

Cystic Kidneys in a Patient with Craniofacial Abnormalities

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Case Description

A 30-year-old woman previously diagnosed with Treacher Collins syndrome presented for operative evaluation of craniofacial abnormalities including microcephaly, cleft palate, nasal stenosis with hypoplasia of the alae, atrophic mandible, lobulated tongue, and ankyloglossia. Preoperative laboratory evaluation revealed BUN of 88 mg/dl, serum creatinine of 6.8 mg/dl (eGFR, 7 ml/min per 1.73 m²), calcium of 5.7 mg/dl, albumin of 3.9 g/dl, intact parathyroid hormone of 976 pg/ml, and hemoglobin of 9 g/dl. Urinalysis was notable for 1+ proteinuria. There was no reported family history of kidney disease, although detailed records were not available. In light of her kidney function, she was admitted for further evaluation.

Physical examination revealed a multilobar tongue (Figure 1A); several missing teeth; brachydactyly and

clinodactyly (Figure 1B); and large, bilateral, nontender abdominal masses. Computed tomography scans performed without intravenous contrast demonstrated polycystic nephromegaly (Figure 1C). Computed tomography imaging of the head showed a hypoplastic vermis. Genetic testing demonstrated a heterozygous splice site mutation NM_003611 c.412+1delG in intervening sequence 5 of *OFD1*, confirming the suspected diagnosis of oral-facial-digital syndrome type 1 (OFD1).

OFD1 is an X-linked ciliopathy that produces a defective centrosome, thereby resulting in ciliary dysfunction and impaired left-right axis determination (1). It is an X-linked dominant condition that has historically been considered embryonic lethal in males, although recent reports indicate some genotypes are compatible with survival into adulthood (2). Structural abnormalities of the face, oral cavity, digits, kidneys,



Figure 1. | Clinical features of oral-facial-digital syndrome type 1 (OFD1). Common features of OFD1 include (A) multilobar tongue, (B) brachydactyly and clinodactyly, and (C) cystic kidney disease.

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and brain, as well as intellectual impairment, are common findings. OFD1 is a rare disease, occurring in 1/50,000–1/250,000 live births, and 75% of mutations may be sporadic. The frequency of polycystic kidney disease in OFD1 is not well established but is estimated to occur in up to 60% of cases (3). Approximately 15%–50% of individuals with OFD1 will progress to ESKD by the fourth decade, although significant intra- and interfamilial variability exists. It is unknown whether sirolimus or tolvaptan—medications with potentially therapeutic effect in other cystic kidney diseases—have any role in OFD1.

OFD1 is one of at least 16 genes known to result in oral-facial-digital syndromes, and significant phenotypic variability and overlap exist across both the different genes as well as other groups of genetic ciliopathies (4). There are at least 35 known disorders caused by ciliary dysfunction, with >187 implicated genes. Clinical manifestations in the renal, skeletal, pulmonary, and neurologic systems are common given ciliary necessity in organogenesis and normal organ function (5). However, massive cystic nephromegaly has a small differential diagnosis, generally limited to autosomal dominant (adult) and recessive (pediatric) polycystic kidney disease, tuberous sclerosis, OFD1, and cystic nephroma. Although Treacher Collins syndrome results in similar facial dysmorphism, it is not associated with abnormalities of the fingers and kidneys.

The patient was initiated on hemodialysis and ultimately underwent dental reconstruction.

Teaching Points

- OFD1 is a multisystem disorder of cilia characterized by structural abnormalities of the face, oral cavity, digits, kidneys, and brain.
- OFD1 should be considered in the differential diagnosis of cystic nephromegaly.
- Significant phenotypic overlap exists among the different ciliary disorders, and genetic testing is often required for a definitive diagnosis.

Disclosures

All authors have nothing to disclose.

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Author Contributions

C. Sperati and A. Tsao conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

References

1. Ferrante MI, Zullo A, Barra A, Bimonte S, Messaddeq N, Studer M, Dollé P, Franco B: Oral-facial-digital type I protein is required for primary cilia formation and left-right axis specification. *Nat Genet* 38: 112–117, 2006
2. Sakakibara N, Morisada N, Nozu K, Nagatani K, Ohta T, Shimizu J, Wada T, Shima Y, Yamamura T, Minamikawa S, Fujimura J, Horinouchi T, Nagano C, Shono A, Ye MJ, Nozu Y, Nakanishi K, Iijima K: Clinical spectrum of male patients with OFD1 mutations. *J Hum Genet* 64: 3–9, 2019
3. Feather SA, Woolf AS, Donnai D, Malcolm S, Winter RM: The oral-facial-digital syndrome type 1 (OFD1), a cause of polycystic kidney disease and associated malformations, maps to Xp22.2-Xp22.3. *Hum Mol Genet* 6: 1163–1167, 1997
4. Bruel AL, Franco B, Duffourd Y, Thevenon J, Jego L, Lopez E, Deleuze JF, Doummar D, Giles RH, Johnson CA, Huynen MA, Chevrier V, Burglen L, Morleo M, Desguerres I, Pierquin G, Doray B, Gilbert-Dussardier B, Reversade B, Steichen-Gersdorf E, Baumann C, Panigrahi I, Fargeot-Espaliat A, Dieux A, David A, Goldenberg A, Bongers E, Gaillard D, Argente J, Aral B, Gigot N, St-Onge J, Birnbaum D, Phadke SR, Cormier-Daire V, Eguether T, Pazour GJ, Herranz-Pérez V, Goldstein JS, Pasquier L, Loget P, Saunier S, Mégarbané A, Rosnet O, Leroux MR, Wallingford JB, Blacque OE, Nachury MV, Attie-Bitach T, Rivière JB, Faivre L, Thauvin-Robinet C: Fifteen years of research on oral-facial-digital syndromes: From 1 to 16 causal genes. *J Med Genet* 54: 371–380, 2017
5. Reiter JF, Leroux MR: Genes and molecular pathways underpinning ciliopathies. *Nat Rev Mol Cell Biol* 18: 533–547, 2017

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