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Smith-Magenis Syndrome

Synonym: del(17)(p11.2)

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Summary

Clinical characteristics

Smith-Magenis syndrome (SMS) is characterized by distinctive physical features (particularly coarse facial features that progress with age), developmental delay, cognitive impairment, behavioral abnormalities, sleep disturbance, and childhood-onset abdominal obesity. Infants have feeding difficulties, failure to thrive, hypotonia, hyporeflexia, prolonged napping or need to be awakened for feeds, and generalized lethargy. The majority of individuals function in the mild-to-moderate range of intellectual disability. The behavioral phenotype, including significant sleep disturbance, stereotypies, and maladaptive and self-injurious behaviors, is generally not recognized until age 18 months or older and continues to change until adulthood. Sensory issues are frequently noted; these may include avoidant behavior, as well as repetitive seeking of textures, sounds, and experiences. Toileting difficulties are common. Significant anxiety is common as are problems with executive functioning, including inattention, distractibility, hyperactivity, and impulsivity. Maladaptive behaviors include frequent outbursts / temper tantrums, attention-seeking behaviors, opposition, aggression, and self-injurious behaviors including self-hitting, self-biting, skin picking, inserting foreign objects into body orifices (polyembolokoilamania), and yanking fingernails and/or toenails (onychotillomania). Among the stereotypic

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behaviors described, the spasmodic upper-body squeeze or "self-hug" seems to be highly associated with SMS. An underlying developmental asynchrony, specifically emotional maturity delayed beyond intellectual functioning, may also contribute to maladaptive behaviors in people with SMS.

Diagnosis/testing

The diagnosis of SMS is established in a proband who has suggestive clinical findings and either a heterozygous deletion at chromosome 17p11.2 that includes *RAI1* or a heterozygous intragenic *RAI1* pathogenic variant.

Management

Treatment of manifestations: Early-childhood intervention programs; individualized special education for school-aged children; speech/language, physical, occupational, and behavior therapy and vocational training support later in life. Affected individuals may also benefit from monitored trials of psychotropic medication to increase attention and/or decrease hyperactivity, and therapeutic management of sleep disorders. Standard treatment for epilepsy, obesity, gastroesophageal reflux disease, constipation, hypercholesterolemia, palatal anomalies, scoliosis, ophthalmologic issues, recurrent otitis media, hearing loss, cardiac anomalies, renal anomalies, mild immunodeficiency, hypothyroidism, and growth hormone deficiency. Individuals with a 17p11.2 deletion that includes *FLCN* may require management of features of Birt-Hogg-Dubé syndrome (BHD). Respite care and psychosocial support for family members are recommended.

Surveillance: Annual multidisciplinary evaluations for general health and well-being and to plan for educational and vocational or other individualized interventions. In particular, periodic neurodevelopmental assessments and/or consultation with a developmental pediatrician to monitor progress and refer for additional services, evaluations, or support. School-aged children should have periodic comprehensive evaluation to give input to the individualized education program. Annual otolaryngology, audiology, and ophthalmology evaluations. Measurement of growth parameters and nutritional status at each visit. Monitor for the development and/or progression of seizures and scoliosis. Annual fasting lipid profile, screening urinalysis for occult urinary tract infections, and thyroid function tests. Annual family psychosocial assessments are also recommended to assess support for caregivers and sibs. Repeat quantitative immunoglobulins / vaccine titers as clinically indicated. Surveillance for complications of BHD in those with a 17p11.2 deletion that includes *FLCN*.

Agents/circumstances to avoid: When starting a new medication, care should be taken to track sleep and behavior changes over several days or weeks to monitor for potential side effects (e.g., increased appetite, weight gain) and adverse reactions and/or to determine potential efficacy.

Genetic counseling

SMS is caused by a heterozygous deletion of or a heterozygous pathogenic variant in *RAI1* on chromosome 17p11.2. The majority of 17p11.2 deletions are *de novo*, while deleterious variants in *RAI1* can be *de novo* or inherited. Complex familial chromosome rearrangements leading to del(17)(p11.2) and SMS occur but are rare. Although SMS usually occurs as the result of a *de novo* deletion of 17p11.2, rare instances of vertical transmission from an affected parent to a child, parental germline mosaicism, and complex familial chromosome rearrangements leading to del(17)(p11.2) and SMS have been reported. If the SMS-related genetic alteration has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. In the rare instance of a complex familial chromosome rearrangement, prenatal testing is possible for a pregnancy at increased risk using prenatal chromosomal microarray analysis (CMA) and sequencing on fetal cells.

Diagnosis

Suggestive Findings

Smith-Magenis syndrome (SMS) **should be suspected** in individuals with the following clinical findings:

- A subtly distinctive facial appearance (see Clinical Description) that becomes more evident with age (see Figure 1, Figure 2, Figure 3)
- Mild-to-moderate infantile hypotonia with feeding difficulties and failure to thrive
- Some level of developmental delay and/or intellectual disability, including early speech delays (expressive greater than receptive speech) with or without associated hearing loss
- A distinct neurobehavioral phenotype that includes stereotypic and maladaptive behaviors
- Sleep disturbance (see Clinical Description)
- Short stature (prepubertal)
- Childhood obesity
- Minor skeletal anomalies, including brachydactyly
- Signs of peripheral neuropathy
- Ophthalmologic abnormalities
- Otolaryngologic abnormalities

Establishing the Diagnosis

The diagnosis of SMS **is established** in a proband with suggestive clinical features and one of the following on molecular genetic testing (see Table 1):

- A heterozygous deletion of 17p11.2
- A heterozygous pathogenic (or likely pathogenic) variant involving *RAI1*

Note: 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.

When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include **chromosomal microarray analysis, single-gene testing,** or use of a **multigene panel**:

- **Chromosomal microarray analysis (CMA)** typically is performed first. CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *RAI1*) that cannot be detected by sequence analysis.

  Note: Although a visible interstitial deletion of chromosome 17p11.2 can be detected in all individuals with the common approximately 3.5-Mb deletion by a routine G-banded analysis provided the resolution is adequate (≥550 band), it is not uncommon for the deletion to be overlooked particularly when the indication for the cytogenetic study is other than SMS. Therefore, CMA has now replaced G-banded cytogenetic analysis and FISH analysis as a first-line test in the diagnosis of SMS.

  If CMA does not detect a deletion of 17p11.2 and the diagnosis of SMS is still suspected, single-gene testing of *RAI1* or a multigene panel that includes *RAI1* may be considered.

- **Single-gene testing.** Sequence analysis of RAI1, which detects small intragenic deletions/insertions and missense, nonsense, and splice site variants, may be considered next. If no pathogenic variant is detected through sequence analysis of RAI1, gene-targeted deletion/duplication analysis, which can detect intragenic deletions or duplications of RAI1, may be considered.

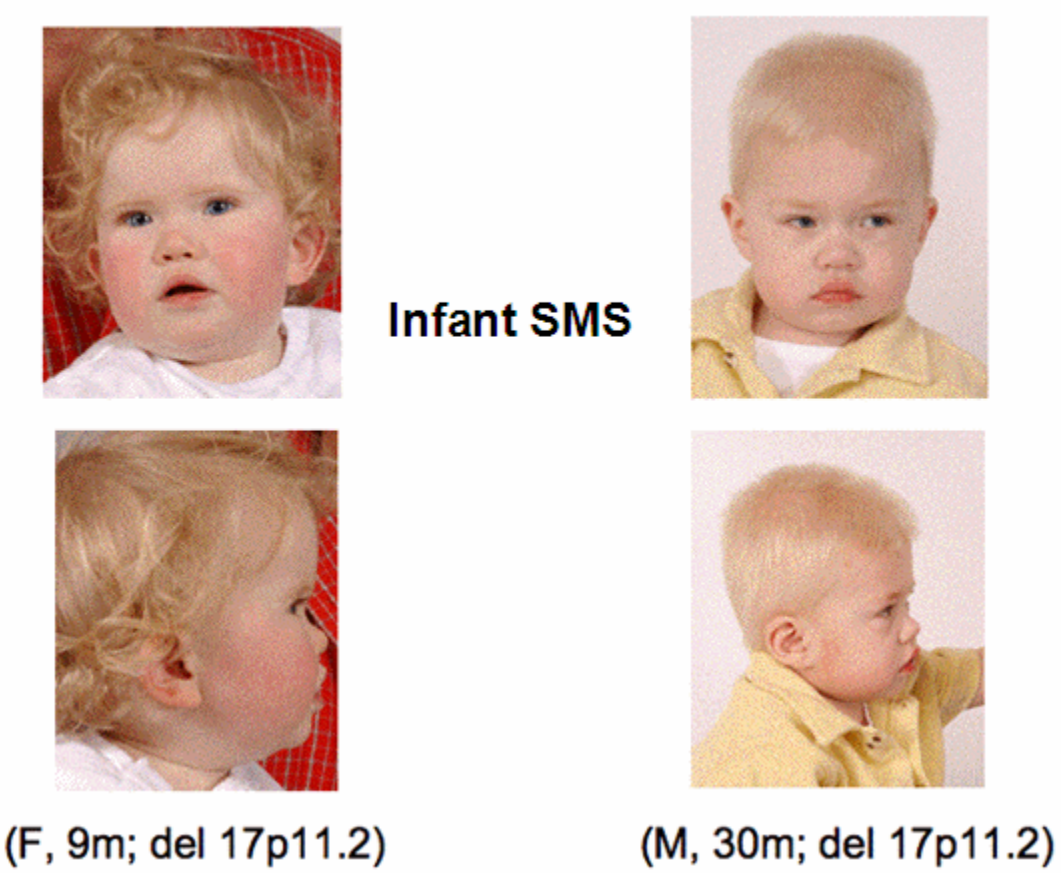

Figure 1. Infants with SMS. Female age nine months (left) and male age 30 months (right). Note brachycephaly, broad forehead, upslanting palpebral fissures, short upturned nose, and characteristic downturned "tent"-shaped vermilion of the upper lip with mild micrognathia. Fair (hypopigmented) complexion with rosy "pudgy" cheeks is also appreciated.

- **An intellectual disability multigene panel** that includes *RAI1* and other genes of interest (see Differential Diagnosis) may also be considered. 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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

When the phenotype is indistinguishable from many other inherited disorders characterized by developmental delay / intellectual disability, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

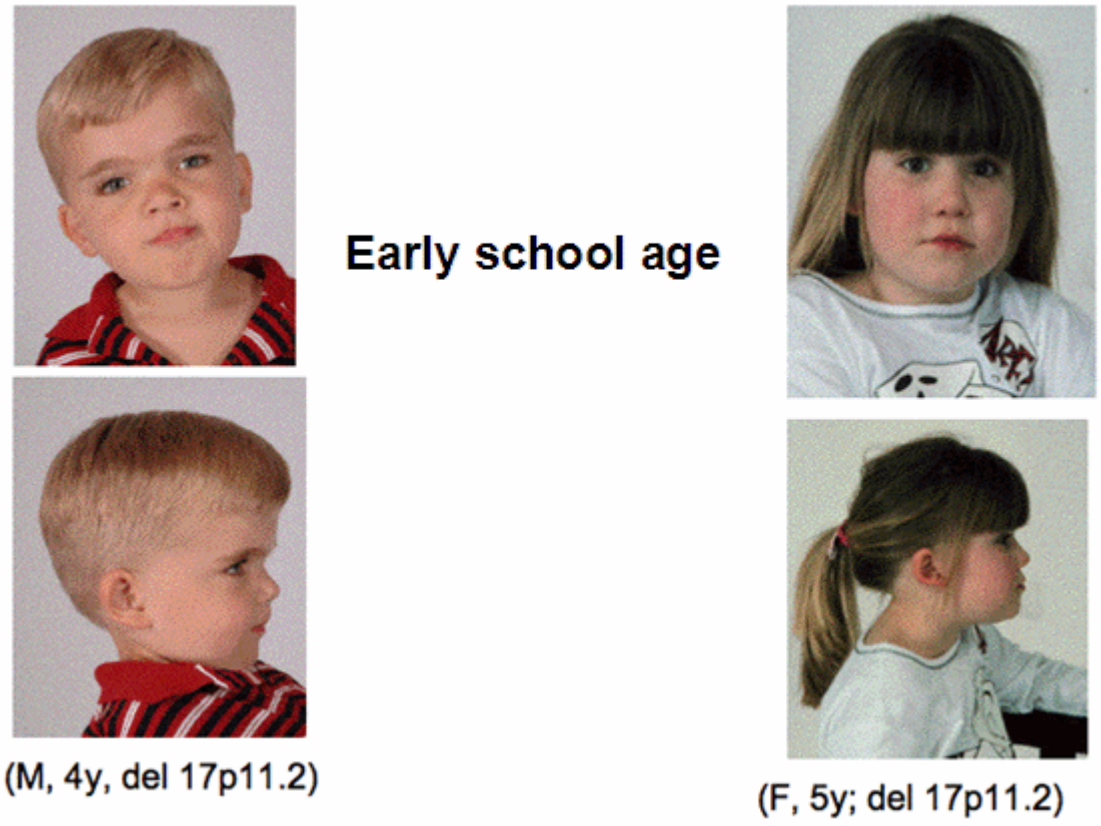

Figure 2. Early school-age SMS showing male age four years (left) and female age five years (right); the female is also pictured at age 15 years in Figure 3. Note broad forehead, deep-set eyes, midface retrusion.

Figure 3. Adolescent females with SMS caused by mutation of *RAI1* (left) and deletion 17p11.2 (right). Note short philtrum with relative prognathism resulting from midface retrusion that persists with age; downturned upper lip is more notable at rest (non-smiling).

Table 1. Molecular Genetic Testing Used in Smith-Magenis Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
RAI1	CMA (recommended first) [3]	~90%-95%
	Sequence analysis [4]	5%-10% [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown

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. A chromosomal microarray (CMA) that includes probe coverage of *RAI1* can detect deletions of 17p11.2 (interstitial deletion, complex rearrangements, or derivative chromosomes).
4. 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.
5. Sequence analysis (particularly of exon 3, in which all pathogenic variants have been found to date) detects *RAI1* pathogenic variants in individuals with SMS when cytogenetic and FISH studies are negative for the 17p11.2 deletion [Vilboux et al 2011, Vieira et al 2012, Dubourg et al 2014, Falco et al 2017].
6. 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. Breakpoints of large deletions and/or deletion of adjacent genes may not be determined.

Clinical Characteristics

Clinical Description

Smith-Magenis syndrome (SMS) has a clinically recognizable phenotype that includes physical, developmental, and behavioral features (Table 2). The phenotypic features can be subtle in infancy and early childhood, frequently delaying diagnosis until school age, when the characteristic facial appearance and behavioral phenotype may be more readily apparent.

Table 2. Clinical Features of Smith-Magenis Syndrome

Frequency	System	Finding
>75% of individuals	Craniofacial/ Skeletal/ Growth	• Brachycephaly • Midface retrusion • Relative prognathism w/age • Broad, square-shaped face • Everted, "tented" vermilion of the upper lip • Deep-set, close-spaced eyes • Short broad hands • Dental anomalies (missing premolars; taurodontism) • >90%ile for weight, w/abdominal fat deposition (esp after age 10 yrs)
	Neurobehavioral	• Infantile hypotonia • Generalized complacency/lethargy (infancy) • Oral sensorimotor dysfunction (early childhood) • Sensory processing issues • Developmental delay / cognitive impairment • Speech/language impairment • Sleep disturbance • Inverted circadian rhythm of melatonin • Attention-seeking behaviors • Inattention ± hyperactivity • Tantrums, behavioral dysregulation • Impulsivity • Stereotypic behaviors • Self-injurious behaviors • Hyporeflexia • Signs of peripheral neuropathy
	Otolaryngologic	• Middle-ear & laryngeal anomalies • Hearing loss (79%) • Hyperacusis (74%) • Hoarse, deep voice
Common (50%-75% of individuals)		• Short stature • Scoliosis • Mild ventriculomegaly of brain • Hyperacusis • Tracheobronchial problems • Velopharyngeal insufficiency • Ocular abnormalities (strabismus, myopia, iris anomalies, &/or microcornea) • REM sleep abnormalities • Hypercholesterolemia/hypertriglyceridemia • Chronic constipation • Abnormal EEG w/out overt seizures • Features of autism spectrum disorder

Table 2. continued from previous page.

Frequency	System	Finding
Less common (25%-50% of individuals)		• Cardiac defects • Thyroid function abnormalities • Seizures (11%-30%) • Immune function abnormalities (esp low IgA)
Occasional (<25% of individuals)		• Renal / urinary tract abnormalities • EEG abnormalities in absence of clinical seizures [1] • Forearm abnormalities • Cleft lip/palate • Retinal detachment

Greenberg et al [1996], Chen et al [1997], Allanson et al [1999], Smith et al [2002], Potocki et al [2003], Gropman et al [2006], Smith et al [2006], Edelman et al [2007], Burns et al [2010], Smith & Gropman [2021]

1. Frequency varies by study.

Facial appearance. The facial appearance is characterized by a broad square-shaped face, brachycephaly, prominent forehead, synophrys, mildly upslanted palpebral fissures, deep-set eyes, broad nasal bridge, midfacial retrusion (formerly known as midfacial hypoplasia), short, full-tipped nose with reduced nasal height, micrognathia in infancy (see Figure 1) changing to relative prognathia with age, and a distinct appearance of the mouth, with fleshy everted vermilion of the upper lip.

The facial appearance of SMS becomes more recognizable in early childhood (see Figure 2, Figure 3), with persisting midfacial retrusion, relative prognathism, and heavy brows with coarsening facial appearance.

Neurologic

- Hypotonia is reported in virtually all infants, accompanied by hyporeflexia (84%) and generalized complacency and lethargy.
- Clinical signs of peripheral neuropathy are seen in approximately 75%, regardless of deletion size [Gropman et al 2006].
- In infancy / early childhood, these include infantile hypotonia, hyporeflexia, relative insensitivity to pain, and mild intention tremor (6-8 Hz) of upper extremity [Gropman et al 2006].
- In later childhood, affected children often exhibit a characteristic appearance of the legs and feet observed in peripheral nerve syndromes or neuropathies (i.e, "inverted champagne bottle appearance") with *pes cavus* or *pes planus* deformity, and unusual broad-based gait (foot flap).
- Toe-walking (60%) may persist despite the absence of tight heel cords [Smith & Gropman 2021].
- By childhood approximately 20% of affected individuals have a head circumference below the third centile [Rive Le Gouard et al 2021, Smith & Gropman 2021].
- Pubertal onset of catamenial seizures has also been observed in some females coinciding with menses [Smith & Gropman 2021].
- Stroke-like episodes have been reported in three individuals with SMS, including:
  - A male born with bilateral cleft lip/palate and congenital heart defect who developed a left hemiparesis at age 4.5 years [Smith & Gropman 2021];
  - A female age ten years with ventricular septal defect, who was diagnosed with Moyamoya disease and had evidence of ischemic changes at age five years [Girirajan et al 2007];

- A female age 32 years with evidence of severe atherosclerotic disease of the intracranial vessels documented after she suffered an ischemic infarct postoperatively following repeat cardiac surgery [Chaudhry et al 2007].

Therefore, pre-surgical evaluation for possible premature cerebrovascular disease is recommended for individuals with SMS who require open-heart surgery in adolescence or adulthood [Chaudhry et al 2007].

Neurodevelopmental features. Developmental delays are evident in early childhood, with the majority of individuals with SMS functioning in the mild-to-moderate range of intellectual disability. Due to the maladaptive behaviors and sleep deficits, true intellectual ability may not be accurately assessed in many individuals and test scores may not be representative of an individual's current level of functioning. When reported, measured developmental or intelligence quotients range from 20 to 78 with a mean score of approximately 50. Individuals with heterozygous deletion of 17p11.2 are more cognitively impaired than those with intragenic *RAI1* pathogenic variants [Edelman et al 2007].

- **Gross and fine motor skills** are delayed in the first year of life and may be exacerbated by generalized hypotonia. Issues related to sensory integration are frequently noted [Hildenbrand & Smith 2012].
- **Speech/language**
  - In infancy, crying is infrequent and often hoarse.
  - The vast majority of infants show markedly decreased babbling and vocalization for age.
  - By age two to three years, significant expressive language deficits relative to receptive language skills are recognized [Wolters et al 2009].
  - With appropriate intervention and a total communication program that includes sign/gesture language and other augmentative communication approaches, verbal speech generally develops by school age; however, articulation problems usually persist. Speech intensity may be mildly elevated with a rapid rate and moderate explosiveness, accompanied by hypernasality and hoarse vocal quality.
- **Cognitive abilities**
  - Affected individuals typically have relative weaknesses observed in sequential processing and short-term memory.
  - Relative strengths are in long-term memory and perceptual closure (i.e., a process whereby an incomplete visual stimulus is perceived to be complete: "parts of a whole").

Behavioral phenotype. The behavioral phenotype, which includes sleep disturbance (see **Sleep disturbance**), maladaptive and self-injurious behaviors (SIB), and stereotypies, is generally not recognized until age 18 months or older and escalates with age, often coinciding with expected life-cycle stages: 18-24 months, school age, and onset of puberty [Gropman et al 2006].

- Maladaptive behaviors in people with SMS reflect a complex interplay between physiology and environment that may be further compounded by an underlying developmental asynchrony: specifically, emotional maturity delayed beyond intellectual functioning [Finucane & Haas-Givler 2009].
  - With age, the gap between intellectual attainment and emotional development appears to widen for many people with SMS, and this disparity poses significant behavioral and programmatic challenges in older children and adults.
  - One study found that 90% of individuals with SMS (between ages 4 and 18 years) demonstrated significant social impairment (35% mild/moderate; 55% severe range per the Social Responsiveness Scale) per parent report, with symptoms that overlap those of children with autistic disorder or other developmental disorders [Laje et al 2010b].
- The degree of sleep disturbance remains one of the strongest predictors of maladaptive behavior [Dykens & Smith 1998, Arron et al 2011, Sloneem et al 2011, Smith et al 2019].

Self-injurious behaviors (SIB) are present in the vast majority of individuals after age two years [Arron et al 2011, Sloneem et al 2011].

- A direct correlation exists between the number of different types, intensity, and frequency of SIB and the level of intellectual impairment.
- Three behaviors distinctive to SMS, nail yanking (onychotillomania), skin picking, and insertion of foreign objects into body orifices (polyembolokoilamania), range from 25% to 90% of affected individuals depending on the age and group studied (see Genotype-Phenotype Correlations).
  - Nail yanking generally does not become a major problem until later childhood.
  - Object insertion in ear(s) is most prevalent in both children and adults; other body orifices (nose, vagina, and rectum) are generally not reported until late teens/adulthood [Gropman et al 2007].
- The overall prevalence of SIB increases with age, as does the number of different types of SIB exhibited [Finucane et al 2001], which may include:
  - Self-hitting (71%)
  - Self-biting (77%)
  - Skin picking (65%)

Note: Given the high rates of SIB, including self-insertion of objects or digits into body orifices, caution must be taken when evaluating individuals with SMS for maltreatment or abuse. Although individuals with intellectual impairment are at high risk for maltreatment, abuse may also be incorrectly suspected due to SIB or self-insertion behaviors.

Sensory integration issues are present and persist throughout childhood. A prominent pattern of sensory processing difficulties is recognized, characterized by an imbalance in neurologic thresholds and a fluctuation between active and passive self-regulation [Hildenbrand & Smith 2012].

Other maladaptive behaviors may include:

- Head banging, which may begin as early as age 18 months
- Frequent outbursts / temper tantrums
- Attention-seeking behaviors (especially from adults)
- Impulsivity, which may increase over time, particularly in females [Martin et al 2006]
- Inattention with or without hyperactivity
- Oppositional behaviors
- Aggression
- Rapid mood shifts
- Anxiety, which can become a major issue in adolescence and adulthood
- Toileting difficulties

Sterotypies common to SMS include:

- The spasmodic upper-body squeeze or "self-hug" behavior, which may provide an effective clinical diagnostic marker for the syndrome.
- Mouthing of hands or objects that persists from early childhood to ages where this is not socially acceptable.
- Teeth grinding
- Body rocking
- Spinning or twirling objects
- Finger lick and repetitive page turning ("lick and flip") behavior [Vieira et al 2012]

Sleep disturbance. The abnormal diurnal (inverted) circadian rhythm of melatonin appears pathognomonic in SMS, documented in an estimated 95% of affected individuals [Boone et al 2011, Spruyt et al 2016]. Further data

[Boudreau et al 2009] suggest that the sleep disturbance cannot be caused solely by aberrant melatonin synthesis and/or degradation as previously suggested [Potocki et al 2000b, De Leersnyder et al 2001, Chik et al 2010, Nováková et al 2012]. While not inverted, the 24-hour circadian rhythm of body temperature is phase advanced by about three hours relative to controls [Smith et al 2019].

The sleep disturbance is characterized by fragmented and shortened sleep cycles with frequent nocturnal and early morning awakenings and excessive daytime sleepiness [Greenberg et al 1996, Smith et al 1998, Potocki et al 2000b, De Leersnyder et al 2001, Smith & Duncan 2005].

- Parents usually do not recognize significant sleep problems before age 12-18 months, although fragmented sleep with reduced total sleep time has been documented as early as age six months [Duncan et al 2003, Gropman et al 2006].
- Disrupted sleep becomes a major problem in early childhood and is a major issue for caregivers, who themselves may become sleep deprived [Foster et al 2010].
- Diminished REM sleep was documented in more than half of those undergoing polysomnography [Greenberg et al 1996, Potocki et al 2000b].
- Actigraphy-based sleep estimates document developmental differences in nocturnal arousal patterns by age and time of night [Gropman et al 2007, Smith et al 2019].
    - Affected individuals have a reduction in 24-hour and night sleep compared to healthy pediatric controls, with estimated sleep about one hour less than expected across all ages.
    - This is evidenced by decreased total night sleep, lower sleep efficiency, earlier sleep onset and final sleep offset, increased waking after sleep onset (WASO), and increased duration of daytime naps (beyond typical age) [Smith et al 2019].
    - Developmental sleep changes from childhood through adolescence/adulthood are evidenced by an age-related variation in the timing of wake onset (but not sleep onset) and WASO [Smith et al 2019].
    - Age differences are also associated with different patterns of sleep for SMS compared to healthy controls [Smith et al 2019]:
        - In those younger than age ten years, late-night activity was greater in individuals with SMS than in pediatric controls.
        - Older individuals with SMS (>10 years) exhibited less late-night activity but increased early-night activity, consistent with poor "settling" and delayed sleep pattern.
- Due to the propensity of weight gain as affected individuals age, obstructive sleep apnea may also develop and can contribute to the overall sleep disturbance.

Growth and feeding

- At birth, weight, length, and head circumference are generally in the normal range.
- Feeding difficulties in infancy leading to failure to thrive are common, including marked oral motor dysfunction with poor suck and swallow and textural aversion.
- In early infancy, length and weight gradually decelerate; short stature (height <5th centile) is frequently observed (67%) especially at young ages but may not persist into adulthood.
- Dietary preferences, hyperphagia, and food foraging at night (especially at older ages), coupled with a general sedentary lifestyle and psychotropic medication side effects (affecting appetite / weight gain), contribute to obesity (increased BMI), typically beginning in school-aged children (ages 6-9 years).
    - Obesity may lead to increased risk for related health issues (e.g., type 2 diabetes) in adulthood.
    - Hypercholesterolemia that is not associated with diet or BMI values is recognized in more than 50% of individuals with SMS [Smith et al 2002].

Gastrointestinal. Gastroesophageal reflux and constipation are frequently reported.

Oral and dental anomalies

- Oral sensorimotor dysfunction is a major issue, including:
  - Lingual weakness, asymmetry, and/or limited mobility
  - Weak bilabial seal (64%)
  - Palatal abnormalities (64%), although cleft lip and/or palate occur in fewer than 25% of affected individuals
  - Open-mouth posture with tongue protrusion and frequent drooling
- A high prevalence (~90%) of dental anomalies, specifically tooth agenesis (especially premolars) and taurodontism, has been reported. This is accompanied by an age-related increase in dental caries and poor gingival health due to decreased oral hygiene, supporting the need for increased dental care in adolescent years [Tomona et al 2006].

Musculoskeletal

- Mild-to-moderate scoliosis, most commonly of the mid-thoracic region, is seen in approximately 60% of affected individuals age four years and older, although vertebral anomalies are seen in only a few.
- Hands and feet remain small.
- Markedly flat or highly arched feet and unusual gait are generally observed.

Ocular abnormalities are present in approximately 85% of affected individuals and include strabismus, progressive myopia, iris anomalies, and/or microcornea. About 20% of affected individuals older than age ten years experience retinal detachment, which may be due to a combination of aggressive/self-injurious behaviors and high myopia.

Ears and hearing

- Otitis media occurs frequently (≥3 episodes/year) and often leads to tympanostomy tube placement (85%).
- Hearing loss is documented in more than 79% [Brendal et al 2017], with conductive loss most common before age ten years.
- A pattern of fluctuating and progressive hearing decline occurs with age, including sensorineural loss (48%) after age 11 years [Brendal et al 2017].
- Hyperacusis, or oversensitivity to certain frequencies/sounds tolerable to listeners with normal hearing, is reported in approximately 74% [Brendal et al 2017].

Laryngeal anomalies, including polyps, nodules, edema, or partial vocal cord paralysis, are common.

- Velopharyngeal insufficiency and/or structural vocal-fold abnormalities without reported vocal hyperfunction are seen in the vast majority of individuals with SMS.
- Functional impairments in voice (hoarseness) may contribute to the marked delays in expressive speech.

Cardiovascular defects are identified in fewer than 50% of affected individuals with SMS who have a deletion of 17p11.2 but have not been reported in those who have a heterozygous pathogenic variant in *RAI1*. Cardiac anomalies may include mild tricuspid or mitral valve stenosis or regurgitation, ventricular septal defects, supravalvular aortic or pulmonic stenosis, atrial septal defects, and tetralogy of Fallot [Smith & Gropman 2021].

Genitourinary anomalies are found in between 15% and 35% of affected individuals who have a deletion of 17p11.2 but have not been reported in those who have a heterozygous pathogenic variant in *RAI1*. Anomalies may include the following [Smith et al 1986, Greenberg et al 1996, Chou et al 2002, Myers et al 2007]:

- Duplicated collecting system
- Unilateral renal agenesis and ectopic kidney
- Ureterovesical obstruction

- Malposition of the ureterovesical junction

Additionally, a vast majority of affected individuals have nocturnal enuresis in childhood. Genital anomalies reported include cryptorchidism, shawl, or undeveloped scrotum in males, and infantile cervix and/or hypoplastic uterus in females [Smith & Gropman 2021].

Immunologic. More than 50% of affected individuals have low serum immunoglobulin profiles, which may increase susceptibility to sinopulmonary infections. Recurrent otitis media (88%), upper respiratory infections (61%), pneumonia (47%), and/or sinusitis (42%) requiring antibiotics are frequently reported [Perkins et al 2017].

Endocrine. The specific incidence of endocrine abnormalities in individuals with SMS remains undefined.

- About 25% of affected individuals have mild hypothyroidism.
- Puberty typically occurs within the normal time frame; however, precocious puberty (premature adrenarche), premature ovarian failure [Smith, personal communication], and delayed sexual maturation have been observed.
- While short stature occurs in SMS, only one published case of isolated growth hormone deficiency has been reported [Itoh et al 2004]. When growth hormone profiles are studied, peak levels appear in the proper phase of the day with levels only slightly below normal controls [De Leersnyder et al 2001, De Leersnyder et al 2006].
- Adrenal aplasia/hypoplasia was described in one affected male age 11 months who died unexpectedly after palatoplasty [Denny et al 1992].

Dermatology. In addition to skin problems due to self-injurious behaviors, a minority of affected individuals have rosy cheeks (which may be related to drooling and/or eczema) and/or hyperkeratosis (~20%) over the hands, feet, or knees.

- Complaints of dry skin remain common especially among those with an *RAI1* pathogenic variant (100%) compared to those with a 17p11.2 deletion (44%) [Edelman et al 2007].
- Hair and skin color often appears fairer compared to other family members.

Malignancy and other features of Birt-Hogg-Dubé (BHD) syndrome. The risk of cancer appears to be no greater than in the general population for most individuals with SMS. However, SMS due to a heterozygous 17p11.2 deletion often results in haploinsufficiency of *FLCN* that is associated with BHD syndrome, an adult-onset hereditary cancer syndrome characterized by cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal tumors. Features of BHD syndrome have been described in several individuals with SMS.

- Typically, BHD-related spontaneous pneumothorax occurs in adults younger than age 40 years [Schmidt & Linehan 2015]. However, among the four reported individuals with SMS caused by a 17p11.2 deletion and spontaneous pneumothorax, the pneumothoraces occurred at younger ages than expected (range 2-22 years) [Finucane et al 2021].
- To date, renal tumors have been reported in three adults with heterozygous deletion of 17p11.2:
  - A male with bilateral renal tumors on imaging (histopathology not available) and no skin or lung findings at age 57 years [Dardour et al 2016];
  - A female with bilateral pathologically confirmed hybrid oncocytic tumors without evidence of skin lesions or lung findings at age 50 years [Smith et al 2014]; and
  - A male who died of unrelated causes at age 45 years, found on autopsy to have oncocytic neoplasm with features of chromophobe renal cell carcinoma, tumor tissue harbored a second *FLCN* pathogenic variant [Smith et al 2014].

- A recent online survey of parents of individuals with SMS (due to either heterozygous deletion of 17p11.2 or *RAI1* pathogenic variant) assessed the prevalence of three features of BHD (spontaneous pneumothorax, pathognomonic skin findings, and renal cancer). Among 117 respondents, five individuals reported spontaneous pneumothorax (4 of the 5 had a deletion of 17p11.2) and two individuals with deletion of 17p11.2 had fibrofolliculoma. No instances of renal cancer were reported [Finucane et al 2021].

Other

- A male with SMS and a confirmed *RAI1* nonsense variant had three spontaneous pneumothoraces between ages five and ten years [Truong et al 2010].
- A female with SMS and a confirmed *RAI1* pathogenic variant had a spontaneous pneumothorax at age nine years [Truong et al 2010, Finucane et al 2021].

Prognosis. Insufficient longitudinal data are available to accurately determine life expectancy. One would expect that, in the absence of major organ involvement, the life expectancy of individuals with SMS would not differ from that of individuals with cognitive impairment at large. Anecdotally, the oldest known individual with SMS lived to age 88 years [Smith & Magenis, personal communication]. In the month prior to her death, she was reportedly her usual alert, happy, "SMS" self with ongoing sleep issues and was being treated for chronic recurrent sinusitis. Four days prior to death, she suffered an apparent right-sided stroke with left-sided weakness. No autopsy was performed.

Genotype-Phenotype Correlations

Deletion of 17p11.2. Parental origin of the 17p deletion has not been documented to affect the phenotype, suggesting that imprinting does not play a role in the expression of the typical SMS phenotype.

Note: See Genetically Related Disorders for information about individuals who have larger deletions of 17p that extend distally to include *PMP22*.

Pathogenic variant in *RAI1*

- Higher rates of onychotillomania and polyembolokoilamania (90%) have been reported in those with a heterozygous pathogenic variant in *RAI1* compared to those with a 17p11.2 deletion (40%) [Edelman et al 2007].
- The risk of obesity and obesity-related health issues is higher in individuals with a heterozygous pathogenic variant in *RAI1* compared to those with a 17p11.2 deletion [Alaimo et al 2014].
- Individuals with a heterozygous pathogenic variant in *RAI1* typically do not have short stature or other organ system involvement [Slager et al 2003, Bi et al 2004, Girirajan et al 2005].

Prevalence

The birth incidence is estimated at 1:25,000 births [Greenberg et al 1991]; the actual prevalence may be closer to 1:15,000 [Smith et al 2005]. The vast majority of individuals have been identified in the last five to ten years as a result of improved whole-genome analysis techniques.

Genetically Related (Allelic) Disorders

Persons with larger deletions extending distally to include *PMP22* are also at risk for hereditary neuropathy with liability to pressure palsies.

Persons with duplication 17p11.2 syndrome (Potocki-Lupski syndrome) harbor the recombination reciprocal of the SMS deletion and differ phenotypically and behaviorally from those with SMS [Potocki et al 2000a, Potocki et al 2007].

Differential Diagnosis

Smith-Magenis syndrome (SMS) should be distinguished from other syndromes that include developmental delay, infantile hypotonia, short stature, distinctive facies, and a behavioral phenotype. The pervasive behavioral aspects and circadian sleep disorder associated with inverted melatonin secretion can help distinguish SMS from other neurodevelopmental disorders. However, because the phenotype of SMS is broad and changes with time, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Management guidelines for SMS have been published by PRISMS. See Medical Management Guidelines and Management Checklist (pdfs).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Smith-Magenis syndrome (SMS), the recommended evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	• EEG in those w/clinical seizures • Neuroimaging (MRI or CT scan) in accordance w/ findings such as seizures &/or motor asymmetry	For those w/o overt seizures, EEG may be helpful to evaluate for possible subclinical events in which treatment may improve attention &/or behavior; a change in behavior or attention warrants reevaluation.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/ language eval • Eval for early intervention / special education
Behavior	Neuropsychological eval	In persons age >12 mos: screen for behavior problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Sleep/ Respiratory	• Sleep history w/particular attention to sleep/wake schedules & signs/symptoms of obstructive sleep apnea • Polysomnogram (overnight sleep study) to evaluate for obstructive sleep apnea in those w/evidence of sleep-disordered breathing	Sleep diaries may prove helpful in documenting sleep/wake schedules.
Growth/ Feeding	Assessment of growth parameters for failure to thrive in infancy & obesity in older individuals	Consider referral to gastroenterologist for those w/ failure to thrive; consider nutrition &/or full feeding eval.
	Consider assessment of oral motor dysfunction & suck/ swallowing issues in infancy.	
	Fasting lipid profile in adolescents & adults	Eval for hypercholesterolemia

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal	Assessment for: • Signs/symptoms of GERD • Constipation • Caloric intake	
Mouth	Assessment for palatal defects & dental anomalies (if teeth have erupted)	Consider referral to pediatric dentist.
Musculoskeletal	Spine radiographs to assess for vertebral anomalies & scoliosis	
Eyes	Ophthalmologic eval	Attention to evidence of strabismus, microcornea, iris anomalies, & refractive error
ENT	• Audiologic assessment for conductive &/or SNHL • Consider eval for velopharyngeal insufficiency in those w/functional impairments	
Cardiovascular	Echocardiogram to assess for a congenital heart defect	
Genitourinary	Ultrasound exam for renal/urologic anomalies	Further urologic evals may be needed if history of frequent urinary tract infections.
Immunologic	Qualitative immunoglobulins [1] incl vaccine titers (incl pneumococcus)	Consider eval by immunologist, as prophylactic strategies to prevent infections may benefit some.
Endocrine	Thyroid function studies to incl TSH & either T4 or free T4 [2]	
Dermatologic	Skin assessment	For evidence of self-injurious behaviors, eczema, & hyperkeratosis
	In those w/17p11.2 deletion incl *FLCN*: • Detailed dermatologic exam • Biopsy of suspicious lesion(s)	To assess for dermatologic features of BHD, incl melanoma
Pulmonary	In those w/17p11.2 deletion incl *FLCN* & signs/symptoms of pneumothorax: • Chest x-ray • Chest CT	
Renal	In those w/17p11.2 deletion incl *FLCN*: abdominal MRI to assess for renal tumors	Beginning at age 21 yrs (See BHD, Management.)
Miscellaneous	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports/resources	Assess need for: • Community or online resources incl Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BHD = Birt-Hogg-Dubé syndrome; GERD = gastroesophageal reflux disease; SNHL = sensorineural hearing loss; TSH = thyroid-stimulating hormone

1. To include quantitative serum immunoglobulins (IgG, IgA, IgM)

2. Screening for adrenal function should be considered in individuals with larger deletions extending into 17p12.

Treatment of Manifestations

The following are appropriate.

Table 4. Treatment of Manifestations in Individuals with Smith-Magenis Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standard treatment w/ASM by an experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for SMS. • Education of parents/caregivers [1]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Speech/ Language delay	• Identify & treat swallowing/feeding problems & optimize oral sensorimotor development. • Develop skills related to swallowing & speech production by ↑ sensory input, fostering movement of articulators, ↑ oral motor endurance, & ↓ hypersensitivity.	
Behavior issues [2]	• Develop comprehensive behavior support plan for home & school at onset of maladaptive behaviors (typically starting in early elementary school). • Develop structured school program w/one-on-one support & curricula matched to known cognitive & behavior profile of SMS. • Behavioral therapies incl special education techniques emphasizing individualized instruction, structure, & routine to minimize behavioral outbursts in school	Insight about vulnerabilities & relative strengths in sensory processing patterns may aid caregivers in adapting activity demands, modifying environments, & facilitating appropriate & supportive social interactions. [3]
Psychiatric disorder	Psychotropic medication & psychological services to ↓ maladaptive behaviors, ↑ attention &/or ↓ hyperactivity, ↓ anxiety, & stabilize mood.	• Atypical patterns of sensory processing & more problematic/atypical behaviors may become more prominent w/↑ age. • No single medication regimen is consistently effective. [4]
Sleep disorder [5]	Melatonin	Early anecdotal reports of therapeutic benefit from melatonin (low dose; <3 mg) taken at bedtime suggest variable improvement of sleep w/o major adverse reactions. [6]
	Tasimelteon	Melatonin receptor agonist: first FDA-approved treatment of nighttime sleep disturbance in SMS. [7]
	Oral beta-1-adrenergic antagonists	A single uncontrolled study reported suppression of daytime melatonin peaks & subjectively improved behavior. [8]
	Acebutolol w/melatonin	An uncontrolled trial combined daytime dose of acebutolol w/evening oral dose of melatonin (6 mg at 8 pm) & found that nocturnal plasma concentration of melatonin was restored & nighttime sleep improved w/disappearance of nocturnal awakenings.[9]
	Enclosed bed system for containment during sleep	
Obesity	Standard treatment [10]	Focus on staying active & fit starting at young age

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Gastroesophageal reflux disease	Standard treatment	
Constipation	Standard treatment	
Hypercholesterolemia	Dietary modifications &/or medication in accordance w/standard practice	
Palatal anomalies	Standard treatment	Consideration of referral to multidisciplinary craniofacial clinic
Scoliosis	Standard treatment per orthopedist	
Ophthalmologic abnormalities	Standard treatment per ophthalmologist &/or optometrist	
Recurrent otitis media	Standard treatment	May incl insertion of tympanostomy tubes
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Cardiac anomalies	Standard treatment	
Renal anomalies	Standard treatment	
Mild immunodeficiency	Standard treatment	May incl prophylactic antibiotics
Hypothyroidism	Thyroid replacement therapy	
Growth hormone deficiency	Growth hormone treatment	Growth hormone treatment has been reported; [11] controlled studies have not evaluated its efficacy.
Clinical manifestations of **BHD in those w/*FLCN* deletion**	See BHD, Treatment of Manifestations.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Impact on parents & sibs	Respite care, annual family psychosocial screenings, & family psychosocial support	• Combination of ID, severe behavioral abnormalities, & sleep disturbance takes a significant toll on parents & sibs. • Incl family support services & resources as essential components of a holistic management plan.

ASM = anti-seizure medication; BHD = Birt-Hogg-Dubé syndrome; ID = intellectual disability; SMS = Smith-Magenis syndrome
1. 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.
2. The potential for more problematic or atypical behaviors with increased age underscores the need for early and ongoing intervention and caregiver education [Hildenbrand & Smith 2012].
3. Parents report high rates of depression and anxiety, and family stress is significantly higher in families of people with SMS than in those of children w/nonspecific developmental disabilities [Hodapp et al 1998, Foster et al 2010].
4. Based on an extensive review of psychotropic medication use in a large cohort of individuals with SMS (n=62), use of polypharmacy and/or serial trials with minimal effectiveness was observed. Benzodiazepines obtained the lowest mean efficacy score in the "slightly worse" range, suggesting that use of these drugs may be detrimental to individuals with SMS [Laje et al 2010a].
5. Sleep management is a challenge for physicians and parents. Prior to beginning any trial, a child's medical status and baseline sleep pattern must be considered.
6. Dosages should be kept low (≤3 mg). However, melatonin dispensed over the counter is not regulated by the FDA; thus, dosages may not be exact. No early and controlled melatonin treatment trials have been conducted. A monitored trial of four to six weeks on melatonin may be worth considering in affected individuals with sleep disturbance.
7. Polymeropoulos et al [2021]
8. Nine individuals with SMS were treated with oral beta-1-adrenergic antagonists (acebutolol 10 mg/kg) [De Leersnyder et al 2001]. This treatment, however, did not restore nocturnal plasma concentration of melatonin.
9. Parents also reported subjective improvement in daytime behaviors with increased concentration. Contraindications to the use of beta-1-adrenergic antagonists include asthma, pulmonary problems, some cardiovascular disease, and diabetes mellitus.
10. Dietary changes with portion management in addition to increased movement and physical activity, limiting sedentary activity, and discouraging nighttime eating
11. Itoh et al [2004], Spadoni et al [2004]

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. Evaluation and referral for services including occupational therapy, physical therapy, speech/language therapy, feeding therapy, special education services, and infant mental health services. In the US, early intervention is a federally funded program available in all states and 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 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 if 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.
- Accommodation for a scheduled nap during the school day (ideally in late morning or after lunch but not after 3 pm) should be included in the IEP.
- Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech/language 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 teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, most school districts in the US are 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., scoliosis).
- Consider use of durable medical equipment and positioning devices as needed (e.g., walkers, orthotics).

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

Oral motor dysfunction should be reassessed 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 based on the principles of applied behavior analysis (ABA). The goals of ABA therapy include teaching and maintaining new skills, generalizing these skills to different environments, reducing maladaptive behaviors, and fostering social interaction. Behavior Support Plans and therapeutic interventions should be developed by a team, often under the supervision of a board-certified behavior analyst (BCBA) or psychologist. The strategies and interventions should be developed by professionals who are familiar with physical, medical, behavioral, and learning characteristics associated with SMS.

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 5. Recommended Surveillance for Individuals with Smith-Magenis Syndrome

System/Concern	Evaluation	Frequency
Neurologic	Monitoring of those w/seizures as clinically indicated [1]	At each visit
Development	Multidisciplinary team eval (incl physical, occupational, & speech therapy evals & psychological assessment) to assist in development of an IEP [2, 3]	Annually
Psychiatric/ Behavioral	Behavior assessment for attention, aggressive or self-injurious behavior	At each visit
Growth/Feeding	Measurement of growth parameters	
	Eval of nutritional status & safety of oral intake	
Gastrointestinal	Fasting lipid profile	Annually in adolescents & adults
ENT/Mouth	Otolaryngologic follow up for assessment & mgmt of otitis media & other sinus abnormalities	Annually
	Audiologic eval to monitor for conductive or SNHL annually or as clinically indicated	
Musculoskeletal	Monitoring for scoliosis	
Eyes	Ophthalmologic eval	
Genitourinary	Routine urinalysis to evaluate for occult urinary tract infections Gynecologic eval per gynecologist	
Endocrine	Thyroid function, incl free T4 & TSH	
Family	Screening of family functioning, mental health, & resource needs leading to provision of appropriate referrals to community agencies	
Immunologic	Repeat qualitative immunoglobulins incl vaccine titers (esp pneumococcus)	As clinically indicated

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Complications of BHD in persons w/*FLCN* deletion	See BHD, Surveillance.	

BHD = Birt-Hogg-Dubé syndrome; IEP = individualized educational program; SNHL = sensorineural hearing loss; TSH = thyroid-stimulating hormone

1. Assess for new manifestations such as seizures or changes in behavior.
2. Particularly in school-aged children
3. Periodic neurodevelopmental assessments and/or developmental/behavioral pediatric consultation can be an important adjunct to the team evaluation.

Agents/Circumstances to Avoid

Use of psychotropic medications in SMS often begins in childhood with use of sleep aids and trials of different psychotropic medications to control behavior, with mixed response; no single regimen has shown consistent efficacy and adverse reactions to some medications have been reported [Laje et al 2010a]. Polypharmacy is also an issue. Weight gain is a concern with many antipsychotics. Lacking well-controlled trials, when starting a new medication, care should be taken to track sleep and behavior changes over several days/weeks to monitor for potential side effects (e.g., increased appetite, weight gain) and adverse reactions and/or to determine potential efficacy.

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.

Other

Pharmacologic intervention should be considered on an individual basis with recognition that some medications may exacerbate sleep or behavioral problems and may cause weight gain.

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

Smith-Magenis syndrome (SMS) is inherited in an autosomal dominant manner and is typically caused by a *de novo* deletion of or pathogenic variant in *RAI1* on chromosome 17p11.2.

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with SMS whose parents have undergone genetic testing have the disorder as a result of a *de novo* 17p11.2 deletion or pathogenic variant in *RAI1*. Rare reports of maternal and paternal transmission of deletion are known, as well as reported parental mosaicism for either the deletion or *RAI1* variant [Campbell et al 2014]. There is no evidence to suggest an obvious parental age contribution for the deletion.
- Evaluation of the parents by genomic or molecular genetic testing that will detect the genetic alteration present in the proband is recommended. In addition, chromosome analysis of the parents should be performed for all newly diagnosed individuals found to have a 17p11.2 deletion; complex familial chromosome rearrangements leading to del(17)(p11.2) and SMS are rare but have been reported [Zori et al 1993, Yang et al 1997, Park et al 1998].
- If the pathogenic *RAI1* variant or 17p11.2 deletion was inherited from a parent, that parent should be assessed for neuropsychiatric and behavior concerns.
- If the deletion or pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the genetic alteration most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a deletion or pathogenic variant from a parent with germline mosaicism. One case reported by Zori et al [1993] identified maternal mosaicism for del(17)(p11.2). Other cases of parental mosaicism are known, including one family with two affected sibs with SMS due to maternal mosaicism for del17p11.2 [Smith et al 2006]; unpublished cases of parental mosaicism for an RAI1 variant are also recognized [Authors, personal observation].

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

- If neither parent is found to have the genetic alteration identified in the proband and parental chromosome analysis is normal, the recurrence risk to sibs is likely less than 1% (recurrence risk attributable to the possibility of germline mosaicism in a parent) [Zori et al 1993].
- If a parent has a balanced structural chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement and the possibility of other variables.
- If a parent of the proband is affected and/or has the genetic alteration identified in the proband, the risk to the sibs is 50%.

Offspring of a proband

- The offspring of an individual with SMS are at a 50% risk of having SMS.
- Individuals (females) with SMS are known to have given birth to a child with SMS [Acquaviva et al 2017; Authors, personal observation].
- Fertility issues in SMS remain unstudied.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an SMS-related genetic alteration or chromosome rearrangement, the parent's family members may be at risk.

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.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults from families in which a chromosome rearrangement has been identified.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies. SMS usually occurs as the result of a *de novo* deletion of 17p11.2; however, rare instances of vertical transmission from an affected parent to a child, parental germline mosaicism, and complex familial chromosome rearrangements leading to del(17)(p11.2) and SMS have been reported.

- If the SMS-related genetic alteration has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.
- In the rare instance of a complex familial chromosome rearrangement, prenatal testing is possible for a pregnancy at increased risk using prenatal chromosomal microarray analysis (CMA) and sequencing on fetal cells.

  Note: Although a visible interstitial deletion of chromosome 17p11.2 can be detected in all individuals with the common approximately 3.5-Mb deletion by a routine G-banded analysis provided the resolution is adequate (≥550 band), this approach is not recommended for prenatal testing because it is not uncommon for the deletion to be overlooked.

Low-risk pregnancies. Unsuspected prenatal detection of del(17)(p11.2) has been reported among women undergoing amniocentesis for other reasons. At least two cases have been detected prenatally following amniocentesis performed because of low maternal serum alpha-fetoprotein (MSAFP) on routine screening [Fan & Farrell 1994; Thomas et al 2000, personal observation]. A large prenatal series identified ten cases from a total of 455,121 consecutive prenatal cytogenetic studies [Qin & Huang 2007].

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.

- **Association of Smith-Magenis France (ASM17)**
  France
  Email: association@smithmagenis.com
  www.smithmagenis17.org
- **MedlinePlus**
  Smith-Magenis syndrome
- **Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS)**
  Phone: 972-231-0035
  www.prisms.org
- **SIRIUS (Germany's Support Network for Smith-Magenis Syndrome)**
  Germany
  Phone: 49 (0)151 201 215 69
  www.smith-magenis.de
- **Smith-Magenis Syndrome Australia**
  Member of PRISMS International Partnership Program
  Australia
  Email: info@smsaustralia.org
  www.smsaustralia.org

- **SMS Foundation UK**
  United Kingdom
  Phone: 0300 101 0034
  www.smith-magenis.co.uk
- **PRISMS Smith-Magenis Syndrome Patient Registry**
  www.prisms.org/research/sms-patient-registry

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. Smith-Magenis Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RAI1	17p11.2	Retinoic acid-induced protein 1	RAI1 @ LOVD	RAI1	RAI1

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 Smith-Magenis Syndrome (View All in OMIM)

182290	SMITH-MAGENIS SYNDROME; SMS
607642	RETINOIC ACID-INDUCED GENE 1; RAI1

Molecular Pathogenesis

Smith-Magenis syndrome is caused by either a microdeletion of 17p11.2 including *RAI1* or a pathogenic variant in *RAI1* (see Table 1). A common deletion interval spanning approximately 3.5 Mb is identified in approximately 70% of individuals [Potocki et al 2003, Vlangos et al 2003], with larger or smaller deletions occurring in approximately 20%.

Consistent with observations in individuals with SMS, studies of mice have shown that *RAI1* haploinsufficiency affects feeding, satiety, and fat deposition patterns [Burns et al 2010].

Gene structure. The *RAI1* transcript NM_030665.3 has six exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in *RAI1* have been identified in individuals with the SMS phenotype who do not have a detectable 17p11.2 deletion [Slager et al 2003, Bi et al 2004, Girirajan et al 2005, Truong et al 2010, Falco et al 2017] (see Table 1).

Normal gene product. The *RAI1* transcript NM_030665.3 encodes a protein of 1,906 amino acids (NP_109590.3). Normal human retinoic acid-induced protein 1 is thought to function in transcription regulation [Bi et al 2004, Burns et al 2010, Carmona-Mora et al 2010]; however, additional studies are required to more fully assess protein function in the cell. Studies of model organisms have confirmed and extended understanding of the functions of retinoic acid-induced protein 1. In murine models, Rai1 is a transcriptional regulator that preferentially binds to promoters and actively transcribes neuronal genes [Huang et al 2016]. Further, mice lacking Rai1 display exaggerated light-induced behaviors and disruption of circadian rhythm

[Diessler et al 2017]. Genetic studies in humans, and experiments in *Xenopus*, have also shown a role for Rai1 in craniofacial development [Claes et al 2014, Tahir et al 2014].

Mechanism of disease causation. Loss of function of retinoic acid-induced protein 1 is thought to result in the SMS phenotype. It is assumed that *RAI1* pathogenic sequence variants result in a nonfunctional protein product by an unknown mechanism.

Chapter Notes

Author Notes

The authors of the Smith-Magenis Syndrome *GeneReview* are members of the PRISMS Professional Advisory Board.

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Revision History

- 10 March 2022 (acms, sg) Revision: extensive updates to Clinical Description and Management
- 5 September 2019 (she) Revision: high-risk pregnancies
- 20 June 2019 (ma) Comprehensive update posted live
- 28 June 2012 (me) Comprehensive update posted live
- 7 January 2010 (me) Comprehensive update posted live
- 11 August 2006 (me) Comprehensive update posted live
- 26 August 2005 (cd) Revision: sequence analysis of *RAI1* clinically available
- 15 March 2004 (me) Comprehensive update posted live
- 15 January 2002 (as) Author revisions
- 22 October 2001 (me) Review posted live
- 23 May 2001 (as) Original submission

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