GENEReviews

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Saethre-Chotzen Syndrome

[*Acrocephalosyndactyly Type III*]

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Summary

Disease characteristics. Classic Saethre-Chotzen syndrome (SCS) is characterized by coronal synostosis (unilateral or bilateral), facial asymmetry (particularly in individuals with unicoronal synostosis), ptosis, and characteristic appearance of the ear (small pinna with a prominent crus). Syndactyly of digits two and three of the hand is variably present. Intelligence is usually normal, although those with large deletions are more likely to have developmental delays. Less common manifestations of SCS include short stature, parietal foramina, vertebral fusions, radioulnar synostosis, cleft palate, maxillary hypoplasia, ocular hypertelorism, hallux valgus, duplicated distal hallucal phalanx, and congenital heart malformations.

Diagnosis/testing. The diagnosis of SCS is primarily based on clinical findings. *TWIST1* is the only gene known to be associated with SCS. *TWIST1* mutations are identified in 46%-80% of affected individuals using a combination of deletion/duplication analysis and sequence analysis. Occasionally, affected individuals have a chromosome translocation involving 7p21 or ring chromosome 7.

Management. *Treatment of manifestations:* cranioplasty in the first year of life to prevent progressive facial asymmetry in those with asymmetric coronal fusion and to prevent increased intracranial pressure (ICP) in those with multiple sutural synostosis, midfacial surgery as needed for dental malocclusion, swallowing difficulties, and respiratory problems. Cleft palate surgery usually follows cranioplasty. As needed: orthodontic treatment and/or orthognathic surgery near the completion of facial growth; developmental intervention; routine treatment of hearing loss. *Prevention of secondary complications:* attention to possible cervical vertebral instability secondary to vertebral anomalies. *Surveillance:* periodic ophthalmologic evaluation for chronic papilledema or brain imaging in later life for evidence of ICP; routine evaluation for facial asymmetry, psychomotor development, and hearing loss.

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 *de novo* mutations is unknown. Each child of an individual with SCS has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-

causing mutation has been identified in the family; however, requests for prenatal testing for conditions such as SCS are not common.

Diagnosis

Clinical Diagnosis

Although the phenotype of Saethre-Chotzen syndrome (SCS) is widely variable, the diagnosis is made primarily on the following clinical findings:

- **Craniosynostosis** (premature fusion of one or more sutures of calvarium. The coronal suture is the most commonly affected. Craniosynostosis often presents with an abnormal skull shape (e.g., brachycephaly [short, broad skull] and acrocephaly [tall skull]).
- **Low frontal hairline, ptosis, strabismus, facial asymmetry**
- **Small ears** with a prominent crus
- **Limb anomalies** including brachydactyly, cutaneous syndactyly of the second and third digits of the hand, hallux valgus, duplicated distal phalanx of the hallux, triangular epiphyses of the hallux [Trusen et al 2003]

  Note: Although the degree of syndactyly or its presence is highly variable, it is nearly diagnostic in the presence of the first three features.

Other findings variably present:

- Lacrimal duct stenosis, vertebral fusion, and short stature [Anderson et al 1997, Trusen et al 2003]
- Family history of abnormal skull shape and/or a combination of other physical findings. Although usually present in SCS, craniosynostosis is not an obligatory finding; therefore, affected relatives may not have been diagnosed with a craniosynostosis syndrome.
- Although learning differences may be noted, severe delay or mental retardation is not typical. In contrast, affected individuals with a microdeletion in 7p21 usually show significant learning deficits.
- Conductive, mixed, and profound sensorineural hearing loss [Lee et al 2002]
- Breast cancer [Sahlin et al 2007] and renal cancer [Seifert et al 2006]

Testing

Cytogenetic testing. Translocations, inversions, or ring chromosome 7 have been reported in individuals with SCS with atypical findings, including developmental delay.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *TWIST1* is the only gene known to be associated with SCS.

Clinical testing

- **Sequence analysis of coding region.** Sequence analysis of exon 1 of the *TWIST1* gene detects all intragenic *TWIST1* mutations identified to date. Exon 1 is the only translated exon in the gene. In a study of 37 unrelated individuals with a clinical diagnosis of SCS, 46% had identifiable mutations in *TWIST1* [Paznekas et al 1998]. In other series, a *TWIST1* mutation was identified in 64%-80% of individuals [Johnson et al 1998, de Heer et al 2005, Kress et al 2006]. (This range likely reflects the experience of the clinician making the diagnosis.)
- **Deletion/duplication analysis.** Other techniques that can detect deletions of *TWIST1* may be used when sequence analysis does not reveal a mutation. Although one study suggested that up to 28.5% of SCS is caused by deletions detectable by Southern blot analysis [Gripp et al 2001], a more recent study revealed 11% with deletions detected by gene dosage and 3.6% with inversions or translocations [Cai, Goodman et al 2003].

In 37 individuals with classic features of SCS, the mutation detection rate was 68% using both sequence analysis and gene dosage studies [Cai, Goodman et al 2003].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Proportion of SCS Attributed to Mutations in This Gene	Mutation Detection Frequency [1]	Test Availability
Sequence analysis of coding region	Mutations in *TWIST1* exon 1 [2]	100%	>50%	Clinical Testing
Deletion/ duplication analysis	Complete deletion of the *TWIST1* gene		11%-28%	
Cytogenetic/FISH	Translocations/inversions		3.6% [3]	

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. All intragenic mutations identified to date are in exon 1, which contains the entire coding region.
3. Cai, Goodman et al 2003

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

Testing Strategy

Confirmation of the diagnosis in a proband requires identification of a disease-causing *TWIST1* mutation.

Depending on the family history and the individual's phenotype, chromosome analysis may be considered if:

- No *TWIST1* mutation can be identified **AND**
- Other disorders such as Muenke syndrome, caused by the p.Pro250Arg mutation in *FGFR3* [Muenke et al 1997], have been excluded **OR**
- The family history is suggestive of a complex chromosome abnormality.

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

Genetically Related (Allelic) Disorders

No other phenotypes have been associated with mutations in *TWIST1*.

Clinical Description

Natural History

With the ability to detect mutations in *TWIST1*, the phenotypic spectrum of Saethre-Chotzen syndrome (SCS) is becoming increasingly broad. Both more severe and milder 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). It is important to note that other sutures (i.e., sagittal, lambdoid, and metopic) can undergo premature fusion in individuals with SCS and that individuals with no evidence of pathologic suture fusion have been described.

Syndactyly of digits two and three of the hand and duplication of the distal hallux are variably present. Less common, but clinically significant, findings include both conductive and sensorineural hearing loss and segmentation defects of the vertebrae. Although mild-to-moderate developmental delay and mental retardation have been reported, normal intelligence is more common.

Less common manifestations of SCS include short stature, parietal foramina, radioulnar synostosis, cleft palate, maxillary hypoplasia, ocular hypertelorism, hallux valgus, and congenital heart malformations.

Although molecular genetic testing was not performed, a recent study of families with the clinical diagnosis of SCS suggests an increased risk of breast cancer in affected individuals [Sahlin et al 2007].

A more severe phenotype, indistinguishable from that of Baller-Gerold syndrome (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]. The individual reported by Seto et al (2001) had a single nucleotide substitution (missense). His affected father demonstrated mild features of SCS (ptosis and mild 2-3 syndactyly).

Milder phenotypes associated with *TWIST1* mutations include the following:

- Blepharophimosis or ptosis with or without craniosynostosis resembling blepharophimosis ptosis epicanthus inversus syndrome (BPES) [de Heer et al 2004]
- Robinow-Sorauf syndrome characterized by mild midfacial hypoplasia, shallow orbits, ocular hypertelorism, orbital asymmetry, and broad or duplicated great toes [Kunz et al 1999; Cai, Shoo et al 2003]

Genotype-Phenotype Correlations

No conclusive evidence of genotype-phenotype correlations exists despite the identification of mutations in each of the functional domains of the TWIST1 protein (5' DNA binding, DNA binding, helix 1, loop, and helix 2 domains). Although insertions, deletions, and nonsense and missense mutations have been described, no genotype-phenotype correlation has been found, suggesting that sequence alterations lead to a loss of functional TWIST1 protein irrespective of the mutation type.

The vast majority of individuals with point mutations 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 mutations [Cai, Goodman et al 2003]. Individuals with a *TWIST1* deletion and normal development have been reported [de Heer et al 2005, Kress et al 2006].

Penetrance

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

Anticipation

There is no evidence of anticipation in individuals clinically diagnosed with SCS or in families with known *TWIST1* mutations.

Nomenclature

Robinow-Sorauf syndrome is now known to be caused by mutations in *TWIST1* [Cai, Shoo et al 2003] 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. It is generally agreed that SCS has approximately the same prevalence as Crouzon syndrome.

Variability of the SCS phenotype may result in underdiagnosis.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Muenke syndrome is "nonsyndromic" coronal craniosynostosis caused by the specific point mutation p.Pro250Arg in *FGFR3* (encoding fibroblast growth factor receptor-3) [Muenke et al 1997]. Muenke syndrome shares features with Saethre-Chotzen syndrome (SCS) [Paznekas et al 1998]. A recent study of 39 pedigrees (71 affected individuals) ascertained on the basis of coronal synostosis demonstrated that individuals with *TWIST1* mutations could be distinguished from those with the *FGFR3* p.Pro250Arg mutations by the presence of a low frontal hairline, ptosis, small ears, parietal foramina, interdigital webbing, and hallux valgus or broad great toe with bifid distal phalanx [Kress et al 2006].

Because clinical findings of Muenke syndrome and Saethre-Chotzen syndrome overlap, testing for the *FGFR3* p.Pro250Arg mutation should be considered if no *TWIST1* mutation is identified in an individual with a presumed diagnosis of Saethre-Chotzen syndrome. The reference sequences for *FGFR3* pathologic variant p.Pro250Arg (c.749C>G) are NM_000142.2 and NP_000133.1 [www.ncbi.nlm.nih.gov/Genbank].

Isolated unilateral coronal synostosis. Coronal synostosis is the second most common form of single-suture fusion after sagittal synostosis. Isolated coronal fusion refers to coronal suture fusion with no evidence of other malformations. Isolated coronal fusion is approximately ten times more common than SCS; if left untreated or incompletely treated, it can result in facial asymmetry resembling SCS.

Baller-Gerold syndrome (BGS) is characterized by coronal craniosynostosis, manifest as abnormal shape of the skull (brachycephaly) with ocular proptosis and bulging forehead; radial ray defect, manifest as oligodactyly (reduction in number of digits), aplasia or hypoplasia of the thumb, and/or aplasia or hypoplasia of the radius; growth retardation and poikiloderma.

RECQL4 is the only gene currently known to be associated with BGS. Findings in individuals with BGS overlap with those of Rothmund-Thomson syndrome (RTS) and RAPADILINO syndrome, also caused by mutations in *RECQL4*. Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Saethre-Chotzen syndrome (SCS), the following evaluations are recommended:

- Determination of the degree of facial asymmetry to establish a baseline for future recognition of progressive facial asymmetry
- Ophthalmologic examination for evaluation of ptosis, strabismus, and the development of amblyopia
- Screening for vertebral (particularly cervical) anomalies using routine radiographs in the first year of life. However, at approximately age two years, increased mineralization of the vertebrae allows for better interpretation of flexion/extension views of the cervical spine in evaluation for functional instability.
- Audiologic screening for hearing loss
- Examination for cleft palate; if cleft palate is present, assessment of feeding ability and growth
- Examination of upper and lower extremities for anomalies; if anomalies are present, x-ray and/or orthopedic evaluation for radial ray or hallux anomalies
- Measurement of height and growth velocity; if short stature and/or reduced linear growth velocity is present, evaluation by an endocrinologist
- Screening developmental assessment on any child demonstrating developmental delays and all children found to have a 7 p microdeletion, if developmental delay is identified, comprehensive developmental assessment
- Breast cancer screening; in view of the recent publication of a case series suggesting an increased risk for breast cancer in women with SCS, the authors recommend that providers emphasize the need for routine screening.

Treatment of Manifestations

As with all children with functional craniofacial malformations, management through an established craniofacial team is recommended.

Although management protocols are likely to differ among craniofacial teams, it is generally accepted that individuals with SCS should undergo cranioplasty in the first year of life. Cranioplasty involves extensive surgery to release fused sutures including repositioning an dreconstruction of the malformed calvaria. It prevents the following:

- Progressive facial asymmetry that can develop in individuals with unilateral or asymmetric coronal fusion
- Increased intracranial pressure (ICP) that can develop in individuals with multiple sutural synostosis (bicoronal or other sutures)

In some circumstances, midfacial surgery is necessary in early childhood to address dental malocclusion, swallowing difficulties, or respiratory problems.

If cleft palate is present, it is treated as in other disorders, including surgical closure, assurance of adequate feeding and weight gain, and speech therapy. In most cases, cranioplasty precedes palatal repair.

Orthodontic treatment and/or orthognathic surgery may be required at or near the completion of facial growth.

If developmental delay is identified, early intervention and/or special education is appropriate.

Hearing loss, if present, should be treated in a standard manner (see Hereditary Hearing Loss and Deafness Overview).

Ophthalmologic abnormalities are treated in a standard fashion.

Prevention of Secondary Complications

Early referral to a craniofacial center with expertise in the management of SCS can minimize the secondary effects of craniosynostosis and other functional deficits.

Tympanostomy tubes are appropriate for children with cleft palate or other causes of persistent middle ear effusion and/or otitis media

Cervical spine radiograph to evaluate for segmentation defects is appropriate before initiating activities that put the spine at risk (e.g., gymnastics, football, soccer).

Surveillance

Because increased intracranial pressure (ICP) can develop even after successful treatment of craniosynostosis, periodic ophthalmologic evaluation for chronic papilledema or brain imaging to evaluate for evidence of ICP should be obtained periodically until age 15 years or at any time symptoms (headache, reduced school performance) are identified.

Examination for progression of facial asymmetry, particularly in individuals with untreated unilateral coronal synostosis should continue until the completion of facial growth (approximately age 16 years).

Audiologic screening throughout childhood is indicated.

Regular ophthalmologic evaluations (frequency determined on the basis of symptoms) should begin before age two years or earlier if strabismus or severe ptosis is identified.

If cleft palate is present, monitor for ear infections and hearing loss.

At least annual assessment of developmental status of preschool aged children is appropriate. If findings suggest developmental delay, comprehensive developmental assessment is indicated.

Routine breast cancer screening should be emphasized for women with SCS.

Testing 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 for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include a complete examination for subtle features (ptosis, mild brachydactyly/2-3 syndactyly) even in the absence of any calvarial pathology and molecular genetic testing of *TWIST1* if a mutation has been identified in the proband.

Note: Although many individuals diagnosed with SCS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members as a result of the wide phenotypic variability of SCS.

Sibs of a proband

- The risk to sibs depends on the genetic status of the parents.
- If a parent has SCS, the risk to each sib of a proband is 50%.
- When the parents are clinically unaffected and do not have a *TWIST1* mutation, the risk to the sibs of a proband appears to be low.
- If a *TWIST1* mutation cannot be detected in DNA extracted from the leukocytes of either parent of the proband, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. The risk to the sibs of the proband depends

on the probability of germline mosaicism in a parent of the proband and the spontaneous mutation rate of *TWIST1*. No instances of germline mosaicism have been reported, although it remains a possibility.

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

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

The widely variable phenotypic manifestations of *TWIST1* mutations (intra- and interfamilial) complicate genetic counseling.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The *TWIST1* disease-causing mutation of an affected family member must be identified before molecular genetic testing can be performed.

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

Requests for prenatal testing for conditions such as SCS are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Saethre-Chotzen Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
TWIST1	7p21	Twist-related protein 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Saethre-Chotzen Syndrome

101400	SAETHRE-CHOTZEN SYNDROME; SCS
601622	TWIST, DROSOPHILA, HOMOLOG OF, 1; TWIST1

Table C. Genomic Databases for Saethre-Chotzen Syndrome

Gene Symbol	Entrez Gene	HGMD
TWIST1	7291 (MIM No. 601622)	TWIST1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Little is known about the mechanism by which alteration in *TWIST1* signaling pathways leads to craniosynostosis. Clinically, Saethre-Chotzen syndrome (SCS) has phenotypic overlap with other craniosynostosis syndromes, particularly Muenke syndrome, caused by the p.Pro250Arg mutation in *FGFR3* [Muenke et al 1997]. Although clinically leading to the same primary malformation, premature fusion of the calvaria, it is not known if the two genes lie in the same, parallel, or independent pathways during calvarial development. Several genes and gene families, including *TWIST1,* FGFs, *FGFRs,MSX2,EFNB1,* BMPs, TGF-ßs, *SHH,* and IGFs regulate suture patency, likely by interacting with one another.

Normal allelic variants: *TWIST1* contains 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 [GenBank Accession NM_000474.3 and NP_000465.1]. At least 50 polymorphisms have been identified within the *TWIST1* gene [Fredman et al 2002]. Of these, eight intragenic polymorphisms have been identified within the coding region [Kasparcova et al 1998, Gripp et al 2000, NCBI Entrez SNP Database 2002]. In addition, Elanko et al (2001) described a variation in the polyglycine tract length of *TWIST1* in individuals with craniosynostosis. None of these rearrangements was consistently associated with clinical disease, and thus they were concluded to be polymorphic or at most weakly pathogenic.

Pathologic allelic variants: To date, 87 mutations in *TWIST1* have been determined to cause SCS, which results from functional haploinsufficiency of *TWIST1*, a basic helix-loop-helix (HLH) transciption factor. These include 49 distinct nucleotide substitutions (missense and nonsense), 40 deletions/insertions/duplications/indels, and complex rearrangements [Johnson et al 1998, Zackai & Stolle 1998, Gripp et al 2000, Chun et al 2002, Human Gene Mutation Database 2007, Seto et al 2007]. All of the point mutations are located within the coding region; no splice mutations, intronic mutations, or changes within the second exon have been reported. Nonsense mutations 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 mutations are clustered within the functional domains. No apparent mutational "hot spot" has been identified.

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 basic domain that mediates specific DNA binding, the HLH domains containing two amphipathic helices that act as dimerization domains [Murre et al 1994], and a loop region that separates the two helices. A motif of mainly basic residues permits HLH protein to bind to a consensus hexanucleotide E-box (CANNTG) [Voronova & Baltimore 1990]. Dimerization is a prerequisite for DNA binding; it depends on the spacing between the helices and leads to the formation of a bipartite DNA-binding groove by the basic domain.

Animal models: Twist-related protein 1 and other bHLH transcription factors play central roles in specifying and maintaining cell identity. Twist-related protein 1 was initially characterized in *Drosophila* as being necessary during gastrulation for the establishment of the mesodermal germ layer, and embryos with *TWIST1* mutations fail to develop mesoderm [Thisse et al 1988]. During mouse development, Twist-related protein 1 is expressed in neural crest cells populating the cephalic region and branchial arches that differentiate into connective tissue, muscle, cartilage, and bone [Wolf et al 1991]. The migratory populations of cephalic neural crest cells were demonstrated to be the origin of the membranous bones of the skull (frontal, parietal, and squamosal), their intervening sutures, overlying dermis, and underlying dura mater [Morriss-Kay 2001; Jiang et al 2002], suggesting an early role in calvarial development.

One defined mechanism through which Twist-related protein 1 exerts its effects on transcription and cellular differentiation in the mouse is through interactions with histone acetyltransferase domains of acetyltransferases, p300 and p300/CBP-associated factor (PCAF), which inhibits acetyltransferase activity [Hamamori et al 1999]. These histone acetyltransferases play a critical role in transcriptional activity by relieving the repressive effects of tightly packed chromatin that hampers access of the transcriptional machinery. It remains to be clarified which downstream genes are regulated by Twist-related protein 1. Like other bHLH transcription factors, *Twist* is thought to play a central role in specifying and maintaining cell identity. *Twist* has been implicated in the inhibition of differentiation of multiple cell lineages, including muscle, bone, and neuronal cells. With regard to osteoblast development, *Twist* binds to the DNA-binding domain of Runx2, reversibly inhibiting its function [Bialek et al 2004]. Runx2 is a major bone regulatory transcription factor that increases the expression of osteocalcin through interaction with the vitamin D receptor [Sierra et al 2003; Paredes, Arriagada, Cruzat, Olate et al 2004; Paredes, Arriagada, Cruzat, Villagra et al 2004]. It is presumed that the de-repression of *RUNX2* in the presence of *TWIST1* mutations is directly related to the pathogenesis of craniosynostosis. Recently, two individuals with isolated single-suture craniosynostosis were described with mutations in the TWIST box. This highly conserved domain interacts with RUNX2, repressing its function [Seto et al 2007].

Abnormal gene product: Mutations of *TWIST1* in SCS lead to haploinsufficiency [el Ghouzzi et al 2000]. Nonsense mutations predict the synthesis of truncated proteins or nonsense-mediated mRNA decay of the mRNA may result in a lack of abnormal protein, thereby leading to functional haploinsufficiency. Missense mutations involving the helical domains lead to a loss of heterodimer formation that alters nuclear translocation. In-frame insertion or missense mutations 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 Twist-related protein 1 function (haploinsufficiency) in individuals with SCS. The suggestion is further supported by the finding of premature fusion of sutures in mice heterozygous for a mutation [el Ghouzzi et al 1997, Bourgeois et al 1998, Carver et al 2002].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

FACES: The National Craniofacial Association
PO Box 11082
Chattanooga TN 37401
Phone: 800-332-2373
Saethre-Chotzen Syndrome
www.faces-cranio.org

AboutFace International
123 Edward Street Suite 1003
Toronto M5G 1E2
Canada
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Society for Deaf Children
3820 Hartzdale Drive
Camp Hill PA 17011
Phone: 800-942-2732 (parent hotline); 717-703-0073 (business V/TTY)
Fax: 717-909-5599
Email: asdc@deafchildren.org
www.deafchildren.org

Children's Craniofacial Association
13140 Coit Road Suite 517
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

National Association of the Deaf
8630 Fenton Street Suite 820
Silver Spring MD 20910
Phone: 301-587-1788 (voice); 301-587-1789 (TTY)
Fax: 301-587-1791
Email: NADinfo@nad.org
www.nad.org

References

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 27 December 2007 (me) Comprehensive update posted to live Web site
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