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Case Report

Familial craniosynostosis due to Pro250Arg mutation in the Fibroblast Growth Factor Receptor 3 gene

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The craniosynostoses, the premature closure of the cranial sutures, are a common heterogeneous group of disorders, affecting about 1 in 2000 children at birth. About 20% have a distinct syndrome defined on clinical and family grounds. The delineation of these syndromes has become more precise with molecular analysis. Mutations in the fibroblast growth factor receptor 1, 2, 3 loci have been identified in craniosynostosis syndromes such as Pfeiffer, Apert, Crouzon, Crouzon with acanthosis nigricans, Jackson-Weiss and Beare-Stevenson. The remainder is isolated non-syndromic craniosynostosis. Recently, a mutation in fibroblast growth factor receptor 3 (FGFR3) gene at chromosome 4 (4p16) has been described in individuals with a variable picture of craniosynostosis.[1] The mutation is at C749G predicting a proline 250 arginine aminoacid substitution in the extracellular domain between the second and third immunoglobulin-like loops. The clinical phenotype of this mutation is variable, involving unilateral and bilateral craniosynostosis. Most affected individuals have normal-appearing hands and feet, but on radiological investigations may have short, broad middle phalanges of the fingers, absent or hypoplastic middle phalanges of the toes, carpal and tarsal fusion and cone-shaped epiphyses. Some authors have described mental retardation, apparently unrelated to the management of the craniosynostosis.[2] This communication describes a family with the FGFR3 Pro250Arg mutation, in which the clinical phenotype encompasses craniosynostosis, macrocephaly, deafness, delayed development, short fingers and toes and proptosis of the eyes.

CASE REPORT A 10 month old girl (Fig.1: V-1) with an "odd-shaped" skull was referred by her

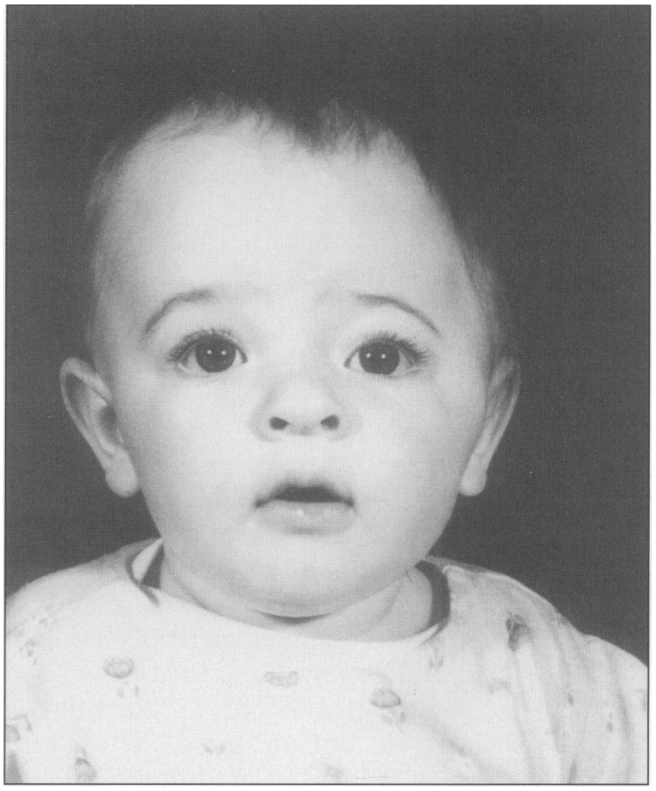

Fig 1. Patient age 10 months showing flattening of left forehead, prominence of left side of face, and left palpebral fissure lower than the right.

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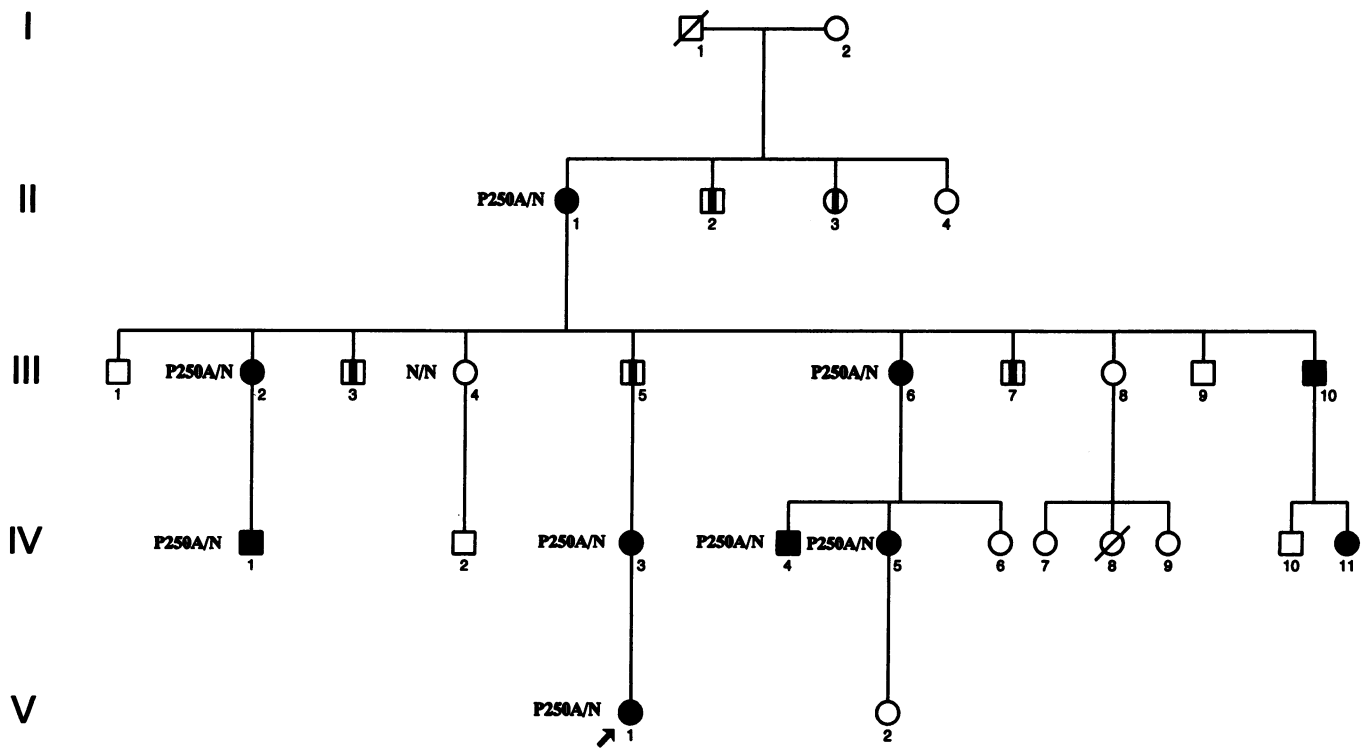

Fig 2. Pedigree of the family (□○ = unaffected male and female; ■● = affected; ◫◑ = not examined but reported affected; P250A = mutant allele; N = normal allele).

family practitioner to the Medical Genetics Clinic because of a family history of craniosynostosis. The mother had noted that her left eye was below the level of that on the right, that the left forehead was flattened and that the left lateral side of the face was more prominent. There were no concerns about hearing or her growth and development patterns. On examination, the left forehead and temple region was flattened (Fig. 1). The anterior fontanelle was of normal size. The skull circumference was 47 cms (91 centile). The tip of the nose was hooked with scalloping of the alae nasi. Fundoscopy was normal, in particular there was no papilloedema. The fingers and toes were short. The x-ray of the skull showed a left coronal synostosis. The anterior-posterior length of the skull is increased. The x-ray of the hands showed shortening of the middle phalanges and to a lesser extent the proximal phalanges of the fingers and thumb. The 4th and 5th metacarpals are short. The changes are symmetrical. The x-rays of the feet showed similar changes to those seen in the hands. There is brachyphalangy with the middle phalanges being most affected. The changes in the distal phalanges are more marked in the feet than the hands. The changes are symmetrical. The patient's mother (IV-3) had no abnormal features apart from slightly proptosed eyes and a similar shaped nose to that of her daughter. The skull circumference was just below 98 centile. Fingers and toes were short. X-ray of her skull showed no craniosynostosis but the x-ray of her hands and feet were similar to those of her daughter.

FAMILY HISTORY

Two relatives had craniosynostoses requiring neurosurgical intervention. The patient's mother (IV-3) had two paternal first cousins, a male (IV-1) with a right coronal synostosis and small auricular appendages and a female (IV-11) with bilateral coronal synostosis, mid-facial hypoplasia and choanal atresia. The Table shows the clinical features of individuals in the family.

MOLECULAR INVESTIGATIONS

Peripheral blood samples were available from nine relatives. The DNA was extracted from lymphocytes and screened using PCR for the FGFR3 Pro250Arg mutation. The eight affected relatives tested proved positive for the mutation. One relative (III,4) who developed breast cancer at age 40 years was negative for the mutation.

TABLE

Clinical Features of affected individuals in the family

RELATIVE (Pedigree ref)	*CLINICAL FEATURE*	*FGFR3 Pro250Arg mutation*
II-1	Mid facial hypoplasia, scoliosis thoracic spine	+
II-2	Facial asymmetry, learning disability	NE
II-3	Facial asymmetry, breast cancer (onset early 40s)	NE
II-4	Breast cancer (onset early 60s)	NE
III-2	Facial asymmetry, flattened R. forehead	+
III-3	Learning disability, deafness	+
III-4	Breast cancer (onset age 40)	–
III-5	Macrocephaly, proptosis	NE
III-6	Macrocephaly, mild proptosis, nerve deafness, short fingers	+
III-7	Macrocephaly, learning disability	NE
III-10	Depressed nasal bridge, treated surgically	NE
IV-I	R. coronal synostosis, small accessory auricles, treated neurosurgically	+
IV-3	Mild proptosis, hook shaped tip of nose, short fingers and toes	+
IV-4	Macrocephaly, sensor – neural deafness	+
IV-5	Macrocephaly, short fingers	+
IV-I I	Fusion coronal sutures, mid-face hypoplasia, hypertelorism, choanal atresia	NE
V-I	L. coronal synostosis, short fingers and toes	NE

+ = mutation present; – = mutation absent; NE = not examined

DISCUSSION

The phenotype of individuals in our family with a FGFR3 Pro250Arg mutation showed wide variability of clinical features (Table). Some individuals had craniosynostosis requiring neurosurgical interventions, whereas others only had minor features such as mild ocular proptosis. It is important to recognise the spectrum of clinical variability as the mutation is transmitted in an autosomal dominant manner.

Mutational analysis of patients with craniosynostosis is not only essential for diagnosis but also is a prerequisite for providing accurate genetic counselling. An individual with the FGFR3 Pro250Arg mutation with a mild clinical expression has a 50% risk of transmitting the gene mutation to children, who may be more severely affected. One report describes a normal individual with FGFR3 Pro250Arg mutation who had a child with bilateral coronal craniosynostosis.[3] Thus with reduced penetrance in some individuals not manifesting the disorder, it is important that both parents of patients with isolated sporadic craniosynostosis due to a mutation should be tested regardless of their clinical status. Any individual with neurosurgical repair of craniosynostosis contemplating having children also should be tested for the mutation in order to estimate the risk.

Mental retardation unrelated to the craniosynostosis has been described with this condition.[2] Deafness has been reported in 33% of affected individuals.[4] The explanation for the learning disability and the hearing loss is unclear. Individuals with this mutation often have macrocephaly.

In our family, four individuals had macrocephaly. Most affected individuals had normal hands and feet on clinical examination but show on x-ray short or broad middle phalanges of fingers and absent or hypoplastic middle phalanges of the toes.[4] Cone shaped epiphyses are also characteristic. The typical appearance of the hands and feet, even in the absence of craniosynostosis should suggest investigation of FGFR3 Pro250Arg mutation. Our patient and her mother had typical finger and toe anomalies. It has been suggested that this syndrome should be designated 'coronal craniosynostosis with brachydactyly and carpal/tarsal coalition due to Pro250Arg mutation in the FGFR3 gene'.[4] The mutation rate at C749G nucleotide which leads to the Pro250Arg change is one of the highest mutation rates in the human genome and makes this an extremely common form of craniosynostosis.[5]

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