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REVIEW

Genetic predisposition to porto-sinusoidal vascular disorder

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Abstract

Porto-sinusoidal vascular disorder (PSVD) is a rare liver disease. The pathophysiological mechanisms underlying the development of PSVD are unknown. Isolated cases of PSVD associated with gene mutations have been reported, but no overview is available. Therefore, we performed an extensive literature search to provide a comprehensive overview of gene mutations associated with PSVD. We identified 34 genes and 1 chromosomal abnormality associated with PSVD in the literature, and we describe here 1 additional gene mutation (*TBL1XR1* mutation, leading to Pierpont syndrome). These gene mutations are associated either with extrahepatic organ involvement as part of syndromes (Adams-Oliver, telomere biology disorders, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations, immune deficiencies, cystic fibrosis, cystinosis, Williams-Beuren, Turner, Pierpont) or with isolated PSVD (*KCNN3*, *DGUOK*, *FOPV*, *GIMAP5*, *FCHSD1*, *TRMT5*, *HRG* gene mutations). Most of the cases were revealed by signs or complications of portal hypertension. When analyzing the cell types in which these genes are expressed, we found that these genes are predominantly expressed in immune cells, suggesting that these cells may play a more important role in the development of PSVD than previously thought. In addition, pathway analyses suggested that there may be 2 types of PSVD associated with gene mutations: those resulting directly from morphogenetic abnormalities and those secondary to immune changes.

Abbreviations: AOS, Adams-Oliver syndrome; CST, CTC1-STN1-TEN1 complex; CVID, common variable immunodeficiencies; GO, Gene Ontology; PSVD, porto-sinusoidal vascular disorder; RAC1, ras-related C3 botulinum toxin substrate 1; RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; TERT, telomerase reverse transcriptase.

Nadia Ciriaci and Lise Bertin share the first authorship.

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KEY POINTS

- An underlying monogenic mutation associated with porto-sinusoidal vascular disorder (PSVD) should be screened in patients diagnosed with PSVD and syndromic diseases, patients diagnosed at a young age, or in case of a family history of PSVD.
- A next-generation sequencing panel can be used, including all genes described in our review.
- Immune cells could play a prominent role in PSVD development, needing further investigation.

INTRODUCTION

Porto-sinusoidal vascular disorder (PSVD) is a rare liver disorder with a prevalence of 2.5 cases per 100.000 inhabitants, characterized by the involvement of intrahepatic vessels at the level of portal venules and/or sinusoids in the absence of cirrhosis. The term PSVD has recently been introduced and regroup several hepatic vascular diseases with portal venules or sinusoids lesions described in the literature (hepatoportal sclerosis, noncirrhotic portal fibrosis, nodular regenerative hyperplasia, or incomplete septal fibrosis/cirrhosis).[1]

PSVD affects young adults (median age 45 y) with a slight male predominance (2/1). PSVD progression can lead to the development of (1) PVT (around 15% at 2 y), which can be complicated with intestinal necrosis or portal cavernoma and its complications; (2) portal hypertension complications (variceal bleeding, ascites, and HE) at a rate of 10%–20% of cases at 2 years. There is currently no treatment able to modify the natural history of PSVD and reduce the incidence of its complications. Therefore, complications are managed using symptomatic treatments and when refractory, they require interventional procedures, such as porto-systemic shunting (4% at 5 y) or liver transplant (5% at 5 y), associated with significant morbidity and mortality. Progress in the management of patients with PSVD is currently hampered by a limited understanding of the pathogenesis of PSVD that impairs the development of mechanistic-based treatments.

Pathophysiological mechanisms underlying PSVD development are unknown. PSVD is often associated with various systemic diseases, including autoimmune (systemic lupus erythematosus and rheumatoid polyarthritis) or blood disorders and infections (HIV), but PSVD can also be associated with genetic diseases. Monogenic mutations associated with PSVD might offer a simplified model to get insight into the pathophysiology of PSVD. Accordingly, this review provides a comprehensive overview of all genetic mutations associated with PSVD, the hepatic and extrahepatic features associated with each mutation, and the cell types and pathways in which these genes are involved.

REVIEW CRITERIA

The following steps were taken to provide a comprehensive overview of genetic mutations associated with PSVD. We initiated our research on DisGeNet database (https://www.disgenet.org), a database of gene-disease associations by reviewing all references published using the following keywords: porto-sinusoidal vascular disease, PSVD, obliterative portal venopathy, incomplete septal fibrosis, incomplete septal cirrhosis, noncirrhotic portal hypertension, idiopathic portal hypertension, intrahepatic noncirrhotic portal hypertension, hepatosclerosis and nodular regenerative hyperplasia. We then searched the Pubmed database (http://www.ncbi.nlm.nih.gov/pubmed) to see if the identified genes had been published as associated with liver involvement suggestive of PSVD. We only included in this review cases with a PSVD diagnosis based on a suitable liver biopsy or a liver explant showing the absence of cirrhosis, along with either specific signs of portal hypertension (ie, esophageal varices, digestive hemorrhage due to portal hypertension and portosystemic collaterals) or histological lesions specific for PSVD (obliterative portal venopathy, nodular regenerative hyperplasia and/or incomplete septal fibrosis)[2,3] (Supplemental Figure S1, http://links.lww.com/HEP/I524). The only exception was families with multiple cases, where family members were considered to have PSVD if they displayed clinical manifestations of PSVD and carried the identified mutation, even in the absence of a liver biopsy, providing the proband had a liver biopsy showing histological lesions of PSVD. We excluded cases with conditions—other than genetic mutations—known to be associated with PSVD (eg, autoimmune diseases, drugs, and HIV) (Table 1).

GENE MUTATIONS ASSOCIATED WITH PSVD AND OTHER ORGAN INVOLVEMENT

Adams-Oliver syndrome

Adams-Oliver syndrome (AOS) is a rare inherited syndrome diagnosed at birth, with 6 recently identified specific genetic mutations, including 4 implicated in the Notch signaling pathways (*RBPJ*, *EOGT*, *NOTCH1*, and *DLL4*) and 2 in the CDC42/RAC1 (ras-related C3 botulinum toxin substrate 1) pathways (*DOCK6* and *ARHGAP31*). These various mutations, whether autosomal dominant or recessive, lead to the same phenotypic manifestations. AOS is characterized by a polymalformative syndrome marked by aplasia cutis congenita, cutis marmorata telangectasia congenita, multiple transverse terminal limb reduction defects, microcephaly, microphtalmia, cleft lip or palate, and rare cardiac or vascular anomalies (Table 2).

We identified 5 case reports of patients with AOS exhibiting liver manifestations of PSVD[4–7] (Table 3).

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TABLE 1 Genetic mutations associated with PSVD

Reference	Genes	Syndrome	Chromosome	Mutation	Transmission
(4–7)	*ARHGAP31*	Adams Oliver	3	N/A	Autosomal dominant or recessive
	DOCK6		19		
	RAC1		7		
	RBPJ		4		
	NOTCH1		9		
	EOGT		3		
	DLL4		15		
(8–11)	*TERT*	Telomere biology disorders	5	K570 - S368F - Gly135Glu - Val170Met - His983Tyr - Lys1050Asn	Autosomal dominant
(10)	*TERC*		3	N/A	
(12)	*NPH2*		5	c.110C>G - c.265G>A	
(13)	*PARN*		16	N/A	
(9,10,14)	*DKC1*		X	IVS1 + 592 C>G	X-linked recessive
(10,13)	*TINF2*		14	N/A	Autosomal dominant
(9,10)	*RTEL1*		20	Arg1010	
(13,15,16)	*CTC1*		17	c.833G>T - c.841T>C	Autosomal recessive
(17,18)	*STN1*		10	c.404G>C - c.469G>T	Autosomal recessive
(19,20)	*TREX1*	RVCL-S	3	V235Gfs*6	Autosomal dominant
(21,22)	*CYBB*	Chronic granulomatous disease	X	N/A	X-linked recessive
	CYBA		16	N/A	Autosomal recessive
	NCF1		7	N/A	Autosomal recessive
	NCF2		1	N/A	Autosomal recessive
(23)	*TACI*	CVID	17	N/A	N/A
(24)	*BTK*	Bruton agammaglobulinemia	X	N/A	X-linked recessive
(25)	*PIK3CD*	APDS	1	N/A	Autosomal recessive
(36–29)	*CFTR*	Cystic fibrosis	7	N/A	Autosomal recessive
(30–34)	*CTNS*	Cystinosis	17	N/A	Autosomal recessive
(35)	*ELN*	Williams Beuren	7	Deletion 7q11.23	Spontaneous
(36–38)	-	Turner	X	Completely or partially missing X	Spontaneous
SDC	*TBL1XR1*	Pierpont	3	Deletion	N/A
(39)	*KCNN3*	-	1	c.1348G>C	Autosomal dominant
(40,41)	*DGUOK*	-	2	c.137A > G - c.831_832del	Autosomal recessive
(42)	*FOPV*	-	4	c.1783G>A - c.4895C>T	Autosomal dominant
(43)	*GIMAP5*	-	7	pI47T - p.P109L - p.L204P - p.L223F	Autosomal recessive
(44)	*FCHSD1*	-	5	c.547C>T	Autosomal dominant
(45)	*TRMT5*	-	14	c.617T>C - c.899A>T	Autosomal recessive
(46)	*HRG*	-	3	c.545G > C,p.R182T	Autosomal dominant

Note: Colors indicate Adams Oliver syndrome (red), telomere biological disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet) and gene mutations associated with isolated PSVD (black).
Abbreviations: APDS, activated PI3K delta syndrome; CVID, common variable immunodeficiency; NA, nonapplicable; PSVD, portosinusoidal vascular disorder; RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SDC, Supplemental Digital Content, http://links.lww.com/HEP/I524.

These manifestations appeared early in childhood, with a median age at diagnosis of 2 years. All the patients had signs of portal hypertension and esophageal varices, with common gastrointestinal bleeding (n = 3/5, 60%). None of them had HE or jaundice. After a median follow-up of 25 months, 2 patients developed PVT, and 1 died because of recurrent gastrointestinal bleeding.

Telomere biology disorders

Telomere biology disorders encompass multiple mutations involving various telomere maintenance genes. The identified mutations affect (Figure 1) (1) the telomerase complex including telomerase reverse transcriptase (*TERT*), *TERC*, *NHP2*, *DKC1*, *PARN*, *NOP10*, *GAR1*, and *TCAB1*; (2) the shelterin complex, consisting of *TINF2*, *RAP1*, *TPP1*, *POT1* and *TRF1*, and *TRF2*; (3) *RTEL1*; or (4) the CST complex, involving *CTC1*, *STN1*, and *TEN1*.

Out of the 46 patients described as having PSVD and telomere biology disorders, the gene involved has been mentioned in 40 patients, including 25 patients with telomerase complex mutations (18 *TERT*,[8–11] 2 TERC,[10] 1 *NPH2*,[12] 1 *PARN*,[13] 5 *DKC1*[9,14]), 5 patients with shelterin mutations (5 *TINF2*[10,13]), 2 patient with

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TABLE 2 Extrahepatic manifestations of patients with genetic predisposition to PSVD

Papers	Genes	Syndrome	Extrahepatic manifestations						
			Malformative	Cutaneous	Pulmonary	Cardiac	Hematological	Neurological	Others
(4–7)	ARHGAP31 DOCK6 RAC1 RBPJ NOTCH1 EOGT DLL4	Adams Oliver	Limb defects, syndactyly, skull defects, malar hypoplasia, growth retardation	Aplasia cutis, cutis marmorata, nail aplasia	-	Fallot tetralogy, valvular dysplasia, atrial septal defect	-	Encephalocele	-
(8–11)	TERT	Telomere biology disorders	-	Graying hair	Pulmonary fibrosis	Visceral arterio-venous malfor-mations	Aplastic anemia, myelodysplasia	-	Retinal detachment
(10)	TERC								
(12)	NPH2		-	Skin telangecta-sia, hyperpigmenta-tion, nail dystrophy, oral leukoplakia	Pulmonary fibrosis	-	Aplastic anemia, immunodeficiency	-	Binocular cataract, oesophageal strictures, knee synovitis
(13)	PARN								
(9,10,14)	DKC1								
(10,13)	TINF2								
(9,10)	RTEL1								
(13,15,16)	CTC1		Skeletal changes, growth retardation	Abnormal skin pigmentation, graying hair, oral leukoplakia	-	-	Bone marrow failure, myelodysplasia	Leukoencephalo-pathy, calcifications and cysts, dilated brain lateral ventricules	Retinopathy, glaucoma
(17,18)	STN1								
(19,20)	TREX1	RVCL-S	-	-	-	Cardiomegaly	-	Cognitive neurodegeneration, vessel ischemic stokes	Vascular retinopathy, atherosclerosis, nephrosclerosis
(26,27)	CYBB CYBA NCF1 NCF2	CGD	-	Cutaneous abscesses	Lung abscesses, pulmonary infections	-	-	-	Staphylococcus infections
(23)	TACI	CVID	-	-	Bacterial and viral respiratory tract infections	-			Enteropathy, lympho-adenopathy
(24)	BTK	Bruton agammaglo-bulinemia	-	-	Pulmonary infection	-	-	Meningoencephalitis	Arthritis, Crohn-like colitis, eosinophilic esophagitis, lympho-proliferative diseases
(25)	PIK3CD	APDS	-	-	Bacterial and viral respiratory tract infections	-			Autoimmune enteropathy
(26–29)	CFTR	Cystic fibrosis	-	-	Cystic fibrosis, pulmonary infections	-	-	-	Pancreatic insufficiency, enteropathy, infertility
(30–34)	CTNS	Cystinosis	Growth retardation	-	-	-	-	Cerebral atrophy	Chronic tubular nephropathy, photophobia, hypothyroidism, diabetes mellitus
(35)	ELN	Williams Beuren	Growth retardation, distinctive facial features	-	-	Valvular stenosis	-	Mental retardation	Cryptorchidia
(36–38)	-	Turner	Short stature, infantilism, short metacarpals, arch palate, webbeb neck	Hypoplastic nails	-	Aortic malformations	-	-	Renal malformations
SDC	TBL1RX1	Pierpont	Growth retardation	-	-	-	-	Mental retardation, autistic spectrum	Waldmann syndrome

Note: Colors indicate Adams Oliver syndrome (red), telomere biological disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet) and gene mutations associated with isolated PSVD (black).
Abbreviations: APDS, activated PI3K delta syndrome; CGD, chronic granulomatous disease; CFTR, cystic fibrosis transmembrane regulator; CVID, common variable immunodeficiency; PSVD, portosinusoidal vascular disorder; RVCL-S: retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SDC, Supplemental Digital Content, http://links.lww.com/HEP/I524.

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RTEL1 mutation,[9,10] 6 patients with *CST* mutations, (3 *CTC1*[13,15,16] and 3 *STN1*[17,18]) (Table 3).

Despite the broad clinical spectrum of telomere biology disorders, an analysis of reported cases revealed 2 distinct clinical patterns based on the affected telomere complex.

Telomerase or shelterin mutations

Deficiencies in telomerase or shelterin complex affect multiple organs (Table 2), the most common being (1) the lungs, with the development of lung fibrosis characterized by a radiological pattern of usual interstitial pneumonia and leading to respiratory insufficiency, (2) the bone marrow, with bone marrow failure, myelodysplasia or aplastic anemia resulting in severe infections and hemorrhages due to neutropenia and thrombocytopenia, respectively, and (3) the skin and hair, with dyskeratosis congenita, abnormal skin pigmentation, nails dystrophy, premature graying of hair. The involvement of these organs might be accounted for by the high proliferative index of epithelial and bone marrow cells, making these cells more susceptible to telomere repair complexes deficiency.

PSVD is the most common liver lesion in this setting, as observed in 48% of liver diseases associated with telomerase or shelterin mutations in the recent work by Sidali et al.[10]

Among the 34 cases with an identified mutation in the literature,[8–14] the median age at diagnosis of PSVD was 25 years (1–50) (Table 3, Figure 2A). No genetic anticipation of PSVD was found in the only reported family with familial aggregation of *TERT* mutations.[8,47] Patients with PSVD and telomere biology disorders commonly had hepatopulmonary syndrome (n = 15/34, 44%), a condition rarely reported with other genetic mutations. Patients with PSVD and telomerase or shelterin mutations were also characterized by a significant prevalence of ascites (n = 4/34, 12%) and a high mortality rate (n = 10/34, 29%), both from hepatic and extrahepatic causes. Liver blood tests were frequently abnormal (n = 28/34, 82%) (Table 3).

CST mutations

Coats-plus syndrome associated with *CST* mutations is characterized by a spectrum of features, including (1) brain abnormalities such as brain calcifications, dilated ventricles, cystic lesions, (2) specific retinopathy, (3) growth retardation and limb defects, (4) graying hair, (5) pancytopenia, and (6) gastrointestinal bleeding (Table 2).

PSVD is the most common liver disease in patients with *CST* mutations. Out of the 6 patients reported in the literature,[13,15–18] the median age at PSVD diagnosis was 14 years (6–25). All patients displayed signs of portal hypertension. A particular feature was the higher frequency of gastrointestinal bleeding (n = 4/6, 67%) than in patients with PSVD associated with other genetic mutations. A splenomegaly was found in only 2 patients (33%), with a much higher frequency of thrombocytopenia (n = 5/6, 83%), probably due to bone marrow failure (Table 3).

In contrast to telomere biology disorders resulting from shelterin or telomerase mutations, as described above, ascites was infrequent in *CST* mutation-associated PSVD. PSVD linked to CST mutation exhibited the highest mortality rate compared to other genetic syndromes, with a 50% (n = 3/6) mortality rate, due to gastrointestinal bleeding.

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is a rare vascular disease caused by *TREX1* mutations, encoding for an exonuclease, resulting in the mislocalization of this latter. Clinically, RVCL-S is characterized by progressive microvasculopathy, leading to ischemic strokes, vascular cognitive impairment, and vision loss (Table 2). Diagnosis occurs around the age of 43. Vascular hepatic involvement and PSVD have been described in 2 series. A study by Stam et al[19] described elevated liver enzymes in 31 out of 40 patients (78%) carrying the mutation, with 10 patients exhibiting liver histopathological abnormalities, the most common being nodular regenerative hyperplasia. A more recent study by Khonde et al[20] reported nodular regenerative hyperplasia at autopsy in 11 patients with RVCL-S. Diagnosis of PSVD was postmortem in all cases, with only 1 patient having a splenomegaly identified when alive. The average age of death was 47 years, primarily due to extrahepatic causes and particularly neurological impairment. Limited knowledge exists regarding the underlying mechanisms leading to liver vascular abnormalities in patients with *TREX1* mislocalization.

Other *TREX1* mutations leading to complete suppression of TREX1 exonuclease activity lead to death early in life without liver involvement or before liver involvement appears. These mutations induce immune changes, particularly in preventing interferon-mediated immune responses, resulting in 3 autoimmune diseases: Aicardi-Goutières syndrome, systemic lupus erythematosus, and autosomal dominant familial chilblain lupus. Although patients with RVCL-S do not exhibit apparent features of autoimmune disorders or vasculitis akin to Aicardi-Goutières

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syndrome, systemic lupus erythematosus, and familial Chilblain lupus, it is conceivable that autoimmunity plays a role in the development of PVSD in RVCL-S. This hypothesis gains further support given the frequent association observed between PSVD and autoimmune disorders.

Immune deficiencies

The association between immunodeficiency and PSVD has been frequently reported, primarily through hypogammaglobulinemia are part of Common Variable Immunodeficiencies (CVIDs) or various hematological disorders.[48–50] We therefore included primary monogenic immune deficiencies in our investigation, even if we cannot rule out that recurrent digestive infections induced by these immunodeficiencies cause PSVD in these patients.[51]

Innate immunity: chronic granulomatous disease

Chronic granulomatous disease is a rare primitive innate immune disorder resulting from mutations in genes encoding NADPH localized on X chromosome (*CYBB*, *NCF1*, *NCF2*, and *CYBA*), a crucial enzyme for bacterial or fungal destruction following phagocytosis by neutrophilic polymorphonuclear cells. The chronic granulomatous disease leads to an increased risk of bacterial infections, particularly abscesses or lymphangitis caused by *Staphylococcus aureus*, as well as fungal infections (ie, *Aspergillus spp*).

Eight patients with PSVD associated with chronic granulomatous disease[21,22] have been described (Table 3). The median age at diagnosis was 19 (Figure 2A). A history of liver infections was associated with a higher rate of PSVD development and progression.[22]

Acquired immunity: CVID/Bruton agammaglobulinemia/activated PI3K delta syndrome

CVID stands out as one of the most prevalent primary immunodeficiencies, characterized by hypo or agammaglobulinemia, with a predominant deficiency in IgG, IgA, or IgM. Although frequently idiopathic and likely polygenic, certain mutations have been identified as potential causes of CVID, notably *TAKI*, *TNFRSF13B*, *TNFRSF13C*, *ICOS*, *CD19*, *CD20*, *MSH5*, and *CD81*. Bruton agammaglobulinemia, distinguished by a complete absence of gamma globulins, results from a mutation of *BTK* gene on the X chromosome. Activated PI3K delta syndrome, arising from mutations in the *PIK3CD* or *PI3KR1* gene, is characterized by a variable degree of hypogammaglobulinemia affecting IgG and IgA, coupled with elevated levels of IgM. Additionally, individuals with activated PI3K delta syndrome exhibit decreased circulating B cells and an altered ratio of CD4/CD8 T cells, marked by an increase in memory and senescent CD8 T cells.

Often manifesting in childhood (Figure 2B), clinical manifestations of primitive hypo or agammaglobulinemia are predominantly marked by infectious syndrome with a heightened susceptibility to bacterial infections, especially of the ear, nose, throat apparatus and the lung. Additionally, manifestations may include lymphoproliferative syndromes, autoimmune disorders, or granulomatous diseases (Table 2).

One case of PSVD associated with monogenic CVID due to a *TACI* mutation was identified.[23] This patient had a hepatic artery aneurysm that ruptured, leading to patient death. Six cases of PSVD associated with Bruton agammaglobulinemia were reported by Nunes-Santos et al,[24] with a median age at diagnosis of 20 years (Table 3). As compared with PSVD associated with other genetic syndromes, splenomegaly was more common, possibly linked to a lymphoproliferative disease on top of portal hypertension. Four cases of PSVD associated with *PI3KCD* mutation were described by Ben Yakov et al,[25] with a median age at diagnosis of 17 years. All patients had elevated liver enzymes and thrombocytopenia. No complication occurred during follow-up (Table 3).

Cystic fibrosis

Mutation in transmembrane protein known as cystic fibrosis transmembrane regulator, a regulator of chloride transport across cell membranes, adversely affects the exocrine function of several organs. Prominent manifestations include lung involvement, such as infectious pneumonia, bronchiectasis, or respiratory insufficiency, as well as pancreatic insufficiency, among others (Table 2). The spectrum of cystic fibrosis-related liver diseases is broad, including small bile duct obstruction, fibrosis, or cirrhosis. Some studies[26–29] also reported vascular liver disease on biopsy or explants. A recent study described a prevalence of liver involvement, based on liver stiffness measurement, of 27% in patients with cystic fibrosis; 81% of them had a suspicion of PSVD.[52] Among the 3 main studies of PSVD in cystic fibrosis, the median age at diagnosis was 18 years (Figure 2A). Esophageal varices were observed in 27/34 patients (79%) and ascites in 4/34 (12%) patients (Table 3). Abnormal liver blood tests were observed in 8/34 (24%) patients. Liver-related mortality in patients with cystic fibrosis was 2/34 (6%).

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TABLE 3 Hepatic clinical and laboratory features of patients with genetic predisposition to PSVD

Papers	Genes (n= cases number)	Syndrome	Median (range) age at diagnosis (years)	Clinical hepatic manifestations					Laboratory features			Death related to liver disease (%)
				Splenomegaly (%)	Esophageal varices (%)	Ascites (%)	HE (%)	PVT (%)	Elevated liver enzymes (%)	Hyperbilirubinemia (%)	Thrombocytopenia (%)	
(4–7)	ARHGAP31 DOCK6 RAC1 RBPJ NOTCH1 EOGT DLL4	Adams Oliver	2 [1-6]	4/5 (80%)	5/5 (100%)	0	0	2/5 (40%)	2/5 (40%)	No	3/5 (60%)	1/5 (20%)
(8–11)	TERT (n=18)	Telomere biology disorders	25 [1-50]	8/34 (24%)	9/34 (26%)	4/34 (12%)	2/34 (6%)	2/34 (6%)	28/34 (82%)	5/34 (16%)	21/34 (62%)	10/34 (29%)
(10)	TERC (n=2)											
(12)	NPH2 (n=1)											
(13)	PARN (n=1)											
(9,10,14)	DKC1 (n=5)											
(10,13)	TINF2 (n=5)											
(9,10)	RTEL1 (n=2)											
(13,15,16)	CTC1 (n=3)		14 [6-25]	2/6 (33%)	4/6 (67%)	0	0	0	2/6 (33%)	1/6 (17%)	5/6 (83%)	3/6 (50%)
(17,18)	STN1 (n=3)											
(19,20)	TREX1 (n=41)	RVCL-S	47	1/11 (9%)	1/11 (9%)	0	0	0	7/11 (64%)	N/A	1/11 (9%)	0
(21,22)	CYBB CYBA NCF1 NCF2	CGD	19	51 %	N/A	8 %	0	0	Yes	0	Yes	0
(23)	TACI (n=1)	CVID	22	Yes	N/A	No	No	0	No	N/A	Yes	Yes
(24)	BTK (n=6)	Bruton agamma-globulinemia	20 [17-31]	6/6 (100%)	3/6 (50%)	0	0	0	Yes	Yes	Yes	0
(25)	PIK3CD (n=4)	APDS	17	No	N/A	1/4 (25%)	No	0	4/4 (100 %)	N/A	4/4 (100%)	0
(26–29)	CFTR (n=34)	Cystic fibrosis	18 [15-26]	26/34 (76%)	27/34 (79%)	4/34 (12%)	N/A	1/34 (3%)	8/34 (24%)	0	23/34 (68%)	2/34 (6%)
(30–34)	CTNS (n=24)	Cystinosis	19 [8-30]	11/24 (46%)	7/24 (29%)	5/24 (21%)	2 (8%)	1/24 (4%)	1/24 (4%)	2/24 (8%)	10/24 (42%)	2/24 (8%)
(35)	ELN (n=1)	Williams Beuren	16	Yes	N/A	No	No	No	Yes	Yes	Yes	0
(36–38)	- (n=12)	Turner	32 [17-46]	6/12 (50%)	5/12 (42%)	3/12 (25%)	No	No	12/12 (100%)	2/12 (17%)	2/12 (17%)	1/12 (8%)
SDC	TBL1XR1 (n=1)	Pierpont	23	Yes	Yes	No	No	0	No	No	Yes	0
(39)	KCNN3 (n=4)	-	7 [1-37]	2/4 (50%)	N/A	1/4 (25%)	No	1/4 (25%)	1/5 (20 %)	N/A	N/A	0
(40,41)	DGUOK (n=4)	-	9 [0,5-12]	4/4 (100%)	3/4 (75%)	No	No	0	1/4 (25 %)	No	2/4 (50%)	0
(42)	FOPV (n=6)	-	1 [1-35]	2/6 (33%)	1/6 (17%)	No	No	0	6/6 (100%)	1/6 (17%)	3/6 (50%)	0
(43)	GIMAP5 (n=9)	-	14 [2-35]	9/9 (100%)	7/9 (78%)	2/9 (22 %)	1/9 (11 %)	0	5/9 (56%)	2/9 (22%)	8/9 (89%)	2/9 (22%)
(44)	FCHSD1 (n=5)	-	25 [13-45]	1/5 (20%)	2/5 (40%)	No	No	0	No	No	N/A	1/5 (20%)
(45)	TRMT5 (n=2)	-	4 [4-5]	2/2 (100%)	1/2 (50%)	N/A	N/A	0	No	1/2 (50%)	2/2 (100%)	0
(46)	HRG (n=1)	-	22	Yes	No	No	No	Yes	No	No	Yes	0

Note: Colors indicate Adams Oliver syndrome (red), telomere biological disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet) and gene mutations associated with isolated PSVD (black).
Abbreviations: APDS, activated PI3K delta syndrome; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; NA, not applicable; PSVD, portosinusoidal vascular disorder; RVCL-S, Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SDC, Supplemental Digital Content, http://links.lww.com/HEP/I524.

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Metabolic disease: cystinosis

Cystinosis is a rare autosomal recessive metabolic disorder, typically diagnosed in infancy (Figure 2B), caused by mutations in *CTNS* gene, resulting in intralysosomal accumulation of cystine in all the cells. Kidneys are particularly vulnerable, exhibiting early tubulointerstitial involvement that presents as Fanconi syndrome and often progresses to end-stage renal failure during childhood. Eyes are also significantly affected, with photophobia as a primary symptom followed by decreased visual acuity, leading to blindness in some cases (Table 2).

Of the 24 cases reported,[30–34] the median age at diagnosis was 19 (8–30) (Figure 2A). Portal hypertension was present in all patients, often accompanied by esophageal varices. Ascites was described in 21% of the patients (n = 5/24), which is higher than for other genetic mutations associated with PSVD. The development of PSVD in patients with cystinosis appears to be a marker of poor prognosis, with liver-related mortality identified in 17% (4/24 cases) (Table 3).

While the possibility of drug-induced PSVD could considered in these patients, as 23/24 received immunosuppression therapy following renal transplantation in childhood, only 2 patients received azathioprine, a drug described as associated with PSVD development; other received tacrolimus or ciclosporin. Regarding the specific treatment of cystinosis called Cysteamine, although it was suggested in 1 article as a possible cause of PSVD due to improvement on discontinuation, it was most often either not used or taken by patients with poor compliance. Finally, the identification of specific histopathological lesions reported by Avner et al,[30] namely occlusive venopathy caused by cysteine-loaden Ito and KCs, supports the idea of direct effect of the storage disease on liver lesions.

Elastine mutation (Williams-Beuren syndrome)

Williams-Beuren syndrome is a rare congenital polymalformative syndrome attributed to elastine haploinsufficiency, typically associated with mental and growth retardation, facial abnormalities, and vascular stenoses (such as supra-aortic stenosis or pulmonary stenosis) (Table 2). We identified one case of Williams-Beuren syndrome displaying lesions suggestive of PSVD.[35] The patient was diagnosed with PSVD at 16 (Figure 2A). He had portosystemic collaterals at imaging and splenomegaly without ascites or HE. Liver biopsy was normal. The patient died from septic shock with *Streptococcus agalactiae* bacteriemia at the age of 29.

Turner syndrome

Turner syndrome is a genetic disorder resulting from X chromosome monosomy, primarily affecting women (with a median age of diagnosis around 14, Figure 2B) and giving rise to a distinctive phenotype characterized by specific facial features, impaired growth, and hormonal development. Turner syndrome is also associated with a diverse array of health conditions, including obesity, diabetes, hypertension, kidney issues, and cardiac defects.

Abnormalities in liver blood tests are common in patients with Turner syndrome, found in 20 to 80% of the cases.[53] The cause of liver blood test abnormalities include metabolic dysfunction-associated steatotic liver disease, linked to the prevalent metabolic syndrome in this patient population, but also PSVD in one-third of the patients.[36] Of the 12 patients with Turner syndrome and PSVD reported in the literature,[36,37,53] median age at diagnosis was 32 years (Figure 2A). Clinical signs of portal hypertension were observed in 50% of them, including splenomegaly (50%), esophageal varices (5/12), or ascites (3/12) (Table 3). One patient died, and 2 required liver transplantation during follow-up.

Pierpont syndrome (TBL1XR1)

The *TBL1XR1* gene mutation is an uncommon genetic anomaly, contributing to a clinical spectrum that spans from Pierpont syndrome, characterized by distinctive facial anomalies and psychomotor developmental delay, to variations within the autistic spectrum (Table 2). We report here (Supplemental Text, Table 1, figure S2 and figure S3 http://links.lww.com/HEP/I524) a patient with PSVD associated with a *TBL1XR1* mutation. The patient had autism spectrum disorder and Waldmann syndrome and was diagnosed as having PSVD at the age of 23, when he bled from esophageal varices. Subsequently, he developed PVT. He was then treated with anticoagulation and received prophylaxis for variceal bleeding recurrence. No additional clinical event occurred after 7 years of follow-up.

GENE MUTATIONS ASSOCIATED WITH ISOLATED PSVD

Genetic mutations associated with PSVD have also been identified in recent years in patients devoid of extrahepatic manifestations using whole-genome sequencing, namely *KCNN3* mutation by Koot et al,[39] *DGUOK* mutation by Vilarinho et al[40] and Li et al,[41] "*Familial Obliterative Portal Venopathy*" (*FOPV*) mutation by Besmond et al,[42] *GIMAP5* mutation by Drzewiecki et al,[43] *FCHSD1* mutation by Shan et al,[44] *TRMT5* mutation by Warasnhe et al,[45] and

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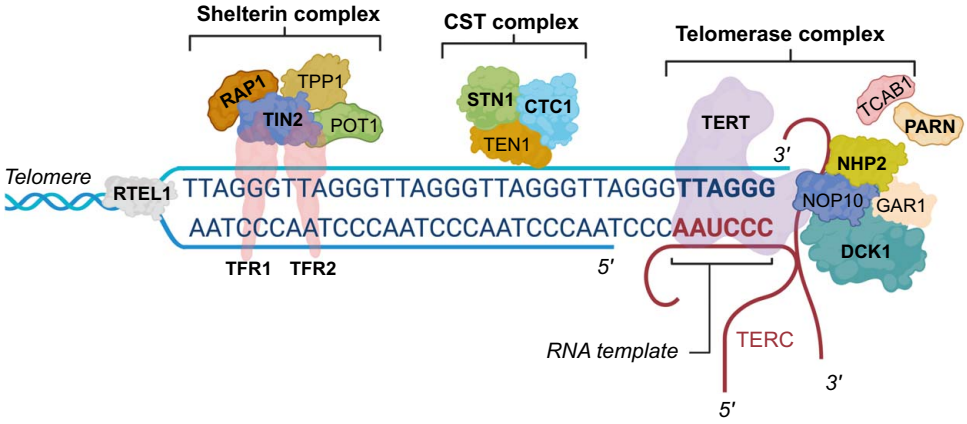

FIGURE 1 Schematic representation of shelterin, CST, and telomerase complexes. Telomeres are tandemly repeated DNA (TTAGGG) structures at the ends of chromosomes that are maintained at each cell division by a telomerase complex and RTEL1 (helicase required in telomere elongation). Telomerase complex includes a TERT catalytic component, an RNA component (TERC), and several accessory proteins (DKC1, NHP2, NOP10, GAR1, PARN, and TCAB1). Telomeres are protected by a shelterin complex consisting of 6 proteins: TRF1, TRF2, TIN2, TPP1, POT1, and RAP1. CST is a trimeric complex composed of CTC1, STN1, and TEN1, which protects telomeres from DNA degradation. Mutations in any of the proteins lead to a broad spectrum of telomere biology disorders. Mutations described in this review are indicated in bold. Abbreviations: CST, CTC1, STN1, TEN1 complex; TERT, telomerase reverse transcriptase.

HRG mutation by Tang et al.[46] The majority of these mutations were reported in only 1 family (ie, *KCNN3*, *TRMT5*, *FCSHD1*, and *HGR*), while *FOPV*, *DGUOK*, and *GIMAP5* mutations were identified in 2, 3, and 4 unrelated families, respectively. Apart from these original cases, the literature search did not reveal any extrahepatic anomaly associated with these specific mutations, yet other mutations in the abovementioned genes (*DGUOK*, *TRMT5*, and *KCNN3*) can be associated with extrahepatic involvement.[54–65]

We can notice that all mutations, but one (*DGUOK*), are missense mutations, resulting in the substitution of 1 amino acid for another (Table 1). These missense mutations have the potential to impair protein expression or to alter protein structure and function. In the latter case, assessing the functional consequences of the mutation might be challenging.

Age at diagnosis of PSVD varies according to the gene mutation (Figure 2A). In patients with *KCNN3*, *DGUOK*, *TRMT5*, and *FOPV* mutations, early clinical manifestations led to a diagnosis in childhood (median ages 7, 9, 4, and 1 y, respectively), although the mutations should also be considered in young adults with PSVD (Table 1). On the other hand, the clinical expression of *FCSHD1* and *GIMAP5* mutations seems to occur later in adolescence or young adulthood (median age 25 and 14 years, respectively). However, caution is needed in interpreting these data, as physicians may have been more prone to perform whole-genome sequencing in children or young adults than in older patients; therefore, systematic screening for these mutations in adult patients may reveal in the future the adult onset of PSVD associated with these mutations. The possibility of genetic anticipation could be explored only for autosomal dominant mutations with multiple cases reported across more than one generation, namely only for *KCNN3*, *FOPV*, and *FCSHD1* gene mutations. Based on the reported age at first symptoms of liver disease, *FCSHD1* and *FOPV* mutations may be associated with genetic anticipation, whereas *KCNN3* mutation is not. However, caution is needed because of the small number of cases, with a maximum of 2 generations involved, and because PSVD diagnosis might have been overlooked in earlier generations.

Signs of portal hypertension were described systematically in patients with these mutations. Splenomegaly and thrombocytopenia were the most common ones. Esophageal varices were present in about half of the patients with *DGUOK*, *TRMT5*, *FCSHD1*, and *GIMAP5* mutations and more rarely (1/6) in those with *FOPV* mutation. Ascites and hepatic encephalopathy are rare and only reported in few patients with *GIMAP5* or KCNN3 mutation (Table 3).

Liver blood tests were mostly normal in patients with *DGUOK*, *TRMT5*, *FCSHD1*, or *HGR* mutations, while patients with *FOPV* and *GIMAP5* mutations had mildly elevated serum transaminases (around 2 times the upper limit of normal values). Alkaline phosphatase and gamma glutamyl transferase levels have been only rarely described in those patients.

Patient outcomes varied according to the mutation. Only one case of HCC was described; it happened in a patient with *GIMAP5* mutation. While no mortality was reported in patients with *KCNN3*, *DGUOK*, *TRMT5*, and *FOPV* mutations (no data for *HGR*), patients carrying *FCSHD1* and those with *GIMAP5* mutation were at risk of liver-related complications and death (around 20% mortality rate). Yet, data on long-term outcome of patients with these mutations are missing.

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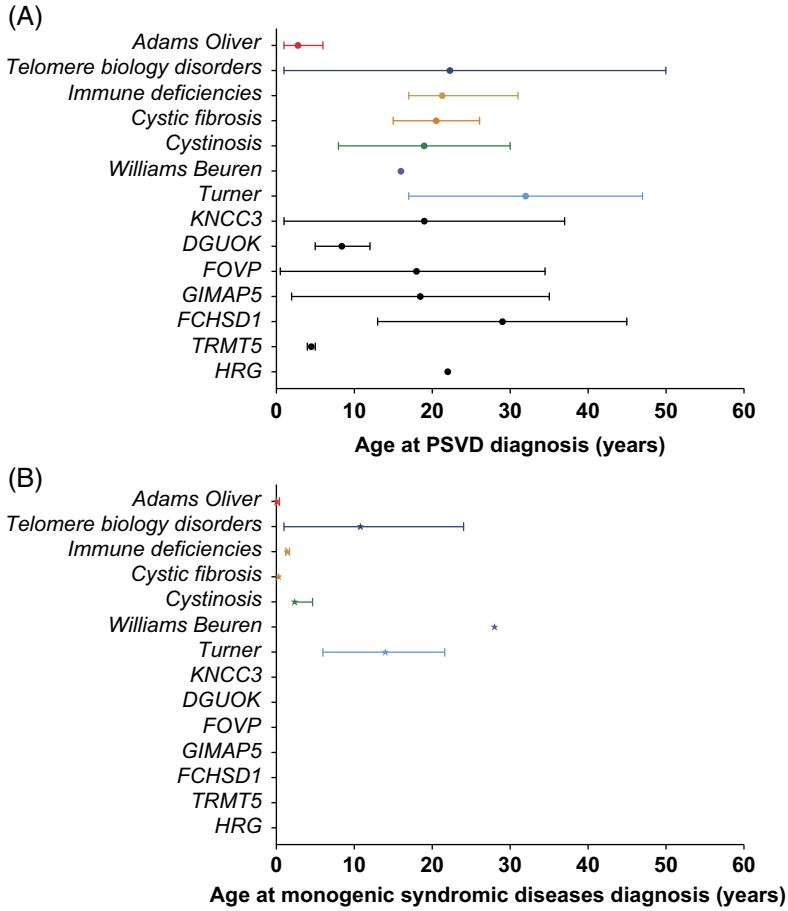

FIGURE 2 (A) Age distribution at PSVD diagnosis in genetic cases studied. Box plots show median age (in years, illustrated by ●) and range (whiskers) of different genetic conditions. (B) Age distribution at monogenic syndromic disease diagnosis. Box plots show median age (in years, illustrated by ★) and range (whiskers) of different genetic conditions. Each genetic condition is color-coded for clarity: Adams Oliver syndrome (red), telomere biology disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet), Turner syndrome (light blue), and gene mutations associated with isolated PSVD (black). Abbreviation: PSVD, porto-sinusoidal vascular disorder.

OTHER GENE MUTATIONS INVESTIGATED BUT NOT CLEARLY ASSOCIATED WITH PSVD

Thrombophilia genetic disorders

Although inherited thrombophilic conditions, including antithrombin, protein C or S deficiency, and factor V or factor II gene mutations, have been described as associated with PSVD,[2] recent data from the Vascular Liver Disease Group network question this concept.[50] Indeed, factor V or factor II mutations were observed in $<2\%$ of 537 patients with PSVD, ie, a prevalence similar to that observed in the general population.[65,66] Antithrombin, protein C, and S deficiencies were slightly more frequent than in the general population (1.5%–2% vs. 0.2%–0.5%).[67–70] Other mutations have been described as slightly more common in a pilot study by Bayan et al,[71] namely *Factor XIII V34L*, *plasminogen Activator Inhibitor-1*, *GPIIIa L33P* (a platelet membrane receptor for fibrinogen and Von Willebrand factor), *MTHFR C677T*, and *MTHFR A1298C* (implicated in hyperhomocyteinemia) mutations. Confirmation is needed.

PIK3CA-related overgrowth spectrum syndrome

PIK3CA-related overgrowth spectrum syndrome comprises a cluster of genetic disorders marked by abnormal growth in different tissues. Vasculature is particularly involved in Klippel-Trenaunay syndrome (congenital malformations of veins and capillaries) and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis, and spinal anomalies syndrome, but no PSVD has been reported in those settings. Klippel-Trenaunay syndrome can yet be associated with portal vein hypoplasia.

PATHOPHYSIOLOGICAL INSIGHT PROVIDED BY PSVD-ASSOCIATED GENE MUTATIONS

As the pathophysiology of PSVD is unknown, we took advantage of the abovementioned PSVD-associated gene mutations to attempt to elucidate the potential mechanisms leading to this disease by the following steps: (1) we

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(A)

	Blood & Immune cells	Liver	Endo-thelial cells	Internal	Secre-tory	Repro-ductive	Ner-vous	Muscle
DOCK6	**100**	14	7	49	50	30	84	30
RAC1	3829	594	172	11968	10573	11158	**16391**	4167
RBPJ	**1318**	68	58	541	553	571	1224	226
NOTCH1	**1418**	70	31	524	266	325	502	172
EOGT	**376**	55	22	208	195	194	286	139
DLL4	**156**	23	11	92	92	57	148	45
TERT	**1554**	251	102	840	848	473	1364	614
NHP2	**13759**	2023	1682	7338	5563	4359	12407	3617
PARN	**132**	16	7	55	62	35	101	32
DKC1	**1726**	102	360	492	502	244	535	243
TINF2	**3652**	139	128	964	821	464	1253	358
RTEL1	**127**	17	8	57	57	34	97	34
CTC1	**257**	14	7	48	49	30	82	29
STN1	**889**	68	24	629	386	210	377	176
TREX1	**614**	33	21	136	116	82	201	76
CYBB	**4110**	18	8	63	61	35	107	40
CYBA	**28539**	538	309	4573	2097	678	881	2835
NCF1	**7439**	12	6	149	42	25	80	89
NCF2	**20981**	21	23	278	74	55	122	44
TACI	376	55	25	190	223	104	**407**	120
PIK3CD	**12106**	15	46	59	58	34	302	50
BTK	**1345**	27	17	93	104	54	167	53
CFTR	126	18	8	81	**1894**	37	108	39
CTNS	**153**	14	7	70	61	79	85	28
ELN	255	89	13	**4156**	1363	187	433	176
KCNN3	**168**	25	11	87	88	104	159	54
DGUOK	**260**	20	21	71	73	61	126	52
GIMAP5	**208**	29	13	93	105	56	167	62
FCHSD1	**144**	21	10	85	84	52	136	41
TRMT5	**38151**	2147	3227	10953	12044	8085	11633	5797
HRG	124	**14884**	8	148	69	34	99	35

Low TPM — High TPM

(B)

	Myeloid cells			Lymphoid cells			
	Myeloid stem cells	Monocy-tes	Dentritic cells	B cells	CD4 T cells	CD8 T cells	NK cells
DOCK6	**8,4**	7,0	7,3	7,0	7,2	6,4	7,9
RAC1	**47,9**	**47,9**	22,0	28,5	21,0	18,5	22,6
RBPJ	**146**	116	79	28	69	52	41
NOTCH1	98	149	41	33	60	66	**163**
EOGT	**32**	25	20	22	23	26	25
DLL4	11,2	**11,4**	11,3	11,2	11,1	11,0	11,1
TERT	**122**	109	98	111	118	101	106
NHP2	802	710	**1599**	1483	825	587	965
PARN	9,1	7,7	14,1	8,8	12,4	7,0	**18,7**
DKC1	69	60	114	146	140	**245**	86
TINF2	373	293	266	508	287	209	**524**
RTEL1	11,2	8,0	**15,6**	8,4	8,4	7,4	9,5
CTC1	8	7	26	20	39	**60**	28
STN1	28	23	100	27	173	**202**	75
TREX1	97	**126**	79	70	25	25	44
CYBB	**1572**	1036	838	165	9	8	33
CYBA	4622	2939	**5703**	2667	956	1089	4163
NCF1	994	**1326**	713	1091	6	5	7
NCF2	**6170**	5238	1387	15	10	9	346
TACI	25,1	23,2	33,8	**52,7**	23,0	18,0	26,0
PIK3CD	1375	852	1460	950	1749	**1761**	1320
BTK	101	405	135	**500**	12	10	22
CFTR	**10,6**	9,5	8,9	8,9	9,1	7,9	9,9
CTNS	8,6	8,7	**54,2**	9,1	7,4	6,6	8,2
ELN	**16,8**	6,9	10,4	11,7	11,0	6,0	13,4
KCNN3	**13,9**	12,1	11,3	11,7	11,7	9,9	12,7
DGUOK	23,0	17,0	22,6	**35,6**	25,3	11,1	27,3
GIMAP5	15,5	12,9	13,2	13,1	**15,8**	14,5	14,3
FCHSD1	10,2	**10,5**	10,4	10,4	10,3	10,3	10,4
TRMT5	**3106**	1688	2495	2829	1828	1750	2283
HRG	**9,8**	8,0	8,3	8,0	8,2	7,1	9,0

Low TPM — High TPM

FIGURE 3 Heatmap showing expression in different cell types and tissues of the identified genes. (A) Gene expression in tissues and cell types, organized into 8 distinct groups: blood and immune cells, liver, endothelial cells, internal, secretory, reproductive, nervous, and muscle, indicated in each row. (B) Gene expression within the immune-specific cluster was analyzed and categorized into myeloid cells (including myeloid stem cells, monocytes, and dendritic cells) and lymphoid cells (comprising B cells, CD4 and CD8 T cells, and NK cells). A color gradient ranging from red (highest value of TPM to gray (lowest value of TPM) is used to depict gene expression levels within groups. The rows represent individual genes, and the numerical values denote their relative expression levels, measured in TPM. TPM in bold indicates the highest expression level. Data were sourced from BioGPS (www.biogps.org), GSEU1133A data set containing information of 79 human tissues. Color code for genetic conditions: Adams-Oliver syndrome (red), telomere biology disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet), and gene mutations associated with isolated PSVD (black). Abbreviations: PSVD, porto-sinusoidal vascular disorder; TPM, transcript per million.

examined the expression of the identified genes in different cell types and human tissues; (2) we analyzed whether the target genes are involved in common cellular pathways or processes; (3) we performed an extensive literature search to identify studies describing the consequences of deletion of these specific genes.

Expression of the identified genes in different cell types and human tissues

To assess the expression of the identified genes across diverse cell types and human tissues, we used the publicly available tissue-specific gene expression microarray provided by the human BioGPS database (http://biogps.org). This database uses the GeneAtlas U133A gcrma data set, which comprehensively examines a panel of 79 human tissues.[72] All the genes identified above were submitted to the BioGPS database, and their tissue-specific and cell-specific expression levels were subsequently downloaded for detailed analysis. The tissues and cell types were organized into 8 distinct groups: blood and immune cells, liver, endothelial cells, internal (ie, adipocyte, colon, kidney, lung, fetal lung, trachea, bronchial epithelial cells, and tongue), secretory (ie, endocrine glands excluding the ovary and testicle, which were categorized under the reproductive group), reproductive, nervous, and muscle (Supplemental Excel, http://links.lww.com/HEP/I525). Following this categorization, the gene expression levels, represented as transcripts per million, were visualized and presented in Figure 3A, with the exception of *ARHGAP13*, *TERC*, and *FOVP* (not found in the data set) and *TBL1XR1*.

Our analysis revealed that 26 out of the 31 examined genes exhibited the highest expression within the cluster of "blood and immune cells." Notably, limited expression was observed in the liver, with the exception of *HRG,* and in the endothelial cell compartment (Figure 3A). This finding was unexpected as PSVD is considered a vascular liver disease.

When focusing specifically on the immune cell clusters, the overall impression was that the identified

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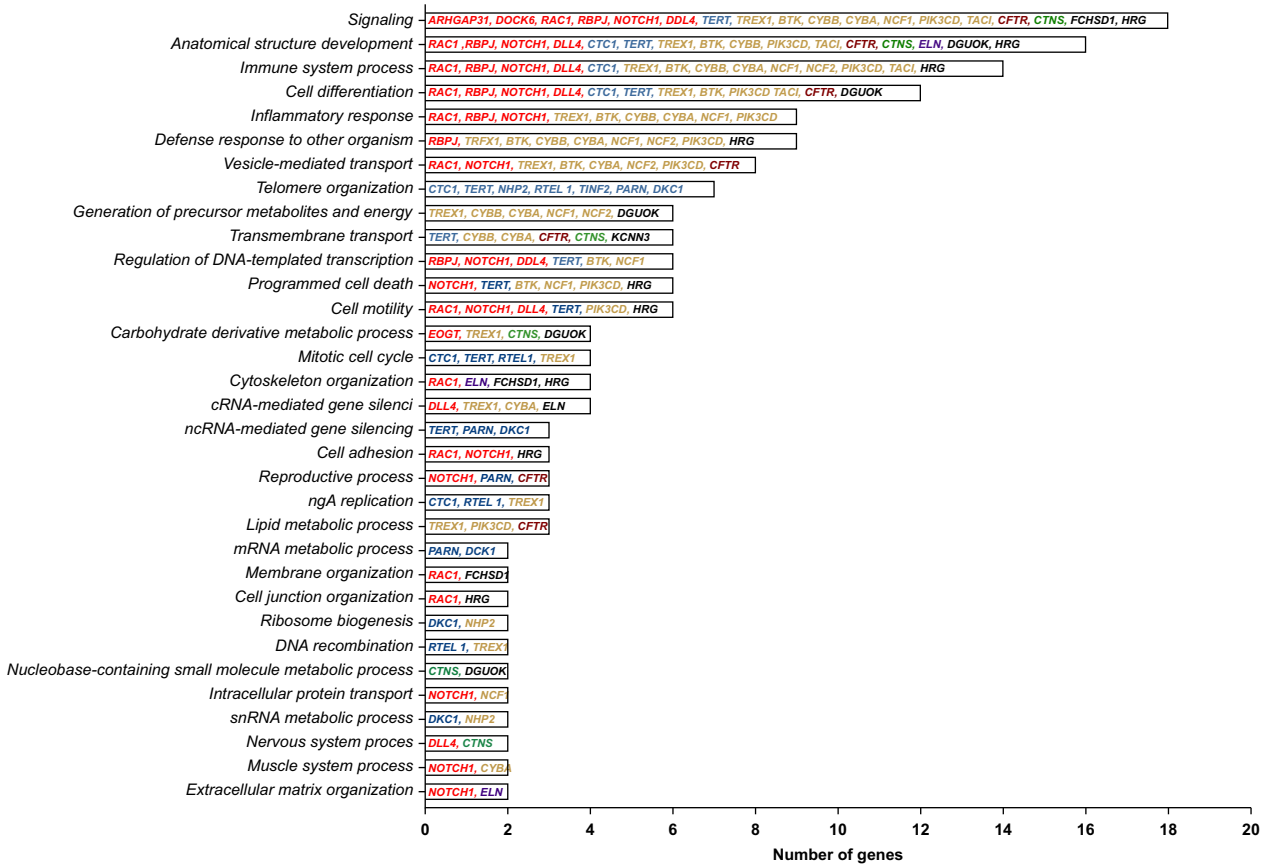

FIGURE 4 Involvement of the identified genes in biological processes. The Gene Ontology terms were ranked based on the number of genes regulating specific biological pathways using Gene Ontology Mapper. Data represents genes related to Adams-Oliver syndrome (red), telomere biological disorders (blue), immune deficiencies (brown), cystic fibrosis (orange), cystinosis (green), Williams-Beuren (violet), and gene mutations associated with isolated porto-sinusoidal vascular disorder (black).

genes were more highly expressed in myeloid cells than in lymphoid cells (Figure 3B). In particular, the highest expression was found in myeloid stem cells, since this cell type ranked first for 12 out of the 31 genes, compared with 2–4 genes for all other cell types. Some patterns support the soundness of our analysis, as they are consistent with our knowledge of the syndromes: *BTK* and *TACI* were mainly expressed in B cells, *PIK3CD* in T cells, and chronic granulomatous disease genes (*CYBB*, *NCF1*, *NCF2*, and *CYBA*) in myeloid cells.

Overall, this analysis suggests that immune cells, and in particular myeloid cells, could be a population that has been neglected so far in the pathophysiology of PSVD. The possible involvement of immune cells in the physiopathology of PSVD is supported by the frequent association of PSVD with autoimmune or immunodeficient disorders. Moreover, Ziol et al[73] reported the intrasinusoidal infiltration of T CD8+ and NK lymphocytes in 14 out of 44 patients with PSVD associated with various underlying conditions, including celiac disease, Sjogren syndrome, CVID, autoimmune neutropenia, ovarian cancer with chemotherapy and radiotherapy, metastatic rectal cancer, Hodgkin lymphoma, T-rich B-cell lymphoma, HIV, and no condition associated. This infiltrate was found near liver endothelial cells undergoing apoptosis. This study focused on lymphoid cells and did not investigate myeloid cells and resident macrophages.

Cellular pathways or processes involving the identified genes

We then delved into the association of differentially expressed genes with specific biological processes. To accomplish this, we used the Gene Ontology (GO) biological process database in conjunction with the GO-mapper tool, which is accessible online (https://go.princeton.edu/cgi-bin/GOTermMapper).[74] This tool quantitatively linked the selected genes to their associated biological processes, molecular functions, or cellular component GO-terms. We compiled a list of 33 GO biological processes, ranking them based on the number of genes regulating each pathway (Figure 4). Strikingly, pathways related to morphogenesis ("signaling," "anatomical structure development," "cell differentiation," "vesicle-mediated transport") and to immune response ("immune system process,"

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"inflammatory response," "defense response to other organisms") emerged at the forefront of the list, with > 8 genes identified each (Figure 4 and Supplemental Figure S4, http://links.lww.com/HEP/I524). This result suggests that there might be 2 types of PSVD associated with gene mutations: those resulting directly from morphogenesis abnormalities and those secondary to immune changes.

When studying molecular functions and cellular components, the majority (16/31) of these genes encoded proteins exhibiting catalytic activities, suggesting their involvement in various biochemical reactions. In terms of cellular localization, a substantial portion of these proteins were in the organelle (24/31) or nuclear compartments (17/31), rather than in the extracellular region (5/31) (Supplemental Figure S5, http://links.lww.com/HEP/I524 and S6, http://links.lww.com/HEP/I524), suggesting a role of these genes in intracellular catalytic processes.

Insight from transgenic mouse models

Genetically modified mouse models allow us to gain insights into whether specific genetic manifestations of PSVD are cell-specific and elucidating the underlying mechanisms involved. We found in the literature in vivo studies that described the causality of genes and their contribution to several biological processes by using constitutive knockout mice a mouse model wherein the target gene is permanently inactivated in every cell of the organism. In this review, with a consideration that mutations previously described could directly impact immune and hepatic cells, we concentrated on and discussed published studies that analyzed the loss of function of a target gene in specific cell types, particularly in immune or hepatic cells. This focused approach enhances our understanding of the causality of genes and their contributions to various biological processes, unraveling the specific cellular mechanisms affected by the mutations associated with PSVD.

Hepatocyte-specific deletion of *RAC1,* described in AOS, by using transgenic mouse models Albumin-Cre-driven knockout,[75] did not exhibit histological features characteristic of PSVD in the liver. Hematoxylin and eosin staining of liver sections revealed no detectable signs of sinusoidal dilatation, fibrosis, or nodular regeneration in the parenchyma. However, intriguingly, the hepatocyte-specific deletion of *RAC1* led to a sustained infiltration and activation of myeloid and lymphoid immune cells in the liver. This was reflected by an enhanced mRNA expression profile of monocytes CD11b, macrophages F4/80, and lymphoid CD4.[75] These findings suggest that while the histological features of PSVD may not be apparent in the liver, the immune response is notably influenced by the hepatocyte-specific deletion of *RAC1*, providing valuable insights into the complex interplay between genetic alterations and immune cell dynamics in the context of PSVD.

The hepatic deficiency of the telomere biology disorders associated with gene *DKC1* was found to induce liver abnormalities. Histological analysis revealed the presence of fibrotic regions, and this was further accompanied by elevated serum alanine aminotransferase levels in *DKC1 Albumin-Cre* mice, as reported in the study by Ge et al.[76] It is worth noting that, in this study, no specific analysis of immune cell populations was conducted. Nonetheless, the observed hepatic abnormalities and fibrosis suggest a potential role for *DKC1* in liver function and highlight the importance of further investigations to comprehensively understand the impact of telomere biology disorders associated genes on both liver morphology and immune responses.

Mice with a targeted deletion of the *RBPJ* gene specifically in bone marrow immune cells, exhibited reduced efficiency in liver regeneration. After partial hepatectomy, these mice displayed significantly diminished hepatocyte proliferation. Furthermore, when bone marrow-derived endothelial progenitor cells deficient in *RBPJ* were isolated, defects in vessel formation were observed, ultimately leading to vessel disruption. This information, derived from the study conducted by Wang et al,[77] underscores the notable impact of gene deletion in immune cells on liver-related functions and phenotypes.

CONCLUSIONS

In conclusion, this comprehensive review of genetic mutations associated with PSVD has identified 35 genes and one chromosomal abnormality associated with this disorder (Table 1). These mutations should be screened (1) in patients with PSVD and a known monogenic syndromic disease or with extrahepatic organ involvement, (2) in patients with PSVD diagnosed at a young age, and (3) when several family members have PSVD. The extension of this screening to patients with PSVD without an identified condition known to be associated with PSVD may, in the future, also reveal the adult onset of genetic forms of PSVD.

Clinical manifestations of PSVD associated with genetic mutations are related to portal hypertension with an intensity varying according to the type of mutation. Only one liver cancer has been described as associated with genetic forms of PSVD.

Our analysis also showed that these genes are predominantly expressed in immune cells, suggesting that this cell type may play a more prominent role in the pathophysiology of PSVD than previously thought.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Lise Bertin, Nadia Ciriaci, and Pierre-Emmanuel Rautou analyzed the data and wrote the manuscript. Pierre-Emmanuel Rautou designed and supervised the research and revised manuscript. All authors reviewed and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

Pierre-Emmanuel Rautou consults for Abbelight, Boehringer Ingelheim, GENFIT, HemostOD, and Mursla. He is on the speakers' bureau for AbbVie and Tillots. He received grants from Terrafirma. The remaining authors have no conflicts to report.

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