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REVIEW

The genetics of portal hypertension: Recent developments and the road ahead

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Abstract

Portal hypertension (PH), defined as a pathological increase in the portal vein pressure, has different aetiologies and causes. Intrahepatic PH is mostly secondary to the presence of underlying liver disease leading to cirrhosis, characterized by parenchymal changes with deregulated accumulation of extracellular matrix and vascular abnormalities; liver sinusoidal endothelial cells and hepatic stellate cells are key players in PH progression, able to influence each other. However, PH may also develop independently of parenchymal damage, as occur in portosinusoidal vascular disorder (PSVD), a group of clinical and histological entities characterized by portal vasculature dysfunctions. In this particular group of disorders, the pathophysiology of PH is still poorly understood. In the last years, several genetic studies, based on genome-wide association studies or whole-exome sequencing analysis, have highlighted the importance of genetic heritability in PH pathogenesis, both in cirrhotic and non-cirrhotic cases. The common *PNPLA3* p.I148M variant, one of the main determinants of the susceptibility to steatotic liver disease, has also been associated with decompensation in patients with PH. Genetic variations at loci influencing coagulation, mainly the *ABO* locus, may directly contribute to the pathogenesis of PH. Rare genetic variants have been associated with familiar cases of progressive PSVD. In this review, we summarize the recent knowledges on genetic variants predisposing to PH development, contributing to better understand the role of genetic factors in PH pathogenesis.

KEYWORDS
cirrhosis, coagulation, genetic, *PNPLA3*, portal hypertension, portosinusoidal vascular disorders, rare variants, vascular abnormalities

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1 | DEFINITION, BURDEN OF THE DISEASE AND CLASSIFICATION OF PORTAL HYPERTENSION

Portal hypertension (PH) is defined as a pathological increase in the portal vein pressure and the gold standard measurement technique is the portal pressure gradient >5 mmHg (the pressure difference between the portal vein and the inferior vena cava). The formation of portosystemic collaterals, which attempts to divert part of the portal blood flow to the systemic circulation,[1] is the hallmark of PH. Patients who develop PH remain usually asymptomatic at the beginning. However, when the portal system and portosystemic collaterals are no longer able to compensate the increased pressure, clinical manifestations such as variceal haemorrhage, ascites or encephalopathy may appear, defining liver decompensation and representing a major turning point in the natural history of the disease. Furthermore, PH may evolve into a systemic process in which maladaptive compensatory responses culminate in dysfunction and failure of multiple organs, with a substantially negative impact on patients' life expectancy and quality of life, ultimately leading to liver transplant or death. Liver disease causes over 2 million deaths annually, ranking as the 11th leading cause of death worldwide and the 15th leading cause of disability-associated life-years. Indeed, complications in patients with chronic liver disease are primarily attributed to PH.[2,3]

The different causes of PH are classified according to the site where primary resistance is established, as reported in Table 1.

Intrahepatic PH is by far the most common form, being cirrhosis the leading cause in Western countries. Intrahepatic PH has been long believed to be a consequence of structural alterations in the liver mainly due to extracellular matrix deposition (i.e. fibrosis). In recent years, the focus of research has shifted towards the study of vascular functional and structural alterations associated with PH, which account for approximately 20%–30% of its severity. Moreover, the notion that PH may occur independently of parenchymal damage (i.e. portosinusoidal vascular disorder, PSVD) opens the door to new pathophysiological explanations, in which endothelial dysfunction might play a major role. The main mechanisms underlying the development of different forms of PH and responsible genes are depicted in Figure 1.

Key points

- Portal hypertension (PH) is mainly secondary to liver cirrhosis, characterized by parenchymal and vascular abnormalities.
- Portosinusoidal vascular disorders (PSVD), characterized by portal vasculature dysfunction, may evolve in PH in the absence of parenchymal damage.
- The pathophysiology of PH in PSVD is still poorly understood.
- Genetic variations are involved in the predisposition to PH development.
- PSVD provides a unique human model for studying the vascular component of PH and to better understand the contribution of genetic factors to PH development.

2 | PORTOSINUSOIDAL VASCULAR DISORDER

In recent decades, a group of diseases that share the possible occurrence of PH in the absence of cirrhosis or other known causes,

TABLE 1 Classification and causes of portal hypertension (PH).

Classification	Site of obstruction	Causes
Pre-hepatic	Extra-hepatic portal vein Splenic vein Mesenteric vein	Vascular obstruction due to thrombosis Neoplastic infiltration Stenosis secondary to inflammatory disease Extraluminal compression
Intra-hepatic	Pre-sinusoidal	Portosinusoidal vascular disorder (PSVD) Primary biliary cholangitis Schistostomiasis Sarcoidosis Polycystic liver disease and congenital liver fibrosis
	Sinusoidal	Cirrhosis Nodular regenerative hyperplasia Infiltrative diseases such as amyloidosis
	Post-sinusoidal	Sinusoidal obstruction syndrome
Post-hepatic	Hepatic venous outflow	Budd-Chiari syndrome Right heart failure Constrictive pericarditis Restrictive cardiomyopathy Pulmonary hypertension

has been reclassified and grouped together under the name of 'portosinusoidal vascular disorder' (PSVD).[4–6] PSVD includes a wide range of clinical and/or histological entities including portal obliterative venopathy, nodular regenerative hyperplasia of the liver, hepatoportal sclerosis, non-cirrhotic portal fibrosis, incomplete septal fibrosis/cirrhosis and early-onset familial non-cirrhotic portal hypertension[6] that may evolve towards the same severe clinical phenotype: idiopathic non-cirrhotic portal hypertension (Figure 1).

The current definition of PSVD, which includes also earlier stages when PH is not yet present, has specific diagnostic criteria and requires a good-quality liver biopsy.[4–6] Diagnosis is based on the presence of 'specific histological features' at liver biopsy (obliterative portal venopathy, nodular regenerative hyperplasia and incomplete septal fibrosis or cirrhosis) and/or 'specific signs of PH' in the absence of cirrhosis. Moreover, the diagnosis is also possible when the combination of 'non-specific' histological signs of PSVD and 'non-specific' signs of PH are present.[4,6]

The clinical course of these patients is mainly characterized by variceal bleeding (20%–40% of cases), development ascites (20%–50% of cases) and portal vein thrombosis (PVT, up to 40% of cases). Encephalopathy, portopulmonary hypertension or hepatopulmonary syndrome have been less frequently reported.[7,8] In the absence of treatments able to halt progression of the disease, complications are managed with symptomatic treatment and, when refractory, interventional procedures are performed, including portosystemic shunt (incidence 4% at 5 years) and liver transplantation (5% at 5 years). Recommendations on prophylaxis, treatment and follow-up are still largely based on knowledge extrapolated from cirrhosis.[7] However, these disorders differ in many aspects from cirrhosis. These patients often present with preserved hepatocellular function, younger age, and associated comorbidities of varying severity that can affect the prognosis and access to liver transplant. Indeed, the lack of knowledge on disease aetiology, physiopathology and determinants of progression makes diagnosis very challenging. Appropriate management is imparied by the limited awareness of the disease, the difficulties of an adequate diagnosis outside centres of expertise and the lack of markers able to predict progression and identify patients at risk of PH-related decompensations, PVT or liver-related death. Moreover, in the absence of prognostic scores/biomarkers, stratifying patients according to their individual risk of decompensation/outcome is not possible in the clinical setting, causing also inequity to access liver transplant (scores used for prioritizing do not reflect PSVD severity). Therefore, the unresolved challenges for this disease are still multiple, and the evidence is still scarce.

3 | PATHOPHYSIOLOGY OF PH AND MECHANISTIC INSIGHT (WHAT IS KNOWN)

The pathophysiology of PH is complex and varies depending on the aetiology and anatomical location of the defect, which can interfere with portal blood flow anywhere between the splanchnic territory and the right atrium.[9] According to Ohm's law, flow and resistance regulate pressure. Therefore, an increase in any or both of these components can result in the establishment of PH. Thus, PH is a disease whose origins and manifestations can be attributable to aberrant mechanical forces induced by alterations of these components, which, in intrahepatic PH, are secondary to hepatic parenchymal and/or vascular changes.

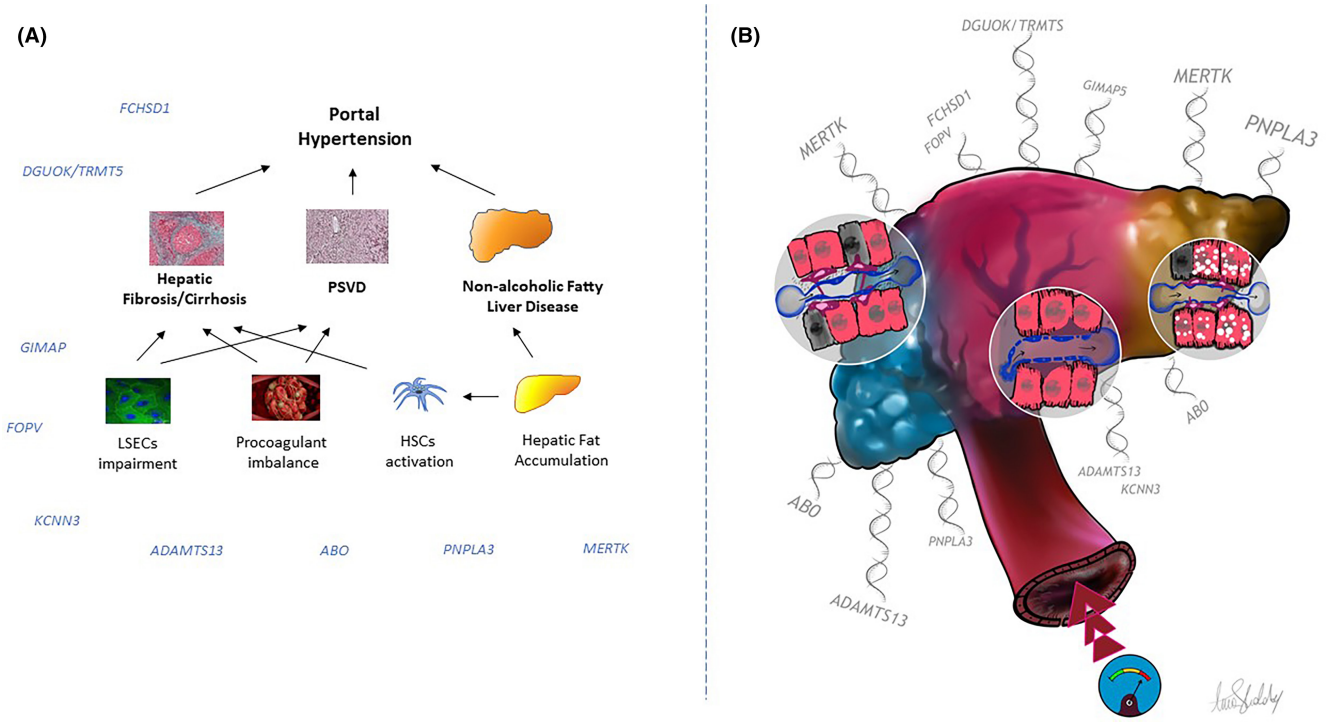

FIGURE 1 Genes and pathophysiological mechanisms involved in portal hypertension development in different diseases: hepatic fibrosis/cirrhosis, portosinusoidal vascular disorder and steatotic liver disease/metabolic associated steatohepatitis. (A) Schematic representation; genes are shown in blue italics. (B) Graphic representation; fibrosis/cirrhosis (left), portosinusoidal vascular disorder (centre) and steatotic liver disease/metabolic associated steatohepatitis (right). HSC, hepatic stellate cells; LSEC, liver sinusoidal endothelial cells; PSVD, porto sinusoidal vascular disease. Fibrosis/cirrhosis, Steatotic liver disease/metabolic associated steatohepatitis, Portosinusoidal vascular disorder, Hepatocyte, Apoptotic hepatocyte, Hepatocyte with fat droplets, Portal vein, Sinusoid, Central vein.

In the past, the onset of intrahepatic PH was thought to be related exclusively to fixed architectural abnormalities due to deregulated deposition of extracellular matrix in the liver.[10] Indeed, as cirrhosis is the most frequent and most characterized cause of PH, clinical studies have been mostly conducted in patients affected by this condition and experimental models of PH were developed reproducing the characteristics of this pathology and have thus allowed for an in-depth study of this component. In chronic liver disease, pronounced and persistent accumulation of extracellular matrix eventually leads to stiffening of the parenchyma, formation of regenerative nodules and microvascular occlusion. The structural changes also involve hepatic sinusoidal endothelial cells (LSEC), which begin to lay down basement membrane, and miss their characteristic fenestrae ('sinusoidal capillarization'). LSEC become dysfunctional, impairing maintenance of hepatic stellate cells (HSC) quiescent state, which change phenotype and transform into fibroblasts.[11] HSC are key players in the progression of fibrosis, as they are not only the main source of extracellular matrix[12] but also actively secrete angiocrine signals that act as paracrine factors unbalancing the liver's response to injury towards fibrosis.[13] These structural derangements were thought to be solely responsible for the increase in intrahepatic vascular resistance to portal blood flow and the onset of PH,[14,15] thus leaving pharmacological research to focus on anti-fibrotic drugs.

Nonetheless, advances in understanding the pathophysiology of PH have revealed the presence of a dynamic vascular component that plays a key role in modulating intrahepatic circulation and could account for about one third of the increased hepatic resistance causing PH in cirrhosis.[16] This component results from the uncontrolled contraction of several elements of the liver, together with the loss of the vasodilatory capacity of LSEC.[17] During prolonged liver injury, LSEC become dysfunctional and acquire a pro-vasoconstrictive, pro-inflammatory, pro-thrombotic, pro-angiogenic and pro-fibrotic phenotype.[18–20] In addition to structural stiffening of the sinusoid, this dysfunctional endothelium loses its role in modulating pressure changes, for example, by reducing nitric oxide (NO) secretion and inducing the release of damage-associated molecular patterns (DAMPs) and endothelin-1. These factors induce HSC to change phenotype, becoming contractile myofibroblasts that, in addition to producing sinusoidal extracellular matrix, act by actively contracting sinusoids.[11,18] These mechanical signals are sensed by mechanoreceptors and transmitted to other nearby cells, which in turn change their phenotype further propagating the damage. Indeed, mechanotransduction is able to influence also gene transcription by opening nuclear pores which increase nuclear transport of proteins,[21–23] and by inducing the transcription of mechanosensitive genes.[24]

Thus, both architectural and vascular abnormalities play a role in the onset of PH in cirrhosis and are also able to influence each

other with a positive feedback process by secreting paracrine factors and stimulating mechanoreceptors, making the progression of PH a self-sustained process.[25] Other conditions such as bacterial translocation, inflammation, neo-angiogenesis and microthrombotic processes also take place, further contributing to perpetuating the damage.[26]

Finally, splanchnic vasodilatation also affects the systemic circulation, leading to a decrease in mean arterial pressure and a reduction in effective arterial blood volume, which in turn leads to activation of neurohumoral systems, sodium and water retention and an increase in cardiac output. This hyperdynamic circulatory state further increases portal pressure and leads to the establishment of clinically significant PH.[27]

4 | HERITABILITY OF PORTAL HYPERTENSION

Heritability is the degree of a phenotype variation in the population that is accounted for by inherited determinants (including genetic variation), in contrast to the environment, random chance and observational error. Heritable factors include both genetic and epigenetic factors. The heritability (h^2) can be determined by twin, familial and multiethnic and epidemiological/genomic studies. For example, through large cohort studies it had been possible to estimate the heritability of systemic and pulmonary arterial blood pressure and of arterial hypertension. Indeed, arterial hypertension is a complex trait, with 15%–40% of systolic and diastolic blood pressure variability being accounted for by polygenic heritability.[28] The advent of genome-wide association studies (GWAS) has allowed to identify the main genetic loci responsible for this blood pressure variation and is already contributing to improve the risk stratification of hypertension and cardiovascular events. Furthermore, these genetic studies have highlighted novel therapeutic targets (e.g. natriuretic peptide receptor 1 – NPR1) that are now being evaluated in clinical trials, as well as the opportunity of repurposing drugs approved for other indications (e.g. endothelin receptor A—EDNRA—antagonists and sodium glutamate transporter 2—SGLT2—inhibitors).[28] However, arterial hypertension can also be due to monogenic conditions. These predominantly involve the renin-angiotensin-aldosterone system and the adrenal glucocorticoid pathway, with a smaller fraction caused by neuroendocrine tumours of the sympathetic and parasympathetic nervous systems.[29] Moreover, polymorphisms in genes coding for therapeutic targets (e.g. *ADRB1* and *ADRB2* encoding for β-adrenergic receptors) are well-known modifiers of the individual response to antihypertensive drugs, potentially contributing to risk stratification and improvement of clinical management with a precision medicine approach.[30]

Pulmonary arterial hypertension can also be due to genetic conditions, and several loci have been identified as causes of primary pulmonary hypertension segregating as an autosomal dominant trait.[31] These are generally involved in the regulation of bone morphogenetic proteins (BMP) signalling, angiogenesis and endothelial function.[31]

Difficulties in accessing the portal venous territory that requires invasive procedures that are ethical only in at-risk individuals, and the complex nature of the syndrome are responsible for the scarcity of available data on the heritability of portal pressure and PH and on the main genetic determinants of this specific driver of liver disease progression. Although genetic variants influencing the individual response to antihypertensive drugs used for PH complications treatment have been described, their possible involvement in PH development has not yet been determined.[32,33] Similarly, the role of genetic variants in PH regression is not known.

5 | THE *PNPLA3* p.I148M VARIANT LINKS LIPOTOXICITY WITH HEPATIC STELLATE CELL ACTIVATION AND PORTAL HYPERTENSION IN CHRONIC LIVER DISEASES

The main genetic determinants of liver disease in the population have been identified in variants of gene regulating hepatic fat metabolism and the predisposition to steatotic liver disease (SLD), bile acid metabolism, endoplasmic reticulum stress and the storage and excretion of transition metals.[34] These data confirm that PH is mostly secondary to the presence of underlying liver disease leading to cirrhosis. However, it should be highlighted that most of the available studies did not evaluate as outcomes clinical phenotypes nor events closely linked to PH.

Recent data suggest that at least some of the inherited risk factors predisposing to SLD may directly contribute to hepatic fibrogenesis and PH independently of their effect on hepatic fat accumulation.[35] Specifically the common rs738409 C>G polymorphism encoding for the p.I148M variant of patatin-like phospholipase domain-containing 3 (*PNPLA3*) accounts for the largest fraction of the inter-individual susceptibility to SLD in the population and is strongly enriched in patients with severe SLD and steatohepatitis, as well as in patients with severe alcohol-related liver disease.[36–38] Among Europeans, more than a quarter of patients with severe SLD and ~40% of those who progressed to hepatocellular carcinoma are homozygous for this genetic variant. Furthermore, the *PNPLA3* p.I148M variant has been identified as one of the main determinants of the susceptibility to endothelial activation and inflammation.[39] In particular, the *PNPLA3* p.I148M variant is the main genetic determinants of circulating levels of ICAM-1, a marker of endothelial cells activation.[39] In addition, in individuals with metabolic dysfunction at high risk of SLD, carriage of the *PNPLA3* p.I148M variant has recently been associated with development of a procoagulant phenotype (higher Factor VIII/Protein C ration).[40] As procoagulant phenotype has been hypothesized to play a causal role in liver fibrogenesis,[41] these data suggest that alterations in hepatic microcirculation may contribute to liver disease predisposition in carriers of the variant. Besides promoting intracellular fat accumulation in hepatocytes, PNPLA3 plays a key role in the trans-activation of HSC,[42] by regulating the dismissal of retinol-esters during HSC activation, and the *PNPLA3* variant

has been linked to a more inflammatory and fibrogenic phenotype in HSC.[43,44] Even though in small initial studies genetic variants in *PNPLA3* do not seem to impact the risk of disease progression and severity in patients with HIV/HCV coinfection, nor the regression of PH in patients with chronic hepatitis C viral eradication,[45,46] carriage of the *PNPLA3* p.I148M variant has been associated with the risk of disease progression and decompensation in patients with portal hypertension due to SLD.[47,48] These data suggest that a large fraction of patients with severe SLD may be predisposed to develop PH due to shared genetic mechanisms with SLD.

6 | OTHER GENETIC VARIANTS INFLUENCING HEPATIC STELLATE CELLS ACTIVATION

Another interesting genetic locus influencing HSC regulation and therefore fibrogenesis and the regulation of portal blood flow, is the one encoding for the c-mer tyrosine kinase gene (*MERTK*). Variation in *MERTK* has been implicated in determining the susceptibility to develop hepatic inflammation and fibrosis in the population, in particular in patients with SLD.[34,35,49] The mechanism linking the minor (less frequent) allele with protection against liver disease has been shown to involve downregulation of MERTK expression in hepatic myeloid cells (macrophages), which determines the secretion of transforming growth factor-β (TGF-β) and activation of HSC.[50] Interestingly, the availability of retinoids, which can be released by HSC, downregulates macrophage MERTK by ADAMTS17-mediated cleavage, providing a feedback mechanism to regulate hepatic fibrogenesis and HSC activation.[50] Additionally, Balcar and colleagues demonstrated that cirrhotic patients carrying the transmembrane 6 superfamily 2 (*TM6SF2*) rs58542926 single nucleotide variant had higher hepatic portal venous gradient and risks of hepatic decompensation and liver-related death, compared to patients with similar baseline liver disease severity.[51] Indeed, in humans, the *TM6SF2* T-allele has been linked to more pronounced hepatic inflammation and activation of HSC, which may increase intrahepatic resistance, thereby potentially aggravating PH and its complications independently of the impact on hepatic fat.[15,52]

All in all, these data confirm a role of HSC activation in response to inflammation in PH pathogenesis in patients with SLD. However, additional studies are required to examine whether the *PNPLA3* p.I148M variant and other common genetic variation responsible for liver disease heritability at population level have a direct effect also on LSEC and coagulation phenotypes.

7 | GENETIC PREDISPOSITION TO PROCOAGULANT IMBALANCE

Microvascular thrombosis occurring in hepatic sinusoids has been suggested to contribute to PH both directly by increasing vascular resistance and indirectly by promoting parenchymal extinction and hepatic fibrogenesis.[41] In keeping, thrombophilic conditions predisposing to abdominal clots are also a risk factor for non-cirrhotic PH.[6] It was recently shown that genetic variation predisposing to procoagulant imbalance, namely *ABO* locus variation through the influence on circulating von Willebrand factor (VWF) and carriage of Factor V^{Leiden} have a causal role in triggering fibrogenesis since the early stage of SLD,[40] and are a risk factor for liver fibrosis at population level.[53] However, the direct contribution to the development of PH is unknown.

Viceversa, the contribution of genetic variation at these loci influencing coagulation to PSVD remains mostly unexplored. However, genetic variant in *ADAMTS13* gene (p.R1277W), encoding for a VWF cleaving protease, associated with decreased secretion and activity of ADAMTS13 protein and high VWF levels, has been reported in a single patient with PSVD with preserved liver function.[54] These anecdotal findings suggest a potential direct contribution of genetic variations at loci influencing coagulation to the pathogenesis of PH; however, up to now the role of these variations remains mostly unexplored in larger cohorts.

The *ABO* locus encoding for the ABO blood group is of particular interest because it is the main genetic determinant of circulating VWF levels, and therefore of coagulation factor VIII concentration and activity, and non-O blood group is a main risk factor for venous thrombosis.[55,56] The mechanism is related to altered glycation and half-life of circulating VWF, which is a substrate of the ABO glycosil transferase.[55,56] Interestingly, together with the *LGALS3* locus itself, the *ABO* was also identified as one of the two genome-wide determinants of circulating levels of Galectin-3, a lectin involved in the pathogenesis of liver fibrosis and PH.[57] The ABO blood group determination is frequently available in clinical practice, especially in patients considered for liver transplantation. Therefore, some studies examined the impact of ABO blood group on clinical outcomes related to PH, although this phenotype underestimates the contribution of the *ABO* genetic locus to circulating VWF levels and the procoagulant imbalance. Indeed, the determination of ABO blood group does only capture qualitative differences in ABO antigen, but it does not reflect quantitative variation of the expression levels.[40] Importantly, PH is associated with increased expression and release of VWF, and higher VWF levels are associated with a worse prognosis.[58,59] The ABO blood group (non-O blood group) was associated with higher VWF levels in patients with cirrhosis, but the impact was smaller than in the general population and did not impact on hard clinical outcomes.[60,61] However, no data on the clinical outcomes in patients with PSVD are yet available.

8 | RARE GENETIC CAUSES OF NON-CIRRHOTIC PORTAL HYPERTENSION, A POSSIBLE CLUE TO SPECIFIC DETERMINANTS?

PSVD alters the portal vasculature and raise portal pressure irrespective of parenchymal liver disease and represents a unique

model for studying the vascular component of PH, allowing an insight into its mechanisms and identification of new therapeutic targets, without the influence of the fibrotic structural component. Therefore, it could be speculated that the discovery of their causes can shed light on the specific mechanism underlying PH development in general.

It has been hypothesized that PSVD may originate from immune and inflammatory mechanisms that induce the activation of LSEC and the onset of local inflammation, leading to damage of small portal vein branches, endothelial dysfunction and activation of HSC, which in turn lead to further endothelial damage, phlebosclerosis, the onset of PH and finally apoptosis of liver cells.[62–67] This hypothesis suggests a central and exclusive role of LSEC in the pathophysiology of PSVD and onset of PH. However, it does not explain why only some patients with PSVD histological lesions develop PH, or why only some patients exposed to PSVD-associated factors develop the disease, while others with the same features do not. Furthermore, vascular damage in patients with PSVD has a patchy distribution in the intrahepatic portal vascular tree, sparing some vascular branches in an apparently random manner. These observations suggest endothelial vulnerability and susceptibility to damage/dysfunction as an important mechanism leading to PH.

In this regard, the similarities with other diseases that originate from primary endothelial dysfunction could provide a hint as to the pathophysiology of PSVD. One example would be pulmonary arterial hypertension, a disease that involves abnormal vascular remodelling of the small branches of the pulmonary artery (including the formation of plexiform and concentric lesions composed of proliferating endothelial cells and myofibroblasts), with subsequent obstruction of small arterioles, leading to increased pulmonary vascular resistance and right ventricular afterload, and eventually to right heart failure.[68] Interestingly, recent data have revealed the acquisition of somatic mutations within the pulmonary endothelium that favour the development of vascular alterations responsible for the onset of hypertension.[69] These abnormalities have been detected in patients with inherited, idiopathic and associated forms of pulmonary arterial hypertension, suggesting that somatic genetic alterations may represent a shared characteristic between the different disease types, which remains independent of parenchymal damage. Of note, no abnormalities were detected in patients with cystic fibrosis or chronic obstructive pulmonary disease.[69]

Similarly, the idea that PSVD may arise from a predisposition of the LSEC to become dysfunctional when exposed to a second hit (immune, neoplastic, infectious, drugs, etc.) might explain its pathophysiology (microvascular damage in the absence of parenchymal damage) and patchy distribution within the intrahepatic vascular tree. In this vision, PSVD could represent a unique opportunity not only for obtaining a more detailed understanding of the pathophysiology of PH in its vascular-derived component, but also for the identification of predisposing factors for endothelial dysfunction.

In this context, the study of determinants, that is the possible genetic and acquired causes of PSVD, may offer a window into the specific mechanisms leading to vascular damage, endothelial dysfunction and PH onset independently of the more common chronic parenchymal disorders of the liver. The advantage of studying genetics is linked to the possibility of deducing the causal link between a hereditary allele associated with a predisposition to the disease, regardless of the presence of confounding factors, and of understanding the cellular and biological mechanism underlying the phenotype by conducting functional studies on candidate genes.

9 | GENETIC ALTERATIONS IN PATIENTS WITH PSVD

Although in most patients PSVD appears to be idiopathic or associated with acquired thrombophilia, immune-mediated disorders or other triggering factors, familial forms of progressive PSVD with development of severe PH have been described.[70–73] The first evidence that PSVD may be transmitted as an autosomal dominant trait was reported in a family living in United Kingdom, with variceal bleeding, hepatic encephalopathy and portopulmonary hypertension manifesting at an early age, associated with histological nodular regenerative hyperplasia and PSVD.[74] These data suggested that mutations of a single gene or small set of genes may be responsible for this condition.

In the last years, the progresses of next-generation sequencing (NGS) technologies are driving exceptional and fast advances in the comprehension of the genetic basis of human disorders, highlighting a major role of rare genetic variants in determining the predisposition not only to rare Mendelian disorders, but also to severe and early presentations of more common and complex conditions. Whole-exome sequencing (WES), targeting the coding portion of the genome, has becoming clinically available in referral centres and is already being applied to the diagnosis of liver disease in adults.[75] By providing complementary findings to clinical, biochemical and histological approaches, WES is already allowing to establish causal diagnosis in at least one third of the cases of adult patients with unexplained liver diseases, especially in early-onset phenotypes associated with a family history.[76–78]

Koot and coworkers identified the first putative gene responsible for PSVD in the *KCNN3* gene, encoding for a potassium channel regulating arterial and venous vascular tone via modulation of the membrane potential of endothelial cells and the contraction of smooth muscle cells.[79] In a proband and three offspring from three different mothers, WES analysis showed that carriage of the de novo c.1348G>C variant, encoding for the amino acid substitution (p.V450L) was associated with PSVD transmitted with and autosomal dominant pattern. However, no further details of the genetic background were provided, and experimental models testing whether genetic manipulation of KCNN3 induces PSVD are not available.

By performing WES in two families, including six patients with PSVD, Besmond and coworkers identified heterozygous variants (p.G595R and p.T1632I) in a novel gene located on chromosome 4

(*C4ORF54*), that they called *FOPV* (from 'Familial Obliterative Portal Venopathy', later redefined PSVD).[80] These variants were predicted to be damaging by in silico analysis and segregated with the disease in families. The pattern of inheritance was suggestive of autosomal dominant inheritance, with incomplete penetrance and variable expression. A deleterious heterozygous *FOPV* missense mutation (c.4244T>C, p.F1415S) was also identified in a patient with non-familial PSVD. Expression study in liver veins showed that *FOPV* transcript was mainly expressed in intrahepatic portal vein.[80] These data suggested for the first time that genetic variants responsible for the predisposition to familial PSVD may also be involved in sporadic cases.

Recently, in four different unrelated families with unexplained PSVD with autosomal recessive inheritance, development of PH was linked to homozygosity for rare damaging variants in the GTPase of the immunity-associated protein family member 5 (*GIMAP5*) gene.[81] Four different variants (p.I47T, p.P109L, p.L204P and p.L223F) accounted for the phenotype in the described families, but they all resulted in loss of protein expression. GIMAP5 is a small GTPase regulating lymphocyte survival, but in experimental models Authors showed that GIMAP5 is also expressed in LSEC, but not in hepatocytes.[81] In mice, loss of *Gimap5* led to LSEC capillarization, due to loss of expression of GATA4 required for LSEC specification, and development of PH, a phenotype that was not influenced by Gimap5 expression in myeloid cells.[81] These findings indicate that LSEC specification is required to prevent the spontaneous development of PH and suggest that LSEC capillarization and loss of fenestration accompanied by reduced GATA4 expression observed during early stages of SLD plays a causal role in PH development.

The same group had previously reported that homozygosity for a rare variant (p.N46S) in deoxyguanosine kinase (*DGUOK*) gene, encoding for a protein required for mitochondrial DNA replication, was responsible for development of PSVD in consanguineous families.[82] Interestingly, exposure to the nucleoside analogue didanosine used to cause the development of PH in a subset of patients with human immunodeficiency viral (HIV) infection, lowers deoxyguanosine kinase levels linking genetic predisposition to acquired causes of PSVD.[82] Other drugs influencing DNA synthesis, such as 5-fluorouracyl, have been implicated in the pathogenesis of PH through a similar mechanism. Homozygosity for *DGUOK* mutations is responsible for hepatocerebral and liver-specific mitochondrial

TABLE 2 Genes associated with familial forms of progressive portosinusoidal vascular disorder (PSVD).

Gene	OMIM ID	Cytogenetic location	Peptide change	Status	Inheritance	Reference
KCNN3	602983	1q21.3	p.V450L	Het	AD	[70]
FOPV (C4ORF54)	617881	4q23	p.G595R p.T1632I p.F1415S0	Het Het Het	AD AD Sporadic case	[71]
GIMAP5	608086	7q36.1	p.I47T p.P109L p.L204P p.L223F	Homo Homo Homo Homo	AR AR AR AR	[72]
DGUOK	601465	2p13.1	p.N46S	Homo	AR	[73]
TRMT5	611023	14q23.1	p.I296T and p.D300V	Comp het	AR	[76]
FCHSD1	617555	5q31.3	p.R183W	Homo	AR	[79]

Abbreviations: Comp het, compound heterozygous; Het, heterozygous; Homo, homozygous.

TABLE 3 Identified research priorities to advance the field of genetics of portal hypertension.

Genetics of portal hypertension	
Research priorities	**Proposed methodology**
Examine the contribution of rare genetic variants linked to familial cases to sporadic PSVD	Whole-exome sequencing (WES) or target sequencing
Identify new genetic determinants of PSVD	Whole-exome sequencing (WES)
Examine the contribution of genetic variation in genes linked to PSVD on the variability of portal blood pressure in individuals at risk of portal hypertension due to chronic liver diseases (e.g. SLD), with similar severity of liver fibrosis	Hepatic Venous Pressure Gradient (HVPG) measurement (or spleen stiffness) in patients with advanced fibrosis; by assessing the presence and grading of varices in patients with cirrhosis
Identify the main genome-wide significant determinants of portal hypertension	Genome-wide association study (GWAS)

Abbreviation: SLD, steatotic liver disease.

DNA depletion syndromes,[83] which can manifest with a spectrum of liver disease conditions including early progressive hepatic failure that may be associated with neurological involvement, and may also present as neonatal hemochromatosis.[84]

Recently, Warasnhe and coworkers reported two siblings, presenting with hepatopulmonary syndrome later diagnosed as PSVD, both with compound heterozygosity for two variants (p.I206T and p.D300V) in mitochondrial tRNA methyltransferase 5 (*TRMT5*) gene.[85] TRMT5 is a methyltransferase responsible for the methylation of Guanosine at 37th position (G37) at mitochondrial-transfer RNA (tRNA). *TRMT5* variants resulted in G37 hypomethylation and consequent mitochondrial DNA translation impairment. *TRMT5* variants were previously associated with different diseases, such as hereditary spastic paraparesis, cerebral palsy and MELAS-like features.[86,87] All these findings suggest that mitochondrial DNA depletion is involved in the pathogenesis of PSVD, but the mechanism remains unclear.

Lastly, Shan and coworkers identified a homozygous rare variant of FCH and double SH3 domains 1 (*FCHSD1*, p.R183W), an uncharacterized gene, as the likely cause of PSVD in a Lebanese family.[88] The variant may increase both messenger RNA (mRNA) and protein stability and its interaction with MTOR-associated protein, LST8 homologue, a key protein of the mechanistic target of rapamycin (mTOR pathway), resulting in increased mTORC1 activity.[88] Furthermore, introduction of the genetic variant in mice led to PH development, confirming the causal role in determining the phenotype, although the mechanism remains to be clarified.[88]

Finally, PSVD may be associated with other rare genetic diseases, such as Adams-Oliver syndrome,[89] cystic fibrosis-related liver disease (CFLD)[90] and Alagille syndrome (ALGS).[91] Although the genetic basis of these disorders, in particular for CFLD and ALGS, is well established and all these conditions affect the development of the biliary tree, suggesting it may secondarily affect liver vascular development, the detailed molecular mechanisms linking genetic variations to PSVD development remains to be clarified.

Genes associated with familial forms of progressive PSVD are summarized in Table 2.

In Table S1 are reported, all data supporting the relevance/lack of relevance of gene variants/polymorphisms in PH development.

10 | CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, genetic variation is likely involved in the specific predisposition to PH development as it has already been robustly demonstrated for other vascular territories. The influence and/or direct contribution of genetic variants in the pathogenesis of PH has only been minimally explored mainly due to (1) the complexity of cirrhosis with multiple changes in parenchymal and non-parenchymal cells (hepatocyte injury, HSC activation, sustained inflammation) and their bidirectional crosstalk with LSEC and (2) the inaccessibility of the portal vein territory and lack of non-invasive approaches to measure portal pressure in large population-based studies and in patients without severe disease.

Identification of subgroup of patients suffering from PH in the absence of parenchymal damage (namely PSVD) and their association with genetic alterations in a familiar and sporadic fashion, provides a unique human model to better understand the contribution of genetic factors to development of PH. In Table 3, we propose ambitious goals as hints for research priorities in this field, for which international multicentric collaborations will be needed to achieve sufficient power.

AUTHOR CONTRIBUTIONS

Conceptualization: Virginia Hernandez-Gea, Luca Valenti. Drafting of the manuscript: Sarah Shalaby, Luisa Ronzoni, Virginia Hernandez-Gea, Luca Valenti. Critical revision of the manuscript for important intellectual content: Sarah Shalaby, Luisa Ronzoni, Virginia Hernandez-Gea, Luca Valenti. All authors approved the final version of the manuscript as submitted, and all authors agree to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are appropriately resolved.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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