Supplemental online file

Zufferey et al,

A 600 kb deletion syndrome at 16p11.2 leads to energy imbalance and neuropsychiatric disorders

16p11.2 European Consortium members:

First name, middle initials	Name	Institution
Sébastien	Jacquemont	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois / University of Lausanne
Marie Claude	Addor	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Joris	Andrieux	Institut de Génétique Médicale, Hopital Jeanne de Flandre
Benoit	Arveiler	Univ. Bordeaux, Maladies Rares : Génétique et Métabolisme (MRGM), EA4576, Bordeaux / Service de Génétique Médicale, CHU de Bordeaux, Bordeaux
Mandy	Barker	Service of Child Psychiatry, SUPEA, Centre Hospitalier Universitaire Vaudois, Lausanne
Noam D.	Beckmann	Service de Génétique, Centre Hospitalier Universitaire Vaudois.
Marco	Belfiore	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Frédérique	Bena	Service of Genetic Medicine, University Hospitals of Geneva, Geneva
Laura	Bernardini	Mendel Laboratory, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo
Patricia	Blanchet	Département de Génétique Médicale, Hopital Arnaud de Villeneuve, CHRU Montpellier
Dominique	Bonneau	Service de génétique médicale, CHU, Anger
Sonia	Bouquillon	Institut de Génétique Médicale, Hopital Jeanne de Flandre
Odile	Boute	Hôpital Jeanne de Flandre, CHRU de Lille, Lille
Patrick	Callier	Service de Cytogénétique, CHU Le Bocage, Dijon
Dominique	Campion	INSERM U614, University of Medicine and Department of Research, Rouvray Psychiatric Hospital, Sotteville-les-Rouen
Jean	Chiesa	Laboratoire de Cytogénétique, CHU Caremeau, Nimes
Philippe	Conus	Department of Psychiatry, Centre Hospitalier Universitaire Vaudois
Marie Pierre	Cordier	Service de génétique, Hôpital Femme Mère Enfant, Lyon
Jean Marie	Cuisset	Service de Neuropédiatrie, Hôpital Roger Salengro, CHRU de Lille, Lille
Albert	David	Service de Génétique Médicale, CHU Nantes, Nantes
Nicole	de Leeuw	Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen
Bert	de Vries	Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen
Bruno	Delobel	Centre de Génétique Chromosomique, Hopital Saint Vincent
Gérard	Didelot	Center for Integrative Genomics, University of Lausanne, Lausanne
Martine	Doco-Fenzy	Service de Génétique, HMB - CHU REIMS, Reims
Bénédicte	Duban Bedu	Centre de Génétique Chromosomique, Hôpital Saint-Vincent de Paul, GHICL, Lille
Christèle	Dubourg	Laboratoire de Cytogénétique, CHU Rennes, Rennes
Sophie	Dupuis Girod	Service de Génétique, Hospices Civils de Lyon, Hôpital Louis pradel, Bron
Christina	Fagerberg	Department of Clinical Genetics Odense Universitetshospital Odense
Laurence	Faivre	Centre de Référence Maladies Rares "Anomalies du Développement et Syndromes Malformatifs", Hôpital d'Enfants, CHU Le Bocage, Dijon
Florence	Fellmann	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne

Bridget A.	Fernandez	Discipline of Genetics, Memorial University of Newfoundland, St John's
Carina	Ferrari	Department of Psychiatry, Centre Hospitalier Universitaire Vaudois
Richard	Fisher	Institute of Human Genetics, International Centre for Life, Newcastle Upon Tyne
Elisabeth	Flori	Service de Génétique Médicale, CHU Strasbourg, Hôpital de Hautepierre, Strasbourg
Alice	Goldenberg	Service de Génétique, Centre Hospitalier Universitaire de Rouen, Hôpital Charles Nicolle, 76031 Rouen Cedex 1
Louise	Harewood	The Babraham Institute, Cambridge, UK
Delphine	Heron	Département de Génétique Cytogénétique et Embryologie AP-HP, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie
Loyse	Hippolyte	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Murielle	Holder	Hopital Jeanne de Flandre, CHRU de Lille, Lille
Juliane	Hoyer	Institute of Human Genetics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen
Bertrand	Isidor	Service de Génétique Médicale, CHU-Nantes, Nantes
Sylvie	Jaillard	Laboratoire de Cytogénétique, CHU Rennes, Rennes
Philippe	Jonveau	Laboratoire de Génétique, CHU-Nancy, Vandoeuvre les Nancy
Sylvie	Joriot	Service de pédiatrie, Hôpital Jeanne de Flandres, Lille
Hubert	Journel	Service de Pédiatrie et de Génétique, Centre Hospitalier Bretagne Atlantique, Vannes
Frank	Kooy	Department of Medical Genetics, University and University Hospital Antwerp, Antwerp
Zoltán	Kutalik	Department of Medical Genetics. University of Lausanne, Lausanne / Swiss Institute of Bioinformatics.
Cedric	Le Caignec	Service de Génétique Médicale, CHU Nantes, Nantes
Sébastien	Lebon	Department of Pediatrics, Centre Hospitalier Universitaire Vaudois, Lausanne
Bruno	Leheup	Service de Médecine Infantile III et Génétique Clinique, CHU-Nancy et PRES de l'Université de Lorraine UHP Nancy, Vandoeuvre les Nancy
Marie-Pierre	Lemaitre	Service de Neuropédiatrie, Centre Hospitalier Régional Universitaire, Lille
Suzanne	Lewis	Department of Medical Genetics. The University of British Columbia, Vancouver
Aurélien	Macé	Department of Medical Genetics. University of Lausanne, Lausanne / Swiss Institute of Bioinformatics.
Anne M.	Maillard	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Valérie	Malan	Département de Génétique et INSERM U781, Université Paris Descartes, Hôpital Necker-Enfants Malades, Paris
Katrin	Mannik	Center for Integrative Genomics, University of Lausanne, Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia
Danielle	Martinet	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Michèle	Mathieu-Dramard	Service de Génétique Clinique, CHU Amiens, Amiens
Andres	Metspalu	Estonian Genome Center, University of Tartu, Tartu
Fanny	Morice-Picard	Service de Génétique Médicale, CHU de Bordeaux, Bordeaux
Mafalda	Mucciolo	Medical Genetics. Dpt. Molecular Biology, University of Siena, Siena

Eve	Oiglane-Slik	Department of Pediatrics, University of Tartu, Tartu/ Children`s Clinic, Tartu University Hospital, Tartu
Katrin	Ounap	Department of Genetics, United Laboratories, Tartu University Hospital, Tartu
Laurent	Pasquier	Service de Medical Genetics, CHU Rennes, Rennes
Florence	Petit	Hopital Jeanne de Flandre, CHRU de Lille, Lille
Anne	Philippe	Département de Génétique et INSERM U781, Université Paris Descartes, Hôpital Necker-Enfants Malades, Paris
Ghislaine	Plessis	Service de Génétique, CHU Clémenceau, Caen
Fabienne	Prieur	Service de génétique médicale, CHU St Etienne
Jacques	Puechberty	Département de génétique médicale, Hôpital Arnaud de Villeneuve, Montpellier
Evica	Rajcan-Separovic	Department of Pathology (Cytogenetics), University of British Columbia, British Columbia
Anita	Rauch	Institute of Medical Genetics, University of Zurich, Schwerzenbach
Alessandra	Renieri	Medical Genetics Unit, Dpt. Molecular Biology, University of Siena, Siena
Claudine	Rieubland	Divison of human genetics, Department of Paediatrics, Inselspital, University of Bern
Caroline	Rooryck	Univ. Bordeaux, Maladies Rares : Génétique et Métabolisme (MRGM), EA4576, Bordeaux / Service de Génétique Médicale, CHU de Bordeaux, Bordeaux
Katharina Magdalena	Rötzer	Institute of Human Genetics, Medizinische Universität Graz, Graz
Mariken	Ruiter	Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen
Damien	Sanlaville	Service de Cytogénétique Constitutionnelle, Hospices Civils de Lyon, CHU de Lyon and Centre de Recherche en Neuroscience de Lyon, UCBL1, U1028 INSERM, UMR 5292 CNRS, Lyon
Stéphanie	Selmoni	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Yiping	Shen	Laboratory Medicine, Children's Hospital Boston, Boston
Vanessa	Siffredi	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Jacques	Thonney	Département de Psychiatrie, Centre Hospitalier Universitaire Vaudois, Lausanne
Louis	Vallée	Service de Neuropédiatrie, Hôpital Roger Salengro, CHRU de Lille, Lille
Ellen	van Binsbergen	Department of Medical Genetics, University Medical Center, Utrecht
Nathalie	Van der Aa	Department of Medical Genetics, University and University Hospital Antwerp, Antwerp
Mieke	van Haelst	Department of Medical Genetics, University Medical Centre Utrecht, Utrecht
Jacqueline	Vigneron	Service de Néonatologie- Génétique, Maternité Régionale Universitaire, Nancy
Catherine	Vincent-Delorme	Génétique Médicale, Centre Hospitalier d'Arras, Arras
Disciglio	Vittoria	Medical Genetics Unit, Dpt. Molecular Biology, University of Siena, Siena
Anneke	Vulto-van Silfhout	Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen
Robert M	Witwicki	Center for Integrative Genomics, University of Lausanne, Lausanne

Flore	Zufferey	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne
Simon	Zwolinski	Institute of Human Genetics, International Centre for Life, Newcastle Upon Tyne
Jacques S.	Beckmann	Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne / Department of medical genetics, University of Lausanne
Alexandre	Reymond	Center for Integrative Genomics, University of Lausanne

Simons VIP consortium members

First name, middle initials	Name	Institution
John E.	Spiro	Simons Foundation
Arthur L.	Beaudet	Baylor College of Medicine
Christie M.	Brewton	Baylor College of Medicine
Zili	Chu	Baylor College of Medicine
Allison G.	Dempsey	Baylor College of Medicine
Yolanda L.	Evans	Baylor College of Medicine
Silvia	Garza	Baylor College of Medicine
Jill V.	Hunter	Baylor College of Medicine
Stephen M.	Kanne	Baylor College of Medicine
Anna L.	Laakman	Baylor College of Medicine
Morgan W.	Lasala	Baylor College of Medicine
Ashlie V.	Llorens	Baylor College of Medicine
Gabriela	Marzano	Baylor College of Medicine
Timothy J.	Moss	Baylor College of Medicine
Kerri P.	Nowell	Baylor College of Medicine
Monica B.	Proud	Baylor College of Medicine
Melissa B.	Ramocki	Baylor College of Medicine
Qixuan	Chen	Mailman School of Public Health, Columbia University
Roger	Vaughan	Columbia University Mailman School of Public Health
Jeffrey	Berman	Department of Radiology, Children's Hospital of Philadelphia
Lisa	Blaskey	Children's Hospital of Philadelphia
Katherine	Hines	Children's Hospital of Philadelphia
Sudha	Kessler	Children's Hospital of Philadelphia
Sarah Y.	Khan	Children's Hospital of Philadelphia
Saba	Qasmieh	Children's Hospital of Philadelphia
Audrey Lynn	Bibb	Emory Healthcare
Andrea M.	Paal	Emory Healthcare
Patricia Z.	Page	Department of Human Genetics, Emory University
Bethanny	Smith-Packard	Genomic Medicine Institute, Geisinger Clinic
Randy	Buckner	Children’s Hospital Boston, Harvard Medical School
Jordan	Burko	Children’s Hospital Boston
Alyss	Lian	Children’s Hospital Boston

	Cavanagh	
Bettina	Cerban	Children's Hospital Boston
Anne V.	Snow	Children's Hospital Boston
P. Ellen	Grant	Children's Hospital Boston, Harvard Medical School
LeeAnne	Green Snyder	Children's Hospital Boston
Rebecca	McNally Keehn	Children's Hospital Boston, Harvard Medical School
David T.	Miller	Children's Hospital Boston, Harvard Medical School
Fiona K.	Miller	University of Michigan
Jennifer	Endre Olson	Children's Hospital Boston
Sarah J.	Spence	Children's Hospital Boston, Harvard Medical School
Christina	Triantafallou	Massachusetts Institute of Technology
Nicole	Visyak	Children's Hospital Boston
Constance	Atwell	Simons Foundation
Marta	Benedetti	Simons Foundation
Gerald D.	Fischbach	Simons Foundation
Marion	Greenup	Simons Foundation
Alan	Packer	Simons Foundation
Jennifer	Tjernagel	Simons Foundation
Polina	Bukshpun	Department of Neurology, University of California, San Francisco
Maxwell	Cheong	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Corby	Dale	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Sarah E.	Gobuty	Department of Neurology, University of California, San Francisco
Leighton	Hinkley	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Rita J.	Jeremy	CTSI Pediatric Clinical Research Center, University of California, San Francisco
Hana	Lee	Department of Neurology, University of California, San Francisco
Tracy L.	Luks	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Elysa J.	Marco	Department of Neurology, University of California, San Francisco
Alastair J.	Martin	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Kathleen E.	McGovern	Department of Neurology, Brain Development Research Program, University of California, San Francisco
Pratik	Mukherjee	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Srikantan S.	Nagarajan	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Julia	Owen	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Brianna M.	Paul	Department of Neurology, University of California, San Francisco
Nicholas J.	Pojman	Department of Neurology, University of California, San Francisco
Tuhin	Sinha	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Vivek	Swarnakar	Department of Radiology and Biomedical Imaging, University of California, San Francisco
Mari	Wakahiro	Department of Neurology, Brain Development Research Program, University of California, San Francisco
Hanalore	Alupay	University of Washington, Seattle

Benjamin	Aaronson	University of Washington, Seattle
Sean	Ackerman	University of Washington, Seattle
Katy	Ankenmann	University of Washington, Seattle
Elizabeth	Aylward	University of Washington, Seattle
Jenna	Elgin	University of Washington, Seattle
Jennifer	Gerdts	University of Washington, Seattle
Kelly	Johnson	University of Washington, Seattle
Beau	Reilly	University of Washington, Seattle
Dennis	Shaw	University of Washington, Seattle
Kyle	Steinman	University of Washington, Seattle
Arianne	Stevens	University of Washington, Seattle
Tracey	Ward	University of Washington, Seattle
Julia	Wenegrat	University of Washington, Seattle
Timothy P. L.	Roberts	The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine
David H.	Ledbetter	Genomic Medicine Institute, Geisinger Clinic
Christa	Lese Martin	Department of Human Genetics / Emory University
Robin P.	Goin-Kochel	Baylor College of Medicine
Raphael	Bernier	University of Washington, Seattle
W. Andrew	Faucett	Genomic Medicine Institute, Geisinger Clinic
Elliott H.	Sherr	Department of Neurology, University of California, San Francisco
Ellen	Hanson	Children’s Hospital Boston, Harvard Medical School
Wendy K.	Chung	Columbia University

Supplementary data: 16p11.2 clinical paper

Supplementary Table S1: A: Influence of co-variates on FSIQ, BMI, HC and height

	FSIQ		BMI Z-score		HC Z-score		Height Z-score	
	Mean (n)	P-value	Mean (n)	P-value	Mean (n)	P-value	Mean (n)	P-value
Inherited	74.0 (14)	0.1	1.8(42)	0.7	0.2(36)	0.3	-0.3 (43)	0.8
De novo	81.4 (30)		1.6(69)		0.6(69)		-0.2 (67)	
Male	76.6 (38)	0.2	1.7(116)	0.3	0.8(99)	0.05	-0.4 (118)	0.9
Female	71.3 (29)		2.1(84)		0.2(56)		-0.4 (78)	
Children	76.2 (55)	0.3	1.7(151)	1.05×10^{-02}	0.5(138)	0.9	**-0.2 (150)**	**2.74×10^{-04}**
Adults	70.6 (9)		2.6 (52)		0.6(18)		**-1.1 (48)**	
"Neurological" cases*	75.8 (21)	0.8	1.6(50)	0.4	0.6(49)	0.8	0 (51)	0.07
"Non neurological" cases	76.8 (37)		1.9(139)		0.5(97)		-0.5 (133)	
Proband	76.1 (59)	0.8	1.8 (186)	0.1	0.6 (146)	0.6	-0.3 (182)	0.08
Relatives	74.6 (9)		2.6 (27)		0.8 (17)		-0.9 (26)	
Total group	76.1 (71)	NA	1.9(221)	NA	0.6(170)	NA	-0.4 (216)	NA

B: Without double hits and point mutations:

	FSIQ		BMI Z-score		HC Z-score		Height Z-score	
	Mean (n)	P-value	Mean (n)	P-value	Mean (n)	P-value	Mean (n)	P-value
Inherited	74.0 (14)	0.1	1.9(39)	0.7	0.3(34)	0.5	-0.1 (40)	0.7
De novo	81.4 (30)		1.7(68)		0.5(68)		-0.2 (66)	
Male	76.6 (38)	0.2	1.8(113)	0.3	0.8(97)	2.66×10^{-02}	-0.3 (115)	0.7
Female	71.3 (29)		2.1(83)		0.1(55)		-0.4 (77)	
Children	76.2 (55)	0.3	1.7(147)	1.38×10^{-02}	0.6(135)	0.9	**-0.1 (146)**	**7.73×10^{-05}**
Adults	70.6 (9)		2.6 (52)		0.6(18)		**-1.1 (48)**	
"Neurological" cases*	75.8 (21)	0.8	1.5(49)	0.3	0.6(48)	0.8	0 (50)	0.1
"Non neurological" cases	76.8 (37)		1.9(136)		0.5(95)		-0.4 (130)	
Proband	76.1 (59)	0.8	1.8 (182)	6.22×10^{-02}	0.6 (143)	0.8	-0.3 (182)	1.05×10^{-02}
Relatives	74.6 (9)		2.7 (26)		0.7 (16)		-0.9 (25)	
Total group	76.1 (71)	NA	2.0(216)	NA	0.6(166)	NA	-0.4 (211)	NA

Relatives were excluded when more than one family member was present in the same group. Significant results surviving Bonferroni correction[1] (threshold = 0.01) are shown in bold.

* A subgroup of patients with significant neurological symptoms was defined by the presence of at least one of the following: seizures (excluding febrile seizures), significant hypotonia and gait, coordination or movement disorders.

Supplementary Table S2: Neurological features

Neurological features		Probands			Relatives	All
		Questionnaire N=76	Full assessment N=54	Literature N=65*	N=38	N=233 (%)
Seizures[1]	Unspecified	6	9	11	3	52 (22.3%)
	Generalized	3	7	1	1	
	Partial	1	6	1	1	
	Infantile spasms	2	0	0	0	
Tone	Spasticity/Hyperreflexia	4	3	1	1	38 (16.3%)
	Hypotonia	9	6	11	3	
Gait, coordination, movements disorders	Dysmetria	1	7	1	0	45 (19.3%)
	Gait disorder/ataxia	5	18	0	1	
	Paroxysmal movements disorder (chorea, athetosis, tremor)	1	7	1	3	
Cranial nerve anomaly	Left abducens nerve aplasia	1	1	0	0	4 (1.7%)
	Unilateral facial palsy	1	1	0	0	
MRI features		**N=24**	**N=34**	**N= unknown****	**N= 7**	N=65**
CNS anomalies	Meningocele/spina bifida occulta	2	0	0	0	57 (87.7%)
	Syringomyelia	0	1	2	0	
	Abnormal corpus callosum/septum pellucidum	2	4	2	0	
	Cerebral atrophy	2	0	1	0	
	Myelinization defect/ unspecific white matter signal changes or decreased white matter volume	2	4	1	0	
	Craniocervical junction abnormalities***	1	16	2	3	
	Abnormal pituitary	0	6	0	1	
	Abnormal hippocampus	0	3	0	0	
	Others****	0	1	1	0	

[1] Febrile seizures (n=7, not shown), *Cases with available data, **We excluded literature cases from the frequency due to unknown count of MRIs, ***Platybasia, abnormal angulation of dens, cerebellar tonsillar ectopia (n=9) and Chiari I malformation (n=4), ****Polymicrogyria (n=1), arachnoid cyst with partial left temporal lobe agenesis (n=1).

Supplementary Table S3: Malformations and other medical conditions

Congenital malformations/medical conditions		Probands			Relatives	All
		Questionnaire N=76	Full assessment N=54	Literature N=65*	N=38	N=233 (%)
Osteo-articular	Hemivertebrae, vertebrae agenesis or fusions, additional, fused rib, Kypho/scoliosis or torticollis	10	28	4	7	59 (25.3%)
	Talipes varus	1	1	0	0	
	Craniosynostosis	0	2	2	1	
	Limb anomaly**	1	1	1	0	
Ophthalmic	Microphthalmia/coloboma/optic nerve hypoplasia/cataract	4	0	1	0	5 (2.1%)
Genitalia	Cryptorchidism, Shawl scrotum, Hypospadias, Micropenis,	6	2	2	0	10 (4.3%)
Urinary tract	Vesico-ureteral reflux/hydronephrosis	2	4	0	0	8 (3.4%)
	Renal agenesis/dysplasia	1	0	1	0	
Digestive	Hypertrophic pyloric stenosis	4	1	2	1	11 (4.7%)
	Hirschprung disease	0	1	1	0	
	Diaphragmatic hernia	0	0	1	0	
Cardiac	Structural***	6	4	3	0	14 (6.0%)
	Cardiomyopathy****	1	0	0	0	
Orofacial	Cleft palate/velopharyngeal insufficiency	1/0	2/1	1/0	0	8 (3.4%)
	Microtia/preauricular tag, cyst	1/2	0	0	0	
Hearing	Sensorineural/ conductive loss	1/2	1/18	1/1	2	26 (11.2%)
Tumor	Seminoma, cholesteatoma, desmoïd tumor, Wilms tumor	2	1	1	0	4 (1.7%)
Infections	Recurrent pneumonia	0	4	0	0	4 (1.7%)

*Cases with available data **Right radius and 1st metacarpals agenesis/polydactyly ***Ventricular/atrial septal defect (VSD/ASD) (n=2), double outlet right ventricle and severe pulmonary stenosis (n=2), supravalvular aortic stenosis/coarctation (n=5), dextrocardia (n=1), tricuspid insufficiency (n=1), endocardial fibroelastosis (n=1), pulmonic stenosis (n=1), ****Hypertrophic.

Conditions seen in a single patient are not present in the table and include: Hashimotos thyroiditis, inflammatory bowel disease, Mullerian agenesis with absent uterus and vaginal atresia, hyperthyroidism and spontaneous pneumothorax. We did not include minor observed medical conditions such as: benign recurrent upper ways infections (n=25) (otitis media, etc.), visual disorders such as strabismus (n=15) and refractive errors (hypermetropia, myopia, astigmatism) (n=37), minor skeletal anomalies (n=10) (pectus excavatum, pes cavus or planus) and gastroesophageal reflux disease (n=20).

Supplementary Table S4: Neonatal data

Mean gestational age	38.8 weeks (n=131*)
Premature births**	10.7% (n=14/131)
Weight at mean gestational age	3048.7 g (n=124; Z-score=-0.61; p=3.3x10^{-11})
Height at mean gestational age	48.9 cm (n=88; Z-score=-0.49; p=1.3x10^{-3})
HC at mean gestational age	33.5 cm (n=58; Z-score=-0.57; p=2.6x10^{-5})
Neonatal complications***	14.9% (n=29/195)

* Including literature cases ** Less than 37 weeks of amenorrhea ***Include: respiratory distress requiring supplemental oxygen/intubation (n=22) and hypotonia (n=7). Z-scores for weight, height and HC at birth were calculated according to gestational ages[2].

Supplementary Table S5: Spearman correlations

	HC		Height		Weight		FSIQ	
	rho	P-value	rho	P-value	rho	P-value	rho	P-value
BMI	0.45	**2.82×10^{-08}**	0.26	**4.03×10^{-04}**	0.89	**1.75×10^{-60}**	-0.05	0.746
HC			0.36	**1.26×10^{-05}**	0.50	**1.71×10^{-10}**	-0.09	0.524
Height					0.51	**2.93×10^{-13}**	-0.13	0.350
Weight							-0.09	0.517

The Spearman correlation values (rho) between FSIQ and anthropometric traits are indicated together with their corresponding P-values. Significant results surviving Bonferroni correction[1] (threshold = 5×10^{-03}) are shown in bold.

Supplementary Table S6: Deletion carriers with multiple medical conditions

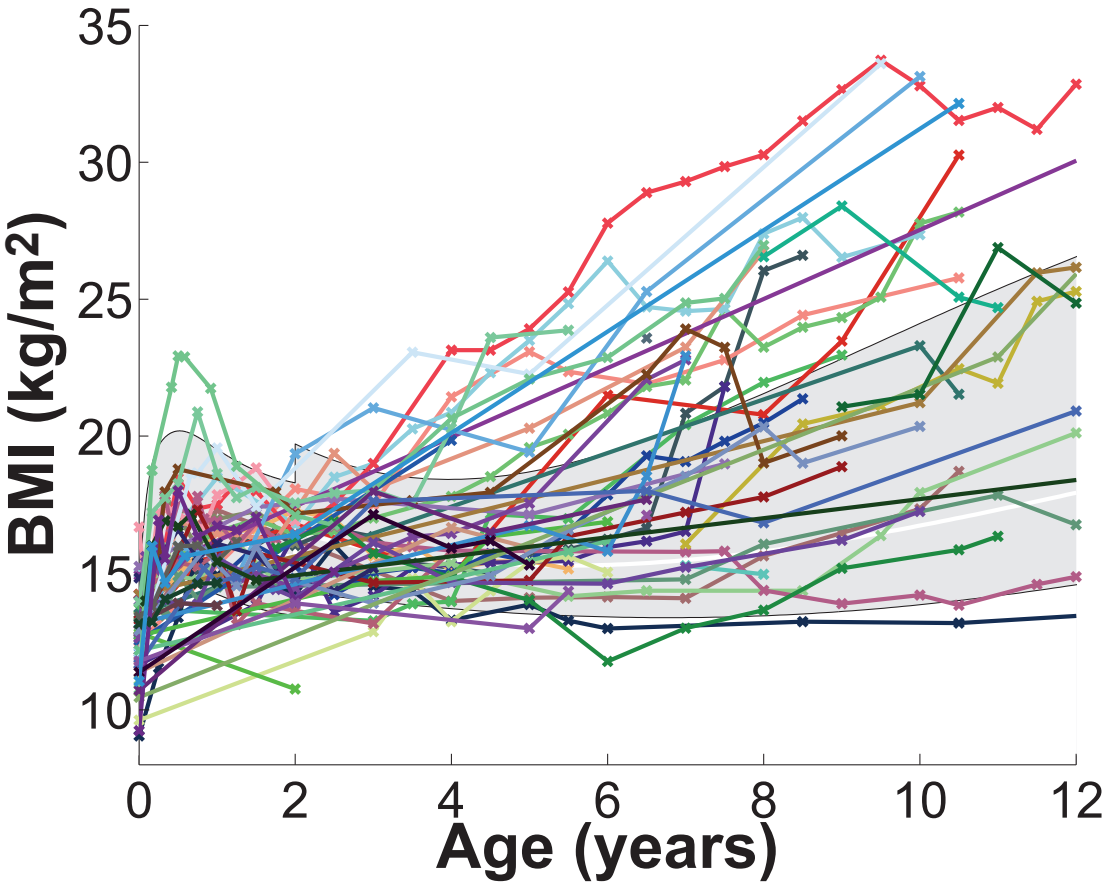
SYSTEMS	Osteo-articular	Cardio-pulmonary	Ophthalmic	Genital	Urinary tract	Digestive	Face	Sensori-neural*	Tumor	Neuro**
Osteo-articular		**4**	**2**	**3**	**4**	**1**	0	0	0	**3**
Cardio-pulmonary	**2**		**1**	**1**	**3**	**1**	**1**	0	**1**	**1**
Ophthalmic	0	0		**1**	**1**	0	0	**1**	0	**1**
Genital	**2**	0	0		**1**	0	0	**1**	0	0
Urinary tract	**1**	0	0	0		0	0	0	0	0
Digestive	0	0	0	0	0		0	0	0	**1**
Face	0	0	0	0	0	0		0	**1**	0
Sensori-neural	0	0	0	0	0	0	0		0	0
Tumor	0	0	0	0	0	0	0	0		0
Neuro**	0	0	0	0	**1**	0	0	0	0	

*Sensorineural deafness; **Include seizures (excluding febrile seizures), gait, coordination or movements disorders and CNS or medullary malformations

Numbers indicate probands presenting 2 or more major medical conditions (according to Supplementary Table S5) affecting various systems. Probands from the European consortium (n=85) and Simons VIP (n=45) series are represented, respectively, in the upper right and lower left parts. In both series, 76/130 patients (58%) had at

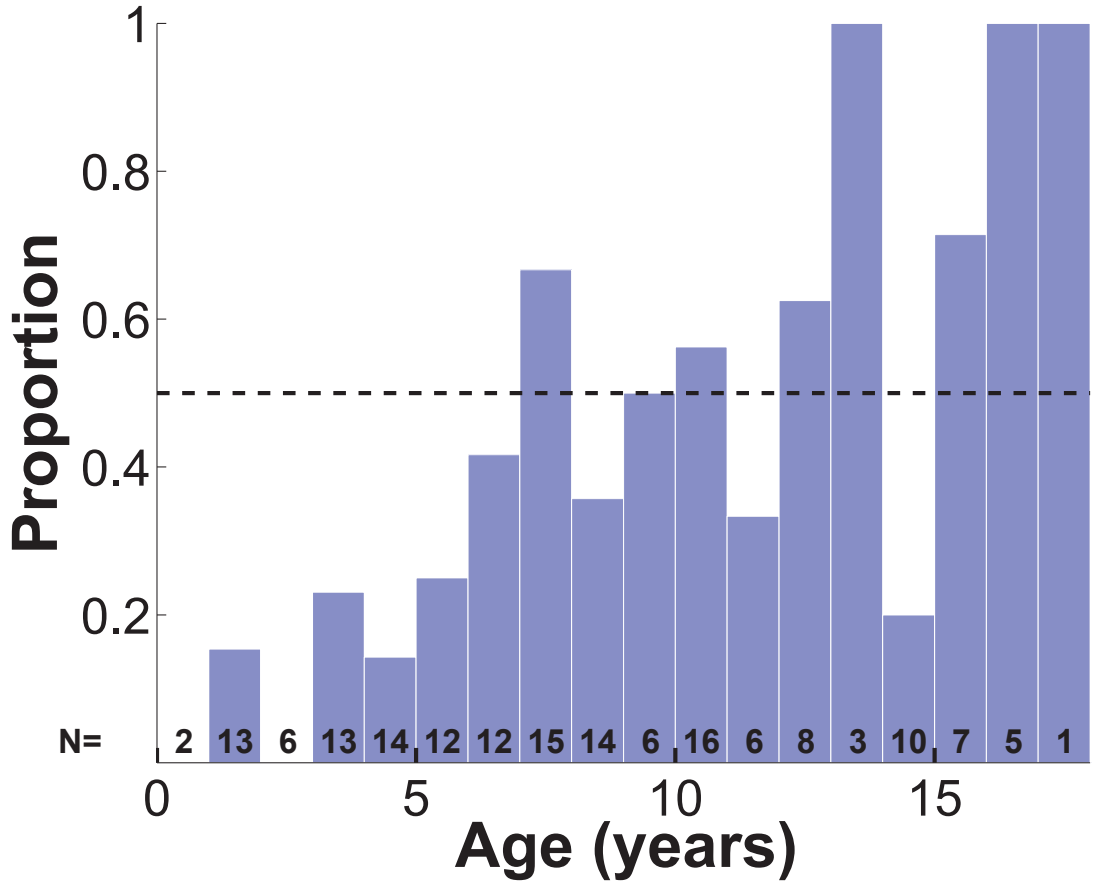
least one malformation or medical problem. Among those, the majority (n=53/76; 70%) had only one. 21% (16/76) had 2, 7.9% (6/76) had 3 and one patient presented 4 (~1%). No recurrent malformation sequence or multisystem involvement is observed.

Supplementary Figure S1: Longitudinal BMI evolution



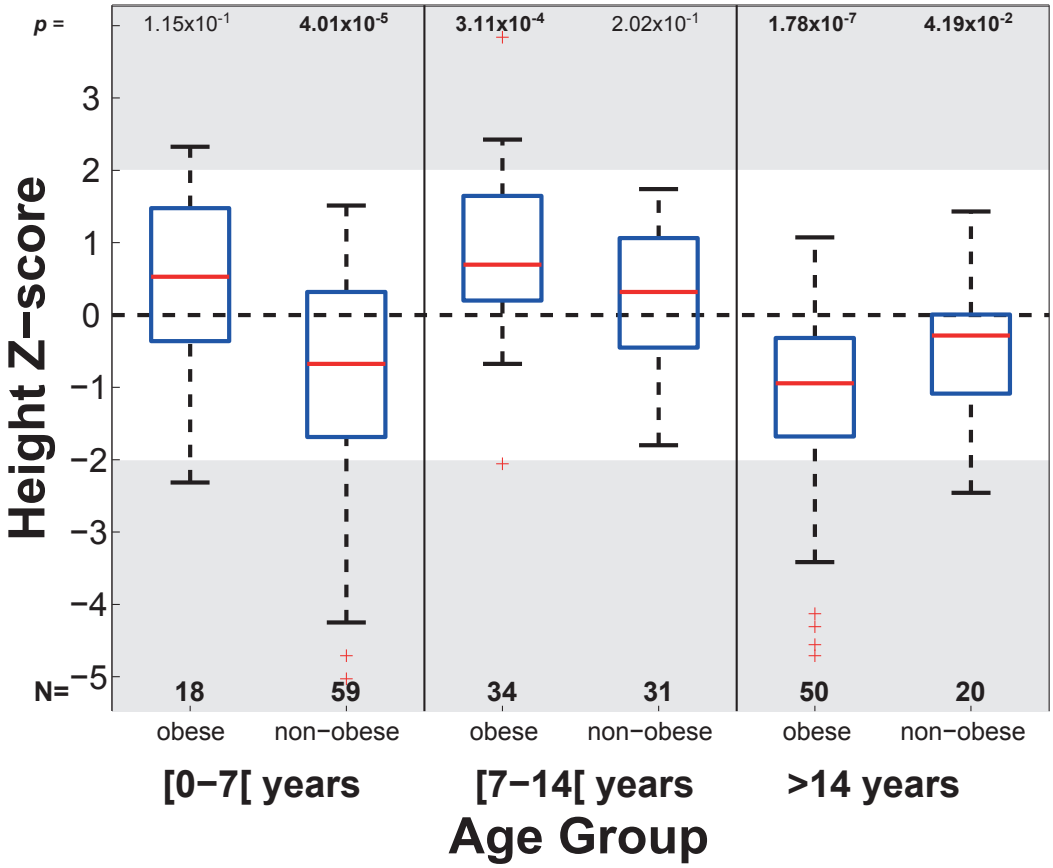
Longitudinal measures of BMI from birth to 12 years of age in 59 carriers of the 16p11.2 BP4-BP5 deletion. Note that BMI acceleration takes place at different ages. The grey area (in background) represents the interval between the 3rd and 97th percentiles using the WHO data (www.who.int/childgrowth/en) between 0-2 years and the Center for Disease Control data above 2 years[3]. The white line is the 50th percentile.

Supplementary Figure S2: Proportion of obese deletion carriers in function of age



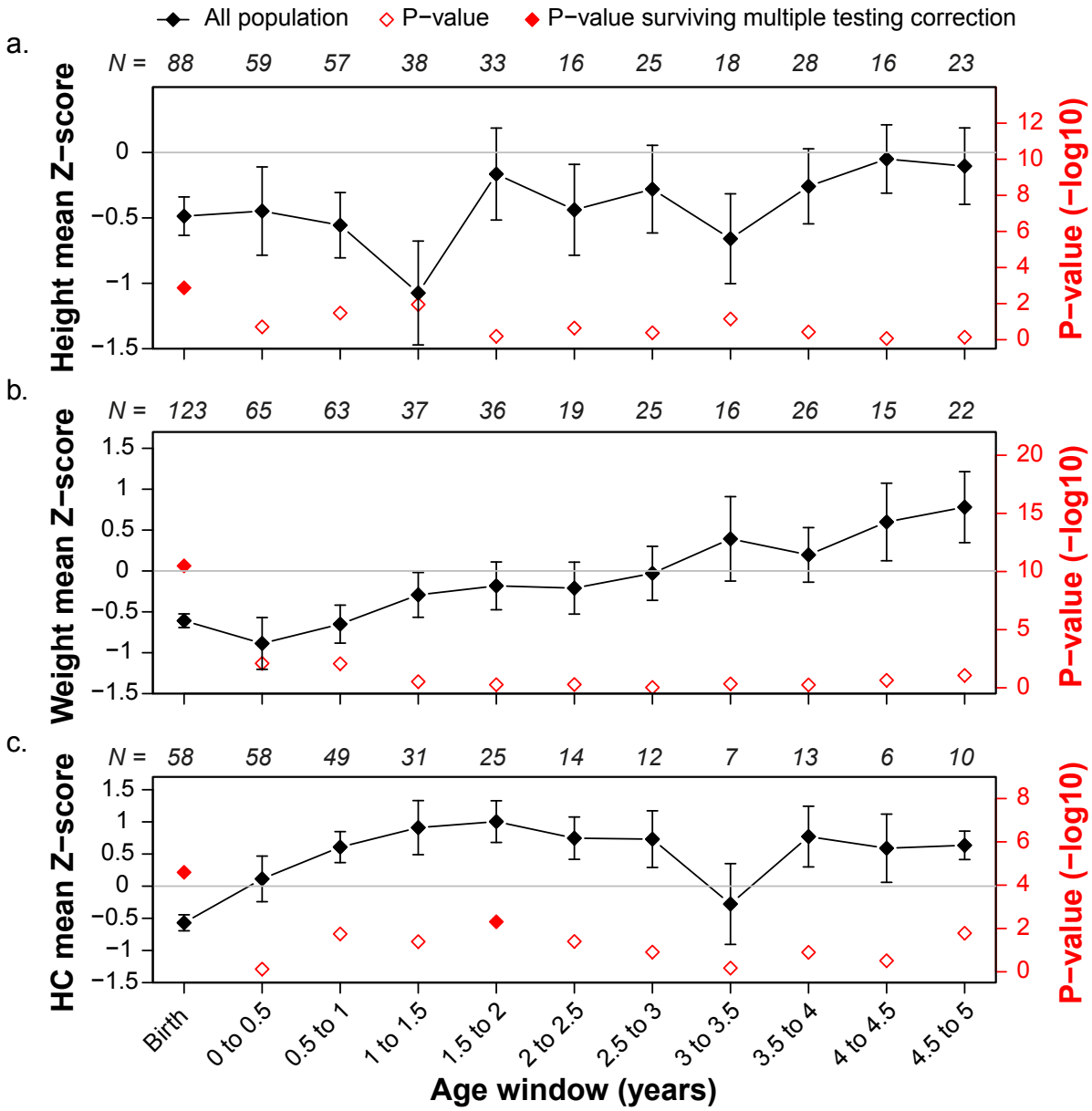
Histogram of crosssectional data showing the proportion of obese 16p11.2 deletion carriers. Number of cases (N) is indicated for each age category above the x axis. The dashed line, which represents 50%, is reached at 7 years of age.

Supplementary Figure S3: Distribution of height in obese and non-obese deletion carriers



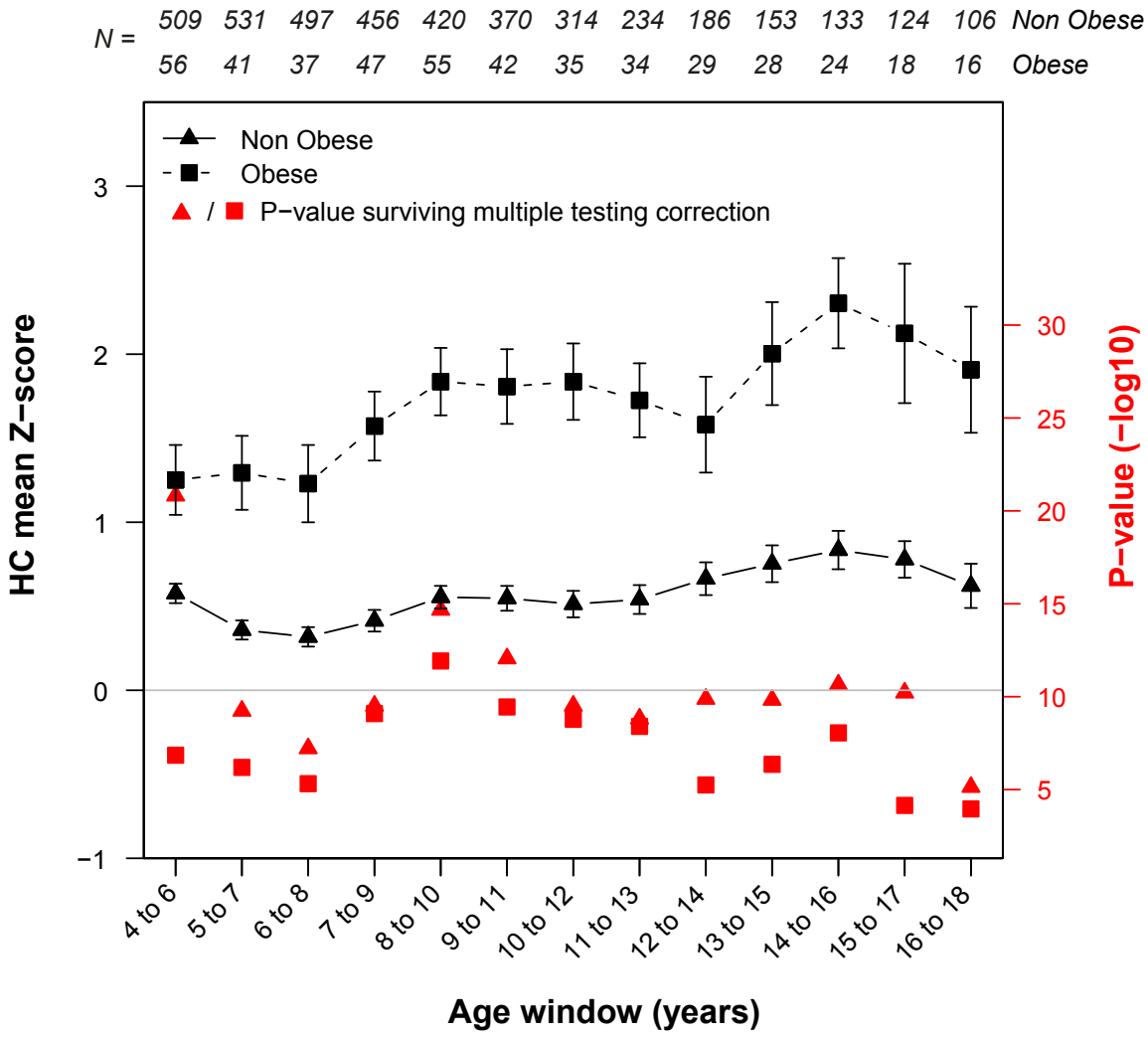
Distribution of cross sectional height Z-scores for 3 age groups. Z-scores, taking into account age and sex, were calculated based on reference population data (cf. methods).
Deletion carriers were stratified as obese, or non-obese. Boxplots represent the 5th, 25th, median, 75th and 95th percentile. Grey backgrounds represent ±2 Z-scores. Two-sided T-tests were performed probing whether mean Z-score is significantly different from 0 (P-values and sample sizes are shown, respectively above and below the boxplots). We observe that (i) non-obese children are significantly smaller than the general population within the 0-7 years window of development, (ii) obese children are taller than the general population within the 7-14 years window and, (iii) all groups above 14 years are significantly smaller than the general population.

Supplementary Figure S4: Early growth parameters



Height (panel a), weight (panel b) and HC (panel c) mean Z-scores and associated P-values as a function of age. Z-scores normalize for the effect of gender and age in the general population (cf methods). Number of cases (N=) is indicated for each age category. A mixed model was used to analyze longitudinal and cross-sectional data together. P-values represent a two-sided T-test. Full red dots are P-values surviving multiple testing correction (significance's threshold at 5.6×10^{-3} for height, at 5.6×10^{-3} for weight and at 5.0×10^{-3} for HC) as opposed to empty red dots. A: HC shows a significant increase during infancy and peaks around the age of 2.25 years. B and C: Height and weight are both significantly decreased at birth

Supplementary Figure S5: Head circumference in the Simon Simplex Collection (SSC)



Mean HC Z-scores as a function of age in patients with ASD from the SSC cohort[4]. Obese (n= 252, black squares) and non-obese (n=2166, black triangles) cases are presented separately. Both categories show increased HC throughout childhood and adolescence. P-values surviving multiple testing corrections are shown in red for each age window and both categories (significance's threshold at 3.9×10^{-3} for both obese and non-obese). Number of cases (N=) is indicated for each age category. Macrocephaly (HC $\geq$ 2 Z-scores) is present in 41.3% of obese individuals and 12.5% of non-obese ASD individuals.

Supplementary references

1. Bland JM, Altman DG (1995) Multiple significance tests: the Bonferroni method. Bmj 310:170
2. Fenton TR (2003) A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC pediatrics 3:13
3. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL (2000) CDC growth charts: United States. Adv Data:1-27
4. Fischbach GD, Lord C (2010) The Simons Simplex Collection: a resource for identification of autism genetic risk factors. Neuron 68:192-195