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REVIEW ARTICLE

Genetic Factors in the Development and Diagnosis of Lymphedema and Lipedema

Aditi S. Gandhi
The Blake School, 511 Kenwood Parkway, Minneapolis, MN, 55403, USA; aditigandhi08@icloud.com

ABSTRACT: Lymphedema and Lipedema are chronic disorders that are often misdiagnosed, leading to complications ranging from infection to impaired mobility. While the genetic basis of lymphedema is well characterized, the genetic contributions to lipedema remain unclear despite clear familial hereditary patterns. This review examines current knowledge on the genetic foundations of both conditions, examining established causative genes in lymphedema and emerging evidence of heritability in lipedema. It also evaluates the role of genetic testing in diagnosis and classification. By emphasizing established findings and highlighting ongoing gaps, this review supports efforts to refine diagnosis and guide therapeutic development.
KEYWORDS: Lymphedema, Lipedema, Genetics, Inheritance, Misdiagnosis, Classification.

Introduction

Lymphedema is a chronic condition characterized by abnormal swelling that affects the arms and legs due to the failure of the lymphatic system, which is one of the important parts of the body that covers the immune system and fluid circulation (Figures 1 and 4). Lymphatic obstruction triggers chronic inflammation, leading to fibrosis and other lymphatic anomalies.[1] Symptoms commonly present swelling in the limbs, feeling heaviness or tightness in the skin, restricted range of motion, and fibrosis (pathologic thickening of the skin due to excess connective tissue) (Figure 1). Lymphedema is diagnosed clinically and based on a comprehensive evaluation and a physical examination. The diagnosis can be supported by >2 cm circumference or >200 mL volume difference between limbs.[2] Volume is measured using a tape (requires consistent technique), water displacement (accurate but unsuitable in patients with open wounds), or perometry (precise but expensive).[3] Non-invasive methods, such as tonometry and bioimpedance spectroscopy, assess tissue resistance and fibrosis.[4] Imaging methods, such as lymphoscintigraphy, ultrasound, CT, and MRI, help detect fluid accumulation and assist in diagnosis, especially when physical findings are unclear.[5]

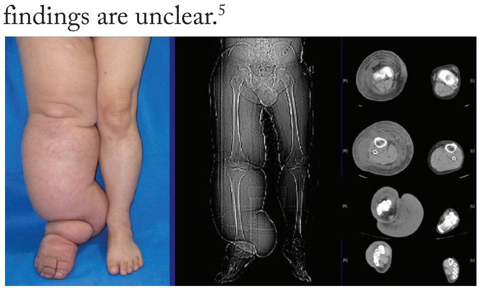

Figure 1: Clinical and radiologic features of unilateral lower-extremity lymphedema. (Left) Marked enlargement of the right leg with dorsal foot hump, papillomatosis, and deep skin folds consistent with advanced-stage lymphedema. (Middle) Coronal CT reconstruction demonstrates diffuse thickening of the subcutaneous compartment without bony abnormalities. (Right) Axial CT images at multiple levels show pronounced subcutaneous fat hypertrophy and fluid accumulation in the affected limb (R) compared with the normal contralateral side (L), with preservation of muscle architecture and absence of discrete mass lesions.

Lipedema, on the other hand, is a fat disorder causing symmetrical, painful fat buildup in mostly legs and sparing feet, but also can be seen in hips, thighs, buttocks, and sometimes upper arms. Lipedema has four distinct stages (Figure 2), each characterized by different cellular and immune characteristics. Pain, tenderness, and swelling may be prevalent in the affected areas. Lipedema diagnosis is also made clinically, but it has fewer validated tools available for confirmation. A basic evaluation consists of an assessment of familial history, manual evaluation, and a visual inspection with a focus on the known clinical features of lipedema. While both conditions rely heavily on clinical evaluation, the availability and use of diagnostic tools differ, with lymphedema having more established objective measures and imaging support than lipedema.[6] The pathophysiology of lipedema remains not fully understood but is thought to involve an interplay of genetic, hormonal, and vascular factors. Estrogen may contribute to lipedema by directly influencing fat storage through its receptors in white adipose tissue, leading to region-specific accumulation in lipedema typical areas such as the hips, legs, and buttocks (gynoid regions).[7] Because estrogen reduces fat breakdown (lipolysis) in these regions, fat gradually accumulates.[8] Additionally, vasculopathy, specifically microangiopathy damage to small blood vessels), has been observed in early stages of lipedema.[8] This may derive from a defect in the endothelial barrier function or from hypoxia (low oxygen), which impairs vascular structure.[10] Increased vascular permeability and abnormal angiogenesis (formation of new blood vessels), triggered by VEGF and other factors, can lead to fragile, leaky vessels that contribute to tissue changes and swelling seen in lipedema.[10]

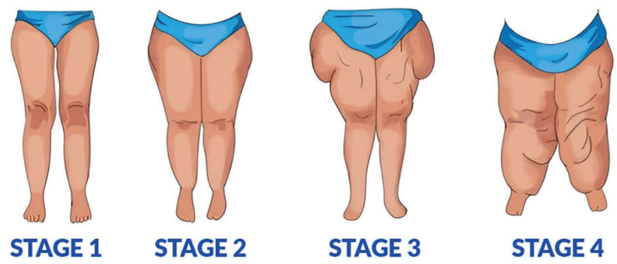

Figure 2: Stages of lipedema: In stage 1, the skin appears smooth, and the subcutaneous adipose tissue is soft and thickened, with small palpable nodules present. Stage 2 is distinguished by irregular skin texture and the occurrence of even larger skin nodules, alongside the development of interstitial fibrosis and gradual adipocyte enlargement. By stage 3, marked fat deposition results in large lobules and apparent limb abnormalities. This stage is also marked by pronounced adipocyte hypertrophy and a thick buildup of fibrous tissue. Stage 4, also known as lipo-lymphedema, includes the development of secondary lymphedema, severe edema, and dermal fibrosis.[12]

Lymphedema and lipedema are frequently misdiagnosed due to limited awareness and overlapping clinical features. Primary lymphedema (Figure 3) is rare, affecting 1 in 100,000 people, whereas secondary lymphedema affects 1 in 1,000 Americans.[13] The epidemiology of lipedema is uncertain, and the lack of data regarding the disease is a key contributor to its frequent misdiagnosis.[14] Prevalence rates vary widely, ranging from 11% to 39% among specific populations. Lipedema is frequently misdiagnosed as obesity due to overlapping clinical features. It predominantly affects women and most often occurs after pregnancy or menopause. Lipedema's specific etiology has not yet been identified, but it likely results from a combination of hormone disruptions, genetic factors, and anatomical irregularities in the lymphatic and vascular systems.[15]

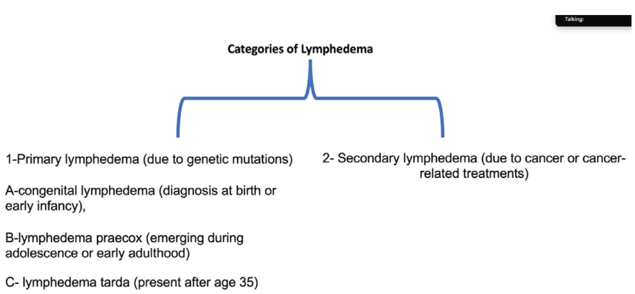

Figure 3: Categories of lymphedema: Lymphedema can be categorized into two types: primary lymphedema and secondary lymphedema.[16] Primary lymphedema is a hereditary disorder that results in deformity of the lymphatic system, caused most often by a genetic mutation.[16] While secondary lymphedema can be derived from injury or obstruction to the lymphatic system, most secondary lymphedema cases often result from cancer or cancer-related treatments. This includes surgical removal of lymph nodes, targeted radiation therapy, and medication-based treatment.[18] Primary lymphedema can be divided into three subcategories: congenital lymphedema (diagnosis at birth or early infancy), lymphedema praecox (emerging during adolescence or early adulthood), and lymphedema tarda (present after age 35).[19]

Lymphedema also has stages, and it is staged according to the increase of interstitial lymphatic fluid in the affected area, which stimulates subcutaneous fibroadipose formation. Its advancement is characterized in four stages. Stage 0 presents with clinically normal limbs, despite impaired lymphatic transport, which can be detected through imaging methods such as lymphoscintigraphy. Stage 1 is seen as early edema, which can be improved with elevation of the affected area. Stage 2 entails pitting edema, which does not improve with elevation, and stage 3 involves increased fibroadipose deposition and accompanied skin changes.[19]

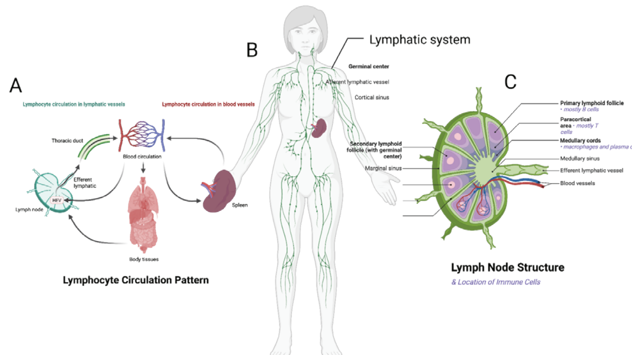

Figure 4: Overview of lymphocyte trafficking, lymphatic anatomy, and lymph node microarchitecture. (A) Schematic of lymphocyte circulation demonstrating coordinated movement between blood and lymphatic vessels. Lymphocytes enter lymph nodes through high endothelial venules (HEVs), transit through cortical and medullary regions, and exit via efferent lymphatics before returning to the bloodstream through the thoracic duct. (B) Anatomical map of the human lymphatic system, highlighting major lymphatic vessels and secondary lymphoid organs. (C) Cross-sectional structure of a lymph node showing the spatial organization of immune cell niches: B-cell–rich primary and secondary follicles, T-cell–dominant paracortex, and macrophage/plasma-cell–rich medullary cords, along with afferent/efferent lymphatic and blood vessel entry points (Figure done in Biorender).

This paper presents clinical features of lymphedema and lipedema, and describes their genetic pathways to highlight differences and different ways of diagnosis despite their similarities. It then explores the genetic and familial components of lipedema, including inheritance patterns and findings from different familial studies. Additionally, this paper integrates genetic findings across lymphedema and lipedema, uncovering shared genetic pathways and hormone-driven mechanisms that offer a new framework for understanding their overlapping features and persistent diagnosis challenges. Finally, it discusses the role of genetic testing in both conditions, including the use of next-generation sequencing in clinical practice. Understanding the genetic basis of lymphedema and advancing research into the genetics of lipedema are critical for preventing the misdiagnosis of these conditions. A confirmed genetic marker for lipedema and a broader clinical adoption of genetic panels for lymphedema are needed to prevent misdiagnosis and further complications.

Discussion

1.1. Genetics of Lymphedema:

Lymphedema can result from genetic mutations in the FLT4 gene, which codes for a protein called vascular endothelial growth factor receptor 3 (*VEGFR-3*).[21] This mutation interferes with lymphatic development and can cause swelling in both legs since birth. Most cases are inherited in an autosomal dominant pattern, but some recessive cases have been reported as well.[22] Mutations in the *VEGFR-3* reduce signaling and can lead to poorly formed lymphatic vessels.[1]

Similar symptoms can also occur from mutations in vascular endothelial growth factor receptor C (*VEGF-C*), the ligand for VEGFR-3, which can also damage lymphatic vessels.[7] Collagen and Calcium- binding EGF domain-containing protein 1 (CCBE1) and Protein Tyrosine Phosphatase Non-Receptor Type 14 (PTPN14) also influence this pathway. Their mutations can lead to more extensive lymphatic irregularities.[8] While lipedema does not have a confirmed genetic cause, it is seen to have an inheritance pattern that is not linked to a single gene. Family studies suggest a strong genetic component, with 60-80% of patients reporting a familial history. Whole-exome sequencing in families identified rare variants across many genes, but no single mutation was found consistent with all cases.[26] Instead, the results show genetic heterogeneity, where different genes contribute to the disease. Some detected genes include pro-opiomelanocortin (*POMC*), Stabilin-1 (*STAB1*), and Tenascin-X (*TNXB*). These genes are involved with connective tissue structure and fat metabolism.[21] Overall, larger population-based studies are needed to clarify the genetic basis of lipedema.

Apart from the the *VEGF-C/VEGFR-3* pathway, there are other essential pathways for lymphedema development. The PI3K/ATK pathway is important for cell proliferation and is activated by both *VEGFR-3* and *HGF/MET* signaling. Mutations in the AKT1 and PIK3CA can cause syndromic lymphatic malformations such as Proteus, CLAPO, and CLOVES syndrome, but other regulators such as *KIF11*, *PIEZO1, ARAP3, SYK, RELN*, and *SVEP1* may also contribute to the disruption of the *PI3K/AKT* pathway, leading to abnormal lymphangiogenesis and the development of primary lymphedema. Similarly, the *RAS/MAPK* pathway is also activated by *VEGFR-3* and HGF/MET signaling.[18] Mutations in *SOS1, RIT1, KRAS, NRAS, HRAS,* and *BRAF* are linked to Noonan spectrum disorders and Costello syndrome, all of which can include lymphedema as a clinical feature. The *HGF/MET* pathways regulate the growth and survival of lymphatic endothelial cells. Mutations in *HGF, MET, CBL,* and *PTPN11* are associated with primary lymphedema or lymphedema as a subset of broader syndromes. The *Rho/ROCK* pathway influences endothelial mobility and lymphatic pumping. Although mutations in this pathway are not directly linked to lymphedema, evidence suggests it may play an important role in lymphatic function through the regulation of endothelial mobility and lymphatic pumping. Additionally, several transcription factors are involved in lymphatic development and valve morphogenesis.[18] Mutations in *SOX18, GATA2*, and *FOXC2* are associated with various forms of syndromic lymphedema as well.[18]

Primary lymphedema can be inherited through both autosomal dominant and autosomal recessive modes of inheritance. Three genes: *FLT4 (VEGFR3)*, Forkhead Box *C2* (*FOXC2*), and SRY-box transcription factor 18 (*SOX18*) are known to cause primary lymphedema. More recent findings suggest hepatocyte growth factor (HGF) and its high-affinity receptor (MET) as additional candidate genes involved in lymphedema. The identification of genes that cause primary lymphedema has advanced both the understanding and diagnosis of the condition. For example, Milroy lymphedema is caused by mutations in the *VEGFR3* gene, whereas similar forms of congenital lymphedema may result from mutations in *VEGF-3* (which codes for the VEGFR3 ligand) or in Kinesin Family Member 11 (*KIF11*), which is associated with microcephaly-lymphedema syndrome.[29] Turner syndrome, caused by the absence or structural alteration of one X chromosome, may also present with congenital lymphedema.[29] Although these conditions appear clinically similar, genetic screening enables a clear diagnosis.

Lymphatic endothelial cell precursors develop from venous endothelial cells, explaining the close genetic and physiological relationship between veins and lymphatic vessels. Mutations in the *FOXC2* gene cause lymphedema-distichiasis syndrome. The underlying cause is lymphatic valve reflux, along with venous valve reflux affecting all superficial veins and about one-third of the deep veins. *FOXC2* was the first gene identified to cause venous disease. Although distichiasis is present at birth, lymphedema typically does not manifest until puberty or later in adulthood. This suggests that the *FOXC2* gene can cause early-onset (praecox) and late-onset (tarda) lymphedema. Other genetic forms, such as Milroy lymphedema, may also present with venous abnormalities, although these do not appear to directly cause swelling. Although treating venous reflux in genetic conditions might appear beneficial because it reduces lymphatic load, the benefits remain uncertain. In patients with *FOXC2* mutations, treatment shows little improvement, indicating that the primary role of the lymphatic system is to regulate chronic edema. Current research also suggests that lymphatic drainage, not venous reabsorption, is the main way for tissue fluid clearance.[29]

1.2. Genetics of Lipedema:

The etiology of lipedema remains clinically unknown, but evidence suggests a likely familial inheritance pattern. One study reported a positive family history in 60-80% of cases. To investigate inheritance patterns, recent research has examined groups of unrelated patients to explore the possibility of shared genetic influences. In a genome-wide association study (GWAS) involving 130 lipedema patients and matched controls, no single-nucleotide polymorphisms (SNPs) met the threshold for statistical significance. Michelini *et al*. developed a panel of 305 candidate genes potentially linked to lipedema, drawing on prior research.[30] Sequencing these genes in a cohort of 167 patients revealed 21 predicted damaging variants in 17 individuals.[31] Although the genetic factors contributing to the development of lipedema are unclear, multigene panels are important for further genetic investigations. Evidence also points to genetic heterogeneity, suggesting that the condition may arise from variants in different genes among affected individuals. While no single gene has been consistently observed in Lipedema cases, several genes have been reported in isolated patients or families, including POU Domain Class 1 Transcription Factor 1 (*POU1F1A*), Nuclear Receptor Binding SET Domain Protein 1 (*NSD1*), and Aldo-Keto Reductase Family 1 Member C1 (*AKR1C1*). Whole-exome sequencing was performed on 31 individuals, and 9 families was done in a study conducted by Morgan *et al*. Using the Genome Analysis

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Toolkit (GATK) best practices pipeline, researchers detected 2,786,094 single-nucleotide variants (SNVs) and indels. These variants were then filtered according to quality metrics, presumed inheritance patterns, gene tolerance to loss of function, predicted pathogenicity, and population allele frequencies. After filtering, the dataset included rare variants in 469 genes. Variants were found among individuals in all nine families studied, with 75 variants appearing in more than one family. However, no single variant was present in more than four families.[31]

Recent genetic studies have begun to clarify the molecular basis of lipedema. But as of right now, genetic testing for lipedema is for research use only.[30] Genetic testing methods of lipedema include: GWAS panels, whole exome sequencing, and candidate gene panels. The goal of these tests is to identify common SNP variants and rare mutations contributing to the disease. The first large-scale genetic analysis of lipedema was a genome-wide association study (GWAS) conducted using UK data. In this study, women clinically diagnosed with lipedema were compared to controls. This identified multiple single-nucleotide polymorphisms (SNPs) with significant associations. Particularly, variants in genes such as *LHFPL6, GATA2, ANGPT2,* and *VEGFA* had the strongest association signals.[33] These genes regulate fat distribution, angiogenesis, and lymphatic vessel development, suggesting that lipedema may stem from an interplay between adipose and lymphatic systems.[21]

Beyond common SNPs, rare variants not captured in GWAS may also drive lipedema, which are more effectively captured through exome sequencing. Candidate pathways linked to extracellular matrix remodeling and vascular signaling can potentially explain both the adipose tissue accumulation and the vascular fragility observed in patients.[33]

Targeted sequencing of genes already linked to lymphatic or adipose disorders has revealed areas of overlap between lipedema and other related conditions.[33] For example, *VEGFA* and *ANGPT2*, previously implicated in primary lymphedema, also appear in lipedema studies, further reinforcing the concept of shared molecular pathways across adipose-lymphatic diseases. Genetic testing for lipedema remains limited to research use only, with no clinically approved methods available. Several approaches are being explored, including genome-wide association studies, whole-exome sequencing, and candidate gene panels. The overarching aim of testing is to identify both common single-nucleotide polymorphisms (SNPs) and rare mutations that contribute to the development and progression of lipedema.[34]

Non-genetics of lipedema: hormonal regulations:

Studies of lipedema fat tissue show that adipocytes are often larger than normal. To investigate this, researchers have examined genes involved in adipocyte growth, metabolism, and hormone regulation. One gene, such as Uncoupling Protein 1 (UCP1), is typically expressed in brown adipose tissue and functions to burn energy and generate heat. Lower levels of UCP1 were expected in lipedema tissue due to slower metabolism in larger adipocytes, but no decrease was observed. Other common fat-related genes, such as leptin (LEP) and adiponectin (ADIPOQ), showed no significant differences between lipedema and healthy samples. However, some genes that regulate adipocyte development, including CCAT/enhancer-binding protein delta (CEBPD), Nuclear Receptor corepressor 2 (NCOR2), and Krüpel-like factor 4 (KLF4), were found at lower levels in lipedema tissue. These genes regulate Peroxisome Proliferator-Activated Receptor Gamma (PPARG), a key controller of fat cell formation.[29] However, not all results have been consistent. In one study, fat stem cells from lipedema patients showed higher levels of PPARG and LEP when grown and stimulated in the lab compared to controls.[29] These differences may be due to variations in study design or sample type.

These gene expression differences in fat tissue may help explain lipedema's inheritance pattern. Although no single genetic variant has been identified, the repeated involvement of genes linked to fat cell growth, hormone signaling, and tissue structure suggests that multiple genetic pathways may be involved in the condition. The strong female predominance in lipedema cases also points to hormonal factors, particularly estrogen, and how they may influence gene activity. One example is the gene Zinc Finger Protein 423 (ZNF423), which is involved in fat cell formation, can be activated by estrogen, and has been found at higher levels in lipedema tissue.[29] This hormonal association may help explain why symptoms often begin or worsen during periods of hormonal change, such as puberty, pregnancy, or menopause, when fluctuations in estrogen and progesterone influence fat distribution, fluid retention, and lymphatic function.[54]

1.3. Diagnosis and Testing of Lymphedema and Lipedema:

Although lymphedema symptoms are commonly prevalent even in early stages, it is often overlooked and insufficiently treated. Diagnosis is primarily done clinically, relying on a detailed and specific familial history of the patient along with a thorough physical examination that includes inspection, palpation, range of motion assessment, and physical evaluation.[35] Functional limitations and impacts on quality of life should be assessed using measurable methods, while psychological factors such as anxiety, depression, and sleep disturbances are also addressed. Lymphedema can be present individually or alongside other conditions such as lipedema, obesity, or chronic venous insufficiency.[35] It can also occur in malignant forms due to tumor infiltration or lymph node metastases.[36] A comprehensive diagnosis should also consider inflammatory disorders, venous disease, deep vein thrombosis, hypoalbuminemia, rheumatic disease, heart or kidney failure, and medication-induced edema.[37] Diagnostic laboratory tests (kidney, liver, thyroid function, D-dimer), chest X-ray, electrocardiography, echocardiogram, venous doppler ultrasonography (US), magnetic resonance imaging (MRI), or computed tomography (CT) may be used to confirm the diagnosis.[37]

Table 1: Imaging-based diagnostic techniques for lymphedema (ref: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.318307?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed)

Technique	Lymphatic application	Resolution	Depth limitation
Contrast lymphography	Central/visceral lymphatic visualization	≈1 mm	No limit
Radionuclide lymphoscintigraphy	Imaging of collecting lymphatic vessels and dermal backflow; quantitative assessment of lymphatic function	≈1.5 mm	No limit
Near infrared lymphography	Imaging of collecting lymphatic vessels and dermal backflow; quantitative assessment of lymphatic function	µm range	1.5 cm
MR lymphography	Central/visceral lymphatic visualization; functional and morphological evaluation of lymphatic vessel status	0.5–2 mm	No limit
CT	Assessment of lymphatic vessel status	50–200 µm	No limit
SPECT	Assessment of lymphatic vessel status	1–2 cm	No limit

Diagnosis of lipedema begins with a thorough clinical history focusing on the onset, duration, and progression of symptoms, factors that worsen them, and any previous treatments such as lymphatic massage, drainage, or compression garments, noting the effect of these treatments, which can indicate lymphatic involvement. Family history is very important, as lipedema often affects other female relatives with similar symptoms.[38] Physical examination should assess swelling in other areas to rule out systemic causes such as cardiac or renal disease and include a detailed evaluation of the lower limbs for asymmetry, prior surgical scars, and the location, extent, and texture of enlargement. The presence of fluid can be tested through pitting with prolonged pressure, though this may be absent in mild cases or those with advanced fibrosis.[39] In lipedema, the fatty tissue may feel soft or doughy, though it may be firmer in long-standing cases, and patients often have a history of easy bruising on the lower extremities, confirmed through history or direct observation.[40]

Clinical methods are available to help distinguish between different genetic forms of primary lymphedema when the causative gene is identified (Figure 6).[56] For cases where the gene is not yet identified, careful phenotyping is used.[57] Some vascular and combined lymphovascular malformations are caused by mosaic mutations, such as those in PIK3CA, which is linked to the mammalian target of rapamycin (mTOR) signaling pathway.[41] Targeting this pathway with drugs like sirolimus has shown promise in reducing symptoms, offering potential new treatment options for specific genetic forms of lymphedema.[18]

Table 2: Genes associated with primary lymphedema and their clinical features. This figure highlights three genes that play a role in primary lymphedema: FOXC2, FLT4/VEGFR3, and SOX18. Each gene is shown with its associated condition, inheritance pattern, function, and common clinical findings.

Gene Name	Associated Condition	Inheritance Pattern	Function/ Pathway	Clinical Features
FOXC2	Lymphedema-Distichiasis Syndrom (LDS)	Autosomal Dominant	regulates gene pathways + necessary for development of lymphatic vessels	• Bilateral lower limb swelling • Distichiasis (extra row of eyelashes) • sometimes varicose veins, ptosis, cleft palate, or heart valve abnormalities
FLT4 (VEGFR3)	Milroy Disease	Autosomal Dominant	necessary for lymphatic vessel formation and cardiovascular development	• Congenital Lymphedema present in adolescence • bilateral swelling in legs + non - pittng edema • may have upslanting toenails or deep creases in toes
SOX18	Hypotrichosis-Lymphedema-Telangiectasia Syndrome (HLTS)	Autosomal Dominant or Autosomal Recessive	regulates blood and lymphatic vessel development during embryonic development and adult blood vessel formation	• scattered or absent scalp and body hair (hypotrichosis) • lymphedema developing in infancy or early childhood • Telangiectasis (small dilated blood vessels , often on upper face or body) • possible congenital heart defects in some cases

Progression flow of Lymphedema and Lipedema symptoms:

Symptoms of lymphedema often appear in early stages and include swelling, heaviness, skin tightness or firmness, pain, aching, soreness, numbness, tingling, stiffness, fatigue or weakness in the affected limb, and reduced mobility of nearby joints. These symptoms can serve as early indicators of rising interstitial pressure linked to the progression of lymphedema. As fluid retention increases, the limb swelling can increase with a noticeable difference in limb size (Figure 1 and Figure 5).[10] Clinicians and researchers have noted that lymphedema symptoms can appear in the earliest stages, even when objective diagnostic tools fail to detect measurable changes. This early phase may persist for months or even years before visible swelling develops. Recent studies show a strong link between individual symptoms and the presence of lymphedema and further indicate that a higher number of reported symptoms is associated with greater limb volume, as measured by infrared perimeter.[10]

In contrast, lipedema begins as abnormal fat deposition in the hips and buttocks and gradually progresses to the thighs and calves but stops at the ankles (Figure 5).[10] Many patients with lipedema are considered overweight or obese, and those who are not may deal with a disproportionate lower body compared to upper body, giving a pear-shaped appearance.[6] Swelling typically does not indent with pressure (pitting edema) unless edema has developed from another condition. Easy bruising, along with varicose veins and small spider veins near the skin surface, is also observed.[42] Swelling does not improve with elevation or weight loss. There is considerable variation in the severity and advancement of lipedema. Some patients obtain mild symptoms with barely any progression, while others can experience measured or accelerated progression.[42]

Figure 5: Clinical comparison of lymphedema and lipedema. Left: Lymphedema characterized by unilateral limb enlargement, distal involvement including the foot, and firm, non–pitting tissue consistent with lymphatic obstruction. Right: Lipedema showing bilateral, symmetrical fatty tissue deposition of the lower extremities with sparing of the feet, a nodular "peau d'orange" texture, and disproportionate adipose accumulation despite unaffected distal anatomy.

Genetic Testing and Diagnosis Yield in Lymphedema:

Genetic testing is important for the diagnosis of lymphedema because of its ability to recognize gene mutations linked to primary lymphedema. But currently, the effectiveness of genetic testing is very low. In a study including 147 patients diagnosed with primary lymphedema, genetic testing confirmed a contributing mutation in only 11 patients, meaning the current diagnostic yield of genetic testing is only 7%. Sev-

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enty-three patients had inconclusive results, while sixty-three had complete negative results, suggesting that current genetic panels are limited and more research is needed to identify additional causative genes. Mutations were most commonly identified in genes that play important roles in signaling pathways that regulate lymphangiogenesis and lymphatic valve development, such as CBL, CELSR1, FAT4, FLT4 (VEGFR-3), HGF, RIT1, and VEGFC.[18]

Discussion:

This review has examined the pathophysiology, diagnostic testing, and clinical treatment of both lymphedema and lipedema. It has also explored the current understandings of genetics in the onset and development of disease, and the impact of testing. Although advances in sequencing technologies have uncovered key mutations and pathways, the overall diagnostic yield of genetic testing remains low. For lymphedema, only a small number of patients receive a confirmed genetic diagnosis, and for lipedema, testing is still confined to research settings. These gaps show that many causative genes and mechanisms remain undiscovered.

At the same time, studies performed so far demonstrate the promise of genetics to reshape how we diagnose and treat these conditions. Shared pathways among lymphatic and adipose biology suggest that future work will need to bridge both paths instead of individual discoveries. Larger cohorts, advanced sequencing technologies (such as GWAS panels, exome sequencing, and targeted gene panels), and functional studies that test the biological impacts of genetic variants are essential for progression in treating vascular diseases.

■ Conclusion

In conclusion, genetic advancements have the potential to not only explain disease origin. They may also allow earlier diagnosis, more precise classification, and the development of targeted therapies. Continued collaboration between researchers and clinicians will be essential to translate these discoveries into benefits for patients.

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Authors

Aditi Gandhi is a high school junior at The Blake School in Minneapolis, Minnesota. Her academic interests include genetics, human biology, and biochemistry. She plans to pursue a career in medicine focused on improving care for individuals with lymphatic disorders.

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