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Milroy Disease

Synonym: Hereditary Lymphedema Type I

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Summary

Clinical characteristic

Milroy disease is characterized by lower-limb lymphedema, present as pedal edema at (or before) birth or developing soon after. Occasionally it presents later in life. The severity of edema shows both inter- and intrafamilial variability. Swelling is usually bilateral but can be asymmetric. The degree of edema can progress but, in some instances, can improve, particularly in the early years. Other features sometimes associated with Milroy disease include hydrocele (37% of males), prominent veins below the knees (23%), upslanting toenails (14%), papillomatosis (10%), and urethral abnormalities in males (4%). Cellulitis, which can damage the lymphatic vessels, occurs in approximately 20% of affected individuals, with infection significantly more likely in males than females.

Diagnosis/testing

The diagnosis of Milroy disease is established in a proband with congenital or infantile-onset lower-limb lymphedema accompanied by lack of uptake of radioactive colloid in the ilioinguinal lymph nodes on lymphoscintigraphy and/or by identification of a heterozygous pathogenic variant in *FLT4* by molecular genetic testing.

Management

Treatment of manifestations: A lymphedema therapist may utilize fitted stockings and massage to improve the cosmetic appearance or decrease the size of the limb and reduce the risk of complications. Improvement in swelling is usually possible with use of properly fitted compression hosiery and/or bandaging and well-fitting,

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supportive shoes. Toe gloves may be of benefit and good skin care is essential. Standard treatment for cellulitis, hydroceles, and urethral abnormalities.

Prevention of secondary complications: Frequency of cellulitis can be reduced through good skin hygiene, prompt treatment of infections with antibiotics, and prophylactic antibiotics for recurrent episodes.

Surveillance: Routine follow up in a clinic specializing in the care of lymphedema is appropriate.

Agents/circumstances to avoid: Wounds to limbs; long periods of immobility with the legs in a dependent position; and medications that can cause increased leg swelling.

Evaluation of relatives at risk: Evaluation of apparently asymptomatic at-risk relatives of an affected individual is appropriate in order to identify those who would benefit from properly fitted compression hosiery and advice on how to reduce the risk of cellulitis of the legs and feet.

Genetic counseling

Milroy disease is inherited in an autosomal dominant manner. Most individuals diagnosed with Milroy disease have an affected parent. If a parent of the proband is affected and/or has an *FLT4* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Intrafamilial variability and reduced penetrance are observed in Milroy disease; a heterozygous sib may be more or less severely affected than the proband. Once the *FLT4* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Ultrasonography during pregnancy may detect swelling of the dorsum of the feet, mild pleural effusions which often resolve, and (very rarely) more extensive edematous states (fetal hydrops) in an affected fetus.

Diagnosis

Suggestive Findings

Milroy disease **should be suspected** in individuals with the following clinical features, radiographic findings, and family history.

Clinical features

- Lower-limb swelling that is:
  - Usually (not always) bilateral
  - Present at birth or develops soon after

    Note: In neonates the swelling predominantly affects the dorsum of the feet; with age, the swelling may improve or progress to affect the below-knee region (rarely extending above the knees).
- Large-caliber veins below the knees
- Upslanting and small, dysplastic toenails
- Deep interphalangeal creases of the feet
- Hydroceles in males
- No internal clinically significant lymphatic issues (e.g., intestinal lymphangiectasia, pleural or pericardial effusions)

Radiographic findings. Lymphoscintigraphy typically demonstrates a lack of uptake of tracer into peripheral lymphatics. Consequently, no drainage channels are visualized nor is there any uptake in the ilio-inguinal nodes. This is referred to as "functional aplasia" and is characteristic of Milroy disease.

Note: The lymphoscintigraphic findings are characteristic and useful for diagnosis, but this test is not absolutely required (see Clinical Description for more detail).

Family history shows similarly affected individuals consistent with an autosomal dominant inheritance pattern.

Note: Absence of a known family history of Milroy disease does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Milroy disease **is established** in a proband with congenital or infantile-onset lower-limb lymphedema accompanied by lack of uptake of radioactive colloid in the ilioinguinal lymph nodes on lymphoscintigraphy and/or identification of a heterozygous pathogenic variant in *FLT4* (*VEGFR3*) by molecular genetic testing (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, 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 Milroy is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with lymphedema are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *FLT4* is performed first. Such testing is able to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. In Milroy disease, most variants are pathogenic missense variants in the tyrosine kinase domain of the gene (see Molecular Genetics).

  Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. However, such variants would not be anticipated to lead to Milroy disease.

- **A lymphedema multigene panel** that includes *FLT4* 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 phenotype is indistinguishable from many other inherited disorders characterized by lymphedema, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible, although not typically done in practice for individuals with a phenotype consistent with Milroy disease.

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 Milroy Disease

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FLT4	Sequence analysis [3]	≤75% in well-phenotyped cohorts [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown [7]	NA	NA

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. Variants detected 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. Connell et al [2009] suggest that a pathogenic variant is detected in 75% of those clearly affected and with a positive family history and in 68% of those with typical Milroy features but without a family history.
5. 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.
6. Gene-targeted deletion/duplication analysis has not identified any deletions or duplications of *FLT4* that are causative of Milroy disease. The molecular mechanism of disease causation is likely dominant negative, such that deletions/duplications of *FLT4* are not likely to cause Milroy disease (see Genetically Related Disorders). Data are derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017].
7. No other loci have been identified, but reports suggest that Milroy disease is genetically heterogeneous [Holberg et al 2001, Evans et al 2003]. Even when the individual has a clear clinical diagnosis, an *FLT4* pathogenic variant is found in up to 75% of affected individuals, suggesting that other genes may be involved [Connell et al 2009]. Rare cases may be caused by pathogenic variants in *VEGFC* [Gordon et al 2013a, Balboa-Beltran et al 2014, Fastré et al 2018, Nadarajah et al 2018].

Clinical Characteristics

Clinical Description

The most common finding in Milroy disease is congenital bilateral, lower-limb lymphedema. The edema is usually present from (or before) birth. Rarely, prenatal pleural effusion and fetal hydrops have been reported [Daniel-Spiegel et al 2005, Boudon et al 2015], but in general Milroy disease is not associated with more widespread lymphatic abnormalities. In neonates the swelling tends to affect primarily the dorsum of the feet (pedal edema). Anecdotal evidence suggests that on rare occasions it develops later in life (see Penetrance).

The amount of edema varies both within and among families. Swelling is often bilateral but can be asymmetric.

The degree of edema sometimes progresses but in some instances can improve, particularly in early years.

Other features sometimes associated with Milroy disease:

- Hydrocele (37% of males)

- Prominent veins (23%) below the knees (with or without venous reflux seen on duplex imaging) [Mellor et al 2010]
- Upslanting (spoon-shaped and/or dysplastic) toenails (14%)
- Papillomatosis located on the toes and/or forefoot (10%)
- Urethral abnormalities, such as hypospadias or urethral stricture, in males (4%)

Cellulitis occurs in approximately 20% of affected individuals, with infection significantly more likely in males than females [Brice et al 2005]. Cellulitis can damage the existing lymphatic vessels, resulting in an increase in the degree of swelling.

Lymphoscintigraphy is a common method of distinguishing Milroy disease from other lymphatic conditions. Radioactive colloid is injected into the toe web spaces and uptake in the ilioinguinal nodes is measured at intervals. Lymphoscintigraphy is performed to determine if there is lack of uptake of radioactive tracer. Milroy disease and other forms of lymphedema can have differing patterns on lymphoscintigraphy [Connell et al 2013, Sarica et al 2019]. In cases of unilateral swelling, lymphoscintigraphy can determine if lymphatic drainage is impaired in the "unaffected" leg.

Genotype-Phenotype Correlations

No genotype-phenotype correlation for Milroy disease has been reported. Most pathogenic variants are missense variants that occur in the tyrosine kinase domain of *FLT4* (see Molecular Genetics).

Penetrance

Approximately 85%-90% of individuals who have a pathogenic variant in *FLT4* develop lower-limb lymphedema by age three years; conversely, 10%-15% of individuals with an *FLT4* pathogenic variant are clinically unaffected.

Nomenclature

Milroy disease is named after William Milroy, who described 97 members of a family, of whom 26 had leg edema [Milroy 1892]. In the family described by Milroy, the edema was painless, non-progressive, and confined to the lower limbs.

Hereditary lymphedema of the legs was also described by Nonne [1891]; hence, the term Nonne-Milroy disease has been used in the past.

Milroy disease may also be referred to as Milroy congenital lymphedema.

Prevalence

The prevalence of Milroy disease is not known but it appears to be one of the more common causes of primary lymphedema, occurring in all ethnic groups.

Genetically Related (Allelic) Disorders

Germline heterozygous loss-of-function pathogenic variants in *FLT4* are associated with congenital heart defects, particularly tetralogy of Fallot (OMIM 618780).

Differential Diagnosis

A list of differential diagnoses can be found in Gordon et al [2020].

Table 2. Genes of Interest in the Differential Diagnosis of Milroy Disease

Gene(s)	DiffDx Disorder	MOI	Lymphedema Phenotype of DiffDx Disorder	Other Clinical Features
ADAMTS3	Hennekam lymphangiectasia-lymphedema syndrome 3 (OMIM 618154)	AR	Congenital generalized edema	Assoc features incl facial dysmorphism & protein-losing enteropathy of variable severity
BRAF *KRAS* *LZTR1* *MAP2K1* *NRAS* *PTPN11* *RAF1* *RIT1* *SOS1*	Noonan syndrome (NS)	AD (AR [1])	May present w/congenital edema of lower limbs which may or may not resolve. Persons w/NS may present again in childhood or adulthood w/ edema of lower limbs & genitalia. There may also be a central conducting lymphatic anomaly presenting w/ chylous reflux, chylothoraces, & chylopericardium which may be progressive.	Characteristic facies, short stature, CHD, & DD of variable degree. Other findings incl broad or webbed neck, unusual chest shape w/superior pectus carinatum & inferior pectus excavatum, cryptorchidism, varied coagulation defects, & ocular abnormalities.
CCBE1	Hennekam syndrome 1 (OMIM 235510)	AR	Congenital or childhood-onset generalized edema; systemic involvement: e.g., intestinal lymphangiectasia (cardinal feature) & pleural or pericardial effusions	ID [2]
FAT4	Hennekam lymphangiectasia-lymphedema syndrome 2 (OMIM 616006)	AR	Childhood- or adult-onset generalized edema	Dysmorphic facial features, microtia, ID
KIF11	Microcephaly-lymphoedema-chorioretinopathy (OMIM 152950)	AD	Edema indistinguishable from that of Milroy disease; identical lymphoscintigraphy pattern. [3] Intestinal lymphangiectasia may be a complication.	Microcephaly, chorioretinopathy, & (in most persons) learning difficulties
PIEZO1	*PIEZO1*-related generalized lymphatic dysplasia w/systemic involvement (OMIM 616843)	AR	Congenital or childhood-onset generalized edema	Fetal hydrops, atrial septal defects; pleural or pericardial effusions
SOX18	Hypotrichosis-lymphedema-telangiectasia syndrome (OMIM 607823)	AR AD	Childhood-onset lower limb lymphedema	Loss of hair & telangiectasia (particularly on the palms); renal defect
VEGFC	*VEGFC* lymphoedema (OMIM 615907)	AD	Clinically indistinguishable from that of Milroy disease; but lymphoscintigraphy pattern is different. [4]	Varicose veins

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart defect; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance

1. Noonan syndrome is most often inherited in an autosomal dominant manner; Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

2. The cognitive impairment with dysmorphic features was originally emphasized as a cardinal clinical sign of *CCBE1*-associated Hennekam syndrome, but less so in more recent publications [Connell et al 2010, Alders et al 2013, Crawford et al 2016, Jackson et al 2016].

3. Ostergaard et al [2012], Jones et al [2014]

4. Two families with a phenotype resembling Milroy disease have been shown to have pathogenic variants in *VEGFC*. Clinically, it is not possible to distinguish these individuals from those with *FLT4* pathogenic variants and testing of *VEGFC* should be considered if *FLT4* testing is negative [Gordon et al 2013a, Balboa-Beltran et al 2014, Fastré et al 2018, Nadarajah et al 2018, Gordon et al 2020].

Chromosomal Disorders and Hereditary Disorders of Unknown Genetic Cause

Turner syndrome is the combination of a characteristic phenotype in females who have one normal X chromosome and either (1) absence of the second sex chromosome (X or Y) with or without mosaicism or (2) partial deletion of the X chromosome. The Turner syndrome phenotype includes short stature, stature disproportion, primary amenorrhea, neck webbing, congenital lymphedema of the hands and feet, high-arched palate, short metacarpals, scoliosis, Madelung deformity, hearing difficulties, cardiac and renal anomalies, hypothyroidism, and glucose intolerance [Batch 2002, Sybert & McCauley 2004]. Lymphedema in this syndrome affects the extremities and often improves over time. Turner syndrome occurs in 1:2,500 to 1:3,000 live female births [Sybert & McCauley 2004] and should always be considered in a female with congenital lymphedema particularly if hands and feet are affected.

Meige disease (OMIM 153200) presents with pubertal-onset lymphedema. No other features appear to be associated. Women are more commonly affected than men. No genes have been identified as yet. Inheritance appears to be autosomal dominant with reduced penetrance.

Lymphedema with yellow nails (yellow nail syndrome, YNS) (OMIM 153300) 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 of any cause. The disorder is thought to be autosomal dominant or non-genetic/acquired [Hoque et al 2007, Maldonado et al 2008].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Milroy disease, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Milroy Disease

System/Concern	Evaluation	Comment
Lymphatic	Referral to a lymphedema therapist	Consider lymphoscintigraphy if not already performed.
Genitourinary	Males: assessment for scrotal edema, hydroceles, & urethral abnormalities	If present, consider referral to urologist.
Integument	Full skin exam	To assess for evidence of cellulitis, papillomatosis, & warts
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Consider use of community or online resources such as Parent to Parent.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Milroy Disease

Manifestation/Concern	Treatment	Considerations/Other
Lower leg edema [1]	• Fitting compression hosiery &/or bandaging • Massage • Supportive shoes • Toe gloves may be of benefit. • Good skin care	Per lymphedema therapist

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cellulitis	Standard treatment	
Hydroceles & urethral abnormalities	Standard treatment per urologist	

1. Although the edema cannot be cured, some improvement is usually possible with the supportive measures listed in the table. Such treatment measures may improve the cosmetic appearance of the limb, decrease the size of the limb, and reduce the risk of complications.

Prevention of Secondary Complications

Secondary cellulitis is prevented through the following measures:

- Prevention of foot infections, particularly athlete's foot or infected ingrown toenails
- Prompt treatment for early cellulitis with appropriate antibiotics. It may be necessary to give the first few doses intravenously.
- Prophylactic antibiotics in recurrent cases (e.g., penicillin V 250 mg 2x daily for 1-2 years). The dose may need to be adjusted for pediatric or obese individuals [British Lymphology Society / Lymphoedema Support Network 2016] (full text).

Surveillance

Routine follow up in a clinic specializing in the care of lymphedema is appropriate.

Agents/Circumstances to Avoid

The following should be avoided:

- Wounds to the swollen limbs, because of a reduced resistance to infection
- Long periods of immobility with the legs in a dependent position (e.g., on a long airplane flight)
- Medications that can cause increased leg swelling in some individuals (particularly calcium channel-blocking drugs)

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment early in the course of the disease. The use of properly fitted compression hosiery and advice to reduce the risk of cellulitis of the legs and feet can be beneficial.

Evaluations can include:

- Molecular genetic testing if the causative pathogenic variant in the family is known;
- Physical examination if the causative pathogenic variant in the family is not known.

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

Pregnancy Management

Ultrasound scanning during pregnancy may indicate if a fetus is affected if swelling of the dorsum of the feet is noted in the second or third trimester. The fetus may have mild pleural effusions which frequently resolve before birth [Gordon et al 2013b]. Very rarely, fetal hydrops is present.

If the mother is affected by Milroy disease there may be an increase in the mother's swelling during the pregnancy.

Therapies Under Investigation

Attempts at overexpressing VEGF-C, the ligand for *FLT4*, have been successful in producing functional lymphatics in mice [Karkkainen et al 2001]. This treatment approach (in combination with microsurgical lymph node transfer surgery) is now being studied in humans in a clinical trial for breast cancer treatment-related secondary lymphedema [Hartiala et al 2020].

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.

Other

Treatment with diuretics is of no proven benefit.

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

Milroy disease is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with Milroy disease have an affected parent.
- An individual diagnosed with Milroy disease may have the disorder as the result of a *de novo FLT4* pathogenic variant. Approximately 10% of individuals with Milroy disease represent simplex cases (i.e., a single affected family member) [Ghalamkarpour et al 2006, Carver et al 2007, Connell et al 2009, Gordon et al 2013b]. However, the proportion of these individuals who have Milroy disease as the result of a *de novo* pathogenic variant (as opposed, for example, to inheritance of a pathogenic variant from a heterozygous parent with reduced penetrance or a parent with germline mosaicism) is not known because parental testing has not been performed in all reported families.
- If a molecular diagnosis has been established in the proband, molecular genetic testing for the *FLT4* pathogenic variant identified in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ cells.

- The family history of some individuals diagnosed with Milroy disease may appear to be negative because of failure to recognize the disorder in family members as a result of variable expression or reduced penetrance.

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 has an *FLT4* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Intrafamilial variability and reduced penetrance are observed in Milroy disease; a heterozygous sib may be more or less severely affected than the proband.
- If the proband has an *FLT4* 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 possibility of parental germline mosaicism [Rahbari et al 2016].
- If the genetic status of the parents is unknown but they are clinically unaffected, the risk to the sibs of a proband appears to be low but greater than that of the general population because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with Milroy disease has a 50% chance of inheriting the *FLT4* pathogenic variant. Intrafamilial variability is observed in Milroy disease; a heterozygous child may be more or less severely affected than the proband.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have a Milroy disease-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 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 *FLT4* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Ultrasound examination. Ultrasonography during pregnancy may detect swelling of the dorsum of the feet, mild pleural effusions which often resolve, and (very rarely) more extensive edematous states (fetal hydrops) in an affected fetus [Franceschini et al 2001, Makhoul et al 2002, Daniel-Spiegel et al 2005].

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.

- **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
- **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
- **Medline Plus**
  Lymphatic diseases
- **VASCERN Patient Group (ePAG)**
  VASCERN - European Reference Network (ERN)
  VASCERN Patient Group
- **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. Milroy Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FLT4	5q35.3	Vascular endothelial growth factor receptor 3	FLT4 database	FLT4	FLT4

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 Milroy Disease (View All in OMIM)

136352	FMS-LIKE TYROSINE KINASE 4; FLT4
153100	LYMPHATIC MALFORMATION 1; LMPHM1

Molecular Pathogenesis

The normal gene product of *FTL4*, VEGFR-3 (vascular endothelial growth factor receptor 3), is a dimeric transmembrane receptor for the ligands VEGFC and VEGFD. The binding of the ligands activates the intracellular kinase domains of the dimer, which then autophosphorylate each other. The trans-autophosphorylation results in recruitment of adaptor proteins such as CRK, SHC, and GRB2, which in conjunction with phosphatidylinositol-3-kinase (PI3K) activate downstream signaling pathways that include the mitogen-activated protein kinase (MAPK) family members AKT, ERK1/2, and JNK (c-Jun N-terminal kinase) [Monaghan et al 2020].

VEGFR-3 is a lymphatic endothelial cell-specific receptor and, when stimulated by the VEGFC ligand, is the key regulator of lymphatic vessel growth and function. The abnormal gene products will form either mutant/mutant type homodimers showing no tyrosine kinase activity or mutant/wild type heterodimers showing some TK activity, leading to an overall decrease in downstream signaling [Irrthum et al 2000, Karkkainen et al 2000]. Studies have shown that the proportion of dimers including a mutant receptor is higher than expected. This is due to a greater stability at the plasma membrane and slower rate of degradation of the mutant receptor compared to wild type receptors, leading to a dominant-negative effect.

Mechanism of disease causation. Dominant negative [Karkkainen et al 2000, Monaghan et al 2020]. All pathogenic variants identified to date have been in exons encoding tyrosine kinase domains. See Gordon et al [2013b] for discussion of variants reported in the literature.

Chapter Notes

Author Notes

St George's University Hospitals

We provide consultations and multidisciplinary approaches for the following medical conditions:

- Primary lymphoedema (genetic/inherited types, and lymphovascular malformations)
- Secondary lymphoedema
- Rapid access appointments for patients with cancer-related lymphoedema
- Complications of lymphoedema, e.g., recurrent cellulitis
- Lipoedema & lipodystrophy

We have a range of diagnostic tools available within our service to aid our phenotyping and assessment process:

- Lymphoscintigraphy

- Genetic screening
- MR lymphography

Our research interest and focus is gene discovery in primary lymphoedema / lymphovascular disease and understanding the mechanism of disease in primary lymphoedema through imaging (e.g., MR lymphography, ICG lymphography), histology, and blood immunophenotyping.

Please check our website for more information about our services: www.stgeorges.nhs.uk/service/lymphoedema. Contact Clinical Lead Dr Gordon for more information: kristiana.gordon@stgeorges.nhs.uk

Information about our research: www.sgul.ac.uk/profiles/pia-ostergaard. Contact Professor Pia Ostergaard directly for more information about our past and current research: posterga@sgul.ac.uk.

VASCERN European Reference Network

The VASCERN European Reference Network is a European platform where health care professionals and patient representatives share expertise and develop consensus and guidelines for rare vascular diseases. The Primary and Pediatric Lymphoedema Working Group is built upon Multidisciplinary Centres of Excellence collaborating and have a long-standing expertise in the diagnosis and management of adults and children with lymphatic problems.

For health care professionals, the VASCERN website contains clinical decision-making tools for pediatric and primary lymphoedema patients such as genetic testing, inter- and multidisciplinary treatment, and cellulitis management. For patients/parents and caregivers, it has resources such as education videos on overall overview of primary lymphoedema, cellulitis management, and compression.

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Revision History

- 18 February 2021 (ma) Comprehensive update posted live
- 25 September 2014 (me) Comprehensive update posted live
- 23 July 2009 (me) Comprehensive update posted live
- 6 April 2007 (gb) Revision: sequence analysis and prenatal testing clinically available
- 27 April 2006 (me) Review posted live
- 19 July 2005 (gb) Original submission

References

Published Guidelines / Consensus Statements

British Lymphology Society / Lymphoedema Support Network. Consensus document on the management of cellulitis in lymphoedema. 2016. Available online. Accessed 2-10-21.

Literature Cited

Alders M, Mendola A, Adès L, Al Gazali L, Bellini C, Dallapiccola B, Edery P, Frank U, Hornshuh F, Huisman SA, Jagadeesh S, Kayserili H, Keng WT, Lev D, Prada CE, Sampson JR, Schmidtke J, Shashi V, van Bever Y, Van der Aa N, Verhagen JM, Verheij JB, Vikkula M, Hennekam RC. Evaluation of clinical manifestations in patients with severe lymphedema with and without CCBE1 mutations. Mol Syndromol. 2013;4:107–13. PubMed PMID: 23653581.

Balboa-Beltran E, Fernández-Seara MJ, Pérez-Muñuzuri A, Lago R, García-Magán C, Couce ML, Sobrino B, Amigo J, Carracedo A, Barros F. A novel stop mutation in the vascular endothelial growth factor-C gene (VEGFC) results in Milroy-like disease. J Med Genet. 2014;51:475–8. PubMed PMID: 24744435.

Batch J. Turner syndrome in childhood and adolescence. Best Pract Res Clin Endocrinol Metab. 2002;16:465–82. PubMed PMID: 12464229.

Boudon E, Levy Y, Abossolo T, Cartault F, Brouillard P, Vikkula M, Kieffer-Traversier M, Ramful D, Alessandri JL. Antenatal presentation of hereditary lymphedema type I. Eur J Med Genet. 2015;58:329–31. PubMed PMID: 25896638.

Brice G, Child AH, Evans A, Bell R, Mansour S, Burnand K, Sarfarazi M, Jeffery S, Mortimer P. Milroy disease and the VEGFR-3 mutation phenotype. J Med Genet. 2005;42:98–102. PubMed PMID: 15689446.

British Lymphology Society / Lymphoedema Support Network. Consensus document on the management of cellulitis in lymphoedema. 2016.

Carver C, Brice G, Mansour S, Ostergaard P, Mortimer P, Jeffery S. Three children with Milroy disease and de novo mutations in VEGFR3. Clin Genet. 2007;71:187–9. PubMed PMID: 17250670.

Connell FC, Gordon K, Brice G, Keeley V, Jeffery S, Mortimer PS, Mansour S, Ostergaard P. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. Clin Genet. 2013;84:303–14. PubMed PMID: 23621851.

Connell F, Kalidas K, Ostergaard P, Brice G, Homfray T, Roberts L, Bunyan DJ, Mitton S, Mansour S, Mortimer P, Jeffery S, et al. Linkage and sequence analysis indicate that CCBE1 is mutated in recessively inherited generalised lymphatic dysplasia. Hum Genet. 2010;127:231–41. PubMed PMID: 19911200.

Connell FC, Ostergaard P, Carver C, Brice G, Williams N, Mansour S, Mortimer PS, Jeffery S, et al. Analysis of the coding regions of VEGFR3 and VEGFC in Milroy disease and other primary lymphoedemas. Hum Genet. 2009;124:625–31. PubMed PMID: 19002718.

Crawford J, Bower NI, Hogan BM, Taft RJ, Gabbett MT, McGaughran J, Simons C. Expanding the genotypic spectrum of CCBE1 mutations in Hennekam syndrome. Am J Med Genet A. 2016;170:2694–7. PubMed PMID: 27345729.

Daniel-Spiegel E, Ghalamkarpour A, Spiegel R, Weiner E, Vikkula M, Shalev E, Shalev SA. Hydrops fetalis: an unusual prenatal presentation of hereditary congenital lymphedema. Prenat Diagn. 2005;25:1015–8. PubMed PMID: 16231305.

Evans AL, Bell R, Brice G, Comeglio P, Lipede C, Jeffery S, Mortimer P, Sarfarazi M, Child AH. Identification of eight novel VEGFR-3 mutations in families with primary congenital lymphoedema. J Med Genet. 2003;40:697–703. PubMed PMID: 12960217.

Fastré E, Lanteigne L-E, Helaers R, Giacalone G, Revencu N, Dionyssiou D, Demiri E, Brouillard P, Vikkula M. Splice-site mutations in VEGFC cause loss of function and Nonne-Milroy-like primary lymphedema. Clin Genet. 2018;94:179–81. PubMed PMID: 29542815.

Franceschini P, Licata D, Rapello G, Guala A, Di Cara G, Franceschini D. Prenatal diagnosis of Nonne-Milroy lymphedema. Ultrasound Obstet Gynecol. 2001;18:182–3. PubMed PMID: 11547763.

Ghalamkarpour A, Morlot S, Raas-Rothschild A, Utkus A, Mulliken JB, Boon LM, Vikkula M. Hereditary lymphedema type I associated with VEGFR3 mutation: the first de novo case and atypical presentations. Clin Genet. 2006;70:330–5. PubMed PMID: 16965327.

Gordon K, Schulte D, Brice G, Simpson MA, Roukens MG, van Impel A, Connell F, Kalidas K, Jeffery S, Mortimer PS, Mansour S, Schulte-Merker S, Ostergaard P. Mutation in vascular endothelial growth factor-C, a ligand for vascular endothelial growth factor receptor-3, is associated with autosomal dominant Milroy-like primary lymphedema. Circ Res. 2013a;112:956–60. PubMed PMID: 23410910.

Gordon K, Spiden SL, Connell FC, Brice G, Cottrell S, Short J, Taylor R, Jeffery S, Mortimer PS, Mansour S, Ostergaard P. FLT4/VEGFR3 and Milroy disease: novel mutations, a review of published variants and database update. Hum Mutat. 2013b;34:23–31. PubMed PMID: 23074044.

Gordon K, Varney R, Keeley V, Riches K, Jeffery S, Van Zanten M, Mortimer P, Ostergaard P, Mansour S. Update and audit of the St George's classification algorithm of primary lymphatic anomalies: a clinical and molecular approach to diagnosis. J Med Genet. 2020;57:653–9. PubMed PMID: 32409509.

Hartiala P, Suominen S, Suominen E, Kaartinen I, Kiiski J, Viitanen T, Alitalo K, Saarikko AM. Phase 1 Lymfactin® study: short-term safety of combined adenoviral VEGF-C and lymph node transfer treatment for upper extremity lymphedema. J Plast Reconstr Aesthet Surg. 2020;73:1612–21. PubMed PMID: 32513642.

Holberg CJ, Erickson RP, Bernas MJ, Witte MH, Fultz KE, Andrade M, Witte CL. Segregation analyses and a genome-wide linkage search confirm genetic heterogeneity and suggest oligogenic inheritance in some Milroy congenital primary lymphedema families. Am J Med Genet. 2001;98:303–12. PubMed PMID: 11170072.

Hoque SR, Mansour S, Mortimer PS. Yellow nail syndrome: not a genetic disorder? Eleven new cases and a review of the literature. Br J Dermatol. 2007;156:1230–4. PubMed PMID: 17459037.

Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. Am J Hum Genet. 2000;67:295–301. PubMed PMID: 10856194.

Jackson CC, Best L, Lorenzo L, Casanova JL, Wacker J, Bertz S, Agaimy A, Harrer T. A multiplex kindred with Hennekam syndrome due to homozygosity for a CCBE1 mutation that does not prevent protein expression. J Clin Immunol. 2016;36:19–27. PubMed PMID: 26686525.

Jones GE, Ostergaard P, Moore AT, Connell FC, Williams D, Quarrell O, Brady AF, Spier I, Hazan F, Moldovan O, Wieczorek D, Mikat B, Petit F, Coubes C, Saul RA, Brice G, Gordon K, Jeffery S, Mortimer PS, Vasudevan PC, Mansour S. Microcephaly with or without chorioretinopathy, lymphoedema, or mental retardation

(MCLMR): review of phenotype associated with KIF11 mutations. Eur J Hum Genet. 2014;22:881–7. PubMed PMID: 24281367.

Karkkainen MJ, Ferrell RE, Lawrence EC, Kimak MA, Levinson KL, McTigue MA, Alitalo K, Finegold DN. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. Nat Genet. 2000;25:153–9. PubMed PMID: 10835628.

Karkkainen MJ, Saaristo A, Jussila L, Karila KA, Lawrence EC, Pajusola K, Bueler H, Eichmann A, Kauppinen R, Kettunen MI, Yla-Herttuala S, Finegold DN, Ferrell RE, Alitalo K. A model for gene therapy of human hereditary lymphedema. Proc Natl Acad Sci U S A. 2001;98:12677–82. PubMed PMID: 11592985.

Makhoul IR, Sujov P, Ghanem N, Bronshtein M. Prenatal diagnosis of Milroy's primary congenital lymphedema. Prenat Diagn. 2002;22:823–6. PubMed PMID: 12224079.

Maldonado F, Tazelaar HD, Wang CW, Ryu JH. Yellow nail syndrome: analysis of 41 consecutive patients. Chest. 2008;134:375–81. PubMed PMID: 18403655.

Mellor RH, Hubert CE, Stanton AWB, Tate N, Akhras V, Smith A, Burnand K, Jeffery S, Makinen T, Levick JR, Mortimer PS. Lymphatic dysfunction, not aplasia, underlies Milroy disease. Microcirculation. 2010;17:281–96. PubMed PMID: 20536741.

Milroy WF. An undescribed variety of hereditary oedema. NY Med J. 1892;56:505–8.

Monaghan RM, Page DJ, Ostergaard P, Keavney BD. The physiological and pathological functions of VEGFR3 in cardiac and lymphatic development and related diseases. Cardiovasc Res. 2020. Epub ahead of print. PubMed PMID: 33067626.

Sarica M, Gordon K, van Zanten M, Heenan SD, Mortimer PS, Irwin AG, Ramachandra V, Ostergaard P, Mansour S. Lymphoscintigraphic abnormalities associated with Milroy disease and lymphedema-distichiasis syndrome. Lymphat Res Biol. 2019;17:610–9. PubMed PMID: 31721633.

Nadarajah N, Schulte D, McConnell V, Martin-Almedina S, Karapouliou C, Mortimer PS, Jeffery S, Schulte-Merker S, Gordon K, Mansour S, Ostergaard P. A novel splice-site mutation in VEGFC is associated with congenital primary lymphoedema of Gordon. Int J Mol Sci. 2018;19:2259. PubMed PMID: 30071673.

Nonne M. Vier Falle von Elephantiasis congenita hereditaria. In: *Archiv fur pathologische Anatomie und Physiologie und fur klinische Medicin.* Berlin, Germany; 1891:189-96.

Ostergaard P, Simpson MA, Mendola A, Vasudevan P, Connell FC, van Impel A, Moore AT, Loeys BL, Ghalamkarpour A, Onoufriadis A, Martinez-Corral I, Devery S, Leroy JG, van Laer L, Singer A, Bialer MG, McEntagart M, Quarrell O, Brice G, Trembath RC, Schulte-Merker S, Makinen T, Vikkula M, Mortimer PS, Mansour S, Jeffery S. Mutations in KIF11 cause autosomal-dominant microcephaly variably associated with congenital lymphedema and chorioretinopathy. Am J Hum Genet. 2012; 2012;90:356–62. PubMed PMID: 22284827.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;351:1227–38. PubMed PMID: 15371580.

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