



## **SATB2-Associated Syndrome**

**Synonyms:** 2q32 Deletion Syndrome, 2q33.1 Microdeletion Syndrome, Glass Syndrome

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## **Summary**

### **Clinical characteristics**

*SATB2*-associated syndrome (SAS) is a multisystem disorder characterized by significant neurodevelopmental compromise with limited to absent speech, behavioral issues, and craniofacial anomalies. All individuals described to date have manifest developmental delay / intellectual disability, with severe speech delay. Affected individuals often have hypotonia and feeding difficulties in infancy. Behavioral issues may include autistic features, hyperactivity, and aggressiveness. Craniofacial anomalies may include palatal abnormalities (cleft palate, high-arched palate, and bifid uvula), micrognathia, and abnormal shape or size of the upper central incisors. Less common features include skeletal anomalies (osteopenia, pectus deformities, kyphosis/lordosis, and scoliosis), growth restriction, strabismus/refractive errors, congenital heart defects, genitourinary anomalies, and epilepsy. While dysmorphic features have been described in individuals with this condition, these features are not typically distinctive enough to allow for a clinical diagnosis of SAS.

### **Diagnosis/testing**

The diagnosis of *SATB2*-associated syndrome (SAS) is established in a proband by detection of one of the following:

- A heterozygous intragenic *SATB2* pathogenic variant (61%)
- A heterozygous deletion at chromosome 2q33.1 that includes *SATB2* (22%)
- An intragenic deletion or duplication of *SATB2* (9%)
- A chromosome translocation with a chromosome 2q33.1 breakpoint that disrupts *SATB2* (8%)

### **Management**

*Treatment of manifestations:* Treatment is symptomatic. Nutritional support for feeding difficulties and management by a cleft/craniofacial team for those with palatal anomalies early in life. Early referral for

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developmental support/special education; standard treatment for dental anomalies, sleep disturbance, skeletal anomalies, seizure disorders, genitourinary anomalies, strabismus and refractive errors, and congenital heart defects.

*Surveillance:* Evaluation of nutritional status, growth, and developmental progress at each visit; routine monitoring by a neurologist for those with epilepsy; annual sleep study in those with a history of sleep disturbance; evaluation for scoliosis/spine deformity at each visit and consideration of screening for osteopenia; routine evaluations by dentistry and ophthalmology.

## Genetic counseling

*SATB2*-associated syndrome (SAS) is an autosomal dominant disorder. Almost all probands with SAS reported to date have the disorder as the result of a *de novo* genetic event. In two families, parental mosaicism seemed likely (given recurrence of SAS in sibs and failure to detect the genetic alteration in parental blood samples). To date, individuals with SAS are not known to reproduce. Once an *SATB2* intragenic pathogenic variant, a 2q33.1 deletion that includes *SATB2*, or a chromosome translocation affecting *SATB2* has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

## Diagnosis

No formal clinical diagnostic criteria have been established for *SATB2*-associated syndrome.

## Suggestive Findings

*SATB2*-associated syndrome (SAS) **should be suspected** in individuals with the following major features [Zarate & Fish 2017]:

- Significant neurodevelopmental disorders in all affected individuals
  - Infantile hypotonia and feeding difficulties (relatively common)
  - Subsequent developmental delay and severe speech delay (including, in some, absence of speech)
- Behavioral issues: autistic tendencies, hyperactivity, and aggressiveness
- Palatal anomalies: cleft palate, bifid uvula, and high-arched palate
- Dental anomalies: prominent upper incisors and other anomalies

Some of the common features can be described using the acronym SATB2: severe speech anomalies; abnormalities of the palate, teeth anomalies, behavioral issues with or without bone or brain anomalies, and onset before age 2.

## Establishing the Diagnosis

The diagnosis of *SATB2*-associated syndrome (SAS) is established in a proband by detection of one of the following: a heterozygous intragenic *SATB2* pathogenic variant, a heterozygous non-recurrent deletion at 2q33.1 that includes *SATB2*, an intragenic deletion or duplication of *SATB2* detectable by chromosomal microarray analysis (CMA), or a chromosome translocation with a 2q33.1 breakpoint that disrupts *SATB2* (see Table 1).

Molecular genetic testing approaches can include a combination of CMA, a multigene panel, comprehensive genomic sequencing, and exome array.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotypes of many inherited disorders with developmental delay / intellectual disability overlap, many children with SAS are diagnosed by the following recommended genomic testing.

**Note:** Because the phenotype of SAS is indistinguishable from a wide range of other developmental disorders, most affected individuals with a 2q33.1 deletion are likely to be diagnosed using **CMA** and individuals with a pathogenic variant detectable by sequence analysis are likely detected by **comprehensive genomic sequencing**.

## Recommended First-Tier Genomic Testing

**Chromosomal microarray analysis (CMA)** using oligonucleotide or SNP arrays is recommended first because deletions/duplications are identified in about 25% of probands (see Table 1). The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 2q33.1 region.

## Options for Second-Tier Genomic Testing

If a chromosome 2q33.1 deletion is not identified on CMA, testing options include the following:

- **A multigene panel** that includes *SATB2* and other genes of interest (see Differential Diagnosis) is recommended because pathogenic sequence variants are identified in 61% of probands (see Table 1). 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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](#).

- **Comprehensive genomic testing** (when clinically available and not previously performed) including **exome sequencing** and **genome sequencing** may be considered.

**Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

## Further Testing to Consider

If a 2q33.1 deletion is not identified on CMA and an intragenic pathogenic variant has not been identified on either a multigene panel or comprehensive genomic testing (genomic sequencing and exome array), additional options for testing include:

- **Karyotype.** A chromosome translocation with a 2q33.1 breakpoint that disrupts *SATB2* has been observed in 8% of person with SAS (Table 1).

Note: Single-gene testing (sequence analysis of *SATB2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

**Table 1.** Molecular Genetic Testing Used in *SATB2*-Associated Syndrome

Gene <sup>1</sup>	Method	Proportion of Probands with a Genetic Alteration <sup>2</sup> Detectable by Method
<i>SATB2</i>	Sequence analysis <sup>3</sup>	46/76 (61%) <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5,6</sup>	See footnote 7.
	CMA <sup>8</sup>	24/76 (31%) <sup>9</sup>
	Karyotype (to detect structural variants)	6/76 (8%) <sup>10</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Almost all individuals with pathogenic missense, nonsense, and frameshift variants have been diagnosed by exome sequencing.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.

7. Note that, although gene-targeted deletion/duplication assays may detect smaller events than genomic deletion/duplication assays, they will detect larger events but may not be able to determine the size. All intragenic deletions and duplications, as well as 2q33.1 deletions, were detected by CMA and would have been detected by a gene-targeted deletion/duplication assay. It is possible that additional smaller deletions and duplications could be detected by these methods.

8. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 2q33.1 region.

9. In addition to detecting the 22q33.1 deletion, CMA technology identified an intragenic duplication in three individuals and an intragenic deletion in four [Rosenfeld et al 2009, Balasubramanian et al 2011, Asadollahi et al 2014, Liedén et al 2014, Kaiser et al 2015].

10. Six individuals with an *SATB2* disruption resulting from a "balanced translocation" have been described [Brewer et al 1999, FitzPatrick et al 2003, Baptista et al 2008, Tegay et al 2009, Talkowski et al 2012, Rainger et al 2014].

## Clinical Characteristics

### Clinical Description

*SATB2*-associated syndrome (SAS) is a multisystem disorder characterized by significant neurodevelopmental compromise with limited or absent speech, behavioral issues, and craniofacial anomalies.

The following clinical findings, based on published reports of 76 individuals with a molecularly confirmed diagnosis of SAS (47 male, 27 female, 2 where sex was not reported), are summarized in Table 2 [Van Buggenhout et al 2005, Leoyklang et al 2007, de Ravel et al 2009, Rosenfeld et al 2009, Urquhart et al 2009, Rifai et al 2010, Balasubramanian et al 2011, Rauch et al 2012, Mc Cormack et al 2013, Tomaszewska et al 2013, Döcker et al 2014, Gilissen et al 2014, Liedén et al 2014, Trakadis et al 2014, Kaiser et al 2015, Yu et al 2015, Zarate et al 2015, Boone et al 2016, Gregoric Kumperscak et al 2016, Lee et al 2016, Bengani et al 2017, Schwartz et al 2017, Zarate et al 2017].

**Table 2.** Summary of the Most Common Clinical Findings in 76 Individuals with *SATB2*-Associated Syndrome

Finding	% of Affected Individuals <sup>1</sup>
Developmental delay / intellectual disability	100%
Speech delay	95%

Table 2. continued from previous page.

Finding	% of Affected Individuals <sup>1</sup>
Craniofacial dysmorphism	89%
Dental anomalies	72%
Behavioral issues	55%
Cleft palate	50%
Abnormal brain MRI	49%
Micrognathia	42%
Hypotonia	42%
Feeding difficulties	39%
Growth restriction	34%
Skeletal anomalies	32%

1. Complete information was not available on some individuals.

**Developmental delay / intellectual disability.** While all known individuals with SAS have some degree of intellectual disability, more than half experience severe developmental delay / intellectual disability with absent speech [Zarate & Fish 2017]. For those with a heterozygous pathogenic variant within *SATB2* (those who do not have a larger deletion of 2q33.1 that includes *SATB2* and other genes), mean age at walking is 20.9 months (range 11-35) and at first word is 19.8 months (range 13-42), although some never achieve verbal communication [Zarate et al 2017].

Developmental regression and/or cognitive decline has been described only once in an adult female with an 8.6-Mb deletion of 2q32.2-q33.1 who progressed from mild to severe intellectual disability and from poor to absent speech between ages six and 12 years [Gregoric Kumperscak et al 2016].

**Mild but nonspecific facial dysmorphism.** In most reports of affected individuals, at least minor facial dysmorphic features have been reported. For those with pathogenic variants within *SATB2*, thin vermilion of the upper lip (20%) and long and smooth philtrum (17%) are the most consistent features (Figure 1 A-E) [Zarate & Fish 2017, Zarate et al 2017]. In those with larger 2q33.1 deletions, the most consistent features include prominent forehead or high anterior hairline (53%), thin vermilion of the upper lip (35%), low-set ears (29%), and/or long face (24%) (Figure 1 F-G) [Zarate & Fish 2017].

**Dental anomalies.** While abnormal shape or size of the upper central incisors is the most common finding (36%), other dental issues can include crowding (36%), hypodontia (16%), delayed primary dentition (6%), and/or diastema (4%). Other issues reported by families include sialorrhea, malocclusion, and fused incisors [Zarate et al 2017].

**Behavioral anomalies.** A broad spectrum of behavioral findings described can include jovial or friendly personality, autistic tendencies, agitation or aggressive outbursts, hyperactivity, difficulties falling asleep or maintaining sleep, and sensory issues [Bengani et al 2017, Zarate et al 2017]. Two affected females were described to have Rett syndrome-like phenotypes with limited purposeful hand movements, stereotyped repetitive movements, and bruxism [Lee et al 2016]. Additional behavioral issues include high pain tolerance, obsessive tendencies, skin picking, and anxiety [Zarate et al 2017].

**Skeletal anomalies.** Pectus deformities, kyphosis/lordosis, and scoliosis have been described in several affected individuals. To date tibial and/or femoral bowing has been described in a few individuals, some with concurrent osteopenia [Zarate et al 2018]. Arachnodactyly, broad thumbs, clinodactyly, small hands/feet, and finger contractures have been infrequently reported.

While routine screening for osteopenia has not been conducted systematically, low bone mineral density or radiographic evidence of osteopenia has been documented to date in several affected individuals as early as age two years [Leoyklang et al 2007, Tegay et al 2009, Talkowski et al 2012, Liedén et al 2014, Rainger et al 2014, Zarate et al 2015, Boone et al 2016, Lee et al 2016, Zarate et al 2018]. Elevated alkaline phosphatase levels have been seen in some individuals with documented osteopenia [Boone et al 2016, Zarate et al 2018].

**Craniofacial anomalies.** Palatal abnormalities documented in 76% of individuals include cleft palate (50%), high-arched palate (23%), and bifid uvula (3%). Micrognathia, diagnosed in 42%, has not required surgical correction. The combination of craniofacial issues and hypotonia is the most likely explanation for the high frequency of feeding issues present during infancy and beyond.

**Neuroimaging.** Brain abnormalities, documented in half of affected individuals who underwent head MRI, include nonspecific findings such as enlarged ventricles (12%), agenesis of the corpus callosum (5%), and prominent perivascular spaces (5%). Of interest, abnormal myelination for age and/or non-progressive white matter abnormalities appear to be particularly common (26%) in those with pathogenic nonsense, frameshift, and missense variants [Zarate & Fish 2017, Zarate et al 2017]. Note that these findings are not sufficiently distinct to specifically suggest the diagnosis of SAS.

### Other neurologic manifestations

- Hypotonia, particularly during infancy (42%)
- Clinical seizures (14%)
- EEG abnormalities without clinically recognizable seizures [Zarate et al 2017]
- Less common neurologic issues include gait abnormalities/ataxia (17%), hypertonicity and/or spasticity (4%), and hyperreflexia (3%).

**Growth restriction.** Pre- and postnatal growth restriction, sometimes with associated microcephaly, can be found in individuals with SAS, particularly in those with large deletions involving *SATB2* and adjacent genes (71%).

**Eye findings.** Both strabismus (18%) and refractive errors (8%) have been described.

**Cardiovascular.** Septal defects have been reported in two affected individuals with large deletions involving *SATB2* and adjacent genes. In one person, echocardiographic evaluation also revealed severe right ventricular volume overload and persistent pulmonary hypertension [Van Buggenhout et al 2005, McCormack et al 2013].

**Genitourinary.** Small or undescended testicles, inguinal hernias, and hypospadias have been described in males with large deletions involving *SATB2* and adjacent genes.

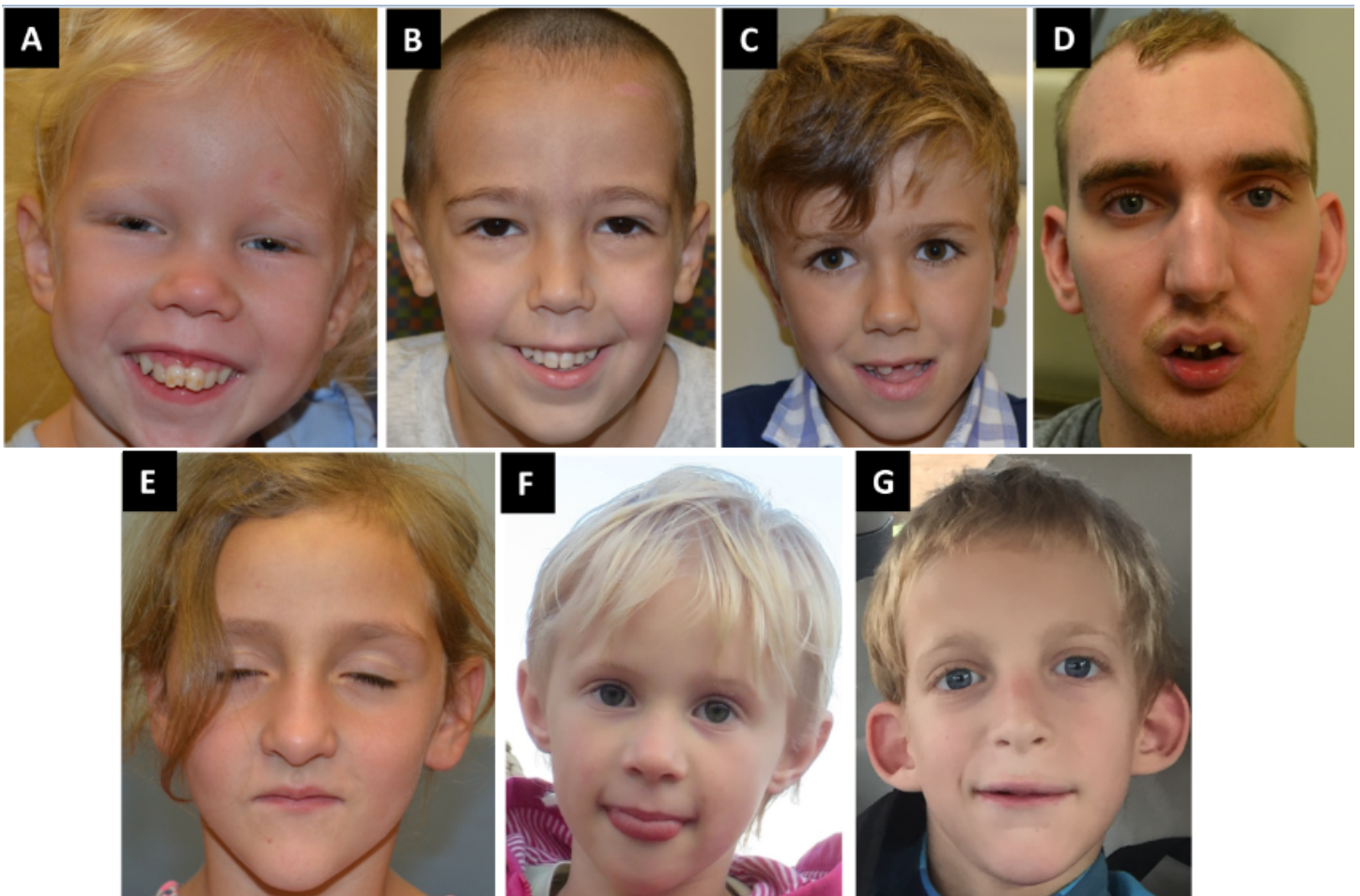
**Ectodermal changes.** Thin skin, reduced subcutaneous fat, and thin or sparse hair have been described in some affected individuals with large deletions involving *SATB2* and adjacent genes.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations for *SATB2* pathogenic variants have been formally established to date; however, it has been suggested that genitourinary anomalies, cardiac defects, and ectodermal changes (other than dental) are more common (or exclusively present) in affected individuals with large deletions involving *SATB2* and adjacent genes [Zarate & Fish 2017].

The number of reported individuals with SAS is still relatively small; genotype-phenotype correlations may emerge as more affected individuals are identified.





**Figure 1.** Facial features of individuals with *SATB2*-associated syndrome caused by intragenic pathogenic variants in *SATB2* (A-D), intragenic deletion of *SATB2* (E), and large deletions that include *SATB2* and other adjacent genes (F-G). Most consistently reported features include thin vermilion of the upper lip, smooth philtrum, long face with prominent chin, and prominent forehead.

## Nomenclature

The name Glass syndrome was suggested after a report of a male with a cytogenetically visible 2q32.2-q33.1 deletion that included *SATB2* was published [Glass et al 1989]. *SATB2* was subsequently identified as the gene associated with this syndrome [FitzPatrick et al 2003]. The designation of *SATB2*-associated syndrome (SAS) was recently proposed as a new clinically recognizable syndrome [Döcker et al 2014].

For *SATB2* alterations, however, the existence of multiple designations for a fairly consistent phenotype – regardless of the underlying pathomechanism – has created some confusion particularly for families of affected individuals [Author, personal experience] such that separate social media support groups exist, one for individuals with deletions of *SATB2* and another for individuals with pathogenic intragenic *SATB2* variants. In this review, the authors have documented a consistent phenotype independent of the underlying *SATB2* genetic alteration. When described, phenotypic differences appear to relate (with few exceptions) to differences in severity rather than in the system affected. Therefore, in an attempt to unify the nomenclature and reduce confusion, the authors support use of the term *SATB2*-associated syndrome.

## Prevalence

The prevalence of SAS is not known. However, two recent studies have estimated the frequency of SAS in large cohorts of individuals with undiagnosed intellectual disability / developmental delay at 0.24%-0.3% [Bengani et al 2017, Zarate et al 2018].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SATB2*.

## Differential Diagnosis

In early infancy the diagnosis of SAS can be particularly difficult to appreciate when developmental delay, hypotonia, feeding difficulties, and palatal issues are the only observable features. During infancy and early childhood, many children with SAS have been tested for Angelman syndrome and related disorders. Over time, the emergence of dental issues and distinctive behavioral issues along with lack of speech progression should lead clinicians to consider this diagnosis. *SATB2*-associated syndrome should be distinguished from other syndromes that include developmental delay and dental abnormalities, such as KBG syndrome.

**Table 3.** Disorders to Consider in the Differential Diagnosis of *SATB2*-Associated Syndrome (SAS)

Disorder	Gene	MOI	DD / ID & Speech Delay	Craniofacial Dysmorphism / Anomalies	Dental Anomalies	Behavioral Findings	Skeletal/Other
<i>SATB2</i> -associated syndrome (the subject of this <i>GeneReview</i> )	<i>SATB2</i>	AD	Some degree of ID in all known patients; severe DD/ID w/absent speech in ~50%	At least minor facial dysmorphic features in most published individuals. <sup>1</sup> Craniofacial anomalies incl cleft palate, high-arched palate	Most common finding: abnormal shape or size of upper central incisors. Other findings (variably seen): crowding, hypodontia, diastema, delayed primary dentition	Jovial or friendly personality, autistic tendencies, agitation or aggressive outbursts, hyperactivity, sleeping difficulties	Pectus deformities, kyphosis/lordosis, scoliosis, osteopenia
<a href="#">Angelman syndrome</a>	See footnote 2.	See footnote 2.	Severe DD or ID, severe speech impairment	Typically not assoc w/anomalies as seen in SAS	Typically not assoc w/ findings seen in SAS	Unique behavior w/inappropriate happy demeanor incl frequent laughing, smiling, excitability	Typically not assoc w/ anomalies seen in SAS



Table 3. continued from previous page.

Disorder	Gene	MOI	DD / ID & Speech Delay	Craniofacial Dysmorphism / Anomalies	Dental Anomalies	Behavioral Findings	Skeletal/Other
KBG syndrome	ANKRD11	AD	DD, ID	Facial dysmorphic features incl triangular face, low anterior & posterior hairlines, bushy eyebrows, large prominent ears, anteverted nostrils w/ hypoplastic alae nasi. Palatal anomalies not common	Macrodontia of upper central incisors	ASD, ADHD, anxiety, temper tantrums, compulsive & aggressive behaviors	Bone age often delayed; short stature prevalent; hand anomalies

AD = autosomal dominant; ADHD = attention deficit/hyperactivity disorder; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

1. Consistent features associated with larger 2q33.1 deletions include: prominent forehead or high anterior hairline, thin vermilion of the upper lip, low-set ears, long face. Consistent features associated with pathogenic missense, nonsense, and frameshift variants include: long and flat philtrum and thin vermilion of the upper lip [Zarate & Fish 2017; Author, personal observation].

2. Angelman syndrome is caused by disruption of maternally imprinted *UBE3A* located within the 15q11.2-q13 Angelman syndrome/Prader-Willi syndrome (AS/PWS) region. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function.

## Management

### Evaluations and Referrals Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SATB2-associated syndrome (SAS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended:

Table 4. Recommended Evaluations and Referrals Following Initial Diagnosis of SATB2-Associated Syndrome

Organ System	Evaluation	Comment
Neurologic	Developmental	W/specific focus on nonverbal language ability
	Neuropsychological assessment	For behavioral problems
	EEG if seizures suspected	Referral to neurologist for seizure disorder management
	Consider head MRI if seizures present	
Oropharynx	Examination for palatal anomalies	Referral to craniofacial team or otolaryngologist as needed
	Dental, for abnormal tooth shape, number, & location	Referral to dentist
Gastrointestinal	Feeding	Consider videofluoroscopic swallowing study
	Growth (weight, length/height, growth velocity)	Consider referral to endocrinologist as needed

Table 4. continued from previous page.

Organ System	Evaluation	Comment
<b>Musculoskeletal</b>	Assessment for skeletal anomalies (e.g., scoliosis, kyphosis, tibial bowing)	Referral to orthopedist as needed
	Assessment for ↓ bone mineralization (e.g., recurrent fractures, ↑ alkaline phosphatase levels)	Consider bone mineral density scan
<b>Genitourinary</b>	For undescended testes, inguinal hernias, & hypospadias in males	
<b>Eyes</b>	Ophthalmology for strabismus & refractive errors	Incl visual acuity & dilated fundus examination
<b>Cardiac</b>	Consider echocardiogram	In those w/larger deletions incl <i>SATB2</i> & adjacent genes
<b>Miscellaneous/ Other</b>	Physical therapy	If hypotonia present
	Consultation w/clinical geneticist &/or genetic counselor	

## Treatment of Manifestations

Treatment is symptomatic; no specific therapy is available. The following are appropriate interventions [Zarate & Fish 2017].

Table 5. Treatment of Manifestations in Individuals with *SATB2*-Associated Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / intellectual disability	Early referral for developmental support / special education	See text following table
Dental anomalies	As per routine	
Cleft palate, bifid uvula, micrognathia	Management by cleft/craniofacial team; surgical correction of cleft palate	
Feeding difficulties	Nutritional support	Referral to gastroenterologist for those w/ persistent issues
Sleep disturbance	Sleep hygiene healthy habits & potential medical management as needed	
Scoliosis, tibial bowing, joint contractures	Standard treatment per orthopedist	
Osteopenia	Treatment remains unclear	Denosumab used in 1 affected patient, pamidronate infusions used in 2 patients; long-term response to these treatments unknown [Boone et al 2016, Zarate et al 2018]
Seizure disorder	Standard treatment per neurologist	
Undescended testes, inguinal hernia, hypospadias	Standard treatment per urologist	
Strabismus & refractive error	Standard treatment per ophthalmologist	
Congenital heart defects	Standard therapy per cardiologist	

## 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 by country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

**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.

### Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

**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.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

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

## Motor Dysfunction

### Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

**Oral motor dysfunction.** Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

**Communication issues.** Consider evaluation for alternative means of communication (e.g., [Augmentative and Alternative Communication](#) [AAC]) for individuals who have expressive language difficulties.

## Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications when necessary.

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

## Surveillance

Periodic reevaluation by a clinical geneticist to apprise the family of new developments and/or recommendations is suggested. Surveillance may also include the following [Zarate & Fish 2017]:

**Table 6.** Recommended Surveillance for Individuals with SATB2-Associated Syndrome

System/Concern	Evaluation	Frequency/Comment
<b>Neurologic</b>	Developmental assessments	Routine intervals to adjust therapies & adapt educational needs
	By neurologist	Per routine for individuals w/epilepsy
<b>ENT/Mouth</b>	Dentistry/orthodontics; audiology	Routine intervals
<b>Growth</b>	Evaluation of nutritional status & growth	At each visit
<b>Respiratory</b>	Sleep study (if history of sleep disturbance)	As needed
<b>Musculoskeletal</b>	Evaluate for scoliosis & spine deformities	At each visit
	Screening for osteopenia	
<b>Eyes</b>	Ophthalmology to screen for refractive errors & strabismus	Routine intervals

## 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](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

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

## Mode of Inheritance

SATB2-associated syndrome (SAS) is inherited in an autosomal dominant manner. Almost all affected individuals reported to date have a *de novo* genetic alteration.

## Risk to Family Members

### Parents of a proband

- Almost all probands with SAS reported in the literature to date have the disorder as a result of a *de novo* genetic alteration (as evidenced by either parental genetic testing or absence of clinical features in the parents).
- Recommendations for the evaluation of parents of an individual with SAS include genetic testing capable of detecting the *SATB2* intragenic pathogenic variant, 2q33.1 deletion, or chromosome translocation identified in the proband.
- If the genetic alteration identified in the proband cannot be detected in either parent, the most likely explanation is that the genetic alteration is a *de novo* pathogenic variant in the proband. Apparent parental germline mosaicism has been observed in several families.
  - A splice variant identified in two brothers with SAS was not detected in the leukocyte DNA of either parent [Bengani et al 2017].
  - Low-level mosaicism for a *SATB2* intragenic pathogenic variant was detected by exome sequencing in the unaffected father of a child with SAS [Author, unpublished].
  - A 2q33.1 duplication (including *SATB2*) identified in two sibs with SAS was not detected in either parent [Author, unpublished].

### Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- Almost all affected individuals reported in the literature to date have had a *de novo* genetic alteration, suggesting a low risk to sibs. However, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism (see **Parents of a proband**).

### Offspring of a proband

- Each child of an individual with a 2q33.1 deletion or *SATB2* pathogenic variant has a 50% chance of inheriting the genetic alteration. Risk to offspring of an individual with a chromosome translocation depends on the specific structural variant.
- To date, individuals with SAS are not known to reproduce.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the SAS-related genetic alteration, his or her 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 the parents of an affected child.

**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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.



## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the 2q33.1 deletion, *SATB2* intragenic pathogenic variant, or chromosome translocation has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

**Ultrasound examination.** Many features of SAS may not be readily identified on ultrasound examination.

## 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](#).*

- **SATB2 Connect**

Australia

**Email:** [hello@satb2.org.au](mailto:hello@satb2.org.au)

[satb2.org.au](http://satb2.org.au)

- **SATB2 Gene Foundation, Inc.**

**Phone:** 678-832-9133

**Email:** [info@satb2gene.org](mailto:info@satb2gene.org)

[satb2gene.org](http://satb2gene.org)

- **SATB2 Portal**

*An interactive resource about SATB2-associated syndrome (SAS) for families, clinicians and researchers.*

**Email:** [yazarate@uams.edu](mailto:yazarate@uams.edu)

[satb2-portal.broadinstitute.org](http://satb2-portal.broadinstitute.org)

- **American Cleft Palate-Craniofacial Association**

**Phone:** 919-933-9044

[acpa-cpf.org](http://acpa-cpf.org)

- **Unique: Understanding Rare Chromosome and Gene Disorders**

United Kingdom

**Phone:** +44 (0) 1883 723356

**Email:** [info@rarechromo.org](mailto:info@rarechromo.org)

[rarechromo.org](http://rarechromo.org)

## 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.** SATB2-Associated Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

<a href="#">SATB2</a>	<a href="#">2q33.1</a>	<a href="#">DNA-binding protein SATB2</a>	<a href="#">SATB2 @ LOVD</a>	<a href="#">SATB2</a>	<a href="#">SATB2</a>
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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 SATB2-Associated Syndrome ([View All in OMIM](#))

<a href="#">608148</a>	<a href="#">SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN 2; SATB2</a>
<a href="#">612313</a>	<a href="#">GLASS SYNDROME; GLASS</a>

**Gene structure.** The *SATB2* transcript variant ([NM\\_001172509](#)) consists of 11 exons and a processed mRNA transcript of 5730 bp sequence. Two alternate transcripts, [NM\\_015265](#) and [NM\\_001172517](#), consist of 12 exons with processed mRNAs of 5306 bp and 5326 bp, respectively. For a detailed summary of gene and protein information, see Table A.

**Pathogenic variants.** In total, approximately 40 distinct intragenic pathogenic variants have been reported in 46 probands including missense, frameshift, nonsense, and splice site variants and a deletion-insertion. Most variants lead to a premature stop codon and a truncated protein [Leoyklang et al 2007]. A nonsense variant in the last exon (p.Glu692Ter) was shown to result in 692-amino-acid C-terminally truncated version of *SATB2* that escape nonsense-mediated decay [Bengani et al 2017].

Pathogenic genomic imbalances resulting from large-scale chromosome 2q33.1 deletions ranging from 2.4 Mb to 26.3 Mb have been reported.

Of interest, most reported pathogenic missense variants are located in the core of the CUT domain and are expected to result in loss of DNA binding activity given the predicted effect on the helical structure of the domain. [Bengani et al 2017, Zarate et al 2017]. A few recurrent variants (p.Arg239Ter, p.Arg283Ter, p.Arg389Cys, p.Arg429Gln, p.Arg459Ter) have been reported.

**Table 7.** *SATB2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.346+2T>G	p.?	NM_015265.3 NP_056080.1
c.715C>T	p.Arg239Ter	
c.748C>T	p.Gln250Ter	
c.847C>T	p.Arg283Ter	
c.1142T>G	p.Val381Gly	
c.1165C>T	p.Arg389Cys	
c.1171C>T	p.Gln391Ter	
c.1186G>C	p.Glu396Gln	
c.1286G>A	p.Arg429Gln	
c.1375C>T	p.Arg459Ter	
c.1945dupT	p.Ser649PhefsTer40	
c.2018dupA	p.His673GlnfsTer16	
c.2074G>T	p.Glu692Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** *SATB2* encodes special AT-rich sequence-binding protein 2 (SATB2) a 733-amino-acid protein with two CUT domains and a homeodomain [FitzPatrick et al 2003]. These functional domains are highly conserved in vertebrates [FitzPatrick et al 2003, Sheehan-Rooney et al 2010].

SATB2 is a transcription factor that binds to nuclear matrix-attachment regions (MARs). MARs are DNA regulatory sequences that are involved in chromatin organization and long-range enhancer function. SATB2 binds MARs and activates transcription of multiple genes simultaneously [Dobrev et al 2003, Gyorgy et al 2008]. In this context, SATB2 can be considered a master regulator of gene regulatory networks (GRNs) critical to the development of multiple tissues including the jaw, brain, and skeleton – tissues affected in humans with SAS [Britanova et al 2006, Dobrev et al 2006, Zarate et al 2015].

**Abnormal gene product.** Haploinsufficiency of SATB2 causes the SAS phenotype [Rosenfeld et al 2009, Leoyklang et al 2013]. In mice, *Satb2* has been shown to act in a dosage-dependent manner [Britanova et al 2006]. Insufficient SATB2 dosage may result in the failure to activate specific genetic programs critical to development. Despite the relatively consistent phenotype of individuals with SAS, variability in the severity of clinical findings has been noted.

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## Chapter Notes

### Author Notes

Website dedicated to SATB2-associated syndrome (SAS): [www.satb2gene.com](http://www.satb2gene.com)

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