U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Verdin H, Matton C, De Baere E. Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome. 2004 Jul 8 [Updated 2022 Mar 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome

Synonyms: Blepharophimosis Syndrome, BPES

Hannah Verdin, MSc, PhD,[1] Charlotte Matton, MSc,[2] and Elfride De Baere, MD, PhD[3]

Created: July 8, 2004; Updated: March 10, 2022.

Summary

Clinical characteristics

*B*lepharophimosis, *p*tosis, and *e*picanthus inversus *s*yndrome (BPES) is defined by a complex eyelid malformation characterized by four major features, all present at birth: blepharophimosis, ptosis, epicanthus inversus, and telecanthus. BPES type I includes the four major features and primary ovarian insufficiency; BPES type II includes only the four major features. Other ophthalmic manifestations that can be associated with BPES include dysplastic eyelids, lacrimal duct anomalies, strabismus, refractive errors, and amblyopia. Other craniofacial features may include a broad nasal bridge and low-set ears.

Diagnosis/testing

The diagnosis of BPES is established in a proband with suggestive findings and a heterozygous pathogenic variant in *FOXL2* or its regulatory domain identified by molecular genetic testing.

Management

Treatment of manifestations: Management requires the input of a multidisciplinary team of specialists. Eyelid surgery traditionally involves a medial canthoplasty for correction of the blepharophimosis, epicanthus inversus, and telecanthus at age three to five years, typically followed a year later by ptosis correction. Primary ovarian insufficiency is managed by hormone replacement therapy; fertility is addressed with reproductive technologies such as embryo donation, egg donation, and cryopreservation strategies.

Author Affiliations: 1 Center for Medical Genetics Ghent University Hospital Ghent, Belgium; Email: hannah.verdin@ugent.be. 2 Department of Biomolecular Medicine Ghent University Ghent, Belgium; Email: charlotte.matton@ugent.be. 3 Center for Medical Genetics Ghent University Hospital; Department of Biomolecular Medicine Ghent University Ghent, Belgium; Email: elfride.debaere@ugent.be.

Surveillance: Ophthalmic follow up depends on age, procedures performed in the past, and results of visual acuity testing. Endocrinologic and gynecologic follow up are advised for affected females. Psychological follow up is recommended.

Genetic counseling

BPES is almost always inherited in an autosomal dominant manner. More than half of individuals diagnosed with BPES have the disorder as the result of a pathogenic variant inherited from an affected parent. Each child of an individual with BPES has a 50% chance of inheriting the pathogenic variant. Once the BPES-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for BPES are possible.

Diagnosis

No consensus clinical diagnostic criteria for *b*lepharophimosis, *p*tosis, and *e*picanthus inversus *s*yndrome (BPES) have been published.

Suggestive Findings

BPES **should be suspected** in individuals with the following clinical findings and family history.

Major clinical findings, all present at birth:

- **Blepharophimosis.** Narrowing of the horizontal aperture of the eyelids
- **Ptosis.** Drooping of the upper eyelid causing a narrowing of the vertical palpebral fissure
- **Epicanthus inversus.** A skin fold arising from the lower eyelid and running inward and upward
- **Telecanthus.** Lateral displacement of the inner canthi and the inferior punctum with normal interpupillary distance

Additionally, primary ovarian insufficiency is present in individuals with BEPS type 1.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of BPES **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *FOXL2* or its regulatory domain identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous variant of *FOXL2* (or its regulatory domain) of uncertain significance does not establish or rule out the diagnosis of this disorder.

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

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

Option 1

Single-gene testing. Sequence analysis of *FOXL2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used,

partial 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 of the *FOXL2* region and its regulatory domain to detect a partial or whole-gene deletion or a noncoding regulatory domain copy number variant (deletion).

Option 2

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

If no variant is detected using exome or genome sequencing, the next step is to perform gene-targeted deletion/duplication analysis of the *FOXL2* region and its regulatory domain to detect a partial or whole-gene deletion or a noncoding regulatory domain copy number variant (deletion).

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

If molecular genetic testing is normal, cytogenetic testing can be considered to identify a balanced translocation associated with an interruption of *FOXL2* or its regulatory domain. This can be evaluated further via newly developed testing techniques such as low-pass whole-genome sequencing of *FOXL2* and its regulatory domain [Yang et al 2014].

Table 1. Molecular Genetic Testing Used in BPES

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
FOXL2	Sequence analysis [4]	72% [5]
	Gene-targeted deletion/duplication analysis [6, 7]	10%-15% [5]
Regulatory regions extragenic to *FOXL2*	Deletion/duplication analysis of the regions upstream or downstream of *FOXL2* [6, 7, 8]	5% [5, 9]

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. Several additional individuals with contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
4. 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, and nonsense variants; typically, partial or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Individuals with BPES and an apparently balanced chromosome translocation and no evidence for a sequence variant or copy number variant in *FOXL2* have been found to have an intragenic or extragenic interruptions of *FOXL2* detected using low-pass whole genome sequencing [Yang et al 2014].
8. MLPA and other methods for deletion/duplication analysis (see footnote 6) may detect partial-, whole-, or contiguous-gene deletions or upstream or downstream regulatory deletions, depending on the experimental design [Beysen et al 2009, D'haene et al 2009].
9. Beysen et al [2005], Beysen et al [2009], D'haene et al [2009], Verdin et al [2013]

Clinical Characteristics

Clinical Description

Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) is defined by complex eyelid malformation characterized by four major features, all present at birth: blepharophimosis, ptosis, epicanthus inversus, and telecanthus.

Two types of BPES have been described [Zlotogora et al 1983]:

- BPES type I includes the four major features and female infertility caused by primary ovarian insufficiency.
- BPES type II includes only the four major features.

Complex eyelid malformation

- **Blepharophimosis.** Narrowing of the horizontal aperture of the eyelids. In normal adults, the horizontal palpebral fissure measures 25-30 mm; in individuals with BPES, it generally measures 20-22 mm.
- **Ptosis.** Drooping of the upper eyelid causing a narrowing of the vertical palpebral fissure. In individuals with BPES, ptosis is secondary to dysplasia of the *musculus levator palpebrae superioris*. To compensate for the ptosis, affected individuals:
  - Use the *musculus frontalis*, wrinkling the forehead to draw the eyebrows upward, which results in a characteristic facial appearance;
  - Tilt their head backward into a chin-up position.
- **Epicanthus inversus.** A skin fold arising from the lower eyelid and running inward and upward
- **Telecanthus.** Lateral displacement of the inner canthi with normal interpupillary distance

Associated ophthalmic manifestations

- Dysplastic eyelids (lack of eyelid folds and thin skin)
- S-shaped border of the upper eyelid and abnormal downward concavity of the lower eyelid with lateral ectropion
- Nasolacrimal drainage problems caused by lateral displacement, duplication, or stenosis of the lacrimal puncta

  Note: A study of ten individuals with molecularly confirmed BPES showed that all had lateral displacement of the inferior punctum (i.e., in the lower eyelid) resulting from a temporal displacement of the entire lower eyelid. This proved to be an important anatomic hallmark in the diagnosis of BPES [Decock et al 2011].
- Strabismus, refractive errors (anisometropic hypermetropia and myopia), and amblyopia are more common in individuals with BPES than in the general population [Beckingsale et al 2003, Dawson et al 2003, Choi et al 2006]. A retrospective study in 204 individuals with BPES showed manifest strabismus in 20%, a significant refractive error in 34%, and bilateral or unilateral amblyopia in 21% and 20%, respectively [Dawson et al 2003].

Other craniofacial features frequently observed in BPES are a broad nasal bridge and low-set ears.

Primary ovarian insufficiency (POI)

- Secondary sexual characteristics are usually normal in both BPES type I and BPES type II.
- In BPES type I, menarche is usually normal, followed by oligomenorrhea and secondary amenorrhea.

- Hypoplastic uterus and small ovaries may be found in some individuals with BPES type I on pelvic ultrasound.
- Ovarian reserve is decreased (characterized by a low atrial follicle count of <4 and decreased serum levels of anti-müllerian hormone) [Huhtaniemi et al 2018].
- Endocrinologic findings of hypergonadotropic hypogonadism include: elevated serum concentrations of follicle-stimulating hormone (>25 IU/L, measured on 2 occasions >4 weeks apart); elevated luteinizing hormone [Huhtaniemi et al 2018]; and decreased serum concentrations of estradiol and progesterone.

Cognitive development is expected to be normal in individuals with BPES unless the disorder occurs as part of a contiguous gene deletion with associated developmental delay / intellectual disability (see Genetically Related Disorders).

Pituitary hormone deficiency. A recent study showed that some individuals with BPES have hypopituitarism with no molecular explanation other than a *FOXL2* pathogenic variant, suggesting a role for *FOXL2* in human pituitary development [Castets et al 2020].

Genotype-Phenotype Correlations

Pathogenic variants predicted to result in proteins truncated before the polyalanine tract preferentially lead to POI (BPES type I). Note: The need for careful interpretation of genotype-phenotype correlations is illustrated by the co-occurrence of BPES type I and isolated POI in a three-generation family [Beysen et al 2008] and the occurrence of both BPES type I and BPES type II within a single family [Yang et al 2017].

Polyalanine expansions preferentially lead to BPES type II.

Penetrance

All individuals heterozygous for a *FOXL2* pathogenic variant have a BPES phenotype; thus, penetrance is complete for the eyelid phenotype.

The exception is a consanguineous Indian family in which heterozygotes for a short polyalanine expansion of 19 alanines are unaffected, but homozygotes have typical BPES (with documented POI in 1 female) [Nallathambi et al 2007].

Prevalence

The prevalence of BPES is estimated at 1:50,000 births in the general population.

No differences in prevalence based on sex, race, or ethnicity have been reported.

Genetically Related (Allelic) Disorders

Nonsyndromic primary ovarian insufficiency (POI). *FOXL2* variants have been identified infrequently in nonsyndromic POI cohorts [Harris et al 2002, Laissue et al 2009].

Contiguous gene deletion. In a series of 17 individuals with deletions encompassing *FOXL2* with a size varying from 29.8 kb to 11.5 Mb, a uniform BPES phenotype was observed with considerable phenotypic variability in associated clinical findings, including developmental delay / intellectual disability (8/17), microcephaly (6/17), and subtle skeletal features (2/17) [D'haene et al 2010]. While the majority of females (10/13) in this study were of prepubertal age, variable degrees of ovarian dysfunction were identified in three females.

Differential Diagnosis

Because of its characteristic phenotype and the absence of extraocular manifestations other than primary ovarian insufficiency, BPES can be distinguished relatively easily from other conditions in which ptosis or blepharophimosis is a major feature (e.g., *NR2F2*-associated 46,XX sex reversal 5 [OMIM 618901] and Say-Barber-Biesecker variant of Ohdo syndrome [see *KAT6B* Disorders]).

Management

No clinical practice guidelines for blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with BPES, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with BPES

System/Concern	Evaluation	Comment
Eyelid malformation	Exam by ophthalmologist & oculoplastic surgeon	Assess for size of palpebral apertures, lacrimal duct abnormality, & eyelid elevation.
Vision		Assess for visual acuity, refractive error, extraocular movement, & amblyopia.
POI	Eval by pediatrician or endocrinologist/ gynecologist	• For females w/BPES during late childhood or early puberty to assess gonadal function & assess/discuss onset & course of POI • See also Genetic Counseling.
Genetic counseling	By genetics professionals [1]	• To inform affected persons & their families re nature, MOI, & implications of BPES to facilitate medical & personal decision making • In females w/BPES, family history can indicate type of BPES (type I inferred by assoc w/subfertility or infertility).

MOI = mode of inheritance; POI = primary ovarian insufficiency

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management requires the input of a multidisciplinary team with specialists including a clinical geneticist, genetic counselor, pediatric ophthalmologist, oculoplastic surgeon, (pediatric or adult) endocrinologist, reproductive endocrinologist, and gynecologist.

Table 3. Treatment of Manifestations in Individuals with BPES

Manifestation/Concern	Treatment	Considerations/Other
Eyelid malformation	Surgery	Traditionally performed in 2 stages: • Age 3-5 yrs: medial canthoplasty for correction of blepharophimosis, epicanthus inversus, & telecanthus • ~1 yr later: ptosis correction, usually requiring brow suspension procedure

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
POI	Standard mgmt for POI (not specific to BPES) [1]	Typically consisting of: • Hormone replacement therapy • Monitoring & optimizing bone health • Eval of options for parenthood (adoption, foster parenthood, embryo donation, egg donation, ovary cryopreservation) Psychological support is important.

POI = primary ovarian insufficiency
1. Current management practices for primary ovarian insufficiency have been reviewed in Moreira & Spritzer [2016] and Kanj et al [2018].

Surveillance

Table 4. Recommended Surveillance for Individuals with BPES

System/Concern	Evaluation	Frequency
Eyelid malformation	Ophthalmic follow up	Based on person's age, past procedures, & results of visual acuity testing
POI	• Endocrinologic & gynecologic follow up to monitor ovarian status • Assess effects of hormone replacement therapy for adjustments as needed. • Psychological follow up	Individualized, but at least annually

POI = primary ovarian insufficiency

Evaluation of Relatives at Risk

It is appropriate to clarify the status of older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from ophthalmic surveillance and, in female relatives, endocrinologic surveillance to monitor ovarian status (see Surveillance). Evaluations can include:

- Molecular genetic testing if a *FOXL2* pathogenic variant has been identified in an affected family member;
- Clinical examination for features of BPES if the pathogenic variant in the family is not known.

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

Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) is almost always inherited in an autosomal dominant manner.

BPES associated with biallelic *FOXL2* pathogenic variants has been reported in one family to date: a consanguineous Indian family in which individuals heterozygous for a short polyalanine expansion are unaffected while individuals homozygous for this expansion have typical BPES [Nallathambi et al 2007].

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- More than half of individuals diagnosed with BPES have an affected parent.

  A recent study showed more female than male probands and a highly significant bias in the parental origin of inherited pathogenic variants, with 20/21 pathogenic variants found to be paternal in origin (95%). The latter may be due to the association of BPES and primary ovarian insufficiency (POI) [Bunyan & Thomas 2019].

- Some probands with BPES have the disorder as the result of a *de novo* pathogenic variant.

- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), 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 proband has BPES as the result of a cytogenetic rearrangement involving 3q23, recommendations for the evaluation of asymptomatic parents include genomic testing to determine if a balanced chromosome rearrangement involving the 3q23 region is present.

- If the pathogenic variant identified in the proband is not found in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:

  - The proband has a *de novo* pathogenic variant.

  - 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 in the germ cells only.

    Parental mosaicism has been observed in BPES [Beysen et al 2005, Beysen et al 2009, Bunyan & Thomas 2019]. In a recent study, presumed parental mosaicism was reported in two of 28 families in whom the pathogenic variant was originally thought to have occurred *de novo* in the proband [Bunyan & Thomas 2019].

- The family history of some individuals diagnosed with BPES may appear to be negative because of failure to recognize the disorder in affected family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish 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 pathogenic variant identified in the proband, the risk to the sibs is 50%. The penetrance of the BPES eyelid phenotype in heterozygous family members is 100%.

- If the proband has a known BPES-causing pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Beysen et al 2005, Beysen et al 2009, Bunyan & Thomas 2019].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism.
- If a parent has a balanced structural chromosome rearrangement involving the 3q23 region, the risk to sibs is increased. The estimated risk depends on the specific chromosome rearrangement.

Offspring of a proband. Each child of an individual with BPES has a 50% chance of inheriting the causative pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the BPES-causing pathogenic variant, his or her family members are 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.
- Women with BPES should be informed regarding the risk of POI and recommendations for endocrinologic surveillance to monitor ovarian status (see Surveillance).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the BPES-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for BPES are possible.

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.

- **MedlinePlus**
  Blepharophimosis, ptosis, and epicanthus inversus syndrome

- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.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. Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FOXL2	3q22.3	Forkhead box protein L2	FOXL2 homepage - FOXL2 @ LOVD	FOXL2	FOXL2

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 Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome (View All in OMIM)

110100	BLEPHAROPHIMOSIS, PTOSIS, AND EPICANTHUS INVERSUS; BPES
605597	FORKHEAD TRANSCRIPTION FACTOR FOXL2; FOXL2

Molecular Pathogenesis

The FOXL2 protein of 376 amino acids belongs to the large family of winged-helix/forkhead transcription factors. Forkhead proteins are present in all eukaryotes and have important functions in the establishment of the body axis and the development of tissues from all three layers in animals.

Mechanism of disease causation. Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) occurs via a loss-of-function mechanism (haploinsufficiency).

***FOXL2*-specific laboratory technical considerations**

- *FOXL2* is a small single-exon gene of 2.7 kb.
- Rearrangements outside the *FOXL2* transcription unit are estimated to account for 5% of all molecular defects found in BPES [Beysen et al 2005] and implicate an effect of long-range *cis*-regulatory elements in regulating FOXL2 expression.
- FOXL2 contains a polyalanine tract of 14 residues, the role of which has not yet been elucidated. Expansions from 14 to 24 alanine residues in this region represent about 30% of all intragenic *FOXL2* pathogenic variants and lead mainly to BPES type II [De Baere et al 2003].

Table 5. Notable *FOXL2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_023067.4 NP_075555.1	c.655C>T	p.(Gln219Ter)	Most common *FOXL2* pathogenic sequence variants [Beysen et al 2009]
	c.672_701dup	p.(Ala224_Ala234dup)	
	c.663_692dup	p.(Ala221_Ala231dup)	
	c.664_693dup	p.(Ala222_Ala231)	
	c.804dup	p.(Gly269ArgfsTer265)	
	c.843_859dup	p.(Pro287ArgfsTer241)	
	c.855_871del	p.(Pro287AlafsTer241)	
	c.855_871dup	p.(His291ArgfsTer71)	

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.

Chapter Notes

Author Notes

Dr Elfride De Baere's research is focused on the molecular pathogenesis of genetically heterogeneous mendelian disorders (such as rare eye diseases) and on noncoding variation of rare eye diseases and transcription factor-associated developmental diseases. Achievements in the field of rare eye disease genomics include identification of novel disease genes for inherited retinal diseases and characterization of new disease mechanisms. For the functional characterization of disease genes, Dr De Baere makes use of integrated omics and cellular and animal models, such as *Xenopus tropicalis*. She has published 34 papers on *FOXL2* and/or BPES: pubmed.ncbi.nlm.nih.gov.

Author websites: www.debaerelab.com and orcid.org

Revision History

- 10 March 2022 (ha) Comprehensive update posted live
- 5 February 2015 (me) Comprehensive update posted live
- 12 November 2009 (me) Comprehensive update posted live
- 15 February 2006 (cd) Revision: prenatal diagnosis available
- 12 July 2005 (me) Comprehensive update posted live
- 8 July 2004 (me) Review posted live
- 1 March 2004 (edb) Original submission

References

Literature Cited

Beckingsale PS, Sullivan TJ, Wong VA, Oley C. Blepharophimosis: a recommendation for early surgery in patients with severe ptosis. Clin Experiment Ophthalmol. 2003;31:138–42. PubMed PMID: 12648048.

Beysen D, De Jaegere S, Mowat D, Laframboise R, Gillessen-Kaesbach G, Fellous M, Veitia RA, Boucard P, Touraine P, Leroy BP, De Cock C, Delbeke P, Leppig K, Ensenauer R, Ebinger F, Barel D, Plomp A, Kimonis V, Hendriks Y, Clayton-Smith J, Grix AW, Van Regemorter N, Hennekam R, Meire F, Oyen N, Wilson LC, De

Paepe A, De Baere E. Mutation in brief: identification of 34 novel and 56 known *FOXL2* mutations in patients with blepharophimosis syndrome. Hum Mutat. 2008;29:E205–19. PubMed PMID: 18642388.

Beysen D, De Paepe A, De Baere E. Mutation update: *FOXL2* mutations and genomic rearrangements in BPES. Hum Mutat. 2009;30:158–69. PubMed PMID: 18726931.

Beysen D, Raes J, Leroy BP, Lucassen A, Yates JR, Clayton-Smith J, Ilyina H, Brooks SS, Christin-Maitre S, Fellous M, Fryns JP, Kim JR, Lapunzina P, Lemyre E, Meire F, Messiaen LM, Oley C, Splitt M, Thomson J, Van de Peer Y, Veitia RA, De Paepe A, De Baere E. Deletions involving long-range conserved nongenic sequences upstream and downstream of FOXL2 as a novel disease-causing mechanism in blepharophimosis syndrome. Am J Hum Genet. 2005;77:205–18. PubMed PMID: 15962237.

Bunyan DJ, Thomas NS. Screening of a large cohort of blepharophimosis, ptosis, and epicanthus inversus syndrome patients reveals a very strong paternal inheritance bias and a wide spectrum of novel FOXL2 mutations. Eur J Med Genet. 2019;62:103668. PubMed PMID: 31077882.

Castets S, Roucher-Boulez F, Saveanu A, Mallet-Motak D, Chabre O, Amati-Bonneau P, Bonneau D, Girardin C, Morel Y, Villanueva C, Brue T, Reynaud R, Nicolino M. Hypopituitarism in patients with blepharophimosis and FOXL2 mutations. Horm Res Paediatr. 2020;93:30–39. PubMed PMID: 32454486.

Choi KH, Kyung S, Oh SY. The factors influencing visual development in blepharophimosis-ptosis-epicanthus inversus syndrome. J Pediatr Ophthalmol Strabismus. 2006;43:285–8. PubMed PMID: 17022162.

Dawson EL, Hardy TG, Collin JR, Lee JP. The incidence of strabismus and refractive error in patients with blepharophimosis, ptosis and epicanthus inversus syndrome (BPES). Strabismus. 2003;11:173–7. PubMed PMID: 14710475.

De Baere E, Beysen D, Oley C, Lorenz B, Cocquet J, De Sutter P, Devriendt K, Dixon M, Fellous M, Fryns JP, Garza A, Jonsrud C, Koivisto PA, Krause A, Leroy BP, Meire F, Plomp A, Van Maldergem L, De Paepe A, Veitia R, Messiaen L. FOXL2 and BPES: mutational hotspots, phenotypic variability, and revision of the genotype-phenotype correlation. Am J Hum Genet. 2003;72:478–87. PubMed PMID: 12529855.

Decock CE, Claerhout I, Leroy BP, Kesteleyn P, Shah AD, De Baere E. Correction of the lower eyelid malpositioning in the blepharophimosis-ptosis-epicanthus inversus syndrome. Ophthal Plast Reconstr Surg. 2011;27:368–70. PubMed PMID: 21562436.

D'haene B, Attanasio C, Beysen D, Dostie J, Lemire E, Bouchard P, Field M, Jones K, Lorenz B, Menten B, Buysse K, Pattyn F, Friedli M, Ucla C, Rossier C, Wyss C, Speleman F, De Paepe A, Dekker J, Antonarakis SE, De Baere E. Disease-causing 7.4 kb cis-regulatory deletion disrupting conserved non-coding sequences and their interaction with the FOXL2 promotor: implications for mutation screening. PLoS Genet. 2009;5:e1000522. PubMed PMID: 19543368.

D'haene B, Nevado J, Pugeat M, Pierquin G, Lowry RB, Reardon W, Delicado A, García-Miñaur S, Palomares M, Courtens W, Stefanova M, Wallace S, Watkins W, Shelling AN, Wieczorek D, Veitia RA, De Paepe A, Lapunzina P, De Baere E. FOXL2 copy number changes in the molecular pathogenesis of BPES: unique cohort of 17 deletions. Hum Mutat. 2010;31:E1332–47. PubMed PMID: 20232352.

Harris SE, Chand AL, Winship IM, Gersak K, Aittomaki K, Shelling AN. Identification of novel mutations in FOXL2 associated with premature ovarian failure. Mol Hum Reprod. 2002;8:729–33. PubMed PMID: 12149404.

Huhtaniemi I, Hovatta O, La Marca A, Livera G, Monniaux D, Persani L, Heddar A, Jarzabek K, Laisk-Podar T, Salumets A, Tapanainen JS, Veitia RA, Visser JA, Wieacker P, Wolczynski S, Misrahi M. Advances in the molecular pathophysiology, genetics, and treatment of primary ovarian insufficiency. Trends Endocrinol Metab. 2018;29:400–19. PubMed PMID: 29706485.

Kanj RV, Ofei-Tenkorang NA, Altaye M, Gordon CM. Evaluation and management of primary ovarian insufficiency in adolescents and young adults. J Pediatr Adolesc Gynecol. 2018;31:13–18. PubMed PMID: 28782660.

Laissue P, Lakhal B, Benayoun BA, Dipietromaria A, Braham R, Elghezal H, Philibert P, Saâd A, Sultan C, Fellous M, Veitia R. Functional evidence implicating FOXL2 in non syndromic premature ovarian failure and in the regulation of the transcription factor OSR2. J Med Genet. 2009;46:455–7. PubMed PMID: 19429596.

Moreira AM, Spritzer PM. Primary ovarian insufficiency: different approaches in three cases and a review of literature. Endocrinol Diabetes Metab Case Rep. 2016;2016:160026. PubMed PMID: 27252868.

Nallathambi J, Moumné L, De Baere E, Beysen D, Usha K, Sundaresan P, Veitia R. A novel polyalanine expansion in FOXL2: the first evidence for a recessive form of the blepharophimosis syndrome (BPES) associated with ovarian dysfunction. Hum Genet. 2007;121:107–12. PubMed PMID: 17089161.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Verdin H, D'haene B, Beysen D, Novikova Y, Menten B, Sante T, Lapunzina P, Nevado J, Carvalho C, Lupski JR, De Baere E. Microhomology-mediated replication-based mechanisms underly non-recurrent pathogenic microdeletions of the FOXL2 gene or its regulatory domain. PLoS Genet. 2013;9:e1003358. PubMed PMID: 23516377.

Yang L, Li T, Xing Y. Identification of a novel FOXL2 mutation in a single family with both types of blepharophimosis-ptosis-epicanthus inversus syndrome. Mol Med Rep. 2017;16:5529–32. PubMed PMID: 28849110.

Yang Y, Yang C, Zhu Y, Chen H, Zhao R, He X, Tao L, Wang P, Zhou L, Zhao L, Tu M, Dong Z, Chen H, Xie Z. Intragenic and extragenic disruptions of FOXL2 mapped by whole genome low-coverage sequencing in two BPES families with chromosome reciprocal translocation. Genomics. 2014;104:170–6. PubMed PMID: 25086333.

Zlotogora J, Sagi M, Cohen T. The blepharophimosis, ptosis, and epicanthus inversus syndrome: delineation of two types. Am J Hum Genet. 1983;35:1020–7. PubMed PMID: 6613996.

License