

Case Reports

Craniofrontonasal Dysplasia: A Report of Two Chinese Families and Literature Review

HM LUK, IFM LO, TMF TONG, STS LAM

Abstract Craniofrontonasal dysplasia (CFND) is a rare X-linked developmental malformation syndrome characterised by frontonasal dysplasia and coronal craniosynostosis. We have reported two Chinese cases of CFND, one isolated and the other familial. By reviewing the literature, the clinical features and the mechanism underlying the "genetic paradox" were discussed. It is hoped that with better understanding of the pathogenesis and application of *EFNB1* gene analysis, CFND can be better recognised, which in turn not only improves the management but is also important for genetic counselling.

Key words Chinese; Craniofrontonasal dysplasia; *EFNB1* gene; Genetic paradox

Introduction

Craniofrontonasal dysplasia (CFND, OMIM#304110) is a rare X-linked developmental malformation syndrome due to mutations of the *EFNB1* gene. It was first described by Cohen in 1979¹ and is characterised by frontonasal dysplasia together with coronal craniosynostosis. With more understanding of its molecular basis, the clinical phenotype of craniofrontonasal syndrome (CFNS) is well delineated. Apart from midline craniofacial abnormalities and craniosynostosis, there are usually associated skeletal and ectodermal malformations. CFND has a peculiar X-linked pattern of inheritance. In most X-linked dominant or recessive conditions, males are more commonly and more severely affected than females. However, the reverse

is true in CFND; more females are affected than males and paradoxically the clinical manifestations are more severe in heterozygous females than hemizygous males. This sex dependent phenomenon is known as a "genetic paradox".² Up to now, only 150 cases are reported in the literature with most of them from western populations.³ We have reported 2 Chinese families with CFND confirmed by *EFNB1* gene analysis in Hong Kong.

Case Report

Case 1

The first was an isolated case. The proband was a girl who was the first child of a non-consanguineous Chinese couple. The maternal and paternal age at delivery were 26 and 29 years, respectively. The antenatal course was uneventful and family history was non-contributory. She was born at 37 weeks' gestation with birth weight of 2.85 kg. She was noted to have facial dysmorphism and abnormal head shape after delivery and was then referred to the genetic service. Physical examination (Figure 1) showed multiple dysmorphic features including brachycephaly, facial asymmetry, sparse and kinky hair, sparse eyebrows, low-set and posteriorly rotated ears, hypertelorism, epicanthic folds, downslanting palpebral fissures, short nose with broad nasal bridge and bifid nasal

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tip, prominent columella, low posterior hairline, and postaxial polysyndactyly of right foot. Other organ systems were normal. Computerised tomography (CT) with 3-dimensional reconstruction was performed and showed premature closure of the left coronal suture. Magnetic resonance imaging (MRI) of the brain was normal. Surgical operation for the left coronal craniosynostosis was done at 6 months of age. Although she had mild developmental delay initially, she caught up afterwards with age-appropriate development now. Based on the characteristic facial gestalt and coronal craniosynostosis, the clinical diagnosis of craniofrontonasal dysplasia was made. *EFNB1* gene analysis showed a *de novo* heterozygous c.29_33dupGCAAG mutation (Reference sequence: NM_004429.4), which was a frameshift mutation predicted to result in premature termination of translation at the 36th codon (p.Trp12Alafs*36). This was a novel mutation not ever reported in other CFND patients before.

Case 2

The second was a familial case. She was the first child of a non-consanguineous Chinese couple, and was born at 38 weeks' gestation with birth weight of 3.1 kg by elective lower segment Caesarean section due to maternal bicornuate uterus. Paternal and maternal age at delivery were 35 and 34 years, respectively. Amniocentesis had been performed for advanced maternal age and showed normal 46,XX. Antenatal ultrasound was normal. The proband was referred to the genetic service soon after birth for dysmorphic facial features namely brachycephaly, frontal bossing, hypertelorism, epicanthic folds, facial asymmetry and bifid nasal tip. There were no digital or nail abnormalities. Other organ systems were normal. Skull X-ray showed right coronal craniosynostosis. MRI of the brain was normal. Upon examination of the mother, hypertelorism and longitudinal grooves on the nails were noted (Figure 1). The clinical diagnosis of CFND was made. The proband subsequently developed repeated vomiting and feeding intolerance. Further investigations including upper gastrointestinal contrast study and CT thorax showed a small diaphragmatic hernia, which was surgically repaired at the age of 8 months. Her craniosynostosis and facial asymmetry were managed conservatively. Her physical growth and development were normal. Two years later, her mother was pregnant again carrying a female fetus. With the knowledge of a 50% recurrence risk, she decided to keep the baby. Although antenatal ultrasound showed normal findings, the second daughter was also found to have similar facial dysmorphism to her elder sister's. CT

scan of brain was normal without evidence of craniosynostosis. She was also diagnosed to have diaphragmatic hernia which manifested as intermittent vomiting, and was repaired at 3 months of age. Subsequent *EFNB1* gene analysis in this family showed a heterozygous c.191C>T mutation (Reference sequence NM_004429.4) which changed the 54th amino acid from Proline to Leucine (p.Pro54Leu) in both daughters and the mother. This mutation has been reported in other CFND patients.⁴

Discussion

The classical description of CFND includes facial asymmetry, hypertelorism, broad or bifid nasal tip and brachycephaly due to coronal craniosynostosis. However, the clinical manifestations are actually highly variable even within a family. Apart from craniofacial malformation, extra-cranial features are not uncommon. This was well illustrated by the presence of postaxial polysyndactyly in case 1, and bicornuate uterus, diaphragmatic hernia and grooved nails in case 2. These extra-cranial features are also important clues to the diagnosis. The clinical findings of CFND are summarised in Table 1.³

The interesting "genetic paradox" associated with CFND can be explained by specific features of the *EFNB1* gene. *EFNB1* was identified as the causative gene for CFND in 2003 and is located on the X chromosome at Xq13.1 region. It consists of 5 exons and encodes the transmembrane protein ephrin-B1, a ligand for ELK. Its main function is to control cell sorting, migration and growth that is crucial for tissue morphogenesis.⁵ In hemizygous males, due to binding promiscuity, the ephrin-B1 deficit can be compensated by other ephrin molecules, which results in a less severe clinical phenotype. However, in heterozygous females, cell-cell interactions become more complicated in the presence of random X-inactivation. With X-inactivation, a mosaic pattern of wide type and mutant ephrin-B1 proteins exists. The mutant protein will interfere with the wide type, a phenomenon known as cellular interference and account for the "genetic paradox" seen in CFND.^{2,5} Different X-inactivation patterns can also account for intrafamilial variability in expressivity.

Although the exact pathogenesis of CFND is not yet completely understood, animal models showed that abnormal neural crest migration and craniofacial morphogenesis might play a role.² Therefore, CFND is now considered an example of neurocristopathy.

Depending on the selection criteria, germline mutations

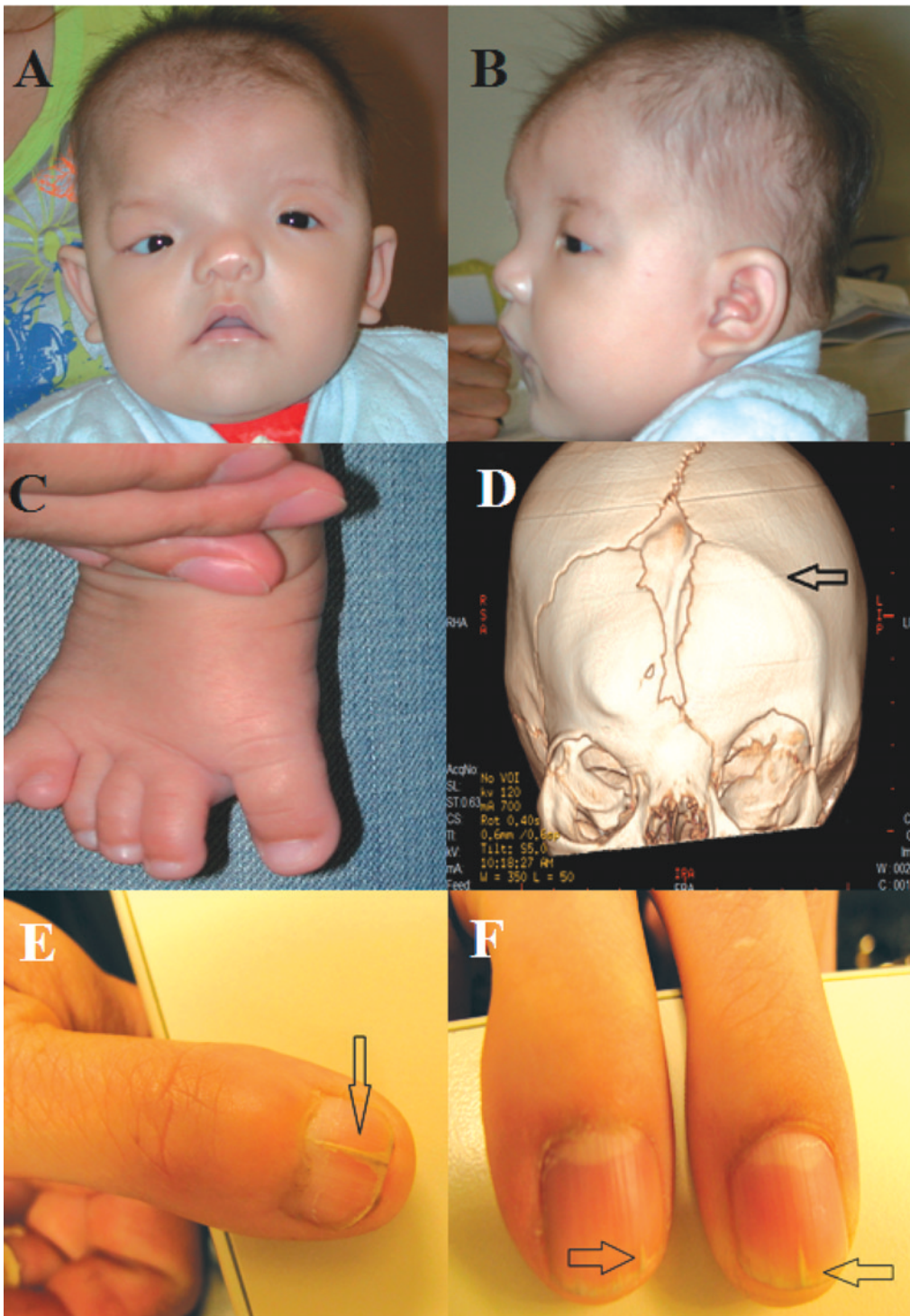


Figure 1 (A and B) Front and lateral views of patient 1 showing brachycephaly, facial asymmetry, sparse and kinky hair, low-set and posteriorly rotated ears, sparse eyebrows, hypertelorism, epicanthic folds, downslanting palpebral fissures, short nose with broad nasal bridge and bifid nasal tip, prominent columella, and low posterior hairline. (C) Postaxial polysyndactyly of the right foot in patient 1. (D) Computerised tomography scan of skull with 3-dimensional reconstruction showed left unilateral coronal craniosynostosis in patient 1. (E and F) Nail examination showed longitudinally grooved nails in mother and daughter of family 2. (Parental consent obtained for use the photos)

Table 1 Clinical features of CFND and their relative frequencies²

Frequency	Craniofacial malformation	Neurological system	Skeletal and genitourinary system	Dermatological system
>50%	Hypertelorism, frontal bossing, facial asymmetry, broad or bifid nasal tip, brachycephaly, coronal craniosynostosis, high-arched palate	Normal development, strabismus		
10-50%	Short neck, webbed neck	Developmental delay, corpus callosum hypoplasia or agenesis	Sprengel anomaly, scoliosis, asymmetric chest, unilateral breast hypoplasia	Asymmetric limbs, digit anomalies like syndactyly, clinodactyly and polydactyly, grooved nails, thick and wiry hair, low anterior hair line, widow's peak
Occasionally	Cleft lip and/or palate, cranium bifidum occultum	Sensorineural hearingloss, cerebellar dysplasia	Asymmetry of pectoralmuscles, axillarypterygium, diaphragmaticernia, umbilicalhernia, bicornuateuterus, duplication of kidney and uterus	Broad hallux, jointlaxity

of *EFNB1* gene are detected in about 80% of CFND cases, with two thirds being *de novo* mutations.^{2,3,6} Up to now, more than 130 distinct *EFNB1* mutations have been reported, with most of the mutations located in exons 2 and 3 that encode the extracellular ephrin domain.^{3,7} No genotype-phenotype correlation can be delineated yet. Unlike other craniosynostotic syndromes, advanced paternal age is not a risk factor for CFND.⁸

As for the two mutations that were identified in these two Chinese families, the 5-bp duplication was a novel mutation that was predicted to result in a truncated protein product without the extracellular domain and thus was likely a null mutation. The missense mutation P54L was a reported mutation.⁴ This mutation was located in exon 2 of the *EFNB1* gene encoding the ephrin extracellular domain that is evolutionarily highly conserved among different species. Missense mutations in such region are predicted to abrogate ephrin-B1 receptor binding function.⁴ However, up till now, no definite genotype-phenotype correlation was reported for *EFNB1* gene

Congenital diaphragmatic hernia (CDH) has been well

described in CFNS, but there are only 5 mutation-confirmed cases reported in the literature.⁹ Our second family is probably the first mutation-confirmed CFND family with recurrent CDH in 2 female siblings. Up to now, the only known gene that is associated with nonsyndromic CDH in humans is the *FOG2* gene. The role of *EFNB1* in CDH is still unknown. Whether it is the main culprit or it requires other unknown modifiers needs further studies.

For familial CFND, genetic counselling is relatively straightforward. However, for spoardic cases, recurrence risk prediction is challenging due to the possibility of occult mosaicism in their apparently normal parents. In one study, about 18% of CFND cases have somatic mosaicism due to post-zygotic mutation in the *EFNB1* gene.¹⁰ If mosaicism is present in the patient, the recurrence risk for subsequent siblings is very low. However, if mosaicism exists in one of the parents, the recurrence risk for the next daughter will be increased significantly, up to 50% and 100% for maternal and paternal mosaicism, respectively. Therefore, during family cascade screening, particular attention should be paid to look for mosaicism. Molecular study of different

tissues like buccal swabs and hair follicles may provide valuable information on mosaicism. If paternal origin of the mutation has been established, molecular analysis of semen would be informative but is only available in research settings.¹¹

The management of CFND is similar to that of other craniosynostotic syndromes and requires a multidisciplinary team approach. Nevertheless, CFND is more demanding on the surgical technique due to variable craniosynostosis, craniofacial asymmetry and hypertelorism. It has been proposed that craniosynostotic correction should be performed between the age of 3 to 6 months to prevent the elevation of intracranial pressure. Facial bipartition for facial asymmetry and hypertelorism should be carried out at around 5 to 6 years of age after the eruption of maxillary central incisors in order to avoid severe disruption of occlusal plane. Correction of nasal and canthal deformities should also be carried out during the time of facial bipartition and be revised during the adolescent period when the skeletal system has become mature.¹² As strabismus and dissociated eye movements are more common in CFND, regular ophthalmological examination is recommended for all CFND patients so as to allow early detection and timely intervention of visual impairment.¹³ Finally, as CDH has been well described in CFNS,⁹ high index of suspicion with appropriate imaging should be performed.

Conclusion

We have reported the first 2 cases of mutation-confirmed CFND in Chinese. The clinical features and the proposed mechanism underlying the "genetic paradox" have been reviewed. With increased awareness among medical professionals and application of *EFNB1* gene molecular testing, CFND can be better recognised, which in turn not only improves the quality of management but is also important for risk assessment during genetic counselling.

Declaration of Interest

There are no conflicts of interest.

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