GENEReviews

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Oral-Facial-Digital Syndrome Type I

[*OFD1, Orofaciodigital Syndrome I*]

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Summary

Disease characteristics. Oral-facial-digital syndrome type I (OFD1) is characterized by the following abnormalities: oral (lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia and other dental abnormalities); facial (ocular hypertelorism or telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft upper lip, micrognathia); digital (brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger; duplicated hallux [great toe]; preaxial or postaxial polydactyly of the hands); brain (intracerebral cysts, corpus callosum agenesis, cerebellar agenesis with or without Dandy-Walker malformation); and kidney (polycystic kidney disease). As many as 50% of individuals with OFD1 have some degree of mental retardation, which is usually mild. Almost all affected individuals are female. However, males with OFD1 have been described, mostly as malformed fetuses delivered by women with OFD1.

Diagnosis/testing. The diagnosis of OFD1 is established 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. Molecular genetic testing of *OFD1*, the only gene currently known to be associated with oral-facial-digital syndrome type I, is available on a clinical basis.

Management. Treatment of OFD1 includes surgery for cleft lip/palate, tongue nodules, accessory frenulas, and syndactyly; removal of accessory teeth, and orthodontia for malocclusion. Treatment is routine for renal disease and seizures. Speech therapy and special education may be warranted. Surveillance includes annual monitoring of renal function and, if cleft lip is present, regular speech and hearing assessment.

Genetic counseling. OFD1 is inherited in an X-linked dominant manner. Approximately 75% of affected individuals are simplex cases (no family history of OFD1). 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. 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%. 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. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males. Prenatal diagnosis for families in which the disease-causing mutation has been identified is available. Prenatal ultrasound examination may detect structural brain malformations and/or duplication of the hallux.

Diagnosis

Clinical Diagnosis

The diagnosis of oral-facial-digital syndrome type I (OFD1) is established 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 [Coll et al 1997].

Oral. Oral findings affect primarily the tongue, palate, and teeth:

- The tongue is lobed and often described as bifid or trifid. 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 occur in more than 50% of affected individuals. Trifurcation of the soft palate has been reported [al-Qattan 1998].
- 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

- Ocular hypertelorism or telecanthus occurs in at least 33% of affected individuals.
- Hypoplasia of the alae nasi, median cleft lip, or pseudocleft upper lip is common.
- Micrognathia and downslanting palpebral fissures are common.

Digital

- 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, but if present is usually unilateral.
- Preaxial or postaxial polydactyly of the hands occurs in 1%-2% of affected individuals.
- Radiographs of the hands often demonstrate fine reticular radiolucencies, described as irregular mineralization of the bone, with or without spicule formation of the phalanges [al-Qattan & Hassanian 1997].

Brain. Structural brain abnormalities may occur in as many as 40% of individuals with OFD1 [Thauvin-Robinet et al 2006]. 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, and berry aneurysms, each of which has been described in a few affected individuals.

Intellect. It is estimated that as many as 50% of individuals with OFD1 have some degree of mental retardation or learning disability. Mental retardation depends in part on the presence of brain abnormalities, but no consistent correlation exists. When present, mental retardation is usually mild. Severe mental retardation in the absence of brain malformations appears to be rare.

Kidney. Polycystic kidney disease occurs in fewer than 50% of individuals with OFD1; the exact frequency is unknown. Renal cysts can develop from both tubules and glomeruli. The age of onset is most often in adulthood, but renal cysts in children have been described.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *OFD1* is the only gene currently known to be associated with oral-facial-digital syndrome type I.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

Sequence analysis. A variety of mutations have been identified, the majority of which result in premature protein truncation. The reported mutation detection rate is 50%-67% [Nowaczyk et al 2003, Thauvin-Robinet et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Methods	Mutations Detected	Mutation Detection Frequency	Test Availability
Sequence analysis	*OFD1* sequence variants	50%-67% [1]	Clinical Testing

1. Direct DNA refers to the use of mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with a specific disorder.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

OFD7, which includes unilateral cleft lip and hydronephrosis, has only been described in one mother-daughter pair, who were later found to have a mutation in *OFD1*; thus, this condition

is either allelic to OFD1 or demonstrates variable expression of OFD1 [Nowaczyk et al 2003].

Clinical Description

Natural History

In addition to the findings described in Clinical Diagnosis, the following may be present:

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

Intellect. As many as half of the individuals with OFD1 have some degree of mental retardation, which is usually mild. Those with brain malformations are more likely to have mental retardation, but the association is not consistent.

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

Skin and hair. The hair is often described as dry, coarse, and brittle. Alopecia, usually partial, is an occasional finding. Alopecia has been described to follow the lines of Blaschko [Del C Boente et al 1999]. Milia, small keratinizing cysts, occur in at least 10%, and likely more, most often appearing on the scalp, ear pinnae, face, and dorsa of the hands. Milia are usually present in infancy and then resolve, but can then leave pitting scars.

Kidney. Although renal cysts have been reported as a prenatal finding [Nishimura et al 1999], the diagnosis is doubtful in these cases. Typically, cysts appear no earlier than late childhood. End-stage renal disease (ESRD) has been reported in affected girls and women ranging in age from 11 to 70 years. Recently it has been emphasized that the risk for significant renal disease may be greater than previously reported [Feather et al 1997, Odent et al 1998]. In addition, liver and pancreatic cysts may be observed.

Other. Rare manifestations include short stature, choanal atresia, tibial pseudarthrosis, and berry aneurysms.

Almost all affected individuals with OFD1 are female; however, a few affected males have been reported. In most cases, these males are described as malformed fetuses delivered by women with OFD1; however, a male described by Goodship et al (1991) survived to term and expired on the first day of life. Virtually all reported males are simplex cases (i.e., a single occurrence in a family); the certainty of the diagnosis is thus unknown. Some of the other reported males with suspected OFD1 may in fact have other diagnoses, such as another OFD or Meckel-Gruber syndrome. It is theoretically possible for an affected male to be born alive.

Genotype-Phenotype Correlations

Some evidence of genotype-phenotype correlation exists [Thauvin-Robinet et al 2006]:

- Renal cysts appear to be correlated with splice mutations.
- Mental retardation is more often associated with mutations in exons 3,8,9,13, and 16.
- Anomalous teeth are more often found in those with mutations in coiled coil domains.

Penetrance

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

Anticipation

No evidence for anticipation exists.

Nomenclature

OFD1 was previously called Papillon-Leage-Psaume syndrome.

Prevalence

Estimates range from 1/50,000 to 1/250,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis includes the other oral-facial-digital syndromes and disorders, including cystic renal disease.

Oral-facial-digital syndromes (see Table 2)

- OFD2, Mohr syndrome, is primarily distinguished by polydactyly. Other manifestations include bifid nasal tip. Affected individuals do not have milia or polycystic kidney disease.
- OFD3 is characterized by seesaw winking (alternate winking of the eyes) and polydactyly. Myoclonic jerks, profound mental retardation, bulbous nose, and apparently low-set ears also occur.
- OFD4 has tibial involvement and polydactyly as the primary manifestations. Other findings include pectus excavatum and short stature.
- OFD5 includes polydactyly and median cleft lip only. Only one affected individual has had hyperplastic frenula.
- OFD6 is distinguished by polydactyly (particularly central) and cerebellar malformations. Renal agenesis and dysplasia have been described.
- OFD8, apparently inherited as an X-linked recessive trait, is characterized by the combination of polydactyly, tibial and radial defects, and epiglottal abnormalities, none of which is seen in the classic form of OFD1.
- OFD9 includes retinal abnormalities and non-median cleft lip.

Cystic renal disease. Autosomal dominant polycystic kidney disease (ADPKD) should be considered in the differential diagnosis of OFD1. The diagnosis of ADPKD has been made in some individuals who later were found to have OFD1 [Scolari et al 1997]. In ADPKD, cysts develop from tubules, whereas in OFD1 cysts develop from both tubules and glomeruli; however, imaging studies cannot always distinguish the renal cystic disease of OFD1 from that of ADPKD and other cystic renal disorders. The cysts are said to be smaller and more uniform in size in OFD1 than in ADPKD, and the kidneys are not as enlarged or malformed in OFD1. Hepatic cysts and berry aneurysms have been observed in OFD1. Other distinguishing features are mode of inheritance and the lack of oral, facial, digital, or brain abnormalities in ADPKD.

Meckel-Gruber syndrome. Meckel-Gruber syndrome is characterized by CNS malformation (posterior encephalocele, cerebral and cerebellar hypoplasia), polycystic or hypoplastic kidneys, preaxial or postaxial polydactyly, and early demise. Additional findings include cleft lip and palate, ambiguous genitalia, microcephaly, and microphthalmia. Ocular histopathology

reveals retinal dysplasia, coloboma, cataract, and corneal dysgenesis. Two loci have been mapped and one gene, *MKS3*, identified. Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with oral-facial-digital syndrome type I (OFD1):

- Examination of the face, especially the mouth, and the hands for characteristic anomalies
- Formal, age-appropriate assessment of development
- Blood pressure and serum creatinine concentration
- Urinalysis, serum chemistries, and ultrasound evaluation of the kidneys, liver, and pancreas for cysts if the individual is age ten years or older

Treatment of Manifestations

- Cosmetic or reconstructive surgery for clefts of the lip and/or palate, tongue nodules, and accessory frenula; treatment as for isolated cleft palate, including speech therapy and assessment for and aggressive treatment of otitis media
- Removal of accessory teeth
- Orthodontia for malocclusion
- Surgery to repair syndactyly, if present
- Routine management of renal disease, which may require hemodialysis or peritoneal dialysis and renal transplantation
- Routine management of seizures
- Special educational evaluation and input to address learning disabilities and other cognitive impairments

Surveillance

- Regular follow-up for assessment of speech and ear infections/hearing loss if cleft lip is present
- Annual determination of blood pressure and serum creatinine concentration to monitor renal function
- Annual assessment of renal function with follow-up by renal ultrasound evaluation to assess cyst development if abnormalities are detected

Testing of Relatives at Risk

Molecular testing of daughters of known gene carriers, even in the absence of oral, facial, and digital anomalies, is reasonable.

Similarly, mothers of affected daughters could benefit from testing 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.

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Oral-facial-digital syndrome type I (OFD1) is inherited in an X-linked dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 25% of females diagnosed with OFD1 have an affected mother.
- A female proband with OFD1 may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Approximately 75% of affected females are simplex cases (i.e., occurrence of OFD1 in a single family member) [Feather et al 1997].
- Recommendations for the evaluation of the mother of a proband with an apparent *de novo* mutation include clinical evaluation and molecular genetic testing if the proband's mutation has been identified. If the mother meets the diagnostic criteria for OFD1 or if she has another affected relative, she is an obligate carrier of an *OFD1* gene mutation.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the mother.
- When the mother of an affected female is also found to be 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. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males.
- 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%. Two possibilities account

for this small increased risk: 1) a new mutation in a second child; or 2) germline mosaicism in a parent [Nishimura et al 1999]. Although germline mosaicism has not been reported, it remains a possibility.

Offspring of a proband. The risk to the offspring of females with OFD1 must take into consideration the presumed lethality to affected males during gestation. At conception, the risk that the disease-causing *OFD1* allele will be transmitted is 50%; however, most male conceptuses with the disease-causing *OFD1* allele miscarry. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males.

Other family members of a proband. The risk to other family members depends upon the status of the proband's mother. If the mother is found to be affected, her family members could be at risk.

Related Genetic Counseling Issues

Specific risk issues. Males described as having OFD1 have been reported. As virtually all are non-familial, the certainty of the diagnosis is unknown. It is theoretically possible for an affected male to be born alive, though this would be exceedingly rare. One family with a peculiar inheritance pattern has been described. In this pedigree, a woman with OFD1 had four unaffected sons, three of whom then had daughters all affected with OFD1.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Ascertainment of affected individuals. Often, mildly affected female relatives are diagnosed only after the identification of a severely affected individual [Thauvin-Robinet et al 2001].

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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 such as porencephaly [Shipp et al 2000, Thauvin-Robinet et al 2001] and/or duplicated hallux.
- **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

(hallucal duplication) should lead to consideration of OFD1. In such instances, it is appropriate to evaluate the mother for manifestations of OFD1.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Oral-Facial-Digital Syndrome Type I

Gene Symbol	Chromosomal Locus	Protein Name
OFD1	Xp22.3-p22.2	Oral-facial-digital syndrome 1 protein

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Oral-Facial-Digital Syndrome Type I

300170	CHROMOSOME X OPEN READING FRAME 5; CXORF5
311200	OROFACIODIGITAL SYNDROME 1; OFD1

Table C. Genomic Databases for Oral-Facial-Digital Syndrome Type I

Gene Symbol	Entrez Gene	HGMD
OFD1	8481 (MIM No. 300170)	OFD1

For a description of the genomic databases listed, click here.

Normal allelic variants: *OFD1* has 23 exons. *OFD1* is on the portion of the X chromosome that escapes X-chromosome inactivation.

Pathologic allelic variants: Exonic and intronic mutations have both been described. Mutations in exons include single base pair changes, frameshifts, and deletions [Stoll & Sauvage 2002, Romio et al 2003]. These changes have occurred to date in exons 3, 11, 13, and 16 only. Abnormal splicing has also been reported in introns 4 and 5 [Ferrante et al 2001, Rakkolainen et al 2002].

Normal gene product: Oral-facial-digital syndrome 1 protein occurs in two forms, Cxorf5-1 and Cxorf5-2, which are differentiated by the use of an alternative splice site. Cxorf5-1 is a 1011-amino acid protein; Cxorf5-2 is a 367-amino acid protein. The two proteins share the first 351 amino acids; Cxorf5-2 then has a C-terminal region of 16 amino acids. The function of the protein is unknown, but thought to be related to a protein-protein interaction mechanism during development. *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 nervous system.

Abnormal gene product: Most of the mutations lead to the premature truncation of the protein and are therefore thought to result in a loss of function. Since the *OFD1* gene is on the portion of the X chromosome that escapes X-chromosome inactivation, the truncated protein may interact with the wild-type product to produce a dominant-negative effect.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

AboutFace International
123 Edward Street Suite 1003
Toronto Ontario
Canada M5G 1E2
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Cleft Palate-Craniofacial Association
Cleft Palate Foundation
1504 East Franklin Street Suite 102
Chapel Hill NC 27514-2820
Phone: 800-242-5338; 919-933-9044
Fax: 919-933-9604
Email: info@cleftline.org
www.cleftline.org

Children's Craniofacial Association
13140 Coit Road Suite 307
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

Let's Face It
PO Box 29972
Bellingham WA 98228-1972
Phone: 360-676-7325
Email: letsfaceit@faceit.org
www.faceit.org

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

National Renal Resource Centre
Sydney Dialysis Centre
37 Darling Point Road
Darling Point NSW 2027

Australia
Phone: (+61) 2 9362 3995 or (+61) 2 9362 3121
Fax: 61 2 9362 4354
Email: d.oshaughnessy@hcn.net.au
www.renalresource.com

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 9 March 2007 (ht,cd) Revision: sequence analysis and prenatal diagnosis clinically available
- 14 August 2006 (me) Comprehensive update posted to live Web site
- 29 June 2004 (me) Comprehensive update posted to live Web site
- 24 July 2002 (me) Review posted to live Web site
- 27 February 2002 (ht) Original submission

Table 2. Oral-Facial-Digital Syndromes

Finding	Oral-Facial-Digital Syndrome								
	OFD I	OFD II	OFD III	OFD IV	OFD V	OFD VI	OFD VII	OFDS VIII	OFDS IX
Oral	Missing teeth, extra teeth, hyperplastic frenula, cleft palate, tongue nodules, cleft tongue	Highly arched or cleft palate, hyperplastic frenula, tongue nodules, tongue clefts	Cleft uvula, tongue nodules, tongue clefts, extra teeth	Highly arched/cleft palate, lobed tongue, tongue nodules, hyperplastic frenula	Hyperplastic frenula (rare)	Highly arched/cleft palate, tongue clefts, tongue nodules, hyperplastic frenula	Highly arched/ cleft palate, tongue nodules, hyperplastic frenula	Highly arched palate, tongue clefts, tongue nodules, absent teeth, hyperplastic frenula	Tongue clefts, tongue nodules, hyperplastic frenula
Facial	Telecanthus or hyper-telorism, median cleft lip, alar hypoplasia	Median cleft lip, bifid nasal tip	Hyper-telorism, bulbous nose, lowset ears	Micrognathia	Median cleft lip	Cleft lip, broad nasal tip	Hyper-telorism, cleft lip, facial asymmetry, preauricular tag	Median cleft lip, telecanthus, bifid/broad nose	Cleft lip
Hand	Clinodactyly, brachy-dactyly, syndactyly	Pre- or postaxial polydactyly, clinodactyly, brachy-dactyly	Postaxial polydactyly	Pre- or postaxial polydactyly, brachy-dactyly, clinodactyly, syndactyly	Postaxial polydactyly	Postaxial or central polydactyly, brachy-dactyly, clinodactyly, syndactyly	Clinodactyly	Pre- and postaxial polydactyly	Brachy-dactyly, syndactyly
Foot	Preaxial polydactyly, usually unilateral	Pre- or postaxial polydactyly	Postaxial polydactyly	Pre- and postaxial polydactyly	Postaxial polydactyly	Preaxial polydactyly		Preaxial polydactyly	Bifid toes
Kidney	Adult-onset polycystic kidneys					Agenesis or dysplasia	Hydronephrosis		
Brain	Agenesis corpus callosum, cerebral or cerebellar hypoplasia, porencephaly	Porencephaly, hydrocephaly	See-saw winking, myoclonus, Dandy-Walker anomaly	Porencephaly, cerebral atrophy		Cerebellar anomalies			
Skeletal			Short sternum	Tibial hypoplasia, pectus excavatum				Tibial and radial defects	
Miscell-aneous				Short stature					Retinal abnormalities
Inheri-tance	XLD	AR	AR	AR	AR	AR	AD or XLD	XLR	AR
Comment				May itself be hetero-geneous		Some overlap with Joubert syndrome		Females have minor manifest-ations	