SnapShot: Genetics of Autism

Neuron

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	CHR GENE	PROTEIN FUNCTION	HUMAN PHENOTYPE (MUTANT MOUSE PHENOTYPES)
Mendelian Syndromes[1]	6q23.3 (AHI1*)	Jouberin; interacts with β-catenin in cilia	**Joubert syndrome.** (Reduced brain and body size. Cerebellar, retinal, and kidney defects. Most die by P10. Neuron-specific loss leads to depressive-like phenotypes.)
	7q35-q36.1 (CNTNAP2*)	Caspr2, a neurexin family member; clusters voltage-gated K+ channels	**Recessive EPI syndrome, ASD, ADHD, TS, OCD.** (Neuronal migration defects. Reduced GABAergic neurons and decreased cortical synchrony. Seizures. Deficits in social, repetitive behaviors, and USV.)
	9q34.13 (TSC1)	Hamartin, a growth inhibitory protein that negatively regulates the mTOR pathway	**Tuberous Sclerosis type I.** (Liver and neural tube defects. Die by E12. Abnormal kidney and liver growth in heterozygotes. Variable brain structure, function and behavior abnormalities in conditional mutants. Die at various postnatal ages. Neuron-specific loss causes abnormal spine morphology and cortical excitability. Loss of LTD.)
	10q23.31 (PTEN)	Protein tyrosine phosphatase; negatively regulates the mTOR pathway	**Cowden disease.** (Placenta and germ cell defects. Die by E9.5. Neuron-specific loss alters synaptic physiology. Heterozygotes have prostate, skin and colon defects, and spontaneous tumors. Macrocephaly, neuronal hypertrophy, abnormal social interaction, and increased survival in conditional mutants.)
	11q13.4 (DHCR7)	Final enzyme in cholesterol biosynthetic pathway	**Smith-Lemli-Opitz syndrome.** (Craniofacial and lung abnormalities. Die by P1. Abnormal cholesterol regulation and enlarged bladders. Hypomorphic mutants are viable and fertile. Compound mutants have fused toes, enlarged ventricles, and 25% embryonic lethality.)
	12p13.33 (CACNA1C)	α-1 subunit of a voltage-dependent Ca2+ channel	**Timothy syndrome.** (Die embryonically. Impaired pancreatic function. Motor defects and antidepressant-like behavior in heterozygotes; anxiety-like deficits in females. Neuron-specific loss, impaired cognition and LTP.)
	15q11.2 (UBE3A)	Ubiquitination ligase; targets protein degradation system	**Angelman syndrome.** (Small brain, seizure susceptibility, motor and learning deficits. Reduced spine density and impaired LTP. Impaired synapse maturation and plasticity.)
	16p13.3 (TSC2)	Tuberin; which negatively regulates the mTOR pathway	**Tuberous Sclerosis type II.** (Heart, neural tube, and motor defects. Purkinje cell death. Die by E12. Various tumors and axon guidance defects in heterozygotes. Dominant-negative mutant has enhanced anxiety-like behaviors; motor, learning, social behavior deficits.)
	17q11.2 (NF1)	Neurofibromin; a GTPase activator and negative regulator of RAS signaling	**Neurofibromatosis.** (Macrocephaly, small eyes, and heart defects. Delayed organ development. Embryonic lethal. Increased astrocytes and tumor susceptibility. LTP and learning and memory deficits in heterozygotes.)
	Xp21.2 (DMD)	Dystrophin; cytoskeletal protein bridging ECM	**Duchenne muscular dystrophy.** (Muscle and heart defects in hemizygous males and homozygous females. Reduced fertility. Abnormal retinal electrophysiology and synapse organization, density, and maturation.)
	Xp21.3 (ARX)	Aristaless-related homeobox protein TF	**LIS, XLID, EPI, ASD.** (Hemizygous males die perinatally. Decreased inhibitory synaptic transmission. Males hemizygous for point mutations or triple repeat expansions have seizures. Defects in behavior and GABAergic neuron generation and migration.)
	Xq27.3 (FMR1)	Fragile X mental retardation protein; an RNA-binding protein that traffics mRNA	**Fragile X syndrome.** (Seizures. Enlarged testes in males. Learning and social behavior defects. Dendritic spine abnormalities. Enhanced LTD and impaired LTP. Altered cortical drive and E/I neuronal cortical networks.)
	Xq28 (MECP2)	MeCP2; involved in transcriptional regulation and chromatin organization	**Rett syndrome.** (Brain, breathing, and motor defects in hemizygous males. Mild cognitive and anxiety-like phenotypes in heterozygous females. Various conditional loss and postnatal reduction mimic null phenotypes in adult hemizygous males. Impaired excitatory synapses and spine morphology. Increased neuronal connectivity.)
Rare Variants	2p16.3 (NRXN1)	A neurexin; forms intracellular junctions through neuroligin binding	**ASD, ID, language delay, SCZ.** (Reduced startle and PPI. Enhanced anxiety-like behavior and motor learning. Impaired spatial memory. Defective LTP. Defects in excitatory synaptic strength and diminished NMDA/AMPA receptor current.)
	3p13 (FOXP1)	A forkhead box TF	**ID, ASD, SLI.** (Cardiovascular defects. Die embryonically.)
	6q16.3 (GRIK2*)	A postsynaptic glutamate receptor subunit	**Recessive ID.** (Increased sensitivity to drug-induced seizures. Elevated startle and pain threshold. Impaired synaptic plasticity and inhibitory transmission.)
	7q31.1 (FOXP2)	A forkhead box TF	**SLI.** (Growth retardation, reduced USV, cerebellar, motor and neurological defects. Perinatal death. Impaired LTD and plasticity.)
	15q11-q13		**ASD, EPI, ID.** (Cleft palate in deletion mutants; die by P3; motor, and cognitive defects. Seizures. Increased newborn USV in maternal heterozygotes. Reduced activity, social interactions, and USV; increased anxiety-like behavior in duplications.)
	16p11.2		**ASD, ADHD, ID, EPI, SCZ.** (Mild structual brain defects and gene dose-dependent behavioral phenotypes.)
	17q11.2 (SLC6A4)	5-HT transporter	**ASD, OCD.** (Heart defects. Hyperactive, aggressive, anxiety-like behaviors, and learning deficits.)
	22q11.21		**DiGeorge syndrome, SCZ, ASD, ID.** (Sensorimotor, learning, and memory deficits. Hyperactivity. Increased anxiety-like behavior.)
	22q13.33 (SHANK3)	A PSD scaffold protein	**ASD.** (Variable phenotypes including excessive grooming, anxiety-like behavior, and disrupted social interactions. Abnormal dendritic spines. Reduced synaptic transmission, LTP, LTD, and NMDAR-dependent responses.)
	Xp22.32-p22.31 (NLGN4X)	A neuroligin; ligand for β-neurexins	**ASD, ID, TS, ADHD.** (Reduced brain size. Social interaction and USV deficits.)
	Xq13.1 (NLGN3*)	A neuroligin; ligand for β-neurexins	**ASD.** (Reduced brain size. Abnormal learning, social behavior, USV, and olfaction. Hyperactivity, altered E/I balance shift caused by increased inhibitory synaptic transmission.)
Common Alleles	1q42.2 (DISC1)	Large transmembrane protein involved in neurite outgrowth and brain development	(Region-specific changes in neuronal morphology. Homozygote and heterozygote learning and memory deficits. Reduced neurogenesis and altered neuron distribution. Abnormal dendritic spines. Reduced short-term plasticity.)
	2q31.1 (SLC25A12)	Mitochondrial Ca2+-binding carrier	(Growth retardation. Tremors, myelination and motor defects. Die E18–P15.)
	3p25.3 (OXTR)	GPCR for oxytocin	(Abnormal maternal behavior. Hypoactivity, increased aggression and USV in males. Social memory defects. Fewer GABAergic synapses.)
	7q31.2 (MET)	Receptor tyrosine kinase	(Muscle, axon guidance, placenta, and liver defects. Die by E14. Abnormal cortical dendrites/spines and hyperconnectivity of local circuits in conditional mutant.)
	7q22.1 (RELN)	Large secreted ECM protein involved in cell-cell interactions	(Reduced body size and premature death in some mutants. Retinal, olfactory, and fertility defects. Various neuron structural, functional, and localization abnormalities. Impaired PPI and LTP and reduced inhibitory tone in heterozygotes.)
	7q36.3 (EN2)	Homeobox TF critical for hindbrain patterning	(Deficits in cerebellar development. Altered DA neuron generation and degeneration. Hyperactivity. Motor, learning, and grooming impairments.)
	12q14.2 (AVPR1A)	GPCR for arginine vasopression	(Impaired spatial memory and reduced PPI. Social deficits in females. Reduced anxiety-like behaviors in males.)
	17q21.32 (ITGB3)	Mediates platelet cell adhesion and cell-surface signaling	(Platelet defects, anemia, internal bleeding, increased bone mass, hypocalcemia, and premature death. 50% die embryonically from placental defects. Altered social and repetitive behaviors.)

See online version for legend and references.

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This SnapShot presents genes and chromosomal regions implicated in risk for autism spectrum disorder and a summary of reported phenotypes of their mouse model counterparts. Due to space limitations, we were unable to show genes for which there is no reported mouse phenotype. These include the following:

TYPE OF SYNDROME/VARIANT	CHR (GENE)	PROTEIN FUNCTION	NEURODEVELOPMENTAL PHENOTYPES
Mendelian Syndrome	Xp22.13 (CDKL5)	Encodes a cyclin-dependent kinase-like 5, a Ser-Thr protein kinase member	X-linked infantile spasm syndrome
Rare variant	1q21.1	N/A	ASD, ID, SCZ, ADHD, EPI
Rare variant	7q11.23	N/A	ASD, ID, language delay
Rare variant	11q13.3-q13.4 (SHANK2)	Encodes a PSD scaffold protein	ASD, ID
Rare variant	16p13.3 (A2BP1)	Encodes an RNA-binding protein; altered splicing in ASD brain	ID, ASD, EPI, SCZ, ADHD
Rare variant	17q12	N/A	ASD, SCZ, EPI
Rare variant	22q13.33	N/A	Phelan McDermid syndrome
Rare variant	Xp22.11 (PTCHD1)	Encodes a transmembrane protein structurally similar to sonic hedgehog	ASD, ID

[1]ASD occurs as a secondary diagnosis in some individuals with these syndromes
*Positive SNP associations with ASD
Abbreviations: CHR, chromosome; LTD, long-term depression; LTP, long-term potentiation; PPI, prepulse inhibition; E/I, excitatory/inhibitory; PSD, postsynaptic density; ASD, autism spectrum disorders; SCZ, schizophrenia; ADHD, attention deficit hyperactivity disorder; ID, intellectual disability; XLID, X-linked intellectual disability; LIS, lissencephaly; EPI, epilepsy; OCD, obsessive compulsive disorder; TS, Tourette syndrome; SLI, speech and language impairment; USV, ultrasonic vocalization; TF, transcription factor; ECM, extracellular matrix; GPCR, G-protein-coupled receptor.

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