SFARI GENE Q3/2023 REPORT

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1. Human Gene Module Quarterly Report, Q3/2023

1.1 Updated Human Gene Dataset

A total of 12 new genes were added to the Human Gene Module for the Q3/2023 release, bringing the overall number of ASD candidate genes in the module to 1,416 (HG_Figure 1, panel A). In-depth annotation of 1311 rare variants and one common variant was completed in this quarter leading to a total of 31,269 rare and 1,407 common variants, respectively (HG_Figure 1, panel B). Annotation of 113 new references was accomplished for the Human Gene module in Q3/2023, bringing the total number of references to 5,608.

HG_Figure 1. Number of ASD-linked genes and variants in the Human Gene Module (A) The number of genes has grown from 1382 to 1416 over the last four quarters. (B) The number of rare variants has increased from 28,619 to 31,269; number of common variants has increased from 1,393 to 1,407.

1.2 Highlights of Q3/2023 Human Gene Dataset

In Q3/2023, we have curated a comprehensive collection of articles reporting genes and variants associated with ASD. These articles span multiple study designs, ranging from large-scale genome-wide studies to more focused investigations highlighting specific genes. This dataset also includes case reports detailing known ASD gene mutations, accompanied by detailed clinical profiles of the probands. The selection of new genes in the Q3 dataset was guided by evidence collected from a variety of sources, encompassing recent genetic findings, prior genetic research, and pertinent functional data. Additionally, several of the existing ASD genes within the database have been updated to incorporate newly reported variants from recent studies.

The Q3/2023 dataset is described in the following sections:

- New genes added in this quarter (HG_Table 1)
- Summary evidence for new genes (Section 1.3)
- New reports added to existing genes (HG_Table 3)
**HG_Table 1. New genes added in Q3/2023**

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Rare*</th>
<th>Syndromic</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHX9</td>
<td>✓</td>
<td>✓</td>
<td>1, 2</td>
</tr>
<tr>
<td>SLC35G1</td>
<td>✓</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>RPH3A</td>
<td>✓</td>
<td></td>
<td>1, 3</td>
</tr>
<tr>
<td>AP2M1</td>
<td>✓</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CACNG2</td>
<td>✓</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>FBXL13</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td>PLEKHA8</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRR25</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLFN5</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNCAIP</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGM1</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPS54</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Rare single gene evidence: Defined as a gene with at least two coding variants identified in individuals diagnosed with ASD. Genes identified by Transmission and De novo Association (TADA) analysis with a false discovery rate (FDR) < 0.1 are in **bold** font.

Syndromic evidence: Presentation of syndromic features in addition to diagnosis of ASD

Functional evidence:
1. Functional assessment of disease-associated variants
2. Animal model
3. Interaction with known ASD candidate genes

### 1.3 Description of Q3/2023 Human Gene Dataset

Genetic and functional evidence collected for selection and annotation of new genes is described below:

**DHX9**: Yamada et al., 2023 demonstrated that two de novo missense variants in the DHX9 gene (a p.Arg1052Gln variant that was previously reported in an ASD proband from the Simons Simplex Collection in Iossifov et al., 2014, and a p.Gly414Arg variant that was identified in a novel patient presenting with developmental delay/intellectual disability, undergrowth, and ventricular non-compaction cardiomyopathy) resulted in aberrant localization and loss-of-function effects in transgenic Drosophila lines. In the same report, the authors also found that mice heterozygous for a p.Gly416Arg variant, which corresponded to the p.Gly414Arg variant, displayed reduced body weight, reduced emotionality, and cardiac conduction abnormalities (prolonged PR interval). Additional de novo variants in the DHX9 gene, including a de novo loss-of-function variant, have been identified in ASD probands from simplex families from the MSSNG cohort (Zhou et al., 2022), while a paternally inherited DHX9 missense variant with a CADD score of 31 was identified in a Chinese ASD proband from the ACGC cohort (Guo et al., 2018). Calame et al., 2023 described 20 individuals with rare monoallelic DHX9 variants presenting with either a neurodevelopmental...
disorder characterized by developmental delay/intellectual disability, neuropsychiatric disorders (including autism spectrum disorder), seizures, axial hypotonia, and dysmorphic features, or Charcot-Marie-Tooth disease; subsequent functional studies demonstrated that DHX9 variants disrupted cellular localization and helicase activity and increased R-loops and double-stranded DNA breaks, while a Dhx9 -/- mice was shown to exhibit behavioral and neurological abnormalities in this report.

**SLC35G1:** SLC35G1 was identified in an ASD candidate gene in Wang et al., 2023 based on reaching a false discovery rate (FDR) threshold of <0.1 following TADA analysis in both a discovery cohort of 1,141 Chinese ASD probands and a combined cohort consisting of the discovery cohort of Chinese ASD probands and 42,607 ASD probands originally published in Zhou et al., 2022. Wang et al., 2023 also demonstrated that mice harboring a heterozygous deletion of Slc35g1 exhibited defects in interactive social behaviors and increased marble-burying activity compared to wild-type mice. In total, four de novo coding variants in SLC35G1 (two loss-of-function variants and two missense variants) have been reported in ASD probands (Yuen et al., 2017; Zhou et al., 2022; Wang et al., 2023).

**RPH3A:** Pavinato et al., 2023 reported six individuals with heterozygous RPH3A missense variants: four individuals with intellectual disability and epileptic seizures, and two individuals with autism spectrum disorder and intellectual disability. Additional functional assessment in this report found that both the ID/epilepsy-associated p.Thr450Ser variant and the ASD/ID-associated p.Asn618Ser variant resulted in reduced synaptic localization of GluN2A, increased GluN2A-dependent NMDAR currents, and alteration of postsynaptic calcium levels in neuronal cultures. A de novo loss-of-function variant and multiple de novo missense variants in the RPH3A gene have also been reported in ASD probands (Iossifov et al., 2014; Yuen et al., 2017; Satterstrom et al., 2020; Trost et al., 2022; Wang et al., 2023). Avagliano Trezza et al., 2021 identified RPH3A as a ubiquitination target of UBE3A and demonstrated that an Angelman syndrome-associated missense variant in UBE3A abrogated the interaction with RPH3A.

**AP2M1:** Analysis of whole-exome sequencing data from 13,091 individuals diagnosed with autism recruited from the SSC, SPARK, and iPSYCH cohorts, 19,488 first-degree relatives of individuals with autism from the SSC and SPARK cohorts, and 194,070 individuals identified from unselected population samples from the iPSYCH and UK Biobank cohorts in Rolland et al., 2023 identified AP2M1 as a novel ASD candidate gene intolerant to loss-of-function variants with an odds ratio greater than 10. Several de novo variants in the AP2M1 gene, including a de novo loss-of-function variant and multiple de novo missense variants, have been identified in ASD probands (Yuen et al., 2017; Satterstrom et al., 2020; Zhou et al., 2022; Wang et al., 2023). A recurrent de novo missense variant in the AP2M1 gene (p.Arg170Trp) that resulted in impaired clathrin-mediated endocytosis was found to be responsible for a form of autosomal dominant intellectual disability (MRD60; OMIM 618587) in four unrelated females in Helbig et al., 2019; all four females presented with global developmental delay, moderate-severe intellectual disability, and seizures, and two of the four individuals with this disorder were also diagnosed with autism spectrum disorder.

**CACNG2:** Analysis of whole-exome sequencing data from 13,091 individuals diagnosed with autism recruited from the SSC, SPARK, and iPSYCH cohorts, 19,488 first-degree relatives of individuals with autism from the SSC and SPARK cohorts, and 194,070 individuals identified from unselected population samples from the iPSYCH and UK Biobank cohorts in Rolland et al., 2023 identified CACNG2 as a novel ASD candidate gene intolerant to loss-of-function variants with an odds ratio greater than 10. Several de novo variants in the CACNG2 gene, including two de novo missense variants and a de novo intragenic deletion that was predicted to result in an in-frame deletion of 30 amino acids from the extracellular AMPA receptor-binding domain, have been identified in ASD probands (Brandler et al., 2016; Lim et al., 2017; Yuan et al., 2023). A de novo missense variant in the CACNG2 gene (p.Val143Leu) was identified in a patient presenting with sporadic non-syndromic intellectual disability in Hamdan et al., 2011; this variant was experimentally demonstrated to result in reduced binding to GluR1 or GluR2 AMPAR subunits, reduced GluR1 cell surface expression, and reduced miniEPSC amplitude and frequency in transfected hippocampal neurons. Subsequent characterization of a knock-in mouse with the p.Val143Leu variant in Caldeira et al., 2022 demonstrated that these mice displayed cognitive and social deficits, as well as hippocampal synaptic transmission defects.

**FBXL13:** Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified FBXL13 as a novel
ASD risk gene with a false discovery rate (FDR) less than 0.1. A de novo loss-of-function variant in this gene has also been observed in a Chinese ASD proband (Yuan et al., 2023).

**PLEKHA8**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified PLEKHA8 as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. De novo missense variants in this gene have also been identified in two ASD probands from the Simons Simplex Collection (Iossifov et al., 2014).

**PRR25**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified PRR25 as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. A de novo missense variant in this gene has also been observed in a Chinese ASD proband (Wang et al., 2023).

**SLFN5**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified SLFN5 as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. De novo missense variants in this gene have also been observed in three ASD probands (Iossifov et al., 2014; Yuen et al., 2017; Zhou et al., 2022).

**SNCAIP**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified SNCAIP as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. De novo missense variants in this gene have also been identified in three ASD probands (De Rubeis et al., 2014; Zhou et al., 2022).

**TGM1**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified TGM1 as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. Additional de novo loss-of-function and missense variants in this gene have been observed in ASD probands (De Rubeis et al., 2014; Zhou et al., 2022).

**VPS54**: Transmission and De Novo Association (TADA) analysis of whole-genome sequencing data from a cohort of 4,551 individuals in 1,004 multiplex families having two or more autistic children identified VPS54 as a novel ASD risk gene with a false discovery rate (FDR) less than 0.1. Additional de novo variants in this gene, including a missense variant and a splice-region variant, have been identified in ASD probands from the Autism Sequencing Consortium (De Rubeis et al., 2014; Satterstrom et al., 2020).

In Q3/2023, the Human Gene module has undergone significant enrichment in terms of the diversity of ethnic backgrounds represented within ASD and NDD individuals. This enhancement is attributed to the inclusion of a series of recently published reports (shown below). These reports have contributed a wealth of genetic data from various ethnic groups, providing a more comprehensive and inclusive repository of information that reflects the global spectrum of individuals impacted by ASD.

- **ASD probands from China**
  - Yuan et al., Neuroscience Bulletin 2023
  - Wang et al., Biological Psychiatry 2023: One of the new candidate genes added to the Human Gene module in this quarter (SLC35G1) was added based on genetic and functional evidence described in this report.

- **ASD probands from India**
  - Sheth et al., BMC Neurology 2023

- **ASD probands of East African ancestry**
  - Tuncay et al., Cell Genomics 2023

- **NDD probands from Kenya and South Africa (the NeuroDev cohort)**
  - Kipkemoi et al., Neuron 2023

- **NDD probands from the NIHR BioResource project**
  - Sanchis-Juan et al., American Journal of Human Genetics 2023
HG_Table 2. Selected examples of new studies added to existing genes in Q3/2023

<table>
<thead>
<tr>
<th>Title</th>
<th>Gene</th>
<th>First Author</th>
<th>Journal/Book</th>
<th>Publication Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Heterogeneity and Different Phenotypes in Patients with SETD2 Variants: 18 New Patients and Review of the Literature</td>
<td>SETD2</td>
<td>Parra A</td>
<td>Genes (Basel)</td>
<td>2023</td>
</tr>
<tr>
<td>SCN1A-deficient excitatory neuronal networks display mutation-specific phenotypes</td>
<td>SCN1A</td>
<td>van Hugte EJH</td>
<td>Brain</td>
<td>2023</td>
</tr>
<tr>
<td>CUX1-related neurodevelopmental disorder: deep insights into phenotype-genotype spectrum and underlying pathology</td>
<td>CUX1</td>
<td>Oppermann H</td>
<td>Eur J Hum Genet</td>
<td>2023</td>
</tr>
<tr>
<td>Characterizing the autism spectrum phenotype in DYRK1A-related syndrome</td>
<td>DYRK1A</td>
<td>Kurtz-Nelson EC</td>
<td>Autism Res</td>
<td>2023</td>
</tr>
<tr>
<td>Intrafamilial variability in SLC6A1-related neurodevelopmental disorders</td>
<td>SLC6A1</td>
<td>Kassabian B</td>
<td>Front Neurosci</td>
<td>2023</td>
</tr>
<tr>
<td>Case Report-An Inherited Loss-of-Function NRXN3 Variant Potentially Causes a Neurodevelopmental Disorder with Autism Consistent with Previously Described 14q24.3-31.1 Deletions</td>
<td>NRXN3</td>
<td>Feichtinger RG</td>
<td>Genes (Basel)</td>
<td>2023</td>
</tr>
<tr>
<td>Large-Scale Whole Genome Sequence Analysis of &gt;22,000 Subjects Provides no Evidence of FMR1 Premutation Allele Involvement in Autism Spectrum Disorder</td>
<td>FMR1</td>
<td>Chubick A</td>
<td>Genes (Basel)</td>
<td>2023</td>
</tr>
<tr>
<td>Case report: Expanding the phenotype of FOXP1-related intellectual disability syndrome and hyperkinetic movement disorder in differential diagnosis with epileptic seizures</td>
<td>FOXP1</td>
<td>Cesaroni CA</td>
<td>Front Neurol</td>
<td>2023</td>
</tr>
</tbody>
</table>

1.4 Gene Highlight: PLPPR4

PLPPR4 was initially included in the Human Gene Module due to compelling functional evidence linking it to ASD. This association was derived from the description of mouse models that faithfully recapitulated core ASD-related phenotypes in studies conducted by Vogt et al. in 2015 and Schneider et al. in 2017. However, at that time, there was a lack of genetic evidence directly linking PLPPR4 to ASD, leading to its removal from the Human Gene Module of SFARI Gene.

In a recently published study by Li et al. in 2023, authors have provided genetic and functional evidence firmly associating PLPPR4 with neurodevelopmental disorders, including ASD. This study detailed the cases of three unrelated patients who presented with a disorder stemming from PLPPR4 haploinsufficiency. This condition was characterized by mild intellectual disability, language delay, motor delay, and autistic behavior, including the diagnosis of autism spectrum disorder in one patient. Further bolstering this link, subsequent functional investigations involving induced pluripotent stem cell (iPSC)-derived neurons from one of the patients with a de novo heterozygous PLPPR4 deletion revealed marked alterations, including a reduced density of dendritic protrusions, shorter neurites, and diminished axon length.
Moreover, upon re-evaluation of genetic data from recent large-scale sequencing studies involving ASD cohorts, a number of de novo variants in PLPPR4 emerged. These included a de novo loss-of-function variant and two de novo missense variants, as reported in studies by Satterstrom et al. in 2020, Zhou et al. in 2022, and Trost et al. in 2022. Considering this compelling new evidence, we propose the reinstatement of PLPPR4 into the Human Gene Module of SFARI Gene.

### 1.5 Human Gene Standardization

We continue to standardize the allele change and residue change data fields to the terminology developed by the Human Genome Variation Society (HGVS) for the Human Gene dataset. All new variant annotations were performed with standardized terminology and include genomic coordinates in GRCh38 genome build for allele change, residue change and correct genome build.

### 1.6 Development of a Candidate Gene Pool

The single line of evidence (SLOE) dataset includes genes and variants that are reported in the scientific literature but for which there is not sufficient evidence to meet our inclusion criteria for the database. We routinely query the SLOE dataset to identify corroborating evidence for newly identified ASD candidate genes. In Q3/2023, we performed harmonization of the variant data in SLOE. Three new articles added in this quarter are shown in HG_Table 3.

**HG_Table 3: New articles added to the SLOE dataset.**

<table>
<thead>
<tr>
<th>Title</th>
<th>First Author</th>
<th>Journal/Book</th>
<th>Publication Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>The contributions of rare inherited and polygenic risk to ASD in multiplex families</td>
<td>Cirnigliaro M</td>
<td>Proc Natl Acad Sci U S A</td>
<td>2023</td>
</tr>
<tr>
<td>Comparative yield of molecular diagnostic algorithms for autism spectrum disorder diagnosis in India: evidence supporting whole exome sequencing as first tier test</td>
<td>Sheth F</td>
<td>BMC Neurol</td>
<td>2023</td>
</tr>
<tr>
<td>The genetics of autism spectrum disorder in an East African familial cohort</td>
<td>Tuncay IO</td>
<td>Cell Genom</td>
<td>2023</td>
</tr>
<tr>
<td>Discovery and Validation of Novel Genes in a Large Chinese Autism Spectrum Disorder Cohort</td>
<td>Wang J</td>
<td>Biol Psychiatry</td>
<td>2023</td>
</tr>
<tr>
<td>Identification of de novo Mutations in the Chinese Autism Spectrum Disorder Cohort via Whole-Exome Sequencing Unveils Brain Regions Implicated in Autism</td>
<td>Yuan B</td>
<td>Neurosci Bull</td>
<td>2023</td>
</tr>
<tr>
<td>Genome sequencing and comprehensive rare-variant analysis of 465 families with neurodevelopmental disorders.</td>
<td>Sanchis-Juan A</td>
<td>Am J Hum Genet</td>
<td>2023</td>
</tr>
</tbody>
</table>
2 Copy Number Variant (CNV) Module Quarterly Report, Q3/2023

2.1 Updated CNV Dataset

A total of 13 new references providing 84 patient records from 66 unique cases were added to the CNV module for the Q3/2023 release. Several articles reporting CNVs have featured ASD probands representing a wide range of ancestral backgrounds. The list of articles added in Q3/2023 are shown in CNV_Table1.

CNV_Table 1. Articles added to the CNV module in Q3/2023

<table>
<thead>
<tr>
<th>PMID</th>
<th>Title</th>
<th>First Author</th>
<th>Journal/Book</th>
</tr>
</thead>
<tbody>
<tr>
<td>36881370</td>
<td>Identification of de novo Mutations in the Chinese Autism Spectrum Disorder Cohort via Whole-Exome Sequencing Unveils Brain Regions Implicated in Autism</td>
<td>Yuan B</td>
<td>Neurosci Bull</td>
</tr>
<tr>
<td>37365192</td>
<td>Elevated levels of FMRP-target MAP1B impair human and mouse neuronal development and mouse social behaviors via autophagy pathway</td>
<td>Guo Y</td>
<td>Nat Commun</td>
</tr>
<tr>
<td>37430334</td>
<td>17q25.3 copy number changes: association with neurodevelopmental disorders and cardiac malformation</td>
<td>Sahajpal NS</td>
<td>Mol Cytogenet</td>
</tr>
<tr>
<td>37492102</td>
<td>The genetics of autism spectrum disorder in an East African familial cohort</td>
<td>Tuncay IO</td>
<td>Cell Genom</td>
</tr>
<tr>
<td>37495270</td>
<td>Integrating RNA-Seq into genome sequencing workflow enhances the analysis of structural variants causing neurodevelopmental disorders</td>
<td>Riquin K</td>
<td>J Med Genet</td>
</tr>
<tr>
<td>37512036</td>
<td>Molecular and Functional Characterisation of a Novel Intragenic 12q24.21 Deletion Resulting in MED13L Haploinsufficiency Syndrome</td>
<td>Siavrienė E</td>
<td>Medicina (Kaunas)</td>
</tr>
<tr>
<td>37541188</td>
<td>Genome sequencing and comprehensive rare-variant analysis of 465 families with neurodevelopmental disorders</td>
<td>Sanchis-Juan A</td>
<td>Am J Hum Genet</td>
</tr>
<tr>
<td>37543562</td>
<td>Comparative yield of molecular diagnostic algorithms for autism spectrum disorder diagnosis in India: evidence supporting whole exome sequencing as first tier test</td>
<td>Sheth F</td>
<td>BMC Neurol</td>
</tr>
<tr>
<td>37550884</td>
<td>PLPPR4 haploinsufficiency causes neurodevelopmental disorders by disrupting synaptic plasticity via mTOR signalling</td>
<td>Li H</td>
<td>J Cell Mol Med</td>
</tr>
<tr>
<td>37563198</td>
<td>A cryptic microdeletion del(12)(p11.21p11.23) within an unbalanced translocation t(7;12)(q21.13;q23.1) implicates new candidate loci for intellectual disability and Kallmann syndrome</td>
<td>Ben-Mahmoud A</td>
<td>Sci Rep</td>
</tr>
<tr>
<td>37595579</td>
<td>Systematic evaluation of genome sequencing for the diagnostic assessment of autism spectrum disorder and fetal structural anomalies</td>
<td>Lowther C</td>
<td>Am J Hum Genet</td>
</tr>
<tr>
<td>37644171</td>
<td>CUX1-related neurodevelopmental disorder: deep insights into phenotype-genotype spectrum and underlying pathology</td>
<td>Oppermann H</td>
<td>Eur J Hum Genet</td>
</tr>
<tr>
<td>37664546</td>
<td>Expanding the mutational and clinical spectrum of Chinese intellectual disability patients with two novel CTCF variants</td>
<td>Tan B</td>
<td>Front Pediatr</td>
</tr>
</tbody>
</table>
3 Animal Models Module Quarterly Report, Q3/2023

3.1 Summary of updated mouse module dataset

In Q3/2023, the mouse module was updated with data from a total of 12 references. New genes added to the Animal Models module in this quarter include Dhx9, Gabrb1, Kmt2c, Map1b, Slc35g1 and Tet2. A total of 34 genetic mouse models were annotated or updated this quarter, including two existing models and ten rescue models, respectively. Allele types modeled in the ASD mouse models that were annotated this quarter include homozygous and heterozygous knockouts, as well as conditional knockouts. The articles annotated this quarter are shown in AM_Table1 and mouse models included in the Q3/2023 release are listed in AM_Table2.

AM_Table1: Articles annotated for AM mouse module in Q3/2023.

<table>
<thead>
<tr>
<th>Gene</th>
<th>PMID</th>
<th>Title</th>
<th>First Author</th>
<th>Journal/Book</th>
<th>Publication Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Map1b</td>
<td>37365192</td>
<td>Elevated levels of FMRP-target MAP1B impair human and mouse neuronal development and mouse social behaviors via autophagy pathway</td>
<td>Guo Y</td>
<td>Nat Commun</td>
<td>2023</td>
</tr>
<tr>
<td>Tet2</td>
<td>37402169</td>
<td>Tet2 acts in the lateral habenula to regulate social preference in mice</td>
<td>Xu X</td>
<td>Cell Rep</td>
<td>2023</td>
</tr>
<tr>
<td>Kmt2c</td>
<td>37538398</td>
<td>KMT2C knockout generates ASD-like behaviors in mice</td>
<td>Brauer B</td>
<td>Front Cell Dev Biol</td>
<td>2023</td>
</tr>
<tr>
<td>Gabrb1</td>
<td>37599823</td>
<td>Increased NMDARs in neurons and glutamine synthetase in astrocytes underlying autistic-like behaviors of Gabrb1(-/-) mice</td>
<td>Wang J</td>
<td>iScience</td>
<td>2023</td>
</tr>
<tr>
<td>Slc35g1</td>
<td>37393044</td>
<td>Discovery and validation of novel genes in a large Chinese ASD cohort</td>
<td>Wang J</td>
<td>Biol Psychiatry</td>
<td>2023</td>
</tr>
<tr>
<td>Dhx9</td>
<td>37467750</td>
<td>Monoallelic variation in DHX9, the gene encoding the DExH-box helicase DHX9, underlies neurodevelopment disorders and Charcot-Marie-Tooth disease</td>
<td>Calame DG</td>
<td>Am J Hum Genet</td>
<td>2023</td>
</tr>
<tr>
<td>Ank2</td>
<td>37321992</td>
<td>Kv7/KCNQ potassium channels in cortical hyperexcitability and juvenile seizure-related death in Ank2-mutant mice</td>
<td>Oh H</td>
<td>Nat Commun</td>
<td>2023</td>
</tr>
<tr>
<td>Ube3a</td>
<td>37389991</td>
<td>Autism-linked UBE3A gain-of-function mutation causes interneuron and behavioral phenotypes when inherited maternally or paternally in mice</td>
<td>Xing L</td>
<td>Cell Rep</td>
<td>2023</td>
</tr>
<tr>
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3.2 Highlights of mouse module annotations

Dhx9: Variation in DHX genes, including DHX9, has been linked to neurodevelopmental disorders including autism spectrum disorder (ASD). The homozygous knockout model shows no change in viability but exhibits decreased body weight compared to sex-matched wildtypes. The model also shows altered behavioral and neurological function. Male and female model mice show decreased locomotion, with a decrease in distance traveled in the periphery of the open field and a decrease in locomotor speed. Additionally, model male and female mice demonstrate decreased grip strength, increased tremor, and decreased auditory functioning, as measured by the auditory brainstem response test. Furthermore, the model shows altered metabolic function, with possible altered renal function, decreased glucose clearance, and decreased cholesterol levels.

Gabrb1: Altered GABAergic inhibitory transmission has been implicated in autism, with mutations in GABA-A receptors having been identified as genetic underpinnings to the disease. The Gabrb1 mutant model provides further evidence of this, exhibiting alterations in behavior. Specifically, mutant mice display decreased social interaction and increased grooming, with no change in general locomotor activity or anxiety. The model also shows upregulated NMDARs and NMDAR-currents, with increased levels of GluN1 and GluN2B in the hippocampus. Additionally, Gabrb1 mutant mice exhibit increased learning, displaying heightened responses to fear conditioning as well as enhanced susceptibility to picrotoxin-induced seizures. Alterations in social interaction, grooming, learning, and seizure susceptibility were all rescued by treatment with the NMDAR antagonist memantine or the glutamine synthetase antagonist methionine sulfoximine.

Kmt2c: Mutations in KMT2C have recently been associated with autism spectrum disorder (ASD) in humans. In the conditional knockout model, there is a 50% reduction in the expression levels of KMT2C in both cortical and hippocampal tissue. Though model mice show no change in growth and general locomotor activity, as measured by the accelerating rotarod test and the open field test, they show increases in anxiety, as measured by a decrease in total distance traveled in the center of the open field. Additionally, the model shows changes in social behavior, with increased time spent engaging with a novel mouse in the three-chamber social approach test and increased social dominance in the tube test of social dominance. Model mice also show alterations in spatial learning and memory in the Barnes maze test, with increased latency to find the escape hole and less time spent in the escape hole target region.

Map1b: To model MAP1B triplication in ASD proband, an overexpression mouse model was developed, in which the Map1b gene is specifically overexpressed in excitatory neurons of the prefrontal cortex. The mouse model shows social approach and social memory deficits in the three-chamber sociability test. This overexpression model, however, shows no changes in locomotor activity, repetitive behavior, anxiety, or spatial memory.

Slc35g1: Recent analysis has identified SLC35G1 as a new autism spectrum disorder (ASD) candidate gene. In line with this finding, the Slc35g1 knockout mouse model shows numerous deficits in social behavior. Heterozygous male mice exhibit significant decreases in social approach and social memory, with a significant decrease in preference for a novel mouse over a familiar mouse in the three-chamber social approach test. Additionally, the model shows a change in repetitive behaviors, with an increase in the number of marbles buried in the marble-burying test. The model shows no change in anxiety, general locomotor activity, or spatial learning, as demonstrated by results in the elevated plus maze test, the open field test, and the Barnes maze test, respectively.

Tet2: Variation in DHX genes, including DHX9, has been linked to neurodevelopmental disorders including autism spectrum disorder (ASD). The homozygous knockout model shows no change in viability but exhibits decreased body weight compared to sex-matched wildtypes. The model also shows altered behavioral and neurological function. Male and female model mice show decreased locomotion, with a decrease in distance traveled in the periphery of the open field and a decrease in locomotor speed. Additionally, model male and female mice demonstrate decreased grip strength, increased tremor, and decreased auditory functioning, as measured by the auditory brainstem response test. Furthermore, the model shows altered metabolic function, with possible altered renal function, decreased glucose clearance, and decreased cholesterol levels.