An Orofaciodigital Syndrome 1 Patient and Her Mother Carry the Same OFD1 Mutation but Have Different X Chromosome Inactivation Patterns

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Abstract:
Orofaciodigital syndrome 1 (OFD-1) is a rare, X-linked, dominantly inherited disorder caused by an OFD1 mutation that can cause polycystic kidneys. A 37-year-old woman on hemodialysis therapy was admitted to our hospital for trans-catheter arterial embolization therapy for enlarged polycystic kidneys. Lobulated tongue and brachydactyly were noticed, prompting an OFD1 sequencing analysis. Sequencing revealed a causal four-base-pair deletion in exon 13, both in the patient and in her mother, whose renal function had been retained. The peripheral leukocyte X chromosome inactivation pattern was skewed in the patient but not in her mother, suggesting some role in their phenotypic difference.

Key words: orofaciodigital syndrome 1, polycystic kidney, X chromosome inactivation

Introduction
Orofaciodigital syndrome type 1 (OFD-1) is an X-linked dominant inherited condition (1) caused by mutations in the cxorf5 gene (OFD1) located at Xp21.3-p22.3 [MIM 311200].

Patients with OFD-1 display oral (e.g., hyperplastic frenulum, tongue hamartoma, cleft palate), facial (e.g., broad nasal ridge, hypertelorism), and digital (e.g., brachydactyly, syndactyly) symptoms, and other organs can be affected (e.g., facial milia, polycystic kidney, and central nervous system anomalies) (2). Despite the monogenic nature of this disease, wide inter- and intra-familial phenotypic variations are common, and types of OFD1 mutations (gene deletion, nonsense mutation, missense mutation, frameshift mutation, splice site mutation) have sometimes been considered in the context of the genotype-phenotype relationship (2-5). Younger patients generally don’t have polycystic kidney disease at the time of the diagnosis (2, 6).

We herein report an OFD-1 patient with early-onset end-stage kidney disease, whose mother shares her OFD1 gene mutation but has retained her renal function.

Case Report
A 37-year-old woman was referred to our hospital seeking trans-catheter arterial embolization (TAE) therapy for enlarged kidneys. She had been receiving hemodialysis therapy for 17 years, since being diagnosed with polycystic kidney disease at her former institution.

She initially presented with lethargy, abdominal distension with marked anemia (blood hemoglobin concentration 5.3 g/dL), and a serum creatinine level of 17.0 mg/dL. Hemodialysis was promptly started, and she has since received hemodialysis three times a week. Before receiving renal TAE, she suffered from anorexia, chronic diarrhea, and lower abdominal pain. She was admitted to our hospital to alleviate her anorexia by performing renal TAE. Her medical history included pneumonia, polydactyly, and cleft palate (0-years old), rubella (8-years old), meningitis (17-years old), external hemorrhoids (32-years old), otitis externa (34-years old).
old), and a large ulcer in her external genitalia and a blistered left hand (35-years old). She had no evident familial history of polycystic kidney disease.

Her abdomen was soft and distended with normal bowel sounds. A lobulated tongue and brachydactyly were noted. Dental pan-tomography showed defects in several mandibular teeth (Fig. 1A). Brain magnetic resonance imaging (MRI) revealed slightly atrophic cerebellar hemispheres (Fig. 1B) and agenesis of the corpus callosum (Fig. 1C). An initial computed tomography (CT) scan showed markedly enlarged kidneys (right: 20.4×13.9×9.5 cm, left: 19.9×12.0×10.8 cm). Abdominal MRI revealed numerous small (several millimeters to 2 cm in diameter) cysts bilaterally present in her kidneys with relatively preserved contours (Fig. 1D). We considered renal TAE therapy to be indicated.

Renal TAE was performed with the patient under epidural anesthesia. The right (left) renal arteries and their branches were embolized with 15 (13) platinum coils. Her kidneys showed moderate bilateral size reduction in serially taken CT scans [right/left: from 18.6×11.4×8.8 cm/17.9×10.7×9.6 cm (August 2014) to 16.9×10.1×8.0 cm/16.1×8.8×7.2 cm (August 2015)].

We obtained written informed consent from the patient and her mother to perform genetic sequencing of \textit{OFD1} to search for a mutation that might have caused OFD-1, which was suspected due to presence of a characteristic pattern of physical signs. This study was in accordance with the Declaration of Helsinki and in compliance with the Toranomon Hospital Institutional Review Board guidelines.

Sequencing of \textit{OFD1} was performed using a 3130 genetic analyzer (Thermo Fisher Scientific, Tokyo, Japan) at Kobe University and revealed a heterozygous four-nucleotide deletion (NM_003611.2: c.1323_1326delAGAA, p.Glu442Argfs*27) in exon 13 of \textit{OFD1}, which resulted in a frameshift (Fig. 2A). This mutation is described in an earlier report [Prattichizzo et al. (2)] and was considered to underlie our patient’s OFD-1 syndrome phenotype.

The proband’s mother’s physical examination was nonremarkable. CT and laboratory tests were performed. Her serum creatinine value was 0.75 mg/dL. CT revealed only a small number of cysts in both kidneys (Fig. 3). To address the severity discordance between the patient and her mother, we performed an X chromosome inactivation pattern analysis by evaluating the human androgen receptor methylation status, as reported previously (7). In short, the methylated androgen receptor gene is not subject to restriction enzyme digestion, so after applying \textit{HpaII} digestion, the inactivated allele is preferentially amplified by

Figure 1. (A) Dental pantomography showed several mandibular tooth defects. (B, C) Brain MRI revealed corpus callosum agenesis. (D) Abdominal MRI showed enlarged kidneys with numerous small (up to 2 cm-diameter) cysts.
polymerase chain reaction. According to Kubota, inactivation of one chromosome in <20% of cells tested is considered to be a non-random pattern (8). A quantitative analysis of 2 peaks revealed a non-random inactivation pattern in the patient’s blood cells (18%:82%) and a random inactivation pattern in her mother’s (44%:56%) (Fig. 2B). The right peak of the patient’s sample, which decreased after HpaII digestion, is close to the right peak in her mother’s. Since the peak position corresponds to the CAG nucleotide repeat number, we can consider some shared mutant allele had likely been preferentially activated in this patient.

**Discussion**

We herein report a patient and her mother, each heterozygous for a previously reported frameshift OFD1 mutation associated with OFD-1. In a retrospective analysis of 34 OFD-1 patients, Saal et al. (6) reported that the estimated median age at which dialysis is initiated is 36-years old, which is younger than that seen in autosomal dominant polycystic kidney disease (57-years old). The present patient began receiving hemodialysis therapy in her teens. By contrast, her mother’s kidney function has been preserved into her seventies. The results of the X chromosome inactivation analysis might help explain their gap in clinical courses. The mutated allele was preferentially activated in the patient’s peripheral blood cells. Although our X inactivation analysis was limited to peripheral blood cells, an example of association between blood cell X inactivation pattern and nephrogenic diabetes insipidus severity has been observed in one
The authors state that they have no Conflict of Interest (COI).

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We obtained written informed consent from the patient and her mother for genetic testing for OFD-1. This study was in accordance with the Declaration of Helsinki and compliant with institutional review board guidelines. The patient gave her fully informed consent for the publication of this case report. All data generated or analyzed during this study are included in this published article.

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Figure 3. An abdominal CT image of the patient’s mother. A small number of cysts were identified.