Germline variants in tumor suppressor *FBXW7* lead to impaired ubiquitination and a neurodevelopmental syndrome

Authors

Sarah E.M. Stephenson, Gregory Costain, Laura E.R. Blok, ..., Paul J. Lockhart, John Christodoulou, Tiong Yang Tan

Correspondence tiong.tan@vcgs.org.au

> Stephenson et al., 2022, The American Journal of Human Genetics 109, 601– 617 April 7, 2022 © 2022 American Society of Human Genetics. https://doi.org/10.1016/j.ajhg.2022.03.002





Germline variants in tumor suppressor FBXW7 lead to impaired ubiquitination and a neurodevelopmental syndrome

Sarah E.M. Stephenson,^{1,2} Gregory Costain,^{3,4,5} Laura E.R. Blok,⁶ Michael A. Silk,^{7,8,9} Thanh Binh Nguyen,^{7,8,9} Xiaomin Dong,¹ Dana E. Alhuzaimi,¹ James J. Dowling,^{10,11} Susan Walker,^{11,12} Kimberly Amburgey,^{5,10} Robin Z. Hayeems,^{13,14} Lance H. Rodan,^{15,16} Marc A. Schwartz,^{17,18,19,20} Jonathan Picker,^{15,21} Sally A. Lynch,²² Aditi Gupta,^{23,24} Kristen J. Rasmussen,²⁵ Lisa A. Schimmenti,^{26,27,28} Eric W. Klee,^{23,24,25,26} Zhiyv Niu,^{25,26} Katherine E. Agre,²⁶ Ilana Chilton,²⁹ Wendy K. Chung,^{29,30} Anya Revah-Politi,³¹ P.Y. Billie Au,³² Christopher Griffith,³³ Melissa Racobaldo,³³ Annick Raas-Rothschild,^{34,35} Bruria Ben Zeev,^{34,36} Ortal Barel,^{37,38}

(Author list continued on next page)

Summary

Neurodevelopmental disorders are highly heterogenous conditions resulting from abnormalities of brain architecture and/or function. *FBXW7* (F-box and WD-repeat-domain-containing 7), a recognized developmental regulator and tumor suppressor, has been shown to regulate cell-cycle progression and cell growth and survival by targeting substrates including CYCLIN E1/2 and NOTCH for degradation via the ubiquitin proteasome system. We used a genotype-first approach and global data-sharing platforms to identify 35 individuals harboring *de novo* and inherited *FBXW7* germline monoallelic chromosomal deletions and nonsense, frameshift, splice-site, and missense variants associated with a neurodevelopmental syndrome. The *FBXW7* neurode-velopmental syndrome is distinguished by global developmental delay, borderline to severe intellectual disability, hypotonia, and gastrointestinal issues. Brain imaging detailed variable underlying structural abnormalities affecting the cerebellum, corpus collosum, and white matter. A crystal-structure model of FBXW7 predicted that missense variants were clustered at the substrate-binding surface of the WD40 domain and that these might reduce FBXW7 substrate binding affinity. Expression of recombinant FBXW7 missense variants in cultured cells demonstrated impaired CYCLIN E1 and CYCLIN E2 turnover. Pan-neuronal knock-down of the *Drosophila* ortholog, *archipelago*, impaired learning and neuronal function. Collectively, the data presented herein provide compelling evidence of an F-Box protein-related, phenotypically variable neurodevelopmental disorder associated with monoallelic variants in *FBXW7*.

Introduction

Neurodevelopment is a complex spatiotemporal process requiring the coordinated action of genetic and environmental cues to regulate a multitude of developmental processes, including cellular proliferation, differentiation, migration, and formation of neural circuits. Neurodevelopmental disorders affect $\sim 2\%$ -5% of children and result in

¹Murdoch Children's Research Institute, Melbourne, VIC 3052, Australia; ²Department of Paediatrics, University of Melbourne, Melbourne, VIC 3052, Australia; ³Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ⁴Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ⁵Department of Paediatrics, University of Toronto, Toronto, ON M5G 1X8, Canada; ⁶Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen 6525, the Netherlands; ⁷Structural Biology and Bioinformatics, Department of Biochemistry and Molecular Biology, University of Melbourne, Melbourne, VIC 3052, Australia; ⁸Australia Cancer Research Funding Facility for Innovative Cancer Drug Discovery, Bio21 Institute, University of Melbourne, Melbourne, VIC 3052, Australia; ⁹Computational Biology and Clinical Informatics, Baker Heart and Diabetes Institute, Melbourne, VIC 3004, Australia; ¹⁰Division of Neurology, Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ¹¹Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ¹²The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ¹³Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ¹⁴Centre for Genetic Medicine, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; ¹⁵Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, United States; ¹⁶Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, United States; ¹⁷Department of Pediatrics, Harvard Medical School, Boston, MA 02115, United States; ¹⁸Cancer and Blood Disorders Center, Boston Children's Hospital, Boston, MA 02115, United States; ¹⁹Department of Pediatric Oncology, Dana Farber Cancer Institute, Boston, MA 02115, United States; ²⁰Broad Institute of MIT and Harvard, Cambridge, MA 02115, United States; ²¹Department of Child and Adolescent Psychiatry, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, United States; ²²Department of Clinical Genetics, Children's Health Ireland at Temple Street, Rotunda, Dublin D01 XD99, Ireland; ²³Center for Individualized Medicine, Mayo Clinic, Rochester, MN 55905, United States; ²⁴Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, United States; ²⁵Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, United States; ²⁶Department of Clinical Genomics, Mayo Clinic, Rochester, MN 55905, United States; ²⁷Otolaryngology—Head and Neck Surgery (Ear, Nose, and Throat), Mayo Clinic, Rochester, MN 55905, United States; ²⁸Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN 55905, United States; ²⁹Department of Pediatrics, Columbia University Irving Medical Center, New York, NY 10032, United States; ³⁰Department of Medicine, Columbia University Irving Medical Center, New York, NY 10032, United

© 2022 American Society of Human Genetics.

Sebastien Moutton, 39,40,41 Fanny Morice-Picard, 42 Virginie Carmignac, 41 Jenny Cornaton, 40 Nathalie Marle,⁴³ Orrin Devinsky,⁴⁴ Chandler Stimach,⁴⁵ Stephanie Burns Wechsler,^{46,47} Bryan E. Hainline,^{48,49} Katie Sapp,^{48,49} Marjolaine Willems,⁵⁰ Ange-line Bruel,⁵¹ Kerith-Rae Dias,^{52,53} Carey-Anne Evans, 52, 53 Tony Roscioli, 52, 53, 54 Rani Sachdev, 54, 55 Suzanna E.L. Temple, 52, 53, 54 Ying Zhu, 52, 56 Joshua J. Baker,⁵⁷ Ingrid E. Scheffer,^{1,2,58} Fiona J. Gardiner,⁵⁸ Amy L. Schneider,⁵⁸ Alison M. Muir,⁵⁹ Heather C. Mefford,⁵⁹ Amy Crunk,⁶⁰ Elizabeth M. Heise,⁶⁰ Francisca Millan,⁶⁰ Kristin G. Monaghan,⁶⁰ Richard Person,⁶⁰ Lindsay Rhodes,⁶⁰ Sarah Richards,⁶⁰ Ingrid M. Wentzensen,⁶⁰ Benjamin Cogné,⁶¹ Bertrand Isidor,⁶¹ Mathilde Nizon,⁶¹ Marie Vincent,⁶¹ Thomas Besnard,⁶¹ Amelie Piton,^{62,63} Carlo Marcelis,⁶ Kohji Kato, 64,65 Norihisa Koyama, 66 Tomoo Ogi, 65,67 Elaine Suk-Ying Goh, 68 Christopher Richmond, 69 David J. Amor, 1,2,69 Jessica O. Boyce, 1,2 Angela T. Morgan, 1,2 Michael S. Hildebrand, 1,58 Antony Kaspi, 70,71 Melanie Bahlo,^{70,71} Rún Friðriksdóttir,⁷² Hildigunnur Katrínardóttir,⁷² Patrick Sulem,⁷² Kári Stefánsson,^{72,73} Hans Tómas Björnsson,^{73,74,75} Simone Mandelstam,^{2,76} Manuela Morleo,^{77,78} Milena Mariani,⁷⁹ TUDP Study Group, Marcello Scala,^{80,81} Andrea Accogli,^{80,81} Annalaura Torella,⁷⁷ Valeria Capra,⁸¹ Mathew Wallis,⁸² Sandra Jansen,⁸³ Quinten Waisfisz,⁸³ Hugoline de Haan,⁸³ Simon Sadedin,^{1,69} Broad Center for Mendelian Genomics, Sze Chern Lim,^{1,69} Susan M. White,^{1,2,69} David B. Ascher,^{7,8,9,84} Annette Schenck,⁶ Paul J. Lockhart,^{1,2} John Christodoulou,^{1,2,69} and Tiong Yang Tan^{1,2,69,*}

variable neurocognitive symptoms.^{1–3} They are genetically and phenotypically heterogeneous and often require untargeted genomic analysis and a genotype-first approach for the discovery of novel phenotypes.⁴ Several neurodevelopmental disorders have been attributed to genes that regulate cell division, underscoring the importance of this process in the development of the central nervous system.^{5,6} F-box (FBX) proteins are essential for regulating the

States; ³¹Institute for Genomic Medicine and Precision Genomics Laboratory, Columbia University Irving Medical Center, New York, NYk, 10032, United States; ³²Department of Medical Genetics and Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, AB T2N 4N1, Canada; ³³Division of Pediatrics, University of South Florida, Tampa, FL 33620, United States; ³⁴Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo 6997801, Israel; ³⁵Institute of Rare Diseases, The Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel; ³⁶Pediatric Neurology Unit, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel; ³⁷The Genomic Unit, Sheba Cancer Research Center, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel; ³⁸The Wohl Institute for Translational Med-icine, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel; ³⁹Centre Pluridisciplinaire de Diagnostic PréNatal, Pôle Mère Enfant, Maison de Santé Protestante Bordeaux Bagatelle, Talence, Nouvelle-Aquitaine 33401, France; ⁴⁰Reference Center for Developmental Anomalies, Department of Medical Genetics, Dijon University Hospital, Dijon, Bourgogne-Franche-Comté 21000, France;⁴¹INSERM U1231, Laboratoire de Neurosciences Cognitives, UMR 1231, Genetic of Development Anomalies, University of Burgundy, Dijon, Bourgogne-Franche-Comté 21078 France; ⁴²Reference Center for Genetic, Complex, and Rare Skin Disorders, Department of Pediatric Dermatology, Bordeaux University Hospital, Bordeaux, Nouvelle-Aquitaine 33000, France; 43 Laboratoire de Génétique Chromosomique et Moléculaire, Pôle de Biologie, Centre Hospitalier Universitaire de Dijon, Dijon, Bourgogne-Franche-Comté 21000 France; ⁴⁴Neurology Department, New York University Langone Medical Center, New York, NY 10016, United States; ⁴⁵Department of Human Genetics, Emory Healthcare, Atlanta, GA 30322, United States; ⁴⁶Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, 30322, United States; ⁴⁷Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, 30322, United States; ⁴⁸Indiana University School of Medicine, Indianapolis, Indiana 46202, United States; 49 Indiana University Health Physicians, Indiana University, Indianapolis, Indiana 46202, United States; ⁵⁰Reference Center for Developmental Disorders, Department of Medical Genetics, Arnaud de Villeneuve Hospital, Montpellier University Hospital, Montpellier, Occitanie 34295, France; ⁵¹Inserm UMR 1231, Genetics of Developmental Anomalies, University of Bourgogne, University Hospital Federation, Translational Medicine in Development Disorders, Dijon, Bourgogne-Franche-Comté 21078, France; 52 New South Wales Health Pathology East Laboratory, Prince of Wales Private Hospital, Sydney, NSW 2031, Australia; ⁵³Neuroscience Research Australia, Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney, New South Wales 2031, Australia; ⁵⁴Centre for Medical Genetics, Sydney Children's Hospital, Sydney Children's Australia; 55 School of Women's and Children's Health, University of New South Wales Medicine, University of New South Wales, Sydney, New South Wales 2052, Australia; ⁵⁶Newcastle Genetics of Learning Disability Service, Hunter Genetics, Newcastle, New South Wales 2298, Australia; ⁵⁷Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, United States; ⁵⁸Epilepsy Research Centre, Department of Medicine, Austin Health, University of Melbourne, Melbourne, VIC 3084, Australia; ⁵⁹Department of Pediatrics, University of Washington, Seattle, WA 98195, United States; ⁶⁰GeneDx, Gaithersburg, MD 20877, United States; ⁶¹Medical Genetic Services, The Thorax Institute, INSERM, Centre National de la Recherche Scientifique, University Hospital of Nantes, Nantes, Pays de la Loire 44007, France; 62 Molecular Genetic Unit, Strasbourg University Hospital, Strasbourg, Illkirch-Graffenstaden 67000, France; 63 Institute of Genetics and Molecular and Cellular Biology, INSERM U964, Centre National de la Recherche Scientifique, UMR 7104, University of Strasbourg, Illkirch-Graffenstaden, Grand Est 67400, France; ⁶⁴Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Chubu 467-8601, Japan; 65 Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Chubu 464-860, Japan; 66 Department of Pediatrics, Toyohashi Municipal Hospital, Toyohashi, Chubu 441-8570, Japan; ⁶⁷Department of Human Genetics and Molecular Biology, Nagoya University Graduate School of Medicine, Nagoya, Chubu 467-8601, Japan; ⁶⁸Laboratory Medicine and Genetics, Trillium Health Partners, Mississauga, ON L5B 1B8, Canada; 69 Victorian Clinical Genetics Services, Melbourne, VIC 3052, Australia; ⁷⁰Population Health and Immunity Division, The Walter and Eliza Hall Institute for Medical Research, Melbourne, VIC 3052, Australia; ⁷¹Department of Medical Biology, University of Melbourne, Melbourne, VIC 3052, Australia; ⁷²deCODE Genetics, Amgen, Reykjavik 101, Iceland; ⁷³Faculty of Medicine, University of Iceland, Reykjavik 101, Iceland; ⁷⁴Department of Genetics and Molecular Medicine, Landspitali University Hospital, Reykjavik 101, Iceland; ⁷⁵McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD 21218, United States; ⁷⁶Department of Medical Imaging, The Royal Children's Hospital, Melbourne, VIC 3052, Australia;⁷⁷Telethon Institute of Genetics and Medicine, Pozzuoli, Naples 80078, Italy;⁷⁸Department of Precision Medicine, University of Campania "Luigi Vanvitelli," Naples 80138, Italy; 79 Department of Pediatrics, Azienda Socio Sanitaria Territoriale, Lariana Sant'Anna Hospital, San Fermo Della Battaglia, Como 22042, Italy; 80 Department of Neurosciences, Rehabilitation, Opthalmology, Genetics, and Maternal and Child Health, University of Genoa, Liguria 16126, Italy; ⁸¹Istituto di Ricovero e Cura a Carattere Scientifico Giannina Gaslini Institute, Genoa, Liguria 16147, Italy; ⁸²Tasmanian Clinical Genetics Services, Royal Hobart Hospital, Hobart, Tasmania 7000, Australia; ⁸³Department of Human Genetics, Amsterdam University Medical Centers, Vrije Universiteit Medical Center Amsterdam, Amsterdam, the Netherlands; ⁸⁴Department of Biochemistry, University of Cambridge, Cambridge, England CB2 1GA, United Kingdom

*Correspondence: tiong.tan@vcgs.org.au

https://doi.org/10.1016/j.ajhg.2022.03.002.

ubiquitination of proteins involved in the cell cycle. There are 69 human FBX proteins, which are classified into three subcategories on the basis of the structural class of their substrate-binding domains: FBXW proteins contain a tryptophan-aspartic acid 40 (WD40) repeat domain; FBXL proteins contain a leucine-rich repeat; and FBXO proteins contain other protein-interaction domains (reviewed in Nguyen et al.⁷ and Zhang et al.⁸). FBX proteins are incorporated as one subunit of a tetrameric SCF (SKP1-CUL1-FBX) ubiquitin ligase complex. First, the FBX protein aggregates the phosphorylated target protein independently of the other complex subunits, then it attaches to the adaptor protein S-phase kinase-associated protein 1 (SKP1), which links it to the major structural scaffold protein cullin 1 (CUL1). CUL1 links SKP1 to the ring-box 1 (RBX1) protein, which facilitates the transfer of a ubiquitin molecule to the protein target, now marked for degradation via the ubiquitin proteasome system (UPS).⁸

To date, germline variants in five genes encoding FBX proteins have been found to underlie neurodevelopmental disorders. De novo missense variants in FBXW11 (MIM: 605651) located in the encoded WD40 domain repeats have been associated with mild to severe neurodevelopmental disability, often accompanied by behavioral abnormalities and mandibular, ocular, and digital features.⁹ De novo frameshift, nonsense, splicing, and missense variants in FBXO11 (MIM: 607871) result in mild to severe intellectual disability with dysmorphic facies and behavioral abnormalities.^{10,11} De novo variants in FBXO28 (MIM: 609100) have been identified in individuals with severe to profound intellectual disability (ID) and epilepsy with various seizure types,^{12,13} confirming the initial suggestions that the gene was the primary phenotypic determinant in chromosome 1q41q42 microdeletion syndrome.^{14,15} Autosomal-recessive inheritance has also been observed in FBX-related phenotypes; biallelic variants in FBXL4 (MIM: 605654) cause mitochondrial DNA depletion syndrome with encephalomyopathy,^{16,17} and in FBXL3 they cause intellectual disability with dysmorphic features and short stature.¹⁸ Additionally, KDM2B (MIM: 609078), also known as FBXL10, is a candidate neurodevelopmental-disease-associated gene with a homozygous variant identified in two siblings with developmental delay, hypotonia, and infantile spasms;¹⁹ additionally, monoallelic single-nucleotide variants and chromosomal microdeletions involving this gene have also been identified in individuals with syndromic intellectual disability.^{20,21}

F-box- and WD-repeat-domain-containing 7 (*FBXW7*; GenBank: NG_029466.2; MIM: 606278) has been extensively studied as a tumor suppressor (reviewed in Yeh et al.²² and Sailo et al.²³). However, it has also been implicated in a variety of diverse biological processes, including the immune response,^{24,25} liver lipid metabolism,²⁶ angiogenesis,^{27,28} cardiac hypertrophy,²⁹ haemopoiesis,³⁰ neurodevelopment^{31–36} and excitotoxicity.^{37,38} Herein we provide a detailed characterization of 35 individuals from 32

families identified through global matchmaking databases and found to have 28 germline *de novo* and inherited monoallelic *FBXW7* variants associated with neurodevelopmental disability and variable features. Evidence from *in silico* protein modeling, cell-based functional studies, and *Drosophila* neuronal knockdown converge to support the discovery that pathogenic variants in *FBXW7* cause an FBX-related neurodevelopmental syndrome.

Subjects and methods

Subjects and FBXW7 variant analysis

All procedures were approved by institutional human research ethics committees, and informed consent was obtained for all individuals. Individuals were clinically evaluated in separate centers, and DNA samples were analyzed by chromosomal microarray or genomic sequencing (exome or genome, with singleton or trio analysis) on a clinical or research basis. Contact between researchers was facilitated with web-based tools Matchmaker Exchange³⁹ and GeneMatcher.⁴⁰ High-confidence candidate variants, categorized as either predicted LoF or damaging candidates, absent from gnomAD and classified as pathogenic according to the American College of Medical Genetics (ACMG) guidelines⁴¹ are reported. The functional outcome of splice-site variants was predicted with BDGP NNSPLICE 0.9,⁴² NetGene2^{43,44} and Splice AI.⁴⁵

In silico modeling of the impact of FBXW7 variant interaction with CYCLIN E1

The structure of CYCLIN E1 (amino acids [aa] 89–395) was built under the default parameters of the i-TASSER website.⁴⁶ The complex between FBXW7 and CYCLIN E1 was then modeled with Schrodinger (2020-3). The highest-resolution experimental X-ray structures of FBXW7 (aa 263–706, PDB: 20VR)⁴⁷ and the modeled CYCLIN E1 from i-TASSER were used for building the complex. A restraint docking approach was applied in Schrodinger. There were four restraints (between 4 and 6 Å) that were applied to the residues between FBWX7 and CYCLIN E1, namely Ser384(CYCLIN E1)-Arg479(FBXW7), Thr380(CYCLIN E1)-Arg505(FBXW7), Thr380(CYCLIN E1)-Arg465(FBXW7), and Thr380(CYCLIN E1)-Arg479(FBXW7).⁴⁷ We then screened the top solutions to evaluate them by their ability to satisfy the experimental data.

FBXW7 missense variants were first annotated for predicted consequences via the Variant Effect Predictor (release 101) including dbNSFP (4.1a) output.^{48,49} MTR scores were included from the MTR-Viewer. We selected a number of these scores to capture conservation, physicochemical properties, and genic intolerance. We examined structural properties by using the mCSM suite to manually map the missense variants to the homology-modeled complex of FBXW7 with CYCLIN E1 bound. We used mCSM to predict changes to thermodynamic stability ($\Delta\Delta G$) and mCSM-PPI2 to predict changes to binding affinity.^{50,51} Additionally, changes to charge, volume, and residue nature were reported for each substitution.

Functional analysis of FBXW7 variants

The open reading frame of *FBXW7* variants (GenBank: NM_001349798.2; c.1267G>A [p.Gly423Arg]; c.1439A>G [p.Asp480Gly]; c.1631T>G [p.Val544Gly]; c.1920C>A [p.Ser640-Arg]; c.2020C>T [p.Arg674Trp]; c.2021G>C [p.Arg674Pro]; and c.2066G>A [p.Arg689Gln]); and known substrates E1 CYCLIN

(GenBank: NM_001238.4) and E2 CYCLIN (GenBank: NM_057749.3) were synthesized, their sequences were verified, and they were cloned inframe into C-terminal- epitope-tagged vectors pcDNA3.1/Myc-His (ThermoFisher, V80020) and pcDNA3.1/V5-His (ThermoFisher, V81020), respectively (Integrated DNA Technologies).

HEK293T cells (American Type Culture Collection CRL-3216) were transiently transfected with an *FBXW7* variant alone or in combination with either a known substrate or empty vector through the use of Fugene HD (Promega, E2311) and harvested at 60–72 h after transfection. Where indicated, cells were treated with 5 μ M MG-132 (Merck, 1474790) or DMSO (Sigma, D2650) at 48 h after transfection and harvested after 16 h. Protein lysates were obtained by resuspension and sonication (Digital Sonifier Cell Disruptor 250, Branson) in 2% SDS, 10 mM TRIS (pH 7.5) with 1× Complete Protease Inhibitor Cocktail (Roche, 11697498001) followed by protein estimation (ThermoFisher, 23225).

Immunoblots were performed on 50 μ g of total protein via the Criterion TGX system (BioRad) and probed sequentially with antibodies to anti-c-Myc (9E10, Abcam, AB32, 1:5000); anti-V5 (ThermoFisher, R960, 1:5000), and GAPDH (1D4, Novus Biologicals, NB300-221, 1:5000). Primary antibodies were detected with goat anti-mouse IgG (H+L, Jackson ImmunoResearch, 115-005-003, 1:10000), and bands were visualized with the Clarity Western ECL Substrate (BioRad, 1705061) and the Amersham Imager 680 (GE Health, 29270772).

Densitometry of detected bands was recorded for semiquantitative analysis between samples. Lanes and bands were identified automatically and then manually modified where appropriate; the rolling-ball method was used for background correction. Individual sample values were first determined by normalization of the intensity of the protein of interest to the housekeeping control protein for each individual sample. To control for individual blot variation, we then normalized each sample to the intensity of the signal of the FBXW7 WT sample before combining samples for statistical significance testing by a two-sample, two-tailed Student's t test; p < 0.05 was considered significant.

Drosophila ago knockdown models

Two *Drosophila* UAS-RNAi lines (RNAi-1, BL34802; and RNAi-2, BL31501), both previously validated^{52,53} and carrying inducible RNAi constructs against the *FBXW7* homolog *archipelago* (*ago*; CG15010; FBgn0041171), and the matching genetic background control (BL36303) were obtained from the Bloomington *Drosophila* Stock Center. *Drosophila* stocks were maintained at room temperature on standard *Drosophila* diet (sugar, cornmeal, agar, and yeast).

The efficiency and relative strength of *ago* RNAi-1 and *ago* RNAi-2 constructs were determined by quantitative real-time-PCR (qPCR) analysis. The *ago* RNAi-1 and *ago* RNAi-2 lines and their genetic background controls were crossed to the ubiquitous Act-Gal4/TM3 Sb Tb driver, and mRNA was extracted from wandering L3 larva of the appropriate genotype with QIAGEN's Rneasy Lipid Tissue Mini Kit. DNase treatment was performed with QIAGEN's RNase-Free DNase Set, and cDNA was synthesized with the Bio-Rad iScript cDNA synthesis kit according to the manufacturer's protocols. PCRs were performed with primers targeting *ago* (5'-GGCCACGACGATCATGTG-3' and 5'-GACTTTGAGC GTGCGATCC-3') and $\beta'COP$ (5'-AACTACAACACCCTGGAGAA GG-3' and 5'-ACATCTTCTCCCAAATTCCAAAG-3') with the GoTaq qPCR Master Mix (Promega) on an Applied Biosystem

Fast 7500 Real-Time machine. The initial denaturation was performed for 10 min at 95°C, followed by 15 s at 95°C and 30 s at 60°C for 40 cycles (qPCR data collection). The products were then denatured at 95°C for 1 min and cooled to 65°C for 1 min (melt curve data collection). For each condition, three biological and three technical replicates were analyzed. Differential gene expression was calculated via the $2^{\Delta\Delta Ct}$ method.⁵⁴ The average Ct value for each sample was calculated and subtracted from the Ct value of the reference gene so that the Δ Ct value could be calculated.⁵⁵ A two-sample t test (equal variance) comparing the $2^{\Delta\Delta Ct}$ values of the RNAi line and genetic background control was performed in Microsoft Excel for calculation of p values).

For inducing neuronal knockdown, the UAS-RNAi lines were crossed to either of two panneuronal promotor lines: (1) $\mathsf{elav}^{(\mathrm{III})}\text{-}$ Gal4 with genotype "w1118; 2xGMR-wIR; elav-Gal4, UAS-Dicer-2" and to (2) $elav^{(I)}$ – Gal4 with genotype "c155-Gal4, GMR-wIR; +; +". The latter is a strong Gal4 insertion into the endogenous elav locus. Crosses were maintained at 25°C, 70% humidity in a 12 h:12 h light:dark cycle. Habituation learning and basal motor function were tested in the light-off jump-reflex habituation and fatigue assays, as previously described.⁵⁶ In brief, three- to four-day-old males were individually placed in semi-transparent vials enclosed by two microphones. The filled vials were inserted into two independent 16-unit light-off jump-habituation systems (Aktogen) and left to acclimatize for 5 min before the start of the habituation paradigm assay, in which 32 flies were simultaneously exposed to 100 light-off pulses of 15 ms with a 1 s inter-trial-interval. The noise amplitude produced by wing vibrations was recorded for 500 ms after each light-off pulse. The measured sound amplitudes were filtered with a threshold to remove background noise, leading to the annotation of a jump at amplitude above 0.8. The jumps were collected and analyzed by a custom-made Labview Software (National Instruments). A high initial jump response to the light-off pulse decreased with the increase of the number of repeated pulses. A fly was considered to have habituated when it failed to jump for five consecutive light-off pulses (no jump criterion). The last jump was then stated as the number of trials needed to reach the no-jump criterion (trials to criterion, TTC). If the fraction of flies jumping to at least one of the first five light-off pulses (initial jump response) was <50%, genotypes were classified as non-performers on the basis of reduced motor performance of the tested population. Habituation per genotype was quantified as the mean trials to criterion (mTTC) of all flies of the same genotype.

The fatigue assay was performed after the habituation assay, which was equivalent to the habituation assay but involved two adaptations; (1) increased inter-trial-interval from 1 to 5 s and (2) shortened trial length from 100 to 50 light-off pulses. The increased inter-trial-interval prevented the flies from habituating and thereby elicited a jump response at each light-off trial. As for the habituation assay, the no-jump criterion was five consecutive pulses without a jump. Failing to jump for five consecutive light-off pulses in this assay was identified as a basal failure to execute jumping and was deemed to be due to increased fatigue. The last jump was scored as the number of trials it took to reach the no-jump criterion (TTC). The TTCs of the simultaneously measured flies of the same genotype were averaged (mean TTC (mTTC)).

Statistics

Protein density and qPCR: statistical significance was assessed by a two-sample, two-tailed Student's t test, and p < 0.05 was considered significant.

Drosophila behavior: the effect of the genotype on habituation and fatigue was scored by comparison of log-transformed TTC values of the mutant versus the control flies after correction for the experimental day and system via a linear-model regression analysis with R statistical software (v.3.0.0).⁵⁶

Results

Monoallelic *FBXW7* variants are associated with neurodevelopmental disability, brain anomalies, hypotonia, and gastrointestinal issues

Using clinical or research-based chromosomal microarrays, genomic sequencing (trio genome or exome), and the global matchmaking platforms Matchmaker Exchange³⁹ and GeneMatcher,⁴⁰ we have identified 35 individuals (26 male, 74.3%) from 32 families with 28 distinct variants in FBXW7. The variants arose de novo in 30 individuals, including two individuals displaying mosaicism and two showing familial transmission from an affected parent (Table S1). The clinical phenotype is characterized by neurodevelopmental disability (34/35; 97.1%), including global developmental delay and intellectual disability ranging from borderline to severe, language disorder, and hypotonia (22/35; 62.9%); individual 21 was severely affected and had episodes of developmental regression and progressive spasticity. Seizures of varying types were reported in 8/35 (22.9%) individuals. Feeding difficulties and constipation were each reported in 16/35 (45.7%) individuals. Growth was generally within normal limits, but macrocephaly was noted in 10/35 (28.6%) and microcephaly in 2/35 (5.7%) individuals. Congenital anomalies were diverse and included palatal, uvular, or laryngeal anomalies (11/35, 31.4%); cardiac anomalies (11/35, 31.4%); and cryptorchidism (5/26 males, 19.2%) (Figure 1, Table 1 and Table S2).

There was no recognizable facial gestalt; however, we noted deeply set eyes with upper eyelid fullness in 9/35 (25.7%) individuals. Other craniofacial features in some individuals included cleft (overt and submucous) or high palate (10/35, 28.6%), midface retrusion with class III malocclusion (1/35, 2.9%), and a tall or broad forehead (4/35, 11.4%). In individual 19 with somatic mosaicism of the *FBXW7* variant, we observed cutaneous Blaschkoid dyspigmentation.

Neuroimaging was undertaken in 17 individuals (15 by MRI, one by CT, and one by both modalities); brain anomalies were identified in 13/17 (76.5%) individuals and included an absent, hypoplastic, or dysplastic corpus callosum (7/17; 41.2%); an abnormal cerebellum (5/17; 29.4%); delayed myelination (2/17; 11.7%); a thick brainstem (2/17; 11.7%); and polymicrogyria (2/17; 11.7%) (Table 1 and Table S2). Scattered small subcortical calcifications were noted on a computed tomography brain scan of individual 22. Ten brain MRI scans of seven individuals (3, 18, 19, 21, 25, 28, and 31) were available for systematic review by a pediatric neuroradiologist (S.M.). The most common anomalies were related to the posterior fossa,

where the cerebellum was enlarged or at the upper limit of the normal range, except in individual 19, who had severe cerebellar atrophy with large folia and a thick dysmorphic corpus callosum and brainstem. Notably, this individual, previously reported as patient IV.1,⁵⁷ also has a familial *CACNA1A* pathogenic variant of variable expressivity, c.835C>T (p.Arg279Cys) (GenBank: NM_023035.2). Although *FBXW7* is a known tumor suppressor, none of the individuals in our cohort has so far developed cancer; the oldest individual is 44 years old. Notably, 13 of the 28 variants observed in this cohort are also reported in somatic form in the COSMIC database, which has collated 1,481 (440 unique) known somatic variants that span the entire coding region of *FBXW7* in various cancer types (Figure S1 and Table S1).

Germline *FBXW7* missense variants identified in this cohort cluster within the substrate-binding surface of the WD40 domain

We identified 28 germline FBXW7 variants in 35 individuals (Figure 2 and Table S1). Two individuals had large chromosomal deletions encompassing FBXW7. One individual had a canonical splice-site variant, c.1236+2T>A, which is predicted to result in donor-site loss. Seven individuals (three de novo and four familial) had frameshift variants affecting the longest transcript (Gen-Bank: NM_001349798.2). Two variants, c.1331_1332del (p.Lys444Serfs*27) and c.1332dup (p.Val445Serfs*27), are predicted to undergo nonsense-mediated decay (NMD) with presumed loss of function (LoF). In contrast, c.1331_1332del (p.Asn572Leufs*32) and c.1939A>T (p.Lys647*) are within the 54 bp upstream of the final intron/exon junction and are predicted to escape NMD.⁵⁸ These truncated proteins might be targeted for degradation via the UPS. The remaining 25 individuals had 21 unique missense variants clustering at the carboxy-terminal half of the protein, and 16/21 (76.2%) of these variants occurred within the WD40 domain. Three variants, c.1267G>A (p.Gly423Arg); c.2020C>T (p.Arg674Trp); and c.2065C>T (p.Arg689Trp), were recurrent in unrelated individuals.

The crystal structure of the FBXW7 and SKP1 complex has been determined with the substrates CYCLIN E1 and DISC1.^{47,59} The F-box domain located in the N-terminal half of FBXW7 mediates interaction with SKP1, whereas the WD40 domain forms a canonical eight-bladed β -propeller structure. Thirteen residues positioned at the top surface of the propeller directly interact with CYCLIN E1 (seven of these also interact with DISC1). The position of the variants identified in this study aligns with the residues required for this interaction: Arg441, Ser462, Arg465, Arg479, Arg505, and Ala599. A further four variants, c.1267G>A ((p.Gly423Arg)); c.1744T>G (p.Ser582Ala); c.2021G>C (p.Arg674Pro); and c.2020C>T (p.Arg674Trp), impact residues adjacent to critical residues Trp425, Leu583, Trp673, respectively.



Figure 1. Characteristics of FBXW7 neurodevelopmental syndrome

(A) Genotype-phenotype matrix of clinical features of key phenotypes associated with *FBXW7* neurodevelopmental variants. Each square represents an individual overlaid with variant class, and each row represents a clinical feature (affected—yellow; unaffected—blue). Variant types are depicted by dots: red (frameshift, stop, whole-gene deletion), blue (missense affecting WD40 domain), and gray (missense not in a WD40 domain).

(B) Clinical features of affected individuals depicting phenotype by variant type: individual 1, aged 3 years, frontal and lateral, with arrow marking preauricular pit; individual 2, aged 3 years 2 months, frontal and lateral; individual 3, aged 14 years 9 months, from family 1, frontal and lateral; individual 4, aged 11 years 9 months, from family 1, frontal and lateral; individual 5, aged 6 years 3 months, from family 1, frontal and lateral; individual 6, aged 44 years, father of individuals 3–5 from family 1, frontal and lateral (note midface retrusion with class III malocclusion); individual 8, aged 5 years, frontal; individual 12 at 12 months, frontal, lateral, and at 26 months, frontal; mother of individual 12, aged 34 years, frontal and lateral; individual 15 at 3 years and 15 years; individual 19 at age 6 years, frontal and lateral; individual 20 at 5 years, frontal and lateral; individual 21 at 3 years; individual 23 at 3 years; individual 24 at 5 years, frontal and lateral; individual 30 aged 15 years, frontal and lateral; individual 32 aged 10 years; individual 34 aged 1 year, frontal, and 12 years, frontal and lateral; individual 35 aged 3 years and 7 years, frontal. Deeply set eyes with upper eyelid fullness are evident in individuals 1, 2, 3, 5, 15, 21, 24, 32 (also in individual 21, not pictured).

(C) Neuroradiological features of selected individuals; sagittal images of T1-weighted brain MRI scans of individuals 3, 20, 27, and 30 and T2-weighted brain scan of individual 24, displaying large cerebellar vermis with tonsillar ectopia (white arrowheads) and thick callosal genu (arrows)—note the generally thinned corpus callosum in individuals 24 and 30; axial T1-weighted brain MRI scans of individuals 20, 27, and 30 and T2-weighted brain scan of individual 24 displaying scattered subcortical white-matter hyperintensities and severely delayed myelination, equivalent to 7–10 months.

To investigate the potential functional impact of the variants observed in this cohort, we mapped the amino acid position to the tertiary structure previously resolved for FBXW7 by crystallography (amino acids 263–706).⁴⁷ This demonstrated fthat the amino acids implicated in disease cluster at the surface of the substrate-binding interface (Figure 2 and Figure S2). Using the mutation Cutoff Scanning Matrix (mCSM) suite, we tested the predicted impact of each missense variant on the stability of FBXW7. Our tests demonstrated that 16/21 (76.2%) vari-

ants are predicted to decrease FBXW7 stability (average $-0.735 \pm 1.05 \Delta\Delta G$; Table S3). Next, we assessed the distance to the interface and the binding affinity to determine the potential of the variants to impact the interaction with CYCLIN E1. This demonstrated that FBXW7 missense variants identified in this cohort are positioned very close to the interaction interface (average 7.80 \pm 5.24 Å) and that 13 (65%) are predicted to decrease the binding affinity of FBXW7 to CYCLIN E1 (average $-0.39 \pm 0.74 \Delta\Delta G$).

Table 1. Demographic and clinical featur individuals	es of affected
Demographic features	
Sex	26 male/9 female
Age range	23 months–44 years, 6 months
Medical history	
Prenatal history	Normal; only one premature birth
Neurologic or CNS features	
Hypotonia (HP: 0001252)	22/35 (62.9%)
Seizures (HP: 0001250)	8/35 (22.9%)
Ataxia (HP: 0001251)	2/35 (5.7%)
Developmental regression (HP: 0002376)	1/35 (2.9%)
Abnormality of brain morphology (HP: 0012443)	13/17 (76.5%)
Macrocephaly (HP: 0000256)	10/35 (28.6%)
Microcephaly (HP: 0000252)	2/35 (5.7%)
Development, cognition, and psychiatric	c features
Neurodevelopmental abnormality (HP: 0012759)	34/35 (97.1%)
Mild-moderate developmental delay or intellectual disability (HP: 0011342, HP: 0011343, HP: 0001256, and HP: 0002342)	27/35 (77.1%)
Severe global developmental delay or intellectual disability (HP: 0011344, HP: 0010864)	3/35 (8.6%)
Delayed speech and language development only (HP: 0000750)	1/35 (2.9%)
Specific learning disability (HP: 0001328)	2/35 (5.7%)
No neurodevelopmental abnormality	1/35 (2.9%)
Ophthalmologic features	
Strabismus (HP: 0000486)	5/35 (14.3%)
Abnormality of refraction (HP: 0000539)	6/35 (17.1%)
Astigmatism (HP: 0000483)	1/35 (2.9%)
Cerebral visual impairment (HP: 0100704)	1/35 (2.9%)
Audiology and hearing	
Mixed hearing impairment (HP: 0000410)	2/35 (5.7%)
Oral, dentition, and other ENT features	
Abnormal palate or uvula morphology (HP: 0000174), (HP: 0000172)	10/35 (28.6%)
Laryngeal cleft (HP: 0008751)	1/35 (2.9%)
Cardiac features	-
Abnormal heart morphology (HP: 0001627)	11/35 (31.4%)

Respiratory features

Recurrent pneumonia (HP: 0006532)	3/35 (8.6%)
Gastrointestinal and feeding features	
Feeding difficulties, including difficulties with nasogastric tube feeding (HP: 0011968, HP: 0040288)	16/35 (45.7%); 5/16 (31.3%)
Constipation (HP: 0002019)	16/35 (45.7%)
Gastresophageal reflux (HP: 0002020)	7/35 (20.0%)
Renal and genitourinary features	
Cryptorchidism (HP: 0000028)	5/26 (19.2%)
Hematologic features	
Neutropenia (HP: 0001875)	2/35 (5.7%)
n = 35; the frequency of clinical features is expresse age) of the number assessed for that feature.	ed as a fraction (and percent-

None of the variants detected in this cohort were observed in the population database, gnomAD v2.1 (140k exomes and genomes); however, for each of three variants-c.1394G>A (p.Arg465His), c.1436G>A (p.Arg479Gln), and c.1796C>T (p.Ala599Val) -an ultra-rare (allele frequency < 0.000005) alternative amino acid substitution, c.1393C>T (p.Arg465Cys), c.1435C>G (p.Arg479Gly), and c.1796C>G (p.Ala599Gly), respectively, has been observed. Nevertheless, these gnomAD substitutions were detected with allele balance rates of \leq 45% where mosaicism could not be excluded (Table S1). To further assess how the variants observed in our cohort differed from variants reported in gnomAD, we investigated the impact of the 78 gnomAD missense variants on the resolved FBXW7 crystal structure. Although the majority of gnomAD variants (69; 89%) are predicted to have a destabilizing effect on the protein (average $-0.723 \pm$ 0.616 $\Delta\Delta G$), these variants are dispersed throughout the structure and positioned much farther from the interface with CYCLIN E1 (average 29.24 \pm 17.24 Å) than the variants identified in this study (Figure S1 and Table S4). Furthermore, the gnomAD variants are predicted to have a very small effect on the binding affinity to CYCLIN E1 (average $-0.064 \pm 0.25 \Delta\Delta G$).

Disease-associated variants impair the ability of FBXW7 to degrade substrates CYCLIN E1 and CYCLIN E2

To experimentally determine the functional consequences of *FBXW7* variants observed in this cohort, we cloned a subset into a mammalian expression vector with a C-terminal Myc tag and exogenously expressed in HEK293T cells. We selected variants within the WD40 domain (p.Gly423Arg, p.Asp480Gly, p.Val544Gly, and p.Ser640-Arg) and outside the WD40 domain (p.Arg674Trp, p.Arg674Pro, and p.Arg689Gln) for cloning. The steadystate amount of FBXW7 protein was assessed by immunoblot, and all mutant proteins were detected (Figure 3A). Relative to FBXW7^{wild type}, FBXW7^{Arg674Trp} and FBXW7^{Arg689Gln} demonstrated a decrease in steady-state



Figure 2. *FBXW7* variants detected in this cohort cluster within the substrate-bind-ing surface of the WD40 domain

(Å) The gene structure surrounding *FBXW7* on chromosome 4 (GRCh37: 4q31–3q32.1) demonstrates the genomic position of two large genomic deletions identified in individuals 8 and 9 (thick red bars above chromosome).

(B) Missense *FBXW7* variants identified in this study cluster within the WD40-repeat domain. Frameshift, stop-gain, or splice-site (red) and missense (blue—within the WD40 domain; and gray—outside the WD40 domain) variants are shown above the protein. Recurrent non-familial (bold); recurrent familial (underlined); F-box domain (orange); and a WD40-repeat domain (beige) derived from DECIPHER.

(C) Representation of the resolved structure of FBXW7 when in complex with a CYCLIN E1 degron (residues 360–390) demonstrating that the residues of FBXW7 that directly interact with CYCLIN E1 span similar residues as disease variants identified in this cohort. The positions of FBXW7 residues that directly interact with CYCLIN E1 are shown below

the schematic depiction. F-box helices (rectangles H-1, H0, and H1–H3), linker α -helical domain (rectangles H4–H5), and the canonical eight-bladed β -propeller structure of the WD40 domain with each blade consisting of four antiparallel β strands (arrows [A–D] are shown,⁴⁷ Amino acids in bold have also been shown to directly interact with DISC1.⁵⁹

(D) *FBXW7* variants associated with neurodevelopmental disorder are predominantly located at the substrate-binding surface of the WD40 repeat domain. The location of residues (in sticks with carbon atoms in purple, nitrogen atoms in blue, and oxygen atoms in red) impacted by mutations is shown on the tertiary structure of FBXW7 (cartoon) in configuration with CYCLIN E1 (surface in gray). The docking location of the conserved FBXW7 substrate-binding TPPXQ motif (cartoon in green) of CYCLIN E1 is demonstrated in close proximity to many of the impacted residues. Figure S1 provides an overlay of the variant residue with the wild-type residue for each individual variant, allowing identification of the change predicted in interaction for each missense variant.

protein amount, 0.42-fold and 0.16-fold, respectively, but only FBXW7^{Arg689Gln} reached statistical significance (p = 0.007) (Figure 3B). After treatment with UPS inhibitor MG-132, only FBXW7^{Arg689Gln} was found to have a steady-state protein amount that was increased relative to those of FBXW7^{wild} type (3.4-fold, p = 0.003; Figure 3C). This suggests that most missense variants tested (six of seven) are unlikely to cause protein instability or consequent degradation by the UPS *in vivo*.

Next, we assessed the functional impact of these missense variants by co-expressing them with C-terminal V5-tagged substrates CYCLIN E1 and CYCLIN E2 in HEK293T cells. As expected, steady-state protein amounts of CYCLIN E1 and CYCLIN E2 were reduced when co-expressed with FBXW7^{wild type} (p = 0.002 and p = 0.0003, respectively). This confirmed that exogenously expressed wild-type FBXW7 retains its ability to ubiquitinate and degrade CYCLIN E1 and CYCLIN E2 in vitro and is provides a suitable way to assess variant effects. Collectively, variants within the WD40 domain appear to have a greater impact on the ability of FBXW7 to degrade CYCLIN E1 and CYCLIN E2 than the variants outside the WD40 domain (Figures 3D and 3E and Figures 3G/and 3H, respectively). FBXW7^{Gly423Arg}, FBXW7^{Val544Gly}, and FBXW7^{Ser640Arg} were less efficient at degrading substrate;

CYCLIN E1 steady-state protein amounts were elevated by 1.7-fold (p = 0.002), 1.4-fold (p = 0.007), and 1.3-fold (p = 0.06), respectively, in comparison to amounts seen with FBXW7^{wildtype} (Figure 3E). Similarly, CYCLIN E2 steady-state protein amounts were elevated by 2.5-fold (p = 5 × 10⁻⁵), 2.6-fold (p = 4.6 × 10⁻⁶), and 2.8-fold (p = 7.5 × 10⁻⁶), respectively. By contrast, FBXW7^{Asp480Gly} did not have a consistent effect on steady-state protein amounts of the two substrates. Although it was more efficient at degrading CYCLIN E1 than FBXW7^{wildtype} (0.6-fold, p = 0.002) it was less efficient at degrading CYCLIN E2 (1.8-fold, p = 0.02).

The variants outside the WD domain have a more subtle impact on CYCLIN E1 and CYCLIN E2 steady-state protein amounts. Although CYCLIN E1 steady-state protein amounts were slightly increased when co-expressed with FBXW7^{Arg674Trp} and FBXW7^{Arg674Pro}, this did not achieve statistical significance. However, the steady-state protein amounts of CYCLIN E2 was found to be elevated 1.6-fold (p = 0.005) and 1.6-fold (p = 0.02), respectively compared to FBXW7^{wildtype}. Notably, FBXW7^{Arg689Gln}, which was found to be turned over by the UPS, had CYCLIN E1 and CYCLIN E2 steady-state protein amounts comparable to FBXW7^{wildtype}, suggesting that the variant protein is able to efficiently degrade CYCLIN E1 and CYCLIN E2.



Figure 3. Disease-associated variants impair the ability of FBXW7 to degrade substrates CYCLIN E1 and CYCLIN E2

(A) The majority of disease-associated FBXW7 variants do not impact steady-state protein amounts. Representative immunoblots of wild-type or mutant FBXW7 with and without inhibition of the ubiquitin proteasome system are shown. HEK293T cells exogenously expressing wild-type FBXW7 or mutant FBXW7 with a C-terminal Myc tag for 32 h were treated with 5 μ M MG-132 for 16 h (four independent replicates).

(B) Quantification of FBXW7:GAPDH from DMSO-treated samples of mutant FBXW7 protein in (A) relative to FBXW7^{wild type}; statistical support for altered steady-state amounts of the mutant FBXW7 protein was only evident for FBXW7^{Arg689GIn} (p = 0.007).

(C) Quantification of FBXW7:GAPDH in MG-132-treated cells and versus their DMSO-treated counterpart in (A), demonstrating the change in steady-state mutant FBXW7 protein relative to FBXW7^{wild type} protein after UPS inhibition; statistical support for altered steady-state protein amount was only evident for FBXW7^{Arg689GIn} (p = 0.003).

(D) Certain FBXW7 mutant proteins demonstrate impaired CYCLIN E1 substrate degradation. Representative immunoblots of wild-type or mutant FBXW7 co-expressed with the substrate CYCLIN E1 are shown. Whole-cell lysates extracted from HEK293T cells that exogenously expressed wild-type FBXW7 or mutant FBXW7 with a C-terminal Myc tag and CYCLIN E1 with a C-terminal V5 tag for 48 h are shown (nine independent replicates).

(E) Quantification of CYCLIN E1:GAPDH in (D) for samples expressing mutant FBXW7 versus FBXW7^{wild type} protein; statistical support for altered steady-state protein amount of CYCLIN E1 was evident for FBXW7^{Gly423Arg} (p = 0.002), FBXW7^{Asp480Gly} (p = 0.002), and FBXW7^{Val544Gly} (p = 0.007).

(F) Quantification of FBXW7:GAPDH in (D) for FBXW7 mutant proteins versus FBXW7^{wild type} protein when cells were co-transfected with CYCLIN E1. Statistical support for altered steady-state protein amount was evident only for FBXW7^{Arg674Pro} (p = 0.005).

(G) The majority of FBXW7 mutant proteins demonstrate impaired CYCLIN E2 substrate degradation. Representative immunoblots of wild-type or mutant FBXW7 co-expressed with the substrate CYCLIN E2 are shown. Whole-cell lysates extracted from HEK293T cells that exogenously expressed wild-type FBXW7 or mutant FBXW7 with a C-terminal Myc tag and CYCLIN E2 with a C-terminal V5 tag for 48 h are shown (ten independent replicates).

(H) Quantification of CYCLIN E2:GAPDH in (G) for samples expressing FBXW7 mutant protein versus FBXW7^{wild type} protein; statistical support for altered steady-state protein amount of CYCLIN E2 was evident for FBXW7^{Gly423Arg} (p = 0.00005), FBXW7^{Asp480Gly} (p = 0.02), FBXW7^{Val544Gly} (p = 0.00005), FBXW7^{Ser640Arg} (p = 0.00007), FBXW7^{Arg674Trp} (p = 0.005), and FBXW7^{Arg674Pro} (p = 0.02).

(I) Quantification of FBXW7:GAPDH in (G) for FBXW7 mutant proteins versus FBXW7^{wild type} protein when cells were co-transfected with CYCLIN E2; statistical support for altered steady-state protein amount was evident for FBXW7^{Arg674Pro} (p = 0.04) and FBXW7^{Arg674Pro} (p = 0.02). All graphs present mean \pm SEM. Student's t test: *p < 0.05; **p < 0.01; and ***p < 0.001.



Figure 4. Knockdown of the *FBXW7 Drosophila* ortholog *ago*, specifically in neurons, can lead to deficits in habituation learning deficits and more severe neuronal dysfunction

(A) Simplified scheme of the habituation assay, used for assessing the stimulus-induced escape response of individual flies upon repeated exposure. In controls, as depicted, the initial high jump response gradually wanes. Of note, in reality, the amplitude of jumps does not wane, but the frequency decreases in the tested population.

B) Knockdown of *ago* with RNAi-1 and either $elav^{(I)}$ -Gal4 or $elav^{(III)}$ -Gal4 severely impairs jumping. Knockdown of *ago* with RNAi-2 driven by either driver is less detrimental, allowing assessment of habituation learning.

(C) Neuronal knockdown of *ago* by elav^(III)-Gal4 and RNAi-2 reduces the ability of flies to habituate to the stimulus (in blue); in ccontrast to their genetic-background controls (in gray), they keep jumping with increased frequency throughout the course of the experiment.

(D) Quantification of habituation according to mean trials to nojump criterion (mTTC). Precise genotypes tested in (C) and (D): w/Y; 2xGMR-wIR/+; elav-Gal4^(III), UAS-Dicer-2/ UAS-RNAi-2 (in blue; n = 71, mTTC = 14.91, p = 0.0015). Genetic background control w/Y; 2xGMR-wIR/+; elav-Gal4^(III), UAS-Dicer-2/+ (in gray; n = 71, mTTC = 7.46). Statistical significance was assessed by a linear-model regression analysis on the log-transformed mTTC values; *p = 0.05, **p = 0.01, and ***p < 0.001.

FBXW7 mutant protein steady state protein amounts when co-expression with CYCLIN E1 or CYCLIN E2 were also assessed and it was found that FBXW7^{Arg674Pro} steady-state protein amounts were increased by 4.1-fold (p = 0.2) and 2.2-fold (p = 0.02) relative to FBXW7^{wildtype,} respectively (Figure 3F and 3I). These studies provide evidence in an *in vivo* cell culture model that FBXW7 missense variants identified in this cohort may destabilize the mutant protein and impact the ability of FBXW7 to degrade target substrates.

Neuronal knockdown of the FBXW7 Drosophila ortholog archipelago causes cognitive and severe neurological deficits

To address the consequences of partial loss of *FBXW7* function (as seen for most of the investigated variants) *in vivo*,

we turned to Drosophila melanogaster as a model. The Drosophila genome encodes a one-to-one FBXW7 ortholog termed archipelago (ago). The two proteins share 61% amino acid similarity, and the F-box domain and the seven WD40 repeats are highly conserved (Figure S3).⁶⁰ The E3 ubiquitin ligase function of FBXW7, its role in cell-cycle progression and growth, and its substrate cyclin e (ortholog of CYCLIN E1/2) have been confirmed in flies.^{60,61} Partial loss of ago function was attempted with the UAS-Gal4 system,⁶² and two previously validated lines carrying ago-specific UAS-RNA interference constructs (RNAi-1 and RNAi-2).^{52,53} We first determined efficiency and relative strength of ago RNAi-1 and ago RNAi-2 constructs by quantitative RT-PCR upon ubiquitous knockdown by using the Act-GAL4 driver. The driver crossed to the genetic background of both RNAi lines served as a control in all experiments. Both lines led to lower levels of ago, albeit to different degrees. The expression level of ago relative to control levels was 19% in ago RNAi-1 (p = 0.005) and 67% (p = 0.11) in *ago* RNAi-2 (Figure S5). Because the latter was also previously shown to be effective in downregulating ago_{1}^{52} we crossed both lines and the control to the pan-neuronal promotor line elav-Gal4^(III) to generate neuron-specific ago knockdown and control animals. Progeny of the appropriate genotypes were selected and subjected to characterization of basal motor function and habituation, a simple form of learning frequently defective in Drosophila models of intellectual disability, 56,63 in the light-off jump reflex habituation paradigm (Figure 4A). In this assay, individual flies are exposed to 100 light-off pulses (trials) with a 1 s inter-trial interval. Wild-type flies will initially startle in response the light-off stimulus, but they learn to suppress their escape response upon repeated, non-harmful stimuli.

Elav-Gal4^(III)-mediated neuronal knockdown of ago with the strong RNAi-1 line severely affected the flies' ability to jump and participate in the assay (23% of initial jumpers, Figure 4B), revealing moderate neurological defects, which precluded an assessment of habituation learning. Knockdown of ago with the mild RNAi-2 line was less detrimental and did not impair the jump response (74% of initial jumpers, Figure 4B), yet caused a deficit in habituation learning (Figure 4C): ago knockdown flies (in blue) adapted incompletely and more slowly to the light-off stimuli in comparison to their genetic background controls (gray). Quantification of habituation via the mean trials to no-jump criterion (mTTC, see "subjects and methods") demonstrated this defect to be significant; ago knockdown flies need on average twice as many trials as their controls to succeed in suppressing their jump response (n = 71, n)p = 0.002, Figure 4D). These results are in agreement with the qPCR results. Using an independent, stronger pan-neuronal promotor line (elav c155^(I)-GAL4)⁶⁴ further confirmed this finding. Elav c155^(I)-GAL4-induced RNAi-1 knockdown completely abolished jumping (0%, Figure 4B), whereas the combination with RNAi-2 affected initial jumping (55%, Figure 4B) but still resulted in

sufficient performance for habituation testing. This combination resulted in a faster decline of the jump response with decreased mTTC in comparison to the control ($p = 1.6 \times 10^{-3}$; Figure S4). Further experiments using a fatigue regime (see "subjects and methods") revealed that this premature decay in the jump response was due to impaired neuronal function, not to faster adaptation ($p = 1.4 \times 10^{-5}$; Figure S4). Together, our results showed that loss of the *FBXW7* fly ortholog *ago* affected learning or compromised neuronal function more severely the higher its level of knockdown.

Discussion

FBXW7 variants are associated with a variable neurodevelopmental syndrome

Here we provide detailed clinical and functional characterization of the neurodevelopmental syndrome associated with germline monoallelic variants in FBXW7. In support of our finding, FBXW7 was recently identified as one of 28 developmental-disorder-associated genes in a large multicenter cohort by bioinformatic analysis for gene-specific enrichment of de novo mutations, but without deep phenotyping.⁶⁵ The neurodevelopmental phenotype involves mild to severe global developmental delay and intellectual disability. At the mildest end of the spectrum, isolated speech delay (n = 1) and learning difficulties or borderline intellect (n = 2) were observed; only one individual was reported to have no neurodevelopmental issues (but had hypotonia). In contrast, the majority of the cohort had mild to moderate intellectual disability (n = 27), and severe neurodevelopmental disability was observed in three individuals, including one with an additional diagnosis of familial CAC-NA1A-related disorder⁵⁷ and another with episodic developmental regression. However, in the latter proband, no other candidate genomic variants were identified as an alternative cause, and the reason for the regressive episodes remains unclear in this individual. After neurodevelopmental disability, the next most frequently observed neurologic feature was hypotonia, common also to the other F-boxrelated neurodevelopmental syndromes associated with germline pathogenic variants in FBXL4. FBXO11, *FBXW11*, and *FBXO28*, ^{9–11,13,16,17}, but not in *FBXL3*.¹⁸

The neurodevelopmental phenotype associated with *FBXW7* has substantial clinical overlap with that of *FBXW11*; areas of overlap include mild to severe neurodevelopmental disability, speech and language delay, microor macrocephaly, and brain anomalies, including corpus callosum hypoplasia, dilated ventricles, and white matter atrophy. However, in contrast to individuals with *FBXW11* variants,⁹ those in the *FBXW7* cohort did not commonly display autistic and/or stereotypical behaviors, psychiatric features, or ocular abnormalities.

It is notable that the *FBXO11*-related neurodevelopmental phenotype is just as variable; its severity ranges from normal cognition to profound disability.^{10,11,66} Individuals with FBXO11 variants were also found to have variability in head size, a similar observation made of the FBXW7 cohort, although we found that macrocephaly was more common than microcephaly. Macrocephaly has been observed in an individual with focal segmental glomerulosclerosis, Wilms tumor, invasive ductal breast carcinoma, and a 157 kb partial chromosomal deletion of FBXW7, but her neurodevelopmental phenotype was not reported.⁶⁷ The DECIPHER database lists five individuals with copy-number losses that are various sizes and involve FBXW7. Three of these individuals have neurodevelopmental disability, and one experiences constipation. Another individual was reported with a 120.84 kb deletion including FBXW7, as well as two deletions in homozygous form on chromosomes 9 and 14, but the only listed phenotype was T cell acute lymphoblastic leukemia.

FBXW7 is a critical tumor suppressor and one of the most commonly mutated genes in human cancer (it is identified in 3.5% of all cancers).⁶⁸ More recently, truncating variants in *FBXW7* have been suggested to predispose the carrier to Wilms tumor in four individuals, and a missense variant was identified in an individual with a rhabdoid tumor; however, the individual's neurodevelopmental phenotype was not well described.⁶⁹ The oldest individual in this cohort is 44 years old, and although no cancer has so far been observed, longer-term follow-up will be necessary if we are to determine whether there is any cancer predisposition risk.

When we compared the frequency of key clinical features between variant types, no genotype-phenotype correlation was apparent, similar to findings for the comparison undertaken in a FBXO11 cohort.¹⁰ We observed three variants (p.Gly423Arg, p.Arg674Trp, and p.Arg689Trp) recurring in unrelated individuals. The degree of neurodevelopmental disability and hypotonia appeared to be consistent between individuals with the same variant. However, there was some variability in head size, and macrocephaly was inconsistently observed in each genotype. The familial cases demonstrated intra-familial variability. For instance, the family carrying the p.Asn572Leufs*32 variant (individuals 3-6) were ascertained from a speech-and-language-disorders cohort. The proband (individual 3) had cleft palate and neurodevelopmental disability, but her sisters were less severely affected. Their father (individual 6) only had borderline-low verbal IQ. Neuroimaging was only undertaken in the proband, but it would be interesting to investigate whether her sisters and father also had similar brain anomalies. Furthermore, the p.Asn572Leufs*32 variant is likely to escape NMD, as is the p.Lys647* variant identified in individual 7, whose phenotype is relatively mild compared to those of the individuals with missense variants. This observation suggests that a truncated FBXW7 might lead to a milder phenotype. We did not identify any individuals with variants affecting FBXW7's N-terminal region, including the F-box. It is possible that the phenotypic consequences of variants in this region are either lethal or sub-clinical, although the latter appears to be more likely given the lack of regional missense constraint relative to the WD40 domain in gnomAD. Addressing this possibility, along with the possibility that milder phenotypes might emerge over time, will require the study of additional affected individuals.

Another explanation for variable expressivity among individuals carrying pathogenic variants in the same gene is the possibility of multiple diagnoses.⁷⁰ This is well illustrated in individuals 19 and 31. Individual 19, in addition to carrying the mosaic FBXW7 variant, is heterozygous for a maternally inherited CACNA1A pathogenic variant.⁵⁷ This combination is responsible for his more severe phenotype compared to that of his relatives carrying the CACNA1A variant alone and that of the other individuals in the FBXW7 cohort, and is likely to also explain the difference in his cerebellar abnormalities. Individual 31 also has a de novo likely pathogenic variant in KMT2D, and this is reflected in his facial features, including long palpebral features characteristic of Kabuki syndrome and the deeply set eyes and upper eyelid fullness observed in other individuals in the FBXW7 cohort. We also considered whether mosaicism for the FBXW7 variant might account for phenotypic attenuation or variable expressivity. We found that individuals 19 and 25 had clinical and genomic features suggestive of mosaicism, yet their phenotype was typical and no less severe than the rest of the cohort, which probably reflects the variable consequences of mosaicism. The emerging phenotype associated with variants in FBX genes appears to be characterized by neurodevelopmental disability with variable involvement of other systems. We speculate that these FBX proteins might function in convergent molecular and/or developmental pathways and that other FBX-related genes might subsequently be identified as playing a role in neurodevelopmental disorders.

FBXW7 missense variants identified in this cohort impair substrate turnover

Individuals harboring germline FBXW7 variants in this study demonstrate considerable phenotypic heterogeneity. FBXW7 encodes three isoforms; FBXW7α, FBXW7β, and FBXW7y. All three contain the F-box and WD40 domain, but they differ at the N-terminal sequences that dictate their subcellular location; nucleus, cytoplasm, and nucleolus, respectively.⁷¹ Studies in mice indicate that the isoforms also demonstrate different tissue specificity.⁷² All variants identified in this study, whole-gene deletions as well as LoF, truncating, and missense variants, are predicted to affect the function of all three FBXW7 isoforms. In addition, FBXW7 has been shown to undergo multiple post-translational modifications, including auto-ubiquitination, de-ubiquitination, and dimerization (reviewed in⁸). There are numerous reported FBXW7 substrates, including CYCLIN E1/E2,61,73,74 PSEN1,75 NOTCH1/2/ 4,^{76,77} MYC,⁷⁸ JUN,^{79,80} REV-ERBα,^{81,82} KLF5,⁷⁹ DISC1,⁵⁹ MCL-1,⁸¹ CCDC6,⁸³ and mTOR.⁸⁴ FBXW7 recognizes substrates upon phosphorylation at a conserved Cdc4 phosphodegron, a short linear motif that is inert until

phosphorylated.⁸ Substrate binding occurs when the degron phosphorylations interact with two FBXW7 β-propeller pockets and upstream phosphodegron residues fit into a hydrophobic groove.⁸⁵ Our in silico protein modeling suggests the amino acids implicated in this neurodevelopmental syndrome mainly cluster at the surface of the substratebinding interface and are likely to impair substrate binding (Figure 2). We have demonstrated that some FBXW7 missense variants can affect steady-state FBXW7 protein amounts, suggesting that in some cases protein instability might lead to degradation of the mutant protein via the UPS. However, the majority of mutant proteins investigated were not turned over by the UPS more than the wild-type protein but demonstrated reduced capacity to turn over known substrates CYCLIN E1 and CYCLIN E2 (Figure 3). Fascinatingly, one mutant, FBXW7^{Asp480Gly}, demonstrated divergent effects: it was less efficient at degrading CYCLIN E2 but more efficient at degrading CYCLIN E1 in comparison to FBXW7^{wild type} and thus acted in a substrate-dependent manner. Collectively, our data suggest that the neurodevelopmental-disability-associated variants observed in this cohort are likely to alter binding affinity to substrates, and we hypothesize that other known substrates are likely to also be impacted.

Within a cell of an individual harboring a neurodevelopmental-disease-associated FBXW7 missense variant, FBXW7 can exist as a monomer (wild type or mutant) or as dimers (either as wild type only and mutant only or as both wild type and mutant) that can function at the cytosol, nucleus, or nucleolus. The impact on protein stability, binding affinity, and ubiquitin-ligase activity is likely to be variant specific, and although we propose that the phenotype is largely reflective of haploinsufficiency or loss of function (evident in those individuals with whole-gene deletions and NMD-predicted variants), we cannot rule out the possibility that some variants might have alternative mechanisms. Interrogation of gnomAD demonstrates that FBXW7 is intolerant of loss-of-function variation (pLI = 1.00), further supporting the notion that haploinsufficiency or loss of function is the predominant mechanism of disease. Some of the phenotypic variability of FBXW7 neurodevelopmental disability might, at least in part, be reflective of the functional consequence of the genotype or other, yet-unidentified modifiers. Identification of additional individuals with a broader spectrum of FBXW7 variants (including predicted LoF variants) associated with neurodevelopmental disability and further molecular characterization will most likely lead to a deeper understanding of genotype-phenotype correlation.

Animal models support a role for FBXW7 in development broadly and specifically in the nervous system

FBXW7 is a critical tumor suppressor and one of the most commonly deregulated ubiquitin-proteasome-system proteins in human cancer. However, this clinical cohort clearly demonstrates that *FBXW7* also functions in human neurological development. Animal *Fbxw7* models—knockout,

haploinsufficient, and knock-in-also support a fundamental role for FBXW7 in development broadly, and in the brain specifically. Fbxw7-knockout mice die in utero at embryonic day 10.5, and they manifest hematopoietic abnormalities as well as abnormalities of vascular development and heart-chamber maturation.^{86,87} Heterozygous knock-in FBXW7 human-cancer mutations p.Arg465Cys and p.Arg482Gln (in mice, affecting residues Arg468 and Arg482) lead to perinatal lethality as a result of abnormal lung development, open eyes at birth (43%), and/or cleft palate (30%).⁸⁷ Notably, heterozygous null animals show no lung abnormality, demonstrating that these missense variants are distinct from null alleles.⁸⁸ Furthermore, heterozygous conditional gut-specific deletion of Fbxw7 (villin-Cre) result in an impaired differentiation of intestinal goblet cells,⁸⁸ providing support for a role for FBXW7 in the development and function of the gut, which is significant because nearly half of individuals in our cohort manifested constipation (16/35, 45.7%).

Fbxw7^{nestin-Cre}-knockout mice that lack expression exclusively in the central and peripheral nervous system (including in precursors of neuronal and glial cells) die in the perinatal period as a result of defective suckling and present with several morphological brain abnormalities, including third-ventricle dilation and distortion, hypoplastic pons, an abnormal cerebellum, and markedly reduced cellularity of the cortex. Notch, a key regulator of glial and neuronal cell fate in the brain, accumulates in cells and skews radial glia differentiation toward the astrocytic lineage by increasing apoptosis of neuronal precursors.^{33,36} Fbxw7 haploinsufficiency in the mouse nervous system has also been investigated with a nestin-Cre system and has been shown to be associated with impaired differentiation of neural stem cells; such an impairment has also been shown to occur via a Notch-dependent mechanism. During development, it is proposed that Fbxw7 haploinsufficiency leads to alterations of Notch-mediated lateral inhibition, an interaction between adjacent cells that drives them toward different final states.⁸⁸ Collectively, these studies provide evidence that Fbxw7 is a key regulator of neural-stem-cell differentiation and maintenance in the brain, and we speculate that dysregulation of Notch lateral inhibition during brain development might underpin the broad spectrum of brain abnormalities identified in FBXW7 neurodevelopmental syndrome.

Several studies have also investigated the role of *FBXW7* orthologs in myelination. *Fbxw7*^{Cre-dhh}-knockout mice that lack expression in Schwann cells of the peripheral nervous system demonstrated enhanced myelination —these mice made thicker myelin sheaths and in some cases, unexpectedly, myelinated multiple axons in a manner similar to the way in which oligodendrocytes of the central nervous system myelinate axons. In addition, *Fbxw7*^{Cre-dhh} knockout led to an early increase in Schwann cells, smaller Remak bundles, and hypermyelination. These effects could be ameliorated by knockout of the substrate mTOR, but had no effect on the myelination of multiple axons.³² In the zebrafish cen-

tral nervous system, *fbxw7^{vu56}* homozygous-mutant larvae and morpholino knockdown of *fbxw7* demonstrate excessive oligodendrocyte cells and hypermyelination as a result of elevated Notch and mTOR signaling.^{31,34}

In this study, in light of the fact that neurodevelopmental disability was the major hallmark of this cohort, we specifically aimed to support the notion of the role of FBXW7 in an intellectual-disability- and cognition-relevant assay. Specifically, we asked whether FBXW7, in addition to its functions in neural stem cells and glia, could also be required more directly, in postmitotic neurons, for basal neuronal and cognitive function. To address this, and also because, as in mice, ago null animals are embryonic lethal,^{60,89} we targeted the gene in a tissuespecific manner. We used two pan-neuronal promotor lines and two independent RNAi lines to generate an allelic series. Our results revealed that the FBXW7 ortholog ago is indispensable in postmitotic neurons; animals with the stronger promotor and UAS-RNAi line were severely impaired, whereas less-stringent conditions kept locomotor function intact and revealed deficits in habituation learning. The gene therefore joins a steeply increasing number of intellectual-disability- and autismspectrum-disorder-associated genes^{56,63,90} that are implicated in this fundamental form of learning that is crucial for information processing, sensory filtering, and cognition. These also include mTOR-pathway genes such as PTEN & TSC1,⁵⁶ to which FBXW7 has already been connected.³¹ Further studies should aim to dissect FBXW7 targets that are mediating the defects in cognitive functioning and study their reversibility; the established Drosophila model is suitable for this purpose. Collectively, the multiple lines of evidence presented herein converge to support the identification of FBXW7 variants as causal for a human neurodevelopmental disorder.

Data and code availability

The datasets supporting the current study have not been deposited in a public repository because of restrictions related to patient consent, but they are available from the corresponding author on request.

Supplemental information

Supplemental information can be found online at https://doi.org/ 10.1016/j.ajhg.2022.03.002.

Acknowledgments

The authors thank the affected individuals and all family members for participating in this research. Please see the supplemental information for a complete list of Acknowledgments and funding.

Declaration of interests

I.E.S. has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded

Therapeutics, Xenon Pharmaceuticals, and Knopp Biosciences; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epygenyx, Encoded Therapeutics and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium and UCB. She may accrue future revenue on pending patent WO2009/086591; her patent for SCN1A testing is held by Bionomics and is licensed to various diagnostic companies; and she has a patent for a molecular diagnostic/therapeutic target for benign familial infantile epilepsy (BFIE) (PRRT2), WO/2013/059884. She receives and/or has received research support from the National Health and Medical Research Council of Australia, Medical Research Future Fund, Health Research Council of New Zealand, CURE, Australian Epilepsy Research Fund, and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. J.P. is co-chief scientific officer for Global Gene Corp. All other authors declare no competing interests.

Received: October 28, 2021 Accepted: February 28, 2022 Published: April 7, 2022

Web resources

DECIPHER, https://www.deciphergenomics.org/ ESP, http://evs.gs.washington.edu/EVS/ ExAC, http://exac.broadinstitute.org GeneMatcher, https://genematcher.org/ Github, https://github.com gnomAD, http://gnomad.broadinstitute.org/ Human Phenotype Ontology, https://hpo.jax.org/app/ Online Mendelian Inheritance in Man, http://www.omim.org UCSC Genome Browser, https://genome.ucsc.edu 1000 Genomes, http://www.internationalgenome.org

References

- 1. Deciphering Developmental Disorders, S.; and Deciphering Developmental Disorders Study (2017). Prevalence and architecture of de novo mutations in developmental disorders. Nature 542, 433–438. https://doi.org/10.1038/nature21062.
- Lemke, J.R. (2020). Predicting incidences of neurodevelopmental disorders. Brain 143, 1046–1048. https://doi.org/10. 1093/brain/awaa079.
- 3. Wilfert, A.B., Sulovari, A., Turner, T.N., Coe, B.P., and Eichler, E.E. (2017). Recurrent de novo mutations in neurodevelopmental disorders: properties and clinical implications. Genome Med. *9*, 101. https://doi.org/10.1186/s13073-017-0498-x.
- Bruel, A.L., Vitobello, A., Tran Mau-Them, F., Nambot, S., Sorlin, A., Denommé-Pichon, A.S., Delanne, J., Moutton, S., Callier, P., Duffourd, Y., et al. (2020). Next-generation sequencing approaches and challenges in the diagnosis of developmental anomalies and intellectual disability. Clin. Genet. *98*, 433– 444. https://doi.org/10.1111/cge.13764.
- Colas, P. (2020). Cyclin-dependent kinases and rare developmental disorders. Orphanet J. Rare Dis. 15, 203. https://doi. org/10.1186/s13023-020-01472-y.

- LiCausi, F., and Hartman, N.W. (2018). Role of mTOR Complexes in Neurogenesis. Int. J. Mol. Sci. 19, E1544. https:// doi.org/10.3390/ijms19051544.
- 7. Nguyen, K.M., and Busino, L. (2020). The Biology of F-box Proteins: The SCF Family of E3 Ubiquitin Ligases. Adv. Exp. Med. Biol. *1217*, 111–122. https://doi.org/10.1007/978-981-15-1025-0_8.
- Zhang, Z., Hu, Q., Xu, W., Liu, W., Liu, M., Sun, Q., Ye, Z., Fan, G., Qin, Y., Xu, X., et al. (2020). Function and regulation of F-box/WD repeat-containing protein 7. Oncol. Lett. 20, 1526–1534. https://doi.org/10.3892/ol.2020.11728.
- 9. Holt, R.J., Young, R.M., Crespo, B., Ceroni, F., Curry, C.J., Bellacchio, E., Bax, D.A., Ciolfi, A., Simon, M., Fagerberg, C.R., et al. (2019). De Novo Missense Variants in FBXW11 Cause Diverse Developmental Phenotypes Including Brain, Eye, and Digit Anomalies. Am. J. Hum. Genet. 105, 640–657. https://doi.org/10.1016/j.ajhg.2019. 07.005.
- Gregor, A., Sadleir, L.G., Asadollahi, R., Azzarello-Burri, S., Battaglia, A., Ousager, L.B., Boonsawat, P., Bruel, A.L., Buchert, R., Calpena, E., et al.; University of Washington Center for Mendelian Genomics; and DDD Study (2018). De Novo Variants in the F-Box Protein FBXO11 in 20 Individuals with a Variable Neurodevelopmental Disorder. Am. J. Hum. Genet. *103*, 305–316. https://doi.org/10.1016/j.ajhg.2018. 07.003.
- 11. Jansen, S., van der Werf, I.M., Innes, A.M., Afenjar, A., Agrawal, P.B., Anderson, I.J., Atwal, P.S., van Binsbergen, E., van den Boogaard, M.J., Castiglia, L., et al. (2019). De novo variants in FBXO11 cause a syndromic form of intellectual disability with behavioral problems and dysmorphisms. Eur. J. Hum. Genet. 27, 738–746. https://doi.org/10.1038/ s41431-018-0292-2.
- 12. Balak, C., Belnap, N., Ramsey, K., Joss, S., Devriendt, K., Naymik, M., Jepsen, W., Siniard, A.L., Szelinger, S., Parker, M.E., et al. (2018). A novel FBXO28 frameshift mutation in a child with developmental delay, dysmorphic features, and intractable epilepsy: A second gene that may contribute to the 1q41-q42 deletion phenotype. Am. J. Med. Genet. A. *176*, 1549–1558. https://doi.org/10.1002/ajmg.a.38712.
- Schneider, A.L., Myers, C.T., Muir, A.M., Calvert, S., Basinger, A., Perry, M.S., Rodan, L., Helbig, K.L., Chambers, C., Gorman, K.M., et al. (2021). FBXO28 causes developmental and epileptic encephalopathy with profound intellectual disability. Epilepsia 62, e13–e21. https://doi.org/10.1111/epi. 16784.
- Au, P.Y., Argiropoulos, B., Parboosingh, J.S., and Micheil Innes, A. (2014). Refinement of the critical region of 1q41q42 microdeletion syndrome identifies FBXO28 as a candidate causative gene for intellectual disability and seizures. Am. J. Med. Genet. A. *164A*, 441–448. https://doi.org/10.1002/ajmg.a.36320.
- Cassina, M., Rigon, C., Casarin, A., Vicenzi, V., Salviati, L., and Clementi, M. (2015). FBXO28 is a critical gene of the 1q41q42 microdeletion syndrome. Am. J. Med. Genet. A. *167*, 1418– 1420. https://doi.org/10.1002/ajmg.a.37033.
- Bonnen, P.E., Yarham, J.W., Besse, A., Wu, P., Faqeih, E.A., Al-Asmari, A.M., Saleh, M.A., Eyaid, W., Hadeel, A., He, L., et al. (2013). Mutations in FBXL4 cause mitochondrial encephalopathy and a disorder of mitochondrial DNA maintenance. Am. J. Hum. Genet. *93*, 471–481. https://doi.org/10.1016/j.ajhg. 2013.07.017.

- 17. Gai, X., Ghezzi, D., Johnson, M.A., Biagosch, C.A., Shamseldin, H.E., Haack, T.B., Reyes, A., Tsukikawa, M., Sheldon, C.A., Srinivasan, S., et al. (2013). Mutations in FBXL4, encoding a mitochondrial protein, cause early-onset mitochondrial encephalomyopathy. Am. J. Hum. Genet. *93*, 482–495. https://doi.org/10.1016/j.ajhg.2013.07.016.
- Ansar, M., Paracha, S.A., Serretti, A., Sarwar, M.T., Khan, J., Ranza, E., Falconnet, E., Iwaszkiewicz, J., Shah, S.F., Qaisar, A.A., et al. (2019). Biallelic variants in FBXL3 cause intellectual disability, delayed motor development and short stature. Hum. Mol. Genet. 28, 972–979. https://doi.org/10.1093/ hmg/ddy406.
- Charng, W.L., Karaca, E., Coban Akdemir, Z., Gambin, T., Atik, M.M., Gu, S., Posey, J.E., Jhangiani, S.N., Muzny, D.M., Doddapaneni, H., et al. (2016). Exome sequencing in mostly consanguineous Arab families with neurologic disease provides a high potential molecular diagnosis rate. BMC Med. Genomics 9, 42. https://doi.org/10.1186/s12920-016-0208-3.
- Labonne, J.D., Lee, K.H., Iwase, S., Kong, I.K., Diamond, M.P., Layman, L.C., Kim, C.H., and Kim, H.G. (2016). An atypical 12q24.31 microdeletion implicates six genes including a histone demethylase KDM2B and a histone methyltransferase SETD1B in syndromic intellectual disability. Hum. Genet. *135*, 757–771. https://doi.org/10. 1007/s00439-016-1668-4.
- Yokotsuka-Ishida, S., Nakamura, M., Tomiyasu, Y., Nagai, M., Kato, Y., Tomiyasu, A., Umehara, H., Hayashi, T., Sasaki, N., Ueno, S.I., and Sano, A. (2021). Positional cloning and comprehensive mutation analysis identified a novel KDM2B mutation in a Japanese family with minor malformations, intellectual disability, and schizophrenia. J. Hum. Genet. *66*, 597–606. https://doi.org/10.1038/s10038-020-00889-4.
- 22. Yeh, C.H., Bellon, M., and Nicot, C. (2018). FBXW7: a critical tumor suppressor of human cancers. Mol. Cancer *17*, 115. https://doi.org/10.1186/s12943-018-0857-2.
- Sailo, B.L., Banik, K., Girisa, S., Bordoloi, D., Fan, L., Halim, C.E., Wang, H., Kumar, A.P., Zheng, D., Mao, X., et al. (2019). FBXW7 in Cancer: What Has Been Unraveled Thus Far? Cancers (Basel) *11*, E246. https://doi.org/10.3390/cancers11020246.
- 24. Song, Y., Lai, L., Chong, Z., He, J., Zhang, Y., Xue, Y., Xie, Y., Chen, S., Dong, P., Chen, L., et al. (2017). E3 ligase FBXW7 is critical for RIG-I stabilization during antiviral responses. Nat. Commun. *8*, 14654. https://doi.org/10.1038/ ncomms14654.
- 25. Zhang, C., Chen, F., Feng, L., Shan, Q., Zheng, G.H., Wang, Y.J., Lu, J., Fan, S.H., Sun, C.H., Wu, D.M., et al. (2019). FBXW7 suppresses HMGB1-mediated innate immune signaling to attenuate hepatic inflammation and insulin resistance in a mouse model of nonalcoholic fatty liver disease. Mol. Med. 25, 29. https://doi.org/10.1186/s10020-019-0099-9.
- Onoyama, I., Suzuki, A., Matsumoto, A., Tomita, K., Katagiri, H., Oike, Y., Nakayama, K., and Nakayama, K.I. (2011). Fbxw7 regulates lipid metabolism and cell fate decisions in the mouse liver. J. Clin. Invest. *121*, 342–354. https://doi. org/10.1172/JCI40725.
- 27. Izumi, N., Helker, C., Ehling, M., Behrens, A., Herzog, W., and Adams, R.H. (2012). Fbxw7 controls angiogenesis by regulating endothelial Notch activity. PLoS ONE 7, e41116. https://doi.org/10.1371/journal.pone.0041116.

- Pronk, M.C.A., Majolée, J., Loregger, A., van Bezu, J.S.M., Zelcer, N., Hordijk, P.L., and Kovačević, I. (2019). FBXW7 regulates endothelial barrier function by suppression of the cholesterol synthesis pathway and prenylation of RhoB. Mol. Biol. Cell *30*, 607–621. https://doi.org/10.1091/mbc. E18-04-0259.
- 29. Gao, W., Guo, N., Zhao, S., Chen, Z., Zhang, W., Yan, F., Liao, H., and Chi, K. (2020). FBXW7 promotes pathological cardiac hypertrophy by targeting EZH2-SIX1 signaling. Exp. Cell Res. 393, 112059. https://doi.org/10.1016/j.yexcr.2020.112059.
- Thompson, B.J., Jankovic, V., Gao, J., Buonamici, S., Vest, A., Lee, J.M., Zavadil, J., Nimer, S.D., and Aifantis, I. (2008). Control of hematopoietic stem cell quiescence by the E3 ubiquitin ligase Fbw7. J. Exp. Med. 205, 1395–1408. https://doi.org/10. 1084/jem.20080277.
- Kearns, C.A., Ravanelli, A.M., Cooper, K., and Appel, B. (2015). Fbxw7 Limits Myelination by Inhibiting mTOR Signaling. J. Neurosci. 35, 14861–14871. https://doi.org/10.1523/ JNEUROSCI.4968-14.2015.
- 32. Harty, B.L., Coelho, F., Pease-Raissi, S.E., Mogha, A., Ackerman, S.D., Herbert, A.L., Gereau, R.W., 4th, Golden, J.P., Lyons, D.A., Chan, J.R., and Monk, K.R. (2019). Myelinating Schwann cells ensheath multiple axons in the absence of E3 ligase component Fbxw7. Nat. Commun. *10*, 2976. https://doi.org/10.1038/s41467-019-10881-y.
- 33. Matsumoto, A., Onoyama, I., Sunabori, T., Kageyama, R., Okano, H., and Nakayama, K.I. (2011). Fbxw7-dependent degradation of Notch is required for control of "stemness" and neuronal-glial differentiation in neural stem cells. J. Biol. Chem. 286, 13754–13764. https://doi.org/10.1074/ jbc.M110.194936.
- 34. Snyder, J.L., Kearns, C.A., and Appel, B. (2012). Fbxw7 regulates Notch to control specification of neural precursors for oligodendrocyte fate. Neural Dev. 7, 15. https://doi.org/10. 1186/1749-8104-7-15.
- Jandke, A., Da Costa, C., Sancho, R., Nye, E., Spencer-Dene, B., and Behrens, A. (2011). The F-box protein Fbw7 is required for cerebellar development. Dev. Biol. 358, 201–212. https://doi. org/10.1016/j.ydbio.2011.07.030.
- Hoeck, J.D., Jandke, A., Blake, S.M., Nye, E., Spencer-Dene, B., Brandner, S., and Behrens, A. (2010). Fbw7 controls neural stem cell differentiation and progenitor apoptosis via Notch and c-Jun. Nat. Neurosci. *13*, 1365–1372. https://doi.org/10. 1038/nn.2644.
- 37. Ko, Y.U., Kim, C., Lee, J., Kim, D., Kim, Y., Yun, N., and Oh, Y.J. (2019). Site-specific phosphorylation of Fbxw7 by Cdk5/p25 and its resulting decreased stability are linked to glutamateinduced excitotoxicity. Cell Death Dis. *10*, 579. https://doi. org/10.1038/s41419-019-1818-4.
- Ko, Y.U., Song, H.Y., Kim, W.K., Yune, T.Y., Yun, N., and Oh, Y.J. (2020). Calpain-mediated cleavage of Fbxw7 during excitotoxicity. Neurosci. Lett. 736, 135265. https://doi.org/10. 1016/j.neulet.2020.135265.
- 39. Philippakis, A.A., Azzariti, D.R., Beltran, S., Brookes, A.J., Brownstein, C.A., Brudno, M., Brunner, H.G., Buske, O.J., Carey, K., Doll, C., et al. (2015). The Matchmaker Exchange: a platform for rare disease gene discovery. Hum. Mutat. *36*, 915–921. https://doi.org/10.1002/humu.22858.
- 40. Sobreira, N., Schiettecatte, F., Valle, D., and Hamosh, A. (2015). GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. Hum. Mutat. *36*, 928–930. https://doi.org/10.1002/humu.22844.

- 41. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., et al.; ACMG Laboratory Quality Assurance Committee (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. *17*, 405–424. https://doi.org/10.1038/gim.2015.30.
- Reese, M.G., Eeckman, F.H., Kulp, D., and Haussler, D. (1997). Improved splice site detection in Genie. J. Comput. Biol. 4, 311–323. https://doi.org/10.1089/cmb.1997.4.311.
- 43. Hebsgaard, S.M., Korning, P.G., Tolstrup, N., Engelbrecht, J., Rouzé, P., and Brunak, S. (1996). Splice site prediction in Arabidopsis thaliana pre-mRNA by combining local and global sequence information. Nucleic Acids Res. 24, 3439–3452. https://doi.org/10.1093/nar/24.17.3439.
- Brunak, S., Engelbrecht, J., and Knudsen, S. (1991). Prediction of human mRNA donor and acceptor sites from the DNA sequence. J. Mol. Biol. 220, 49–65. https://doi.org/10.1016/ 0022-2836(91)90380-o.
- 45. Jaganathan, K., Kyriazopoulou Panagiotopoulou, S., McRae, J.F., Darbandi, S.F., Knowles, D., Li, Y.I., Kosmicki, J.A., Arbelaez, J., Cui, W., Schwartz, G.B., et al. (2019). Predicting Splicing from Primary Sequence with Deep Learning. Cell *176*, 535–548.e24. https://doi.org/10.1016/j.cell.2018.12. 015.
- 46. Yang, J., and Zhang, Y. (2015). I-TASSER server: new development for protein structure and function predictions. Nucleic Acids Res. 43 (W1), W174–W181. https://doi.org/10.1093/nar/gkv342.
- 47. Hao, B., Oehlmann, S., Sowa, M.E., Harper, J.W., and Pavletich, N.P. (2007). Structure of a Fbw7-Skp1-cyclin E complex: multisite-phosphorylated substrate recognition by SCF ubiquitin ligases. Mol. Cell 26, 131–143. https://doi.org/10.1016/ j.molcel.2007.02.022.
- McLaren, W., Gil, L., Hunt, S.E., Riat, H.S., Ritchie, G.R., Thormann, A., Flicek, P., and Cunningham, F. (2016). The Ensembl Variant Effect Predictor. Genome Biol. *17*, 122. https://doi.org/10.1186/s13059-016-0974-4.
- Liu, X., Jian, X., and Boerwinkle, E. (2011). dbNSFP: a lightweight database of human nonsynonymous SNPs and their functional predictions. Hum. Mutat. 32, 894–899. https:// doi.org/10.1002/humu.21517.
- Pires, D.E., Ascher, D.B., and Blundell, T.L. (2014). mCSM: predicting the effects of mutations in proteins using graph-based signatures. Bioinformatics *30*, 335–342. https://doi.org/10. 1093/bioinformatics/btt691.
- Rodrigues, C.H.M., Myung, Y., Pires, D.E.V., and Ascher, D.B. (2019). mCSM-PPI2: predicting the effects of mutations on protein-protein interactions. Nucleic Acids Res. 47 (W1), W338–W344. https://doi.org/10.1093/nar/gkz383.
- Li, L., Anderson, S., Secombe, J., and Eisenman, R.N. (2013). The Drosophila ubiquitin-specific protease Puffyeye regulates dMyc-mediated growth. Development *140*, 4776– 4787. https://doi.org/10.1242/dev.096941.
- 53. Nam, S., and Cho, K.O. (2020). Wingless and Archipelago, a fly E3 ubiquitin ligase and a homolog of human tumor suppressor FBW7, show an antagonistic relationship in wing development. BMC Dev. Biol. 20, 14. https://doi.org/10. 1186/s12861-020-00217-1.
- 54. Livak, K.J., and Schmittgen, T.D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and

the 2(-Delta Delta C(T)) Method. Methods *25*, 402–408. https://doi.org/10.1006/meth.2001.1262.

- Qureshi, R., and Sacan, A. (2013). A novel method for the normalization of microRNA RT-PCR data. BMC Med. Genomics 6 (Suppl 1), S14. https://doi.org/10.1186/1755-8794-6-S1-S14.
- Fenckova, M., Blok, L.E.R., Asztalos, L., Goodman, D.P., Cizek, P., Singgih, E.L., Glennon, J.C., IntHout, J., Zweier, C., Eichler, E.E., et al. (2019). Habituation Learning Is a Widely Affected Mechanism in Drosophila Models of Intellectual Disability and Autism Spectrum Disorders. Biol. Psychiatry 86, 294–305. https://doi.org/10.1016/j.biopsych.2019.04. 029.
- 57. Angelini, C., Van Gils, J., Bigourdan, A., Jouk, P.S., Lacombe, D., Menegon, P., Moutton, S., Riant, F., Sole, G., Tournier-Lasserve, E., et al. (2019). Major intra-familial phenotypic heterogeneity and incomplete penetrance due to a CACNA1A pathogenic variant. Eur. J. Med. Genet. *62*, 103530. https://doi.org/10.1016/j.ejmg.2018.08.011.
- Pawlicka, K., Kalathiya, U., and Alfaro, J. (2020). Nonsense-Mediated mRNA Decay: Pathologies and the Potential for Novel Therapeutics. Cancers (Basel) *12*, E765. https://doi. org/10.3390/cancers12030765.
- Yalla, K., Elliott, C., Day, J.P., Findlay, J., Barratt, S., Hughes, Z.A., Wilson, L., Whiteley, E., Popiolek, M., Li, Y., et al. (2018). FBXW7 regulates DISC1 stability via the ubiquitinproteosome system. Mol. Psychiatry 23, 1278–1286. https:// doi.org/10.1038/mp.2017.138.
- Moberg, K.H., Bell, D.W., Wahrer, D.C., Haber, D.A., and Hariharan, I.K. (2001). Archipelago regulates Cyclin E levels in Drosophila and is mutated in human cancer cell lines. Nature 413, 311–316. https://doi.org/10.1038/35095068.
- Koepp, D.M., Schaefer, L.K., Ye, X., Keyomarsi, K., Chu, C., Harper, J.W., and Elledge, S.J. (2001). Phosphorylation-dependent ubiquitination of cyclin E by the SCFFbw7 ubiquitin ligase. Science 294, 173–177. https://doi.org/10.1126/science.1065203.
- 62. Brand, A.H., and Perrimon, N. (1993). Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. Development *118*, 401–415.
- 63. Stessman, H.A., Xiong, B., Coe, B.P., Wang, T., Hoekzema, K., Fenckova, M., Kvarnung, M., Gerdts, J., Trinh, S., Cosemans, N., et al. (2017). Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental-disability biases. Nat. Genet. 49, 515–526. https:// doi.org/10.1038/ng.3792.
- 64. Gonzales, E.D., Tanenhaus, A.K., Zhang, J., Chaffee, R.P., and Yin, J.C. (2016). Early-onset sleep defects in Drosophila models of Huntington's disease reflect alterations of PKA/ CREB signaling. Hum. Mol. Genet. *25*, 837–852. https://doi. org/10.1093/hmg/ddv482.
- 65. Kaplanis, J., Samocha, K.E., Wiel, L., Zhang, Z., Arvai, K.J., Eberhardt, R.Y., Gallone, G., Lelieveld, S.H., Martin, H.C., McRae, J.F., et al.; Deciphering Developmental Disorders Study (2020). Evidence for 28 genetic disorders discovered by combining healthcare and research data. Nature 586, 757–762. https://doi.org/10.1038/s41586-020-2832-5.
- 66. Fritzen, D., Kuechler, A., Grimmel, M., Becker, J., Peters, S., Sturm, M., Hundertmark, H., Schmidt, A., Kreiß, M., Strom, T.M., et al. (2018). De novo FBXO11 mutations are associated with intellectual disability and behavioural anomalies. Hum. Genet. *137*, 401–411. https://doi.org/10.1007/s00439-018-1892-1.

- 67. Roversi, G., Picinelli, C., Bestetti, I., Crippa, M., Perotti, D., Ciceri, S., Saccheri, F., Collini, P., Poliani, P.L., Catania, S., et al. (2015). Constitutional de novo deletion of the FBXW7 gene in a patient with focal segmental glomerulosclerosis and multiple primitive tumors. Sci. Rep. *5*, 15454. https:// doi.org/10.1038/srep15454.
- Consortium, A.P.G.; and AACR Project GENIE Consortium (2017). AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 7, 818–831. https://doi.org/10.1158/2159-8290.CD-17-0151.
- Mahamdallie, S., Yost, S., Poyastro-Pearson, E., Holt, E., Zachariou, A., Seal, S., Elliott, A., Clarke, M., Warren-Perry, M., Hanks, S., et al. (2019). Identification of new Wilms tumour predisposition genes: an exome sequencing study. Lancet Child Adolesc. Health *3*, 322–331. https://doi.org/10.1016/ S2352-4642(19)30018-5.
- Posey, J.E., Harel, T., Liu, P., Rosenfeld, J.A., James, R.A., Coban Akdemir, Z.H., Walkiewicz, M., Bi, W., Xiao, R., Ding, Y., et al. (2017). Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. N. Engl. J. Med. *376*, 21–31. https://doi.org/10.1056/NEJMoa1516767.
- Welcker, M., Orian, A., Grim, J.E., Eisenman, R.N., and Clurman, B.E. (2004). A nucleolar isoform of the Fbw7 ubiquitin ligase regulates c-Myc and cell size. Curr. Biol. *14*, 1852–1857. https://doi.org/10.1016/j.cub.2004.09.083.
- Matsumoto, A., Onoyama, I., and Nakayama, K.I. (2006). Expression of mouse Fbxw7 isoforms is regulated in a cell cycle- or p53-dependent manner. Biochem. Biophys. Res. Commun. *350*, 114–119. https://doi.org/10.1016/j.bbrc.2006.09. 003.
- 73. Strohmaier, H., Spruck, C.H., Kaiser, P., Won, K.A., Sangfelt, O., and Reed, S.I. (2001). Human F-box protein hCdc4 targets cyclin E for proteolysis and is mutated in a breast cancer cell line. Nature 413, 316–322. https://doi.org/10.1038/ 35095076.
- Klotz, K., Cepeda, D., Tan, Y., Sun, D., Sangfelt, O., and Spruck, C. (2009). SCF(Fbxw7/hCdc4) targets cyclin E2 for ubiquitindependent proteolysis. Exp. Cell Res. *315*, 1832–1839. https:// doi.org/10.1016/j.yexcr.2008.11.017.
- 75. Li, J., Pauley, A.M., Myers, R.L., Shuang, R., Brashler, J.R., Yan, R., Buhl, A.E., Ruble, C., and Gurney, M.E. (2002). SEL-10 interacts with presenilin 1, facilitates its ubiquitination, and alters A-beta peptide production. J. Neurochem. *82*, 1540–1548. https://doi.org/10.1046/j.1471-4159.2002.01105.x.
- 76. Wu, G., Lyapina, S., Das, I., Li, J., Gurney, M., Pauley, A., Chui, I., Deshaies, R.J., and Kitajewski, J. (2001). SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. Mol. Cell. Biol. 21, 7403–7415. https://doi.org/10.1128/mcb.21.21.7403-7415.2001.
- 77. Fukushima, H., Shimizu, K., Watahiki, A., Hoshikawa, S., Kosho, T., Oba, D., Sakano, S., Arakaki, M., Yamada, A., Nagashima, K., et al. (2017). NOTCH2 Hajdu-Cheney Mutations Escape SCF^{FBW7}-Dependent Proteolysis to Promote Osteoporosis. Mol. Cell *68*, 645–658.e5. https://doi.org/10.1016/j. molcel.2017.10.018.
- Popov, N., Herold, S., Llamazares, M., Schülein, C., and Eilers, M. (2007). Fbw7 and Usp28 regulate myc protein stability in response to DNA damage. Cell Cycle *6*, 2327–2331. https:// doi.org/10.4161/cc.6.19.4804.
- 79. Zhao, D., Zheng, H.Q., Zhou, Z., and Chen, C. (2010). The Fbw7 tumor suppressor targets KLF5 for ubiquitin-mediated

degradation and suppresses breast cell proliferation. Cancer Res. *70*, 4728–4738. https://doi.org/10.1158/0008-5472.Can-10-0040.

- Nateri, A.S., Riera-Sans, L., Da Costa, C., and Behrens, A. (2004). The ubiquitin ligase SCFFbw7 antagonizes apoptotic JNK signaling. Science 303, 1374–1378. https://doi.org/10. 1126/science.1092880.
- Tong, J., Tan, S., Nikolovska-Coleska, Z., Yu, J., Zou, F., and Zhang, L. (2017). *FBW7*-Dependent Mcl-1 Degradation Mediates the Anticancer Effect of Hsp90 Inhibitors. Mol. Cancer Ther. *16*, 1979–1988. https://doi.org/10.1158/1535-7163. Mct-17-0032.
- 82. Zhao, X., Hirota, T., Han, X., Cho, H., Chong, L.W., Lamia, K., Liu, S., Atkins, A.R., Banayo, E., Liddle, C., et al. (2016). Circadian Amplitude Regulation via FBXW7-Targeted REV-ERBα Degradation. Cell *165*, 1644–1657. https://doi.org/10.1016/j. cell.2016.05.012.
- Morra, F., Luise, C., Merolla, F., Poser, I., Visconti, R., Ilardi, G., Paladino, S., Inuzuka, H., Guggino, G., Monaco, R., et al. (2015). FBXW7 and USP7 regulate CCDC6 turnover during the cell cycle and affect cancer drugs susceptibility in NSCLC. Oncotarget 6, 12697–12709. https://doi.org/10.18632/oncotarget.3708.
- 84. Okazaki, H., Matsunaga, N., Fujioka, T., Okazaki, F., Akagawa, Y., Tsurudome, Y., Ono, M., Kuwano, M., Koyanagi, S., and Ohdo, S. (2014). Circadian regulation of mTOR by the ubiquitin pathway in renal cell carcinoma. Cancer Res. 74, 543–551. https://doi.org/10.1158/0008-5472.CAN-12-3241.
- Welcker, M., Larimore, E.A., Swanger, J., Bengoechea-Alonso, M.T., Grim, J.E., Ericsson, J., Zheng, N., and Clurman, B.E. (2013). Fbw7 dimerization determines the specificity and robustness of substrate degradation. Genes Dev. 27, 2531– 2536. https://doi.org/10.1101/gad.229195.113.
- 86. Ikenoue, T., Terakado, Y., Zhu, C., Liu, X., Ohsugi, T., Matsubara, D., Fujii, T., Kakuta, S., Kubo, S., Shibata, T., et al. (2018). Establishment and analysis of a novel mouse line carrying a conditional knockin allele of a cancer-specific FBXW7 mutation. Sci. Rep. *8*, 2021. https://doi.org/10.1038/s41598-018-19769-1.
- 87. Davis, H., Lewis, A., Spencer-Dene, B., Tateossian, H., Stamp, G., Behrens, A., and Tomlinson, I. (2011). FBXW7 mutations typically found in human cancers are distinct from null alleles and disrupt lung development. J. Pathol. *224*, 180–189. https://doi.org/10.1002/path.2874.
- 88. Sancho, R., Blake, S.M., Tendeng, C., Clurman, B.E., Lewis, J., and Behrens, A. (2013). Fbw7 repression by hes5 creates a feedback loop that modulates Notch-mediated intestinal and neural stem cell fate decisions. PLoS Biol. *11*, e1001586. https://doi.org/10.1371/journal.pbio.1001586.
- 89. Mortimer, N.T., and Moberg, K.H. (2013). The archipelago ubiquitin ligase subunit acts in target tissue to restrict tracheal terminal cell branching and hypoxic-induced gene expression. PLoS Genet. *9*, e1003314. https://doi.org/10.1371/journal.pgen.1003314.
- 90. McDiarmid, T.A., Belmadani, M., Liang, J., Meili, F., Mathews, E.A., Mullen, G.P., Hendi, A., Wong, W.R., Rand, J.B., Mizumoto, K., et al. (2020). Systematic phenomics analysis of autism-associated genes reveals parallel networks underlying reversible impairments in habituation. Proc. Natl. Acad. Sci. USA 117, 656–667. https://doi.org/10.1073/ pnas.1912049116.

The American Journal of Human Genetics, Volume 109

Supplemental information

Germline variants in tumor suppressor FBXW7

lead to impaired ubiquitination

and a neurodevelopmental syndrome

Sarah E.M. Stephenson, Gregory Costain, Laura E.R. Blok, Michael A. Silk, Thanh Binh Nguyen, Xiaomin Dong, Dana E. Alhuzaimi, James J. Dowling, Susan Walker, Kimberly Amburgey, Robin Z. Hayeems, Lance H. Rodan, Marc A. Schwartz, Jonathan Picker, Sally A. Lynch, Aditi Gupta, Kristen J. Rasmussen, Lisa A. Schimmenti, Eric W. Klee, Zhiyv Niu, Katherine E. Agre, Ilana Chilton, Wendy K. Chung, Anya Revah-Politi, P.Y. Billie Au, Christopher Griffith, Melissa Racobaldo, Annick Raas-Rothschild, Bruria Ben Zeev, Ortal Barel, Sebastien Moutton, Fanny Morice-Picard, Virginie Carmignac, Jenny Cornaton, Nathalie Marle, Orrin Devinsky, Chandler Stimach, Stephanie Burns Wechsler, Bryan E. Hainline, Katie Sapp, Marjolaine Willems, Ange-line Bruel, Kerith-Rae Dias, Carey-Anne Evans, Tony Roscioli, Rani Sachdev, Suzanna E.L. Temple, Ying Zhu, Joshua J. Baker, Ingrid E. Scheffer, Fiona J. Gardiner, Amy L. Schneider, Alison M. Muir, Heather C. Mefford, Amy Crunk, Elizabeth M. Heise, Francisca Millan, Kristin G. Monaghan, Richard Person, Lindsay Rhodes, Sarah Richards, Ingrid M. Wentzensen, Benjamin Cogné, Bertrand Isidor, Mathilde Nizon, Marie Vincent, Thomas Besnard, Amelie Piton, Carlo Marcelis, Kohji Kato, Norihisa Koyama, Tomoo Ogi, Elaine Suk-Ying Goh, Christopher Richmond, David J. Amor, Jessica O. Boyce, Angela T. Morgan, Michael S. Hildebrand, Antony Kaspi, Melanie Bahlo, Rún Friðriksdóttir, Hildigunnur Katrínardóttir, Patrick Sulem, Kári Stefánsson, Hans Tómas Björnsson, Simone Mandelstam, Manuela Morleo, Milena Mariani, TUDP Study Group, Marcello Scala, Andrea Accogli, Annalaura Torella, Valeria Capra, Mathew Wallis, Sandra Jansen, Quinten Waisfisz, Hugoline de Haan, Simon Sadedin, Broad Center for Mendelian Genomics, Sze Chern Lim, Susan M. White, David B. Ascher, Annette Schenck, Paul J. Lockhart, John Christodoulou, and Tiong Yang Tan

Acknowledgements

UDP-Vic acknowledges financial support from the Murdoch Children's Research Institute and the Harbig Foundation. The Rare Disease Flagship acknowledges financial support from the Royal Children's Hospital Foundation, the Murdoch Children's Research Institute, and the Harbig Foundation. The research conducted at the Murdoch Children's Research Institute and Baker Heart and Diabetes Institute was supported by the Victorian Government's Operational Infrastructure Support Program. Sequencing and analysis of Individual 1 were provided by the Broad Institute of MIT and Harvard Center for Mendelian Genomics (Broad CMG) and was funded by the National Human Genome Research Institute, the National Eye Institute, and the National Heart, Lung and Blood Institute grant UM1 HG008900 to Daniel MacArthur and Heidi Rehm.

The research pertaining to Individual 18 was supported by Telethon Undiagnosed Diseases Program (TUDP, GSP15001).

Sequencing of Individual 31 was funded by CREGEMES and Sanger validated by Claire Feger.

The research conducted at The Hospital for Sick Children (Canada) was supported in part by the Norm Saunders Complex Care Initiative, SickKids Centre for Genetic Medicine, and University of Toronto McLaughlin Centre.

The Chair in Genomic Medicine awarded to J.C. is generously supported by The Royal Children's Hospital Foundation.

This work was in part supported by a grant awarded under the Australian National Health & Medical Research Council (NHMRC) Centre for Research Excellence Scheme (APP1117394) to L.E.R.B., A.S., T.R., K-R.D., C-A.E. and by a personal Vici grant (09150181910022) from The Netherlands Organization for Scientific Research (NWO) to A.S.

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number T32CA136432. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

D.B.A, T.B.N. and M.S. were supported by an Investigator Grant from the National Health and Medical Research Council (NHMRC) of Australia (GNT1174405).

This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1TR001873. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

M.S.H., M.B. and A.T.M. are funded by a National Health and Medical Research Council (NHMRC) Centre of Research Excellence Grant (1116976). M.B. was funded by an NHMRC Senior Research Fellowship (ID:1102971).



Figure S1: Distribution of neurodevelopment variants within FBXW7 relative to known COSMIC and gnomAD variants. (**A**) Location of patient-ascertained missense variants (red) and stop-gained and frameshift variants (purple). (**B**) Distribution of 1481 (440 unique) Catalogue Of Somatic Mutations In Cancer (COSMIC) somatic mutations (red) in FBXW7, where bubble size corresponds to the number of observations.

(C) Distribution of 280 missense variants (277 unique) in FBXW7 gnomAD v2.1 (140k exomes and genomes) variants with bubble size corresponding to the number of observations. (D) Comparison of structural predictors of neurodevelopmental disease variants to gnomAD variants. The gnomAD dataset was filtered to only those within the FBXW7 experimental structure, which includes residues 263 - 706, giving 78 variants only. Of these, the majority are very rare in the population (Allele Count: No. observations – 1:55, 2:14, 3:5, 6:2, 7:1, 12:1). Protein stability, determined using mutation Cutoff Scanning Matrix (mCSM), predicted the majority of gnomAD variants to also have a destabilizing effect, and to be similarly distributed to the patient cohort variants. Binding affinity, determined using mCSM-Protein–protein interactions (PPI) 1&2 ($\Delta\Delta$ G), suggests that gnomAD variants have a much smaller effect on binding affinity compared to the patient variants. Additionally, the gnomAD variants are dispersed throughout the structure and are, on average, further from the predicted interface with CYCLIN E1. See Table S3 for individual variant data.







Figure S2: Change in interaction with CYCLIN E1 predicted by each variant

Zoom-in of the interaction of wild-type/variant residues of FBXW7 and its surrounding residues. The variant residues are overlaid on wild-type residues to identify the changes in interaction when variant occurs. FBXW7 is shown in brown ribbon, while CYCLIN E1 is shown in a light gray surface. All wild-type, and variant residues are shown in magenta and cyan sticks, respectively, while surrounding residues of FBXW7 and TPPXS motif of CYCLIN E1 are shown in brown and green sticks. The Oxygen and Nitrogen atoms are in red, and blue, respectively. Hydrogen bond interactions are shown in the red dash lines. Variants that reoccur are indicated by the bold title.

ENSP00000474725/1-707	
FBpp00/3101/1-1326	MERGCPAASSESVTSAGERTQSAVTSSTSTWVKSQASTSRKTEASEESGLGAVDAEVGAG
ENSP00000474725/1-707 FBpp0073101/1-1326	RTG-GSL REAFVSMSTLREDVEDVCVSSNSQHGFAVVLDDESSTFEISSSNSLPTSAGAASTVGVVA
ENSP00000474725/1-707	RGNPSSSQVQVQV
FBPP007310171-1320	VDD3351D1LNGGHPDLGHFASSENSNQGFINEDNEDFFVVCLINDDDDDEEFEFEEDDE .:.**: : :* *
ENSP0000047472571-707 FBpp0073101/1-1326	NKVVEEEQQQQLRQQEEEHIARNG EELIEDEDEDAVDIVTGAISCPNTSQLALADGTIMAADGSKIFLETPVVEE :.::*:* :*
ENSP00000474725/1-707 FBpp0073101/1-1326	PRPGGQNDS AQPHPGQVVTTGSQSELTGKPKRLSDEFLLGEEDQAENLALGRCIKSEPVNPVDDNPSEG * * *
ENSP00000474725/1-707 FBpp0073101/1-1326	QQGQLEENNNRFISVDEDSS DDGATCFSLHDRLMSVRLKQMSLTANTVSNPSPAASANAAAPEEASTSNSSST
ENSP00000474725/1-707 FBpp0073101/1-1326	GNQEEQEEDEEHAGEQ SSSALSRADIESMDLIERRDFETEQRLTGGIILRTSSMVSQNKLNLSLIKSMAGGSKAAN
ENSP00000474725/1-707	··· *· : *: . *: ·
FBpp00/3101/1-1326	GSGTANSDDwPSSSNGRTVSSDSKYTYKDLSTTPTSSRKYTNSRLSKSTAKLNLGSSLGA
ENSP00000474725/1-707 FBpp0073101/1-1326	ESDDFDQSDDSSRED SSCSQHRSGSSSTSKSMESSTSCTGAARTDVYTNTNSNDYPSLAPTTSGSSTSGGSCQQD :.*:. **:.
ENSP00000474725/1-707 FBpp0073101/1-1326	EHTHTNVDLPVHQLSSP QEENVSASVSYSSVGSQTSQESGCSRTTAINPTAACSTGSACLGDSQASTSASTSSGAGA
ENSP00000474725/1-707 FBpp0073101/1-1326	FYTK-TTKMKRKLD-HGSE-VR-SFSLGKKP SNRCQYATTSTTKAARQVNASAQTQERFLTRSNPPAASGAGSVGANPTASVRQRRNGSSD
ENSP00000474725/1-707 FBpp0073101/1-1326	CKVSEYT-S VVHLEVVVEEGAGGGDGGVVEPGDFSAEEPWANCDEENNCSDLEEICTCQNGNGSSYGGS *: *.* *
ENSP00000474725/1-707 FBpp0073101/1-1326	TTGLVPCSA-TPTTFGDLRAANGQG NASLSETFDMDAMDPDEPISLSLSSASAGFTEYSLTNPSSLMSHQRKRKFNEGRLLDGGD
ENSP00000474725/1-707 FBpp0073101/1-1326	QQRRRITSVQP- YSVTISSSGEVGGPGSGVSDNCRKRIAYDFASTPRSSQHLGPTAVLSVTPSSHLTSSTPG *:** * *
ENSP00000474725/1-707 FBpp0073101/1-1326	PTGLQEWLKMFQSWSGPEKLLALDELIDSCEPTQVKHMMQVIE SALGRRTPRSVPSRDNPPPELQHWLAQFQRWSHVERLLALDRLIDHCDPSQVRHMMKVIE *. **.** ** ** *:**********************
ENSP00000474725/1-707 FBpp0073101/1-1326	PQFQRDFISLLPKELALYVLSFLEPKDLLQAAQTCRYWRILAEDNLLWREKCKEE-GIDE PQFQRDFISLLPRELALFVLSYLEPKDLLRAAQTCRSWRFLCDDNLLWKEKCRKAQILAE
ENSP00000474725/1-707 FBpp0073101/1-1326	PLHIKRRKV-IKPGFIHSPWKSAYIRQHRIDTNWRRGELKSPKVLKGHDDHVITCLQF PRSDRPKRGRDGNMPP-IASPWKAAYMRQHIIEMNWRSRPVRKPKVLKGHDDHVITCLQF * ** : * * ****:*** *: ***
ENSP00000474725/1-707 FBpp0073101/1-1326	CGNRIVSGSDDNTLKVWSAVTGKCLRTLVGHTGGVWSSQMRDNIIISGSTDRTLKVWNAE SGNRIVSGSDDNTLKVWSAVNGKCLRTLVGHTGGVWSSQMSGNIIISGSTDRTLKVWDMD
ENSP00000474725/1-707 FBpp0073101/1-1326	TGECIHTLYGHTSTVRCMHLHEKRVVSGSRDATLRVWDIETGQCLHVLMGHVAAVRCVQY SGACVHTLQGHTSTVRCMHLHGSKVVSGSRDATLRVWDIEQGSCLHVLVGHLAAVRCVQY
ENSP00000474725/1-707 FBpp0073101/1-1326	DGRRVVSGAYDFMVKVWDPETETCLHTLQGHTNRVYSLQFDGIHVVSGSLDTSIRVWDVE DGKLIVSGAYDYMVKIWHPERQECLHTLQGHTNRVYSLQFDGLHVVSGSLDTSIRVWDVE
ENSP00000474725/1-707 FBpp0073101/1-1326	TGNCIHTLTGHQSLTSGMELKDNILVSGNADSTVKIWDIKTGQCLQTLQGPNKHQSAVTC TGNCKHTLMGHQSLTSGMELRQNILVSGNADSTVKVWDITTGQCLQTLSGPNKHHSAVTC **** *** ************
ENSP00000474725/1-707 FBpp0073101/1-1326	LQFNKNFVITSSDDGTVKLWDLKTGEFIRNLVTLESGGSGGVVWRIRASNTKLVCAVGSR LQFNSRFVVTSSDDGTVKLWDVKTGDFIRNLVALDSGSSGVVWRIRANDTKLICAVGSR ******:****************************
ENSP00000474725/1-707 FBpp0073101/1-1326	NGTEETKLLVLDFDVDMK NGTEETKLMVLDFDVEGACVKCS ********:******: :*

Figure S3: Amino acid alignment of human FBXW7 and Drosophila Ago sequences

Uniprot (www.uniprot.org) sequence alignment of Homo sapiens (ENSP00000474725/1-707) and Drosophila melanogaster (FBpp0073101/1-1326) FBXW7 (ago) proteins. Highlighted in yellow the F-Box, in gray the seven D40 repeats of the WD40 domain.





The knockdown of ago leads to a lower mTTC compared to the controls. Increasing the inter-trial interval in the fatigue assay, preventing habituation from being formed, demonstrates that this lower TTC is not due to improved habituation but due to motor fatigue. Precise genotypes tested in the fatigue assay: elav^(I) C155-Gal4, GMR-wIR /Y; +/+; +/+ of genetic background control gray and elav^(I) C155-Gal4. GMR-wIR /Y; +/+; UAS-RNAi-2/+ of RNAi-2 knockdown in in blue. N_{control} = 42, N_{RNAi-2} = 48, mTTC_{control} = 44.53, mTTC_{RNAi-2} = 25.85, p = 1.35E-5. Statistical significance a linear model regression analysis on was assessed by the log transformed mTTC values, * P < 0.05, ** P < 0.01, *** P < 0.001.



Figure S5: Relative expression of ago in Drosophila knockdown lines

Quantitative RT-PCR was performed on wandering L3 larva from RNAi-1 and RNAi-2 lines crossed to the ubiquitous Act-Gal4/TM3 Sb Tb driver to determine the level of *ago* expression using exon spanning primers to *ago* and β 'COP. Error bars represent standard deviation.

Table S1: Analysis of FBXW7 neurodevelopmental syndrome variants

							gnom	AD - germline variants	COSMIC - s	somatic variants	CA	ADD	FATH	MM	GERP++	RS N	IPC	MTR	м	utationA	ssessor		PROVEAN	4	Polyp	hen2		SIFT		VEST4
Individua	Inheritance	gDNA (Chr4; GRCh37)	Exon	cDNA	Protein	Occurs within WD40 domain	Same variant	Alternative change at same amino acid residue	Same variant	Alternative change at same amino acid residue	score	rank score scor	re rank score	predicted conseq- uence	score s	ank core score	rank score	score sco	nk re score	rank score	predicted conseq- uence	score	rank score	redicted conseq- sc uence	ore score	predicted conseq- uence	score	rank score	predicted conseq- uence	ore rank score
1	de novo	g.153249446_153249447del	11	c.1331_1332del	p.(Lys444Serfs*27)	NMD predicted	Absent	3 LoF variants upstream	Absent	p.(Lys444Glyfs*55), p.(Lys444Argfs*32), p.(Lys444fs*2), more than 10 NMD predicted variants	-		-	-	-		-		-	-	-	-	-	-	-	-	-	-		
2	de novo	g.153249446dup	11	c.1332dup	p.(Val445Serfs*27)	NMD predicted	Absent	3 LoF variants upstream	Absent	p.(Val445Cysfs*53), p.(Val445Aspfs*27), more than 10 NMD predicted variants	-		-	-	-		-		-	-	-	-	-	-	· -	-	-	-		
3 4 5 6	familial	g.153245477_153245478del	13	c.1713_1714del	p.(Asn572Leufs*32)	Truncation predicted	Absent	3 LoF variants upstream	Absent	More than 10 NMD predicted variants	-		-	-	-		-		-	-	-	-	-	-		-	-	-		
7	de novo	g.153244218T>A	14	c.1939A>T	p.(Lys647*)	Truncation predicted	Absent	3 LoF variants upstream	Absent	p.(Lys647Asnfs*5) in stomach carcinoma, more than 10 NMD predicted variants	-		-	-	-		-		-	-	-	-	-	-	-	-	-	-		
8	de novo	g.153250822A>T	intron 10	c.1236+2T>A	p.?	N/A	Absent	Alternative change at same nucleotide: Absent	Present (stomach carcinoma)	Alternative change at same nucleotide: c.1236+2T>C (large intestine adenocarcinoma)																				
9	de novo	arr[GRCh37] 4q31.3(152720434_153661857)x1 dn	N/A	N/A	Entire gene deleted	N/A	N/A	N/A	N/A	N/A	-		-	-	-		-		-	-	-	-	-	-	-	-	-	-		
10	de novo	arr[GRCH37] 4q31.3q32.1(152854578_156285170)x1 dn,4q32.1q34.1(161464002_175617314)x3 dn,4q34.1q34.3(175858796_179802170)x3 dn	N/A	N/A	Entire gene deleted	N/A	N/A	N/A	N/A	N/A	-		-	-	-		-		-	-	-	-	-	-	-	-	-	-		
11	de novo	g.153249531G>A	11	c.1247C>T	p.(Thr416lle)	Yes	Absent	Absent	Absent	Absent	4.22	0.86 0.13	3 0.61	т	5.90 0	0.95 2.78	0.99	0.56 0.9	7 1.37	0.34	L	-5.66	0.87	D 1.	0.92	D	0.05	0.56	D 0.	.78 0.80
12	familial	g.153249532T>C	11	c.1246A>G	p.(Thr416Ala)	Yes	Absent	Absent	Absent	Absent	4.08	0.81 0.04	4 0.62	Т	5.90 (0.95 2.40	0.97	0.56 0.9	7 1.71	0.44	L	-4.80	0.81	D 0.	98 0.81	D	0.02	0.59	D 0./	.80 0.81
13	de novo	g.153249519T>A	11	c.1259A>T	p.(His420Leu)	Yes	Absent	Absent	Absent	Multiple	4.13	0.83 -1.5	0 0.81	D	5.90 0	0.95 3.08	0.99	0.87 0.5	9 4.72	1.00	Н	-10.92	0.99	D 1.	0.97	D	0.00	0.91	D 0.'	.94 0.95
14 15	de novo	g.153249511C>T	11	c.1267G>A	p.(Gly423Arg)	Yes	Absent	Absent	Present (multiple tissue types)	Multiple	4.35	0.89 0.16	6 0.61	т	5.90 (0.95 3.01	0.99	0.67 0.9	1.21	0.30	L	-7.94	0.96	D 1.	0.97	D	0.00	0.91	D 0.9	.94 0.96
16	de novo	g.153249457G>C	11	c.1321C>G	p.(Arg441Gly)	Yes	Absent	Absent	Present (lung carcinoma,	Multiple	3.72	0.70 2.02	2 0.21	т	4.08 0	0.47 3.14	0.99	0.55 0.9	0.42	0.13	N	-6.83	0.93	D 0.	0.80	D	0.03	0.91	D 0.	.84 0.86
17	de novo	a.153249394A>G	11	c.1384T>C	p.(Ser462Pro)	Yes	Absent	Absent	Absent	p.(Ser462Tvr), p.(Ser462Phe)	4.33	0.89 0.86	3 0.74	т	6.05 (.98 2.78	0.99	0.54 0.9	7 2.65	0.77	М	-4.96	0.82	D 0.	0.92	D	0.00	0.78	D 0.	87 0.89
19	do novo	a 1522492840 - T	11	0.1294G>A	p.(Arg465Hic)	Voc	Abcont	p.(Arg465Cys)	Procent (more than 5 ticsue types)	Multiple	4 17	0.84 0.0	7 0.42	т	6.05 (109 2.09	0.00	0.61 0.0	5 1 26	0.22		4.96	0.92	- ···	0 0 97		0.02	0.01		79 0 70
19	de novo (mosaic 14%)	g.153247366C>T	12	c.1436G>A	p.(Arg479Gln)	Yes	Absent	(allele balance 45% or lower) p.(Arg479Giy) (allele balance 25-30%)	Present (more than 5 tissue types)	Multiple	4.17	0.84 1.02	2 0.41	т	5.72 (0.89 2.93	0.99	0.80 0.3	5 0.84	0.32	L	-3.97	0.74	D 1.	0.97	D	0.02	0.51	D 0.	.64 0.65
20	de novo	g.153247363T>C	12	c.1439A>G	p.(Asp480Gly)	Yes	Absent	Absent	Present (colon adenocarcinoma)	Multiple	4.46	0.91 -2.4	9 0.89	D	5.72 (0.89 3.19	0.99	0.86 0.6	i0 3.93	0.96	Н	-6.95	0.93	D 1.	0 0.97	D	0.00	0.91	D 0./	.99 0.99
21	de novo	g.153247288C>T	12	c.1514G>A	p.(Arg505His)	Yes	Absent	Absent	Present (more than 5 tissue types)	Multiple	4.17	0.85 0.05	5 0.62	т	4.87 (0.63 3.08	0.99	0.55 0.9	7 1.50	0.38	L	-4.96	0.82	D 1.	0 0.97	D	0.01	0.78	D 0.	.75 0.75
22	de novo	g.153247171A>C	12	c.1631T>G	p.(Val544Gly)	Yes	Absent	Absent	Present (large intestine adenocarcinoma)	p.(Val544Asp) (mouth squamous cell carcinoma)	4.29	0.88 -0.7	9 0.74	Т	5.72 (0.89 3.18	0.99	0.55 0.9	4.32	0.98	н	-6.95	0.93	D 1.	0 0.92	D	0.00	0.91	D 0.0	.64 0.66
23	de novo	g.153245453G>A	13	c.1738C>T	p.(His580Tyr)	Yes	Absent	Absent	adenocarcinoma)	Multiple	4.09	0.82 -1.4	9 0.81	т	5.70 (0.89 2.95	0.99	0.75 0.8	4 4.04	0.97	н	-5.96	0.89	D 1.	0.97	D	0.01	0.56	D 0.f	.89 0.89
24	de novo	g.153245447A>C	13	c.1744T>G	p.(Ser582Ala)	Yes	Absent	Absent	Absent	Multiple	4.02	0.79 1.00	0.41	Т	5.70 (0.89 0.97	0.97	0.76 0.8	3 1.46	0.37	L	-2.70	0.61	D 0.	98 0.75	D	0.10	0.59	T 0./	.66 0.67
25	de novo (mosaic 23%)	g.153245395G>A	13	c.1796C>T	p.(Ala599Val)	Yes	Absent	p.(Ala599Gly) (allele balance 35-40%)	Absent	Absent	4.29	0.88 0.94	4 0.44	т	5.45 (0.80 2.69	0.99	0.86 0.6	0.86	0.21	L	-3.96	0.74	D 1.	00 0.84	D	0.02	0.78	D 0.0	.63 0.64
26	de novo	g.153244280G>A	14	c.1877C>T	p.(Ala626Val)	Yes	Absent	Absent	Present (large intestine adenocarcinoma)	p.(Ala626Thr), p.(Ala626Pro), p.(Ala626Asp)	4.13	0.83 0.96	6 0.43	т	5.67 (0.88 2.73	0.99	0.63 0.9	4 1.71	0.44	L	-3.91	0.74	D 1.	00 0.91	D	0.00	0.78	D 0.	.74 0.76
27	de novo	g.153244237G>T	14	c.1920C>A	p.(Ser640Arg)	Yes	Absent	Absent	Absent	Absent	3.40	0.62 0.97	7 0.43	Т	3.03 0	0.34 2.87	0.99	0.81 0.	2 2.58	0.75	М	-4.91	0.82	D 1.	0.92	D	0.06	0.60	T 0.f	.87 0.92
28	de novo	g.153245369T>C	13	c.1822A>G	p.(Ile608Val)	No	Absent	Absent	Absent	Absent	2.43	0.40 0.90	0 0.45	т	5.45 (0.80 1.39	0.85	0.37 0.9	9 0.18	0.09	N	-0.86	0.23	N 0.	0.30	В	0.22	0.19	T 0.5	.36 0.41
29	de novo	g.153244136C>G	14	c.2021G>C	p.(Arg674Pro)	No	Absent	Absent	Absent	p.(Arg674Trp), p.(Arg674Gln)	4.13	0.83 2.21	1 0.18	Т	4.82 (0.62 3.35	1.00	0.52 0.9	8 2.67	0.78	М	-6.83	0.93	D 1.	0.89	D	0.00	0.78	D 0.8	.81 0.85
30 31	de novo	g.153244137G>A	14	c.2020C>T	p.(Arg674Trp)	No	Absent	Absent	Present (glioma, cervix squamous cell carcinoma, atypical meningioma, prostate adenocarcinoma)	p.(Arg674Gln) (colon adenocarcinoma, stomach adenocarcinoma)	3.77	0.71 2.20	0.19	т	1.62 (0.23 2.77	0.99	0.52 0.9	8 2.67	0.78	М	-7.80	0.96	D 1.	00 0.92	D	0.00	0.91	D 0.f	.80 0.88
32	de novo	g.153244091C>T	14	c.2066G>A	p.(Arg689Gln)	No	Absent	Absent	Present (more than 5 tissue types)	p.(Arg689Glu), p.(Arg689Trp)	4.14	0.83 2.25	5 0.18	т	4.82 (0.62 2.62	0.98	0.40 0.9	9 2.70	0.79	М	-3.92	0.73	D 1.	0.89	D	0.03	0.68	D 0./	.82 0.87
33 34 35	de novo	g.153244092G>A	14	c.2065C>T	p.(Arg689Trp)	No	Absent	Absent	Present (more than 5 tissue types)	p.(Arg689Glu), p.(Arg689Gln)	4.22	0.86 2.20	0 0.19	т	5.67 (0.88 2.77	0.99	0.40 0.9	9 2.70	0.79	м	-7.88	0.96	D 1.	00 0.97	D	0.03	0.91	D 0.1	.86 0.91

Tolerated (T); Deleterious (D); Low (L); Medium (M); High (H); Combined Annotation Dependent Depletion (CADD); Functional Analysis through Hidden Markov Models (FATHMM); Genomic Evolutionary Rate Profiling (GERP) ++ rejected substitutions* (RS) score; missense badness, PolyPhen-2; Sorting Intolerant From Tolerant (SIFT); Variant Effect Scoring Tool (VEST).

Table S2: Clinical details of Individuals with FBXW7 neurodevelopmental syndrome

| INDIVIDUAL

 | 1 | 2 | 3 | 4
 | 5

 | 6 | 7
 | 8 | 9

 | 10 | 11 | 12 | 13
 | 14 | 15 | 16 | 17
 | 18

 | 19 | 20

 | 21 | 22 | 23 | 24 | 25
 | 26 | 27 | 28
 | 29 | 30 | 31
 | 32 | 33 | 34 35 |

--
--
---|---|---|--
--
--
--
--
--|--|---|--
--
--
--
--|--|--|--|---
---|--|--
--
--

--
--
--|--
--|---|--|--|---

--|--|---|--
---|--|
| VARIANT TYPE
Variant Details

 | | | | Predicted Los
 | ss of Function

 | |
 | | GENE DE

 | ELETION SNP way (thereing infinite | | |
 | | | |
 | MISSENSE,

 | AFFECTING WD40 | DOMAIN

 | | | | |
 | | |
 | | MISS | ENSE, NOT AFFECT
 | ING WD40 DOMAIN | | |
| Mode of discovery Tri

 | o WES (Broad) | ome sequencing with parental
variant segregation | Pamily-based WGS | Family-based WGS
 | Family-based WGS

 | Family-based WGS | Solo WES
 | Trio WES | Array CGH Aglient 180K

 | CoreDome-24 vf. 1, hg19)
[VCG5] | Gene Dx Trio WES | Solo WES | Trio WES (GeneDil)
 | Trio WES | Trio WES | Trio WES | Trio WGS
 | This WES W

 | WES on skin biopey; normal
depth for patient blood | Trio WES (DDD)

 | Trio WES (Mayo) | Tio WES | Trio WES (GeneDx) | Trio WES | Trio Exome
 | Trio WES | Trio WGS (research) | Trio WES
 | Trio WES (GeneDx) | Trio WES | Trio WES
 | Trio WES | Solo WES | trio WES Trio WE |
| cDNA (NM_001349798.2) c

 | 1331_13329el | c. 1332dup | c.1713_1714del | c.1713_1714del
 | c.1713_1714del

 | c.1713_1714del | c.1939A-T
 | c.1236+27>A | NA

 | NA | c.1247G>T | c. 1246A-G | c.1259AoT
 | c. 1267GoA | c.1267G>A | c.13210-G | c.13847C
 | c.1394QaA

 | c.1439QrA | c.1429A-G

 | c.1514GaA | c.16317>G | c.1738G>T | c.1744T>G | c.1796G>T
 | c.1877C>T | c.1920C>A | c.1822A-G
 | c 2021GrC | c.2020C>T | c.2020C>T
 | c.2055Ga-A | c 2065C>T | c.2055C>T c.2055C |
| gDNA (Chr4; GRCh37) g.1532-

 | 9446_1532N9447dal | g.153249446dup | g.153245477_153245478del | g.153245477_153245478del
 | g.153245477_153245478del

 | g 153245477_153245478del | g-1532H4218T-A
 | g 153250822A-T | arr [GRD:b37]
4q31.3(152720434_153661857)x

 | 4q31.3q32.1(152854578_15628
5170(x1
dn,4q32.1q34.1(161464032_175 | g-153249531G-A | g-1532495327>C | g.15324951975-A
 | g. 15304951 1C>T | g-153249511C>T | g. 153249457G2-C | g-153249394A-G
 | g-15324833MC>T

 | g.153247366C>T | g.1532473637>C

 | g.153247288C>T | g-153247171A-C | g 153045453G-A | g.153245447A-C | g-153045395G-A
 | g.153244280Gr-A | g 153244237G-T | g 153245369T>C
 | g 153244138C>G | g.1532441370-A | g. 153244137GrA
 | g.153244091C>T | g. 153244092G-A | g.153244092G-A g.153244092 |
|

 | | | |
 |

 | |
 | | 1 dn

 | 617314)x0
dn,4q34.1q34.3(175858796_179
802170)x0 dn | | |
 | | | |
 |

 | |

 | | | | |
 | | |
 | | |
 | | | |
| Protein level p.(
Same variant in gnomAD
Atemative change at same
3 Loft

 | Absent
Absent
veriants upstream | p.(VsH46Sents*27)
Absent
3 Loff variants upstream | p.(Asr672Lauts*32)
Absert
3 LoF variants upstream | p.(Asr672Leuts'32)
Absent
3 LoF variants upstream
 | p.(Aer572.euts'32)
Absort
3 LoF variants upstream

 | p.(Am572Leuts'32)
Absent
3 LoF variants upstream | p.(Lye647*)
Absent
3 Loff variants upstream
 | p.?
Absent
Absente change at some | DEL
NA
NA

 | DEL
NA
NA | p.(Trr4168e)
Absent
Absent | p.(Ttr415Als)
Absent
Absent | p.(Ha422Lex)
Absent
Absent
 | p.(Gy423Arg)
Absent
Absent | p. (Gy423Arg)
Absert
Absert | p. (Arg441Gy)
Absert
Absert | p.(Ser40291c)
Absert
Absert
 | p.(Arg465Hs)
Absent
p.(Arg465Cys)

 | p.(Arg479Gh)
Absent
p.(Arg479Gly) | p.(Aep480Gy)
Absent
Absent

 | p.(Arg522Hz)
Absent
Absent | p.(Va544Gy)
Absent
Absent | p.(His5807)r)
Absent
Absent | p.(Ser562Ala)
Absent
Absent | p.(Ab599Va)
Absent
p.(Ab599Giy)
 | p.(Alat22Val)
Absent
Absent | p. (SerE4DArg)
Absert
Absert | p.(Be608Val)
Absert
Absert
 | p. (ArgG74Pro)
Absert
Absert | p.(ArgET4Trp)
Absent
Absent | p.(Arg674Ttp)
Absent
Absent
 | p. (Arg689Gir)
Absert
Absert | p.(Arg689Trp)
Absent
Absent | p.(Arg6027rp) p.(Arg6027
Absent Absent
Absent Absent |
| amino acid residue in gnomAD
Same variant in COSMIC

 | Absert | Absert | Absert | Absent
 | Absert

 | Absent | Absent
 | Present (stomach carcinoma | a) NA

 | NA | Absent | Absent | Absent
 | Present (multiple tissue types) | Present (multiple tissue types) | Present (lung carcinoma, | Absert
 | (allele balance 45% or lower) Present (more than 5 tissue P

 | (alele balance 25-30%)
Present (more than 5 tissue Pro | vesent (colon adenocarcinoma)

 | Present (more than 5 tissue | Present (large intestine | Present (large intestine | Absent | (allele balance 35-40%)
Absent
 | Present (large intestine | Absort | Absent
 | Absert | Present (glioma, cervix
squarrous cell carcinoma, | Present (gloma, cents
aquamous cell carcinoma,
 | Present (more than 5 tissue | Present (more than 5 tissue Pre | ent (more than 5 tissue Present (more than |
| pij

 | ys444Glyts*55). | p.(Val445Cysts*53), | |
 |

 | | p.(Lys647Asnts'5) in storract
 | ch Marrie abarro al arra |

 | | | |
 | | | mabdomyosarcoma) |
 | (ypec)

 | types) |

 | t/pec) | adenoca/cinoma) | adenoca/cinona) | |
 | adenocarcinoma) | |
 | | adenocarcinoma) | adenocarcinoma)
 | (ypec) | dbeel | type) (tpes) |
| Atemative change at same Pro
amino acid residue in COSMIC P
more th

 | (Lys444fs*2),
in 10 NMD predicted
variants | p.(VsH45Aspts*27),
more than 10 NMD predicted
variants | More than 10 NMD predicted
variants | More than 10 MMD predicted
variants
 | More than 10 NMD predicted
variants

 | More than 10 NMD predicted
variants | carcinoma,
more than 10 NMD predicted
variants
 | nucleotide: c. 1236-27-C (br)
intestine adenocarcinoma) | ge NA

 | NA | Absent | Absent | Multiple
 | Multiple | Multiple | Multiple | p.(Ser4627yr), p.(Ser4629he)
 | Multiple

 | Multiple | Multiple

 | Multiple P | p.(Val544Asp) (mouth squarrous
cell carcinoma) | Multiple | Multiple | Absent
 | p.(Ala6267hr), p.(Ala626Pro),
p.(Ala626Asp) | Yes (one in NCI's GDC) | Absent
 | p.(Arg674Trp), p.(Arg674Gh) | adenocarcinoma, stomach
adenocarcinoma) | adenocarcinoma, stomach
adenocarcinoma)
 | p.(Arg689GU), p.(Arg689Tp) | p.(Arg689Gb),
p.(Arg689Gb) | p. (Arg689Gb), p. (Arg689G
p. (Arg689Gb) p. (Arg689G |
| Exen (WI, 001349798.2)
Occurs within WD40 domain

 | 11
MD predicted
De novo | 11
NMD predicted
De novo | 13
Truncation predicted
Paternal | 13
Truncation predicted
Paternal
 | 13
Truncation predicted
Paternal

 | 13
Truncation predicted
Unknown | 14
Truncation predicted
De novo
 | intron 10
NA
De novo | NA
NA
De novo

 | NA
NA
De navo | 11
Yes
De rovo | 11
Yes
Inherited from mother with ID | 11
Yes
De nao
 | 11
Yes
De navo | 11
Yes
De novo | 11
Yes
De novo | 11
Yes
De novo
 | Tes
De novo De

 | 12
Yes
Se novo, posi-zygolic (mosaic: | 12
Yes
De rovo

 | 12
Yes
De rovo | 12
Yes
De novo | 13
Yes
De rovo | 13
Yes
De noio | 13
Yes
De novo (mossic: 23.3% of 103
 | 14
Yes
De rovo | 14
Yes
De rovo | 13
No
De roio
 | 14
No
De roio | 14
No
De rovo | 14
No
De novo
 | 14
No
De novo | 14
No
De navo | 14 14
No No
De nos |
|

 | | | |
 |

 | |
 | |

 | | | Yes
NCOR1.NM_001190440:exen27: |
 | | | |
 |

 | 14%) |

 | | | | | reads)
 | | | |
 | | |
 | | | |
| Other candidate variants PDP2:

 | de novo LoF variant | No | No | No
 | No

 | No | No
 | No | Other inherited CNV (see below)

 | No | arr[GRCh37]
22q11.22q11.23(22997609_249
61234)x3 pat | c.3734GrA;p.Arg1245Gh (mat)
NCOR1:NM_001190440;exend:c | No
 | No | No | No | No
 | No CA

 | Yes
ACNA1A:NM_022035.2:c.835
C>T p.(Arg279Cys) | No

 | No | No | No | No | No
 | No | No | No
 | No | No | No
 | KMT2D: de novo
NM_003482.4:c 16012T>C
p.(Cys5338Arg) | No | No No |
| Demographic Features

 | | | |
 |

 | |
 | |

 | | | 244CSA(p.(Prote21tr) [no
known disease association] |
 | | | |
 |

 | |

 | | | | |
 | | |
 | | |
 | | | |
| Sex
Age at last assessment

 | 11 years | lible
3 years 2 months | Ferrale
14 years 9 months | Female
11 years 9 months
 | Ferrale
6 years 3 months

 | Mble
44 years 6 months | Maie
Py
 | Fernale
5 years | Male
7 years 2 months

 | Male
2 years 2 months | Male
18 yo | Partale
Jy | Mais
10 years, 2 months
 | Male
14 yo | Main
15 | Male
5 years o | Mais
Information gathered from
clinical record and obtained from
 | Partais
9.5 years

 | Mole
(currently 6 years) | Mbin
15 years

 | Main
3 years | Perrait
23 months | Male
3 years | Fernale
6 years | Male
22 months
 | Male
3 yrs | Farais
7 years | tible
11 years
 | Male
2 years (currently 4 years) | Male
15 years | Male
14 years
 | Mala
2 years | Male
10 years | Male Male
12 years 7 y |
| Other
Medical History

 | | | |
 |

 | |
 | |

 | | | |
 | | Macedonian | | parens
 |

 | | COD4K02105 in DOD paper

 | | | | |
 | Caucasian | | Caucasian
 | Born at 42ake in a C2PE Alter | |
 | | | |
|

 | | | |
 |

 | |
 | | Feet maposition during

 | | | |
 | | | | Planned Casearean after 42
 |

 | |

 | | | | | 1565g. 33 weeks premature.
 | | Low material second DATE A | |
 | mother, BW = 7bs, Length =
48.5cm, HC = 34.5cm, NCU to
2 days due to mild respiratory | or
V |
 | | | |
| Prenabal history norm

 | d nuchal fold at 12/40;
I chromosomes on | suspicion of preeclampela | NAD | NAD
 | NAD

 | NAD | NAD
 | Born at 36+5 weeks, birth
weight 3390 gr, Apgar scores
and 8. Neonatal joundice | syphile serology. Born at 40
weeks: (weight 4,000g; height 51

 | 40+2/40 Emergency LUSCS for
non-reassuring CTG. NI
antenatal concerns. Growth | Unremarkable | no | ron-contributory, born at 38
weeks 1 day
 | uneventul | Urremarkable | complicated pregnancy and
term delivery | tize and drop in fetal movement,
weight at birth: 5230 g (<59
percentile, +3.4 SD), length: 57
 | normal p

 | Born at 40 weeks. Uneventful
pregnancy. Weight at birth : No | formal (well bar ear infection in num and she took ear drops)

 | Delivered at 35 weeks, induced
for maternal cholestasis. BW
Bbs. 15oz., hospitalized for 6 | Normal | Unremarkable. Term delivery,
Gesarean section for breech | Normal | dx of IUGR, Vaginal, Mother
G1PD, 30years old, NCU for 19
days for jaundice, hypoglycemia
 | Born at 41+4 wks.
Uncomplicated pregnancy and | Velamentous cord insertion;
Term birth and Apgars 9/9; Birth
weight, length, and head | Normal
 | distress and poor feeding.
Parents report a history of
increased nuchal fold and extra
doin table is fee back of the work | Unremarkable pregnancy. Born
at term. BW 3450g. Apgans 8.9
a Mom recalls concerns re being | Normal
 | Normal | Normal | Normal Hyperschogenic
hypotonia and re
detress at birth (J |
|

 | | | |
 |

 | |
 | treated with phototherapy. | jaundice. Negative syphilis
serckogy at age 4 years

 | scans normal | | |
 | | | | cm (<99 percentile, +2.6 SD),
head circumference: 40 cm (99
percentile, +2.5 SD)
 |

 | |

 | | | | | and feeding difficulties.
Abnormal newborn hearing
screen.
 | | circumference within normal
range | |
 | at birth, which resolved. Mothe
took Philosec for GEIPD during
pregnancy. Newborn screen we | er resuscitation needed. |
 | | | 3) |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | |
 | Hypolonia. Tonic upgaze eye | |
 | normal. NHS was completed 3
times. | |
 | | | |
| Neurological problems Hypo

 | onia, tactile issues | Hypotonia | Hypolonia | NAD
 | NAD

 | NAD | NAD
 | No hypotonia | No neurological signs at testing.

 | Early hypotonia. No seizures. No | After onset of seizures at age 7
years, his academic and
intellectual functions | Unsteady gait, Broad-based gait | hypotonia diagnosed shortly
after birth
 | history of seizures; hypotonia | Hypotonia; macrocephaly | Generalized hypotonia | hypotonia
 | eonatal hypotonia and failure to Ge

 | Reneralized severe hypotonia; | apgars 8 (01 min, 10 at 5 min.
rome day 4 fine, ducky episode
day 12, floppy, generalised

 | Hypotonia | Severe progressive spasticity; | Hypotonia. Broad-based gait but
not trankly absic. No seizures. | no hypotonia, no seizures | motor developmental delay, mild
hypotonia. Pocal seizures (left
anterior temporal area)
 | Myoclonic and myoclonic-lonic
seizures from 4-5 months of
ana JEC findings successive ci | Generalized hypotonia;
Transment-references | Early Onset Absence Epilepe
(EOAE); rare leolated myoclor
 | ay
onic Generalized hypotonia | Normal tone on exam (from 8
years). Achilles tendon
contracture (tight heel cords).
Abnormality of coordination | epilepsy started at 4yGm;
hypotonix; atsxis; upper hand
distribution insubstary
 | Normal | hypotonia, language trouble | hypotonia Global DD, hyp |
|

 | | | |
 |

 | |
 | |

 | | deteriorated. Now in special ed. | |
 | | | |
 |

 | | hypotonia; on CB2 for his
seizures which has stabilised;

 | | | Norral EMG/NCS. | | on antiepleptic medication
 | developmental epileptic
encephakpathy with multifocal
and generalised discharges. | , | seizunes
 | | Possible atxxis. Has history of
migraines with photophobia. | movements and stereotypies
 | | | |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | |
 | | Brain MFI x3 - Large cerebelum
with crowded posterior tasks at 9 |
 | | |
 | | | |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | Train MEI (2 years of anal |
 |

 | | Crowded posterior fossa with

 | | | | |
 | | grow from 42mm to 46mm at 3.5
years, thereafter it mildly shrinks
in 41mm at 9 years - this could |
 | | cerebeilum 46mm with crowded
posterior fossa and tonsils low |
 | | Brain MFI (2 ye) : non
specific while matter
hypersignals, widening of | |
| Brain imaging CT brain abro

 | n only - no structural
mailties reported | NA | Large cerebellar vermis with low-
lying tonsils 3.6 mm below
foramen magnum (Arnold-Chiari | e
ni NA
 | NA

 | NA | NA
 | NA | NA

 | NA | NA | thin corpus callosum | NA
 | NA | agenesis of corpus callosum c | shows dysmorphic corpus
allosum, scattered foci of T2
olongation in periventricular | NA
 | NA bu

 | tain MRI: cerebellar hypoplasia ve
aut large folia and big cisterna ai | enlarged cerebelium and thick
wermis with low-lying tonsits just
above foramen magnum; thick to

 | Brain: abnormal suical pattern
suggestive of polymicrogynia,
thin corpus callosum, delayed | Brain Atrophy per MRI
Scattered small subcortical
calcifications (Brain CT) | Normal brain MRU/spine with MRS. | Delayed myelination; generally
thin corpus calceum | Brain MRI 3/2018: prominent
extraoutal fluid but otherwise
normal for age.
 | MRI brain abronnal suical
pattern suggestive of
polymicrogyria. | be related to antieplepay
medications. The dysmorphic
corpus callosum is not thickened | NA
 | NA | brainstern, scattered bilateral
11T2 hyperintensities in
subcortical while matter frontal, | normal brain MRI
 | NA | Virchow-Robin spaces,
ventris upper limits 41mm,
low right tonsil, mega | NA Brain MR: n |
|

 | | | maromatory |
 |

 | |
 | |

 | | | |
 | | | white matter |
 |

 | | calosum

 | - Harden and - | | | |
 | | at 9 months but is thick at 3.5
and 9 years. On the last scan
there is generalised mild |
 | | parietal and temporal similar to
Individual 25. Volume and
myelination ok; thin corpus |
 | | brainsten; normal
myelination and corpus
callosum | |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | |
 | | size of the extra-solal CSF
spaces |
 | | caldeum |
 | | | |
|

 | | encoded analysis differ data | |
 |

 | |
 | | the design of the local sector

 | | | |
 | | | |
 |

 | |

 | | | | | Developmental concerns at 2 months when he was not litting
 | | | |
 | Mid-moderate global
developmental delay (Sitting at | e. |
 | | | |
|

 | | delayed motor milestones :
crawled on four legs at 18
moths walked interemotently at | Circled developmental debu- |
 |

 | |
 | Waking 18 months, first word
18 months.
Snearch development devode | ds sit alone between 9 and 11
months, wak at age 15 months,
an mild delived mouth learning

 | Moderate global developmental | | |
 | | | |
 |

 | |

 | | | | | his head or tracking. Roled over
at 9 months, sat on own at 10
months, pulled to stand at 14
 | | | |
 | Bro, taking at 13mo and wakin
at 24mo). El evaluation showed
average cognition with delayed | ng
d Moderate ID. GDD - welked at
d 29 months. Speech delay with |
 | | moderate global
developmental delay. | |
| Giobal de
Developmental / cognitive / bors

 | elopmental delay ; now h
lerline IQ, attends ye | 21 months hypotonia and
hyperbolly. first words at 2,5
sars. But at 3y 2 months : can | learning difficulty, ID,
speech/language problems;
delayed fine motor skills; | Delayed language; late walker;
delayed socially; attention,
mood; learning disorder;
munchistriat involved; 7ASD, no.
 | Delayed language; poor gross
mator skille; attention/mood.

 | Exclusion enclusive ID | walk at 14m/speech
 | At the age of 4 years serienc
of 3-4 words. Problems with
pronounciation. | tes difficulties and global
needucation since age 4 years
(speech therapy, psychomolor

 | delay. Early gross motor delays
with minimal weight-bearing and
lower limb use prior to age 2
wars. East independent store | Very mild delays in gross motor
skills, mild cognitive delays (eg,
color naming) until onset of
salinges states 7 vo. then more | Global moderate developmental
delay, walking at 20m Enter | 0007781
 | Developmental delay waled at
age 3; intellectual disability. Very | Giobal dev delay al M | oderate global developmental
Inv. (Incourse limited and has | mator developmental delay,
 | Girbai dessivemental dalar

 | icbal developmental delay with
marked generalized hypotonia,
only subhers for smarth | Severe gibbal developmental
seay (babbling, mama dada but

 | Mater and assorth datas | Severe progressive
developmental delay with | Global developmental delay: I
gross motor (walking | Moderate global developmental
delay (4 months head control | months, crawled at 14 months,
cruising at 16 months, walking at
22 months is very wobbly and
still needs support. Sneech , at
 | Motor and speech delay.
Walkeri at 1920 months of some | Global developmental delay (non- | Learning difficulties Borderin
 | expression language and moto
skills. At 22mo his pediatrician
reported that he was able to
ne point and uscaling to show his | or first words at 4 years and
sentence at 6 years, still not
tully understandable at age 9. In
provide 9 was operation at grant 4 | severe delay; no words;
 | Second data | walking at 23 mo, global
motor delay, global and
facial hypotonia, fine motor
throuble, fat excels at days | derale developmental Global mod |
| psychiatric problems mainshi
assist

 | am school with some sol
snce; some anxiety so | one letters, can count to five,
ecognizes colours. Can stay | sensory processing: 7ASD, no
dx - paed says not enough for
diagnosis, but all have mild | dx - paed says not enough for
diagnosis, but all have mild
symptoms
 | Austin health

 | | delay/learning difficulties
 | Non-verbal development at lo
average level.
Problems with loud noises, Iw | w fterapy, psychological therapy).
Anxiety, low self-confidence,
less impulsivity, low treatment speed

 | 22 months. No reported fine
motor concerns. Severe speech
delay: grunts / vocalises. Only | learning, attentional and
cognitive delays. Still with
impaired coordination | words at 2y |
 | few words. Dx of Autism
spectrum disorder | disability is | peech apraxis, ambulatory) | normal fine motor development
 | (4

 | walking independently after 4 years) | ot consistent, non ambulatory);
Sleep disturbance

 | | episodes of regression | independently after 2 years) and
expressive speech | 9 months sitting
31 months walking) | 22 months has 2-3 spontaneous
words, but usually only repeats
or echos. Developmental delay.
 | Minimal speech at 3yrs of age. | verbal, non-ambulatory) | IQ F5IG-70
 | wants, as well as use two word
combinations, but he could no
run without failing. By 25mo | d 5 level for academics, and is in
if a skills program at achool.
Has computative behaviours. | walked at 32 m;
 | | can say words, language
trouble, good non-verbal
communication, good level | delay and limited speed |
|

 | s | Speech lompediment but can
soluce more than 50 significant
verds | symptoms. |
 |

 | |
 | dagnosis of ASD.
Mid sleeping problems. | (between 88 and 97) of WPPSI-
IV testing at age 5 years 3
months

 | "mum" and "dad" at 2 years. | | |
 | | | |
 |

 | |

 | | | | | global, mild and making
progress. Cruising age 16 mos;
not walking yet 22 mos. Few
 | | | |
 | months he could use pronouns
and verbalize immediate
experiences, but he could not | s paricularly tricholikomania. ND
autom.
t |
 | | of understanding of simple
orders, not tollet-trained | |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | | 22 mos. Social and affectionate.
 | | | |
 | wak up and down stars one se
at a time. | ep. |
 | | | |
| Ophthalmologic problems

 | No | Astignatism | No | No
 | No

 | No | No
 | Hypermetropia, ambiyopia | Hypernebopia, strabismus
(orthopic therapy)

 | No | No | stabismus | No
 | No B | Bilateral esotropia hypermetropia Mil | t hypermetropia, rasolacrimal
duct obstruction | No
 | No

 | No | Esophoria

 | No | No | No reported concerns | No | Hypermetropia but no rx for
glasses. Amblyopia and treated
 | No | Visual impairment; Bilateral
ptosis; Contical visual impairment | Myopia
 | No | Hypermetropia | No
 | No | No | No No |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | | Sdb bilateral SNHL: Hs 2 ear
Infections. Tubes placed at 17
 | | | |
 | | |
 | | | |
| Audiology / hearing

 | Normal | Normal | Acute CME, x2 sets of
grommets, no concerns with | Normal
 | Acute CM as baby, no goramete,
no concerns with hearing

 | Normal | Normal
 | Normal | Normal

 | Normal | Normal | Normal | bilateral mixed hearing loss
requiring hearing aids
 | Normal | Normal | Chronic CM s/p TM tubes,
normal audiometry | Normal
 | Normal

 | moderate conductive hearing | Normal

 | Normal | Normal | Normal | Normal | monthe, would rearing loss with
mild sensorineural hearing loss,
conductive hearing loss with
chronic middle ear effusion sib
 | Normal newborn hearing
assessment. Normal | Unclear | Normal
 | Failed NHS, but eventually had
normal ABR in both ears | a Normal | Normal
 | Normal | Normal | Normal Normal |
|

 | | | hearing |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | | ear tubes. "Note: pt is also
compound heteropygote for 2
different pathogenic variants in
 | assessment at 1 year of age. | | |
 | | |
 | | | |
| Out dealing (shar D/T

 | | | tonallisctomy; cieft soft paixle; | Colorana and antico
 | tonellectorry and superior
adenoidectorry after speech

 | Core II estenticizatoria (|
 | |

 | Ankylogiossia. Poor | | |
 | | | |
 |

 | |

 | | | | | GUE2"
 | Terrer in character of 3 months | | |
 | Date and dented exception. And | |
 | | | Dyamorphic ea |
| problems Subr

 | succus cleft palate Hi; | gh palala, widely spaced leeth | orthodontics; on WL for
rhinoplasty | tonsilectomy; orhodontics
 | speech did not improve after
T&As on waiting list for
pharynopolasty

 | midface retrusion | Normal
 | Normal | 10

 | Obstructive/holey upper airway
breathing. | No | hypoplastic uvula | rormal
 | High palate | High palais | Normal dentition, no carles | No Ar
 | Interior open-bite malocolusion

 | No | Carlous teeth

 | Laryngeal cleft | High palate | No reported concerns | No | unusual order
 | of age. | Dental carles | No
 | tooth at 12mo | No | Normal
 | te at birth - clipped | Nerrow palate | No usula, nasal voli
septum devi |
| Bour

 | d aprilic valve, PDA | | |
 | Heartmumur when born,

 | |
 | |

 | No/referred for echocardiogram. | | |
 | interrupted acrtic arch; multiple | | | deby in ductus arteriosus di
ciosure after birth, but normal
 | Surgical correction for patent
ductus arteriosus, now she has
minimal shurts for

 | |

 | | Persistent left superior vena | | |
 | Small PFO noted at birth. | Ventricular septal defect |
 | | |
 | | | Patent locame |
| Carbiac proberts requir

 | ng surgical closure | Ana sepa desc | NO | NO
 | ECG and echo normal

 | NO | NO
 | NO | 10

 | pending) | NO | spontaneously resound vs.D | NO
 | denosis. Severe LV dysfunction. | NO | NOTAL LUFU | echocardiogram at 3 weeks of pe
age
 | erimembrancus interventricular
delect and celium secundum
interstrial defect.

 | 10 | NO

 | NO | cava to coronary sinus | NO | Arria Septe Derect | ND
 | Normal DCHO at 2yrs of age. | (sponsneousy cosed);
Mesocardia | ND
 | ND | ND | NO
 | seculpid sonic vave | ND | ND interatrial d |
| Respiratory problems

 | No | No | Moderate OSA; no asthma | QSA and anoring; hospitalised
for pneumonia at 3, no asthma
 | CISA, now resolved

 | Mid asthma as child, fares up
every once in a shile | No
 | No | No

 | No | No | No | respiratory distress at birth, no
current issues
 | No | No | No | No Pa
 | ecurrent pneumonia, low cillar
functioning

 | No | No

 | No | recurrent pneumonia | No | No | No
 | Recurrent upper respiratory trac
infections | Recurrent aspiration
pneumonias: Reactive sirway
disease; Sinuses essentially | No
 | No | No | No
 | CT scan performed secondary
to frequent sinus infections
showed "underdeveloped | No | No No |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | |
 | | unremarkable on brain MPI |
 | | |
 | maillay sinus'. | | |
|

 | | | |
 |

 | |
 | |

 | | | |
 | | | |
 |

 | |

 | | | | |
 | | |
 | He poor sucking and feeding
difficulties as infant leading to | |
 | | | |
| Gastrointeelinel renhierer/ Poor fee

 | ing in newborn period | neorabil sucking difficulties. | Calculated faceling differ disc. |
 | y

 | |
 | |

 | Early difficulties with latching | | 1 | feeding dysfunction in infancy
requiring Glube, Nasen
 | | 54 | were feeding difficulties with |
 |

 | | Chemic constraints cashs.

 | Constigation (negative testing for
Manchements' Gabba | | Searce controline Mersian | | Hx teeding difficulty. Still
struggles with hard foods due to
delayed teeth eruption. Prefers
 | | Constitution: On main lawless | |
 | Hs poor sucking and feeding
difficulties as infant leading to
FTT by 3mo. Formulas were
tried with no success. Barium
swallow showed GERD - to | linerellieri dashaa idurriaa |
 | FTT and poor suck/swallow
coordination. GERD and blood i
stool prompting several formula
changes. Ma was discrossed with | | |
| Gastrointestinal problems/
feeding difficulties

 | ling in newborn period
NGT feeds; Chronic
constipation co | neoratal sucking difficulties.
Nocturnal salva seallowing
difficulties responsible for
ughing and nocturnal wakings | Clefi-rebied feeding difficulties;
fuesy eater; mainly carbs | Hyperphagia; eats good variety
of loods and lextures;
constipation
 | y
fuzzy saler

 | No | No
 | No | No

 | Early difficulties with latching
and ongoing poor coordination
of suck and availow. Early
difficulty initiating solids. | No | No h. | feeding dystunction in infancy
requiring Glubs, Nasen
fundsplication (CERE), currently
east by mouth with no ventiling,
damhea or constipation
 | Glube fed; Constipation | Severe persistent constipation w | vers feeding difficulties with
hispharyogeal insufficiency,
GERD, constipation | poor feeding, constipation
 | Episodic constipation

 | Constipation | Chronic constipation, gastro-
oseophageal reflux

 | Constigation (negative testing for
Hrachprung): G-tube
dependence; GEIRD | failure to gain weight | Severe constpation. Negative
rectal biopsy for Hinchprung. | No | Ho feeding difficulty. Sell
struggles with hard foods due to
delayed teath enuption. Prefers
soft foods and struggles a little to
chew and rawlow hard foods:
uses a sippy cup and can drink
 | Diantoea | Constipution; Oro-motor feeding
dysfunction; GEIFD; G-table fed | No
 | Hs poor sucking and feeding
difficulties as infant leading to
FTT by 3mc. Formulas were
tried with no success. Barken
seallow showed GERD - to
Provacid and Zantac with
minimal improvement. Normal
upper GI and small bowel series | itientilient danhea, of unclear
elisiogy | No
 | FTT and poor suckinealow
coordination. GERD and blood i
stool prompting several formula
changes. He was diagnosed with
mik protein allergy as infant, bu-
skin test negative and now able
to tolerate mik without symptom | in
a
dh Constipation
at
ss | severe constipation Constipat |
| Gastrointestinal problems'
feeding difficulties

 | ling in newborn period
NGT feeds; Chronic
constipation co | neoratal sucking difficulties.
Nocturnal salva availowing
difficulties responsible for
sughing and necturnal weikings | Cleft-rebled feeding difficultes;
fuzzy ester; mainly carbs | K Hyperphagia: exits good variety
of loods and textures:
constipation
 | y
fussy ealer

 | No | No
 | No | No

 | Early difficulties with latching
and organing poor coordination
of suck and avealow. Early
difficulty initiating solids. | No | No No | feeding dystancion in intency
requiring Glube, Mesen
fundoplication (GERG), currently
easts by mouth with no sceniting,
diamhea or constipation
 | Glube fed; Constipation | Severe persistent constpation 9 | nere feeding difficulties with
http://aryngesi.insufficiency,
GERD, constipation | poor feeding, constipation
 | Episodic constipution

 | Contribution C | Chronic constipation, gastro-
oesophageal reliux

 | Constitution (negative testing for
Hinschprung): G-tube
dependence; GERD | failure to gain weight | Severe constipation. Negative
rectal biopsy for Himchprung. | No | He feeding difficulty. Still
struggles with hard foods due to
delayed seth explore. Prefers
soft foods and struggles a life to
chew and seallow hard foods;
uses a sigpy cup and can drink
from a straw
 | Danhoes | Constigation; Oro-motor feeding
dysfunction; GEPD; G-tube fed | No
 | He poor sucking and feeding
difficulties as infart leading to
17 TG yim. Formulas were
hind with no success. Darkan
seekee whore GERD - to
neismit improvement. Normal
comport G and small bound and
support G and small bound and
influentation. Just use diversion
influentation. Just use diversion
well. He chronic constipation. | internitioni danhea, o' unclear
etislogy
a:
d
se | No
 | FTT and poor suckineellow
coordination. CEIPD and blood
titol pronepting assend formul
changes. He was diagnoand will
mitk problem allergy as initiant, bu
dido test negative and now abd
to lotensis mitk without symptom
/ blood in stools. | in
h
Constipation
s | severe constpation Constpat |
| Gastrointestinal problems'
feeding difficulties
Renal / genitourinary problems
function
difficulties

 | ing in newborn period
NGT feeds, Chronic
contiguition co
crypterchidem; non-
ing right multicystic rc
splastic kidney | neorabi sucking difficulties.
Nocturnal salva sealboxing
difficulties responsible for
sughing and nocturnal weikings
initial inguinal feetils but new
onnal. Normal abdominal and
kidneys US | Cleft-selded feeding difficulties:
fussy eater; mainly carbs
No | Hyperphasics sels good sariety
of looks and textures;
constipation No
 | y fussy eater

 | No | No
No
 | No | No
No

 | Early difficulties with latching
and ongoing poor coordination
of suck and asolices Early
difficulty initiating solids.
No | No
No | No h
No | feeding dystancion in infancy
requiring Gluba, Neare
Judgipcation (GETR), currently
eats by mouth with no isoniting,
diarrhea or constipation
No
 | Glube fed; Constipation | Severe pensistent constipation w | nere feeding difficultes with
high-aryregael insufficiency.
GEIRD, constipation
Nocturia /
Nocturia / | poor feeding, constpation
 | Epicodic constipation

 | Constpation C | Chronic constipation, gastro-
ossophageal reflux
Cryptorchidam

 | Centipation (negative testing for
Heschpung): G-tube
dependence; GERD
No | failure to gain weight
No | Severe constpation. Negative
rectal biopsy for Hinchprung.
No | No
No | No feeding difficulty. Still
struggles with hard loods due to
delayed seet englos. Profess
and loods and druggles a tille to
chere and sealbay hard foods;
uses a stippr count can driv
from a straw
No
 | Dianhoea
No | Constigation; Oro-motor feeding
dysfunction; GE/RD; G-lube fed
Biblecol inguinal hernias | No
Incontinence, resolved at 8 y
with seizure control
 | Heppor sucking and leading
difficulties as infart leading
by the second second second second
bird with reaccess. Barban
minimal improvement. Narmal
opper Cl and 2 Antice with
minimal improvement. Narmal
opper Cl and 2 Antice with
information, but was derived
information. Narmal
second second second second second
information, but was derived
with the church conseptation.
³⁷ No | internitioni dianhea, of unclear
ediology
at
dia
Small peris and tesicies
(history of delayed publy).
bormal was diseased | No
 | FTT and poor suck/texellew
coordination. CEFID and blood i
ticic) promping several formul-
changes. Ne was disproved with
mitig protein along yas tirtart, bo-
sidor text negative and noue able
to loterate mitik. Without symptom
/ blood in stocie.
Elideeral cryptorchidam | In Constipation | avere constpation Constpation |
| Cedebinistinal problems ²
Isoding difficulties ²
Pendi / gentlaurinary problems ³
Hermologic problems ⁴

 | ling in newborn period
NAT feeds: Chronic
constipution
cryptorchalam; non-
ing split mulicystic
splatel; kidney
No | nervatol sucking difficulties.
Noctional solve readlowing
difficulties responsible for
sughing and necturnal wakings
initial inguinal testile but now
contral. Normal addominal and
kidways US
No | Cleft-selded feeding difficultary
fusity eatler; mainly carbs
No
No | Nperphagic, etiti good sarvity
of loads and teatures:
constipation No No Reemby Endo at RCH statow 75
 | 7 Aussy axis

 | No
No
No | No
No
No
 | No
No
No | No
No
No

 | Early difficulties with hickneys
and regarding poor coordination
of such and exercise. Early
difficulty initialing solids. | No
No | No h | feeding dyslanction in Infancy
requiring Gluba. Nasen
Munopication (Graffic, Lorented)
easi by mouth with no verifig-
dianthea or consignition
No
No
 | Glube fed: Constipation
Cryptorchidem I
Neutropenta: Thrombacy/openta | Severa paraisteri constpation vi
Nephromegaly/Normal function
No ini | nere heding difficulies with
highenyngel insufficiency,
CEPD, consignion
Nocturia
Nocturia
nichtoperia (resolved) and
amitient normocylic aventa | poor feeding, constipution
normal remai ultrasound at 14 mo
ren deliciency (4 prolit, at 5
mo)
 | Epitodic constpation
No
neoretal anertia

 | Constpation C
No
No | Chronic constipation, gastro-
oexophogest influx
Cryptorchidem
No

 | Constipation (regative testing for
Heardprong): G-bibe
dependence: CETED
No
No | failure to gain weight
No
No | Seem contipatos. Negalve
recisi biopsy for Histoprurg.
No
No | No
No | No teading attroaty, Sall
anggine with hard book due to
delayed bank neption. Privato
chara wat anaboli water for data
uses a tappy cup and can drink
from a straw
No
No
 | Diamhoea
No
No | Constgation: One-mater feeding
dystanction; GERD; G-table feed
Biblensi inguinal herritas
No | No
Incontinence, resolved at 8 y
with secure control
No
 | Hypecon matching and heating Hotel State Market Hotel State Hotel State Hotel State Hotel State Hotel State Hotel State Hotel Hotel State Hotel Hotel No No | reservitient danheas, of unclear
edology
8:
d
5real pents and tealchea
(history of dolayed public)
Normel renal ubsecurd
No | No
No
 | FTT and poor suck/investore
coordination. CRETD and block
inder prompting servers for much
changes. If is was disposed with
the server prompting of your block
is blockraite mitk without symptom
/ blood in stroks.
Blateral cryptorchidam
No | in Constipation at incomplete foreskin | severe constpation Constpat
No Increased confor
differentia
No No |
| Cestroinistical problems' Proc Tee
Intelling difficulties Proc Tee
Result's genticulties Proceedings
Hernalogic problems (School
Hernalogic problems)
Endocrine problems

 | Ing in newborn partod r
NET feeds; Chronic
constipation
cryptorchidam; non-
ing right multicpatic
No | neorabi sucking difficulties.
Noctures adva seallowing
difficulties responsible for
sugging and nocturnal sealings
tottal traditional facility of the
second sealing of the
Normal Modernian and
Modernian Second Second Second
No. | Cleft-related functions
fluxing address relation of the second se | Normalization and a second sec | Aussy easter No Overally a start of the charts on neast-annexity of bocause of COVID, but Mark and Panding

 | No
No
No | No
No
No | No
No
No | No.
No.
No.

 | Early difficulties with hickning
and anging poor coordination
of such and examines. Early
difficulty initialing solids.
No
No
No | No
No | No N | feeding dystanciion in Infancy
meaiuring Gaba, Naissen
Van Statution (San Statution)
diarrhea or constipation
No
No
No | Glube fed: Constipation I
Cryptorchidem I
Neutropenia, Thrombacy/spenia
No | Severe penaleter i constpation Se
NeghronegalyNamed function
No Internet
No
 | nera tedrag difficultus ella
high-proposi fescalicanoy,
GERC, consignation
Noclarita
Noclarita
No
No | poor feeding, constipation
romal renal ultracound at 14 mo
rom difficiency (4 prosit, at 5
mo)
No | Episodic constpution
No
reconstruit america
No

 | Constpation C
No
No
No | Chronic constipution, guate
oexploaged refus
Crypterchidsen
No
Vitamin D deficiency

 | Constipution (registive statisticg for
Hashbyrung): G Julies
dependence: (S2PD)
No
No
No | falurs to gain weight
No
No
No
 | Severe constpation. Negative
rectal biopsy for Hischpung.
No
No
No | No
No
No | No leading difficulty. Sell
enrugges with hard load care
bidlighed sells enclosed. Prefers
and tools and enclosed
uses a topic cross and can drive
from a shaw
No
No
No | Diarrhean
No
No | Constigation; Dio-mator feeding
dynamictor; CEPID; G-abe feed
Biblenal inguinat hermias
No
Nacostat inguinat hermias
(sacostation) | No
Incontinence, resolved at if y
with rescure correct
No
No
 | Hypoon sucking and intellig
Hind State and the subscription of the
HT DB yars. Formulas were
tind with no success. But unit
were subscription of the subscription
method by the subscription of the
method subscription of
 | internitient danheas, of unclear
edocgy
st.
d
Senal parts and testician
(biatery of oblight of palent)
Normal Senal Senatorial
Normal Senatorial
Normal Senatorial
Normal Senatorial
Dailyyed puberty | No
No
No | PTT and poor suck/investore
coordination. GERED and blood
india prompting assesses it tomake
million promoting assesses it to the
risk potential aslenge and now abit
to block and now abit
block and constraints.
Bitsternal constraints and
No
No | Constpation incompiles foresion No No
 | awere constpation Constpat
No Increased cortice
attraversion
No No |
| Cast-orienter polarer
Institute getto aller
Penel getto aller
Hematige polarer
Dedorine polarer

 | Eng in needers period in Narr Reads, Chronic contribution contribution contribution contribution of the second contribution of th | normati aucling difficular.
Recturn and an availability
difficularies responsible for
difficularies responsible and
address and address and
kidneys CS
No
No | Cleft-skiled feeding difficulties:
Rany editr; mitrly carbs
No
No
No | Nyperinhapise and good working
consequences
consequences
No
No
Search by East 2017 (Search Search Se | Y Duary eater No

 | No
No
No
No | No
No
No | No
No
No | No
No
No

 | Early difficulties with latching
and englishing develope. Early
difficulty initialing welds. | No
No
No | No h | Inding dysherdate in Inforcy
requiring Galaxy, Nasan
Undigdiading (GETR), currently
daritae or configued
No
No
No | Clube fed. Constipation
Cryptochidaen I
Nouhrspenis; Thioribocylopenia
No | Severe persistent constpasion of we way to be a severe persistent constpasion of we
way to be a severe persistent persist | New function with
single arranged insufficiency,
(ZERD, conseption
Noclusta
Noclusta
No
No | poor feeding, constipation
normal nema ultrasound at 14 mo
Fee deticiency (Hymrait, at 5
mo)
No | Episodic consipation
No
neorotal anertia
No

 | Constipution C
No
No
No | Chrotic contiguitor, gastionegatagast refus
omsghagast refus
Cryptorchidam
No
Watmin D deficiency

 | Instantion (registre testing for
Mexigning): G-Libe
dependence: GERD
No
No
No | Failure to gain weight
No
No
No | Seare contiputor. Negative
rectal biopy for Heschpung.
No
No
 | No
No
No | No leading difficulty, SB
errugges with hard loads due to
dilugid testin - outro, Praints
actives and seeklow trans frances
unsen an expect one and can drive
from a strave
No
No
No | Dantees
No
No
No | Constigution: On-Instan Reading
dynhanction; CEXID; G-tube Red
Bitternal Inguinal Nerritas
No
Nacontal Ingrojecenta
(Installed) | No
Incontinues, teaclost at 8
with values control
No
No
 | Hypoton sacking and Hendry
difficulties as intervention leading to
FTT TDy Sime, Florendae users
mediae diverse in the same
manual and and a same
manual and a sa | starrillant danhas, of urclas
elokgy
d
d
G
G
G
G
G
G
G
G
G
G
G
G
G
G
G
G
G
 | No
No
No | PTT and poor and knowledge
interfamilia. PECI and their
interfamilia. The May and PH
milk protein allenge as inferts. No
milk protein allenge as inferts. No
is beinner milk where a protein
is binner milk where a protein
binner in the interfamilies.
Binemal cryster children
No
No | Contigation Contigation Incomplete foreskin No No | Assere contabulor Constant
No breased cortic
different
No No
No No
 |
| Gedenseksion problems Proje trike Besel gerinultare Makeur Prest gerinultare Address Deducte problems Address Deducte problems Address Deducte problems Sprange

 | Ing in neakon partial (* 1967 Reads Chronic conteption conteption conteption context) (* 1977 Reads Chronic context) (* 1977 | nervitet androg efficiently
Rective at define employing
difficulties separatelies for
upplying and rection real
relations of the second second second
liability of G
Re
Re | Celt-valed feeding difficulter.
Tury estir, menty cate
No
No
No | Hypothologi, and yoor an only
of bolic and basis or
constpation No No Remarky finds at ROL suburs 1
class to sub-high and
only built at ROL suburs 1
bolic works and a sub-respective
subbasis on boggers hind in with
Default ROL
 | Y Ausry enter No No No No Name entering of biocast of
a mass memory of biocast of biocast of
a mass memory of biocast of biocast of
a mass memory of biocast of biocast of biocast of
a mass memory of biocast o

 | No N | No
No
No | No
No
No
No | No
No
No

 | Sary ditudes with backing
and nak with website Sary
ditude yinthing solds. | No
No
No | No n
No n
Jacobie and palls
ultrasend normal | Indeling dystantion in Many
requiring Gaba, Nasan
Undeplication (GZRC), carently
aller hear of condipition
diameter of condipition
No
No | Clube fet, Contigution Cryptorchidee No No
 | Sever perioder contpation
Nationagia, Nama function
No
No
No
No
No
No
No
No | Notification with
lightworping insufficiency.
CARD, ourseption
Notification of
Manageness (mechad) and
another reprovide works
No. | peor leading, condipation
ormat leads and as 14 mp
montal character of approx. as 3
Mp
No. | Episod: constpation No Image: Constpation of the image:

 | Constpation C
No
No
No
docrete treb langt asympty | Chronic constipution, game
osciphagust refux
Orystanchidem
No
Vitamin D deliciency

 | Interprete insight wing to
Renegaring: G-base
dependence: GDD
No
No | hallues to gain weight | Severe confloctor Magning
rectal biopsy for Heachpoing
No
No
No
 | No
No
No | No heading atticuty. Self
margane with the data load and
headings the short point, where
in the second second second second
cheve and second second second
the second second second
the second second second
headings and second
headings and second second second
headings are and second second
headings are and second second
headings are and second second second
headings are and second second second
headings are and second second second second
headings are and second second second second second second second
headings are and second se | Dantees
No
No
No
No
Mid kystees. Hysterins hes | Constantion; Dio notion teeding
dynamication; CEVID; G value feer
Italianed regularita ferminas
Nor
Namonala hyperogleamia
(rescuber) | No
Incontinues, resoluted at 8
with assume control
No
No
 | Hipper auching est-frequency languages of the second | eternitet darba, d'uclas
elidiqu
brat jenis autisticas
binty d'object public,
binte d'objec | No
No
No | PTT or dot or accidenced in
mod property general favore of el
mod property general favore of el
beneral results el construction
beneral results el
hop
hop
 | Constitution Constitution Constitution Constitution Constitution Constitution No No No No No | Assesses constigation Constigat
No Increased confor
differentia
No No
No No
No
No
No
No
No
No
No
No
No |
| Gadronisation (instance) Projection Heading diffulding Projection Parent (perfutures) Locks Versiteigin produme Locks Disburite produme Locks Machaelabel produme Sprent

 | Ing in newborn period 7 Not Teede Chronic contripation contribution for the second sec | normal analog of locates
Proceed and an analog of locates
and tradies expossible for
updating and exciting and analog
end angular data and analog
biology of an
biology of an
biology of an analogy of an
biology of an analogy of an analogy of an
analogy of an analogy of an analogy of an
analogy of an analogy of an analogy of an
analogy of an analogy of an analogy of an analogy of an
analogy of an analogy of an analogy of an analogy of an
analogy of an analogy of an analogy of an analogy of an
an an a | Dart-united herding afficializes
Namy ester: matrix carbs
No
No
No | Hystophyck, etc. good worky
forch and features:
consistent
to be an experiment
to be an exper | 7 Lussy exter 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100

 | No
No
No
No | No
No
No
No | No
No
No
No | 10
10
10
10
10

 | Early difficulties with highling
and anguing poor constraints
of and an adults. Early
afficulty instrume posts.
No
No
Small Togers, brand
Puerlas. | No
No
No
No | No P | Needing dystancias in intercom-
response (Data, Ellisan
eraping (Data, Ellisan
eraping (Data, Ellisan)
esti by monochi tho unstituy,
dantes or consequence
No
No
No
mucch fulgue | Gade Net, Constgation Cryptorchideen I No No Tai | Searce persister company. Searce persister company. Neural Income of the Searce
 | Inter Fredrig difficulies with
digital regulations (Internet),
ICERS, consequence
Noctures (Internet)
Noctures
No
No
No | per feeing contipation
errors (real ubsecut at 14 no
errors (real ubsecut at 14 no
not addressing of priors, at 1
No
No
No | Epitodic constipution No I No I No I No I No I No I Depitrion access EXP + pectal cannot exp + pectal

 | Constpation C No I No I docrets line langh asymptyr
(Lath Shipt) Lath Shipt) | Chronic consignation, games of the consignation of the constraint of the con

 | Controller) regulate lassing be
dependence. CERD
No
No
No | helue to gain weight No | Sears computes legaler
recal lengts for Heartpoor | No
No
No
No
 | No testing atticuty SII
margine with the toto take to
margine with the toto take to
the atticute and the toto
the atticute and the toto
the atticute atticute
tota a the
No
No
No
No | Damheas
No
No
No
Mid kyphosis. Hypotenia heas
sepremel with insu. | Contpation, Oio endor Handing
dysfanction, CEPC), O data Har
Bitteriol regulard herrites
No
Northol Typoglycemits
(mailed)
Right calcumovalgue deformity
at birth (mailed) | No
Incontinues, resoluted at 8 1
with assume control
No
No
 | Hyper maching on Heading The Market Heading Hitching and the Market Barket Heading Hitching and the Heading Hitching and Heading Hitching and Heading Hitching Heading | Internetient diarties, of unclear
address
Deall parts and selection
(Named and Selection
Named and Selection
Res
Design of parts and selection
Res
Design of parts and selection
Res
Design of parts and selection
Named and Selection
Design of parts | No
No
No | HTT order set-Scheder
and perspectives. CELE to a tot tool
and perspectives. CELE to a tot tool
and perspective and too a too
perspective and too a too
perspective and too a too
be been received and to a too
be been received and too
Bob
Ro
 | Contipation Contipation Contipation Contipation Continuent Recorded transfer Recorde | ever contigutor Contigutor
No Decement control
No Decement con |
| Onderstanding of pillings Page Mark Name of a pilling of the data Page Mark Partial of pillings of pillings Status Tended op or pillings Of Deducting on pillings Of Deducting on pillings Of Deducting on pillings Of Deducting on pillings Strenge

 | Ing in revolution period of social so | second sucking difficular
difficular workshold of the subburg
difficular workshold of the subburg
difficular and subburg
restores for a subburg of the subburg
workshold of the subburg
here and subburg of the
here and subbu | Dart-unked bendrug afflucities;
Nany ester: marky carbs
No
No
No | Typenblogs, ests pool works,
di bolt et de taksus;
consignation No No Senar ly foots at FCH along at an
dische bit sich integration
dische sich at sich restere
destates obligen at and
pools at FCH. No No | 7 Namy ester 100 No 200 No

 | No | No | No
No
No
No
No
No | 10
10
10
10

 | Early difficulties with backing and expeription constrained on a series.
Early difficulties with an experimental experimentat experimentat experimentat experimental experimental experimen | No | No P | Needing dystancias in intercep-
regaring Calas, Taman
and you want the second second
ask by model with our westing,
advertee or consignition
No
No
No
No
No
No | Glube Net, Constigution Cryptocrividien I No No Tai | Searce periater company. Searce periater company. Neural Income of the I | Notaria Parkana ang A
 | per feeing contipation
error (real phased at 14 mp
and addressing of phase at 3
No
No
No
No | Episode constipution No Image: Constipution No Image: Constitution of the constane constitution of the constituti

 | Constpation C
No No N | Chronic constiguities, games
complement rules.
Crysterchidem
No
Numin D deficiency
Distances rtip

 | Instanton Ingelie I taking br
dependence. GERD
No
No
No
No
No | helure to gate weight No No No No Increased muscle tone | Sears completes. Negative
recal brance for Heartproce
No.
No.
No. | No
No
No
No | No heading atticutey data
margine with the of both and and
the state of the state of the state
in the state of the state of the state
in the state of the state of the state
in the state of the state of the state
No
No
No
No
No
No
No
No
No
No
No
No
No
 | Dantees No No No No Mdf lephons. Hypotenia hes approach with line. | Contpatino, Oro endor Handing
dysfanstano, CEPE), O Lato Har
Bitteriod regulard herrites
No
Neurotal Hypotoglasmits
(mainted)
Regist calculateouslyse deformity
at bitth (mainted) | No
Incontinuos, resultad al 4 p
Mo
No
No
No
 | Hyper maching on Hendrey
Hindler and Hendrey Britten
Hindler Anderson
Hindler Anderson
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hindler
Hind | Internetient diarties, of unclear
addrogs
Smith period and addrogs addrogs
Network and addrogs addrogs
Network addrogs addrogs
Network addrogs addrogs
Network addrogs addrogs
Designed publicly
Designed publicly
Designed publicly
Designed publicly
Designed publicly
Designed publicly
Designed publicly
Designed addrogs of the
Designed addrogs | No
No
No | FTT or oper sub-chemised
and perspectives. CEID and Mooil
and perspectives.
And perspectives
in the second second second
in the second second second
becomes and the second second
becomes and the second second
becomes and the second second
becomes and the second second second
becomes and the second second second second second
becomes and the second secon | Constpantor Constp
 | een craigebr Contact
No Incented contact
No No
No No
een hystore Jan to |
| Substantial problem Pare Ministra Read politicity problem Read Read politicity problem Read Read-spectration Read Read Deducting problem Read Read Deducting problem Read Read Menocalization problem Read Read Menocalization problem Read Read

 | Ing in readout part of 100 mm (and a model on part of 100 mm (and a mm (and | second sucking difficulties
difficulties weards to
difficulties weards to
the second second second
weards and advantage of
the second second second
to the second second second
to the second second second
to the second second second second
to the second second second second
to the second second second second second
to the second second second second second second
to the second second second second second second second
to the second s | Cash-select feeding difficulties
Nery etter; mility cartes
No
No
No
No
No
No
No
No | Hyperplays, we goal and your action of the second sec | Charry enter Construction

 | 10
10
10
10
10
10
10
10 | No
No
No
No | No | 10
10
10
10
10

 | Early diffusion with backing on degrees particular or degrees part | No
 | No. | Nacing dysheridion in sharpy
Understanding dysheridion in sharpy
Understanding (SERIE), Surveyly
and an average of molecular
and average of molecular
No
No
No
No
No | Olden fest, Constigation Cryptorolidae No Tail No No No | Sever particle's conjuster
Natrongaly Neural Locks
No Novel Link Schlass Alley S
Novel Link Schlass Alley S
N | Notaria feadra di Califandia ad
CERD, condiçation
Notaria di
Notaria di
Storgenezi pestodo dal
amber correcpita aneste
No
Leti adad hambyseptosia
Hynogenemgikbuhamia | part heading constipation
worst until characteria 114 ray
model charac
 | Epitende conviljadem
 | Consignation II Consignation II Consignation II Consignation II Constrained II Co | Chante constiguitor, gaselo
osseptingent relax. C
Organizatione
No
Veamin D deficiency
Datacaset hg
26 / 26 / 26 / 26 / 26 / 26 / 26 / 26 /

 | ontparter register stering for
Herebrandig C Aske
algorithms, GETO
No
No
No
No
No
No
No
No
No
No
No
No
No | Indues to gate weight No
 | Searce conductors Negative
relatibility for Negative
No
No
No
No
No | No
No
No
No
No | No heading atticuty, Sall
margament have local back and
these and explosions atticute
these and explosions atticute
to an atticute the same same
back atticute
No
No
No
No
No
No
No
No | Dantees No No No No Mdf lephons: Hypotenia hese sepresed with lines. No | Conduction: C2x with teaching
systems (C2K); C share for
Balancel regularit herman
to
Neurosci hypergelacentes
(Neurosci hypergelacentes)
Regific calcinenseligies deforming
at birth presided
Rescinent infectione | No
Incontinues, resulted at 8
with acture control of
No
No
No
No
 | Hispan analog of Headra Stranger (1997)
Headra (1997)
(1997) (19 | Annual and Annual Annua | No
No
No
No
No | FTF or oper seck-based
adoption and provide the section of
adoption of the section of the section of
adoption of the section of the section of the
model of the section of the section of the
section and the section of the section of the
No No | Constpator
Constpator
Constpator
Constpator
Constpator
No
No
No
No
No
No
No
 | esen constato
No Promotional Sectors
No No
No No
No Justica
No No
No Justica
No No |
| Contractantian proteins
Menter personany proteins
Menter personany proteins
Menter personany proteins
Collaborar publics
Instructional publics
Dos

 | In it seeks and a seek of | version action of the cubes
intervention and a second any off
intervention of the constraints
intervention of the cubes of the cubes
intervention of the cubes of the cubes
Normal Market of the cubes of the cubes
Normal Network of the cubes of the cubes
Normal Network of the cubes of the cubes of the cubes
Normal Network of the cubes | Cash-saked heading difficulties
Nany estim malky cashs
No
No
No
No
No
No
No
No
No | Hyperphysics and post analysis Hyperphysics and post analysis constraints No | Natry enter No

 | 10
10
10
10
10
10
10
10 | No
No
No
No
No | No | 10 10 10 10 10 10 10 10 10 10 10 10 10 1

 | Early diffusion with backing or dependent on the factor of | No
 | No. | Nating systems to sharpy
undestability (SERE, Survey)
and y reactions (SERE, Survey)
and y reactions
derives or indexident
No
No
No
No
No
No
No | Obdan Hat, Constigution Crystervisidam No Tool of the Constigution No | Seens particle's conjuster
Nathonautic conjuster
Nathonautic construction
Nathonautic constructi | nen hadig dittalise of
even hadig dittalise of
Notaria (name) (| per feeling contiputors
unrar until cheatran 4 14 mp
res delicerar of priority and 1
200
300
300
300
300
300
300
300 | Episode convliption No

 | Consignation of Consignation of Consignation of Consignation of Constraints of Co | Charac consistents and
onestingent relax. C
Crysterohiden
No
Vitamin D deficiency
Delecated hp
No
Normal

 | Interpretent inter | No. | Searce caracteria Negative
recell heaps for Heaptive
No
No
No
No
No
No
No
No
No
No
No
 | No
No
No
No
No
No | No heading attracky 101
marging and inclusion. The second
marging and the second marging attraction
to the second marging attraction.
Non at track
Non
No
No
No
No
No
No
No
No
No
No
No
No
No | Dantess Dantess No No No No No No Cores Cores | Conduction: C2x while Yearing
geta-status: C2400; C shale for
Billatori Ingulari formas
Ingulari
Neurolal Yearing
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registration
Registra | No
Incontence, resultant el 1
antibaticas consel
No
No
Normal
 | Harmen auching and Hearmen's Marken and Harmen's Marken's M | International distributions of unchanged and a sections of a section of the secti | No N
 | HTT order an schwarten
meinen stand and several and several
meinen stand and several and several
methods and several and several
methods and several and several
methods and several and several
function of any several several
field of the several several several
field of the several several several
field of the several several several several
field of the several several several several
field of the several several several several several several
field of the several severa | Constpation Constpation Recompilie formation Recompilie Recompilie formation Recompilie Reco | Anne contestanto
No Contesta conte
Series Series Se |
| Controletario professo
Intelligenti control professo
Presidenti professo
Presidenti professo
Presidenti professo
Control professo
Intervisitigati professo
Intervisiti
Intervisitigati professo
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervisiti
Intervis

 | In it medica and a second and a | nontel using disular
financial using disular
financial disult disult
resolution and a state of the
state of the state of the
state of the state of the
state of t | Calit-stated Seading diffusitive
Large effer, ranky cetter
No
No
No
No
No
No
No
No
No
No
No
No
No | Providence, we good a way
consignation. Providence, we good a way
consignation. Providence, we good a way
the constraint of the constraint of the constraint of the
constraint | Juary earlier No No Hopp and States and
control of State Units are
research more of Interscore of
Controls. Let Units and
controls. Let Uni

 | 50
50
50
50
50
50
50
50
50
50
50
50
 | 10
10
10
10
10
10
10
10
10
10 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | No N

 | Early deficiency of heatings
of adds of adds and adds for y
attraction of adds of adds and y
boots for y
No
No
No
No
No
No
No | No
No
No
No
No
No
No | No. | Nacional de la conservación de l | Ouke fut Conduction Crypterindian No Startgents, Translag years No Tal Tal No
 | Severe perceiter conteption P Severe perceiter conteption P National P Nati | ner hang Afrika uh
an hang Afrika uh
an hang an hang an hang an
Nacht
An
An
An
An
An
An
An
An
An
An
An
An
An | par heading consignation
within const. diseased at 11 min
the disclose of particle at 25
min
The disclose of the disclose of the
No.
No.
No.
No.
No.
No.
No.
No.
No. | Episodi: sovaljavlari
No

 | Considentian Construction Const | Chronic consignation, passion
consentinguarder relations
Organizational and
No
Utablication high
No
Normal
No

 | Anongeneric internet | Indues to gain weight No | Searce conduction Negative
receivablesper for Negative
No
No
No
No
No
No
No
No
No
No
No
No
No | No
No
No
No
No
No
No
No
No
No
No
No
No
N
 | No hashing afficulty, SII
market water couples, Provide
and an operation of the second
test of the second and the second and the
second and the second and the
second and the second and the second and the second and the
second and the second and the second and the second and the
second and the second and the second and the second and the
second and the second and the second and the second and the
second and the second and the second and the second and the
second and the second and the second and the second and the second and the
second and the second and the second and the second and the second and the
second and the second and the | Dentres
No
No
Mill Synder, Ny preside an ins
respond an ins
No
Ecome | Constantion, On endor transforg
applications, GEVID, O clusters
Eliberal inguinal fearing
No.
Noncommunication
(clusters)
Regist accommodiges adversing
at the Ty insulation
Registration and applications
Registrations and applications
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations
Registrations | Po
Nontroor, realist if 5
No
Po
Po
None
Normal
 | A point marking of releases of the second point of the second | elevative davies, el united
elevative davies, el united
berge per est actual
berge per est actual
berg per | No
No
No
No
No
No
No
No
No
No
No | HTT and your sub-balance and the second s | Constpation Incomplete formability Non Non All Juster banky Bernell Remeilt
 | anne contestan
No Possible
No Strategi
No No
No No
No No
Nord
No No
Nord
No No |
| Contracted or professor
Interf gendencing professor
Preself gendencing professor
Preself gendencing professor
Reconcentration

 | Ing in readow
particle
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constraints
constra | Investigation of the second se | Celonate level get muches
Jacque des celonates
No
No
No
No
No
No
No
No
No
No
No
No
No | Programme and programme a | kun

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10 | N | No

 | Englishment enhange
in the and and an and an and an and
an an and an and an and
an an an
an an a
 | N
N
N
N
N
N
N | N N N N N N N N N N N N N N N N N N N | heing gold share in Fary
building dol share in Fary
building dol share in Fary
building dol share in Fary
and the second share
No.
No.
No.
No.
No.
No.
No.
No.
No.
No. | Gale hat Condpain Cospitulation Cospitulation Normal Norma | Severe percenter contegetion
Severe percenter contegetion
National severe s | ever bedrog filtedate with
opportunity of the second second
(ETC) compared
by the second second second second
by the second second second second
by the second second second second second
by the second second second second second second
by the second seco | par haling analysis
and out absorbed it to
the default of the
the default of the default
of default of the default
No
 | Egisted: contiputor
No
No
No
No
No
No
No
No
No
No
 | Conductor P
 | Ommer caretysten gener
mentingen of the
Cognomial of the
Network Distances
Discussifier
Started Startes
Startes
Startes
Startes
 | Instruction house a level of the
Theorem (C action of
No. 100 No. 10 | blue to per wept No
 | Search caraligates. Negative
excelutions for Noncolor
No.
No.
No.
No.
No.
No.
No.
No.
No.
No. | No
No
No
No
Normal
No | A basing all outy of all outy | Darhes No No No No No No No No No N | Cardiation Connects Heating
systemetric (CPHC) Collection
Internet Anguined Hermite
Net Collection (CPHC)
Internet Hyperspectra
With the Hypersection
Processor Hermite
Report Hermitegianes
Processor | No
Nontroes, realist if if
with above reals if
No
No
No
No
No
No
No
No
No
No
No
No
No
 | Processing and sections of endown of the section of the se | envention derivery of vectors
design of vectors
between the second second second second
terms of vectors and second second second second second
terms of vectors and second secon | No
No
No
Normal
Normal | n FT states analysedes TT states analysedes TT states and the stat | Contputer
in Contputer
in Contputer
in Contputer
No
No
No
No
No
No
No
No
No
No
 | Anne conteston
No estante contesto
No esta forma
Anno |
| Contensative pressure
Next operations and the second
Next operation of the second
Meter operation of the second
Meter operation of the second
Next oper

 | Ing in reacher particle
constitution
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
constrained
const | Next the space of the later
and the space of the later
of the space of the later of the space
of the space of the later of the space
of the later of the later of the later
of the later of the later of the later
of the later of the later of the later of the later
of the later of the later of the later of the later of the later
of the later of the later of the later of the later of the later
of the later of | Advalanted up gifticalling
adjuster many cardinal
file
file
file
file
file
file
file
fil | Number of the second seco | Name water No

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10
10
10 | 16
16
16
16
16
16
16
16
16
16 | No N

 | Englishmen schladinger
an den an orden schladinger
andre an andre andre andre andre
No
Seal Bagers, Insel André,
No
No
No
No
No
No
No
No
No
No
 | N
N
N
N
N
N
N | N | Hang da da da hara hara
angel da da da hara hara
angel da da da da da da da
da da da da da da da da da
na da da da da da da da da da da
na da da
na da | Gala ta Gangadan
Ogaponaka
Norta-rapin
No
No
No
No
No
No
No
No
No
No
No
No
No | Severe persistent contigution
Martineaugity Neural location
National Severe location
National Se | een bedrog Bitcales with
Bitcales with the second second
CEC compared and the second
Bitcale compared and the second second
bitcale second second second second second
bitcale second second second second second second second
bitcale second s | par haling conductor
event was also and of the
control and allowed of the
control and and of the
field of the control and the control and the control and the
field of the control and the control and the control and the
field of the control and the control and the control and the
field of the control and the control and the control and the
field of the control and the control and the control and the
field of the control and the control and the control and the
field of the control and the control and the control and the control and
the
field of the control and the co | Specie computer
N Sector American
N Sector Americ
 | Conjuter P N N N N N N N N N N N N N N N N N N N | Overcentpeline P Overcentpeline Over

 | Interpret California Series and Series Serie | Nuture to proceeding | Searce cardigates. Negative enablemps for Neuropation Negative Searce Se | No
No
No
No
No
No
No
No
No
No
No | Houseney attrices, so of the second sec | Danhas
No
No
No
No
No
No
Scars
No
No
No
No
No
No
No
No
No
No
No
No
No | Contestion (c) and/or leave
generation (c)
 | Posteres central el 19
Posteres central el 19
Poster
 | Approximately and reading the second se | environ dan han, ul vinan
altan
han yang bang bang bang
han yang bang bang bang bang bang
han yang bang bang bang bang bang
han yang bang bang bang bang bang bang
han yang bang bang bang bang bang bang
han yang bang bang bang bang bang bang bang b | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 117 Sector and Annual Sector S | Constants
Constants
Constants
Constants
Constants
Ne
Justi banky
Constants
Ne
Constants
Ne
Constants
Ne
Constants
Ne
Constants
Constants
Ne
Constants
Constants
Ne
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Constants
Con | exercication Content
No Content
No Content
No No
No No
No No
No
No No
No
No
No
No
No
No
No
No
No
No
No
No
N
 |
| Contensative protone
Network protone
Network protone
American p

 | ing in mattern parts of the second se
 | reported particular displayed and an experimental or a second sec | An orient leading shifting and a second seco | Norman and an and a series of the series of | Name state:
Name

 | No N | No
No
No
Normal
Normal | N
N
N
N
N
N
N
N
N
N
N
N
N
N | No N

 | Say diffusion and instruments
to an and robusts of an and robusts
within a minimum scale
in the second scale of the second scale
in the second scale of the second scale of the second
scale scale of the second scale of the second scale
is scale scale of the second scale of the second scale of the second scale
is scale scale of the second scale o | N N N N N N N N N N N N N N N N N N N | N N
N N
N N N
Jachary
Jachary
N N | Manage de de de la Serier
angeneral de la Serier
angeneral de la Serier
de la Serier
No
No
No
No
No
No
No
No
No
No | Galantic Conductor
Cogenerations
Non-Angeneration
Non-
Non-
Non-
Non-
Non-
Non-
Non-
No | Severe parather i contiguitori
Severe parather i contiguitori
Net i
Net i
N | ser heling fillsalte aft
gifter, omgeden
gifter, omgeden
men er forste er forste er
helinger instander er forste er
helinger er forste er
helinger er forste er
her er
her
her
her
her
her
her er
her er
her er
her er
her er
her
her
her
her er
her
her
her
her
her
her
her
her
her
h
 | par balang sendipatan
mererenan dan sendipatan
mererenan dan sendipatan
mererenan dan sendipatan
Na
Na
Na
Na
Na
Na
Na
Na
Na
Na
Na
Na
Na | Equals conjutine
No. 1
No. 2
No. 2
N
 | Consignation of
No
 | Overceneption per a
operand of the
operand of the
operand of the
operand operand o
 | Initiative register and the set of the set o | blue to gen empt | Reart cardigates hegeline
excelutions for these parts
No
 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | No hashing attractly (20)
The second | Damkes An An An An An An An An An A | Constantino, Constantino Constantino, Cardio Sola Ante Ante
Cardio Cardio Constantino Cardio Constantino
Della del Paparate International
Neuroscie Constantino Constantino
Personali constantino
Pers | No
Proprietores model al 4 y
house source model
No
No
No
No
No
No
No
No
No
No
No
No
No
 | Appendix matching of behavior The second s | enversion danses of union
active
sectors of union
enversion danses of union
enversion danses of union
to the sector of union
enversion danses of union
of union danses of union danses of union danses of union
of union danses of union danses of union danses of union
of union danses of union danses of union danses of union danses of union
of union danses of union | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 117 Torque auxiliaria
117 Torque auxiliaria
auxiliaria del constructiones
auxiliaria
auxiliaria
118 Torque auxiliaria
118 Torque | Contputer
A
A
A
A
A
A
A
A
A
A
A
A
A
 | eene creigion Conjunt
No Energia
No Energia
No John
No John
No Long
No No
No No
No No
No No
No No
No No
No No
No
No No
No
No No
No
No
No
No
No
No
No
No
No
No
No
No
N |
| Antenendry prilow Region
Rect: prilowny prilow Rect
Rect: prilowny prilow Rect
Rect: prilowny prilow Rect
Rect: prilown Rect
Rect: prilow Rect: prilow Rect
Rect: prilow Rect: pril

 | ing in matter parts of the second sec | reporter particular distribution
and constrained and constrained and constrained and
and constrained and constrained and constrained
and constrained and constrained and constrained and
and constrained and constrained and constrained
and constrained and constrained and constrained
and constrained and constrained and constrained and
and constrained and constrained and constrained and constrained and
a | Advector factor get (California)
California (California)
The The The The The The The The The The | Normality of the second seco | Non care No No No Second

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N
 | 10
10
10
10
10
10
10
10
10
10
10
10
10
1 | N N N N N N N N N N N N N N N N N N N | 10 10 10 10 10 10 10 10 10 10 10 10 10 1

 | Grightfolm of sprong
Grightfolm of sprong
etc.sprong of the sprong
etc.sprong of the sprong
No.
South Spron, braid Purch
No.
No. | N N N N N N N N N N N N N N N N N N N | N N
N N
N N N
N N N N N N N N N N N N N | Name of the Annual Annu | Oute hit Congetor Coppendide Non-constraints No
 | Seeing particles contigution
Seeing particles contigution
Nation complex Natural Location
Nation Section 2014 (Section 2014)
National Section 2014 (Section 2014)
Na | een tealing diricular and
diricul an appendix
diricul an appendix
diricul and appendix
head of the strength of appendix
the above the strength of appendix
the above the strength of appendix
the st | por balang analysis
ever vegetabandari k kan
ever vegetabandari k kan
ever vegetabandari k kan
ever vegetabandari k kan
ever vegetabandari k kan
kan ever da kalan
ever da kalan | Epecto conjugate
No Epecto anoma
Personal an

 | Consignation of
No | Overcongetion gene 0
output of the second s

 | Instruction Paged to a left to the
Response De La des
No.
No.
No.
No.
No.
No.
No.
No. | blue to gen weyf 1 No | Seare caratigates hegeline
exclusions for Headphire
No | No
No
No
Normal
No | He hashing affords y DFI Service and another sectors. Provide the sectors and the sec | Cantas No | Conteplier On each leave
generation. Gene O de service
Recer argunal works.
Normal Ingene Annues.
Normal Ingene Annues.
Records Handle and Annues.
 | No
meteresis candod at 5 yr
meteresis candod at 5 yr
meteresis candod at 5 yr
meteresis candod at 5 yr
No
Normal
No
No
 | Approximation of the sector of the sect | Herniteria daria, et areas Stargaria da selatoria Stargaria da selatoria Stargaria da selatoria No Stargaria da selatoria Stargaria Stargaria | No N | n 117 separation 000 or white a set should be a set of the set of | Conteption
Conteption
Note
Note
Note
Note
Note
Note
Note
Note | exercication Contract Contract
N Contract Contract Contract
N Contract Contract Contract
N Contract Contract Contract Contract
N Contract Contract Contract Contract
N Contract Contract Contract Contract Contract
N |
| Contracted system Per sign Resc: period: Period: Resc: period: Period: Debatistic period: Period: Debatistic period: Period: Debatistic period: Period: Maccularistic period: Period: Debatistic Period: Period:

 | Ing is maken paint of the second seco | representation of the second s | A characterized of processing of the characteristic of the charact | Number of the second se | kan san
ban san
ban
san
ban san
ban san
ban san
ban san
ban

 | No N | 10
10
10
10
10
10
10
10
10
10
10
10
10
1 | N
 | No N

 | Englishment sharing of second | 30
10
10
10
10
10
10
10
10
10
1 | N N N N N N N N N N N N N N N N N N N | Interpretent of the second sec | Gala Na Congestion Coppendation Coppendation NoteCoppendation NoteCoppenda | Severe periodic contiguition
Severe periodic contiguition
National control contains in
National control contains in
National control contains in
National control control control control
Severe control control
Severe control control
Severe control control
Severe control control
Severe control control
Severe control control control
Severe control
S | een today dhalan ah
ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah ah
ah ah ah ah ah ah ah ah ah ah
ah ah ah
ah ah a
 | par balang analysis
analysis and analysis and
analysis and analysis
by
By abbas as an as an
By
By abbas as an as an
By abbas as an as an
By abbas as an
B | Equation consequences of the second s
 | Consignator P
N
N
N
N
N
N
N
N
N
N
N
N
N | Conscientingional and a consequence of a

 | Network Parks and a very series of the serie | No. 10 per empt
No.
No.
No.
No.
No.
No.
No.
No.
No.
No. | Search consignition. Negative
Networks of the Network of Network o | N | He heading afficulty (2) Heading afficulty (2) Heading afficulty (2) Heading afficulty (2) Heading afficient (2) Heading af | Euritus |
Contraction: Call to call the leave
of the contraction of Call Contraction of Call Contractions
In the contraction of Call Contraction of Call Contractions
In the contraction of Call Contraction of Call Contractions
Contraction of Call Contractions of Call Contractions
Contractions of Call Contractions of Call Contractions
Contractions of Call Contractions of Call | To an
 | A province and a province of the second provi | Investigation of a constraint of | No N | If TF approximations, BM or end and the second s | Contigutor Contigutor | exercication Content of the Content |
| Subschaft of pulsary Per sign Heart's pristoring pulsaries See

 | Ing in readers paired and an angle of the second se | representa particular distribution
distribution sequenciation and
distribution sequence and
distribution sequence and
distribution and distribution
distribution and distribution
distribu | Anterior lead of produces
and anterior and anterior anter | Nargang ang pang p | kun

 | No
No
No
No
No
No
No
No
No
No | 16
10
10
10
10
10
10
10
10
10
10 | 10
10
10
10
10
10
10
10
10
10 | No N

 | Englishment sharing of second | No
No
No
No
No
No
No
No
No
No
No
No
No
N
 | N N N N N N N N N N N N N N N N N N N | hanne gedor dans en Reyr,
server an Werker and State State State
and the server and state server
and the server and state server
and the server and state server
for the server and server and server
for the server and server and server and server
for the server and server and server and server and server and server
for the server and server an | Gale Na Congeline
Cogenitation in
Teleparent Territoryami
No
No
No
No
No
No
No
No
No
No
No
No
No | Severy persistent contigents
Severy persistent contactor
National several several several
National several
National several
National Several Several
National Several
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
National
N | een tedrog dirichen wit
dirit verweense
dirit verweense
bestelen omstelen die verstelen
bestelen die verstelen die verstelen die verstelen
bestelen die verstelen die verstelen die verstelen die verstelen
bestelen die verstelen d | por backing stratighter
even area descented in the
Constraints of the second strate
No
No
No
No
No
No
No
No
No
No | Sands conjution

 | Consident of a constraint of a | Ommersnepsing P

 | Interded Fundamental Angle of Marine State | blub type weft No | Search consigning, heighting
No
 | No.
No.
No.
No.
No.
No.
No.
No. | A basing attachy attach | Dartes
No
No
No
No
No
No
No
No
No
No | Conduction (c) an order to heavy
operation (c) COID (c) does
not a set of the set of the set of the set of the set
of the set of the set of the set of the set of the set
of the set of the | 10
10 contract on calculated all
10 contract on calculated a
 | A point matching on teaching the teaching th | Mentanda da kalan di kalan | 10
10
10
10
10
10
10
10
10
10 | 11 TT engine analysedue
methods (SB of end that and the set of the | Contputer | anan contention and a contention of the second of the seco |
| Contensation pressure
Next of pressure and the second
Next of pressure pressure
Next of pressure pressure
Next of pr

 | No. Produces performance of the second secon
 | Terretaria de la construita de la constr | Advantanteredary prilocine
alogic desire many constraints
in the second se | National and a set of | Name and Participants Name and Participants State Participants

 | No N | N N N N N N N N N N N N N N N N N N N | 10
10
10
10
10
10
10
10
10
10
 | No No No No No No No No No No No No No

 | See definition of highling
is a start or or other local
in the start or other local
in the start or other local
is a
finite layer, beat hurds,
finite layer, beat hurds,
file
beat layer, beat hurds,
beat layer,
beat lay | N N N N N N N N N N N N N N N N N N N | N N N N N N N N N N N N N N N N N N N | And a second sec | Galanta Gangadan Copercisada Opercisada Notacingan Nota | Severe persistent cantigation
Severe personnels for any severe | err being dhugha sh
art being dhugha sh
Dachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nachar
Nach
 | par balag sundjada
erent sun abaued at 14 m
erent sun abaued at 14 m
erent
son
Rent
Rent
Rent
Rent
Rent
Rent
Rent
Re | Speaks complete
No

 | Conjute 1 N N N N N N N N N N N N N | Ome company of a c
 | Interdent Funds and a with a w | Nuclea to proceedings
 | Search caralignes. Negative
non-beinger for Neuropean
No.
No.
No.
No.
No.
No.
No.
No.
No.
No. | No | No series attracts, tain
No series attracts of the series
No series at the series of the series
No series | Durines | Carlyster, () and ar leave
generative (CHC) of the second
Second Second Second Second
Name
Part of the second Second Second
Research Second Second Second
Carlos Internet Second Second
Second Second Second Second Second
Second Second Second Second Second
Second Second Second Second Second Second
Second Second Second Second Second Second
Second Second | No
Incontrol or section of a l
No
No
No
No
No
No
No
No
No
No
 | Import processing of the design of | member danka if what skills member danka if what ski | n
n
n
n
n
n
n
n
n
n
n
n
n
 | 11 TT engine analysedue
methods (SE of the Mark Service)
of the Mark Service of the Mark Service of the Mark Service of the
Service of the Mark Service of the Mark Service of the Mark Service of the
Service of the Mark Service of the Mark Service of the Mark Service of the
Service of the Mark Service of the Mark Service of the Mark Service of the
Service of the Mark Service of the
Service of the Mark Service of the Mark Se | Contputer of a contpu | exer creigion Control |
| Contensative proteins
Next generative proteins
Next generative proteins
Detects proteins
Next Annual Prote

 | Ing in readers parter of a consistent of a constraint of a con
 | recent of set of | Advatanted up pricing
and up the many control
to the second second second second second
to the second secon | Hysrange means and ender
scenpters
scenpters
Second Second Second Second Second Second
Second Second Secon | Non-sector Non-sector

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | No
No
No
No
No
No
No
No
No
No
No
No
No
N | No
 | 10 10 10 10 10 10 10 10 10 10 10 10 10 1

 | Early diffusion and highling of a set of an and a set of | N N N N N N N N N N N N N N N N N N N | N N N N N N N N N N N N N N N N N N N | Hange de dates to Hange
angeste States and
angeste States and
A | Galanta Congelier
Oppervision
National Nontracipation
National Nontracipation | Severe perceiver consigneets Severe perceiver consigneets Nation services Nation service | ere todag ditudite och
diffe ordination och
diffe ordination
social and today and
today and today and
toda | par helding conductor
event mata distance of 1 (1)
me
metal distances of profiles
me
and
big pathene and me and a serie
to
the
metal distances
and
the
helding conductor
to
the
the
helding conductor
to
the
helding conductor
to
the
heldin
to
the
heldin
helding
to
the
heldi | Specific computer
N Sector Annual An

 | Completer P N N N N N N N N N N N N N | Overcentreplement P P P P P P P P P P P P P P P P P P P

 | Interpret a set to set | blub ti pro wegt
No
No
No
No
No
No
No
No
No
No
No
No
No | Seare cardigate. Negative enablement of the theorement of the theo | No | No hashing affinally, 201
The second | Durites | Conteption: On early leaving of early early early early early early leave the early | No
Incontract, results of 4
period
No
Po
No
No
No
No
No
No
No
No
No
No
No
No
No | Approximation of the section of | eventer dansa et visa
dans
Service dansa et visa
Service dansa et
 | Ro
Ro
Ro
Roma
Roma
Roma
Roma
Roma
Roma | 11 TT encoderable difference of the sector o | Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler
Conspiler | exer creipine Contract
No Contract Contract |
| Contensative protocol
Network protocol
Merical protocol
Merical protocol
Delectro protocol
Merical protocol
Merica

 | ing in readers products of a consequence
 | Increde capitage dipulation
increde capitage dipulation
increde and an executive to a series
of the series of the series of the
series of the series of the series of the
series of the series of the series of the
series of the series of the series of the series of the
series of the series of the series of the series of the
series of the series of the series of the series of the
series of the series of the series of the series of the series of the
series of the series of the series of the series of the series of the
series of the series of the | An-index level applicables
adaption in the second s | Normany employee Normany employee No No Status between the first sector to the sector t | Name and No

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10
10
 | No
No
No
No
No
No
No
No
No
No | No N

 | Say diffusion and happing
to an ad robust to a set of ad robust to
all the set of ad robust to all
set of address that have it
is
not fugue. In all fugues to all have it
is
not | No N | N N N N N N N N N N N N N N N N N N N | An and performance of | Gala tei, Congenitation
Cogenitation 2.
Notice 2.
No | Severe parather contigutors
Severe parather contigutors
National and the severe se | err heling filtsalte eth
andre en der heling ether eth
andre ether eth
en der heling ether eth
ether ether ether ether
ether ether ether ether
ether ether ether ether
ether ether ether ether ether
ether ether ether ether ether
ether ether ether ether ether
ether ether ether ether ether ether
ether ether ether ether ether ether
ether ether ether ether ether ether ether
ether ether ether ether ether ether ether ether ether
ether ether ether ether ether ether ether ether ether ether
ether ether ether ether ether ether ether ether ether
ether ether ether ether ether ether ether ether ether ether
ether ether e | par heling sortigeton
ever versi even densitier i 1 ever
200 allen ever termine
200 allen ever term | Fands conjution No

 | Consignation of
No
 | Overcentrepletion and a segment of a se
 | Interfactor Pageta sales are
Interfactor and an an and an an and an | htun ti per mejri
No
No
No
No
No
No
No
No
No
No
No
No
No | Sever cardigates hegeline exceptions in the several se | No
No
No
No
No
No
No
No
No
No
No
No
No
N
 | No hashing attracts, 125
Market and scales, Production
No. 100
No. 100 | Daritus | Constantion Constantisti Constantion Constantion Constantion Constantion Const | No
Proprietores model al 6 y
and and any model
No
No
No
No
No
No
No
No
No
No
No
No
No
 | Appendix matching of begins of the second seco | eventeer damage of unique e | 10
10
10
10
10
10
10
10
10
10 | 117 Tergina exhauses
and the second of the second of the second
of the second of the second of the second of the
second of the
second of the second of the
second of th | Conteplation | exer create of a set |
| Contrasting problem Per Negation Next (problem) Next (problem) Next (problem) Next (problem) Debeter problem Per Next (problem) Next (problem) Per Next (problem) Next (proble

 | Ing is readers paired a consequence of the second s | Increase of particular display | Advised ledge plicities
and units and units
by the main data
by
the
the
the
the
the
the
the
the
the
the | Norman and an one of the second secon | Name case No

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10
10 | No | No N

 | Say diffulture and highly and a set of an other set of an othe | No N | N N N N N N N N N N N N N N N N N N N | And and a second | Gale tel
Congenitador
Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-Coperentador
Non-C | Severy particle of contigution 5
Severy particle of contigution 5
Nath company future of location 1
Nath company future of location | en heling fillighte eff
giftig en opporte
giftig en opporte
en opporte
heling fillighte eff
heling fillighte
heling fillighte | por backing conduction
ever over development of the second
meter over development over deve | Equals conjugates and annual sector sector annual sector a

 | Contiputor II All II | Americanspation (Company)
Americanspation (Company)
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
Americans
A
 | Interfactor Angeles and a feet of
Record of Control o | blue to gen empt
No
No
No
Processed much for
No
No
No
No
No
No
No
No
No
No
 | Reart cardigates hegeline
Reart cardigates hegeline
Reart lange for Machine
Reart lange for Machine
Reart lange for
Reart lange | No N | No hashing attracky, 100
The sector of a state of the sector of the sec | Dantess Are | Senderliken, Oan onder beering
deriverse of Sender Sender
Beiter of Species Hornes
Beiter of Species Hornes
Record Properties Andreen
Record Contracting and Andreen
Record Contracting an | Non-services, model at 6 1 Non-services, model at 6 1 Non-services Non-services <tr< td=""><td>Appendix matching on beginning of the second s</td><td>eventer danks of units eventer danks of units</td><td>No
No
No
No
No
No
No
No
No
No
No
No
No
N</td><td>117 Torigina exclusions
and the second second second second
second second second second second
second second second second second second
second second second second second second second second
second second second second second second second second
second second second second second second second second second
second second second
second second se</td><td>Conteption
Conteption
Neuropeake to make
Neuropeake to make
Ne</td><td>exer categorian No Description No Description</td></tr<> | Appendix matching on beginning of the second s | eventer danks of units | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 117 Torigina exclusions
and the second second second second
second second second second second
second second second second second second
second second second second second second second second
second second second second second second second second
second second second second second second second second second
second second second
second second se | Conteption
Conteption
Neuropeake to make
Neuropeake to make
Ne
 | exer categorian No Description |
| Contrasterio de particulos Per el mesorie Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitonis Rendri gentarrony patitonis Rendri gentarrony patitonis Son de la manualización patitoni patitonis

 | Ing is readers paired of a second sec | reporter particular display di | An other head on particular, and a second se | Normany on part of the second secon | Non-color Non-color

 | No
 | 16
10
10
10
10
10
10
10
10 | No | 10 No 10 <

 | Exp diffusion of saving
Exp diffusion of saving
diffusion of saving saving
diffusion of saving saving
Saving Saving Saving Saving
Saving Saving Saving Saving Saving
Saving Saving Saving Saving Saving Saving Saving Saving
Saving Saving Savin | No | N N N N N N N N N N N N N N N N N N N | Manage do chance a server
and a server and a server
a server a server a server a server
a server a server a server a server a server
a server a server a server a server a server
a server a server a server a server a server a
server a server a server a server a server a server a server
a server a server | Oda hit Congenitation 1 Coppendulation 1 Nationality Nonline Japane 1 | Severy particles contigutes 9 Severy particles contigutes 9 Representation of the severy se | en rading diriche adv
dirich andre adv
dirich andre adv
dirich andre adv
behalten en energie (a serie
Regenergie). Autor
adv
diriche adverse (a serie
Regenergie). Autor
adverse diriche adv
regenergie
diriche adverse diriche
adverse diriche adv
regenergie
diriche adverse diriche
adverse diriche adv
regenergie
diriche adverse diriche
adverse diriche adverse diriche adverse diriche
adverse diriche adverse diriche
 | par being under an office of the second seco | Sands conjution N N N N N N N N N N N N N N N N N N N
 | Consident of
No
 | Ommersnepsinger Paral
Oppensender
Neren 2 delateurs
Neren 2 delateu
 | Interdet Pupils and a very series of the ser | blue to per weet | Search consignion. Negative
No
 | No | Notaring attachy, 22
Notaring attachy, 23
No
No
No
No
No
No
No
No
No
No | 30 30 30 30 30 30 30 30 30 30 30 30 30 30 30 30 31 32 32 32 32 32 32 32 32 33 | Consistent of an exist in leaving of an exist in exist in leaving of an exist in leaving of | 10
10000000000000000000000000000000000
 | Approximation of the sector of the sect | Herniter danka if water danka if water | No | 117 State and should be a set of the set | * Contpate 1 Horizabe formation 80 1 80 1 80 1 80 1 80 1 80 1 80 1 9 3000 Horizabe 80
 3000 Horizabe 9 3000 Horiz | America contigation Contigation No. Proceeding contig No. One No. Jump contig No. |
| Contensities pressure
Next of pressure y publics of the first
Next of pressure y publics of the first
Next of pressure y publics of the first
Next of pressure of the first
Next of the first of the first of the first
Next of the first of the first
Next of the first of the first of the first
Next of the first of the first of the first
Next of the first of the first of the first of the first
Next of the first of the fir

 | An and and | result of a share security of a second secon | An observed by physics,
and observed by physics,
by observed by an observed
by observed by an observed
by an observed by an observed by an
observed by an observed by an observed
by an observed by an observed by an observed
by an observed by an observed by an observed by an
observed by an observed by an observed by an observed
by an observed by an observed by an observed by an observed
by an observed by an ob | Normany and part of the second part of the seco | Name and P Na

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N
 | 10
10
10
10
10
10
10
10
10
10 | No | N0

 | Reg distances and highly and a set of a | Ib III III IIII IIII IIII IIII IIIII IIIII | N N N N N N N N N N N N N N N N N N N | Angele de de la presentación de | Galanta
Gangkalan
Departmakan
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta
Notarianta | Severe persistent caterity and a severe persistent caterity and a severe persistent caterity and a severe persistent of the severe persistence of th | ent heing dhugha and
and a long dhugha and
and a long dhugha and
and a long dhugha and
and a long heing dhugha and
and a long heing dhugha and
high ageneragida barris.
A long dhugha and
high ag | par haling conductor
event out abauted at 1 for
the second second second second
out and the second second second
biological second second second second
second second seco | Speech computer
Notes and average
Second ave

 | Consignate 1 | Americanspino da Caracteriza da Cara
 |
 | Nuclea to pore weeks | Seart cardigate. Night in
Nicholsey for National
Nicholsey for National
Nic | No.
No.
No.
No.
No.
No.
No.
No. | Notaring attracts, 201
Notaring attracts, 201
Notari | Durtees | Cashpillen () an eiler kenne
die eiler de prodet kenne
Ne
Net de prodet kenne
Ne
Cashpillen () and de prodet
Cashpillen ()
Ne
Cashpillen ()
Ne
Ne
Ne
Ne
Ne
Ne
Ne
Ne
Ne
Ne | 10
Increases and a final sector of a final sect
 | Import an exciting of elegands Import and the exciting of elegands Import and the elegands< | eventer danka d'alas | 76
76
76
76
76
76
76
76
76
76
76
76
76
7
 | | Contputer
Contputer
Formation
No
No
No
No
No
No
No
No
No
No | Americanitami Scientification No Scientification |
| Contensity proteins Part Mark Mark of generating proteins Annual Part of generating proteins Annual Dedicitie proteins

 | Ing in readers produces produces of the second seco | recent of a sharp all public designs | Activate level by philoses
any setting and activates
in the setting and activates
in the setting and activates
in the setting activates
activates and activates
activates activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activates
activa | Normany end of end end of en | Name and
Name and Name and
Name and Name and
Name and Name and
Name and Name and
Name Name and
Name
and
Name Name and
Name Name and
Name Name
and
Name Name Name Name and
Name Name Name Name

 | No No No No No No No No O No O No Jaugetore No Aper CY (12) or (10) or (10) or or (10) or (1 | 10 10 10 10 10 10 10 10 10 10 10 10 10 1 | No No | N0 N0 N0 <

 | Any diffusion of highly of a set of a s | Part International Control of Con | N N N N N N N N N N N N N N N N N N N | Hange de dates to havy,
angeste de dates to havy,
angeste de dates to have,
angeste de dates to have
and and an angeste date
and and angeste dates
and angeste dates
and angeste dates
angeste dates
a | Galanta Canapatan
Oquennaan
Natarana Nantarayan
Na
Na
Na
Na
Na
Na
Na
Na
Na
Na | Severe perceiver contentions for a severe perceiver contentions for a severe perceiver contention of the severe perceiver content of the severe perceiver cont | An and a set of | par helds an objective
event was dealered at 1 feet
and an objective program of 1
feet and 1
feet an object and 1
feet and 1
feet an object and 1
feet and 1
feet and 1
feet an object and 1
feet an object and 1
feet and 1
feet and 1
feet an object an object an object an object and 1
feet an object and 1
feet an | Speck complete
No Experimental Sector Secto

 | Company P | Ome company of a c

 | Interest of the second | blue to per empt
No
No
Common Anno
No
No
No
No
No
No
No
No
No
N | Seare cardigate. Negative environment of the second of the | No
No
No
No
No
No
No
No
No
No
No
No
No
N | Hotelang attracky (20) Hotelang attrack | Durites | Contegritor, con estar leave
generalistic colors, colors, and
la Barrier de yanterior
leave de yanterior
lea | No
Normal Advances of Advances
 | Approximation of the section of | eventer danag of units eventer danag of units eventer danag of units eventer danage eventer danage eventer danage eventer danage eventer danage eventer eventer danage eventer | No No No < | 11 TT approximation of the second | * Constants * Nacropakes transits
 | ANN CAPAGANAN CA |
| Contensities produce
Next of personal personal produce
Next of personal per

 | ing is readers product of a consequence
 | recent of share any share and share any share and share any share | Advision feeding philology
and philology and philology
and philology and philology
and | Netrongen metal ende
netropies
netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Netropies
Net | Name and Name and Name and Name and Market States of States and Market States and

 | 10
10
10
10
10
10
10
10
10
10 | 10
10
10
10
10
10
10
10
10
10
 | No No No < | No No Other services No No No No <th>See affording and injury of a set of an other set of an other</th> <th>No. No. No. No. No. No. No. No. No. No.</th> <th>N N N N N N N N N N N N N N N N N N N</th> <th>hange de date se berey
angenet 2000 kerne
angenet 2000 kerne
de date au onderdet
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend</th> <th>Gala te Congenerate
Cogenerate
No
No
No
No
No
No
No
No
No
No</th> <th>Severy particle f contigues
Severy particle f contigues
Severy</th> <th>err tedag dirude och
diffe och erregelse
diffe och erregelse
sollter erregelse
tedagen i statute och
sollter erregelse tedagen
i erregelse
i erregelse</th> <th>par heling sortigiston
even resultationed at 14 feet
See allocation of provide
See allocation of provide
Resultation of the set of the
Resultation of the
Resultation of the
Resultation of the set of the
Resultation of the
Resultation of th</th> <th>Speaks complete No N</th> <th>Consignation of
No No No No No No No No</th> <th>Overcentrapies of a sequence o</th> <th>Interaction in parties and in a series with
Reservery of the Reservery o</th> <th>blue ti per mejet
No
No
Versenie Aucho tre
No
No
No
No
No
No
No
No
No
No
No
No
No</th> <th>Seare cardigate. Negative exceedences of the search of the</th> <th>No No No No No No No No No No</th> <th>Nested at Sub 2, 25 Minutes of Sub 2, 25 Minutes of</th> <th>Durites
No
No
So
Particular
So
So
So
So
So
So
So
So
So
So</th> <th>Sendardin Constant heavy
devices (SHC) and an even
heavy services (SHC)
heavy services (SHC)</th> <th>Non-street and all all all all all all all all all al</th> <th>Appendix matching of beginning of the second s</th> <th>environt damage of union environt damage of union envinterveo damage of union environt damage of union environt</th> <th>30
30
30
30
30
30
30
30
30
30</th> <th>If T equivalence difference in the second difference of the second d</th> <th>Conteption - Neuropation - Neuropation - No - No - Jone (mit) - Jone (mit) - No - No</th> <th>ANAL CARENT CARE</th> | See affording and injury of a set of an other | No. | N N N N N N N N N N N N N N N N N N N | hange de date se berey
angenet 2000 kerne
angenet 2000 kerne
de date au onderdet
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend
Rend | Gala te Congenerate
Cogenerate
No
No
No
No
No
No
No
No
No
No
 | Severy particle f contigues
Severy | err tedag dirude och
diffe och erregelse
diffe och erregelse
sollter erregelse
tedagen i statute och
sollter erregelse tedagen
i erregelse
i erregelse | par heling sortigiston
even resultationed at 14 feet
See allocation of provide
See allocation of provide
Resultation of the set of the
Resultation of the
Resultation of the
Resultation of the set of the
Resultation of the
Resultation of th | Speaks complete No N

 | Consignation of
No No No No No No No No | Overcentrapies of a sequence o
 | Interaction in parties and in a series with
Reservery of the Reservery o | blue ti per mejet
No
No
Versenie Aucho tre
No
No
No
No
No
No
No
No
No
No
No
No
No
 | Seare cardigate. Negative exceedences of the search of the | No | Nested at Sub 2, 25 Minutes of | Durites
No
No
So
Particular
So
So
So
So
So
So
So
So
So
So | Sendardin Constant heavy
devices (SHC) and an even
heavy services (SHC)
heavy services (SHC) | Non-street and all all all all all all all all all al
 | Appendix matching of beginning of the second s | environt damage of union envinterveo damage of union environt damage of union environt | 30
30
30
30
30
30
30
30
30
30 | If T equivalence difference in the second difference of the second d | Conteption - Neuropation - Neuropation - No - No - Jone (mit) - Jone (mit) - No
 | ANAL CARENT CARE |
| Contrasting problem Per line Next (problem) Result Next (problem) Result Next (problem) Result Debeter problem Result Next (problem) Result State (problem) Result </td <td>ing is reader product of a constraint of a con</td> <td>Increase of a second se</td> <td>An in the last of photons,
and photons, and an intervention of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the</td> <td>National and a set of the set of</td> <td>Name and Name and Name and Name and Name and Anti-Anti-Anti-Anti-Anti-Anti-Anti-Anti-</td> <td>No No No No No No Ornitation Ornitation Aparts State Aparts Aparts Aparts Aparts Aparts Aparts Aparts NA</td> <td>10
10
10
10
10
10
10
10
10
10</td> <td>No No No</td> <td>No No No <</td> <td>Say diffultion of highling
Say diffultion of highling
say diffultion of highling
say diffultion of highling
say
Say
Say
Say
Say
Say
Say
Say
S</td> <td>No No N</td> <td>N N N N N N N N N N N N N N N N N N N</td> <td>المالية المالية المالية
مالية المالية المال
المالية المالية الماليالية المالية المالية المالية المالية المالية المالية</td> <td>Gala bit, Congenitation Coperindian Non-operative Non-o</td> <td>Seem parather contigetion 5 Seem parather contigetion 5 Nather contigeti</td> <td>en telang dirigina adı
diriyi avayatır
diriyi avayatır
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
ba</td> <td>pa halog andpaha
ener ener den de se de se
ener ener de se de se de se
ener ener de se de se de se
ener ener de se de se
ener de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se de se de se
ener de se d</td> <td>Spack couple 1 No 1 nonad omba 1 No 1 <!--</td--><td>Consignation of
No</td><td>Overce comparison of an an</td><td>Interface parties and a set of with a set of</td><td>Nahara tepen menjet
Nahara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakar
Manakara Manakara Manakar</td><td>Seen caragalas. Nagain e
Na</td><td>No
No
No
No
No
No
No
No
No
No</td><td>Plansing attracts, 121 See and the set of the</td><td>Danhasi
An
In
In
In
In
In
In
In
In
In
I</td><td>Cardipation, Can capita leaving
approximation, Califord, Sanking
Balander Spraces Investi-
tion
Balander Spraces Investi-
Balander Spraces Internet
Research Spraces Internet
Capitality Homospheres, Team
Capitality Homos</td><td>No No No</td><td>Appendix matching on belonging Processing and second se</td><td>eventered darkes of union
action
of the second dark of union
the second dark of union
the second dark of the second
test of the second dark of the second
test of the second dark of the second dark
of the second dark of the second dark of the
second dark of the</td><td>Po
- Au
- Po
- Po
- Po
- Rome
- Rome
-</td><td></td><td>Contiguitar </td><td>America contegration Scientification No No No No <tr< td=""></tr<></td></td> | ing is reader product of a constraint of a con | Increase of a second se
 | An in the last of photons,
and photons, and an intervention of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the last of the last
and an intervention of the last of the | National and a set of the set of | Name and Name and Name and Name and Name and Anti-Anti-Anti-Anti-Anti-Anti-Anti-Anti-

 | No No No No No No Ornitation Ornitation Aparts State Aparts Aparts Aparts Aparts Aparts Aparts Aparts NA | 10
10
10
10
10
10
10
10
10
10 | No | No No No <

 | Say diffultion of highling
Say diffultion of highling
say diffultion of highling
say diffultion of highling
say
Say
Say
Say
Say
Say
Say
Say
S | No N | N N N N N N N N N N N N N N N N N N N | المالية المالية
مالية المالية المال
المالية المالية الماليالية المالية المالية المالية المالية المالية المالية | Gala bit, Congenitation Coperindian Non-operative Non-o | Seem parather contigetion 5 Seem parather contigetion 5 Nather contigeti | en telang dirigina adı
diriyi avayatır
diriyi
avayatır
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
barina
ba | pa halog andpaha
ener ener den de se de se
ener ener de se de se de se
ener ener de se de se de se
ener ener de se de se
ener de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se de se
ener de se de se de se de se de se
ener de se de se de se de se de se de se de se
ener de se d | Spack couple 1 No 1 nonad omba 1 No 1 </td <td>Consignation of
No</td> <td>Overce comparison of an an</td> <td>Interface parties and a set of with a set of</td> <td>Nahara tepen menjet
Nahara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakar
Manakara Manakara Manakar</td> <td>Seen caragalas. Nagain e
Na</td> <td>No
No
No
No
No
No
No
No
No
No</td> <td>Plansing attracts, 121 See and the set of the</td> <td>Danhasi
An
In
In
In
In
In
In
In
In
In
I</td> <td>Cardipation, Can capita leaving
approximation, Califord, Sanking
Balander Spraces Investi-
tion
Balander Spraces Investi-
Balander Spraces Internet
Research Spraces Internet
Capitality Homospheres, Team
Capitality Homos</td> <td>No No No</td> <td>Appendix matching on belonging Processing and second se</td> <td>eventered darkes of union
action
of the second dark of union
the second dark of union
the second dark of the second
test of the second dark of the second
test of the second dark of the second dark
of the second dark of the second dark of the
second dark of the</td> <td>Po
- Au
- Po
- Po
- Po
- Rome
- Rome
-</td> <td></td> <td>Contiguitar </td> <td>America contegration Scientification No No No No <tr< td=""></tr<></td> | Consignation of
No | Overce comparison of an

 | Interface parties and a set of with a set of | Nahara tepen menjet
Nahara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara
Nahara Manakara Manakara Manakara Manakara Manakara Manakara Manakara
Nahara Manakara Manakar
Manakara Manakara Manakar | Seen caragalas. Nagain e
Na | No
No
No
No
No
No
No
No
No
No | Plansing attracts, 121
 See and the set of the | Danhasi
An
In
In
In
In
In
In
In
In
In
I | Cardipation, Can capita leaving
approximation, Califord, Sanking
Balander Spraces Investi-
tion
Balander Spraces Investi-
Balander Spraces Internet
Research Spraces Internet
Capitality Homospheres, Team
Capitality Homos | No
 | Appendix matching on belonging Processing and second se | eventered darkes of union
action
of the second dark of union
the second dark of union
the second dark of the second
test of the second dark of the second
test of the second dark of the second dark
of the second dark of the second dark of the
second dark of the | Po
- Au
- Po
- Po
- Po
- Rome
- | | Contiguitar | America contegration Scientification No No No No <tr< td=""></tr<> |
| Consequent products Pare Marine Nextly productively produce Sector Detects products Sector Sector products Sector Sector products Sector Sector products Sector Sector Sector <t< td=""><td>The area water and a second se</td><td>receive and a second and a seco</td><td>An enter head of produces
and an enter of the second secon</td><td>National control of mail intervention of the mai</td><td>Kan same Kan same</td><td>No No No</td><td>16</td><td>No No No</td><td>No No No No No No No No Status in a second seco</td><td>Registrations and highly and an an an and an and an an</td><td>Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
P</td><td>N N N N N N N N N N N N N N N N N N N</td><td>Angele de de ter a la segurar de la segurar</td><td>Gala NG Gardpeller
Ceptorshaften
N
N
N
N
N
N
N
N
N
N
N
N
N</td><td>Seeue parather contigutor. See
Seeue parather contigutor. See
Not contigutor have of baseline
Not contiget
Not contiget
Not contiget</td><td>ent taking disular ada
add a constrained
balance and a constrained
add a constrained
balance and a constrained
add a local test parabalance
add a loca</td><td>par halog outputse
out of out abased of 1 out
to additional program (1 out
additional program (1 out))</td><td>Spands: computer N No </td><td>Consident of a constraint of a</td><td>Omme companye in all of the second second</td><td>Interest Part of the Section of the</td><td>bile type weyt
N
N
N
N
N
N
N
N
N
N
N
N
N</td><td>Search caralights: Register
Residuency for Handberg
Residuency for Ha</td><td>No No No</td><td></td><td>Durines</td><td>Contention (control heavy
and control control heavy
and control control heavy
and control control heavy
and control heav</td><td>No No No</td><td>Important participant Important Important</td><td> Herniter danial of class data o</td><td>No No No</td><td></td><td>* Contigutor - 10 Fouriestical formation - 50 50 - 50 Jacrit barly - 4 Jacrit barly - 4 Jacrit barly - 5 Jacrit barly - 7 Farmat - 50 Farmat - 50 Farmat - 6 Farmat - 7 Farmat - 70 Fa</td><td>Marce conteption Scientist of the sector of th</td></t<> | The area water and a second se | receive and a second and a seco | An enter head of produces
and an enter of the second secon | National control of mail intervention of the mai | Kan same

 | No
 | 16 | No | No No No No No No No No Status in a second seco

 | Registrations and highly and an an an and an and an | Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
P | N N N N N N N N N N N N N N N N N N N | Angele de de ter a la segurar de la segurar | Gala NG Gardpeller
Ceptorshaften
N
N
N
N
N
N
N
N
N
N
N
N
N | Seeue parather contigutor. See
Seeue parather contigutor. See
Not contigutor have of baseline
Not contiget
Not contiget
Not contiget | ent taking disular ada
add a constrained
balance and a constrained
add a constrained
balance and a constrained
add a local test parabalance
add a loca | par halog
outputse
out of out abased of 1 out
to additional program (1 out
additional program (1 out)) | Spands: computer N No

 | Consident of a constraint of a | Omme companye in all of the second
 | Interest Part of the Section of the | bile type weyt
N
N
N
N
N
N
N
N
N
N
N
N
N | Search caralights: Register
Residuency for Handberg
Residuency for Ha | No |
 | Durines | Contention (control heavy
and control control heavy
and control control heavy
and control control heavy
and control heav | No
 | Important participant Important | Herniter danial of class data o | No | | * Contigutor - 10 Fouriestical formation - 50 50 - 50 Jacrit barly - 4 Jacrit barly - 4 Jacrit barly - 5 Jacrit barly - 7 Farmat - 50 Farmat - 50 Farmat - 6 Farmat - 7 Farmat - 70 Fa
 | Marce conteption Scientist of the sector of th |
| Containanti prismu Par Million Next of prisminanti
Next of prisminanti
Next of prisminanti
Deducing prisminanti
Deducing prisminanti
Next of prisminanti
Next of prisminanti
Deducing prisminanti
Next of prisminanti
Deducing pris

 | No control of a co | result of a visual share we we have a visual share we we have a visual share we we have a visual share we have a v | An extent test by philose,
and set of the se | Norman en par en p | Kan same

 | No | 16
10
10
10
10
10
10
10
10
10
10 | No | No No No No No No No No State bargescripts charts charts
regester of a cognitable
soft of relevant of relevant of a cognitable
soft of relevant of a cognitable
soft of relevant of relev

 | See definition of highling of an and an an an and a | Particular Section 2014 (Constraints)
 | N N N N N N N N N N N N N N N N N N N | Angele de de la presentación de | Gala NG Gangkelon
Copercision
No
No
No
No
No
No
No
No
No
No | Severe personnel cantingener. Severe personnel cantingener. Not can applied the severe here and the severe | err being disults of
Discher and
Discher | par halog outdyddi
erwl outdyddiol
yg
b
b
b
b
b
b
b
b
b
b
b
b
b
b
b
b
b
b | Spands: computed Image: Computed in the section of the s

 | Complete F No In No | Ommergingen (Lasse) D Oppersonale - Oppersonale - Name - Datacati fly - Name - Name </td <td>Interest Parks and a very series of the seri</td> <td>blue to per empt No No No No No No No No No N</td> <td>Seart cardigate. Negative exceptions in the search of the</td> <td>No No No <</td> <td>Abadegathedy, 20 Abadegathedy, 20 Abad</td> <td>Dartes</td> <td>Cardyalan () an air heirig
Berefarante () Mit () Mit ()
Net () Mit () Mit ()
Net () Mit ()
Net () Mit ()
Net () Mit ()
Restrict () Mit ()
Restrict ()
Net () Mit ()
Net ()
N</td> <td>No No No</td> <td>Approximation of the second seco</td> <td>eventer danka di visa
eventer danka di visa
Parto di visa
Parto</td> <td>No No No</td> <td></td> <td>Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitettion Image: Constitution Imag</td> <td>ana craigian Sana drain an an</td> | Interest Parks and a very series of the seri | blue to per empt No No No No No No No No No N
 | Seart cardigate. Negative exceptions in the search of the | No No No < | Abadegathedy, 20 Abad | Dartes | Cardyalan () an air heirig
Berefarante () Mit () Mit ()
Net () Mit () Mit ()
Net () Mit ()
Net () Mit ()
Net () Mit ()
Restrict () Mit ()
Restrict ()
Net () Mit ()
Net ()
N | No
 | Approximation of the second seco | eventer danka di visa
eventer danka di visa
Parto | No | | Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitution Image: Constitettion Image: Constitution Imag
 | ana craigian Sana drain an |
| Contensity protein Part of any protein of any prote

 | In a in readers produces produ | recent of a share sequent way | An observed by physically
and server and ser | Norman en un | Name and the second s

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10
10
 | No | N0 N0 N0 <

 | And September 2014 and September | IN I | N N N N N N N N N N N N N N N N N N N | Na selection of the sel | Gala tel Conspector
Cogenovalent
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-Star
Norter-St | Severe provide t contiguente
Severe provide t contiguente
National and the severe severe
National and the severe
Na | An and a set of setting efficiency effi | par halog ondpain
even out attached of 1 for
the
second attack of particular
the
for
for
for
for
for
for
for
for
 | Species computer Image: Computer computer No Image: Computer co
 | Company P N N N N N N N N N N N N N
 | Ome company of a
Operation of a
Operation of a
Decent ing
Neurol Defaury
Neurol D
 | Interesting and a series with a series of | Nut is para megit
Nut is para m | Search caretypins, Negative search se | No | Abadegation, 20 A | Durites | Cardipatini, O an other leaving
distribution, Cardini, O and Series
National Cardini, O and Series
National Cardinal Cardinal
National Cardinal Cardinal
Cardinal International
Cardinal
International
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors
Sectors | No
 | Appendix metaling and heading of the second se | eventer danka di vike
eventer danka di vike
Party da vike
Party | Ро
- Ло
- Ло | | Constpation
 | ana craigian Canaga Canag
Canaga Canaga Cana |
| Contensity protein Part of
second second s

 | Ing in readers parter of a consequence o | receive and a second and a seco | An observed of processes
and processes of the second of the second
region of the second of the second of the second
region of the second of th | Netronyce metada endy
conference
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section
Section | Non Non Non Non Name of the state

 | No | 10
10
10
10
10
10
10
10
10
10 | No N
 | N0 N0 N0 <

 | See diffusion and highling of a set of an other set of a | No. | N N N N N N N N N N N N N N N N N N N | Interpretent of the second sec | Gala te Congenitaria
Opportunation
Nationess Technologies
Nationess Technol | Severe parather t contiguents
Severe parather t contiguents
National severe | ere today display of
diffe outputs of
diffe outputs of
today ou | par helding somehaden
even varia daskande at 14 km
met varia daskande at
met varia daskande | Specie compares

 | Conteptant P N N N N N N N N N N N N N N N N N N | Orace company of an

 | Interaction in parties and any term
Mathematical Country
Name of the second s | blub tipe megt | Seare cardigate. Nigethe
No
 | No | Plansing attrack, till men senser, terms attrack men senser, term | Durines | Contaption: On early leaving of early leaving leav | No Normal Advancements No Normal No
 | Approximation of the section of | eventeric danage of units description descrip | No | If TT encoderable, SEC or Market and Sector Sect | Contractor Image: Contractor Image: Contractor Image: Contr | aan corigion Constant
No. Constant
No. Constant
Anti-
Anti-
No. Constant
Anti-
No. Constant
No. Constant |
| Contrasting product Per significant Per significant Per of production product Earned
of production product Earned
of production product Decomposition product Earned
of production product Earned
of production product Manuscript product Earned
of production production Earned
of production production Manuscript production Earned
of production production Earned
of production production Decision production production Earned
of production production Earned
of production production Decision production production Earned
of production production Earned
of production production Decision production production production Earned
of production production Earned
of production production Decision production production production production Earned
of production production Earned
of production production Decision production pro

 | ing is readers produce produces of the second secon | result of years of the second | Advision feeding pricipang
adviser international
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro | Netropy of the second sec | Name and the second s

 | No
 | No | No No No No In < | No No No No No No No No No No Second

 | See diffusion and injury of a set of an other | No. | N N N N N N N N N N N N N N N N N N N | August of a data of a second sec | Gala te Congenerate e
Cogenerate e
No e | Sever parather contigues in the several parather contigues in the several seve | er telang dingka ung
gang bang dingka ung
gang bang ung
telang dingka ung
telang ding | par heleig undebalen
ener undebalend it fan
See defaarte gener
See defaarte gener
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler
Regeler | Species computers No

 | Conteptants II Contep | Overse carequise (and any oper of any oper of any oper of any oper oper oper oper oper oper oper oper

 | Interest of a set of | Naka tepen weekt | Seare cardigate. Negative search sear | No | Abadegation, 20 A | Durines |
Cardipation: Can stage in leasing of the leasing of the least of the l | Non-theorem is and all all all all all all all all all al
 | Appendix matching on beginning of the section of the secti | eventeen dampa of units
advanced and units
eventeen dampa of units
eventeen dampa o | No | | Contpate - Nonrelate branch - Nonrelate branch - Nonrelate branch - Jant Work - Jant Work - Jant Work - Branch - <t< td=""><td>Anar craigen S Conjert
N Conjert</td></t<> | Anar craigen S Conjert
N Conjert |
| Contrasting problem Per significant Next (problem) Per significant Next (problem) Per significant Debeter (problem) Per significant Next

 | ing is reader product of a conservation of a con | Increduction and an and an | An estantication performance
in a second se | Number of the second se | Kum ckm K

 | No
| No | No | No No No No No No No No No No See bengenites charactures and second sec

 | Say distance of largery and la | No. | N N N N N N N N N N N N N N N N N N N | In the second se | Gala bit, Congenitation Cogenitation Non-output Non-output < | Seem parather conjustes. See A | en telang dirigina edi
dirigina editoria
dirigina editoria
telana editoria
telana editoria
telana telana telana editoria
telana telana telana editoria
telana telana telana editoria
telana telana telana telana editoria
telana telana telana telana editoria
telana telana telana telana editoria
telana telana telana telana telana telana telana telana telana telana telana
telana telana tela | pa halog analysis
and analysis of the
metric statistical of the
metric s | Sanda: compation No No No No No Sanda: Sa

 | Consident of a constraint of a | Ome: campaigned, and any

 | Industry hype and a way | blah type weet | Searce caregistics. Negative
No. 1999
No. 1999
N | No | Abadegation, 20 A | Durtes | Candidati (an exist here of a second | No
 | Appendix and any of ending of the second secon | Herniter danka if water danka if water | No |
 | * Contpate - * Naritzééé formanie - * Naritzééé formanie - * Naritzéé formanie - | ANAL CALLER OF C |
| Outside prised of the set o

 | Normal Carlos and Annual Annua | nordina selection de la construction de la construc | An end of the second of the se | Narrange en auto en en | Lan care Lan care Barton and an an and an and an an and an an an and an an an and an an and an an an and an an and an an an and an an

 | No | 16
 | No | No No No No No No No No No No No No No

 | See design of the set | Parent of descendences of the sector of the | N N N N N N N N N N N N N N N N N N N | Angele des la parte de la part | Gala Na Gangkalan
Copuscilata
Na
Na
Na
Na
Na
Na
Na
Na
Na
N | Severe persistent cantingener
Martraungein honraut knatter
Martraungein höheraut knatter
M | err being structure etc.
BER omtigener
BER omtigener
Autor terms of the structure etc.
Autor at the structure etc.
Autor at the structure etc.
Autor at the structure etc.
To an at the structure | par haling conductor
event out abates of 1 m
10
10
10
10
10
10
10
10
10
10
 | Spands: computed N Normal series R Normal series R Spands: series R No R No R No R Spands: series R
 | Consigned on a first sector of the sector of | Ommersheeting of a second seco

 | | blah type megt | Seart caragelis. Negative
No
 | No | Abadegation, 20 A | Dartes | Cardpatin () and ar heart
Betra space turns
Net
Cardpatin () and () and ()
Net
Cardpatin () and ()
Net () and ()
Cardpatin () and ()
Cardpatin ()
C | No
 | Image: An analysis of elements of the second seco | eventext database of values eventext database of values eventext database eventext as eventext database eventex | No | | Contputer
 | ANAL GORDEN CONTRACTOR CONTRACTON |
| Contension property Part of the second property Marcing contraction property Table of the second property Marcing contractin property

 | An and an analysis of the second seco | Teacher and a second and a seco | An observed by physics,
any description (and a second sec | Norman en un | Lang ADF Non Non Non- September 24, so and distance of the sector of the sect

 | No
No
No
No
No
No
No
No
No
No
No
No
No
N | 10
10
10
10
10
10
10
10
10
10 | No | No No No No No No No No No No Status bargestates (status)
metabolic

 | See distance with highly and a second | Ib
Ib
Ib
Ib
Ib
Ib
Ib
Ib
Ib
Ib | N N N N N N N N N N N N N N N N N N N | Angele de la conservation de la | Gala NG Canagadan
Cogamoniana
Norta - Tonda - Tonda
Na
Na
Na
Na
Na
Na
Na
Na
Na
N | Severe prositient candingtons
Severe prositient candingtons
Networks and a severe | en todag display ak
Balan ak
B | par balang analysis
and analysis of the
analysis of the
analys | Space compares Image: Space compares Im

 | Consigner of
No. No. No. No. No. No. No. No. | Ome capacity of a sequence of a seq

 | | blab type menter
No
No
No
No
No
No
No
No
No
No | Seart cardigate. Negative scale scal | No | Number all the second s | Durites | Cardpalan, Canada Kang
Baran apara ana ana ana ana ana ana ana ana ana
 | No
 | Image: constraint of the second sec | Herniteria data, al d'altar
data Harrison da trabati
Partire da | Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa
Pa | <pre>rtf regionacioned to the second to the</pre> | Contputer of a second s | aas contention and a co |
| Contensity protein Part of the second seco

 | Ing is readers produces produces of the second seco | Result of a share share the share sh | Autoritariative processor
Autoritariative processor
Records and an autoritaria
Records and au | Norman en | Name and Participants Name and Partity <t< td=""><td>No No No</td><td>No No No</td><td>No No No</td><td>N0 N0 N0 <</td><td>See definition of holes of the second of the</td><td>IN IN I</td><td>N N N N N N N N N N N N N N N N N N N</td><td>Angele de de la presenta de la companya de la de</td><td>Galanta Conspector
Cognorolater
Northerrow
Northerrow
Northerrow
Northerrow
Northerrow
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North</td><td>Exemple product contiguous for a set of the set of the</td><td>Approximation of the second seco</td><td>par halong understand
men understand under star
men under</td><td>Species computer Image: Species computer No Image: Species computer No Image: Species computer Species computer Image: Species computer No Image: Species computer</td><td>Company P
No
No
No
No
No
No
No
No</td><td>Ome company of a c</td><td>Interest of a second se</td><td>bba b par weys
N
N
N
N
N
N
N
N
N
N
N
N
N</td><td>Seare cardigate. Negative and an an an and an and an and an and an an an and an an and an an</td><td>No No No</td><td></td><td>Durines</td><td>Cardipatine, Canara Internet
Batter departed water
Name
Rest of a particular sector
Name
Cardinal Internet
Cardinal Internet
Cardinal Internet
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa</td><td>No No No No</td><td>Image: constraints of elements of the second seco</td><td>eventer danag d view
deventer danag d view
Provide development
Provide development
Provid</td><td>Ро
- Колина
- Колина
-</td><td></td><td>Constpate </td><td>ana carigan Ca</td></t<> | No | No No | No
 | N0 N0 N0 <

 | See definition of holes of the second of the | IN I | N N N N N N N N N N N N N N N N N N N | Angele de de la presenta de la companya de la de | Galanta Conspector
Cognorolater
Northerrow
Northerrow
Northerrow
Northerrow
Northerrow
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North
North | Exemple product contiguous for a set of the | Approximation of the second seco | par halong understand
men understand under star
men under | Species computer Image: Species computer No Image: Species computer No Image: Species computer Species
computer Image: Species computer No Image: Species computer
 | Company P
No
No
No
No
No
No
No
No | Ome company of a c

 | Interest of a second se | bba b par weys
N
N
N
N
N
N
N
N
N
N
N
N
N | Seare cardigate. Negative and an an an and an and an and an and an an an and an an and an | No |
 | Durines | Cardipatine, Canara Internet
Batter departed water
Name
Rest of a particular sector
Name
Cardinal Internet
Cardinal Internet
Cardinal Internet
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa
Sa | No No
 | Image: constraints of elements of the second seco | eventer danag d view
deventer danag d view
Provide development
Provide development
Provid | Ро
- Колина
- | | Constpate
 | ana carigan Ca |
| Community and and a second and

 | Ing in readers produces of the second | Result of a sharp a sharp has | Advancementary processes
Advancementary processes
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pro-
Pr | National and an and a second an | Name and Participants Name and Partitipants

 | No | No
 | No | N0

 | Any diffusion of highly and a set of a | In I | N N N N N N N N N N N N N N N N N N N | Na San San San San San San San San San Sa | Gala tel
Congestione
Cogestiones
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
Nationes
N | Severe parather tandiques
Severe parather tandiques
National and the severe severe
National a | erer belag ditude of
STEC ourspecter
The Construction of
Nachon in
Second of the Construction of
Automatic terration of the
Automatic terration of the | par heling underland
ever space destander of 1.5 m
Territorica (1.5 m)
Territorica (1.5 m) | Species computer Image: Species computer No Image: Species computer No Image: Species computer Species computer Image: Species computer No Image: Species computer Species computer Image: Species computer <

 | Company P
No
No
Company P
Address to the height summer
paragram parameters of the summer
parameters and the summer of th | Ome company of a c
 | Interest in terms of the second secon | blan type ment
 | Seare cardigate. Negation
No | No | Abadeq attrack, till of the second attracts of the second attra | Durites | Cardiplich, Can card in lawy
generalised, Card C, Card I,
Bard argunt was
not card in the second
network of th | No Normal No
 | Image: constraints of elements | eventent danka of visual eveettent danka of visual eveettent danka of visual eveettent | P0 N0 |
 | Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Controleter
Contr | ABAR CATEGORIAN
NO CATEGORIAN
NO CATEGORIAN
AND CATEGORIAN |

Table S3: HPO terms associated with FBXW7 Neurodevelopmental syndrome

Thickened nuchal skin fold HP:00 Jaundice HP:0000952 Breech presentation HP:0001623 Neonatal hypoglycemia HP:00016 Hyperechogenic kidneys HP:0004 Neonatal respiratory distress HP:0004	00474 98 719 002643	Global developmental delay HP:0001263 Intellectual disability, borderline HP:0006889 Anxiety HP:0000739 Poor suck HP:0002033 Motor delay HP:0001270 Specific learning disability HP:0001328 Lelayed speech and language development HP:0000750	Cardiac problems	Bicuspid aortic valve HP:0001647 Patent ductus arteriosus HP:0001643 Atrial septal defect HP:0001631 Ventricular septal defect HP:0011629 Interrupted aortic arch HP:0011611 Subvalvular aortic stenosis HP:0001682 Abnormal left ventricular function HP:0005162	Hematologic problem	Neutropenia HP:0001875 Thrombocytopenia HP:0001873 is Normocytic anemia HP:0001897 Iron deficiency anemia HP:0001891 Anemia HP:0001903 Low levels of vitamin D HP:0100512	Growth	Short stature HP:0004322 Tall stature HP:000098 Obesity HP:0001513 Macrocephaly HP:0000256 Microcephaly HP:0000252 Broad forehead HP:0000337	Hands/foot	Tapered finger HP:0001182 Single transverse palmar crease HP:0000954 Short foot HP:0001773 Pes planus HP:0001763 Overlapping toe HP:0001845 Clinodactlyly HP:0030084 Metatarsus adductus HP:0001840
Hypotonia HP:0001252 Seizure HP:0001250 Progressive spasticity HP:000219 Unsteady gait HP:0002317 Broad-based gait HP:0002136 Paroxysmal tonic upgaze HP:003 Early onset absence seizures HP: Neurological problems Achilles tendon contracture HP:00 Abnormality of coordination HP:00 Migraine HP:0002076 Photophobia HP:0001251 Dyskinesia HP:0100660	1980 0011152 01771 11443	 Speech articulation difficulties HP:0009088 Sleep disturbance HP:0002360 Impulsivity HP:0100710 Short attention span HP:0000736 Autistic behavior HP:0000729 Speech apraxia HP:011098 Developmental regression HP:0002376 Hair-puling HP:0012167 Depression HP:0000746 Astigmatism HP:0000483 Hypermetropia HP:0000540 Amblyopia HP:000646 	Respiratory problem	Secundum atrial septal defect HP:0001684 Persistent left superior vena cava HP:0005301 Patent forarmen ovale HP:0001655 Mesocardia HP:0011599 Obstructive sleep apnea HP:0002870 Snoring HP:0025267 Astima HP:0025267 Recurrent pneumonia HP:0006532 Recurrent sinusitis HP:0011108 Abnormality of the maxillary sinus HP:0430023 Recurrent upper respiratory tract infections HP:0002788 Bronchits HP:0012367	Endocrine problem	s Neonatal hypoglycemia HP:0001998 Hypothyroidism HP:0000821 Sprengel anomaly HP:0000912 Webbed neck HP:0000465 Joint Laxity HP:0001388 Short finger HP:0009381 Broad thumb HP:0011304 Increased muscle tatiguability HP:0003750 Pectus exavatum HP:0000767 Pectus carinatum HP:0000768 Hemihypertrophy HP:0001528 Scoliosis HP:0002650		Abnormal nasal bridge morphology HP:0000422 Periorbital fullness HP:0000629 Malar flattening HP:0000272 Deeply set eye HP:0000490 Thin vermilion border HP:0000233 Underdeveloped superior crus of antihelix HP:0011246 Preauricular pit HP:0004467 Epicanthus HP:0000286 Thick eyebrow HP:0000574 Synophys HP:0000664 Large earlobe HP:0009748 Downturned corners of mouth HP:0002714 Prominent forehead HP:0011220	Other	2-3 toe syndactyly HP:0004691 Prominent fingertip pads HP:0001212 Finger swelling HP:00025131 Short 5th finger HP:0009237 Interphalangeal joint contracture of finger HP:0001220 Prominent calcaneus HP:0012428 Abnormality of the 2nd toe HP:0010319 Supernumerary nipple HP:0002558 Narrow chest HP:0000774 Umbilical hernia HP:0001537
Stereotypy HP:0000733 Drooling HP:0002307 Atonic seizure HP:0010819 Enlarged cerebellum HP:001208 Arnold-Chiari type I malformation Thin corpus callosum HP:003372	PP:0007099	ogic Strabismus HP:000486 Nasolacrimal duct obstruction HP:0000579 Esophoria HP:0025312 Bilateral ptosis HP:0001488 Cerebral visual impairment HP:0100704 Myopia HP:0000545	Gastrointestinal problems/ feeding difficulties	Feeding difficulties HP:0011968 Nasogastric tube feeding in infancy HP:0011470 Chronic constipation HP:0012450 Polyphagia HP:0002591 Gastroesophageal reflux HP:000220 Velopharynegal insufficiency HP:0000220	Immunological	Hip dislocation HP:0002827 Hypertonia HP:0001276 Kyphosis HP:0002808 Calcaneovalgus deformity HP:0001848 Genu valgum HP:0002857 Decreased circulating antibody level HP:0004313		Hypertelorism HP:0000316 Telecanthus HP:0000506 Almond-shaped palpebral fissure HP:0007874 Low-set, posteriorly rotated ears HP:0000368 Prominent metopic ridge HP:0005487 Dolichocephaly HP:0000268 Fiat occiput HP:0005469		
Agenesis of corpus callosum HP: Abnormal corpus callosum norph Punctate periventricular 72 hyperi Aplasia/Hypoplasia of the cerebel Enlarged cisterna magna HP:000 Brain Imaging	001274 ology HP:0001273 ttense foci HP:0030081 um HP:0007360 2280 HP:0002363	Mixed hearing impairment HP:0000410 earing Conductive hearing impairment HP:0000405 Sensorineural hearing impairment HP:000407 Otitis media with effusion HP:0031353 Submucus cleft of soft and heart palate HP:0410031		Constipation HP:0002019 Failure to thrive HP:0001508 Diarrhea HP:0002014 Bilateral cryptorchidism HP:0008689 Multicystic kinoey dyscipacia HP:0000003	problems	Recurrent fever HP:0001954 Acne HP:0001061 Telangiectasia HP:0001009 Blue nevus HP:0100814 Hwnertrichosis HP:0000998	Facial features	Wide nasal bridge HP:0000431 Eversion of lateral third of lower eyelids HP:0007655 Thickened helices HP:000391 Microtia HP:0008551 Micrognathia HP:0000347 Smooth britium HP:0000319		
Brain atrophy HP:001244 Subcortical white matter calcificat Delayed myelination HP:0012448 Extra-avial cerebrospinal fluid acc Polymicrogyria HP:0002119 Ventriculomegaly HP:0002119 Dilation of Virchow-Robin spaces	ns 502200 pns HP:0007346 jmulation HP:0012510 HP:0012520	High palate HP:0000218 Widely spaced teeth HP:0000687 Cleft soft palate HP:0000185 Dental malocclusion HP:0000689 Midtace retrusion HP:0011800 Ankyloglossia HP:0012096 Poor suck HP:0002033 Imnaired oronbaronceal swallow response HP:0031162	Renal / genitourinar problems	Enlarged kidney HP:0000105 Nocturia HP:0000017 Unguial hernia HP:0000023 Urinary incontinence HP:0000020 Micropenis HP:0000054 Decreased testicular size HP:0008734 Ventral shortening of foreskin HP:0012435 Abnormal renal conticomedullaru differentiation HP:0005932	Skin problems	Melanocytic nevus HP:0000995 Poliosis HP:0002290 Hypopigmentation of the skin HP:0001010 Distributed along Blaschko lines HP:0025293 Cafe-au-lait spot HP:000957 Hyperpigmentation of the skin HP:0000953 Nevus flammeus HP:0001052 Canillary bemangingm BP:000506		Highly arched eyebrow HP:0002553 Myopathic facies HP:0002058 Hypotelorism HP:0000601 Prominent eyelashes HP:0011231 Long palpebral fissure HP:0000637 Downslanted palpebral fissures HP:0000494 Anteverted nares HP:0000463 Overdidet beix HP:0000396		
	Oral / dentition ENT proble	/ other Episodic upper airway obstruction HP-0012271 ms Short uvula HP:0010812 Anterior open-bite malocclusion HP:0009102 Carious teeth HP:0000670 Laryngeal cleft HP:0008751 Delayed eruption of teeth HP:0000684 Laryngomalacia HP:0001601 Narrow palate HP:0001601 Narrow palate HP:000189	L				-	Prominent inferior crus of antihelix HP:0011238 Narrow mouth HP:0000160 Short nose HP:0003196 Prominent masal tip HP:0005274 Tented upper lip vermilion HP:0010804 Deep philtrum HP:0002002 Scaphocephaly HP:0030799 Prominent occiput HP:0000269 Actemented oner HP:001090		
		Abromma ear morphology HP3031703 Bifd uvula HP:0000193 Nasal speech HP:0001611 Deviated nasal septum HP:0004411						Antevented ears Hri 2040/080 Depressed nasal bridge HP:0005280 Low anterior hairline HP:000294 Thick vermilion border HP:0012471 Incisor macrodontia HP:0011081	l	

	mCSM- Stability (ΔΔG) - previous structure	mCSM- Stability (ΔΔG)	Change in protein stability	Distance to interface (Å)	mCSM- PPI 1&2 (ΔΔG)	Change in PPI binding affinity	Δ Charge	Δ Volume	Δ Residue nature
p.(Thr416lle)	-0.134	-0.179	Decrease	15.1	-0.07	Decrease	0	50.6	Polar -> Hydrophobic
p.(Thr416Ala)		-0.788	Decrease	15.1	-0.134	Decrease	0	-27.5	Polar -> Hydrophobic
p.(His420Leu)		-0.823	Decrease	12.4	-0.469	Decrease	Partial	13.5	Partial charge -> Neutral
p.(Gly423Arg)	-1.031	-0.985	Decrease	7.8	-0.264	Decrease	1	113.3	Neutral -> Basic
p.(Arg441Gly)	-1.258	-1.367	Decrease	2.8	0.179	Increase	-1	-113.3	Basic -> Neutral
p.(Ser462Pro)		0.973	Increase	2.6	-2.449	Decrease	0	23.7	Polar -> Hydrophobic
p.(Arg465His)		-1.834	Decrease	5.1	0.286	Increase	Partial	-20.2	Basic -> Partial charge
p.(Arg479Gln)	-0.625	-1.346	Decrease	3.1	0.054	Increase	-1	-29.6	Basic -> Unchanged
p.(Asp480Gly)	0.327	1.401	Increase	4.5	-1.998	Decrease	1	-51	Acidic -> Neutral
p.(Arg505His)	-2.019	-2.032	Decrease	5.4	-0.038	Neutral	Partial	-20.2	Basic -> Partial charge
p.(Val544Gly)	-3.203	-3.16	Decrease	9.1	-1.114	Decrease	0	-79.9	Hydrophobic -> Hydrophobic
p.(His580Tyr)	-0.414	-0.422	Decrease	9.1	0.311	Increase	Partial	40.4	Partial charge -> Aromatic
p.(Ser582Ala)		0.033	Increase	3.54	-0.422	Decrease	0	-0.4	Polar -> Hydrophobic
p.(Ala599Val)	-0.451	-0.093	Neutral	4	0.265	Increase	0	51.4	Hydrophobic -> Hydrophobic
p.(Ala626Val)		-0.106	Decrease	4.4	0.291	Increase	0	51.4	Hydrophobic -> Hydrophobic
p.(Ser640Arg)	-0.639	-0.586	Decrease	11.1	-0.355	Decrease	1	84.4	Polar -> Basic
p.(Ile608Val)		-2.019	Decrease	22.3	-0.244	Decrease	0	-33.4	Hydrophobic -> Hydrophobic
p.(Arg674Pro)	-0.648	-0.614	Decrease	8.1	-0.321	Decrease	-1	-60.7	Basic -> Neutral
p.(Arg674Trp)	-0.283	-0.157	Decrease	8.1	0.013	Neutral	-1	54.4	Basic -> Aromatic
p.(Arg689GIn)	-0.079	-0.353	Decrease	3.4	-0.54	Decrease	-1	-29.6	Basic -> Neutral
p.(Arg689Trp)		-0.357	Decrease	3.4	-0.437	Decrease	-1	54.4	Basic -> Aromatic

Table S4: Impact of neurodevelopmental syndrome variants on protein stability and interaction with CYCLIN E1.

mutation Cutoff Scanning Matrix (mCSM); Protein-protein interactions (PPI)

Tabl	e S5	: Com	parison o	f the in	npact of	neurodeve	elopmental	svnd	rome val	riants and	anomA	D variants on	protein sta	bilitv an	d substr	ate b	indina

Variant	Amino acid reference	Amino acid position	amino acid change	mCSM- Stability (ΔΔG)	Distance to interface (Å)	mCSM-PPI 1&2 (ΔΔG)	Allele Count	Class	Chromosome	Position	rsID	Reference	Alternate	Source	Protein Consequence	Transcript Consequence
T416A	Т	416	A	-0.788	15.1	-0.134	1	clin	4	153247315	-	G	A	This study	p.(Thr416lle)	c.1247C>T
T416I	T	416		-0.179	15.1	-0.07	1	clin	4	153249532	-	T T	C	This study	p.(Thr416Ala)	c.1246A>G
G423B	G	420	B	-0.823	7.8	-0.469	2	clin	4	153249519	-	C	T	This study	p.(His420Leu)	c.1259 A>1
R441G	R	441	G	-1.367	2.8	0.179	1	clin	4	153249457	-	Ğ	Ċ	This study	p.(Arg441Gly)	c.1321C>G
S462P	S	462	Р	0.973	2.6	-2.449	1	clin	4	153249394	-	A	G	This study	p.(Ser462Pro)	c.1384T>C
R465H	R	465*	Н	-1.834	5.1	0.286	1	clin	4	153249384	-	C	T	This study	p.(Arg465His)	c.1394G>A
D480G	D	480	G	1.401	4.5	-1.998	1	clin	4	153247363	-	T	C	This study	p.(Asp480Gly)	c.1439A>G
R505H	R	505	Н	-2.032	5.4	-0.038	1	clin	4	153247288	-	С	Т	This study	p.(Arg505His)	c.1514G>A
V544G	V	544	G	-3.16	9.1	-1.114	1	clin	4	153247171	-	A	С	This study	p.(Val544Gly)	c.1631T>G
H580Y	H	580	Y	-0.422	9.1	0.311	1	clin	4	153245453	-	G	A	This study	p.(His580Tyr)	c.1/38C>1
1608V	A	608	V	-2.019	22.3	-0.244	1	clin	4	153245369	-	T	C	This study	p.(Ile608Val)	c.1822A>G
S640R	S	640	R	-0.586	11.1	-0.355	1	clin	4	153244237	-	G	T	This study	p.(Ser640Arg)	c.1920C>A
R674P	R	674	Р	-0.614	8.1	-0.321	1	clin	4	153244136	-	С	G	This study	p.(Arg674Pro)	c.2021G>C
R674W	R	674	W	-0.157	8.1	0.013	1	clin	4	153244137	-	G	A	This study	p.(Arg674Trp)	c.2020C>T
R689W	R	689	Ŵ	-0.357	3.4	-0.437	2	clin	4	153244091	-	G	A	This study	p.(Arg689Trp)	c.2065C>T
V265I	V	265	I	-1.029	57.368	0.119	1	gnomad	4	153259022	rs1393933844	С	Т	gnomAD Genomes	p.Val265lle	c.793G>A
H267R	Н	267	R	-0.581	61.633	-0.111	1	gnomad	4	153259015	rs1172754641	Т	C	gnomAD Exomes	p.His267Arg	c.800A>G
V271M	V	2/1	M	-0.254	64.686	-0.311	1	gnomad	4	153259004	rs/640/4483	C T		gnomAD Exomes	p.Val2/1Met	c.811G>A
L288F	L	288	F	-0.908	59.843	0.132	6	gnomad	4	153253869	-	C	A	gnomAD Exomes	p.Leu288Phe	c.864G>T
A289S	А	289	S	-1.765	57.647	0.121	6	gnomad	4	153253868	rs1444335835	С	A	gnomAD Exomes	p.Ala289Ser	c.865G>T
Y291C	Y	291	С	-0.467	55.112	-0.254	2	gnomad	4	153253861	rs948405432	T	C	gnomAD Exomes	p.Tyr291Cys	c.872A>G
1291N K299F	r K	291 299	N F	-0.601	55.112 40.936	-0.017	<u> </u>	gnomad	4 4	153253852	rs750051282	A T	I C	gnomAD Exomes	p. i yr∠91Asn p.I vs299Glu	c.895A>G
L302I	L	302		-0.922	44.101	-0.084	1	gnomad	4	153253829	rs150506693	G	T	gnomAD Exomes	p.Leu302lle	c.904C>A
T307I	Т	307		-0.413	54.949	-0.006	1	gnomad	4	153253813	rs764174613	G	A	gnomAD Exomes	p.Thr307lle	c.920C>T
R309H	R	309	H	-0.992	59.667	0.003	1	gnomad	4	153253807	rs760675122	C	T T	gnomAD Conces	p.Arg309His	c.926G>A
K326R	K	326	R	-0.333	39.317	0.12	1	gnomad	4 4	153253756	rs773325030	T	C	gnomAD Genomes	p.Leu3 19lle p.Lvs326Ara	c.95505A
K326T	K	326	Т	-0.52	39.317	-0.056	1	gnomad	4	153253756	rs773325030	<u> </u>	G	gnomAD Exomes	p.Lys326Thr	c.977A>C
E327D	E	327	D	-0.513	37.333	0.1	1	gnomad	4	153253752	rs148769501	Т	G	gnomAD Exomes	p.Glu327Asp	c.981A>C
G329E 1330V	G -	329	E V	-1.067	34.737	0.145	1	gnomad	4	153252020	rs767438108	с т	I C	gnomAD Genomes	p.Gly329Glu p.lle330Val	C.986G>A
1336M	i	336	Ň	-0.569	45.102	0.19	1	gnomad	4	153251998	rs1046708929	G	C	gnomAD Exomes	p.lle336Met	c.1008C>G
K337Q	K	337	Q	-0.295	47.538	0.194	1	gnomad	4	153251997	rs750480880	Т	G	gnomAD Exomes	p.Lys337Gln	c.1009A>C
R338K	R	338	K	-0.216	50.737	0.251	3	gnomad	4	153251993	rs1185005670	C	T C	gnomAD Exomes	p.Arg338Lys	c.1013G>A
1342T	1	342	T	-0.67	57.24	-0.602	2	gnomad	4	153251984	rs765495879	A	G	gnomAD Exomes	p.lle342Thr	c.10221>C
I342V	I	342	V	-0.424	57.24	0.344	1	gnomad	4	153251982	rs1247097813	Т	C	gnomAD Exomes	p.lle342Val	c.1024A>G
1347V	1	347	V	-0.956	53.902	-0.016	1	gnomad	4	153251967	rs762013076	T	С	gnomAD Exomes	p.lle347Val	c.1039A>G
H359H T363N	Т	359	R N	-0.889	35.47	-0.035	1	gnomad	4	153251930	rs1381320045	I G	с т	gnomAD Genomes	p.HIS359Arg	c.10/6A>G
N364S	N	364	S	-1.14	29.412	-0.243	2	gnomad	4	153251915	rs775885576	T	Ċ	gnomAD Exomes	p.Asn364Ser	c.1091A>G
R367Q	R	367	Q	-0.102	29.26	-0.019	7	gnomad	4	153251906	rs745418631	C	T	gnomAD Exomes,gnomAD Genomes	p.Arg367Gln	c.1100G>A
K371R P373B	K P	371	R	-0.371	27.686	0.115	1	gnomad	4	153251894	rs748952220	I G	C	gnomAD Exomes	p.Lys3/1Arg	c.1112A>G
K374E	ĸ	374	E	0.473	21.263	-0.168	1	gnomad	4	153251886	rs937391131	T	C	gnomAD Exomes	p.Lys374Glu	c.1120A>G
L387V	L	387	V	-1.645	13.766	0.063	1	gnomad	4	153250901	rs1338105130	A	С	gnomAD Exomes	p.Leu387Val	c.1159T>G
S407L	S	407	L	-0.153	23.243	-0.1	1	gnomad	4	153250840	-	G	A	gnomAD Genomes	p.Ser407Leu	c.1220C>T
V418L	v	418	M	-0.517	15.903	-0.098	2	anomad	4	153249526	rs755422880	c	T	anomAD Exomes	p.Val418Met	c.1252G>A
N432I	Ν	432	I	0.078	26.504	-0.075	2	gnomad	4	153249483	rs772668762	Т	A	gnomAD Exomes	p.Asn432lle	c.1295A>T
1433F		433	F	-1.662	23.411	0.361	3	gnomad	4	153249481	rs761173677	T	A	gnomAD Exomes	p.lle433Phe	c.1297A>T
1435V		435	v	-1.87	16.772	-0.377	1	gnomad	4	153249475	rs1190126709	T	c	gnomAD Exomes	p.lle435Val	c.1303A>G
V445L	V	445	L	-0.729	18.426	-0.093	1	gnomad	4	153249445	rs776371212	С	A	gnomAD Exomes	p.Val445Leu	c.1333G>T
T456N	Ť	456	N	-0.895	14.647	-0.131	1	gnomad	4	153249411	rs775244232	G	Ť	gnomAD Exomes	p.Thr456Asn	c.1367C>A
G459V	G	459	V	-0.347	9.584	-0.311	1	gnomad	4	153249407	rs772056210	C	A	gnomAD Exomes	p.Ceu457Phe p.Gly459Val	c.1376G>T
R465C	R	465*	С	-1.48	5.148	0.035	1	gnomad	4	153249385	rs867384286	G	А	gnomAD Exomes	p.Arg465Cys	c.1393C>T
E471G	E	471	G	-0.856	25.356	-0.243	12	gnomad	4	153249366	rs756238684	Т	C	gnomAD Exomes	p.Glu471Gly	c.1412A>G
V485I	ri V	479	- G - I	-0.014	17.029	-0.053	2	gnomad	4 4	153247367	rs1325363774	G C	T	gnomAD Exomes	p.Val485lle	c.1453G>A
1488T		488	Ť	-2.861	20.45	-0.025	1	gnomad	4	153247339	rs1222797439	Ă	G	gnomAD Exomes	p.lle488Thr	c.1463T>C
H495R	Н	495	R	-1.47	17.376	0.073	3	gnomad	4	153247318	rs750717620	T	C	gnomAD Exomes	p.His495Arg	c.1484A>G
Y509C	Y	509	C I	-2.06	19.683	-0.627	2	gnomad	4	15324/276	rs1334352027	I C	C T	gnomAD Exomes	p. Lyr509Cys	c.1526A>G
T532I	Ť	532		-0.371	20.341	-0.005	1	gnomad	4	153247207	rs1179476070	G	A	gnomAD Exomes	p.Thr532lle	c.1595C>T
T541S	Т	541	S	-0.708	6.634	0.083	1	gnomad	4	153247181	rs1184403966	Т	А	gnomAD Exomes	p.Thr541Ser	c.1621A>T
N542S	N	542	S	-1.271	3.775	-0.02	1	gnomad	4	153247177	rs1462861861	T	C	gnomAD Exomes	p.Asn542Ser	c.1625A>G
T576M	T	576	M	0.072	16.356	-0.448	2	gnomad	4	153245501	rs1429385222	G	A	anomAD Exomes	p.Arg564Cys p.Thr576Met	c.1727C>T
M587I	М	587	I	-0.303	12.55	-0.345	1	gnomad	4	153245430	rs1269436440	C	Т	gnomAD Exomes	p.Met587lle	c.1761G>A
E588D	E	588	D	-1.234	15.447	0.029	2	gnomad	4	153245427	rs751435265	T	A	gnomAD Exomes	p.Glu588Asp	c.1764A>T
K590E	ĸ	590	B	-0.309	22.181	-0.234	1	gnomad	4	153245423	- rs1290448722	T	C	gnomAD Exomes	p.Lys590Giu	c.1768A>G
A599G	A	599*	G	-0.412	3.998	-0.372	1	gnomad	4	153245395	rs766088325	G	C	gnomAD Exomes	p.Ala599Gly	c.1796C>G
P620S	Р	620	S	-0.557	16.899	-0.062	1	gnomad	4	153244299	rs1375643251	G	A	gnomAD Exomes	p.Pro620Ser	c.1858C>T
N633S	N	633	S	-0.757	23.914	-0.073	3	gnomad	4	153244259	rs758163453	T	C	gnomAD Exomes	p.Asn633Ser	c.1898A>G
K652O	r. K	652	н О	0.026	21.347	-0.05	1	gnomad	4 4	153244256	rs1182453513	T	G	gnomAD Genomes	p.∟ys634Arg p.Lvs652Gln	c.1901A>G c.1954A>C
T653K	T	653	ĸ	-0.363	24.831	-0.116	1	gnomad	4	153244199	rs775781675	G	Ť	gnomAD Exomes	p.Thr653Lys	c.1958C>A
T653M	T	653	М	0.115	24.831	0.066	1	gnomad	4	153244199	rs775781675	G	A	gnomAD Genomes	p.Thr653Met	c.1958C>T
F656Y	F R	656 658	Y O	-0.584 -0 906	18.778	-0.201	1	gnomad	4	153244190	rs11/6237755 rs759610240	A C	I T	gnomAD Exomes	p.Phe656Tyr	c.196/1>A
T662A	T	662	A	-0.612	17.859	-0.022	1	gnomad	4	153244173	rs974902950	Т	Ċ	gnomAD Exomes	p.Thr662Ala	c.1984A>G
S665I	S	665		-0.629	11.47	-0.132	1	gnomad	4	153244163	rs957874517	С	A	gnomAD Exomes	p.Ser665lle	c.1994G>T
1675V	1	675	V T	-2.065	14.286	0.097	1	gnomad	4	153244134	rs1446303596	Т	C T	gnomAD Exomes	p.lle675Val	c.2023A>G
N679D	N	679	D	0.186	20.339	0.000	1	gnomad	4 4	153244128	rs746489993	T	C	gnomAD Exomes	p.Alao77111 p.Asn679Asn	c.2029G>A
V686I	V	686	I	-0.703	11.334	-0.086	1	gnomad	4	153244101	rs1307998016	C	Ť	gnomAD Genomes	p.Val686lle	c.2056G>A
N690S	N	690	S	-0.255	4.292	-0.391	1	gnomad	4	153244088	rs1237327125	Т	C	gnomAD Genomes	p.Asn690Ser	c.2069A>G
WI/06T	M	/06		-0.185	41.053	-0.248	1	griomad	4	153244040	rs/04051432	A	G	gromAD Exomes	p.iviet/061hr	c.211/1>C

*residue affected in both clincal cohort and gnomAD. Mutation Cutoff Scanning Matrix (mCSM); Protein-protein interactions (PPI).