Supplemental Information

SUPPLEMENTAL TABLE 14 Recurrent CNVs Most Commonly Identified in Cohorts With ASD by Using CMA Analysis

CNV Region	Frequency[a]	Common Clinical Features
16p11.2 deletion	1 in 304	ASD, DD or ID, expressive language impairment, relative or absolute macrocephaly, overweight
16p11.2 duplication	1 in 396	ASD, schizophrenia, bipolar disorder, ADHD, relative or absolute microcephaly, underweight
15q11.2-q13 (BP2–BP3) duplication	1 in 494	ASD, DD or ID, epilepsy, hypotonia, ataxia, behavior problems
15q13.2-q13.3 (BP4–BP5) deletion	1 in 659	ASD, DD or ID, epilepsy, schizophrenia, cardiac defects
1q21.1 duplication	1 in 659	ASD, DD or ID, schizophrenia, ADHD, relative macrocephaly, hypertelorism
22q11.2 duplication	1 in 659	ASD, DD or ID, hypotonia, motor delay
16p13.11 deletion	1 in 791	ASD, DD or ID, epilepsy, schizophrenia, congenital anomalies
7q11.23 duplication	1 in 989	ASD, DD or ID, growth retardation, hypotonia
16p12.2 deletion	1 in 989	ASD, DD or ID, schizophrenia, epilepsy, growth retardation, cardiac defects, microcephaly, hypotonia
17q12 deletion	1 in 1978	ASD, DD or ID, schizophrenia, renal cysts, mature-onset diabetes of the young type 5
15q13.2–13.3 (BP4–BP5) duplication	1 in 1978	ASD, DD or ID, obesity

BP2 breakpoint 2; BP3 breakpoint 3; BP4 breakpoint 4; BP5 breakpoint 5; DD developmental delay; ID intellectual disability.

[a] Moreno-De-Luca D et al[631]; the frequency of each CNV among 3955 probands with ASD from the Autism Genetic Resource Exchange, Autism Genome Project, and Simons Foundation Autism Research Initiative Simplex Collection cohorts.

SUPPLEMENTAL TABLE 13 Selected Genetic Syndromes Associated With ASD

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
Fragile X syndrome	Long face, prominent forehead and jaw, large ears, joint laxity, macroorchidism after puberty in boys	*FMR1* (CGG repeat expansion, abnormal methylation)	Targeted mutation analysis (PCR and Southern blot)	Genetic counseling (X-linked dominant inheritance); all mothers of individuals with an *FMR1* full mutation are carriers of an *FMR1* premutation or full mutation; extended family counseling is necessary; premutation carriers are at risk for fragile X–associated tremor/ataxia syndrome and *FMR1*-related primary ovarian insufficiency in female patients; several targeted pharmacologic therapies are under investigation
Neurofibromatosis 1	Multiple café-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, cutaneous neurofibromas	*NF1*	Clinical criteria; optimized protein truncation testing, sequence analysis, and deletion or duplication analysis are available but infrequently required	Genetic counseling (autosomal dominant inheritance); 50% de novo, 50% inherited; associated problems requiring investigation or monitoring (optic gliomas, other CNS tumors, peripheral nerve sheath tumors, vasculopathy, hypertension, orthopedic issues, osteopenia)
PTEN hamartoma tumor syndrome (includes Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome)	Marked macrocephaly, skin hamartomas, pigmented macules of the glans penis	*PTEN*	*PTEN* sequence analysis, deletion or duplication analysis	Genetic counseling (autosomal dominant inheritance with highly variable expression); associated problems requiring investigation or monitoring (significant risk of benign and malignant tumors of the thyroid, breast, and endometrium as well as intestinal polyps, colorectal cancer, renal cell carcinoma, cutaneous melanoma, and cerebellar dysplastic gangliocytoma)
Rett syndrome	Deceleration of head growth velocity, acquired microcephaly, loss of purposeful hand use, prominent hand stereotypies (especially hand wringing or clasping), apraxia, hyperventilation or breath-holding, seizures	*MECP2*	*MECP2* sequence analysis, deletion or duplication analysis	Genetic counseling (>99% de novo, <1% germline mosaicism); associated problems requiring investigation or monitoring and anticipatory guidance (failure to thrive, gastroesophageal reflux, respiratory problems, osteopenia, sudden death); targeted pharmacologic therapy under investigation
Smith-Lemli-Opitz syndrome	Characteristic facial features (narrow forehead, low-set ears, ptosis, epicanthal folds, short nose, anteverted nares), microcephaly, cleft palate, 2- to 3-toe syndactyly, postaxial polydactyly, hypospadias in male	*DHCR7*	7-dehydrocholesterol level (elevated); *DHCR7* sequence analysis available	Genetic counseling (autosomal recessive inheritance); potential role for treatment with cholesterol

SUPPLEMENTAL TABLE 13 Continued

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
	patients, prenatal and postnatal growth retardation			
Timothy syndrome	Long QT interval, other ECG abnormalities (atrioventricular block, macroscopic T-wave alternans), congenital heart defects, cutaneous syndactyly, low-set ears, flat nasal bridge, thin upper lip, round facies, baldness for the first 2 y of life followed by thin scalp hair, dental abnormalities, frequent infections because of altered immune response, intermittent hypoglycemia	*CACNA1C*	Targeted mutation analysis, sequence analysis, deletion or duplication analysis	Genetic counseling, autosomal dominant, usually de novo, but parental germline mosaicism has been observed; treatment related to long QTc (β-blocker, pacemaker, implantable defibrillator) and avoidance of hypoglycemia
Tuberous sclerosis	Hypopigmented macules, angiofibromas, shagreen patches (connective tissue nevi), ungual fibromas, retinal hamartomas	*TSC1*, *TSC2*	Clinical criteria; *TSC1* and *TSC2* sequencing available	Genetic counseling (autosomal dominant inheritance); associated problems requiring investigation or monitoring (CNS tumors, seizures, renal angiomyolipomas or cysts, cardiac rhabdomyomas and arrhythmias); potential role for targeted pharmacologic therapy (mTOR inhibitors)

CACNA1C, calcium channel, voltage-dependent, L-type, α-1c subunit; CGG, cytosine-guanine-guanine; CNS, central nervous system; *DHCR7*, 7-dehydrocholesterol reductase; ECG, electrocardiogram; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; *PTEN*, phosphatase and tensin homolog; QTc, corrected QT interval; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2. Adapted with permission from Myers SM, Challman TD. Autism Spectrum Disorders. In: Voigt RG, Macias MM, Myers SM, eds. *Developmental and Behavioral Pediatrics*. Elk Grove Village, IL: American Academy of Pediatrics; 2011:249–291.

SUPPLEMENTAL TABLE 15 Selected ASD Risk Genes Identified or Confirmed in Whole-Exome Studies

Gene	Gene Name	Broad Functional Categorization
SCN2A	sodium channel, voltage-gated, type II, α subunit	Synaptic functions (eg, ion channels, neurotransmitter receptors, cell adhesion molecules, microtubule assembly, scaffolding proteins, actin cytoskeleton)
GRIN2B	glutamate receptor, ionotropic, N-methyl-D-aspartate 2B	
KATNAL2	katanin p60 subunit A-like 2	
ANK2	ankyrin 2, neuronal	
DSCAM	Down syndrome cell adhesion molecule	
NRXN1	neurexin 1	
SHANK2	SH3 and multiple ankyrin repeat domains 2	
SHANK3	SH3 and multiple ankyrin repeat domains 3	
PTEN	phosphatase and tensin homolog	Intracellular signaling, activity-dependent synaptic protein synthesis and degradation
SYNGAP1	synaptic Ras GTPase activating protein 1	
DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	
POGZ	pogo transposable element with ZNF domain	
CUL3	cullin 3	
CHD2	chromodomain helicase DNA binding protein 2	Transcription regulation, chromatin remodeling
CHD8	chromodomain helicase DNA binding protein 8	
ADNP[a]	activity-dependent neuroprotector homeobox	
ARID1B	AT rich interactive domain 1B (SWI1-like)	
ASH1L	ASH1 (absent, small, or homeotic)-like	
KDM5B	lysine-specific demethylase 5B	
KMT2C	lysine-specific methyltransferase 2C	
SETD5	SET domain containing 5	
TBR1	T-box, brain, 1	

Based on de novo loss of function variants and small de novo deletions (false discovery rate < 0.01). Adapted from Sanders SJ, He X, Willsey AJ, et al; Autism Sequencing Consortium. Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron.* 2015;87(6):1215–1233; Krumm N, O'Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. *Trends Neurosci.* 2014;37(2):95–105; Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. *Annu Rev Med.* 2015;66:487–507; De Rubeis S, He X, Goldberg AP, et al; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature.* 2014;515(7526):209–215; Bourgeron T. From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nat Rev Neurosci.* 2015;16(9):551–563; and Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature.* 2012; 485(7397):237–241.

[a] Also involved in microtubule dynamics at the synapse.

SUPPLEMENTAL TABLE 16 Selected Metabolic Conditions That May (Rarely) Be Associated With an ASD Phenotype

Disorders of amino acid metabolism
Phenylketonuria (untreated)
Homocystinuria
Branched-chain ketoacid dehydrogenase kinase deficiency
Disorders of γ-aminobutyric acid metabolism
Succinic semialdehyde dehydrogenase deficiency
Disorders of cholesterol metabolism
Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)
Disorders associated with cerebral folate deficiency
Folate receptor 1 gene mutations
Dihydrofolate reductase deficiency
Disorders of creatine transport or metabolism
Arginine-glycine amidinotransferase deficiency
Guanidinoacetate methyltransferase deficiency
X-linked creatine transporter deficits
Disorders of carnitine biosynthesis
6-*N*-trimethyllysine dioxygenase deficiency
Disorders of purine and pyrimidine metabolism
Adenylosuccinate lyase deficiency
Adenosine deaminase deficiency
Cytosolic 5′-nucleotidase superactivity
Dihydropyrimidine dehydrogenase deficiency
Phosphoribosyl pyrophosphate synthetase superactivity
Lysosomal storage disorders
Sanfilippo syndrome (mucopolysaccharidosis type III)
Mitochondrial disorders
Mitochondrial DNA mutations
Nuclear DNA mutations
Others
Biotinidase deficiency
Urea cycle defects

Adapted from Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013;15(5):399–407; Legido A, Jethva R, Goldenthal MJ. Mitochondrial dysfunction in autism. *Semin Pediatr Neurol.* 2013;20(3):163–175; Jiang YH, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit Rev Clin Lab Sci.* 2014;51(5):249–262; and Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. *Epilepsy Behav.* 2015;47:147–157.

SUPPLEMENTAL REFERENCES

631. Moreno-De-Luca D, Sanders SJ, Willsey AJ, et al. Using large clinical data sets to infer pathogenicity for rare copy number variants in autism cohorts. *Mol Psychiatry.* 2013;18(10):1090–1095