Craniosynostosis refers to the premature fusion of cranial sutures. This condition occurs with an incidence of 1:2500 live births and can be present in isolation or as a component of various syndromes. Some forms of syndromic craniosynostosis are caused by discrete genetic mutations (for example, FGFR, Twist, and EFNB) that impact suture patency. Nevertheless, the molecular basis for many forms of syndromic and nonsyndromic craniosynostosis are unknown. Identification of additional associations may offer further clues about the complex biology of bone growth and the pathology of premature suture fusion.

There is no known association between Down syndrome and craniosynostosis. The authors report 2 infants with trisomy 21 and right unilateral coronal craniosynostosis. Both patients were clinically asymptomatic but displayed characteristic craniofacial features associated with each disorder. One patient underwent a bilateral fronto-orbital advancement and the other underwent an endoscopically assisted strip craniectomy with postoperative helmet therapy. Both patients demonstrated good cosmesis at follow-up.

**Case Reports**

**Case 1**

A 22-month-old girl born at 39 weeks’ gestation, in whom a prenatal diagnosis of trisomy 21 Down syndrome had been made, was referred to our clinic for evaluation of forehead asymmetry, with right frontal flattening (Fig. 1). She had no symptoms of increased intracranial pressure. Her head circumference was about the 60th percentile. Head CT scanning confirmed a right unilateral coronal craniosynostosis (Fig. 2). The patient underwent a fronto-orbital advancement and placement of autologous bone graft. She tolerated the procedure well and was discharged without incident. She has had an uneventful recovery and frontal symmetry was excellent almost 1 year after surgery.

**Case 2**

A 4-month-old boy, born at term, also with a prenatal diagnosis of trisomy 21 Down syndrome, was examined for right forehead asymmetry (Fig. 3). Head CT scanning was significant for a right unilateral coronal craniosynostosis (Fig. 4). He was otherwise asymptomatic, and his head circumference was in the 30th percentile. Again, there were no examination findings to support syndromic craniosynostosis. The patient underwent an endoscopically assisted strip craniectomy of the fused right coronal suture and tolerated the procedure well. He was fitted with a cranial molding orthosis shortly after the procedure and underwent postoperative helmet therapy to direct cranial growth. The patient had excellent phenotypic improvement almost 1 year after surgery.

**Discussion**

Large cohort studies have found genetic abnormalities
Craniosynostosis in Down syndrome

Fig. 1. Case 1. Preoperative photographs of a 22-month-old girl with Down syndrome showing frontal asymmetry with right frontal flattening, consistent with right unilateral coronal craniosynostosis.

Fig. 2. Case 1. Preoperative head CT reconstruction demonstrating right unilateral coronal craniosynostosis.

in 21% of patients with craniosynostosis, of which 86% and 15% were attributed to single gene and chromosomal abnormalities, respectively.23 A key clinical distinction is the diagnosis of craniosynostosis in the setting of a syndrome, as it can be associated with other anomalies. Genetic studies of the so-called syndromic craniosynostoses, which may account for approximately 15% of patients,9,23 have provided key insights into the physiology of suture formation and its premature closure.23 Familial linkage studies have implicated genetic roles for FGFR family, TWIST-1, MSX-2, EFNB-1, and RAB-23.5,16,17

The contemporaneous occurrence of these 2 conditions raises the question of a possible causal association. Down syndrome occurs in 1 in 690 live births and is the most common chromosomal condition.6,7,25 The incidence of unilateral coronal synostosis is less well defined but is estimated to occur in roughly 1 in 10,000 live births.10,11 Thus, the likelihood of both diagnoses occurring randomly together is around 1 in 6.9 million live births. If there were a causal link, the incidence would be higher. Although it is difficult to conclusively extrapolate, the lack of prior descriptions seems to suggest that the concurrence in our patients might be random. Nevertheless, it is intriguing that the fusion involved the coronal suture in both patients instead of the more commonly fused sagittal or metopic sutures. A more esoteric causal link, possibly related to epigenetic influences, cannot be excluded.

The biology of cranial suture fusion is complex, and thus the root cause of any phenotypic aberrancy is likely to be multifactorial. The cranial sutures are made up of undifferentiated mesenchymal tissue composed of highly proliferative osteoprogenitors, which respond to a multitude of signaling molecules that promote transdifferentiation into osteoblasts to induce skull growth and subsequent suture fusion.14 It is likely that only a subset of key mediators has been elucidated, with additional mediators that remain unidentified. In support of this is the lack of a clear genetic basis for many individuals initially diagnosed with nonsyndromic craniosynostosis, and it may likely be a phenotypic manifestation of multiple genetic and environmental factors.5,22 Subsequent studies of nonsyndromic patients have identified genetic and chromosomal abnormalities in up to 5% of cases.12,18,21 The identification of other associations with craniosynostosis can provide additional insights.

While patients with trisomy 21 exhibit characteristic craniofacial abnormalities,20 an association with craniosynostosis is unknown. Trisomy 21 has been theorized to
promote a generalized genetic imbalance. Recently, several candidate genes on chromosome 21 were identified that regulate bone development. DSCR1 and DYRK1A are genes located in the Down syndrome critical region and act to synergistically inhibit nuclear translocation of NFAT, a transcription factor important in normal skeletal development. Some studies have shown that NFAT inhibition results in increased osteoblast activity, while other studies have pointed to a more stimulatory role.

The disparity may lie in timing of the expression, but it does underscore a genetic basis for overexpression of effectors found in chromosome 21 that modulate bone development and could increase the risk of craniosynostosis. An additional candidate gene located on chromosome 21 is COL18A1, whose cleavage product is endostatin. It has been shown to affect osteoblast activity. Additionally, endostatin can inhibit Wnt signaling, which has been implicated in the development of a craniosynostosis phenotype in animal models. Further characterization of this pathway is necessary to determine the role in the human phenotype.

Conclusions

The association between trisomy 21 and craniosynostosis remains to be elucidated. While the paucity of described cases refutes the possibility of a direct causal link, the fact that both of our patients had fusion of a single coronal suture suggests that a less direct molecular interaction may be operative.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Magge, Rogers. Acquisition of data: Siu. Analysis and interpretation of data: Magge, Siu, Rogers, Khalsa, Keating. Drafting the article: Magge, Siu, Rogers, Khalsa. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Magge. Statistical analysis: Siu. Study supervision: Magge, Rogers.

References

2. Behr B, Longaker MT, Quarto N: Craniosynostosis of coronal suture in twist1 mice occurs through endochondral ossification recapitulating the physiological closure of posterior frontal suture. *Front Physiol* **2**:37, 2011


Manuscript submitted October 1, 2013. Accepted February 17, 2014.

Please include this information when citing this paper: published online March 21, 2014; DOI: 10.3171/2014.2.PEDS13504. Address correspondence to: Suresh N. Magge, M.D., 111 Michigan Ave. NW, Washington, DC 20010-2970. email: smagge@cnmc.org.