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A Newborn with Cloverleaf Skull and Sacrococcygeal Eversion due to a Rare FGFR2-Related Craniosynostosis Disorder: Beare-Stevenson Syndrome

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Case Summary:

A Genetics consultation was requested for a term female infant with a cloverleaf skull and multiple congenital anomalies. She was born by Cesarian section at 38 weeks 5 days gestation to a 29-year-old G2P1 mother. Father was 30 years old. Pregnancy was complicated by maternal obesity, polyhydramnios, prenatal diagnosis of fetal ventriculomegaly, and Chiari 1 malformation.

The physical exam was noteworthy for major and minor anomalies:

- Cloverleaf skull with turricephaly (Figure 1a); moderately tense anteriorly displaced fontanelle; flat midface; maxillary hypoplasia, class III malocclusion with excess tissue on the lower alveolar ridge (Figure 1b), with a prominence at the midline; intact, high arched palate, shallow and widely spaced orbits, posterior auricular pits and indentations, bilateral preauricular and lobular pits and excess nuchal skin
- Broad adducted thumbs and great toes (Figure 1c) without syndactyly and with a range of motion of all joints.
- The caudal appendage at the base of the spine has a blind central pit with a hard, bony consistency (Figure 1d)
- Thick umbilical stump with excess epithelialization extending 2-3 cm up the cord (Figure 1e)
- Anteriorly placed anus at the base of the introitus; edematous and widely separated labia; unable to visualize clitoris.
- Hyperkeratotic palms and soles (Figure 1f); deep palmar and plantar creases with many accessory creases and rugae on the face

"During her 3-month hospitalization, she required a ventriculoperitoneal shunt, tracheostomy, and gastrostomy tube. The first step in the surgical correction of her craniosynostosis, a posterior distraction, is planned at about four months of age."

Brain imaging with CT and MRI showed multisuture craniosynostosis (coronal and lambdoid) with cloverleaf skull, dysmorphic bilateral cerebral hemispheres with scalloping along the posterior parieto-occipital lobes, thinning of the corpus callosum, hypoplastic posterior fossa with low-lying cerebellar tonsils, midfacial hypoplasia, and shallow orbits with associated proptosis and hypertelorism and lateral ventriculomegaly. A patent foramen ovale was visualized at 8 days by echocardiogram. She was treated with positive pressure ventilation for upper airway obstruction. During her 3-month hospitalization, she required a ventriculoperitoneal shunt, tracheostomy, and gastrostomy tube. The first step in the surgical correction of her craniosynostosis, a posterior distraction, is planned at about four months of age.

Family history was not significant. The parents are both of Mexican ancestry, and consanguinity was denied.

A craniosynostosis gene panel testing revealed a recurrent *de novo* pathogenic variant in *FGFR2*: c.1124A>G, p.Tyr375Cys. Chromosome microarray was negative.

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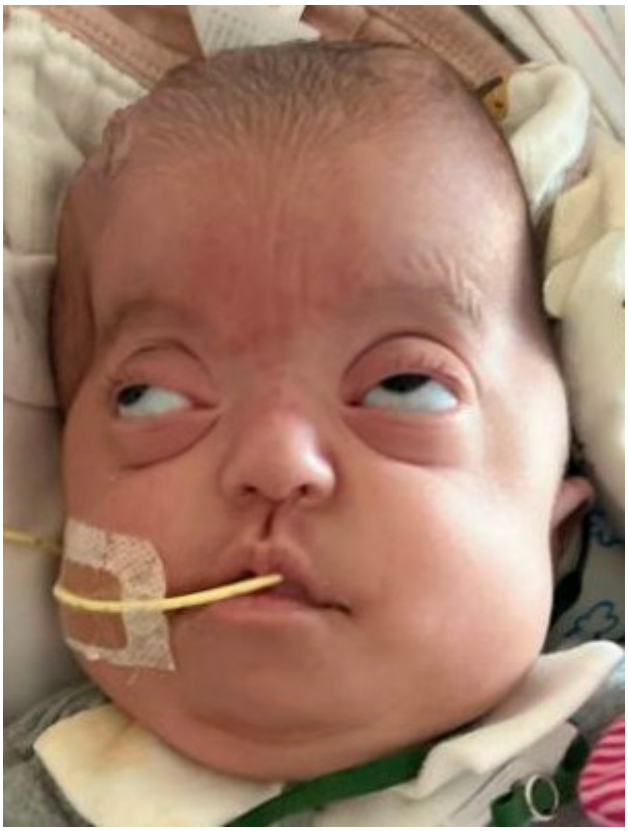
Discussion:

Craniosynostosis is a relatively common congenital anomaly that affects about 1 in 2000 children. (1) Although most cases of craniosynostosis involve a single suture and are not associated with other anomalies, approximately 5% involve multiple sutures, which are more often syndromic with a genetic etiology (Figure 2). (2) This infant has the most severe manifestation of craniosynostosis with premature fusion of both coronal and lambdoidal sutures, causing a cloverleaf-shaped skull. The genetic cause in her case is a heterozygous *de novo* pathogenic variant (p.Tyr375Cys or Y375C) in the *FGFR2* gene, which encodes the fibroblast growth factor receptor type 2. Activating variants in this family of genes (*FGFR1, FGFR2,* and *FGFR3)* are responsible for many craniosynostosis and chondrodysplasia syndromes.

"The pathogenic FGFR2 variants responsible for craniosynostosis cause a gain of function in either a ligand-dependent or ligand-independent manner."

Like the other members of this class, FGFR2 is a transmembrane tyrosine kinase signaling factor that usually forms a dimer and activates a growth-stimulating signal when ligands bind to its extracellular domains (Figure 3). (3) The pathogenic *FGFR2* variants responsible for craniosynostosis cause a gain of function in either a ligand-dependent or ligand-independent manner. Two tissue-specific isoforms of FGFR2 have different ligand binding domains (IIIb, KGFR, IIIc, and BEK) and selectively target epithelial and mesenchymal tissues. The Y375C variant adds a cysteine residue, which is thought to increase ligand-independent dimerization in both the mesenchymal and epithelial isoforms, constitutively activating the growth-stimulating pathway in both tissue types.

The Y375C variant in *FGFR2* is the most common variant responsible for Beare-Stevenson syndrome (BSS; OMIM #123790). (4) The incidence of BSS is unknown, and only about 25 cases have been reported worldwide. In this rare condition, cloverleaf skull occurs in the context of cutis gyrata on the scalp or elsewhere, skin tags, creases on the ears, skin furrows on the palms and soles, enlarged and elongated umbilical stump, anal and genital anomalies. (5) A caudal appendage or pseudotail, described more accurately as a sacrococcygeal eversion, has been reported in many affected individuals with BSS and the Y375C variant. (6-8)



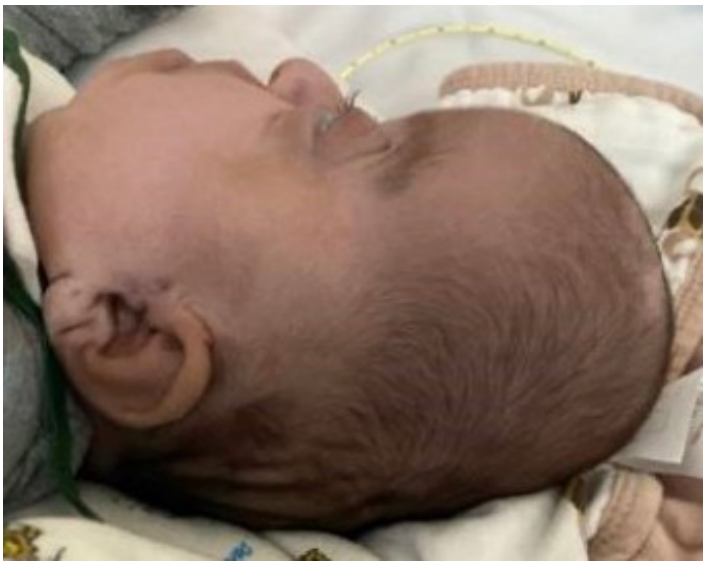


Figure 1a: Cloverleaf skull with turricephaly. Note the rugae on the forehead. Photo taken about 11 weeks.

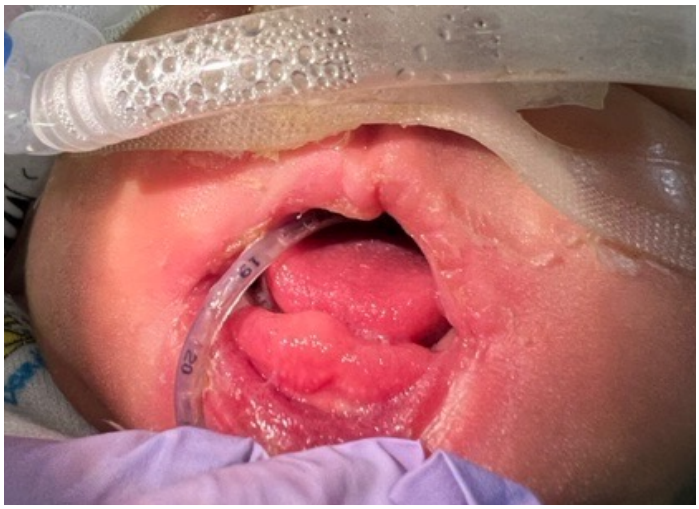


Figure 1b: Exuberant gingival tissue growth on the lower alveolar ridge.

Figure 1c: The great toe is wide and there is excess soft tissue around the toenail and rugae of the foot. The thumbs are broad but not deviated

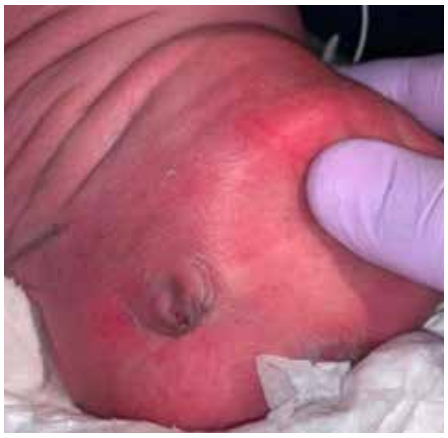


Figure 1d (left): Caudal appendage at the base of the spine has a blind central pit.

Figure 1e (right): The umbilical stump is large with excess epithelialization and soft tissue.

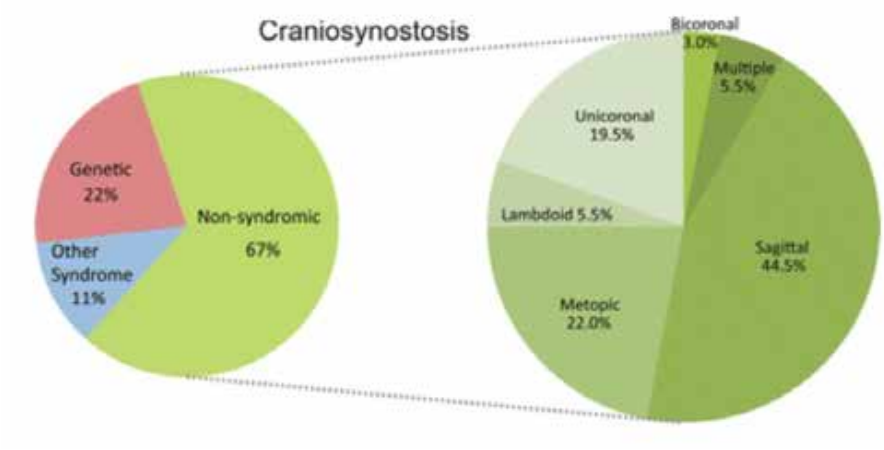
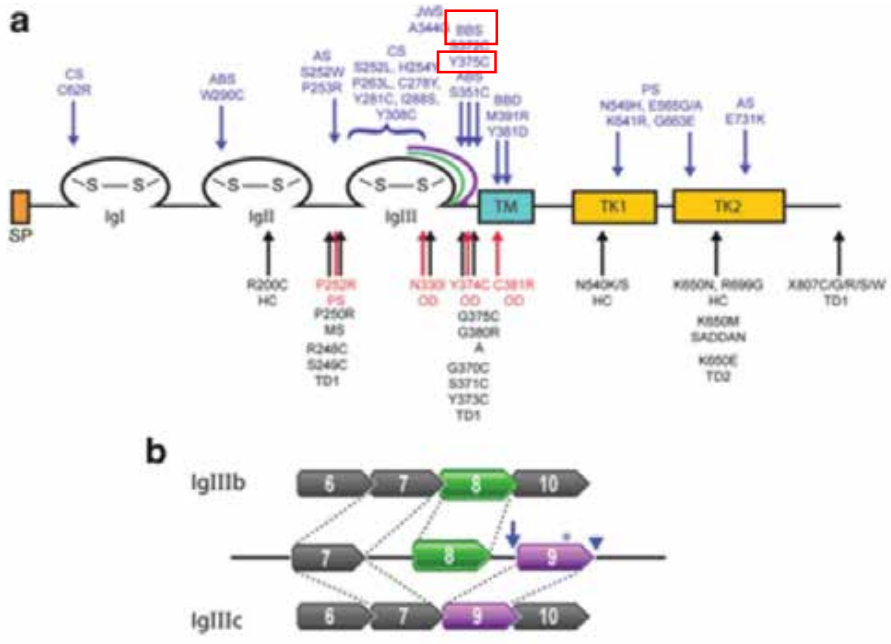


Figure 2: The prevalence of different forms of craniosynostosis was derived from a cohort of 215 patients. (2)



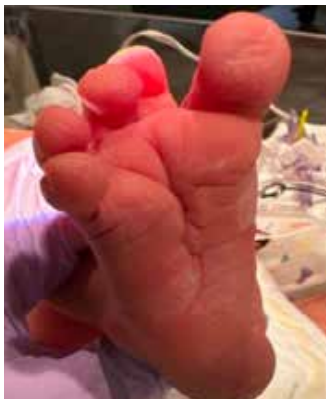


Figure 1f: Hyperkeratotic soles and deep plantar creases.

Figure 3a: This schematic of the FGFR protein structure illustrates the functional domains: three immunoglobulin-like loops in the extracellular space (IgI, IgII, and IgIII), responsible for ligand binding, the transmembrane domain (TM) and the intracellular tyrosine kinase domains (TK1, TK2). Mutations in different functional domains cause Crouzon syndrome (CS), Antley-Bixler syndrome (ABS), Apert syndrome (AS), Pfeiffer syndrome (PS), and other craniofacial disorders. Note that the *FGFR2* variant identified in this patient (red box), abbreviated Y375C is in the juxtramembrane domain, listed under BSS, Beare-Stevenson syndrome. (3)

Figure 3b: This illustrates the alternate splicing of exons 8 and 9 that determines ligand binding in the third immunoglobulin loop in the two isoforms of FGFR2: IgIIIb, which contains exon 8 (green) and IgIIIc, which contains exon 9 (purple). The juxtamembrane region, where this patient's variant is found, is shared by both isoforms, which is why this Y375C variant is expected to enhance FGFR2 signaling and cause excess growth in both mesenchymal and epithelial tissues. (3)

Pfieffer syndrome (PS; OMIM# 101600) was initially considered because of the baby's broad great toes and thumbs, but her features are more compatible with BSS even in the absence of cutis gyrate of the scalp. (9) There is considerable phenotypic overlap between BSS and other craniosynostosis syndromes like PS, such as a cloverleaf skill, airway obstruction, hydrocephalus, and Chiari malformation. (10) Compared to other craniosynostosis syndromes, the prognosis for BSS is worse. To our knowledge, there have been no survivors beyond the age of 13. Fifty percent of individuals with the Y375C variant have not survived past two years of age. (11).

Practical applications:

1. Pay attention to minor anomalies. They can be the keys to a correct diagnosis. The presence of facial rugae, a long epithelialized umbilical stump, multiple ear creases, and deep furrows on the palms and soles established the diagnosis of Beare-Stevenson syndrome in this child.
2. Seek a unifying diagnosis. Beare-Stevenson syndrome is caused by enhanced signaling of mesenchymal (bone) and epithelial (skin) isoforms of FGFR2, explaining its varied effects on different tissue types.
3. Order genetic testing when craniosynostosis is severe (cloverleaf skull), involves multiple sutures or is associated with extraskeletal anomalies.

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Disclosures: The authors have no relevant disclosures

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