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. Three clinical subtypes have been delineated 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.

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.
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 bicornal 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, proptosis, 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...
PFEIFFER SYNDROME WITH FGFR2 GENE MUTATION

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 Pfeiffer.

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 explanation. 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

Table 1

<table>
<thead>
<tr>
<th>Gene-Exon</th>
<th>Primers</th>
<th>Annealing temperature</th>
<th>Product size</th>
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<tr>
<td>FGFR1-Exon 5</td>
<td>5′-GGAATTCATCTCCACAGAGCGG-3′ and 5′-GGAATTCCTCAAGATCTGGACATAAGGAC-3′</td>
<td>60</td>
<td>216</td>
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<tr>
<td>FGFR2-Exon 8</td>
<td>5′-GGTAGTGTTCTGTCATTCTCCCATC-3′ and 5′-AATCAAAGAACCTGTGGCAAACCC-3′</td>
<td>60</td>
<td>322</td>
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<tr>
<td>FGFR2-Exon 10</td>
<td>5′-AGCCCTCCACAATCCTTTCTG-3′ and 5′-TAAAGGGGCAATGTTGATAACAG-3′</td>
<td>60</td>
<td>303</td>
</tr>
</tbody>
</table>

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).
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.

ACKNOWLEDGEMENTS

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REFERENCES


