

## Approach to Familial Lymphoedema

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Abstract

Lymphoedema is the build-up of lymphatic fluid leading to swelling in the tissues. Most commonly it affects the peripheries. Diagnosis is based on clinical assessment and imaging with lymphoscintigraphy. Treatment is supportive with compression garments, massage, good skin hygiene and prompt use of antibiotics to avoid the complication of cellulitis. Most commonly lymphoedema occurs **secondary** as a result of damage to the lymphatic system, following surgery, trauma, radiation, or infection. However, it can be primary, often associated with a genetic defect causing disruption to the development of the lymphatic system. Common genetic conditions associated with lymphoedema include Turner syndrome and Noonan syndrome, however there are numerous others that can be classified based on their clinical presentation and associated features. Herein we discuss how to diagnose and classify the known primary lymphoedema conditions, and how best to investigate and manage this group of patients.

Keywords: Primary lymphoedema, hereditary, single gene, chromosomal, lymphatic

**Key points**

Primary lymphoedema is caused by abnormal development or function of the lymphatic system
Primary lymphoedema can be classified according to age of onset, pattern of lymphoedema, and associated features
There are many chromosomal or genetic conditions in which lymphoedema is a reported feature
Management of lymphoedema is mainly supportive with massage, compression garments and personal care, however with better understanding of the genetic basis, targeted therapies may be an option for some conditions
Genetic testing may help to clarify the diagnosis and allow accurate risk assessment for relatives

## Introduction

The lymphatic system is a network of connected vessels, nodes and tissues, whose main function is in the body's defence against infection. It also returns excess fluid from the tissues and fatty acids from the bowel to the bloodstream<sup>1</sup>. Disruption of the normal flow of the lymphatic system leads to swelling (oedema). Most commonly lymphoedema occurs ~~secondary~~ as a result of damage to the lymphatic system, following surgery, trauma, radiation, or infection. However, it can be primary, associated with a disruption to the development or the function of the lymphatic system causing impaired drainage of lymph, and this group of conditions will be the focus of the current review.

## Clinical Presentation

The presentation is most commonly with swelling in the extremities, however, it may involve any body site (e.g. facial or genital oedema). In addition, there may be systemic (or visceral) involvement with chylothoraces, pericardial effusions, chylous reflux or intestinal lymphangiectasia (Fig 1). In primary lymphoedema, the underlying abnormality is usually present at birth but the swelling, although often congenital, may not develop until puberty or adulthood. Lower limb lymphoedema can be confirmed by a positive Stemmer's sign, which is a thickened cutaneous fold of the second toe or second finger that can be gently pinched and lifted<sup>2</sup>. There may also be skin changes, such as papillomatosis (Fig 1B), lymphangiectasia or lymphorrhoea in chronic lymphoedema and deep interphalangeal creases and nail changes with small, dysplastic, 'ski-jump' nails (Fig 1A & 1B).

## Genetic basis of primary lymphoedema

For many years it was known that there were some families where there was likely inherited lymphoedema with or without additional features. However, it was not until 2000 that the

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7 gene for Milroy syndrome *FLT4 (VEGFR3)* was discovered<sup>3,4</sup>. Following this, numerous  
8 other genes have been discovered that are associated with lymphatic disease. Connell *et al.*,  
9 2013 detailed a classification system and diagnostic algorithm based on onset and site of  
10 lymphoedema, and associated features<sup>5</sup>. There are five main subgroups: syndromic,  
11 lymphoedema with systemic/visceral involvement, overgrowth/vascular malformation  
12 syndromes, congenital onset (<1yr), and later onset (>1yr). Since then, two new genes,  
13 *PIEZO1* and *EPHB4* have been identified as a cause of generalized lymphatic dysplasia<sup>6,7</sup>,  
14 and the overgrowth/vascular malformation syndromes are now collectively known as the  
15 *PIK3CA*-related overgrowth spectrum (PROS) disorders because they are caused by somatic  
16 mutations in the phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway<sup>8</sup>. An adapted  
17 classification system is presented in Figure 2. We will now detail the features and  
18 presentations of some of the conditions within each category. A summary can be found in  
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### 33 **Syndromes associated with lymphoedema**

#### 34 *Turner syndrome*

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36 Turner syndrome is a genetic condition affecting females who have only one normal X  
37 chromosome. Common features include antenatal hydrops or cystic hygroma, short stature,  
38 mild learning difficulties, congenital heart disease (commonly coarctation of the aorta),  
39 congenital renal anomalies, lymphoedema and infertility. Examination may identify low  
40 posterior hairline with webbed neck, widely spaced nipples and increased carrying angle.  
41 Lymphoedema typically presents at birth with four-limb lymphoedema, which often resolves,  
42 but may recur later in life. Lymphoscintigraphy suggests that the lymphatic phenotype of  
43 Turner syndrome may be due to a failure of initial lymphatic (capillary) function<sup>9</sup>.  
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### Noonan syndrome

Noonan syndrome is a relatively common condition that follows an autosomal dominant condition-pattern of inheritance. It is associated with alterations in genes encoding the Ras/MAPK pathway. Common features include antenatal hydrops or cystic hygroma, short stature, mild learning difficulties, congenital heart disease (commonly pulmonary stenosis or hypertrophic cardiomyopathy), cryptorchidism, hernias, and bleeding diathesis. Examination may identify distinct facial features (down slanting palpebral fissures, ptosis, low set posteriorly rotated ears), and webbed neck. Congenital lymphoedema is fairly common in this disorder but a few patients may develop lymphoedema in childhood, with a characteristic pattern of bilateral lower limb lymphoedema, genital swelling with chylous reflux and frequent systemic involvement, including intestinal lymphangiectasia and chylothoraces (Fig 1E), which may be progressive. Lymphoscintigraphy demonstrates reflux and/or rerouting of lymphatic drainage associated with incompetent veins on the venous duplex scans<sup>10</sup>.

### Generalised lymphatic dysplasia

#### Hennekam syndrome

Hennekam syndrome is a rare condition with an autosomal recessive pattern of inheritance condition associated with alterations in the *CCBE1* and *FAT4* genes<sup>11,12</sup>, which account for approximately 50% of cases. Presentation is usually with congenital, or antenatal onset (hydrops) of generalised severe lymphoedema, lymphangiectasia, learning difficulties, seizures, microcephaly, short stature and characteristic facial features (puffy eyelids, flattened facial profile, hypertelorism, gingival hypertrophy and microstomia) (Fig 1D).

#### *PIEZO1*-related lymphatic-related hydrops/generalised lymphatic dysplasia

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7 This is a newly described ~~autosomal recessive~~ condition following autosomal recessive  
8 inheritance related to alterations in the *PIEZO1* gene<sup>6</sup>. It is characterized by a uniform,  
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10 widespread lymphoedema affecting all segments of the body, with systemic involvement  
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12 such as pulmonary lymphangiectasia, pleural effusions, chylothoraces and/or pericardial  
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14 effusions (Fig 1E). Presentation may be with non-immune hydrops. In comparison to  
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16 Hennekam syndrome, intelligence is normal, with no seizures or distinct facial features other  
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18 than swelling.  
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#### 20 21 *EPHB4*-related lymphatic-related hydrops

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23 In 2016, Martin-Almedina *et al.*, reported two unrelated autosomal dominant families with *in*  
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25 *utero* hydrops/neonatal deaths found to be due to heterozygous missense mutations in *EPHB4*  
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27 on exome sequencing<sup>7</sup>. There was a high incidence of atrial septal defects in these families.  
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29 *EPHB4* was found to be an important regulator of early lymphatic vascular development and  
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31 mutations in the gene can cause an autosomal dominant form of non-immune hydrops with  
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33 variable expressivity but associated with high mortality rate.  
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#### 39 **Lymphoedema associated with overgrowth and/or vascular malformations**

##### 40 *PIK3CA*-related overgrowth spectrum (*PROS*)

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42 In 2015, Keppler-Noreuil *et al* delineated *PROS*, a heterogeneous group of disorders  
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44 associated with somatic activating mutations in the PI3K/AKT/mTOR pathway<sup>8</sup>. This group  
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46 encompasses many conditions that were previously thought to be distinct (Proteus,  
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48 Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi,  
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50 Scoliosis/Skeletal and Spinal (CLOVES) syndrome, macrodactyly, and the related  
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52 megalencephaly syndromes, including megalencephaly-capillary malformation (MCAP or M-  
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CM)). However, it is now known that there is significant overlap in the clinical features which include overgrowth (adipose, muscle, nerve, skeletal), vascular malformations (capillary, venous, arteriovenous malformation, lymphatic), and epidermal naevi.

### **Congenital Lymphoedema**

#### *Milroy disease*

Milroy disease is ~~an autosomal dominant~~ condition that follows an autosomal dominant pattern of inheritance, characterised by antenatal or congenital onset of bilateral lower limb lymphoedema. Large calibre veins, and upslanting ‘ski-jump’ toenails are commonly seen (Fig 1A). Lymphoscintigraphy identifies functional aplasia, either due to paucity of the lymphatic vessels or abnormal function of the vessels in the lower limbs<sup>13</sup> (Fig 1C).

Alterations in the *FLT4* (*VEGFR3*) gene are causative<sup>3,4</sup>. In 2013, Gordon *et al.*, 2013 ascertained that mutations in *VEGFC*, which is a ligand for *VEGFR3* are responsible for Milroy-like lymphoedema<sup>14</sup>.

#### *Microcephaly-Chorioretinopathy-Lymphoedema-Mental Retardation (MCLMR)*

MCLMR is ~~an autosomal dominant syndrome~~ associated with alterations in the *KIF11* gene<sup>15</sup> and follows an autosomal dominant pattern of inheritance. It is included in this section as there is a very high incidence of congenital lower limb lymphoedema (46%). It is characterised by primary microcephaly, chorioretinal dysplasia, typically congenital bilateral pedal lymphoedema, and mild to moderate learning difficulties. Epilepsy and congenital heart disease may also be associated. There is significant variability in presentation and reduced penetrance has been reported<sup>16</sup>.

### **Late onset Lymphoedema**

### *Lymphoedema-distichiasis syndrome (LDS)*

This ~~autosomal dominant~~ condition follows an autosomal dominant pattern of inheritance and is characterised by lower-limb lymphoedema, usually of pubertal onset, and distichiasis (aberrant extra eyelashes originating from the meibomium glands). This may be a whole additional row of eyelashes or a single hair. Distichiasis may lead to corneal irritation, recurrent conjunctivitis, and photophobia. Other commonly associated features include ptosis, congenital heart disease and cleft palate<sup>17</sup>. *FOXC2* is the only gene, to date, in which mutations are known to cause LDS<sup>18</sup>. The lymphatic and venous valves in this condition are dysplastic and leaky so there is a high incidence of varicose veins and lymphoscintigraphy shows dermal backflow, suggestive of lymph reflux into the lower limbs (Fig 1C).

### *Emberger syndrome*

Emberger syndrome is ~~an autosomal dominant condition~~ characterised by the combination of lymphoedema and predisposition to development of myelodysplasia and acute myeloid leukaemia (AML) with autosomal dominant inheritance. It is caused by alterations in the *GATA2* gene<sup>19</sup>. Presentation is typically with childhood onset (although may be prenatal or congenital), bilateral, pedal +/- genital oedema which usually predates the haematological abnormalities. There may be immune dysfunction, myelodysplasia (karyotypic anomalies include monosomy 7) which may progress to AML.

### *GJC2-related lymphoedema*

In 2010, alterations in the *GJC2* gene were identified as a cause of autosomal dominant lymphoedema<sup>20</sup>. Ostergaard et al., 2011 further characterised the features of this ~~autosomal dominant~~ condition, which presents in the first or second decade with four limb lymphoedema and increased incidence of varicose veins<sup>21</sup>.



### *Meige syndrome*

This condition presents with lower limb lymphoedema in adolescence or adulthood. There are a number of families suggestive of autosomal dominant inheritance. There are usually no associated features. It is probably the most common form of primary lymphoedema.

Lymphoscintigraphy demonstrates poor uptake at 2 hours and rerouting through the deep lymphatics, with the presence of popliteal lymph nodes (which are not usually visualised). No specific genes have been found for this condition.

There are numerous other conditions in which lymphoedema is a reported feature. These may have a chromosomal or single gene cause, however in some the cause is unknown. A detailed list of these conditions can be found in Connell *et al.*, 2013.

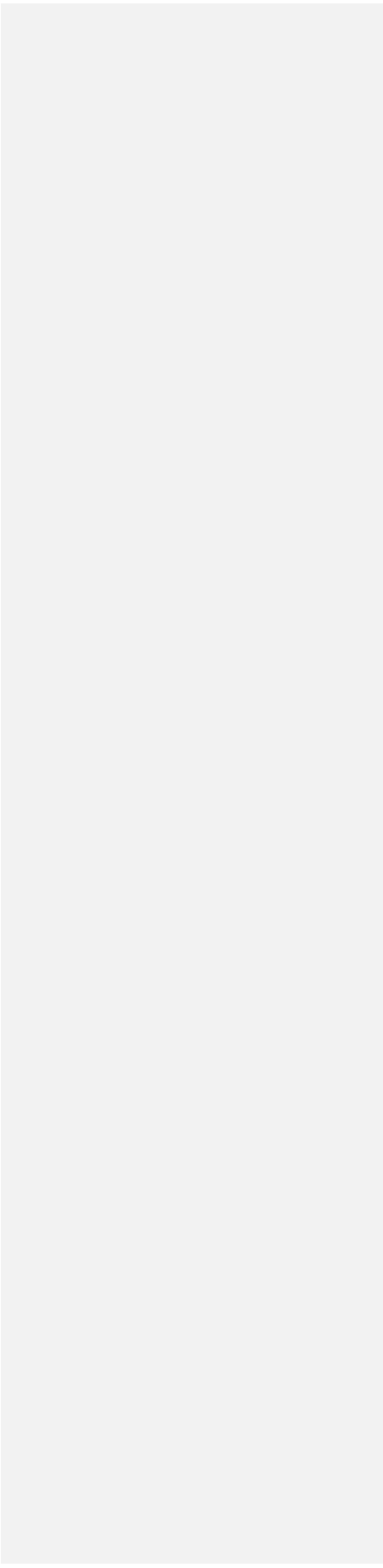
### Investigations and Management

Following a detailed family history and examination, investigation of lymphoedema includes lymphoscintigraphy examination. This is the imaging of the lymphatic system by injecting radioactive isotope into the web spaces between the toes (or fingers) and quantification of uptake into the inguinal (or axillary) lymph nodes after 2 hours (Fig 1C). Decreased uptake suggests abnormal lymphatic drainage. If a specific genetic diagnosis is suspected, genetic testing can be arranged. This includes chromosomal analysis, or karyotype (for Turner syndrome), single gene or gene panel testing if available. These tests can be performed on a peripheral blood sample, however if PROS is suspected, a skin biopsy should be taken from an affected area and sent for genetic testing<sup>22</sup>. In view of the somatic nature of this condition, testing of blood may not yield the diagnosis.

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In the main, the treatment of lymphoedema is supportive. It includes manual lymphatic drainage and compression hosiery/garments along with skin hygiene advice, and appropriate footwear to reduce the risk of complications. Surgical treatment is largely unsuccessful, and is not generally recommended. There are currently no effective drug therapies available for the management of primary lymphoedema. However, the use of drugs targeting the PI3K/AKT/mTOR signalling pathway, such as mTOR inhibitors, provide an exciting prospect for patients with PROS<sup>23</sup>.

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8 Figure 1. A: Bilateral pedal oedema, deep interphalangeal creases and small, dysplastic, 'ski-  
9 jump' toenails in an individual with Milroy disease. B: Longstanding pedal oedema with  
10 papillomatosis in a female with Turner syndrome. C: Lymphoscintigraphy after 2 hours in a  
11 normal control, an individual with LDS demonstrating lymphatic reflux, and an individual  
12 with Milroy disease showing paucity of lymphatic vessels. D: Generalised lymphoedema  
13 affecting the face, hands and feet in a patient with Hennekam syndrome (*CCBE1*). E: Facial  
14 oedema in a patient with *PIEZO1* related-lymphoedema. F: A chest radiograph demonstrating  
15 bilateral chylothoraces in a patient with Noonan syndrome.  
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26 Figure 2. Classification criteria for diagnosis of primary lymphoedema (adapted from Connell  
27 *et al.*, 2013). Genes marked in italics.  
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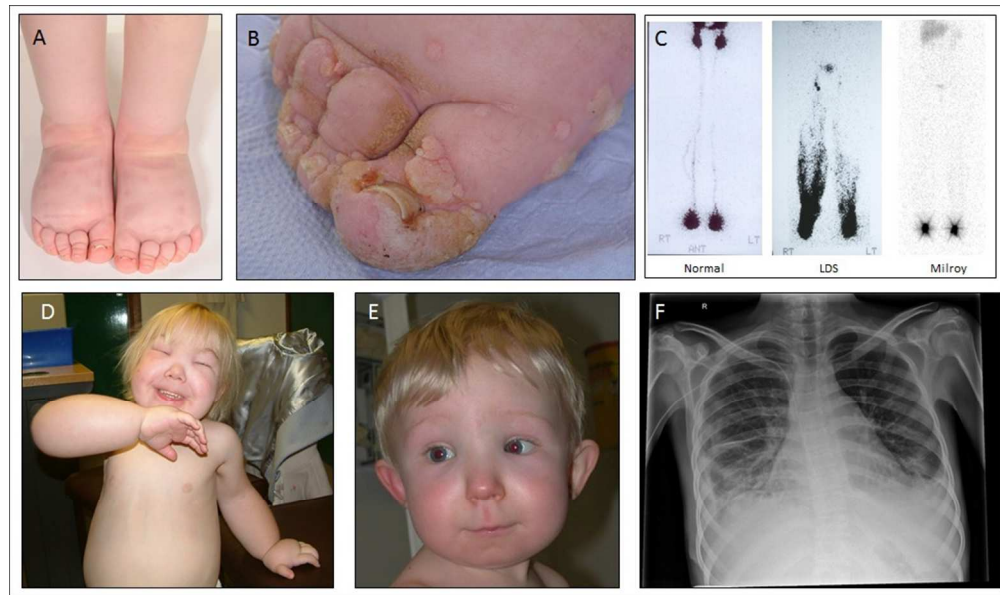


Figure 1. A: Bilateral pedal oedema, deep interphalangeal creases and small, dysplastic, 'ski-jump' toenails in an individual with Milroy disease. B: Longstanding pedal oedema with papillomatosis in a female with Turner syndrome. C: Lymphoscintigraphy after 2 hours in a normal control, an individual with LDS demonstrating lymphatic reflux, and an individual with Milroy disease showing paucity of lymphatic vessels. D: Generalised lymphoedema affecting the face, hands and feet in a patient with Hennekam syndrome (CCBE1). E: Facial oedema in a patient with PIEZO1 related-lymphoedema. F: A chest radiograph demonstrating bilateral chylothoraces in a patient with Noonan syndrome.

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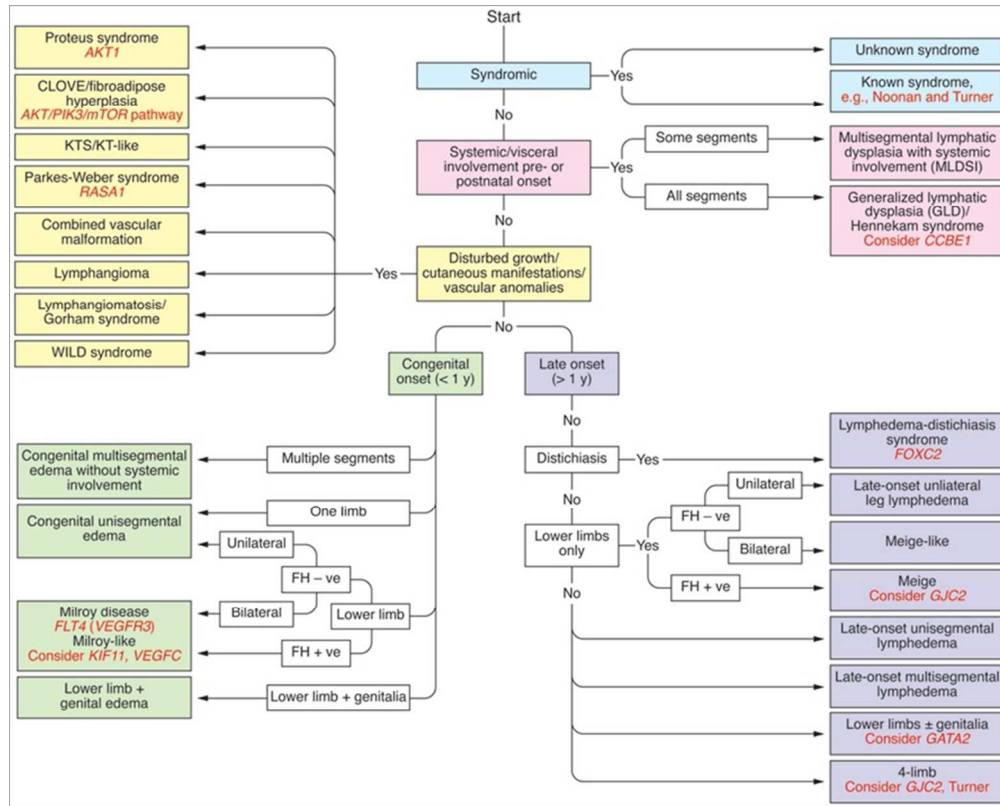


Figure 2. Classification criteria for diagnosis of primary lymphoedema (adapted from Connell et al., 2013). Genes marked in italics.

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Table 1: Summary of primary lymphedema conditions, including genetic basis and inheritance, onset and nature of lymphedema and associated features. Genes written in italics. AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart disease.

Condition	Genetic basis	Inheritance	Onset and nature of lymphedema	Associated features
Turner syndrome	45,X (or similar)	Sporadic	Congenital ( <i>may be prenatal</i> ), hands and feet	Short stature, webbed neck, widely spaced nipples and increased carrying angle, CHD (coarctation of aorta), renal anomalies, primary infertility, mild intellectual disability
Noonan syndrome	>23 <i>rasopathy genes including: PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1</i>	AD	Congenital ( <i>may be prenatal</i> ), lower limb Later onset genital oedema, chylous reflux, intestinal lymphangiectasia, and/or chylothoraces	Short stature, webbed neck, CHD (pulmonary stenosis or hypertrophic cardiomyopathy), dysmorphic features, bleeding tendency, intellectual disability, cryptorchid testes, pectus deformities
Hennekam syndrome	<i>CCBE1</i>	AR	Congenital, multi-segment, facial, lymphangiectasia	Microcephaly, distinct facial features, intellectual disability, short stature, respiratory problems, skeletal anomalies, anaemia, polysplenia, renal anomalies. Systemic lymphatic involvement
<i>PIEZO1</i> -related lymphatic-related hydrops/generalised lymphatic dysplasia	<i>PIEZO1</i>	AR	Non-immune hydrops, childhood onset multisegment	Systemic involvement (chylothoraces and/or pericardial effusions)
<i>EPHB4</i> -related lymphatic-related hydrops	<i>EPHB4</i>	AD	Non-immune hydrops	Atrial septal defects
<i>PIK3CA</i> -related overgrowth spectrum (PROS)	PI3K/AKT/mTOR pathway	Somatic	Congenital	Hypertrophy/overgrowth of bone and soft tissues resulting in asymmetry, vascular malformations, naevi/pigmentation
Milroy syndrome	<i>VEGFR3, VEGFC</i>	AD	Congenital, pedal, lower limb	Hydrocele, prominent veins, upslanting toenails, papillomatosis, and urethral abnormalities in males
Microcephaly-Chorioretinopathy-Lymphedema-Mental Retardation (MCLMR)	<i>KIF11</i>	AD	Congenital, lower limb	Microcephaly, chorioretinopathy, intellectual disability, epilepsy, CHD
Lymphedema distichiasis	<i>FOXC2</i>	AD	Pubertal, lower limb	Distichiasis, varicose veins, ptosis, cleft palate, CHD, renal anomalies

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Emberger syndrome	GATA2	AD	Childhood, lower limb and/or genital	Myelodysplasia, sensorineural hearing loss
Primary lymphedema	GJC2	AD	Childhood/adolescence or postnatal, four limb	

For Review Only