



# Oral-Facial-Digital Syndrome Type 1 with Fibrocystic Disease of the Liver and Pancreas

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## Abstract

Oral-facial-digital syndrome type 1 is a developmental disorder associated with malformation of the oral cavity, face and digits. This syndrome is an X-linked dominant condition with embryonic male lethality. The case is here reported of a 6-year old girl who presented with facial dysmorphology in addition to a cleft palate operation history and digital abnormalities. In addition, she had visceral involvement of the kidney, liver and pancreas. A new splice site mutation of OFD1 gene was detected. To the best of our knowledge, there has been no reported case of oral-facial-digital syndrome type 1 with liver and pancreatic involvement and with this mutation. The aim of this case report was to discourse this new clinical entity in the light of literature.

**Keywords:** Liver cysts; Novel mutation; Oral facial digital syndrome; Pancreatic cysts; Polycystic kidney disease

## Abbreviations

OFDSs: Oral-Facial-Digital Syndromes; OFDS1: Oral-Facial-Digital Syndrome type 1; ADPRD: Autosomal Dominant Polycystic Renal Disease

## Introduction

Oral-Facial-Digital Syndromes (OFDSs) are a group of diseases divided into nine categories with similar clinical findings [1]. Because of the unique X-linked dominant inheritance pattern and associated polycystic kidney disease, OFDS type 1 (OFD1) is different from the other forms. OFD1 is the most common form of OFDSs, affecting 1 in 250,000 live births. It is a rare developmental syndrome and especially characterized with various deformities of the oral cavity, face and digits [1]. In addition to these external features, although polycystic kidney disease is a well-known visceral involvement, liver and pancreatic cysts are under-recognized features [2]. The disorder caused by mutations in the Cxorf5 transcript, was later named OFD1 gene [3]. The case reported here is of OFD1 with kidney, liver and pancreatic cysts and a new mutation in OFD1 gene, and through discussion of this case, it is hoped to contribute to literature.

## Case Presentation

A 6-year old girl presented at our clinic for evaluation. She was born to non-consanguineous parents with a normal pregnancy and delivery, with birth weight of 2900 g, and length 50 cm. She had an operation history of cleft palate, and tongue hamartoma, together with agenesis of the corpus callosum, mild intellectual disability and renal cystic disease. Micrognathia, facial asymmetry, hypertelorism, broad nasal root, malar hypoplasia, hypoplastic teeth, and sequelae arising from surgical closure of the cleft palate and bifid tongue were detected in physical examination (Figure 1a and b). Digital features included brachydactyly of both hands (Figure 2). Abdominal ultrasonography showed renal cystic disease. Renal function tests and other biochemical tests were normal. Blood pressure monitoring was normal. The karyotype was 46, XX. Borderline mental function (IQ test score of 80) was diagnosed. Echocardiography was normal and there was no musculoskeletal problem on physical examination. The mother was determined with renal cysts and accessory gingival frenulae had a history of abortus of male fetus (Figure 3). The complete family history, clinical and radiological examination confirmed the presence of OFD1 in the patient. Full gene sequence analysis showed a novel splice site mutation in heterozygous form at OFD1 gene such as IVS13+1G>A (OFD1c.1411+1G>A) (Figure 4). Abdominal ultrasonography performed at 1 year after the diagnosis showed multiple cysts in the intrahepatic bile ducts and in addition to renal cysts,

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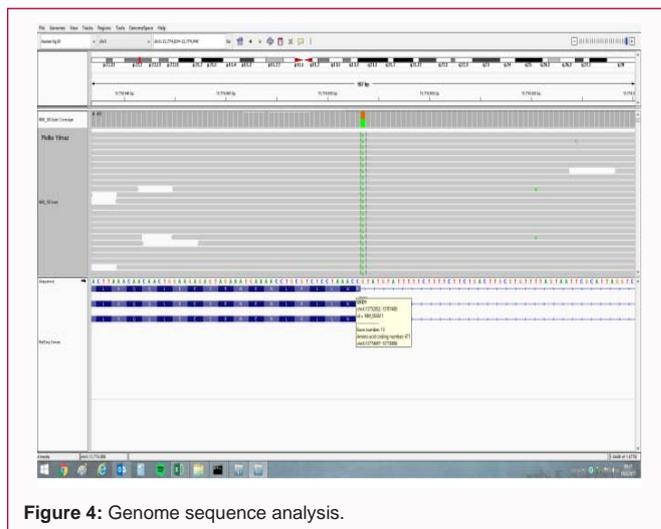
**Figure 1:** (a) Bifid tongue, Hypoplastic teeth and Hypertelorism (b) Facial asymmetry.



**Figure 3:** Accessory gingival frenulae of the mother.



**Figure 2:** Brachydactyly of both hands.



**Figure 4:** Genome sequence analysis.

the largest cyst located in the pancreatic uncinata process measured  $2 \times 3$  cm. Diagnosis was confirmed with magnetic resonance imaging of the abdomen (Figure 5a,b and c). Liver and pancreatic enzymes (AST, ALT, ALP, GGT, amylase and lipase) were within the normal range. A fine needle aspiration of the pancreatic cyst was done and no malignant cells were detected. The patient was followed up in our clinic for 2 years without the development of any new problems. Written informed consent was obtained from the patient's mother.

## Discussion

Mohr reported a family with highly arched palate, lobate tongue with papilliform outgrowths, broad nasal root, hypertelorism, and digital anomalies and so OFDS was first defined by him in 1941 [4]. A subtype of this is OFD1, which was described by two French dentists Papillon-Leage E and Psaume Jean in 1954 after a study of 22 cases and hence, the syndrome was also named Papillon-Leage and Psaume Syndrome [5]. OFD1 is a rare ciliopathy syndrome and is caused by dysfunction of primary cilia and characterized with oral, facial and digital abnormalities and visceral involvements [6]. Oral manifestations are a lobed tongue, hamartoma or lipoma of the tongue, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia, and other dental abnormalities. Facial abnormalities include telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft upper lip, and micrognathia [7]. Digital manifestations are brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger, duplicated hallux, preaxial or postaxial polydactyly of the hands [8]. Central nervous system involvement includes intellectual disability and a wide range of brain structural abnormalities such as intracerebral cysts, corpus callosum agenesis, and cerebellar agenesis with or without Dandy-Walker malformation [9]. OFD1 is inherited as an X-linked dominant condition with embryonic male lethality. In the current case, the mother had a history of miscarriage of a male fetus. Primary cilia are significant

for the improvement of the bile ducts and renal tubules, and various ciliopathies are known to result in Hepato renal fibrocystic disease [10]. The renal involvement of OFD1 is polycystic renal disease and this condition is now considered a feature distinguishing OFD1 from the other eight forms of the syndrome. It occurs in most of the patients, and the prognosis is associated with renal involvement in such patients. It is difficult to differentiate from other causes of renal cystic diseases on imaging techniques. Compared to Autosomal Dominant Polycystic Renal Disease (ADPRD), the cysts are smaller and more similar in OFD1. In ADPRD, the cysts are comprised of tubules, whereas they originate from both tubules and glomerulus in OFD1 and are different from ADPRD both microscopically and macroscopically [11]. Renal injury can be present at birth but in 63% of patients renal cysts develop older than 18 years, and it is clear that the cystic kidney disease is often seen after the second decade of life [12]. In particular, the current patient and her mother both had renal cystic disease and the patient was 6 years of age. Thus, performing renal function tests and periodically follow-up from the early ages is very important. Hepatic and pancreatic cysts may occur, similar to ADPRD, but the lack of these cysts does not exclude the diagnosis. The liver and pancreas are not routinely evaluated in OFD1 patients. The better known visceral involvement in OFD1 is polycystic renal disease and majority of the patients are followed-up for this reason. In the current patient, an abdominal ultrasonography showed asymptomatic liver and pancreatic cysts. Enzyme levels were normal and needle aspiration showed no malignant cells. A PubMed based literature scan revealed a newborn that died at 4 hours and an 11-year old female OFD1 case reported with kidney and liver cysts and a 26-



**Figure 5:** (a) Magnetic resonance images (b) multiple cysts in the kidneys (c) liver and pancreas.

year old female with multiple liver and pancreatic cysts [11]. Another case was reported of a 15-year old female patient who died of renal failure and massive cerebral hemorrhage. That patient had different visceral anomalies including biliary cyst adenomatous proliferation in the liver and pancreatic cysts in addition to renal cysts [13]. To the best of our knowledge, the current case is the only reported pediatric alive OFD1 case with pancreatic cyst in addition to renal and liver cysts in the literature. OFD1 is usually diagnosed at birth with the characteristic oral, facial, and digital malformations [1]. In spite of the severe phenotypic findings the current case had not been diagnosed until she was 6 years of age. OFD1 is the only gene in which mutations are known to reason of oral facial digital syndrome type 1. The gene for the disorder was mapped to Xp22.3-p22.2. Mutation analysis identified *Cxorf5*, which was renamed OFD1 as the gene responsible for this disorder which comprises 23 exon encoding a 1011 amino acid protein [3]. Until today, various mutations have been described and some genotype-phenotype correlations have been suggested. Intellectual disability has been more often associated with mutations in exon 3, 8, 9, 13, 16. Polycystic renal disease correlated with splice mutations is often located in 9 and 12 exon. Cleft palate has been found to be associated with missense and splice site mutations [14]. Patients with tongue abnormalities have been reported to more often have a mutation in exon 12 [1]. In addition, a new splice site mutation was found in this gene which is IVS13+1G>A (OFD1c.1411+1G>A). This mutation was previously defined as Lowe syndrome, infantile spasm and Rett syndrome [15]. To the best of our knowledge, this is the first report of IVS13+1G>A (OFD1c.1411+1G>A) mutation for OFD1 in the OFD1 gene.

## Conclusion

This case report is important because of this novel mutation and as it is the first reported pediatric OFD1 patient with pancreatic cyst in the literature. It was aimed to draw attention to the importance of visceral monitoring involving the liver and pancreas in addition to the kidneys in OFD1 patients, because follow-up of visceral complications is essential for timely and accurate treatment. It is hoped that the case can contribute to literature in these aspects.

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