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Oral-Facial-Digital Syndrome Type I

Synonyms: OFD1, Orofaciodigital Syndrome I

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Summary

Clinical characteristics

Oral-facial-digital syndrome type I (OFD1) is usually male lethal during gestation and predominantly affects females. OFD1 is characterized by the following: oral features (lobulated tongue, tongue nodules, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia, and other dental abnormalities); facial features (widely spaced eyes, telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft of the upper lip, micrognathia); digital features (brachydactyly, syndactyly, clinodactyly of the fifth finger, duplicated great toe); polycystic kidney disease; brain MRI findings (intracerebral cysts, agenesis of the corpus callosum, cerebellar agenesis with or without Dandy-Walker malformation); and intellectual disability (in approximately 50% of affected individuals).

Diagnosis/testing

The diagnosis of OFD1 is established in a female proband with suggestive findings and a heterozygous *OFD1* pathogenic variant identified by molecular genetic testing. The diagnosis of OFD1 is established in a male proband with suggestive findings and a hemizygous pathogenic variant in *OFD1* identified by molecular genetic testing.

Management

Treatment of manifestations: Surgery for cleft lip/palate, tongue nodules, accessory frenulae, syndactyly, and polydactyly; speech therapy and aggressive treatment of otitis media as needed; removal of accessory teeth; orthodontia for malocclusion; routine treatment for seizures and renal disease; early intervention and

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individualized education plan as needed; standard treatments for attention-deficit/hyperactivity disorder and/or autistic features; hearing aids and community hearing services as needed.

Surveillance: Annual audiology evaluation and assessment of speech development in children with cleft lip and/or cleft palate; annual dental evaluation or as recommended by the dentist; assessment for new seizures or changes in seizures as recommended by neurologist in those with brain involvement. Annual blood pressure; serum creatinine; and renal, liver, pancreas, and ovarian ultrasound for cystic disease beginning at age ten years. Assess developmental progress, educational needs, and behavioral manifestations at each visit.

Evaluation of relatives at risk: It is appropriate to evaluate the genetic status of apparently asymptomatic female relatives (even in the absence of oral, facial, and digital anomalies) to determine if they are at risk for renal disease.

Pregnancy management: Careful monitoring of blood pressure and renal function during pregnancy is warranted.

Genetic counseling

OFD1 is inherited in an X-linked manner with, typically, male lethality. The full OFD1 phenotype has not been described in males beyond the perinatal period. Approximately 75% of affected females represent simplex cases (i.e., the occurrence of OFD1 in a single family member) and have a *de novo* pathogenic variant; approximately 25% of females diagnosed with OFD1 have an affected mother (mildly affected females may be diagnosed after the identification of a severely affected individual). If the mother of the proband has an *OFD1* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%; however, most male conceptuses with the *OFD1* pathogenic variant miscarry. It is possible for an affected male to be born alive, though this is exceedingly rare. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males. Once the *OFD1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for oral-facial-digital syndrome type I (OFD1) have been published.

Suggestive Findings

OFD1 **should be suspected** in females with typical oral, facial, and digital findings, polycystic kidney disease, and/or milia. The oral, facial, and digital findings are also found in other oral-facial-digital syndromes. OFD1 is characterized by renal cystic disease in approximately 50% of individuals and by the X-linked inheritance pattern in families with more than one affected individual. Almost all individuals with OFD1 are female; however, a few affected males have been reported. Most affected males are described as malformed fetuses delivered by an affected female.

Clinical Features

Oral

- Tongue anomalies (e.g., lobulated, nodules, ankyloglossia)
- Cleft palate
- Alveolar clefts and accessory gingival frenulae
- Dental anomalies (e.g., missing teeth, extra teeth)

Facial

- Widely spaced eyes, telecanthus, downslanting palpebral fissures

- Hypoplasia of the alae nasi
- Median cleft lip, pseudocleft of the upper lip
- Micrognathia

Digital

- Brachydactyly, syndactyly
- Clinodactyly of the fifth finger
- Radial or ulnar deviation of the other fingers, particularly the third
- Unilateral duplicated hallux (great toe)

Other

- Polycystic kidney disease
- Intellectual disability
- Milia

Imaging Features

- **Hand x-rays** often demonstrate fine reticular radiolucencies, described as irregular mineralization of the bone, with or without spicule formation of the phalanges.
- **Renal ultrasound** examination shows renal cysts in at least 50% of individuals.
- **Brain MRI** most commonly shows intracerebral cysts, agenesis of the corpus callosum, and cerebellar agenesis with or without Dandy-Walker malformation.

Family History

Family history is consistent with X-linked inheritance predominantly affecting females due to male lethality. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Female proband. The diagnosis of OFD1 **is established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *OFD1* identified by molecular genetic testing (see Table 1).

Male proband. The diagnosis of OFD1 **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *OFD1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this section is understood to include any likely pathogenic variant. (2) Identification of a heterozygous or hemizygous *OFD1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of OFD1 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *OFD1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *OFD1* and other genes of interest (see Differential Diagnosis) is recommended if no pathogenic variant is identified on single-gene testing. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Oral-Facial-Digital Syndrome Type I

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
OFD1	Sequence analysis [3]	~80% [4]
	Gene-targeted deletion/duplication analysis [5]	~20% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Nowaczyk et al [2003], Thauvin-Robinet et al [2006], Prattichizzo et al [2008]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. One study found that six of 131 individuals with OFD1 had a deletion ranging in size from one to 14 exons. None had the same deletion. Within this group, 23% of those who did not have a pathogenic variant identified on gene sequencing were found on qPCR to have a single- or multiexon deletion [Thauvin-Robinet et al 2009].

Clinical Characteristics

Clinical Description

The diagnosis of oral-facial-digital syndrome type I (OFD1) is suspected at birth in some infants on the basis of characteristic oral, facial, and digital anomalies; in other instances, the diagnosis is suspected only after polycystic kidney disease is identified in later childhood or adulthood. Almost all affected individuals with OFD1 are female; however, a few affected males have been reported. Most affected males are described as malformed fetuses delivered by a female with OFD1. To date, 234 individuals have been identified with a pathogenic variant in *OFD1* [Pezzella et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Oral-Facial-Digital Syndrome Type I: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Oral manifestations	97%-100%	Dental & tongue abnormalities, aberrant oral frenulae, bifid uvula
Facial features	60%-80%	Dysmorphisms, frontal bossing, cleft lip / pseudocleft of upper lip
Digit anomalies	50%-60%	Syndactyly, clinodactyly, polydactyly, brachydactyly
Brain malformations	65%	Hydrocephalus, porencephaly, corpus callosum abnormalities, cortical dysgenesis
Polycystic kidney disease	>50%	
Intellectual disability	~50%	Mild to severe
Milia	>10%	

Oral manifestations. The tongue is lobulated. Tongue nodules, which are usually hamartomas or lipomas, also occur in at least one third of individuals with OFD1. Ankyloglossia attributable to a short lingual frenulum is common. Cleft hard or soft palate, submucous cleft palate, or highly arched palate occurs in more than 50% of affected individuals. Alveolar clefts and accessory gingival frenulae are common. These fibrous bands are hyperplastic frenulae extending from the buccal mucous membrane to the alveolar ridge, resulting in notching of the alveolar ridges. Dental abnormalities include missing teeth (most common), extra teeth, enamel dysplasia, and malocclusion.

Facial features. Widely spaced eyes (telecanthus) occurs in at least 33% of affected individuals. Hypoplasia of the alae nasi, median cleft lip, or pseudocleft of the upper lip is common. Micrognathia and downslanting palpebral fissures are common.

Digital anomalies. Brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger are common. The other fingers, particularly the third (i.e., middle finger), may show variable radial or ulnar deviation. Duplicated hallux (great toe) 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 affected individuals.

Brain malformations. Structural brain abnormalities may occur in as many as 65% of individuals with OFD1 [Bisschoff et al 2013, Del Giudice et al 2014]. Anomalies most commonly include intracerebral cysts, agenesis of the corpus callosum, and cerebellar agenesis with or without Dandy-Walker malformation. Other reported anomalies include type 2 porencephaly (schizencephalic porencephaly), pachygyria and heterotopias, hydrocephalus, cerebral or cerebellar atrophy, hypothalamic hamartomas, and berry aneurysms, each of which has been described in a few affected individuals.

Structural brain abnormalities may be accompanied by seizures and ataxia, especially in those with cerebellar atrophy.

Kidney manifestations. Renal cysts can develop from both tubules and glomeruli. The age of onset is most often in adulthood, but renal cysts in children as young as age two years have been described. Although renal cysts have been reported as a prenatal finding [Nishimura et al 1999], the diagnosis is doubtful in these cases. The risk for significant renal disease appears to be higher than 60% after age 18 years [Prattichizzo et al 2008, Saal et al 2010]. End-stage kidney disease has been reported in affected girls and women ranging in age from 11 to 70 years.

Intellectual disability and neurobehavioral manifestations. It is estimated that as many as 50% of individuals with OFD1 have some degree of intellectual disability or learning disability. Intellectual disability depends in part on the presence of brain abnormalities, but no consistent correlation exists. When present, intellectual disability is usually mild. Severe intellectual disability in the absence of brain malformations appears to be rare [Del Giudice et al 2014]. Rarely, behavioral issues (e.g., attention-deficit/hyperactivity disorder, autistic features) are observed.

Milia, small keratinizing cysts, occur in at least 10% of individuals, and are likely more common than reported. Milia most often appears on the scalp, ear pinnae, face, and dorsa of the hands. Milia are usually present in infancy and then resolve, but they can leave pitting scars.

Hair. The hair is often described as dry, coarse, and brittle. Alopecia, usually partial, is an occasional finding. Alopecia following the lines of Blaschko has been described [Del C Boente et al 1999].

Hearing loss from recurrent otitis media, usually associated with cleft palate, has been reported. On occasion, speech can be affected.

Other. Liver, pancreatic, and ovarian cysts may be observed [Macca & Franco 2009, Chetty-John et al 2010].

Phenotypic variability is often seen in affected females, possibly as a result of random X-chromosome inactivation [Morleo & Franco 2008].

Genotype-Phenotype Correlations

No convincing genotype-phenotype correlations have been reported. The majority of *OFD1* pathogenic variants are localized within exon 16.

Penetrance

OFD1 appears to be highly penetrant, although highly variable in expression. In some reports, renal cysts are the only apparent manifestation in affected females [McLaughlin et al 2000].

Nomenclature

OFD1 was previously called Papillon-Léage-Psaume syndrome.

Prevalence

Prevalence estimates range from 1:50,000 to 1:250,000.

Genetically Related (Allelic) Disorders

OFD1 pathogenic variants have been reported in males with Joubert syndrome, primary ciliary dyskinesia, and retinitis pigmentosa (see Table 3; reviewed in [Pezzella et al 2022]).

Table 3. *OFD1* Allelic Disorders

Disorder	References
OFD1-related Joubert syndrome	Coene et al [2009], Field et al [2012], Juric-Sekhar et al [2012], Thauvin-Robinet et al [2013], Bachmann-Gagescu et al [2015], Srour et al [2015], Suzuki et al [2016], Wentzensen et al [2016], Kane et al [2017], Meng et al [2017], Linpeng et al [2018], Aljeaid et al [2019], Zhang et al [2021], Huang et al [2022], Li et al [2023]
OFD1-related primary ciliary dyskinesia	Bukowy-Bieryllo et al [2019], Hannah et al [2019], Hasegawa et al [2021], Yang et al [2022]
OFD1-related retinitis pigmentosa	Webb et al [2012], Wang et al [2017], Chen et al [2018]

OFD1 pathogenic variants have also been described in the following reports:

- An *OFD1* pathogenic variant was reported in male family members with intellectual disability, macrocephaly, obesity, skeletal abnormalities, and a primary ciliary dyskinesia phenotype [Budny et al 2006]. These findings represent the first indication of a role for *OFD1* in motile cilia function. Note: The phenotype in this family has been classified as Simpson-Golabi-Behmel type 2 (SGBS2; OMIM 300209); however, subsequent studies have demonstrated that the SGBS2 locus is associated with pathogenic variants in *PIGA* [Fauth & Toutain 2017].
- An *OFD1* pathogenic variant was reported in a family in which males had a lethal congenital malformation syndrome characterized by oral, facial, digital, cerebral, and renal anomalies and in utero lethality; disease was caused by a novel splicing variant in intron 17 of *OFD1*. Heterozygous females were described to have hyperplastic frenulae and dental anomalies only [Tsurusaki et al 2013].
- A male fetus with a hemizygous *OFD1* truncating variant c.2101C>T (p.Gln701Ter) displayed a severe multisystemic condition including severe hypoplasia of the left cardiac ventricle; pregnancy was terminated at 16 1/7 weeks' gestation [Bouman et al 2017].

Differential Diagnosis

The differential diagnosis of oral-facial-digital syndrome type I (OFD1) includes other oral-facial-digital syndromes and cystic renal diseases.

Table 4. Genes of Interest in the Differential Diagnosis of Oral-Facial-Digital Syndrome Type I

Gene(s)	Disorder	MOI	Distinctive Features / Comment
C2CD3	*C2CD3*-related OFD (OMIM 615948) / JS-OFD	AR	Severe microcephaly & ID. Brain MRI shows vermis hypoplasia & MTS.
CEP164	*CEP164*-related OFD [1]	AR	Postaxial polydactyly, hypotonia, cerebral malformations, hydronephrosis, & urogenital abnormalities. (*CEP164* is also assoc w/nephronophthisis.)
CLUAP1	*CLUAP1*-related JS-OFD [2]	AR	Epiglottis cleft, short limbs, ID. Brain MRI shows MTS. One individual reported to date.
CPLANE1 (*C5orf42*)	*CPLANE1*-related OFD (OMIM 277170) / JS-OFD	AR	Polydactyly (particularly central) & cerebellar malformations. Renal agenesis & dysplasia have been described. Brain MRI may show MTS. [3]
DDX59	*DDX59*-related OFD (OMIM 174300)	AR	Polydactyly & median cleft lip only. Hyperplastic frenula reported in 1 person.
FAM149B1	*FAM149B1*-related JS (OMIM 618763)	AR	Macrocephaly. Brain MRI shows MTS. Reported in 1 family to date.
IFT57	*IFT57*-related OFD (OMIM 617927)	AR	Short stature, skeletal dysplasia, & brachymesophalangia

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Distinctive Features / Comment
INTU	*INTU*-related OFD (OMIM 617926)	AR	Cardiac defects, deafness, polydactyly. (Also assoc w/*INTU*-related SRPS [OMIM 617925].)
KIAA0753 (*OFIP*)	*KIAA0753*-related OFD (OMIM 617127)	AR	Polydactyly (particularly postaxial). Brain MRI shows vermis hypoplasia & MTS. (Also assoc w/*KIAA0753*-related short-rib thoracic dysplasia [OMIM 619479] & JS [OMIM 619476].)
NEK1	*NEK1*-related OFD2 (Mohr syndrome) [4]	AR	Dental agenesis, maxillary hypoplasia, conductive hearing loss, & bilateral tortuosity of retinal veins. (Also assoc w/*NEK1*-related SRPS [OMIM 263520].)
SCLT1	*SCLT1*-related OFD [4]	AR	Microcephaly, coloboma, choanal atresia, congenital heart disease, agenesis of corpus callosum
SCNM1	*SCNM1*-related OFD (OMIM 620107)	AR	Postaxial polydactyly, tongue nodules, abnormalities of incisors, cleft palate, & retrognathia
TBC1D32	*TBC1D32*-related OFD [4]	AR	Microcephaly, coloboma, choanal atresia, agenesis of corpus callosum, congenital heart disease, & seizures. 1 person described to date.
TCTN1	*TCTN1*-related JS	AR	Polydactyly & cerebellar malformations
TCTN3	*TCTN3*-related OFD4 (Mohr-Majewski) (OMIM 258860) / JS-OFD	AR	Tibial involvement & polydactyly are primary manifestations. Micrognathia. Other findings incl pectus excavatum & short stature.
TMEM107	*TMEM107*-related OFD (OMIM 617563) / JS-OFD	AR	Postaxial polydactyly. ID. Brain MRI shows vermis hypoplasia & MTS.
TMEM138	*TMEM138*-related OFD [4]	AR	Brain MRI shows vermis hypoplasia & MTS. (*TMEM138* is also assoc w/ JS.)
TMEM216	*TMEM216*-related OFD [4] / JS-OFD	AR	Polydactyly, nephronophthisis, & cystic kidneys. Brain MRI shows MTS.
TMEM231	*TMEM231*-related OFD [4]	AR	Brain MRI shows vermis hypoplasia & MTS. (*TMEM231* is also assoc w/ JS.)
TOPORS	*TOPORS*-related OFD [1]	AR	Postaxial polydactyly, hypotonia, cerebral malformations, & urogenital abnormalities. (*TOPORS* is also assoc w/retinitis pigmentosa.)
B9D1 *B9D2* *CC2D2A* *CEP290* *KIF14* *MKS1* *NPHP3* *RPGRIP1L* *TCTN2* *TMEM107* *TMEM216* *TMEM231* *TMEM67* *TXNDC15*	Meckel syndrome (OMIM PS249000)	AR	CNS malformation (posterior encephalocele, cerebral & cerebellar hypoplasia), polycystic or hypoplastic kidneys, preaxial or postaxial polydactyly, & early demise. Additional findings incl cleft lip & palate, ambiguous genitalia, microcephaly, & microphthalmia. Ocular histopathology reveals retinal dysplasia, coloboma, cataract, & corneal dysgenesis.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Distinctive Features / Comment
ALG5 *ALG9* *DNAJB11* *GANAB* *IFT140* *PKD1* *PKD2*	Autosomal dominant polycystic kidney disease (ADPKD)	AD	ADPKD has been diagnosed in some persons who later were found to have OFD1. [5] In ADPKD, cysts develop from tubules; in OFD1, cysts develop from both tubules & glomeruli (imaging studies cannot always distinguish the renal cystic disease of OFD1 from that of ADPKD & other cystic renal disorders). OFD1 cysts are said to be smaller & more uniform in size than in ADPKD & kidneys are not as enlarged or malformed in OFD1. ADPKD is not assoc w/oral, facial, digital, or brain abnormalities.
PRKACB	Cardioacrofacial dysplasia 2 (OMIM 619143)	AD	Postaxial polydactyly, brachydactyly, oral frenulae, dental abnormalities, ID, & seizures. Additional findings incl long thorax & heart defects.

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; ID = intellectual disability; JS = Joubert syndrome; JS-OFD = Joubert syndrome with oral-facial-digital features; MOI = mode of inheritance; MTS = molar tooth sign; OFD = oral-facial-digital; SRPS = short-rib polydactyly syndrome

1. Strong et al [2021]
2. Johnston et al [2017]
3. Romani et al [2015]
4. Bruel et al [2017]
5. Scolari et al [1997]

Note: *TMEM17* may also be of interest in the differential diagnosis of OFD1. A homozygous *TMEM17* variant – expected to be damaging based on variant analyses – was reported in one individual with vermis hypoplasia and the molar tooth sign on brain MRI and postaxial polydactyly [Shamseldin et al 2020].

OFD types of unknown genetic cause include the following:

- OFD3 (OMIM 258850) is characterized by seesaw winking (alternate winking of the eyes) and polydactyly. Myoclonic jerks, profound intellectual disability, bulbous nose, and apparently low-set ears also occur.
- OFD8 (OMIM 300484), apparently inherited in an X-linked manner, is characterized by the combination of polydactyly, tibial and radial defects, and epiglottal abnormalities, none of which are typical of OFD1.
- OFD9 (OMIM 258865) includes retinal abnormalities and non-median cleft lip.
- OFD10 (OMIM 165590) includes short limbs with bilateral radial shortening and fibular agenesis.
- OFD11 (OMIM 612913) includes odontoid and vertebral abnormalities.
- OFD12 is described in only one individual with brain malformations, myelomeningocele, short tibiae, and central Y-shaped metacarpal [Franco & Thauvin-Robinet 2016].
- OFD13 is described in only one individual with neuropsychiatric disturbances and leukoaraiosis [Franco & Thauvin-Robinet 2016].

Management

No clinical practice guidelines for oral-facial-digital syndrome type I (OFD1) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with OFD1, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Oral-Facial-Digital Syndrome Type I: Recommended Evaluations

System/Concern	Evaluation	Comment
ENT	Exam for oral manifestations that may affect feeding & speech	
Dental	Dental eval	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Digit anomalies	Assess for digit anomalies.	
Neurologic	• Eval of CNS involvement incl brain MRI • Neurologic eval w/movement disorder specialist for ataxia • EEG in those w/suspected seizures	
Renal	• Blood pressure • Serum creatinine concentration • Serum chemistries • Urinalysis	
	Ultrasound exam of kidneys for cysts	Incl ultrasound of liver, ovary, & pancreas in those age ≥10 yrs
Development/ Behavior	Formal, age-appropriate assessment of development & behavior	
Hearing	Audiology eval if cleft palate is present	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of OFD1 to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CNS = central nervous system; MOI = mode of inheritance; OFD1 = oral-facial-digital syndrome type I
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Oral-Facial-Digital Syndrome Type I: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Oral manifestations	• Reconstructive surgery for clefts of lip &/or palate, tongue nodules, & accessory frenulae • Treatment is the same as as that for isolated cleft palate, incl speech therapy & assessment for & aggressive treatment of otitis media.	
Dental anomalies	• Removal of accessory teeth • Orthodontia for malocclusion	
Syndactyly/ Polydactyly	Surgical repair as recommended by orthopedist	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Renal disease	Routine mgmt of renal disease, which may require hemodialysis or peritoneal dialysis & renal transplantation	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Development / Behavioral manifestations	• Early intervention & IEP for those w/developmental issues, learning disabilities, & other cognitive impairments • Standard treatments for ADHD &/or autistic features	
Hearing impairment	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district

ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; IEP = individualized education plan
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Table 7. Oral-Facial-Digital Syndrome Type I: Recommended Surveillance

System/Concern	Evaluation	Frequency
ENT	Assessment of speech development & frequency of ear infections	Annually in children if cleft lip &/or cleft palate is present
Dental	Dental eval	Annually or as recommended by dentist in presence of dental abnormalities
Neurologic	Assess for new seizures or changes in seizures.	As recommended by neurologist in those w/brain involvement
Renal	• Blood pressure exam • Serum creatinine concentration • Renal ultrasound for renal cysts • Incl ultrasound of liver, pancreas, & ovaries for cystic disease	Annually in individuals age ≥10 yrs
Development/ Behavior	Monitor developmental progress, educational needs, & for behavioral manifestations.	At each visit
Hearing	Audiology eval	Annually

Evaluation of Relatives at Risk

It is appropriate to evaluate the genetic status of apparently asymptomatic female relatives (even in the absence of oral, facial, and digital anomalies) to determine if they are at risk for renal disease.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Affected pregnant women should undergo careful monitoring of their blood pressure and renal function during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Oral-facial-digital syndrome type I (OFD1) is inherited in an X-linked manner with, typically, male lethality. Almost all affected individuals with OFD1 are female.

The full OFD1 phenotype has not been described in males beyond the perinatal period. Males with a hemizygous *OFD1* pathogenic variant who survive present a phenotype characterized by only some of the clinical features of OFD1, Joubert syndrome, retinitis pigmentosa, or primary ciliary dyskinesia, or with a clinical phenotype that is a combination of the different disorders [Sakakibara et al 2019, Sharma et al 2016, Zhang et al 2020, Pezzella et al 2022].

Risk to Family Members

Parents of a female proband

- A female proband may have inherited the *OFD1* pathogenic variant from her mother or the pathogenic variant may be *de novo*. (Theoretically, a female proband may have inherited an *OFD1* pathogenic variant from a father with germline mosaicism; however, this has not been reported to date.)
  - Approximately 75% of affected females represent simplex cases (i.e., the occurrence of OFD1 in a single family member) and have a *de novo* pathogenic variant [Pezzella et al 2022].
  - Approximately 25% of females diagnosed with OFD1 have an affected mother. (Mildly affected females may be diagnosed after the identification of a severely affected individual.)
- Recommendations for the evaluation of the mother of a proband with an apparent *de novo* pathogenic variant include clinical evaluation and molecular genetic testing for the pathogenic variant in the proband. (Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.)

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents.

- If the mother of the proband has an *OFD1* pathogenic variant, the chance of transmitting the causative *OFD1* pathogenic variant in each pregnancy is 50%; however, most male conceptuses with the *OFD1* pathogenic variant miscarry [Macca & Franco 2009]. It is possible for an affected male to be born alive, though this is exceedingly rare. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males.
- If the proband represents a simplex case and if the *OFD1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Maternal mosaicism for an *OFD1* pathogenic variant has been reported [Wentzensen et al 2016, Gangaram et al 2022]. Paternal germline mosaicism has not been reported to date but remains a possibility.

Offspring of a female proband. Women with an *OFD1* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy; however, the expected sex ratio of offspring at delivery is 33% unaffected females, 33% affected females, and 33% unaffected males because of the presumed lethality to affected males during gestation (most male conceptuses with an *OFD1* pathogenic variant miscarry).

Other family members. The risk to other family members depends on the status of the proband's mother: if the mother has an *OFD1* pathogenic variant, the mother's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of having an *OFD1* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *OFD1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination

- **High-risk pregnancies.** In pregnancies of a female with OFD1, which are at 50% risk, prenatal ultrasound examination may detect structural brain malformations (e.g., porencephaly) [Carss et al 2014, Alamillo et al 2015] and/or skeletal defects.
- **Low-risk pregnancies.** In pregnancies not known to be at increased risk for OFD1, the findings of structural brain anomalies **and** unilateral polydactyly of the great toe (duplicated hallux) should lead to consideration of OFD1. In such instances, it is appropriate to evaluate the mother for manifestations of OFD1.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Cleft Palate-Craniofacial Association**
  Phone: 919-933-9044
  acpa-cpf.org
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **Friendly Faces**

Email: smile@friendlyfaces.org
www.friendlyfaces.org

- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca

- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Oral-Facial-Digital Syndrome Type I: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
OFD1	Xp22.2	Centriole and centriolar satellite protein OFD1	OFD1 @ LOVD	OFD1	OFD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Oral-Facial-Digital Syndrome Type I (View All in OMIM)

300170	OFD1 CENTRIOLE AND CENTRIOLAR SATELLITE PROTEIN; OFD1
311200	OROFACIODIGITAL SYNDROME I; OFD1

Molecular Pathogenesis

Oral-facial-digital syndrome 1 protein (also called centriole and centriolar satellite protein OFD1) occurs in two forms, OFD1-1 (Cxorf5-1) and OFD1-2 (Cxorf5-2), which are differentiated by the use of an alternative splice site. OFD1-1 is a 1,012-amino acid protein (reference sequence NP_003602.1); OFD1-2 is a 367-amino acid protein. The two proteins share the first 351 amino acids; OFD1-2 then has a C-terminal region of 16 amino acids. OFD1 was expressed in all adult tissues that were examined by de Conciliis et al [1998]. However, during early development, expression is exclusively in the genital ridges, soon followed by expression in craniofacial structures and the nervous system [Ferrante et al 2001]. Functional in vivo and in vitro studies have demonstrated that OFD1 is required for ciliogenesis and determination of left-right asymmetry [Ferrante et al 2006, Singla et al 2010]. Recent studies reviewed in Morleo & Franco [2020] demonstrated that OFD1 has a role in microtubule organization and cell cycle progression [Alfieri et al 2020] and protein quality balance [Iaconis et al 2017, Morleo et al 2021]. A more recent report also indicated that OFD1 acts as a class II nucleation-promoting factor to promote Arp2/3 complex-mediated actin branching [Cao et al 2023].

Mechanism of disease causation. Most *OFD1* pathogenic variants predict a premature truncation of the protein and apparent loss of function, which is further supported by *OFD1* intragenic deletions causing the phenotype. However, the *OFD1* transcript escapes X-chromosome inactivation; thus, the abnormal protein may theoretically interact with the wild type product to produce a dominant-negative effect.

***OFD1*-specific laboratory technical considerations.** In females without a pathogenic variant identified on *OFD1* sequence analysis, gene-targeted deletion/duplication analysis should be done, as the deletion could be masked by the wild type allele.

Chapter Notes

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References

Literature Cited

Alamillo CL, Powis Z, Farwell K, Shahmirzadi L, Weltmer EC, Turocy J, Lowe T, Kobelka C, Chen E, Basel D, Ashkinadze E, D'Augelli L, Chao E, Tang S. Exome sequencing positively identified relevant alterations in more than half of cases with an indication of prenatal ultrasound anomalies. Prenat Diagn. 2015;35:1073–8. PubMed PMID: 26147564.

Alfieri M, Iaconis D, Tammaro R, Perone L, Calì G, Nitsch L, Dougherty GW, Ragnini-Wilson A, Franco B. The centrosomal/basal body protein OFD1 is required for microtubule organization and cell cycle progression. Tissue Cell. 2020;64:101369. PubMed PMID: 32473706.

Aljeaid D, Lombardo RC, Witte DP, Hopkin RJ. A novel pathogenic variant in OFD1 results in X-linked Joubert syndrome with orofaciodigital features and pituitary aplasia. Am J Med Genet A. 2019;179:1010–14. PubMed PMID: 30895720.

Bachmann-Gagescu R, Dempsey JC, Phelps IG, O'Roak BJ, Knutzen DM, Rue TC, Ishak GE, Isabella CR, Gorden N, Adkins J, Boyle EA, de Lacy N, O'Day D, Alswaid A, Ramadevi A R, Lingappa L, Lourenço C, Martorell L, Garcia-Cazorla À, Ozyürek H, Haliloğlu G, Tuysuz B, Topçu M, Chance P, Parisi MA, Glass IA,

Shendure J, Doherty D, et al. Joubert syndrome: a model for untangling recessive disorders with extreme genetic heterogeneity. J Med Genet. 2015;52:514–22. PubMed PMID: 26092869.

Bisschoff IJ, Zeschnigk C, Horn D, Wellek B, Rieß A, Wessels M, Willems P, Jensen P, Busche A, Bekkebraten J, Chopra M, Hove HD, Evers C, Heimdal K, Kaiser AS, Kunstmann E, Robinson KL, Linné M, Martin P, McGrath J, Pradel W, Prescott KE, Roesler B, Rudolf G, Siebers-Renelt U, Tyshchenko N, Wieczorek D, Wolff G, Dobyns WB, Morris-Rosendahl DJ. Novel mutations including deletions of the entire OFD1 gene in 30 families with type 1 orofaciodigital syndrome: a study of the extensive clinical variability. Hum Mutat. 2013;34:237–47. PubMed PMID: 23033313.

Bouman A, Alders M, Oostra RJ, van Leeuwen E, Thuijs N, van der Kevie-Kersemaekers A, van Maarle M. Oral-facial-digital syndrome type 1 in males: congenital heart defects are included in its phenotypic spectrum. Am J Med Genet A. 2017;173:1383–89. PubMed PMID: 28371265.

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. 2017;54:371–80. PubMed PMID: 28289185.

Budny B, Chen W, Omran H, Friegauf M, Tzschach A, Wisniewska M, Jensen LR, Raynaud M, Shoichet SA, Badura M, Lenzner S, Latos-Bielenska A, Ropers HH. A novel X-linked recessive mental retardation syndrome comprising macrocephaly and ciliary dysfunction is allelic to oral-facial-digital type I syndrome. Hum Genet. 2006;120:171–8. PubMed PMID: 16783569.

Bukowy-Bieryllo Z, Rabiasz A, Dabrowski M, Pogorzelski A, Wojda A, Dmenska H, Grzela K, Sroczynski J, Witt M, Zietkiewicz E. Truncating mutations in exons 20 and 21 of OFD1 can cause primary ciliary dyskinesia without associated syndromic symptoms. J Med Genet. 2019;56:769–77. PubMed PMID: 31366608.

Cao M, Zou X, Li C, Lin Z, Wang N, Zou Z, Ye Y, Seemann J, Levine B, Tang Z, Zhong Q. An actin filament braching surveillance system regulates cell cycle progression, cytokinesis and primary ciliogenesis. Nat Commun. 2023;14:1687. PubMed PMID: 36973243.

Carss KJ, Hillman SC, Parthiban V, McMullan DJ, Maher ER, Kilby MD, Hurles ME. Exome sequencing improves genetic diagnosis of structural fetal abnormalities revealed by ultrasound. Hum Mol Genet. 2014;23:3269–77. PubMed PMID: 24476948.

Chen X, Sheng X, Liu Y, Li Z, Sun X, Jiang C, Qi R, Yuan S, Wang X, Zhou G, Zhen Y, Xie P, Liu Q, Yan B, Zhao C. Distinct mutations with different inheritance mode caused similar retinal dystrophies in one family: a demonstration of the importance of genetic annotations in complicated pedigrees. J Transl Med. 2018;16:145. PubMed PMID: 29843741.

Chetty-John S, Piwnica-Worms K, Bryant J, Berbardini I, Fisher RE, Heller T, Gahl WA, Gunay-Aygun M. Fibrocystic disease of liver and pancreas; under-recognized features of the X-linked ciliopathy oral-facial-digital syndrome type 1 (OFDI). Am J Med Genet Part A. 2010;152A:2640–5. PubMed PMID: 20818665.

Coene KLM, Roepman R, Doherty D, Afroze BM, Kroes HY, Letteboer SJF, Ngu LH, Budny B, van Wijk E, Gorden NT, Azhimi M, Thauvin-Robinet C, Veltman JA, Boink M, Kleefstra T, Cremers FPM, van Bokhoven H, de Brouwer APM. OFD1 is mutated in X-linked Joubert syndrome and interacts with LCA5- encoded lebercilin. Am J Hum Genet. 2009;85:465–81. PubMed PMID: 19800048.

de Conciliis L, Marchitiello A, Wapenaar MC, Borsani G, Giglio S, Mariani M, Consalez GG, Zuffardi O, Franco B, Ballabio A, Banfi S. Characterization of Cxorf5 (71-7A), a novel human cDNA mapping to Xp22 and

encoding a protein containing coiled-coil alpha-helical domains. Genomics. 1998;51:243–50. PubMed PMID: 9722947.

Del C Boente M, Primc N, Veliche H, Rosales S, Carrero-Valenzuela R, Saleme C, Asial R. A mosaic pattern of alopecia in the oral-facial-digital syndrome type I (Papillon-Léage and psaume syndrome). Pediatr Dermatol. 1999;16:367–70. PubMed PMID: 10571835.

Del Giudice E, Macca M, Imperati F, D'Amico A, Parent P, Pasquier L, Layet V, Lyonnet S, Stambou-Darmency V, Thauvin-Robinet C, Franco B, et al. CNS involvement in OFD1 syndrome: a clinical, molecular, and neuroimaging study. Orphanet J Rare Dis. 2014;9:74. PubMed PMID: 24884629.

Fauth C, Toutain A. Comment on "Whole exome sequencing and array-based molecular karyotyping as aids to prenatal diagnosis in fetuses with suspected Simpson-Golabi-Behmel syndrome.". Prenat Diagn. 2017;37:1055–6. PubMed PMID: 29057530.

Ferrante MI, Giorgio G, Feather SA, Bulfone A, Wright V, Ghiani M, Selicorni A, Gammaro L, Scolari F, Woolf AS, Sylvie O, Bernard L, Malcolm S, Winter R, Ballabio A, Franco B. Identification of the gene for oral-facial-digital type I syndrome. Am J Hum Genet. 2001;68:569–76. PubMed PMID: 11179005.

Ferrante MI, Zullo A, Barra A, Bimonte S, Messaddeq N, Studer M, Dolle P, Franco B. Oral-facial-digital type I protein is required for primary cilia formation and left-right axis specification. Nat Genet. 2006;38:112–7. PubMed PMID: 16311594.

Field M, Scheffer IE, Gill D, Wilson M, Christie L, Shaw M, Gardner A, Glubb G, Hobson L, Corbett M, Friend K, Willis-Owen S, Gecz J. Expanding the molecular basis and phenotypic spectrum of X-linked Joubert syndrome associated with OFD1 mutations. Eur J Hum Genet. 2012;20:806–9. PubMed PMID: 22353940.

Franco B, Thauvin-Robinet C. Update on oral-facial-digital syndromes (OFDS). Cilia. 2016;5:12. PubMed PMID: 27141300.

Gangaram B, Devine WP, Slavotinek A. Expanding the phenotype of males with OFD1 pathogenic variants-a case report and literature review. Eur J Med Genet. 2022;65:104496. PubMed PMID: 35398350.

Hannah WB, DeBrosse S, Kinghorn B, Strausbaugh S, Aitken ML, Rosenfeld M, Wolf WE, Knowles MR, Zariwala MA. The expanding phenotype of OFD1-related disorders: hemizygous loss-of-function variants in three patients with primary ciliary dyskinesia. Mol Genet Genomic Med. 2019;7:e911. PubMed PMID: 31373179.

Hasegawa R, Suzuki S, Nishimata S, Kashiwagi Y, Inagaki N, Kawashima H. A case of primary ciliary dyskinesia caused by a mutation in OFD1, which was diagnosed owing to Clostridium difficile infection. Pediatr Rep. 2021;13:241–4. PubMed PMID: 34068458.

Huang L-X, Lu X-G, Liu J-X, Xu L, Shang N, Guoa L, OuYang Y-C. Case report and a brief review: analysis and challenges of prenatal imaging phenotypes and genotypes in Joubert syndrome. Front Genet. 2022;13:1038274. PubMed PMID: 36468023.

Iaconis D, Monti M, Renda M, van Koppen A, Tammaro R, Chiaravalli M, Cozzolino F, Pignata P, Crina C, Pucci P, Boletta A, Belcastro V, Giles RH, Surace EM, Gallo S, Pende M, Franco B. The centrosomal OFD1 protein interacts with the translation machinery and regulates the synthesis of specific targets. Sci Rep. 2017;7:1224. PubMed PMID: 28450740.

Johnston JJ, Lee C, Wentzensen IM, Parisi MA, Crenshaw MM, Sapp JC, Gross JM, Wallingford JB, Biesecker LG. Compound heterozygous alterations in intraflagellar transport protein CLUAP1 in a child with a novel Joubert and oral-facial-digital overlap syndrome. Cold Spring Harb Mol Case Stud. 2017;3:a001321. PubMed PMID: 28679688.

Juric-Sekhar G, Adkins J, Doherty D, Hevner RF. Joubert syndrome: brain and spinal cord malformations in genotyped cases and implications for neurodevelopmental functions of primary cilia. Acta Neuropathol. 2012;123:695–709. PubMed PMID: 22331178.

Kane MS, Davids M, Bond MR, Adams CJ, Grout ME, Phelps IG, O'Day DR, Dempsey JC, Li X, Golas G, Vezina G, Gunay-Aygun M, Hanover JA, Doherty D, He M, Malicdan MCV, Gahl WA, Boerkoel CF. Abnormal glycosylation in Joubert syndrome type 10. Cilia. 2017;6:2. PubMed PMID: 28344780.

Li C, Wang X, Li F, Ding H, Liu L, Xiong Y, Yang C, Zhang Y, Wu J, Yin A. A novel non-sense variant in the OFD1 gene caused Joubert syndrome. Front Genet. 2023;13:1064762. PubMed PMID: 36704348.

Linpeng S, Liu J, Pan J, Cao Y, Teng Y, Liang D, Li Z, Wu L. Diagnosis of Joubert syndrome 10 in a fetus with suspected Dandy-Walker variant by WES: a novel splicing mutation in OFD1. BioMed Res Int. 2018;2018:4032543. PubMed PMID: 30581852.

Macca M, Franco B. The molecular basis of oral-facial-digital syndrome, type 1. Am J Med Genet C Semin Med Genet. 2009;151C:318–25. PubMed PMID: 19876934.

McLaughlin K, Neilly JB, Fox JG, Boulton-Jones JM. The hypertensive young lady with renal cysts--it is not always polycystic kidney disease. Nephrol Dial Transplant. 2000;15:1245–7. PubMed PMID: 10910455.

Meng C, Zhang KH, Ma J, Gao X, Yu K, Zhang HY, Wang Y, Zhang ZX, Li WG, Liu Y, Gai ZT. Zhonghua Er Ke Za Zhi. 2017;55:131–4. [Clinical and genetic analysis of a family with Joubert syndrome type 10 caused by OFD1 gene mutation]. PubMed PMID: 28173652.

Morleo M, Brillante S, Formisano U, Ferrante L, Carbone F, Iaconis D, Palma A, Buonomo V, Maione AS, Grumati P, Settembre C, Franco B. Regulation of autophagosome biogenesis by OFD1-mediated selective autophagy. EMBO J. 2021;40:e105120. PubMed PMID: 33368531.

Morleo M, Franco B. Dosage compensation of the mammalian X-chromosome influences the phenotypic variability of X-linked dominant male-lethal disorders. J Med Genet. 2008;45:401–8. PubMed PMID: 18463129.

Morleo M, Franco B. OFD Type I syndrome: lessons learned from a rare ciliopathy. Biochem Soc Trans. 2020;48:1929–39. PubMed PMID: 32897366.

Nishimura G, Kuwashima S, Kohno T, Teramoto C, Watanabe H, Kubota T. Fetal polycystic kidney disease in oro-facio-digital syndrome type I. Pediatr Radiol. 1999;29:506–8. PubMed PMID: 10398784.

Nowaczyk MJ, Zeesman S, Whelan DT, Wright V, Feather SA. Oral-facial-digital syndrome VII is oral-facial-digital syndrome I: a clarification. Am J Med Genet. 2003;123A:179–82. PubMed PMID: 14598343.

Pezzella N, Bove G, Tammaro R, Franco B. OFD1: one gene, several disorders. Am J Med Genet C Semin Med Genet. 2022;190:57–71. PubMed PMID: 35112477.

Prattichizzo C, Macca M, Novelli V, Giorgio G, Barra A, Franco B. Mutational spectrum of the oral-facial-digital type I syndrome: a study on a large collection of patients. Hum Mutat. 2008;29:1237–46. PubMed PMID: 18546297.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Romani M, Mancini F, Micalizzi A, Poretti A, Miccinilli E, Accorsi P, Avola E, Bertini E, Borgatti R, Romaniello R, Ceylaner S, Coppola G, D'Arrigo S, Giordano L, Janecke AR, Lituania M, Ludwig K, Martorell L, Mazza T, Odent S, Pinelli L, Poo P, Santucci M, Signorini S, Simonati A, Spiegel R, Stanzial F, Steinlin M, Tabarki B, Wolf NI, Zibordi F, Boltshauser E, Valente EM. Oral-facial-digital syndrome type VI: is C5orf42 really the major gene? Hum Genet. 2015;134:123–6. PubMed PMID: 25407461.

Saal S, Faivre L, Aral B, Gigot N, Toutain A, Van Maldergem L, Destree A, Maystadt I, Cosyns JP, Jouk PS, Loeys B, Chauveau D, Bieth E, Layet V, Mathieu M, Lespinasse J, Teebi A, Franco B, Gautier E, Binquet C, Masurel-Paulet A, Mousson C, Gouyon JB, Huet F, Thauvin-Robinet C. Renal insufficiency, a frequent complication with age in oral-facial-digital syndrome type I. Clin Genet. 2010;77:258–65. PubMed PMID: 19817772.

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. 2019;64:3–9. PubMed PMID: 30401917.

Scolari F, Valzorio B, Carli O, Vizzardi V, Costantino E, Grazioli L, Bondioni MP, Savoldi S, Maiorca R. Oral-facial-digital syndrome type I: an unusual cause of hereditary cystic kidney disease. Nephrol Dial Transplant. 1997;12:1247–50. PubMed PMID: 9198060.

Shamseldin HE, Shaheen R, Ewida N, Bubshait DK, Alkuraya H, Almardawi E, Howaidi A, Sabr Y, Abdalla EM, Alfaifi AY, Alghamdi JM, Alsagheir A, Alfares A, Morsy H, Hussein MH, Al-Muhaizea MA, Shagrani M, Al Sabban E, Salih MA, Meriki N, Khan R, Almugbel M, Qari A, Tulba M, Mahnashi M, Alhazmi K, Alsalamah AK, Nowilaty SR, Alhashem A, Hashem M, Abdulwahab F, Ibrahim N, Alshidi T, AlObeid E, Alenazi MM, Alzaidan H, Rahbeeni Z, Al-Owain M, Sogaty S, Seidahmed MZ, Alkuraya FS. The morbid genome of ciliopathies: an update. Genet Med. 2020;22:1051–60. PubMed PMID: 32055034.

Sharma S, Kalish JM, Goldberg EM, Reynoso FJ, Pradhan M. An atypical presentation of a male with oral-facial-digital syndrome type 1 related ciliopathy. Case Rep Nephrol. 2016;2016:3181676. PubMed PMID: 27651963.

Singla V, Romaguera-Ros M, Garcia-Verdugo JM, Reiter JF. OFD1, a human disease gene, regulates the length and distal structure of centrioles. Dev Cell. 2010;18:410–24. PubMed PMID: 20230748.

Srour M, Hamdan FF, McKnight D, Davis E, Mandel H, Schwartzentruber J, Martin B, Patry L, Nassif C, Dionne-Laporte A, Ospina LH, Lemyre E, Massicotte C, Laframboise R, Maranda B, Labuda D, Décarie JC, Rypens F, Goldsher D, Fallet-Bianco C, Soucy JF, Laberge AM, Maftei C. Care4Rare Canada Consortium; Boycott K, Brais B, Boucher RM, Rouleau GA, Katsanis N, Majewski J, Elpeleg O, Kukolich MK, Shalev S, Michaud JL. Joubert syndrome in French Canadians and identification of mutations in CEP104. Am J Hum Genet. 2015;97:744–53. PubMed PMID: 26477546.

Strong A, Simone L, Krentz A, Vaccaro C, Watson D, Ron H, Kalish JM, Pedro HF, Zackai EH, Hakonarson H. Expanding the genetic landscape of oral-facial-digital syndrome with two novel genes. Am J Med Genet A. 2021;185:2409–16. PubMed PMID: 34132027.

Suzuki T, Miyake N, Tsurusaki Y, Okamoto N, Alkindy A, Inaba A, Sato M, Ito S, Muramatsu K, Kimura S, Ieda D, Saitoh S, Hiyane M, Suzumura H, Yagyu K, Shiraishi H, Nakajima M, Fueki N, Habata Y, Ueda Y, Komatsu Y, Yan K, Shimoda K, Shitara Y, Mizuno S, Ichinomiya K, Sameshima K, Tsuyusaki Y, Kurosawa K, Sakai Y, Haginoya K, Kobayashi Y, Yoshizawa C, Hisano M, Nakashina M, Saitsu H, Takeda S, Matsumoto N. Molecular genetic analysis of 30 families with Joubert syndrome. Clin Genet. 2016;90:526–35. PubMed PMID: 27434533.

Thauvin-Robinet C, Cossee M, Cormier-Daire V, Van Maldergem L, Toutain A, Alembik Y, Bieth E, Layet V, Parent P, David A, Goldenberg A, Mortier G, Heron D, Sagot P, Bouvier AM, Huet F, Cusin V, Donzel A, Devys D, Teyssier JR, Faivre L. Clinical, molecular, and genotype-phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: a French and Belgian collaborative study. J Med Genet. 2006;43:54–61. PubMed PMID: 16397067.

Thauvin-Robinet C, Franco B, Saugier-Veber P, Aral B, Gigot N, Donzel A, Van Maldergem L, Bieth E, Layet V, Mathieu M, Teebi A, Lespinasse J, Callier P, Mugneret F, Lasurel-Paulet A, Gautier E, Huet F, Teyssier JR, Tosi M, Frebourg T, Faivre L. Genomic deletions of OFD1 account for 23% of oral-facial-digital type 1 syndrome after negative DNA sequencing. Hum Mutat. 2009;30:E320–9. PubMed PMID: 19023858.

Thauvin-Robinet C, Thomas S, Sinico M, Aral B, Burglen L, Gigot N, Dollfus H, Rossignol S, Raynaud M, Philippe C, Badens C, Touraine R, Gomes C, Franco B, Lopez E, Elkhartoufi N, Faivre L, Munnich A, Boddaert N, Van Maldergerm L, Encha-Razavi F, Lyonnet S, Vekemans M, Escudier E, Attié-Bitach T. OFD1 mutations in males: phenotypic spectrum and ciliary basal body docking impairment. Clin Genet. 2013;84:86–90. PubMed PMID: 23036093.

Tsurusaki Y, Kosho T, Hatasaki K, Narumi Y, Wakui K, Fukushima Y, Doi H, Saitsu H, Miyake N, Matsumoto N. Exome sequencing in a family with an X-linked lethal malformation syndrome: clinical consequences of hemizygous truncating OFD1 mutations in male patients. Clin Genet. 2013;83:135–44. PubMed PMID: 22548404.

Wang X, Zheng C, Liu W, Yang H. Retinitis pigmentosa and bilateral idiopathic demyelinating optic neuritis in a 6-year-old boy with OFD1 gene mutation. Case Rep Ophthalmol Med. 2017;2017:5310924. PubMed PMID: 28191358.

Webb TR, Parfitt DA, Gardner JC, Martinez A, Bevilacqua D, Davidson AE, Zito I, Thiselton DL, Ressa JH, Apergi M, Schwarz N, Kanuga N, Michaelides M, Cheetham ME, Gorin MB, Hardcastle AJ. Deep intronic mutation in OFD1, identified by targeted genomic next-generation sequencing, causes a severe form of X-linked retinitis pigmentosa (RP23). Hum Mol Genet. 2012;21:3647–54. PubMed PMID: 22619378.

Wentzensen IM, Johnston JJ, Patton JH, Graham JM, Sapp JC, Biesecker LG. Exome sequencing identifies a mutation in OFD1 in a male with Joubert syndrome, orofaciodigital spectrum anomalies and complex polydactyly. Hum Genome Var. 2016;3:15069. PubMed PMID: 27081566.

Yang B, Lei C, Yang D, Lu C, Xu Y, Wang L, Guo T, Wang R, Luo H. Identification of a novel variant in a patient with primary ciliary dyskinesia. Pharmgenomics Pers Med. 2022;15:697–704. PubMed PMID: 35847568.

Zhang H-W, Su B-G, Yao Y. OFD1 mutation induced renal failure and polycystic kidney disease in a pair of childhood male twins in China. World J Clin Cases. 2020;8:331–6. PubMed PMID: 32047782.

Zhang YW, Qu H, Long N, Leng X, Liu Y, Yang Y. A rare mutant of OFD1 gene responsible for Joubert syndrome with significant phenotype variation. Mol Genet Genomics. 2021;296:33–40. PubMed PMID: 32944789.

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