Familial nonsyndromic craniosynostosis with specific deformity of the cranium

Case report

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An otherwise healthy, developmentally normal 3-week-old male infant presented with complex multisuture craniosynostosis involving the metopic suture and bilateral coronal sutures with frontal prominence and hypotelorism. Frontal craniotomy and bilateral frontoorbital advancement remodeling were performed at the age of 5 months. The postoperative course was uneventful. The child’s development was normal up to 8 months after the operation. His father and grandfather had similar specific deformities of the cranium, but no anomaly of the extremities was found, and conversation suggested that their intelligence was normal, excluding the possibility of syndromic craniosynostosis. A DNA analysis revealed large-scale copy number polymorphism of chromosome 4 in the patient and his family, which may include the phenotype of the cranium. Neither FGFR mutation nor absence of a TWIST1 mutation in the sequence from 291 to 1087, which includes DNA binding, Helix1, Loop, and Helix2, was identified. The patient apparently had a rare case of familial nonsyndromic craniosynostosis. The authors plan further genomic analysis of this family and long-term observation of the craniofacial deformity of this patient.

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KEY WORDS • craniosynostosis • hypotelorism • familial case • gene search • congenital anomaly

Craniosynostosis syndrome is a congenital anomaly of the cranium with an incidence of 4–5 per 10,000 live births.3 Craniosynostosis occurs as 2 types: nonsyndromic craniosynostosis, involving only dysmorphology of the cranium with no familial history, and familial syndromic craniosynostosis, which shows autosomal-dominant inheritance and is associated with other anomalies such as facial hypoplasia or anomaly of the extremities. We treated a young boy who presented with complex multisuture craniosynostosis involving the metopic suture and bilateral coronal sutures with frontal prominence and hypotelorism. The boy’s father and grandfather had similar specific deformities of the cranium; consequently we examined the genetic characteristics of this familial case.

Case Report

History and Presentation. This 3-week-old boy was born at 41 weeks and 3 days of gestation. The pregnancy was uneventful, and his birth weight was 3620 g. He was referred by his physician for evaluation of cranial deformation and protrusion of the forehead, which was noticed immediately after birth.

On admission, physical examination revealed brachycephaly, protrusion of the forehead, hypotelorism, and a high-arched palate (Fig. 1), but no signs of intracranial hypertension such as papilledema or pitting edema; no deformities of the extremities were identified. The patient was developmentally normal for his age of 4 months. Analysis

Abbreviations used in this paper: CNV = copy number variation; FGFR = fibroblast growth factor receptor; SNP = single-nucleotide polymorphism.
of a blood sample revealed no abnormalities. Skull radiography, 2D CT, and 3D CT revealed premature fusion of the bicoronal and metopic sutures and hypotelorism (Fig. 2). Magnetic resonance imaging showed that the underlying brain appeared normal and that the protrusion of the forehead contained cerebral parenchyma.

The patient’s father and grandfather had similar specific deformities of the cranium (Fig. 3), but his mother and elder sister had normal facial features. Therefore, we suspected syndromic craniosynostosis, but physical examination detected no anomaly of the extremities, and interviews with the father and grandfather suggested normal intelligence. However, no neuropsychological testing, IQ testing, or radiological examinations were performed, and the details of their craniosynostosis remained unknown.

Operation. Frontal craniectomy and bilateral fronto-orbital advancement remodeling were performed when the patient was 5 months old. To reshape the hypotelorism, part of the parietal bone was grafted to the center of the supraorbital bar, which was detached from the skull, and the reshaped supraorbital bar was relocated 1.5 cm anterior to its previous position and fixed to the temporal bone using absorbable plates. The parietal bone was detached and grafted to the frontal area of the supraorbital bar. The parietal bone defect was repaired using a flattened graft of the deformed frontal bone, an absorbable mesh plate, and parts of the parietal bone. The detached bone from the protrusion area was also flattened and grafted again (Fig. 4).
Postoperative Course. Eight months after surgery, the protrusion of the forehead had become more rounded, the upper half of the orbit was extended, and the shape of the cranium was improved (Fig. 5). The patient’s development was normal up to 8 months after surgery, and his appearance was satisfactory for his family.

Genetic Analysis. A genome-wide study of the patient, his father, and his grandfather was performed using the GeneChip Genome-Wide Human SNP Array 6.0 (Affymetrix, Inc.). We also performed DNA analysis for the TWIST1 mutation. The SNP array examines the copy number of the genomic DNA and analyzes the area of large-scale CNVs, which indicates the loss or gain area of the genomic DNA. In this case, we compared the common CNV for of the patient, his father, and his grandfather with that of the Japanese population and screened for the genomic anomaly on a large scale. This genomic analysis revealed a common copy number loss area on 4p14, which includes NEDD4-binding protein 2 (N4BP2) (Fig. 6); such a copy number loss is absent in the normal Japanese population. To examine further genetic backgrounds, we screened for mutations in the FGFR1–3 genes by using direct DNA sequencing. No FGFR mutation was identified in this family. Our investigation of this family revealed another female relative with similar cranial deformity, confirming the presence of autosomal dominant inheritance (Fig. 7).

Discussion

Nonsyndromic craniosynostosis involving only dysmorphology of the cranium usually occurs as solitary cases, whereas familial syndromic craniosynostosis is associated with other anomalies such as facial hypoplasia or anomaly of the extremities. Therefore, the present familial case of nonsyndromic craniosynostosis is rare.

Apert syndrome, Crouzon syndrome, and Pfeiffer syndrome all show autosomal-dominant inheritance in syndromic craniosynostosis. However, our patient had facial anomaly, no anomaly of the extremities, and normal development, indicating the absence of these syndromes. The diagnosis of Saethre–Chotzen syndrome is based on the presence of bilateral craniosynostosis, blepharoptosis, anomaly of the ears, syndactyly, and normal intelligence. The appearance of our patient and his father and
grandfather was different from that of patients with Saethre-Chotzen syndrome. However, because a previously reported patient with Saethre-Chotzen syndrome had a very similar cranial deformation and facial anomaly,3 we performed DNA analysis. Because no TWIST1 mutation was identified, Saethre-Chotzen syndrome can probably be excluded.

Genetic examination with the GeneChip Genome-Wide Human SNP Array 6.0 compared the common CNV area for the patient, his father, and his grandfather with that for the normal Japanese population and screened for the genomic anomaly on a large scale. Recently, the importance of CNVs, such as loss, duplication, and triplication of a gene, has been recognized as an interindividual genetic variation across the human genome.5 We found such a loss or low copy number of N4BP2 in this family, but whether this information includes the phenotype of the cranium remains unclear. We plan further genomic analysis in this family. Chromosome 4 contains not only the common CNV area, but also the FGFR3 gene on 4p16.3. Recent studies have demonstrated that mutations in 3 or 4 known FGFR genes are responsible for craniosynostoses, including Crouzon, Apert, Pfeiffer, and Jackson-Weiss syndromes, and specific mutations in the FGFR1, FGFR2, and FGFR3 loci have been identified.2,4 Therefore, we screened for mutations in the FGFR1–3 genes by using direct DNA sequencing but identified no FGFR mutation in this family. Further genetic analysis may, however, identify another genetic anomaly.

Our patient showed not only deformity of the skull, but also protrusion of the forehead, which was the reason for referral to our hospital. Generally, a congenital protruding lesion in a medial area of the head is likely to be diagnosed as a manifestation of cranium bifidum cysticum, such as meningocele or encephalocele. In our case, the protrusion of the forehead was perfectly covered with

Fig. 6. Genomic analysis showing a common copy number polymorphism area on chromosome 4 including genetic information. Blue arrowheads pointing up indicate copy number gain; red arrowheads pointing down indicate copy number loss.

Fig. 7. Genealogical tree of the patient showing a female relative (dark circle) with similar cranial deformity, indicating autosomal dominant inheritance.
dura mater, bone, and skin and did not change with crying, so our diagnosis was protrusion of the forehead with cerebral parenchyma and not cranium bifidum cysticum.

Patients with trigonocephaly or oxycephaly may suffer intellectual disability because of premature fusion of the metopic suture leading to narrowing of the space for the frontal lobe. In our patient, the reason for the protrusion of the forehead is unclear, so the deformity of the cranium may change over several years, and this patient will require a long follow-up.

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: Shimizu. 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: Shimizu. Study supervision: Komuro, Miyajima, Arai.

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