Supplementary Table S1. Clinical and genetic features of the subjects.

Patient ID	Chromosome Designation [GRCh38] Size	ASD/ ADHD	Brain anomaly	Macro-cephaly	ID-Learning Difficulty/Language problem	Seizures/ Epilepsy*	NMD delay/ Hypotonia	Skeletal findings	Obesity/ Hyperphagia Weight Percentile	Dysmorphism	Hearing loss	Cardiac finding	Psychiatric problems	Miscellaneous
P1	16p11.2 (29616028-30188392) 572Kb	+/+	MR:N	-	Mild/+ Both receptive and expressive language delay	+/Absence seizure	N/N	Mild Bilateral PEV	+/+ 3.89 SD	Ear lobes prominent, medial flare, synophrys, wide palpebral spaces, groove in columella, deep philtrum, fusiform fingers, genu valgum, buried penis	N	N	Tics, Aggressive behaviour	Pale optic disc and drusen in the left eye, bilateral papilledema, hepatic steatosis, elevated CSF pressure, sister had tics and anomaly of arcus aorta without genetic diagnosis
P2	16p11.2 (29584162-30188392) 604Kb	NE	MR:N	-	NE	+/ EEG: Focal epileptic activity	+/+ severe MMR	N	-/-	Hyperpigmentation around nipples and acral areas, tracheostomy	N	N	NE	Polyhydramnios, macroglossia, frequent vomiting in early infancy, constipation, PEG feeding. Patient had aspirated and followed in intensive care unit for a long time in early infancy
P3	16p11.2 (29616028-30188392)x1 572Kb	-/+	MR:N	-	Mild-moderate/+ receptive language mild, expressive severely delayed	+	N/N	N	+/+ 2.25 SD	N	+	NA	Aggressive behaviour since infancy	Transient mild anaemia, brother had bipolar disorder
P3 Father	16p11.2 (29616028-30188392)x1 621Kb	-/-	MR:NA	-	Mild/+ receptive language mild, expressive mildly delayed	N	N	N	N	-	N	N	N	-
P4	16p11.2 (29616028-30188392)x1 572Kb	+/+	MR: Idiopathic intracranial hypertension, left optic nerve tortuoused	+	Moderate/+ Non Verbal-Non Receptive	N	+/+ Moderate NM delay,	Bilateral PEV	-/+ 0.62 SD	Narrow forehead, anteverted ears, down slanted palpebral fissures, small hands, syndactyly, bilateral sandal gap, micropenis	N	N	Stereo-typical movements, Aggression	Prenatal macrocephaly and hyperechoic colon, chronic bilateral papilledema (grade 4), pseudotumor cerebri, (father had macrocephaly also), frequent infection
P5	16p11.2 (29401121-30188392)x1 787Kb	-/+	MR: ulegyria and gliosis in both occipital lobes consistent with neonatal hypoglycaemia sequelae	+	Moderate/+ Receptive language normal, non-verbal	+/ EEG:Gene-ralized epileptic activity	+/N Moderate NM delay	N	-/- 0.43 SD	N	+	N	Stereo typical movements	Strabismus, nystagmus (right eye), neonatal hypoglycaemia, transient prenatal relative macrocephaly
P5 Mother	16p11.2 (29401121-30188392)x1 787Kb	-/+	NA	-	-/-	+	N/N	n	-/- BMI: 21.8	N	N	N	Aggression	-

† 292Kb deletion.
*Characterisation of the seizure and EEG findings were also depicted if available.
§ Family stated hyperphagia coincided with epilepsy treatment
N: Normal; NA: Not available; NE: Not evaluated; ASD: Autism Spectrum Disorder; ADHD: Attention deficiency and hyperactivity disorder; ID: Intellectual Disability; EEG: Electroencephalogram; NM/D: Neuromotor/Development; MR: Magnetic resonance imaging; SD; Standard deviation; CC: Corpus Callosum, OCD: Obsessive compulsive disorder, PEV: Pes equinovarus; W: Week.

Supplementary Table S1. Continued.

Patient ID	Chromosome Designation [GRCh38] Size	ASD/ ADHD	Brain anomaly	Macro-cephaly	ID-Learning Difficulty/Language problem	Seizures/ Epilepsy*	NMD delay/ Hypotonia	Skeletal findings	Obesity/ Hyperphagia Weight Percentile	Dysmorphism	Hearing loss	Cardiac finding	Psychiatric problems	Miscellaneous
P6	16p11.2 (28794374_29026493)x1 232Kb†	+/+	NA	-	Mild-moderate/+ Receptive moderate-severe, expressive severely affected	N	+/+ NM delay, No walking	N	-/- 1.28 SD	N	+	NA	Stereo-typical movements	Preeclampsia, 35W preterm birth, constipation, hypopigmented lesion(paternal)
P6 Mother	16p11.2 (28814728-29083829)x1 269Kb†	-/-	NA	-	N	N	N/N	N	+/+ BMI: 31.3	N	N	N	N	Constipation, hepatic steatosis,
P7	16p11.2 (29616028-30204297)x1 558Kb	NE	NE	-	NE	NE	NE	Bilateral PEV	N	N	NE	N	NE	Fetal distress, polyhydramnios, preterm labour, abnormal presentation, cleft palate, short neck, deceased in 2nd day
P7 Mother	16p11.2 (29423424_30209095)x1 786Kb	-/-	NA	-	N	N	N/N	N	-/- BMI: 29.7	N	N	N	N	-
P8	16p11.2 (29574786_30188396)x1 614Kb	-/+	NA	-	-/+ Receptive language normal, expressive delayed moderately	-	+/N Mild NM delay	N	+/+ 2.57 SD	N	N	NA	N	Vitiligo, elevated TSH levels, short stature(-3.03SD), abnormal presentation at birth, frequent urinary infection in infancy
P9	16p11.2 (29584162-30188392)x1 604Kb	NE/NE	MR:NA	-	-/+ Receptive language normal, expressive delayed mildly	+/ Febrile-nonfebrile seizures	+/+ Mild-moderate NM delay	N	-/- 0.98 SD	N	N	N	N	Single café au lait, delayed teething, constipation, increased abortus risk in pregnancy
P10	16p11.2 (29401121-30188392)x1 787Kb	+/+	MR: N	-	Mild/- Receptive language mild, expressive moderately affected	N	+/+ Moderate NM delay	Bilateral PEV	-/- -1.61 SD	Hypospadias, pectus excavatum, umbilical hernia	N	N	N	Feeding difficulty, preterm birth, small for gestational age, vomiting seldomly, increased abortus risk in pregnancy, frequent infection
P11	16p11.2 (29616028-30188392)x1 572Kb	-/+	MR: Expansion in bilateral perivascular spaces, right periventricular deep white gliotic focus approximately 3 mm in size	+	Mild/+ Both receptive and expressive language affected moderately	+/ EEG:Gene-ralized epileptic activity	+/N Mild nm delay	N	+/- 3.29 SD	Gynecomastia, buried penis, acanthosis	N	N	N	Constipation, hepatomegaly grade 2 steatosis, meconium aspiration, faecal incontinence -sister had obesity without genetic testing

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P11 Mother	16p11.2 (29584162-30188392)x1 604Kb	-/-	NA	-	-/+	N	N/N	N	+/+ BMI: 43.9	N	N	NA	N	Preeclampsia history, insulin resistance, astigmatism, frequent infection in infancy
P12	16p11.2 (29584162-30188392)x1 604Kb	NE/NE	MR:CC hypoplasia	-	NE/NE Delayed speech, single words in 18mo	+/ Generalize clonic EEG: multifocal epileptic activity	N/N	N	-/+ 0.03 SD	N	N	N	N	Cleft palate, increased nuchal translucency in 2nd trimester
P13	16p11.2 (29616028-30188392)x1 572Kb	-/+	MR:N	+	Mild-moderate/+ Receptive language moderate, expressive severely affected	+	+/N Moderate nm delay	N	+/+ 5.82 SD	Epicanthus, almond eyes, brachydactyly	N	NA	Aggression Stubborn-ness	Bilateral pale nasale optic disc
P13 Mother	16p11.2 (29548822-30188392)x1 640Kb	-/-	MR:N	-	-/+ Receptive language normal, expressive moderately affected	N	N/N	N	+/- BMI: 51.1	N	N	N	N	Constipation in adulthood
P14	16p11.2 (29584162-30200636)x1 616Kb	-/+	MR: Colloid cyst	-	-/+	N	N/N	N	-/+ 0.77 SD	Broad forehead, horizontally placed eyebrows, synophrys, deep philtrum, thin upper lip	N	N	N	Hypothyroidism, hepatosplenomegaly, liver steatosis, frequent infection in infancy, short stature(-2.19sd), elevated Lp(a)-LDL
P15	16p11.2 (29616028-30315642)x1 700 kb	-/-	MR:NA	-	Mild/+ Receptive language mildly, expressive severely affected	+/ Generalized clonic	N/N	Pes valgus	+/+ BMI: 49.3	Round face, low nasal bridge, full cheek, thin upper lip, small hands and feet, brachydactyly, hypertrichosis	N	N	OCD	Primary amenorrhea, hypogonadism, myopia, cholecystectomy, hepatosplenomegaly, liver steatosis, small uterus, insulin resistance-Mother had ID, short stature without genetic testing
P16	16p11.2 (29599861_30369165)x1 769Kb	+/+	MR:N	+	Mild/+ Receptive language mild expressive severely affected	+/2 times febrile seizures	N/N	Mild scoliosis	+/+ 3.35 SD	Thick eyebrows eyelashes, high forehead, down-slanting palpebral fissures, long face philtrum, thin upper lip, micrognathia, short neck, brachy-clinodactyly, post axial bilateral polydactyly, toenails mildly dystrophic and deeply seated	N	N	Aggressive behaviour, biting fingers seldomly	Prenatal fetal distress, increased LpA-triglyceride, neonatal transient hydrocephalus Height: 2.16SD

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P17	16p11.2 (29584162-30188392)x1 604Kb	-/-	MR:N	-	-/+ Receptive language moderate expressive severely affected	+	+/N Moderate NM delay	N	-/- 0.71 SD	Downslanting palpebral fissures, low set ears, pectus carinatum, strabismus of the left eye	N	N	N	Myopia, astigmatism
P17 Father	16p11.2 (29595483_30199713)x1 604Kb	-/-	MR:NA	-	N	N	N	N	N	-	N	N	N	-
P18	16p11.2 (29627349_30209531)x1 582Kb	-/+	MR:N	-	-/- Moderate speech delay	+	N/N	N	N/+$ -1.14SD	Long face, upslanted palpebral fissures, nostrils anteverted, downturned corners of mouth	N	N	Stereo-typical movements	Frequent infection

[ǂ] 292Kb deletion.
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