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Supplemental Data

Deletion 17q12 Is a Recurrent Copy Number Variant that Confers High Risk of Autism and Schizophrenia

Daniel Moreno-De-Luca, SGENE Consortium, Jennifer G. Mulle, Simons Simplex Collection Genetics Consortium, Erin B. Kaminsky, Stephan J. Sanders, GeneSTAR, Scott M. Myers, Margaret P. Adam, Amy T. Pakula, Nancy J. Eisenhauer, Kim Uhas, LuAnn Weik, Lisa Guy, Melanie E. Care, Chantal F. Morel, Charlotte Boni, Bonnie Anne Salbert, Ashadeep Chandrareddy, Laurie A. Demmer, Eva W.C. Chow, Urvashi Surti, Swaroop Aradhya, Diane L. Pickering, Denae M. Golden, Warren G. Sanger, Emily Aston, Arthur R. Brothman, Troy J. Gliem, Erik C. Thorland, Todd Ackley, Ram Iyer, Shuwen Huang, John C. Barber, John A. Crolla, Stephen T. Warren, Christa L. Martin, and David H. Ledbetter

Consortia Members

The following authors are included under:

SGENE Consortium: H Stefansson (deCODE genetics, Reykjavik, Iceland), O Gustafsson (University of Oslo, Oslo, Norway), OP Pietiläinen (Institute of Molecular Medicine, Helsinki, Finland and Wellcome Trust Sanger Institute, Cambridge UK), E Sigurdsson (National University Hospital, Reykjavik, Iceland), U Thorsteinsdottir (deCODE genetics, Reykjavik, Iceland), A Kong (deCODE genetics, Reykjavik, Iceland), M Ruggeri (University of Verona, Verona, Italy), S Tosato (University of Verona,Verona, Italy), S Cichon (University of Bonn, Bonn, Germany), OA Andreassen (University of Oslo, Oslo, Norway), T Werge (Copenhagen University Hospital, Roskilde, Denmark), RA Ophoff (UCLA, Los Angeles, CA, USA and University Medical Center Utrecht, Utrecht, The Netherlands), D St Clair (University of Aberdeen, Aberdeen UK), DA Collier (Institute of Psychiatry, London, UK), D Rujescu (Ludwig-Maximilians-University, Munich, Germany), J Halldorsson (Psychological Health Services, Landspitali University Hospital, Reykjavik, Iceland), E Saemundsen (State Diagnostic and Counseling Center, Kópavogur, Iceland) and K Stefansson (deCODE genetics, Reykjavik, Iceland).

Simons Simplex Collection Genetics Consortium: MW State (Child Study Center and Departments of Psychiatry and Genetics, Yale University School of Medicine, New Haven, CT, USA), B Devlin (University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, PA, USA), JS Sutcliffe (Departments of Molecular Physiology & Biophysics and Psychiatry, Vanderbilt University, Nashville, TN, USA), CA Walsh (Division of Genetics, Children's Hospital, Howard Hughes Medical Institute, Harvard Medical School, Boston, MA, USA) D Geschwind (Programs in Neurogenetics and Neurobehavioral Genetics, Neurology Department, and Semel Institute for Neuroscience and Behavior, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA), EH Cook Jr (Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA), RM Cantor (Department of Human Genetics, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA) DE Grice (Division of Child and Adolescent Psychiatry, Columbia University and the New York State Psychiatric Institute, New York, NY, USA), AL Beaudet (Department of

Molecular & Human Genetics, Baylor College of Medicine, Houston, TX, USA), DM Martin (Departments of Pediatrics and Human Genetics, The University of Michigan, Ann Arbor, MI, USA), E Morrow (Developmental Disorders Genetics Research Program, Brown University, Providence, RI, USA).

GeneSTAR: LR Yanek, LC Becker, DM Becker (The Johns Hopkins GeneSTAR Research Program, The Johns Hopkins University School of Medicine, Baltimore, MD, USA)

Table S1. Extended clinical phenotypes of nine patients with 17q12 deletions.

Abbreviations: WNL, within normal limits; U, unknown; y, years; %, percentile; HC, head circumference; CT, computed tomography; IGF-1, insulin-like growth factor-1; IGFBP3, insulin- like growth factor binding protein-3; Hb, hemoglobin; EEG, electroencephalogram; ECG, electrocardiogram; ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observational scale, SCQ, social communication questionnaire; Q-CHAT, quantitative checklist for autism in toddlers; IQ, intelligence quotient; DQ, developmental quotient; KBIT-2, Kaufman Brief Intelligence Test, Second Edition; ABAS-II, Adaptive Behavior Assessment Scale, Second Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Male	Male	Male	Female
Current age	19 y	4 y	7 y	12 y	37 y
Inheritance of the deletion	*de novo*	*de novo*	*de novo*	*de novo*	U
Pregnancy					
Gestation	Term delivery. Delivered by cesarean section due to cephalopelvic disproportion.	Preterm delivery (35 weeks). Oligohydramnios, possible renal anomalies, poor fetal growth. Two prior miscarriages.	Low alpha-fetoprotein. Uncomplicated term delivery.	Term delivery (41 weeks). Meconium staining. Eight prior miscarriages.	U
Birth weight	3,377 g (25th - 50th %)	2,580 g (50th %)	3,340 g (25th %)	3,120 g (10th - 25th %)	U
Birth length	U	48.2 (50th - 75th %)	U	50.8 cm (50th %)	U
Birth HC	U	35 cm (>97th %)	U	U	U
Development					
Age at sitting	U	5 months	U	U	U
Age at walking	16 months	10 months	15 months	2 years	U
Physical exam					
Weight	55.35 kg (25 - 50th%)	17.9 kg (75th %)	25.5 kg (55th %)	34.5 kg (25th - 50th)	59 kg (50th - 75th %)
Height	159.9 cm (25 - 50th%)	105.8 cm (75th %)	125.7 cm (75th %)	137.6 cm (10th - 25th %)	160 cm (25th - 50th %)
Head	HC: 55 cm (50th %) High forehead. Narrow face. Normal	HC: 52.25 (90th %), frontal bossing.	HC: 54.5 cm (>97th %). Dolichocephaly.	HC: 55.5 cm (90th %). High forehead, turricephaly.	High forehead
Eyes	Short, slightly upslanting palpebral fissures. Arched eyebrows.	Deep-set eyes. Mildly downslanting palpebral fissures. High, arched eyebrows.	Slightly downslanting palpebral fissures. Arched eyebrows.	Stellate irides, hypertelorism, telecanthus, downslanting palpebral fissures. High, arched eyebrows.	Arched eyebrows
Ears	WNL	WNL	Recurrent otitis media and persistent middle ear effusion, tympanostomy tubes.	Long with prominent lobes	WNL
Nose	Tubular	Depressed nasal bridge	Depressed nasal bridge at young age; presently tubular nose.	Depressed nasal bridge at young age; presently tubular nose.	Depressed nasal bridge at young age; presently bulbous nasal tip.
Mouth and jaw	Retrognathia. Narrow upper lip. Slight asymmetry of nasolabial folds. Mandibular surgery. Irregularly placed teeth, odd spacing on upper teeth.	WNL	WNL	Micrognathia	Poor dentition
Musculoskeletal	12-degree angle stable scoliosis. Increased joint mobility in hands and knees. Reflex neurovascular dystrophy.	WNL	WNL	Very long fingers in hands and feet, left single palmar crease. Increased small and large joint mobility. Mild pectus excavatum. Bilateral hip dysplasia and pes planovalgus.	Decreased range of motion, pain and stiffness in joints.
Skin and integuments	Several melanocytic nevi on abdomen. Easy bruising. Acanthosis nigricans in neck. Normal nail development.	Irregular café-au-lait spot anterior to right axilla. Mildly hirsute back. Slightly hypoplastic and thick toenails.	Surgery for ingrown toenail	Left scalp mass of overgrown, redundant, folded normal skin	WNL
Abdomen/ gastrointestinal	Irritable bowel syndrome, gastroesophageal reflux, ileitis, abdominal migraines.	Frequent constipation	WNL	U	WNL
Cardiorespiratory	Syncopal episodes. Normal ECG and Holter monitor.	WNL	Frequent upper respiratory infections	WNL	WNL
Genitourinary	Amenorrhea, uterus didelphis. Bilateral nephrocalcinosis, small kidney stones, recurrent urinary tract infections, right simple cyst, mild renal insufficiency. Vesicoureteral reflux on prenatal ultrasound. Residual renal cortical thinning. Multiple ovarian follicular cysts. Endometriosis found in laparotomy.	Echogenic renal calyces with normal kidney size seen on ultrasound. Normal renal function.	Normal renal ultrasound. Normal renal function tests.	Urethral stenosis. Normal renal ultrasound.	Echogenic, multicystic kidneys. Episodes of renal failure during pregnancy. Pyelonephritis due to proteus mirabilis.
Endocrine	Amenorrhea. Normal thyroid hormones, cortisol, prednisolone, and androstenone.	No mention of signs or symptoms of diabetes or any endocrine disorder.	No mention of signs or symptoms of diabetes or any endocrine disorder.	Normal aldolase, IGF-1, IGFBP3, insulin level, C-peptide, HbA1C, and UA.	Diabetes mellitus type 1. Hyperlipidemia.
Neurological exam					
Muscle tone	WNL	WNL	Mild hypotonia	Hypotonia	WNL
Seizures	No	No	No	No	No
Gait	WNL	WNL	WNL	Slightly wide-based	WNL
Sensory deficits	Unspecified visual accuity problems	No. Normal vision exam.	No	Auditory hypersensitivity and decreased pain sensitivity. Hypermetropia.	No
Coordination and motor skills	U	Delayed fine motor skills	Minor coordination problems	Coordination problems	U
Behavior and cognition					
Autism	Not mentioned or suspected	Yes	Yes	Yes	Not mentioned or suspected
Diagnostic criteria, supportive tests	DSM-IV	DSM-IV. ADI-R. ADOS. Mullen Scales of Early Learning, Vineland Adaptive Behavior Scales, and Child Behavior Checklist for Ages 1.5 - 2.	DSM-IV. SCQ total score: 25.	DSM-IV	DSM-IV
Other behaviors and neuropsychiatric comorbidities	Depression. Migraines.	Unusual phobias, hand flapping, spitting, mild hyperactivity, temper tantrums. Short attention span. Extremely selective diet. Aggresive behavior.	Prominent anxiety. No pointing. Behavioral rigidity and repetitive behavior. Occasional unmotivated giggling. Extremely selective diet.	Anxiety. Mood changes. Aggressive and obsessive-compulsive behaviors.	Bipolar disorder, depressive mood. Anxiety and sleep disturbances.
Cognition, adaptive behavior, language	In College. Unremarkable speech development.	Mild to moderate intellectual disability. Delayed speech. Verbal skills (severe delay) more severely compromised than non-verbal skills (mild delay). First word: ~18 months; sentences: 4 y.	Mild delay in non-language abilities, but marked expressive and receptive speech delay. Verbal IQ 44; nonverbal IQ 73 (KBIT-2). General Adaptive Composite 40 (ABAS-II). Communicates in single words and 2- to 3-word phrases.	IQ in low 50s, not tested in detail. Delayed speech; speaks in 2- to 3-word sentences.	Developmental delay. Unremarkable speech development.

	Case 6	Case 7	Case 8	Case 9
Sex	Male	Female	Male	Male
Current age	1 y 9 months	1 y 10 months	10 y	22 y
Inheritance of the deletion	Maternal (son of case 5)	*de novo*	*de novo*	*de novo*
Pregnancy				
Gestation	Preterm delivery (30 weeks). Uncontrolled maternal diabetes mellitus. Corioamnionitis. Pulmonary hypoplasia, respiratory distress syndrome. Small right periventricular hemorrage. Enterococcal meningitis.	Preterm delivery (35 weeks); premature rupture of membranes. Abnormal maternal screening. Two prior miscarriages.	Threatened preterm labor. Term delivery (38 weeks). Cesarean section for fetal distress following prolonged labor.	Term delivery (37 weeks)
Birth weight	1,815 g (50th - 90th %)	2,350 g (25th - 50th %)	2,270 g (<5th %)	2,770 g (10th %)
Birth length	38 cm (10th - 50th %)	45.7 cm (50th %)	48.3 cm (25th - 50th %)	U
Birth HC	27.75 cm (10th - 50th %)	34 cm (90th %)	U	U
Development				
Age at sitting	11 months	10 months	U	U
Age at walking	19 months	15 months	12 months	U
Physical exam				
Weight	10.4 kg (7th %)	At 1 y 7 months: 11.1 kg (50th - 75th %)	32 kg (25th - 50th %)	56 kg (5th - 10th %)
Height	75.5 cm (<1st %)	At 1 y 7 months: 78 cm (10th - 25th %)	134 cm (25th - 50th %)	170.2 cm (10th - 25th %)
Head	HC: 48 cm (42nd %), relative macrocephaly, dolichocephaly, mild plagiocephaly (right posterior flattening). Malar flattening.	At 1 y 7 months: HC: 50.5 cm (>97th %), frontal bossing, dolicocephaly. CT: Extra-axial fluid collections. MRI: bilateral patchy areas of abnormal signal intensity in subcortical white matter suggestive of gliosis. Most marked in frontal lobe.	HC: 54 cm (75th %). Normocephalic.	HC: 58.5 (>97th %), dolichocephaly, bitemporal narrowing and frontal bossing. Widow's peak. Long face. Malar flattening.
Eyes	Bilateral epicanthal folds, upslanted palpebral fissures. High, arched eyebrows.	Deep-set eyes. Bilateral epicanthal folds. Mildly downslanting palpebral fissures. Normal fundoscopic exam.	High, arched eyebrows. Frequent episodes of conjunctivitis.	Normal ophthalmological exam. Arched eyebrows.
Ears	Protruding ear lobes. Recurrent otitis media. Tympanostomy. Incompletely folded and hypoplastic helices.	Mildly low-set	Frequent ear infections	Fleshy ear lobes
Nose	Depressed nasal bridge, upturned tip, slightly anteverted nares.	Slightly depressed nasal bridge	Slightly depressed nasal bridge	Tubular
Mouth and jaw	Micrognathia, long philtrum.	Gap between central incisors	WNL	Teeth removal due to dental malocclusion, prognathia. High arched palate.
Musculoskeletal	Short stature, short arms and legs, short hands and feet. Proximally placed thumbs. Normal skeletal x-ray survey. Kyphosis on sitting.	Right leg 1.5 cm shorter than left leg	WNL	Increased joint mobility, but no hyperextensibility (Beighton score 2/9). Small S-shaped scoliosis in thoracolumbar spine.
Skin and integuments	Deep plantar creases. Hyperconvex nails.	Mildly hypoplastic nails. Decreased size of the distal phalanges of all fingers in hands. Mild 2-3 toe syndactyly. Nevus flammeus over glabella.	Persistent fetal pads	Diffuse telangiectasias over upper chest. Normal nails. Two hyperpigmented spots in right calf and inner thigh.
Abdomen/ gastrointestinal	Diastasis recti	Frequent constipation	WNL	WNL
Cardiorespiratory	Pneumonia	Recurrent chest congestion	WNL	WNL
Genitourinary	Multicystic dysplastic right kidney, left kidney with increased echogenicity, 3 tiny cysts and poor corticomedullary differentiation.	Left vesicoureteral reflux and hydronephrosis, and bilateral subcapsular renal cysts (largest 7 mm in size, left kidney). Recurrent urinary tract infections. Normal female Tanner stage 1.	Moderate left hydronephrosis and severe dilatation of the left renal pelvis. Left pyeloplasty performed.	Bilateral innumerable small renal cysts, with normal function. Tanner 5 pubertal development. Urinary tract infection.
Endocrine	No mention of signs or symptoms of diabetes or any endocrine disorder.	No mention of signs or symptoms of diabetes or any endocrine disorder.	Blood glucose level of 99 mg/dL, HbA1C: 5.2 %, unremarkable urinalysis.	No mention of signs or symptoms of diabetes or any endocrine disorder.
Neurological exam				
Muscle tone	Mild hypotonia	WNL	WNL	Mild hypertonia in upper extremities. Brisk tendon reflexes, 3 beats of clonus in ankles.
Seizures	No	No	One episode of febrile seizures. Normal EEG.	No
Gait	Wide-based, no ataxia.	Walks with a limp, normal radiographs.	WNL	WNL
Sensory deficits	Moderate to severe bilateral sensorineural hearing loss. Absence of connexin 26 or connexin 30 mutations.	No	Hypermetropia	No
Coordination and motor skills	Gross motor delay. Immature grasp.	Delayed fine and gross motor skills	Good gross motor skills, but difficulties in single-limb activities, bilateral integration skills, and coordination.	On WISC-3, slow motor speed, but visual and motor processing skills are average or better. Problem lies on motor output. Difficulty with fine motor tasks.
Behavior and cognition				
Autism	Autistic features: deficits in social responsivity and joint attention, mild stereotypy, high pain threshold; however, good eye contact and some communivative gesture use. Autism probable, but not settled yet.	Not currently exhibiting autism symptoms in formal behavioral assessment, but too young to completely rule out.	Yes	Autistic features: Unusual affect and late-onset social difficulties, decreased eye contact, emotional irritability, gets stuck in several tasks.
Diagnostic criteria, supportive tests	DSM-IV. Q-CHAT total score: 57.	DSM-IV. Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales. Too young for ADI-R or ADOS.	DSM-IV. Vineland Adaptative Behavior Scales, Asperger's Diagnostic Rating Scale, Behavior Assessment System for Children - 2nd edition.	DSM-IV. ADOS. SCQ.
Other behaviors and neuropsychiatric comorbidities	Flat affect. Mild intermitent irritability. Minimal response to pain.	No	Anxiety. Self-injurious behaviors. Pica. Nail biting. Short attention span.	Anxiety. Unusual affect and social skills. Mood changes.
Cognition, adaptive behavior, language	Global developmental delay. Marked speech delay, no words at 21 months. At age 21 months (18.5 months corrected for prematurity): receptive language age equivalent 12 months; expressive language age equivalent 9 months; problem-solving age equivalent 17 months.	Nonverbal cognitive skills at age-appropriate level. Delays in receptive and expressive language skills, 2 words at 1 y, 10 words at 22 months.	Developmental delay. Speech delay; speaks in 3-word phrases. Echolalia. Uses 50 to 80 words.	Nonverbal learning disability. At age 22 y: Low average cognitive skills (overall IQ: 85, performance IQ: 78). Average language skills (verbal IQ: 91). Finished high school.

Figure S1. Probe coverage of the 17q12 region across different array platforms.

Schematic of the 17q12 genomic interval deleted in our patients, along with the genes within the region and the flanking segmental duplications (blue bars). The probe coverage of the different array platforms used in this study is shown for comparative purposes. These include the custom-designed Agilent ISCA oligonucleotide arrays (44K, 105K, and 180K), and the commercially available Illumina and Affy SNP arrays (Illumina 1M, 550K, 370K, 317K and Affy 6.0).