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Distinct Craniofacial-Skeletal-Dermatological Dysplasia in a Patient With W290C Mutation in *FGFR2*

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Mutations in the fibroblast growth factor receptor genes (*FGFR*) have been known to be associated with many craniosynostosis syndromes with overlapping phenotypes. We studied a 15-year-old Thai boy with an unspecified craniosynostosis syndrome characterized by multiple suture craniosynostoses, a persistent anterior fontanel, corneal scleralization, choanal stenosis, atresia of the auditory meatus, broad thumbs and great toes, severe scoliosis, acanthosis nigricans, hydrocephalus, and mental retardation. Radiography revealed bony ankyloses of vertebral bodies of T9–12, humero-radio-ulnar joints, intercarpal joints, distal interphalangeal joints of fifth fingers, fibulo-tibial joints, intertarsal joints, and distal interphalangeal joints of the first toes. The patient was a heterozygous for a 870G → T change resulting in a W290C amino acid substitution in the extracellular domain of the fibroblast growth factor receptor 2 gene (*FGFR2*). This mutation has previously been reported in a patient with severe Pfeiffer syndrome type 2 that is distinct from the craniosynostosis in our patient. These findings emphasize locus, allelic, and phenotypic heterogeneity of craniofacial-skeletal-dermatological syndrome due to *FGFR2* mutations.

KEY WORDS: fibroblast growth factor receptor 2 gene (*FGFR2*); craniosynostosis; acanthosis nigricans; ankyloses; hydrocephalus; corneal scleralization

INTRODUCTION

At least 100 syndromes are associated with craniosynostosis and are classified based upon clinical features [Muenke and Wilkie, 2001]. Recently, many of the craniosynostosis syndromes, including Crouzon syndrome (MIM 123500), Apert syndrome (MIM101200), Pfeiffer syndrome (MIM 101600), Muenke syndrome (MIM 602849), Jackson-Weiss syndrome (MIM 123150), and Beare-Stevenson syndrome (MIM 123790) were discovered to be associated with mutations in the fibroblast growth factor receptor genes (*FGFR*) [Passos-Bueno et al., 1999]. Here we present a case of unspecified craniosynostosis with an *FGFR2* mutation.

MATERIALS AND METHODS

Clinical Report

The patient was a 15-year-old Thai boy. He was born at full-term by natural spontaneous vaginal delivery after an uncomplicated pregnancy with a birth weight of 2,850 g to a 28-year-old, gravida 2, para 1 mother and her 28-year-old unrelated husband. Family history was unremarkable. At birth, the patient was noted to have craniosynostosis of several cranial sutures, severe midface hypoplasia and noisy breathing. Bilateral inguinal hernias were also noted, which was surgically corrected at age 10 months. At age seven months, a ventriculoperitoneal (VP) shunt was placed for hydrocephalus. At four years, he underwent total calvarial vault reconstruction with fronto-orbital advancement. At approximately 10 years of age, he developed

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hyperpigmentation at skin areas and hyperkeratosis consistent with the diagnosis of acanthosis nigricans.

When evaluated by us at age 15 years, physical examination revealed a weight of 38 kg (-1.5 SD), height of 124.5 cm (-6 SD), and OFC of 52 cm (-2 SD). The anterior fontanel was still open and measured 0.5 × 0.5 cm. He had turribrachycephaly, several surgical scars on his scalp, high forehead, depression over the supraorbital ridges and temporal areas, down-slanting palpebral fissures, shallow orbits with severe ocular proptosis, exotropia, bilateral corneal scleralization, and corneal scars with vascularization of corneae and conjunctivae (Fig. 1A–B). Bilateral choanal stenosis, maxillary hypoplasia, severe underbite, inverted-V-

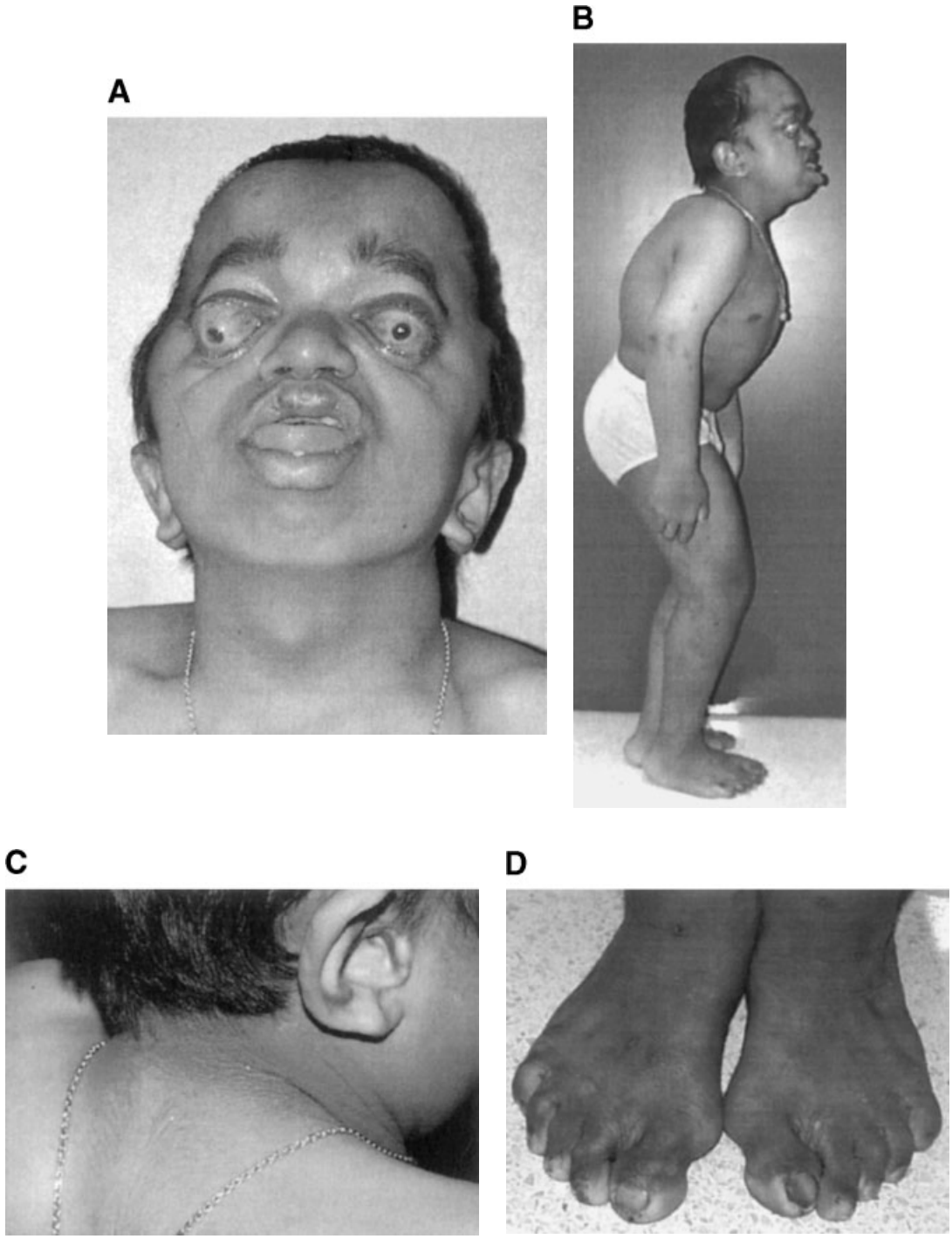

Fig. 1. Postoperative appearance of the patient at age 15 years. **A:** Note cloverleaf skull, severe ocular proptosis, scleralization of corneae, low-set ears, severe prognathia, acanthosis nigricans of periorbital, perinasal, and periorbital areas. **B:** Note abnormal position of joints. **C:** Acanthosis nigricans of the neck. **D:** Broad and laterally deviated halluces.

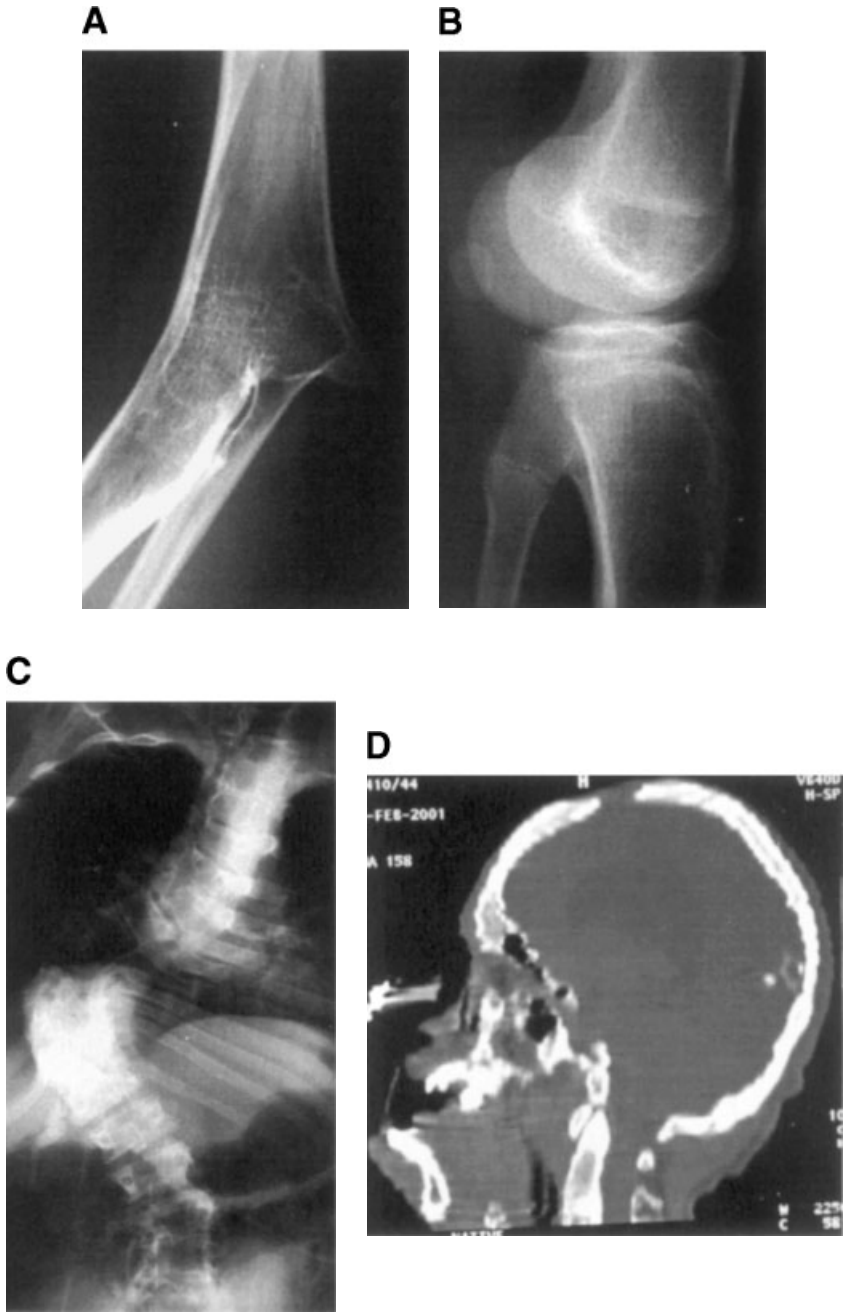

Fig. 2. Radiographs. **A:** Note complete fusion of the humerus, radius, and ulna prohibiting any motion at the right elbow. **B:** Tibulofibular fusion at the right knee. **C:** Severe scoliosis and fusion of vertebral bodies of T9 to T12. **D:** Brain computer tomography with two-dimension multiplanar reconstruction showing microcephaly and severe maxillary hypoplasia.

shaped palate, and noisy breathing were noted. Ears were low-set and external auditory canals were atretic. Acanthosis nigricans involved the periorbital, perinasal, perioral areas, and neck and axillae (Fig. 1C). The chest wall was asymmetric and severe scoliosis was detected. Examinations of his heart and lungs were unremarkable. His elbows, hips, and knees were fixed at approximately 150 degrees. His thumbs and great toes were broad with the great toe/second toe ratio of 2.0 on the left and 2.12 on the right. The halluces were in valgus position (Fig. 1D). He was unable to talk but able to follow simple commands. His vision and hearing were severely impaired. He had light perception. Brain stem auditory-evoked potentials revealed hearing at approximately 45 and 60 decibels on the right and left, respectively. Electrocardiogram showed no evidence of right heart hypertrophy. Routine laboratory tests were all within the normal limits. Radiography revealed

bony ankyloses of T9–12 vertebral bodies, the humero-radio-ulnar, intercarpal, and distal interphalangeal joints of the fifth fingers and first toes, and of the fibulo-tibial and intertarsal joints (Fig. 2A–C). Computed tomography of the skull and brain revealed microcephaly, hydrocephalus with a ventriculoperitoneal shunt, and severe maxillary hypoplasia (Fig. 2D).

Mutation Analysis

After informed consent was obtained in accordance with the standards set by the local institutional review boards, DNA was extracted from the patient and his parents by a standard method. *FGFR2* exon 8 and *FGFR2* exon 10 were PCR-amplified. Primers, annealing temperatures and PCR procedures were as described previously [Shotelersuk et al., 2001]. PCR products were electrophoresed on a 2% agarose gel (Promega, Madison, WI) and stained with ethidium bromide. DNA on visualized bands was extracted with a kit (Bio 101, Carlsbad, CA), and sequenced in both directions with an automated DNA sequencer (ABI Prism 310 Genetic Analyzer, Perkin Elmer, Foster City, CA).

A heterozygous G → T transversion at nucleotide 870 was identified in *FGFR2* exon 8 of the patient (data not shown). Nucleotide sequence of *FGFR2* exon 10 of the patient, and those of *FGFR2* exons 8 and 10 of his parents, were normal (data not shown).

DISCUSSION

The salient features in our patient were multiple suture craniosynostoses, corneal scleralization, choanal stenosis, atresia of auditory meatus, broad thumbs and great toes, multiple bony ankyloses, severe scoliosis, acanthosis nigricans, hydrocephalus and mental retardation. These clinical features do not fit any known craniosynostosis syndromes (Table I).

Although acanthosis nigricans can be associated with type II diabetes mellitus (DM), patients with acanthosis nigricans and congenital disorders such as Crouzon syndrome did not have DM [Wilkes et al., 1996]. Our patient had a normal fasting glucose level and an oral glucose tolerance test showing no evidence of abnormal glucose metabolism. Craniosynostoses with acanthosis nigricans can result from either of mutations in *FGFR2* (Beare-Stevenson syndrome), or in *FGFR3* (Crouzon syndrome and acanthosis nigricans, CAN) [Passos-Bueno et al., 1999].

Our patient was heterozygous for an 870 G-to-T mutation in *FGFR2*, leading to a substitution of a cysteine for the normal tryptophan at codon 290 (W290C). The mutation was not found in either of his parents, the finding indicating that the mutation was de novo type. The same mutation has previously been reported in a female patient with Pfeiffer syndrome [Schaefer et al., 1998]. Unlike our patient, she had normally formed corneae, a urogenital septum defect, bilateral temporal encephaloceles, patent ductus arteriosus, atrial septal defect, and no fusion of the vertebral, fibulo-tibial,

TABLE I. Clinical Features in Patients With Craniosynostosis

Clinical findings	Our patient	Previously reported patient with W290C	Crouzon with acanthosis nigricans	Pfeiffer syndrome	Crouzon syndrome	Antley-Bixler syndrome	Apert syndrome	Beare-Stevenson syndrome
Craniosynostosis	+	+	+	+	+	+	+	+
Hydrocephalus	+	+	+	+/–	+/–	+/–	+/–	+/–
Acanthosis nigricans	+	–	+	–	–	–	–	+
Broad thumbs and great toes	+	+	–	+	–	–	+	–
Deviation of great toes	Valgus	Varus	–	Varus	–	–	Varus	–
Choanal atresia/stenosis	+	+	+	+/–	–	+	+	+
Atresia of auditory meatus	+	?	+/–	+/–	+	+	–	–
Ankyloses	+	+	–	+/–	–	+	+/–	–
Ocular anterior chamber dysgenesis	+	–	+/–	+/–	+/–	–	+/–	–
Radiographic findings of achondroplasia	–	–	+	–	–	–	–	–
Mental retardation	+	?	+/–	+/–	+/–	+/–	+	?
Early death	–	+	–	+/–	–	+	+/–	+
Inheritance	AD	AD	AD	AD	AD	AR	AD	AD
Mutation	*FGFR2* W290C	*FGFR2* W290C	*FGFR3* A391E	*FGFR1/2* Several	*FGFR2* Several	?	*FGFR2* S252W P253R Others	*FGFR2* S372C Y375C

+, common or present; +/–, occasional; –, uncommon or not present; ?, unknown.

intercarpal, intertarsal, and interphalangeal joints; she died at the age of 10 days. If she had survived to an older age, acanthosis nigricans and bony fusion, which are present in our patient, might have been observed. In contrast to our patient with halluces extended a valgus deviation, the halluces in the patient by Schaefer et al. [1998] were in varus position. Even though clinical manifestations were similar between the two patients with W290C, the natural history was quite different: one died at age 10 days, the other has survived to adolescence. This observation emphasizes phenotypic heterogeneity of the mutation, which could be accounted for by different modifier genes and diverse environmental factors.

Other amino acid changes, e.g., a substitution of tryptophan to arginine or to glycine, at the same codon of *FGFR2* resulted in milder forms of craniosynostosis, such as either classic Crouzon syndrome or an atypical Crouzon syndrome [Oldridge et al., 1995; Park et al., 1995; Meyers et al., 1996; Steinberger et al., 1996]. Cysteine crosslinking forming immunoglobulin-like hoops typifies the region around codon 290 of the fibroblast growth factor receptor [Zhang et al., 1999], and an additional cysteine predicted by the mutation in our patient may lead to aberrant crosslinking and severe changes in the secondary and tertiary structure of the protein.

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