Molecular Analysis of Patients with Synostotic Frontal Plagiocephaly (Unilateral Coronal Synostosis)

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Mutations in genes known to be responsible for most of the recognizable syndromes associated with bilateral coronal synostosis can be detected by molecular testing. The genetic alterations that could cause unilateral coronal synostosis are more elusive. It is recognized that FGFR and TWIST mutations can give rise to either bilateral or unilateral coronal synostosis, even in the same family. The authors undertook a prospective study of patients presenting with synostotic frontal plagiocephaly (unilateral coronal synostosis) to Children’s Hospital Boston during the period from 1997 to 2000. Mutational analysis was performed on all patients and on selected parents whenever familial transmission was suspected. Intraoperative anthropometry was used in an effort to differentiate those patients in whom a mutation was detected from those in whom it was not. The anthropometric measures included bilateral sagittal orbital-globe distance, inter medial canthal distance, and nasal angulation. Macrocephaly and palpebral angulation were also considered possible determinants. There was a 2:1 female preponderance in 47 patients with synostotic frontal plagiocephaly. Mutations were found in eight of 47 patients: two patients with different single-amino-acid changes in FGFR2, three patients with FGFR3 Pro250Arg, and three patients with TWIST mutations. Another patient had craniofrontonasal syndrome for which a causative locus has been mapped to chromosome X, although molecular testing is not yet available. Two features were strongly associated with a detectable mutation in patients with synostotic frontal plagiocephaly: asymmetrical brachycephaly (retrusion of both supraorbital rims) and orbital hypertelorism. Other abnormalities in the craniofacial region and extremities were clues to a particular mutation in FGFR2, FGFR3, TWIST, or the X-linked mutation. Neither macrocephaly nor degree of nasal angulation nor relative vertical position of the lateral canthi correlated with mutational detection. An additional four patients in this study had either unilateral or bilateral coronal synostosis in an immediate relative and had anthropometric findings that predicted a mutation, and yet no genetic alteration was found. This suggests either that the authors’ screening methods were not sufficiently sensitive or that perhaps there are other unknown pathogenic loci. Nevertheless, molecular testing is recommended for infants who have unilateral coronal synostosis, particularly if there are the anthropometric findings highlighted in this study or an otherwise suspicious feature in the child or a parent. Infants with either an identified or a suspected mutation usually need bilateral asymmetric advancement of the bandeau and may be more likely to require frontal revision in childhood. (Plast. Reconstr. Surg. 113: 1899, 2004.)

Synostotic frontal plagiocephaly is the phenotypic designation for premature closure of the frontoparietal and frontosphenoidal sutures on one side of the coronal ring. Unilateral coronal synostosis is the more commonly used clinicopathologic term. This disorder is characterized by elevation and posteroslateral displacement of the affected orbit, ipsilateral deviation of the nasal root, and contralateral compensatory frontal bossing. There is also a contralateral rotation of the middle face and mandible, as evidenced by anteriorly positioned auricle, malar eminence, and temporomandibular joint. There are also rare instances of synostotic frontal plagiocephaly in which the frontoparietal suture is open and only the frontosphenoidal suture is fused. This localized synostosis in the basal coronal ring results in a flat forehead with minimal orbital displacement, straight nasal dorsum (or slight contralateral deviation), and minor midfacial rotation.
Synostotic frontal plagiocephaly is generally not considered to be inheritable. However, mutations have been found in some patients, the most common being \textit{FGFR3} Pro250Arg. An \textit{FGFR2} mutation was discovered in a family with variable sutural synostosis, including asymmetric coronal fusion presenting as frontal plagiocephaly. Asymmetric coronal synostosis, manifesting as synostotic frontal plagiocephaly, also occurs in approximately one-fourth of patients with Saethre-Chotzen syndrome, which is caused by various mutations in \textit{TWIST}. In addition, synostotic frontal plagiocephaly is exhibited by one-half of patients with the rare craniofrontonasal syndrome, which is inherited as an X-linked trait.

This study analyzed a consecutive series of patients with synostotic frontal plagiocephaly who were admitted for primary surgical correction or seen for postoperative follow-up evaluation. The parents also were examined for dysmorphic features suggestive of coronal synostosis. Blood samples were drawn for mutational analysis in \textit{FGFR1}, \textit{FGFR2}, \textit{FGFR3}, and \textit{TWIST}. In those patients who were found to have a mutation, phenotypic findings, anthropometric data, and family history were reviewed, looking for clues that could have predicted the molecular change.

\section*{Patients and Methods}

\subsection*{Mutational Analysis}

Blood samples were drawn on all infants undergoing operative correction for synostotic plagiocephaly during the period 1997 to 2000. In addition, mutational analysis was performed on children evaluated during this period following repair of this condition. Blood was taken from the parents of the child if there was any evidence of a cranial abnormality, such as unilateral or bilateral frontal retrusion, macrocephaly, hypertelorism, or anomalies of the hands or feet.

Ethylendiaminetetraacetic acid blood samples were analyzed by extracting DNA according to standard procedures. Analysis for the \textit{FGFR1} Pro252Arg and the \textit{FGFR3} Pro250Arg mutations was performed by polymerase chain reaction amplification, followed by restriction enzymatic digestion and agarose gel electrophoresis. Exons 7 and 9 of the \textit{FGFR2} gene were amplified using primers and conditions described by Steinberger et al. and by Meyers et al., followed by single-strand conformation polymorphism analysis. Sequence analysis was performed either manually using the 33P-Thermo Sequenase radiolabeled terminator for cycle sequencing kit (Amersham Pharmacia Biotech, Piscataway, N.J.) or on an ABI 377 automated DNA sequencer. Sequence analysis of the \textit{TWIST} gene coding region was performed, as described previously.

\subsection*{Clinical and Anthropometric Analysis}

The patients’ records were reviewed, documenting head circumference, midfacial hypoplasia, blepharoptosis, cant of the palpebral fissures, and possible auricular and hand anomalies. Any dysmorphic features in the parents were also noted. Intraoperative anthropometric measures included sagittal distance from orbitale superius to apex corneae, inter medial canthal dimension, and nasal angulation. Instruments used for measuring included a metric ruler for the distance from orbitale superius to apex corneae, a sliding Vernier caliper for inter medial canthal dimension, and a nasal protractor for angulation of the root, as previously described. All measurements were performed three times by a single examiner (Mulliken) and the average or identical value was recorded. Accuracy was to the nearest 1 mm for distance from orbitale superius to apex corneae and the nearest 0.5 mm for the inter medial canthal distance. Anthropometric measures and the other physical findings were compared between infants discovered to have a mutation and those in whom a mutation was not found.

\section*{Results}

\subsection*{Mutational Analysis}

A total of 47 patients with synostotic frontal plagiocephaly were evaluated during the 4-year study: there were 32 girls and 15 boys, for a 2:1 female preponderance. Mutations were found in eight patients, and a ninth patient was clinically diagnosed as syndromic, although the
The mutated gene is unknown. These findings are summarized in Table I. The most common mutation was FGFR3 Pro250Arg (n = 3) (Fig. 1). Two patients had different mutations in FGFR2 (Fig. 2). Three of these five patients had a first-degree relative with either unilateral (n = 1) or bilateral frontal retrusion (n = 2). The parents of the other two patients with FGFR mutations were normal by physical examination and molecular screening.

Three patients had a mutation in TWIST (Fig. 3). The diagnosis of Saethre-Chotzen syndrome had been predicted for two of these subjects because each had an affected parent. The parents of the third child with a TWIST mutation were considered to be phenotypically

### TABLE I

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Family</th>
<th>Distance from Orbitale Superior to Apex Corneae</th>
<th>Nasal Angle</th>
<th>Mutation (gene and amino acid change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ipsilateral/Contralateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 mo</td>
<td>Mother: UCS</td>
<td>–1/+8</td>
<td>28</td>
<td>FGFR3 Pro250Arg</td>
</tr>
<tr>
<td>2</td>
<td>2 yr</td>
<td>Negative</td>
<td>+4/+9</td>
<td>34.5</td>
<td>FGFR3 Pro250Arg</td>
</tr>
<tr>
<td>3</td>
<td>33 yr</td>
<td>Daughter: BCS</td>
<td>–1/+6</td>
<td>40.5</td>
<td>FGFR3 Pro250Arg</td>
</tr>
<tr>
<td>4</td>
<td>9 mo</td>
<td>Mother: BCS (inter medial canthal dimension 32 mm)</td>
<td>–6/+4</td>
<td>35</td>
<td>FGFR2 Ala344Ala</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sister: pansynostosis</td>
<td>(inter medial canthal dimension 35 mm at 20 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10 mo</td>
<td>Negative</td>
<td>–3/+0</td>
<td>27</td>
<td>FGFR2 Cys542Tyr</td>
</tr>
<tr>
<td>6</td>
<td>10 yr</td>
<td>Father: SCS</td>
<td>–6/+0</td>
<td>25</td>
<td>TWIST 417insLysIleIleProThrLeuPro (in-frame duplication)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sister: SCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9 mo</td>
<td>Father: SCS</td>
<td>–5/+2</td>
<td>34</td>
<td>TWIST Glu122STOP (nonsense)</td>
</tr>
<tr>
<td>8</td>
<td>10 mo</td>
<td>Mother: normal phenotype, same genetic alteration</td>
<td>–3/+0</td>
<td>26</td>
<td>TWIST delAla87-Gly92 (in-frame deletion)</td>
</tr>
<tr>
<td>9</td>
<td>1 yr</td>
<td>Mother: CFNS</td>
<td>–2/+5</td>
<td>36</td>
<td>Causative gene on chromosome X</td>
</tr>
</tbody>
</table>

UCS, unilateral coronal synostosis; BCS, bilateral coronal synostosis; SCS, Saethre-Chotzen syndrome; CFNS, craniofrontonasal syndrome.

**FIG. 1.** Synostotic frontal plagiocephaly caused by FGFR3 Pro250Arg mutation. (**left**) Patient 1 and (**right**) patient 2. Both have first-degree orbital hypertelorism.
FIG. 2. Two infants with synostotic frontal plagiocephaly. (Left) Patient 4 (FGFR2 Ala344Ala) with second-degree hypertelorism; (right) patient 5 (FGFR2 Cys342Tyr) with normal medial canthal dimension.

FIG. 3. Three infants with synostotic frontal plagiocephaly and TWIST mutations. (Left) Patient 6; note blepharoptosis. (Center) Patient 7; note low, upturned frontal hairline and second-degree hypertelorism. (Right) Patient 8; note contralateral rotation of midface and chin and incidental infantile hemangioma.
normal; however, molecular testing revealed that one had the same genetic alteration. One child had craniofrontonasal syndrome, as did her mother (Fig. 4).

Four patients with synostotic frontal plagiocephaly had a relative with typical features of either unilateral or bilateral coronal synostosis—yet DNA testing was negative for FGFR1, FGFR2, FGFR3, and TWIST (Fig. 5). The findings in this subset of putative patients are summarized in Table II.

Anthropometry

Intraoperative anthropometry was available in eight patients with a mutation, another patient with a putative locus, and in 23 of 38 patients without a mutation, including two of four patients who were suspected of having a mutation.

Orbitale Superius-Apex Cornea

The findings in the sagittal dimension are summarized in Table III. The difference in the distance from orbitale superius to apex cornea between the fused and nonfused sides was the same for both groups (approximately 6 mm), defined as with or without a detected mutation. However, the distance from orbitale superius to apex cornea for both the non-
fused and fused sides was significantly different between the two groups. This means there was a significant difference in the frontal projection between the patients with a mutation and those in whom a mutation was not found. On the normal side in the patients without a mutation, the mean distance from orbitale superius to apex cornea was 5.4 mm, whereas on the nonfused side in the mutated group, the mean was 2.6 mm. On the fused side in the patients without a mutation, the mean distance from orbitale superius to apex cornea was −0.50 mm, as compared with −3.6 mm in the patients with a mutation. In summary, there was no difference in the relative sagittal position of the supraorbital rims between the two groups. However, both sides of the supraorbital region were more retruded in those patients with a detectable mutation (and in the patients suspected of having a mutation) (Fig. 6).

Endocanthion-Endocanthion

Seven of eight patients found to have a mutation and the one infant with craniofrontonasal syndrome had orbital hypertelorism, defined as inter medial canthal dimension more than 2 SD for age- and sex-matched controls (Table I). Hypertelorism was also noted in all four patients suspected of having a mutation, although their molecular test results were negative (Table II). In contrast, the inter medial canthal distance was normal in the group without a mutation.

Nasal Angulation and Other Physical Findings

There was no significant difference in preoperative angulation of the nasal root for patients found to have a mutation versus those whose test results were negative (Table III), nor was there a consistent pattern in the position of the affected-side lateral canthus (relative to the medial canthus) that differentiated those infants with or without mutation. Macrocephaly also did not predict the finding of a mutation. None of the patients evidenced midfacial retrusion at the time of the study. Clino-
dactyly of the fifth finger was noted in one family suspected of having a mutation (patient 4); however, this is a common autosomal dominant trait.

![Fig. 4. Patient 9 with craniofrontonasal syndrome. Note left synostotic frontal plagiocephaly, short, bifid nose, second-degree hypertelorism, eurycephaly, and strabismus.](image-url)
Revisions

Although the numbers are small, of possible importance was the finding that two of the five patients with an FGFR molecular diagnosis required revision of the forehead. Patient 2 had a second fronto-orbital advancement (the initial procedure was performed at another hospital) and patient 5 had a foreheadplasty in our unit. Furthermore, of the four patients suspected of having a mutation, one had a second fronto-orbital advancement and another will need a foreheadplasty. In contrast, to date, only six of 34 patients in whom a mutation was not identified either have had or will need frontal revision.

TABLE II
Clinical and Anthropometric Findings in Patients with Synostotic Frontal Plagiocephaly and Suspected Mutation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Family</th>
<th>Distance from Orbitale Superius to Apex Corneae (mm)</th>
<th>Inter Medial Canthal Dimension (mm)</th>
<th>Nasal Angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5 mo</td>
<td>Mother: UCS, hypertelorism</td>
<td>N/A</td>
<td>30</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal grandmother: hypertelorism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>7 mo</td>
<td>Maternal grandmother: BCS</td>
<td>–1</td>
<td>+5</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>22 mo</td>
<td>Mother: frontal retrusion</td>
<td>–4</td>
<td>+2</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>10 yr</td>
<td>Father: UCS</td>
<td>N/A</td>
<td>35</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A, not available; BCS, bilateral coronal synostosis; UCS, unilateral coronal synostosis.

FIG. 5. Two infants with synostotic frontal plagiocephaly suspected of having a mutation because of anthropometric findings and positive family history, but no mutation detected. (Left) Patient 10; note high forehead, first-degree orbital hypertelorism. (Right) Patient 11 has borderline hypertelorism.

DISCUSSION

Genes Causing Bilateral Coronal Craniosynostoses

Many different mutations in genes coding for FGFR1, FGFR2, or FGFR3 cause bilateral synostosis of the coronal ring, often in combination with fusion of other cranial sutures. When mutations in FGFR2 first were detected in Crouzon syndrome, it was thought that the genetic change (genotype) would predict the phenotype. This assumption turned out to be correct in Apert syndrome, which is caused by one of two adjacent mutations in the linker region between the immunoglobulin-like loops II and III of FGFR2. Another example of mo-
molecular-clinical correlation is FGFR3 (Ala391Glu), which is consistently found in patients with crouzonoid craniosynostosis and acanthosis nigricans.22–24 However, there is no clear genotype-phenotype correlation in most patients with bilateral coronal synostosis. Different mutations in one of the three FGFR genes can cause identical phenotypes, and mutations in the same genes can beget highly variable features (and different eponymous labels).25 Even identical mutations in the same family can produce a wide spectrum of craniofacial manifestations that range from subtle dysmorphism, such as minor hypertelorism and minimally broad toes, to major changes caused by pansynostosis.26

Mutations are known for the major “syndromic” craniosynostoses. In a study of 50 patients with bilateral coronal synostosis, a molecular alteration in genes encoding fibroblast growth factor receptors 1, 2, and 3 was found in all those patients who had a clinical diagnosis of either Apert, Crouzon, or Pfeiffer syndrome.24 A mutation was discovered in 75 percent of patients with unclassified brachycephaly, the most common being FGFR3 Pro250Arg (Muenke syndrome).24 In patients with a clinical diagnosis of Saethre-Chotzen syndrome, sequence analysis and Southern blot analysis or fluorescent in situ hybridization detected mutations in TWIST in 80 percent, including point mutations and deletions.17,27

Table III
Anthropometric Measures: Comparison between Patients with and without a Detected Mutation

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of Patients</th>
<th>Mean</th>
<th>SD</th>
<th>No. of Patients</th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal angle (degrees)</td>
<td>23</td>
<td>8.52</td>
<td>2.13</td>
<td>9</td>
<td>8.50</td>
<td>1.07</td>
<td>0.27</td>
<td>NS</td>
</tr>
<tr>
<td>Distance from orbitale superius to apex corneae (mm), nonfused side</td>
<td>23</td>
<td>5.43</td>
<td>1.24</td>
<td>9</td>
<td>2.63</td>
<td>2.88</td>
<td>2.68*</td>
<td>0.03</td>
</tr>
<tr>
<td>Distance from orbitale superius to apex corneae (mm), fused side</td>
<td>23</td>
<td>−0.50</td>
<td>2.09</td>
<td>9</td>
<td>−3.63</td>
<td>2.00</td>
<td>3.68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Distance from orbitale superius to apex corneae (mm), difference nonfused versus fused side</td>
<td>23</td>
<td>5.95</td>
<td>1.71</td>
<td>9</td>
<td>6.25</td>
<td>2.49</td>
<td>0.40</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Variances were not equal across groups. The t test procedure does not assume equal variances was used for this measure. In all other measures, the variances were not significantly different and the standard t test assuming equal variances was applied.

Imprecise usage of the designation “nonsyndromic” can cause confusion because it implies that a disorder is not genetic or not familial.1 For example, this term is often misapplied to patients with bilateral coronal synostosis who do not have an easily recognizable eponymous phenotype.28 Nonsyndromic is sometimes used in reference to single sutural synostosis involving either sagittal, coronal, metopic, or lambdoid junctures.29 Indeed, a genetic abnormality is rarely found in a patient who has an isolated sutural fusion. However, such a patient could have an underlying genetic cause for the synostosis. Our current screening techniques have limitations and, furthermore, it is likely that there are undiscovered gene loci responsible for craniosynostosis.

Sagittal synostosis is the most common type of single sutural fusion. To date, no known mutations causing scaphocephaly have been identified, although this abnormality can be familial. In a large series of scaphocephalic patients, Lajeunie and colleagues determined that only 6 percent were familial, and segrega-
tion analysis indicated autosomal dominant transmission. In Crouzon syndrome, sagittal and coronal synostosis can occur together in 19 percent of patients and combined sagittal-coronal-lambdoidal synostosis in 75 percent of patients. Metopic synostosis can occur with many other anomalies, some of which are known to be genetic. Lajeunie et al. found that only 5.6 percent of patients with isolated trigonocephaly were familial, 23 percent were syndromal, and 17 percent had trigonocephaly in association with other anomalies, usually involving the limbs, heart, genitourinary system, and brain. Chromosomal analysis is indicated in evaluating a trigonocephalic infant because there is an association with a number of deletions and with aneuploidy. Unfortunately, karyotyping was available in only a small number of patients in the large series of Lajeunie et al.

**Genes Causing Unilateral Coronal Synostosis**

Unilateral fusion of the coronal ring, involving the frontoparietal and frontosphenoidal sutures, is usually considered to be nongenetic and nonsyndromic. However, a small proportion of these patients will be found to have an identifiable mutation in FGFR 2, FGFR 3, or TWIST, either de novo or inherited. The parents may be unaware of an inheritable condition until the birth of a child with synostotic frontal plagiocephaly. The first step is to examine the child and parents for evidence of bilateral frontal retrusion (distance from orbitale superius to apex corneae), orbital hypertelorism (inter medial canthal dimension), macrocephaly (cranial circumference), and hand and foot anomalies. Bilateral frontal recession and orbital hypertelorism could have a common pathogenesis. Although the frontoparietal suture is open on the contralateral side, there could be an abnormality in the basilar coronal suture. Thus, bilaterally diminished growth at the frontosphenoid and/or sphenethmoid could restrict supraorbital expansion and also cause transverse (compensatory) overgrowth of the ethmoidal complex.

There are other physical findings that are specific to patients who have one of the mutations known to cause syndromic unilateral coronal synostosis. In addition, a detailed family history may identify relatives with an abnormal cranial shape or those with a record of having had an operation for craniosynostosis.

**FGFR2**

Two patients with synostotic frontal plagiocephaly were identified as having an FGFR2 mutation. Patient 4 had a G1032A transition (Ala344Ala), a common mutation for Crouzon syndrome. This does not result in an amino acid substitution but rather an abnormal splicing of the FGFR2 transcript and a deletion of 12 amino acids in the immunoglobulin IIIc domain. The same mutation was detected in the mother who had bilateral frontal retrusion and in the sister who had pansynostosis, which required total calvarial modeling. All three had second-degree orbital hypertelorism and minor hand anomalies (which are probably not associated with the mutation). A Turkish pedigree has been described with the same FGFR2 Ala344Ala mutation. As in our family, there was a wide spectrum from minor to severe manifestations of craniosynostosis, but none of the affected members had synostotic frontal plagiocephaly. Another child (patient 5) in our series had nonfamilial synostotic frontal plagiocephaly had the amino acid alteration FGFR2 Cys342Tyr, another common mutation causing Crouzon syndrome. He had borderline orbital hypertelorism (1 SD above normal) but no hand abnormalities. There is also a documented family with another mutation in FGFR2 (Lys292Glu) that caused variable phenotypes ranging from minor brachycephaly to synostotic frontal plagiocephaly.

**FGFR3**

It has been suggested that FGFR3 Pro250Arg is among the most common mutations in the human genome. Approximately 10 percent of patients with the FGFR3 Pro250Arg mutation have unilateral, rather than bilateral, coronal suture fusion, and both phenotypes can occur in the same family. Clues to this mutation include a broad, high forehead with macrocephaly, down-slanting palpebral fissures, minor brachydactyly, and anomalous toes. Carriers of this mutation can have a subtle phenotype or they can be clinically normal. On the basis of previous reports, the likelihood of finding the FGFR3 mutation in patients with synostotic frontal plagiocephaly is low, for example, four of 37 (11 percent), two of 27 (7 percent), and three of 46 (6 percent). Indeed, we found only three of 47 patients with FGFR3 Pro250Arg; two were female and none had macrocephaly or digital
needed a frontal revision. In the group suspected of having a mutation needed a foreheadplasty. Two of four patients as asymmetry and recession, and a second child formed elsewhere) to correct frontal advancement (the initial procedure was performed in very large families, but it is not diagnostic. One patient in our series (patient 9) had craniofrontonasal syndrome, as did her mother. The infant had typical features, including eurycephaly, third-degree orbital hypertelorism, a broad, short nose with bifid tip, scaphomaxillism, short neck, and narrowed, sloping shoulders. Low hairline, frizzy hair, and grooved nails did not become obvious until the child was older.

Craniofrontonasal Syndrome

Synostotic frontal plagiocephaly is reported to occur in 54 percent of patients who have the rare craniofrontonasal syndrome. In large families, craniofrontonasal syndrome was found to be transmitted as an X-linked dominant trait. The putative locus of the gene was initially mapped to the short arm, but it was more recently linked to the pericentric region of the X chromosome. This condition is unusual in that, in contrast to other X-linked disorders, boys are typically less severely affected than girls. Linkage analysis can only be performed in very large families, but it is not diagnostic. One patient in our series (patient 9) had craniofrontonasal syndrome, as did her mother. The infant had typical features, including eurycephaly, third-degree orbital hypertelorism, a broad, short nose with bifid tip, scaphomaxillism, short neck, and narrowed, sloping shoulders. Low hairline, frizzy hair, and grooved nails did not become obvious until the child was older.

Familial Coronal Synostosis without an Identifiable Mutation

Neither FGFR nor TWIST mutations were found in four patients with synostotic frontal plagiocephaly. This is curious because all patients had craniosynostosis in an immediate relative and had phenotypic findings suggestive of an FGFR mutation. For example, all had orbital hypertelorism. Patient 12 had bilateral, asymmetrical supraorbital retrusion (distance from orbitale superius to apex corneae was only 2 mm on the “normal” side), whereas her mother had symmetrical frontal retrusion. The mother of patient 10 also had synostotic frontal plagiocephaly and hypertelorism; the latter was also documented in the maternal grandmother. Another infant in this putative group (patient 11) had normal sagittal projection of the contralateral supraorbital rim and his mother was considered normal, but his maternal grandmother had had a coronal “strip” craniectomy in infancy.

It is likely that each of these four children has a causative mutation. The mutations could be in the known genes that were missed be-
cause we did not sequence the entire coding region. An alternative and more likely explanation is that these families segregate bilateral and unilateral coronal craniosynostosis linked to an unknown locus. Another, and believed to be least likely, interpretation is somatic mosaicism for a mutation affecting one side of the frontoparietal-frontosphenoidal suture.

CONCLUSIONS

Given the current state of our knowledge, discovery of a molecular change in a child with synostotic frontal plagiocephaly is infrequent. Nevertheless, every child with this phenotype and the child’s parents should be carefully examined and a detailed family history should be obtained. Molecular testing is available on a clinical basis. DNA analysis is particularly indicated if there is a positive family history of craniosynostosis, suspicious features in a parent, or additional findings in the child, such as a broad forehead, bilateral (asymmetrical) supraorbital retrusion, minor hypertelorism, or subtle anomalies of the hands. The finding of a dominant mutation in FGFR2, FGFR3, or TWIST in such a circumstance has obvious importance for counseling the parents and the patient.42

Knowledge of a molecular diagnosis also alerts the surgeon. Preoperative anthropometric documentation of supraorbital rim-to-corneal apex (distance from orbitale superius to apex corneae) has technical implications. Those infants with synostotic frontal plagiocephaly without an identifiable mutation usually have a normal distance from orbitale superius to apex corneae on the contralateral side and, consequently, fronto-orbital advancement is only necessary on the affected side. However, those infants found to have a mutation (or suspected of having a mutation) exhibit bilateral supraorbital recession and, consequently, bilateral (asymmetrical) advancement of the bandeau is necessary.

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REFERENCES


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