A Review of Familial, Genetic, and Congenital Aspects of Primary Varicose Vein Disease

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Varicose veins are a common manifestation of chronic venous disease (CVD) and present as excessively dilated, tortuous, and elongated superficial veins in the lower limbs.

Varicose veins arise either secondary to vein wall remodeling or valvular incompetence leading to blood stasis and venous hypertension.1 Patients may experience lower limb pain, muscle cramps, bleeding, swelling, and skin changes, which include lipodermatosclerosis and eventual ulceration.2 To date, no specific cause for the development of varicose veins has been identified. However, various genetic and environmental risk factors have been ascribed to their formation.

Primary varicose veins have been shown to affect up to one third of the Western adult population and are a major cause of morbidity. Estimates of prevalence range from 2% to 56% in men and 1% to 60% in women.3,4 This inconsistency between reports may be due to heterogeneity of study populations, study designs, and experimental methodologies used as well as actual variations in the general population. Some reports suggest that varicose veins are more common in women than men,5–8 whereas others have shown the opposite.2,3,9,10 A cross-sectional survey in Edinburgh, UK, involving a total of 1566 patients, showed an age-adjusted prevalence of Grade 1 truncal varices in 33.3% of men compared with 26.2% of women.10 It has also been reported that there is a significant correlation between CVD onset and sex with females showing first symptoms at a mean age of 30.8 years and males at 36.8 years.8 Besides sex, the prevalence of varicose veins increases with age. The Edinburgh Vein Study reported the prevalence of varicose veins increases from 11.5% in 18 to 24 year olds age to 55.7% in 55 to 64 year olds.10 Similarly, other studies have reported a direct relationship between the prevalence of varicose veins and age,2,3,7,10 whereas an inverse relationship has also been observed between CVD severity and the age of disease onset.4 There is a suggestion of a trend toward a higher prevalence of varicose veins in developed countries, although this remains debatable.11

There are several established risk factors associated with varicose veins, including age, sex, pregnancy,6 raised body mass index in women,10 obesity, and family history of varicose veins.4 Although these risk factors may contribute to varicose vein formation, many individuals exposed to these risk factors do not develop the disease. Furthermore, the so-called environmental risk factors may also contain substantial genetic components. For example, obesity has an estimated heritability of up to 80%.12 Thus, varicose veins could be associated with distal mutation in these genetic determinants. In one study, a positive family history of varicose veins in first-degree relatives of patients was recalled in 17% of patients, which estimated the additive genetic component of CVD at 17%.8

The aim of this review was to collate the findings of primary research investigating the genetics and heredity of varicose vein disease, discuss the current level of understanding, and highlight areas warranting further investigation. This article also aimed to discuss the congenital disorders associated with varicose veins and review the genetics of primary dermal ulceration, an important and debilitating complication of varicose veins.

Methods

A PubMed and Medline search was performed using the terms: “genetics” or “inheritance” or “heritability” or “heredity” and “varicose veins” or “chronic venous disease” or “chronic venous insufficiency” or “venous ulcers.” The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology13 was applied to systematically identify relevant articles (Figure 1). The search was expanded using the “related articles” function and by scrutinizing article reference lists. Only English language articles were considered. Other studies discussing congenital disorders linked to varicose vein disease was also included. Those transcriptomics studies focusing on the differential genes expression in varicose veins were not included if it was not clear that the differential expression was the cause or the effect of varicose vein disease.

Familial Component to Varicose Veins

Epidemiological research has highlighted a trend of familial clustering for varicose vein disease. One study conducted in Japan demonstrated that 42% of women with varicose veins reported a positive family history as compared with 14% without the disease.14 In another case–control study in the United Kingdom, Scott and colleagues15 reported a positive family history of varicose veins in 85% of patients with varicosities as opposed to 22% in individuals...
Genes Associated With Varicose Veins

Given the frequent observation of a positive family history of varicose veins in some studies, scientific effort has led to the identification of specific genes that may be linked to venous function. One study investigated the heritability of venous function measured by impedance, and it has been stipulated that this separation of muscle fibers may cause loss of vascular tone leading to venous dilatation.

Studies also suggest that the downregulation of desmuslin in the vein wall may be responsible for a smooth muscle cell phenotypic switch from the contractile to synthetic phenotype and hence cellular weakness. In a recent study, desmuslin gene knockdown in cultured human saphenous vein smooth muscle cells by RNA interference led to a reduction in the expression of various smooth muscle cell proteins that regulate their phenotype. An increase in matrix metalloproteinase-2 and collagen activity has also been reported, further supporting the proposed role of desmuslin in smooth muscle cell differentiation and structural integrity in veins.

Thrombomodulin, involved in the control of thrombus formation through the regulation of thrombin, is thought to be associated with varicose veins. In a case–control study involving 327 patients with a history of venous thromboembolism (deep venous thrombosis or pulmonary embolism) and 398 control subjects, thrombomodulin mutation (−1208/−1209 TT deletion) was associated with a history of varicose veins. However, because this study primarily examined the biological risk factors of deep venous thrombosis, further studies are required to ascertain the involvement of thrombomodulin in primary varicose veins.

It is important to note that a number of studies have demonstrated differences between varicose and nonvaricose veins in the expression of numerous other genes including structural genes regulating the extracellular matrix (ECM), cytoskeletal proteins, and myofibroblasts. Importantly, it remains unclear if the differential expression of these genes is a cause or the effect of varicosities.

Varicose Veins Linked to Genetic Disorders

Varicose veins have been found to be associated with several congenital disorders, some of which have a strong hereditary component (Table 1; Figure 2).

### Table 1. Disorders, Genes, and Specific Mutations Associated With Varicose Vein Development

<table>
<thead>
<tr>
<th>Conditions With Chromosomal Defects</th>
<th>Conditions With Gene Mutations or Defects</th>
<th>Single Nucleotide Polymorphism or Gene Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal trisomies (7, 12 and 18) or monosomies (14)</td>
<td>Chuvash polycythemia (Von-Hippel Lindau gene)</td>
<td>Notch3 mutation in pedigree of CADASIL (12796T)</td>
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<tr>
<td></td>
<td>Lymphoedema distichiasis (FOXC2 gene)</td>
<td>Desmuslin</td>
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<tr>
<td></td>
<td>Severe congenital neutropenia type 4 (G6PC3)</td>
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CADASIL indicates cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
syndrome. KTS is considered a paradigmatic disorder; heterozygotes are asymptomatic, whereas homozygote mutations are lethal. The disorder manifests when a loss of heterozygosity mutation occurs early in embryonic development leading to 2 distinct cell lines in the individual. No ethnic or racial predisposition has been reported, but increased parental age and number of pregnancies have been considered likely contributing factors. A de novo balanced translocation involving chromosome 8q22.3 and 14q13 has also been reported. Other mutations such as chromosome translocation t (5;II) and mutations of the E13K gene and the VQ5Q gene on chromosome 5 (coding for the angiogenic factor VQ5Q) have also been reported in some patients with KTS. An insult at the sixth week of gestation during the process of vascular differentiation and invasion of the limb bud or failure of embryonic lateral border veins to regress at the eighth week of gestation have been postulated to lead to features of KTS.

Varicose veins are found in 76% to 100% of patients with KTS. An abnormal vein is sometimes obvious at birth traveling in the lateral aspect of the affected leg, draining through the gluteal vein into the profunda femoris or internal iliac system. Extensive varicosities can be visible on the extremities. Infrequently, varicosities may be present in other organs including the bladder, colon, and pulmonary veins. Some of these patients demonstrate venous hypoplasia including an absence of venous valves or the deep venous system. Some of the deep venous system anomalies including atresia, agenesis, or compression of the deep system due to fibrous bands have also been seen in patients with KTS. Venous obstruction and malformations are seen at popliteal or femoral regions and rarely at the ilioc or inferior vena cava level.

Lymphoedema Distichiasis and FOXC2 Mutations
Lymphoedema distichiasis (LD) syndrome is a form of lymphoedema linked with distichiasis (extra eyelashes from meibomian glands). Other associated features of the syndrome include varicose veins, congenital heart defects, vertebral anomalies, extradural cysts, ptosis, and cleft palate. The haplo insufficiency (when one copy of the gene is inactive and the remaining functioning copy is unable to produce sufficient gene product to allow a healthy condition) of FOXC2 genes from the forkhead family of transcription factors was found responsible for LD and was mapped to chromosome locus 16q24.3. FOXC2 is expressed on mesenchymal cells and is involved in the development of endothelial and smooth muscle cells of blood vessels, including venous and lymphatic valve leaflets. Homozygous mutations of FOXC2 in mice have been reported to cause death during development or immediately after birth. Heterozygous mutations in FOXC2 genes were noted in additional families with LD. Brice et al examined 74 subjects from 18 families of LD syndrome and 6 isolated cases of LD, in which approximately half of
patients with LD were found to have varicose veins. A cohort study involving 2060 pairs of female twins aged 18 to 80 years compared the incidence of varicose veins and hemorrhoids in relation to a candicate marker D16S520 on chromosome 16q24.4. In this study, phenotyping was assessed using a self-administered questionnaire (response rate of 60%–65%), whereas genotyping was performed using venous blood samples. This study showed an association of dizygotic twins with a candidate marker D16S520 on chromosome 16q24.4, located in close proximity to a functional variant of gene FOXC2. Concordance was significantly higher within monozygotic twins compared with dizygotic twins, suggesting a substantial genetic contribution for varicose veins. Genotyping revealed a strong association of this marker with varicose veins. The authors concluded that a functional variant within the vicinity of FOXC2 may be responsible for the predisposition of individuals to developing varicose veins.

In another study involving 18 participants with the FOXC2 mutation, including 3 without lymphoedema, every patient showed reflux in the great saphenous vein in comparison with 12 control subjects, 10 of whom were family members (P<0.0001). Deep venous reflux was recorded in 14 of 18 patients with the FOXC2 mutation. This study suggested that FOXC2 is strongly associated with primary venous valve failure in both superficial and deep venous systems.

Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy
In a study investigating a family with a history of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), for patients with venous insufficiency, clinical details were recorded, and imaging and genetic analyses were performed. A novel heterozygous mutation (1279G>T) in the 3 splice acceptor site of intron 15 of the Notch3 gene was isolated. The mutation of Notch3 in this lineage with varicose veins suggests that the gene may have a role in determining smooth muscle cell phenotype in varicose veins.

Chuvash Polycthemia
Chuvash polycthemia is an autosomal-recessive disorder caused by homozygous mutation of the von Hippel-Lindau gene (598>T) on chromosome 3p25. Chuvash polycthemia results in a defective oxygen sensing mechanism and is associated with increased levels of hypoxia-inducible factor-1α despite blood normoxia, leading to increased serum erythropoietin and hemoglobin concentrations. Although the disorder was first described in the Chuvash population of central Russia, similar mutations have also been identified in other populations. Patients with Chuvash polycthemia are predisposed to vertebral hemangiomas, thrombosis, bleeding, and stroke. Hypoxia-inducible factors are nuclear transcriptional factors that regulate genes mediating oxygen homeostasis. A matched cohort study showed varicose veins were found in 32 of 43 von Hippel-Lindau homozygote as compared with the 2 of 9 heterozygote and 30 of 77 unaffected individuals. There was an increased expression of hypoxia-inducible factor-regulated genes including vascular endothelial growth factor, plasminogen activator inhibitor-1, erythropoietin, glucose transporter GLUT-1, transferrin, and transferring receptor in patients with varicose veins.

Other Related Genetic Abnormalities
Another Mendelian disorder that has been shown to be associated with varicose vein development includes severe congenital neutropenia type 4. Severe congenital neutropenia type 4 is caused by a mutation in the G6PC3 gene. In addition to varicose veins, individuals with severe congenital neutropenia type 4 also develop leg ulcers. Because severe congenital neutropenia type 4 is a multisystem disease, it is not known whether the mutation is directly causing CVD or whether it is a secondary effect.

Chromosomal aberrations have been observed in cell culture lines taken from patients with varicose veins. These include structural abnormalities; clonal trisomies of chromosomes 7, 12, and 18; and monosomy of chromosome 14.

Genes Associated With Venous Ulceration
One of the major complications of CVD is the development of venous ulceration, with approximately 10% of patients with varicose veins going on to develop ulcers. Although ulcers are often multifactorial in development, variations in their severity and response to treatment have been observed, suggesting genetic factors may be responsible for such differences. The variations seen in leg ulcers are hypothesized to originate primarily from the subversion of the tissue injury response and the mutation of genes central to the repair of tissue damage. This malfunction is the underlying factor leading to ulcer development and persistence. Factor XIII (FXIII), encoded by the F13A1 gene, is one of the many proteins involved in the fibrinolytic system. It is also involved in tissue damage repair by regulating extracellular matrix regeneration. Fibrin protein complexes consisting of FXIII provide a temporary matrix at the site of injury. Furthermore, fibroblast migration and growth is greatly improved by the presence of FXIII. FXIII is thought to be highly polymorphic. Deficiency of FXIII has been shown to delay the healing of superficial wounds. Although F13A1 gene variants have yet to be directly linked with ulcer development, an inverse relationship between FXIII protein concentration and ulcer size and healing time has been observed (Table 2). Furthermore, high concentrations of specific F13A1 gene variants, Leu34 and Leu564, have been linked to increased ulcer healing rate. Iron deposits (hemosiderosis) are frequently a sign observed on the legs of individuals with CVD and venous ulceration and are thought to originate from the catabolism of hemoglobin due to chronic blood stasis. The hemochromatosis gene codes for a membrane receptor, structurally similar to major histocompatibility complex Class I and is thought to facilitate iron uptake. Mutations of the hemochromatosis gene, including the common variants C282Y and H63D, cause a deficiency of iron metabolism, which is known to exacerbate ulceration.

Although it has been demonstrated that heterozygous carriers of these mutations remain asymptomatic, there is an approximately 5-fold increased risk
for venous leg ulcer development in carriers who also have CVD.64 This is an important example of conditions overlapping and the gene–environment interaction resulting in disease progression and iron aggregation coupled with a reduction in iron uptake capability underlying disease pathogenesis.

Another susceptibility locus for ulcer development is the methylenetetrahydrofolate reductase gene, which codes for the enzyme methylene tetrahydrofolate reductase that is involved in the folate cycle. Mutations in this gene have been linked to various vascular diseases such as peripheral arterial disease. A specific exonuclease polymorphism (SNP) in methylene tetrahydrofolate reductase, C677T, previously associated with hyperhomocysteinemia, has been observed significantly more frequently (20%) in complicated CVD of Clinical Severity Etiology Anatomy and Pathophysiology Score (CEAP) C4–6 when compared with CEAP C2–3 (10%).57 A case–control study that used DNA analysis also found that the same missense mutation was also strongly associated with venous ulcer (P<0.005).58

Other SNPs have been linked to venous leg ulcers. SLC40A1 encodes ferroportin, a solute carrier transmembrane protein thought to be involved in the export of iron from duodenal epithelial cells. A SNP in the promoter region of this gene, S65G, is thought to affect gene expression; a recent study showed that carriers of this SNP have an increased risk of CVD (4-fold) and primary leg ulcer development (5-fold).59 Because the role of impaired iron metabolism has been implicated in the etiology of CVD and venous ulceration, these results further support this hypothesis. The same group also investigated a SNP in matrix metalloproteinase-12, a peptidase responsible for the breakdown of the ECM. The said SNP—82AA—located in the coding region of the gene, increased the risk of ulcer formation by 2-fold.59

Nagy et al60 investigated SNPs in the fibroblast growth factor receptor-2 gene. Fibroblast growth factor receptor-2 protein product is a membrane-bound receptor integral to the wound healing process. The extracellular domain of the fibroblast growth factor receptor-2 protein interacts with fibroblast growth factors, instigating mitogenesis and differentiation. SNP 2451AG, located in the 3′ untranslated region, was found to be associated with nonhealing ulcers.61 It is noteworthy that mutations in the untranslated regions of genes are thought to cause mRNA instability, leading to its degradation (see Table 2 for the genes associated with venous ulcer).

### Discussion

Genetic medical research has progressed significantly from the immature and impractical beginnings of positional cloning, chromosome walking, and linkage analysis in humans, which, with the exception of the cystic fibrosis gene, cystic fibrosis transmembrane conductance regulator, yielded few breakthroughs and proved to be an inadequate approach. After decoding the human genome, genetic studies may be either hypothesis-driven approaches such as gene-candidate studies or hypothesis-free (also known as nonhypothesis-driven or hypothesis-generating) approaches, including genomewide association studies. Although the candidate gene approach is appealing, it requires sufficient knowledge of disease etiology for a hypothesis to be synthesized. Conversely, genomewide association studies is a flexible approach, which is able to detect components of complex traits, but it is limited by its low statistical power, necessitating large sample sizes. Furthermore, the problem of missing heritability, the inability of genomewide association studies to determine variants with clinically significant effects, has been well documented.62

A number of environmental risk factors have been associated with the development of varicose veins, namely age, female sex, obesity, and possibly occupations requiring prolonged periods of standing.5 However, primary varicose veins are also seen in young adults with no specific cause. Current evidence suggests a strong association of varicose veins with a positive family history. Although it is apparent that there are critical genetic components involved in the disease etiology, there is still limited information on this important aspect of CVD pathophysiology.

Genes including desminulin and thrombomodulin can directly affect vein function with mutations implicated in the development and progression of varicose veins.52,57 Although some genetic SNP array analyses have been used to directly investigate the role of genetics in varicose vein formation, the majority of the studies have been qualitative epidemiological studies and have failed to identify specific susceptibility genes or variants. Nonetheless, there are many hereditary single gene disorders and genetic syndromes, which may include varicose veins as part of the (often complex) clinical presentation. These syndromes are multisytem diseases that are well understood and, in most cases, the genetic determinants have been described. With this information as a starting point, further genetic components contributing to CVD have been elucidated such as the FOXC mutations associated with LD.41 Although this can be insightful, these are monogenic forms of varicose veins and, as such, represent a small minority of disease burden. CVD is a complex, multifactorial disease, and this needs to be considered in the planning of future genetic and epigenetic studies.

Genetic research in venous ulceration has highlighted the importance of understanding the pathophysiological mechanisms that underlie disease development. Mutations in the F13A1 gene as well as variants of the hemochromatosis gene directly affect venous ulcer progression through the inhibition of physiological tissue healing processes.54,56 SNP array technology through a candidate gene approach has been used to identify further susceptibility loci including SLC40A1, methylenetetrahydrofolate reductase, and fibroblast growth factor receptor-2.59,60 Although dermal ulceration is linked to varicose veins, there are insufficient data to link ulcer-related genes to varicosity formation.

Patient-reported quality of life is reduced in patients with CVD64 and the cost of treating CVD has been estimated at 1% to 3% of the total annual healthcare budget of many Western countries.65 Varicose veins are the most common manifestation of CVD, although up to 4% of patients aged ≥65 years may experience venous ulceration.65,64 Recurrence rates for varicose veins after surgical treatment have been reported to be as high as 20% to 40%.65 Therefore, there is a pressing need to improve our understanding of the underlying causes of varicose veins and to identify high-risk groups. This involves recognizing both rare and frequent genetic variants that influence risk of CVD and relate these to quantitative phenotypes according to severity of disease (including, but not limited to, the CEAP classification). This will enable researchers to establish the critical functions of the susceptibility genes and the translation pathways leading to disease. This approach has the potential to provide improved medical treatment for patients and personalized, targeted preventive measures tailored to those identified to be at high risk. These preventive measures may include lifestyle changes, occupational advice, use of preventative compression stocking, or a pharmacotherapeutic treatment to prevent the progression of the disease. Identification of these specific genes will require large-scale
population-based studies with objective evidence of varicose veins and analysis of blood or other appropriate samples for genetic testing. Genomewide association studies have already been used for the investigation of a number of common complex diseases. Such studies have revealed several susceptibility loci associated with conditions such as Type 2 diabetes mellitus66 and colorectal cancer.67 However, such an approach will undoubtedly require significant resources and planning. Researchers should also strive to produce simple yet informative animal models for the observation of the inheritance of susceptibility genes and the long-term effects of any proposed treatments.

The use of alternative emerging technologies may help by reducing the cost and time requirement for analysis of patients’ phenotypes and offer an indirect picture of their genotypes. One of the technologies frequently used in the pharmaceutical industry is metabolomics, using nuclear magnetic resonance spectrometry and mass spectrometry. These techniques have been found to be very useful in discovering novel biomarkers for the disease, elucidation of cellular pathways, and functions of enzymes and genes.68,69 Examination of the metabolic profiles of varicose vein tissue and urine or plasma of patients with varicose veins using metabolomics techniques may unlock new disease-related cellular pathways and genes through the combination of the observation of genetically determined metabolic endophenotypes, and classical genetic research. It has been shown that variation in metabolic profile is stably controlled by genetic and environmental factors70 and by introducing a case–control study methodology, we can directly correlate disease phenotypes with biomarkers and the genetic components that underlie them. There have been various studies that support the potential of such an approach.71,72

In conclusion, it is apparent that there is a limited understanding of the complex underlying genetic factors contributing to varicose vein formation.

Disclosures

None.

References

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466


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