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SUPPLEMENTARY INFORMATION

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A framework for the investigation of rare genetic disorders in neuropsychiatry

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Supplementary Information for

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Materials and Methods

Estimating the effect size of copy number variants (CNVs)

Large samples of cases and controls provide an opportunity to estimate the effect size on specific neuropsychiatric symptoms of some of the more common rare genetic disorders. We extending the approach described previously[1], to estimate the frequency of these variants in defined cohorts systematically assessed for neurodevelopmental delay[2,3], autism spectrum disorder[4,5], and schizophrenia[2,6,7] and in general population controls from UK Biobank[8]. These estimates of frequency in cases and controls were compared to estimate odds ratios for each neuropsychiatric diagnosis at each CNV locus. These numbers are shown in Table S2 and plotted as a polar plot in Fig. 2 of the main text. For highly penetrant CNVs we lack sufficient population controls to accurately define the odds ratio, therefore we limited the plot to a maximum odds ratio of ≥30.

Estimating the effect size of single gene rare genetic disorders (RGDs)

On average, the population frequency of a specific single gene RGD is lower than the population frequency of the most well-defined CNV loci, due to the higher mutation rate of non-allelic homologous recombination (NAHR). Accordingly, larger populations of control samples will be needed to accurately define the effect size by an odds ratio. Furthermore, the completeness of reporting for specific neuropsychiatric domains varies (Fig. 2). As an estimate of the relative impact of each single gene RGD on different neuropsychiatric symptoms, we used the data systematically collected from the literature in the Developmental Brain Disorder Genes Database hosted at Geisinger (https://dbd.geisingeradmi.org) to quantify the relative frequency of different symptoms. The raw data are shown in Table S4 and plotted as a polar plot in Extended Data Fig. 1.

Estimating the number of *de novo* PTVs for genome-wide significance for a given population size.

The rate at which germline *de novo* mutations arise in each gene is highly correlated with gene size (cDNA) and sequence context, especially GC content[9,10]. We used previously published estimates of per gene mutation rates for protein-truncating variants (PTVs) in 18,224 protein-coding genes based on exome sequencing of over 60,000 general population samples in ExAC[10–12]. To estimate the expected number of *de novo* PTVs in controls, we assessed the total number of *de novo* PTVs identified in 1,807 unaffected siblings from the Simons Simplex Collection, identifying 187 such mutations (187 / 1807 = 0.103). The PTV mutations rates and estimate of *de novo* PTV rate in controls were combined to estimate the expected number of *de novo* PTVs per individual per gene. Multiplying these values by a given population size provided the expected number of *de novo* PTVs per gene in a cohort; this was used as the Lambda value (λ) for a Poisson distribution. The probability of observing a specific number of *de novo* PTVs in the population was assessed using the cumulative density function (CDF) for a Poisson distribution with the estimated λ value. To reach genome-wide significance, this probability had to be lower than 2.7×10^{-6} based on a Bonferroni correction for all genes assessed (p=0.05/18,224). We also considered searching only the 1,528 genes with high "probability loss-of-function intolerance" scores (pLI ≥ 0.995), giving a p-value threshold for high-pLI significance of 3.3×10^{-5} with Bonferroni correction (p=0.05/1,528), however we would advocate for using the genome-wide significant threshold or a more conservative threshold.

Using this approach, we searched across a range of observed *de novo* PTVs (3, 5, 10, 20) and eight p-value thresholds (3.3×10^{-5} to 2.7×10^{-12}) to find the cohort size at which such at observation would result in a probability lower than the p-value threshold. To limit the compute required, we down-sampled to one in 15 genes. The results are shown in Extended Data Fig. 2.

In the main text (Fig. 3), we show a simplified version of this approach using a single p-value threshold (2.7×10^{-6}) and three cohort size (50,000, 100,000, and 200,000) to represent the effective cohort size of existing clinical exome sequencing (i.e. the total number of cases who could be reported in the literature). We note that these are estimates of the true number of individuals sequencing for a neuropsychiatric phenotype, and that the exact number is unknown, however current research cohorts include over 27,000 ASD cases between the Autism

Sequencing Consortium[12] and SPARK (https://sparkforautism.org), over 14,000 cases of severe developmental delay[13] (https://decipher.sanger.ac.uk/ddd), and over 5,000 cases of schizophrenia[14]. This sets a lower bar for the true number of cases sequenced at 46,000; adding smaller research cohorts and clinical exome sequencing leads to an estimate of 100,000 effective cases with neuropsychiatric symptoms and exome sequencing that could contribute to case reports. We also note that GeneDx describes an exome- and genome-sequencing database of over 155,000 samples (https://www.genedx.com), though many of these are likely to be controls or parents.

Table S3. Attendee list of the "Rare Genetic Disease Workshop: Window into Genomic Risk and Resilience of Mental Disorders" held at the NIMH Sept. 2017.

ATTENDEE LIST

Attendee Name	Title	Affiliation
Anjené Addington	Branch Chief, Genomics Research Branch	National Institute of Mental Health
Alan Anticevic	Assistant Professor, Psychiatry and of Psychology; Director, Anticevic Lab, Clinical Neuroscience Research Unit	Yale University
Alexander Arguello	Program Officer, Genomics Research Branch	National Institute of Mental Health
Christopher Austin	Director, Office of the Director	National Center for Advancing Translational Sciences
Shelli Avenevoli	Deputy Director, Office of the Director	National Institute of Mental Health
Paul Avillach	Assistant Professor, Pediatrics & Biomedical Informatics	Harvard University
Carrie Bearden	Professor, Department of Psychiatry & Biobehavioral Sciences; Department of Psychology	University of California, Los Angeles
Bettina Buhring	Chief, Learning and Memory Program, Division of Neuroscience and Basic Behavioral Science	National Institute of Mental Health
Andrea Beckel-Mitchener	Acting Director, Office of Research Disparities and Global Mental Health	National Institute of Mental Health
Sarah Bergen	Senior Researcher, Department of Medical Epidemiology and Biostatistics	Karolinska Institutet
Raphael Bernier	Associate Professor, Department of Psychiatry & Behavioral Sciences; Clinical Director, Seattle Children's Autism Center; Associate Director, Center on Human Development and Disability	University of Washington
Julia Berzhanskaya	Scientific Review Officer, Scientific Review Branch	National Institute on Drug Abuse
Diana Bianchi	Director, Office of the Director	National Institute of Child Health and Human Development
Lora Bingaman	Program Analyst, Office of Genomics Research Coordination	National Institute of Mental Health
Linda Brady	Director, Division of Neuroscience and Basic Behavioral Science	National Institute of Mental Health
Kristin Cadenhead	Psychiatrist; Professor of Psychiatry	University of California, San Diego
Wendy Chung	Kennedy Family Professor of Pediatrics and Medicine	Columbia University

Attendee Name	Title	Affiliation
John Constantino	Professor of Psychiatry and Pediatrics; Director, William Greenleaf Eliot Division of Child & Adolescent Psychiatry; Co-Director, Intellectual and Developmental Disabilities Research Center	Washington University in St. Louis
Ricardo Dolmetsch	Global Head, Neuroscience	Novartis Institutes for Biomedical Research
Tara Dutka	Program Officer, Office of Genomics Research Coordination	National Institute of Mental Health
Tuba Fehr	AAAS Science and Technology Policy Fellow	National Institute of Child Health and Human Development
Guoping Feng	Investigator, Department of Brain and Cognitive Sciences; McGovern Institute for Brain Research	Massachusetts Institute of Technology
Daniel Geschwind	Director, Center for Autism Research and Treatment (CART); Gordon and Virginia MacDonald Distinguished Chair, Human Genetics; Professor, Neurology; Professor, Psychiatry and Biobehavioral Sciences; Co-Director, Center for Neurobehavioral Genetics; Professor In-Residence, Tennenbaum Center for the Biology of Creativity; Professor In-Residence, Human Genetics	University of California, Los Angeles
David Glahn	Professor of Psychiatry and Psychology, Department of Psychiatry, Olin Neuropsychiatry Research Center; Co-Director, Neurocognition, Neurocomputation and Neurogenetics (n3) Division	Yale University
David Goldstein	Director of the Institute for Genomic Medicine, Professor of Genetics and Development	Columbia University
Rashmi Gopal-Srivastava	Director, Extramural Research Program, Office of Rare Diseases Research	National Center for Advancing Translational Sciences
Joshua Gordon	Director, Office of the Director	National Institute of Mental Health
Raquel Gur	Professor of Psychiatry Neurology and Radiology; Neuropsychiatry Section; Schizophrenia Research Center; Department of Psychiatry	University of Pennsylvania
Stephen Hooper	Adjunct Professor, Psychiatry and Behavioral Sciences	University of North Carolina – Chapel Hill

Attendee Name	Title	Affiliation
Sébastien Jacquemont	Associate Professor, Department of Pediatrics, Faculty of Medicine; Medical Geneticist, CHU Sainte Justine; Scientific Director, CARTaGENE, 2015	University of Montréal
Alice Kau	Program Director, Research on Autism Spectrum Disorders, Intellectual and Developmental Disabilities Branch	National Institute of Child Health and Human Development
Tracy King	Medical Officer, Intellectual and Developmental Disabilities Branch	National Institute of Child Health and Human Development
Susan Koester	Deputy Director, Division of Neuroscience and Basic Behavioral Science	National Institute of Mental Health
Danuta Krotoski	Program Officer, Intellectual and Developmental Disabilities Branch	National Institute of Child Health and Human Development
David Ledbetter	Executive Vice President and Chief Scientific Officer	Geisinger Health System
Thomas Lehner	Director, Office of Genomics Research Coordination	National Institute of Mental Health
Holly Lisanby	Director, Division of Translational Science	National Institute of Mental Health
Christa Martin	Director and Professor, Autism and Developmental Medicine Institute	Geisinger Health System
Doug Meinecke	Program Officer, Division of Translational Science	National Institute of Mental Health
Jennifer Mulle	Assistant Professor, Department of Epidemiology	Emory University
Stanley Nelson	Professor In-Residence, Human Genetics; Director, DNA Microarray Technology; Co-Director, Center for Duchenne Muscular Dystrophy	University of California, Los Angeles
David Panchision	Program Chief, Developmental Neurobiology Program, Division of Neuroscience and Basic Behavioral Science	National Institute of Mental Health
Enrique Michelotti	Program Director, Molecular Biology, Division of Neuroscience and Basic Behavioral Science	National Institute of Mental Health
Anne Pariser	Deputy Director, Office of Rare Diseases Research	National Center for Advancing Translational Sciences
Sergiu Pasca	Assistant Professor, Psychiatry and Behavioral Sciences, Stanford Center for Sleep Sciences and Medicine	Stanford University

Attendee Name	Title	Affiliation
Alan Percy	Professor and Director, Neurology, Rett Syndrome Clinic	University of Alabama at Birmingham
Kevin Pelphrey	Carbonell Family Professor; Director of Autism and Neurodevelopmental Disorders Institute	The George Washington University
Erin Ramos	Program Director, Division of Genomic Medicine	National Human Genome Research Institute
Armin Raznahan	Chief, Developmental Neurogenomics Unit, Human Genetics Branch, Intramural Research Program	National Institute of Mental Health
Judith Rumsey	Chief, Brain Imaging Clinical Research Program	National Institute of Mental Health
Mustafa Sahin	Professor, Department of Neurology, Harvard Medical School; Director, Translational Neuroscience Center	Boston Children's Hospital
Rodney Samaco	Assistant Professor, Department of Molecular and Human Genetics; Associate Director, BCM Intellectual and Developmental Disabilities Research Center (IDDRC); Director, BCM IDDRC & TCH Rodent Neurobehavioral Cores	Baylor College of Medicine
Stephan Sanders	Assistant Professor, Department of Psychiatry; Institute of Human Genetics; Director, Psychiatry Bioinformatics Core	University of California, San Francisco
Christian Schaaf	Assistant Professor, Molecular and Human Genetics	Baylor College of Medicine
Jonathan Sebat	Chief, Beyster Center for Molecular Genomics of Neuropsychiatric Diseases; Professor of Psychiatry and Cellular and Molecular Medicine	University of California, San Diego
Geetha Senthil	Program Director, Office of Genomics Research Coordination	National Institute of Mental Health
Vandana Shashi	Professor of Pediatrics, Department of Pediatrics	Duke University
David Sommers	Scientific Review Officer, Extramural Review Branch	National Institute of Mental Health
Randall Stewart	Program Director, Channels, Synapses, and Circuits, Division of Neuroscience	National Institute of Neurological Disorders and Stroke

Attendee Name	Title	Affiliation
Edmund Talley	Program Director, Channels, Synapses, and Circuits, Division of Neuroscience	National Institute of Neurological Disorders and Stroke
Audrey Thurm	Clinical Psychologist, Pediatrics and Developmental Neuroscience Branch	National Institute of Mental Health
Lu Wang	Program Director, NHGRI Genome Sequencing Program	National Human Genome Research Institute
Lois Winsky	Chief, Molecular, Cellular, and Genomic Neuroscience Research Branch	National Institute of Mental Health
Anastasia Wise	Epidemiologist, Division of Genomic Medicine	National Human Genome Research Institute
Susan Wright	Program Officer, Office of Genomics Research Coordination	National Institute of Mental Health

Table S5. Stakeholders in rare genetic disorders.

Stakeholder	Possible Roles	Examples
Patients and caregivers	• Work with advocacy groups to connect to multiple researchers • Advocate that health systems participate in research	• Most advocacy groups for RGDs are created and run primarily by parents and caregivers, e.g. Phelan-McDermid Syndrome Foundation (https://www.pmsf.org)
Advocacy groups	• Work with funders to design maximally effective initiatives • Work with multiple research groups to facilitate communication	• For a listing of groups, see: https://rarediseases.org/for-patients-and-families/connect-others/find-patient-organization/

Clinical Research groups	• Advance theoretically driven-efforts to collect and share systematically obtained data from a variety of genetics-first approach studies to:
	  • Merge and integrate available databases
	  • Define best data formats for prospective studies
	  • Mobilize existing data for cross-disorder analyses
		• Mind and Genes http://www.minds-genes.org
		• Imagine https://imagine-id.org
		• International 22q11.2 Brain Behavior Consortium http://www.22q11-ibbc.org/
		• The Investigation of Genetic Exome Research (TIGER) Study https://depts.washington.edu/rablab/research-studies-2/research-studies/tiger/
		• ECHO Study CNV Research https://www.cardiff.ac.uk/mrc-centre-neuropsychiatric-genetics-genomics/research/themes/developmental-disorders/echo-study-cnv-research
		• FIND (Further Information on Neurogenic Disorders) http://www.findresources.co.uk/professionals

Healthcare systems	• Organize efforts around rare disorders to collect systematic data on phenotypes • Implement consistent genotyping in patients • Implement broad neuropsychiatric measures to facilitate retrospective data harmonization	• Deciphering Developmental disorders (DDD) https://decipher.sanger.ac.uk/ddd#overview • Institute for Molecular Medicine Finland (FIMM) https://www.fimm.fi • Vanderbilt Genetics Institute https://www.vumc.org/vgi/ • Geisinger Genomic Medicine Institute https://www.geisinger.edu/research/departments-and-centers/gmi
Collaborations across health systems	• Partner with other health care systems to expand the reach of their initiatives • Work with other researchers to consolidate data and harmonize existing data • Implement broad neuropsychiatric measures to facilitate retrospective harmonization	• EU-Aims https://www.eu-aims.eu • SPARK https://sparkforautism.org • Genome to Brain (G2B) https://geisingeradmi.org/care-innovation/studies/the-genome-to-brain-network-g2b/

Funding agencies	• Emphasize and support the need for implementation of core phenotypic measures that span diagnostic categories
	• Emphasize need for use of broad neuropsychiatric measures to facilitate retrospective harmonization
	• Emphasize early collaboration and coordination across groups working in this space
		• NCATS funded Rare Disease Clinical Research Networks (RDCRN) trans-diagnostic, 'genetic first' projects, Consortia and organizations, e.g.:
		  • Full list: https://ncats.nih.gov/rdcrn/consortia
		  • Rett Syndrome Natural History (*MECP2* and related genes) https://ncats.nih.gov/rdcrn/consortia#rett
		  • Developmental Synaptopathies (*TSC*, *PTEN*, *SHANK3*) https://ncats.nih.gov/rdcrn/consortia#developmental
		• Simons VIP Connect https://simonsvipconnect.org/

Pharmaceutical Companies	• Facilitate the pre-clinical focused consortia or consortia with pre-clinical elements in partnership with other groups	• Novartis (e.g. *TSC*) https://www.novartis.co.uk/rare-diseases
Trans-diagnostic, 'genetic first' projects, networks consortia, and organizations	• Foster complementary approaches for building resources and establishing cohorts (e.g. mining Electronic Medical Records, focused clinical recruitment, patient advocacy groups) • Increase infrastructure for coordination and collaboration • Expand use of consistent broad and deep phenotyping across projects to facilitate harmonization efforts • Coordinate investments to be synergistic – invest in operations with quality control to leverage existing resources	• National Organization for Rare Disorders https://rarediseases.org/ • Global Genes RARE Foundation Alliance https://globalgenes.org/foundation-alliance-2list/ • AGENDA – Alliance for Genetic Etiologies in Neurodevelopmental Disorders and Autism https://www.gdaac.org/ • The Society for the Study of Behavioral Phenotypes http://www.ssbp.org.uk/index.html • Rare Disease Foundation https://www.rarediseasefoundation.org/ • UK Biobank http://www.ukbiobank.ac.uk • Matchmaker Exchange https://www.matchmakerexchange.org/ • International Rare Diseases Research Consortium (IRDiRC)
Trans-diagnostic Phenotypic Ontology projects, networks, consortia and organizations	• Create and standardize ontologies for use in phenotypic studies • Integrate, standardize and analyze heterogenous data from healthcare and research, via open-source, open-data community	• Phenotips (https://phenotips.org/) • PhenX toolkit (https://www.phenxtoolkit.org/about) • i2b2 tranSMART Foundation (https://transmartfoundation.org)

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