U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Gallagher ER, Ratisoontorn C, Cunningham ML. Saethre-Chotzen Syndrome. 2003 May 16 [Updated 2019 Jan 24]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Saethre-Chotzen Syndrome

Synonym: Acrocephalosyndactyly Type III

Emily R Gallagher, MD, MPH,[1] Chootima Ratisoontorn, DDS, PhD,[2] and Michael L Cunningham, MD, PhD[3]

Created: May 16, 2003; Updated: January 24, 2019.

Summary

Clinical characteristics

Classic Saethre-Chotzen syndrome (SCS) is characterized by coronal synostosis (unilateral or bilateral), facial asymmetry (particularly in individuals with unicoronal synostosis), strabismus, ptosis, and characteristic appearance of the ear (small pinna with a prominent superior and/or inferior crus). Syndactyly of digits two and three of the hand is variably present. Cognitive development is usually normal, although those with a large genomic deletion are at an increased risk for intellectual challenges. Less common manifestations of SCS include other skeletal findings (parietal foramina, vertebral segmentation defects, radioulnar synostosis, maxillary hypoplasia, ocular hypertelorism, hallux valgus, duplicated or curved distal hallux), hypertelorism, palatal anomalies, obstructive sleep apnea, increased intracranial pressure, short stature, and congenital heart malformations.

Diagnosis/testing

The diagnosis of SCS is established in a proband with typical clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *TWIST1* identified by molecular genetic testing.

Management

Treatment of manifestations: Ongoing management by an established craniofacial team which may include cranioplasty in the first year of life and midface surgery in childhood as needed for dental malocclusion, swallowing difficulties, and respiratory problems. If a cleft palate is present, surgical repair usually follows cranioplasty. As needed: orthodontic treatment and/or orthognathic surgery at the completion of facial growth; developmental intervention; routine treatment of hearing loss; ophthalmologic evaluation and, if ptosis is present, intervention to prevent amblyopia, with surgical repair during early childhood as needed.

Author Affiliations: 1 Children's Craniofacial Center Seattle Children's Hospital; Department of Pediatrics University of Washington, Seattle, Washington; Email: egalla@uw.edu. 2 Department of Operative Dentistry Chulalongkorn University, Bangkok, Thailand. 3 Medical Director, Children's Craniofacial Center Seattle Children's Hospital; Departments of Pediatrics, Biological Structure, Pediatric Dentistry, and Oral Biology University of Washington Schools of Medicine and Dentistry, Seattle, Washington; Email: mcunning@uw.edu.

Surveillance: Annual ophthalmologic evaluation for papilledema; brain imaging for additional evaluation when there is evidence of increased intracranial pressure; clinical examination for facial asymmetry as needed; annual speech evaluation starting at age 12 months in those with a cleft palate. Audiology evaluations every 6-12 months; annual clinical evaluation for sleep-disordered breathing and developmental delays.

Agents/circumstances to avoid: If cervical spine abnormality with instability is present in an individual, activities that put the spine at risk should be limited.

Genetic counseling

SCS is inherited in an autosomal dominant manner. Many individuals diagnosed with SCS have an affected parent; the proportion of cases caused by a *de novo* pathogenic variant is unknown. The family history of some individuals diagnosed with SCS may appear to be negative because of failure to recognize the disorder in family members (wide phenotypic variability is observed within families with SCS) or reduced penetrance. Each child of an individual with SCS has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the pathogenic variant has been identified in the family.

Diagnosis

Suggestive Findings

Saethre-Chotzen syndrome (SCS) **should be suspected** in individuals with a combination of the following features:

- Craniosynostosis (premature fusion of one or more sutures of the calvarium)
  - The coronal suture is the most commonly affected, although any or all sutures can be affected.
  - Craniosynostosis often presents with an abnormal skull shape (e.g., brachycephaly [short, broad skull], acrocephaly [tall skull], anterior plagiocephaly [flat skull]).
- Low frontal hairline, ptosis, strabismus, facial asymmetry
- Small ears with a prominent crus, hearing loss
- Parietal foramina
- Vertebral anomalies
- Limb anomalies [Trusen et al 2003] including the following:
  - Partial cutaneous syndactyly of the second and third digits of the hand

    Note: Although the degree of syndactyly or its presence is highly variable, it is effectively diagnostic in the presence of the first three features: craniosynostosis, low frontal hairline (...), and small ears (...).
  - Radioulnar synostosis
  - Brachydactyly
  - Hallux valgus
  - Duplicated distal phalanx of the hallux
  - Triangular epiphyses of the hallux

Establishing the Diagnosis

The diagnosis of SCS **is established** in a proband with typical clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *TWIST1* identified by molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of SCS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with craniosynostosis or those in whom the diagnosis of SCS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of SCS, molecular genetic testing approaches can include **single-gene testing**, **chromosomal microarray analysis (CMA)**, or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TWIST1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TWIST1*) that cannot be detected by sequence analysis.

  Note: The risk for developmental delay with large deletions involving *TWIST1* is approximately 90%, or eight times greater than with intragenic pathogenic variants [Cai et al 2003a, Fryssira et al 2011]; therefore, CMA should be considered in individuals with features of SCS and developmental delay.
- **A craniosynostosis multigene panel** that includes *TWIST1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For 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.

Note: A **karyotype** should be considered if a diagnosis of SCS is strongly suspected despite normal results on molecular testing, since chromosome rearrangements disrupting *TWIST1* (e.g., translocations, inversions, or

ring chromosome 7 involving 7p21) have been reported in individuals with SCS with atypical findings, including developmental delay [Shetty et al 2007, Touliatou et al 2007].

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by craniosynostosis, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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.

Table 1. Molecular Genetic Testing Used in Saethre-Chotzen Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TWIST1	Sequence analysis [3]	72% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	23% [4]
	CMA [6, 7]	23% [4, 8]
	Karyotype	5% [9]

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. Gripp et al [2000], Cai et al [2003a], de Heer et al [2005], Kress et al [2006], Foo et al [2009], Roscioli et al [2013], Paumard-Hernández et al [2015], The Human Gene Mutation Database
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. 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 (e.g., those described by Cai et al [2003a] or Tahiri et al [2015]) may not be detected by these methods.
6. Note that most reported deletions and duplications are large enough to likely be detected by CMA; however, gene-targeted deletion/duplication analysis does have a higher resolution.
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TWIST1*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 7p21 region. CMA designs in current clinical use target the 7p21 region.
8. CMA should be considered in individuals with features of SCS and developmental delay.
9. Cai et al [2003a], Shetty et al [2007], Touliatou et al [2007], The Human Gene Mutation Database

Clinical Characteristics

Clinical Description

With the ability to detect pathogenic variants in *TWIST1*, the phenotypic spectrum of Saethre-Chotzen syndrome (SCS) is increasingly broad. Both milder and more severe phenotypes are recognized.

Classic Saethre-Chotzen syndrome is characterized by coronal synostosis (unilateral or bilateral), facial asymmetry (particularly in individuals with unicoronal synostosis), strabismus, ptosis, and characteristic

appearance of the ear (small pinna with a prominent superior and/or inferior crus). Partial cutaneous syndactyly of digits two and three of the hand is common and may be subtle.

- It is important to note that other cranial sutures (i.e., sagittal, lambdoid, and metopic) can undergo premature fusion in individuals with SCS.
- However, individuals with SCS with no evidence of pathologic suture fusion have been described; thus, craniosynostosis is not an obligatory finding.
- There may be a family history of abnormal skull shape, but affected relatives may not have been diagnosed with a craniosynostosis syndrome.
- Whereas mild-to-moderate developmental delay and intellectual disability have been reported in some individuals with SCS, normal cognitive development is more common. However, those with a large genomic deletion involving *TWIST1* are at an increased risk for intellectual challenges. See Genotype-Phenotype Correlations.

Findings variably present include the following:

- Maxillary hypoplasia, ocular hypertelorism, and lacrimal duct stenosis
- Palatal anomalies, including narrow palate, bifid uvula, and cleft palate [Stoler et al 2009]
- Conductive, mixed, and profound sensorineural hearing loss [Lee et al 2002]
- Obstructive sleep apnea (OSA). Mild OSA, defined by changes in nocturnal oxygen saturation, was diagnosed in 5% of individuals with SCS in one recent study [de Jong et al 2010].
- Increased intracranial pressure (ICP). A recent study found that 21% of individuals with SCS had increased ICP based on the finding of papilledema that persisted more than one year after surgery [de Jong et al 2010].
- Skeletal concerns such as segmentation defects of the vertebrae, parietal foramina, radioulnar synostosis, duplication of the distal hallux, and hallux valgus
- Congenital heart malformation
- Short stature

A more severe phenotype, indistinguishable from that of Baller-Gerold syndrome (BGS) (see Differential Diagnosis), has been observed. This phenotype includes severe craniosynostosis, radial ray hypoplasia/agenesis, vertebral segmentation defects, and other anomalies [Gripp et al 1999, Seto et al 2001]. Two individuals with clinical features consistent with BGS were found to have novel *TWIST1* pathogenic variants.

Genotype-Phenotype Correlations

Most pathogenic variants causing SCS are intragenic and cause haploinsufficiency of the protein product, Twist-related protein 1. No specific genotype-phenotype correlations have been identified except for the following.

The vast majority of individuals with single-nucleotide variants have normal intelligence. The risk for developmental delay in individuals with deletions involving *TWIST1* is approximately 90%, or eightfold greater than in individuals with intragenic pathogenic variants [Cai et al 2003a]; individuals with a *TWIST1* deletion and normal development have been reported [de Heer et al 2005, Kress et al 2006].

Penetrance

Precise penetrance data are not available; however, wide phenotypic variability and incomplete penetrance are well described [Dollfus et al 2002, de Heer et al 2005].

Nomenclature

Robinow-Sorauf syndrome is now known to be caused by pathogenic variants in *TWIST1* [Cai et al 2003b] and is considered part of the mild end of the phenotypic spectrum of SCS.

Prevalence

SCS is one of the more common forms of syndromic craniosynostosis. Prevalence estimates range from 1:25,000 to 1:50,000 [Howard et al1997, Paznekas et al 1998]. It is generally agreed that SCS has approximately the same prevalence as Crouzon syndrome [Cohen &Kreiborg 1992].

Variability of the SCS phenotype may result in underdiagnosis.

Genetically Related (Allelic) Disorders

Pathogenic variants in the TWIST box, the highly conserved C-terminus that binds and inhibits RUNX2 transactivation, are associated with isolated sagittal or unilateral coronal synostosis, not SCS [Kress et al 2006, Seto et al 2007].

Blepharophimosis or ptosis with or without craniosynostosis resembling blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) was reported in association with a *TWIST1* pathogenic variant [De Heer et al 2004].

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Saethre-Chotzen Syndrome (SCS)

Disorder	Gene(s)	MOI	Clinical Features		Comment
			Overlapping	Distinguishing	
Muenke syndrome	*FGFR3* [1]	AD	Unilateral/bilateral coronal synostosis	In SCS: [2] • Low-set frontal hairline • Downward-sloping palpebral fissures • Ptosis • Ear abnormalities • Interdigital webbing In Muenke syndrome: • Higher prevalence of DD (35%, vs 5% in SCS) • SNHL (34%, vs rare in SCS)	Consider testing for *FGFR3* p.Pro250Arg if a *TWIST1* pathogenic variant is not identified in a person w/a presumed diagnosis of SCS.
Isolated unilateral coronal synostosis (IUCS) [3, 4] (OMIM PS123100)	*ALX4* *ERF* *MSX2* *SMAD6* *TCF12* *TWIST1* *ZIC1*	AD	If left untreated or incompletely treated, IUCS can → facial asymmetry resembling SCS.	By definition, IUCS is not assoc w/other clinical findings of SCS.	• Coronal synostosis is 2nd most common form of single-suture fusion (after sagittal synostosis). • Isolated coronal fusion is ~10x more common than SCS.

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features		Comment
			Overlapping	Distinguishing	
Baller-Gerold syndrome (BGS)	*RECQL4*	AR	Bilateral coronal craniosynostosis → brachycephaly w/ocular proptosis & flat forehead	In BGS: • Radial ray defect, usually w/oligodactyly (↓ # of digits), aplasia or hypoplasia of the thumb, &/or aplasia or hypoplasia of the radius • Growth restriction • Poikiloderma	Rothmund-Thomson syndrome & RAPADILINO syndrome (OMIM 266280), also caused by *RECQL4* pathogenic variants, have overlapping clinical features w/ BGS.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; SNHL = sensorineural hearing loss

1. Muenke syndrome is defined by the presence of the specific *FGFR3* pathogenic variant c.749C>G, which results in the protein change p.Pro250Arg.

2. In their study of 39 families (71 affected individuals) ascertained on the basis of coronal synostosis, Kress et al [2006] determined that individuals with a *TWIST1* pathogenic variant could be distinguished from those with the *FGFR3* p.Pro250Arg pathogenic variant based on differences in facial features.

3. Isolated coronal synostosis refers to coronal suture fusion with no evidence of other malformations.

4. In an analysis of 186 individuals with isolated single-suture craniosynostosis, 7.5% had at least one rare deletion or duplication found using CMA [Mefford et al 2010].

Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with SCS

Organ System	Evaluation	Comment
Constitutional	Measure height & growth velocity.	If short stature &/or ↓ linear growth velocity, eval by an endocrinologist
Eyes	Ophthalmologic evaluation	Evaluate for ptosis, strabismus, amblyopia, lacrimal duct stenosis, & papilledema as evidence of ↑ ICP.
ENT/Mouth	Evaluate for cleft palate.	If present, assess for feeding ability & growth.
	Audiologic screening for hearing loss	If present, assess for hearing aid.
Cardiovascular	Routine cardiac exam	Refer if suspicion of cardiac disease.
Respiratory	Assess for sleep apnea.	If suspected, refer for polysomnogram.

Table 3. continued from previous page.

Organ System	Evaluation	Comment
Musculoskeletal	Evaluate for craniosynostosis & facial asymmetry.	CT scan if suspected clinically
	Screen for vertebral (particularly cervical) anomalies.	• At age ~2 yrs, ↑ mineralization of vertebrae allows for better interpretation of flexion/extension views of cervical spine in eval for functional instability. • Such screening is appropriate before initiating activities that put the spine at risk (e.g., surgeries w/long duration, gymnastics, football, soccer).
	Examine upper & lower extremities for anomalies.	If suspected, follow up w/radiographic & orthopedic evaluations
Miscellaneous/ Other	Developmental assessment	Esp in those w/chromosome deletion involving *TWIST1*. If delay suspected, refer for early intervention.
	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with SCS

Manifestation	Treatment	Considerations/Other
Craniofacial malformation	Ongoing management by an established craniofacial team	• Typical cranioplasty occurs in 1st yr of life. • In some individuals midfacial surgery is needed during childhood to address dental malocclusion, swallowing difficulties, or respiratory problems. • Orthodontic treatment &/or orthognathic surgery may be required at or near completion of facial growth.
Cleft palate (if present)	Surgical treatment	In most cases, cranioplasty precedes palatal repair.
Ophthalmologic abnormalities	Standard treatment as recommended by ophthalmologist	Ptosis & strabismus should be corrected in early childhood to prevent amblyopia, either w/patching or surgery. If papilledema is detected, consider cranioplasty.
Hearing loss	Treated in standard manner	
Developmental delay	Early intervention &/or special education as appropriate	

Surveillance

Table 5. Recommended Surveillance for Individuals with SCS

Medical Concern	Evaluation	Frequency
Increased intracranial pressure (ICP)	• Ophthalmologic evaluation • Brian imaging (MRI or CT scan)	• Annual, if synostosis is not treated • If ↑ ICP a concern, perform imaging (preferably MRI) for additional assessment
Craniofacial asymmetry	• Clinical exam • Preoperative CT scan	As needed
Cleft palate	Speech evaluations	• Annual starting at age 12 mos • Frequency after age 6 yrs based on symptoms of palatal dysfunction

Table 5. continued from previous page.

Medical Concern	Evaluation	Frequency
Strabismus &/or ptosis	Ophthalmologic evaluation	As needed if strabismus or ptosis is present
Hearing loss	Audiology	• Annual through age 6 yrs, then as needed • Up to every 6 mos in patients w/cleft palate or known hearing loss
Sleep-disordered breathing	Clinical evaluation	Annual (polysomnogram if indicated by history)
Developmental delay (DD)	Clinical evaluation	• Annual for preschool-age children, then as indicated • If screening suggests DD, comprehensive assessment & referral to early intervention

Agents/Circumstances to Avoid

If cervical spine abnormality with instability is present in an individual, activities that put the spine at risk should be limited.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

Saethre-Chotzen syndrome (SCS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with SCS have an affected parent.
- A proband with SCS may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include the following:
  - Complete examination for subtle features (ptosis, mild brachydactyly / 2-3 syndactyly) even in the absence of any calvarial pathology
  - Molecular genetic testing of *TWIST1* if a pathogenic variant has been identified in the proband

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with SCS may appear to be negative because of failure to recognize the disorder in family members (wide intrafamilial phenotypic variability is observed in SCS) or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

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

- If a parent has SCS and/or is known to have the pathogenic variant identified in the proband, the risk to sibs is 50%.
- If the proband has a known *TWIST* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *TWIST* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for SCS because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SCS has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- The widely variable phenotypic manifestations of *TWIST1* pathogenic variants (intra- and interfamilial) complicate genetic counseling.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TWIST1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **FACES: The National Craniofacial Association**
  PO Box 11082
  Chattanooga TN 37401
  Phone: 800-332-2373 (toll-free)
  Email: faces@faces-cranio.org
  Saethre-Chotzen Syndrome
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.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. Saethre-Chotzen Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TWIST1	7p21.1	Twist-related protein 1	TWIST1 database	TWIST1	TWIST1

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 Saethre-Chotzen Syndrome (View All in OMIM)

101400	SAETHRE-CHOTZEN SYNDROME; SCS
601622	TWIST FAMILY bHLH TRANSCRIPTION FACTOR 1; TWIST1

Molecular Pathogenesis

Several genes and gene families including *TWIST1*, *TCF12*, *ERF*, *FGF*s, *FGFR*s, *MSX2*, *ALX4*, *EFNB1*, *EFNA4*, *NELL1*, *RUNX2*, *BMP*s, *TGF-βs*, *SHH*, *IGF*s, *IGFRs*, and *IGFBPs* regulate patency of the sutures of the calvarium, likely by interacting with one another. Clinically, Saethre-Chotzen syndrome (SCS) has phenotypic overlap with other craniosynostosis syndromes, particularly Muenke syndrome, caused by the p.Pro250Arg pathogenic variant in *FGFR3* [Muenke et al 1997]. While the two genes lead clinically to the same primary malformation – premature fusion of the calvaria – it is not known if they lie in the same, parallel, or independent pathways during calvarial development.

Gene structure. *TWIST1* comprises two exons and one intron. The first exon contains an open reading frame encoding a 202-amino acid protein, followed by a 45-bp untranslated portion, a 536-bp intron, and a second untranslated exon (reference sequences NM_000474.3 and NP_000465.1).

Pathogenic variants. To date, more than 209 variants in *TWIST1* have been reported to cause SCS, which results from functional haploinsufficiency of Twist-related protein 1, a basic helix-loop-helix (HLH) transcription factor. The majority of reported pathogenic variants are missense, nonsense, or frameshift (i.e., deletions/insertions/duplications/indels); however, a significant number of large deletion or chromosome rearrangements have also been reported [Gripp et al 2000, Cai et al 2003a, de Heer et al 2005, Kress et al 2006, Foo et al 2009, Roscioli et al 2013, Paumard-Hernández et al 2015, The Human Gene Mutation Database (registration required)]. All *TWIST1* pathogenic variants cause functional haploinsufficiency.

All of the disease-associated variants are located within the coding region; no splice variants, intronic variants, or changes within the second exon have been reported. No apparent mutational "hot spot" has been identified.

- Nonsense variants that preclude translation of the DNA binding domain and the HLH domain have been identified from the 5' end of the coding sequence to the end of the HLH motif.
- Missense variants are clustered within the functional domains.
- Four persons have been identified with pathogenic variants in the C-terminus, known as the TWIST box, a highly conserved region that binds and inhibits RUNX2 activation [Kress et al 2006, Seto et al 2007, Peña et al 2010]. RUNX2 is considered the "master switch" for osteoblast differentiation and activity.
- Functional haploinsufficiency of TWIST1, whether due to mutation in the DNA binding, HLH, or TWIST box domains, results in disinhibition of RUNX2 and enhances osteogenesis.

Normal gene product. The Twist-related protein 1 is a member of a large family of basic helix-loop-helix (bHLH) transcriptional regulators. The bHLH motif is identified by the following:

- The basic domain that mediates specific DNA binding to a consensus hexanucleotide E-box (CANNTG)
- The HLH domains containing two amphipathic helices that act as dimerization domains (dimerization is required for DNA binding)
- A loop region that separates the two helices, spacing them appropriately for DNA binding and causing formation of a bipartite DNA-binding groove by the basic domain

Abnormal gene product. *TWIST1* pathogenic variants lead to haploinsufficiency [El Ghouzzi et al 2000]. Haploinsufficiency of Twist-related protein 1 changes the ratio of dimers and, therefore, the expression of downstream signaling molecules.

- Nonsense and frameshift variants have been associated with disease.

- Missense variants involving the helical domains lead to a loss of heterodimer formation that alters nuclear translocation.
- In-frame insertion or missense variants within the loop domain alter dimer formation, but not the nuclear location of the protein.

These data suggest that protein degradation and altered subcellular localization account for the loss of functional Twist-related protein 1 from the abnormal allele in individuals with SCS. This model also supports the finding that the coronal sutures are predominantly fused in SCS, since these sutures have a higher level of gene expression of downstream activators, as shown in *Twist*-null/+ mice models [el Ghouzzi et al 1997, Bourgeois et al 1998, Carver et al 2002, Connerney et al 2008, Miraoui & Marie 2010].

Chapter Notes

Revision History

- 24 January 2019 (ha) Comprehensive update posted live
- 14 June 2012 (cd) Revision: mutation scanning no longer available clinically
- 21 June 2011 (me) Comprehensive update posted live
- 27 December 2007 (me) Comprehensive update posted live
- 1 August 2005 (me) Comprehensive update posted live
- 30 July 2004 (mc) Revision: testing methods
- 16 May 2003 (me) Review posted live
- 21 January 2003 (mc) Original submission

References

Literature Cited

Bourgeois P, Bolcato-Bellemin AL, Danse JM, Bloch-Zupan A, Yoshiba K, Stoetzel C, Perrin-Schmitt F. The variable expressivity and incomplete penetrance of the twist-null heterozygous mouse phenotype resemble those of human Saethre-Chotzen syndrome. Hum Mol Genet. 1998;7:945–57. PubMed PMID: 9580658.

Cai J, Goodman BK, Patel AS, Mulliken JB, Van Maldergem L, Hoganson GE, Paznekas WA, Ben-Neriah Z, Sheffer R, Cunningham ML, Daentl DL, Jabs EW. Increased risk for developmental delay in Saethre-Chotzen syndrome is associated with TWIST deletions: an improved strategy for TWIST mutation screening. Hum Genet. 2003a;114:68–76. PubMed PMID: 14513358.

Cai J, Shoo BA, Sorauf T, Jabs EW. A novel mutation in the TWIST gene, implicated in Saethre-Chotzen syndrome, is found in the original case of Robinow-Sorauf syndrome. Clin Genet. 2003b;64:79–82. PubMed PMID: 12791045.

Carver EA, Oram KF, Gridley T. Craniosynostosis in Twist heterozygous mice: a model for Saethre-Chotzen syndrome. Anat Rec. 2002;268:90–2. PubMed PMID: 12221714.

Cohen MM Jr, Kreiborg S. Birth prevalence studies of the Crouzon syndrome: comparison of direct and indirect methods. Clin Genet. 1992;41:12–15. PubMed PMID: 1633640.

Connerney J, Andreeva V, Leshem Y, Mercado MA, Dowell K, Yang X, Linder V, Friesel RE, Spicer DB. Twist1 homodimers enhance FGF responsiveness of the cranial sutures and promote suture closure. Dev Biol. 2008;318:323–34. PubMed PMID: 18471809.

de Heer IM, de Klein A, van den Ouweland AM, Vermeij-Keers C, Wouters CH, Vaandrager JM, Hovius SE, Hoogeboom JM. Clinical and genetic analysis of patients with Saethre-Chotzen syndrome. Plast Reconstr Surg. 2005;115:1894–902. PubMed PMID: 15923834.

De Heer IM, Hoogeboom AJ, Eussen HJ, Vaandrager JM, De Klein A. Deletion of the TWIST gene in a large five-generation family. Clin Genet. 2004;65:396–9. PubMed PMID: 15099347.

de Jong T, Bannink N, Bredero-Boelhouwer HH, van Veelen MLC, Bartels MC, Hoeve LJ, Hoogeboom AJM, Wolvius EB, Lequin MH, van der Muelen JJNM, van Adrichem LNA, Vaandrager JM, Ongkosuwito EM, Joosten KFM, Mathijssen IMJ. Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. J Plast Reconstr Aesthet Surg. 2010;63:1635–41. PubMed PMID: 19913472.

Dollfus H, Biswas P, Kumaramanickavel G, Stoetzel C, Quillet R, Biswas J, Lajeunie E, Renier D, Perrin-Schmitt F. Saethre-Chotzen syndrome: notable intrafamilial phenotypic variability in a large family with Q28X TWIST mutation. Am J Med Genet. 2002;109:218–25. PubMed PMID: 11977182.

el Ghouzzi V, Le Merrer M, Perrin-Schmitt F, Lajeunie E, Benit P, Renier D, Bourgeois P, Bolcato-Bellemin AL, Munnich A, Bonaventure J. Mutations of the TWIST gene in the Saethre-Chotzen syndrome. Nat Genet. 1997;15:42–6. PubMed PMID: 8988167.

El Ghouzzi V, Legeai-Mallet L, Aresta S, Benoist C, Munnich A, de Gunzburg J, Bonaventure J. Saethre-Chotzen mutations cause TWIST protein degradation or impaired nuclear location. Hum Mol Genet. 2000;9:813–9. PubMed PMID: 10749989.

Foo R, Guo Y, McDonald-McGinn DM, Zackai EH, Whitaker LA, Bartlett SP. The natural history of patients treated for TWIST1-confirmed Saethre-Chotzen syndrome. Plast Reconstr Surg. 2009;124:2085–95. PubMed PMID: 19952666.

Fryssira H, Makrythanasis P, Kattamis A, Stokidis K, Menten B, Kosaki K, Willems P, Kanavakis E. Severe developmental delay in a patient with 7p21.1-p14.3 microdeletion spanning the TWIST gene and the HOXA gene cluster. Mol Syndromol. 2011;2:45–9. PubMed PMID: 22570644.

Gripp KW, Stolle CA, Celle L, McDonald-McGinn DM, Whitaker LA, Zackai EH. TWIST gene mutation in a patient with radial aplasia and craniosynostosis: further evidence for heterogeneity of Baller-Gerold syndrome. Am J Med Genet. 1999;82:170–6. PubMed PMID: 9934984.

Gripp KW, Zackai EH, Stolle CA. Mutations in the human TWIST gene. Hum Mutat. 2000;15:479. PubMed PMID: 10790211.

Howard TD, Paznekas WA, Green ED, Chiang LC, Ma N, Ortiz de Luna RI, Garcia Delgado C, Gonzalez-Ramos M, Kline AD, Jabs EW. Mutations in TWIST, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. Nat Genet. 1997;15:36–41. PubMed PMID: 8988166.

Kress W, Schropp C, Lieb G, Petersen B, Busse-Ratzka M, Kunz J, Reinhart E, Schafer WD, Sold J, Hoppe F, Pahnke J, Trusen A, Sorensen N, Krauss J, Collmann H. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet. 2006;14:39–48. PubMed PMID: 16251895.

Lee S, Seto M, Sie K, Cunningham M. A child with Saethre-Chotzen syndrome, sensorineural hearing loss, and a TWIST mutation. Cleft Palate Craniofac J. 2002;39:110–4. PubMed PMID: 11772178.

Mefford HC, Shafer N, Antonacci F, Tsai JM, Park SS, Hing AV, Rieder MJ, Smyth MD, Speltz ML, Eichler EE, Cunningham ML. Copy number variation analysis in single-suture craniosynostosis: multiple rare variants Including RUNX2 duplication in two cousins with metopic craniosynostosis. Am J Med Genet Part A. 2010;152A:2203–10. PubMed PMID: 20683987.

Miraoui H, Marie PJ. Pivotal role of Twist in skeletal biology and pathology. Gene. 2010;468:1–7. PubMed PMID: 20696219.

Muenke M, Gripp KW, McDonald-McGinn DM, Gaudenz K, Whitaker LA, Bartlett SP, Markowitz RI, Robin NH, Nwokoro N, Mulvihill JJ, Losken HW, Mulliken JB, Guttmacher AE, Wilroy RS, Clarke LA, Hollway G, Ades LC, Haan EA, Mulley JC, Cohen MM Jr, Bellus GA, Francomano CA, Moloney DM, Wall SA, Wilkie

AO, et al. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. Am J Hum Genet. 1997;60:555–64. PubMed PMID: 9042914.

Paumard-Hernández B, Berges-Soria J, Barroso E, Rivera-Pedroza CI, Pérez-Carrizosa V, Benito-Sanz S, López-Messa E, Santos F, García-Recuero II, Romance A, Ballesta-Martínez JM, López-González V, Campos-Barros Á, Cruz J, Guillén-Navarro E, Sánchez Del Pozo J, Lapunzina P, García-Miñaur S, Heath KE. Expanding the mutation spectrum in 182 Spanish probands with craniosynostosis: identification and characterization of novel TCF12 variants. Eur J Hum Genet. 2015;23:907–14. PubMed PMID: 25271085.

Paznekas WA, Cunningham ML, Howard TD, Korf BR, Lipson MH, Grix AW, Feingold M, Goldberg R, Borochowitz Z, Aleck K, Mulliken J, Yin M, Jabs EW. Genetic heterogeneity of Saethre-Chotzen syndrome, due to TWIST and FGFR mutations. Am J Hum Genet. 1998;62:1370–80. PubMed PMID: 9585583.

Peña WA, Slavotinek A, Oberoi S. Saethre-Chotzen syndrome: a case report. Cleft Palate Craniofac J. 2010;47:318–21. PubMed PMID: 19860490.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roscioli T, Elakis G, Cox TC, Moon DJ, Venselaar H, Turner AM, Le T, Hackett E, Haan E, Colley A, Mowat D, Worgan L, Kirk EP, Sachdev R, Thompson E, Gabbett M, McGaughran J, Gibson K, Gattas M, Freckmann ML, Dixon J, Hoefsloot L, Field M, Hackett A, Kamien B, Edwards M, Adès LC, Collins FA, Wilson MJ, Savarirayan R, Tan TY, Amor DJ, McGillivray G, White SM, Glass IA, David DJ, Anderson PJ, Gianoutsos M, Buckley MF. Genotype and clinical care correlations in craniosynostosis: findings from a cohort of 630 Australian and New Zealand patients. Am J Med Genet C Semin Med Genet. 2013;163C:259–70. PubMed PMID: 24127277.

Seto ML, Hing AV, Chang J, Hu M, Kapp-Simon KA, Patel PK, Burton BK, Kane AA, Smyth MD, Hopper R, Ellenbogen RG, Stevenson K, Speltz ML, Cunningham ML. Isolated sagittal and coronal craniosynostosis associated with TWIST box mutations. Am J Med Genet A. 2007;143A:678–86. PubMed PMID: 17343269.

Seto ML, Lee SJ, Sze RW, Cunningham ML. Another TWIST on Baller-Gerold syndrome. Am J Med Genet. 2001;104:323–30. PubMed PMID: 11754069.

Shetty S, Boycott KM, Gillan TL, Bowser K, Parboosingh JS, McInnes B, Chernos JE, Bernier FP. Cytogenetic and molecular characterization of a de-novo cryptic deletion of 7p21 associated with an apparently balanced translocation and complex craniosynostosis. Clin Dysmorphol. 2007;16:253–6. PubMed PMID: 17786117.

Stoler JM, Rogers GF, Mulliken JB. The frequency of palatal anomalies in Saethre-Chotzen syndrome. Cleft Palate Craniofac J. 2009;46:280–4. PubMed PMID: 19642760.

Tahiri Y, Bastidas N, McDonald-McGinn DM, Birgfeld C, Zackai EH, Taylor J, Bartlett SP. New pattern of sutural synostosis associated with TWIST gene mutation and Saethre-Chotzen syndrome: peace sign synostosis. J Craniofac Surg. 2015;26:1564–7. PubMed PMID: 26114524.

Touliatou V, Mavrou A, Kolialexi A, Kanavakis E, Kitsiou-Tzeli S. Saethre-Chotzen syndrome with severe developmental delay associated with deletion of chromosomic region 7p15→pter. Genet Couns. 2007;18:295–301. PubMed PMID: 18019370.

Trusen A, Beissert M, Collmann H, Darge K. The pattern of skeletal anomalies in the cervical spine, hands and feet in patients with Saethre-Chotzen syndrome and Muenke-type mutation. Pediatr Radiol. 2003;33:168–72. PubMed PMID: 12612814.

License