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 (p.S372C) in 2 patients and c.1124C→G (p.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 FGFR-1-3 genes have been identified in several syndromic craniosynostoses, including the Apert, Crouzon, Pfeiffer, Jackson-Weiss, BSS, Antley-Bixler, Muenke and Crouzono-dermoskeletal 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 NF1 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,
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 (IgIII) 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 Pfeiffer 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

Table I. Involvement of the FGFR gene family members in syndromic craniosynostosis with known mutationsa.

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM</th>
<th>Chromosomal location</th>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mutationsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>136350</td>
<td>8p11.2-p11.1</td>
<td>Pfeiffer</td>
<td>101600</td>
<td>P252R</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Apert</td>
<td>101200</td>
<td>S252W, S252F, P253R</td>
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<tr>
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<td></td>
<td></td>
<td>Antley-Bixler</td>
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<td>C342R, C342S, S351C</td>
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<tr>
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<td>P250R</td>
</tr>
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</tr>
</tbody>
</table>

aBased on previous reviews (15-17). bIncludes only amino acid substitutions. cReduced penetrance or uncertain pathogenicity (17). ND, not determined.
References


