# Oro-facio-digital syndrome type 1

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**Abstract**
*Oro-facio-digital syndrome type 1 (OFD1) is an X-linked dominant condition that is lethal for males, and characterized by malformations of the face (frontal bossing, facial asymmetry, hypertelorism, broadened nasal bridge, facial milia), oral cavity (pseudoclefting of the upper lip, cleft palate and tongue, high arched palate, tethering of the tongue by frenulae, abnormal dentition), and digits (syndactyly, brachydactyly, clinodactyly, polydactyly). Malformation of the brain and polycystic kidney disease are commonly associated with the syndrome. Usually, the renal cystic changes represent a late manifestation of the OFD1 syndrome, and the diagnosis is generally made when an advanced renal failure has already developed. The etiopathogenesis of OFD1 syndrome is obscure: how the underlying genetic abnormality leads to renal disease is unknown. Recently, it was found that mutations in the* Cxorf5 *gene, located in the Xp22 region, may cause OFD1 syndrome. Since no sequence homologies with other proteins with known functions either in mammals or lower organisms have been found, it is difficult to predict the function of the gene product responsible for OFD1. OFD1 is a rare syndrome, occurring in approximately 1/250,000 live births. Surgical correction of the dysmorphic features is the usual approach. End-stage renal failure is treated with dialysis and renal transplantation.*

**Keywords**
dysmorphic features, oro-facio-digital syndrome type 1, polycystic kidney disease, X-linked dominant inheritance.

## Disease name

- Oro-facio-digital syndrome type 1 (OFD1; MIM 311200)
- OFD1 syndrome

## Diagnosis criteria

OFD1 syndrome is an X-linked dominant condition that is lethal for males. The disorder is characterized by malformations of the face, oral cavity, and digits, and shows a highly variable expressivity even within the same family. Malformation of the brain and polycystic kidney

disease (PKD) are commonly associated with the syndrome. OFD1 syndrome is usually diagnosed in early childhood, when most patients with dysmorphic features consult for medical follow-up. However, at the time of diagnosis, kidney involvement may not be apparent. Since the renal disease may be a delayed manifestation of the OFD1 syndrome, all children the dysmorphic features of OFD1 should be undergo with renal ultrasound scans and simple evaluations of renal function (*e.g*. blood pressure and plasma creatinine) to detect PKD and its clinical consequences. Moreover, since variable phenotypic expression is a well recognized feature of the syndrome and the disease is transmitted as an X-linked dominant condition that is lethal for males, the presence of OFD1 syndrome should be looked for in families in wich only females have PKD. To detect renal cystic changes, both ultrasound and computed tomography (CT) imaging are reliable and sensitive techniques. Renal cysts are numerous, smaller and more uniform in size compared with patients with autosomal dominant polycystic kidney disease (ADPKD); thus, the kidneys are less enlarged and the renal contour is not grossly deformed. Liver and pancreatic cysts may be also found.

**Differential diagnosis**

The differential diagnosis of OFD1 with PKD should include cystic kidney diseases inherited in an autosomal dominant manner, such as ADPKD, tuberous sclerosis (TSC) and von Hippel-Lindau disease (vHL). Generally, recognition of the accompanying dysmorphic features is the key to a diagnosis of OFD1 in a female child or adult who presents with PKD. Due to the presence of minor clinical features of the syndrome, OFD1 with PKD may be misdiagnosed as ADPKD. However, in OFD1 with PKD, the kidneys are usually of normal size and contour. Moreover, a closer inspection of kindreds with OFD1 suggests that the mode of inheritance is X-linked dominant. Finally, OFD1 is almost exclusively diagnosed in females because males carrying OFD1 mutations die *in utero*, usually during the first or second trimester. The renal cystic changes of TSC and vHL are usually correctly diagnosed on the basis of the specific clinical features (represented by the formation of angiomyolipomas or tubers in the skin, brain and kidneys in TSC; by the occurrence of cerebellar and retinal hemangioblastoma, renal carcinoma, pancreatic cysts and pheocromocytoma in vHL) which allow them to be clearly distinguished from both OFD1 and ADPKD.

**Prevalence**

OFD1 is a rare syndrome, occurring in approximately 1/250,000 live births.

**Clinical description**

The term OFD syndrome designates a group of heterogeneous clinical patterns of which nine different types have been described. The syndrome is characterized by oral, facial and digital malformations and a considerable overlap of the features of the various forms gives rise to difficulties in precise clinical differentiation. OFD1 is the most common pattern, and it can be easily identified because of its X-linked dominant inheritance pattern and PKD which seems to be specific to type 1. OFD1 was first described by Papillon-Leage and Psaume in 1954, who reported on eight girls with a syndrome characterized by oral, facial and digital malformations. Gorlin and Psaume further delineated this condition, suggesting an X-linked dominant inheritance, with the trait lethal in the hemizygous male. In 1964, Doege *et al*. first reported a mother and daughter with OFD1 syndrome and PKD. Since then, the combination of the OFD-1 syndrome with PKD has been reported in other patients and is now considered a distinguishing feature of OFD1 syndrome. The dysmorphology of OFD1 is characteristic, with facial features that include frontal bossing, facial asymmetry, hypertelorism (widely spaced eyes), a broadened nasal bridge and facial milia. Oral features include pseudoclefting of the upper lip, cleft palate and tongue, high arched palate, tethering of the tongue (ankyloglossia) by frenulae, together with abnormal dentition. The digital abnormalities, which affect the hands (50-70%) more often than the feet (25%) include syndactyly (fusion), brachydactyly (shortening), clinodactyly (curvature) and, more rarely, pre or post-axial polydactyly (extra digits). These dysmorphic features can vary within a kindred; this variation has been attributed to the generation of mosaics of somatic cells due to random X chromosome inactivation early during embryogenesis. Central nervous system disease occurs in 40% of OFD1 individuals, with mental retardation, seizures, hydrocephalus, cerebellar anomalies, porencephaly, and agenesis of the corpus callosum. In recent years, the introduction of renal ultrasound scan revealed that PKD is commonly associated with OFD1 and, in some patients, the renal involvement may completely dominate the clinical course of the disease. Usually, the renal cystic changes represent a late complication of the OFD1 syndrome, and PKD is generally diagnosed when advanced chronic renal failure has already developed. Variability in the severity of the kidney disease has also been observed,

characterized by occurrence of unilateral PKD, probably due to random X chromosome inactivation, as mentioned above.

**Management including treatment**
There is no specific therapy for OFD1 syndrome other than surgical correction of the dysmorphic features. Dialysis followed by renal transplantation is the preferred approach for end-stage renal failure.

**Etiology**
The etiopathogenesis of OFD1 syndrome is still obscure and how the underlying genetic abnormality leads to renal disease is unknown. The *OFD1* locus was first mapped by linkage analysis to a 19.8 cM interval flanked by crossovers with markers DXS996 and DXS7105 in the Xp22 region. Subsequently, the interval was narrowed down to a 12-Mb interval of the same region. More recently, it has been demonstrated that mutations in the *Cxorf5* gene may cause the OFD1 syndrome. Thus, the protein has been named OFD1. Because it shares no sequence homologies with other proteins with known functions either in mammals or lower organisms, it is difficult at this time to predict its function. Available data support the hypothesis that the OFD1 protein may have widespread influence on organogenesis and be essential for fetal survival. The presence of several coiled-coil domains suggests that OFD1 acts *via* a protein-protein interaction mechanism. Identification of OFD1 protein interactors may lead to the discovery of novel genes involved in mammalian development and possibly implicated in other types of OFD syndromes. Furthermore, as OFD1 is often associated with polycystic kidney, it is intriguing to note that *PKD1* and *PKD2*, the genes responsible for ADPKD, physically interact through a coiled-coil domain. In conclusion, the identification of the first gene involved in OFD syndrome will be instrumental for the elucidation of the molecular mechanisms underlying this complex group of developmental disorders and may shed new light on the pathogenesis of PKD.

**Genetic counseling**
Approximately 75% of OFD1 cases are sporadic and these occur almost exclusively in females; in this setting, the female with OFD1 has a new *Cxorf5* gene mutation. The remaining cases are familial and these too are essentially limited to females who may have inherited the maternal *Cxorf5* mutation. The mode of inheritance is X-linked dominant, with prenatal death of males carrying a single, mutated, OFD1 gene encoding. The cause of death *in utero* is currently unknown but affected fetuses usually spontaneously abort during the first or second trimester. These observations have important implications for genetic counseling of PKD patients with OFD1. In an established kindred with OFD1, an affected female will transmit the mutation to 50% of her female progeny and these heterozygotes will exhibit the clinical syndrome. In principle, all live-born boys will be normal because males who harbor a mutated gene OFD1 encoding would be expected to die in utero. In addition, 50% of female siblings of an index case will carry the mutation, while all living brothers will be unaffected. If the disease-causing *Cxorf5* gene mutation has been identified in the probed, molecular genetic testing of the mother, the search in female siblings and female progeny with clinical findings is warranted. The probability that an individual with sporadic OFD1 will produce affected offspring is currently unknown; these patients, however, should be counselled as in familial cases.

**Antenatal diagnosis**
For pregnancies of women with OFD1, prenatal diagnosis using molecular genetic testing is available if the disease-causing *Cxorf5* gene mutation has been identified. The usual procedure is to determine fetal sex by chromosome analysis using fetal cells obtained by amniocentesis at 16 to 18 weeks gestation or chorionic villus sampling (CVS) at 9 to 11 weeks gestation. If the fetal karyotype is 46, XY, counseling should include discussion of the increased risk of miscarriage of affected males. If the fetus is found to be female, molecular genetic testing can be offered.

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