

**SUPPLEMENTARY TABLE 1 Summary of genetically modified models of ASD**

<b>Gene</b>	<b>Whole brain</b>	<b>Neocortex</b>	<b>Hippocampus</b>	<b>Amygdala</b>	<b>Cerebellum</b>	<b>Striatum</b>
<i>Nlgn3</i>	Volume↓[71]	(M-Excitatory spine turnover↑[41] GABAergic synapses↔[80])	(M-Volume↓, Dendrite complexity↑, Spine density↔, PSD length↔, Presynaptic bouton size↓, Presynaptic vesicle number↓, Presynaptic spine area↓[22, 23])			(M-Volume↓[20])
<i>Nlgn4</i>	Volume↓[42]		Excitatory & inhibitory synapse markers↓[32]		Volume↓ [42]	
<i>Nrxn1</i>	(2KO- gross anatomy↔ [16])	(2KO- inhibitory synapse density↓[58] Volume↓, Cell density↑, Dendrite length↓, Synapse ultrastructure↔ [16])			(3KO- inhibitory synapse density↓[58])	
<i>Shank3</i>		NMDAR↓,  Spine density↔[17]	GluR1↓[5] Perforated synapse density↑ or ↔ [85] Dendrite complexity↔, Spine density↔[53, 88, 89] or ↓[89] Spine length↑ or ↓[89] PSD length↔, PSD thickness↔[88]		Dendrite complexity↑, Spine density↓[51]	Dendrite length↑,  Dendrite complexity↑, Spine density↓[66, 88] PSD length↓, PSD thickness↓[88]
<i>Mecp2</i>	Brain weight↓[9, 29]	Volume↓[26, 49, 74] Cell density↑[26, 49, 78] Cell size↓[49, 73, 87] Dendrite length↓ [43, 49, 74, 78, 87] or ↔ [76] Dendrite complexity↓[43, 49, 74, 78, 87]. Spine density↓[26, 74, 76, 78] Abnormal axon orientation[3] Glutamatergic synapse density↓[3, 8] (KI-Dendrite length↑, Dendrite complexity↑[45] Glutamatergic synapse density↑[3, 8])	Cell density↑[43] Cell size↓[9, 29]  Spine density↓[3, 77] Spine head size↓[3]		Cell density↑[43] Cell size↓[9]  Spine density↓[51]	

Gene	Whole brain	Neocortex	Hippocampus	Amygdala	Cerebellum	Striatum
<i>Fmr1</i>		Dendrite complexity↔, but directional↑[27] Spine density↑[11, 13, 38-40, 63] or ↔[12, 28, 33, 83] Spine length↑[13, 63] or ↔[12, 28, 33, 83] Spine motility↑[13] Spine turnover↑[12, 13, 60] Filopodia↑, Mature spines↓[12, 28, 56, 65, 83]  (KI-Dendrite complexity↔, Spine density↑, Spine length↑[70], Atypical cell orientation during neuron migration[14])	Spine density↔[30, 31]  Spine length↑[30, 67] or ↓[67]  Filopodia↑[30, 54] or ↔[54] or ↓[31] Mature spines↓[30, 54] or ↔[54] or ↑[31] Presynaptic active zone size↓, Presynaptic docked vesicle number↓[50] (KI-Dendrite complexity↓, Spine density↑, Spine length↑[70])	Inhibitory synapses↓[64]  (KI-Dendrite complexity↓, Spine density↑, Spine length↑[70])		PSD density↑, PSD length↔,  Spine length↑[62]
<i>Ube3a</i>	Brain weight↓ [46]	Tissue weight ↓[46] Cortical thickness↔, Cell density↔[75, 86] Spine density↓[15, 48, 75] Thin spines↑, Stubby spines↓ [48] Presynaptic GABAergic vesicle density↑[86] (KI: Spine density↑[92])	Spine density↓, Spine length↓[79]  Presynaptic vesicle density↓[79]		Tissue weight ↓[46] Cell density↔, Dendrite complexity↔ [15]	
<i>Tsc1</i>		Cell size↑[24, 57]/↔[81] Dendrite complexity↔, Spine density↑[81]	Cell size↑[57, 82] Spine length↑, Spine density↓[82]		Cell density↓, Cell size↑, Spine density↑[84]	
<i>Tsc2</i>		Cell size↔, Dendrite complexity↔, Spine density↑[81]	Spine length↑, Excitatory synapse number↓[91]		Cell density↓[72]	
<i>Chd8</i>		Dendrite complexity↓, Spine density↓[18]				

Gene	Whole brain	Neocortex	Hippocampus	Amygdala	Cerebellum	Striatum
<i>Syngap1</i>		Dendritic complexity early, Spines formed early and pruned prematurely, Spine size↑[1] Bouton density↓, Axon terminal branching↓[4]	Dendritic complexity↔, Spines formed early and pruned prematurely Spine size↑[10] Thin and stubby spines↔, Mushroom spines↑[7] Spine density↔, Spine types↔[2]			
<i>Arid1b</i>		Dendrite length↓, Dendrite complexity↓, Spine density↓, Spine head size↓[47]	Dendrite length↓, Dendrite complexity↓[47]			
<i>Grin2b</i>		Neuron migration delayed, Dendrite length↑, Dendrite complexity↑[44]	Spine density↓[6]			
<i>Dscam</i>		Volume↓, Apical dendrite complexity↑, Dendrite length↓, Spine density↑ (all transient changes)[55]				
<i>Tbr1</i>		Defective cortical morphology, Abnormal neuron migration, Flawed axonal projection[34, 35]		Defective neuron differentiation [37]		
15q13.3 microdeletion	Volume↑[52]					
15q11-13 duplication	Gross morphology↔ [61]	Turnover of excitatory spines↑[41]	Volume↓[21]			
16p11.2 deletion	Volume↑ [36] Weight↓ [69] or↔[68]	Cortical size↓[69] Dopaminergic cell number↓[68]				Volume↑, Cell density↑, Dendrite complexity↔, Spine density↔[68]
16p11.2 duplication	Volume↓[36]					

Gene	Whole brain	Neocortex	Hippocampus	Amygdala	Cerebellum	Striatum
22q11.2 deletions		Cell number↓, Inhibitory neurons↓, Cell size↔, Basal: dendrite length↓, dendrite complexity↓, Spine density↓, mushroom spines↓, spine width↑[90] Apical: dendrite complexity↔, spine density↔, spine length↔, mushroom spines↓, spine width↓, spine turnover↑[25]	Dendrite complexity↔[19] Spine length↔[19] or↓[59],  Spine width↔[19]or↓[59]  Spine density↔, PSD length↔[19] Mushroom spines↓, Excitatory synapse↓, Presynaptic vesicle density↓[59]			

Neuropathologic changes observed following reduced expression of specific genes or chromosomes are indicated for each brain area (see text for details explaining the differences between and within models). Changes due to overexpression (knock-in, KI) or expression of a mutant version (M) of the gene are indicated in parentheses. The direction of the arrows indicates increase (↑), decrease (↓), or no change (↔) compared to controls. The apparently contradictory results within a model can be explained by transient changes that occur with age, differences in location of the cells, or altered spine turnover rate.

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**SUPPLEMENTARY TABLE 2 Summary of clinical features of various ASD subtypes against behavioral phenotypes in genetically modified models**

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
<i>NLGN3/4</i>	<ul style="list-style-type: none"> <li>• Non-syndromic X-linked ASD</li> <li>• Intellectual disability [52, 70, 91]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Nlgn3</i> KO mice: normal social interaction in pairs, normal sociability, reduced social novelty preference, decreased ultrasonic vocalizations [114]</li> <li>• <i>Nlgn3</i> KO in striatal neurons expressing dopamine receptor 1, not dopamine receptor 2: repetitive behaviors [120]</li> <li>• <i>Nlgn3</i> KO rats: reduced juvenile social play [61]</li> <li>• <i>Nlgn3</i><sup>R451C</sup> KI mice: (129S2/SvPasCrl background) social interaction deficits [72, 134], repetitive behavior [17]. (C2J background) normal sociability, reduced ultrasonic vocalizations [20]</li> <li>• <i>Nlgn4</i> KO mice: reduced reciprocal social interaction in dyads, very mild difference in sociability, lack of preference for social novelty, reduced juvenile and adult ultrasonic vocalizations and impaired nest-building, increased self-grooming, compulsive marble burying and repetitive circling [43, 71, 76]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Nlgn3</i> KO mice: no perseveration on the hole-board test, normal spatial learning and inflexibility in the Morris water maze, locomotor hyperactivity in the open field, normal motor performance on the rotarod and normal levels of anxiety [114]</li> <li>• Conditional <i>Nlgn3</i> KO in Purkinje cells: hyperactivity [120]</li> <li>• <i>Nlgn3</i><sup>R451C</sup> mice: (129S2/SvPasCrl background) enhanced cognitive function, [72, 134], increased aggression [17]. (C2J background) developmental delays and impaired motor learning [20]</li> <li>• <i>Nlgn4</i> KO mice: No inflexibility during reversal spatial learning, normal anxiety-like behavior, activity and motor coordination [43, 71, 76]</li> </ul>
<i>NRXN1/3</i>	<ul style="list-style-type: none"> <li>• Intellectual disability, developmental delay, language problems, ASD [7, 49, 80, 133]</li> <li>• <i>NRXN1</i>: higher risk for schizophrenia [68]</li> <li>• Seizures, hypotonia and facial dysmorphism [7, 49, 80, 133]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Nrxn1</i> <math>\alpha</math> KO mice: (129/SvJ x C57BL/6J background) normal social behavior but increased self-grooming and impaired nest building [46]. (C57BL/6J background) enhanced sociability (both genders) and preference for social novelty (females only) in the 3-chamber test [54]</li> <li>• <i>Nrxn2</i> <math>\alpha</math> KO mice: decreased social interactions and increased grooming as well as increased anxiety phenotypes in both the open field and the novel object interaction task [11, 32]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Nrxn1</i> <math>\alpha</math> KO mice: (C57BL/6J background) increased aggression with adult and juvenile conspecifics (males only), hypoactivity (females), and anxiety-like behavior (males) [54]</li> </ul>
<i>CNTNAP2</i>	<ul style="list-style-type: none"> <li>• Intellectual disability and/or ASD [3, 4, 131]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Cntnap2</i> KO mice: reduced communication, decrease in social interaction in the 3-chamber task during reciprocal interactions and in home cage nesting, and elevated repetitive behaviors [111], no changes in social or repetitive behaviors [16]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Cntnap2</i> KO mice: inflexibility during reversal training in the water maze and a reduction of spontaneous alternation in the T-maze, increased hyperactivity [16]</li> <li>• <i>Cntnap2</i> KO rats and mice: severe epileptiform activity [111, 136]</li> </ul>

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
<i>SHANK3</i>	<ul style="list-style-type: none"> <li>• ASD [40]</li> <li>• Phelan-McDermid syndrome [63], showing global developmental delay, intellectual disability, delay or absence of speech, and ASD, as well as low motor tone and minor dysmorphic features [112, 145]</li> </ul>	<p><i>Shank3</i>-deficient mice:</p> <ul style="list-style-type: none"> <li>• Stereotypies, notably abnormally elevated levels of self-grooming [28, 62, 73, 74, 84, 110, 140-142, 149], mild deficits in social approach and/or reciprocal interactions [73, 84, 110, 141, 142, 149], abnormal ultrasonic vocalizations [12, 110, 141, 142, 149]</li> <li>• Genetic background does not appear to have a major impact on ASD behaviors in <i>Shank3</i>-deficient rodent models [37]</li> </ul>	<p><i>Shank3</i>-deficient mice:</p> <ul style="list-style-type: none"> <li>• Motor deficits and learning delays reminiscent of those seen in Phelan-McDermid syndrome [13, 73, 84, 92, 99, 110, 140-142, 149]</li> <li>• Decreased attention [28, 64]</li> </ul> <p><i>Shank3</i>-deficient rat:</p> <ul style="list-style-type: none"> <li>• Decreased attention [28, 64]</li> </ul>
<p><i>MECP2</i></p> <p><i>MECP2</i> duplication</p>	<ul style="list-style-type: none"> <li>• Primarily affects females [2, 118]</li> <li>• Developmental regression at 6-18 months, loss of sensory, motor and cognitive functions</li> <li>• &lt; 60% meet ASD criteria [119], with repetitive hand movements, social withdrawal and loss of verbal communication</li> <li>• Males with <i>MECP2</i> duplications have a syndromic manifestation including intellectual disability, language deficits, anxiety, and ASD [115]</li> </ul>	<ul style="list-style-type: none"> <li>• Conditional mutations in mice: impaired social behavior [22, 51, 57, 90, 94, 122]</li> <li>• Mice overexpressing <i>Mecp2</i> (<i>Mecp2<sup>Tg1</sup></i>): social interaction deficits [121]</li> <li>• Marmoset monkey model of <i>MECP2</i> duplication: deficits of social interaction (more pronounced in males), stereotypical behavior [5, 93]</li> </ul>	<ul style="list-style-type: none"> <li>• Constitutive <i>Mecp2</i> deletion in mice: embryonic lethality</li> <li>• Conditional mutations in mice: Stiff and uncoordinated gait, hind-limb claspings, seizures, breathing irregularities, deficits in learning and memory, and reduced anxiety [22, 51, 57, 90, 94, 122].</li> <li>• Mice overexpressing <i>Mecp2</i> (<i>Mecp2<sup>Tg1</sup></i>): enhanced learning [26]</li> </ul>
<i>FMR1</i>	<ul style="list-style-type: none"> <li>• Intellectual disability, delayed speech, anxiety, attention deficit disorder and hyperactivity, seizure and body dysmorphism [24]</li> <li>• ~22% of all carriers and 30% of males with <i>FMR1</i> mutations meet ASD criteria [58, 119]</li> </ul>	<p><i>Fmr1</i> KO mice:</p> <ul style="list-style-type: none"> <li>• ASD-related behaviors including abnormal sociability and social recognition, deficit in the establishment of social dominance, decrease of ultrasonic vocalizations and repetitive behaviors [48, 97, 128]</li> <li>• Degree of behaviors strongly affected by the genetic background [127]</li> </ul> <p><i>Fmr1</i> KO rats</p> <ul style="list-style-type: none"> <li>• Low levels of social play behavior and high levels of a repetitive block chewing [61]</li> </ul>	<p><i>Fmr1</i> KO mice:</p> <ul style="list-style-type: none"> <li>• Score poorly in learning and memory tasks, impaired spatial working memory [139, 148], impaired reversal learning and increased perseverance in both spatial navigation tasks and touch-screen visual discrimination [31, 35], impaired contextual fear memory [36, 55]</li> <li>• Comorbid behaviors such as hyperactivity, impulsivity and perseverance [86], prone to seizures [21]</li> <li>• Low anxiety-like behaviors [128]</li> </ul>

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
<i>TSC1/2</i>	<ul style="list-style-type: none"> <li>• Benign tumors (tubers) in brain and kidneys, increased risk for malignant tumors</li> <li>• Seizures, intellectual disability and ASD [18]</li> <li>• ASD in 36% carriers of <i>TSC</i> mutations [119]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Tsc1</i><sup>+/-</sup> mice: significantly reduced social approach and nest building behavior [53, 124, 137]</li> <li>• <i>Tsc2</i><sup>+/-</sup> mice: reduced sociability and reduced preference for social novelty, reduced dyadic reciprocal interaction in pairs and abnormal mother-pup interaction, reflected by altered ultrasound vocalization [116, 124, 150]</li> <li>• Cerebellar KO of <i>Tsc1</i>: impaired social interaction, increased grooming and higher ultrasonic vocalizations [137]</li> <li>• <i>Tsc2</i> KO in Purkinje cells: increased repetitive behaviors and impaired social behavior [116]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Tsc1</i> or <i>Tsc2</i> KO in mice: lethal, with severe neurological abnormalities and seizures beginning at postnatal day 5 and a median age of 35 days [89, 100]</li> <li>• <i>Tsc1</i><sup>+/-</sup> mice: impaired in hippocampus-dependent versions of both spatial and fear-conditioned tests of learning and memory [53, 124, 137]</li> <li>• <i>Tsc2</i><sup>+/-</sup> mice: impaired spatial learning and memory and contextual fear conditioning [42, 124]</li> <li>• <i>Tsc1</i><sup>+/-</sup> and <i>Tsc2</i><sup>+/-</sup> mice: no seizures, or the brain anatomic abnormalities characteristic of TSC in human [53]</li> <li>• Cerebellar KO of <i>Tsc1</i>: deficits in reversal learning [137]</li> <li>• <i>Tsc2</i> KO in Purkinje cells: progressive Purkinje cell degeneration [116]</li> </ul>
<i>CHD8</i>	<ul style="list-style-type: none"> <li>• High-penetrance ASD risk gene [33, 69, 107, 135]</li> <li>• Also a risk gene for schizophrenia [81]</li> <li>• Global developmental delay, macrocephaly, ASD, facial dysmorphism, sleep disturbances, gastrointestinal problems [9, 130, 151]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Chd8</i>-deficient mice: social deficits [39, 78, 113], but not repetitive behaviors [113]</li> </ul>	<ul style="list-style-type: none"> <li>• Knock-down of the <i>CHD8</i> ortholog: macrocephaly and decreased gut mobility in zebrafish [9, 132], increased brain weight and volume [78, 113] and decreased gut length [78] in mice</li> <li>• <i>Chd8</i>-deficient mice: anxiety [78, 113], persistent behavior during learning [78], and an absence of learning deficits [39, 113]</li> </ul>
<i>SCN2A</i>	<ul style="list-style-type: none"> <li>• Infantile seizures, epileptic encephalopathy, epileptic syndromes (reviewed in [146])</li> <li>• Intellectual disability and ASD without epilepsy [33, 69, 143]</li> </ul>	<ul style="list-style-type: none"> <li>• Mice expressing adult <i>Scn2a</i> isoform: social behavior was normal [50]</li> <li>• Mice with <i>Scn2a</i> GAL879-881QQQ mutation: repetitive behaviors [79]</li> </ul>	<ul style="list-style-type: none"> <li>• Mice expressing adult <i>Scn2a</i> isoform: no spontaneous seizures but increased susceptibility to proconvulsant-induced seizures, reduced anxiety and increased risk-taking behavior [50]</li> <li>• Mice with <i>Scn2a</i> GAL879-881QQQ mutation: spontaneous and handling-induced seizures [79]</li> </ul>

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
<i>SYNGAP1</i>	<ul style="list-style-type: none"> <li>• Several neurodevelopmental disorders, including non-syndromic intellectual disability in 100% of carriers and ASD in 50% of carriers [33, 60, 69]</li> <li>• Encephalopathy, epilepsy, hypotonia, stereotypical behaviors and aggression (reviewed in [101])</li> </ul>	<p><i>Syngap1</i>-deficient mice:</p> <ul style="list-style-type: none"> <li>• Increased stereotypical behaviors, increased social isolation [56]</li> </ul>	<p><i>Syngap1</i>-deficient mice:</p> <ul style="list-style-type: none"> <li>• Reduced social memory, hyperactive, greater risk-taking behavior, increased startle reaction, and reduced pre-pulse inhibition [56], improved long-term memory [1], poor performance on amygdala-dependent cued fear conditioning and working memory [56] and dentate gyrus-driven learning [25]</li> <li>• Susceptible to seizures and show abnormalities on electroencephalogram recording [56]</li> </ul>
<i>ARID1B (or BAF250B)</i>	<ul style="list-style-type: none"> <li>• Coffin-Siris syndrome</li> <li>• Developmental delay, hypotonia, feeding problems, and physical features such as anomalous nails or shorter fingers, hirsutism, sparse scalp hair and facial dysmorphism (reviewed in [123])</li> <li>• ASD [30, 33, 59, 69, 106, 138]</li> </ul>	Behavioral testing not reported yet.	
<i>GRIN2B</i>	<ul style="list-style-type: none"> <li>• Neurodevelopmental disorders, including epileptic encephalopathy, intellectual disability and ASD [33, 44, 45, 69]</li> </ul>	ASD phenotypes not tested.	<ul style="list-style-type: none"> <li>• <i>Grin2b</i> full KO mice: no suckling response and therefore die shortly after birth [88]</li> <li>• Cortical and hippocampal CA1 <i>Grin2b</i> KO mice: impaired performance on the Morris water maze, T-maze spontaneous alternation, and Pavlovian trace fear conditioning tests [15]</li> <li>• Corticostriatal or striatal <i>Grin2b</i> KO mice: impairment in choice learning [14]</li> <li>• Cortical <i>Grin2b</i> KO mice: impaired shifting in pairwise visual discrimination and reversal tests [14]</li> </ul>
<i>DSCAM</i>	<ul style="list-style-type: none"> <li>• ASD risk gene [33, 69]</li> </ul>	ASD phenotypes not tested.	<ul style="list-style-type: none"> <li>• <i>Dscam</i><sup>del17</sup> mutant mice: decreased motor function, impaired motor learning ability [147]</li> </ul>
<i>TBR1</i>	<ul style="list-style-type: none"> <li>• Intellectual disability and ASD [33, 34, 104, 107]</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Tbr1</i><sup>+/-</sup> mice: social deficits, and reduced ultrasonic vocalization [67].</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Tbr1</i><sup>+/-</sup> mice: impaired associative memory and cognitive flexibility [67].</li> </ul>

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
<p>15q11-q13 deletions and 15q13.3 microdeletions</p>	<p>Angelman syndrome: <i>de novo</i> deletions on the maternal copy, paternal uniparental disomy, or defective imprinting on chromosome 15q11.2-q13 or <i>UBE3A</i> mutations [82]</p> <ul style="list-style-type: none"> <li>• Developmental delay at 6 to 12 months of age. Ataxia or tremor, speech and motor deficits, inappropriate happiness with hand flapping, seizures, microcephaly, hypotonia, misaligned eyes, drooling, protruding tongue, disturbed sleep and anxiety [77, 95]</li> <li>• ASD in 34% cases [82]</li> </ul> <p>Prader-Willi syndrome: deletion, uniparental disomy, or an imprinting center defect on the paternal chromosome 15q11.2-q13 [23, 38]</p> <ul style="list-style-type: none"> <li>• Extremely low motor tone</li> <li>• Difficulty in feeding during infancy, uncontrolled eating and development of obesity in early childhood</li> <li>• Cognitive impairment</li> <li>• ASD in ~25% cases [8], with social deficits and increased repetitive and ritualistic behaviors [19, 77]</li> </ul> <p>15q13.3 microdeletion:</p> <ul style="list-style-type: none"> <li>• Increased risk for ASD, intellectual disability and other disorders including schizophrenia and epilepsy [6, 68, 108, 125]</li> </ul>	<p>Microdeletion model:</p> <ul style="list-style-type: none"> <li>• Heterozygous deletion D/+ mice: deficits in social interaction, increased grooming and fewer ultrasonic vocalizations [83]</li> </ul>	<p>Angelman syndrome model:</p> <ul style="list-style-type: none"> <li>• Mice with maternal <i>Ube3a</i> deletions (<i>Ube3amKO</i>): decreased motor coordination, susceptibility to audiogenic seizures, and impaired learning and memory [66, 75, 102, 126], severity of those behaviors varies with genetic background and age [66]</li> </ul> <p>Prader-Willi models:</p> <ul style="list-style-type: none"> <li>• Mice with paternal deletion: lethal [47], small, weak, and feed poorly (reviewed in [10])</li> <li>• <i>Snrpn</i> mutant mice: decreased locomotor activity and impaired attention functioning in the five-choice serial reaction time task, normal fear reactivity [117]</li> <li>• <i>Magel2</i>-null mice: increased anxiety in response to new stimuli, intact learning and memory capacities [85]</li> </ul> <p>Microdeletion model:</p> <ul style="list-style-type: none"> <li>• Heterozygous deletion D/+ mice: normal cognition and no seizures [83]</li> </ul>

ASD gene	Clinical features	ASD behavioral phenotypes in animal models	Comorbidities in animal models
15q11-13 duplication, often of maternal origin	<ul style="list-style-type: none"> <li>• Neurodevelopmental and neurological phenotypes with features of both Prader-Willi syndrome and Angelman syndrome</li> <li>• Hypotonia, speech disorder, developmental delay, seizures and ASD [27]</li> </ul>	<ul style="list-style-type: none"> <li>• Mice with maternally derived duplication (<i>matDp/+</i>): no impairment on ASD-associated behaviors [103]</li> <li>• Mice with paternally derived duplication (<i>patDp/+</i>): reduced sociability, abnormal ultrasound vocalization [103]</li> <li>• Mice with triplication of <i>Ube3a</i>: decreased sociability, reduction of ultrasonic vocalizations and repetitive self-grooming [126]</li> </ul>	<ul style="list-style-type: none"> <li>• Mice with paternally derived duplication (<i>patDp/+</i>): behavioral inflexibility, increased anxiety [103]</li> </ul>
16p11.2 deletions and duplications	<ul style="list-style-type: none"> <li>• ASD, schizophrenia and other neurodevelopmental manifestations [87, 96, 144]</li> <li>• Speech and language delays, cognitive impairment and facial dysmorphism</li> <li>• ASD in 16% of subjects with deletion and 20% of those with duplication [29]</li> </ul>	<ul style="list-style-type: none"> <li>• Mice carrying a deletion, Df(7)16, or the reciprocal duplication, Dp(7)16: only mild ASD-like behaviors, more severe phenotype in deletion compared to duplication model [65]</li> <li>• Df(7)16 mice: normal sociability and preference for social novelty, prominent stereotypies in climbing behaviors [65]</li> <li>• Dp(7)16 mice: normal sociability and preference for social novelty, no prominent stereotypies [65]</li> </ul>	<ul style="list-style-type: none"> <li>• Df(7)16 mice: impaired post-natal survival, novelty-induced hyperactivity [65]</li> <li>• Dp(7)16 mice: no viability problems, hypoactivity in a modified home cage environment [65]</li> </ul>
22q11.2 deletion syndrome	<ul style="list-style-type: none"> <li>• Velocardial facial or DiGeorge syndrome</li> <li>• Congenital or late-onset features including mild dysmorphism, inability to seal the nasopharynx, heart defects, and impaired cognition</li> <li>• High risk for neuropsychiatric disorders, including attention deficit hyperactivity disorder, schizophrenia, intellectual disability and ASD [105]</li> <li>• ASD in ~11% cases [119]</li> </ul>	Social behavior has not been reported yet.	<ul style="list-style-type: none"> <li>• 22q11.2DS mice: Learning and memory deficits, including impaired spatial learning in the T-maze or the water maze [41, 129], impaired fear conditioning [109, 129], improved early-phase reversal learning, impaired late-phase and overall touchscreen reversal learning, impaired discrimination performance [98]</li> </ul>

Clinical features observed in patients are compared to the behavioral phenotype of animal models carrying various ASD risk genes.

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**SUPPLEMENTARY TABLE 3 Summary of ASD-behavioral phenotypes in models of idiopathic ASD**

<b>Model</b>	<b>Behavioral phenotype</b>
BTBR-T <sup>+</sup> tf/J	<ul style="list-style-type: none"> <li>• Low sociability [9, 22, 23], reduced reciprocal social interactions in dyads [19, 25, 38], aberrant vocalizations, and impairments in several social settings such as scent marking and social transmission of food preference [19, 27-29]</li> <li>• High level of stereotypies or repetitive behaviors, including jumping, digging, self-grooming, perseverative marble burying and unusual hole board exploration [1, 19, 21, 25, 31, 32, 36, 37]</li> <li>• Comorbidities: cognitive rigidity in reversal learning tasks, hyperactivity in the open field, impaired motor performance on the rotarod, and inconsistent performance in tests of anxiety-like behavior [14, 23, 35]</li> </ul>
BALB/cByJ	<ul style="list-style-type: none"> <li>• Significant social deficits compared to inbred mouse strains with high sociability, such as C57BL/6J and FVB/NJ mice [8, 22, 23], including juvenile social interactions [5, 8], low levels of sociability in the social approach assay ([8, 9, 12, 22, 23], reduced reciprocal social interactions [6, 24]</li> <li>• No repetitive self-grooming [33]</li> </ul>
Prenatal sodium valproate (VPA) exposure	<ul style="list-style-type: none"> <li>• Social deficits, with reduced social exploration, and low numbers of isolation-induced ultrasonic vocalizations in both mouse and rat pups, low levels of juvenile rough and tumble play in rats [13, 20, 30, 34]</li> <li>• Increased frequency of motor stereotypies and repetitive marble burying, decreased sensitivity to pain, increased anxiety [34]</li> <li>• Sexual divergence in behavior, with males being more affected than females [15, 26]</li> </ul>
Maternal autoantibodies	<ul style="list-style-type: none"> <li>• Deficits in development, increased ultrasonic vocalizations, and increased stereotypical behaviors in mice [7, 10, 11]</li> <li>• Increased stereotypies and atypical social behavior in rhesus monkeys [2, 4, 18]</li> </ul>
Maternal immune activation	<ul style="list-style-type: none"> <li>• Reduced ultrasonic vocalizations, decreased social interaction, and repetitive behaviors in mice [17]</li> <li>• Stereotypical behavior, increased vocalizations, atypical social interactions [3], deficits in social attention in rhesus monkeys [4, 16]</li> </ul>

Behavioral phenotypes observed in ASD models derived from inbred strains and environmental interventions are summarized to depict the ASD phenotypes seen in these models.

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