SATB2 Syndrome (Glass syndrome)

https://www.ncbi.nlm.nih.gov/books/NBK458647/

SummaryClinical 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 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.

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DiagnosisNo formal clinical diagnostic criteria have been established for SATB2-associated syndrome.Suggestive FindingsSATB2-associated syndrome (SAS) should be suspected in individuals with the following major features [Zarate & Fish 2017]:Significant neurodevelopmental disorders in all affected individualsInfantile 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 aggressivenessPalatal anomalies: cleft palate, bifid uvula, and high-arched palateDental anomalies: prominent upper incisors and other anomaliesSome 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 DiagnosisThe 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 TestingChromosomal 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

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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].

Suggestive FindingsSATB2-associated syndrome (SAS) should be suspected in individuals with the following major features [Zarate & Fish 2017]:Significant neurodevelopmental disorders in all affected individualsInfantile 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 aggressivenessPalatal anomalies: cleft palate, bifid uvula, and high-arched palateDental anomalies: prominent upper incisors and other anomaliesSome 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.

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Establishing the DiagnosisThe 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

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

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].

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 CharacteristicsClinical DescriptionSATB2-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 SyndromeView in own windowFinding% of Affected Individuals 1Developmental delay / intellectual disability100%Speech delay95%Craniofacial dysmorphism89%Dental anomalies72%Behavioral issues55%Cleft palate50%Abnormal brain MRI49%Micrognathia42%Hypotonia42%Feeding difficulties39%Growth restriction34%Skeletal anomalies32%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

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Genetically Related (Allelic) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with germline pathogenic variants in SATB2.

Differential DiagnosisIn 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)View in own windowDisorderGeneMOIDD / ID &Speech DelayCraniofacial Dysmorphism / AnomaliesDental AnomaliesBehavioral FindingsSkeletal/OtherSATB2-associated syndrome (the subject of this GeneReview)

SATB2

ADSome 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. 1Craniofacial anomalies incl cleft palate, high-arched palateMost common finding: abnormal shape or size of upper central incisors.Other findings (variably seen): crowding, hypodontia, diastema, delayed primary dentitionJovial or friendly personality, autistic tendencies, agitation or aggressive outbursts, hyperactivity, sleeping difficultiesPectus deformities, kyphosis/lordosis, scoliosis, osteopenia

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See footnote 2.See footnote 2.Severe DD or ID, severe speech impairmentTypically not assoc w/anomalies as seen in SASTypically not assoc w/findings seen in SASUnique behavior w/inappropriate happy demeanor incl frequent laughing, smiling, excitabilityTypically not assoc w/anomalies seen in SAS

KBG syndrome

ANKRD11

ADDD, IDFacial dysmorphic features incl triangular face, low anterior & posterior hairlines, bushy eyebrows, large prominent ears, anteverted nostrils w/hypoplastic alae nasi.Palatal anomalies not commonMacrodontia of upper central incisorsASD, ADHD, anxiety, temper tantrums, compulsive & aggressive behaviorsBone age often delayed; short stature prevalent; hand anomaliesAD = autosomal dominant; ADHD = attention deficit/hyperactivity disorder; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance1. 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.

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ManagementEvaluations and Referrals Following Initial DiagnosisTo 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 SyndromeView in own windowOrgan SystemEvaluationComment

Neurologic

DevelopmentalW/specific focus on nonverbal language abilityNeuropsychological assessmentFor behavioral problemsEEG if seizures suspectedReferral to neurologist for seizure disorder managementConsider head MRI if seizures present

Oropharynx

Examination for palatal anomaliesReferral to craniofacial team or otolaryngologist as neededDental, for abnormal tooth shape, number, & locationReferral to dentist

Gastrointestinal

FeedingConsider videofluoroscopic swallowing studyGrowth (weight, length/height, growth velocity)Consider referral to endocrinologist as needed

Musculoskeletal

Assessment for skeletal anomalies (e.g., scoliosis, kyphosis, tibial bowing)Referral to orthopedist as neededAssessment for ↓ bone mineralization (e.g., recurrent fractures, ↑ alkaline phosphatase levels)Consider bone mineral density scan

Genitourinary

For undescended testes, inguinal hernias, & hypospadias in males

Eyes

Ophthalmology for strabismus & refractive errorsIncl visual acuity & dilated fundus examination

Cardiac

Consider echocardiogramIn those w/larger deletions incl SATB2 & adjacent genes

Miscellaneous/

Other

Physical therapyIf hypotonia presentConsultation w/clinical geneticist &/or genetic counselorTreatment of ManifestationsTreatment 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/OtherDevelopmental delay /intellectual disabilityEarly referral for developmental support / special educationSee text following tableDental anomaliesAs per routineCleft palate, bifid uvula, micrognathiaManagement by cleft/craniofacial team; surgical correction of cleft palateFeeding difficultiesNutritional supportReferral to gastroenterologist for those w/persistent issuesSleep disturbanceSleep hygiene healthy habits & potential medical management as neededScoliosis, tibial bowing, joint contracturesStandard treatment per orthopedistOsteopeniaTreatment remains unclearDenosumab 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 disorderStandard treatment per neurologistUndescended testes, inguinal hernia, hypospadiasStandard treatment per urologistStrabismus & refractive errorStandard treatment per ophthalmologistCongenital heart defectsStandard therapy per cardiologistDevelopmental Delay / Intellectual Disability Management IssuesThe 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 ConcernsConsultation 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.SurveillancePeriodic 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 SyndromeView in own windowSystem/ConcernEvaluationFrequency/Comment

Neurologic

Developmental assessmentsRoutine intervals to adjust therapies & adapt educational needsBy neurologistPer routine for individuals w/epilepsy

ENT/Mouth

Dentistry/orthodontics; audiologyRoutine intervals

Growth

Evaluation of nutritional status & growthAt each visit

Respiratory

Sleep study (if history of sleep disturbance)As needed

Musculoskeletal

Evaluate for scoliosis & spine deformitiesAt each visitScreening for osteopenia

Eyes

Ophthalmology to screen for refractive errors & strabismusRoutine intervalsEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Evaluations and Referrals Following Initial DiagnosisTo 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 SyndromeView in own windowOrgan SystemEvaluationComment

Neurologic

DevelopmentalW/specific focus on nonverbal language abilityNeuropsychological assessmentFor behavioral problemsEEG if seizures suspectedReferral to neurologist for seizure disorder managementConsider head MRI if seizures present

Oropharynx

Examination for palatal anomaliesReferral to craniofacial team or otolaryngologist as neededDental, for abnormal tooth shape, number, & locationReferral to dentist

Gastrointestinal

FeedingConsider videofluoroscopic swallowing studyGrowth (weight, length/height, growth velocity)Consider referral to endocrinologist as needed

Musculoskeletal

Assessment for skeletal anomalies (e.g., scoliosis, kyphosis, tibial bowing)Referral to orthopedist as neededAssessment for ↓ bone mineralization (e.g., recurrent fractures, ↑ alkaline phosphatase levels)Consider bone mineral density scan

Genitourinary

For undescended testes, inguinal hernias, & hypospadias in males

Eyes

Ophthalmology for strabismus & refractive errorsIncl visual acuity & dilated fundus examination

Cardiac

Consider echocardiogramIn those w/larger deletions incl SATB2 & adjacent genes

Miscellaneous/

Other

Physical therapyIf hypotonia presentConsultation w/clinical geneticist &/or genetic counselor

Table 4. Recommended Evaluations and Referrals Following Initial Diagnosis of SATB2-Associated SyndromeView in own windowOrgan SystemEvaluationComment

Neurologic

DevelopmentalW/specific focus on nonverbal language abilityNeuropsychological assessmentFor behavioral problemsEEG if seizures suspectedReferral to neurologist for seizure disorder managementConsider head MRI if seizures present

Oropharynx

Examination for palatal anomaliesReferral to craniofacial team or otolaryngologist as neededDental, for abnormal tooth shape, number, & locationReferral to dentist

Gastrointestinal

FeedingConsider videofluoroscopic swallowing studyGrowth (weight, length/height, growth velocity)Consider referral to endocrinologist as needed

Musculoskeletal

Assessment for skeletal anomalies (e.g., scoliosis, kyphosis, tibial bowing)Referral to orthopedist as neededAssessment for ↓ bone mineralization (e.g., recurrent fractures, ↑ alkaline phosphatase levels)Consider bone mineral density scan

Genitourinary

For undescended testes, inguinal hernias, & hypospadias in males

Eyes

Ophthalmology for strabismus & refractive errorsIncl visual acuity & dilated fundus examination

Cardiac

Consider echocardiogramIn those w/larger deletions incl SATB2 & adjacent genes

Miscellaneous/

Other

Physical therapyIf hypotonia presentConsultation w/clinical geneticist &/or genetic counselor

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

Organ SystemEvaluationComment

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Cardiac

Consider echocardiogramIn those w/larger deletions incl SATB2 & adjacent genes

Miscellaneous/

Other

Physical therapyIf hypotonia presentConsultation w/clinical geneticist &/or genetic counselor

Treatment of ManifestationsTreatment 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 SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/OtherDevelopmental delay /intellectual disabilityEarly referral for developmental support / special educationSee text following tableDental anomaliesAs per routineCleft palate, bifid uvula, micrognathiaManagement by cleft/craniofacial team; surgical correction of cleft palateFeeding difficultiesNutritional supportReferral to gastroenterologist for those w/persistent issuesSleep disturbanceSleep hygiene healthy habits & potential medical management as neededScoliosis, tibial bowing, joint contracturesStandard treatment per orthopedistOsteopeniaTreatment remains unclearDenosumab 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 disorderStandard treatment per neurologistUndescended testes, inguinal hernia, hypospadiasStandard treatment per urologistStrabismus & refractive errorStandard treatment per ophthalmologistCongenital heart defectsStandard therapy per cardiologistDevelopmental Delay / Intellectual Disability Management IssuesThe 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 ConcernsConsultation 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.

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Treatment of Manifestations in Individuals with SATB2-Associated Syndrome

ManifestationConcernTreatmentConsiderationsOtherDevelopmental delay /intellectual disabilityEarly referral for developmental support / special educationSee text following tableDental anomaliesAs per routineCleft palate, bifid uvula, micrognathiaManagement by cleft/craniofacial team; surgical correction of cleft palateFeeding difficultiesNutritional supportReferral to gastroenterologist for those w/persistent issuesSleep disturbanceSleep hygiene healthy habits & potential medical management as neededScoliosis, tibial bowing, joint contracturesStandard treatment per orthopedistOsteopeniaTreatment remains unclearDenosumab 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 disorderStandard treatment per neurologistUndescended testes, inguinal hernia, hypospadiasStandard treatment per urologistStrabismus & refractive errorStandard treatment per ophthalmologistCongenital heart defectsStandard therapy per cardiologist

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Ages 5-21 years

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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.

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Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

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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.

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SurveillancePeriodic 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 SyndromeView in own windowSystem/ConcernEvaluationFrequency/Comment

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Dentistry/orthodontics; audiologyRoutine intervals

Growth

Evaluation of nutritional status & growthAt each visit

Respiratory

Sleep study (if history of sleep disturbance)As needed

Musculoskeletal

Evaluate for scoliosis & spine deformitiesAt each visitScreening for osteopenia

Eyes

Ophthalmology to screen for refractive errors & strabismusRoutine intervals

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Eyes

Ophthalmology to screen for refractive errors & strabismusRoutine intervals

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.Mode of InheritanceSATB2-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 TestingMolecular 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.

Mode of InheritanceSATB2-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

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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].

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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,

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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.

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.

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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).

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.

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.

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.

Prenatal Testing and Preimplantation Genetic TestingMolecular 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 Portal

An interactive resource about SATB2-associated syndrome (SAS) for families, clinicians and researchers.
Email: yazarate@uams.edu
satb2-portal.broadinstitute.org

American Cleft Palate-Craniofacial Association
Phone: 919-933-9044

www.acpa-cpf.org

Unique: Understanding Rare Chromosome and Gene Disorders

United KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

SATB2

2q33.1

DNA-binding protein SATB2

SATB2 @ LOVD

SATB2

SATB2

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) View in own window

608148SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN 2; SATB2

612313GLASS SYNDROME; GLASSGene 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 GeneReviewView in own windowDNA Nucleotide ChangePredicted Protein ChangeReference Sequencesc.346+2T>Gp.? NM_015265.3

NP_056080.1

c.715C>Tp.Arg239Terc.748C>Tp.Gln250Terc.847C>Tp.Arg283Terc.1142T>Gp.Val381Glyc.1165C>Tp.Arg389Cysc.1171C>Tp.Gln391Terc.1186G>Cp.Glu396Glnc.1286G>Ap.Arg429Glnc.1375C>Tp.Arg459Terc.1945dupTp.Ser649PhefsTer40c.2018dupAp.His673GlnfsTer16c.2074G>Tp.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). 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 [Dobreva 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, Dobreva 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.

Table A.SATB2-Associated Syndrome: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

SATB2

2q33.1

DNA-binding protein SATB2

SATB2 @ LOVD

SATB2

SATB2

Data are compiled from the following standard references: gene from

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chromosome locus from

OMIM;

protein from UniProt.

For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

SATB2-Associated Syndrome: Genes and Databases

GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

SATB2

2q33.1

DNA-binding protein SATB2

SATB2 @ LOVD

SATB2

SATB2

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.

Data are compiled from the following standard references: gene from

HGNC;

chromosome locus from

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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) View in own window

608148SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN 2; SATB2

612313GLASS SYNDROME; GLASS

OMIM Entries for SATB2-Associated Syndrome (View All in OMIM)

608148SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN 2; SATB2

612313GLASS SYNDROME; GLASS

Table 7. SATB2 Pathogenic Variants Discussed in This GeneReviewView in own windowDNA Nucleotide ChangePredicted Protein ChangeReference Sequencesc.346+2T>Gp.?

NM_015265.3

NP_056080.1

c.715C>Tp.Arg239Terc.748C>Tp.Gln250Terc.847C>Tp.Arg283Terc.1142T>Gp.Val381Glyc.1165C>Tp.Arg389Cysc.1171C>Tp.Gln391Terc.1186G>Cp.Glu396Glnc.1286G>Ap.Arg429Glnc.1375C>Tp.Arg459Terc.1945dupTp.Ser649PhefsTer40c.2018dupAp.His673GlnfsTer16c.2074G>Tp.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). See Quick Reference for an explanation of nomenclature.

SATB2 Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide ChangePredicted Protein ChangeReference Sequencesc.346+2T>Gp.?

NM_015265.3

NP_056080.1

c.715C>Tp.Arg239Terc.748C>Tp.Gln250Terc.847C>Tp.Arg283Terc.1142T>Gp.Val381Glyc.1165C>Tp.Arg389Cysc.1171C>Tp.Gln391Terc.1186G>Cp.Glu396Glnc.1286G>Ap.Arg429Glnc.1375C>Tp.Arg459Terc.1945dupTp.Ser649PhefsTer40c.2018dupAp.His673GlnfsTer16c.2074G>Tp.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). See Quick Reference for an explanation of nomenclature.

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