Classification & Molecular Biology of Orofaciodigital Syndrome Type I

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Abstract
Orofaciodigital syndrome (OFDS) is an umbrella term for the apparently distinctive morphogenetic disorders, affecting invariably the mouth, face and digits. Polycystic kidney disease has been shown to be one of the distinct feature of this syndrome. It has X-linked dominant inheritance with lethality in males. Orofaciodigital syndrome type 1 (OFD1) was mapped to Xp22.3-22.2 and the gene for OFD1 i.e. cxorf5 was identified some years back where several mutations have been reported. Appertaining to different prognosis and mode of inheritance, thirteen specific types of OFDS are distinguished Oral-facial-digital syndrome 1 (OFD1) which being the most usual of the thirteen, is symbolized by its X linked dominant mode of inheritance with lethality in males. Keeping this in view, a comprehensive review of OFDS types and the genetics and molecular data of OFD1 are reviewed. Selected pathological variants of OFD1 are also tabularized.

Keywords: OFD Syndrome/Orofaciodigital Syndrome, Syndromes, OFD1 Gene, Autosomal Dominant, Autosomal Recessive, X-Linked Dominant.

Introduction:
The orofaciiodigital syndrome (OFDS) is a generic name for the morphogenetic impairment that leads to congenital condition virtually limited to females. Its classical features include deformities of oral cavity, face and limbs like hamartomatous lobulated tongue, cleft lip, cleft palate, hypertelorism, hyperplastic alar cartilage, polydactyly, syndactyly, frontal bossing, hydroencephaly to name a few.1,2

Mohr gave the first description of OFDS in 1941 when he reported a family with significant OFD findings, including highly arched palate, lobate tongue with papilliform outgrowths, a broad nasal root, and hypertelorism.1 In 1954, Papillon-Leage and Psaume reported a hereditary malformation of the buccal mucous membrane and abnormal frenae and suggested that the syndrome was inherited as a complete recessive trait.2 Other French and German authors have since published full accounts of this condition, and Gorlin and Pindborg (1964) have summarized their knowledge of the syndrome in textbook in the 60’s. They described it under the heading of orodigitofacial dystosis, but as there was involvement of other tissues than bone, the term oral-facial-digital (OFD) syndrome was preferred.3,4 Apart from a single case report by Nesbitt (1965), British authors were unaware of the syndrome, but then Smithells (1964) drew attention to it in a British journal without adding any further examples.5-7 This paucity of references is surprising, as the first account of the syndrome was probably given by Murray in 1860. He described a Scottish female infant with characteristic features in his case report of a somewhat similar familial disorder.4,7

Classification: Thirteen different types of OFD have been described in the literature; of these OFD1 has the highest incidence. All the thirteen types have been summarized and a proposed classification have been tabularized (Table 1).1, 2, 8-22
**Table No. 1: Classification of Orofaciodigital Syndrome**

<table>
<thead>
<tr>
<th>OFD Subtype</th>
<th>MIM</th>
<th>Inheritance pattern/Cause</th>
<th>Clinical features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFD I (Papillon-Leage Psaume Syndrome)</td>
<td>311200</td>
<td>X linked dominant inheritance Mutations in OFD1 gene</td>
<td>Facial dysmorphism with oral, tooth, and distal abnormalities, polycystic kidney disease, and central nervous system malformations.</td>
<td>Papillon-Leage, Psaume (1954)(2)</td>
</tr>
<tr>
<td>OFD II (Mohr Syndrome)</td>
<td>252100</td>
<td>Autosomal recessive inheritance Mutations in an as yet unidentified gene.</td>
<td>Milia of the face, the absence of deafness, and bilateral preaxial polydactyly.</td>
<td>Mohr (1941)(1)</td>
</tr>
<tr>
<td>OFD III (Sugarman Syndrome)</td>
<td>258850</td>
<td>Autosomal recessive inheritance</td>
<td>Mental retardation, eye abnormalities, lobulated hamartomatous tongue, dental abnormalities, bifid uvula, postaxial hexadactyly of hands and feet, pectus excavatum, short sternum, and kyphosis.</td>
<td>Sugarman et al. (1971)(8)</td>
</tr>
<tr>
<td>OFD IV (Baraitser-Burn Syndrome)</td>
<td>258860</td>
<td>Autosomal recessive inheritance</td>
<td>Severe tibial dysplasia differentiate type IV from type I</td>
<td>Baraitser (1986)(9)</td>
</tr>
<tr>
<td>OFD V (Thurston Syndrome)</td>
<td>174300</td>
<td>Autosomal recessive inheritance</td>
<td>Polydactyly, postaxial, with median cleft of upper lip.</td>
<td>Thurston (1909)(10)</td>
</tr>
<tr>
<td>OFD VI (Varadi-Papp Syndrome)</td>
<td>277170</td>
<td>Autosomal recessive inheritance</td>
<td>Polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation.</td>
<td>Varadi et al. (1980)(11), Papp and Varadi (1985)(12)</td>
</tr>
<tr>
<td>OFD VII (Whelan Syndrome)</td>
<td>608518</td>
<td>X-linked dominant inheritance</td>
<td>Oral (tongue nodules, bifid tongue, midline cleft of the lip), facial (hypertelorism, alar hypoplasia), and digital abnormalities</td>
<td>Whelan et al. (1975)(13), Nowaczyk et al. (2003)(14)</td>
</tr>
<tr>
<td>Syndrome</td>
<td>OMIM Number</td>
<td>Mode of Inheritance</td>
<td>Core Findings</td>
<td>References</td>
</tr>
<tr>
<td>----------</td>
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<tr>
<td>OFD VIII (Edwards Syndrome)</td>
<td>300484</td>
<td>X-linked recessive inheritance</td>
<td>Hypertelorism or telecanthus, broad, bifid nasal tip, median cleft lip, tongue lobulation and/or hamartomas, oral frenula, high-arched or cleft palate, bilateral polydactyly, and duplicated hallucs.</td>
<td>Edwards et al. (1988)(15), Toriello (1993)(16)</td>
</tr>
<tr>
<td>OFD IX (Gurrieri Syndrome)</td>
<td>258865</td>
<td>Autosomal recessive inheritance</td>
<td>Retinal colobomata in addition to core oral, facial and digital findings.</td>
<td>Gurrieri et al. (1992)(17)</td>
</tr>
<tr>
<td>OFD X (Figuera Syndrome)</td>
<td>165590</td>
<td>-</td>
<td>Mesomelic limb shortening due to radial hypoplasia and fibular agenesis apart from oral, facial and digital findings.</td>
<td>Figuera et al. (1993)(18), Taybi and Lachman (1996)(19)</td>
</tr>
<tr>
<td>OFD XI (Gabreilli Syndrome)</td>
<td>-</td>
<td>-</td>
<td>Presence of craniovertebral anomalies in association with the oral, facial, and digital anomalies.</td>
<td>Gabrielli et al. (1994)(20)</td>
</tr>
<tr>
<td>OFD XII (Moran Barroso Syndrome)</td>
<td>-</td>
<td>-</td>
<td>Myelomeningocele, stenosis of the aqueduct of Sylvius, and cardiac anomalies.</td>
<td>Moran-Barroso et al. (1998)(21)</td>
</tr>
<tr>
<td>OFD XIII (Degner Syndrome)</td>
<td>-</td>
<td>-</td>
<td>Psychiatric symptoms (major depression), epilepsy, and brain MRI findings of leukoaraiosis (patched loss of white matter of unknown pathogenetic origin, possibly of ischemic nature, considered to increase the risk of stroke) in association with core oral, facial, and digital findings.</td>
<td>Degner et al. (1999)(22)</td>
</tr>
</tbody>
</table>

**OFDI – Papillon-Leage-Psaume Syndrome:** OFD1 is characterized by malformations of the face, oral cavity, and digits with embryonic male lethality. The embryonic male lethality is because OFD1 is caused due to mutations in gene ofd1. Ofd1 encodes a protein that localizes to the distal end of centrioles...
where it functions as a cap to regulate centriole length.\textsuperscript{22, 23} As OFD1 is X-linked, males lacking OFD1 do not form cilia, resulting in prenatal lethality.\textsuperscript{22} Although these clinical features resemble the reported features of other forms of OFDS, OFD1 can be easily distinguished from others by its X-linked dominant inheritance pattern and by polycystic kidney disease, which seems to be explicit to type I.\textsuperscript{23-25}

**Clinical features:** The list of facial features cover tongue hamartomas, bifid tongue, cleft lip and palate, multiple hypertrophic frenulae, thick alveolar bands, absence of central and lateral incisor, aplasia of nasal alae. Digital features entails polydactyly: mostly unilateral or asymmetrical, (bilateral, preaxial polydactyly has been reported once), syndactyly: skin or bone, brachydactyly, clinodactyly. Central nervous system features append mental retardation; pathological features include cerebral atrophy, porencephaly, hydrocephaly, hydranencephaly.\textsuperscript{1} Whereas facial milia, coarse thin hair, sometimes alopecia accounts for the features listed for skin manifestations.\textsuperscript{26}

Polycystic kidney disease is another feature annexed to OFD1 symptoms.\textsuperscript{27, 28} It is a multisystem disorder characterized by bilateral renal cysts, renal manifestations like hypertension, renal pain and renal insufficiency. Cysts formation in organs like liver, seminal vesicles, pancreas, and arachnoid membrane, few vascular abnormalities which include intracranial aneurysms, dissection of the thoracic aorta, mitral valve prolapsed, dilatation of the aortic root and abdominal wall hernias.\textsuperscript{29}

**Diagnosis:** OFD1 is diagnosed in few infants at the time of the birth based on characteristic oral, facial and digital anomalies and molecular genetic testing. In case isn’t diagnosed at the time of birth, the diagnosis is suspected only after polycystic kidney disease is identified in later childhood or adulthood. In a worldwide cohort of 120 individuals clinically diagnosed with OFD1, cleft palate / high-arched palate was present in 23.5\%, tongue anomalies in 90.1\%, aberrant frenula in 65.4\%, and abnormal teeth in 42\%.\textsuperscript{30} None of these abnormalities is specific to OFDS, and accessory frenula, for instance, may be more suggestive of Pallister–Hall syndrome.\textsuperscript{31}

**Oral findings:** The disease affects predominantly the tongue, palate, and teeth. The tongue is lobed and described as bifid or trifid depending on its state. Tongue nodules are usually hamartomas or lipomas, they also occur in at least one third of individuals with OFD1. Ankyloglossia which give rise to a short lingual frenulum is common in this condition. Cleft of hard or soft palate, submucous cleft palate, or highly arched palate, this condition is observed to be in more than 50\% of diseased cases. Trifurcation of the soft palate has also been reported. Alveolar clefts and accessory gingival frenulae are common which are hyperplastic frenulae, these extends from the buccal mucous membrane to the alveolar ridge, thus leading to formation of notch in the alveolar ridges. Other oral findings include missing teeth which is most common when considering only teeth, then, supernumerary teeth, enamel dysplasia, and malocclusion.\textsuperscript{32, 33}

**Facial findings:** Ocular hypertelorism or telecanthus occurs in at least 33\% of affected individuals. Hypoplasia of the alae nasi, median cleft lip, or pseudo-ocleft upper lip, micrognathia and downslanting palpebral fissures are commonly observed.\textsuperscript{32}

**Digital findings:** These include clinodactyly of the fifth finger, brachydactyly and syndactyly of varying degrees. The other fingers, chiefly the third one may show variable radial or ulnar deviation. Duplicated hallux occurs in fewer than 50\% of affected individuals, and if present is usually unilateral. Preaxial or postaxial polydactyly of the hands occurs in 1-2\% of afflicted people. Radiographs of the hands often demonstrate fine reticular radiolucencies, which is described as irregular mineralization of the bone, may be with or without spicule formation of the phalanges.\textsuperscript{32, 33}

**Neural findings:** Structural brain abnormalities may occur in as many as 65\% of individuals with OFD1.\textsuperscript{33} Anomalies most commonly include agenesis of the corpus callosum, intracerebral cysts and cerebellar
agenesis with or without Dandy-Walker malformation. Other reported anomalies include type 2 porencephaly (schizencephalic porencephaly), hydrocephalus, pachygyria and heterotopias, cerebral or cerebellar atrophy and berry aneurysms, each of which has been described in a few affected individuals.

**Renal findings:** Renal cysts can develop from both glomeruli and tubules. Polycystic kidney disease occurs in at least 50% of individuals with OFD1 although the exact frequency is unknown. Data indicate that renal cystic disease is present in 60% of affected individuals older than age 18 years.\(^30\) The age of onset is most often in adulthood, but renal cysts in children as found in young age of two years have been illustrated.

**Molecular Genetic Testing** Gene: OFD1 is the only gene currently known to be associated with oral-facial-digital syndrome type I.\(^23\)

**Clinical testing:** Sequence analysis: A variety of mutations have been identified, the majority of which predict premature protein truncation. The reported mutation detection rate is about 80% (30). Deletion/duplication analysis: One study found that six of 131 individuals with OFD1 had a deletion which has a size ranging from one to fourteen exons but not even a single had the same deletion. In this group, 23% of the individuals who did not have a mutation identified on gene sequencing were found on qPCR to have an exonic or multiexonic deletion.\(^34\)

**Prevalence:** It is a rare disease with an estimated incidence of 1:50,000–250,000 live births with description in multifarious ethnic backgrounds.\(^35,\)\(^36\) Penetration and Anticipation: OFD1 appears to have high penetrance, though it has high variability in expression. Few have reported that renal cysts are the only probable manifestation in diseased females but no evidence for such forethought is available.\(^37\)

**Inheritance:** Seeing the reported cases it can be said that OFD1 is *especifico par alas hembras* (specific to females) with few exceptional cases seen in males. OFD1 is considered lethal to males and the condition described by Wahran et al., in 1966 in an XXY male strengthened the idea of male-lethal X-linked dominant inheritance.\(^35,\)\(^37\) Vaillaud et al in 1968 described a pedigree in which 10 females had OFD. One female along with 9 of her granddaughters through 3 unaffected sons had OFD. The 9 affected included all daughters of the 3 carrier sons. The most plausible theory appears to be that of an x-linked dominant gene with lethality in the hemizygous males and this theory has been applied to earlier published pedigrees. In order to explain the findings in this specific family, they presupposed that the OFD gene is on a terminal segment of the X chromosome homologous with a segment of the Y chromosome and the 3 carrier males had inherited a Y chromosome which in a way concealed the expression of the OFD gene.\(^38\)

**Risk to Family Members**

**Parents of a proband:** Approximately 25% of females diagnosed with OFD1 have an affected mother. A female proband with OFD1 may have the disorder as the result of a *de novo* gene mutation. Approximately 75% of affected females are simplex cases (i.e., occurrence of OFD1 in a single family member). Recommendations for the evaluation of the mother of a proband with an apparent *de novo* mutation add up clinical evaluation and molecular genetic testing if the mutation in the proband has been recognized. Literature suggests that if the mother of the proband fulfills the diagnostic criteria required for OFD1 or if she has an afflicted relative, she is a carrier of an *OFD1* gene mutation.\(^39-41\)

**Siblings of a proband:** The risk to siblings depends on the genetic status of the mother. When the mother of an affected female is also racked by this baleful disease, the risk to siblings of inheriting the disease-causing *OFD1* allele at conception is 50%; however, most male conceptuses with the disease-causing *OFD1* allele miscarry.\(^41\) If there is no family history of the disease, there is 1% probability that the unaffected mother of an affected female will give
birth to another affected female. Two possibilities account for this minor increased risk, first, a new mutation in a second child and second, germline mosaicism in a parent. Although germline mosaicism has not been reported, it remains a possibility.42

**Offspring of a proband:** The risk to the offspring of females with OFD1 must take into consideration the presumed lethality to afflicted males during the gestation period. At the time of conception, there are 50% chances that the *OFD1* allele will be carried on and most of the male fetuses affected get miscarry. At the time of the birth the expected gender ratio of the offspring is 1/3 unaffected females, 1/3 affected females, 1/3 unaffected males.41, 42

**Other family members of a proband:** The risk to other family members depends on the status of the proband's mother, if her mother is also affected, her other family members depends on the proband’s father, if his father is also affected, his other family members might be at risk of having the disease.

**Molecular Genetics:** The locus of *Ofd1* was first mapped by linkage analysis to a 19.8 cm interval, flanked by crossovers with markers DXS996 and DXS7105 in the Xp22 region.40 The causative mutations of *Ofd1* were labeled in the *CXORF5* transcript and so *CXORF5* was renamed as *Ofd1*23, 40 *Ofd1* comprises of 23 exons encoding a 1011 amino acid protein. The gene encodes a centrosomal protein found in the primary cilia43 and consequently, OFD1 has been considered a ciliopathy.44 It is widely expressed in metanephros, brain, tongue, and limb43 which could explain the clinical expression of the syndrome.

Mutations of *Ofd1*, located on the X chromosome account for most cases of OFD1 syndrome with most mutations tracked down in the first half of the gene.23, 41, 43, 45 Human *Ofd1* is a region on X-chromosome where transcript frequently escapes X inactivation and the affected females are probably composed of cells with reduced levels of normal OFD1 protein.46 *Ofd1* is the first gene for an X-linked dominant male lethal disorder found to escape X inactivation.47 Apparently, in affected females, one normal copy is not adequate to give protection from the disorder to occur. It is convincing to theorize that unaffected males who carry only one normal copy of OFD1 may exhibit a surpassing expression of the transcript on the single active X chromosome, but more studies are warranted to comment on the level of expression of this transcript in both the genders.43 An alternative hypothesis is that *Ofd1* undergoes X inactivation in the tissues affected in OFD1 syndrome at developmental stages when its function is necessary. Therefore, some tissues of affected females at certain stages during development may result in *Ofd1* functional nullisomy, by inactivation of the normal X. Individual variation in the X-inactivation pattern of this gene may also explain the clinical variability observed in OFD1 syndrome.

There remain, however, some OFD1 syndrome individuals for which *OFD1* mutations cannot be detected.44 In human embryos, *OFD1* is expressed in many organs, accomodating those that develop abnormally in the syndrome.43, 45 *Ofd1* gene has been identified in the olfactory and respiratory epithelium of the nasal cavities and nasopharynx, in the endoderm-derived surface epithelium of the tongue and oropharynx and in a number of ectodermally derived structures of the mouth and palate enlisting upper labial structures, the surface epithelium of the gingiva and tooth primordial.27 In the embryonic nervous system, *Ofd1* gene is observed in telencephalic primordia of the cerebral cortex and striatum and even in cranial and dorsal root ganglia. In postnatal brain, *Ofd1* gene is detected in all the underlying structures, with a higher expression in the hippocampal region. *Ofd1* expression is also observed in the thymus, lungs, kidney, surface ectoderm and vibrissae follicles. This expression leads to alopecia and hair problems and nephrotic abnormalities.43, 45

*Ofd1* gene has 23 exons and generates two main splice variants, *Ofd1a* and *Ofd1b*, the latter coding for an unstudied putative protein of 367 amino acids derived from exons 1–11.46 More is avowed about *Ofd1a* (OFD1), the protein encoded by exons 1–23, itself with a variant lacking exon 10, with a predicted molecular weight of ~110 kDa. The
existence of several coiled-coil domains suggests that OFD1 execute through a protein-protein interaction mechanism. The recognition of OFD1 protein interactors might provide identification of of novel genes involved in mammalian development and conceivable implications in other types of OFD syndromes.  

OFD1 protein contains an N-terminal Lis1 homology (LisH) motif and an extended C-terminal domain containing what have been alternatively indicated as either five or six putative coiled-coils (47,48,50-52). These C-terminal regions, which are sighted as containing six coiled-coils based on SMART analysis (http://smart.embl-heidelberg.de/), is essential for localizing OFD1 to the centrosome. It is also cardinal for interaction with the LCA5-encoded ciliary protein, lebercilin, itself mutated in Leber congenital amaurosis. LisH motifs present in proteins are responsible for dimerization, stability and/or OFD1 regulates centriolar satellites localization and protein–protein interactions. Along with this LisH motif may even control the microtubule dynamics directly or indirectly through cytoplasmic dynein.

It is interesting to note that the genes leading to autosomal dominant polycystic renal have been observed to interact via a coiled-coil domain and it has been already stated that OFD1 is often associated with polycystic kidney. Interestingly, Miller–Dieker lissencephaly and Treacher Collins syndrome are caused by mutations in genes encoding LisH-containing proteins, and both disorders have been attributed to incorrect cell migration resulting from cytoskeletal defects. Hence, certain neuronal components of the OFD1 syndrome might involve aberrant cell migration. In addition, missense mutation of the OFD1 LisH domain deregulates centriole elongation.

Ciliopathies: Intriguingly, OFD1 mutations have recently been associated with other disease phenotypes, including the nephronophthisis (NPHP)-related ciliopathy, Joubert Syndrome.
*Hoxa* and *Hoxd* genes in the limb buds of mice lacking.\(^5\)

In another experiment OFD1 function was analyzed using zebrafish embryonic development. In the experiment Disruption of OFD1 using antisense morpholinos led occurrence of bent in the body axes, hydrocephalus, and edema. The laterality was randomized in the brain, viscera and heart. This was supposed to be an effect of shortening of cilia along with disruption of axonemes and disruption of intravesicular fluid flow in Kupffer vesicle. The embryos which were injected with OFD1 antisense morpholinos led to convergent extension defects and it was also observed that pronephric glomerular midline fusion was compromised in Vangl2 and OFD1 loss-of-function embryos. This led to the conclusion that OFD1 is required for ciliary motility and function in zebrafish and also that OFD1 is cardinal for convergent extension during gastrulation.\(^6\)

**Pathologic allelic variants:** To date, 99 different mutations (92 point mutations and 7 genomic deletions) have been identified.\(^23, 34, 43, 51-54\) Both exonic and intronic pathologic allelic variants have been described. Point mutations in exons encompass single base-pair changes, frameshifts, and deletions. These changes have been identified in exons 2 through 17 and Seven different genomic deletions in the exons 1-23 have been stated till date;\(^41, 57\) (Table no. 2)\(^23, 58-62\)

### Table No. 2: Selected Pathologic Allelic Variants of OFDSI

<table>
<thead>
<tr>
<th>Allelic Variant</th>
<th>Mutation</th>
<th>Protein amino acid change</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>.0004 OROFACIODIGITAL SYNDROME I</td>
<td>IVS5AS, T-G, -10</td>
<td>(Abnormal Splicing)</td>
<td>Rakkolainen et al. (2002)(59)</td>
</tr>
<tr>
<td>.0005 OROFACIODIGITAL SYNDROME I</td>
<td>2-BP INS, 1887AT, Exon16</td>
<td>p.N630IfsX666</td>
<td>Rakkolainen et al. (2002)(59)</td>
</tr>
<tr>
<td>.0006 OROFACIODIGITAL SYNDROME I</td>
<td>4,094-BP DEL, 14-BP DEL</td>
<td>(Frameshift)</td>
<td>Morisawa et al. (2004)(60)</td>
</tr>
<tr>
<td>.0007 SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 2</td>
<td>4-BP DUP, 2122AAGA</td>
<td>p.N711KfsX713</td>
<td>Budny et al. (2006)(61)</td>
</tr>
<tr>
<td>.0008 JOUBERT SYNDROME 10</td>
<td>7-BP DEL, NT2841</td>
<td>p.K948NfsX8</td>
<td>Coene et al. (2009)(62)</td>
</tr>
<tr>
<td>.0009 JOUBERT SYNDROME 10</td>
<td>1-BP DEL, 2767G</td>
<td>p.E923KfsX3</td>
<td>Coene et al. (2009)(62)</td>
</tr>
</tbody>
</table>
References:


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