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Schaaf-Yang Syndrome

Synonym: Chitayat-Hall Syndrome

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Summary

Clinical characteristics

Schaaf-Yang syndrome (SYS) is a rare neurodevelopmental disorder that shares multiple clinical features with the genetically related Prader-Willi syndrome. It usually manifests at birth with muscular hypotonia in all and distal joint contractures in a majority of affected individuals. Gastrointestinal/feeding problems are particularly pronounced in infancy and childhood, but can transition to hyperphagia and obesity in adulthood. Respiratory distress is present in many individuals at birth, with approximately half requiring intubation and mechanical ventilation, and approximately 20% requiring tracheostomy. Skeletal manifestations such as joint contractures, scoliosis, and decreased bone mineral density are frequently observed. All affected individuals show developmental delay, resulting in intellectual disability of variable degree, from low-normal intelligence to severe intellectual disability. Other findings may include short stature, seizures, eye anomalies, and hypogonadism.

Diagnosis/testing

The diagnosis of Schaaf-Yang syndrome is established in a proband by identification of a heterozygous pathogenic variant in the paternally derived *MAGEL2* allele by molecular genetic testing. The 15q11.2 locus that includes *MAGEL2* is maternally imprinted, meaning that only the paternally derived allele is expressed while the maternally derived allele is inactivated.

Management

Treatment of manifestations: Feeding therapy or supplemental tube feeding may be required for persistent feeding issues; assisted ventilation to include either noninvasive or invasive intervention; CPAP for sleep apnea; growth hormone therapy in those with short stature and/or linear growth concerns; standard therapy for gastroesophageal reflux disease, metabolic syndrome, constipation, skeletal abnormalities, low bone mineral density, developmental delay/cognitive impairment, seizures, eye anomalies, undescended testes, hypogonadism and pubertal abnormalities, and hypothyroidism.

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Surveillance: At each visit: measurement of growth parameters and evaluation of nutritional status & safety of oral intake; assessment of developmental progress, educational needs, and self-help skills; monitor for signs and symptoms of constipation, sleep apnea, respiratory insufficiency, scoliosis, progression of contractures, and puberty (from ages 10-17 years). Behavioral assessment annually; DXA scan every two years starting at the age five years, transitioning to every three to five years in adulthood; ophthalmology evaluation as recommended by an ophthalmologist; polysomnography annually for those on long-term GH therapy or as recommended by a sleep specialist.

Genetic counseling

Schaaf-Yang syndrome is inherited in an autosomal dominant, maternally imprinted manner (i.e., a heterozygous pathogenic variant on the paternally derived *MAGEL2* allele results in disease; a pathogenic variant on the maternally derived *MAGEL2* allele does not result in disease because normally the maternally derived *MAGEL2* allele is silenced). Approximately 50% of individuals diagnosed with SYS inherited a *MAGEL2* pathogenic variant from a clinically unaffected father and the remainder are *de novo*. If the father of the proband is heterozygous for the *MAGEL2* pathogenic variant identified in the proband, the risk to both male and female sibs is 50%. The recurrence risk within the family of the proband's mother is that of the general population. Once the *MAGEL2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for Schaaf-Yang syndrome (SYS) have not been established.

Suggestive Findings

SYS **should be suspected** in individuals with the following clinical and suggestive laboratory findings.

Clinical findings

- Generalized hypotonia of infancy
- Respiratory distress in infancy
- Infant feeding difficulties with failure to thrive
- Hyperphagia with subsequent obesity in childhood or adolescence
- Mild-to-profound developmental delay or intellectual disability
- Autism spectrum disorder or autistic features
- Nonspecific dysmorphic facial features, including a pointed chin, frontal bossing, and low-set ears
- Short stature
- Joint contractures of variable severity, ranging from mild contractures of the distal phalanges of the hands to severe arthrogryposis multiplex congenita
- Endocrinopathy, including:
  - Hypopituitarism
  - Growth hormone deficiency
  - Hypogonadism and/or undervirilization in males

Suggestive laboratory findings

- Normal methylation analysis of the 15q11.2 region (Prader-Willi/Angelman syndrome locus)
- Any of the following hormonal or metabolic findings [McCarthy et al 2018b]:
  - Low IGF-1 levels despite normal weight and adequate nutrition
  - Elevated glucose levels on oral glucose tolerance testing (OGTT)
  - Elevated fasting ghrelin levels

Establishing the Diagnosis

The diagnosis of Schaaf-Yang syndrome **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in the paternally derived *MAGEL2* allele by molecular genetic testing (see Table 1).

Note: (1) The 15q11.2 locus that includes *MAGEL2* is maternally imprinted, meaning that only the paternally derived allele is expressed while the maternally derived allele is inactivated. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of a heterozygous *MAGEL2* variant of uncertain significance in the paternal allele neither establishes nor rules out a diagnosis of SYS.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive combination of findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SYS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of SYS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**. If a pathogenic *MAGEL2*-variant is detected, **parental origin of the mutated allele** should be determined by parental testing or methylation-sensitive sequencing in the proband. If testing of both parents does not identify the pathogenic variant found in the proband, methylation-sensitive testing is required to confirm the diagnosis.

- **Single-gene testing.** Sequence analysis of *MAGEL2* is performed first to detect pathogenic single-nucleotide variants or small intragenic deletions/insertions in the paternally derived allele.

  Note: Depending on the sequencing method used, larger deletions/duplications or whole-gene deletions may not be detected.

  If no variant is detected by the sequencing method used, a gene-targeted deletion/duplication analysis to detect larger deletions/duplications or whole-gene deletions may be performed (e.g., by quantitative PCR, MLPA, or chromosome microarray testing). Parental/methylation-sensitive testing may be required to confirm the diagnosis.

- **A neonatal hypotonia, congenital contractures, intellectual disability (ID), or autism spectrum disease multigene panel** that includes *MAGEL2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by infantile hypotonia and/or intellectual disability, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved.

- **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not.
- **Genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Schaaf-Yang Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MAGEL2	Sequence analysis [3]	≥99% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	Single cases [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Note: *MAGEL2* is a single-exon gene.
6. Larger deletions of the paternally derived 15q11.2 region that include *MAGEL2* typically lead to Prader-Willi syndrome (see Genetically Related Disorders).
7. A 22-kb inversion and 3-kb deletion, which removed the last 852 bp of *MAGEL2*, has been described in an individual diagnosed clinically with Chitayat-Hall syndrome [Jobling et al 2018] (see Nomenclature).

Clinical Characteristics

Clinical Description

Schaaf-Yang Syndrome (SYS) is a rare, paternally derived neurodevelopmental disorder that shares multiple clinical features with the genetically related Prader-Willi syndrome. It usually manifests at birth with muscular hypotonia in all and distal joint contractures in a majority of affected individuals.

To date, more than 250 individuals have been identified with a paternally derived pathogenic variant in *MAGEL2* [Schaaf et al 2013, Fountain et al 2017, McCarthy et al 2018a, McCarthy et al 2018b]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Schaaf-Yang Syndrome

Feature	% of Persons w/Feature	Comment
DD/ID	100%	
Muscular hypotonia	100%	
Infantile hypotonia	95%-100%	
Feeding difficulties in infancy	95%-100%	
Flexion contractures	>85%	
Autistic behavior	75%-85%	
Dysmorphic features	75%-85%	Incl pointed chin, frontal bossing, low-set ears
Ocular anomalies	75%-85%	Incl esotropia, myopia, strabismus
Behavioral abnormalities	70%-80%	Incl impulsivity, compulsivity, stubbornness, manipulative behavior, skin picking / automutilation
Sleep apnea	70%-80%	
Respiratory distress	65%-75%	
Small hands	65%-75%	Other hand anomalies: tapered fingers, clinodactyly, camptodactyly, brachydactyly, adducted thumbs
Chronic constipation	65%-75%	
Temperature instability	60%-70%	
Short feet	55%-65%	
↓ fetal movement	55%-65%	
GERD	50%-60%	
Scoliosis	50%-60%	
Short stature	50%-60%	
Polyphagia/Obesity	30%-40%	Onset in late childhood/adolescence. Frequency of this feature ↑ w/age.
Seizures	30%-40%	
Kyphosis	25%-35%	
Hypogonadism	15%-65%	15%-25% of females & 55%-65% of males, based on appearance of external genitalia

DD = developmental delay; GERD = gastroesophageal reflux; ID = intellectual disability

Muscular hypotonia is, to a variable degree, present in almost all neonates with SYS, and can be severe in some instances. Reduced fetal movements may be reported prenatally. Hypotonia also contributes to different aspects of the neonatal phenotype, such as feeding difficulties and respiratory distress.

Gastrointestinal/feeding problems are particularly pronounced in infancy and childhood, but can transition to hyperphagia and obesity in adulthood.

- Almost all affected individuals have feeding problems in infancy. Most infants are dependent on special feeding techniques (special nipple, nasogastric tube feeding) during the first months of life.
- While feeding problems resolve in about half during the first year of life, insufficient oral food uptake remains a problem in the other half, and these affected individuals eventually require gastrostomy tube placement, which could be continued into childhood.

- Although not a hallmark of SYS in childhood, hyperphagia and obesity can be found in a significant proportion of affected adults, and the incidence of hyperphagia appears to increase with age [Schaaf et al 2013, McCarthy et al 2018a, McCarthy et al 2018b].
- Chronic constipation is present in the majority of affected individuals.
- Gastroesophageal reflux is present in more than half of affected individuals.

Stature. Approximately 50%-60% of individuals with SYS have short stature, defined as height below the third percentile. In a cohort of 78 affected individuals reported by McCarthy et al [2018a], average height was on the 22nd percentile for age.

- Growth hormone (GH) treatment has been effective in some affected individuals [McCarthy et al 2018b].
- A retrospective analysis of GH treatment in children with SYS including 14 treated and 12 untreated individuals found a significant increase in body height in the treated group over a course of six months (improvement of mean height z-scores from -2.6 before to -1.7 after treatment) [Hebach et al 2021].
- Satisfaction with GH therapy was high among parents of treated individuals, who reported a subjective increase or strong increase in muscle strength in 13 of 14 individuals.
- Based on seven individuals for whom sufficient data was available, a non-significant improvement of mean weight for stature Z-scores (decrease by 0.8 after 6 months on GH therapy) was noted. The authors hypothesized that this may indicate a positive effect of GH treatment on body composition, which would be in line with established effects of GH therapy in children with Prader-Willi syndrome [Lindgren et al 1998].
- Worsening of sleep apnea was reported in one individual with SYS who was on GH, and worsening of scoliosis/kyphosis was reported in two individuals in the treatment group, without the need to interrupt or discontinue GH therapy.
- The authors proposed that the same precautions should be taken in individuals with SYS undergoing GH therapy that apply for individuals with Prader-Willi syndrome (see Management).

Head circumference. Most individuals with SYS have a normal head circumference.

Respiratory abnormalities. Respiratory distress is present in many individuals with SYS at time of birth, with approximately half of all individuals requiring intubation and mechanical ventilation, and approximately 20% requiring tracheostomy.

- More than half of the individuals reported by McCarthy et al [2018a] required mechanical ventilation during the first two months of life.
- Central apnea and/or obstructive sleep apnea is seen in approximately 75% of all affected individuals.
- Episodes of apnea or severe respiratory distress can occur, especially during the first year of life [McCarthy et al 2018a], and contribute to a higher mortality compared to the general population during infancy.

Musculoskeletal features. Skeletal manifestations such as joint contractures, scoliosis, and decreased bone mineral density are frequently observed. Joint contractures may be detected prenatally.

- Distal joint contractures of the upper limbs are present in the majority of affected individuals. The severity of this symptom varies from isolated contractures of the interphalangeal joints to severe arthrogryposis multiplex congenita [Mejlachowicz et al 2015].
- Scoliosis is present in more than half of affected individuals. Exaggerated kyphosis can be observed in some.
- Low bone mineral density (>2 SD below the mean) was reported in the majority of affected individuals studied by McCarthy et al [2018b].

Developmental delay (DD) / intellectual disability (ID). All individuals with SYS show DD, resulting in ID of variable degree, from low-normal intelligence to severe ID. The severity of ID is likely influenced by an individual's *MAGEL2* genotype (see Genotype-Phenotype Correlations).

- Motor milestones are usually delayed – on average, children with SYS sit independently at age 18 months, crawl at 31 months, and walk at 50 months.
- First words are spoken at an average age of 36 months, and the first two-word sentence at an average of 40 months.
- However, affected individuals vary greatly with regard to motor and language development, and some adults with SYS do not acquire speech or independent walking [McCarthy et al 2018a].
- A few affected individuals have borderline intellectual function [Marbach et al 2020].
- Neurologic deterioration following febrile illness has been reported in four individuals with SYS [Negishi et al 2019].

Behavioral problems. Autistic behavior is present in about three quarters of affected individuals.

- Common findings include social withdrawal, restricted interests/fascinations, or stereotypic behavior such as hand flapping when stressed.
- 75%-80% of affected individuals meet the formal clinical diagnostic criteria of autism spectrum disorder (ASD) [McCarthy et al 2018a].
- Additionally, skin picking and self-injurious behavior, which are frequent among individuals with ASD, are present in 70%-80% of those with SYS. Whether this behavior coincides with other features of ASD or whether it occurs as an isolated symptom is as yet unknown.

Seizures of focal or generalized onset have been reported in a minority of affected individuals [Fountain et al 2017, McCarthy et al 2018a].

Two of the four individuals with neurologic deterioration following febrile illness reported by Negishi et al [2019] developed seizures after two to three days of fever. Cranial MRIs revealed unilateral white matter hyperintensities on diffusion-weighted imaging in one individual, while the other showed bilateral high signal intensity areas in the putamen and globus pallidus on T_2-weighted imaging [Negishi et al 2019].

Eye abnormalities are found in the majority of affected individuals, and may include esotropia, myopia, and/or strabismus, as well as nystagmus and microcornea. The number and severity of eye anomalies varies among individuals.

Genitourinary abnormalities. Hypogonadism may be apparent at the time of birth, with undescended testicles and a small penis in males, or may become apparent later in childhood or adolescence.

- Hypogonadism is reported in 15%-25% of females and 55%-65% of males, although McCarthy et al [2018b] reported that values of follicle-stimulating hormone, luteinizing hormone, and testosterone in nine individuals (2 postpubertal and 7 prepubertal individuals) were within the normal range for sex and pubertal status.
- While true hypogonadotropic hypogonadism is among the cardinal features of PWS, it may be less frequent among individuals with SYS.

Facial features. Facial dysmorphisms are mostly nonspecific. A few features are seen with frequency; these include a pointed, prominent chin and frontal bossing (see Suggestive Findings).

Other associated features

- Temperature instability has been reported, with a majority of affected individuals experiencing excessive cold or excessive sweating [McCarthy et al 2018a].
- Hypothyroidism has been observed in some affected adults (see Prader-Willi Syndrome).

Phenotype in adults. Based on data from a group of seven adults, the phenotype of SYS appears to be variable.

- Cognitive abilities vary from complete dependence on external care to mild ID or borderline cognitive function.
- Most affected adults reported to date are verbal and have basic reading skills, and some are able to work in a structured environment.
- Frequent behavioral issues include a lack of activity and motivation, stubbornness, and social withdrawal. Features of ASD are present in most, and heightened anxiety is reported in almost all cases.
- Obsessive-compulsive disorder and attention-deficit disorder are also reported, and one affected adult has been diagnosed with schizophrenia [Marbach et al 2020].
- Overeating and obesity characterizes the majority of adults with SYS. While variable, the onset of obesity appears to be later than in PWS, where it usually occurs in childhood.
- Obesity in adulthood can lead to features of metabolic syndrome, including hyperlipidemia and insulin resistance.

Prognosis. The overall life expectancy of individuals with SYS is reduced due to a greater risk of fatal complications, mostly during infancy and childhood. These include severe respiratory distress due to central and/or obstructive apnea. Sleep monitoring, pulse oximetry, and increased vigilance for breathing irregularities may mitigate these risks to some extent. Survival into adulthood is possible: one reported individual is alive at age 36 years [Marbach et al 2020]. Similar to Prader-Willi syndrome (see Genetically Related Disorders), adults with SYS may suffer from obesity and asssociated complications such as metabolic syndrome. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are under-recognized and under-reported.

Genotype-Phenotype Correlations

The c.1996dupC variant is the most prevalent pathogenic variant, found in 40%-50% of affected individuals. Compared to affected individuals who have other truncating variants, those with the c.1996dupC variant display a more severe phenotype, including a higher prevalence of joint contractures, more severe respiratory complications, more pronounced DD, and a higher rate of profound ID [McCarthy et al 2018a].

The pathogenic c.1996delC variant has been found to be pre- or perinatally lethal in all nine individuals with the variant reported to date [Mejlachowicz et al 2015, Fountain et al 2017, Guo et al 2019].

Penetrance

Penetrance is considered to be 100% for individuals with a pathogenic *MAGEL2* variant on their paternal allele, regardless of the sex of the affected individual (i.e., all should display symptoms associated with SYS). Individuals with a pathogenic *MAGEL2* variant on their maternal allele will be unaffected.

Nomenclature

Jobling et al [2018] demonstrated that Chitayat-Hall syndrome, which was first described in 1990 [Chitayat et al 1990], is caused by a heterozygous pathogenic variant on the paternal allele of *MAGEL2,* demonstrating a common genetic etiology with SYS.

Prior to the description of SYS as a distinct genetic condition, individuals with Schaaf-Yang syndrome may have been diagnosed with Prader-Willi-like syndrome (PWLS). PWLS is considered to be an umbrella term for a genetically heterogeneous group of disorders with phenotypic similarities to PWS [Cheon 2016].

Prevalence

More than 250 individuals with SYS have been reported to date. SYS affects both sexes and all ethnicities equally.

Genetically Related (Allelic) Disorders

Prader-Willi syndrome (PWS) is caused by the absence of paternally expressed, maternally silenced genes at 15q11-q13 (deletions, maternal uniparental disomy 15, or imprinting defects). This region contains several paternally expressed protein-coding genes, including *MAGEL2*. There is significant clinical overlap between PWS and Schaaf-Yang syndrome (see Differential Diagnosis).

Differential Diagnosis

Table 3. Neurodevelopmental Disorders of Interest in the Differential Diagnosis of Schaaf-Yang Syndrome (SYS)

Gene(s) / Genetic Mechanism	DiffDx Disorder	MOI	Occurrence of Feature in Persons w/DiffDx Disorder				
			ID/DD	ASD	Neonatal hypotonia	Infantile feeding problems	Distal joint contractures
Deletions, maternal UPD, imprinting errors w/in PWCR [1]	Prader-Willi syndrome	See footnote 2.	+++	++	+++	+++	±
ERGIC1 *LGI4* *SCYL2* *SYNE1* *TOR1A*	Arthrogryposis multiplex congenita (See *SYNE1* Deficiency & OMIM PS617468.)	AR	++	–	Variable	Variable	+++
SMN1	Spinal muscular atrophy type 1	AR	–	–	+++	+++	–
Interstitial deletions on chromosome 16q22 [3]	Chromosome 16q22 deletion syndrome (OMIM 614541)	AD (isolated cases)	++	–	++	+++	–
AGRN *ALG2* *ALG14* *CHAT* *CHRNA1* *CHRNB1* *CHRND* *CHRNE* *COL13A1* *COLQ* *DOK7* *DPAGT1* *GFPT1* *LRP4* *MUSK* *MYO9A* *PREPL* *RAPSN* *SCN4A* *SLC18A3* *SLC5A7* *SLC25A1* *SNAP25*	Congenital myasthenic syndromes [4]	AD AR	+	–	++	++	++

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	DiffDx Disorder	MOI	Occurrence of Feature in Persons w/DiffDx Disorder				
			ID/DD	ASD	Neonatal hypotonia	Infantile feeding problems	Distal joint contractures
SYT2 *VAMP1*							

+++ = core feature in this disorder; ++ = variable feature of this disorder; + = rare feature of this disorder; – = not typically associated with this disorder; AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; PWCR = Prader-Willi critical region; UPD = uniparental disomy

1. See Genetically Related Disorders.

2. The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

3. Infants may present with clenched or flexed fingers.

4. See also Phenotypic Series: Congenital Myasthenic Syndrome for genes associated with this phenotype in OMIM.

C syndrome (OMIM 211750). An individual with distal contractures, trigonocephaly, neonatal respiratory difficulties, hypotonia, and severe developmental delay, who was tentatively diagnosed at age two years with C syndrome (an autosomal dominant disorder caused by pathogenic variants in *CD96*) based on clinical features, was later (age 19 years) diagnosed with SYS after exome sequencing revealed a *de novo* pathogenic variant in *MAGEL2* (c.1912C > T; p.Gln638Ter) [Urreizti et al 2017].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Schaaf-Yang syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Schaaf-Yang Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To evaluate for growth deficiency in infancy/childhood & obesity in adulthood
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval for aspiration risk, nutritional status, & signs & symptoms of GERD & constipation • May require use of special nipple &/or nasogastric tube in infancy • Consider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.
Respiratory	Polysomnography	To assess for obstructive &/or central sleep apnea [1]

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	AP & lateral radiographs of spine in children & adolescents	To evaluate for scoliosis
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	DXA scan of hips & lower spine beginning in childhood [2]	To assess bone mineral density
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/ language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Neurologic	Neurologic eval	Consider EEG if seizures are a concern.
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
Genitourinary	Assessment for genital hypoplasia &/or pubertal development (in adolescents & adults) on physical exam	Consider referral to: • Urologist in males w/undescended testes; • Endocrinologist in those w/evidence of hypoplastic genitalia &/or hypogonadism.
Endocrine system & lipid metabolism	Baseline laboratory testing [3]	
Genetic counseling	By genetics professionals [4]	To inform affected persons & families re nature, MOI, & implications of Schaaf-Yang syndrome to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; DXA = dual-energy x-ray absorptiometry; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. This is particularly important for those who may be considering growth hormone (GH) therapy and should be completed, along with an adenotonsillar evaluation, prior to the initiation of GH therapy [Berini et al 2013, Deal et al 2013].

2. McCarthy et al [2018b]

3. The following laboratory studies should be considered, depending on the age of the affected individual: fasting blood glucose and glucose tolerance after 120 mins; insulin-like growth factor 1 / insulin-like growth factor binding protein 3; random growth hormone level; follicle-stimulating hormone and luteinizing hormone; total testosterone (in males); thyroid-stimulating hormone and thyroxine; a lipid panel to include total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol; uric acid level.

4. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Schaaf-Yang Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	• Feeding therapy • A special nipple or nasogastric tube may be required. • Gastrostomy tube placement may be considered for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Obesity w/metabolic syndrome	• Nutritional intervention incl restricted caloric intake • Standard treatment for insulin resistance / diabetes • Standard treatment for hyperlipidemia	
GERD	Standard therapy	
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Short stature	Consideration of GH therapy	• Affected persons w/short stature should benefit from off-label GH supplementation to improve body height. GH therapy may also have positive effects on muscle strength & body composition. • Polysomnography & adenotonsillar eval should be completed prior to initiation of GH therapy.[1]
Acute respiratory distress in infancy	Invasive or noninvasive assisted ventilation for acute respiratory distress	Tracheostomy may be required for severe, prolonged respiratory compromise.
Sleep apnea	Overnight application of noninvasive ventilation (e.g., CPAP)	Low threshold for performing addl sleep apnea tests / sleep studies
Skeletal abnormalities	Standard treatment for contractures, clubfoot, & scoliosis per orthopedist	
Low bone mineral density	Standard treatment per endocrinologist	• Optimization of Ca^{2+} & vitamin D levels • Bisphosphonates may be considered.
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist	Community vision services through early intervention or school district
Undescended testes	Standard treatment per urologist	
Hypogonadism	Consideration of short course of testosterone therapy in early infancy for males w/small penis (stretched penile length <–2 SD)	
Pubertal abnormalities	Standard hormonal treatment per endocrinologist	
Hypothyroidism	Thyroid hormone replacement therapy	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CPAP = continuous positive airway pressure; DD = developmental delay; GERD = gastroesophageal reflux disease; GH = growth hormone; ID = intellectual disability; OT = occupational therapy; PT = physical therapy
1. Berini et al [2013], Deal et al [2013]
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with Schaaf-Yang Syndrome

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for signs & symptoms of sleep apnea, aspiration, & respiratory insufficiency.	
	Polysomnography	Annually for those on long-term GH therapy [1] or per sleep specialist
Musculoskeletal	• Monitor for scoliosis & for progression of contractures. • OT/PT assessment of mobility & self-help skills	At each visit
	DXA scan	Every 2 yrs starting at age 5 yrs, transitioning to every 3-5 yrs in adulthood
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for signs of ASD, anxiety, attention, & aggressive or self-injurious behavior	Annually
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures & changes in tone.	At each visit
Eyes	Assessment by ophthalmologist	Per ophthalmologist
Endocrine	Assessment for signs & symptoms of puberty & appropriate pubertal development from ages 10-17 yrs	At each visit
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

ASD = autism spectrum disorder; DXA = dual-energy x-ray absorptiometry; GH = growth hormone; OT = occupational therapy; PT = physical therapy
1. Berini et al [2013], Deal et al [2013]

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Schaaf-Yang syndrome (SYS) is inherited in an autosomal dominant, maternally imprinted manner (i.e., a heterozygous pathogenic variant on the paternally derived *MAGEL2* allele results in disease; a pathogenic variant on the maternally derived *MAGEL2* allele does not result in disease because normally the maternally derived *MAGEL2* allele is silenced).

Risk to Family Members

Parents of a proband

- Approximately 50% of individuals diagnosed with SYS inherited a *MAGEL2* pathogenic variant from a clinically unaffected father.
- Approximately 50% of individuals diagnosed with SYS have the disorder as the result of a *de novo* pathogenic variant on the paternally derived *MAGEL2* allele.
- Molecular genetic testing is recommended for the biological father of the proband to confirm his genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is situated on the paternal allele but is not identified in paternal DNA, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a father with germline (or somatic and germline) mosaicism. Paternal somatic/germline mosaicism has been reported [Patak et al 2019].

      Note: Testing of paternal leukocyte DNA may not detect all instances of somatic mosaicism.
- The mother of a proband will not be affected with SYS nor will she be heterozygous for a *MAGEL2* pathogenic variant.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's father:

- If the father of the proband is heterozygous for the *MAGEL2* pathogenic variant identified in the proband, the risk to both male and female sibs is 50%. The penetrance of SYS is considered to be complete (i.e., a person who is heterozygous for a *MAGEL2* pathogenic variant on the paternal allele will show features of the disorder). However, some interfamilial clinical variability is to be expected.
- If the *MAGEL2* pathogenic variant is not detected in the leukocyte DNA of the biological father of the proband, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of paternal germline mosaicism [Soden et al 2014, Patak et al 2019].

Offspring of a proband. Each child of a proband with SYS has a 50% chance of inheriting the *MAGEL2* pathogenic variant: if the proband is male, heterozygous offspring will be affected; if the proband is female, heterozygous offspring will remain asymptomatic (see Penetrance).

Other family members. Because SYS is inherited in an autosomal dominant, maternally imprinted manner:

- The recurrence risk within the family of the proband's mother is that of the general population.
- If the father of the proband is heterozygous for a *MAGEL2* pathogenic variant, or if the genetic status of the father is unknown, the recurrence risk to members of the father's family is increased. Targeted genetic testing of the father's mother (the paternal grandmother of the proband) may indicate increased recurrence risks for offspring of the father's sibs.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- Genetic counseling (including discussion of potential risks to offspring and reproductive options) should be offered to the parents of affected individuals and to males who are heterozygous for a maternally inherited *MAGEL2* pathogenic variant.
- Genetic counseling is also recommended for members of the paternal family of the proband (such as the father's mother and sibs) if the proband's father is heterozygous for a *MAGEL2* pathogenic variant.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *MAGEL2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Foundation for Prader-Willi Research**
  340 Lemon Ave
  Suite 3620
  Walnut CA 91789
  Phone: 888-322-5487
  Fax: 888-559-4105
  Email: info@fpwr.org
  www.fpwr.org/about-schaaf-yang-syndrome
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Schaaf-Yang Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
MAGEL2	15q11.2	MAGE-like protein 2	MAGEL2	MAGEL2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Schaaf-Yang Syndrome (View All in OMIM)

605283	MAGE-LIKE 2; MAGEL2
615547	SCHAAF-YANG SYNDROME; SHFYNG

Molecular Pathogenesis

MAGEL2 is a maternally imprinted (silenced), paternally expressed, single-exon gene located within the Prader-Willi critical region (PWCR) on chromosome 15q11.2. It encodes the MAGEL2 protein, which belongs to the MAGE protein family. MAGEL2 binds to and regulates the activity of the E3 RING ubiquitin ligase TRIM27 (tripartite motif containing 27). MAGEL2, USP7 (ubiquitin-specific peptidase 7), and TRIM27 are known to colocalize at endosomes where they form the MUST (*M*AGEL2-*U*SP7-*T*RIM27) protein complex, which facilitates retromer-mediated endosomal protein recycling by ubiquitination of the WASH actin nuclear promoting factor [Tacer & Potts 2017]. Disruption of MAGEL2 protein function is predicted to impair autophagy and potentially other ubiquitination-dependent cellular processes. Indeed, truncating variants in *MAGEL2* have been shown to result in decreased autophagy and increased expression of mammalian target of rapamycin (mTOR) in fibroblasts derived from affected individuals. iPSC-derived neurons (iNeurons) derived from patient cells exhibited elevated mTOR activity and defective dendrite formation [Crutcher et al 2019], suggesting that SYS manifests on the cellular level as a disorder of neuronal development.

Given its position within the PWCR, it is remarkable that individuals with *MAGEL2* pathogenic variants on the paternally derived allele show, on average, more pronounced cognitive deficits than those who have PWS as a result of a contiguous gene deletion within the PWCR on the paternally derived chromosome 15. Additionally, individuals who have smaller, atypical deletions within the PWCR on the paternally derived chromosome that include *MAGEL2* but not the SNORD116 cluster may show even milder phenotypes than individuals with typical PWS [Kanber et al 2009]. This suggests either a neomorphic or dominant-negative effect of truncated MAGEL2 proteins, when compared to simple loss of protein expression from the paternal allele. Alternatively, "leaky" expression of the maternal allele of *MAGEL2* in the absence of a paternal allele has been discussed as a possible explanation [Buiting et al 2014].

Mechanism of disease causation. Loss of function (paternal allele)

***MAGEL2*-specific laboratory technical considerations.** *MAGEL2* is an imprinted gene. Only paternally inherited pathogenic variants cause disease; therefore, parental testing is important for variant interpretation.

Table 7. Notable *MAGEL2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_019066.4 NP_061939.3	c.1996dupC	p.Gln666ProfsTer47	Recurrent severe pathogenic variant [McCarthy et al 2018a]
	c.1996delC	p.Gln666SerfsTer36	Pre- or perinatally lethal in all reported affected persons [Mejlachowicz et al 2015, Fountain et al 2017, Guo et al 2019]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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