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Clinical Spotlight

Craniofacial dysmorphism, what is your diagnosis?

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A 12-year-old girl, presented to the Outpatient Department with congenital non- progressive cranial-facial-digital abnormalities and normal developmental milestones, had a past medical history of congenital heart disease (atrial septal defect, tricuspid valve regurgitation) under long-term follow-up. Clinically, specific phenotype was characterized by widely separated eyes (hypertelorism), broad nasal root, bifid nasal tip, clinodactyly over left 5th finger and slim fingers Fig. 1 (Panel A,B and C). Computed tomography of her head revealed no skull asymmetry or brachycephaly (Panel D). Her mother showed similar characteristics but with facial asymmetry (Panel E) due to isolated right coronal suture craniosynostosis that had received surgical correction. Although craniofrontonasal dysplasia was our first impression of diagnosis according to the index case's clinical manifestations, mode of inheritance (most likely autosomal dominant or X-linked dominant disorder) and a hint of isolated craniosynostosis from her mother, several disorders having similar symptoms to those of craniofrontonasal dysplasia, including Aarskog syndrome (widely spaced eyes and broad nose; but lack of low-set ear, short, broad hands with stubby hands, genital malformations and mental retardation), Frontonasal dysplasia (for her hypertelorism, broad nose, vertical grove down the tip of the nose; fall short of nose split into two, brachycephaly, cleft lip and/or palate, microphthalmia and mental retardation; sporadic occurrence), Frontofacionasal dysplasia (wide space between the eyes, no cleft lip and/or palate, telecanthus, brachycephaly, mid-face hypoplasia; autosomal recessive inheritance), Greig cephalopolysyndactyly syndrome (widely separated eyes; but no prominent forehead, polydactyly and/or syndactyly) and a variety of craniosynostosis (not seen in this index patient, but her mother had prematurely closed right coronal skull suture) syndromes, should be on the list of differential diagnoses. Craniofrontonasal dysplasia has an X-linked dominant inheritance mode. Direct sequencing of all exons and exon-intron boundaries of the *EFNB1* gene subsequently revealed C-to-G transversion at nucleotide 354 in exon 2 [*EFNB1* (Xq12), exon2: c.354C>G, p.S118R] (Panel F). This disease-causing novel mutation was inherited from her mother with intrafamilial phenotypic variability. Craniofrontonasal dysplasia is inherited as an X-linked dominant pattern. A female inherits one X chromosome from each parent, while a male gets an X chromosome from the mother and a Y from the father. The male

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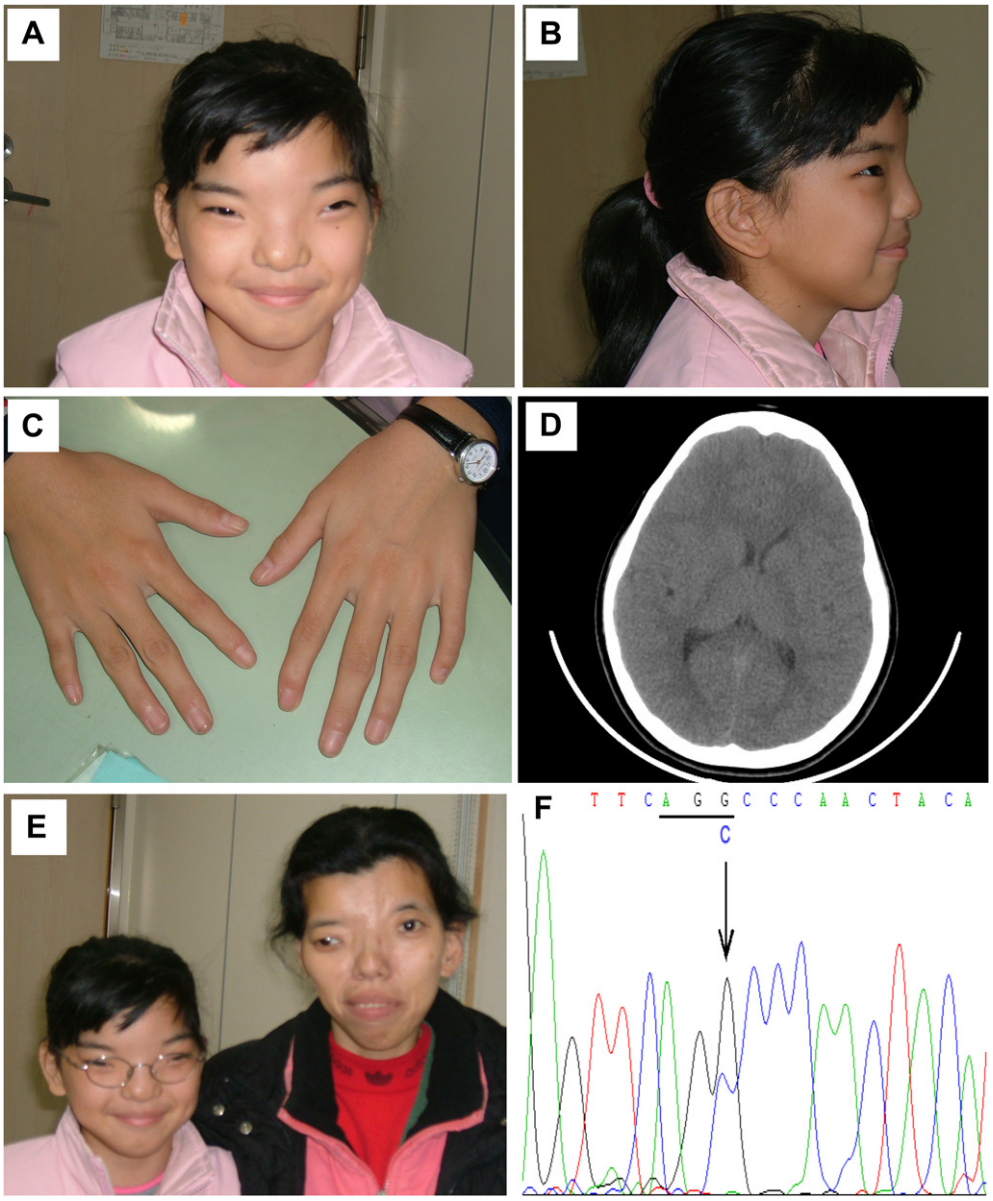

Fig. 1 – Panel A,B,C - peculiar phenotypes of the index patient; Panel D - neuroimage of index case; Panel E - index patient's mother on right side of the picture; Panel F - mutated nucleotide of EFNB1 gene depicted.
(Note: Informed consent to publish patient photographs was obtained.)

thus displays X-linked trait from the mother, while a female may have X-linked traits from either parent. Because of dominantly inherited pattern, only one copy of defective gene *EFNB1* is necessary for the disease to appear. No definite therapy for craniofrontonasal dysplasia is available so far, except for plastic surgery.