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SHORT REPORT

Apert Syndrome

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Apert syndrome is a developmental malformation characterized by craniosynostosis, a cone shaped calvarium, midface hypoplasia, pharyngeal attenuation, ocular manifestations and syndactyly of the hands and feet (1). Mutations of either Ser252Trp or Pro253Arg in fibroblast growth factor receptor 2 (FGFR2) are responsible for nearly all known cases of Apert syndrome (2).

We report a Turkish case of Apert Syndrome confirmed for the FGFR2 mutation.

Case Report

A 2-day-old infant was referred to Pamukkale University Hospital because of an atypical facial appearance and syndactyly. The infant was born at 38 weeks of gestational age and was the first child of a second-degree cousin marriage. His mother was 20 years old and his father was 24 years old. It was learned that prenatal ultrasound was normal. He weighed 2400 g (25th-50th percentile), was 48 cm (50th-75th percentile) long and had a cranial circumference of 33 cm (50th-75th percentile). The baby had a short anteroposterior diameter with high, full forehead and flat occiput, flat facies, shallow orbits, proptosis, hypertelorism, downslanting palpebral fissures, a small nose, maxillary hypoplasia, a cleft palate, bifid uvula, low set ears, and cutaneous syndactyly of the fingers and toes (Figures 1, 2). Syndactyly was present in fingers 2 through 5 and also at the toes in all digits symmetrically. An X-ray of the head revealed craniosynostosis of the coronary suture. Atrial septal defect was observed in echocardiogram. Cranial, abdominal, and urinary system ultrasonographies were normal. The diagnosis of Apert syndrome was confirmed by molecular genetic analyses. The patient was heterozygous for the FGFR2 Ser252Trp mutation.

Molecular genetic analysis of FGFR2 Ser252Trp mutation was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The FGFR2-specific 318 bp long sequence was PCR-amplified using the forward 5'-TGACAGCCTCTGACAACACAAC-3' and reverse 5'-GGAAATCAAAGAACCTGTGGC-3' primers. PCR amplifications were performed in a total volume of 50 µl containing extracted DNA, 20 pmol of each primer (forward, and reverse), and 25 µl of HotStarTaq Master Mix (containing 2.5 units of HotStarTaq DNA polymerase, 1x PCR buffer with 1.5 mM $MgCl_2$, and 200 µM each of dNTP; and Qiagen). The thermal cycling conditions were as follows: initial activation of HotStarTaq DNA polymerase at 95 °C for 15 min, followed by 30 cycles of denaturation at 94 °C for 1 min, annealing at 57 °C for 1 min, and extension at 72 °C for 1 min, with final

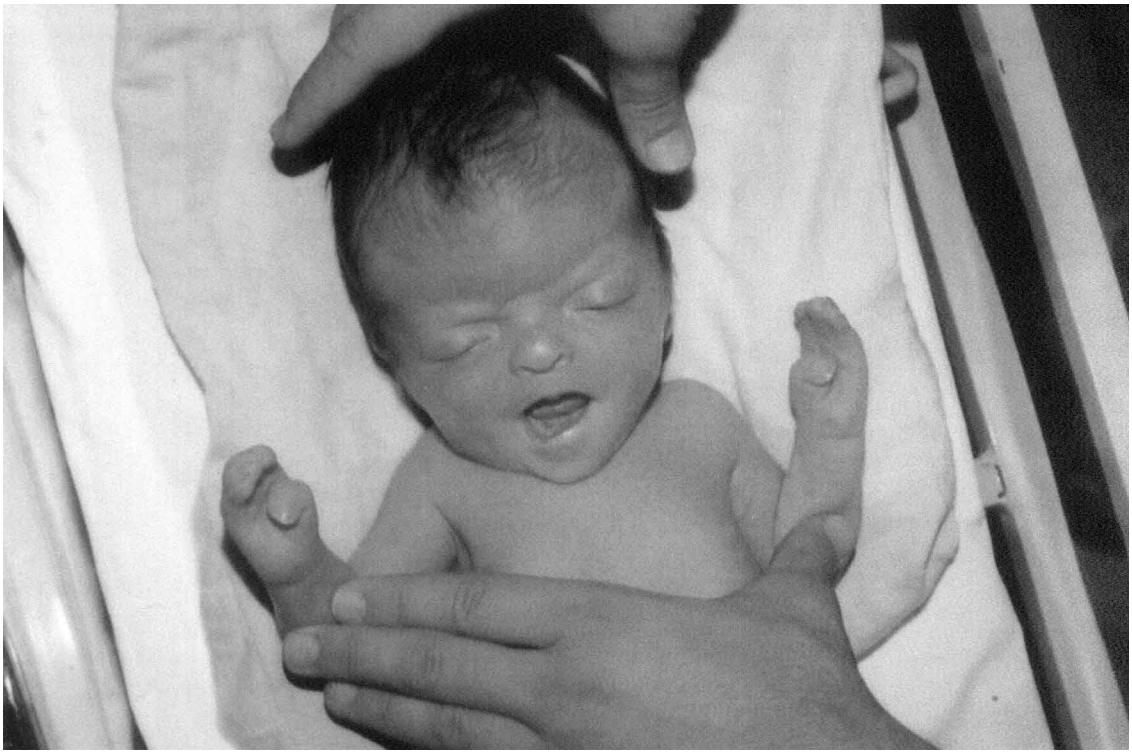

Figure 1. Facial appearance and syndactyly in the hand.

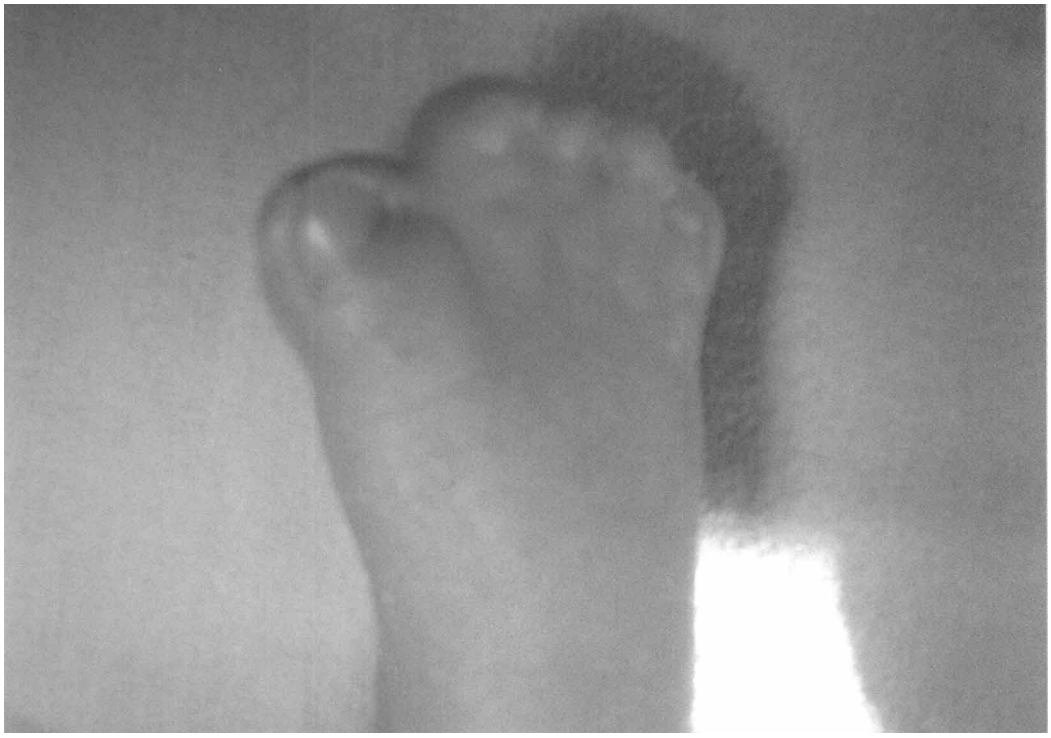

Figure 2. Syndactyly in the feet.

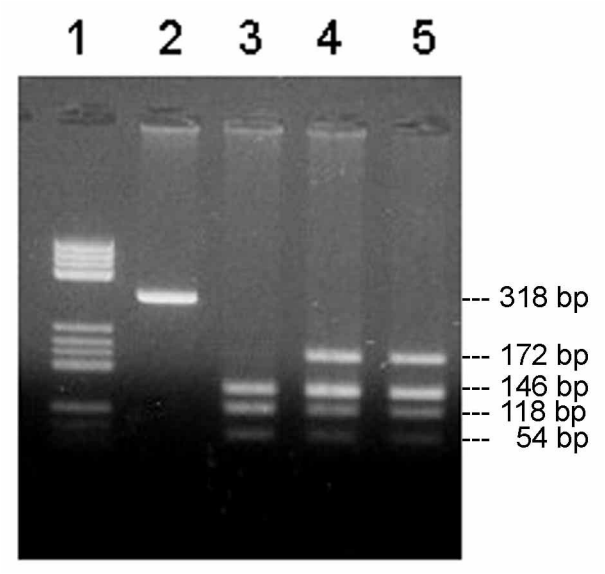

Figure 3. Molecular genetic analysis of FGFR2 Ser252Trp mutation by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).
Mutation analysis of the FGFR2 gene was performed using whole blood genomic DNA of the patient that confirmed a substitution of 755C → G (Ser252Trp), consistent with Apert syndrome. In normal control samples the undigested PCR product was 318 bp long as shown in lane 2. When the same control PCR product was enzymatically digested with MboI restriction endonuclease 146 bp, 118 bp, and 54 bp long bands were identified on the agarose gel as shown in lane 3. In thecase of heterozygous 755C → G (Ser252Trp) mutation as in our patient, MboI restriction endonuclease digest resulted in an additional 172 bp long band as shown in lanes 4 and 5. Lane 1; molecular weight standard.

extension at 72 °C for 10 min. The PCR amplification products were separated by 2% agarose gel electrophoresis and visualized by exposure to ultraviolet light after ethidium bromide staining.

When the 318 bp long control PCR product was enzymatically digested with MboI restriction endonuclease according to the manufacturer's (New England BioLabs Inc.) protocol, 146 bp, 118 bp, and 54 bp long bands were identified on the agarose gel confirming the 2 cut sites of MboI on this 318 bp long PCR product (Figure 3, lane 3). However, in the case of heterozygous 755C → G (Ser252Trp) mutation, as in our patient, MboI restriction endonuclease digest resulted in 4 distinct bands with an additional bp long band as shown in Figure 3, lanes 4 and 5, confirming the elimination of 1 of the MboI cut sites on 1 allele of the FGFR2 gene of the patient.

Apert syndrome or acrocephalosyndactyly syndromes are extremely rare conditions. In 1906, Apert described the skull, facial and hand deformities of several patients characteristic of this syndrome that now bears his name (3). The incidence of infants born with Apert syndrome is approximately 1 in 50,000 to 80,000 live births (4,5).

The inheritance of Apert syndrome is usually autosomal dominant, but sporadic cases are also frequent. Sporadic transmission indicates that a family may have a child with Apert when no other member of the family is affected. The recurrence risk of having another child with Apert syndrome for 2 unaffected parents is negligible. However, there is a higher mutation rate in males because the germ-cell divisions in males are greater than those in females. Hence, the mutation rate increases with paternal age. In contrast, Glaser et al. reported a significantly greater mutation rate in a group of young men who had children with Apert syndrome and suggested that there are many other relevant environmental factors in addition to paternal age (6). In the absence of a family history, prenatal diagnosis may be difficult based on sonography alone (7). In our case, Apert syndrome was not detected prenatally.

Holten et al. (8) conclude that there is a genetic anomaly causing variable and uncoordinated differentiation of the mesenchyme at the time of embryologic separation into various skeletal components, particularly in the distal limb bud and craniofacial skeleton. The disease process continues postnatally, especially in endochondral bone growth.

Apert syndrome results from a mutation in the fibroblast growth factor-2 (FGFR2) gene, a tyrosine kinase receptor gene. Upon ligand binding the FGRF2 receptor dimerises followed by activation of the intracellular tyrosine kinase domains initiating a cascade of signals that influence cell division and differentiation. FGFR2 mutations have been found in the Apert, Crouson, and Pfeiffer craniosynostosis syndromes. Most mutations are gain-of-function mutations, including ligand-independent receptor activation or altered ligand binding. With the exception of Apert syndrome, there is no clear genotype-phenotype correlation (9).

Two missense mutations have been reported in exon IIIa of the FGFR2 gene, resulting in Ser252Trp or Pro253Arg (10). Park et al. (10) concluded that there were no differences between these 2 mutations with

respect to their phenotypic features. In contrast, the severity of the syndactyly and the presence of cleft palate were significantly correlated with mutations in the series published by Slaney et al. (11). The syndactyly was more severe with the Pro253Arg mutation, for both the hands and the feet. In contrast, cleft palate was significantly more common in Ser252Trp patients (11). The Pro253Arg mutation appears to be associated with the more severe forms of Apert Syndrome with regard to the forms of syndactyly and to mental outcome (9). Of 203 patients, the proportions of the 2 types of mutation were 65% Ser252Trp and 34% Pro253Arg (9). The phenotype analyses in that study show that there were significant differences in the frequency of cleft palate in patients with the Ser252Trp mutation and in the severity of syndactyly in patients with the Pro253Arg mutation. Those patients with Pro253Arg mutation have a higher probability of suffering from more severe syndactyly, although some patients with Ser252Trp mutation also had type 3 syndactyly. Our patient, with Ser252Trp mutation, had a cleft palate, type 2 syndactyly in the hands and type 3 syndactyly in the feet.

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References

1. Batra P, Duggal R, Parkash H. Dentofacial characteristics in Apert syndrome: a case report. J Indian Soc Pedod Prev Dent 20: 118-23, 2002.
2. Chen L, Li D, Li C et al. A ser250trp substitution in mouse fibroblast growth factor receptor 2 (FGFR2) results in craniosynostosis. Bone 33: 169-78, 2003.
3. Jones KL. Apert syndrome. In: Smith's Recognizable Patterns of Human Malformation. 4th ed. WB Saunders Company, Philadelphia, USA, 1997, pp. 418-9.
4. Cohen MM Jr, Kreiborg S, Lammer EJ et al. Birth prevelance study of Apert syndrome Am J Med Genet 42: 655-9, 1992.
5. Rebelo N, Duarte R, Costa MJ et al. Acrocephalosyndactyly-the coalesced hand. Eur J Pediatr Surg 12: 49-55, 2002.
6. Glaser RL, Broman KW, Schulman RL et al. The paternal-age effect in Apert syndrome is due, in part, to the increased frequency of mutations in sperm. Am J Hum Genet 73: 939-47, 2003.
7. Mahieu-Caputo D, Sonigo P, Amiel J et al. Prenatal diagnosis of sporadic Apert syndrome: a sequential diagnostic approach combining three-dimensional computed tomography and molecular biology. Fetal Diagn Ther 16: 10-2, 2001.
8. Holten IW, Smith AW, Bourne AJ et al. The Apert syndrome hand: pathologic anatomy and clinical manifestations. Plast Reconstr Surg 96: 1681-7, 1997.
9. Lajeunie E, Cameron R, el Ghouzzi V et al. Clinical variability in patients with Apert syndrome. J Neurosurg 90: 443-7, 1999.
10. Park WJ, Theda C, Maestri NE et al. Analyses of phenotypic features and FGFR2 mutations in Apert syndrome. Am J Hum Genet 57: 321-8, 1995.
11. Slaney SF, Oldridge M, Hurst JA et al. Differential effects of FGFR2 mutations on syndactyly and cleft palate in Apert syndrome. Am J Hum Genet 58: 923-32, 1996.