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# Clinical Insights Into a Rare *SETD2* Disorder: Report of a Novel Variant

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## ABSTRACT

The *SET domain containing the 2* (*SETD2*) gene encodes a histone methyltransferase responsible for H3K36me3 modification, playing key roles in transcriptional regulation, RNA splicing, and DNA repair. Pathogenic variants in *SETD2* have been linked to variable phenotypes, including Luscan–Lumish syndrome (LLS, OMIM #616831), autosomal dominant intellectual developmental disorder 70 (MRD70, OMIM #620157), and Rabin–Pappas syndrome (RAPAS, OMIM #620155). Defining the severity of intellectual disability/developmental delay caused by *SETD2* variants is important for accurate genetic counseling. This study aims to present a patient carrying a novel de novo nonsense variant in the *SETD2* gene and to expand the clinical phenotype spectrum associated with *SETD2* variants. A 17-year-old male with dysmorphic features, epilepsy, attention deficit and hyperactivity disorder (ADHD), and moderate intellectual disability underwent a detailed clinical and genetic evaluation. A novel de novo heterozygous nonsense variant in the *SETD2* gene, NM_014159.7:c.7084C>T (NP_054878.5:p.Gln2362Ter), was identified by whole-exome sequencing. This variant was classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines. The patient exhibited clinical features overlapping with LLS. Further research is warranted to elucidate the mechanistic differences underlying various *SETD2* variants, which will be essential for improving our understanding of *SETD2*-related disorders and for providing accurate genetic counseling and targeted management strategies.

## 1 | Introduction

The *SET domain containing the 2* (*SETD2*) gene is located on chromosome 3p21.31 and has two different transcripts, NM_014159.7 and NM_001349370.3 (Wu et al. 2023). Functionally, *SETD2* mediates the trimethylation of lysine 36 on histone H3 through its *SET* domain. This trimethylated histone plays a crucial role in the elongation phase of RNA polymerase II-mediated transcription. *SETD2* is known to participate in various biological processes, including maintaining transcriptome integrity, preventing aberrant transcription initiation, RNA splicing, and DNA repair (Wagner et al. 2025). Moreover, the loss of *SETD2* function sensitizes cells to epigenetic targeting of H3K36 methylation mediated by NSD1. Similar to other members of the histone methyltransferase family (e.g., *DNMT3A*, *BRWD3*), *SETD2* has been associated with overgrowth syndromes (Wagner et al. 2025; Parra et al. 2023). However, the specific function of this epigenetic regulator that underlies disease pathogenesis has not yet been fully elucidated (Suda et al. 2021).

*SETD2* has been shown to play a critical role in neurodevelopmental processes. Xu et al. (2021) demonstrated that *SETD2* is essential for cortical arealization and the formation of the cortico-thalamo–cortical circuits. Indeed, mouse models carrying *SETD2*

variants exhibited neurological phenotypes such as impaired social interaction, motor learning deficits, and spatial memory impairments (Xu et al. 2021). Clinically, pathogenic *SETD2* variants have been associated with three distinct genetic disorders: Luscan–Lumish syndrome (LLS; OMIM #616831), autosomal dominant intellectual developmental disorder 70 (MRD70; OMIM #620157), and Rabin–Pappas syndrome (RAPAS; OMIM #620155).

LLS is characterized by a clinical presentation that typically includes macrocephaly with or without ventriculomegaly, brain malformations (e.g., Chiari type I malformation, syringomyelia), marked developmental delay (particularly in speech development), mild-to-moderate intellectual disability, behavioral problems (including autism spectrum disorder and aggression), obesity, and overgrowth (Lucain et al. 2025). RAPAS, on the other hand, is defined by microcephaly, congenital heart malformations, urogenital anomalies, ocular findings (notably Coats disease of the retina), severe growth retardation, hypotonia, hyponatremia, respiratory issues (such as tracheomalacia, frequent aspiration, and hypoventilation), epilepsy, severely limited or absent speech development, profound intellectual disability, and distinctive craniofacial dysmorphism (Pappas and Rabin 2022). MRD70 is typically characterized by mild global developmental delay, speech difficulties, and moderate intellectual disability. These three syndromes related to the *SETD2* gene present variability in the severity of intellectual disability/developmental delay and the presence of comorbid multi-organ abnormalities. The degree of intellectual disability in MRD70 is more severe than in individuals with LLS but not as profound as in those with RAPAS (Rabin et al. 2020). These phenotypic differences may be attributed to a potential gain-of-function mechanism or distinct effects in the epigenetic regulation mediated by *SETD2* (Parra et al. 2023) (Table 1).

Emerging evidence supports a clear genotype-phenotype correlation among *SETD2* variants. Notably, amino acid substitutions at codon 1740 have been shown to result in distinct clinical outcomes: The p.Arg1740Trp variant is associated with RAPAS, characterized by severe neurodevelopmental delay, microcephaly, and multi-organ anomalies, whereas the p.Arg1740Gln variant correlates with MRD70, exhibiting a milder neurodevelopmental phenotype and relatively normal head circumference (Rabin et al. 2020). In contrast, variants affecting other codons in *SETD2*, which do not perturb these critical residues, have been associated with LLS, typically manifesting macrocephaly, overgrowth, mild-to-moderate intellectual disability, and the absence of major congenital malformations (Parra et al. 2023; Wu et al. 2023).

In this study, a case carrying a novel heterozygous nonsense variant in the *SETD2* gene was evaluated in the context of the three known *SETD2*-related syndromes. In addition, it was systematically compared with the phenotypic features reported in the literature for these conditions to clarify the clinical and mechanistic spectrum associated with *SETD2* variants.

## 2 | Materials and Methods

### 2.1 | Case

Ethical approval for this study was obtained from the Balıkesir University Ethics Committee on August 8, 2025, under decision number 2025/291. Written informed consent was also obtained from the patient's legal guardians.

A 17-year-old male with dysmorphic features, epilepsy, attention deficit and hyperactivity disorder (ADHD), and moderate intellectual disability was referred to our clinic for evaluation of a potential genetic etiology. He had previously been followed for developmental delay, epilepsy, ADHD, and moderate intellectual disability. The patient's medical records, clinical findings, physical examination results, and family history were thoroughly reviewed. Clinical assessment was performed jointly by a clinical geneticist and a child psychiatrist.

### 2.2 | Genetic Testing

Genomic DNA was isolated from peripheral blood leukocytes of the patient and his parents. In the first stage of genetic analysis, the whole-exome sequencing (WES) was performed. The identified variant was confirmed, and familial segregation analysis was conducted using the Sanger sequencing method.

Genomic DNA isolation was carried out automatically using the HiPurA pre-filled clinical multi-purpose nucleic acid purification kit and the HIMEDIA InstaN Mag-96 system. The concentration of the extracted DNA was measured using the Qubit fluorometer (Thermo Fisher Scientific, USA). The WES analysis was conducted using the Roche KAPA HyperExome 96 rxn kit and the MGI DNBSEQ-G400 platform. Bioinformatic analysis of the resulting FastQ files was performed using the Genomize SEQ platform (v8.7.0).

### 2.3 | Variant Analysis and Classification

Raw data were analyzed using the Genomize data analysis platform (https://seq.genomize.com). A two-step filtering strategy was applied to identify potentially pathogenic variants associated with the clinical findings: (1) nonsense, missense, frameshift, splice-site, indel, in-frame, and synonymous variants were filtered; and (2) variants with a minor allele frequency (MAF) of less than 1% in population databases 1000 Genomes (1000G), ESP, ExAC, and the Genome Aggregation Database (gnomAD) were selected.

Visualization of sequencing data was performed using the Integrative Genomics Viewer (IGV) software. Novel variants were queried in the HGMD and ClinVar (http://ncbi.nlm.nih.gov/clinvar) databases for validation purposes, and their pathogenicity was assessed using in silico prediction tools such as

**TABLE 1** | A comparative table of clinical findings between the three phenotypes (MRD70, LLS, and RAPAS, adapted from the OMIM database) associated with the SET domain containing the 2 (*SETD2*) gene variants and our case.

| | | Intellectual developmental disorder, autosomal dominant 70; MRD70 (OMIM #620157) | Luscan–Lumish syndrome; LLS (OMIM #616831) | Rabin–Pappas syndrome; RAPAS (OMIM #620155) | Our case |
|---|---|---|---|---|---|
| **Growth** | Tall stature | | + | | |
| | Short stature | | + | | |
| | Obesity | | + | | + |
| **Head** | Low-normal head circumference | + | | | + |
| | Brachycephaly | + | | | |
| | Macrocephaly | | + | | |
| | Microcephaly | | | + | |
| **Face** | Hypotonic facies | + | | | |
| | Malar flattening | + | | | |
| | Retrognathia | + | | | + |
| | Malar hypoplasia | | + | | |
| | Long face | | + | | + |
| | Pointed chin | | + | | |
| | Prominent mandible | | + | | |
| | Flat face | | | + | |
| | Small forehead | | | + | |
| | Biparietal narrowing | | | + | |
| | Micrognathia | | | + | + |
| | Maxillary hypoplasia | | | + | |
| | Mandibular hypoplasia | | | + | |
| **Ears** | Recurrent otitis media | | + | | + |
| | Hearing loss | | | + | |
| | Forward-facing ears | | | + | + |
| **Eyes** | Upslanting palpebral fissures | + | | + | |
| | Downslanting palpebral fissures | | + | | + |
| | Hypertelorism | | | + | + |
| | Straight eyebrows | + | | | + |
| | Myopia | + | | | |
| | Strabismus | + | | + | |
| | Arched eyebrows | | | + | |
| | Short palpebral fissures | | | + | + |
| | Telangiectasia of the retina | | | + | |
| | Optic nerve coloboma | | | + | |
| | Cataracts | | | + | |
| | Retinal exudates | | | | |
| **Nose** | Long nose | | + | | |
| | Small upturned nose | | | + | |
| | Wide nasal bridge | | | + | |

(Continues)

**TABLE 1** | (Continued)

| | | Intellectual developmental disorder, autosomal dominant 70; MRD70 (OMIM #620157) | Luscan–Lumish syndrome; LLS (OMIM #616831) | Rabin–Pappas syndrome; RAPAS (OMIM #620155) | Our case |
|---|---|---|---|---|---|
| | Broad nasal tip | | | + | + |
| | Low-hanging columella | | | + | |
| **Mouth** | High-arched palate | + | | | |
| **Teeth** | Crowded teeth | + | | | |
| **Cardiovascular** | Congenital heart defects | | | + | + |
| **Chest** | Hypoventilation | | | + | |
| | Thoracic dysplasia | | | + | |
| **Gastrointestinal** | Feeding difficulties | | | + | |
| **Genitourinary** | Cryptorchidism | | | + | |
| | Polycystic ovaries | | + | | |
| | Multicystic-dysplastic kidneys | | | + | |
| **Skeletal** | Scoliosis | | | + | |
| | Fifth finger clinodactyly | + | | | |
| | Camptodactyly | + | | + | |
| | Hyperlaxity of hands | | + | | |
| | Hypoplastic distal phalanges | | | + | |
| **Central nervous system** | Global developmental delay | + | | + | + |
| | Hypotonia | + | + | + | + |
| | Delayed walking | + | | | + |
| | Impaired fine motor skills | + | | | |
| | Impaired intellectual development | + | | | + |
| | Learning difficulties | + | | | + |
| | Speech delay | + | + | | + |
| | Impaired speech | + | | | + |
| | Intellectual disability | | + | | + |
| | Absent speech | | | + | |
| | Inability to walk | | | + | |
| | Seizures | | + | + | + |
| | Chiari malformation | | + | | |
| | Ventriculomegaly | | + | | |
| | Syringomyelia | | + | | |
| | Hypoplasia of the corpus callosum | | | + | |
| | Shallow sulci | | | + | |
| | Enlarged ventricles | | | + | |
| | Pontocerebellar hypoplasia | | | + | |
| **Behavioral psychiatric manifestations** | Behavioral abnormalities | + | | | + |
| | Autism spectrum disorder | | + | | |
| | Anxiety disorder | | + | | |
| | Behavior troubles | | + | | + |

(Continues)

**TABLE 1** | (Continued)

| | | Intellectual developmental disorder, autosomal dominant 70; MRD70 (OMIM #620157) | Luscan–Lumish syndrome; LLS (OMIM #616831) | Rabin–Pappas syndrome; RAPAS (OMIM #620155) | Our case |
|---|---|---|---|---|---|
| | Hyperphagia | | + | | + |
| | Behavioral outbursts | | + | | + |
| | Compulsions | | + | | |
| **Prenatal manifestations** | Polyhydramnios | + | | | |
| | Premature delivery | | | + | |

*Note:* '+' describes the presence of the symptom among the syndromes and our case.

MutationTaster and Combined Annotation Dependent Depletion (CADD).

The pathogenicity of the variants was classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015). Finally, segregation analysis was conducted using DNA samples obtained from available family members.

## 3 | Results

### 3.1 | Case Presentation

The patient was a 17-year-old male referred to our clinic for the evaluation of the etiology of developmental delay, epilepsy, and ADHD. During prenatal follow-up, oligohydramnios had been detected, and he was delivered by cesarean section at 39 weeks of gestation. His birth weight was 2700 g (−1.84 SD), and his length was 50 cm (−0.05 SD); head circumference at birth was not recalled by the family. The patient's developmental milestones were as follows: He established eye contact at 3 months of age, sat with support at 13 months, and sat independently at 22 months. He began to walk with support at 4.5 years and achieved independent walking at age 7. He spoke his first word at age 7, was able to form two-word phrases by age 8, and developed fluent speech by age 14. However, he was still unable to perform self-care tasks independently. He had been receiving special education support since he was 17 months old. However, over time, significant progress was achieved in both motor and cognitive domains, ultimately allowing the patient to walk independently, construct sentences, and, by the age of 14, acquire basic reading and writing skills. At 6 months of age, the patient experienced a febrile seizure. Due to neuromotor developmental delay and seizure history, he was evaluated by the Pediatric Neurology Department. Electroencephalography (EEG) revealed paroxysmal activity originating from the right centrotemporal region, leading to a diagnosis of epilepsy. Brain magnetic resonance imaging (MRI) performed at ages 14 and 17 was evaluated as normal, with no structural abnormalities identified. Cardiac evaluation by the pediatric cardiology department revealed asymmetric septal hypertrophy on echocardiography. From a psychiatric perspective, the patient was followed by the child and adolescent psychiatry clinic due to aggression, temper tantrums, and hyperactivity. He was diagnosed with ADHD, moderate intellectual disability, irritability, and episodes of anger outbursts. Additionally, he was under follow-up in the pediatric endocrinology clinic for hypothyroidism. He also had a history of myringotomy due to recurrent otitis media during childhood. On physical examination, the patient's weight was 102 kg (+2.35 SD), height was 188 cm (+1.92 SD), head circumference measured 59 cm (+0.87 SD), and body mass index (BMI) was calculated as 28.86 kg/m$^2$ (+1.53 SD). Dysmorphic features included multiple nevi on the scalp, a broad forehead, thick and straight eyebrows, a wide nasal bridge, a broad nasal tip, downslanting palpebral fissures, retrognathia, an open mouth posture, anteriorly positioned ears, a narrow and high-arched palate, complex dental architecture, pes planus, and a broad right hallux (Figure 1).

Table 1 presents a comparative overview of our case and the three phenotypes associated with *SETD2* gene variants (MRD70, LLS, and RAPAS). The clinical data regarding these three syndromes were compiled and adapted from the OMIM database.

### 3.2 | Genetic Findings

Previous genetic evaluations performed at an external center, including karyotype analysis, FMR1 CGG repeat analysis, and chromosomal microarray analysis, were reported as normal. WES analysis conducted for the patient identified a novel heterozygous nonsense variant in the *SETD2* gene: NM_014159.7:c.7084C>T (NP_054878.5:p.Gln2362Ter). We presented exon locations of the *SETD2* gene variants for our case and the previous reports in Figure 2. According to the ACMG guidelines, this variant was classified as likely pathogenic (LP; PVS1, PM2).

Evolutionary conservation analysis demonstrated that the region harboring the variant is highly conserved (phyloP100way score: 8.641; PhastCons100way score: 1.0). According to the Human Gene Mutation Database Professional 2023.4, a total of 119 different variants in the *SETD2* gene have been reported to date, including 87 missense/nonsense, 2 splice-site, 19 small deletions, 9 small insertions, 1 small indel, and 1 complex variant. As of June 2025, the identified variant has not been reported in the gnomAD or ClinVar databases and is therefore considered a novel variant.

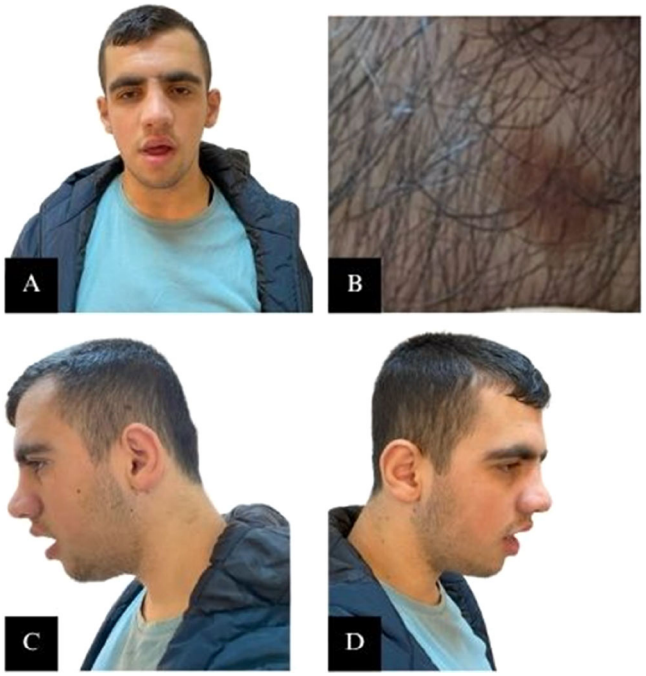


**FIGURE 1** | Clinical photographs of the patient during follow-up at the Medical Genetics Outpatient Clinic. (A, C, and D) Dysmorphic features include a broad forehead, thick and straight eyebrows, a wide nasal bridge, a broad nasal tip, down-slanting palpebral fissures, retrognathia, an open-mouth posture, and anteriorly positioned ears. (B) A nevus observed on the scalp.

Family segregation analysis revealed that neither parent carried the variant, confirming its de novo origin. Pedigree and Sanger sequencing results showing a de novo heterozygous *SETD2* variant identified in the proband, NM_014159.7:c.7084C>T (NP_054878.5:p.Gln2362Ter), are shown in Figure 3.

## 4 | Discussion

In this study, a novel heterozygous nonsense variant in the *SETD2* gene was identified at NM_014159.7:c.7084C>T (NP_054878.5:p.Gln2362Ter) using WES. This variant is absent from the gnomAD and ClinVar databases and has not been previously reported in the literature. To date, 52 cases related to *SETD2* have been described in the literature; among these, 34 were associated with LLS, 14 with RAPAS, and 3 with MRD70 phenotypes (Parra et al. 2023). One case could not be categorized into any of these three phenotypes (Lucain et al. 2025). The presented case represents the first reported *SETD2*-related case in the Turkish population and the 53rd case worldwide.

Features, such as long facial structure, recurrent otitis media history, down-slanting palpebral fissures, hypothyroidism, developmental delay, speech and language impairments, intellectual disability, seizures, and behavioral problems, align well with the LLS phenotype. Conversely, retrognathia supports the MRD70 phenotype. The MRD70 phenotype has been described in the literature for three individuals carrying the same c.5219G>A (p.Arg1740Gln) variant (Rabin et al. 2020). Although retrognathia, which was implied as a specific feature for MRD70 (Parra et al. 2023), was present in our case, most features of our case were related to the LLS phenotype.

Parra et al. highlighted marked clinical heterogeneity depending on the type and location of the variant: Loss-of-function variants distributed throughout the gene cause LLS, whereas specific missense substitutions at residue 1740 lead to RAPAS (p.Arg1740Trp) or MRD70 (p.Arg1740Gln). Moreover, variants outside residue 1740, such as p.Glu1718Lys and p.Asp2251Glu, were associated with RAPAS-like features, suggesting that nearby amino acid changes may mimic the same phenotype. In silico modeling supported a structural interaction between residues 1718 and 1744, potentially explaining these phenotypic effects (Parra et al. 2023). Both patients with p.Glu1718Lys and p.Asp2251Glu variants were diagnosed as RAPAS syndrome by Parra et al., and the authors explained these phenotypes as a compatible RAPAS-like phenotype without the typical neuroimaging findings (cerebellar, pontine, or corpus callosum hypoplasia) that characterize classical RAPAS. So, these variants should be treated with caution, as evidenced by classical RAPAS. Consistent with the report by Parra et al. (2023), the complete RAPAS phenotype appears to occur only in individuals carrying the p.Arg1740Trp variant in *SETD2*.

The patient initially exhibited a severe clinical course, characterized by the absence of speech onset and independent ambulation before the age of seven. However, over time, significant progress was achieved in both motor and cognitive domains, ultimately allowing the patient to walk independently, construct sentences, and, by the age of 14, acquire basic reading and writing skills. This remarkable developmental improvement highlights the potential for considerable variability in clinical outcomes among patients with the same *SETD2* variant, suggesting that early intervention and supportive therapies may substantially influence functional prognosis. Moreover, the variability in the severity of intellectual disability among SETD2-related syndromes directly affects the quality of life and genetic counseling. Future studies systematically evaluating the relationship between the severity of intellectual disability will provide deeper insights into the pathogenesis of these rare genetic conditions and facilitate the development of personalized management strategies.

The occipital nevi reported by Parra et al. (2023) are supported by the multiple scalp nevi observed in our case. Additionally, hypothyroidism reported by Marzin et al. (2019) was also detected in our patient, consistent with existing data. On the other hand, findings, such as oligohydramnios detected during the prenatal period and a broad right hallux observed postnatally, have not been previously described in the literature and appear unique to this case.

Furthermore, whereas *SETD2* gene variants are frequently associated with autism spectrum disorder in the literature, our patient did not exhibit autistic features; instead, behavioral symptoms, such as ADHD, temper outbursts, and irritability, were predominant. This suggests that the behavioral symptoms related to *SETD2* variants may be broader than currently understood.

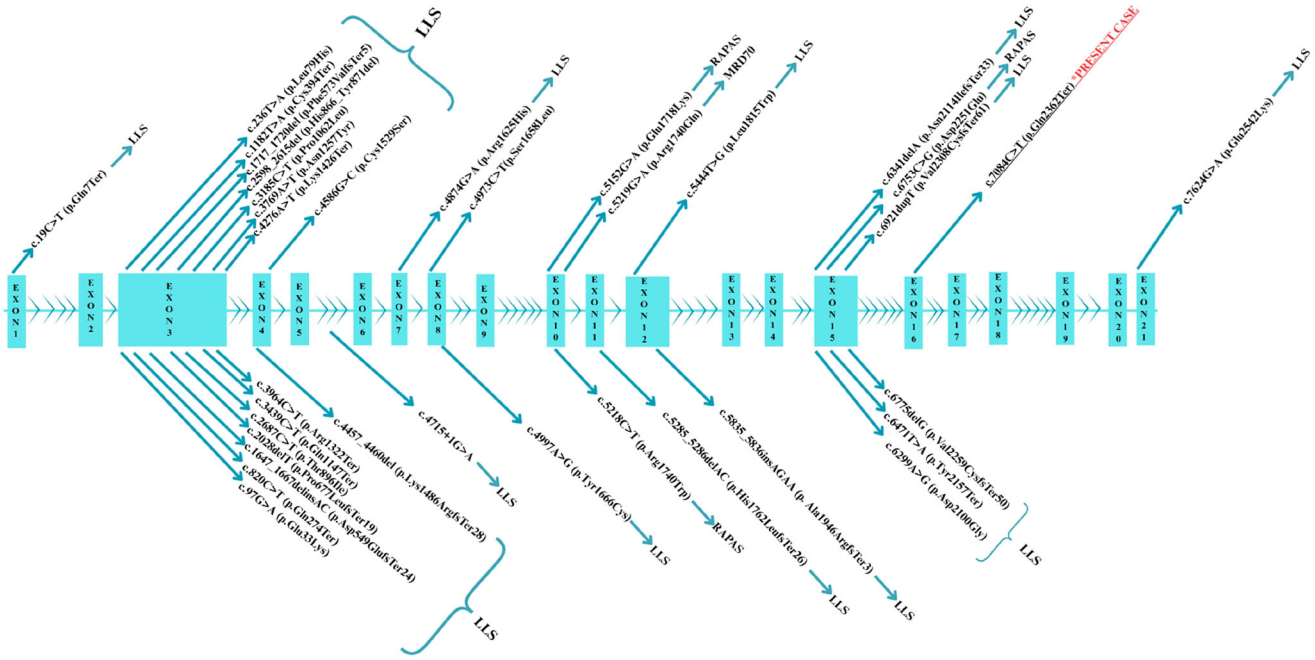


**FIGURE 2** | Exon locations of the *SETD2* gene variants identified in our case and in previously reported cases. LLS, Luscan–Lumish syndrome; RAPAS, Rabin–Pappas syndrome; MRD70, autosomal dominant intellectual developmental disorder 70. *Source:* ClinVar database; Parra et al. (2023); Lucain et al. (2025).

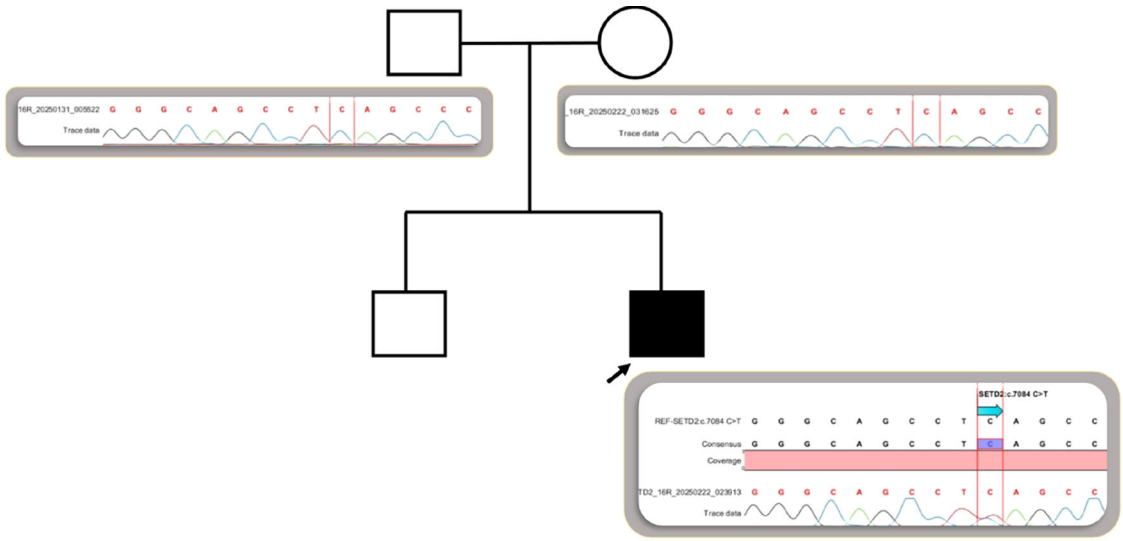


**FIGURE 3** | Pedigree and Sanger sequencing results showing a de novo heterozygous *SETD2* variant identified in the proband: NM_014159.7:c.7084C>T (NP_054878.5:p.Gln2362Ter).

## 5 | Conclusion

As a conclusion, the strong selective pressure of p.Arg1740 variants in RAPAS (p.Arg1740Trp) and MRD70 (p.Arg1740Gln) suggests a distinct mechanism from the LLS phenotype. Although there are shared phenotypic features, the evidence suggests that loss-of-function variants (such as our variant) cause LLS, whereas recurrent variants affecting p.Arg1740 cause either MRD70 or RAPAS. The underlying mechanism related to different *SETD2* variants needs further investigation.


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The authors have nothing to report.


### Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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