GENEReviews

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Lymphedema-Distichiasis Syndrome

[*Lymphedema with Distichiasis*]

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Summary

Disease characteristics. Lymphedema-distichiasis syndrome is characterized by lower-limb lymphedema and distichiasis (aberrant eyelashes ranging from a full set of extra eyelashes to a single hair). Lymphedema typically appears in late childhood or puberty, is confined to the lower limbs, and is often asymmetric; severity varies within families. Males develop edema at an earlier age and have more problems with cellulitis than females. Distichiasis, which may be present at birth, is observed in 94% of affected individuals. About 75% of affected individuals have ocular findings including corneal irritation, recurrent conjunctivitis, and photophobia; other common findings include varicose veins, congenital heart disease, and ptosis. About 25% of individuals are asymptomatic.

Diagnosis/testing. The diagnosis of lymphedema-distichiasis syndrome is made clinically and is based on the presence of primary lymphedema and distichiasis. *FOXC2* is the only gene known to be associated with lymphedema-distichiasis syndrome. Molecular genetic testing of the *FOXC2* gene is clinically available.

Management. *Treatment of manifestations:* lubrication, plucking, cryotherapy, electrolysis, or lid splitting for treatment of distichiasis; fitted stockings and bandages to improve swelling and discomfort associated with edema. *Prevention of secondary complications:* To prevent secondary cellulitis treat athlete's foot and other infections promptly; treat early cellulitis with antibiotics. *Other:* Diuretics are not effective in the treatment of lymphedema.

Genetic counseling. Lymphedema-distichiasis syndrome is inherited in an autosomal dominant manner. Approximately 75% of affected individuals have an affected parent; about 25% have *de novo* mutations. Each child of an individual with lymphedema-distichiasis syndrome has a 50% chance of inheriting the mutation. Disease severity cannot be predicted and is variable even within the same family. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation has been identified in an affected family member;

however, it is rarely requested. Fetal echocardiography is recommended because of the increased risk of congenital heart disease.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of lymphedema-distichiasis syndrome is based on the presence of the following:

- **Primary lymphedema** (chronic swelling of the extremities caused by an intrinsic dysfunction of the lymphatic vessels)
- **Distichiasis** (aberrant, extra eyelashes arising from the meibomian glands)

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. *FOXC2* is the only gene known to be associated with lymphedema-distichiasis syndrome [Fang et al 2000].

Other loci. Four affected families with no mutation identified in *FOXC2* have been reported. Brice et al (2002) reported one family out of 18 families and six simplex cases (i.e., single occurrences of lymphedema-distichiasis syndrome in a family) in whom linkage was compatible with the *FOXC2* locus but no mutation was identified. Finegold et al (2001) reported three small families out of 14 with no identifiable mutation; however, no linkage data were available.

Clinical testing

- **Sequence analysis** of the entire coding region detects mutations in about 95% of individuals with lymphedema-distichiasis syndrome. Over 90% of mutations are small deletions or insertions. Four possible missense mutations (one of which has uncertain pathogenesis) and a small number of nonsense mutations have been reported. No entire gene deletions have been reported.

Research testing. For those in whom no mutation is detected in the coding region by sequence analysis, the 5' and 3' regions of the *FOXC2* gene can be sequenced and analyzed. Detection rate for coding region mutations should be 100%, other than laboratory error.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Lymphedema-Distichiasis Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	Small insertions, small deletions, missense mutations in *FOXC2*	~95% of probands	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Testing Strategy

To confirm the diagnosis in a proband

- Physical examination for the cardinal findings of lymphedema and distichiasis
- Molecular genetic testing of *FOXC2*

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with *FOXC2* mutations. However, a recent twin study suggested a link between *FOXC2* and early onset of varicose veins [Ng et al 2005].

Clinical Description

Natural History

The most common findings in lymphedema-distichiasis syndrome are lower-limb lymphedema and distichiasis.

Lymphedema. Lymphedema is present in most individuals with lymphedema-distichiasis syndrome. It typically appears in late childhood or puberty (age range 7-40 years) [Erickson et al 2001, Brice et al 2002], although congenital onset has been reported [Finegold et al 2001; Brice, unpublished observations].

Lymphedema is confined to the lower limbs, is often asymmetric, and can be unilateral. The severity of the lymphedema varies within families. Males develop edema at a significantly earlier age and have more problems with cellulitis than females. Sixty-five percent of males in one series complained of recurrent cellulitis in the edematous leg, compared to 25% of females [Brice et al 2002].

Primary lymphedema is usually associated with hypoplasia or aplasia of the lymphatic vessels. However, individuals with lymphedema-distichiasis syndrome have an increased number of lymphatic vessels and inguinal lymph nodes [Dale 1987, Brice 2003]. Although present, the lymphatic vessels do not appear to function properly.

Isotope lymphoscintigraphy can be used to demonstrate that the swelling is caused by lymphedema. Radioactive colloid is injected into the toe web spaces and uptake in the ilioinguinal nodes is measured at intervals. Low uptake can be demonstrated in most affected individuals in association with dermal backflow, indicating lymph reflux into the lower limbs. This technique replaces lymphangiography (x-ray after injection of dye into the lymphatic vessels in the foot).

Distichiasis. Distichiasis describes the presence of aberrant eyelashes arising from the meibomian glands on the inner aspects of the inferior and superior eyelids. These range from a full set of extra eyelashes to a single hair. Distichiasis is observed in 94% of individuals with lymphedema-distichiasis syndrome [Brice et al 2002]. Although distichiasis may be present at birth, it may not be recognized until early childhood.

About 75% of affected individuals have ocular problems related to distichiasis including corneal irritation, recurrent conjunctivitis, and photophobia. About 25% of individuals have no symptoms from distichiasis and are thus not aware of it. Therefore, any individual with

primary lymphedema of the lower limbs should be examined carefully for the presence of distichiasis.

Finegold et al (2001) described one family with a *FOXC2* mutation with lymphedema only; however, only three individuals were affected and no comment was made as to whether they were examined by slit lamp for evidence of distichiasis. Sometimes the distichiasis can be very subtle. In a study of 23 probands reported to have Meige disease (see Differential Diagnosis) only one was found to have a mutation in *FOXC2*. More extensive examination of the individuals in this family revealed that although the proband did not have distichiasis, four affected relatives had evidence of distichiasis on slit-lamp examination [Rezaie et al, personal communication].

In one family described distichiasis was associated with a mutation in *FOXC2* but none of the affected individuals had evidence of lymphedema. However, the two affected individuals in the family were the 13-year-old proband (who could still develop lymphedema) and her father [Brooks et al 2003].

Varicose veins. The incidenceof varicose veins is much higher, and onset earlier, in individuals with lymphedema-distichiasis syndrome than in the general population. About 50% of individuals with lymphedema-distichiasis syndrome have varicose veins [Brice et al 2002]. In one family, light-reflective rheography and Doppler studies showed bilateral incompetence at the sapheno-femoral junction and long saphenous vein, which were presumed to be congenital abnormalities affecting both deep and superficial veins [Rosbotham et al 2000]. Ongoing studies of venous abnormalities suggest that they are present in all individuals with *FOXC2* mutations [Mellor et al 2007].

Ptosis. Approximately 30% of individuals with lymphedema-distichiasis syndrome have unilateral or bilateral congenital ptosis of variable severity.

Congenital heart disease. Congenital heart disease occurs in 7% of individuals with lymphedema-distichiasis syndrome. Structural abnormalities include ventricular septal defect, atrial septal defect, patent ductus arteriosis, and tetralogy of Fallot. Cardiac arrhythmia, most commonly sinus bradycardia, may also occur.

Cleft palate. About 4% of individuals have cleft palate with or without Pierre-Robin sequence.

Other findings. Other abnormalities include scoliosis, spinal extradural cysts [Kanaan et al 2006], neck webbing, uterine and renal anomalies, strabismus, and synophrys. Neonatal chylothorax has been reported in one case only in association with congenital heart disease [Chen et al 1996]. One paper suggested an association with yellow nails, but discolored nails are often a feature of chronic lymphedema regardless of cause.

Genotype-Phenotype Correlations

No genotype-phenotype correlation for the major clinical signs has been reported; however, a preliminary study suggested that asymptomatic anomalies of the anterior chamber of the eye are more extensive if the mutation is in the forkhead domain rather than in other regions of the gene [Lehmann et al 2003].

Penetrance

Approximately 80% of individuals with lymphedema-distichiasis syndrome have lymphedema by early adulthood (age 30 years), although a few individuals may develop lymphedema later.

About 94% of affected individuals have distichiasis. In all families reported with mutations in *FOXC2*, at least one individual has had distichiasis.

Anticipation

No evidence of anticipation has been reported.

Nomenclature

Lymphedema and ptosis, described as a separate entity in OMIM (153000), is thought to be the same as lymphedema-distichiasis syndrome [Finegold et al 2001].

Prevalence

The prevalence of lymphedema-distichiasis syndrome is not known; however, it is a well-recognized cause of autosomal dominant primary lymphedema.

Differential Diagnosis

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

Lymphedema. The presence of lymphatic vessels in lymphedema-distichiasis syndrome contrasts with other causes of primary lymphedema such as Milroy disease and Meige disease, which show aplasia or hypoplasia of the lymphatic vessels.

- In **Milroy disease**, lymphedema is usually present at birth and very rarely presents later. Distichiasis is not present. Milroy disease results from mutations in the gene *VEGFR3*, encoding vascular endothelial growth factor receptor 3 [Karkkainen et al 2000, Irrthum et al 2000]. Inheritance is autosomal dominant.
- **Meige disease** presents with primary lymphedema at puberty. Distichiasis is not observed. Meige disease predominantly affects women, but inheritance is autosomal dominant. The causative gene(s) has/have not yet been confirmed.
- **Hypotrichosis-lymphedema-telangiectasia syndrome** is the association of childhood-onset lymphedema in the lower limbs, loss of hair, and telangiectasia, particularly in the palms. Inheritance is either autosomal dominant or autosomal recessive. Mutations in *SOX18* are causative [Irrthum et al 2003].
- **Lymphedema with yellow nails** (yellow nail syndrome, YNS) often presents after age 50 years. The nails in YNS are very slow growing, with transverse over-curvature and hardening of the nail plate. The nail changes are different from the typically discolored nails that are often associated with chronic lymphedema. Inheritance is said to be autosomal dominant; however, most cases are simplex (i.e., a single occurrence in a family) [Hoque et al 2007].

Distichiasis

- **Blepharocheilodontic syndrome** is the association of lagophthalmos (inability to fully close eyes), cleft lip and palate, atrial septal defect, and oligodontia. Distichiasis is a feature; lymphedema is not observed.
- Only one family has been reported with **isolated distichiasis** (i.e., absence of other malformations and/or lymphedema) [Brooks et al 2003]. Familial distichiasis has been described [OMIM 123000], but may not represent a separate genetic disorder. Others have noted individuals with "distichiasis only" in the context of a family in which both lymphedema and distichiasis were present [Falls & Kertesz 1964].

- Distichiasis should also be clinically distinguished from **trichiasis**, a more common condition in which lashes arise normally from the anterior lamella of the eyelids but are misdirected. The misdirected lashes can cause symptoms similar to distichiasis (e.g., corneal irritation and photophobia).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with lymphedema-distichiasis syndrome, the following evaluations are recommended:

- Referral to an ophthalmologist (preferably one familiar with distichiasis) for slit-lamp examination, as the extra lashes may be subtle and easily missed on clinical examination
- Physical examination to document the presence of manifestations and identify evidence of cellulitis
- Isotope lymphoscintigraphy to confirm underlying abnormality of the lymphatics as the cause of the edema
- Physical examination of the heart and possible echocardiography if murmur or arrhythmia is identified

Treatment of Manifestations

- Conservative management of symptomatic distichiasis with lubrication or epilation (plucking), or more definitive management with cryotherapy, electrolysis, or lid splitting [O'Donnell & Collin 1993]. Recurrence is possible even with more definitive treatment.
- Referral to a lymphedema therapist regarding management of edema (fitting stockings, massage). Although the edema cannot be cured, some improvement may be possible with the use of carefully fitted stockings and/or bandaging, which may reduce the size of the swelling as well as the discomfort associated with it.
- Surgery for ptosis if clinically indicated (e.g., obscured vision, cosmetic appearance)
- Referral to neurosurgery for individuals with symptomatic spinal cysts (i.e., any neurologic signs or symptoms especially in the lower limbs)
- Conservative management of varicose veins if possible, as surgery could aggravate the edema and increase the risk of infection or cellulitis
- Standard treatment for scoliosis

Prevention of Secondary Complications

- Prevention of secondary cellulitis in areas with lymphedema, particularly as cellulitis may aggravate the degree of edema. Prophylactic antibiotics (e.g., penicillin V 500 mg daily) are recommended for recurrent cellulitis.
- Prompt treatment of early cellulitis with appropriate antibiotics (See the British Lymphology Society Consensus Statement for information on appropriate antibiotics.) It may be necessary to give the first few doses intravenously if there is severe systemic upset.
- Prevention of foot infections, particularly athlete's foot/infected eczema by treatment with appropriate creams/ointments

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Diuretics are not effective in the treatment of lymphedema.

Cosmetic surgery is often associated with disappointing results.

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

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

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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

Lymphedema-distichiasis syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with lymphedema-distichiasis syndrome have an affected parent.
- A proband with lymphedema-distichiasis syndrome may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is about 25% [Brice et al 2002].

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include slit-lamp examination for distichiasis and clinical examination for lymphedema. Lymphoscintigraphy may be helpful [Rosbotham et al 2000].

Note: Although most individuals diagnosed with lymphedema-distichiasis syndrome have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members as a result of the variable expressivity.

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, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in DNA extrated from leukocytes of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with lymphedema-distichiasis syndrome has a 50% chance of inheriting the mutation. Disease severity cannot be accurately predicted and is variable even within the same family.

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

Related Genetic Counseling Issues

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.

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 or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. 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 banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible in the US (availability may vary by country) by analysis of DNA extracted from fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation. The disease-causing

mutation of an affected family member must be identified before prenatal testing can be performed. Although available, prenatal diagnosis for lymphedema-distichiasis syndrome is rarely requested.

Ultrasonography. Fetal echocardiography at 16 to 20 weeks' gestation is recommended because of the increased risk for congenital heart disease.

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

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. 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 Lymphedema-Distichiasis Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
FOXC2	16q24.3	Forkhead box protein C2

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 Lymphedema-Distichiasis Syndrome

153400	LYMPHEDEMA-DISTICHIASIS SYNDROME
602402	FORKHEAD BOX C2; FOXC2

Table C. Genomic Databases for Lymphedema-Distichiasis Syndrome

Gene Symbol	Entrez Gene	HGMD
FOXC2	2303 (MIM No. 602402)	FOXC2

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

Normal allelic variants: The *FOXC2* gene is composed of a 1.5-kb single exon. SNPs reported in the 5' region of the gene include -512C>T [Ridderstrale et al 2002] and -350G>T [Osawa et al 2003], and in the 3' region, 1548C>T and 1702C>T [Kovacs et al 2003]. 1761G>A has been identified [Sholto-Douglas-Vernon et al 2005].

Pathologic allelic variants: Information on at least 35 different insertions and deletions situated throughout the gene has been published to date. The region 900-920 bp appears to be a "hot spot" for mutations, possibly because of the presence of a repeated GCCGCCGC element [Jeffery, unpublished data]. Several nonsense mutations have been reported, as well as four missense mutations: p.Ser125Leu [Bell et al 2001], p.Arg121His [Brice et al 2002], p.Trp116Ala, and p.Ser235Ile [Sholto-Douglas-Vernon et al 2005]. The first three are presumed to be causative; the status of p.Ser235Ile is unknown.

Mutations in *FOXC1* give rise to Axenfeld-Rieger anomaly and congenital glaucoma. Mutations analogous to p.Ser125Leu and p.Arg121His in *FOXC2* have been shown to inactivate *FOXC1* [Saleem et al 2003].

Normal gene product: Because the gene has no introns, no isomers exist. The normal product is active as a transcriptional regulator during embryonic development and is also expressed in white adipose tissue in adults and in human adult lymphatics [Petrova et al 2004].

Abnormal gene product: The assumed method of pathogenesis is haploinsufficiency. It is not clear whether the frameshift mutations produce a protein product with novel amino acids or whether the mRNA or proteins are degraded.

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.

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.

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Chapter Notes

Revision History

- 2 August 2007 (me) Comprehensive update posted to live Web site

- 4 January 2007 (sm) Revision: *FOXC2* mutations and Meige disease
- 16 June 2006 (cd) Revision: prenatal testing clinically available
- 6 March 2006 (cd) Revision: *FOXC2* testing clinically available
- 29 March 2005 (me) Review posted to live Web site
- 13 September 2004 (sm) Original submission