Atlas of Genetic Diagnosis and Counseling
DOI 10.1007/978-1-4614-6430-3_184-2


# Oral-Facial-Digital Syndrome

Harold Chen*
Medical Genetics, Shriners Hospitals for Children, Shreveport, LA, USA
Department of Pediatrics, Perinatal and Clinical Genetics, LSU Health Sciences Center, Shreveport, LA, USA

In 1941, Mohr reported a family in which the propositus had oral (high-arched palate, lobate tongue with papilliform outgrowths), facial (broad nasal root, hypertelorism), and digital (syndactyly, brachydactyly, polydactyly of the hands and feet) findings. This report was the first description of an oral-facial-digital syndrome (OFD). Mohr concluded that the condition was due to sex-linked recessive sublethal gene. A later report of the same family identified a similarly affected individual born to consanguineous parents, thus leading to the conclusion that the condition was inherited as an autosomal recessive trait, now known as OFD II or Mohr syndrome.

A similar phenotype, described by Papillon-Leage and Psaume in 1954, was identified as an X-linked dominant trait, now known as OFD I. After the identification of OFD I and OFD II, the phenotype spectrum was further expanded with extra oral-facial-digital manifestations, leading to the definition of the new types (Toriello 1988; Al-Qattan and Hassanain 1997). To date, 13 types have been distinguished based on the characteristic clinical manifestations. The oral-facial-digital syndromes result from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face, and digits.

## Synonyms and Related Disorders

OFD I (papillon-Leage-Psaume syndrome); OFD II (Mohr syndrome); OFD III (Sugarman syndrome); OFD IV (Baraitser-Burn syndrome or Mohr-Majewski syndrome); OFD V (Thurston syndrome); OFD VI (Varadi-Papp syndrome); OFD VII (Whelan syndrome); OFD VIII (Edwards syndrome); OFD IX (Gurrieri syndrome); OFD X (Figuera syndrome); OFD XI (Gabrielli syndrome); OFD XII (Moran-Barroso syndrome); OFD XIII (Degner syndrome); OFD XIII (Degner syndrome); OFD XIV; Orofaciodigital syndrome (OFD)

## Genetics/Basic Defects

1. OFD I (Papillon-Leage-Psaume syndrome) (Wahrman et al. 1966): X-linked dominant (lethal in males): *OFD1* is the only gene currently known to be associated with oral-facial-digital syndrome type I. Caused by mutation in the OFD1 protein gene (Rakkolainen et al. 2002; Romio et al. 2003)
2. OFD II (Mohr syndrome): autosomal recessive
3. OFD III (Sugarman syndrome): autosomal recessive
4. OFD IV (Mohr-Majewski syndrome, Baraitser-Burn syndrome): autosomal recessive, caused by mutation in the TCTN3 gene
5. OFD V (Thurston syndrome): autosomal recessive, caused by mutation in the DDX59 gene
6. OFD VI (Varadi-Papp syndrome): autosomal recessive, caused by mutation in the C5ORF42 gene
7. OFD VII (Whelan syndrome): autosomal or X-linked dominant

*Email: hchen@lsuhsc.edu

DOI 10.1007/978-1-4614-6430-3_184-2


8. OFD VIII (Edwards syndrome): X-linked recessive
9. OFD IX (Gurrieri syndrome): X-linked recessive
10. OFD X (Figuera syndrome): autosomal dominant
11. OFD XI (Gabrielli syndrome): isolated cases
12. OFD XII (Moran-Barroso syndrome): autosomal recessive
13. OFD XIII (Degner syndrome): autosomal recessive
14. OFD XIV: autosomal recessive, caused by mutation in the C2CD3 gene on chromosome 11q13 (Thauvin-Robinet et al. 2014)

## Clinical Features

1. OFD I (Papillon-Leage-Psaume syndrome) (Gorlin and Psaume 1962; al-Qattan and Hassanain 1997; Ferrante et al. 2001; Thauvin-Robinet et al. 2006; Gurrieri et al. 2007; Papagrigoraskis et al. 2010; John et al. 2013; Toriello and Franco 2013)
    1. Characterized by anomalies of the face, oral cavity, and digits with a high degree of phenotypic variability even within the same family, possibly due to different degrees of somatic mosaicism resulting from random X-inactivation
    2. Abnormalities of the oral cavity: primarily affecting the tongue, palate, and teeth
        1. Lobed tongue often described as bifid or trifid.
        2. Tongue nodules, usually hamartomas or lipomas, also occur in at least one third of individuals.
        3. Ankyloglossia attributable to a short lingual frenulum common
        4. Cleft hard or soft palate, submucous cleft palate, or highly arched palate: occurring in more than 50 % of affected individuals.
        5. Trifurcation of the soft palate reported.
        6. Alveolar clefts and accessory gingival frenula are common. These fibrous bands are hyperplastic frenula extending from the buccal mucous membrane to the alveolar ridge, resulting in notching of the alveolar ridges.
        7. Dental abnormalities include missing teeth (most common), extra teeth, enamel dysplasia, and malocclusion.
    3. Craniofacial abnormalities
        1. Median pseudoclefting of the upper lip
        2. Irregular margin of the lips
        3. Facial asymmetry
        4. Downslanting palpebral fissures
        5. Ocular hypertelorism
        6. Telecanthus
        7. Micrognathia
        8. Broadened nasal ridge
        9. Hypoplasia of the malar bones and nasal alar cartilages
        10. Frontal bossing
        11. Vanishing milia of the face and ears, usually disappear before the third year of life
        12. Dryness, brittleness, and/or alopecia of the scalp hair
    4. Digital abnormalities
        1. Brachydactyly.
        2. Syndactyly of varying degrees.

DOI 10.1007/978-1-4614-6430-3_184-2


3. Clinodactyly of the fifth finger.
4. The third (i.e., middle ) finger showing variable radial or ulnar deviation.
5. Duplicated hallux (great toe) occurs in fewer than 50 % of affected individuals but if present is usually unilateral.
6. Preaxial or postaxial polydactyly of the hands occurring in 1–2 % of affected individuals.
7. Radiographs of the hands often demonstrate fine reticular radiolucencies, described as irregular mineralization of the bone, with or without spicule formation of the phalanges.

5. Other associated anomalies
   1. CNS anomalies (Towfighi et al. 1985; Holubu et al. 2005):
      1. Microcephaly
      2. Intracerebral cysts
      3. Agenesis of the corpus callosum
      4. Cerebellar agenesis with or without Dandy-Walker malformation
      5. Type 2 porencephaly (schizencephalic porencephaly)
      6. Pachygyria and heterotopias
      7. Hydrocephalus
      8. Cerebral or cerebellar atrophy
      9. Berry aneurysms
   2. Intelligence: about 50 % of individuals with OFD1 with some degree of mental retardation or learning disability.
   3. Polycystic kidney disease (Connacher et al. 1987; Donnai et al. 1987; Feather et al. 1997): occurring in fewer than 50 % of individuals with OFD1. Renal cysts can develop from both tubules and glomeruli, most often in adulthood.

2. OFD II (Mohr syndrome) (Mohr 1941; Rimoin and Edgerton 1967; Goldstein and Medina 1974; Silengo et al. 1987; Gillerot and Koulischer 1988; Prpic et al. 1995; Balci et al. 1999; Hsieh and Hou 1999)
   1. Oral anomalies
      1. Lobulated/cleft tongue
      2. Tongue hamartomas
      3. Duplicated frenulum
      4. Absent central incisors
   2. Facial anomalies: bifid nasal tip
   3. Digital anomalies (Michels et al. 1985)
      1. Hands: clinodactyly, syndactyly, polydactyly
      2. Feet: preaxial or postaxial polydactyly, synpolydactyly, of both big toes
   4. CNS anomalies
      1. Hydrocephalus
      2. Porencephaly
      3. Mental retardation
   5. Features overlapping with OFD I
      1. Orofacial manifestations: tongue nodules, midline clefts of the lip, thick frenula, and dystopia canthorum
      2. Digital manifestations: clinobrachydactyly, syndactyly, and polydactyly
   6. Subtle clinical differences between types I and II
      1. Greater thickness of the alveolar ridge than in type I, which is normal in type II.
      2. Presence of hair and skin abnormalities in type I.

DOI 10.1007/978-1-4614-6430-3_184-2


3. Presence of bilateral polysyndactyly of the halluces in type II rather than unilateral polysyndactyly, which is usually found in type I.
4. Conductive hearing impairment may occur in type II.
5. Central nervous system can also be affected in this form mainly with porencephaly and hydrocephaly.

7. Distinctive difference in the mode of inheritance: OFD type II is caused by mutations of an as yet unidentified autosomal recessive gene versus X-linked dominant inheritance in OFD type I.
8. Expanding phenotype spectrum in OFD type II: congenital heart defects such as atrioventricular canal and endocardial cushion defects.
9. A Y-shaped central metacarpal, usually considered typical of OFD type VI, has also been reported in patients with clinical characteristics falling within the OFD II spectrum, suggesting the existence of transitional OFD types that may turn out to be allelic forms once the genetic defects of all OFD types are discovered.

3. OFD III (Sugarman syndrome) (Sugarman et al. 1971; Sugarman 1983; Smith and Gardner-Medwin 1993)
   1. Oral anomalies
      1. Lobulated tongue with hamartoma
      2. Cleft palate
      3. Extra small teeth
   2. Facial anomalies
      1. Hypertelorism
      2. Broad nose
      3. Choanal atresia
      4. Low-set ears
   3. Digital anormalies
      1. Hands: oligodactyly, syndactyly
      2. Feet: postaxial polydactyly
   4. CNS anomalies
      1. Dandy-Walker malformation
      2. Cerebellar anomalies
      3. Ceaseless seesaw (continuous alternating) winking of the eyelids
      4. Myoclonic jerks
      5. Mental retardation
   5. Other features: short sternum, hyperconvex nails
4. OFD IV (Mohr-Majewski syndrome, Baraitser-Burn syndrome) (oral-facial-digital syndrome with tibial defects) (Burn et al. 1984; Baraitser et al. 1986; Nevin and Thomas 1989; Meinecke and Hayek 1990; Nevin et al. 1992; Ades et al. 1994; Digilio et al. 1995; Toriello et al. 1997; Moerman and Fryns 1998; Tuysuz et al. 1999)
   1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
   2. Minor facial anomalies: hypertelorism, broad nose, epicanthal folds, micrognathia, low-set ears
   3. Digital anomalies: hands (polydactyly), feet (preaxial and postaxial polydactyly, clubfoot)
   4. Mesomelic limb shortening limited to tibial defects (tibial dysplasia)
   5. Other features: joint dislocations, pectus excavatum, short stature
   6. Expansion of phenotypic spectrum
      1. Occipitoschisis
      2. Brain malformation (porerncephaly, cerebral atrophy)
      3. Hearing loss

DOI 10.1007/978-1-4614-6430-3_184-2


4. Ocular colobomas
5. Hypoplastic epiglottis
6. Intrahepatic cyst
7. Renal cysts
8. Anal atresia
9. Joint dislocations

5. OFD V (Thurston syndrome) (Thurston 1909; Khoo and Saad 1980; John et al. 2013)
   1. The mildest form within the OFD group
   2. Oral anomalies
      1. Median cleft lip
      2. Duplicated frenulum
      3. Enamel hypoplasia
      4. High-arched palate
      5. Supernumerary teeth
   3. Postaxial polydactyly of the hands and feet
   4. Normal intelligence
   5. Reported exclusively in individuals of Indian ethnicity
6. OFD VI (Varadi-Papp syndrome) (Varadi et al. 1980; Muenke et al. 1990, 1991; Toriello 1993; Stephens et al. 1994; Wey et al. 1994; Doss et al. 1998)
   1. Distinguished features
      1. First report in endogamic gypsies
      2. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip, deep palate
      3. Facial anomalies: microphthalmia, micrognathia
      4. Digital anomalies
         1. Clinodactyly and syndactyly of the hands
         2. Y-shaped metacarpals/metatarsals: forked third or fourth metacarpals/metatarsals, indicating central polydactyly
      5. Expanded phenotype spectrum
         1. Penile agenesis (Yildirim et al. 2002).
         2. Abnormal clavicles.
         3. Vermis hypoplasia/aplasia.
         4. Dandy-Walker anomaly.
         5. Absent pituitary gland (Al-Gazali et al. 1999).
         6. Hypothalamic hamartoma with precocious puberty, which is almost constantly found in Pallister-Hall syndrome, an autosomal dominant condition characterized by postaxial polydactyly, imperforate anus, and hypothalamic hamartoma. The phenotypic overlap between OFD VI and Pallister-Hall syndrome has been noted, and lumping of the two conditions as the same entity has been proposed.
         7. GLI3 mutations identified in Pallister-Hall syndrome suggest that GLI3 analysis should also be carried out in patients with OFD VI to find out if these two conditions are allelic.
         8. A single report of neuropathologic findings in OFD VI showed disruption or dysgenesis of glial architecture, suggesting a primary glial cell defect. This observation is interesting in light of the recent discovery that OFD I is caused by a failure of the ciliary system, which is involved in cellular migration during embryogenesis.
      6. Represents a rare phenotypic subtype of Joubert syndrome and related disorders

DOI 10.1007/978-1-4614-6430-3_184-2


2. Diagnostic criteria (Poretti et al. 2012)
    1. Molar tooth sign (a neuroanatomical feature characterized by thickened, elongated, and horizontally located superior cerebellar peduncles and an abnormally deep interpeduncular fossa) and one or more of the following:
    2. Tongue hamartoma(s) and/or additional frenula and/or upper lip notch
    3. Mesoaxial polydactyly of one or more hands or feet
    4. Hypothalamic hamartoma
7. OFD VII (Whelan syndrome) (Whelan et al. 1975; Nowaczyk et al. 2003): a single report of mother and daughter
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, cleft palate, median cleft lip
    2. Facial anomalies: asymmetry of the face, hypertelorism
    3. Digital anomalies: clinodactyly of the hands
    4. Preauricular skin tag
    5. Hydronephrosis
    6. Possibly same entity as OFD 1 since mother and daughter later developed cystic kidney disease, although mutation analysis for OFD I failed to detect a pathogenic mutation
8. OFD VIII (Edwards syndrome) (Edwards et al. 1988; Toriello 1993)
    1. Oral anomalies: lobulated tongue with hamartoma, median cleft lip, missing teeth
    2. Facial anomalies: telecanthus, broad/bifid nose
    3. Digital anomalies: hands (pre- or postaxial polydactyly), feet (preaxial polydactyly)
    4. Limb anomalies: short tibiae and radii
    5. Other features: delay of developmental milestones, hypoplastic epiglottis
    6. Distinguished from OFD II by X-linked recessive inheritance
9. OFD IX (Gurrieri syndrome) (Gurrieri et al. 1992; Nevin et al. 1994; Nagai et al. 1998)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. Facial anomalies: hypertelorism
    3. Retinal anomaly (colobomata): a distinctive feature
    4. Digital anomalies: hands (brachydactyly, postaxial oligodactyly), feet (usually consist of hallucal duplication detectable radiologically)
10. OFD X (Figuera syndrome) (Figuera et al. 1993)
    1. Oral anomalies: Cleft palate, duplicated frenulum
    2. Facial anomalies: telecanthus
    3. Digital anomalies: hands and feet (preaxial polydactyly and postaxial oligodactyly)
    4. Limb anomaly: fibular agenesis
11. OFD XI (Gabrielli syndrome) (Gabrielli et al. 1994; Ferrero et al. 2002): in addition to the oral, facial, and digital anomalies, this type is characterized by following craniovertebral anomalies:
    1. Oral anomalies: bifid tongue, duplicated frenulum, median cleft lip, cleft palate, midline cleft extending to ethmoid and crista galli
    2. Facial anomalies: wide nose, bulbous tip, hypertelorism, blepharophimosis, deformed earlobes
    3. Digital anomalies: postaxial polydactyly of the hands and feet
    4. Additional anomalies
        1. Apophysis
        2. Vertebral malformations
            1. Fusion of vertebral arches in C1, C2, and C3
            2. Clefts of vertebral bodies
        3. Conductive deafness, cardiac interventricular septal hypertrophy, mucosal subaortic spur

DOI 10.1007/978-1-4614-6430-3_184-2


12. OFD XII (Moran-Barroso syndrome) (Moran-Barroso et al. 1998)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. Myelomeningocele
    3. Stenosis of the aqueduct of Sylvius
    4. Cardiac anomalies
13. OFD XIII (Degner syndrome) (Degner et al. 1999)
    1. Oral anomalies: lobulated tongue with hamartoma, duplicated frenulum, median cleft lip
    2. CNS anomalies
        1. Psychiatric symptoms (major depression)
        2. Epilepsy
        3. 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)
14. OFD XIV (Thauvin-Robinet et al. 2014)
    1. Craniofacial: microcephaly, trigonocephaly, facial dysmorphism, telecanthus, upslanting palpebral fissures, retinitis, cleft palate, cleft tongue, lobulated tongue, lingual hamartoma, buccal frenule, absent epiglottis, supernumerary teeth
    2. Genitourinary: micropenis
    3. Skeletal; postaxial polydactyly of hands, broad/duplicated halluces
    4. CNS: severe intellectual disability, corpus callosum hypoplasia, vermian hypoplasia, molar tooth sign, subarachnoid cysts, incomplete myelinization

## Diagnostic Investigations

1. Diagnostic approach
    1. First, ascertain oral, facial, and digital findings.
    2. Obtain family history to determine if a mode of inheritance can be established.
    3. In patients with clear X-linked dominant transmission and even in sporadic female patients, it is necessary to rule out mutations in the OFD1 gene.
    4. Additional studies to delineate specific type, given the fragmentary nosology of OFD.
        1. Brain MRI
        2. Abdominal ultrasound
        3. Skeletal survey
        4. Ophthalmologic evaluation
        5. Audiometric test
        6. Chromosome analysis to detect submicroscopic rearrangements by array-CGH analysis
2. Diagnosis of OFD I (Toriello and Franco 2013)
    1. Established at birth in some infants on the basis of characteristic oral, facial, and digital anomalies
    2. Diagnosis is suspected in some patients only after polycystic kidney disease is identified in later childhood or adulthood
    3. Molecular genetic testing (sequence analysis and duplication/deletion analysis) of *OFD1*, the only gene currently known to be associated with OFD I: clinically available for confirmatory diagnostic testing and prenatal diagnosis of OFDI
3. Diagnosis of OFD VII (includes unilateral cleft lip and hydronephrosis, only been described in one mother-daughter pair, who were later found to have a mutation in *OFD1*): either allelic to OFD1 or demonstrates variable expression of OFD1

DOI 10.1007/978-1-4614-6430-3_184-2


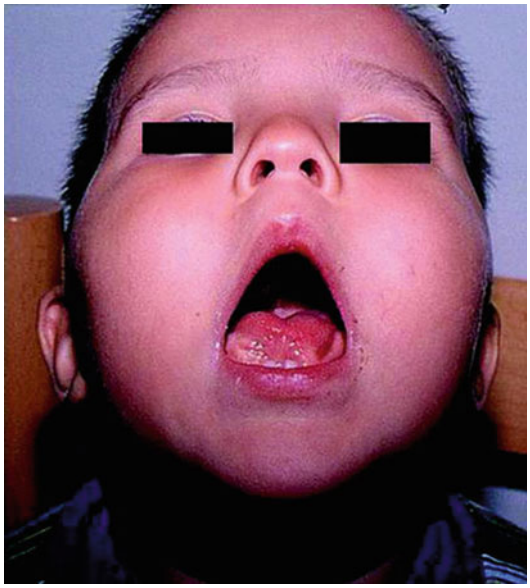

**Fig. 1** Patient 1 with OFD I. Note the lingual frenulum and hypoplastic alar nasi

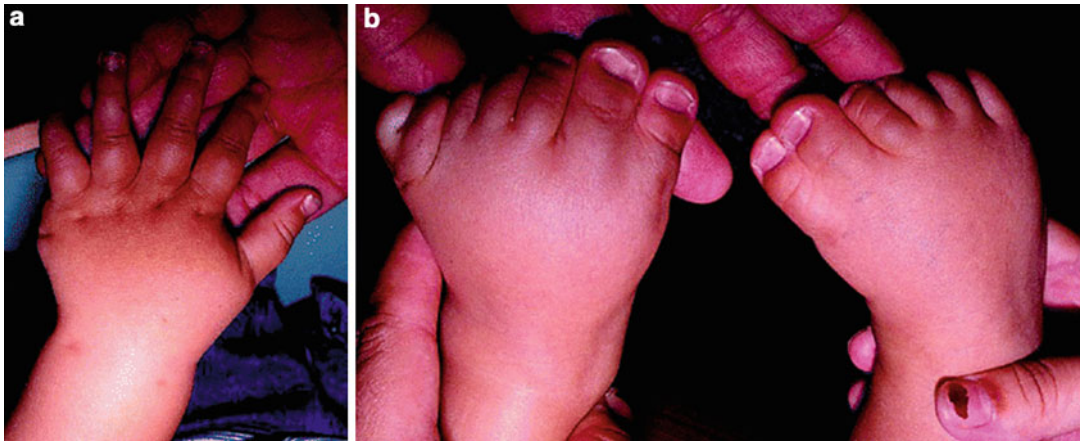


**Fig. 2** (**a**, **b**) The patient's bilateral postaxial polydactyly of both hands, duplicated hallux of both feet, and postaxial polydactyly of the left foot

## Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive (OFD types II, III, IV, V, VI, possibly types XI, XII, XIII)
            1. A 25 % risk
            2. A 50 % risk of being a carrier
        2. Autosomal dominant (OFD X)
            1. A small recurrence risk if neither parent is affected
            2. A 50 % risk if one parent is affected
        3. X-linked dominant with male lethality (OFD I, OFD VII) (Toriello and Franco 2013)
            1. Approximately 75 % of affected individuals are simplex cases (no family history of OFD1).

DOI 10.1007/978-1-4614-6430-3_184-2


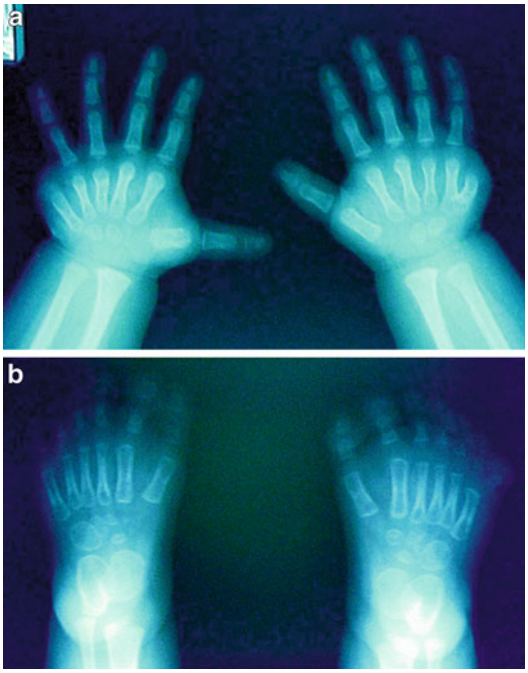


**Fig. 3** (**a**, **b**) Radiographs of hands and feet of patient 1

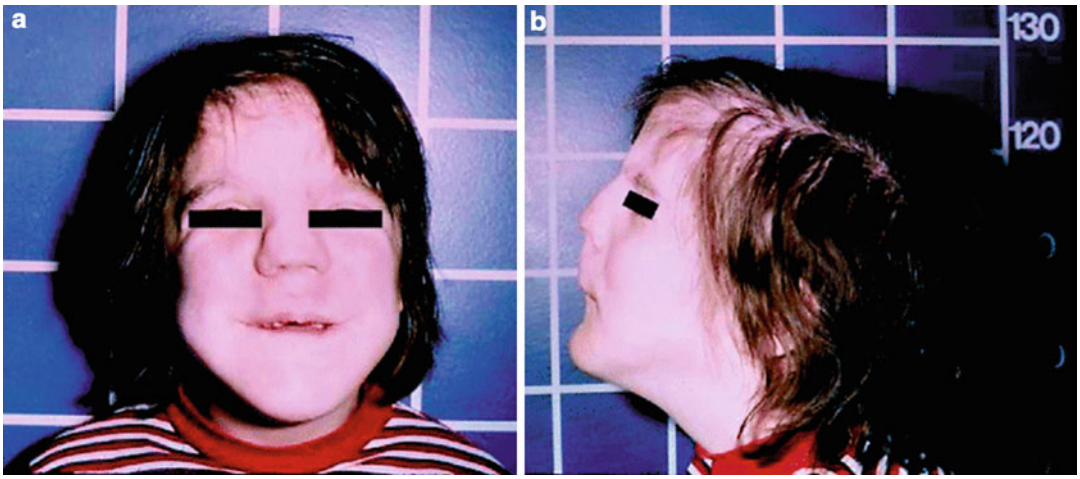


**Fig. 4** (**a**, **b**) Patient 2 with OFD II. Note bifid nasal tip, medial cleft of the upper lip, and ocular hypertelorism

2. A female proband with OFD1 may have the disorder as the result of a de novo gene mutation; however, the proportion of cases caused by de novo mutations is unknown.
3. When the mother of an affected female is also affected, the risk to sibs of inheriting the disease-causing *OFD1* allele at conception is 50 %; however, most male conceptuses with the disease-causing *OFD1* allele miscarry (Macca and Franco 2009). Thus, at delivery the expected sex ratio of offspring is 33 % unaffected females; 33 % affected females; 33 % unaffected males.
4. If no family history of OFD1 exists, the risk that the unaffected mother of an affected female will have another female with OFD1 is less than 1 %.

DOI 10.1007/978-1-4614-6430-3_184-2


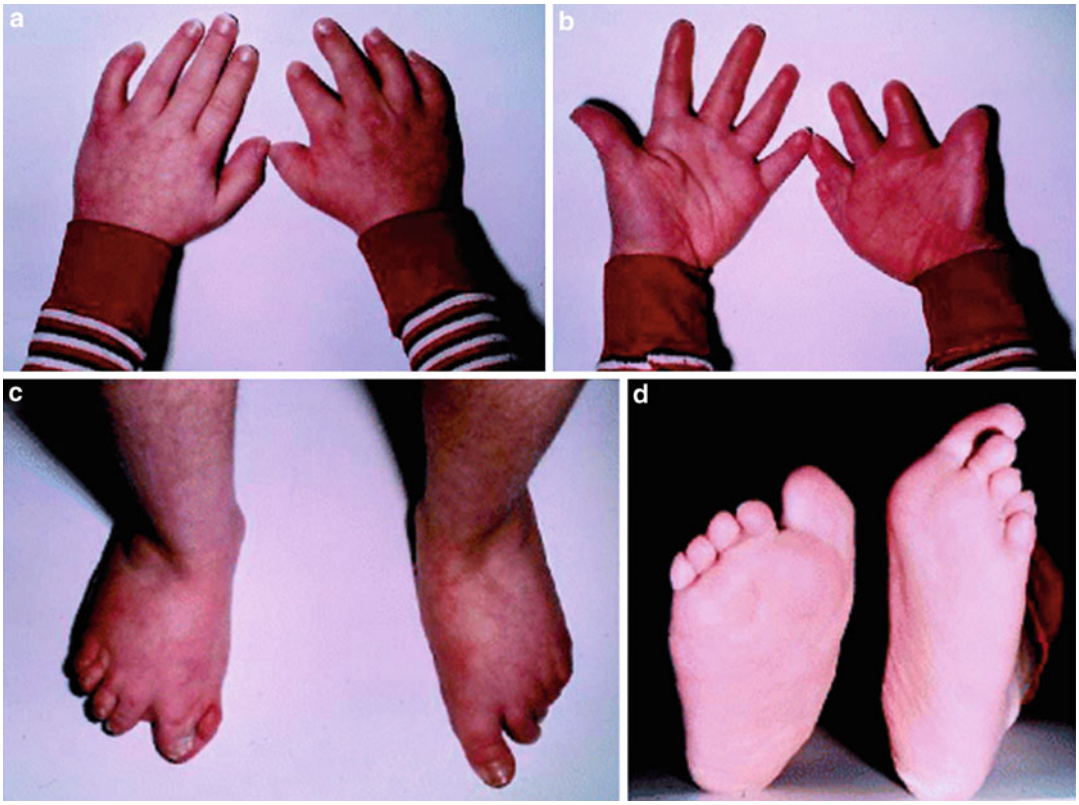


**Fig. 5** (**a**–**d**) Note the clinobrachydactyly and syndactyly of the hands and polydactyly of the right hallux

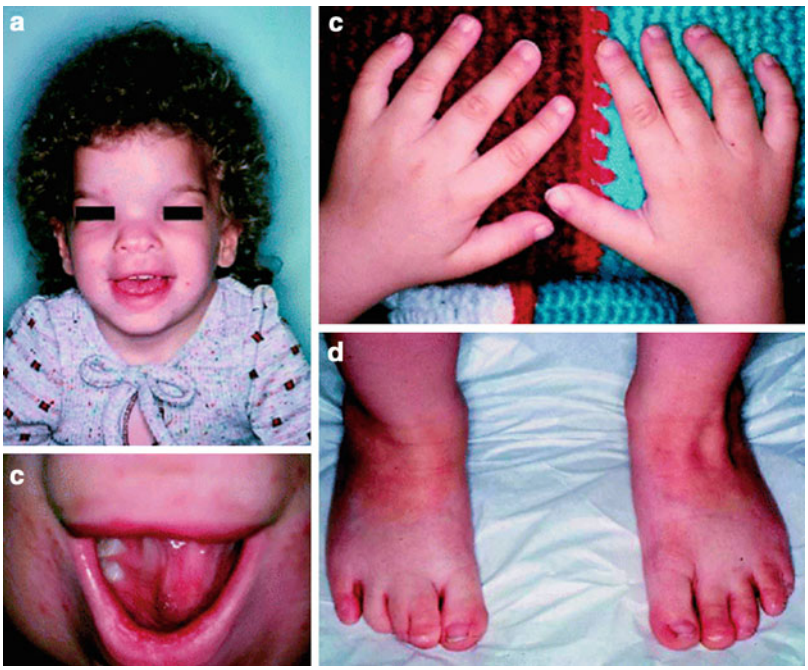


**Fig. 6** (**a**–**d**) Patient 3 with OFD II. Note the ocular hypertelorism, bifid tip of the nose, lingual frenulum, and brachysyndactyly

DOI 10.1007/978-1-4614-6430-3_184-2


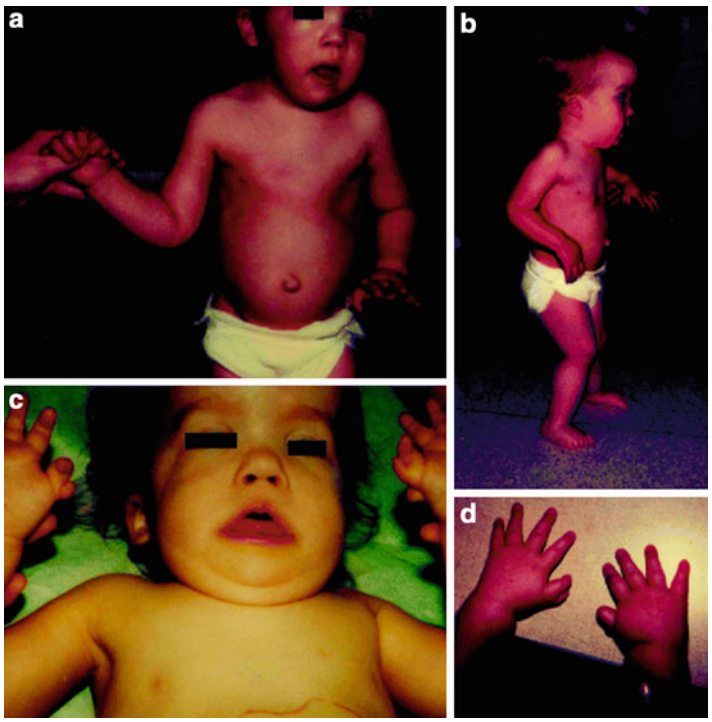


**Fig. 7** (**a**–**d**) Patient 4 with unclassified OFD. Note frontal bossing, ocular hypertelorism, strabismus, pseudocleft of the upper lip, preaxial polydactyly of the hands, hepatomegaly, and genu valgum

4. X-linked recessive (OFD VIII): risk to the sibs depending on the carrier status of the mother
    1. Mother is a carrier: a 50 % of risk of having a male sib with OFD VIII
    2. Mother is not a carrier: a low recurrence risk
2. Patient's offspring
    1. Autosomal recessive: a low recurrence risk unless the spouse is also affected or a carrier
    2. Autosomal dominant: a 50 % risk if the spouse is normal
    3. X-linked dominant with male lethality (Toriello and Franco 2013)
        1. At conception, the risk to the offspring of females with OFD1 of inheriting the disease-causing OFD1 allele is 50 %; however, most male conceptuses with the disease-causing allele miscarry.
        2. At delivery, the expected sex ratio of offspring: 33 % unaffected females, 33 % affected females, and 33 % unaffected males.
    4. X-linked recessive
        1. No sons will be affected.
        2. All daughters will be carriers.
2. Prenatal diagnosis
    1. Prenatal ultrasound
        1. Prenatal diagnosis of OFD type II reported in a fetus
            1. Polydactyly with bifid thumbs in both hands
            2. Bilateral polysyndactyly of halluces
            3. Lateral polysyndactyly and bilateral pes equinovarus
        2. Prenatal diagnosis of OFD type IV (Mohr-Majewski) possible: findings showing overlap between OFD type II (Mohr) and lethal short rib-polydactyly syndrome type II (Majewski) (Rosing et al. 2008)

DOI 10.1007/978-1-4614-6430-3_184-2


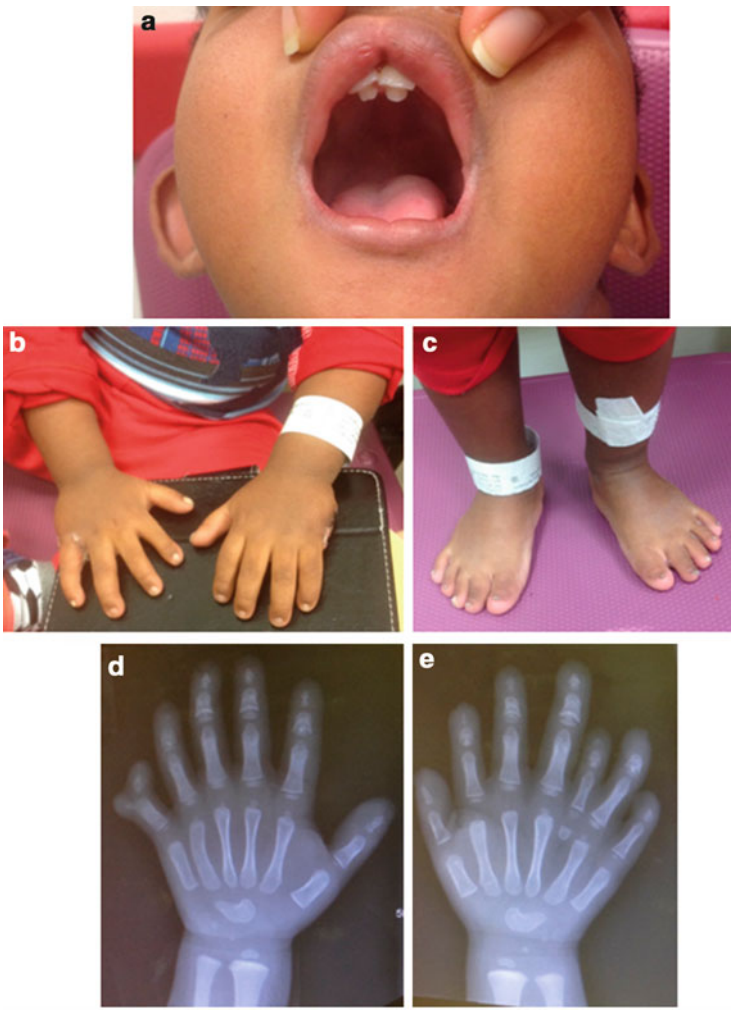


**Fig. 8** (**a**–**e**) This 3-year-old Hispanic boy from Panama was seen for abnormal dentition and brachydactyly and polydactyly of both hands. Orofacial features were characterized by slight hypertelorism, flat nasal bridge, and presence of median pseudocleft of the upper lip and double rows of upper central incisors with absence of other teeth (**a**). Radiographic imaging of oromandibular areas with panoramic and cephalometric projection showed no permanent maxillary laterals and complete absence of all central and lateral mandibular teeth (not shown). The fingers were short with postaxial polydactyly of both hands (seven fingers on the right and six fingers on the left with duplicated distal end of the last finger) (Status post incision of polydactylies and post reconstruction of both hands is shown here) (**b**). There was no polydactyly of the toes, but the great toes were slightly broad. Radiograph of left hand (**d**) showed duplication of the fifth ray with dysplasia and hypoplasia of the distal and middle phalanges. Radiograph of the right hand (**e**) showed duplication of the fourth and fifth rays with dysplasia and hypoplasia of the distal and middle phalanges. Dysplastic fusion of the capitate and hamate was present in both wrists (**d, e**)

    3. Prenatal ultrasound examination of OFD type I (Toriello and Franco 2013) may detect structural brain malformations (Shipp et al. 2000) and/or duplication of the hallux.
  2. Molecular genetic analysis: prenatal diagnosis and preimplantation genetic diagnosis for families in which the disease-causing mutation has been identified is clinically available.
3. Management (Toriello and Franco 2013)
  1. Surgery
    1. Cleft lip/palate
    2. Tongue nodules
    3. Accessory frenula

DOI 10.1007/978-1-4614-6430-3_184-2


4. Polysyndactyly
5. Removal of accessory teeth
6. Orthodontia for malocclusion

2. Management of renal disease and seizures
3. Speech therapy
4. Special education
5. Surveillance
    1. Annual monitoring of renal function
    2. Speech and hearing assessment if cleft palate is present

## References

Ades, L. C., Clapton, W. K., Morphett, A., et al. (1994). Polydactyly, campomelia, ambiguous genitalia, cystic dysplastic kidneys, and cerebral malformation in a fetus of consanguineous parents: A new multiple malformation syndrome, or a severe form of oral-facial-digital syndrome type I. *American Journal of Medical Genetics, 49*, 211–217.

Al-Gazali, L. I., Sztriha, L., Punnose, J., et al. (1999). Absent pituitary gland and hypoplasia of the cerebellar vermis associated with partial ophtalmoplegia and postaxial polydactyly: A variant of orofaciodigital syndrome type VI or a new syndrome? *Journal of Medical Genetics, 36*, 161–166.

Al-Qattan, M. M., & Hassanain, J. M. (1997). Classification of limb anomalies in oral-facial-digital syndromes. *Journal of Hand Surgery, 22B*(2), 250–252.

Balci, S., Guler, G., Kale, G., et al. (1999). Mohr syndrome in two sisters: Prenatal diagnosis in a 22-week-old fetus with postmortem findings in both. *Prenatal Diagnosis, 19*, 827–831.

Baraitser, M. (1986). The orofaciodigital (OFD) syndromes. *Journal of Medical Genetics, 23*(116–119), 1986.

Burn, J., Dezateux, C., Hall, C. M., et al. (1984). Orofaciodigital syndrome with mesomelic limb shortening. *Journal of Medical Genetics, 21*, 189–192.

Connacher, A. A., Forsyth, C. C., & Stewart, W. K. (1987). Orofaciodigital syndrome type 1 associated with polycystic kidneys and agenesis of the corpus callosum. *Journal of Medical Genetics, 24*, 116–118.

Degner, D., Bleich, S., RIegel, A., et al. (1999). Orofaciodigital syndrome: A new variant? Psychiatric neurologic and neuroradiological findings. *Fortschritte der Neurologie-Psychiatrie, 67*, 525–528.

Digilio, M. C., Giannotti, A., Pagnotta, G., et al. (1995). Joint dislocation and cerebral anomalies are consistently associated with oral-facial-digital syndrome type IV. *Clinical Genetics, 48*, 156–159.

Donnai, D., Kerzin-Storrar, L., & Harris, R. (1987). Familial orofaciodigital syndrome type I presenting as adult polycystic kidney disease. *Journal of Medical Genetics, 24*, 84–87.

Doss, B. J., Jolly, S., Qureshi, F., et al. (1998). Neuropathologic findings in OFDS type VI (Varadi syndrome). *American Journal of Medical Genetics, 77*, 38–42.

Edwards, M., Mulcahy, D., & Turner, G. (1988). X-linked recessive inheritance of an orofaciodigital syndrome with partial expression in females and survival of affected males. *Clinical Genetics, 43*, 325–332.

Feather, S. A., Winyard, P. J., Dodd, S., et al. (1997). Oral-facial-digital syndrome type 1 is another dominant polycystic kidney disease: Clinical, radiological and histopathological features of a new kindred. *Nephrology, Dialysis, Transplantation, 12*, 1354–1361.

Ferrante, M. I., Giorgio, G., Feather, S. A., et al. (2001). Identification of the gene for oral-facial-digital type I syndrome. *American Journal of Human Genetics, 68*, 569–576.

DOI 10.1007/978-1-4614-6430-3_184-2


Ferrero, G. B., Valenzise, M., Franco, B., et al. (2002). Oral, facial, digital, vertebral anomalies with psychomotor delay: A mild form of OFD type Gabrielli? *American Journal of Medical Genetics, 113*, 291–294.

Figuera, L. E., Rivas, F., & Cantu, J. M. (1993). Oral-facial-digital syndrome with fibular aplasia: A new variant. *Clinical Genetics, 44*, 190–192.

Gabrielli, O., Ficadenti, A., Fabrizzi, G., et al. (1994). Child with oral, facial, digital, and skeletal anomalies and psychomotor delay: A new OFDS form? *American Journal of Medical Genetics, 53*, 290–293.

Gillerot, Y., & Koulischer, L. (1988). Oro-facial-digital syndrome II. *Clinical Genetics, 33*, 141–142.

Goldstein, E., & Medina, J. L. (1974). Mohr syndrome or oral-facial-digital II: Report of two cases. *The Journal of the American Dental Association, 89*, 377–382.

Gorlin, R. J., & Psaume, J. (1962). Orofaciodigital dysostosis: A new syndrome. A study of 22 cases. *Journal of Pediatrics, 61*, 520–530.

Gurrieri, F., Sammito, V., Ricci, B., et al. (1992). Possible new type of oral-facial-digital syndrome with retinal abnormalities: OFDS type VIII. *American Journal of Medical Genetics, 42*, 789–792.

Gurrieri, F., Franco, B., Toriello, H., et al. (2007). Oral-facial-digital syndromes: Review and diagnostic guidelines. *American Journal of Medical Genetics Part A, 143A*, 3314–3323.

Holub, M., Potocki, L., & Bodamer, O. A. (2005). Central nervous system malformations in oral-facial-digital syndrome, type 1. *American Journal of Medical Genetics Part A, 136A*, 218.

Hsieh, Y., & Hou, J. (1999). Oral-facial-digital syndrome with Y-shaped fourth metacarpals and endocardial cushion defect. *American Journal of Medical Genetics, 86*, 278–281.

John, J. R., Kumar, P., & Sharma, R. K. (2013). Thurston syndrome: an uncommon disorder presenting with common abnormalities. *The Journal of Craniofacial Surgery, 24*, e132–e134.

Khoo, C. T. K., & Saad, M. L. (1980). Median cleft of the upper lip in association with bilateral hexadactyly and accessory toes. *British Journal of Plastic Surgery, 33*, 407–409.

Macca, M., & Franco, B. (2009). The molecular basis of oral-facial-digital syndrome, type 1. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 151C*, 318–325.

Meinecke, P., & Hayek, H. (1990). Orofaciodigital syndrome type IV (Mohr-Majewski syndrome) with severe expression expanding the known spectrum of anomalies. *Journal of Medical Genetics, 27*, 200–202.

Michels, V. V., Suther, A. A., & Puffer, M. J. (1985). Polysyndactyly in the orofacial digital syndrome, type II. *The Journal of Clinical Dysmorphology, 3*, 2–9.

Moerman, P., & Fryns, J. P. (1998). Oral-facial-digital syndrome type IV (Mohr-Majewski syndrome): A fetopathological study. *Genetic Counseling, 9*, 39–43.

Mohr, O. L. (1941). A hereditary sublethal syndrome in man. *Skr Norske Vidensk Akad, I Mat-Naturv, 14*, 3.

Moran-Barroso, V., Valdes Flores, M., Garcia-Cavazos, R., et al. (1998). Oral-facial-digital (OFD) syndrome with associated features: A new syndrome or genetic heterogeneity and variability? *Clinical Dysmorphology, 7*, 55–57.

Muenke, M., McDonald, D. M., Cronister, A., et al. (1990). Oral-facial-digital syndrome type VI (Varadi syndrome): Further clinical delineation. *American Journal of Medical Genetics, 35*, 360–369.

Muenke, M., Ruchelle, E. D., Rorke, L. B., et al. (1991). On lumping and splitting: A fetus with clinical findings of the oral-facial-digital syndrome type VI, the hydrolethalus syndrome and Pallister-Hall syndrome. *American Journal of Medical Genetics, 41*, 548–556.

Nagai, K., Nagao, M., Yanai, S., et al. (1998). Oral-facial-digital syndrome type IX in a patient with Dandy-Walker malformation. *Journal of Medical Genetics, 35*, 342–344.

DOI 10.1007/978-1-4614-6430-3_184-2


Nevin, N. C., & Thomas, P. S. (1989). Orofaciodigital syndrome type IV: Report of a patient. *American Journal of Medical Genetics, 32*, 151–154.

Nevin, N. C., Magee, A. C., Mudenda, V., & Thomas, P. S. (1992). Orofaciodigital syndrome type IV: Report of a patient. *American Journal of Medical Genetics, 43*, 902–904.

Nevin, N. C., Silvestri, J., Kernohan, D. C., et al. (1994). Oral-facial-digital syndrome with retinal abnormalities: OFDS type IX. A further case report. *American Journal of Medical Genetics, 51*, 228–231.

Nowaczyk, M. J. M., Zeesman, S., Whelan, D. T., et al. (2003). Oral-facial-digital syndrome VII is oral-facial-digital syndrome I: A clarification. *American Journal of Medical Genetics Part A, 123A*, 179–182.

Papagrigorakis, M. I., Fotos, S., Damanakis, G., et al. (2010). Orofaciodigital (OFD)syndromes: report of a case with OFDS type I. *Hellenic Orthodontic Review, 13*, 43–68.

Papillon-Leage, M., & Psaume, J. (1954). Une malformation hereditaire de la muquese buccale: Brides et freins anomaux. *Revue de Stomatologie, 55*, 209–227.

Poretti, A., Vitiello, G., Hennekam, R. C. M., et al. (2012). Delination and diagnostic criteria of oral-facial-digital syndrome type VI. *Orphanet Journal of Rare Diseases, 7*, 4–17.

Prpic, I., Cekada, S., & Franulovic, J. (1995). Mohr syndrome (oro-facial-digital syndrome type II) – A familial case with different phenotypic findings. *Clinical Genetics, 48*, 304–307.

Rakkolainen, A., Ala-Mello, S., Kristo, P., et al. (2002). Four novel mutations in the OFD1 (Cxorf5) gene in Finnish patients with oral-facial-digital syndrome 1. *Journal of Medical Genetics, 39*, 292–296.

Rimoin, D. L., & Edgerton, M. T. (1967). Genetic and clinical heterogeneity in the oral-facial-digital syndromes. *Journal of Pediatrics, 71*, 94–102.

Romio, L., Wright, V., Price, K., et al. (2003). OFD1, the gene mutated in oral-facial-digital syndrome type 1, is expressed in the metanephros and in human embryonic renal mesenchymal cells. *Journal of the American Society of Nephrology, 14*, 680–689.

Rosing, B., Kempe, A., Berg, C., et al. (2008). Orofaciodigital syndrome Type IV (Mohr-Majewski): Early prenatal diagnosis in siblings. *Ultrasound in Obstetrics & Gynecology, 31*, 457–460.

Shipp, T. D., Chu, G. C., & Benacerraf, B. (2000). Prenatal diagnosis of oral-facial-digital syndrome, type I. *Journal of Ultrasound in Medicine, 19*, 491–494.

Silengo, M. C., Bell, G. L., Biagioli, M., & Franceschini, P. (1987). Oro-facial-digital syndrome II. Transitional type between the Mohr and the Majewski syndromes: Report of two new cases. *Clinical Genetics, 31*, 331–336.

Smith, R. A., & Gardner-Medwin, D. (1993). Orofacialdigital syndrome type III in two sibs. *Journal of Medical Genetics, 30*, 870–872.

Stephan, M. J., Brooks, K. L., Moore, D. C., et al. (1994). Hypothalamic hamartoma in oral-facial-digital syndrome type VI (Varadi syndrome). *American Journal of Medical Genetics, 51*, 131–136.

Sugarman, G. I. (1983). Orofacial defects and polysyndactyly. *The Journal of Clinical Dysmorphology, 1*, 16–19.

Sugarman, G. I., Kutakia, M., & Menkes, J. (1971). See-saw winking in a familial oral-facial-digital syndrome. *Clinical Genetics, 2*, 248–254.

Thauvin-Robinet, C., Cossee, M., Cormier-Daire, V., et al. (2006). Clinical, molecular, and genotype-phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: A French and Belgian collaborative study. *Journal of Medical Genetics, 43*, 54–61.

Thauvin-Robinet, C., Franco, B., Saugier-Veber, P., et al. (2009). Genomic deletions of OFD1 account for 23% of oral-facial-digital type 1 syndrome after negative DNA sequencing. *Human Mutation, 30*, E320–E329.

DOI 10.1007/978-1-4614-6430-3_184-2


Thauvin-Robinet, C., Lee, J. S., Lopez, E., et al. (2014). The oral-facial-digital syndrome gene C2CD3 encodes a positive regulator of centriole elongation. *Nature Genetics, 46*, 905–911.

Thurston, E. O. (1909). A case of median hare-lip associated with other malformations. *Lancet, 174*, 996–997.

Toriello, H. V. (1988). Heterogeneity and variability in the oral-facial-digital syndromes. *American Journal of Medical Genetics, 4*, 149–159.

Toriello, H. V. (1993). Oral-facial-digital syndromes, 1992. *Clinical Dysmorphology, 2*, 95–105.

Toriello, H. V., & Franco, B. (2013). Oral-facial-digital syndrome type I. *GeneReviews*. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1188/. Updated 28 Feb 2013.

Toriello, H. V., Carey, J. C., Suslak, E., et al. (1997). Six patients with oral-facial-digital syndrome IV: The case for heterogeneity. *American Journal of Medical Genetics, 69*, 250–260.

Towfighi, J., Berlin, C. M., Jr., Ladda, R. L., et al. (1985). Neuropathology of oral-facial-digital syndromes. *Archives of Pathology & Laboratory Medicine, 109*, 642–646.

Tuysuz, B., Arapoglu, M., Seven, M., et al. (1999). Mohr-Majewski syndrome (orofaciodigital syndrome type IV) in five sibs. *Genetic Counseling, 10*, 189–192.

Varadi, V., Szabo, L., & Papp, Z. (1980). Syndrome of polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation in endogamic Gypsies. *Journal of Medical Genetics, 17*, 119–122.

Wahrman, J., Berant, M., Jacobs, J., et al. (1966). The oral-facial-digital syndrome: A male-lethal condition in a boy with 47/XXY chromosomes. *Pediatrics, 37*, 812–821.

Wey, P. D., Neidich, J. A., Hoffman, L. A., et al. (1994). Midline defects of the orofaciodigital syndrome type VI (Varadi syndrome). *The Cleft Palate-Craniofacial Journal, 13*, 397–400.

Whelan, D. T., Feldman, W., & Dost, I. (1975). The oro-facio-digital syndrome. *Clinical Genetics, 8*, 205–212.

Yildirim, S., Akan, M., & Deviren, A. (2002). Penile agenesis and clavicular anomaly in a child with an oral facial digital syndrome. *Clinical Dysmorphology, 11*, 29–32.