Saethre-Chotzen syndrome

Authors: Professor L. Clauser[1] and Doctor M. Galié
Creation Date: June 2002
Update: July 2004

Scientific Editor: Professor Raoul CM. Hennekam

[1]Department of craniomaxillofacial surgery, St. Anna Hospital and University, Corso Giovecca, 203, 44100 Ferrara, Italy. csr@dns.unife.it

Abstract
Saethre-Chotzen Syndrome (SCS) is an inherited craniosynostotic condition, with both premature fusion of cranial sutures (craniostenosis) and limb abnormalities. The most common clinical features, present in more than a third of patients, consist of coronal synostosis, brachycephaly, low frontal hairline, facial asymmetry, hypertelorism, broad halluces, and clinodactyly. The estimated birth incidence is 1/25,000 to 1/50,000 but because the phenotype can be very mild, the entity is likely to be underdiagnosed. SCS is inherited as an autosomal dominant trait with a high penetrance and variable expression. The TWIST *gene located at chromosome 7p21-p22, is responsible for SCS and encodes a transcription factor regulating head mesenchyme cell development during cranial tube formation. Some patients with an overlapping SCS phenotype have mutations in the* FGFR3 *(fibroblast growth factor receptor 3) gene; especially the Pro250Arg mutation in* FGFR3 *(Muenke syndrome) can resemble SCS to a great extent. Significant intrafamilial and interfamilial phenotypic variability is present for* TWIST *mutations.*

Keywords
craniosynostosis, craniostenosis, limb abnormalies, locus 7p21-22, *TWIST* gene

Disease name and synonyms

Saethre-Chotzen syndrome (SCS)
Acrocephalosyndactyly type III (ACS III)

Excluded diseases

SCS belongs to a group of autosomal craniosynostosis syndromes (see below) that have numerous major clinical features in common and diagnostic dilemmas continue to arise, with single cases being particularly difficult to classify (1).

- Apert syndrome, ACS I
- Vogt syndrome, ACS II
- Waardenburg syndrome, ACS IV
- Pfeiffer syndrome, ACS V
- Carpenter syndrome, ACS VI
- Jackson-Weiss syndrome
- Muenke syndrome

Furthermore, it can be difficult to differentiate SCS from the Rubinstein-Taybi syndrome and related entities, that also go along with brachycephaly, a certain facial resemblance, and limb anomalies including broad thumbs and halluces.

Definition
Saethre-Chotzen Syndrome (SCS) is an autosomal dominant inherited craniosynostotic condition, with both premature fusion of cranial sutures (craniostenosis) and limb abnormalities (2). The most common phenotype features, present in more than a third of patients, consist of coronal synostosis, brachycephaly, low frontal hairline, facial asymmetry, hypertelorism, broad halluxes, and clinodactyly. In the topographic and anatomic classification of craniofacial syndromes, Tessier describes the SCS as related to group 4 affecting the cranial vault (level A), the orbitocranial region (level B), and the lower orbits with body of maxilla and zygomas (level C) (3).

Prevalence
The estimated birth prevalence is 1/25,000 to 1/50,000. However, the phenotype is remarkably variable and can be so mild, that recognition can be difficult. Hence, it is likely to be underdiagnosed.

Clinical description
Brachycephaly or acrocephaly with coronal sutural synostosis is frequently observed. Suture involvement is often asymmetric, producing plagiocephaly and facial asymmetry. Trigonocephaly has also been observed, as well as large and late-closing fontanels, parietal foramina, ossification defects, and enlargement of the sella turcica. Various vertebral abnormalities, including progressive vertebral fusion have been reported in patients affected by SCS (4). Flattened nasofrontal angle with supraglabellar depression and platybasia are present in some instances. Maxillary hypoplasia with relative mandibular prognathism may be evident. The midface may also be broad and flat in some cases. The nose is often beaked, and deviation of the nasal septum is common. The palate is usually high-arched and a cleft may be occasionally present. There is often malocclusion associated with various dental anomalies including supernumerary teeth, enamel hypoplasia, and peg teeth (5, 6-8).
Ocular findings apart from ptosis of superior lids could also include strabismus, shallow orbits, telecanthi or epicanthal folds, downward slanting of the palpebral fissures, blepharophimosis, dacryostenosis, optic atrophy, refractive errors, and both hypotelorism as hypertelorism (5, 7, 9, 10).
Mild external ear malformation is common, typically manifesting as small round ears that may be posteriorly rotated with low setting and prominent helical crura (2, 11, 12). Hearing impairment (conductive type of hearing loss in majority of the cases), which is thought to reflect nerve compression, is an occasional finding (5). Intelligence is usually normal. However, mild to moderate mental retardation has been reported in several cases, sometimes in association with enlarged lateral ventricles, tremor, and other slight cerebral dysfunctions. Usually the behaviour of patients is normal, but there are reports regarding patients with SCS who have speech disorders, disturbed communication skills, and personality disorders including an increased irritability and depressions (5, 11).
Mild syndactyly of the second interdigital space of the fingers was described by Saethre and in subsequent reports. Syndactyly of other fingers is uncommon; thumbs may be short (brachydactyly) and angled (clinodactyly) or flattened. Cutaneous syndactyly of toes two to three is a frequently reported symptom, but the main limb symptoms in SCS are a broad thumb and / or a broad hallux with a valgus deformity (5, 6, 8, 11, 13-15).
Short stature has been documented in some instances. Other findings have included radioulnar synostosis, short clavicles, small ilium, large ischia, coxa valga, cryptorchidism, and congenital heart defects (5, 6, 11).

Management including treatment
Treatment consists mainly of surgical repair of craniosynostosis (cranial remodelling). Cranioplasty involves extensive surgery to release fused sutures including repositioning and reconstruction of the malformed calvaria. Rarely the cutaneous syndactyly will need correction. Plastic surgical correction of some of the facial dysmorphisms, such as ptosis or deviated nasal septum has been performed. Facial asymmetry can be progressive, particularly in patients with untreated unilateral coronal synostosis. Patients may require orthodontic treatment and/or orthognathic surgery at or near the completion of facial growth. In some circumstances, midfacial surgery is necessary in early childhood to address dental malocclusion, swallowing difficulties, or respiratory problems. Because hearing loss occurs in SCS, audiologic screening throughout childhood is warranted. Screening for vertebral anomalies (particularly cervical) should be done because of their functional significance. Although these can be evaluated with routine radiographs in the first year of life, evaluation at approximately age two to three years is recommended due to increased mineralization of the vertebrae and improved ability to interpret flexion/extension views of the cervical spine to evaluate for functional instability.

Etiology

SCS has a genetic etiology with an autosomal dominant inheritance pattern, a high penetrance and a remarkable variability of expression.
Chromosomal rearrangement and linkage analysis have mapped the locus for SCS to chromosome 7p21-p22. The causative gene in this region proved to be *TWIST*, which encodes a basic helix-loop-helix (b-HLH) transcription factor regulating head mesenchyme cell development during cranial tube formation (16, 17). More than 35 different TWIST mutations have been identified in SCS patients, in most cases involving the b-HLH domain of the protein. The mutations are nonsense, missense, and frameshift insertion / deletion mutations either truncating or disrupting the b-HLH domain.
A significant proportion of patients with SCS had large (megabase sized) deletion in the region 7p21 encompassing the region that codes for *TWIST*. The risk for developmental delay in patients with deletions involving the *TWIST* gene is approximately 90% or eight times more common than in patients with intragenic mutations (23). These patients have significant learning difficulties in addition to the clinical features of SCS, which suggests that this mutation may define a new microdeletion syndrome (18).
Most patients with SCS have been demonstrated to harbour a mutation in the *TWIST* gene. Some patients with an overlapping phenotype have mutations in the *FGFR3* (fibroblast growth factor receptor 3) gene, and at least one individual has been described with a mutation in the *FGFR2* gene. Some investigators have diagnosed all these patients as having SCS, but nowadays most colleagues separate these patients from the SCS group. Especially patients with the Pro250Arg mutation in *FGFR3* (Muenke syndrome) may resemble patients with SCS to a great extent. Significant intrafamilial and interfamilial phenotypic variability is present for the *TWIST* mutations. The families in which a Pro250Arg mutation segregates can show a similar variability. The detection rate for *TWIST* mutations in patients with SCS is approximately 68%. New strategy to screen for *TWIST* mutation has been proposed (23) by using polymerase chain reaction (PCR) amplification with subsequent sequencing to identify point mutations and small insertions or deletions in the and real-time PCR-based gene dosage analysis to identify large deletions encompassing the gene, with confirmation by microsatellite and fluorescence in situ hybridization (FISH) analyses.

Diagnostic methods

Diagnosis is based on dysmorphology examination and radiographic evaluation (X-rays, computed tomography (CT) scan of the skull and MRI). Pathognomonic radiographical signs for SCS are the triangular shape of the epiphysis and duplicated distal phalanx of the hallux. The clinical diagnosis can be confirmed by a DNA analysis in which patients should be tested for *TWIST* mutations (mutations in the *TWIST1*, chromosomal locus 7p21, are identified in 46-80% of patients using a combination of Southern blot analysis and sequence analysis of the coding region (exon one). Such testing is clinically available. If negative, the patients should be tested for the Muenke syndrome by *FGFR3* mutation analysis.

Genetic counseling

The risk that an affected individual will have affected offspring is 50%. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Antenatal diagnosis

This is available through identification of the syndrome-causing *TWIST* mutation using CVS (chorionic villus sampling) at about 10-12 weeks' gestation or amniocentesis at 16-18 weeks' gestation.

Unresolved questions

The overlap in the clinical features caused by mutations in different genes, and on the other hand the presence within the same gene of mutations associated with a variety of craniosynostotic conditions, such as Crouzon syndrome and Pfeiffer syndrome, support the hypothesis that the causative gene products are components of the same molecular pathway involved in the modulation of craniofacial and limb development in humans (1, 16-22). Little is known about how alteration in *TWIST1* signaling pathways leads to craniosynostosis. Clinically, Saethre-Chotzen syndrome has phenotypic overlap with other craniosynostosis syndromes, particularly Muenke syndrome, caused by a P250R mutation of *FGFR3*. Although clinically leading to the same primary malformation (premature fusion of the calvaria) it is not understood whether these genes lie in the same, parallel, or independent pathways during calvarial development.

References

1. Brueton LA, van Herwerden L, Chotai KA, Winter RM. The mapping of a gene for craniosynostosis: evidence for linkage of the

Saethre-Chotzen syndrome to distal chromosome 7p. J Med Genet. 1992; 29:681-5
2. von Gernet S, Schuffenhauer S, Golla A, Lichtner P, Balg S, Muhlbauer W, Murken J, Fairley J, Meitinger T. Craniosynostosis suggestive of Saethre-Chotzen syndrome: clinical description of a large kindred and exclusion of candidate regions on 7p. Am J Med Genet. 1996; 63:177-84
3. Tessier P. Craniofacial surgery in syndromatic craniosynostosis. In: Cohen MM (ed). Craniosynostosis: Diagnosis, Evaluation and Management. New York: Raven Press, 1986: 321-411
4. Anderson PJ, Hall CM, Evans RD, Hayward RD, Harkness WJ, Jones BM. The cervical spine in Saethre-Chotzen syndrome. Cleft Palate Craniofac J. 1997; 34:79-82
5. Gorlin RJ, Cohen MM, Hennekam RCM. Saethre-Chotzen syndrome. Syndromes of the head and neck. 4th ed. Oxford / New-York: Oxford University Press. 2001; 664-666
6. Bartsocas CS, Weber AL, Crawford JD. Acrocephalosyndactyly type 3: Chotzen syndrome. J Pediatr. 1970; 77:267-72
7. Gellis SS, Feingold M. Picture of the month. Acrocephalosyndactyly type Saethre-Chotzen (Saethre-Chotzen syndrome). Am J Dis Child. 1975;129:227-8
8. Marchesi A, Leoni R. Multiple peg-shaped teeth associated with acrocephalosyndactyly. A variant of the Saethre-Chotzen syndrome? A clinical case. Minerva Stomatol. 1993;42:169-72
9. Cristofori G, Filippi G. Saethre-Chotzen syndrome with trigonocephaly. Am J Med Genet. 1992; 44:611-4
10. Posnick JC. The craniofacial dysostosis syndromes. Current reconstructive strategies. Clin Plast Surg. 1994; 21:585-98
11. Reardon W, Winter RM. Saethre-Chotzen syndrome. J Med Genet. 1994; 31:393-6
12. Ma HW, Lajeunie E, de Parseval N, Munnich A, Renier D, Le Merrer M. Possible genetic heterogeneity in the Saethre-Chotzen syndrome. Hum Genet. 1996; 98:228-32
13. Galluzzi F, Salti R, Marianelli L, La Cauza C. The Saethre-Chotzen syndrome. Clinical case. Minerva Pediatr. 1980; 32:325-8
14. Stricker M, van der Meulen JC, Raphael B, *et al*. Classification of craniofacial malformations. In: Craniofacial Malformations. Edinburgh / London / Melbourne / New York/ Churchill Livingstone, 1987: 44-269
15. Wilkie AO, Yang SP, Summers D, Poole MD, Reardon W, Winter RM. Saethre-Chotzen syndrome associated with balanced translocations involving 7p21: three further families. J Med Genet. 1995; 32:174-80
16. 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
17. 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
18. Johnson D, Horsley SW, Moloney DM, Oldridge M, Twigg SR, Walsh S, Barrow M, Njolstad PR, Kunz J, Ashworth GJ, Wall SA, Kearney L, Wilkie AO. A comprehensive screen for TWIST mutations in patients with craniosynostosis identifies a new microdeletion syndrome of chromosome band 7p21.1. Am J Hum Genet. 1998; 63:1282-93
19. Lewanda AF, Green ED, Weissenbach J, Jerald H, Taylor E, Summar ML, Phillips JA 3rd, Cohen M, Feingold M, Mouradian W, *et al*. Evidence that the Saethre-Chotzen syndrome locus lies between D7S664 and D7S507, by genetic analysis and detection of a microdeletion in a patient. Am J Hum Genet. 1994; 55:1195-201
20. 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
21. Robin NH. Molecular genetic advances in understanding craniosynostosis. Plast Reconstr Surg. 1999; 103: 1060-70
22. Zackai EH, Stolle CA. A new twist: some patients with Saethre-Chotzen syndrome have a microdeletion syndrome. Am J Hum Genet. 1998; 63:1277-78
23. 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. 2003; 114:68-76