A CASE OF PFEIFFER SYNDROME TYPE 1 WITH AN A344P MUTATION IN THE *FGFR2* GENE

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Abstract. Pfeiffer syndrome, an autosomal dominant disorder, consists of craniosynostosis, broadening of the thumbs and great toes, and partial soft tissue syndactyly of the hands and feet. Three clinical subtypes have been classified mainly for the purpose of genetic counseling. Mutations in *FGFR1* and *FGFR2* are known to be associated with the syndrome. However, the correlation between genotype and phenotype is not well defined. Only one patient with Pfeiffer syndrome with no other clinical information has been reported to have had an A344P mutation of the *FGFR2*. Here we report a Thai male patient with sporadic Pfeiffer syndrome type 1 with impaired intelligence (IQ = 77). Mutation analysis revealed A344P in *FGFR2*. Identification of the clinical features and molecular defects in more patients is required to better correlate the genotype and phenotype of this complex syndrome.

INTRODUCTION

Pfeiffer syndrome (MIM 101600), an autosomal dominant disorder, consists of craniosynostosis, broadening of the thumbs and great toes, and partial soft tissue syndactyly of the hands and feet (Martsolf *et al*, 1971). Three clinical subtypes have been delineated by Cohen (1993). Patients with type 1 have the classical phenotype with normal to near normal intelligence. Affected individuals with type 2 have a cloverleaf skull, severe CNS involvement, and do poorly with early death. Type 3 is similar to type 2 with the absence of a cloverleaf skull. Most cases of Pfeiffer syndrome are sporadic. In familial cases, autosomal dominant inheritance with complete penetrance is characteristic. Variable expressivity has involved mostly the presence and the degree of syndactyly (Cohen, 1993).

On the molecular level, Pfeiffer syndrome displays locus heterogeneity. The first gene identified to be responsible for the syndrome was *FGFR1* (MIM 136350) (Muenke *et al*, 1994). A year later, a second locus, *FGFR2* (MIM 176943), was found (Schell *et al*, 1995). At least 24 different mutations in *FGFR2* associated with the Pfeiffer phenotype have been characterized (Passos-Bueno *et al*, 1999). Some mutations have been reported to cause a specific clinical type such as Ser351Cys which was found in a patient with Pfeiffer syndrome type 3 (Gripp *et al*, 1998). Only one patient with Pfeiffer syndrome has been reported to have an A344P mutation of the *FGFR2* (Meyers *et al*, 1996). No other information about this patient was given. Identification of the clinical features and molecular defects in more patients is required to better correlate the genotype and phenotype of this complex syndrome.

Here we report a Thai male patient with sporadic Pfeiffer syndrome type 1 with impaired intelligence. Mutation analysis revealed A344P in *FGFR2*. He represents the second

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case of this mutation reported to date.

MATERIALS AND METHODS

Case report

A male patient was born at term to a 41-year-old G2P1 Thai mother and a 40-year-old unrelated Thai father. Prenatal history was unremarkable. A cesarean section was performed because of premature rupture of membranes. Birth weight was 3400 g (75th centile), birth length 51 cm (75th centile), and head circumference 37 cm (>90th centile). Physical examination at 4 months of age revealed bicoronal synostosis, proptosis, midface hypoplasia, micrognathia, and enlarged great toes. A diagnosis of Pfeiffer syndrome was given. The patient underwent frontoorbital advancement at 7 months old. The patient had obstructive sleep apnea requiring adenoidectomy and uvuloplasty at 1½ years old. His IQ at 3 years and 2 months old was 77. His last clinic visit was at 6 years of age (Fig 1). At this time his height was 108 cm (25th centile), his weight 15 kg (10th centile), and his head circumference 50.5 cm (between 10th and 25th centile). Turribrachycephaly, protosis, and midface hypoplasia were noted. His thumbs were slightly broadened. The great toe/second toe ratios were 1.96 on the right and 1.74 on the left. The physical features of his parents and brother revealed no major malformations.

Mutation analysis

After informed consent was obtained in accordance with the standards set by local institutional review boards, six ml of peripheral blood was obtained for DNA isolation by a standard method. *FGFR1* exon 5, *FGFR2* exon 8, and *FGFR2* exon 10 were PCR amplified. Primers, annealing temperatures and PCR product sizes are shown in Table 1. The PCR products were electrophoresed on a 2% agarose gel (Promega) and stained with ethidium bromide. The visualized band was extracted and purified with a kit (Bio 101), and sequenced in both directions by using an automated DNA sequencer (ABI Prism 310 Genetic

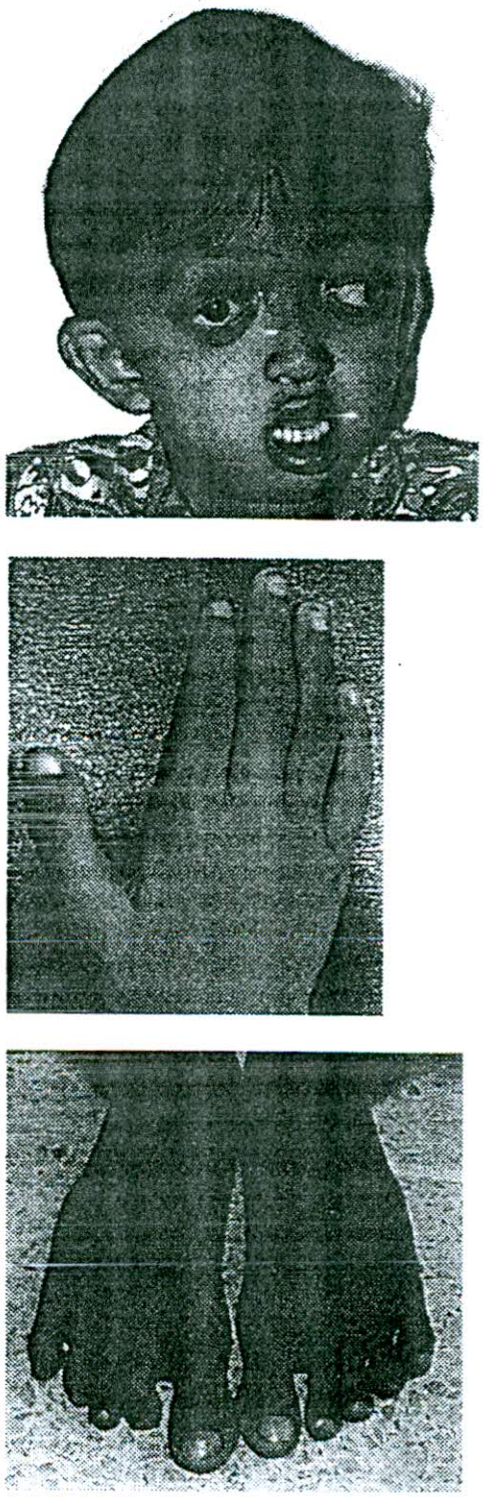

Fig 1–A. Face B. Right hand C. Feet of the patient.

Table 1
Primers, the optimal annealing temperatures, and the PCR product sizes of the exons of the FGFR genes studied.

Gene-Exon	Primers	Annealing temperature	product size
FGFR1-Exon 5	5′-GGAATTCCATCTTCCACAGAGCGG-3′ and 5′- GGAATTCCTCAAGATCTGGACATAAGGCAG-3′	60	216
FGFR2-Exon 8	5′-GGTAGTGGTCTGTCATTCTCCCATC-3′ and 5′-AATCAAAGAACCTGTGGCCAAACCC-3′	60	322
FGFR2-Exon 10	5′-AGCCCCCTCCACAATCATTCCTG-3′ and 5′-TAAAAGGGGCCATTTCTGATAACAG-3′	60	303

Analyser, Perkin Elmer).

RESULTS

A G->C transversion at nucleotide 1209 of the *FGFR2* gene exon 10 was detected (Fig 2). This change substitutes a proline for an alanine residue at amino acid position 344. Sequence tracings of both directions confirmed the mutation. Nucleotide sequences of the *FGFR1* exon 1 and the *FGFR2* exon 8 were normal (data not shown).

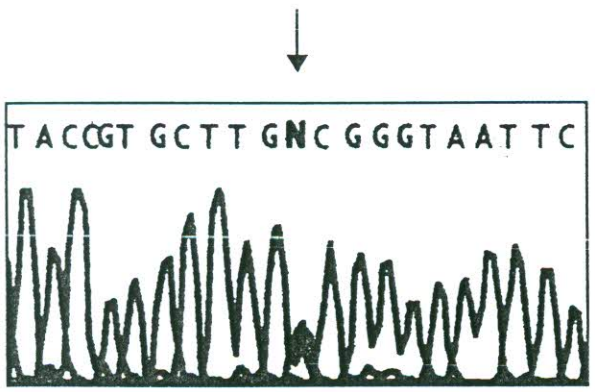

Fig 2–The backward strand sequence of the *FGFR2* exon 10 revealed a G->C transversion (indicated in the figure by an arrow).

DISCUSSION

This patient had craniosynostosis, down-slanting palpebral fissures, proptosis and broadening of the thumbs and great toes consistent with Pfeiffer syndrome (Cohen, 1995). The ratios of his hallucal width to second toe width were 1.96 on the right and 1.74 on the left. These are within the range (1.72-2.23) of patients with Pfeiffer syndrome (Cohen, 1993). Although the patient did not have deviation of the thumbs and great toes or syndactyly, these features are not essential for diagnosis. Patients with Crouzon syndrome have normal hands and feet, Jackson-Weiss syndrome is defined by foot anomalies without hand involvement, and broad toes in Saethre-Chotzen syndrome are in the valgus position. Thus, these syndromes may be distinguished from Pfieffer.

Our patient's features are consistent with Pfeiffer syndrome type 1. However, his intelligence seems to be more severely affected by the disease than others. No other family members had similar clinical features. *De novo* mutation is the most likely explaination. His father was 40 years old at the time the patient was born. Advanced paternal age is known to be the risk of *de novo* mutation with the average paternal age of 34.5 ± 7.65 years (Glaser *et al*, 2000).

Molecular study revealed an A344P mutation in *FGFR2* making him the second

case of Pfeiffer syndrome with this mutation. Comparison of the phenotypes between the two patients is not feasible due to no clinical data being available for the first case. Participation with clinical and molecular geneticists in phenotype-genotype studies is necessary to provide more accurate information for genetic counseling.

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