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Review

A *HRG* novel mutation associated with idiopathic portal hypertension: Case report and literature review

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ABSTRACT

Idiopathic portal hypertension (IPH) is defined as the presence of portal hypertension in the absence of a common cause. IPH can have several etiologies, one of which is a genetic disorder. Some genetic mutations, such as KCNN3 and DGUOK, were shown to be related to IPH pathogenesis. This is the first case report of a 22-year-old man who was diagnosed with IPH with a novel heterozygous mutation in the histidine-rich glycoprotein gene (c.545G > C, p.R182T). Using bioinformatics analysis and the protein quantification method, we showed that this novel mutation has a pathogenetic role in IPH. Our study broadens the mutation spectrum of the histidine-rich glycoprotein gene and provides new ideas for IPH etiology.

1. Introduction

Idiopathic portal hypertension (IPH) mainly presents with signs and symptoms of portal hypertension in the absence of an obvious hepatic disorder, where the hepatic venous pressure gradient is normal or near normal but the intrasplenic and intravariceal pressure is markedly increased, and the portal vein and hepatic veins are patent [1]. The most common IPH characteristic is esophageal-gastric variceal bleeding. Hepatic encephalopathy and portal vein thrombosis are also common IPH complications [2]. IPH etiopathogenesis is poorly understood. In addition to infections, prothrombotic states, immunologic disorders, and toxins, gene mutations are also considered to be an IPH etiology, including mutations in the telomerase complex gene [3], autosomal dominant inherited mutations in the KCNN3 gene [4], and recessive inherited mutations in the DGUOK gene [5]. IPH is considered to be a rare disease, and to date, few case series have been published. Here, we aimed to report an interesting case of a 22-year-old man with a novel mutation in the histidine-rich glycoprotein (*HRG*) gene that was associated with IPH.

2. Case presentation

2.1. Case description

A 22-year-old man was admitted to our hospital with the abdominal discomfort for 3 months and a stomachache for 10 days. He had taken traditional Chinese medicine for 3 years because of acne and stopped 1 year before hospital admission. He drank 80 g of alcohol per day two to three times a week for 7 years. His vital signs (blood pressure, heart rate, body temperature, and respiratory rate) on admission were stable and within normal limits. On physical examination, he had no jaundice or bleeding. Auscultation of his heart and lungs was normal. His abdomen was soft and flat, with obvious splenomegaly. No edema was found in the upper and lower limbs.

Table 1 shows the patient's laboratory findings on admission. A complete blood count analysis revealed low platelet levels (109×10^9/L). Aspartate aminotransferase, alanine aminotransferase, total bilirubin and direct bilirubin levels, and the glomerular filtration rate were normal. Prothrombin activity was slightly low (79%). Hepatitis B surface antigen

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Table 1
The patient's laboratory test results at admission and at the 1-year follow-up.

	On admission	1 year later	Normal range
Alanine aminotransferase (U/L)	11.5	12	7–40
Aspartate aminotransferase (U/L)	12.8	15	13–35
Total bilirubin (μmol/L)	10.2	19.6	5–21
Direct bilirubin (μmol/L)	4.6	7.8	0–7
Total bile acid (μmol/L)	7.9	10.9	0–10
Alkaline phosphatase (U/L)	57	55	50–135
γ-glutamyltransferase (U/L)	14	12	7–45
Total protein (g/L)	67	64.2	65–85
Creatine phosphohykinase (U/L)	55.2	None done	40–200
Lactic dehydrogenase (U/L)	128	None done	120–250
Albumin (g/L)	46.7	43	40–55
Globulin (g/L)	20.3	21.2	20–40
Creatinine (μmol/L)	75.7	71	41–53
Glomerular filtration rate (mL/min/1. 73m^2)	123.31	125.7	> 90
Serum Uric Acid (μmol/L)	361.3	377	220–547
Cholesterol (mmol/L)	3.04	2.39	< 5.18
Triglycerides (mmol/L)	0.66	0.61	< 1.7
White cells (*10^9/L)	5.463	5	3.5–9.5
Red cells (*10^{12}/L)	4.77	4.7	4.3–5.8
Hemoglobin (g/L)	157	155	130–175
Platelets (*10^9/L)	109	101	125–350
INR	1.17	None done	0.8–1.2
Na^+ (mEq/L)	143.2	140.9	137–147
K^+ (mEq/L)	4.07	3.88	3.5–5.3
Prothrombin activity (%)	79	None done	80–120

INR, international normalized ratio.

and hepatitis C virus antibody test results were both negative. Antinuclear antibody and anti-smooth muscle antibody test results were negative. Immunoglobulin (Ig) levels, including those of IgG, IgA, IgM, and IgE, were normal. The ceruloplasmin level was also normal.

Upper gastrointestinal endoscopy results showed stomach mucosal inflammation, edema, and erythema, which were consistent with the manifestations of portal hypertension gastropathy (Fig. 1). Abdominal magnetic resonance imaging and computed tomography results both showed incomplete intrahepatic portal vein thrombus, splenomegaly, cavernous transformation of the portal vein, collateral circulation formation, and perfusion defects (Fig. 2). The extrahepatic portal vein and the inferior vena cava were not obstructed.

A needle liver biopsy was then obtained to exclude cirrhosis and other causes. Liver tissue samples were examined by an experienced pathologist. Histology showed mild periportal inflammation and fibrosis (G1S1). In the smaller portal tract, the portal vein branch showed compensatory peripheral venule dilatation, and these venules appeared to herniate into the adjacent parenchyma. The portal tracts lacked appropriately sized portal veins. The lobular structure was preserved, with occasional small necrotic foci (Fig. 3).

The patient had portal hypertension that manifested as portal hypertension gastropathy, splenomegaly, and collateral circulation formation, and it was confirmed using computed tomography, magnetic resonance imaging, and upper digestive tract endoscopy. Pathological examination showed no cirrhosis or parenchymal damage in the patient's liver. The patient received no special treatment and his condition was stable.

Liver histology showed the absence of cirrhosis or parenchymal injury, and there was no known cause of liver disease.

2.2. Genetic testing results and bioinformatics analyses

To understand the genetic predisposition to IPH, the panel sequencing of liver metabolism genes was performed. This analysis identified a novel heterozygous mutation c.545G > C (p.R182T) in the *HRG* gene. This mutation was further confirmed using Sanger sequencing (Fig. 4A). Potential functional effects of the detected missense mutations were predicted by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), SIFT (http://sift.jcvi.org/), PROVEAN (http://provean.jcvi.org/index.php), MutationTaster (http://mutationtaster.org/), and FATHMM (http://fathmm.biocompute.org.uk/) (Table 2). All software programs except FATHMM and InterVar showed that the mutation R182T was damaging. The inheritance mode of the *HRG* c.545G > C (p.R182T) mutation is autosomal dominant. The PhastCons score for the mutation was 0.992, and the corresponding PhyloP value was 1.81, suggesting a high conservation of the amino acid.

Wild-type and mutated *HRG* gene structure models were constructed and assessed using SWISS-MODEL (https://swissmodel.expasy.org/interactive) (Fig. 4B, C). The QMEAN score was −0.63, and there was no electricity in the blank space in the model evaluation graph (Fig. 4D), indicating that the model quality was good. The graphics were retouched using Pymol software (Schrödinger, 2015). The secondary structure of this protein was not affected in the predicted mutation structure.

2.3. Evaluation of the HRG level

Serum was separated from the blood samples and frozen at −80 °C. A commercially available enzyme-linked immunosorbent assay kit (Abcam, Cambridge, UK) was used to analyze the serum HRG level in accordance with the manufacturer's instructions. The serum samples were diluted 1:1000 before the experiment. The patient's HRG level was significantly decreased compared with that of 20 healthy controls (Fig. 5; average value, 52.85 μg/mL vs. 145.69 μg/mL, respectively).

3. Discussion

IPH is a rare disorder with several issues that remain to be clarified, including its etiology and pathogenesis [6]. Many theories including a genetic disorder have been proposed to explain the etiology of IPH. Abernethy malformation and Turner's disease have been widely suggested as a genetic background for this disorder [7]. In the present study, we describe a Chinese Han patient with IPH and a *HRG* gene mutation. To

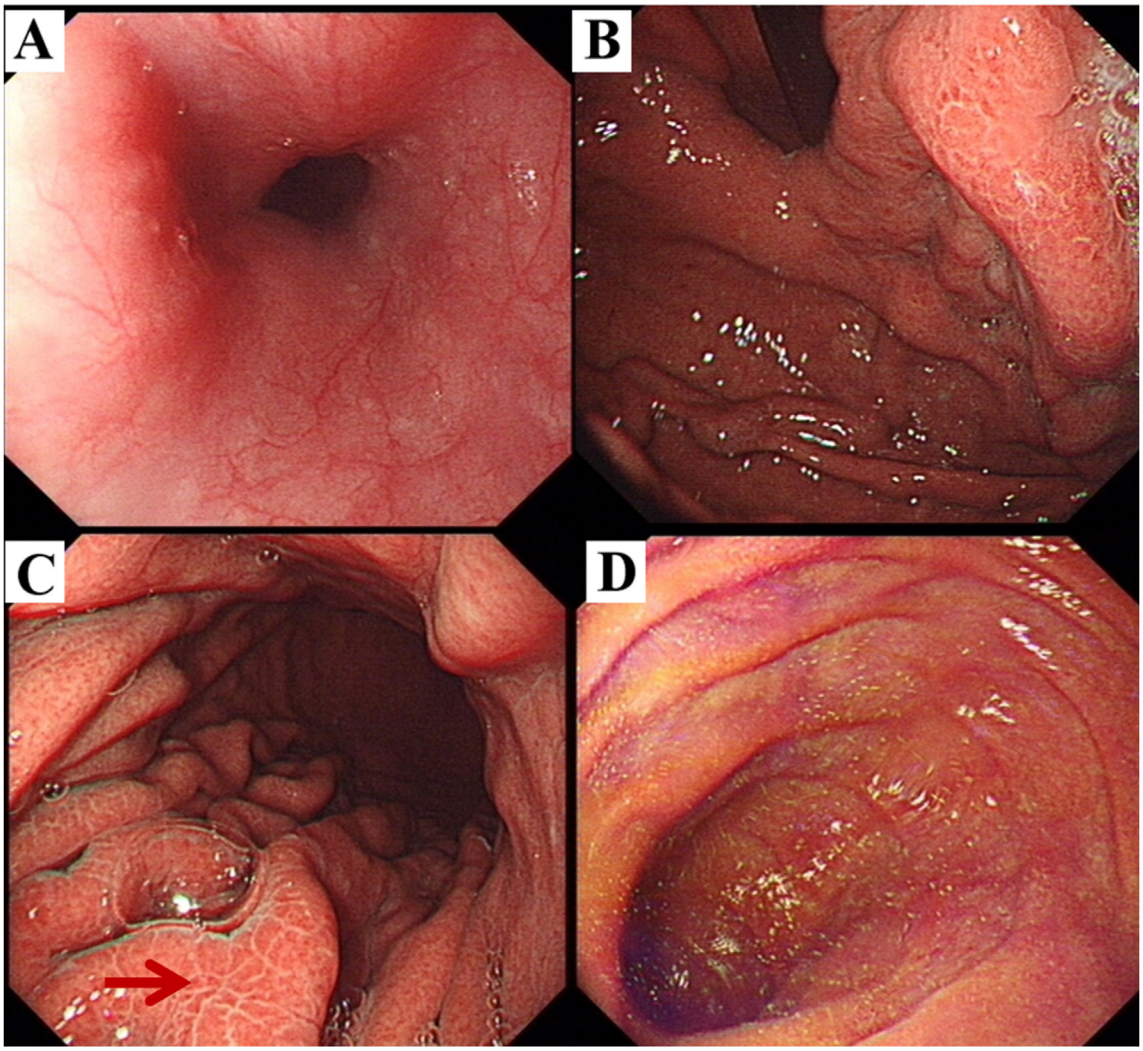

Fig. 1. The gastroscopy reveals portal hypertension gastropathy. (**A**) esophagus; (**B**) fundus of stomach; (**C**) body of stomach; (**D**) duodenum.

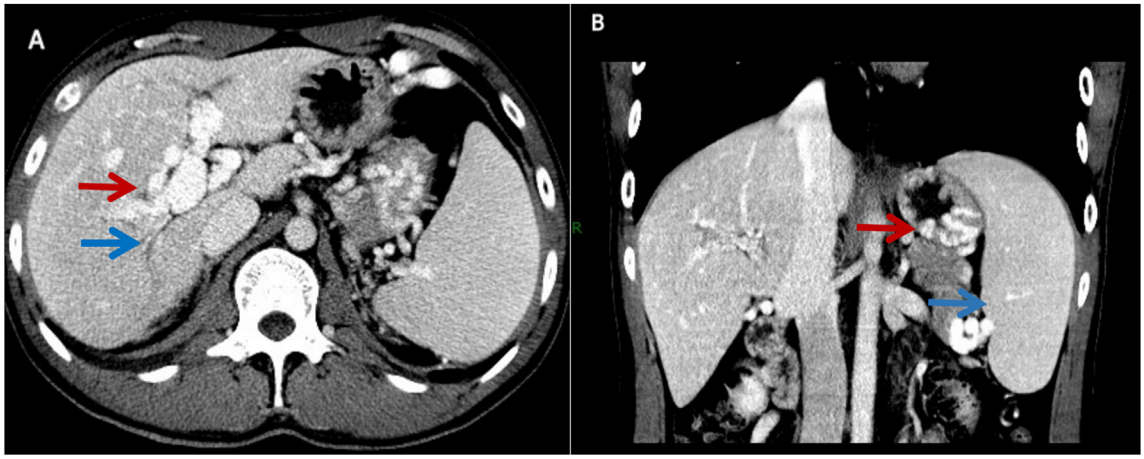

Fig. 2. Computed tomography (CT) of the patient. (**A**) CT shows cavernous transformation of portal vein (red arrow); (**B**) the reconstructed maxium intensity projection (MIP) image shows splenomegaly (blue).

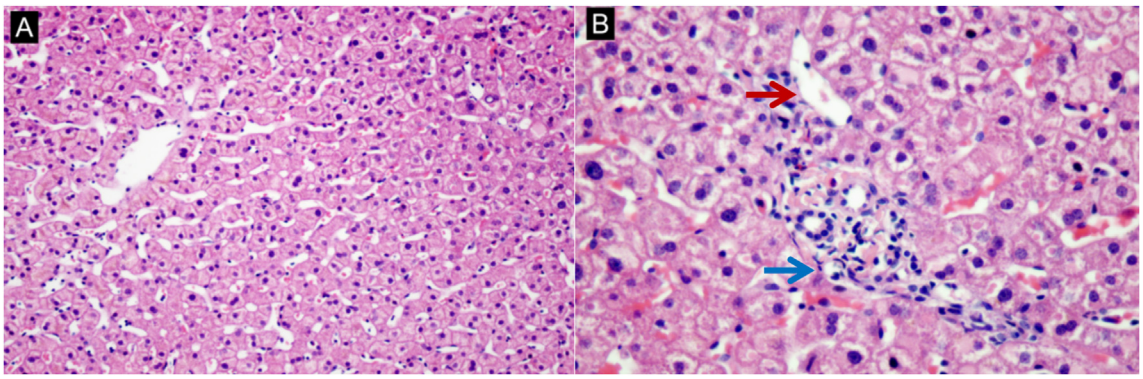

Fig. 3. The liver histopathology reveals IPH. (A) H&E 200 × ; (B) H&E 400 × ; compensatory dilatation. IPH, idiopathic portal hypertension; H&E, hematoxylin-eosin.

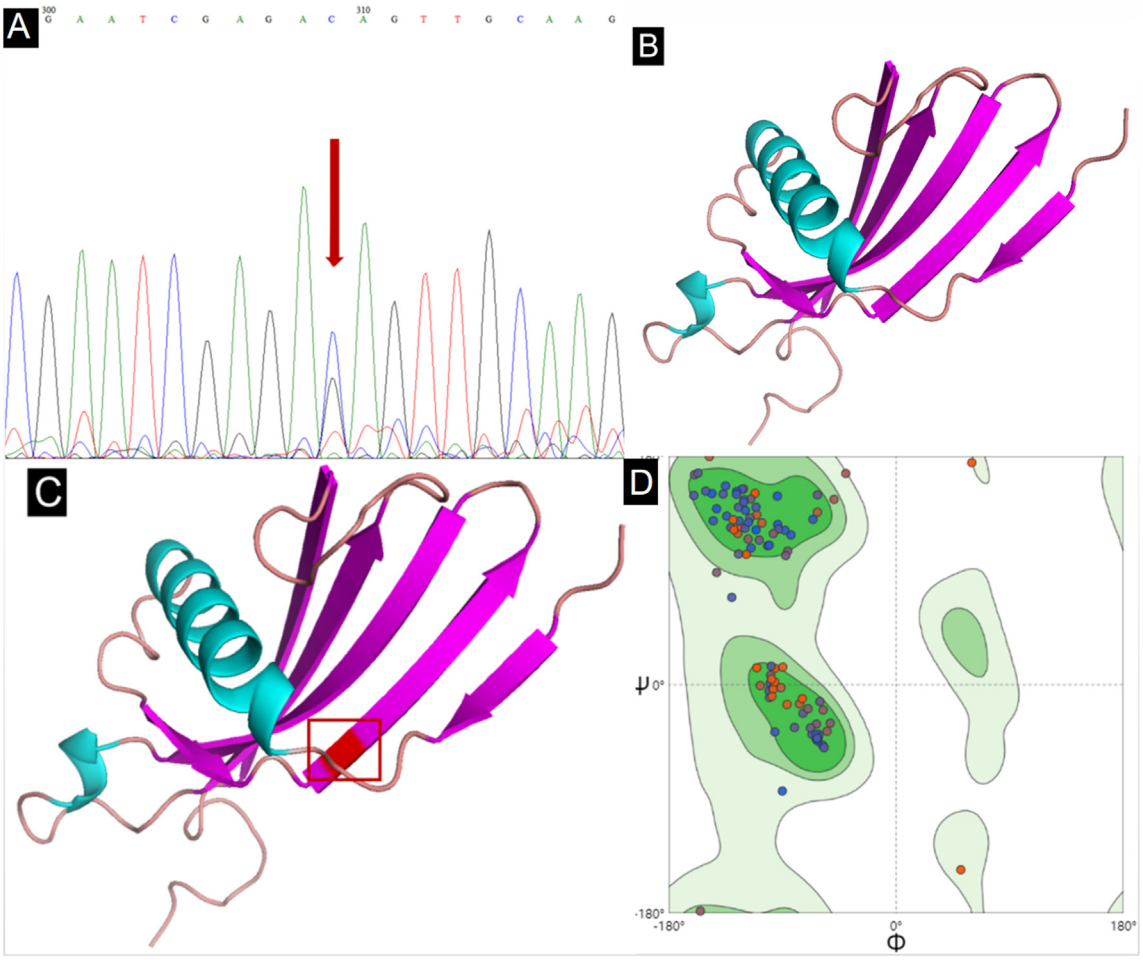

Fig. 4. 3D structure of HRG protein and sanger sequencing reveals heterozygous mutations in HRG gene, c.G545C (p.R182T). (**A**) heterozygous mutations in HRG gene. HRG, histidine-rich glycoprotein.

Table 2
Bioinformatics analysis of the *HRG* mutations.

Mutation	PolyPhen-2		SIFT		PROVEAN		MutationTaster		FATHMM		InterVar
	Score	prediction	Score	prediction	Score	prediction	Score	prediction	Score	prediction	prediction
c.G545C p.R182T	0.864	probably damaging	0.018	deleterious	−4.56	deleterious	0.913	polymorphism	2.58	tolerated	Uncertain significance

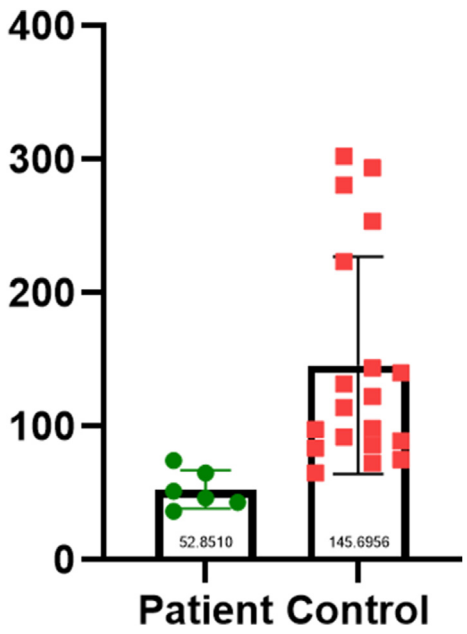

Fig. 5. Comparison of serum HRG concentration. HRG, histidine-rich glycoprotein.

multidomain polypeptide with 507 amino acids including two cystatin-like regions at the N-terminus, which is a histidine-rich region flanked by proline-rich regions, and a C-terminal domain [17]. Its domain structure can bind with ligands and regulate many important biological processes including coagulation and fibrinolysis. HRG was found to modulate various components of the coagulation cascade. HRG can bind to heparin, preventing mast cell-induced heparin release and inhibiting monocyte procoagulant activity at sites of inflammation and thrombosis [18]. Plasma is the main reservoir for HRG. The plasma HRG concentration is 100–150 μg/mL [19], and the patient's HRG plasma concentration was 52.85 μg/mL. This shows that the R182T mutation in the *HRG* gene causes phenotypic changes. Patients with underlying thrombophilia may develop IPH [20], as shown by Hillaire et al. [21]. They investigated 23 patients with IPH and found that among these patients, 12 patients had a prothrombotic disorder. We suggest that our patient's IPH may be related to the coagulation disorder caused by the *HRG* gene mutation.

The patient was followed-up 1 year later, and there was no significant change in the patient's condition (Table 1). The influence of *HRG* gene mutation on IPH requires further observation.

In conclusion, we performed panel sequencing of liver metabolism genes in a Chinese patient with IPH and identified a novel mutation (c.G545C p.R182T) in the *HRG* gene. The mutation might cause a decrease in circulating HRG protein levels. Our study broadened the *HRG* gene mutation spectrum and identified a possible link between the *HRG* gene and IPH, which helps us better understand the causes of IPH.

Table 3
List of patients with *HRG* gene mutations.

Report Number	Ancestry	Age	Sex	Exon	Codon change	Amino acid change	plasma HRG level (patient/normal)	Disease	Reference
1	Japanese	43	Female	Exon 3	308G > A	G103E	20%	right transverse sinus thrombosis	Shigekiyo et al. [10].
2	Japanese	76	female	Exon 6	721T > C	C241R	50%	dural arteriovenous fistula	Shigekiyo et al. [11]
3	Chinese	19	male	Exon 2	271C > T	P91S	50%	Deep venous thrombosis	Luo et al. [12].
4	Chinese	–	–	Exon 1	125G > A	R42Q	–	venous thromboembolism	Lee et al. [13]
5	American	–	–	Exon 1	167C > T	A56V	–	pulmonary arterial hypertension	Song et al. [14]
6	Sweden	–	female	Exon 5	610C > T	P204S	–	Poor pregnancy outcome	Nordqvist et al. [15].

the best of our knowledge, this is the first time that a novel heterozygous mutation such as c.545G > C (p.R182T) in the *HRG* gene was reported to be associated with IPH. However, the ACMG/AMP (American College of Medical Genetics and Genomics/Association for Molecular Pathology) guidelines [8] indicate that the *HRG* c.545G > C (p.R182T) mutation has an uncertain significance (PM1+PM2+PP2) and the HRG protein's role in the mutation's pathogenesis is unknown.

The human *HRG* gene has been mapped to chromosome 3, position 3q28–q29, and it spans approximately 11 kb [9]. To date, six pathogenic *HRG* mutations have been described in the Human Gene Mutation Database (Table 3). In the first case, the patient had a right transverse sinus thrombosis caused by a single G to A point mutation on exon 3 of the *HRG* gene, which resulted in a Gly103 to Glu substitution [10]. In the second case, the patient had a dural arteriovenous fistula, and a single nucleotide substitution of T to C was found at exon 6 in the HRG gene, which switched Cys 241 to Arg [11]. In the third case, the patient had deep vein thrombosis, and a missense variant, c.271C > T (p. Pro91Ser), in exon 2 of the *HRG* gene was identified [12]. In the fourth report, the *HRG* mutation c.125G > A (R42Q) played a significant role in venous thromboembolism [13]. In the fifth report, a new specific gene panel was developed for pulmonary arterial hypertension including a *HRG* c.167C > T (A56V) mutation [14]. The sixth report showed that *HRG* gene mutation is involved in establishing and maintaining pregnancy [15]. Briefly, the low HRG plasma concentration may be related to the thrombosis. In this case, the *HRG* gene mutation that causes IPH may also be related to coagulation dysfunction.

HRG is a single polypeptide chain α-plasma glycoprotein that is approximately 75 kDa, and it is mainly synthesized in liver parenchymal cells [16]. The primary structure of human HRG is predicted to be a

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Author contributions

All authors listed have made substantial, direct, and intellectual contributions to the work and approved it for publication.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

The raw data supporting the conclusions in this article will be made available by the authors, without undue reservation.

Ethics statement

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institute Ethical Committee of Beijing You An Hospital, Capital Medical University, Beijing, China and with the Declaration of Helsinki (as revised in 2013).

Informed consent

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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