SFARI GENE Q4/2025 REPORT

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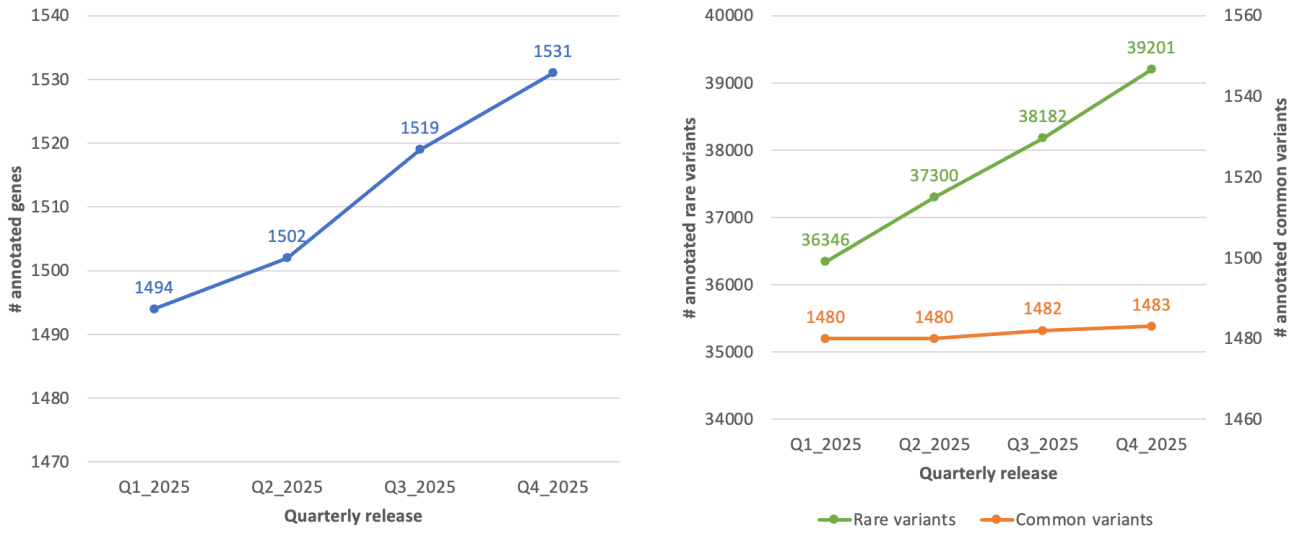
1. Human Gene Module
Quarterly Report, Q4/2025

1.1 Updated Human Gene Dataset

A total of ***twelve*** new genes were added to the Human Gene Module for the Q4/2025 release, bringing the overall number of ASD candidate genes in the module to **1,531** (HG_Figure 1, panel A). In-depth annotation of **1,019** rare variants and one common variant were completed in this quarter leading to a total of **39,201** rare and **1,483** common variants, respectively (HG_Figure 1, panel B). Annotation of **131** new references was accomplished for the Human Gene module in Q4/2025, bringing the total number of references to **6,698**.



HG_Figure 1. Number of ASD-linked genes and variants in the Human Gene Module over the last four quarters. (A) The number of genes has grown from 1,494 to 1,531 (B) The number of rare variants has increased from 36,346 to 39,201; number of common variants has increased from 1,480 to 1,483.

1.2 Highlights of Q4/2025 Human Gene Dataset

In **Q4/2025**, we curated newly reported ASD-associated genes and variants from recently published studies, ranging from large-scale genome-wide analyses to smaller, focused cohort investigations. Gene inclusion was stringently guided by multiple independent lines of evidence derived from recent literature, together with variant data reported in large-scale genome-wide studies in ASD (see below for details). In addition, several previously curated ASD genes were updated to incorporate newly identified variants. Notably, multiple studies reported rare variants from ethnically and geographically diverse populations, thereby expanding ancestral representation and presenting a more comprehensive view of the global genetic architecture of ASD.

The Q4/2025 dataset is described in the following sections:

- **New genes added in this quarter (HG_Table 1)**
- **Summary evidence for new genes (Section 1.4)**
- **New reports added to existing genes (HG_Table 2)**
- **New articles added to the SLOE dataset (HG_Table 3)**

HG_Table 1. New genes added in Q4/2025

Gene Symbol	Gene Name
DPYSL5	dihydropyrimidinase like 5
KMT2D	lysine methyltransferase 2D
MKRN1	makorin ring finger protein 1
PRMT9	protein arginine methyltransferase 9
PTCH1	patched 1
SF1	splicing factor 1
SMARCA1	SNF2 related chromatin remodeling ATPase 1
SPTAN1	spectrin alpha, non-erythrocytic 1
TCF12	transcription factor 12
ZEB2	zinc finger E-box binding homeobox 2
ZFYVE9	zinc finger FYVE-type containing 9
ZNF865	zinc finger protein 865

1.3 Description of Q4/2025 Human Gene Dataset

Newly curated publications in the Q4_2025 release broaden the ASD genetic landscape by adding rare variant findings from ethnically and geographically diverse cohorts, highlighting both the marked genetic heterogeneity of ASD and the importance of comprehensive sequencing strategies across populations.

Across European cohorts, Repiská et al. (2025) analyzed whole-exome sequencing data from 117 Slovakian ASD probands and demonstrated that the cumulative burden of rare variants was significantly associated with variability in social affect and adaptive behavior measures (ADOS-2 and VABS). These results support a polygenic burden model in which aggregated rare variation contributes to phenotypic diversity in ASD beyond strictly pathogenic variants.

Multiple large Chinese cohorts further strengthened ASD gene discovery and diagnostic frameworks. Wu et al. (2025) evaluated trio-WES data from 226 individuals with low-functioning ASD across two centers and developed a robust, clinically actionable nomogram to predict diagnostic yield prior to sequencing. Genetic evidence from this study contributed to the addition of four ASD candidate genes: **SPTAN1, ZEB2, TCF12, and PTCH1**, highlighting the utility of phenotype-informed sequencing strategies. Complementarily, Qin et al. (2025) retrospectively analyzed WES data from 128 individuals with neurodevelopmental disorders, showing that integrating CNV information with SNV/Indel analysis substantially improved diagnostic yield. This study identified recurrent pathogenic variants in established ASD/NDD genes (e.g., *SHANK3*, *ASXL3*, *EHMT1*) and functionally validated a deleterious *NLGN3* variant, reinforcing the importance of dual-dimension genomic analysis.

Finally, Suspitsin et al. (2025) reported results from 110 Russian individuals with ASD using chromosomal microarray analysis and clinical exome sequencing. Pathogenic CNVs and monogenic syndromic variants were identified in a subset of cases, while a large proportion of individuals carried rare variants of uncertain significance across high-confidence ASD genes, including recurrent findings in *TRIP12, AUTS2, ARID1B, PCDH19,* and *EP300*. Notably, hemizygous *PCDH19* missense variants were observed in affected males without epilepsy, expanding the phenotypic spectrum associated with this gene.

Collectively, these studies emphasize the global diversity of ASD genetic architecture, validate the contribution of rare and uncertain variants to phenotypic variability, and support integrated sequencing and analytical approaches for improved diagnosis and gene discovery in ASD.

1.4 Summary Evidence of New Genes

DPYSL5

Desprez et al. (2025) reported six distinct missense variants in **DPYSL5** across three male fetuses and six postnatal individuals up to 10 years of age. These variants included the previously identified recurrent p.Glu41Lys variant, which was experimentally validated as a loss-of-function allele by Jeanne et al., 2021. All living individuals in the Desprez et al. cohort exhibited developmental delay (6/6), including language delay (5/6) and mild to severe intellectual disability (5/5); four individuals were additionally diagnosed with autism spectrum disorder. Functional characterization of the novel DPYSL5 missense variants in differentiating mouse and human neuronal cultures demonstrated deficits in dendritic arborization, axonal elongation, and synaptic density. Consistent with these findings, among nine individuals with Ritscher–Schinzel syndrome 4 reported by Jeanne et al., 2021, one was diagnosed with ASD and two others exhibited stereotypic movements. Additionally, a de novo DPYSL5 missense variant was identified in an ASD proband from the Autism Sequencing Consortium (De Rubeis et al., 2014).

KMT2D

Shangguan et al., 2025 assembled genotype and phenotype data for 9 affected individuals from 9 unrelated families with predicted deleterious KMT2D variants through literature curation (Parisi et al., 2015; Sertçelik et al., 2016; Luo et al., 2021) and two web-based databases (ClinVar and DECIPHER). All 9 probands were diagnosed with autism and presented with intellectual disability and dysmorphic facial features. In the same report, the authors observed that selective knockdown of Kmt2d in the mouse hippocampus resulted in defects in social behaviors and increased repetitive behavior, as well as decreased excitatory and increased inhibitory synaptic transmission. De novo variants in the KMT2D gene, including a loss-of-function variant and several potentially deleterious missense variants, have also been identified in ASD probands from the Simons Simplex Collection, the SPARK cohort, the Autism Sequencing Consortium, the MSSNG cohort, and a Korean ASD cohort (Iossifov et al., 2014; Yuen et al., 2017; Krupp et al., 2017; Satterstrom et al., 2020; Zhou et al., 2022; Kim et al., 2024; Tan et al., 2024).

MKRN1

Plassmeyer et al. (2025) identified an ASD-associated 5′UTR variant in **MKRN1** through functional assessment of de novo variants from Simons Simplex Collection probands using a massively parallel reporter assay (MPRA) on polysome fractions. The variant showed reduced relative polysome/80S enrichment in both HEK cell–based in cellulo MPRA assays and patient-derived lymphoblastoid cell lines and was associated with decreased protein expression in patient-derived LCLs and in a dual-luciferase reporter assay (FDR-adjusted $p < 0.05$). A de novo missense variant with a CADD score > 30 was identified in a female ASD proband from the SPARK cohort (Zhou et al., 2022). Rare deletions affecting the MKRN1 gene (defined as those found in <0.1% of 10,851 population control samples) were identified in two individuals diagnosed with ASD and one diagnosed with schizophrenia from a cohort of 2,691 subjects diagnosed with a neurodevelopmental disorder (Zarrei et al., 2019).

PRMT9

Kroll-Hermi et al., 2025 reported 35 individuals from 26 families with biallelic loss-of-function variants in PRMT9 presenting with a neurodevelopmental disorder characterized by global developmental delay, learning disabilities, mild to severe intellectual disability, autism spectrum disorder, epilepsy, and hypotonia. Furthermore, skin fibroblasts from affected individuals exhibited reduced expression at the RNA and/or protein level and subsequent aberrant methylation activity, as well as anomalies in the length of primary cilia under ciliogenesis conditions. A prmt9 knockout zebrafish model displayed abnormal social preference in adult animals. A de novo loss-of-function variant and a de novo missense variant in PRMT9 had previously been reported in ASD probands from the SPARK cohort (Zhou et al., 2022). Using a Prmt9 conditional knockout (cKO) mouse, Shen et al., 2024 demonstrated that knockout

of Prmt9 in hippocampal neurons caused alternative splicing of ~1900 genes, which likely accounted for the aberrant synapse development and impaired learning and memory observed in Prmt9 cKO mice; furthermore, the authors identified a methylation-sensitive protein-RNA interaction between the arginine 508 (R508) of the splicing factor SF3B2, the site that is exclusively methylated by PRMT9, and the pre-mRNA anchoring site, a cis-regulatory element that is critical for RNA splicing.

PTCH1

Whole-exome sequencing of 168 patients with low-functioning ASD using a trio-based study design at Sun Yat-sen Memorial Hospital in Wu et al., 2025 identified a paternally inherited loss-of-function variant in the PTCH1 gene in a patient clinically diagnosed with ASD based on DSM-5 criteria and presenting with global developmental delay/intellectual disability. A number of de novo variants in PTCH1, including a de novo loss-of-function variant and several de novo missense variants that are predicted to be deleterious, have been identified in ASD probands from the Simons Simplex Collection, the SPARK cohort, the MSSNG cohort, the Autism Sequencing Consortium, the iHART cohort, and a Japanese cohort of 262 ASD probands (Iossifov et al., 2014; Yuen et al., 2016; Takata et al., 2018; Ruzzo et al., 2019; Zhou et al., 2022; Fu et al., 2022). Autism spectrum disorder or autistic traits have been reported in a subset of individuals with PTCH1-associated disorders, including basal cell nevus syndrome and somatic overgrowth with macrocephaly (Delbroek et al., 2011; Klein et al., 2019; Mashayekhi et al., 2023). Alterations in hippocampal and cortical layer structure, activity, and social behavior were observed in female Ptch1 +/- mice (Jackson et al., 2020). A prevalence estimate of autism of 4% was made in a cohort of 109 individuals from Norway with basal cell naevus syndrome caused by pathogenic PTCH1 variants (Brandtzæg et al., 2025).

SF1

Bou-Rouphael et al., 2025 described a cohort of 15 unrelated individuals with de novo likely deleterious variants in the SF1 gene presenting with neurodevelopmental disorders of variable severity. All individuals presented with developmental delay during the first years of life and mild facial features, and autism spectrum disorder was the most common neurodevelopmental disorder among individuals aged 3 years of older (n=9). Additional functional studies in neuronal progenitor cells in this report demonstrated that SF1 downregulation altered gene expression and alternative splicing programs, particularly in genes involved in neuronal differentiation, synaptic transmission, and axonal guidance. Ultra-rare de novo non-coding variants in the SF1 gene have been previously reported in ASD probands from the Simons Simplex Collection (Iossifov et al, 2014).

SMARCA1

Mirzaa et al., 2025 described 35 individuals from 26 families with de novo or maternally-inherited variants in the SMARCA1 gene presenting with an X-linked neurodevelopmental disorder characterized by mild to severe developmental delay/intellectual disability, delayed or regressive speech development, behavioral abnormalities, facial dysmorphisms, and other variable features, including macrocephaly; almost one-third of patients (31%; 11/35) received an ASD diagnosis. Mirzaa et al., 2025 also demonstrated that individuals with SMARCA1 truncating variants exhibited a mildly unique genome-wide DNA methylation profile with a high penetrance of macrocephaly, while genetic dissection of the NURF complex using single and double knockouts of Smarca1 and other NURF complex genes demonstrated the importance of NURF composition and dosage for proper forebrain development. Damaging de novo missense variants in the SMARCA1 gene have also been identified in a female ASD proband from the SPARK cohort (Zhou et al., 2022), as well as in a severely autistic Portuguese female with a clinical presentation significantly overlapping Rett syndrome (Lopes et al., 2016).

SPTAN1

Trio-based whole-exome sequencing of 168 patients with low-functioning ASD at Sun Yat-sen Memorial Hospital in Wu et al., 2025 identified a de novo in-frame insertion variant in the SPTAN1 gene that was classified as likely pathogenic in ClinVar in a patient clinically diagnosed with ASD based on DSM-5 criteria and presenting with global developmental delay/intellectual disability. A de novo loss-of-function variant and multiple de novo missense variants, many of which are predicted to be deleterious by one or more in silico tools, have been identified in SPTAN1 in ASD probands from the Simons Simplex Collection, the SPARK cohort, the Autism Sequencing Consortium, the MSSNG cohort, the iHART cohort, and a cohort of 22 Bulgarian ASD probands (Iossifov et al., 2014; Ruzzo et al., 2019; Feliciano et al., 2019; Satterstrom et al., 2020; Zhou et al., 2022; Fu et al., 2022; Tan et al.,

2025; Belenska-Todorova et al., 2025). Autism spectrum disorder has also been reported in a subset of individuals presenting with SPTAN1-associated disorders, including DEE5 and DEVEP (Syrbe et al., 2017; Marco Hernandez et al., 2022; Luongo-Zink et al., 2022).

TCF12
Trio-based whole-exome sequencing of 168 patients with low-functioning ASD at Sun Yat-sen Memorial Hospital in Wu et al., 2025 identified a de novo loss-of-function variant in the TCF12 gene in a patient clinically diagnosed with ASD based on DSM-5 criteria and presenting with global developmental delay/intellectual disability. Additional de novo loss-of-function variants, as well as a de novo missense variant predicted to be deleterious by CADD, REVEL, and MPC, were previously reported in TCF12 in ASD probands from the MSSNG cohort, the SPARK cohort, and the Autism Sequencing Consortium (Yuen et al., 2016; Zhou et al., 2022; Fu et al., 2022; Trost et al., 2022). TCF12 was identified in Wang et al., 2020 as an novel NDD risk gene, with ultra-rare likely gene-disruptive variants reaching FDR significance following a combined analysis of new ASD and NDD cases with published data. Autism spectrum disorder has been reported in a subset of individuals with craniosynostosis 3 (Sharma et al., 2013; Paumard-Hernández et al., 2015).

ZEB2
Trio-based whole-exome sequencing of 168 patients with low-functioning ASD at Sun Yat-sen Memorial Hospital in Wu et al., 2025 identified a de novo loss-of-function variant in the ZEB2 gene in a patient clinically diagnosed with ASD based on DSM-5 criteria and presenting with global developmental delay/intellectual disability. De novo missense variants in the ZEB2 gene, including one predicted to be deleterious by CADD, REVEL, and MPC, were previously reported in an ASD proband from the Simons Simplex Collection and a proband from the SPARK cohort (Iossifov et al., 2014; Zhou et al., 2022). ZEB2 was identified as a top gene with ASD-associated noncoding de novo mutations (DNMs) in the SPARK cohort, with validation in the SSC cohort, using point-based statistical tests (CADD score > 15) in Zhang et al., 2025. Evans et al., 2012 evaluated the behavioral phenotype in 61 individuals with Mowat-Wilson syndrome (MWS) and found an increased rate of repetitive behaviors compared with those for individuals selected from an epidemiological sample of people with intellectual disability from other causes; the authors also found that 40% of the MWS participants and 42.62% of contrast participants scored above the cut-off score for the DBC-Autism Screening Algorithm.

ZFYVE9
Plassmeyer et al. (2025) identified an ASD-associated 5′UTR variant in **ZFYVE9** through functional assessment of de novo variants from Simons Simplex Collection probands using a massively parallel reporter assay (MPRA) on polysome fractions. The variant showed reduced relative polysome/80S enrichment in both HEK cell–based in cellulo MPRA assays and patient-derived lymphoblastoid cell lines and was associated with decreased protein expression in patient-derived LCLs and in a dual-luciferase reporter assay (FDR-adjusted $p < 0.05$). Several de novo variants in this gene, including a de novo loss-of-function variant and a de novo missense variant that was predicted to be deleterious by CADD and REVEL, have been identified in ASD probands from the Simons Simplex Collection and the SPARK cohort (Iossifov et al., 2014; Zhou et al., 2022).

ZNF865
Bradbrook et al., 2025 described a cohort of 18 patients with protein-truncating variants in the ZNF865 gene (the majority of which were de novo in origin and clustered toward the C-terminus) presenting with a neurodevelopmental disorder characterized by speech delay, cognitive delay or intellectual disability, hypotonia, brain MRI abnormalities, and dysmorphic features; seven patients were reported to have been diagnosed with autism spectrum disorder, with two additional patients having autistic features without a confirmed diagnosis. Additional de novo variants in ZNF865, including two protein-truncating variants and four missense variants, have been reported in ASD probands from the Simons Simplex Collection, SPARK, the Autism Sequencing Consortium, MSSNG, and a Chinese ASD cohort (Satterstrom et al., 2020; Zhou et al., 2022; Wang et al., 2023).

HG_Table 2. Selected examples of new studies added to existing genes in Q4/2025

Gene	Title	First Author	Journal
ANK3	Impaired AIS plasticity in ankyrin-G mutant mice alters cortical excitability and behavior	Li M	Proc Natl Acad Sci U S A
ASH1L	A novel de novo missense variant in ASH1L associated with mild autism spectrum disorder and an uneven cognitive profile: a case report	Pulatov O	J Med Case Rep
DMD	Conditional Dmd ablation in muscle and brain causes profound effects on muscle function and neurobehavior	Karuppasamy M	Commun Biol
LEO1	LEO1 haploinsufficiency is associated with developmental delays and autism spectrum disorder	Ung EC	J Hum Genet
MEF2C	Transcriptional and epigenetic targets of MEF2C in human microglia contribute to cellular functions related to autism risk and age-related disease	Nguyen C	Nat Immunol
MYT1l	De novo missense mutation in MYT1l leading to autosomal dominant intellectual disability 39 and autism spectrum disorder: a case report	Wang X	Front Pediatr
PSMC5	Investigating the neuronal role of the proteasomal ATPase subunit gene PSMC5 in neurodevelopmental proteasomopathies	Küry S	Nat Commun
RNU2-2	Pathogenic Variants in RNU2-2, a Non-coding Spliceosomal RNA, Cause a Distinctive Developmental and Epileptic Encephalopathy	Chiu ATG	Ann Neurol
RNU4-2	Monoallelic and biallelic RNU4-2 variants in neurodevelopmental disorders	Hayashi Y	J Hum Genet
RNU4-2	Reanalysis of Undiagnosed Neurodevelopmental Disorder Cases: From RNU4-2 Variants to Clinical Phenotypes	Di Letto P	Neurol Genet
SATB2	Expanding Clinical and Genetic Landscape of SATB2-Associated Syndrome	Pullano V	Genes (Basel)
SETD1A	Mutations of schizophrenia risk gene SETD1A dysregulate synaptic function in human neurons	Su X	Mol Psychiatry

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.

1.5 Development of a Candidate Gene Pool

The Single Line of Evidence (SLOE) dataset comprises genes and variants reported in the scientific literature that lack sufficient evidence to meet the established inclusion criteria for the database. This dataset serves as a repository for genetic findings that may have potential relevance but have not been fully validated or sufficiently supported by robust data. Regular queries of the SLOE dataset play a crucial role in gene selection process by facilitating cross-

referencing and validating newly identified ASD candidate genes. By systematically examining the SLOE dataset, we compare recently discovered variants against existing evidence, allowing for a thorough assessment of their relevance and significance.

In Q4/2025, we updated SLOE dataset by adding eight new articles, detailed in HG_Table 3.

HG_Table 3: New articles added to the SLOE dataset.

PMID	Title	First Author, Year
40869941	Rare Variant Burden and Behavioral Phenotypes in Children with Autism in Slovakia	Repiská G, 2025
41010044	De Novo Variants Predominate in Autism Spectrum Disorder	Boles RG, 2025
41107264	Neurometabolic profiles of autism spectrum disorder patients with genetic variants in specific neurotransmission and synaptic genes	Vilela J, 2025
41127290	Predicting the diagnostic efficacy of trio-based whole exome sequencing in children with low-function autism spectrum disorders: a multicenter study	Wu R, 2025
41134724	Genetic Characterization of 128 Chinese Individuals with Neurodevelopmental Disorders via Whole-Exome Sequencing	Qin Y, 2025
41255692	Monogenic defects in Russian children with autism spectrum disorders	Suspitsin EN, 2025
41344325	Approaches for identification of 5' UTR mutations impacting translation and protein production from neurodevelopmental disorder genes	Plassmeyer SP, 2025