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Smith-Magenis Syndrome

Synonym: del(17)(p11.2)

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Initial Posting: October 22, 2001; Last Update: June 28, 2012.

Summary

Disease characteristics. Smith-Magenis syndrome (SMS) is characterized by distinctive physical features (particularly facial features that progress with age), developmental delay, cognitive impairment, and behavioral abnormalities. 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 integration issues are frequently noted. Children and adults typically have inattention, distractibility, hyperactivity, impulsivity, maladaptive behaviors including frequent outbursts/temper tantrums, attention seeking, disobedience, aggression, toileting difficulties, and self-injurious behaviors (SIB) including self-hitting, self-biting, and/or skin picking, inserting foreign objects into body orifices (polyembolokoilamania), and yanking fingernails and/or toenails (onychotillomania). Among the stereotypic behaviors described, the spasmodic upper-body squeeze or "self-hug" seems to be highly associated with SMS. The finger lick and page flipping ("lick and flip") behavior may be less prevalent than initially reported. An underlying developmental asynchrony, specifically between intellectual functioning and emotional maturity, may also contribute to maladaptive behaviors in people with SMS.

Diagnosis/testing. The diagnosis of SMS is based on clinical findings and confirmed by either detection of an interstitial deletion of 17p11.2 or by molecular genetic testing of *RAI1*. A visible interstitial deletion of chromosome 17p11.2 can be detected in all individuals with the common 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 not SMS. Molecular cytogenetic analysis by FISH using a DNA probe specific for the SMS critical region or aCGH is required in cases of submicroscopic deletions and/or to resolve equivocal cases. Mutation or deletion of *RAI1* accounts for the majority of features in SMS.

Management. *Treatment of manifestations:* Early childhood intervention programs; special education; vocational training/supports later in life; and speech/language, physical, occupational, behavioral, and sensory integration therapies. Affected individuals may also benefit from use of psychotropic medication to increase attention and/or decrease hyperactivity, and therapeutic management of sleep disorders. Respite care and psychosocial support for family members are recommended.

Surveillance: Annual multidisciplinary evaluations to assist in development of an individualized education program (IEP), evaluation of thyroid function, fasting lipid profile, routine urinalysis to evaluate for occult urinary tract infection, monitoring for scoliosis, ophthalmologic examination, periodic neurodevelopmental assessments and/or developmental/behavioral pediatric consultations, otolaryngologic follow-up for assessment and management of otitis media and other sinus abnormalities, and audiologic evaluation to monitor for conductive or sensorineural hearing loss annually or as clinically indicated.

Genetic counseling. Smith-Magenis syndrome (SMS) is caused by deletion or mutation of *RAI1* on chromosome 17p11.2. Virtually all occurrences are *de novo*. Complex familial chromosomal rearrangements leading to del(17)(p11.2) and SMS occur but are rare. If parental chromosome analysis is normal, the risk to sibs of the proband is likely to be less than 1%. The small recurrence risk takes into account the possibility of germline mosaicism, which has been documented in at least two families. If a parent of the proband has a balanced chromosome rearrangement, at-risk family members can be tested by chromosome analysis and FISH. In the rare instance of a complex familial chromosomal rearrangement, prenatal testing is possible for pregnancies at increased risk using a combination of routine cytogenetic studies and FISH.

Diagnosis

The diagnosis of SMS depends on genetic testing that demonstrates either a 17p11.2 deletion that includes *RAI1* or a mutation of *RAI1*.

Smith-Magenis syndrome (SMS) is suspected in individuals who present with a complex pattern of findings including the following:

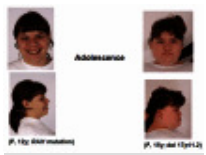
- A subtly distinctive facial appearance (see Clinical Description) that becomes more evident with age (see Figures 1, 2, 3)
- Mild-to-moderate infantile hypotonia with feeding difficulties and failure to thrive
- Minor skeletal anomalies
- Short stature (prepubertal)
- Brachydactyly
- Ophthalmologic abnormalities
- Otolaryngologic abnormalities
- Early speech delays with or without associated hearing loss
- Peripheral neuropathy
- Some level of cognitive impairment and developmental delay
- A distinct neurobehavioral phenotype that includes sleep disturbance and stereotypic and maladaptive behaviors [Finucane et al 1994, Dykens & Smith 1998, Smith et al 1998a, Finucane et al 2001, Martin et al 2006]. Sleep disturbance is chronic and associated with an abnormal diurnal circadian rhythm of melatonin [Potocki et al 2000b, De Leersnyder et al 2001, Boone et al 2011].

Figure

Figure 1. Infants with SMS. Nine-month-old female (left) and 30-month-old male (right). Note brachycephaly, broad forehead, upslanting palpebral fissures, short upturned nose, and characteristic down-turned “tent” shaped upper lip vermilion (more...)

Figure

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



Figure

Figure 3. Adolescent females with Smith-Magenis syndrome caused by *RAI1* mutation (left) and deletion 17p11.2 (right). Note short philtrum with relative prognathism resulting from midface retrusion that persists with age; down-turned upper lip is more (more...)

Renal anomalies and cleft lip and/or palate occur in fewer than 25% of individuals.

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.

Testing

Cytogenetic testing. SMS is typically diagnosed by detection of an interstitial deletion of 17p11.2 by G-banded cytogenetic analysis and/or by FISH analysis. Probes for FISH testing must include *RAI1* [Vlangos et al 2005]. A visible interstitial deletion of chromosome 17p11.2 can be detected in all individuals with the common deletion by a routine G-banded analysis provided the resolution is adequate (≥550 band). Studies indicate that approximately 90% of individuals with SMS have a FISH-detectable deletion, with approximately 70% having the common approximately 3.5-Mb deletion [Potocki et al 2003, Vlangos et al 2003, Girirajan et al 2006].

Note: It is not uncommon for the deletion to be overlooked particularly when the indication for the cytogenetic study is other than SMS. Thus, repeat cytogenetic study including FISH or aCGH is indicated for individuals with prior "normal" routine cytogenetic analysis in whom a diagnosis of SMS is strongly suspected.

Molecular Genetic Testing

Gene. *RAI1* is the only gene in which mutation or deletion is known to account for the majority of features in Smith-Magenis syndrome (SMS) [Slager et al 2003, Bi et al 2004, Girirajan et al 2005, Truong et al 2010, Vilboux et al 2011].

Clinical testing

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

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]
RAI1	FISH [2]	Deletion 17p11.2 involving *RAI1* [3]	~95%
	Sequence analysis	Sequence variants [4]	5%-10% [5]
	Deletion / duplication analysis [6]	Deletions involving *RAI1* [3]	~95% [7]

Note: A few individuals with clinical features of SMS but without confirmed deletions and/or *RAI1* mutations may represent an SMS-like syndrome yet to be defined.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. FISH probe that contains *RAI1* or *D17S258*. Note: Not all commercially available FISH probes contain *RAI1* [Vlangos et al 2005].

3. Extent of deletion detected may vary by method and by laboratory. *RAI1*deletions have been detected by aCGH, real-time PCR, and MLPA [Truong et al 2008]. Deletion/duplication analysis of the critical region and beyond will define the size of the deleted region.

4. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole-gene deletions/duplications are not detected.

5. Sequence analysis (particularly of exon 3, in which all mutations have been found to date) detects *RAI1* mutations in individuals with SMS when cytogenetic and FISH studies are negative for the 17p11.2 deletion [Slager et al 2003, Bi et al 2004, Girirajan et al 2005, Truong et al 2010, Vilboux et al 2011].

6 Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex

ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

7. Wide availability of CMA testing may lead to increased diagnostic detection of previously unsuspected cases.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Information on specific allelic variants may be available in Molecular Genetics (see Table A. Genes and Databases and/or **Pathologic allelic variants**).

Testing Strategy

To confirm/establish the diagnosis in a proband

- Array CGH should be performed as an initial study. This test will identify all 17p11.2 deletions and will also identify phenotypically overlapping genomic disorders.
- If there is a strong clinical suspicion of SMS and aCGH is normal, deletion/duplication analysis specific for *RAI1* may be performed.
- If the above deletion analyses are normal, sequencing of *RAI1* should be considered.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing deletion or mutation in the family.

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 (HNPP).

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].

Clinical Description

Natural History

Smith-Magenis syndrome (SMS) has a clinically recognizable phenotype that includes physical, developmental, and behavioral features (Table 2). Males and females are affected equally. The facial appearance is characterized by a broad square-shaped face, brachycephaly, prominent forehead, synophrys, mildly upslanting 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 changing to relative prognathia with age, and a distinct appearance of the mouth, with fleshy everted vermilion of the upper lip.

With progressing age, the facial appearance becomes more distinctive and coarse, with persisting midfacial retrusion, relative prognathism, and heavy brows with a "pugilistic" appearance. An increased frequency of dental anomalies, specifically tooth agenesis (especially premolars) and taurodontism, has been reported [Tomona et al 2006].

SMS has a wide degree of variability in cognitive and adaptive functioning, with the majority of individuals with SMS functioning in the mild-to-moderate range of intellectual disability.

The behavioral phenotype, which includes sleep disturbance, stereotypies, and maladaptive and self-injurious behaviors, is generally not recognized until age 18 months or older and continues to change throughout early childhood to adulthood [Dykens & Smith 1998, Smith et al 1998a, Sarimski 2004, Gropman et al 2006]. 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 1998b, Potocki et al 2000b, De Leersnyder et al 2001, Smith & Duncan 2005]. Fragmented sleep with reduced total sleep time has been documented as early as age six months [Duncan et al 2003, Gropman et al 2006] and remains

a chronic issue into adulthood. Actigraphy-based sleep estimates document developmental differences in nocturnal arousal patterns by age and time of night [Gropman et al 2007].

The abnormal diurnal (inverted) circadian rhythm of melatonin appears pathognomic in SMS; it is documented in 95% (26/28) of individuals with a deletion studied to date [Potocki et al 2000b, De Leersnyder et al 2001, Boudreau et al 2009], in addition to individuals with mutation of *RAI1* [Boone et al 2011]. New 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].

Table 2. Clinical Features of Smith-Magenis Syndrome

Frequency	System	Finding
>75% of individuals	Craniofacial/skeletal	Brachycephaly Midface retrusion Relative prognathism with 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)
	Otolaryngologic	Middle ear and laryngeal anomalies Hoarse, deep voice
	Neuro/behavioral	Cognitive impairment/developmental delay Generalized complacency/lethargy (infancy) Infantile hypotonia Sleep disturbance Inverted circadian rhythm of melatonin Attention seeking Attention deficit (+/-hyperactivity) disorder Tantrums, behavioral outbursts Impulsivity Stereotypic behaviors Self-injurious behaviors Speech delay Hyporeflexia Signs of peripheral neuropathy Oral sensorimotor dysfunction (early childhood) Sensory processing issues
Common (50%-75% of individuals)		Hearing loss Short stature Scoliosis Mild ventriculomegaly of brain Hyperaccusis Tracheobronchial problems Velopharyngeal insufficiency (VPI) Ocular abnormalities (iris anomalies; microcornea) REM sleep abnormalities Hypercholesterolemia/hypertriglyceridemia History of constipation Abnormal EEG without overt seizures Autism spectrum disorder (ASD)
Less common (25%-50% of individuals)		Cardiac defects Thyroid function abnormalities Seizures [1] Immune function abnormalities (esp. low IgA)

Occasional (<25% of individuals)		Renal/urinary tract abnormalities 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], Edelman et al [2007], Smith et al [2007], Smith & Gropman [2010]

1. Frequency varies by study.

Infancy

Physical features. Prenatal histories are notable for decreased fetal movement in 50%. The infant with SMS is generally born at term, with normal birth weight, length, and head circumference. Length and weight gradually decelerate in early infancy. In approximately 20% of children with SMS, the head circumference is less than the third percentile for age [Smith & Gropman 2010].

The subtle facial dysmorphology in infancy, often characterized by midface retrusion, short upturned nose, fleshy everted vermilion of the upper lip with a "tented" appearance, and micrognathia, may be recognizable in early infancy (see Figure 1). Feeding difficulties leading to failure to thrive are common, including marked oral motor dysfunction with poor suck and swallow, textural aversion, and gastroesophageal reflux. Hypotonia is reported in virtually all infants, accompanied by hyporeflexia (84%) and generalized lethargy and complacency, similar to that found in Down syndrome.

Neurobehavioral features. Gross and fine motor skills are delayed in the first year of life. Issues related to sensory integration are frequently noted [Hildenbrand & Smith 2012].

Prospective assessment of infants younger than age one year document generalized hypotonia, oral-motor dysfunction, and middle ear abnormalities with age-appropriate social skills and minimal maladaptive behaviors [Wolters et al 2009]. Crying is infrequent and often hoarse, and the vast majority of infants show markedly decreased babbling and vocalization for age. By age two to three years, global developmental delays, significant expressive language deficits relative to receptive language skills, and emerging maladaptive behaviors are recognized [Gropman et al 2006, Wolters et al 2009].

Parents usually do not recognize significant sleep problems before age 12-18 months; they often describe their infants as "perfect" babies with "smiling" dispositions, who cry infrequently and are "good sleepers." However, actigraphy-estimated sleep suggests that the disrupted sleep pattern begins as early as age nine months and worsens progressively from infancy through childhood [Duncan et al 2003, Gropman et al 2006].

Childhood/School Age

Physical features. The facial appearance of SMS becomes more recognizable in early childhood (see Figure 2, Figure 3) and is accompanied by the emergence of the SMS behavioral phenotype. Ocular abnormalities, including strabismus, progressive myopia, iris anomalies, and/or microcornea, are usually recognized and may progress with age. Mild-to-moderate scoliosis, most commonly of the mid-thoracic region, is seen in approximately 60% of affected individuals age four years and older. Underlying vertebral anomalies are seen in only a few. Hands and feet remain small, and short stature (height <5th percentile) is frequently observed (67%). Markedly flat or highly arched feet and unusual gait are generally observed. Constipation is frequently reported.

Hypercholesterolemia is recognized in over 50% of individuals with SMS [Smith et al 2002].

Otolaryngologic problems are common throughout childhood. Otitis media occurs frequently (≥3 episodes/year) and often leads to tympanostomy tube placement (85%) and risk for conductive hearing loss (65%). Hyperacusis, or oversensitivity to certain frequencies/sounds tolerable to listeners with normal hearing, is reported in 78% [Smith et al 2007]. 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. Oral sensorimotor dysfunction is a major issue, including lingual weakness, asymmetry and/or limited

mobility, weak bilabial seal (64%), palatal abnormalities (64%), and open-mouth posture with tongue protrusion and frequent drooling. Sinusitis requiring antibiotics is frequently reported.

The high incidence of otolaryngologic findings provides a physiologic explanation for the functional impairments in voice (hoarseness) and may contribute to the marked delays in expressive speech. With appropriate intervention and a total communication program that includes sign/gesture language, 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. Hearing impairment is found in more than two thirds of affected individuals.

Neurobehavioral features. Developmental delays are evident in early childhood, and the majority of older children and adults function within the mild-to-moderate range of intellectual disability. A cognitive profile has been described with relative weaknesses observed in sequential processing and short-term memory; relative strengths were found 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").

The behavioral phenotype of SMS is evident by early childhood/school age and escalates with age, often coinciding with expected life-cycle stages: 18-24 months, school age, and onset of puberty. Head banging may begin as early as age 18 months. Sensory integration issues are present and persist throughout childhood. A prominent pattern of sensory processing is recognized that is characterized by an imbalance in neurologic thresholds and a fluctuation between active and passive self-regulation [Hildenbrand & Smith 2012]. Most individuals with SMS exhibit inattention with or without hyperactivity.

A recent study using the SRS (Social Responsiveness Scale) found that 90% of individuals with SMS had scores within the autism range (35% mild/moderate; 55% severe range) and, from a clinical perspective, met criteria for an axis I diagnosis of pervasive developmental disorder [Laje et al 2010b]. The diagnosis of SMS should be considered in the differential diagnosis of children with autism spectrum disorders, especially those with characteristic behaviors or stereotypies recognized in SMS, significant feeding problems and oromotor dysfunction, or sleep disturbance associated with excessive daytime sleepiness [Smith & Gropman 2010]. Therapeutic interventions for autism are likely to benefit individuals with SMS.

Maladaptive behaviors are prevalent and represent the major management problem for families and caretakers. These include frequent outbursts/temper tantrums, attention seeking (especially from adults), impulsivity, distractibility, disobedience, aggression, self-injury, and toileting difficulties. While age and degree of developmental delay correlate with maladaptive behaviors, the degree of sleep disturbance remains a strong predictor of maladaptive behavior [Dykens & Smith 1998, Arron et al 2011, Sloneem et al 2011]. Due to the maladaptive behaviors, true intellectual ability may not be accurately assessed in many individuals.

Self-injurious behaviors (SIB) occur in the vast majority of individuals with SMS after age two years [Arron et al 2011, Sloneem et al 2011]. The most common include self-hitting (71%), self-biting (77%), and/or skin picking (65%) [Dykens & Smith 1998]. The overall prevalence of SIB increases with age, as does the number of different types of SIB exhibited [Finucane et al 2001]. A direct correlation exists between the number of different types and extent of SIB exhibited and the level of intellectual functioning. Two behaviors distinctive to SMS, nail yanking (onychotillomania) [Greenberg et al 1991] and insertion of foreign objects into body orifices (polyembolokoilamania), are seen in 25%-30% of affected individuals. Nail yanking generally does not become a major problem until later childhood. Mouthing of hands or objects appears to persist from early childhood to ages where this is not socially acceptable.

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 between intellectual functioning and emotional maturity [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.

The spasmodic upper-body squeeze or "self-hug" behavior may provide an effective clinical diagnostic marker for the syndrome [Dykens et al 1997, Dykens & Smith 1998]. Additional stereotypies include mouthing objects or insertion of hand in mouth (54%-69%), teeth grinding (54%), body rocking (43%), and spinning or twirling objects (40%). The finger lick and page flipping ("lick and flip") behavior first recognized by Dykens et al [1997] may be less prevalent than initially reported [Authors, personal observation].

Sleep disturbance is a major issue for caretakers, who themselves may become sleep deprived [Foster et al 2010]. Disrupted sleep becomes a major problem in early childhood. Studies of individuals with SMS confirm

difficulties falling asleep, frequent and prolonged night-time awakenings, and excessive daytime sleepiness. With increasing age, the number and frequency of naps increases and total sleep time at night decreases. Diminished REM sleep was documented in over half of those undergoing polysomnography [Greenberg et al 1996, Potocki et al 2000b]. Actigraphy-based sleep estimates from infancy (age <1 year) to age eight years demonstrate a reduction in 24-hour and night sleep in SMS when compared to healthy pediatric controls [Gropman et al 2006]. Children younger than age ten years show few difficulties getting to sleep (settling), but exhibit increased activity (arousals) in the second half of the night [Gropman et al 2007]. Older children and adolescents show more difficulties settling to sleep [Gropman et al 2007].

Sexual and/or child abuse may be wrongly suspected secondary to self-inflicted injuries and/or insertion of objects in body orifices (e.g., vaginal insertion).

Adolescence

Physical features. The facial appearance (Figure 3) becomes more angulated, with persisting midface retrusion and relative prognathism, frontal bossing with synophrys, heavy brows (often pugilistic), and a general coarsening. Puberty typically occurs within the normal time frame; however, precocious puberty and delayed sexual maturation have been seen.

Neurobehavioral features. Behaviors often escalate with onset of puberty, and sleep disturbance remains a concern. Actigraphy-based sleep estimates indicate more difficulties settling to sleep than in earlier childhood [Gropman et al 2007]. Increased impulsivity, especially in females, is recognized [Martin et al 2006]. Rapid mood shifts, increased anxiety with/without tendency for fright/flight reaction becomes a major issue in adolescence and adulthood. Aggressive outbursts are common, escalating with age. Pubertal onset of catamenial seizures has also been observed in some females coinciding with menses [Smith & Gropman 2010]. Polyembolokoilamania and onychotillomania may become more prevalent. 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 [Finucane et al 2001].

Adulthood

Insufficient longitudinal data are available to accurately determine life expectancy; however, the oldest known individual with SMS lived to age 88 years [Magenis, personal communication]. In the month prior to her death she was her usual alert happy “SMS” self 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.

One would expect that, in the absence of major organ involvement, the life expectancy would not differ from that of the cognitively impaired population at large.

Physical features. The facial appearance is coarser with persisting midface retrusion and relative prognathism as a result of pointed chin. Scoliosis becomes more severe with age, and short stature may or may not persist [Smith et al 2004]. Behavioral outbursts, aggression, and SIB may continue, but many have noted a relative "calming" of behavior in adulthood.

Genotype-Phenotype Correlations

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.

Individuals so far reported with *RAI1*-specific mutations are obese, do not exhibit short stature, and do not have organ system involvement [Slager et al 2003, Bi et al 2004, Girirajan et al 2005]. All other features typically associated with SMS are seen in individuals with mutations in *RAI1*. The effects of possible modifier genes within 17p11.2 are not known.

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 cytogenetic techniques.

The syndrome has been identified worldwide in all ethnic groups.

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 most common of these include the following, which can be distinguished using cytogenetic (FISH) and/or molecular analysis:

- 22q11.2 deletion syndrome (including velocardiofacial [VCF] syndrome, DiGeorge syndrome)
- Prader-Willi syndrome (PWS)
- Williams syndrome
- Down syndrome (trisomy 21; in the newborn period)
- Fragile X syndrome
- 2q37 deletion syndrome
- 2q23.1 deletion syndrome
- Kleefstra syndrome (9q34.3 deletion or intragenic *EHMT1* mutation)

Clinically, many children with SMS are given psychiatric diagnoses — including autism/autism spectrum disorders (ASD), attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and/or mood disorders.

Accurate diagnosis is more difficult in the presence of speech delays and maladaptive or stereotypic behaviors.

Delayed diagnosis of SMS is common. Repeat cytogenetic analysis using aCGH or FISH-specific probes for SMS is warranted in individuals suspected of having SMS who had a prior "normal" chromosome analysis. Current clinical use of aCGH in children referred with “developmental delay” alone has led to increased detection of clinically unsuspected SMS deletion cases [Authors’ experience].

Infants with SMS are often thought to have Down syndrome based on the findings of infantile hypotonia, facial stigmata suggestive of this diagnosis (brachycephaly, flat midface, upslanting palpebral fissures), and/or congenital heart disease. Failure to confirm trisomy 21 in a child with suggestive findings warrants further analysis by FISH using an SMS-specific probe [Smith et al 2005].

Note to clinicians: For a patient-specific ‘simultaneous consult’ related to this disorder, go to **SimulConsult®**, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Smith-Magenis syndrome (SMS), the following evaluations are recommended:

- Complete review of systems at the time of diagnosis
- Physical and neurologic examination
- Renal ultrasound examination to evaluate for possible renal/urologic anomalies (~20% of individuals with SMS), including urologic workup if a history of frequent urinary tract infections exists
- Echocardiogram to evaluate for possible cardiac anomalies (<45% of individuals with SMS); follow-up depending on the severity of any cardiac anomaly identified
- Spine radiographs to evaluate for possible vertebral anomalies and scoliosis (~60%)
- Routine blood chemistries, qualitative immunoglobulins, fasting lipid profile (evaluation for hypercholesterolemia), and thyroid function studies

- Ophthalmologic evaluation with attention to evidence of strabismus, microcornea, iris anomalies, and refractive error
- Comprehensive speech/language pathology evaluation
- Assessment of caloric intake, signs and symptoms of gastroesophageal reflux disease (GERD), swallowing abilities, and oral motor skills with referral as warranted for full diagnostic evaluation
- Otolaryngologic evaluation to assess ear, nose, and throat problems, with specific attention to ear physiology and palatal abnormalities (clefting, velopharyngeal insufficiency)
- Audiologic evaluation at regular intervals to monitor for conductive and/or sensorineural hearing loss
- Multidisciplinary developmental evaluation, including assessment of motor, speech, language, personal-social, general cognitive, and vocational skills
- Early evaluation by physical and/or occupational therapists
- Sleep history with particular attention to sleep/wake schedules and respiratory function. Sleep diaries may prove helpful in documenting sleep/wake schedules. Evidence of sleep-disordered breathing warrants a polysomnogram (overnight sleep study) to evaluate for obstructive sleep apnea.
- EEG in individuals who have clinical seizures to guide the choice of antiepileptic agents. For those without overt seizures, EEG may be helpful to evaluate for possible subclinical events in which treatment may improve attention and/or behavior; a change in behavior or attention warrants reevaluation.
- Neuroimaging (MRI or CT scan) in accordance with findings such as seizures and/or motor asymmetry
- In individuals with SMS documented to have larger deletions extending into 17p12:
    - Specific screening for adrenal function
    - Detailed assessment and attention to peripheral neurologic function in individuals with SMS with large deletions involving *PMP22*, which is associated with hereditary neuropathy with liability to pressure palsy (HNPP)
- Assessment of family support and psychosocial and emotional needs to assist in designing family interventions
- Medical genetics consultation

Treatment of Manifestations

The following are appropriate:

- Ongoing pediatric care with regular immunizations
- From early infancy, referrals for early childhood intervention programs, followed by ongoing special education programs and vocational training in later years
- Therapies including speech/language, physical, occupational, and especially sensory integration:
    - During early childhood, speech/language pathology services should initially focus on identifying and treating swallowing and feeding problems as well as optimizing oral sensorimotor development.
    - Therapeutic goals of increasing sensory input, fostering movement of the articulators, increasing oral motor endurance, and decreasing hypersensitivity are needed to develop skills related to swallowing and speech production.
    - The use of sign language and total communication programs, such as computer assisted devices and tablets, as adjuncts to traditional speech/language therapy is felt to improve communication skills and also to have a positive impact on behavior. The ability to develop expressive language appears dependent on the early use of sign language and intervention by speech/language pathologists.

    - Atypical patterns of sensory processing may become more prominent with increased age. Insight about the vulnerabilities and relative strengths in patterns of sensory processing may aid caregivers of individuals with SMS in adapting activity demands, modifying the environment, and facilitating appropriate and supportive social interactions. In addition, 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].
    - A comprehensive behavior support plan for home and school should be considered as soon as problem behaviors arise, typically starting in early elementary school. A structured school program with one-on-one support and curricula matched to the known cognitive and behavioral profile of SMS can be effective in addressing the needs of these students.
    - The combination of intellectual disability, severe behavioral abnormalities, and sleep disturbance takes a significant toll on parents and siblings. 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 with nonspecific developmental disabilities [Hodapp et al 1998, Foster et al 2010]. Family support services and resources should be included as essential components of a holistic management plan for people with SMS.
- Use of psychotropic medication to increase attention and/or decrease hyperactivity. No single regimen shows consistent efficacy [Laje et al 2010a]. 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].
- Behavioral therapies including special education techniques that emphasize individualized instruction, structure, and routine to help minimize behavioral outbursts in the school setting
- Therapeutic management of the sleep disorder. Sleep management in SMS remains a challenge for physicians and parents. No well-controlled treatment trials have been reported:
    - Early anecdotal reports of therapeutic benefit from melatonin taken at bedtime remain encouraging, providing variable improvement of sleep without reports of major adverse reactions. 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.
    - A single uncontrolled study of nine individuals with SMS treated with oral ß-1-adrenergic antagonists (acebutolol 10 mg/kg) reported suppression of daytime melatonin peaks and subjectively improved behavior [De Leersnyder et al 2001]. This treatment, however, did not restore nocturnal plasma concentration of melatonin.
    - A second uncontrolled trial by the same group [De Leersnyder et al 2003] combined the daytime dose of acebutolol with an evening oral dose of melatonin (6 mg at 8pm) and found that nocturnal plasma concentration of melatonin was restored and nighttime sleep improved with disappearance of nocturnal awakenings. Parents also reported subjective improvement in daytime behaviors with increased concentration. Contraindications to the use of ß-1-adrenergic antagonists include asthma, pulmonary problems, some cardiovascular disease, and diabetes mellitus.
    - Prior to beginning any trial, the child's medical status and baseline sleep pattern must be considered.
- Enclosed bed system for containment during sleep
- Respite care and family psychosocial support to help assure the optimal environment for the affected individual
- Monitoring of hypercholesterolemia (recognized in >50% of individuals with SMS); treatment with diet or medication as indicated
- Treatment with corrective lenses as indicated for ophthalmologic abnormalities

- Treatment of recurrent otitis media with tympanostomy tubes as needed
- Auditory amplification if hearing loss is identified
- Management of seizures in accordance with standard practice
- Treatment of cardiac and renal anomalies and scoliosis in accordance with standard medical care. While growth hormone treatment has been reported [Itoh et al 2004, Spadoni et al 2004], controlled studies have not evaluated its effectiveness.

Surveillance

Recommended annually:

- Multidisciplinary team evaluation (including physical, occupational, and speech therapy evaluations and pediatric assessment) to assist in development of an individualized educational program (IEP). Periodic neurodevelopmental assessments and/or developmental/behavioral pediatric consultation can be an important adjunct to the team evaluation.
- Thyroid function, including free T4 and TSH
- Fasting lipid profile
- Routine urinalysis to evaluate for occult urinary tract infections
- Monitoring for scoliosis
- Ophthalmologic evaluation
- Otolaryngologic follow-up for assessment and management of otitis media and other sinus abnormalities
- Audiologic evaluation to monitor for conductive or sensorineural hearing loss annually or as clinically indicated

Agents/Circumstances to Avoid

In at least one case, a teenage female with SMS was documented to have a serious adverse event taking Strattera® (atomoxetine hydrochloride) with extreme escalation of behaviors and aggression leading to hospitalization. Significant changes in her sleep pattern were also documented. Care should be taken to track sleep parameters and behavior with this medication.

Evaluation of Relatives at Risk

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

Pregnancy Management

To date, there are no published cases of individuals with SMS who have had children.

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Smith-Magenis syndrome (SMS) is caused by deletion or mutation of *RAI1* on chromosome 17p11.2.

Risk to Family Members

Parents of a proband

- Virtually all cases of SMS occur *de novo*. There is no evidence to suggest an obvious parental age contribution for the deletion.
- One case reported by Zori et al [1993] identified maternal mosaicism for del(17)(p11.2). Other cases of parental mosaicism are known but not reported [Smith et al 2006].
- Complex familial chromosomal 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]. Consequently, chromosome analysis of the parents should be performed for all newly diagnosed individuals.

Sibs of a proband

- The risk to sibs depends on the results of parental chromosome analysis.
- If parental chromosome analysis is normal, the risk to sibs of the proband is likely less than 1% (recurrence risk attributable to the possibility of germline mosaicism in a parent).
- 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.

Offspring of a proband

- No instances of individuals with SMS having an affected child have been reported.
- Theoretically, the offspring of an individual with SMS are at a 50% risk of having SMS.
- Fertility issues in SMS remain unstudied.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent has a chromosome abnormality, his or her family members are at risk and can be offered chromosome analysis and FISH.

Carrier Detection

If a parent of the proband has a balanced chromosome rearrangement, testing of at-risk family members is possible by chromosome analysis and FISH.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

High-risk pregnancies. Because SMS usually occurs as the result of a *de novo* deletion of 17p11.2, virtually all individuals with SMS represent a simplex case (i.e., a single occurrence in a family). In the rare instance of a complex familial chromosomal rearrangement, prenatal testing is possible for at-risk pregnancies using a combination of routine cytogenetic studies and FISH on fetal cells obtained by chorionic villus sampling (usually performed at ~10-12 weeks' gestation) or amniocentesis (usually performed at ~15-18 weeks' gestation). Note: It is essential to include FISH studies when performing prenatal diagnosis.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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 AFP (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].

Preimplantation genetic diagnosis (PGD) may be an option for some families in whom the disease-causing deletion or mutation has been identified.

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 (ASM France)**
  France
  Email: association@smithmagenis.com
- **National Library of Medicine Genetics Home Reference**
  Smith-Magenis syndrome
- **Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS)**
  21800 Town Center Plaza
  Suite 266A-633
  Sterling VA 20164
  Phone: 972-231-0035
  Fax: 972-499-1832
  Email: info@prisms.org
  www.prisms.org
- **Smith-Magenis Syndrome Foundation**
  57 Allen Road
  Northants NN10 0DY
  United Kingdom
  Phone: +44 01933 389951
  Email: info@smith-magenis.co.uk
  www.smith-magenis.co.uk
- **National Institutes of Health (NIH) SMS Research Registry and Tissue Bank**
  Ann C. M. Smith, MA, DSc (Hon)
  Phone: 301-435-5475
  Fax: 301-496-7184
  Email: acmsmith@mail.nih.gov
  SMS Research Registry and Tissue Bank

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 Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
RAI1	17p11.2	Retinoic acid-induced protein 1	RAI1 @ LOVD	RAI1

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) 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 Genetic Pathogenesis

Smith-Magenis syndrome is a contiguous gene deletion syndrome. A common deletion interval spanning approximately 3.5 Mb is identified in approximately 70% of individuals [Potocki et al 2003, Vlangos et al 2003]. The SMS critical region maps to 17p11.2 and spans fewer than 650 kb [Schoumans et al 2005, Vlangos et al 2005]. SMS also results from intragenic mutations of *RAI1* (see Table 3).

Normal allelic variants. The gene has six exons

Pathologic allelic variants. Dominant mutations 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]. See Table 3.

Table 3. Selected *RAI1* Pathologic Allelic Variants

Nucleotide Change	Amino Acid Change [1]	Reference Sequences
c.253_271del19	p.Leu85Cysfs*55	NM_030665.3 NP_109590.3
c.1119delC	p.Gln374Serfs*65	
c.1449delC	p.Glu484Lysfs*35	
c.2773_2801del29	p.Val1925Argfs*9	
c.2878C>T	p.Arg960X	
c.3103delC	p.Gln1035Argfs*29	
c.3103dupC	p.Gln1035Profs*31	
c.3801delC	p.Thr1268Profs*47	
c.4649delC	p.Ser1550Phefs*37	
c.4685A>G	p.Gln1562Arg	
c.4933_4936del	p.Ala1645Glyfs*35	
c.5423G>A	p.Ser1808Asn	
c.5265delC	p.Arg1756Glyfs*94	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

References for pathologic variants: Slager et al [2003], Bi et al [2004], Girirajan et al [2005], Girirajan et al [2006], Truong et al [2010]

1. Nomenclature for frameshift mutatons includes the amino acid change occurring at the site of the frame shift (fs), followed by an "X#" indicating the codon position at which the new reading frame ends in a stop codon (X). The position of the stop in the new reading frame is calculated starting at the first changed amino acid that is created by the frame shift, and ending at the first stop codon (X#) (See www.hgvs.org).

Normal gene product. Normal retinoic acid-induced protein 1 is thought to function in transcriptional 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.

Abnormal gene product. The mechanisms by which the mutations in *RAI1* affect gene/protein function are not known. The mechanism by which retinoic acid-induced protein 1 is thought to result in disease phenotype is haploinsufficiency; thus it is assumed that intragenic mutations result in a nonfunctional protein product.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

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Revision History

- 28 June 2012 (me) Comprehensive update posted live
- 7 January 2010 (me) Comprehensive update posted live
- 11 August 2006 (me) Comprehensive update posted to live Web site
- 26 August 2005 (cd) Revision: sequence analysis of *RAI1* clinically available
- 15 March 2004 (me) Comprehensive update posted to live Web site
- 15 January 2002 (as) Author revisions
- 22 October 2001 (me) Review posted to live Web site
- 23 May 2001 (as) Original submission

Bookshelf ID: NBK1310 PMID: 20301487