Published in final edited form as:

Plast Reconstr Surg. 2009 June ; 123(6): 1801–1810. doi:10.1097/PRS.0b013e3181a3f391.

REOPERATION FOR INTRACRANIAL HYPERTENSION IN *TWIST1* CONFIRMED SAETHRE-CHOTZEN SYNDROME: A 15 YEAR REVIEW

Roger H Woods, MBBS FRACS¹, Ehtesham UI-Haq, MBBS FCPS(Surg) FCPS(Plast)¹, Andrew OM Wilkie, DM FRCP FMedSci², Jayaratnam Jayamohan, BSc MBBS FRCS(SN)¹, Peter G Richards, FRCPCH FRCS¹, David Johnson, BMBCh DM FRCS(Plast)¹, Tracy Lester, PhD FRCPATH³, and Steven A Wall, MBBCh(rand) FRCS FCS(SA)plast¹

¹Oxford Craniofacial Unit, John Radcliffe Hospital, Oxford, UK

²Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK

³Oxford Medical Genetics Laboratories, Churchill Hospital, Oxford, UK

Abstract

Background—Saethre-Chotzen syndrome (SCS) is a syndromic craniosynostosis defined by a genetic mutation affecting the *TWIST1* gene on chromosome 7p21. SCS is typically associated with uni- or bi-coronal synostosis, eyelid ptosis, dysmorphic external ears and other variable facial and limb abnormalities. Surgical management of the craniosynostosis addresses the calvarial deformity and may relieve or reduce risk of intracranial hypertension. The aim of this study was to assess surgical intervention, with particular consideration of reoperation rate for intracranial hypertension, in SCS patients.

Method—A retrospective casenote analysis was performed on all patients with a confirmed *TWIST1* gene abnormality, who attended the Oxford Craniofacial Unit over a 15-year period. Each patient's mutation and clinical features were recorded. Surgical intervention and sequelae were examined in greater detail.

Results—Thirty-four patients with genetically confirmed SCS were identified. All had craniosynostosis (bicoronal 76%, unicoronal 18%, bicoronal and sagittal 6%), and the majority had eyelid ptosis, low frontal hairline and external ear anomalies. Thirty-one cases had received surgical intervention. Nine of 26 patients (35%) with minimum 12 month follow-up after primary intervention, and 8 of 19 patients (42%) with minimum 5 year follow-up, developed intracranial hypertension necessitating secondary calvarial surgery.

Conclusions—Despite standard surgical intervention, patients with SCS have a high rate (35 - 42%) of recurrent intracranial hypertension necessitating further surgical expansion. All patients with either bicoronal synostosis or unicoronal synostosis with syndromic features, should be screened for *TWIST1* mutations as this confers a greater risk than non-syndromic synostosis of the same sutures. Regular follow-up of SCS patients throughout the childhood years is essential.

Corresponding Author: Roger Woods, Email: rogerwoods1@gmail.com, Address: Oxford Craniofacial Unit, Level LG1 West Wing, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom. Phone: +44 (0)1865 231085, Fax: +44 (0)1865 231091.

FINANCIAL DISCLOSURE

Wellcome Trust -provision of grant support for Professor AOM Wilkie

None of the authors have a financial interest in the products described in the manuscript.

BACKGROUND

Craniosynostosis is a congenital disorder characterised by abnormal craniofacial growth due to premature fusion of calvarial sutures. Saethre-Chotzen syndrome (SCS) is one of the major craniosynostosis syndromes, described by Saethre in 1931¹ and Chotzen in 1932². It was subsequently delineated in greater detail by Pantke *et al.* in 1975³.

SCS is inherited as an autosomal dominant condition with high penetrance and variable expressivity, although cases do occur due to new mutations. The genetic basis is now well understood: heterozygous intragenic mutations, microdeletions or translocations affecting the *TWIST1* gene, located on the short arm of chromosome 7 (7p21.1), lead to the syndrome⁴⁻⁷. SCS has an estimated incidence of 1:25,000 to 1:50,000 live births. Some authors have suggested that this is an underestimate as many cases are mild and do not attend a specialised treatment centre⁸. However there is equally the possibility of overestimation as many previous clinical studies of SCS are likely to have inadvertently included patients with Muenke syndrome (caused by heterozygous P250R mutation in fibroblast growth factor receptor type 3, encoded by the *FGFR3* gene), which has a similar phenotype but a distinct genetic basis⁹⁻¹¹.

The clinical features of *TWIST1*-confirmed SCS have been extensively studied, as there is no single pathognomonic feature associated with the syndrome^{7,8,10,12-14}. Typically, the synostosis affects one or both of the coronal sutures, and usually leads to a pattern of frontal plagiocephaly or brachycephaly. The most consistent facial findings include low set frontal hairline, eyelid ptosis, broad and indented nasal bridge, and external ear anomalies^{8,10,12,14} (Figure 1). Common limb anomalies include soft tissue syndactyly and broad great toes^{10,13,14}.

Surgery for the psychosocial benefits associated with an improved craniofacial appearance is widely accepted. The potential for intracranial hypertension (elevated intracranial pressure, ICP) is also a significant concern in SCS. Intracranial hypertension in SCS is typically due to cranio-cephalic disproportion, as other causes (including hydrocephalus and venous hypertension) are rare^{15,16}. Presently, the frequency of primary intracranial hypertension in SCS is not known. Kress *et al.*¹⁴ described a rate of intracranial hypertension of 35% in their *TWIST1*-confirmed SCS group of 71 patients, although in most cases the diagnosis was based solely on clinical signs.

Unrelieved intracranial hypertension can lead to neurological impairment, including visual loss or developmental delay. This may progress to seizures and even death. Calvarial surgery addresses cranio-cephalic disproportion to relieve or prevent intracranial hypertension. Despite primary surgical intervention, many SCS patients require re-operation due to symptomatic elevated ICP, due to restenosis. Previous small studies of clinically diagnosed SCS cases suggested that this occurs in 18-20% of patients¹⁷⁻¹⁹. Wong *et al.*²⁰ described 20 clinically diagnosed SCS patients who required reoperation in 65% for supraorbital rim position, but do not comment on ICP. There exists no previous study that has assessed the frequency of intracranial hypertension following surgical intervention in genetically confirmed SCS.

The aim of this study was therefore to assess the morbidity and outcome following surgical treatment of SCS, with particular respect to incidence of subsequent intracranial hypertension and necessity for secondary procedures.

METHOD

A retrospective casenote review of all patients with a diagnosis of *TWIST1*-positive SCS, attending the Oxford Craniofacial Unit during a 15 year period between July 1993 and June 2008, was performed. Genetic testing of *TWIST1* for intragenic mutations, deletions and mutations was performed either at the University of Oxford (until 2003) or by the Oxford Medical Genetics Laboratories (after 2003)^{7,21-23}. Thirty-four patients were identified and the clinical features of these patients assessed. Criteria for clinical suspicion of intracranial hypertension included headache, aggressive behaviour or deteriorating school performance, slowing cranial growth on serial head circumference assessment, and papilloedema on fundoscopy. All patients underwent CT radiography for assessment of calvarial shape, synostosis and intracranial space. Radiological features of intracranial hypertension included copperbeating of the inner calvarial surface, small ventricles with effaced basal cisterns and sulcal spaces, and tonsillar herniation.

The timing and rationale for operative intervention were recorded. This included documentation of all ICP assessments performed for clinical or radiological signs suggestive of intracranial hypertension. ICP measurement was obtained by placing an intraparenchymal Codman Microsensor (Codman; LeLochle, Switzerland) in the right frontal lobe via a small burrhole under general anaesthetic²⁴. The pressure was monitored for a period of 24 hours while the child performed normal activities. It was recorded as elevated if 24 hour monitoring showed a mean pressure equal to, or greater than, 20 mm Hg, or 4 or more B waves during this period. If the initial 24 hour reading was neither clearly elevated nor entirely normal, a further 24 hour period of monitoring was performed.

Primary surgical intervention was performed between 9 and 15 months of age where possible, and comprised two main groups. Most patients were treated with a standard fronto-orbital advancement and remodelling (FOAR) as a single definitive procedure. More recently, severely turribrachycephalic patients have been managed with planned dual-stage intervention: primary posterior calvarial release to increase intracranial volume and prevent progressive deformity, followed by standard FOAR²⁵.

Follow-up was performed in a multidisciplinary clinic at 3 months after surgery, then annually unless the parents requested earlier review. Sequelae of surgery were assessed. Where reoperation was required for raised ICP, clinical and radiological features were noted. Secondary surgery was individualised to address recurrent intracranial hypertension in the optimal aesthetic manner. The frequency of secondary surgery in comparative groups was analysed statistically using Fisher's exact test, except, in the case of analysis by position within the *TWIST1* gene, a runs test was used.

RESULTS

Genetic and clinical features

All patients included in the study had a confirmed heterozygous mutation in the *TWIST1* gene. Thirty-four patients (18 male, 16 female) met this criterion during the 15-year study period. The genetic change present in each patient is recorded in Table 1. Our series included four previously unreported mutations of *TWIST1*. One of these (cases 20,21) was a single nucleotide deletion, and therefore unequivocally pathogenic. Three cases with single nucleotide substitutions encoded missense changes (p.I135M, case 8; p.P139T, case 7; p.I156N, case 31) of the highly conserved helix1-loop-helix2 domain of the TWIST1 protein. One of these (p.P139T) arose *de novo*, the other two were inherited from the father, who was clinically affected in each case. The naturally occurring amino acids at these

positions exhibit 100% sequence conservation in the TWIST1 orthologues of a wide variety of metazoan species, indicating that these novel mutations are highly likely to be pathogenic.

All 34 patients had craniosynostosis. The affected sutures were bicoronal in 26 (77%), right unicoronal in 4 (12%), left unicoronal in 2 (6%) and combined bicoronal and sagittal in 2 cases (6%). The patient group had variable expression of the other features of SCS, as summarised and compared to previous studies of genetically confirmed SCS in Table 2. The most common clinical features in our group included ear malformation with prominent transverse crus (88%), low set frontal hairline (77%), and eyelid ptosis (62%). Ten patients (29%) had convergent squint, and 2 (6%) had a palatal cleft (one hard palate cleft, one submucous cleft).

Primary intervention

Twenty-eight patients were cared for primarily at the Oxford Craniofacial Unit. The remaining 6 patients received primary care outside our unit, but had care transferred to the Oxford Craniofacial Unit. Thirty-one patients have had surgical intervention; of the remainder, two are infants and planned for surgery within the next 12 months, and one presented as an adult with mild calvarial abnormality and no features of intracranial hypertension.

Although not a routine part of our protocol, 4 patients had ICP monitoring prior to any surgical intervention. Two of these had acceptable calvarial morphology despite synostosis and were under clinical surveillance, and 2 presented as adults. ICP monitoring was performed due to clinical and radiological (Figure 2) concern of intracranial hypertension, and confirmed its presence in all cases. These individuals were aged 1.2, 4.8, 20.6 and 26.5 years, and included the 3 oldest patients at the time of primary intervention.

Of the 31 patients receiving primary surgical intervention, 25 underwent primary FOAR (median age 1.2 years, range 0.5 - 26.5 years), 5 had planned dual-stage procedures (median age 0.6 years, range 0.5 - 0.8 years), and one (managed primarily outside of Oxford) had multiple strip craniectomies prior to FOAR.

Four of the 25 patients (16%) who received primary surgery at the Oxford Craniofacial Unit had complications following FOAR procedures. One patient developed intraoperative cerebral swelling that required the initial procedure to be halted; a CT Scan revealed a small intraventricular haemorrhage that did not require intervention, and the procedure was completed uneventfully one week later. Another patient developed an acute subdural haematoma that was drained intraoperatively, and the procedure completed without further problems. Two patients (8%) required removal of prominent wires. Documentation of surgical complications in cases initially managed at other units is incomplete; one patient required a minor procedure to remove a bony prominence causing discomfort.

Secondary intervention

Five of the 31 patients who had surgery were excluded due to follow-up of less than 12 months (in 3 cases, primary surgical intervention occurred in the final year of the study and the other 2 cases were siblings who moved abroad within 12 months of their surgery). Of the remaining 26 patients, median follow-up after primary surgery was 6.8 years (range 1.3 - 19.3 years). Thirteen underwent ICP monitoring on 16 occasions due to clinical and radiological (Figure 3) suspicion of intracranial hypertension (3 patients underwent monitoring on 2 separate occasions). Nine of these monitoring episodes confirmed elevated ICP.

Further calvarial surgery to address cranio-cephalic disproportion was thus performed in 9 patients (35%). This included 7 of the 20 cases (35%) with primary surgery performed at the Oxford Craniofacial Unit, and 2 of the 6 cases (33%) with primary surgery elsewhere. Nineteen patients have been followed up for more than 5 years after primary surgery: 8 (42%) had required secondary surgery for elevated ICP. Secondary surgery was performed at median 4.3 years after primary surgery (range: 1.3 - 8.5 years). This comprised calvarial expansion targeting the area of constriction or associated aesthetic deformity: repeat fronto-orbital advancement for frontal constriction, posterior remodelling for posterior constriction and lateral expansion for non-specific space restriction. All procedures were equivalent to grade IV by the Whitaker classification (major craniofacial procedure of same or greater magnitude as the original surgery) 29.

An additional 2 patients (7.7%) without clinical suspicion of intracranial hypertension required secondary calvarial surgery for aesthetic reasons. One patient had surgery for calvarial deformity due to progressive synostosis of the lambdoid sutures, 14 months after FOAR (also equivalent to grade IV by the Whitaker classification), the other required forehead recontouring with bone substitute at growth completion.

Further analysis was carried out on those patients receiving primary surgical intervention at the Oxford Craniofacial Unit. For the single stage (FOAR) group of 16 patients, reoperation rates for elevated ICP were compared in relation to age at primary intervention. Those undergoing intervention before 12 months of age had a significantly higher reoperation rate for intracranial hypertension (4 of 5, 80%) than those operated on after 12 months of age (2 of 11, 18%) [Fisher's exact test, $p=0.04$]. All patients requiring secondary operations for elevated ICP had initial intervention at less than 15 months of age.

The clinical and radiological features of all nine patients who had developed confirmed intracranial hypertension following primary intervention are displayed in Table 3. Symptoms of headache and aggression were reported in 5 (56%), slowed cranial growth on serial head circumference measurements in 6 (67%) and papilloedema was present on fundoscopy in 3 patients (33%). CT imaging showed evidence of raised pressure in 8 (88.9%), without features of hydrocephalus.

Finally, we examined whether the type and position of *TWIST1* mutation had any influence on the reoperation rate. Dividing the mutations into complete deletions or intragenic disruptions [nonsense mutations, frameshifts, in-frame insertions] ($n=17$) and missense mutations ($n=9$), there was no difference in reoperation rate (Fisher's exact test, $p>0.05$). For the intragenic mutations ($n=21$) we also examined whether the position of the mutation ($5' \rightarrow 3'$) influenced reoperation rate, but again no significant effect was observed (runs test, $p>0.08$).

DISCUSSION

SCS is a genetically determined condition with a variable clinical phenotype. Genetic testing is indicated to confirm the diagnosis, and to distinguish SCS from clinically similar disorders, especially Muenke syndrome. It allows accurate genetic counselling regarding recurrence risk and enables prenatal testing. All 34 patients in the study group had genetically confirmed abnormalities in the *TWIST1* gene.

No previous studies of surgical outcome have comprised only *TWIST1*-confirmed SCS patients 17-20. Hence, previous series may inadvertently have included patients with Muenke syndrome. Indeed, several studies of clinically diagnosed "Saethre-Chotzen syndrome" have identified cases with the FGFR3 P250R mutation in their initial patient groups 9, 10, and Clauser *et al.* have reported a case of "Saethre-Chotzen syndrome" with

genetic detection of the FGFR3 P250R mutation, confirming an actual diagnosis of Muenke syndrome¹¹. The distinction between these conditions is clinically significant. Kress *et al.* compared the phenotypes of the two syndromes and found that intracranial hypertension was more common in SCS, while developmental delay and sensorineural hearing loss were more common in Muenke syndrome¹⁴.

The clinical features in our SCS group are consistent with previous reports and highlight the wide phenotypic variation in this disorder^{7,8,10,12-14}. While it is common for patients with SCS to exhibit asymmetric bicoronal synostosis, it is notable that 6 of the 34 patients in our group had isolated unicoronal synostosis and 2 had additional sagittal synostosis.

All four patients who had ICP monitoring prior to any calvarial surgery, had evidence of raised ICP. One child presented with intracranial hypertension aged 4.8 years despite acceptable calvarial shape, reinforcing the need to monitor SCS patients who do not receive early operative intervention.

The overall reoperation rate with minimum 12 month follow-up for intracranial hypertension was 35%. When patients with longer follow-up (minimum 5 years) are considered, the rate was 42% suggesting that the lifetime risk may be up to 50%. These results are compared with other studies in Table 4. These other studies offer at best a guide to intracranial hypertension rates following primary surgery in SCS patients, as they have two clear confounding issues. First, none state that identification of a *TWIST1* mutation, confirming SCS, was performed in all patients¹⁷⁻²⁰. This may lead to inaccuracy due to inclusion of other syndromes (notably Muenke syndrome). Second, the technique for ICP monitoring was inconsistent in these studies. Intraparenchymal pressure monitoring is the accepted gold standard²⁴. It is more accurate than extra-dural or subdural monitoring, or assessment on clinical or radiological grounds²⁴. Siddiqi *et al.*, Foster *et al.* and Pollack *et al.* all used clinical or radiological features for diagnosis and do not describe intraparenchymal pressure monitoring¹⁷⁻¹⁹. The group of Wong *et al.*²⁰, which was the only other large series with long-term follow-up, quotes a 65% reoperation rate for supra-orbital rim position, but describes no assessment for intracranial hypertension. Our study provides the most accurate assessment of intracranial hypertension in the SCS population to date. The oldest patient requiring reoperation for intracranial hypertension was 9.1 years of age, and had received primary intervention 8.3 years earlier. This highlights the need to follow these children in the long term. We believe our protocol of annual reviews until maturity, with prioritized review if new symptoms develop in the interim, is sufficient in this regard and should be encouraged.

Patients with SCS, who had primary surgical intervention before 12 months of age, were much more likely to develop subsequent intracranial hypertension necessitating reoperation. This finding may be biased, as often infants with severely abnormal craniofacial morphology will receive early surgery to prevent progression of abnormal head shape. Though clearly the decision for surgical intervention must be based on clinical and radiological findings, in the absence of extreme morphology or intracranial hypertension, the optimal timing appears to be 12 to 15 months.

The need for reoperation due to raised ICP was higher in our SCS group than in other patients with coronal craniosynostosis treated with identical techniques. The lack of genotype-phenotype correlation that we observed for both the type and position of *TWIST1* mutation fits with the haploinsufficiency (heterozygous loss of function) mechanism proposed for SCS³⁰. In a previous study from our unit, Thomas *et al.*³¹ showed that the reoperation rate for Muenke syndrome was 20.7%, and for mutation-negative non-syndromic coronal synostosis it was 4.3%. When compared to the Muenke group, the SCS

group appears to be at increased risk, though this does not reach statistical significance (Fisher's exact test, $p=0.20$). The SCS group is at significantly higher risk than the non-syndromic group (Fisher's exact test, $p=0.001$). The fact that the same surgical protocol was used in all 3 groups indicates that differences are not due to surgical variation. Our results highlight the importance of genetic assessment and molecular genetic analysis in patients with coronal suture synostosis.

Review of the presenting features in patients with intracranial hypertension after surgical intervention confirmed that screening history and fundoscopy are useful tools in diagnosis. Parental education is also an important adjunct to aid early detection of problems. With the assistance of an experienced neuroradiologist, features on CT imaging can be highly suggestive of raised ICP, and were present in 8 of 9 cases (88.9%). ICP monitoring remains the gold standard to investigate suspected intracranial hypertension. Expertise and modern practice have enabled ICP monitoring to be performed at our unit with extremely low morbidity²⁴.

CONCLUSION

SCS patients are at high risk of developing intracranial hypertension due to cranio-cephalic disproportion. Screening of all patients with either bicoronal craniosynostosis, or unicoronal craniosynostosis with syndromic features for *TWIST1* abnormalities will assist in identifying this group. Close monitoring for symptoms and signs of raised ICP is essential in allowing prompt intervention to minimize sequelae. Postoperatively these patients should be closely followed throughout childhood as there is a high risk of recurrent intracranial hypertension.

Acknowledgments

We wish to recognise the contributions of Mr M. Poole and Mr M. Briggs, consultant surgeons at the Oxford Craniofacial Unit 1980-1994. We also thank Dr P. Anslow for his expert CT interpretation.

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Figure 1. Clinical images of 8 month old girl with asymmetric bicoronal synostosis in Saethre-Chotzen syndrome. She has brachycephaly, right eyelid ptosis, and mild facial asymmetry (slight elevation of left eyebrow and deviation of nose and chin point to the right). The lateral view displays the indented nasal bridge, and dysmorphic external ear with prominent transverse crus.

Figure 2.

CT imaging of a 4.8 year old girl with acceptable calvarial morphology despite bicoronal synostosis (upper left, AP reconstruction; upper right, lateral reconstruction). Right frontal bone defect is present from burrhole for ICP monitoring at the same presentation, which confirmed intracranial hypertension. Axial image displaying copperbeating and reduced intracranial space suggestive of intracranial hypertension (bottom).

Figure 3.

CT imaging of a 5.4 year old boy with acceptable calvarial morphology 4.4 years after fronto-orbital advancement and remodelling for bicoronal synostosis (upper left, AP reconstruction; upper right, lateral reconstruction). Inner calvarial reconstruction (lower left) and axial image (lower right) display copperbeating and reduced intracranial space suggestive of intracranial hypertension. ICP monitoring confirmed intracranial hypertension.

Table 1
Genetic analysis of SCS patients

Case	<i>TWIST1</i> mutation (all patients heterozygous)	Reference
1	Microdeletion	Johnson <i>et al.</i> 7, case SA
2	Intragenic mutation (c.465C>A, p.Y155X)	Elanko <i>et al.</i> 21, case CRS126
3	Intragenic mutation (c.368C>G, p.S123W)	Johnson <i>et al.</i> 7, case SB
4	Intragenic mutation (c.[230delA;232T>C], p.K77SfsX48)	Johnson <i>et al.</i> 7, case LB
5	Intragenic mutation (c.[230delA;232T>C], p.K77SfsX48)	Sibling of case 4
6	Intragenic mutation (c.376G>T, p.E126X)	Gripp <i>et al.</i> 26 described mutation, independent occurrence
7	Intragenic mutation (c.415C>A, p.P139T)	Novel mutation in loop, <i>de novo</i> in patient
8	Intragenic mutation (c.405C>G, p.I135M)	Novel mutation in helix 1, inherited from mildly affected father
9	Intragenic mutation (c.379_381dup, p.A127dup)	Elanko <i>et al.</i> 21, case SC25
10	Intragenic mutation (c.355delC, p.Q119fsX6)	Elanko <i>et al.</i> 21, case C19
11	Intragenic mutation (c.421G>T, p.D141Y)	Johnson <i>et al.</i> 7, case DE
12	Intragenic mutation (c.421G>T, p.D141Y)	Sibling of case 11
13	Intragenic mutation (c.421G>T, p.D141Y)	Half-sibling of case 11
14	Intragenic mutation (c.283delAinsCG, p.S95RfsX143)	Elanko <i>et al.</i> 21, case C12
15	Microdeletion	Wilkie <i>et al.</i> 23, table I
16	Atypical intragenic mutation (c.115C>G, p.R39G)	Funato <i>et al.</i> 22
17	Intragenic mutation (c.472T>C, p.F158L)	Elanko <i>et al.</i> 21 described mutation, independent occurrence
18	Intragenic mutation (c.472T>C, p.F158L)	Sibling of case 17
19	Intragenic mutation (c.406C>T, p.P136S)	De Heer <i>et al.</i> 8 described mutation, independent occurrence
20	Intragenic mutation (c.331delG, p.V111SfsX14)	Novel mutation
21	Intragenic mutation (c.331delG, p.V111SfsX14)	Maternal aunt of case 20
22	Deletion (karyotype 46,XY, del(7)(p21p21))	Wilkie <i>et al.</i> 23, table I
23	Intragenic mutation (c.362C>T, p.T121I)	Wilkie <i>et al.</i> 23, table I
24	Intragenic mutation (c.310G>T, p.E104X)	Johnson <i>et al.</i> 7, case LM
25	Intragenic mutation (c.396_416dup, p.K133_P139dup)	Wilkie <i>et al.</i> 23, table I
26	Intragenic mutation (c.396_416dup, p.K133_P139dup)	Sister of case 25
27	Intragenic mutation (c.485_488del, p.V162AfsX68)	Elanko <i>et al.</i> 21, case SC19
28	Intragenic mutation (c.396_416dup, p.K133_P139dup)	Wilkie <i>et al.</i> 23, table I
29	Intragenic mutation (c.329_333del, p.R110HfsX126)	Wilkie <i>et al.</i> 23, table I
30	Intragenic mutation (c.340A>G, p.N114D)	Carbonara <i>et al.</i> 27 described mutation, independent occurrence
31	Intragenic mutation (c.467T>A, p.I156N), also Down syndrome (karyotype 47,XY,+21)	Novel mutation in helix 2, inherited from mildly affected father
32	Intragenic mutation (c.397_417dup, p.K133_P139dup)	El Ghouzzi <i>et al.</i> 5 described mutation, independent occurrence
33	Microdeletion associated with chromosome translocation (karyotype 46,XY, t(7;8)(p21;q13))	Johnson <i>et al.</i> 7, case CP
34	Large chromosome 7 interstitial deletion (karyotype 46,XX, del(7)(p15.1p21.3))	Similar to deletions described by Chotai <i>et al.</i> 28

Table 2

Clinical features of *TWIST1* confirmed SCS

Clinical features	Oxford group (n=34)	De Heer ⁸ (n=16)	Paznekas ¹⁰ (n=39)	El Ghouzzi ¹² (n=22) ^a	Trusen ¹³ (n=27)	Kress ¹⁴ (n=71)
Brachycephaly	79%	76%	59%	45%	-	46%
Plagiocephaly	18%	24%	23%	36%	-	37%
Low frontal hairline	77%	24%	36%	41%	-	55%
Prosis	62%	53%	59%	100%	-	45%
Prominent crus helices	88%	47%	-	91%	-	51%
Syndactyly, hands	18%	35%	33%	100%	61%	52% ^b
Syndactyly, feet	6%	-	-	-	52%	52% ^b
Broad big toe	9%	-	54%	82%	44%	55%

^aCalculated from Table 1 in El Ghouzzi *et al.*¹² study including all patients with mutations affecting *TWIST1*

^bKress *et al.*¹⁴ reported a 52% incidence of syndactyly, without specifying whether the hands or feet were involved

Table 3
Features of SCS patients requiring reoperation for intracranial hypertension

Case	Sex	Suture involved	Primary procedure	Age of primary procedure (years)	Secondary procedure	Age of secondary procedure (years)	Headache/Aggression	Slowed cranial growth	Fundoscopy	CT features of elevated intracranial pressure
1	M	Left unicoronal	FOAR	0.9	CE	8.9	+	+	-	+
2	F	Bicoronal	FOAR	0.6	Re-FOAR	5.4	-	+	-	+
4	F	Bicoronal	FOAR	1.2	PR	5.3	-	+	papilloedema	+
11	M	Bicoronal	FOAR	0.8	CE	9.1	+	-	papilloedema	+
17	M	Bicoronal	Dual stage	0.5; 1.3	CE	5.8	+	+	-	+
18	F	Bicoronal	FOAR	0.9	PR	2.1	-	+	-	+
19	M	Bicoronal	FOAR	1	Re-FOAR	5.4	+	+	-	+
24	M	Bicoronal	FOAR	0.7	Re-FOAR	3.5	-	-	papilloedema	+
27	F	Bicoronal	FOAR	0.8	CE	4.3	+	-	-	-

FOAR = Fronto-orbital advancement and remodelling, Dual stage = Posterior release followed by FOAR, PR = Posterior remodelling, CE = Calvarial expansion with lateral panel release, Re-FOAR = Repeat FOAR

Reoperation rate for SCS

Table 4

Author	Follow up	SCS cases ^a	SCS cases undergoing primary surgery	Reoperations (total)	Reoperations (intracranial hypertension) ^b
Siddiqi17	24-61 months	11	11	2 (18%)	2 (18%)
Pollack18	Median 30 months	5	5	1 (20%)	1 (20%)
Foster19	Mean 38 months	5	5	1 (20%)	1 (20%)
Wong20	Minimum 5 years	25	20	13 (65%)	unknown
Oxford (this work)	Median 6.8 years	34	31 (26) ^c	11 (42%)	9 (35%)

^a Oxford -all cases genetically confirmed. All other groups diagnosed clinically with incomplete genetic confirmation.

^b Intracranial hypertension confirmed by intraparenchymal monitoring in this work. Other groups diagnosed elevated intracranial pressure on clinical and radiological grounds.

^c Of 31 cases in the Oxford group, 5 had follow-up of less than 12 months and were excluded from statistical analysis.