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CASE REPORT

Case Report: Schaaf-Yang Syndrome Milder Phenotype Due to Potential Pathogenic Novel Missense Variant as an Unusual Cause of Obesity in a Pediatric Patient

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Abstract: According to OMIM and Orphanet databases, Schaaf-Yang syndrome (SYS) (OMIM: 615547, ORPHA: 398069) is a rare genetic disorder that shares certain clinical features with Prader-Willi syndrome (PWS), including hypotonia, developmental delay, and early-onset obesity. However, SYS often exhibits a more complex and variable phenotype. Missense variants in MAGEL2 have been reported only rarely, and their phenotypic spectrum appears milder and more variable than that of truncating mutations. Data on early-onset obesity as a dominant feature in such patients are limited. In this case report, we describe a child with mild phenotype (SYS) carrying the novel missense variant *MAGEL2(NM_019066.5)*:c.1265C>T (p.Pro422Leu) presenting with severe early-onset obesity and a comparatively neurodevelopmental phenotype. We present a case of a boy with neonatal hypotonia, diagnosed with (SYS) at age 9 years, with follow-up to age 11 years. The boy was born at 34+3 weeks of gestation with hypotonia, feeding difficulties, and a persistent ductus arteriosus that required surgical ligation in early infancy. In the following years, he developed severe early-onset obesity, already evident by age 2 despite multidisciplinary care. Genetic testing performed at age 9 years identified a novel missense variant (NM_019066.5)c.1265C>T in the *MAGEL2* gene, which was not inherited from his mother, thereby confirming the diagnosis of (SYS). At the time of the most recent evaluation, at age 11 years, he remained under long-term follow-up. Clinical management over this period included endocrine therapy, cardiac surgery, physical rehabilitation, and dietary interventions, and despite the complexity of his condition, long-term stabilization of his BMI percentile was achieved with consistent non-pharmacological interventions. This case highlights the importance of early multidisciplinary investigation and intervention in SYS, particularly when obesity is the dominant feature. Effective long-term weight stabilization is possible through structured lifestyle management.

Keywords: Schaaf-Yang syndrome, pediatric obesity, *MAGEL2* mutation, hypothyroidism, developmental delay, physical activity

Introduction

Schaaf-Yang syndrome (SYS) is a rare imprinting disorder (prevalence < 1/1,000,000) which was described in 2013[1] and it is caused by almost always truncating or termination mutations in the paternally expressed *MAGEL2* gene (chromosome 15q11.2–q13).[2]

The *MAGEL2* gene (OMIM 605283) consists of a single exon and belongs to the MAGE protein family of RING E3 ubiquitin ligase regulators.[3–5] It encodes a ubiquitin ligase enhancer required for endosomal protein recycling[1,6] and plays an essential role in retrograde transport[7] as well as endosomal trafficking.[8–10]

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MAGEL2 is thought to have evolved as a mammalian-specific regulator of hypothalamic neuroendocrine functions, crucial for maintaining physiological balance and behavior through hypothalamic signaling, thereby enabling adaptation to environmental changes.[11]

Expression of the *MAGEL2* gene occurs predominantly in the hypothalamus and pituitary between the 6th and 8th weeks of gestation.[12] This timing corresponds with neurogenesis and the formation of neuronal precursors.[5]

While overlapping phenotypically with PWS, SYS often presents distinct features such as arthrogryposis, autism spectrum disorder traits, and a wider range of endocrine abnormalities. Early-onset obesity, exacerbated by hypotonia and neurodevelopmental impairment, is a core manifestation.

Common endocrine manifestations include:

- Short stature: Reported in 50–60% of SYS patients, with a median height near the 22nd percentile. Recombinant growth hormone (rhGH) therapy may improve stature and muscle strength, although effects on weight are limited. As with PWS, careful monitoring for sleep apnea during rhGH therapy is essential.
- Hypogonadism: Frequently presents as micropenis, cryptorchidism, or delayed puberty. Unlike PWS, true hypogonadotropic hypogonadism is less common in SYS. Management may include orchiopexy and hormonal replacement therapy.
- Central hypothyroidism: Similar to PWS, an increased incidence is suspected. Diagnosis requires thorough endocrinological evaluation, including TSH and peripheral thyroid hormone levels. Levothyroxine therapy is indicated if diagnosed.[7–10]
- Temperature dysregulation and episodes of hypothermia or hyperthermia are frequently reported in children with PWS and SYS, and accumulating evidence suggests underlying oxytocin pathway dysfunction.[1,2]

Recombinant growth hormone (rhGH) is commonly used in Prader–Willi syndrome and increasingly in Schaaf–Yang syndrome to improve linear growth, body composition, and muscle strength.[1,2]

Case Presentation

A male patient was born in 2014 via cesarean section at 34+3 weeks of gestation due to breech presentation. Birth weight was 1870 g and length 40 cm. The neonatal period was complicated by hypotonia, poor sucking reflex, and a hemodynamically significant patent ductus arteriosus (PDA), which was unresponsive to pharmacological closure and later required surgical ligation at 2.5 months of age. Other anomalies included a duplicated right renal pelvis and non-autoimmune congenital hypothyroidism, managed with levothyroxine until age 7. At age 3, the patient developed strabismus and global developmental delay. Ophthalmological evaluation revealed astigmatism and esotropia. Cognitive testing (SON-R) showed mild intellectual disability (IQ = 57), with developmental delay in both reasoning and perception scales. Initial genetic analysis excluded Prader–Willi syndrome, DiGeorge syndrome, and Bardet–Biedl syndrome. Conventional karyotyping revealed a normal male chromosomal complement (46, XY). Whole-genome sequencing performed at the age of nine identified a previously unreported heterozygous missense variant, *MAGEL2(NM_019066.5)*:c.1265C>T (p.Pro422Leu, rs1484822926), thereby probably confirming the diagnosis of SYS. Genetic testing in the mother showed that the variant was absent and paternal genetic testing could the father was not in contact with the patient's family. An overview of the genetic testing performed in individual family members is provided in Table 1.

Obesity developed early: by age 3, weight was 24.7 kg (BMI 29.8) (Figure 1).

Table 1 Summary of Genetic Testing

Individual	Cytogenetics	Molecular-Cytogenetics	NGS Finding	Sanger Sequencing
Child with SYS	46,XY *	Not detected**	*MAGEL2*(NM_019066.5): c.1265C>T	Confirmed
Mother	Not tested	Not tested	Not tested	Not detected
Father	Not tested	Not tested	Not tested	Not tested

Notes: Table shows genetic tests performed and their results. * karyotyping. **Prader–Willi syndrome, DiGeorge syndrome, and Bardet–Biedl syndrome.

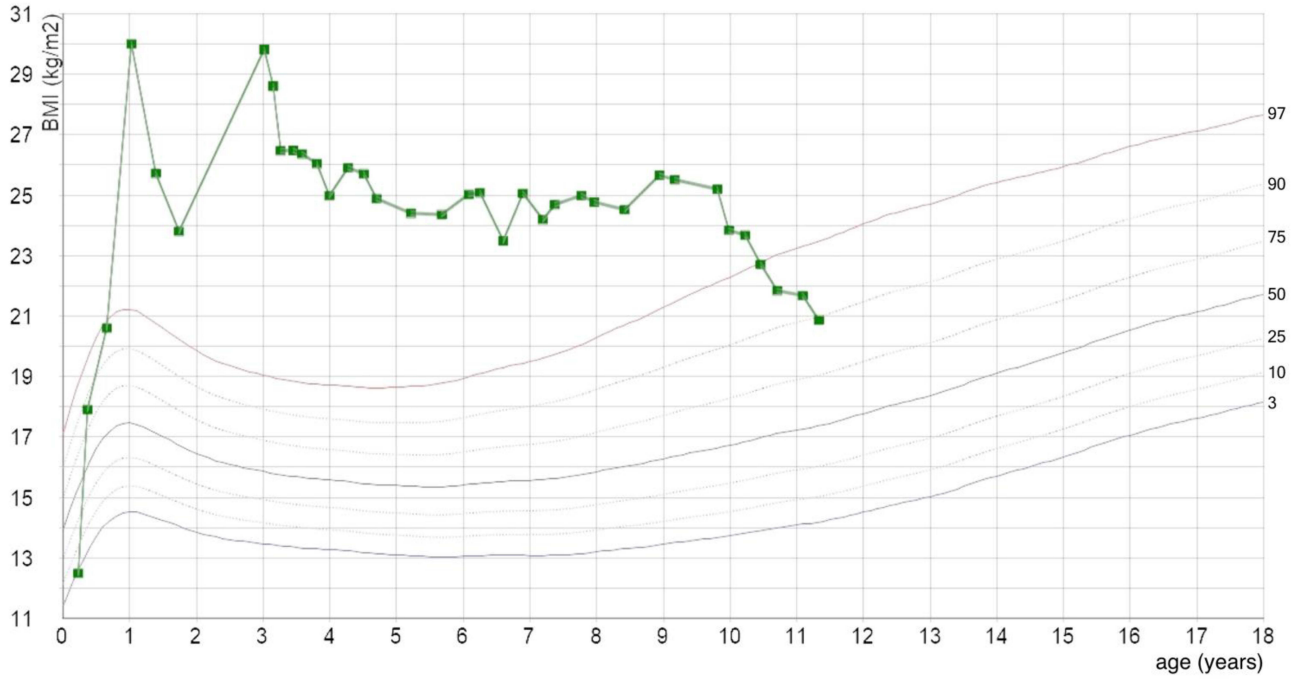

Figure 1 Trajectory of body mass index (BMI).

Despite -SPA based interventions (balneotherapy, supervised physical activity, dietary counseling, and lifestyle education as part of obesity management) and nutritional counseling, obesity persisted (BproMI 25.9 at age 4, waist circumference >97th percentile). Nutritional intervention was comprehensive, individualized, and family-centred. A key component was educating the entire family on the principles of healthy eating, dietary habits, and the promotion of an active lifestyle. Emphasis was placed on the gradual adjustment of energy intake, increasing the proportion of fresh vegetables, fruits, whole grains, and quality protein sources, while simultaneously reducing energy-dense, nutrient-poor foods (such as sweets, sugar-sweetened beverages).

Endocrine follow-up began at 6 months of age, when non-autoimmune mild hypothyroidism was detected (TSH 10.786 mIU/l [0.350–4.940], FT4 9.0 pmol/l [9.1–19.1], TGAB 3.3 kU/l [0.0–4.1], TPOAB <1.0 kU/l [0.0–5.6]). The boy needed a small dose of levothyroxine (25mcg per day) to achieve euthyroid state. This treatment was discontinued at 7 years of age without recurrence of the hypothyroidism. The patient was growing around 3rd percentile. His mid-parental height is 170 cm. Last endocrinological evaluation (June 2024) showed spontaneous pubertal onset at age 10 (Tanner stage G2, testicular volume 4–5 mL, LH 1.01 IU/l, FSH 3.4 IU/l), with stable thyroid function (TSH 4.2 mIU/L, fT4 10.8 pmol/L) without substitution treatment.

Rehabilitation interventions included proprioceptive neuromuscular facilitation (PNF) and dynamic neuromuscular stabilization (DNS), aiming to improve motor control and postural stability. Initially, gross motor limitations (eg, unstable gait) precluded increased physical activity. Through consistent physiotherapy and strong family engagement, the patient achieved functional mobility and joined a swimming club, participating in regular swim training and coordination exercises (eg, TRX, gym ball workouts).

Discussion

This case illustrates the multisystemic complexity of SYS. Early-onset obesity—already evident at 1 year of age—was a central challenge, worsened by hypotonia, feeding issues, and global developmental delay. Although major congenital cardiac defects are rare in SYS, this patient required early cardiac surgery for PDA. SYS leads to a complex phenotype, characterized by profound ID/DD, Autism spectrum disorder (ASD), respiratory dysfunction, feeding difficulties, digestive complications, skeletal abnormalities, sleep dysfunction, hypogonadism, and temperature instability.

However, the severity of the SYS phenotype is highly variable, and may depend on the particular type and location of the mutation in *MAGEL2*.[2] *MAGEL2* loss-of-function explains a broad range of symptoms in SYS and PWS, but incompletely accounts for the severity observed in SYS.[13] *MAGEL2*, together with USP7 and TRIM27, activates the WASH (WASP and SCAR Homolog) complex through K63-linked ubiquitination, thereby controlling the formation of F-actin on endosomes. This process is essential for proper endosomal cargo sorting and transport.[8] *MAGEL2* is crucial for the proper regulation of secretory granules and neuropeptide production.[10] Loss of *MAGEL2* disrupts endosomal transport and causes misrouting of secretory granule proteins to lysosomal degradation. Consequently, the number of granules decreases, leading to reduced synthesis and release of neuropeptides. Impaired neuropeptide signaling may therefore contribute to the hormonal imbalances observed in PWS patients. In *MAGEL2* knockout mice, symptoms include growth retardation, altered circadian regulation,[13] and excessive weight gain.[14] Similarly, rats with paternal truncation of *MAGEL2* exhibit alterations in body composition, cardiac structure and function, respiration, and social behavior and anxiety—symptoms that resemble those seen in individuals affected by SYS. McCarthy described 78 patients with 39 different types of mutations in the *MAGEL2* gene and identified a mutational hotspot within nucleotides c.1990–c.1996, where the highest density of pathogenic variants was observed.[2] The c.1996dupC mutation was associated with a more severe phenotype compared with other reported variants. Different mutations in *MAGEL2* have been associated with distinct clinical presentations. Truncating mutations have been reported in patients with arthrogryposis multiplex congenita[15,16] as well as in those diagnosed with Opitz Trigonocephaly C syndrome.[17]

Molecular findings and variant interpretation of *MAGEL2(* NM_019066.5):c.1265C>T

The *MAGEL2* gene is a paternally expressed, imprinted gene, and pathogenic variants have been associated with SYS and related phenotypes. In the study, we identified a previously undescribed missense variant, *MAGEL2* (NM_019066.5): c.1265C>T, p.(Pro422Leu, rs1484822926). This variant was absent in the mother and is therefore presumed to be of paternal or de novo origin. Given paternal imprinting in this genomic region, both of these facts represent a strong argument for its potential pathogenicity.

The variant has not been reported in population and annotation databases, including gnomAD Exomes, gnomAD Genomes or ClinVar. It is located within a moderately phylogenetically conserved region (PhyloP = 1.9) corresponding to a disordered segment of the protein, situated outside the main MAGE homology domain that is crucial for *MAGEL2*'s molecular function. Nevertheless, intrinsically disordered regions may also play important regulatory roles, such as mediating post-translational modifications or serving as flexible linkers between structured domains.

According to the ACMG/AMP criteria, the variant meets the PS2 moderate criterion, as it is not inherited from the mother and is presumed to be of paternal or de novo origin. The PM2 supporting criterion is fulfilled because the variant is novel and absent from population databases. Computational evidence consistently predicts a deleterious effect, meeting the PP3 supporting criterion (DANN 0.93; PrimateAI 0.80; GenoCanyon 1.0). The PP4 supporting criterion is partially met, since the patient's phenotype partially overlaps with the typical SYS spectrum, including hypotonia, developmental delay, and hypogonadism, though joint contractures and ASD are absent. No benign evidence or increased population frequency was identified, and thus the BS1–BP4 criteria are not met.

Based on the combination of these criteria (PS2 strong + PM2 supporting + PP3 supporting + PP4 supporting + PM6 moderate), the MAGEL2*(NM_019066.5)*:c.1265C>T (p.Pro422Leu, rs1484822926) variant may be classified as likely pathogenic. Summary of the variant classification is shown in Table 2.

Although this variant meets the criteria for likely pathogenic classification, it is supported only by moderate and supporting evidence per ACMG guidelines and should therefore be interpreted with caution.

The amino acid substitution of proline to leucine may locally alter the structure of this region and lead to partial functional impairment of the protein, due to a slight decrease in protein stability. This could result in weakened interactions with TRIM27 or USP7, although the overall complex formation is likely maintained.

Regarding the phenotype–genotype correlation, the relatively mild neurodevelopmental presentation in our patient and the absence of typical SYS features such as arthrogryposis and ASD may be related to the nature and localization of the identified missense variant. Truncating mutations within the established mutational hotspot (c.1990–c.1996) are generally associated with a severe SYS phenotype, whereas the p.Pro422Leu variant lies outside the critical MAGE

Table 2 The Variant Classification According to ACMG/AMP Guidelines (Richards et al, 2015[18])

Pathogenic Criteria		
Strength	Code	+/–
Very strong	PVS1	–
Strong	PS1	–
	PS2	+
	PS3	–
	PS4	–
Moderate	PM1	–
	PM2	+
	PM3	–
	PM4	–
	PM5	–
	PM6	+ (de novo or paternally imprinted)
Supporting	PP1	–
	PP2	–
	PP3	+
	PP4	+
	PP5	–
Benign criteria		
Strength		
Stand-alone	BA1	–
Strong	BS1	–
	BS2	–
	BS3	–
	BS4	–
Supporting	BP1	–
	BP2	–
	BP3	–
	BP4	–
	BP5	–
	BP6	–
	BP7	–

Notes: Table shows evaluation of MAGEL2(NM_019066.5):c.1265C>T variant according to ACMG/AMP guidelines.

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homology domain, in a less conserved and likely disordered region of MAGEL2. This suggests that the variant may cause only partial functional impairment or a modest reduction in protein stability, which could be sufficient re major skeletal and social deficits. In contrast, the missense variant reported by Patak et al (2019) (p.Ala538Glu), located in a more functionally relevant region, was associated with the different phenotypic SYS spectrum (Table 3). Interestingly, early-onset obesity was the dominant clinical feature in our patient (BMI 30 at 1 year of age), which is less typical for SYS than for Prader–Willi syndrome. This observation raises the possibility that certain missense variants may preferentially disrupt hypothalamic pathways regulating energy balance while leaving other *MAGEL2*-dependent functions relatively intact.

Table 3 Comparison of Phenotypic Characteristics in Schaaf–Yang Syndrome

Clinical Feature	SYS – Literature Review	Patient 2 (Patak et al, 2019)	Our Patient
Neonatal muscle hypotonia	Almost universal finding, often the first symptom.	Marked hypotonia after birth.	Admitted to neonatal intensive care unit for cardiorespiratory stabilization and thermoregulation support.
Feeding difficulties in infancy	Common, often requiring tube feeding.	Feeding difficulties in infancy, need for nutritional support.	No feeding difficulties.
Developmental delay and intellectual disability	Average IQ ≈ 38; wide range.	Mild to moderate developmental delay, limited communication, IQ not specified.	At the age of 4.8 years, according to SON-R IQ 57, developmental age 3.1 on the reasoning scale and developmental age 2.1 on the perception scale. Significant dyslalia in speech.
Hypogonadism Autism spectrum disorder	Described in most male patients.	Clinical signs of hypogonadism.	Clinical signs of hypogonadism
(ASD)	Very high prevalence (~78%).	Autistic traits, stereotypical behaviour, social deficit.	No ASD symptoms.
Joint contractures (arthrogryposis)	A key and very common feature, present in more than 85% of patients. It can range from mild finger contractures to severe generalised arthrogryposis.	Mild – distal finger contractures, without generalised arthrogryposis.	No arthrogryposis.
Hyperphagia and obesity	It occurs less frequently and with a later onset of hyperphagia. Hyperphagia occurs in approximately 25% of patients and obesity in 22–40% of patients.	No hyperphagia or obesity described.	Early development of significant obesity BMI in the first year of life 30 kg/m^2
Severe respiratory distress in the neonatal period	Higher prevalence, approximately 58% of patients require intubation	Short-term need for oxygen support, no long-term ventilation.	No respiratory distress.
Characteristic facial features	These are non-specific. They may include a pointed chin, prominent forehead (frontal bossing), thick eyebrows or low-set ears.	Mild dysmorphia (low-set ears, broad nasal bridge).	No characteristic facial features.

Notes: Comparison of SYS symptoms reported in the literature, symptoms of the patient with the MAGEL2(NM_019066.5):c.1613C>A variant (Patak et al, 2019), and symptoms of our patient with the MAGEL2:c.1265C>T variant.
Abbreviation: ASD, Autism spectrum disorder.

Conclusion

The first missense mutation in *MAGEL2* associated with *MAGEL2*-related disorders was reported in a patient exhibiting an overall milder phenotype compared to truncating cases, although he presented with severe autism spectrum disorder, dysmorphic facial features, and developmental delay.[19]

We also compared the clinical manifestations of our patient with those reported by Patak, who described a patient harboring the missense variant *MAGEL2*:c.1613C>A (p.Ala538Glu) (Table 3). Both patients share several core features of Schaaf-Yang syndrome, including neonatal hypotonia, developmental delay, and signs of hypogonadism. However, they differ in the presence of autistic traits, dysmorphic features, and arthrogryposis multiplex congenita, which were observed in the patient reported by Patak et al but were absent in our case. Conversely, our patient exhibited obesity, which was not reported in the previously described case. These findings illustrate the variable expressivity and potentially distinct functional consequences of different *MAGEL2* missense variants.[19] Cells with mutant *MAGEL2* display abnormal subcellular localization. *MAGEL2* has been shown to participate in the regulation of transcription factors and chromatin remodeling, which may in turn affect gene transcriptional activity in the 15q11–q13 region. Furthermore, impaired interactions between mutant *MAGEL2* and SMN, FMRP, KHSRP, and FUS proteins have been observed, leading to disruption of RNA stability and processing, including transcripts originating from the PWS region.[20] Endocrine abnormalities, including non-autoimmune hypothyroidism and short stature, are common in SYS and warrant proactive monitoring. Notably, spontaneous pubertal development occurred, albeit at the lower end of growth percentiles.[21] In children with early-onset obesity and neurodevelopmental features not explained by common syndromes, testing for *MAGEL2* mutations should be considered. Genetic confirmation facilitates prognosis and guides coordinated multidisciplinary care. Parents play a crucial role as behavioural models — their own lifestyle changes have a direct positive influence on the child's motivation and long-term adherence. Intervention should be delivered by a multidisciplinary team (paediatrician, dietitian, psychologist, and, where appropriate, physiotherapist) and include regular follow-up.

In accordance with standard genetic counseling recommendations, parental testing would be warranted; however, the father is unavailable for genetic testing. Consequently, the observed mutation may be either paternally inherited or *de novo* in origin.

This case underscores the complexity of managing early-onset obesity in the context of a rare genetic disorder. It is suggested that the early use of whole genome sequencing, particularly in critical situations such as the early development of significant obesity in combination with other multi-organ involvement, could facilitate early diagnosis of rare conditions such as SYS. This could help save time and resources and contribute to improved clinical outcomes for patients. Multidisciplinary surveillance—particularly in endocrinology, rehabilitation, cardiology, and nutrition—is essential. Genetic testing for *MAGEL2* mutations should be part of the diagnostic algorithm for children with severe hypotonia, obesity, and syndromic features. Currently, the patient attends regular swim training, participates in mainstream school without support needs, and successfully completed a 400m charity athletic event.

In case of planning future offspring, it is advisable to discuss the possibility of in vitro fertilization (IVF) with preimplantation genetic testing for monogenic disorders (PGT-M) to prevent recurrence of the pathogenic variant.

Data Sharing Statement

The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to ethical restrictions and the privacy of the patients.

Ethics

The study was approved by the Ethics Committee of the University Hospital Ostrava (approval no. 16/2025). Institutional approval was required for the publication of anonymized case details.

Informed Consent Statement

Informed consent was obtained from the parents (legal guardians) of the child described in this case report for participation in the study and publication of anonymized clinical data and images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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