CASE REPORT

FGFR2 mutation in a patient with Apert syndrome associated with humeroradial synostosis

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ABSTRACT Most cases of Apert syndrome are due to S252W or P253R mutations in the fibroblast growth factor receptor 2 (FGFR2) gene. Differences in the effects of S252W and P253R mutations on the clinical features of Apert syndrome have been studied, but little is known about the type of FGFR2 mutation in Apert syndrome with humeroradial synostosis. To study a correlation between the FGFR2 mutations and the clinical complications, we examined the FGFR2 gene in a patient with Apert syndrome associated with humeroradial synostosis, and found that the mutation was S252W. This report suggested that S252W mutation in FGFR2 may cause humeroradial synostosis in Apert syndrome.

Key words: Apert syndrome, fibroblast growth factor receptor 2 (FGFR2), humeroradial synostosis, elbow abnormalities, congenital craniosynostosis syndrome

INTRODUCTION

Apert syndrome is a severe malformation syndrome characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly of the hands and feet (Apert, 1906). Upton et al. (1991) reported that radiography revealed elbow abnormalities in less than half of patients with this syndrome. However, Anderson et al. (1998) reported that the incidence of elbow abnormalities in Apert syndrome was higher than that previously suggested in the literature. Radiographs of patients with Apert syndrome have frequently shown elbow abnormalities such as hypoplasia of the capitulum humeri and radial head, subluxation or dislocation of the radial head, and humeroradial synostosis. Among these abnormalities, slight hypoplasia of the capitulum humeri is the most common, and humeroradial synostosis is the least common (Cohen and Kreiborg, 1993; Cohen, 1995; Kasser and Upton, 1991; Upton, 1991; Wood et al., 1995). The reported incidences of humeroradial synostosis among Apert patients for whom elbow radiographs have been obtained have varied from 2 among 19 patients (Kasser and Upton, 1991), 3 among 38 (Cohen and Kreiborg, 1993), 3 among 68 (Upton, 1991), and 1 among 33 (Anderson et al., 1998). Although Upton (1991) reported that elbow function was normal in the majority of Apert patients, those patients with humeroradial synostosis have suffered severe limitation of daily living activities, and Anderson (1998) has advocated that orthopaedic review of the management of this condition might be necessary.

Wilkie et al. (1995) first reported that Apert syndrome was caused by a S252W or P253R mutation within exon 7 of the fibroblast growth factor receptor 2 (FGFR2) gene. Recently, differences in the clinical features between the genotypic subgroups assigned to S252W and P253R mutations have been studied (Cohen, 1995; Matsumoto et al., 1998; Oldridge et al., 1997; Park et al., 1995; Slaney et al., 1996). Syndactyly was more severe with P253R, whereas cleft palate was significantly more common with S252W (Slaney et al., 1996). To correlate elbow abnormalities with genotype, Park et al. (1995) studied 36 patients with Apert syndrome and found that the proportion of patients with decreased range of motion (ROM) at the elbows was 35% with S252W and 33% with P253R, the difference being non-significant. However, they did not investigate humeroradial synostosis, and the possible association of FGFR2 mutation with this condition appears to have received little attention. Therefore, we examined the FGFR2 gene in a patient with Apert syndrome, showing humeroradial synostosis.
Apert Syndrome with humeroradial synostosis

CASE REPORT

Clinical finding
This female patient was born after an uneventful pregnancy to a 23-year-old mother and a 28-year-old father. The couple was healthy, non-consanguineous, and had no contributory family history. Delivery was by cesarean section at term, and the Apgar score was 8. Birth weight was 2.66 kg, and body length was 49 cm. Craniofacial, upper, and lower limb anomalies were noted at birth. Examination showed a brachycephalic skull, a prominent forehead, midfacial hypoplasia, bulging eyes, severe proptosis of the eye and a cleft palate. There was symmetrical syndactyly of the hands and feet (Figs. 1a and 1b). Neither active nor passive motion of the bilateral elbows was recognized, the elbows being fixed in about 45 degrees of flexion. Based on these clinical findings, Apert syndrome was diagnosed. Radiograph of the hand at the age of 6 months showed osseous fusion between the distal portions of the long and ring fingers, and absence of the proximal interphalangeal (PIP) joints of the index, long, and ring fingers (Fig. 2). According to Upton’s classification (Upton, 1991), the syndactyly was classified as Type 1, which is the most common and least severe.

Radiograph of the elbow showed a narrow space between the humerus and radius. In view of the absence of elbow motion, the space did not appear to be a joint space, but the distal humeral growth plate (Fig. 3a). At the age of 2 years and 6 months, elbow radiograph showed complete osseous humeroradial synostosis (Fig. 3b). Syndactyly of the second web space was released at the age of 1 year, and that of the third web space was released at the age of 2 years. Her elbows remained untreated. At the age of 4 years, she underwent reconstruction of the radially deviated thumb, and at this time samples of her venous blood were taken for study of the FGFR2 mutation. Informed consent was obtained from her parents after the study had been fully explained.

SSCP analysis and DNA sequencing
Genomic DNA was prepared from venous blood using PureGene (Gentra). Primer pairs for amplifying all individual exons of
FGFR2 were designed and used for PCR. The PCR conditions were 95°C for 1 min to begin the reaction, followed by 35 cycles at 94°C for 30 sec, 60°C for 1 min, 72°C for 2 min, and an additional 10 min at 72°C to complete the reaction. The PCR products were analyzed on 2% agarose gels and then subjected to SSCP analysis with the GeneGel Excel 12.5/24 kit (Amersham Pharmacia Biotech AB). The amplification products were directly sequenced using Sequencing High (Toyobo Co., Ltd.).

**Mutation detection of FGFR2**

With genomic DNA from the patient and an unaffected control, all exons of FGFR2 were amplified by PCR and subjected to SSCP analysis. No altered patterns of migration were observed except for the PCR product obtained with the primer pair amplifying exon 7 of FGFR2. As shown in **Fig. 4a**, the patient had an additional band that was not present in the control. To identify the mutation at the DNA level, the PCR product was directly sequenced (**Fig. 4b**). This revealed a C to G transversion at the 5th nucleotide from the 5′ end of exon 7, resulting in an amino acid substitution of tryptophan (W) for serine (S) at codon 252 (S252W). Thus, the FGFR2 mutation in this patient was revealed to be S252W.

**DISCUSSION**

This is the first reported study of FGFR2 mutation in a patient with Apert syndrome associated with humeroradial synostosis. The FGFR2 mutation in this case was S252W. Slaney et al. (1996) reported that syndactyly associated with the S252W mutation was less severe. In our patient with S252W mutation, the syndactyly was the least severe and most common type according to Upton’s classification (Upton, 1991). Concerning the correlation between syndactyly severity and humeroradial synostosis in Apert syndrome, Ogino et al. (1995) reported that syndactyly with humeroradial synostosis appeared to be less severe than that without humeroradial synostosis. Based on these observations and our results, we speculate that S252W mutation in Apert syndrome may be associated with more severe elbow abnormalities and less severe syndactyly.

Abnormalities of the elbow have been detected in congenital craniosynostosis syndromes including Apert syndrome, Pfeiffer syndrome, and Antley-Bixler syndrome (Antley and Bixler, 1975; Chun et al., 1998; Cohen, 1993; Gripp et al., 1998; Plomp et al., 1998; Schaefer et al., 1998; Schell et al., 1995). Recent studies have revealed that in Pfeiffer syndrome (Cohen, 1993; Gripp et al., 1998; Plomp et al., 1998; Schaefer et al., 1998; Schell et al., 1995) and Antley-Bixler syndrome (Chun et al., 1998) elbow synostosis can be caused by FGFR2 mutation including T290C, C342R, and S351C. These results suggest that FGFR2 mutation may have an important causative role in humeroradial synostosis. The present study suggests that S252W mutation in FGFR2 may also cause humeroradial synostosis in Apert syndrome.

Recent analysis has indicated that Apert syndrome arises as a result of increased affinity of mutant receptors for specific FGF ligands, leading to activation of signaling under conditions where ligand availability is limited (Anderson et al., 1998). Increased activation of FGF signaling during limb development can cause limb abnormalities such as syndactyly, osseous fusion between fingers, lack of PIP joints, and humeroradial synostosis. However, further study is necessary to determine the pathological conditions leading to these abnormalities.

**REFERENCES**


