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Lymphedema-Distichiasis Syndrome

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Summary

Clinical characteristics

Lymphedema-distichiasis syndrome (referred to as LDS in this *GeneReview*) 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 with or without involvement of the external genitalia, 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 and ptosis.

Diagnosis/testing

The clinical diagnosis of LDS is established in a proband with either lymphedema and distichiasis, distichiasis and a family history of lower-limb lymphedema, or lower-limb lymphedema and a family history of distichiasis. If clinical findings are not diagnostic, the identification of a heterozygous *FOXC2* pathogenic variant by molecular genetic testing confirms the diagnosis.

Management

Treatment of manifestations: Lubrication, plucking, cryotherapy, electrolysis, or lid splitting for treatment of distichiasis; fitted compression garments and bandaging to improve swelling and discomfort associated with edema. To prevent secondary cellulitis, good skin care and prompt treatment of infected skin lesions; prompt treatment of cellulitis with antibiotics. The implementation of hosiery prior to the development of lymphedema may help reduce the extent of edema. Diuretics are not effective in the treatment of lymphedema.

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Genetic counseling

LDS is inherited in an autosomal dominant manner. Approximately 75% of affected individuals have an affected parent; about 25% have a *de novo* pathogenic variant. Each child of an individual with LDS has a 50% chance of inheriting the pathogenic variant. Disease severity cannot be predicted and is variable even within the same family. If the *FOXC2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Fetal echocardiography is recommended because of the increased risk for congenital heart disease, renal abnormalities, cleft palate, and hydrothoraces or hydrops fetalis.

Diagnosis

Suggestive Findings

Lymphedema-distichiasis syndrome (LDS) **should be suspected** in individuals with the following clinical findings:

- **Primary lymphedema** (chronic swelling of the extremities caused by an intrinsic dysfunction of the lymphatic vessels) typically affecting the lower limbs ± genitalia with onset in late childhood or puberty
- **Distichiasis** (aberrant, extra eyelashes arising from the meibomian glands on the inner aspects of the inferior and/or superior eyelids, ranging from a full set of extra eyelashes to a single hair
- **Varicose veins** in the lower limbs presenting at puberty or early adulthood
- **Ptosis** (drooping upper eyelid) of one or both eyes
- Other less frequent findings:
  - Congenital heart disease including bicuspid aortic valves
  - Cleft palate ± Pierre Robin sequence
  - Renal anomalies
  - Spinal extradural arachnoid cysts
  - Nonimmune hydrops fetalis
  - Antenatal hydrothoraces
  - Neck webbing

Establishing the Diagnosis

The clinical diagnosis of LDS **is established** in a proband with **one** of the following:

- Distichiasis and lymphedema (although a young child may have no evidence of lymphedema)
- Distichiasis and a family history of lower-limb lymphedema
- Lower-limb lymphedema and a family history of distichiasis

If clinical findings are not diagnostic, the identification of a heterozygous pathogenic variant in *FOXC2* by molecular genetic testing can confirm the diagnosis (see Table 1).

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of LDS can be specific to this condition, 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 diagnosis of LDS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of LDS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FOXC2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A primary lymphedema multigene panel** that includes *FOXC2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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.

Option 2

When the diagnosis of LDS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FOXC2	Sequence analysis [3]	~95%
	Gene-targeted deletion/duplication analysis [4]	Unknown; none reported [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Lymphedema-distichiasis syndrome (LDS) is characterized by lymphedema with onset in late childhood or puberty and is confined to the lower limbs and/or genitalia. Varicose veins are a frequent association and may develop before the onset of the lymphedema. Distichiasis, which may be present at birth, can be associated with ocular problems such as corneal irritation, recurrent conjunctivitis, and photophobia. Congenital ptosis involving one or both eyes may be present. Other less common findings include congenital heart disease, cleft palate, webbed neck, and renal anomalies. Severity varies within and between families, with some affected neonates presenting with hydrops fetalis.

Lymphedema is present in most individuals with LDS. While it typically appears in late childhood or puberty (age range: 7-40 years) [Erickson et al 2001, Brice et al 2002], congenital onset has been reported [Finegold et al 2001]. In females, pregnancy or use of oral contraceptives may precipitate the onset of swelling.

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].

Whereas primary lymphedema is usually associated with hypoplasia or aplasia of the lymphatic vessels, LDS is associated with an increased number of lymphatic vessels and inguinal lymph nodes [Dale 1987, Brice 2003]. The valves in the lymphatic vessels and veins are small and dysplastic, resulting in reflux and edema [Petrova et al 2004].

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 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 LDS [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* pathogenic variant with lymphedema only; however, only three individuals were affected and it is not known whether they were examined by slit lamp for evidence of distichiasis, which can sometimes be very subtle. In a study of 23 probands reported to have Meige disease (see Differential Diagnosis) only one had a pathogenic variant 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 2008].

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

Varicose veins. The incidence of varicose veins is much higher (and onset earlier) in individuals with LDS than in the general population. About 50% of individuals with LDS have clinically evident 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* pathogenic variants [Mellor et al 2007]. *FOXC2* is essential for lymphatic and venous valve formation in the embryo [Lyons et al 2017].

Ptosis. Approximately 30% of individuals with LDS have unilateral or bilateral congenital ptosis of variable severity.

Congenital heart disease occurs in 7%-10% of individuals with LDS. Structural abnormalities include ventricular septal defect, atrial septal defect, patent ductus arteriosis, bicuspid aortic valve, 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 [Papoff et al 2016].

Other findings

- Nonimmune hydrops fetalis or antenatal hydrothoraces have been reported as a rare complication of LDS. Hydrops fetalis can be caused by lymphatic abnormalities [Bellini et al 2015]. If the fetus or neonate survives, the hydrops may resolve completely. It has been suggested that the hydrops and respiratory failure may be due to severe pulmonary lymphangiectasia [de Bruyn et al 2012, Sargent et al 2014].
- Spinal extradural arachnoid cyst (SEDAC) is a cyst in the spinal canal that protrudes into the epidural space from a defect in the dura mater. Thus, SEDAC caused by a heterozygous *FOXC2* loss-of-function variant should be considered a feature of LDS. It may manifest as the sole finding, but more frequently the family history is positive for SEDAC, distichiasis, and/or lymphedema [Kanaan et al 2006, Ogura et al 2013].
- Renal anomalies include hydronephrosis, ectopic kidney, and renal agenesis, which may be detected by antenatal ultrasound examination [Jones et al 2017].

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

Genotype-Phenotype Correlations

No genotype-phenotype correlations for the major clinical signs have been reported.

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.

Approximately 94% of affected individuals have distichiasis. In all families with *FOXC* pathogenic variants reported, at least one individual has had distichiasis.

Nomenclature

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

Prevalence

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

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Lymphedema-Distichiasis Syndrome (LDS)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/LDS	Distinguishing from LDS
Milroy disease	*FLT4*	AD	Lymphedema [1]	• Typically congenital-onset lymphedema (very rarely presents later) • Absence of distichiasis
Meige disease (OMIM 153200)	Unknown	AD		• Absence of distichiasis
Hypotrichosis-lymphedema-telangiectasia syndrome (OMIM 607823)	*SOX18*	AR		• Loss of hair • Telangiectasia, particularly in the palms • Absence of distichiasis
Hypotrichosis-lymphedema-telangiectasia-renal defect syndrome (OMIM 137940)		AD		
Lymphedema microcephaly (OMIM 152950)	*KIF11*	AD		• Small head circumference • May be associated w/ chorioretinopathy &/or ID • Absence of distichiasis
Yellow nail syndrome (OMIM 153300)	Unknown	AD [2]		• Very slow-growing nails w/ transverse overcurvature & hardening of the nail plate [3] • Absence of distichiasis
Emberger syndrome (OMIM 614038)	*GATA2*	AD		• Myelodysplasia • Immunodeficiency • Absence of distichiasis

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/LDS	Distinguishing from LDS
Blepharocheilodontic syndrome (OMIM PS119580)	*CDH1* *CTNND1*	AD	Distichiasis [4]	• Lagophthalmos (inability to fully close eyes) • Cleft lip & palate • Atrial septal defect • Oligodontia • Absence of lymphedema

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. The presence of lymphatic vessels on lymphoscintigraphy in LDS contrasts with other causes of primary lymphedema, including Milroy disease and Meige disease, which show aplasia or hypoplasia of the lymphatic vessels.

2. Inheritance is said to be autosomal dominant; most affected individuals represent simplex cases (i.e., a single occurrence in a family) [Hoque et al 2007].

3. Nail changes are different from the typically discolored nails often associated with chronic lymphedema.

4. 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 and needs of in an individual diagnosed with lymphedema-distichiasis syndrome (LDS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Lymphedema-Distichiasis Syndrome

System/ Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	• Slit lamp eval for distichiasis & related problems of corneal irritation, recurrent conjunctivitis, & photophobia • Assess for ptosis. • Assess for strabismus.
Lymphedema	Physical exam of lower legs to document presence of lymphedema & any evidence of cellulitis	Isotope lymphoscintigraphy to detect lymphatic weakness before onset of swelling
Vascular	Physical exam of varicose veins w/young onset (adolescence / early adulthood)	Venous duplex scans
Cleft palate	Assess for cleft palate or Pierre Robin sequence.	
Cardiovascular	Assess for congenital heart defects.	• Echocardiogram • Further eval if clinical evidence suggests arrhythmias
Spine	Assess for spinal extradural arachnoid cyst.	• Cysts can result in fluctuating symptoms (e.g., when enlarged, they may compress the root or cord & result in pain or weakness). • Spinal MRI if symptomatic
	Assess for scoliosis.	
Renal	Renal ultrasound eval	Assess for renal anomalies.

Table 3. continued from previous page.

System/ Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Eyes

- 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.
- Surgery for ptosis if clinically indicated (e.g., obscured vision, cosmetic appearance)

Lymphedema. Refer to a lymphedema therapist for management of edema (fitting hosiery, massage). Although the edema cannot be cured, some improvement may be possible with the use of carefully fitted hosiery and/or bandaging, which may reduce the size of the swelling as well as the associated discomfort. The implementation of hosiery prior to the development of lymphedema may be beneficial in reducing the extent of edema [P Mortimer, personal communication].

The following are appropriate:

- 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/day) are recommended for recurrent cellulitis.
- Prompt treatment of early cellulitis with 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

Note: (1) Diuretics are not effective in the treatment of lymphedema. (2) Cosmetic surgery is often associated with disappointing results.

See fact sheet for more information.

Varicose veins. Manage varicose veins conservatively with compression garments if possible, as surgery could aggravate the edema and increase the risk of infection or cellulitis.

Cardiac anomalies/arrhythmia. Manage as per standard practice.

Spine

- **Spinal extradural arachnoid cyst.** Refer individuals with symptomatic spinal cysts (i.e., any neurologic signs or symptoms, especially in the lower limbs) to a neurosurgeon.
- **Scoliosis.** Standard treatment

Renal malformations. Standard treatment

Surveillance

Table 4. Recommended Surveillance for Individuals with Lymphedema-Distichiasis Syndrome

System/Concern	Evaluation	Frequency
Eyes	Slit lamp exam of the eyes	As required for control of symptoms from distichiasis

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Lymphedema	Lymphoscintigraphy at diagnosis, then clinical assessment	1-2x/yr, but regular lymphedema therapy (every 6 mos) [1]
Varicose veins	Clinical assessment	1-2x/yr
Cleft palate	Per craniofacial team	
Cardiovascular	Per cardiologist	
Spine	Investigate w/spine MRI; only if symptomatic.	
Renal	Per treating nephrologist/urologist	

1. See fact sheet for more information.

Evaluation of Relatives at Risk

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

Pregnancy Management

Edema may be exacerbated during pregnancy, but often improves after delivery. The patient should continue compression and bandage treatment as long as possible but this should be adapted to the patient's needs (e.g., thigh-length compression garments instead of tights). See fact sheet for more information.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

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

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with LDS have an affected parent.
- A proband with LDS may have the disorder as the result of a *de novo FOXC2* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is about 25% [Brice et al 2002].
- If the *FOXC2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with LDS may appear to be negative because of failure to recognize the disorder in family members as a result of variable expressivity. Therefore, an apparently

negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of 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%. Manifestations of the disorder in sibs who inherit a *FOXC2* pathogenic variant cannot be accurately predicted and may be variable within the same family.
- If the parents are clinically unaffected and/or the proband has a known *FOXC2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with LDS has a 50% chance of inheriting the *FOXC2* pathogenic variant. Manifestations of the disorder in offspring who inherit a *FOXC2* pathogenic variant cannot be accurately predicted and may be variable within the same family.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *FOXC2* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *FOXC2* pathogenic variant has been detected in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing for LDS are possible.

Ultrasonography

- Fetal echocardiography at 16 to 20 weeks' gestation is recommended because of the increased risk for congenital heart disease.
- Additional fetal scans may be warranted because of the increased risk for cleft palate.
- An additional scan in the third trimester is recommended because of the increased risk of hydrothoraces or hydrops fetalis.

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.

- **LE&RN**
  Lymphatic Education and Research Network
  261 Madison Avenue
  9th Floor
  New York NY 10016
  Phone: 516-625-9675
  Fax: 516-625-9410
  Email: lern@lymphaticnetwork.org
  Living with lymphedema and lymphatic disease
- **Lymphoedema Support Network (LSN)**
  St. Luke's Crypt
  Sydney Street
  London SW3 6NH
  United Kingdom
  Phone: 020 7351 4480 (Information and Support); 020 7351 0990 (Administration)
  Fax: 020 7349 9809
  Email: adminlsn@lymphoedema.freeserve.co.uk
  www.lymphoedema.org
- **National Lymphedema Network (NLN)**
  116 New Montgomery Street
  Suite 235
  San Francisco CA 94105
  Phone: 800-541-3259 (toll-free); 415-908-3681
  Fax: 415-908-3813
  Email: nln@lymphnet.org
  www.lymphnet.org
- **Medline Plus**
  Lymphatic diseases
- **The International Lymphatic Disease and Lymphedema Patient Registry & Biorepository**
  www.lernregistry.stanford.edu

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. Lymphedema-Distichiasis Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

FOXC2	16q24.1	Forkhead box protein C2	FOXC2 database	FOXC2	FOXC2

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 Lymphedema-Distichiasis Syndrome (View All in OMIM)

153400	LYMPHEDEMA-DISTICHIASIS SYNDROME; LPHDST
602402	FORKHEAD BOX C2; FOXC2

Molecular Pathogenesis

FOXC2 has a major role in the formation of the lymphatic and venous valves [Petrova et al 2004] and in cardiac neural crest cell migration [Inman et al 2018].

Mechanism of disease causation. *FOXC2* variants causing lymphedema-distichiasis syndrome are thought to be loss-of-function variants. Evidence in support of a loss-of-function mechanism would be a large partial- or whole-gene *FOXC2* deletion; no such variants have been described. However, a 256-kb contiguous gene deletion, involving *FOXC2* and multiple adjacent genes, was reported; a number of clinical features of this individual were likely caused by the deletion of *FOXC2* [Butler et al 2012].

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Chapter Notes

Revision History

- 4 April 2019 (bp) Comprehensive update posted live
- 24 May 2012 (me) Comprehensive update posted live
- 2 August 2007 (me) Comprehensive update posted live
- 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 live
- 13 September 2004 (sm) Original submission

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