GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

IRF6-Related Disorders

Bryan Cary Bjork, PhD
Brigham and Women's Hospital
Harvard Medical School
bbjork@rics.bwh.harvard.edu

Katherine Nash Krahn, MS
Pediatrics Department
University of Iowa
k.b.n.krahn@tue.nl

Brian C Schutte, PhD
Pediatrics Department
University of Iowa
brian-schutte@uiowa.edu

Jeffrey C Murray, MD
Pediatrics Department
University of Iowa
jeff-murray@uiowa.edu

Initial Posting: October 30, 2003.
Last Update: May 15, 2006.

Summary

Disease characteristics. *IRF6*-related disorders span a spectrum from isolated cleft lip and palate and Van der Woude syndrome (VWS) at the mild end to popliteal pterygium syndrome (PPS) at the more severe end. Individuals with VWS show one or more of the following anomalies: (1) congenital, usually bilateral, paramedian lower-lip fistulae (pits) or sometimes small mounds with a sinus tract leading from a mucous gland of the lip; (2) cleft lip (CL); or (3) cleft palate (CP). Both cleft types — cleft lip with or without cleft palate (CL±P) and CP only — occur in individuals with VWS in the same proportions as in the general population, about two to one respectively. The PPS phenotype includes CL±P, fistulae of the lower lip, webbing of the skin extending from the ischial tuberosities to the heels, bifid scrotum and cryptorchidism in males, hypoplasia of the labia majora in females, syndactyly of fingers and/or toes, and anomalies of the skin around the nails. Filiform synechiae may connect the upper and lower jaws (syngnathia) or the upper and lower eyelids (ankyloblepharon). A characteristic pyramidal fold of skin overlying the nail of the hallux is almost pathognomonic. In both phenotypes, growth and intelligence are normal.

Diagnosis/testing. Diagnosis is based on clinical findings. Mutations in the *IRF6* gene are known to be associated with *IRF6*-related disorders. Genetic variants in *IRF6* contribute risk for isolated cleft lip and palate. Sequence analysis of the *IRF6* coding region (exons 1-9) detects mutations in approximately 70% of individuals with the Van der Woude syndrome phenotype and approximately 97% of individuals with the popliteal pterygium syndrome phenotype. Such testing is clinically available.

Management. Treatment is supportive/symptomatic, and may include: surgery, orthodontia, speech therapy, feeding and hearing evaluation, physical therapy, and orthopedic care.

Genetic counseling. *IRF6*-related disorders are inherited in an autosomal dominant manner. Most individuals diagnosed with an *IRF6*-related disorder have an affected parent; however, penetrance is incomplete. The risk to the sibs of the proband depends upon the genetic status of the proband's parents. If a parent of the proband is affected or has an *IRF6* mutation, the risk to the sibs of inheriting the mutation is 50%. Prenatal diagnosis for pregnancies at increased risk is possible. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. Prenatal ultrasound examination may detect a cleft lip in some fetuses later in pregnancy, but it is less likely to detect a cleft palate or lip pits.

Diagnosis

Clinical Diagnosis

IRF6-related disorders span a spectrum from isolated cleft lip and palate and Van der Woude syndrome (VWS) at the mild end to popliteal pterygium syndrome (PPS) at the more severe end.

To make the diagnosis of **Van der Woude syndrome**, at least one of the following findings must be present:

- **Lip pits and cleft lip AND/OR palate (CLP).** Lip pits must be paramedian on the lower lip, and can include mounds with a sinus tract leading from a mucous gland of the lip.
- **Lip pits alone and a first-degree relative with CLP**
- **CLP and a first-degree relative with lip pits**

Note: Presence of psychomotor delay does not exclude Van der Woude syndrome or popliteal pterygium syndrome but suggests the presence of a microdeletion, which has been observed in only one of 310 families studied or which occurs from an unrelated cause.

To make the diagnosis of **popliteal pterygium syndrome**, an individual must have one or more of the following in addition to features of Van der Woude syndrome listed above:

- Popliteal pterygia
- Syndactyly
- Abnormal external genitalia
- Ankyloblepharon
- Pyramidal skin on the hallux
- Intraoral adhesions

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.

Gene. Mutations in the *IRF6* gene are known to be associated with Van der Woude syndrome and popliteal pterygium syndrome. Genetic variants in *IRF6* contribute risk for isolated cleft lip and palate.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

- **Sequence analysis**

  For Van der Woude syndrome, sequence analysis of the *IRF6* coding region (exons 1 through 9) detects mutations in approximately 70% of individuals. Mutations in exons 3, 4, and 7-9 account for 80% of known VWS-causing mutations (N-310) [B Shutte & J Murray, personal communication].

  Note: Whole gene deletions, present in at least 2% of individuals affected with VWS, are not detected by this test method.

  For popliteal pterygium syndrome, sequence analysis of exon 4 of the *IRF6* coding region detects mutations in approximately 72% of individuals. Additional sequencing of the entire coding region of the *IRF6* gene detects mutations in approximately 97% of individuals with PPS (N=37) [B Schutte & J Murray, personal communication].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *IRF6*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Sequence analysis	*IRF6* mutations in exons 1-9	VWS ~70%	Clinical Testing
	IRF6 mutations in exons 1-9	PPS ~97%	

1. B Schutte & J Murray, personal communication

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

Testing Strategy for a Proband

- Clinical evaluation by a medical geneticist is generally performed first to verify the presence of lip pits in at least one family member before undertaking molecular genetic testing.
- Presence of cleft lip (CL) or cleft lip and palate (CL+P) together with cleft palate (CP) only in the same family should also suggest VWS and should prompt a close search for lip pits and consideration of molecular testing even in their absence.

Genetically Related (Allelic) Disorders

No syndromes other than Van der Woude syndrome and popliteal pterygium syndrome have been related to mutations in *IRF6*. However, recent studies demonstrated that normal genetic variation in *IRF6* contributes risk for isolated cleft lip and palate.

Zucchero and colleagues performed the transmission disequilibrium test (TDT) with the nonsynonymous SNP V274I on 8003 individuals with isolated CLP from nine geographically distinct populations [Zucchero et al 2004]. The V274 allele was significantly over-transmitted in seven of the populations. Since V274I is a less informative SNP in populations originating from Northern Europe, haplotype analysis was also performed. Significant association was observed between isolated CLP and the common haplotype for *IRF6*, even in populations from

northern Europe. Thus, genetic variation in *IRF6* contributes risk for isolated cleft lip and palate.

Subsequently, four studies confirmed the association between genetic variation in *IRF6* and isolated CLP [Blanton et al 2005, Ghassibe et al 2005, Scapoli et al 2005, Srichomthong et al 2005]. One study did not find an association between V274I and isolated CLP [Hering & Grundmann 2005]. However, Murray et al (2005) attributed the failure to detect such an association to the low frequency of V274I in the population under study.

To determine the genetic variant in *IRF6* that is the risk allele, the entire *IRF6* gene was sequenced in 23 individuals homozygous for the risk haplotype. No missense or protein truncation mutations were detected [Zucchero et al 2004]. Based on the haplotype block structure around *IRF6*, the most likely location for the variant is within 200 kb. A comparative genomic approach should allow the identification of sequence elements that regulate *IRF6*, and may also contain genetic variants.

Clinical Description

Natural History

The craniofacial features of PPS and VWS form a continuum such that it is often difficult to distinguish between mildly affected individuals with PPS and those with VWS [Bixler et al 1973, Soekarman et al 1995, Lees et al 1999, Kondo et al 2002].

Van der Woude syndrome. Individuals with VWS show one or more of three anomalies: congenital, usually bilateral, paramedian lower-lip fistulae (pits) or sometimes small mounds with a sinus tract leading from a mucous gland of the lip; cleft lip (CL); or cleft palate (CP) [Van der Woude 1954].

Van der Woude (1954) observed that 27% of the offspring of affected parents had lip fistulae alone and 21% had fistulae associated with CL and/or CP. Burdick et al (1985) gathered information on 864 affected individuals from 164 families. In this population, 44% had lip pits only, 37% had cleft lip (with/without lip pits and with/without cleft palate), 16% had cleft palate only (with/without lip pits), and 3% had no apparent phenotype. Overall, lip pits were observed in 86% of affected individuals.

Both cleft types, cleft lip with or without cleft palate (CL±P) and CP only, occur in indivduals with VWS in the same proportions as in the general population, about two to one respectively [Burdick et al 1987]. The *IRF6*-related disorders are especially interesting as it is unusual for a single syndrome or genetic disorder to include both types of clefting. This type of mixed clefting can also occur with *MSX1* [van den Boogaard et al 2001] and *FGFR1* mutations.

The sex ratio is nearly equal in VWS for CP and CL±P, as well as for the presence of lip pits. It was also noted that CL±P and CP co-occur both vertically and horizontally in pedigrees. Forty percent of families with at least three affected individuals have both forms of clefting; in those, 75% have both forms of clefting in sibs.

Oberoi & Vargervik (2005) suggest that individuals with VWS are more likely to have hypoplasia of the mandible and maxilla than isolated cases with the same cleft phenotype.

Non-classic forms of the VWS phenotype that have been described [Soricelli et al 1966, Ranta et al 1983, Ranta & Rintala 1983, Schinzel & Klausler 1986, Burdick et al 1987, Kantaputra et al 2002] include:

- Conical elevations (CE) of the lip

- Single unilateral lip pits
- Hypodontia
- Submucous cleft
- Bifid uvula
- Ankyloglossia
- Limb abnormalities
- Hearing loss

Growth and intelligence are normal. The single exception is a pedigree in which affected individuals have developmental delay and a large deletion that spans the *IRF6* gene [Sander et al 1994]. In two other pedigrees, individuals with large deletions have normal intelligence [Schutte et al 1999, Kayano et al 2003]. In one of the latter cases, the deletion is even larger than the deletion described by Sander et al (1994), suggesting that developmental delay in the family of Sander et al (1994) is not related to deletion of *IRF6*.

Popliteal pterygium syndrome. The PPS phenotype includes cleft lip and/or palate (91-97% of individuals); fistulae of the lower lip (45.6% [Froster-Iskenius 1990]); webbing of the skin extending from the ischial tuberosities to the heels, bifid scrotum and cryptorchidism in males, hypoplasia of the labia majora in females, syndactyly of fingers and/or toes, and anomalies of the skin around the nails [Lewis 1948, Rintala et al 1970]. A characteristic pyramidal fold of skin overlying the nail of the hallux is almost pathognomonic.

Filiform synechiae may connect the upper and lower jaws (syngnathia) or the upper and lower eyelids (ankyloblepharon).

Growth and intelligence are normal.

Genotype-Phenotype Correlations

Van der Woude syndrome. Whole gene deletions and nearly all protein truncation mutations cause a VWS phenotype. Missense mutations that cause VWS are evenly divided between the two protein domains encoded in exons 3, 4, and 7-9. Two missense mutations at Arginine 84, R84G [Item et al 2005] and R84P [B Schutte, M Dixon & J Murray, personal communication], are only found in individuals with VWS, suggesting that R84G and R84P affect *IRF6* function differently from R84H and R84C, which are seen most commonly in PPS.

Popliteal pterygium syndrome. Most missense mutations that cause PPS are located in exon 4.

It appears likely that certain mutations (R84H, R84C) are more apt to cause PPS than VWS. A cluster of missense mutations in the DNA binding domain are more commonly seen in families with PPS ($p<0.01$; e.g., W60, K66, Q82, R84, K89). However, families may include individuals with features of only VWS and other members with the additional features of PPS.

Penetrance

Van der Woude syndrome. Additional studies have supported Van der Woude's observation of dominant inheritance with variable expressivity and high, but incomplete, penetrance [Cervenka 1967, Janku et al 1980, Shprintzen et al 1980, Burdick et al 1985]. In the most current and extensive literature review of VWS [Burdick et al 1985], a citation list search and manual search of Index Medicus starting from 1965 revealed data on 864 affected individuals

in 164 families reported since Demarquay (1845) first observed VWS. Based on these data, penetrance was estimated at 92%.

Lip pit phenotype. The penetrance of the lip pit phenotype is estimated at 86%.

Anticipation

There are no data to suggest anticipation in *IRF6*-related disorders.

Prevalence

Van der Woude syndrome. VWS represents the most common single-gene cause of cleft lip and cleft palate, accounting for about 2% of all individuals with CL+P [Cohen & Bankier 1991, Murray et al 1997] or roughly one in 35,000 to one in 100,000 in the European and Asian populations [Cervenka et al 1967, Rintala & Ranta 1980, Burdick 1986].

Popliteal pterygium syndrome. Prevalence is approximately one in 300,000 [Murray, unpublished data].

Differential Diagnosis

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

Van der Woude syndrome should be considered in every child born with an orofacial cleft, even in the absence of lip pits, and the parents should be examined for isolated pits, submucous cleft palate, and hypodontia.

Pits of the lower lip similar to those seen in VWS also occur in Kabuki syndrome (OMIM 147920) and branchiooculofacial syndrome (OMIM 113620).

Kabuki syndrome (KS) (also Kabuki make-up syndrome or Niikawa syndrome) includes short stature, mental retardation, facies characterized by long palpebral fissures with eversion of the lateral third of the lower eyelids, a broad and depressed nasal tip, large prominent ears, high-arched palate, or cleft palate (40%) [Burke & Jones 1995]. The facial appearance resembles that of the actors of Kabuki, a Japanese traditional theatrical form [Niikawa et al 1988]. Several individuals with KS who have lower-lip pits have been identified [Matsumura et al 1992, Franceschini et al 1993, Kokitsu-Nakata et al 1999, Makita et al 1999]. In particular, Makita et al (1999) reported a five-year-old Japanese girl with both the KS and VWS clinical phenotypes.

Although KS is proposed to be autosomal dominantly inherited with variable expressivity [Ilyina et al 1995], little, if any, evidence exists that it is a result of a chromosomal or Mendelian genetic abnormality. To date, no microdeletions or point mutations involving *IRF6* have been observed in KS [Makita et al 1999, Kondo et al 2002].

Branchiooculofacial syndrome (BOFS) is inherited in an autosomal dominant manner. Features include abnormal (pseudocleft) upper lip, malformed nose with broad bridge and flattened tip, lacrimal duct obstruction, malformed ears, and branchial cleft sinuses and/or linear skin lesions behind the ears [Lee et al 1982, Hall et al 1983, Fujimoto et al 1987]. Clefts of the lip and palate with varying severity and lip pits can also contribute to the phenotype [Fujimoto et al 1987, McCool & Weaver 1994, Richardson et al 1996].

Isolated CLP. Ranta & Rintala (1983) examined the lower lips of 397 children with CP, 518 with CL+P, and 1000 with no cleft phenotype. In addition to lip pits in these groups, 39.3% of CP, 0.8% of CL+P, and 0.7% of noncleft cases had conical elevations (CE) of the lower lip

[Ranta & Rintala 1983]. The finding was interesting in that the familial occurrence of clefts among those in the CP group with CE (30%) was statistically higher than in those without them (20.7%). In addition, the incidence of hypodontia was significantly higher among 251 children with CP and CE (40%) than in those without them (25%) [Ranta et al 1983]. In all, 56% of children with CP had an associated hypodontia or CE phenotype. It is unknown how many of these may represent an *IRF6*-related disorder.

Direct sequence analysis of *IRF6* exons 1-10 was performed in 160 individuals with isolated CLP. No mutations in *IRF6* exons were detected [Zucchero et al 2004], suggesting that *de novo* mutations in *IRF6* do not make a major contribution to nonsyndromic clefting.

Mixed clefting (cleft lip with or without cleft palate (CL±P) and CP only). The mixed clefting seen in IFR6-related disorders can also occur with disorders caused by mutations in *MSX1* [van den Boogaard et al 2000], *p63* and *FGFR1*. Although lip pits are absent in these disorders, they lack sufficient additional features to exclude VWS without lip pits [van den Boogaard et al 2000, Dode et al 2003, Jezewski et al 2003]. These disorders should be considered in evaluating any family in which multiple members have orofacial clefts.

Wong et al (2001) presented a family in which ten of eleven affected family members had CP and one had cleft lip and palate; only one of the eleven affected individuals clinically examined had lip pits. Two of the affected individuals had a "wave-like" lower lip in addition to CP. Although the authors suggested that this could be a novel finding of VWS, linkage to *IRF6* at 1q32-q41 was excluded (multipoint lod scores < -13.0 for markers across this region). The locus was subsequently mapped to a 30-cM region on the short arm of chromosome 1 in 1p32-p36 [Koillinen et al 2001].

Management

Evaluations at Initial Diagnosis to Establish Extent of the Disease

Individuals diagnosed with VWS should be evaluated for the characteristic features of PPS: webbing behind the knee, syndactyly of the toes, and the pyramidal skin-fold on the nail of the hallux.

Feeding and hearing should be evaluated.

Treatment of Manifestations

Management is supportive/symptomatic.

- Cleft lip. Management is surgical and orthodontic.
- Cleft palate. In addition to surgery and orthodontics, speech therapy and audiologic evaluation are usually needed.
- Lip pits. Surgery may be indicated for cosmetic purposes or for lip function.
- Popliteal pterygium. Management is surgical and orthopedic.
- Synechiae may require surgical removal.
- Abnormal genitalia rarely require surgery but may result in infertility.
- Syndactyly may require surgery.
- Orthopedic care and physical therapy may be needed.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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

IRF6-related disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with an *IRF6*-related disorder have an affected parent. However, penetrance is incomplete.
  - The penetrance for VWS is estimated at 92% [J Murray, personal communication]. Thus, unaffected parents and sibs of individuals with VWS are at risk for having the *IRF6* mutation.
  - Similarly, the lip pit phenotype is estimated at 86% penetrance. Thus, parents and sibs of individuals with VWS who have an orofacial cleft, but no lip pits, are at risk for having the *IRF6* mutation.
- A proband with an *IRF6*-related disorder may have the disorder as the result of a new gene mutation.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination of both parents with special attention to evaluation for lip pits and/or clefts, especially submucous clefts that may be asymptomatic, and molecular genetic testing if the mutation has been identified in the proband.

Note: Although most individuals diagnosed with an *IRF6*-related disorder have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or incomplete penetrance of the *IRF6* mutation.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected or has an *IRF6* mutation, the risk to the sibs of inheriting the mutation is 50%. Approximately 92% of individuals with an *IRF6* mutation will manifest the phenotype [J Murray, personal communication]. About 70% of individuals with a mutation will have an orofacial cleft requiring surgical intervention [J Murray, personal communication]. However, the clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in the sibs.

- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low but the possibility of incomplete penetrance in a parent or of germline mosaicism need to be considered.
- If a disease-causing mutation found in the proband cannot be detected in the DNA extracted from the leukocytes of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband.

Offspring of a proband. Each child of an individual with an *IRF6* mutation has a 50% chance of inheriting the mutation. The clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in the offspring.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have an *IRF6* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation, it is likely that the proband has a *de novo* mutation or germline mosaicism. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

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

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 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 10-12 weeks' gestation. The disease-causing allele of an affected family member 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. Prenatal ultrasound examination may detect a cleft lip in some fetuses later in pregnancy, but it is less likely to detect a cleft palate or lip pits. A level 2 targeted ultrasound examination at a center that routinely performs such procedures is most accurate.

Requests for prenatal testing for conditions such as *IRF6*-related disorders are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate. Prenatal testing may provide the benefit of preparing the parents

and family for a child with a facial difference or disability. In addition, the clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in the offspring.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. 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 IRF6-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
IRF6	1q32-q41	Interferon regulatory factor 6

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 IRF6-Related Disorders

119300	VAN DER WOUDE SYNDROME; VWS
119500	POPLITEAL PTERYGIUM SYNDROME; PPS
607199	INTERFERON REGULATORY FACTOR 6; IRF6

Table C. Genomic Databases for IRF6-Related Disorders

Gene Symbol	Entrez Gene	HGMD
IRF6	3664 (MIM No. 607199)	IRF6

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

Molecular Genetic Pathogenesis

Further functional analyses to identify downstream target genes and interacting proteins is important to the understanding of the role of *IRF6* in palatal development, especially given the overlap of *Irf6* gene expression at the medial edge of the palatal shelves immediately before and during fusion with that of *Tgfb3* in mouse and the proposed role of the SMIR domain of *IRF6* in mediating interactions between IRFs and Smads, a family of transcription factors known to transduce TGF-beta signals [Fitzpatrick et al 1990, Brivanlou & Darnell 2002].

Normal allelic variants: There are ten exons and nine introns. Two common SNPs were found in the coding sequence for *IRF6*. Rare variants found in unaffected controls include L3L, D19N, A61P, V113V, T224S, Y237Y, T242T, and L385L [B Schutte & J Murray, personal communication].

Pathologic allelic variants: Protein truncation (nonsense and frameshift) mutations, missense mutations, and whole gene deletions are known to cause disease. Mutations have now been identified in more than 260 of 358 families with VWS and PPS, representing 235 different alleles [Sander et al 1994; Schutte et al 1999; Kondo et al 2002; Kayano et al 2003; Kim et al 2003; Shotelersuk et al 2003; Wang et al 2003; Gatta et al 2004; Ghassibe et al 2004; Matsuzawa et al 2004; Item et al 2005; Mostowska et al 2005; Peyrard-Janvid et al 2005; Wang et al 2005; Ye et al 2005; Du et al 2006; B Schutte & J Murray, personal communication].

Normal gene product: The function of the normal gene product of *IRF6* is currently unknown. However, IRF6 belongs to the interferon regulatory factor family of transcription factors. This protein family shares a highly conserved helix-loop-helix DNA binding domain (amino acids 13-113) and a less well conserved protein binding domain (amino acids 226-394). The DNA binding domain contains a unique penta-tryptophan motif. The IRFs form homo- and heterodimers through the protein binding domain, called IRF association domain (IAD). This domain is also called the SMIR (SMAD/IRF) domain because the secondary structure of this protein binding domain is shared in the two families [Eroshkin & Mushegian 1999]. Most IRFs, including IRF6, are broadly, but not ubiquitously, expressed. The expression of IRF4 and IRF8 is restricted to hematopoietic cells.

The IRFs are best known to regulate the expression of interferon-alpha and interferon-beta after viral infection [Taniguchi et al 2001]. Following a viral infection, the latent IRF proteins in the cytoplasm are activated by multiple phosphorylation events at serine residues in the C terminus. They form homo- and heterodimers, accumulate in the nucleus, bind to the promoters of the interferon and interferon-stimulated genes, and are active in transcription [Lin et al 1998].

Mouse knockout studies support the role for *Irf1*, *Irf2*, *Irf3*, *Irf4*, *Irf5*, *Irf7*, *Irf8*, and *Irf9* in the immune response, and none of these mutant strains has embryologic abnormalities [Matsuyama et al 1993, Holtschke et al 1996, Kimura et al 1996, Mittrucker et al 1997, Sato et al 2000, Honda et al 2005, Takaoka et al 2005]. However, IRF1, IRF2, IRF3, IRF4, and IRF7 also regulate cell growth or arrest [Iida et al 1997, Harada et al 1998, Heylbroeck et al 2000, Zhang & Pagano 2002]. Although IRF6 was identified as a homolog of IRF4, which is required for B- and T-cell development and homeostasis [Mittrucker et al 1997], its function remains unknown. Mice deficient for *Irf6* have abnormal skin, limb, and craniofacial development [B Schutte, M Dixon, J Murray, personal communication].

Abnormal gene product: The mutations in individuals with VWS are consistent with haploinsufficiency. The missense mutations that cause VWS localize to the regions encoding the DNA binding domains (exons 3 and 4) and the protein binding domain (exons 7, 8, and 9) and most likely result in loss of function.

The mutations found in many individuals with PPS are highly localized to amino acid residues in the DNA binding domain (exons 3 and 4). Based on structural similarity to IRF1 [Escalante et al 1998], these residues (including W60, K66, Q82, R84, K89) are predicted to directly contact the DNA target. Missense mutations at these positions abrogate DNA binding in IRF1 [Escalante et al 1998] but do not affect protein binding. Consequently, these mutations are predicted to have a dominant negative effect on IRF function and may explain the broader phenotype observed in PPS [Kondo et al 2002]. Not all missense mutations at R84 are highly associated with PPS; R84G and R84P are only found in individuals with VWS, suggesting a different effect on IRF6 function for these mutations.

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; 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

References

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.

Literature Cited

Bixler D, Poland C, Nance WE. Phenotypic variation in the popliteal pterygium syndrome. Clin Genet. 1973;4:220–8. [PubMed: 4203060]

Blanton SH, Cortez A, Stal S, Mulliken JB, Finnell RH, Hecht JT. Variation in IRF6 contributes to nonsyndromic cleft lip and palate. Am J Med Genet A. 2005;137:259–62. [PubMed: 16096995]

Brivanlou AH, Darnell JE Jr. Signal transduction and the control of gene expression. Science. 2002;295:813–8. [PubMed: 11823631]

Burdick AB. Genetic epidemiology and control of genetic expression in van der Woude syndrome. J Craniofac Genet Dev Biol Suppl. 1986;2:99–105. [PubMed: 3491128]

Burdick AB, Bixler D, Puckett CL. Genetic analysis in families with van der Woude syndrome. J Craniofac Genet Dev Biol. 1985;5:181–208. [PubMed: 4019732]

Burdick AB, Ma LA, Dai ZH, Gao NN. van der Woude syndrome in two families in China. J Craniofac Genet Dev Biol. 1987;7:413–8. [PubMed: 3429616]

Burke LW, Jones MC. Kabuki syndrome: underdiagnosed recognizable pattern in cleft palate patients. Cleft Palate Craniofac J. 1995;32:77–84. [PubMed: 7727492]

Cervenka J, Gorlin RJ, Anderson VE. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. Am J Hum Genet. 1967;19:416–32. [PubMed: 6026934]

Cohen MM Jr, Bankier A. Syndrome delineation involving orofacial clefting. Cleft Palate Craniofac J. 1991;28:119–20. [PubMed: 2004090]

Demarquay J. Quelques considerations sur le bec-de-lievre. Gaz Med. 1845;13:52–4.

Dode C, Levilliers J, Dupont JM, De Paepe A, Le Du N, Soussi-Yanicostas N, Coimbra RS, Delmaghani S, Compain-Nouaille S, Baverel F, Pecheux C, Le Tessier D, Cruaud C, Delpech M, Speleman F, Vermeulen S, Amalfitano A, Bachelot Y, Bouchard P, Cabrol S, Carel JC, Delemarre-van de Waal H, Goulet-Salmon B, Kottler ML, Richard O, Sanchez-Franco F, Saura R, Young J, Petit C, Hardelin JP. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nat Genet. 2003;33:463–5. [PubMed: 12627230]

Du XY, Tang W, Tian WD, Li XY, Liu L, Zheng XH. [Identification of three novel mutations of IRF6 in Chinese families with Van der Woude syndrome] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2006;23:82–3. [PubMed: 16456794]

Eroshkin A, Mushegian A. Conserved transactivation domain shared by interferon regulatory factors and Smad morphogens. J Mol Med. 1999;77:403–5. [PubMed: 10426188]

Escalante CR, Yie J, Thanos D, Aggarwal AK. Structure of IRF-1 with bound DNA reveals determinants of interferon regulation. Nature. 1998;391:103–6. [PubMed: 9422515]

Fitzpatrick DR, Denhez F, Kondaiah P, Akhurst RJ. Differential expression of TGF beta isoforms in murine palatogenesis. Development. 1990;109:585–95. [PubMed: 2401212]

Franceschini P, Vardeu MP, Guala A, Franceschini D, Testa A, Corrias A, Chiabotto P. Lower lip pits and complete idiopathic precocious puberty in a patient with Kabuki make-up (Niikawa-Kuroki) syndrome. Am J Med Genet. 1993;47:423–5. [PubMed: 8135293]

Froster-Iskenius UG. Popliteal pterygium syndrome. J Med Genet. 1990;27:320–6. [PubMed: 2352260]

Fujimoto A, Lipson M, Lacro RV, Shinno NW, Boelter WD, Jones KL, Wilson MG. New autosomal dominant branchio-oculo-facial syndrome. Am J Med Genet. 1987;27:943–51. [PubMed: 3321995]

Gatta V, Scarciolla O, Cupaioli M, Palka C, Chiesa PL, Stuppia L. A novel mutation of the IRF6 gene in an Italian family with Van der Woude syndrome. Mutat Res. 2004;547:49–53. [PubMed: 15013698]

Ghassibe M, Bayet B, Revencu N, Verellen-Dumoulin C, Gillerot Y, Vanwijck R, Vikkula M. Interferon regulatory factor-6: a gene predisposing to isolated cleft lip with or without cleft palate in the Belgian population. Eur J Hum Genet. 2005;13:1239–42. [PubMed: 16132054]

Ghassibe M, Revencu N, Bayet B, Gillerot Y, Vanwijck R, Verellen-Dumoulin C, Vikkula M. Six families with van der Woude and/or popliteal pterygium syndrome: all with a mutation in the IRF6 gene. J Med Genet. 2004;41:e15. [PubMed: 14757865]

Hall BD, deLorimier A, Foster LH. Brief clinical report: a new syndrome of hemangiomatous branchial clefts, lip pseudoclefts, and unusual facial appearance. Am J Med Genet. 1983;14:135–8. [PubMed: 6829601]

Harada H, Taniguchi T, Tanaka N. The role of interferon regulatory factors in the interferon system and cell growth control. Biochimie. 1998;80:641–50. [PubMed: 9865486]

Hering R, Grundmann K. The IRF6 p.274V polymorphism is not a risk factor for isolated cleft lip. Genet Med. 2005;7:209. [PubMed: 15775759]

Heylbroeck C, Balachandran S, Servant MJ, DeLuca C, Barber GN, Lin R, Hiscott J. The IRF-3 transcription factor mediates Sendai virus-induced apoptosis. J Virol. 2000;74:3781–92. [PubMed: 10729153]

Holtschke T, Lohler J, Kanno Y, Fehr T, Giese N, Rosenbauer F, Lou J, Knobeloch KP, Gabriele L, Waring JF, Bachmann MF, Zinkernagel RM, Morse HC III, Ozato K, Horak I. Immunodeficiency and chronic myelogenous leukemia-like syndrome in mice with a targeted mutation of the ICSBP gene. Cell. 1996;87:307–17. [PubMed: 8861914]

Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N, Taniguchi T. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature. 2005;434:772–7. [PubMed: 15800576]

Iida S, Rao PH, Butler M, Corradini P, Boccadoro M, Klein B, Chaganti RS, Dalla-Favera R. Deregulation of MUM1/IRF4 by chromosomal translocation in multiple myeloma. Nat Genet. 1997;17:226–30. [PubMed: 9326949]

Ilyina H, Lurie I, Naumtchik I, Amoashy D, Stephanenko G, Fedotov V, Kostjuk A. Kabuki make-up (Niikawa-Kuroki) syndrome in the Byelorussian register of congenital malformations: ten new observations. Am J Med Genet. 1995;56:127–31. [PubMed: 7625432]

Item CB, Turhani D, Thurnher D, Yerit K, Sinko K, Wittwer G, Adeyemo WL, Frei K, Erginel-Unaltuna N, Watzinger F, Ewers R. Van Der Woude syndrome: variable penetrance of a novel mutation (p.Arg 84Gly) of the IRF6 gene in a Turkish family. Int J Mol Med. 2005;15:247–51. [PubMed: 15647839]

Janku P, Robinow M, Kelly T, Bralley R, Baynes A, Edgerton MT. The van der Woude syndrome in a large kindred: variability, penetrance, genetic risks. Am J Med Genet. 1980;5:117–23. [PubMed: 7395906]

Jezewski PA, Vieira AR, Nishimura C, Ludwig B, Johnson M, O'Brien SE, Daack-Hirsch S, Schultz RE, Weber A, Nepomucena B, Romitti PA, Christensen K, Orioli IM, Castilla EE, Machida J, Natsume N, Murray JC. Complete sequencing shows a role for MSX1 in non-syndromic cleft lip and palate. J Med Genet. 2003;40:399–407. [PubMed: 12807959]

Kantaputra PN, Sumitsawan Y, Schutte BC, Tochareontanaphol C. Van der Woude syndrome with sensorineural hearing loss, large craniofacial sinuses, dental pulp stones, and minor limb anomalies: report of a four-generation Thai family. Am J Med Genet. 2002;108:275–80. [PubMed: 11920830]

Kayano S, Kure S, Suzuki Y, Kanno K, Aoki Y, Kondo S, Schutte BC, Murray JC, Yamada A, Matsubara Y. Novel IRF6 mutations in Japanese patients with Van der Woude syndrome: two missense mutations (R45Q and P396S) and a 17-kb deletion. J Hum Genet. 2003;48:622–8. [PubMed: 14618417]

Kim Y, Park JY, Lee TJ, Yoo HW. Identification of two novel mutations of IRF6 in Korean families affected with Van der Woude syndrome. Int J Mol Med. 2003;12:465–8. [PubMed: 12964020]

Kimura T, Kadokawa Y, Harada H, Matsumoto M, Sato M, Kashiwazaki Y, Tarutani M, Tan RS, Takasugi T, Matsuyama T, Mak TW, Noguchi S, Taniguchi T. Essential and non-redundant roles of p48 (ISGF3 gamma) and IRF-1 in both type I and type II interferon responses, as revealed by gene targeting studies. Genes Cells. 1996;1:115–24. [PubMed: 9078371]

Koillinen H, Wong FK, Rautio J, Ollikainen V, Karsten A, Larson O, Teh BT, Huggare J, Lahermo P, Larsson C, Kere J. Mapping of the second locus for the Van der Woude syndrome to chromosome 1p34. Eur J Hum Genet. 2001;9:747–52. [PubMed: 11781685]

Kokitsu-Nakata NM, Vendramini S, Guion-Almeida ML. Lower lip pits and anorectal anomalies in Kabuki syndrome. Am J Med Genet. 1999;86:282–4. [PubMed: 10482881]

Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, de Lima RL, Daack-Hirsch S, Sander A, McDonald-McGinn DM, Zackai EH, Lammer EJ, Aylsworth AS, Ardinger HH, Lidral AC, Pober BR, Moreno L, Arcos-Burgos M, Valencia C, Houdayer C, Bahuau M, Moretti-Ferreira D, Richieri-Costa A, Dixon MJ, Murray JC. Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet. 2002;32:285–9. [PubMed: 12219090]

Lee WK, Root AW, Fenske N. Bilateral branchial cleft sinuses associated with intrauterine and postnatal growth retardation, premature aging, and unusual facial appearance: a new syndrome with dominant transmission. Am J Med Genet. 1982;11:345–52. [PubMed: 7200726]

Lees MM, Winter RM, Malcolm S, Saal HM, Chitty L. Popliteal pterygium syndrome: a clinical study of three families and report of linkage to the Van der Woude syndrome locus on 1q32. J Med Genet. 1999;36:888–92. [PubMed: 10593995]

Lewis E. Congenital webbing of lower limbs. Proc R Soc Med. 1948;41:64.

Lin R, Heylbroeck C, Pitha PM, Hiscott J. Virus-dependent phosphorylation of the IRF-3 transcription factor regulates nuclear translocation, transactivation potential, and proteasome-mediated degradation. Mol Cell Biol. 1998;18:2986–96. [PubMed: 9566918]

Makita Y, Yamada K, Miyamoto A, Okuno A, Niikawa N. Kabuki make-up syndrome is not caused by microdeletion close to the van der Woude syndrome critical region at 1q32-q41. Am J Med Genet. 1999;86:285–8. [PubMed: 10482882]

Matsumura M, Yamada R, Kitani Y, Nishi T, Yamamoto H, Oahama Y, Kuroki Y. Anorectal anomalies associated with Kabuki make-up syndrome. J Pediatr Surg. 1992;27:1600–2. [PubMed: 1469590]

Matsuyama T, Kimura T, Kitagawa M, Pfeffer K, Kawakami T, Watanabe N, Kundig TM, Amakawa R, Kishihara K, Wakeham A, et al. Targeted disruption of IRF-1 or IRF-2 results in abnormal type I IFN gene induction and aberrant lymphocyte development. Cell. 1993;75:83–97. [PubMed: 8402903]

Matsuzawa N, Yoshiura K, Machida J, Nakamura T, Niimi T, Furukawa H, Toyoda T, Natsume N, Shimozato K, Niikawa N. Two missense mutations in the IRF6 gene in two Japanese families with Van der Woude syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:414–7. [PubMed: 15472655]

McCool M, Weaver DD. Branchio-oculo-facial syndrome: broadening the spectrum. Am J Med Genet. 1994;49:414–21. [PubMed: 8160736]

Mittrucker HW, Matsuyama T, Grossman A, Kundig TM, Potter J, Shahinian A, Wakeham A, Patterson B, Ohashi PS, Mak TW. Requirement for the transcription factor LSIRF/IRF4 for mature B and T lymphocyte function. Science. 1997;275:540–3. [PubMed: 8999800]

Mostowska A, Wojcicki P, Kobus K, Trzeciak WH. Gene symbol: IRF6. Disease: Van der Woude syndrome. Hum Genet. 2005;116:534. [PubMed: 15988826]

Murray JC, Daack-Hirsch S, Buetow KH, Munger R, Espina L, Paglinawan N, Villanueva E, Rary J, Magee K, Magee W. Clinical and epidemiologic studies of cleft lip and palate in the Philippines. Cleft Palate Craniofac J. 1997;34:7–10. [PubMed: 9003905]

Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. Am J Med Genet. 1988;31:565–89. [PubMed: 3067577]

Oberoi S, Vargervik K. Hypoplasia and hypodontia in Van der Woude syndrome. Cleft Palate Craniofac J. 2005;42:459–66. [PubMed: 16149825]

Peyrard-Janvid M, Pegelow M, Koillinen H, Larsson C, Fransson I, Rautio J, Hukki J, Larson O, Karsten AL, Kere J. Novel and de novo mutations of the IRF6 gene detected in patients with Van der Woude or popliteal pterygium syndrome. Eur J Hum Genet. 2005;13:1261–7. [PubMed: 16160700]

Ranta R, Rintala AE. Correlations between microforms of the Van der Woude syndrome and cleft palate. Cleft Palate J. 1983;20:158–62. [PubMed: 6573981]

Ranta R, Stegars T, Rintala AE. Correlations of hypodontia in children with isolated cleft palate. Cleft Palate J. 1983;20:163–5. [PubMed: 6573982]

Richardson E, Davison C, Moore AT. Colobomatous microphthalmia with midfacial clefting: part of the spectrum of branchio-oculo-facial syndrome? Ophthalmic Genet. 1996;17:59–65. [PubMed: 8832722]

Rintala A, Gylling U, Lahti A, Soivio A. On sarcomas of the mandibular region. Scand J Plast Reconstr Surg. 1970;4:109–13. [PubMed: 5531996]

Rintala AE, Ranta R. Lower lip sinuses: I. Epidemiology, microforms and transverse sulci. Br J Plast Surg. 1981;34:26–30. [PubMed: 7459520]

Sander A, Schmelzle R, Murray J. Evidence for a microdeletion in 1q32-41 involving the gene responsible for Van der Woude syndrome. Hum Mol Genet. 1994;3:575–8. [PubMed: 8069301]

Sato M, Suemori H, Hata N, Asagiri M, Ogasawara K, Nakao K, Nakaya T, Katsuki M, Noguchi S, Tanaka N, Taniguchi T. Distinct and essential roles of transcription factors IRF-3 and IRF-7 in response to viruses for IFN-alpha/beta gene induction. Immunity. 2000;13:539–48. [PubMed: 11070172]

Scapoli L, Palmieri A, Martinelli M, Pezzetti F, Carinci P, Tognon M, Carinci F. Strong evidence of linkage disequilibrium between polymorphisms at the IRF6 locus and nonsyndromic cleft lip with or without cleft palate, in an Italian population. Am J Hum Genet. 2005;76:180–3. [PubMed: 15558496]

Schinzel A, Klausler M. The Van der Woude syndrome (dominantly inherited lip pits and clefts). J Med Genet. 1986;23:291–4. [PubMed: 3746828]

Schutte BC, Basart AM, Watanabe Y, Laffin JJ, Coppage K, Bjork BC, Daack-Hirsch S, Patil S, Dixon MJ, Murray JC. Microdeletions at chromosome bands 1q32-q41 as a cause of Van der Woude syndrome. Am J Med Genet. 1999;84:145–50. [PubMed: 10323740]

Shotelersuk V, Srichomthong C, Yoshiura K, Niikawa N. A novel mutation, 1234del(C), of the IRF6 in a Thai family with Van der Woude syndrome. Int J Mol Med. 2003;11:505–7. [PubMed: 12632105]

Shprintzen RJ, Goldberg RB, Sidoti EJ. The penetrance and variable expression of the Van der Woude syndrome: implications for genetic counseling. Cleft Palate J. 1980;17:52–7. [PubMed: 6928118]

Soekarman D, Cobben JM, Vogels A, Spauwen PH, Fryns JP. Variable expression of the popliteal pterygium syndrome in two 3-generation families. Clin Genet. 1995;47:169–74. [PubMed: 7628117]

Soricelli DA, Bell L, Alexander WA. Congenital fistulas of the lower lip. A family case report. Oral Surg Oral Med Oral Pathol. 1966;21:511–6. [PubMed: 5218157]

Srichomthong C, Siriwan P, Shotelersuk V. Significant association between IRF6 820G>A and non-syndromic cleft lip with or without cleft palate in the Thai population. J Med Genet. 2005;42:e46. [PubMed: 15994871]

Takaoka A, Yanai H, Kondo S, Duncan G, Negishi H, Mizutani T, Kano S, Honda K, Ohba Y, Mak TW, Taniguchi T. Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. Nature. 2005;434:243–9. [PubMed: 15665823]

Taniguchi T, Ogasawara K, Takaoka A, Tanaka N. IRF family of transcription factors as regulators of host defense. Annu Rev Immunol. 2001;19:623–55. [PubMed: 11244049]

van den Boogaard MJ, Dorland M, Beemer FA, van Amstel HK. MSX1 mutation is associated with orofacial clefting and tooth agenesis in humans. Nat Genet. 2000;24:342–3. [PubMed: 10742093]

VAN DER WOUDE A. Fistula labii inferioris congenita and its association with cleft lip and palate. Am J Hum Genet. 1954;6:244–56. [PubMed: 13158329]

Wang X, Liu J, Zhang H, Xiao M, Li J, Yang C, Lin X, Wu Z, Hu L, Kong X. Novel mutations in the IRF6 gene for Van der Woude syndrome. Hum Genet. 2003;113:382–6. [PubMed: 12920575]

Wang XF, Xiao MZ, Shi JN, Zhang HB, Hu LD, Kong XY. [IRF6 gene mutation analysis in a van Der Woude syndrome family in Henan province] Shanghai Kou Qiang Yi Xue. 2005;14:234–7. [PubMed: 15995766]

Wong FK, Koillinen H, Rautio J, Teh BT, Ranta R, Karsten A, Larson O, Linder-Aronson S, Huggare J, Larsson C, Kere J. Genetic heterogeneity and exclusion of a modifying locus at 17p11.2- p11.1 in Finnish families with van der Woude syndrome. J Med Genet. 2001;38:198–202. [PubMed: 11303516]

Ye XQ, Jin HX, Shi LS, Fan MW, Song GT, Fan HL, Bian Z. Identification of novel mutations of IRF6 gene in Chinese families with Van der Woude syndrome. Int J Mol Med. 2005;16:851–6. [PubMed: 16211254]

Zhang L, Pagano JS. Structure and function of IRF-7. J Interferon Cytokine Res. 2002;22:95–101. [PubMed: 11846980]

Zucchero TM, Cooper ME, Maher BS, Daack-Hirsch S, Nepomuceno B, Ribeiro L, Caprau D, Christensen K, Suzuki Y, Machida J, Natsume N, Yoshiura K, Vieira AR, Orioli IM, Castilla EE, Moreno L, Arcos-Burgos M, Lidral AC, Field LL, Liu YE, Ray A, Goldstein TH, Schultz RE, Shi M, Johnson MK, Kondo S, Schutte BC, Marazita ML, Murray JC. Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate. N Engl J Med. 2004;351:769–80. [PubMed: 15317890]

Chapter Notes

Revision History

- 15 May 2006 (me) Comprehensive update posted to live Web site
- 30 October 2003 (me) Review posted to live Web site
- 27 May 2003 (jcm) Original submission