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Research Letter

Pfeiffer syndrome with *FGFR2* W290C mutation perinatally presenting extreme proptosis

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The male propositus was the first child of a healthy unrelated couple. The mother was 31 years old. There was no family history of congenital malformations. The pregnancy was uncomplicated except that big eyes, especially the right, and prominent forehead were noted during prenatal ultrasound examination. He was born at 37 weeks by cesarean section due to breech presentation. Birth weight was 3500 g, length 51 cm, and head circumference 37 cm. After birth, he was found to have scaphocephaly, broad big toes and thumbs, midface hypoplasia, hypertelorism, low-set ears, and severe proptosis (Fig. 1). Radiographs showed radio–ulnar–humeral synostosis, multisynostoses of sagittal and coronal sutures, brachycephaly, and ventriculomegaly (Fig. 2). A diagnosis of type 3 Pfeiffer syndrome was made. Molecular analysis of peripheral blood revealed a heterozygous c.870G>C, TGG>TGC transversion, leading to a p.Trp290Cys (W290C) mutation in the *FGFR2* gene (Fig. 3).

Pfeiffer syndrome (OMIM 101600) is an autosomal dominant disorder characterized by craniosynostosis, broad and deviated thumbs, big toes, and partial syndactyly on hands and feet, and affects about one in 100,000 individuals [1]. Three subtypes of Pfeiffer syndrome have been identified [2]. Types 2 and 3 are more common and severe than type 1. Type 1 is classic Pfeiffer syndrome with mild manifestations of brachycephaly, midface hypoplasia, and abnormalities of the digits, and has normal intelligence, a good outcome, and a familial history of inheritance. Types 2 and 3 are associated with severe neurological compromise, poor prognosis, early death, and sporadic occurrence. Type 2 consists of cloverleaf skull, extreme proptosis, digital abnormalities, ankylosis of elbows, and developmental delay. Type 3 is similar to type 2 but without cloverleaf skull. Type 1 Pfeiffer syndrome is caused by mutations in *FGFR1* (5%) or *FGFR2* (95%), whereas types 2 and 3 Pfeiffer syndrome are caused by mutations in *FGFR2* (100%) only [3]. Hearing loss and hydrocephalus can be seen in type 1, and choanal stenosis/atresia,

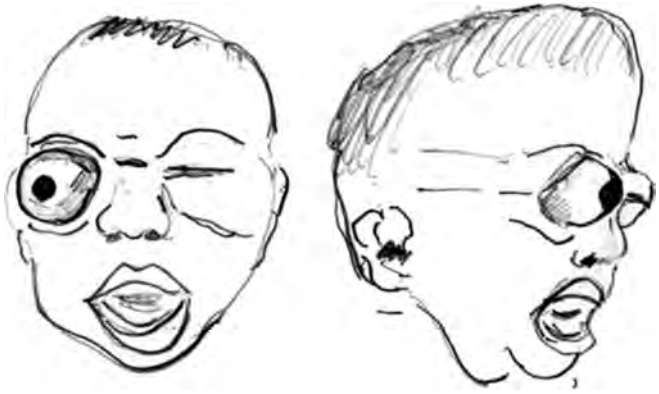

Fig. 1. Craniofacial appearance and extreme proptosis at birth.

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laryngotracheal abnormalities, cleft palate, hydrocephalus, seizures, sacrococcygeal eversion/appendage, and early death can be seen in types 2 and 3 [3–7].

Prenatal diagnosis of craniosynostosis associated with digital abnormalities should include a differential diagnosis of Apert syndrome and Pfeiffer syndrome, both of which can be caused by *FGFR2* mutations. Apert syndrome is usually associated with *FGFR2* S252W and P253R mutations, and severe syndactyly of hands and feet, but no cloverleaf skull or proptosis. Pfeiffer syndrome is usually associated with *FGFR2* W290C, Y340C, C342R, and S351C mutations, and can be associated with cloverleaf skull, proptosis, and broad great toes and thumbs [5,8].

The present case was associated with the *FGFR2* W290C mutation and type 3 Pfeiffer syndrome. To date, at least 16 cases of Pfeiffer syndrome with the *FGFR2* W290C mutation have been reported [5,9–17]. All were associated with type 2 or 3 Pfeiffer syndrome and had severe phenotypic features. The

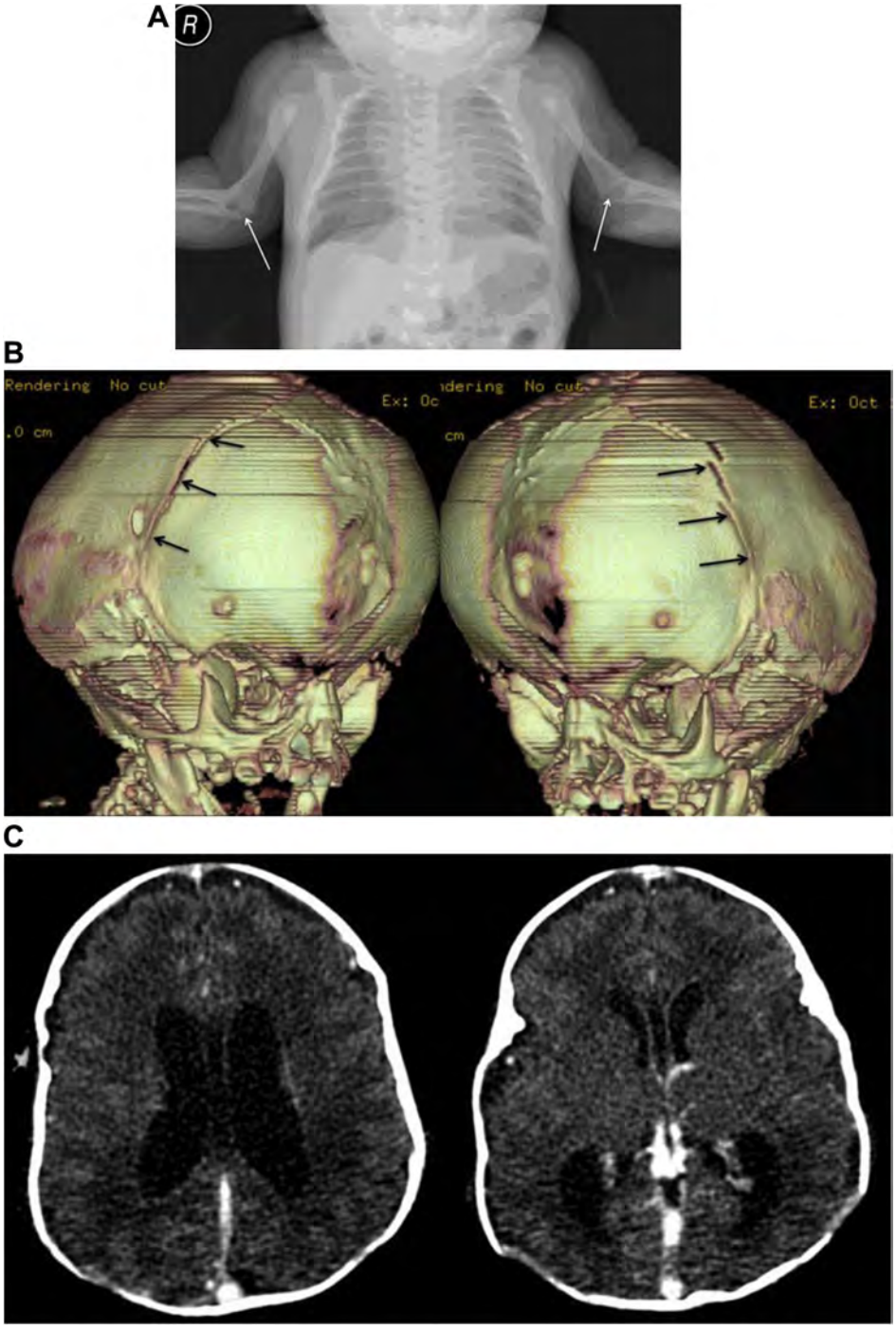

Fig. 2. Radiographs show (A) radio–ulnar–humeral synostosis (white arrows); (B) multisynostoses of sagittal and coronal sutures (black arrows), shallow orbits, and brachycephaly; and (C) ventriculomegaly.

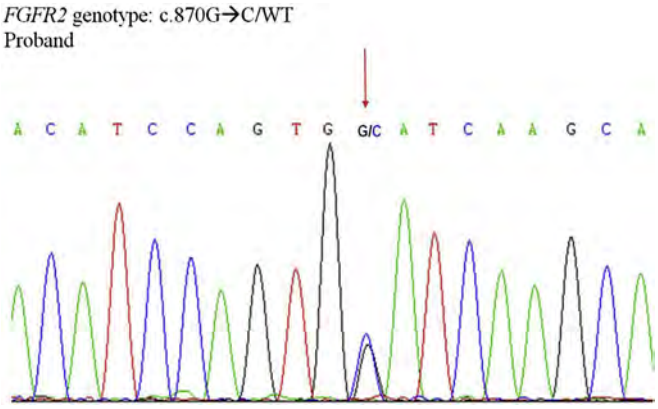

Fig. 3. Molecular analysis of the *FGFR2* gene shows a heterozygous c.870G>C, TGG>TGC transversion, leading to a p.Trp290Cys (W290C) mutation in the proband. WT = wild type.

FGFR2 mutations of W290C (p.Trp290Cys), Y340C (p.Tyr340Cys), C342R (p.Cys342Arg), and S351C (p.Ser351-Cys) have been associated with severe phenotypic features of Pfeiffer syndrome such as cloverleaf skull, extreme proptosis, midface hypoplasia, hydrocephalus, tracheal sleeve, Chiari malformation, radio–ulnar–humeral synostosis, and early infant death [3–5,13,14,16,18–21]. W290C (p.Trp290Cys) creating cysteine residue has been noted to cause severe Pfeiffer syndrome, whereas W290G (p.Trp290Gly) and W290R (p.Trp290Arg) cause mild Crouzon syndrome; the same is true for Y340C (p.Tyr340Cys) versus Y340H (p.Tyr340His) [16]. Y340C causes severe Pfeiffer syndrome, whereas Y340H causes mild Crouzon syndrome.

Ocular manifestations play an essential role in the diagnosis and management of Pfeiffer syndrome. The present case presented ocular manifestations of shallow orbits, proptosis, and hypertelorism. Types 2 and 3 Pfeiffer syndrome tend to have more severe ocular proptosis secondary to a shallow orbit, an increased incidence of spontaneous globe subluxation, and a less favorable prognosis. Okajima et al [22] demonstrated that *FGFR2* mutation is associated with ocular anterior chamber dysgenesis. In a study of 55 cases with craniosynostosis syndromes, Tay et al [23] found a 35.5% prevalence of bilateral visual impairment and a 9.1% prevalence of unilateral visual impairment. The reported causes of visual impairment included amblyopia (16.7%), ametropia (25%), optic atrophy (16.7%), exposure keratopathy (4.2%), and infantile nystagmus syndrome (4.2%) [23]. Proptosis and strabismus are the hallmark ocular signs of Pfeiffer syndrome. Multidisciplinary management of ocular signs of Pfeiffer syndrome includes artificial tears, a lubricating ointment, eye care to prevent amblyopia, craniotomy for repair of craniosynostosis, and cosmetic reconstruction for facial dysmorphisms [24,25].

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