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Review Article

The Role of *MAGEL2* Gene on Schaaf-Yang Syndrome

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ABSTRACT

Schaaf-Yang Syndrome (SYS) is an imprinted neurodevelopmental disorder caused by truncating variants in the paternally expressed *MAGEL2* gene within chromosome 15q11-q13. Early clinical features overlap with Prader-Willi Syndrome (PWS), yet SYS is characterized by distal joint contractures and a higher prevalence of autistic traits. Recent molecular and animal studies have advanced the understanding of *MAGEL2* function and identified potential therapeutic targets. Molecular confirmation through *MAGEL2* sequencing remains the diagnostic gold standard. Current treatments are primarily supportive; early oxytocin administration has demonstrated partial behavioral improvements in animal models, likely via modulation of hypothalamic circuits, though human evidence is lacking. Comprehensive natural history data and genotype-phenotype correlations are still limited. Effective management requires a coordinated, multidisciplinary approach, and further translational studies are essential to guide targeted therapies.

Keywords: Schaaf-Yang syndrome; *MAGEL2* gene; Neurodevelopmental disorder; Prader-Willi syndrome; Oxytocin

INTRODUCTION

Schaaf-Yang Syndrome (SYS) is an ultra-rare genetic disorder first described by Dr. Christian Patrick Schaaf in 2013. The condition is caused by truncating mutations in the paternally inherited *MAGEL2* gene. *MAGEL2* belongs to the Melanoma Antigen (MAGE) family and is located within the Prader-Willi critical region on chromosome 15q11-q13. These nonsense or frameshift variants lead to the production of a truncated protein, disrupting normal *MAGEL2* function and resulting in the characteristic clinical manifestations of the syndrome [1]. Both Schaaf-Yang Syndrome (SYS) and Prader-Willi Syndrome (PWS) share several clinical characteristics, including neonatal hypotonia, feeding difficulties during infancy, and global developmental delay. Still, some important characteristics distinguish the two diseases; autistic spectrum disorder and joint contractures are somewhat more prevalent in SYS [2]. We hope to increase knowledge of the phenotypic spectrum and underlying molecular basis by filling in the present clinical recognition and regional epidemiological data gaps, by providing a thorough examination of its clinical and genetic characteristics, and mechanisms of Schaaf-Yang Syndrome

Clinical features

Primarily targeting the muscular, neurological, and circulatory systems, Schaaf-Yang Syndrome (SYS) presents itself as a broad but distinct clinical profile. Early-life hypotonia and feeding difficulties sometimes mimic Prader-Willi Syndrome (PWS), but later characteristics, such as joint contractures and behaviors related to the autism spectrum, can help to differentiate SYS from PWS. The range in symptom severity reflects the several developmental effects of *MAGEL2* failure.

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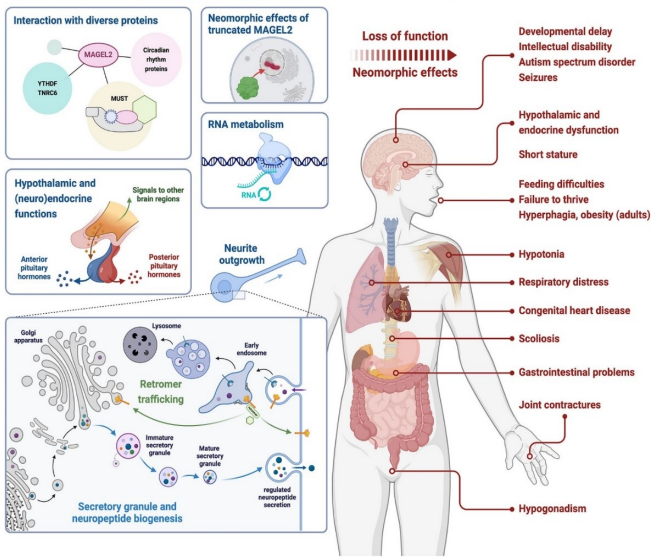

Figure 1: *MAGEL2* physiology and SYS. *MAGEL2* engages in diverse protein complexes and interactions to facilitate a range of processes spanning RNA metabolism, retromer trafficking, secretory granule and neuropeptide biogenesis, neurite outgrowth, and the fine-tuning of hypothalamic and (neuro) endocrine activities. In addition to loss-of-function mechanisms, the emergence of neomorphic effects from truncated *MAGEL2*, which is encoded by typical SYS variants, probably contributes to the complex SYS phenotype [2,3]. Abbreviations: MUST: MAGEL2-USP7-TRIM27 protein complex; SYS: Schaaf-Yang Syndrome.

Neonatal and early-life

They often display significant hypotonia and poor sucking reflexes during the neonatal stage. Patients with Schaaf-Yang Syndrome (SYS) need specific or assisted feeding methods. Like these early-life diseases, Prader-Willi Syndrome (PWS) results from frequent gene losses in the 15q11-q13 area. Additional distinguishing features of SYS from the classic PWS phenotype [4] are congenital joint contractures, especially those impacting the little finger joints, and the lack of or delayed onset of hyperphagia. Besides hypotonia and eating disorders, afflicted newborns often do not develop normally and gain weight abnormally, hence they need continuous dietary assistance [1,2]. Early muscle hypotonia's systemic effects show themselves in the prevalence of respiratory problems during the first several weeks of birth, including transient. An elevated chance of infection and apnoea [1]. Moreover, several cases have shown slight prenatal symptoms suggesting unusual neuromuscular development may happen before delivery, including lowered foetal activity or lessened intrauterine activity [2]. Together, these early-life and neonatal features define the first clinical sign of SYS and emphasise the great importance of early detection for timely management and compassionate care.

Growth and endocrine

People with Schaaf-Yang syndrome most often have a lack of growth hormone. This shortage shows early in infancy as hypoglycemia, which sometimes causes seizures or poor growth. Furthermore, some patients show further hormonal abnormalities such as central hypothyroidism, which points to more general pituitary malfunction. Early diagnosis and therapy are crucial to avoid metabolic problems and encourage normal development [5], although certain endocrine deficiencies disappear with time. Schaaf-Yang syndrome testing often shows a growth hormone shortage; stimulation tests, such as clonidine and GHRH-arginine certifications, confirm a diagnostic peak GH level under 20 mU/L. Along established medical standards, pubertal abnormalities, including late or early onset, should also be evaluated. Some patients also show the need for a comprehensive hormonal examination and quick treatment to help with metabolic stability and development. They have thyroid disorders or central adrenal insufficiency [6].

Neurodevelopmental and behavioral

In patients with Schaaf-Yang syndrome, hypotonia, global neurodevelopmental delay, and early-life autonomic anomalies are common. Certain individuals may have underlying hypothalamic dysfunction, as evidenced by their unique EEG patterns, which correlate with both motor and behavioural disorders. Even though certain neurodevelopmental abnormalities may gradually improve, persistent issues with eating, adaptive reflexes, and motor coordination are frequently reported [7]. Neurodevelopmental and behavioural features may vary significantly even among patients with the same *MAGEL2* mutation. Common symptoms include social communication deficits and behaviours like those of autism spectrum disorder. This clinical heterogeneity highlights the importance of early supportive interventions and personalised assessment to maximise developmental outcomes for afflicted individuals [8].

Dysmorphic and musculoskeletal

Schaaf-Yang syndrome patients often have unique dysmorphic and musculoskeletal characteristics. Almost universal early symptom of neonatal hypotonia is feeding difficulties. Hand abnormalities include tapering fingers, clinodactyly, camptodactyly, brachydactyly, and adducted thumbs are frequently seen, as are joint contractures that range from minor interphalangeal involvement to severe arthrogryposis. Small hands and feet, short stature, and spinal abnormalities like kyphosis or scoliosis are frequently found during skeletal evaluations. In addition to early signs of hypogonadism in males and delayed sexual development in females, dysmorphic traits can include strabismus, esotropia, and myopia in the eyes. Affected individuals also frequently experience sleep difficulties, especially sleep apnoea, which reflects the systemic effects of these dysmorphic and musculoskeletal abnormalities [4]. Schaaf-Yang syndrome's long-term morbidity is significantly increased by severe musculoskeletal anomalies such as scoliosis and obvious joint contractures. These anatomical anomalies may result in decreased mobility, the development of hypotonia-related functional limits, and increased vulnerability to secondary issues such as respiratory disorders or sleep disturbances [9].

Systemic and additional

Beyond early-life complications, SYS can affect multiple organ systems throughout development. Sleep disturbances, including obstructive sleep apnea, are prevalent, and gastrointestinal dysmotility may contribute to chronic feeding difficulties. Additionally, some patients exhibit metabolic or endocrine abnormalities that interact with systemic health, highlighting the importance of longitudinal monitoring to anticipate and manage multisystem involvement [4]. Long-term morbidity in Schaaf-Yang syndrome often arises from the cumulative effects of musculoskeletal, respiratory, and endocrine complications. Severe joint contractures, spinal deformities, and persistent hypotonia can exacerbate functional limitations, while systemic issues such as recurrent infections and respiratory insufficiency may contribute to increased mortality risk. These findings underscore the need for ongoing, coordinated care to address the multisystemic impact of the syndrome and improve long-term outcomes [9].

Comparison with PWS

Schaaf-Yang syndrome shares several clinical features with Prader-Willi Syndrome, including neonatal hypotonia, feeding difficulties, and global developmental delay. However, truncating *MAGEL2* mutations in SYS result in distinctive phenotypes that help differentiate it from classical PWS. Autism spectrum disorder and congenital joint contractures are markedly more prevalent in SYS, whereas features typical of PWS, such as pronounced hyperphagia and subsequent obesity, are often absent or only mildly expressed. Genetic analyses further underscore these differences, as SYS arises specifically from pathogenic variants in the paternally expressed *MAGEL2* gene, while PWS involves larger deletions or disruptions of multiple genes within the 15q11-q13 region. Collectively, these observations highlight both the phenotypic overlap and the distinguishing features that are critical for accurate diagnosis and management [10]. While Schaaf–Yang Syndrome (SYS) and Prader-Willi Syndrome (PWS) share a common genetic locus within the 15q11-q13 region, the pathogenic mechanisms underlying these disorders differ substantially. SYS results from truncating mutations in the paternally expressed *MAGEL2* gene, whereas PWS arises from larger deletions or maternal uniparental disomy affecting multiple imprinted genes in the same chromosomal region. This distinction explains the overlap in clinical features, such as hypotonia and developmental delay, alongside key differentiating traits, including joint contractures and autism spectrum behaviors that are characteristic of SYS. The comparative molecular analyses of these syndromes provide deeper insights into the role of individual imprinted genes, particularly *MAGEL2*, in hypothalamic and neurobehavioral regulation [11].

In summary, the clinical phenotype of SYS is diverse but characterized by consistent neurodevelopmental and behavioral features. Understanding its genetic basis is crucial for clarifying this variability and improving diagnostic accuracy. The next section, therefore, focuses on the molecular mechanisms underlying *MAGEL2*-related pathology.

Genetic basis and pathophysiology

Schaaf-Yang syndrome arises from truncating mutations in the paternally expressed *MAGEL2* gene within the 15q11-q13 region. These mutations lead to a loss of normal *MAGEL2* function, which plays a crucial role in hypothalamic development, protein ubiquitination, and neuronal maturation. Disruption of these processes contributes to the multisystem phenotype observed in SYS, including neurodevelopmental delay, endocrine abnormalities, and musculoskeletal anomalies [12,13].

Research focused on the cellular level, notably by Castilla-Vallmanya, et al. demonstrates that *MAGEL2* dysfunction hinders endosomal recycling and ubiquitin-mediated protein degradation [1]. This impairment is strongly implicated as a mechanism for the abnormal neuronal connectivity and altered neurotransmission observed in SYS patients. Furthermore, investigations into the protein's function suggest that the N-terminal domain of *MAGEL2* is integral to RNA metabolism and post-transcriptional control. It is hypothesized that mutations within this domain disrupt crucial processes like mRNA handling and protein translation, potentially explaining the early-onset symptoms such as hypotonia, feeding difficulties, and cognitive deficits [14,15].

Truncating mutations in *MAGEL2* generate phenotypes that partially overlap with Prader-Willi Syndrome but are distinguished by joint contractures and autism spectrum traits. Studies indicate that specific *MAGEL2* variants contribute directly to hypothalamic dysfunction, affecting thermoregulation, appetite regulation, and endocrine homeostasis. Beyond intracellular mechanisms, *MAGEL2* dysfunction impacts systemic physiology, particularly through oxytocin-mediated pathways, which may impair social behaviors, stress responses, and thermoregulation. These genotype-phenotype correlations emphasize the importance of precise molecular characterization in predicting clinical outcomes [16,17].

Epidemiology

Schaaf-Yang Syndrome (SYS) is an ultra-rare neurodevelopmental disorder with an estimated prevalence of less than 1 in 50,000 individuals worldwide. Over 250 patients with paternally inherited pathogenic variants in the *MAGEL2* gene have been identified to date, although only approximately 120 cases had been reported in the literature as of September 2020 [4,9]. The rarity of SYS is further reflected in its variable phenotypic presentation, which includes neurodevelopmental delay, hypotonia, feeding difficulties, and musculoskeletal anomalies. Particularly during the neonatal period, the degree of multisystem involvement influences mortality and morbidity, therefore highlighting the need for early diagnosis and clinical surveillance [9].

Even with global case studies, some regions are still underreported. More clinical awareness, thorough genetic testing, and epidemiological research are needed to reliably ascertain prevalence, discover new *MAGEL2* variations, and guide patient treatment choices [1].

While Schaaf-Yang syndrome (SYS) is still widely accepted as a very rare disease, recent multicenter studies have identified more than a few genetically confirmed cases, suggesting limited clinical exposure and lack of access to testing may result in underreported prevalence. Data from longitudinal cohorts suggest many individuals are first misdiagnosed with Prader-Willi Syndrome or some other neurodevelopmental condition, delaying genetic confirmation and epidemiological reporting. Additionally, advances in next-generation sequencing technologies and the expansion of genetic testing panels have contributed to a growing detection of *MAGEL2* mutations in recent years. These cases illustrate the fluid and dynamic aspects of SYS epidemiology and highlight the need for global databases for more accurate case reporting and genotype-phenotype association [18].

Diagnostic approach and differential diagnosis

Diagnosing Schaaf-Yang Syndrome (SYS) depends mostly on molecular validation of truncating mutations in the paternally expressed *MAGEL2* gene. Prenatal and early postnatal diagnosis remains challenging because newborn hypotonia, feeding problems, and mild dysmorphic traits are all general in nature. Although these findings are neither sensitive nor specific, diminished foetal movements may occasionally be observed on prenatal ultrasonography. Comprehensive genetic testing, such as targeted *MAGEL2* analysis or whole-exome sequencing, is required for correct diagnosis and timely clinical therapy [19].

Because of phenotypic heterogeneity, distinguishing SYS patients from overlapping syndromes, including Prader-Willi Syndrome (PWS) and Chitayat-Hall syndrome, can be difficult. Even those with the same *MAGEL2* mutations may show different clinical characteristics, including the degree of developmental delays, joint contractures, and actions linked to autism spectrum disorders. Integrative, thorough clinical evaluation with molecular testing is necessary to distinguish SYS from related neurodevelopmental disorders and to guide appropriate treatment options [8].

Management and therapeutic strategies

The management of Schaaf-Yang Syndrome (SYS) often requires the involvement of many specialists. Many symptoms are different in each case and may have a wide range of potential severity levels that can affect several areas of function, including the neurologic, hormonal, and musculoskeletal areas. It will be important to ensure diagnosis as early as possible to lessen the effects on the future and make an attempt at treatment as early as possible. This is especially true in infancy when hypotonia and feeding are of greatest concern. Early diagnosis will often also require a session with multiple specialists, such as a neurologist, endocrinologist, geneticist, and inclusion of rehabilitation staff, including physical and/or occupational therapists. Regular monitoring of growth parameters, nutritional status, and neurodevelopmental milestones should continue to maximize long-term outcomes and enhance quality of life [1,9].

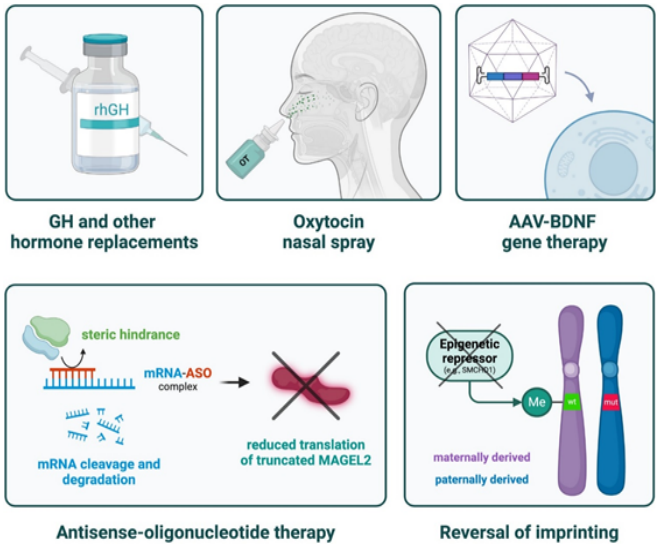

Figure 2: Therapeutic strategies for SYS. This figure summarizes some promising therapeutic advances with potential efficacy in addressing SYS, transcending symptomatic management. Notably, antisense oligonucleotides directed at truncated *MAGEL2* could specifically address potential neomorphic effects [2,3]. **Abbreviations:** AAV-BDNF: Adeno-Associated Virus-BDNF gene; ASO: Antisense Oligonucleotide; GH: Growth Hormone; Me: Methylation signal; Mrna: Messenger RNA; mut: Mutation; OT: Oxytocin; rhGH: Recombinant Human Growth Hormone; SYS: Schaaf–Yang Syndrome; WT: Wild Type.

Endocrine dysregulations are among the most treatable elements of SYS, and their management can make an important contribution to developmental progress. For instance, in a select group of patients with Growth Hormone deficiency (GH), growth hormone replacement therapy can have a positive impact on muscle tone, length growth, and metabolism. Similarly, thyroid or adrenal insufficiencies can be assessed and treated using standard assays for hormonal levels in addition to clinical findings. In cases of delayed or atypical development of puberty, hormone replacement therapy can be envisaged to help achieve appropriate sexual maturation and bone health. Thus, a systemic endocrine follow-up is an essential component of clinical management in SYS [5].

Beyond endocrine therapy, rehabilitative and behavioral interventions form the cornerstone of long-term management. Early implementation of physiotherapy and occupational therapy aids in improving joint mobility and reducing the impact of congenital contractures, while speech and feeding therapy can address dysphagia and communication difficulties. Behavioral therapy and structured educational support are essential for managing autistic traits and social communication deficits, which are prevalent in SYS. Family counseling and social support services are equally important to address the psychosocial aspects of living with a chronic rare disorder, underscoring the value of sustained, individualized, and multidisciplinary care [4,9].

Research directions and future perspectives

Despite significant progress in understanding Schaaf-Yang Syndrome (SYS), numerous gaps remain in elucidating its full molecular, neurodevelopmental, and clinical spectrum. Future research should focus on comprehensive genotype-phenotype correlations to predict individual patient outcomes and identify potential biomarkers for early diagnosis. Longitudinal studies are needed to characterize developmental trajectories and multisystem involvement, which could guide personalized therapeutic interventions. Additionally, exploration of novel molecular pathways, including synaptic regulation and neuroendocrine signaling, may reveal targeted strategies to mitigate behavioral, cognitive, and endocrine manifestations. Collaborative, multicenter studies and shared patient registries will be essential to expand sample sizes, validate findings, and accelerate translation from molecular insights to effective clinical management.

CONCLUSION

This comprehensive review affirms that Schaaf-Yang Syndrome (SYS) is a distinct neurodevelopmental disorder, predominantly caused by truncating mutations in the paternally expressed *MAGEL2* gene. Its unique phenotype, marked by neonatal hypotonia, joint contractures, global developmental delay, and a high prevalence of Autism Spectrum Disorder (ASD), is crucial for differentiating it from the phenotypically overlapping Prader-Willi Syndrome (PWS). Moving forward, research must pivot from purely supportive care toward targeted molecular therapies. The discovery that the truncated *MAGEL2* protein is stable and localizes to the nucleus suggests a pathogenic neomorphic effect. This insight, combined with the need to explore biomarkers like OXTR methylation to personalize oxytocin-based behavioral therapies, defines the cutting edge of translational research for SYS, aiming to elucidate the full pathophysiology and guide precision medicine strategies.

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