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IRF6-Related Disorders

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Summary

Clinical characteristics

Most commonly, *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. In rare instances, *IRF6* pathogenic variants have also been reported in individuals with nonsyndromic orofacial cleft (18/3,811; 0.47%) and in individuals with spina bifida (2/192).

Individuals with VWS show **one or more** of the following 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)
- Cleft palate (CP)

  Note: Cleft lip with or without cleft palate (CL±P) is observed about twice as often as CP only.
- Submucous cleft palate (SMCP)

The PPS phenotype includes the following:

- CL±P
- Fistulae of the lower lip
- Webbing of the skin extending from the ischial tuberosities to the heels
- In males: bifid scrotum and cryptorchidism
- In females: hypoplasia of the labia majora
- Syndactyly of fingers and/or toes

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- Anomalies of the skin around the nails
- A characteristic pyramidal fold of skin overlying the nail of the hallux (almost pathognomonic)
- In some nonclassic forms of PPS: filiform synechiae connecting the upper and lower jaws (syngnathia) or the upper and lower eyelids (ankyloblepharon)
- Other musculoskeletal anomalies may include spina bifida occulta, talipes equinovarus, digital reduction, bifid ribs, and short sternum.

In VWS, PPS, *IRF6*-related neural tube defect, and *IRF6*-related orofacial cleft, growth and intelligence are typical.

Diagnosis/testing

Diagnosis of an *IRF6*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic variant in *IRF6* identified by molecular genetic testing. A heterozygous pathogenic variant in *IRF6* is identified in approximately 72% of individuals with the VWS phenotype, approximately 97% of individuals with the PPS phenotype, and fewer than 1% of individuals with a neural tube defect or orofacial cleft.

Management

Treatment of manifestations: Supportive/symptomatic treatment of VWS and PPS may include surgical treatment of lip pits and cleft lip and palate pediatric dentistry, orthodontia, speech therapy, feeding therapy, timely treatment of otitis media due to eustachian tube dysfunction to prevent secondary hearing loss, physical therapy, orthopedic care, and surgical treatment for cryptorchidism. Surgical treatment may be needed for those with oral and/or eyelid synechiae. *IRF6*-related neural tube defects are treated in a standard manner as per neurosurgeon. *IRF6*-related orofacial clefts are treated in a standard manner.

Surveillance: Surveillance for those with cleft lip and/or cleft palate includes weekly assessment of nutritional intake and weight gain during the first month of life; otolaryngologic evaluation within the first six months of life and continued throughout adolescence; audiologic evaluation with infant's first visit to cleft clinic, with the frequency of subsequent evaluations based on the history of ear disease or hearing loss; speech-language pathology evaluation by age six months, twice during the first two years of life, at least annually until age six years, at least annually until after adenoid involution, and at least every two years until dental and skeletal maturity; dental evaluation within six months of the first tooth erupting and no later than age 12 months, and routine dental evaluation continued throughout life. In individuals with myelomeningocele, assessment of walking and mobility and bowel and bladder management with each visit throughout life.

Genetic counseling

IRF6-related disorders are inherited in an autosomal dominant manner. Most individuals diagnosed with an *IRF6*-related clefting disorder (e.g., VWS or PPS) inherited an *IRF6* pathogenic variant from a heterozygous parent who may or may not have manifestations of the disorder. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if a parent of the proband is affected and/or has an *IRF6* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Once an *IRF6* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Prenatal ultrasound examination may detect a cleft lip with/without cleft palate in some fetuses later in the second trimester, but it is much less likely to detect an isolated cleft palate or lip pits.

GeneReview Scope

IRF6-Related Disorders: Included Phenotypes
• Van der Woude syndrome (VWS) • Popliteal pterygium syndrome (PPS) • *IRF6*-related neural tube defect • *IRF6*-related orofacial cleft

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Van der Woude syndrome (VWS)

- **Lip pits*** in combination with one of the following:
  - Cleft lip with or without cleft palate (CL±P)
  - Cleft palate (CP)
  - Submucous cleft palate (SMCP)
- **Lip pits*** alone and a first-degree relative with **CL±P, CP, or SMCP**
- **CL±P, CP, or SMCP** and a first-degree relative with **lip pits***
- CL or CL+P and CP in the same family

* Lip pits are most often paramedian on the lower lip, and can include mounds with a sinus tract leading from a mucous gland of the lip.

Popliteal pterygium syndrome (PPS)

- Popliteal pterygia
- Syndactyly
- Abnormal external genitalia
- Ankyloblepharon
- Pyramidal skin on the hallux
- A spectrum of intraoral adhesions, the most severe of which is complete syngnathia
- Musculoskeletal anomalies are rarely reported (e.g., talipes equinovarus, digital reduction, spina bifida occulta, bifid ribs, short sternum).

***IRF6*-related neural tube defect.** Two individuals with an *IRF6* pathogenic variant and spina bifida have been reported. Neural tube defects due to an *IRF6* pathogenic variant cannot be clinically distinguished from neural tube defects of other etiologies.

***IRF6*-related orofacial cleft.** Eighteen individuals with an *IRF6* pathogenic variant and orofacial cleft have been reported. Orofacial cleft due to an *IRF6* pathogenic variant cannot be clinically distinguished from orofacial clefts of other etiologies.

Establishing the Diagnosis

The diagnosis of an *IRF6*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *IRF6* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches include single-gene testing or a multigene panel.

- **Single-gene testing.** Sequence analysis of *IRF6* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants; analysis of the *IRF6* regulatory region should be included (see Molecular Genetics). Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes sequence analysis and gene-targeted deletion/duplication analysis of *IRF6* (see Molecular Genetics), *GRHL3,* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

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

Gene [1]	Phenotype	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method	
		Sequence analysis [3]	Deletion/duplication analysis [4]
IRF6	VWS	~72% [5]	<2% [6]
	PPS	~97% [7]	Unknown [8]
	Isolated NTD	2 persons [9]	None reported
	Isolated OFC	18 persons [10]	None reported

NTD = neural tube defect; OFC = orofacial cleft; PPS = popliteal pterygium syndrome; VWS = Van der Woude syndrome

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Sequence analysis of *IRF6* (exons 1-9) detects pathogenic variants in approximately 68% of individuals with VWS [de Lima et al 2009]. Pathogenic variants in exons 3, 4, 7, and 9 account for 80% of known VWS-causing variants (N=307) [de Lima et al 2009].

6. Whole- and partial-gene deletions have been identified in several families with VWS [Sander et al 1994, Schutte et al 1999, Kayano et al 2003, Osoegawa et al 2008, Tan et al 2008, de Lima et al 2009, Salahshourifar et al 2011, Mbuyi-Musanzayi et al 2020].

7. Sequence analysis of exon 4 of the *IRF6* coding region detected pathogenic variants in approximately 72% of individuals with PPS [de Lima et al 2009]. Additional sequencing of the entire coding region of *IRF6* detected pathogenic variants in approximately 97% of individuals with PPS (N=37) [de Lima et al 2009].

8. Incidence of deletions/duplications unknown; likely rare as pathogenic variants were identified on sequence analysis in 36 of 37 individuals with PPS [de Lima et al 2009].

9. Kousa et al [2019]

10. IRF6 pathogenic variants were identified in 0.47% (18/3,811) of individuals with nonsyndromic orofacial cleft [Leslie et al 2016, Khandelwal et al 2017].

Clinical Characteristics

Clinical Description

The craniofacial features of nonsyndromic orofacial clefting, Van der Woude syndrome (VWS), and popliteal pterygium syndrome (PPS) form a continuum such that it is often difficult to distinguish mildly affected individuals with VWS from those with nonsyndromic orofacial clefting, and mildly affected individuals with PPS from those with VWS. To date, pathogenic variants in *IRF6* have been found in 648 families [Kondo et al 2002, de Lima et al 2009, Leslie et al 2013, Alade et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *IRF6*-Related Disorders: Comparison of Phenotypes by Select Features

Feature	VWS [1]	PPS [2]	*IRF6*-Related Isolated NTD [3]	*IRF6*-Related Isolated OFC [4]
Lip pits	86%	46%	–	–
Cleft lip ± cleft palate	37%	91%-97%	–	>60%
Cleft palate	16%	–	–	<30%
Hypodontia	10%-20%	–	–	–
Popliteal pterygia	–	Common	–	–
Syndactyly	–	59%	–	–
Pyramidal skin on hallux	–	Common	–	–
Abnormal external genitalia	–	Common	–	–
NTD – spina bifida occulta	–	Rare	–	–
NTD – myelomeningocele	–	–	100%	–

– = not reported; NTD = neural tube defect; OFC = orofacial cleft; PPS = popliteal pterygium syndrome; VWS = Van der Woude syndrome
1. Burdick et al [1985]
2. Froster-Iskenius [1990]
3. Kousa et al [2019]
4. Leslie et al [2016], Khandelwal et al [2017]

Van der Woude Syndrome

Individuals with VWS show one or more of the following anomalies: lip pits, cleft lip (CL), cleft palate (CP), and submucous cleft palate (SMCP) [Van der Woude 1954].

Lip abnormalities. Individuals with VWS often have congenital, usually bilateral, paramedian lower-lip fistulae (pits) or sometimes small mounds with a sinus tract leading from a mucous gland of the lip. Lip manifestations are variable and can include single unilateral lip pits, conical elevations of the lip, or bulges located below the vermilion border.

CL and/or CP. The ratio of CL with or without CP (CL±P) to CP only is about two to one in individuals with VWS [Burdick et al 1985]. Of note, this is the same relative proportion as in the general population. The *IRF6*-related disorders are among very few single-gene disorders or genetic syndromes in which individuals from the same family have both types of clefting (i.e., one family member having cleft palate alone and another having cleft lip and palate) (see Differential Diagnosis). he sex ratio is nearly equal in VWS for CP and CL±P. 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. Submucous cleft and bifid uvula have also been reported in individuals with *IRF6*-related VWS.

Hypodontia. Typically consists of absent second incisors and second molars in the deciduous or permanent teeth. Approximately 10%-20% of individuals with VWS have hypodontia [Schinzel & Kläusler 1986].

Other

- Growth and intelligence are normal.
- In a small study, Jones et al [2010] found that following surgery for their clefts, eight (47%) of 17 individuals with VWS had wound complications compared to 13 (19%) of 68 individuals with nonsyndromic cleft lip and palate (NSCLP).

Popliteal Pterygium Syndrome

The PPS phenotype includes cleft lip and/or palate, fistulae of the lower lip, pterygia, genital anomalies, and characteristic digit anomalies.

Pterygia. Webbing of the skin extending from the ischial tuberosities to the heels

Genital anomalies. Bifid scrotum and cryptorchidism in males, hypoplasia of the labia majora in females

Digits. 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.

Other

- Filiform synechiae connecting the upper and lower jaws (syngnathia) and/or the upper and lower eyelids (ankyloblepharon) may occur.
- Musculoskeletal anomalies are rarely reported (e.g., talipes equinovarus, digital reduction, spina bifida occulta, bifid ribs, short sternum).
- Growth and intelligence are normal.

IRF6-Related Neural Tube Defect

Two individuals with spina bifida were found to have a heterozygous *IRF6* pathogenic variant [Kousa et al 2019] (see Table 7).

IRF6-Related Isolated Orofacial Cleft

Eighteen individuals with orofacial cleft were found to have a heterozygous *IRF6* pathogenic variant [Leslie et al 2016, Khandelwal et al 2017].

Genotype-Phenotype Correlations

VWS. Whole-gene deletions and nearly all protein truncation variants cause a VWS phenotype. Missense variants that cause VWS are evenly divided between the two protein domains encoded in exons 3, 4, and 7-9. Two pathogenic missense variants at arginine 84, p.Arg84Gly [Item et al 2005] and p.Arg84Pro [de Lima et al 2009], are found only in individuals with VWS, suggesting that p.Arg84Gly and p.Arg84Pro differ from p.Arg84His and p.Arg84Cys (which are seen most commonly in PPS) in their effect on *IRF6* protein function.

PPS. Most PPS-associated variants are missense (78%) and are located in exon 4 (72%).

It appears likely that certain pathogenic variants (p.Arg84His, p.Arg84Cys) are more apt to cause PPS than VWS. A cluster of pathogenic missense variants in the DNA binding domain that are predicted to directly contact the DNA are more commonly seen in families with PPS ($p<0.01$); these include amino acid residues Trp60, Lys66, Gln82, Arg84, and Lys89. However, families may include individuals with features of VWS only and others with the additional features of PPS.

There are examples of variable expressivity, where at least one member of the same family is diagnosed with PPS, while at least one other member is diagnosed with VWS.

Penetrance

IRF6-related disorders have high, but incomplete, penetrance.

VWS. 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% [Burdick et al 1985].

PPS. Of approximately 40 pedigrees with individuals diagnosed with PPS, there were no instances of incomplete penetrance.

Nomenclature

The following terms were used in the original description of Van der Woude syndrome by Anne Van der Woude [1954], but are no longer used:

- Congenital pits of the lower lip
- Fistula labii inferioris congenita
- Congenital fistulae of the lower lip

Current nomenclature is "lip pits," "lip eminences," or more inclusively "lip abnormalities."

Prevalence

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 1:35,000 to 1:100,000 in the European and Asian populations [Cervenka et al 1967, Rintala & Ranta 1981, Burdick 1986].

PPS. A prevalence of approximately 1:300,000 has been suggested [Froster-Iskenius 1990].

Genetically Related (Allelic) Disorders

Large contiguous gene deletions that include *IRF6* have been reported in several families; affected individuals in one family had developmental disabilities [Sander et al 1994]. In two other families, individuals with large deletions had normal intelligence [Schutte et al 1999, Kayano et al 2003]. In one of the latter cases, the deletion was even larger than that described by Sander et al [1994].

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *IRF6*-Related Disorders

Gene(s)	Disorder	MOI	Lip Pits	Cleft Lip / Cleft Palate	Other Clinical Characteristics / Comment
CHD7	*CHD7* disorder (CHARGE syndrome)	AD	Absent	Mixed clefting (CP±L or CP only)	Although lip pits are absent, disorder lacks sufficient addl features to exclude VWS w/o lip pits & should be considered in evaluating any family in which multiple members have orofacial clefts.
FGFR1	*FGFR1*-related hypogonadotropic hypogonadism (OMIM 147950)	AD	Absent	Mixed clefting (CL±P or CP only)	
GRHL3 [1]	VWS 2 (OMIM 606713)	AD	± (upper lip)	±CL/±CP	"Wave-like" lower lip

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Lip Pits	Cleft Lip / Cleft Palate	Other Clinical Characteristics / Comment
KDM6A *KMT2D*	Kabuki syndrome	AD XL	± (upper lip)	±CL/±CP	Typical facial features (long palpebral fissures w/eversion of lateral 3rd of lower eyelid; arched & broad eyebrows; short columella w/depressed nasal tip; large, prominent, or cupped ears), minor skeletal anomalies, persistence of fetal fingertip pads, mild-to-moderate ID, & postnatal growth deficiency
MSX1	*MSX1* disorders [2]	AD	Absent	Mixed clefting (CL±P or CP only)	Although lip pits are absent, disorder lacks sufficient addl features to exclude VWS w/o lip pits & should be considered in evaluating any family in which multiple members have orofacial clefts.
RIPK4	Bartsocas-Pappas syndrome (PPS, lethal type) (OMIM 263650)	AR	± (upper lip)	±CL/±CP	Cutaneous webbing across ≥1 major joints, syndactyly, genital hypoplasia, ankyloblepharon, syngnathia, & ectodermal defects (e.g., alopecia, absent eyelashes/eyebrows, & brittle nails)
	CHAND syndrome (OMIM 214350)	AR	± commissural	±CL/CP	Ankyloblepharon, [3] curly hair, nail dysplasia
TFAP2A	Branchiooculofacial syndrome	AD	± (upper lip)	CL±P (or "pseudocleft lip" [4])	Branchial skin defects (barely perceptible thin skin/hair patch or erythematous "hemangiomatous" lesions or large weeping erosions), ocular anomalies, & facial anomalies; malformed/prominent pinnae & hearing loss from inner ear &/or petrous bone anomalies are common.
TP63	*TP63* disorders (e.g., AEC syndrome, EEC3, Rapp-Hodgkin syndrome)	AD	Absent	Mixed clefting (CL±P or CP only)	Ankyloblepharon [3] may be present; although lip pits are absent, disorder lacks sufficient addl features to exclude VWS w/o lip pits & should be considered in evaluating any family in which multiple members have orofacial clefts.

AD = autosomal dominant; AEC = ankyloblepharon-ectodermal defects-cleft lip/palate; AR = autosomal recessive; CL = cleft lip; CL±P = cleft lip with or without cleft palate; CP = cleft palate; EEC3 = ectrodactyly, ectodermal dysplasia, cleft lip/palate 3; ID = intellectual disability; MOI = mode of inheritance; PPS = popliteal pterygium syndrome; VWS = Van der Woude syndrome; XL = X-linked

1. *GRHL3* pathogenic variants appear to account for 17% of individuals w/clinical features of Van der Woude syndrome (VWS) who lack a pathogenic variant in *IRF6* & ~5% of all VWS [Peyrard-Janvid et al 2014].

2. van den Boogaard et al [2000], Jezewski et al [2003]

3. Ankyloblepharon (or eyelid synechiae) present at birth is seen occasionally in popliteal pterygium syndrome.

4. Prominent philtral pillars that give the appearance of a repaired cleft lip (formerly called "pseudocleft lip").

Other disorders

- The mixed clefting seen in *IFR6* disorders (cleft lip with or without cleft palate and cleft palate only) can also occur in **22q11.2 deletion syndrome** and **fetal alcohol syndrome** [Shaw & Lammer 1999].
- Ankyloblepharon (or eyelid synechiae) present at birth is seen occasionally in popliteal pterygium syndrome. These may also be seen in **ectrodactyly**, **ectodermal dysplasia**, **cleft lip/palate syndrome 1** (OMIM 129900), and **trisomy 18**.

Management

No clinical practice guidelines for *IRF6*-related disorders have been published. Individuals with a cleft lip and/or palate should be evaluated and treated by a multidisciplinary team of craniofacial specialists.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *IRF6*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *IRF6*-Related Disorders

System/Concern	Evaluation	Comment
Lip pits	Referral to plastic surgeon for clinical eval & treatment	
Cleft lip/palate	Clinical eval by multidisciplinary team of specialists incl feeding eval	In infancy at diagnosis
	Otolaryngologic eval	In infancy at diagnosis to evaluate for eustachian tube dysfunction
	Audiologic eval	In infancy at diagnosis to evaluate for hearing loss related to cleft palate
	Eval by speech-language pathologist	In infancy at diagnosis to assess prelinguistic speech-language development & to provide parents w/info about speech & language development
	Dental eval	In infancy w/1st visit to cleft clinic
Musculoskeletal manifestation of PPS phenotype	Clinical eval for knee contractures w/webbing behind knee & syndactyly of toes w/referral to orthopedic surgery &/or plastic surgery	
Genital anomalies assoc w/PPS phenotype	Clinical eval w/referral to urologist as necessary	
Hypodontia	Dental eval w/eruption of primary teeth	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *IRF6* disorders to facilitate medical & personal decision making
Family support/ resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; PPS = popliteal pterygium syndrome
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management is supportive/symptomatic.

Table 5. Treatment of Manifestations in Individuals with *IRF6*-Related Disorders

Manifestation/ Concern	Treatment	Considerations/Other
Lip pits	Surgery may be indicated for cosmetic purposes or for lip function.	Lip pits may be connected to mucous-secreting glands & may be excised for this.
Cleft lip	Mgmt is surgical, dental, & orthodontic.	
Cleft palate	• In addition to surgery, dentistry, & orthodontics, speech therapy & audiologic eval are usually needed. • Otolaryngology eval is needed for mgmt of middle ear effusions. • Speech therapy or other interventions are appropriate for child w/secondary hearing loss.	• Timely treatment of otitis media secondary to eustachian tube dysfunction due to cleft palate to prevent secondary hearing loss • Some may have pressure-equalizing tubes placed.
Popliteal pterygium	Mgmt involves PT & surgical & orthopedic intervention as necessary.	
Syndactyly	May require surgery	
Abnormal genitalia	• May require surgery esp in presence of cryptorchidism • Genital anomalies may result in infertility.	
Oral synechiae (incl syngnathia)	Syngnathia often requires emergent release due to feeding & respiratory concerns & may require tracheotomy.	
Eyelid synechiae (ankyloblepharon)	May require surgical excision.	
Neural tube defect	Standard mgmt per neurosurgeon	

PT = physical therapy

Surveillance

The following surveillance guidelines are adapted from the American Cleft Palate-Craniofacial Association [2009] parameters for evaluation and treatment of individuals with cleft lip/palate or other craniofacial anomalies. Click here for full text.

Table 6. Recommended Surveillance for Individuals with *IRF6*-Related Disorders

System/Concern	Evaluation	Frequency
Cleft lip/palate	Assessment of nutritional intake & weight gain	Weekly during 1st mo of life
	Otolaryngologic eval	• Follow-up eval w/in 1st 6 mos of life • Continue evals throughout adolescence.
	Audiologic eval	• Follow-up eval w/infant's 1st visit to cleft clinic • Timing & frequency of follow-up evals based on person's history of ear disease or hearing loss • Routine evals through adolescence
	Speech-language pathology eval	• Follow up by age 6 mos for assessment of prelinguistic speech-language development • During 1st 2 yrs of life, evaluate children at least twice, then at least annually until adenoid involution. • After adenoid involution, evaluate at least every 2 yrs until dental & skeletal maturity.
	Dental eval	• Follow-up eval w/in 6 mos of 1st tooth erupting; no later than age 12 mos • Continue routine dental eval throughout life.
Neural tube defect	Assess walking/ mobility & bowel/ bladder mgmt	At each visit throughout life in those w/history of meningocele or myelomeningocele

Evaluation of Relatives at Risk

Offspring and/or sibs of an affected individual should be clinically examined for evidence of cleft palate including submucous cleft, lip abnormalities (pits or mounds), and the pyramidal skin fold on the nail of the hallux, given the variable expressivity and incomplete penetrance of VWS and PPS.

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

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

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 clefting disorder (e.g., Van der Woude syndrome [VWS] or popliteal pterygium syndrome [PPS]) have the disorder as the result of a pathogenic variant inherited from a heterozygous parent. Because penetrance of *IRF6*-related disorders is incomplete, a heterozygous parent may not have manifestations of the disorder (see Penetrance).
- A proband with an *IRF6*-related disorder may have the disorder as the result of a *de novo* pathogenic variant.
  - In a study of 16 families with VWS and one family with PPS, two individuals with VWS who represented simplex cases (i.e., a single affected family member) had a *de novo IRF6* pathogenic variant [Peyrard-Janvid et al 2005].
  - A female born with ankyloblepharon and lip pits, diagnosed as a mild form of PPS, had a *de novo* pathogenic variant [Houweling et al 2009].
  - *De novo* pathogenic variants in *IRF6* have been identified as a rare cause of orofacial cleft [Leslie et al 2016, Khandelwal et al 2017].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ cells.
- The family history of some individuals diagnosed with an *IRF6*-related disorder may appear to be negative because of failure to recognize the disorder in family members or incomplete penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *IRF6* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted in a sib who inherits an *IRF6* pathogenic variant.
  - **Reduced penetrance.** Approximately 92% of individuals with an *IRF6* pathogenic variant have clinical signs of an *IRF6*-related disorder [Burdick et al 1985]. About 70% of individuals with a pathogenic variant have an orofacial cleft requiring surgical intervention [Murray, personal communication].
  - **Intrafamilial clinical variability** is observed in *IRF6* disorders. Some affected family members may have cleft palate alone while others have cleft lip and palate. In addition, families may include individuals with features of only VWS and others with the additional features of PPS.
- If the parents have not been tested for the *IRF6* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for an *IRF6*-related disorder because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with an *IRF6*-related disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has an *IRF6* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once an *IRF6* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. The clinical manifestations of *IRF6*-related disorders are variable and cannot be predicted based on family history or the presence of an *IRF6* pathogenic variant identified on prenatal testing.

Ultrasound examination. Prenatal ultrasound examination may detect a cleft lip with or without cleft palate in some fetuses later in the second trimester, but it is much less likely to detect an isolated cleft palate or lip pits. A level 2 targeted ultrasound examination at a center that routinely performs such procedures is most accurate.

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

Resources

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

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

Molecular Genetics

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

Table A. IRF6-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
IRF6	1q32.2	Interferon regulatory factor 6	IRF6 database	IRF6	IRF6

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

Table B. OMIM Entries for IRF6-Related Disorders (View All in OMIM)

119300	VAN DER WOUDE SYNDROME 1; VWS1
119500	POPLITEAL PTERYGIUM SYNDROME; PPS
607199	INTERFERON REGULATORY FACTOR 6; IRF6

Molecular Pathogenesis

The function of the normal gene product of *IRF6* is currently unknown. However, IRF6 protein belongs to the interferon regulatory factor family of transcription factors. This protein family shares a highly conserved helix-loop-helix DNA binding domain (IRF6 amino acids 13-113) and a less-well-conserved protein binding domain (IRF6 amino acids 226-394). The DNA binding domain contains a unique pentatryptophan 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 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].

Mice deficient for *Irf6* have abnormal skin, limb, and craniofacial development [Ingraham et al 2006, Richardson et al 2006]. Murine embryos that are heterozygous for the null allele [Ingraham et al 2006] or the PPS-associated p.Arg84Cys allele [Richardson et al 2006] have oral epithelial adhesions. The extent and severity of the oral adhesions is greater in the p.Arg84Cys mice than in the mice with the null allele, providing further evidence that the p.Arg84Cys allele has a dominant-negative effect (see **Mechanism of disease causation**). Molecular and histologic analyses showed that *Irf6*-mutated embryos lack periderm cells at the sites of oral adhesions [Richardson et al 2009]. In the absence of periderm the underlying basal epithelial cells express E-cadherin on their surface, which provides a mechanism for aberrant interactions between adjacent tissues. These aberrant interactions could prevent timely elevation and apposition of the palatal shelves, leading to cleft palate. Peyrard-Janvid et al [2014] also observed similar oral epithelial adhesions and absence of periderm in murine embryos that were heterozygous for a mutated allele of *Grhl3*. These observations support the role of proper periderm development during palatogenesis.

Mechanism of disease causation

- **Haploinsufficiency.** The pathogenic variants in individuals with VWS are consistent with haploinsufficiency. The missense pathogenic variants 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.

- **Dominant-negative effects.** The pathogenic variants 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 Trp60, Lys66, Gln82, Arg84, Lys89) are predicted to directly contact the DNA target. Pathogenic missense variants at these positions abrogate DNA binding in IRF1 [Escalante et al 1998] but do not affect protein binding. Consequently, these pathogenic variants are predicted to have a dominant-negative effect on IRF function and may explain the broader phenotype observed in PPS [Kondo et al 2002, de Lima et al 2009]. Not all pathogenic missense variants at Arg84 are highly associated with PPS; p.Arg84Gly and p.Arg84Pro are found only in individuals with VWS, suggesting a different effect on IRF6 function for these variants.

***IRF6*-specific laboratory technical considerations.** Sequence analysis of *IRF6* should include the upstream 5'UTR regulatory region, including the enhancer element designated as MCS9.7, located 9,700 bp upstream of the transcriptional start site for *IRF6*. Single-nucleotide substitutions and small duplications in the 5'UTR have been identified in individuals with VWS [Kondo et al 2002, Rahimov et al 2008, de Lima et al 2009, Fakhouri et al 2014].

Table 7. Notable *IRF6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_006147.4 NP_006138.1	c.250C>G	p.Arg84Gly	Seen only in persons w/VWS [1]
	c.251G>C	p.Arg84Pro	
	c.251G>A	p.Arg84His	Most commonly seen in persons w/ PPS [1]
	c.250C>T	p.Arg84Cys	
	c.-3-3C>A	–	Reported in 1 person w/spina bifida [Kousa et al 2019]
	c.1279G>T	p.Asp427Tyr	Reported in 1 person w/spina bifida [Kousa et al 2019]

PPS = popliteal pterygium syndrome; VWS = Van der Woude syndrome
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.

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