SFARI GENE Q1/2026 REPORT

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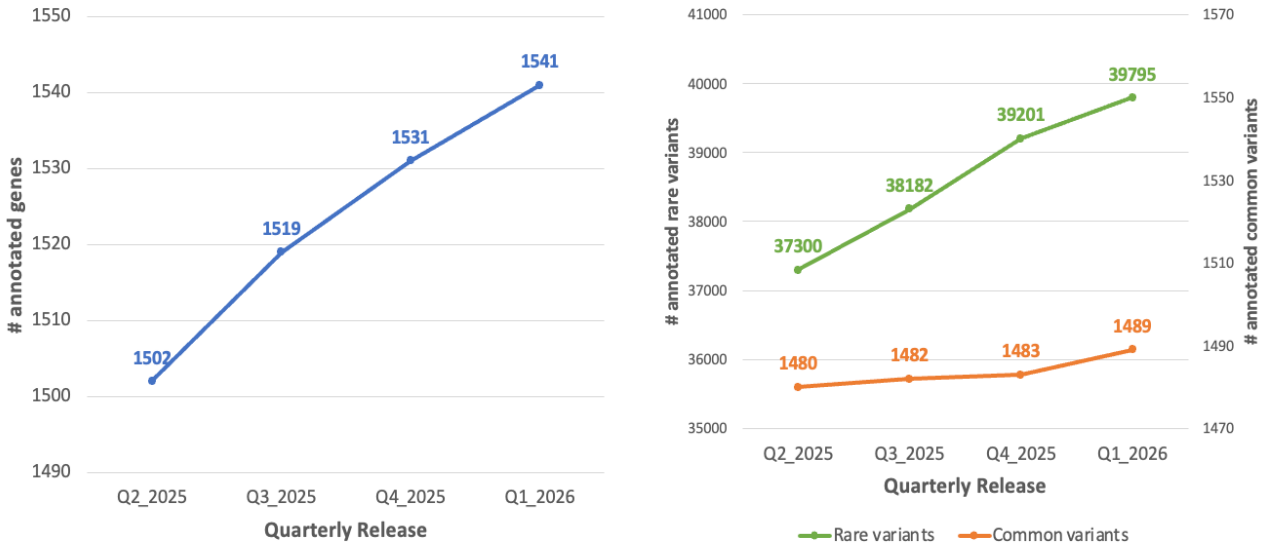
1. Human Gene Module
Quarterly Report, Q1/2026

1.1 Updated Human Gene Dataset

A total of ***ten*** new genes were added to the Human Gene Module for the Q1/2026 release, bringing the overall number of ASD candidate genes in the module to **1,541** (HG_Figure 1, panel A). In-depth annotation of **594** rare variants and six common variants were completed in this quarter leading to a total of **39,795** rare and **1,489** common variants, respectively (HG_Figure 1, panel B). Annotation of **113** new references was accomplished for the Human Gene module in Q1/2026, bringing the total number of references to **6,811**.



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 1,502 to 1,541 (B) The number of rare variants has increased from 37,300 to 39,795; number of common variants has increased from 1,480 to 1,489.

1.2 Highlights of Q1/2026 Human Gene Dataset

The identification and evaluation of emerging ASD risk genes in the Q1 2026 release were guided by an integrative framework that synthesizes multiple lines of genetic evidence across large-scale and targeted studies. Gene-level assessment incorporates signals from established ASD cohorts including Autism Sequencing Consortium (ASC), Simons Simplex Collection (SSC), SPARK, and MSSNG, alongside data from ancestrally diverse and broad neurodevelopmental cohorts. Importantly, when a gene is newly reported in smaller or less-established cohorts, we systematically evaluate its genetic evidence within established ASD cohorts to assess recurrence and consistency of association. Evidence is further evaluated across variant classes (loss-of-function and missense), inheritance patterns (de novo, inherited, and X-linked), and replication across independent datasets, with particular emphasis on concordance of signals across cohorts. This multi-dimensional approach enables robust prioritization of candidate genes within SFARI Gene database.

The Q1/2026 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 2)**
- **New articles added to the SLOE dataset (HG_Table 3)**

HG_Table 1. New genes added in Q1/2026

Gene	Evidence from Primary Ref	Additional Cohort Support	Mutation Type	Inheritance	NDD phenotype
ASTN1	Large-scale NDD gene discovery study	SPARK, iHart, Chinese ASD cohort	Missense, LoF	Biallelic, De novo present	Yes
GSPT2	Genotype-Phenotype study	X-linked NDD cohort (multiple affected males)	Protein-altering (missense, LoF)	X-linked, de novo	Yes
RAPGEF2	Large-scale sequencing study	ASC, SPARK, MSSNG	LoF + missense	De novo enriched	Yes
RSF1	NDD cohort sequencing study	ASC, SPARK	LoF + missense	De novo enriched	Yes
SF3B3	Clinical + molecular cohort study	SSC, SPARK	Missense (primarily)	Mixed (de novo + inherited)	Yes
MAN1B1	WES of Turkish cohort	MSSNG, SPARK, mAGRE	LoF (recessive)	Biallelic, de novo + inherited	Yes
DLG3	Ancestrally diverse cohort	SPARK, MSSNG	Missense + LoF	X-linked (inherited + de novo)	Yes
BPTF	WES of Turkish cohort	ASC, SPARK, MSSNG, REACH	LoF (dominant)	De novo	Yes
PPP2R1A	WES of Turkish cohort	ASC, MSSNG	Missense (recurrent hotspots)	De novo	Yes
RALGAPA1	WES of Turkish cohort	SSC, SPARK, ASC	LoF (recessive)	Biallelic	Yes

1.3 Summary evidence for new genes

ASTN1

Levine et al., 2026 described eighteen individuals from twelve unrelated families with biallelic, ultra-rare, predicted damaging variants in ASTN1 and one individual with heterozygous variants in both ASTN1 and ASTN2 presenting with a variable neurodevelopmental disorder characterized by mild to profound developmental delay or intellectual disability, autism or autistic features, ADHD, epilepsy, dysmorphic facial features, hypotonia, spasticity, ataxia, and structural brain abnormalities. A homozygous missense variant in the ASTN1 gene was previously identified in an ASD proband born to consanguineous Middle Eastern parents in Tuncay et al., 2022, while additional de novo heterozygous

variants in the ASTN1 gene, including a de novo loss-of-function variant and several de novo missense variants, have been reported in ASD probands from the iHART cohort, the SPARK cohort, and a Chinese ASD cohort (Ruzzo et al., 2019; Zhou et al., 2022; Yuan et al., 2023).

GSPT2

Wei et al., 2025 described six individuals from six unrelated Chinese families carrying hemizygous missense variants in the GSPT2 gene presenting with severe intellectual disability/learning disability (5/5), developmental delay with severely delayed speech development (5/5), autism spectrum disorder (3/5), ADHD (3/5), seizures (3/5), and brain malformations (3/5); functional assessment of these variants by Western blot analysis of GSPT2-deficient H4 neuroglioma cells transfected with wild-type or mutant HA-GSPT2 demonstrated either reduced or increased protein expression compared to wild-type. Furthermore, Wei et al., 2025 found that GSPT2-deficient H4 cells displayed a slower growth rate and downregulation of cell proliferation and neurodevelopmental markers compared to wild-type cells. A maternally-inherited hemizygous missense variant in GSPT2 was previously identified in a male ASD proband from a simplex family of Middle Eastern ancestry (Gogate et al., 2024), while copy number variation affecting the GSPT2 gene has been previously reported in individuals presenting with syndromic and non-syndromic intellectual disability (Whibley et al., 2010; Grau et al., 2017; Al-Shehhi et al., 2019).

RAPGEF2

Bereshneh et al., 2026 identified five unrelated individuals carrying de novo heterozygous variants (three missense variants, a frameshift variant, and a nonsense variant) in the RAPGEF2 gene presenting with a neurodevelopmental disorder characterized by developmental delay, intellectual disability, behavioral abnormalities (including autism in two individuals), seizures, and dysmorphic features; functional assessment of the three missense variants and the nonsense variant in PDZ-GEF mutant Drosophila found that, while wild-type RAPGEF2 was able to rescue phenotypes associated with loss of PDZ (lethality, severe locomotion defects, aberrant microtubular stability in motor neurons axons, and synaptic overgrowth at neuromuscular junctions in third instar larvae), mutant RAPGEF2 with these variants failed to do so, indicating a loss-of-function effect. De novo missense variants in the RAPGEF2 gene have been previously reported in ASD probands from the Autism Sequencing Consortium, the MSSNG cohort, and the SPARK cohort (De Rubeis et al., 2014; Yuen et al., 2017; Zhou et al., 2022).

RSF1

Jost et al., 2026 identified a total of 11 unrelated individuals harboring predominantly de novo heterozygous variants in the RSF1 gene; all individuals presented with a neurodevelopmental disorder, whether intellectual disability, autism spectrum disorder, or developmental delay, and from the seven individuals with detailed clinical information, unspecific and inconsistent associated features were described, including craniofacial dysmorphism, musculoskeletal, digestive, vision, and tone-associated phenotypes, epilepsy, and brain MRI anomalies. De novo missense variants in the RSF1 gene have previously been identified in ASD probands from the Autism Sequencing Consortium and the SPARK cohort (De Rubeis et al., 2014; Zhou et al., 2022).

SF3B3

Musante et al., 2026 collected clinical and molecular information from 24 unrelated individuals with mostly heterozygous missense variants in the SF3B3 gene exhibiting a congruent phenotype including autism spectrum disorder, developmental delay, intellectual disability, language and motor delay,

multiple congenital anomalies, and distinctive craniofacial features confirmed by GestaltMatcher analysis; three of the individuals included in this report were ASD probands from the Simons Simplex Collection and the SPARK cohort previously reported in Satterstrom et al., 2020, Zhou et al., 2022, and Trost et al., 2022. Additional functional assessment of fibroblasts from a subset of individuals with SF3B3 missense variants in Musante et al., 2026 identified reduced SF3B3 protein levels, differential gene expression, increased alternative splicing events, and cell-cycle abnormalities compared to controls.

DLG3

Maternally-inherited hemizygous variants in the DLG3 gene have been identified in male ASD probands from ancestrally diverse cohorts, including ASD cohorts from China, Bulgaria, and most recently Turkey (Hu et al., 2022; Gogate et al., 2024; Belenska-Todorova et al., 2025; Eser et al., 2026), while de novo variants in this gene were previously reported in ASD probands from the SPARK and MSSNG cohorts (Zhou et al., 2022). Two of the seven males with X-linked epilepsy resulting from maternally inherited hemizygous DLG3 missense variants described in He et al., 2024 were reported to also present with ASD. More recently, Malbos et al., 2025 described 17 novel individuals with 16 different DLG3 variants (10 with pathogenic loss-of-function and 6 variants of uncertain significance) and found that ASD was present in 1/10 individuals with a loss-of-function variant and 3/7 individuals with a variant of uncertain significance. The protein encoded by the DLG3 gene (often referred to as SAP102) has been shown to interact with proteins encoded by other ASD candidate genes, including GRIN2B (Muller et al., 1996), APC (Makino et al., 1997), SYNGAP1 (Kim et al., 1998), DLG4 (Masuko et al., 1999), ERBB4 (Garcia et al., 2000), and NBEA (Lauks et al., 2012).

BPTF

Missense variants in the BPTF gene have been identified in ASD probands from the MSSNG cohort, the SPARK cohort, the Autism Sequencing Consortium, and most recently in a cohort of 75 Turkish patients diagnosed with ASD (Yuen et al., 2017; Zhou et al., 2022; Fu et al., 2022; Kayhan et al., 2026). De novo loss-of-function variants in this gene have been reported in ASD probands from the REACH cohort and a Spanish ASD cohort, as well as in an individual with autism from an ethnically diverse pediatric patient population (Ji et al., 2019; Antaki et al., 2022; Blázquez et al., 2025). ASD has also been reported in a subset of individuals with NEDDFL (2/10 in Stankiewicz et al., 2017, and 3/26 individuals in Glinton et al., 2021).

PP2R1A

Missense variants in the PPP2R1A gene have been identified in ASD probands from the Autism Sequencing Consortium and, more recently, from a cohort of 75 Turkish patients diagnosed with ASD (Satterstrom et al., 2020; Marques et al., 2022; Fu et al., 2022; Kayhan et al., 2026), while de novo coding-synonymous variants in this gene were previously reported in ASD probands from the MSSNG cohort (Yuen et al., 2017). Lenaerts et al., 2021 described 30 individuals with 16 different PPP2R1A variants presenting with a variable neurodevelopmental disorder characterized by developmental delay with language delay, hypotonia, behavioral problems (including ASD or autistic features in 6 individuals), dysmorphic features, joint hypermobility, and hypoplasia/agenesis of the corpus callosum. Subsequent functional assessment of a subset of disease-associated variants of Lenarets et al., 2021 demonstrated altered PP2A B-type subunit binding, altered C subunit binding, and/or impaired overall PP2A activity, while the ASD-associated p.Ser152Phe variant was shown to cause a reduction in dendritic spine number following expression in hippocampal neurons.

RALGAPA1
Whole exome sequencing of 75 Turkish patients diagnosed with ASD (based on DSM-5 criteria) identified a homozygous missense variant in the RALGAPA1 gene in a 10-year-old male presenting with ASD and developmental delay in Kayhan et al., 2026. Additional de novo variants in this gene, including a de novo loss-of-function variant and multiple de novo missense variants, have been reported in ASD probands from the Simons Simplex Collection, the SPARK cohort, the Autism Sequencing Consortium, and a Chinese ASD cohort (De Rubeis et al., 2014; Iossifov et al., 2014; Zhou et al., 2022; Fu et al., 2022; Yuan et al., 2023), while maternally-inherited loss-of-function variants in this gene were identified in two unrelated multiplex ASD families from the mAGRE cohort in Cirnigliaro et al., 2023.

1.4 New additions to existing genes in Q1/2026

Recent gene discovery and cohort-based studies further expand the genetic landscape of ASD by leveraging sequencing approaches across clinically stratified populations. In a cohort of minimally verbal individuals with ASD, Guerrera et al., 2026 identified a higher-than-expected prevalence of genetic syndromes compared to the general autistic population (22.6% *versus* 10%), highlighting the contribution of genetic risk factors in this severe phenotypic subgroup. Population-scale whole genome sequencing in an underrepresented mixed NDD cohort by Spirito et al., 2026 reported a diagnostic yield gradient, with the lowest yield in ASD, intermediate in ASD-ID, and the highest in ID. Similarly, Mancuso et al., 2026 applied whole-exome sequencing and burden testing in pediatric NDD cases, identifying a diagnostic yield of 7.4% within the ASD subgroup. Complementing these findings, Van Niel et al., 2026 analyzed a cohort of 153 children with motor speech disorders, among whom a subset presented with ASD or autistic features; notably, ASD was less commonly associated with a genetic diagnosis in this cohort. Collectively, these studies highlight the power of integrating cohort-based sequencing and phenotype stratification to identify both known and emerging genetic contributors to ASD and related conditions.

In parallel, the Q1 2026 update incorporates evidence from a diverse range of study types to strengthen the characterization of existing ASD genes. These include large multi-individual cohort expansions, detailed case series, and integrative functional studies spanning in vitro systems, organoids, and in vivo animal models. Clinical reports further refine phenotypic profile and inheritance patterns, including variable expressivity and genotype–phenotype correlations.

HG_Table 2. Selected examples of new studies added to existing genes in Q1/2026

Gene	Title	First Author	Study type
SCN2A	Human microglia in brain assembloids display region-specific diversity and respond to hyperexcitable neurons carrying SCN2A mutation	Wu J, 2026	Brain assembloid
TRIO	Common Genetic Variants in TRIO Are Associated With Autism in Chinese Han Population	Shen H, 2025	Genetic association
RNU4-2	Longitudinal Behavior Phenotype Hallmarks in RNU4-2 Syndrome: Implications for Clinical Management	Ajmone PF, 2026	GenPhen/Case series
ADNP	A Systematic Review Illustrates the Expanding Clinical and Molecular Landscape of Helsmoortel-Van der Aa Syndrome	Harutyunyan L, 2025	GenPhen/Case series

KMD5C	Individuals with reported and novel KDM5C variants present with seizures, a feature recapitulated in a Drosophila model	Terry BK, 2026	GenPhen/Case series
KDM2A	De novo variants in KDM2A cause a syndromic neurodevelopmental disorder	Anderson EN, 2026	GenPhen/Case series
CHD3	In vivo base editing of Chd3 rescues behavioural abnormalities in mice	Yang K, 2026	Mouse model
SCN2A	Autism-related phenotypes in a heterozygous Scn2a(R854Q) mouse model and their partial rescue via a potassium channel opener	Ismail H, 2026	Mouse model/Humanized

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 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 Q1/2026, 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	Journal/Book	Publication Year
41507692	Whole Exome Sequencing in Patients With Developmental Delay/Intellectual Disability (DD/ID), Epilepsy and the First Turkish Patient Diagnosed With BCL11A-Related Intellectual Disability	Akkus N	Mol Genet Genomic Med	2026
41751633	Genetic Traces in Autism Spectrum Disorders: A Whole Exome Sequencing Study from Türkiye	Kayhan G	Genes (Basel)	2026
41577710	Using the linear references from the pangenome to discover missing autism variants	Sui Y	Nat Commun	2026
41629344	New insights into neurodevelopmental disorders by whole genome sequencing of 100 families from Italy	Spirito G	NPJ Genom Med	2026