

Isolated Sagittal Synostosis in a Boy with Craniofrontonasal Dysplasia and a Novel *EFNB1* Mutation

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Summary: Craniofrontonasal syndrome (CFNS) is a rare X-linked disorder that shows greater severity in females and is largely attributed to mutations in *EFNB1*. A 7-year-old boy presented with hypertelorism, broad nasal root, midfacial hypoplasia, mandibular prognathia, ptosis, and scaphocephaly was clinically diagnosed with CFNS. Three-dimensional computed tomographic scans confirmed the isolated sagittal synostosis. His mother also showed clinical features of CFNS, but less severe. Genetic tests uncovered a novel C to T mutation at nucleotide 466 (c.466C>T) in exon 1 of *EFNB1* for both. To the best of our knowledge, this is the only reported incident of CFNS in a male child exhibiting isolated sagittal synostosis. (*Plast Reconstr Surg Glob Open* 2015;3:e427; doi: 10.1097/GOX.0000000000000369; Published online 19 June 2015.)

Craniofrontonasal syndrome (CFNS) is a rare X-linked syndrome commonly associated with mutations in *EFNB1*.¹⁻³ It is characterized by a more severe phenotype in heterozygous females,⁴ which typically display dysmorphic features including bicoronal synostosis, hypertelorism, broad nasal root with bifid tip, brachycephaly, frontal bossing, corpus callosum agenesis, and thick wiry hair with orbital asymmetry and strabismus.⁵ The extracranial features include multiple skeletal malforma-

tions, such as sloping shoulders, dysplastic clavicles, thoracic skeleton asymmetry, and unilateral breast hypoplasia, in addition to longitudinally grooved fingernails, mild cutaneous syndactyly, and umbilical or diaphragmatic hernia. Sagittal synostosis has been reported in one female with CFNS, where the sagittal synostosis was accompanied by bicoronal synostosis.⁶ Hemizygous males usually manifest hypertelorism, cleft lip, and/or cleft palate.⁷ However, unilateral or bilateral coronal craniosynostosis among 8 male children with CFNS have been reported.⁸⁻¹² Herein, we report a 7-year-old boy diagnosed with a novel CFNS phenotype, chiefly isolated sagittal synostosis, arising from a previously unreported *EFNB1* mutation.

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CLINICAL REPORT

A 7-year-old boy with sagittal synostosis was referred for ophthalmic evaluation to rule out raised intracranial pressure. His family history was

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unremarkable. However, on examination, his mother was noted to have hypertelorism and a broad nasal tip along with a medical history of an umbilical hernia and widely spaced incisors. The patient's initial symptoms included frequent headaches, history of obstructive sleep apnea, and abnormal head shape. Examination confirmed scaphocephaly, microcephaly, midfacial hypoplasia, mandibular prognathia, ptosis with upslanting palpebral fissures, large ears (>97th percentile), broad nasal root and bridge with an inner canthal distance of 3.7 cm (>97th percentile), and interpupillary distance of 6.9 cm (>97th percentile) suggestive of hypertelorism (Fig. 1). His intraoral examination revealed an intact palate with class III malocclusion and widely spaced incisors. A three-dimensional computed tomographic scan of the head (Fig. 2) revealed fusion of the sagittal suture only and mandibular prognathia with crowding of the teeth. Fundus examination was negative for papilledema, but revealed bilateral mild exocyclotorsion of the fundi. The patient also exhibited hyperopia with astigmatism in both eyes. The facial appearance together with the eye findings pointed to a diagnosis of CFNS.

GENETIC TESTING

All genetic testing were conducted in laboratories certified under the Clinical Laboratory Improvement Amendments of 1988. Previous genetic testing of the patient included a karyotype at a 600 G-band level of resolution and an oligoarray, both of which demonstrated a normal chromosomal complement. After the ophthalmic examination, venous blood was drawn and genomic DNA extracted. Sequencing of exons 1 through 5 of *EFNB1* revealed a novel C to T mutation at nucleotide 466 in exon 1 (c.466C>T) (Fig. 3A), which changes a codon for the nonpolar arginine to the polar cysteine at amino acid

156 (p.Arg156Cys) (Fig. 3B). This arginine is highly conserved from mammals, chicken, frogs, and zebrafish in addition to being conserved in *EFNB2* and *EFNB3*. The amino acid change is at the terminus end of the *EFNB1* ephrin receptor-binding domain, the main functional domain. The mother was found to have the same mutation with a less severe phenotype, whereas the younger brother was negative for site-specific mutation analysis and had no signs of CFNS. Written informed consent was obtained from the mother of the child for being included in the study.

DISCUSSION

Although sagittal synostosis has been previously reported in a girl with CFNS, the synostosis was multisutural and included bilateral coronal synostosis.⁶ CFNS is associated with mutations in 1 of 5 exons in *EFNB1* at chromosome Xq13.1, 42% of which are missense changes in exons 2 or 3 that encode the extracellular domain. Mutations in the cytoplasmic domain encoded by exons 4 and 5 (Fig. 3B) have also resulted in CFNS.^{7,13} Previously described mutations in the gene have accounted for coronal craniosynostosis,^{2,13,14} and a review of the literature failed to reveal any individual (male or female) affected by isolated sagittal synostosis.

Genetic testing revealed a missense mutation at position 466 of *EFNB1* from a C to a T in exon 1, leading to an amino acid substitution of an arginine to a cysteine at amino acid 156 (p.Arg156Cys). This arginine is highly conserved not only among several vertebrate species, ranging from fish to primates, but also among human *EFNB* members 1–3.

EFNB1 has several basic functions in cell adhesion, migration, and patterning^{15–18} to regulate many developmental roles, including bone formation,^{19,20} skeletogenesis,²¹ neuronal wiring,^{22,23} angiogenesis,²⁴ and retinocollicular mapping,²⁵ in addition to disease monitoring such as inflammation²⁶ and blood



Fig. 1. Seven-year-old boy with CFNS. A, Frontal view of the 7-year-old boy displaying microcephaly, hypertelorism, broad nasal root, ptosis, mandibular prognathia, and midface hypoplasia. B, Side profile of the boy showing large ears, mandibular prognathia, midface hypoplasia, and, together with the left-hand panel, scaphocephaly.

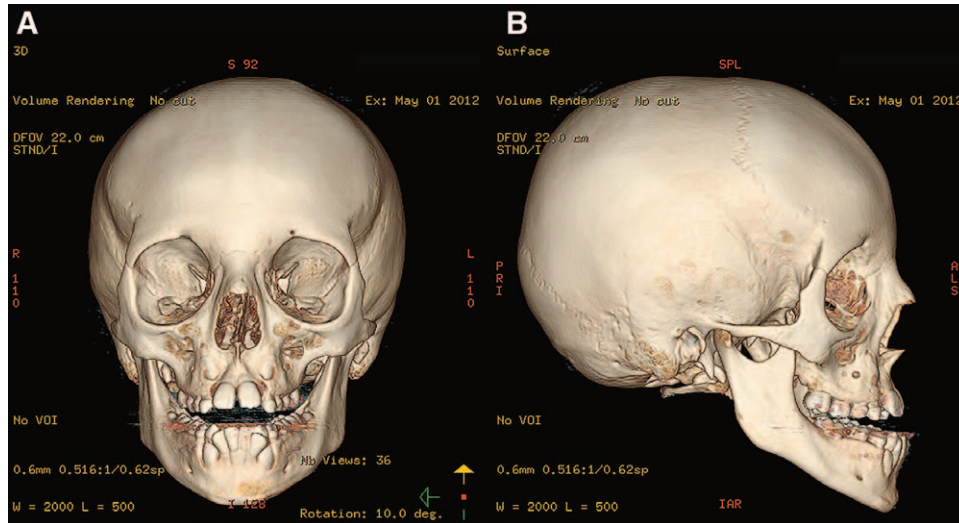


Fig. 2. Computed tomography scans demonstrating sagittal synostosis, mandibular prognathia, and dental crowding in the lower mandible. A, Front view. B, Right-side profile.

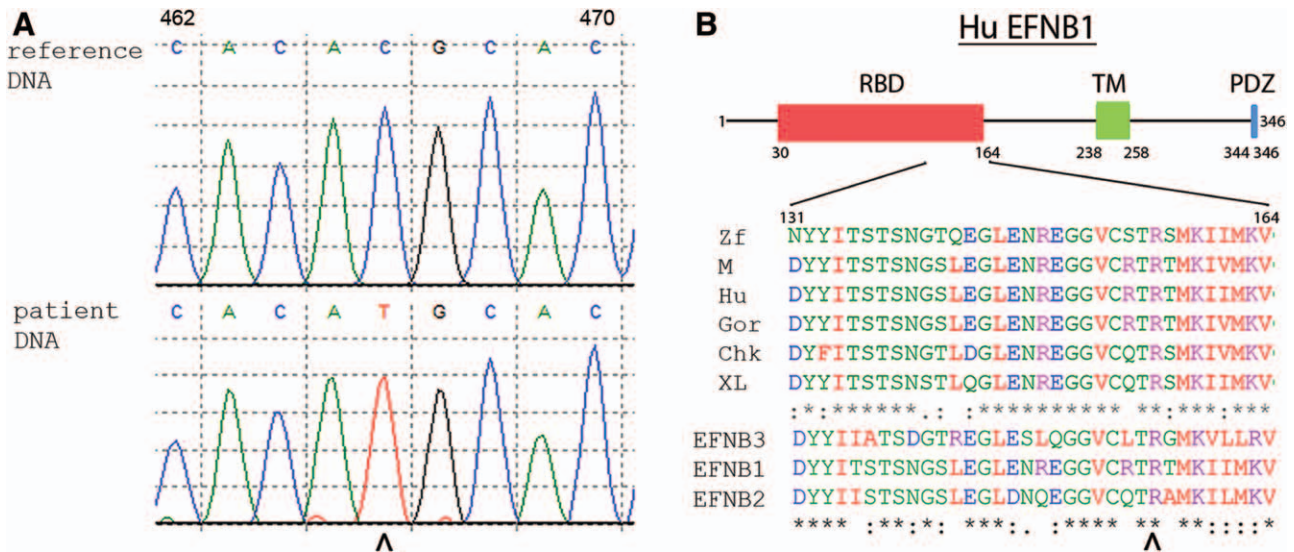


Fig. 3. A, Chromatogram showing the C to T missense mutation at nucleotide 466 (c.466C>T) in *EFNB1*. The top portion is the reference genome and the bottom portion is the patient sample showing the missense mutation at position 466 (denoted by ^). B, Missense mutation, p.Arg156Cys (denoted by ^), in the RBD of *EFNB1*. The protein structure of human *EFNB1* is shown at the top. Amino acid sequence alignments from several vertebrate species in the region of the missense mutation are at the bottom, together with the human sequence alignments for human *EFNB1*, 2, and 3 in the same region. The numbers refer to amino acid positions for the human *EFNB1* protein. Chk indicates chicken; Gor, gorilla; Hu, human; M, mouse; RBD, receptor-binding domain; TM, transmembrane; XL, *Xenopus laevis* (frog); Zf, zebrafish.

pressure monitoring.²⁷ Previous characterization of the *EFNB1* protein structure²⁸ enabled the location of the highly conserved arginine to be determined within the essential receptor-binding domain in the extracellular region. This domain binds to the Eph receptor, and loss of binding to the receptor leads to craniofacial defects such as CFNS.² The mechanism explaining the more severe phenotype in affected heterozygote females compared with homozygous males is unclear, but the random X-inactivation in

heterozygote females leading to the mosaic state is the most likely explanation. This is because with transmembrane proteins, such as *EFNB1*, cellular interference between normal and mutant *EFNB1*-expressing cell populations leads to the diseased condition.⁹

CONCLUSIONS

We present a case of isolated sagittal synostosis in a male child with a novel mutation in the *EFNB1*.

This case is significant when providing genetic diagnosis and counseling in families suspected of CFNS or in females with known *EFNB1* mutations. Also unusually, the child is more severely affected when compared with his mother who shares the same mutation. We propose the differential diagnosis of CFNS be expanded to include isolated sagittal synostosis in the presence of other suggestive facial dysmorphology, such as hypertelorism, broad nasal tip, or widely spaced incisors, and that this diagnosis be considered in both males and females with suggestive symptoms.

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PATIENT CONSENT

Parents or guardians provided written consent for the use of the patient's image.

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