Atypical Skin Manifestations in *FGFR2*-Related Craniosynostosis Syndromes Broaden the Phenotypic Spectrum

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Keywords

Beare-Stevenson syndrome · Craniosynostosis · Crouzon syndrome · *FGFR2*

Abstract

Crouzon syndrome (CS) and Beare-Stevenson syndrome (BSS) are craniosynostosis syndromes caused by mutations in the fibroblast growth factor 2 (*FGFR2*) gene. CS is more common (1 in 60,000 live births) than BSS, where fewer than 20 individuals have been reported. The cardinal features of BSS are craniosynostosis, cutis gyrata, acanthosis nigricans, skin furrows, skin tags, anogenital anomalies, and a prominent umbilical stump. Previously described individuals with BSS have typically had mutations in exon 11 of *FGFR2*. Here, we present 2 patients with CS who have significant skin manifestations and some phenotypic overlap with BSS. De novo mutations in exon 8 of *FGFR2* were identified in both; one is a mutation (c.799T>C; p.Ser267Pro) previously identified in individuals with CS and the other a novel in-frame deletion (c.820_824delinsTT; p.Val274_Glu275delinsLeu). No mutations in exon 11 of *FGFR2*, where previously reported BSS

mutations have been located, were identified. This case expands the phenotypic spectrum of CS and highlights the overlap between conditions caused by mutations in *FGFR2*.

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Crouzon syndrome (CS; OMIM 123500) and Beare-Stevenson syndrome (BSS; OMIM 123790) are craniosynostosis syndromes caused by mutations in the fibroblast growth factor 2 (*FGFR2*) gene [Reardon et al., 1994; Przy-lepa et al., 1996]. CS is clinically differentiated from the other craniosynostosis syndromes by characteristic facial dysmorphism, the degree of proptosis, maxillary hypoplasia, and the absence of limb abnormalities [Reardon et al., 1994; Wilkes et al., 1996]. Skin manifestations have not been typically associated with CS [Reardon et al., 1994; Wilkes et al., 1996]. BSS is a rare *FGFR2*-related craniosynostosis syndrome, identifiable by its specific cutaneous features of cutis gyrata, acanthosis nigricans, unusual skin and ear furrows, deep palmar and plantar creases, and a prominent umbilical stump. Here, we present 2 patients with different *FGFR2* mutations and significant skin man-

ifestations; one is a novel mutation and the other was previously associated with CS but with significant clinical overlap with BSS. These patients broaden the phenotypic spectrum of *FGFR2*-related craniosynostosis.

Patients and Methods

Patient 1 is the first child born to non-consanguineous parents following a healthy pregnancy. The family history was non-contributory. First-trimester screening demonstrated low PAPP-A (0.3 multiples of the median) and increased nuchal translucency (4.6 mm at 12 weeks) corresponding to a 1-in-3 risk of Trisomy 21. The 16-week ultrasound was reported as normal, while the 20-week ultrasound showed normal morphology other than a bowed ulna. Delivery occurred at 39 weeks of gestation via caesarean section, with a birth weight of 4.4 kg (>97th centile). At birth, an abnormal head shape was noted, and a subsequent CT scan demonstrated premature fusion of the sagittal suture in the middle third and posteriorly together with almost complete premature fusion of the left coronal suture and incomplete inferior fusion of right coronal suture.

The patient was referred to the clinical genetics service at 4 months of age, at which time his head circumference was 45 cm (97th centile), weight 7.42 kg (80th centile), and his length was 65 cm (75th centile). He had marked turribrachycephaly, hypertelorism, and bilateral proptosis. Both thumbs were slightly broad with radial deviation at the distal interphalangeal joint. The halluces were slightly broad. There was a prominent deep transverse natal cleft adjacent to the central natal cleft.

The infant had skin manifestations consistent with BSS including lip and perioral linear rugations similar to cutis gyrata as well as deep ear lobe linear creases (Fig. 1). He had deep palmar and plantar creases, a prominent umbilical stump and generalised redundant skin (Fig. 1). There were no cardiovascular, respiratory or gastrointestinal abnormalities. His hearing was normal. Post-natal upper abdominal and spinal ultrasounds and X-rays of both ulnas were normal. The patient underwent a successful craniofacial repair (fronto-orbital advancement) at 6 months of age.

The second patient was the fourth child to non-consanguineous Iraqi parents. His 3 older siblings are healthy, and there is no relevant medical history in the extended family. The pregnancy was uncomplicated with normal ultrasound scans. Patient 2 was born at 42 weeks of gestation by normal delivery. Birth weight was 3,730 g, length 50 cm, and his head circumference was 36 cm. A possible diagnosis of Costello syndrome was considered at birth due to the presence of coarse facial features and loose, excessive skin. Additional features of hypertelorism, prominent posterior and anterior earlobe creases, a bifid uvula, deep plantar and palmar creases as well as soft excessive skin on his hands and feet were noted after referral to a clinical geneticist at 2 weeks of age (Fig. 1). He had a long great toe, minimal 2/3 toe syndactyly, small inset nails on his hands and feet, and a preauricular ear pit on the right side. Bilateral epicanthic folds and a degree of micrognathia were present. He had thickened gums. His skin was generally soft and loose. His genitalia were abnormal with a shawl scrotum, scrotal rugations, and a raphe between the anus and the scrotum. His testes were descended.

By 4 months of age, the infant had mild hypotonia but was otherwise developmentally normal. At 6 months of age, he started to

Fig. 1. Clinical photographs of patient 1. **A** Evidence of marked turribrachycephaly. **B** Linear rugations very similar to cutis gyrata involving the lips. **C, D** Deep linear creases/rugations involving the ear lobes as seen in Beare-Stevenson syndrome. **E, F** Deep palmar and plantar creases, prominent umbilical stump and redundant skin as seen in Beare-Stevenson syndrome. **G, H** Marked redundant scalp skin, also seen on the 3D reconstructed CT scan.

roll over and would weight bear but could not sit alone. At 1 year of age, he was standing with support and taking a few steps, had 2 words (“mama” and “dada”), and was babbling. At 18 months, he was seen in the craniofacial clinic and diagnosed with craniosynostosis. At 2 years and 1 month, he had surgical correction of bilateral coronal craniosynostosis. At 15 months of age, he had bilateral proptosis, more obvious on the right side, with a right exotropia. He had elevated disc oedema associated with shallow orbits. MRI of his brain and orbits showed a normal cerebrum, brainstem, and ventricles but tortuous optic nerves with some dural ectasia bilaterally. His hearing was normal.

Table 1. Clinical and molecular features of Crouzon syndrome and Beare-Stevenson syndrome and those observed in Patient 1 and Patient 2 in this study

	Crouzon syndrome	Beare-Stevenson syndrome	Patient 1, this study	Patient 2, this study
Gene	<i>FGFR2</i>	<i>FGFR2</i>	<i>FGFR2</i>	<i>FGFR2</i>
Location of mutation	exon 8, 10	exon 8, 11	exon 8	exon 8
Sutures involved	sagittal, coronal, lamboid	sagittal, coronal, lamboid	sagittal, coronal	coronal
Facial dysmorphism	frontal bossing, maxillary hypoplasia, mandibular prognathism, proptosis, hypertelorism	midface hypoplasia, low-set posteriorly rotated ears, preauricular skin furrows, hypertelorism, proptosis, down-slanting palpebral fissures	midface hypoplasia, low-set posteriorly rotated ears, periauricular skin furrows, hypertelorism, proptosis, down-slanting palpebral fissures	midface hypoplasia, preauricular skin furrows, hypertelorism, proptosis, bifid uvula, thickened gums, bilateral epicanthic folds, micrognathia
Respiratory	sleep apnoea	respiratory distress	normal	normal
Hearing/ENT	conductive hearing loss, atretic external auditory canals	choanal atresia/stenosis, hearing usually normal	normal	normal
Umbilicus	normal	prominent umbilical stump	prominent umbilical stump	normal
Genitourinary/gastrointestinal	normal	anteriorly placed anus, bifid scrotum, prominent scrotal raphe	prominent scrotal raphe	prominent scrotal raphe, shawl scrotum, scrotal rugations
Palate	lateral palatal swellings, occasional cleft palate	usually normal	normal	normal
Cognitive outcome/neurological	mental retardation, occasional seizures, hydrocephalus	hydrocephalus, agenesis of the corpus callosum, developmental delay	normal	normal
Hand abnormalities	usually normal, occasional carpal fusion	deep palmar creases, furrowed palms, bones usually normal	deep palmar creases, furrowed palms, broad thumbs	deep palmar creases, furrowed palms
Foot abnormalities	normal	deep plantar creases, furrowed soles	deep plantar creases, furrowed soles, broad halluces	deep plantar creases, furrowed soles, 2/3 toe syndactyly
Skin abnormalities	normal	cutis gyrata, acanthosis nigricans, cutaneous and mucosal skin tags, furrowed palms and soles, small nails	cutis gyrata, furrowed palms and soles, small nails, deep transverse natal cleft	furrowed palms and soles, small nails, loose excessive skin

ENT, ears, nose, and throat.

Methods

Karyotyping and chromosome microarray (Affymetrix 750k array) were performed on DNA from patient 1. In both patient 1 and patient 2, genomic DNA was amplified by PCR and screened by bidirectional sequencing followed by semi-automated software analysis for variants in “hotspot” exons of *FGFR1*, *FGFR2*, and *FGFR3*. Human genome variation society (HGVS) nomenclature was utilised relative to NCBI reference sequences NM_023110.2, NM_000141.4, NM_000142.4, and NM_000474.3, respectively.

Results

Patient 1 had a normal male karyotype and normal microarray. Molecular sequencing of *FGFR2* identified a NM_000141.4 (*FGFR2*):c.799T>C (p.Ser267Pro) mutation, which has previously been reported in Crouzon and

Pfeiffer syndromes and has been classified as a pathogenic mutation [Oldridge et al., 1995; Cornejo-Roldan et al., 1999]. Previously reported Beare-Stevenson-associated mutations in exon 11 of *FGFR2* were not identified.

Patient 2 had a previously unreported in-frame deletion in exon 8 of the *FGFR2* gene, NM_000141.4 (*FGFR2*):c.820_824delinsTT (p.Val274_Glu275delinsLeu). The *FGFR2* mutation was de novo.

Discussion

Mutations in *FGFR2* are associated with a number of congenital craniosynostosis syndromes including CS, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome, Antley-Bixler syndrome, BSS, and Saethre-Chot-

zen syndrome. Missense mutations in *FGFR2* in these syndromic forms of craniosynostosis are clustered around the third immunoglobulin-like domain or within the tyrosine kinase domains [Katoh, 2009; Jezela-Stanek and Krajewska-Walasek, 2013]. CS is typically caused by mutations in *FGFR2* exons 8 and 10, BSS is typically caused by 1 of 2 recurrent mutations in exon 11 of *FGFR2* (Tyr375Cys and Ser372Cys); however, a deletion involving *FGFR2* exon 8 has also been described in patients with typical features of BSS [Przylepa et al., 1996; Roscioli et al., 2001; Eun et al., 2007; Fonseca et al., 2008; Slavotenik et al., 2009] (Table 1). CS is much more common (1 in 60,000 live births) than BSS, where fewer than 20 cases have been reported [Slavotenik et al., 2009].

The *FGFR2*-related craniosynostosis syndromes are characterised by uni- or multisutural craniosynostosis or cloverleaf skull, distinctive facial features, and variable hand and foot findings [Robin et al., 2011]. With the exception of BSS and Apert syndrome, very few cutaneous features have been reported in association with these syndromes. Pfeiffer syndrome, Jackson-Weiss syndrome, and Antley-Bixler have not been associated with any particular cutaneous features. Individuals with Saethre-Chotzen syndrome have been described to have a typically lower frontal hairline, but no other recurrent cutaneous features are reported [Robin et al., 2011]. Muenke syndrome has a phenotypic overlap with Pfeiffer, Jackson-Weiss, and Saethre-Chotzen syndromes with cutaneous features reported uncommonly [Roscioli et al., 2001; Robin et al., 2011].

In addition to craniosynostosis, the cardinal features of BSS involve the skin (Table 1). Cutis gyrata, acanthosis nigricans, skin furrows, skin tags, and deep palmar and plantar creases are usual [Przylepa et al., 1996; Akai et al., 2002; Vargas et al., 2003; McGaughan et al., 2006; Slavotinek et al., 2009; Robin et al., 2011]. The mechanisms by which cutis gyrata and acanthosis nigricans are caused by the *FGFR2* mutations remain unclear. However, it is clear that *FGFR* is expressed in skin, and loss of IIIb splice variants in *FGFR2* in keratinocytes cause a range of skin abnormalities including acanthosis and keratinocyte hyperproliferation [Kawano et al., 2005]. A knock-in mouse model of BSS has identified p38 MAPK as an important signalling pathway mediating the skin abnormalities in BSS [Wang et al., 2012]. In this study, in addition to craniosynostosis, *Fgfr2*^{±/Y394C} mice exhibited epidermal hyperplasia due to abnormal cell proliferation and differentiation. The authors demonstrated ligand-independent phosphorylation of *FGFR2* and activation of p38 signalling in mutant skin and calvarial tissues. One possible ex-

planation for the interesting cutaneous manifestations in our patients is that the mutations in exon 8 have led to constitutive activation of the *FGFR2* receptor and activation of MAPK p38 signalling in the epidermis. Wang et al. [2012] proposed inhibition of p38 signalling as a potential future therapy. Another possible mechanism is that the mutations lead to expression of a *FGFR* protein lacking one or more extracellular domains, with a resultant effect on signalling. This mechanism has been reported as a modifier of phenotypic outcome [Poot, 2017].

BSS features have also been described in a girl with the *FGFR3* P250R mutation [Roscioli et al., 2001], which is usually associated with Muenke syndrome (coronal craniosynostosis, deafness, brachydactyly, and carpal/tarsal coalition) [Graham et al., 1998]. This patient's father had the same mutation and only subtle cutaneous features, suggesting that while skin manifestations are a rare feature of *FGFR3*-coronal craniosynostosis, subtle cutaneous features may be overlooked or appear later in life.

CS with acanthosis nigricans is a distinct entity caused by a recurrent mutation, Ala391Glu, in *FGFR3* [Przylepa et al., 1996; Wilkes et al., 1996; Nigase et al., 2000]. While the molecular genetic aetiology differs to that of BSS, the 2 syndromes have overlapping cutaneous phenotypes [Akai et al., 2002]. Cutaneous features in CS with acanthosis nigricans include diffuse hyperpigmentation without hyperplasia, diffuse skin thickening, generalised xerosis, desquamation, hypopigmented prominent scars after surgery, multiple melanocytic nevi, warty acanthomas, and rarely, café-au-lait spots [Gines et al., 1996; Di Rocco et al., 2011].

The BSS-like cutaneous features seen in our patients with CS expand the phenotypic spectrum of *FGFR2*-related craniosynostosis syndromes. One limitation of our report is that exome sequencing has not been performed on either of these patients. Given the recent literature indicating that approximately 5% of the patients referred for exome sequencing have dual molecular diagnoses, the small possibility of a second diagnosis in our patients (or digenic inheritance) has not been fully excluded [Posey et al., 2017].

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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