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Identification of a *De Novo* *MAGEL2* Pathogenic Variant in Schaaf–Yang Syndrome and the Importance of Paternal Allele Confirmation

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ABSTRACT

Background: Schaaf–Yang syndrome (SYS) is a rare genetic disorder caused by pathogenic variants in *MAGEL2*, a paternally expressed and maternally imprinted gene on 15q11.2. Genetic diagnosis of SYS is challenging due to clinical features that overlap with those of other rare syndromic disorders and limited clinician awareness regarding the diagnosis of imprinting disorders.

Methods: We present a neonate presenting with respiratory distress and joint contractures, diagnosed with SYS through comprehensive genetic testing. Whole-exome sequencing identified a heterozygous *de novo* nonsense variant in *MAGEL2* c.2092G>T [p.(Gly698Ter)]. To confirm the paternal origin of this variant, methylation-sensitive restriction enzyme digestion followed by long-range PCR, nested PCR, and Sanger sequencing was performed.

Results: The *MAGEL2* c.2092G>T was absent in both parents, indicating a *de novo* mutation. Methylation analysis confirmed that the variant resided on the paternal allele, establishing its pathogenicity. A proband diagnostic approach integrating sequence analysis, parental testing, and methylation assays effectively delineates *MAGEL2* variants and their inheritance patterns.

Conclusion: Our study underscores the importance of combining genomic sequencing with methylation assay to accurately diagnose SYS, especially for *de novo* variants. The proposed diagnostic workflow facilitates reliable identification of pathogenic *MAGEL2* mutations and their parental origin, improving diagnostic precision in clinical settings. Further research is needed to elucidate the molecular mechanisms underlying *MAGEL2*-related disorders and develop targeted therapies.

1 | Introduction

Schaaf–Yang syndrome (SYS, OMIM #615547) is a rare and heterogeneous disorder characterized by neonatal hypotonia, feeding difficulties, joint contractures, and developmental

delays (DDs) or intellectual disabilities (IDs) [1–3]. Additional common manifestations of SYS include respiratory distress, occurring in 65%–75% of cases, and autism spectrum disorder, affecting 75%–85% of individuals [4]. Episodes of apnea or severe respiratory distress may occur during the first year of life,

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resulting in a significantly higher mortality rate compared to that of the general infant population [1] and profoundly impacting the lives of SYS patients, their primary caregivers, and their families [5].

SYS is caused by pathogenic variants in *MAGEL2*, an imprinted gene located within the 15q11–q13 chromosomal region associated with Prader–Willi syndrome (PWS, OMIM #176270) [4]. This region contains several paternally expressed protein-coding genes, including *MAGEL2*, as well as *SnoRNA* clusters, and long noncoding RNA transcripts, all of which are not expressed in PWS patients [6]. This lack of expression in PWS is associated with clinical manifestations such as hypotonia, feeding difficulties, and global developmental delay. In contrast, pathogenic variants in *MAGEL2* alone are associated with SYS, which shares some clinical features with PWS but presents with distinct phenotypes, including autism spectrum disorder and joint contractures, which are not typically seen in PWS [1, 6]. Pathogenic variants in *MAGEL2* primarily consist of paternally truncating mutations [7]; however, the underlying molecular mechanisms—whether they lead to haploinsufficiency, exert a dominant-negative effect, or involve other pathways [2]—remain unclear, contributing to the poorly understood clinical manifestations of SYS.

Recently, with the routine use of genomic sequencing technologies such as whole-exome sequencing (WES) for diagnosing rare diseases, there has been increase in reported cases of truncating variants in *MAGEL2*. This increase in reported cases, however, belies the inherent diagnostic challenge posed by SYS. Its rarity and the necessity for specific molecular confirmation (i.e., determining the parental origin of the variant) often complicate and delay a definitive diagnosis. In a previous study by Ahn et al. [8], four patients with SYS were identified among 460 pediatric patients with DDs/IDs who underwent WES. Two of these SYS patients were confirmed to have inherited the truncating variant from their father, while, in the other two cases, the truncating variants were not detected in either parent, indicating *de novo* occurrences. However, the latter two cases were diagnosed with SYS without additional genetic studies for paternal confirmation of the variant [8]. Furthermore, highly variable and overlapping clinical presentations with other syndromes complicate the diagnosis of SYS. Urreizti et al. [9] reported a patient with hypotonia, arthrogryposis, and seizures who was initially diagnosed with Optiz trigonocephaly C syndrome (OTCS, OMIM #211750). However, genetic testing later identified a *MAGEL2* pathogenic variant inherited from the patient's father, confirming the diagnosis of SYS. In the same study, *MAGEL2* testing was conducted on nine additional OTCS patients, and a *MAGEL2* c.1894G>A variant was identified in one patient; however, upon confirmation that this variant was inherited from the patient's mother, it was predicted to be silenced and therefore did not alter the diagnosis of OTCS.

In this study, we present a patient with SYS who was found to have a *de novo* pathogenic variant in *MAGEL2*, and we provide a detailed description of the genetic testing workflow implemented for this patient. Furthermore, we propose a diagnostic strategy that can be applied in clinical laboratories for the accurate diagnosis of SYS.

2 | Methods

2.1 | Study Patient

Our patient was born at 40 weeks and 2 days via elective cesarean section, with a birth weight of 3210 g (50–75th percentile) and a head circumference of 35.5 cm (25–50th percentile). Her parents were healthy and unrelated, and the family history was unremarkable. She was born at a local obstetrics clinic and received oxygen supplementation due to desaturation during the first day. Although her desaturation resolved, she was transferred to another neonatal intensive care unit due to decreased activity and feeding intolerance on the second day of life. She received gastric tube feeding but experienced aspiration episodes. She also required invasive mechanical ventilation for 3 days, followed by noninvasive ventilation with oxygen supplementation and caffeine therapy due to mixed apnea (combined central and obstructive). Also, a left humerus fracture was discovered at 2 weeks of age, and a splint was applied. By the age of 2 months, she was transferred to our hospital for further evaluation and treatment of her feeding problems and apnea. Upon examination, she exhibited dysmorphic facial features, including low-set ears, frontal bossing, and almond-shaped eyes. Additional findings included wrist and elbow joint contractures with camptodactyly of both hands, limitation of both hip abduction, and hypotonia. Pendular nystagmus was noted on ophthalmologic examination. For the first 3 months of life, she received laparoscopic Nissen fundoplication and gastrostomy due to poor sucking and severe gastroesophageal reflux. She was diagnosed with mild laryngomalacia via direct laryngoscopy under general anesthesia, which required no treatment; however, she was discharged with a portable positive pressure ventilator due to central apnea. Sonographic evaluations of the brain, heart, and abdomen, as well as radiographic assessments of the skeletal survey, revealed no structural anomalies except for dislocation of the right hip and healing fracture of the left humerus. Electroencephalography showed no abnormalities. Results of karyotype analysis were normal, while chromosomal microarray revealed a 3.3-Mb duplication at 4p16.1, which was classified as a copy number variant of uncertain significance that did not explain the patient's clinical presentation. Because the neonate presented with hypotonia accompanied by swallowing difficulty and respiratory failure, and, characteristically, severe joint contractures, SYS, OTCS, Escobar syndrome, and other arthrogryposis spectrum disorders were considered, and WES was performed.

2.2 | WES and Sanger Validation

Genomic DNA was extracted from a sample of the patient's peripheral blood. Exome capture was performed using the xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, IA, USA) with the addition of the xGen human mtDNA panel and the xGen custom hyb panel v1. Sequencing was carried out using the NovaSeq X system (Illumina, San Diego, CA, USA). The target region was sequenced with a mean depth of 134.67×, and 99.40% of the sequences were covered at a depth of 20× or greater. The sequence reads were aligned to human reference genome GRCh38 (hg38), and

subsequent preprocessing and variant calling were performed according to the Genome Analysis Toolkit v4.4.0 workflow. Variants were annotated using Variant Effect Predictor v104.2 and classified in accordance with the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) variant interpretation guideline [10]. To validate the candidate *MAGEL2* variant identified in the patient through WES and confirm the mode of inheritance, genomic DNA was extracted from the patient and both of her parents, then underwent polymerase chain reaction (PCR) amplification and Sanger sequencing. Primer pairs for the target region were designed by authors and are provided in Table 1.

2.3 | Phasing the *De Novo* Candidate Variant in *MAGEL2*

To determine the phase of the *de novo* pathogenic *MAGEL2* variant identified by WES and Sanger validation, methylation analysis was conducted in the patient following established protocols. In detail, genomic DNA from both the patient and a nonrelative control (an adult healthy female with no reported clinical conditions) was digested with the methylation-sensitive restriction endonuclease *SmaI* and rCutSmart Buffer (New England Biolabs, Ipswich, MA, USA), which was followed by long-range PCR amplification. The DNA primer sequences for long-range PCR, encompassing the pathogenic variant and methylation sites in *MAGEL2*, were adapted from the study by Urreizti et al. [9]. The PCR amplification of a 2.28-kb region was conducted using 200 ng of genomic DNA in a 25- μ L reaction volume, which included 12.5- μ L of Platinum SuperFi II PCR master mix (ThermoFisher Scientific, Waltham, MA, USA), 4- μ L of distilled water, and the long-range PCR primers. The PCR reaction was performed on a Thermal Cycler 9700 (Applied Biosystems, Foster City, CA, USA) under the following conditions: 1 cycle at 98°C for 30 s, followed by 32 cycles at 98°C for 10 s, 60°C for 10 s, and 72°C for 2 min; then, 1 cycle at 72°C for 5 min was performed. PCR products were assessed for quality by agarose gel electrophoresis and subjected to nested PCR to determine the sequence of the pathogenic variant. Nested PCR was performed in a 25- μ L reaction volume using the Platinum SuperFi II PCR master mix (ThermoFisher Scientific). The reaction was carried out on a Thermal Cycler 9700 (Applied Biosystems) under the following conditions: 1 cycle at 98°C for 30 s, followed by 32 cycles at 98°C for 10 s, 62°C for 10 s, and 72°C for 1 min; then,

1 cycle at 72°C for 5 min was performed. The detailed information for long-range and nested PCR is provided in Table 1. After treating the amplification product with shrimp alkaline phosphatase and exonuclease I (USB Corporation, Cleveland, OH, USA), sequencing was performed using the BigDye Terminator v3.1 (Applied Biosystems). The product was purified and analyzed on an ABI 3730xl DNA Analyzer (Applied Biosystems). Chromatograms were analyzed using Sequencer v5.0 (Gene Codes, Ann Arbor, MI, USA) and compared with the *MAGEL2* reference sequence (NM_019066.5).

3 | Results

3.1 | A Novel Pathogenic Variant in *MAGEL2* Identified by WES and Methylation Analysis

A heterozygous c.2092G>T in *MAGEL2* was identified in the patient's WES and considered a primary candidate variant associated with the patient's disease phenotype (Figure 1A). This variant was a nonsense-type (p.Gly698Ter) predicted to generate a premature termination codon (PTC). The full-length *MAGEL2* protein consists of 1249 amino acids (NP_061939.3). This variant is located within the proline-rich domain and is expected to eliminate the C-terminal 551 amino acids (~44% of the protein). This significant truncation, along with the presence of multiple pathogenic variants downstream of the PTC at the 698th amino acid codon (<https://www.hgmd.cf.ac.uk/ac/gene.php?gene=MAGEL2>), strongly suggests that it may disrupt the normal function of the protein. In addition, the identified *MAGEL2* c.2092G>T variant was absent from population databases such as gnomAD v4.1.0 (Genome aggregation database, <https://gnomad.broadinstitute.org/>) and KOVA v2 (Korean variant archive for a reference database, <https://kobic.re.kr/kova/>). According to ACMG/AMP guideline, this variant was classified as likely pathogenic, fulfilling the criteria PVS1 (predicted null variant in a gene where loss-of-function is a known mechanism of disease) and PM2 (absent from population databases).

Sanger sequencing of the patient's parents confirmed that neither carried the *MAGEL2* variant identified in their child, indicating that this variant occurred *de novo* (Figure 1B), constituting a significant evidence of the variant pathogenicity. However, even if the *MAGEL2* c.2092G>T variant is considered pathogenic, if it is derived from a maternally methylated allele, it would not account for the disease manifestation. Therefore, additional molecular genetic

TABLE 1 | Primers of molecular study for determination of pathogenic variant c.2092G>T in *MAGEL2* in this study.

PCR	Primer name	Sequence (5' → 3')	Direction	Product size
Targeted PCR and Sanger sequencing for family study	MAGEL2-e01F	GTGCCACACGAGATTCCAAC	F	591 bp
	MAGEL2-e01R	AGCTGGGAAGACACTTGAGG	R	
Long-range PCR ^a	MAGEL2-LR-F	ACTCACTTCTATTTCAGCATTCAGC	F	2.3 kb
	MAGEL2-LR-R	CTGATGGAGTCATCAATGATTTAGC	R	
Nested PCR ^a	MAGEL2-4-F	CCACCCCCACCTCCACTG	F	604 bp
	MAGEL2-LR-R	CTGATGGAGTCATCAATGATTTAGC	R	

Abbreviations: F, forward; R, reverse.

^aPrimer sequences for long-range and nested PCR were adapted from the study of Urreizti et al. [9] and modified for optimization.

workup to determine the parental origin of the *de novo* pathogenic *MAGEL2* variant is essential for the accurate diagnosis of SYS. Following *SmaI* digestion, a 2.3-kb region encompassing the candidate c.2092G>T variant and methylation sites in *MAGEL2* was amplified, while a subsequent 604-bp DNA fragment was amplified to cover the c.2092G>T variant prior to Sanger sequencing (Figure 1C). In sequence chromatogram, the c.2092G>T variant was no longer observed after *SmaI* digestion, confirming that it is located on the paternal unmethylated allele (Figure 1C).

3.2 | Diagnostic Strategy for SYS Using Paternal Confirmation of the *MAGEL2* Variant

To accurately detect the pathogenic *MAGEL2* variant associated with SYS, we propose a diagnostic strategy suitable for use in a

diagnostic laboratory. When the phenotypic and laboratory findings suggest a clinical diagnosis of SYS, sequence analysis for *MAGEL2* is performed first to identify potential pathogenic variants. In more than 99% of SYS patients, pathogenic variants are identified as detectable by sequence analysis [4, 11]. If a pathogenic *MAGEL2* variant is detected, the parental origin of the mutated allele should be determined through parental testing. Approximately 50% of patients diagnosed with SYS inherit a *MAGEL2* pathogenic variant from a clinically unaffected father [7]. If testing of both parents does not identify the pathogenic variant found in the patient, methylation-sensitive sequencing in the patient is necessary to confirm the diagnosis. Alternatively, long-read sequencing technologies (e.g., Oxford Nanopore sequencing) may be used to simultaneously resolve methylation patterns and phase variants in a single assay where resources are available [12, 13]. This diagnostic strategy is illustrated in Figure 2.

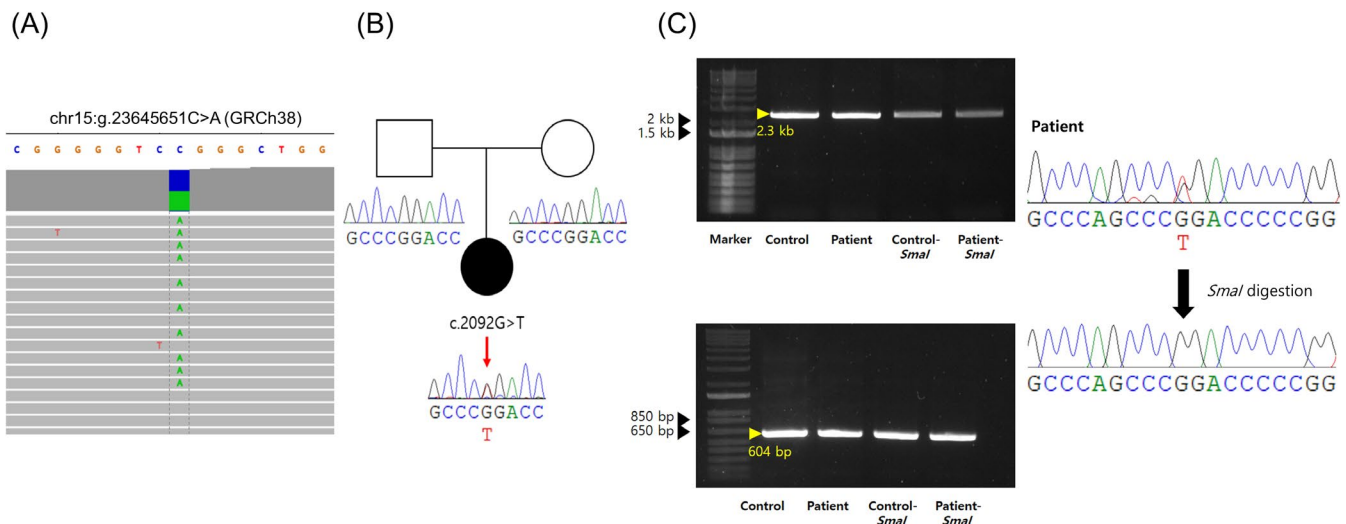


FIGURE 1 | *De novo* pathogenic *MAGEL2* variant associated with Schaaf–Yang syndrome (SYS). (A) Integrative Genomics Viewer snapshot of the variant in *MAGEL2* identified by whole-exome sequencing. (B) Sanger sequencing revealed that neither parent carried the variant identified in the child, confirming its *de novo* occurrence. (C) The 2.3-kb DNA fragments (yellow arrowhead in upper panel) observed in all lanes of the electrophoresis following long-range PCR, along with the 604-bp fragments (yellow arrowhead in lower panel) from nested PCR, contained the target variant c.2092G>T. This variant was absent in the sequence chromatogram after *SmaI* digestion, indicating its presence on the paternal allele and allowing for the diagnosis of SYS in the patient. All samples were derived from the same experiment, and gels were processed in parallel.

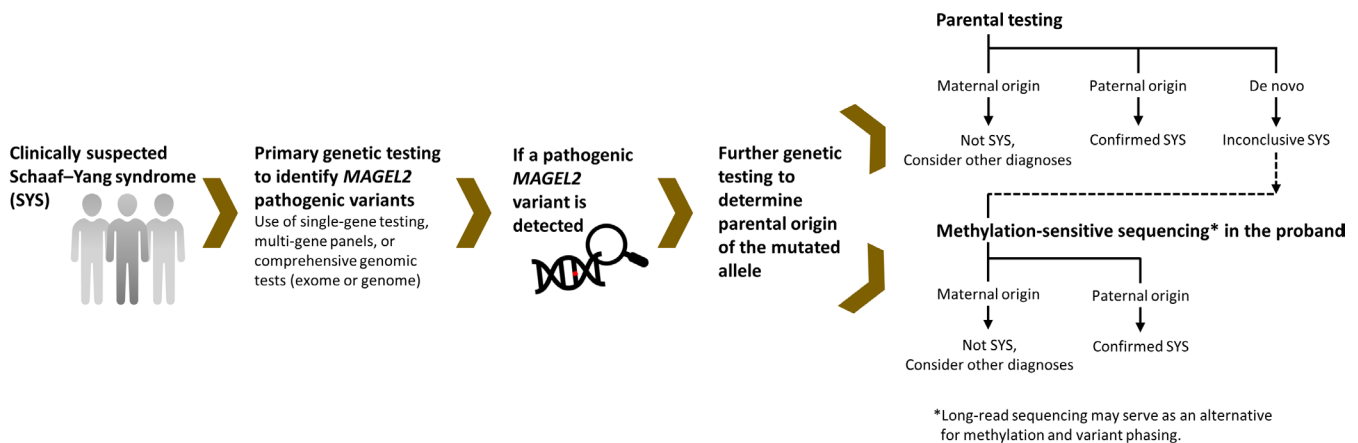


FIGURE 2 | Strategy for genetic diagnosis of Schaaf–Yang syndrome (SYS). If SYS is clinically suspected, sequence analysis of *MAGEL2* should be performed. Upon finding a pathogenic variant, additional testing should be conducted to determine the parental origin of the mutated allele. If parental testing confirms a *de novo* occurrence, methylation-sensitive sequencing should be performed to definitively diagnose SYS. Alternatively, long-read sequencing (e.g., Oxford Nanopore) can simultaneously assess methylation and phase variants where available.

4 | Discussion

In this study, we diagnosed a neonate with SYS by identifying a *de novo* pathogenic variant, specifically located on the paternal allele in *MAGEL2*, who presented with respiratory distress and joint contractures. This report highlights that the diagnosis of SYS is not solely reliant on identifying the variant through genomic sequencing. Particularly, comprehensive molecular investigations—such as methylation enzyme digestion, long-range PCR, nested PCR, and Sanger sequencing—are essential for confirming the diagnosis of SYS in cases of *de novo* occurrence.

MAGEL2 is a relatively GC-rich, single-exon gene located on chromosome 15, featuring CpGs sites that are methylated on the maternal allele and expressed exclusively from the unmethylated paternal allele [7]. The coding sequence of *MAGEL2* contains four restriction sites (5'-CCCGGG-3') for the methylation-sensitive restriction endonuclease *SmaI* [3]. The unmethylated allele is digested by *SmaI*, while the methylated maternal allele remains intact. Consequently, a candidate pathogenic variant that is undetectable by PCR amplification and sequencing following *SmaI* digestion is demonstrated to be located on the paternal allele and is therefore considered a pathogenic variant, as seen in our case.

Interestingly, the WES data from our patient revealed additional potential variants in *CHRNA*, which are primarily associated with joint contracture observed in the patient's phenotypes, thereby complicating the diagnostic process alongside the variant identified in *MAGEL2*. The *CHRNA* is a causative gene for Escobar syndrome (ES, OMIM #265000), following an autosomal recessive inheritance pattern [14]. The identified *CHRNA* variants are NM_005199.5:c.1021C>T [p.(Arg341Ter)] and c.752C>T [p.(Pro251Leu)] in a potential compound heterozygous state, which are interpreted as a pathogenic variant and a variant of uncertain significance, respectively. In both SYS and ES, clinical manifestations such as multiple joint contractures, facial dysmorphism, and muscle weakness overlap significantly [14]. However, our patient did not exhibit the multiple pterygia typically observed in most cases of ES. In addition, the respiratory distress noted in our patient is less frequently reported in ES patients [14], suggesting a greater likelihood of SYS than ES in this case. Among the *CHRNA* variants identified in our patient, the c.752C>T [p.(Pro251Leu)] was extremely rare in population databases, and *in silico* prediction showed a damaging effect, with a REVEL score of 0.951 points [15]. However, in *CHRNA*, truncating variants are primarily reported as disease-causing [11]. Even if the other identified truncating variant c.1021C>T [p.(Arg341Ter)] is found *in trans* with the c.752C>T, this variant is unlikely to be reclassified as a pathogenic or likely pathogenic variant due to a lack of evidence to support its pathogenicity. Furthermore, given the confirmation of the c.2092G>T variant in *MAGEL2* as pathogenic, we conclude that our patient is diagnosed with SYS.

Accurate diagnosis of rare genetic disorders is essential for the effective application of therapeutic agents. Recently,

significant progress has been made in the research and development of epigenetic therapies targeting imprinting disorders. Wang et al. [16] successfully developed an euchromatic histone lysine N-methyltransferase-2 (EHMT2/G9a) inhibitor that can reactivate repressed PWS-associated genes on the maternal chromosome by epigenetic modulations [16]. Notably, validation experiments using mice revealed that some paternally expressed genes, including *Magel2* located on the distal side of the PWS imprinting center, exhibit inconsistent gene upregulation [17]. This finding suggests the possibility of an unknown mechanism influencing the regulation of *Magel2*. Current research on the molecular mechanisms underlying pathogenic variants in *MAGEL2* and the treatment of SYS is still lacking.

SYS is a rare neurodevelopmental disorder characterized by broad phenotypic variability, with severity ranging from mild developmental delay to profound motor impairment [1]. The core features—neonatal hypotonia, feeding difficulties, and joint contractures—were all present in our patient. At the current age of 14 months, the patient shows severe limitation of movement, as the elbow and hip contractures and scoliosis have become more pronounced over time, and no gross motor milestones, including rolling over, have been achieved. In addition, the patient has shown minimal speech output, rarely producing intentional vocalizations. These findings further underscore the phenotypic heterogeneity of SYS, as the degree of motor limitation in our patient appears more severe than that reported in most previously published cases (Table 2).

It is noteworthy that while our analysis confirmed the *de novo* origin of the *MAGEL2* variant through Sanger sequencing of parental blood-derived DNA, the possibility of gonadal mosaicism in a parent or somatic mosaicism in the patient cannot be entirely ruled out. Gonadal mosaicism is a recognized phenomenon in genetic disorders and has critical implications for recurrence risk counseling [18]. Although the variant was absent from the somatic cells of the parents tested, the potential for a parent to harbor the variant in their germline cells means the recurrence risk, while low, is not zero and is estimated to be up to 1% for *de novo* variants in imprinting genes [19]. This underscores the importance of discussing this possibility with families during genetic counseling, ensuring they understand the small but existing risk for future pregnancies.

We herein present a patient diagnosed with SYS who was found via comprehensive molecular investigation to have a *de novo* pathogenic variant in *MAGEL2*. Parental testing and/or methylation assays are essential for determining the parental origin of *de novo* *MAGEL2* variants and ensuring precise molecular diagnosis of SYS. Methods for determining parental origin can include various approaches beyond the methylation analysis proposed in the diagnostic strategy of this study, including the use of SNP genotype information adjacent to the location of the pathogenic *MAGEL2* variant. We hope that our report will inspire new research efforts to further investigate the function and clinical significance of *MAGEL2*, ultimately benefiting individuals with SYS.

TABLE 2 | Clinical features of the present patient compared with previously reported patients of Schaaf–Yang syndrome.

Feature	Present patient	Total <i>n</i> / <i>N</i> ^a (%) for McCarthy et al. [1]
Neurologic problem		
Neonatal hypotonia	+	66/68 (97)
Seizures	–	21/64 (33)
Sleep apnea	+	38/50 (76)
Temperature instability	+	40/60 (67)
Skeletal problem		
Joint contractures	+	69/78 (88)
Scoliosis	+	26/46 (57)
Feeding problem		69/71 (97)
Poor suck in infancy	+	62/64 (97)
Dysphagia	+	48/57 (84)
Use of nasogastric tube	+	45/60 (75)
Use of gastric tube	+	28/53 (53)
GERD	+	34/60 (57)
Chronic constipation	–	39/55 (71)
Respiratory distress		41/58 (71)
Intubation	+	32/55 (58)
Mechanical ventilation	+	30/55 (55)
Tracheostomy	–	9/50 (18)
Gross motor delay		
No sitting	+ (currently 14 months)	7/48 (15), achieved at mean 18 months
No crawling	+	22/47 (47), achieved at mean 31 months
No walking	+	19/54 (35), achieved at mean 50 months
Speech delay		
First word	+	23/53 (43), achieved at mean 36 months
Intellectual disability	Not yet assessed	70/70 (100)

Abbreviation: GERD, gastroesophageal reflux disease.

^a*n*/*N* indicates the ratio of the number of positive patients and the total number of examined patients.

5 | Conclusion

In conclusion, this study underscores that a definitive diagnosis of SYS extends beyond variant detection to require confirmation of its parental origin, a step critical for addressing the epigenetic complexity of imprinting disorders. Future research should prioritize establishing clear genotype–phenotype correlations and developing targeted therapeutic approaches to improve outcomes for individuals with SYS.

Author Contributions

Youn-Ji Hong: conceptualization, data curation, writing – original draft. **Misun Yang:** investigation, writing – original draft. **Hyeon Jeong Kwon and Jooyoung Cha:** investigation, methodology, writing – review and editing. **Ja-Hyun Jang:** conceptualization, methodology, writing – review and editing. **Sung Eun Wang:**

conceptualization and writing – review and editing. **Eun Sun Lee:** investigation, writing – review and editing. **Mi-Ae Jang:** conceptualization, investigation, methodology, supervision, writing – original draft and review and editing.

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Ethics Statement

This study was approved by the Institutional Review Board of Samsung Medical Center (approval no. 2025–04-068).

Consent

Informed consent was obtained from all participants for genetic testing and the research use of biological data. However, explicit consent for the publication of clinical photographs was not granted; therefore, such images have been omitted.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support findings of this study are available from the corresponding author upon reasonable request.

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