Presence of the Apert canonical S252W FGFR2 mutation in a patient without severe syndactyly

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Abstract

Apert syndrome, characterised by craniosynostosis, craniofacial anomalies, and symmetrical syndactyly of the digits (cutaneous and bony fusion), has been associated with two canonical mutations in the FGFR2 gene (S252W, P253R) in the great majority of cases. Since these two alterations have been observed exclusively among these patients, it has been suggested that the S252W and P253R changes may play an important role in the occurrence of syndactyly. In order to verify which the mutations S252W and P253R could cause a milder phenotype, without involvement of the limbs, we have screened 22 patients with clinical characteristics compatible with Crouzon or Pfeiffer syndrome for these two particular changes. Surprisingly, we identified a Pfeiffer-like patient with the mutation S252W, and therefore we have shown for the first time the occurrence of one of the canonical Apert mutations without severe abnormalities of the upper and lower extremities.


Keywords: Apert syndrome; Pfeiffer syndrome; FGFR2 mutations

Apert syndrome is a relatively rare condition characterised by craniosynostosis, craniofacial anomalies, and symmetrical syndactyly of the digits (cutaneous and bony fusion). It has been considered one of the most severe forms of the craniosynostotic syndromes.

Fibroblast growth factor receptor 2 (FGFR2) mutations have been associated with the Apert phenotype as well as with other craniosynostotic conditions, such as Crouzon, Pfeiffer, and Jackson-Weiss syndromes. Several missense and splicing mutations in exons IIIa and IIIc of the FGFR2 gene have been found in patients with Crouzon, Pfeiffer, and Jackson-Weiss syndromes. In contrast, 98.6% of Apert syndrome patients have the S252W or P253R changes, which are located in FGFR2 exon IIIa. Since these two alterations have been observed exclusively among Apert patients, it has been suggested that these specific changes always result in syndactyly of the upper and lower limbs.

In order to verify whether the mutations S252W and P253R could cause a milder phenotype, without severe involvement of the extremities, we have screened 17 Crouzon and five Pfeiffer syndrome patients for these two particular changes, according to methods previously reported. Surprisingly, we identified the S252W change in a Pfeiffer-like subject, and this finding was confirmed in two independent DNA samples (fig 1). Subsequently, we sequenced the 5′ portion of exon IIIa of this patient which allowed us to confirm the presence of this mutation and to verify that there was no other change in this region of exon IIIa. In addition, we have sequenced FGFR2 exon IIIc of this patient, which was found to be normal (data not shown).

This patient, an African-Brazilian boy, currently aged 4 years (fig 2), is the only affected child of a non-consanguineous, clinically normal couple (mother aged 28 years, father aged 37 years). The pregnancy was normal and delivery was at term by caesarean section. Birth weight was 3900 g (75th centile) and total body length 52 cm (50th centile). Craniofacial and upper and lower limb anomalies were noted at birth. Examination at 5 months of age showed an active child. Height was 67.5 cm (50th centile), weight was 7.9 kg (50th centile), and OFC was 44 cm (<50th centile). He had brachycephaly, a prominent forehead, wide anterior fontanelle and metopic suture, large ears, hypertelorism, sparse eyebrows and lashes, flat supraorbital ridges, prominent eyes, broad nasal root, short neck, brachydactyly, bilateral skin syndactyly between fingers 3 and 4, short and broad terminal phalanges, radial deviation of the fingers, club foot, and short toes with talib deviation. CT head scan showed mild dilatation of the frontal horn of the lateral ventricles and coronal and lambdoid sutures; the anterior cranial fossa was also slightly wider than the posterior. X rays of the...
conformation of the ligand binding site or both, and hence accentuate binding of fibronec-
tropin growth factors (FGFs).6 Oldridge et al4 have recently described three new mutations in
residues 252 and 253; however, only one is
associated with Apert syndrome, suggesting
that the critical conformation of FGFR2 giving
rise to this more severe phenotype also depends
on specific amino acids at neighbouring sites.

The present finding of one of the canonical
mutations of Apert syndrome not associated
with severe syndactyly is intriguing, showing
for the first time that S252W may be associated
with mild limb anomalies. Since the 5' end
of exon III of this patient has no other nucleotide
alteration, this milder phenotype is not
the result of changes in amino acids bordering
residue 252. FGFR2 mutations seem to cause
the phenotype according to a gain of function
or dominant negative models.7 Therefore, we
could speculate that this patient may have
another mutation in some other gene, which is
decreasing the function of the mutated FGFR2
molecule. The analysis of other genes in this
particular patient, such as the ligands that bind
to this receptor, would be important to improve
our understanding of the function of FGFR2
as well as for the identification of the
mechanisms causing limb malformations.

Variability of the clinical phenotype in
subjects carrying the same mutation has been
shown for other FGFR2 mutations as well as in
other diseases.7 16-20 Recently, Asher et al21
showed through genetic crosses between two
mice species that the Pax3 mutation can
produce distinct phenotypes depending on the
genetic background. Interestingly, the non-
Apert patient reported here is of African
Brazilian descent, suggesting that different
racial backgrounds, which may reflect variability
in some molecules that interact with
FGFR2, might interfere differently in the
expression of the mutated allele. It will be
important to verify if there are other patients
with these canonical Apert mutations and
absence of severe syndactyly.

In addition to the difficulties in establishing a
genotype-phenotype correlation for these condi-
tions, as previously discussed,14 22 23 the de-
scription of this patient provides further
evidence for the existence of other factors (or
genes) playing an important role in the
determination of the phenotype.

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2 Gorlin RJ, Cohen MM, Levin LS. Syndromes of the head and
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4 Wilkie AOM. Cranioectodermal anomalies: diagnosis, evalu-

Wilkie et al4 first reported that Apert
syndrome was caused by mutations S252W or
P253R within exon IIIa of the FGFR2 gene.
This narrow spectrum of mutations was
confirmed by other studies, since 284 out of
the reported 288 Apert syndrome patients have
one of these two mutations.6-11 It is important
to point out that although mutation S252W
was associated with a milder syndactyly than
was P253R, all these patients had fusion of
three or more digits in both hands and feet.10
These DNA alterations lie in the region linking
the immunoglobulin (Ig)-like domains II and
III of FGFR2, which is a highly conserved
sequence among the different FGFRs. It has
been proposed that the S252W and P253R
substitutions alter the relative orientation of
Ig-like domains II and III or the local

Figure 2 Photographs of the patient with the S252W
mutation and a phenotype more compatible with Pfeiffer
syndrome. Note the typical facial features of prominent
forehead, hypertelorism, and midface hypoplasia. Only soft
syndactyly between fingers 3-4 and between toes 2-3 was
observed. Hand and foot x ray findings are detailed in the
text.

hands showed shortening of the proximal,
middle, and distal phalanges of all digits,
particularly of the distal phalanges, proximally
set and adducted thumbs, and soft tissue
syndactyly between fingers 3-4. X rays of the
feet showed shortened phalanges of all toes, a
short big toe, an increased distance between
the first and second toes, and soft tissue
syndactyly between toes 2-3. Based on these
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