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Research Letter

Pfeiffer syndrome with *FGFR2* C342R mutation presenting extreme proptosis, craniosynostosis, hearing loss, ventriculomegaly, broad great toes and thumbs, maxillary hypoplasia, and laryngomalacia

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Dear Editor,

The male propositus was the first child of a healthy unrelated couple. The mother was 32 years old, and the father was 37 years old at his birth. There was no family history of congenital malformations. The pregnancy was uncomplicated and associated with unremarkable prenatal ultrasound findings. He was born at 39 weeks by cesarean section due to breech presentation. Birth weight was 2740 g, length was 49 cm, and head circumference was 33.5 cm. After birth, he was found to have severe proptosis, bilateral hearing loss, brachycephaly, hypertelorism, broad big toes and thumbs, low-set ears, and midface hypoplasia (Figs. 1 and 2). He had suffered from respiratory distress and cardiac arrest because of laryngomalacia that required a surgery to release and repair larynx. Radiographs showed multisynostoses of sagittal and coronal sutures, shallow orbits, brachycephaly and ventriculomegaly (Fig. 3). A diagnosis of type 3 Pfeiffer syndrome was made. Cytogenetic analysis revealed a karyotype of 46,XY. Molecular analysis of peripheral blood at age three months revealed a heterozygous c.1024T>C, TGC>CGC transition, leading to a p.Cys342Arg (C342R) mutation in the *FGFR2* gene (Fig. 4).

We previously reported Pfeiffer syndrome with *FGFR2* mutation in two infants [1,2]. In this presentation, we additionally report a case of Pfeiffer syndrome with a *FGFR2* C342R mutation. Both Apert syndrome and Pfeiffer syndrome can be caused by *FGFR2* mutations. Apert syndrome is usually associated with *FGFR2* S252W and P253R mutations, and may manifest severe syndactyly of hands and feet but no cloverleaf skull or proptosis, whereas Pfeiffer syndrome is usually associated with *FGFR2* W290C, Y340C, C342R and S351C mutations, and can be associated with a cloverleaf skull, proptosis and broad great toes and thumbs [3,4]. The *FGFR2* mutations of W290C (p.Trp290Cys), Y340C (p.Tyr340Cys), C342R (p.Cys342Arg) and S351C (p.Ser351Cys) have been reported to be associated with severe phenotypic features of Pfeiffer syndrome such as a cloverleaf skull, extreme proptosis, midface hypoplasia, hydrocephalus, tracheal sleeve, Chiari malformation, radio-ulnar-humeral synostosis and early infant death [3,4]. In a review of 25 patients with *FGFR2* C342R mutation, Lajeunie et al [3] found 22 cases with Pfeiffer syndrome, two cases with Crouzon syndrome and one case with Jackson-Weiss syndrome. *FGFR2* C342R mutation has been occasionally observed in patients with Crouzon syndrome [5,6], Jackson-Weiss syndrome [7] and Antley-Bixler syndrome [8], but frequently in patients with severe Pfeiffer syndrome [3,9].

In a review of 18 cases with prenatal diagnosis of Pfeiffer syndrome, Giancotti et al [10] found frequent sonographic features of skull shape anomalies (72.2%), nasal abnormalities (50%), proptosis and hypertelorism (44.4%), frontal bossing (22.2%), thumbs' anomalies (33.3%) and toes' abnormalities (38.9%). However, our

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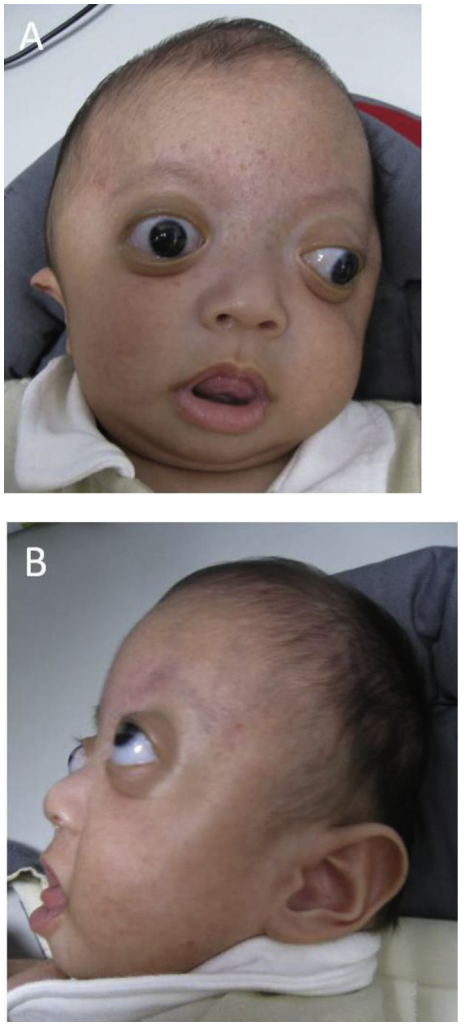

Fig. 1. (A) and (B). Craniofacial appearance of extreme proptosis, brachycephaly, midface hypoplasia, hypertelorism and low-set ears of the propositus at age 3 months.

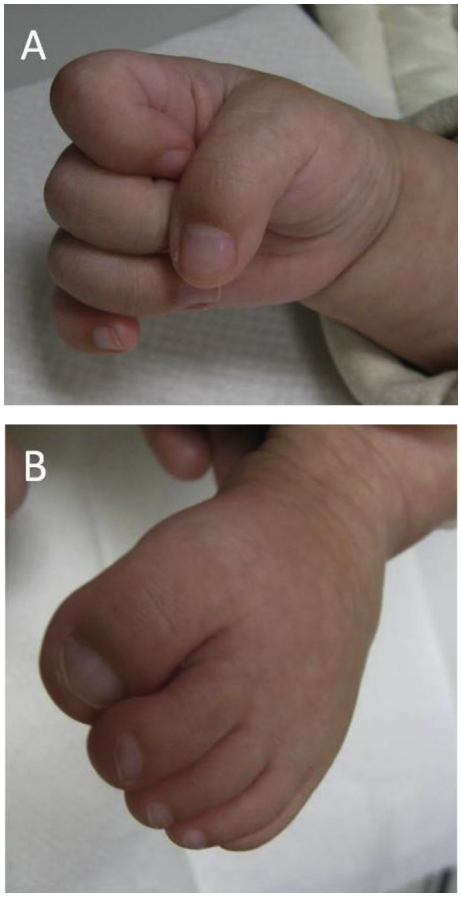

Fig. 2. (A) Broad thumb and (B) broad big toe.

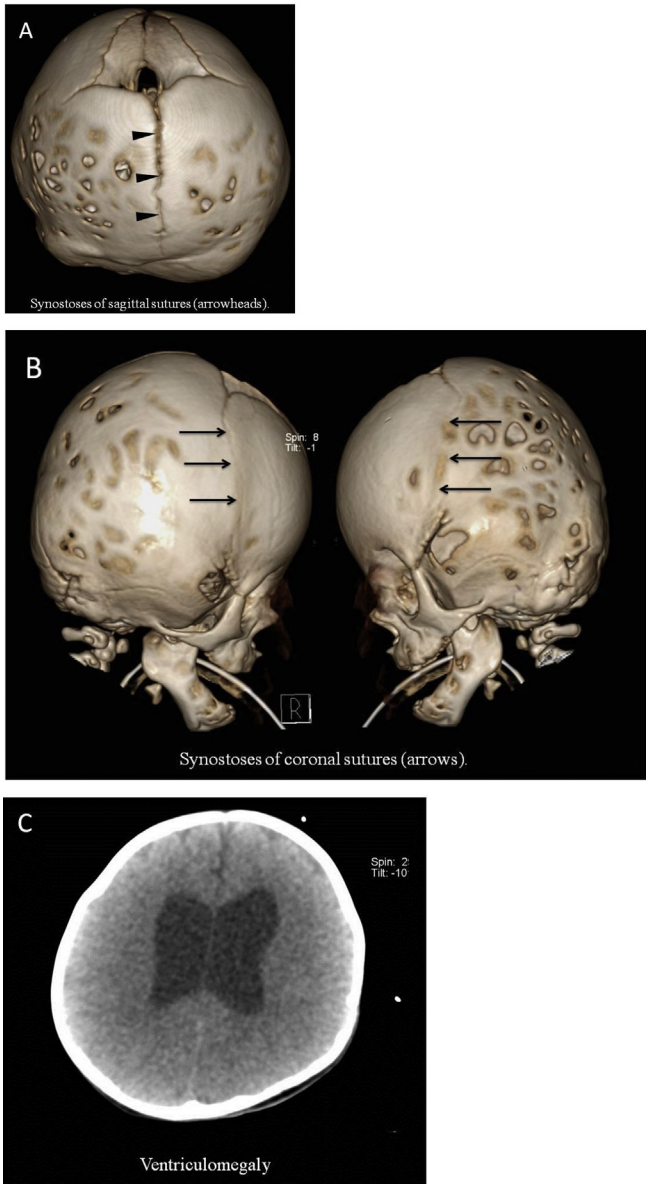

Fig. 3. Radiographs show multisynostoses of (A) sagittal and (B) coronal sutures (arrows) and shallow orbits, and (C) ventriculomegaly.

case did not manifest identifiable abnormalities on prenatal ultrasound indicating that prenatal diagnosis of Pfeiffer syndrome simply by ultrasound screening is not easy.

In summary, we demonstrate a genotype-phenotype correlation of *FGFR2* C342R mutation with severe Pfeiffer syndrome. We suggest a mutational analysis of *FGFR2* is helpful in genetic counseling of newborns with severe Pfeiffer syndrome.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

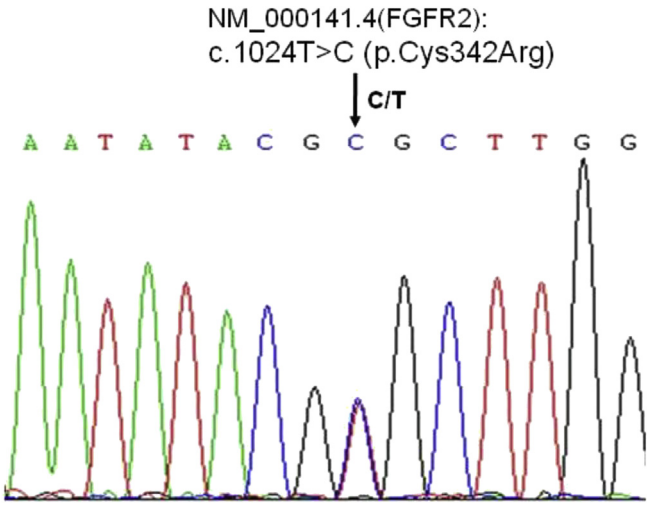

Fig. 4. Mutational analysis of the *FGFR2* gene shows a heterozygous c.1024T>C, TGC>CGC transition, leading to a p.Cys342Arg (C342R) mutation in the proband. WT = wild type.

Acknowledgements

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