Beare-Stevenson cutis gyrata syndrome: A new case of a c.1124C→G (Y375C) mutation in the *FGFR2* gene

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Abstract. Beare-Stevenson syndrome (BSS) (MIM#123790) is a rare disorder characterized by craniofacial anomalies and cutis gyrata associated with anogenital anomalies and prominent umbilical stump. There are few reports on the syndrome, and molecular analysis has revealed the involvement of two closely spaced mutations within the *FGFR2* gene: c.1115C→G (p.S372C) and c.1124C→G (p.Y375C). We herein describe a new case of a c.1124C→G mutation in a BSS patient.

Introduction

Beare-Stevenson syndrome (BSS) is a rare disorder characterized by a series of symptoms, recognizable at birth, which include cutis gyrata, craniosynostosis, acanthosis nigricans and craniofacial, umbilical and anogenital anomalies (1-5). These symptoms overlap with other disorders, such as Crouzon syndrome; however, the prognosis for BSS is worse than in these other disorders (6). BSS cases are sporadic, and a paternal age effect has been suggested (4,7,8). Molecular analysis of BSS cases has revealed two closely spaced mutations in exon 11 of the *FGFR2* gene: c.1115C→G (S372C) in 2 patients and c.1124C→G (Y375C) in 9 patients (4,6,8-14).

Fibroblast growth factor receptors (FGFRs) comprise a family of tyrosine kinase receptors. Four of their members have been identified in humans, and three of these are associated with developmental disorders. Heterozygous mutations in *FGFR1-3* genes have been identified in several syndromic craniosynostoses, including the Apert, Crouzon, Pfeiffer, Jackson-Weiss, BSS, Antley-Bixler, Muenke and Crouzonodermoskeletal syndromes, and at least 40 allelic variants of *FGFR2* have been described to date (Table I) (15-17). Other genes have also been implicated in syndromic craniosynostosis, including *MSX2* in Boston type craniosynostosis (18), *TWIST* in Saethre-Chotzen syndrome (19), *POR* in Antley-Bixler syndrome (20) and *NFB1* in craniofrontonasal syndrome (21,22).

In the present study, we describe a new case of a c.1124C→G (Y375C) mutation in a BSS patient.

Case report

The patient was the product of a 41-week gestation to a G2P2Ab0 23-year-old mother and a 30-year-old unrelated father. Delivery was by cesarian section. At birth, the head circumference was 35 cm, birth weight was 3,985 g and birth length was 50.5 cm. Clinical examination showed several anomalies, among them a cloverleaf skull, high forehead, low-set ears, corrugated skin overlying the scalp, face, ears, palms, soles and labia majora, mild face hypoplasia, choanal atresia, neonatal teeth, corrugated high palate, globulous abdomen, prominent umbilical stump, perineal fissure from genital to anal mucosa and lumbosacral dimple.

Chromosomal analysis by GTG banding revealed a normal 46,XX karyotype. Blood samples were obtained from the patient and her mother. The child died on day 1, and a post-mortem examination was refused.

Results

After informed consent was obtained, molecular screening was performed by PCR-direct sequencing. DNA was extracted according to standard procedures (23), and 100 ng was used to amplify a segment containing exon 11 of *FGFR2*. PCR was conducted in an MJ PTC200 thermocycler (Waltham, MA,

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Table I. Involvement of the *FGFR* gene family members in syndromic craniosynostosis with known mutations[a].

Gene	MIM	Chromosomal location	Syndrome	OMIM	Mutations[b]
FGFR1	136350	8p11.2-p11.1	Pfeiffer	101600	P252R
			Crouzon	123500	Y105C, S252L[c], P253L, H254Y, P263L, S267P, F276V, C278F, C278Y[c], Y281C, I288S, Q289P, W290R, W290C, W290G, L292E, Y308C, D321A, Y328C, A337P, G338R, Y340S, Y340H, C341P, C342F, C342Y, C342R, C342S, C342W, A344A, S347C, S354C, S354F, A326S[c], K526E[c], N549H
FGFR2	176943	10q26	Pfeiffer	101600	A172F, S252L, P253S, S267P, C278F, W290C, Y340C, T341P, C342R, C342S, C342Y, S351C, S352P, Y375C, N549T, E565A, E565G, K641R, G663E
			Apert	101200	S252W, S252F, P253R
			Beare-Stevenson	123790	S372C, Y375C
			Jackson-Weiss	123150	C342R, C342S, A344G
			Antley-Bixler	207410	C342R, C342S, S351C
FGFR3	134934	4p16.3	Muenke	602849	P250R[c]
			Crouzon with acanthosis nigricans	123500	A391E
FGFR4	134935	5q35.1-qter	ND	-	-

[a]Based on previous reviews (15-17). [b]Includes only amino acid substitutions. [c]Reduced penetrance or uncertain pathogenicity (17). ND, not determined.

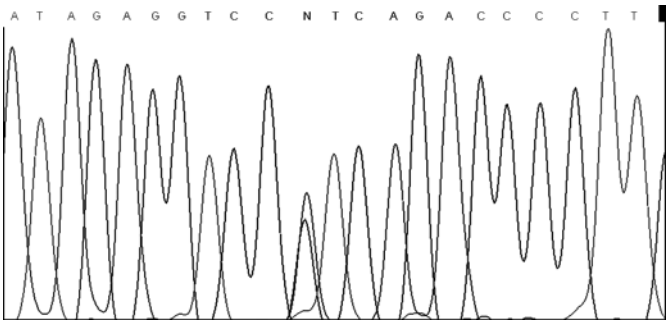

Figure 1. Chromatogram showing the presence of a transition (c.1124A→G) in the proposita.

USA) using the Enhancer Kit (Invitrogen, Carlsbad, CA, USA) with cycling conditions and primers as described elsewhere (12). Sequencing was performed using Dyenamic™ ET Dye Terminator Kit Megabace™ (GE Healthcare Biosciences, Buckinghamshire, UK) according to the manufacturer's instructions in a Megabace 1000™ (GE Healthcare Biosciences), and revealed a heterozygous transition at nucleotide 1124 (c.1124A→G) (Fig. 1) that promotes the substitution of a tyrosine by a cysteine residue (p.Y375C). This mutation was not found in the mother.

Discussion

To date, *FGFR2* mutations have been reported in 11 BSS patients. Two cases harbored a c.1115C→G transversion (9,14) located in the carboxyl-terminal end of the linker region between the immunoglobulin III-like (Iglll) and transmembrane domains of the protein, and 9 cases harbored a c.1124A→G transition (4,8-13) located in the transmembrane region of the protein. In 2 patients, no *FGFR2* mutations were detected, suggesting further genetic heterogeneity (9). One unique report revealed a chromosomal abnormality with a 46XY,t(7;18)(q35;q21) karyotype (24); however, no molecular analysis was performed in this case.

While the Crouzon and Pffeifer syndromes can be caused by an impressive number of different *FGFR2* mutations, the Apert, Beare-Stevenson, Jackson-Weiss and Antley-Bixler syndromes are caused by a restricted number of *FGFR2* mutations. The same mutation can, however, occur in different syndromes. For example, p.C342R has been described in the Crouzon, Pfeiffer, Jackson-Weiss and Antley-Bixler syndromes. The p.Y375C substitution in the *FGFR2* gene has also been described in a patient with severe Pfeiffer syndrome presenting a cloverleaf skull, prominent labia majora and sacral appendage, but without cutis gyrata (26). On the other hand, a mutation in the *FGFR3* gene (p.P250R) was described

in a man and his daughter affected with atypical BSS-like features (25).

The phenotypic spectrum of BSS is wide; however, to date all patients harboring *FGFR2* mutations have been reported to present preauricular creases, umbilical stump, abnormal cranial shape, craniosynostosis, midface hypoplasia, and proptosis. Our patient presented neonatal teeth, a feature that has only been previously described once (1).

Our case confirms the high morbidity and fatal outcome generally associated with BSS, irrespective of the *FGFR2* mutation involved. The oldest patient reported reached 13 years of age (1), while over 60% of the patients with *FGFR2* mutations die before 2 years of age. The mean paternal age reported in the literature seems to be high (38.7±11.5, range 24-62, in accordance with the notion that *FGFR2* mutations arise from the male chromosome (5). However, no paternal age effect can be assumed in the present case, and further analysis of additional patients is necessary for an association to be established.

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