Genetics Corner: A Lethal Ciliopathy Affects Two Siblings with Renal Dysplasia and Oligohydramnios

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A Case History:

A genetics consultation was requested for a one-day-old 38-week gestation male because of prenatal diagnosis of multiple congenital anomalies: severe oligohydramnios, IUGR, renal dysplasia (renal cysts, pelviectasis, calyceal dilatation, dilated ureters), microcephaly, Dandy-Walker malformation, and bilateral club feet. A fetal MRI at 37-weeks' gestation also showed a mega cisterna magna. The fetal echocardiogram was normal.

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The parents denied consanguinity. The family history was positive for a similarly affected female fetus, with a normal chromosome microarray that was electively aborted at 20 weeks gestation at another facility in 2017. An autopsy was not performed, but an external exam showed micrognathia, thick nuchal fold, and preaxial polydactyly of the toes, which were medially deviated and duplicated halluces with a wide sandal gap. A photograph of that fetus is shown in Figure 1.

A genetic counselor and I had met with this Spanish-speaking couple during gestation. A fetal microarray was normal. A trio whole-exome sequencing test revealed two variants in C2CD3, a gene on chr 11q13.4 linked to an autosomal recessive ciliopathy: Orofaciodigital syndrome XIV (MIM 615948; OFD14). A likely pathogenic variant in C2CD3: c.994dupG was maternally-derived and a variant of uncertain significance: c. 2504A>T was paternally-derived.

The baby was born at term by vaginal delivery to a 24-year-old G2P1 healthy mother. B.W. was 2775 g (11th%ile, Z -1.35), B.L. was 46 cm (2nd %ile, Z -2.05), H.C. was 30 cm (Z -3.51). Apgar scores were 1^{1}, 7^{5}, and 9^{10}. He did not cry spontaneously at birth, his color was blue, and his tone was flaccid. He was treated initially with positive pressure ventilation and then successfully intubated and mechanically ventilated. He did not pass urine. He lacked a urethral meatus and a urethral catheter could not be passed. The renal U.S. showed irregular echogenicity in the renal fossae suggesting bilateral dysplastic kidneys. He was ineligible for peritoneal dialysis. His parents agreed to withdraw support. He was extubated and died at nine days of age. Post mortem photographs are shown in Figure 2.

Genetics evaluation:

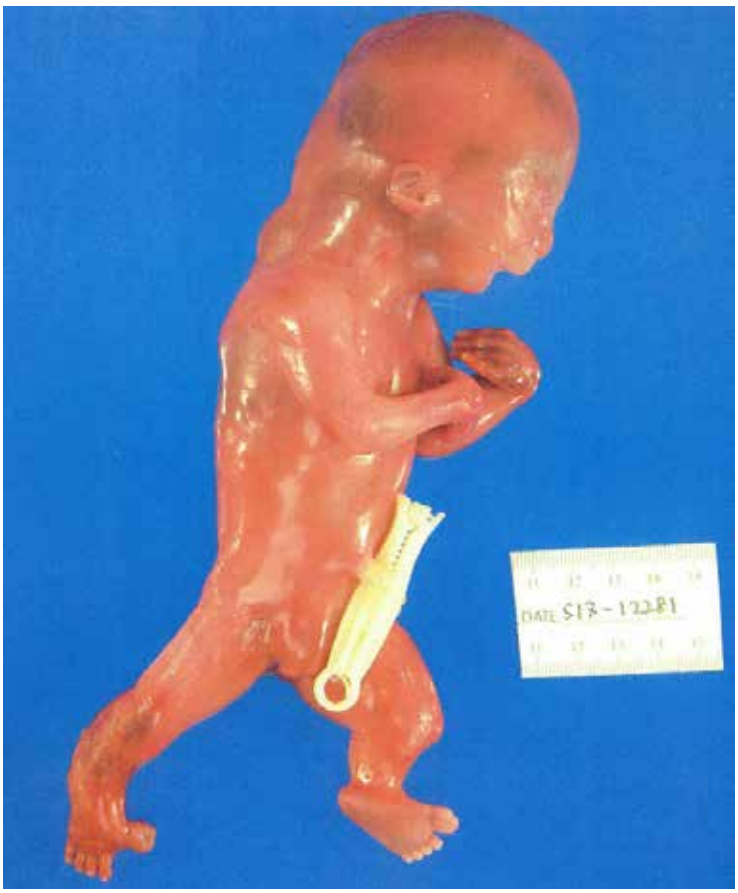

Figure 1. Similarly affected female fetus at 20 weeks gestation

On physical exam, the baby had microcephaly and deformations consistent with intrauterine compression due to severe oligohydramnios, including bilateral club feet. He also had micrognathia, microglossia, and a high arched palate. A subtle midline notch was evident in the upper lip post mortem (when all tape had been removed). The intraoral exam was pertinent for microglossia, multiple accessory frenulae, abnormal adhesions between the tongue, the mandibular alveolar ridge, and the buccal mucosa with several pearly hamartomatous nodules in the mucosal webs. The maxillary and mandibular alveolar ridges were irregular and notched. There was no polydactyly.

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Figure 2a. Post-mortum facial photograph

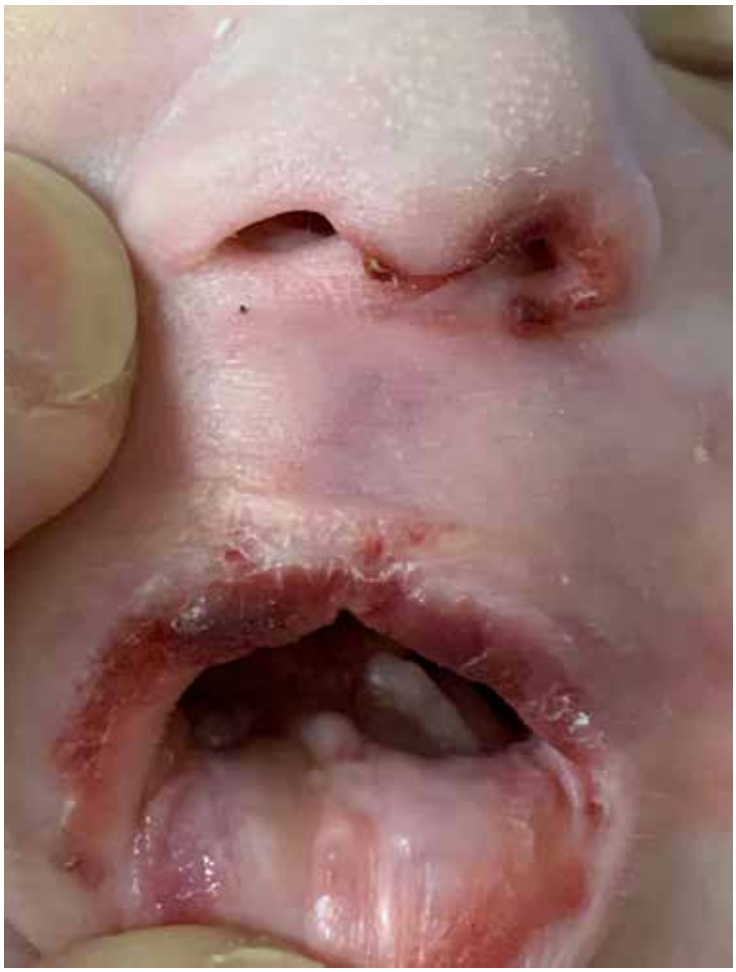

Figure 2b. Post-mortum facial photograph

Discussion:

The primary cilia are microtubular-based organelles that project from the cytoplasmic membrane of almost all cells in vertebrates. They function in many developmental processes and a broad range of sensory functions. Ciliopathies encompass a diverse group of disorders, including the rare orofaciodigital (OFD) syndromes, of which 16 causal genes have been delineated. (1) Each OFD subtype has a distinct phenotype, but they share characteristic craniofacial (hypertelorism), oral (lingual hamartoma, abnormal frenulae, and lobulated tongue) and digital (polydactyly, brachydactyly) anomalies as well as other (CNS, renal, skeletal) malformations. Of these 16 subtypes, OFD14 is among the rarest and also one of the most recently described. In 2014, Thauvin-Robinet et al. reported two affected families with severe microcephaly and cerebral malformations who had pathogenic variants in the evolutionarily conserved gene, C2CD3, which is required for centriole assembly. (2)

The Orofaciodigital syndromes are among the many ciliopathies that can present in the newborn period, including situs inversus, polycystic kidney disease (autosomal recessive ARPKD and autosomal dominant ADPKD), Joubert syndrome, Jeune syndrome (thoracic dystrophy), Bardet-Biedl syndrome, and Meckel syndrome. The shared pattern of anomalies in this group includes renal cysts, polydactyly, and cerebellar anomalies. Other features are only apparent in the older child or adult, such as intellectual disability, retinal deterioration, anosmia, obesity, and infertility.

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Although their paper does not include a discussion of orofaciodigital syndromes, Hildebrandt et al. published a useful review of ciliopathies in 2011. (3) Their excellent figures illustrate the anatomy of cilia, which are microtubule-based structures that are found on almost all vertebrate cells. They originate from a basal body, a modified centrosome, which is the organelle that forms the spindle poles during mitosis. Microtubules extend from the centriole, constituting the basal body, and form the axoneme. The surrounding membrane is called the ciliary membrane, distinct from other membranes. Unlike motile cilium with a 9+2 microtubular structure, the primary cilium has a 9+0 structure. The important role

that the cilium-centrosome complex plays in the normal function of most tissues appears to account for the involvement of multiple organ systems in ciliopathies. As of 2017, there were 35 known ciliopathies, and with hundreds of ciliary proteins, the number is sure to grow. (4)

OFD14 is not uniformly fatal, and the phenotype is variable. Boczek et al. (2018) described five affected children with biallelic C2CD3 variants in three families, identified by Whole Exome Sequencing. (5) Three of these children survived. In addition to the classic oral and digital anomalies (including postaxial polydactyly), they exhibited a wide variety of brain and CNS anomalies: simplified gyral pattern, molar tooth sign, cerebellar hypoplasia, encephalocele, gray matter heterotopia, and retinal colobomas.

Interestingly, our patient and his sister have both overlapping and distinctive features that are not shared. Her duplicated great toes and his subtle midline upper lip defect, lingual hamartomas, and accessory frenulae are typical of OFD, and both had renal dysplasia. By adding their features, we might have been able to make a clinical diagnosis of OFD and determine the gene involved by using a gene panel for diagnosis. However, we did not have access to the fetal photograph until our evaluation was nearly complete.

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Practical Applications:

1. Be aware that Whole Exome Sequencing (WES) is now increasingly available, both prenatally and postnatally. This test can identify rare single-gene disorders that cause multiple congenital anomalies and lethal disorders, that would have gone undiagnosed even a few years ago.
2. Recognize the pattern of anomalies associated with ciliopathies that present in the newborn period. Suspect ciliopathies when brain malformations occur with renal cysts and polydactyly in an autosomal recessive pattern of inheritance. In the absence of a whole-exome sequencing test, this diagnosis can be made with a gene panel designed to detect ciliopathies.
3. Request an autopsy whenever a deceased fetus or infant has congenital anomalies. If the family declines an autopsy, offer a more limited or focused examination (e.g., percutaneous renal biopsy), an external exam with photographs, or ask for permission to take a blood or tissue sample for DNA banking.
4. When an autopsy is not possible, perform a careful physical examination yourself. Document unusual features with photographs whenever possible.
5. Understand that the phenotype of a genetic disorder can vary, even between affected individuals within the same family, due to differences in gene expression patterns caused by gene-gene or gene-environment effects.

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The authors have no relevant disclosures.

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