






## RESEARCH ARTICLE

# High penetrance of inferior vena cava system atresia in severe thrombophilia caused by homozygous antithrombin Budapest 3 variant: Description of a new syndrome

María E. de la Morena-Barrio<sup>1</sup>  | Réka Gindele<sup>2</sup> | Carlos Bravo-Pérez<sup>1</sup>  | Péter Ilonczai<sup>3</sup> | Isabel Zuazu<sup>1</sup> | Marianna Speker<sup>2</sup> | Zsolt Oláh<sup>4</sup> | Juan J. Rodríguez-Sevilla<sup>5</sup>  | Laura Entrena<sup>6</sup> | Maria S. Infante<sup>7</sup>  | Belén de la Morena-Barrio<sup>1</sup>  | José M. García<sup>7</sup> | Ágota Schlammadinger<sup>8</sup> | Rosa Cifuentes-Riquelme<sup>1</sup> | Asunción Mora-Casado<sup>9</sup> | Antonia Miñano<sup>1</sup> | Jose Padilla<sup>1</sup> | Vicente Vicente<sup>1</sup> | Javier Corral<sup>1</sup> | Zsuzsanna Bereczky<sup>2</sup>

<sup>1</sup>Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonación, Universidad de Murcia, IMIB-Arrixaca, CIBERER, Murcia, Spain

<sup>2</sup>Division of Clinical Laboratory Science, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

<sup>3</sup>Jósa Teaching Hospital of University of Debrecen, Nyíregyháza, Hungary

<sup>4</sup>Department of Anaesthesiology and Intensive Care, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

<sup>5</sup>Servicio de Hematología, Hospital del Mar, Barcelona, Spain

<sup>6</sup>Servicio de Hematología, Hospital Virgen de las Nieves, Granada, Spain

<sup>7</sup>Servicio de Hematología y Unidad Central de Radiodiagnóstico, Hospital Infanta Leonor, Madrid, Spain

<sup>8</sup>Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

<sup>9</sup>Servicio de Hematología, Hospital Clínico San Carlos, Madrid, Spain

## Correspondence

Javier Corral, Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonación, Universidad de Murcia, IMIB-Arrixaca, Ciberer, Murcia, Spain.  
Email: javier.corral@carm.es

Zsuzsanna Bereczky, Division of Clinical Laboratory Science, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.  
Email: zsbereczky@med.unideb.hu

## Funding information

Fundación Séneca, Grant/Award Number: 19873/GERM/15; Hungarian National Research Development and Innovation Office, Grant/Award Number: OTKA K116228;

## Abstract

Atresia of inferior vena cava (IVC) is a rare congenital malformation associated with high risk of venous thrombosis that still has unknown etiology, although intrauterine IVC thrombosis has been suggested to be involved. The identification of IVC atresia in a case with early idiopathic venous thrombosis and antithrombin deficiency caused by the homozygous *SERPINC1* c.391C > T variant (*p.Leu131Phe*; antithrombin Budapest 3) encouraged us to evaluate the role of this severe thrombophilia in this vascular abnormality. We have done a cross-sectional study in previously identified cohorts of patients homozygous for the Budapest 3 variant ( $N = 61$ ) selected from 1118 patients with congenital antithrombin deficiency identified in two different populations: Spain ( $N = 692$ ) and Hungary ( $N = 426$ ). Image analysis included computed tomography and phlebography. Atresia of the IVC system was observed in

María E. de la Morena-Barrio, Réka Gindele, Carlos Bravo-Pérez and Péter Ilonczai contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *American Journal of Hematology* published by Wiley Periodicals LLC.

Instituto de Salud Carlos III & FEDER, Grant/Award Number: PI18/00598; Ministry of National Economy, Hungary, Grant/Award Number: GINOP-2.3.2-15-2016-00039

17/24 cases (70.8%, 95% confidence interval [CI]: 48.9%–87.3%) homozygous for antithrombin Budapest 3 with available computed tomography (5/8 and 12/16 in the Spanish and Hungarian cohorts, respectively), 16 had an absence of infrarenal IVC and one had atresia of the left common iliac vein. All cases with vascular defects had compensatory mechanisms, azygos-hemiazygos continuation or double IVC, and seven also had other congenital anomalies. Short tandem repeat analysis supported the specific association of the IVC system atresia with *SERPINC1*. We show the first evidence of the association of a severe thrombophilia with IVC system atresia, supporting the possibility that a thrombosis in the developing fetal vessels is the reason for this anomaly. Our hypothesis-generating results encourage further studies to investigate severe thrombophilic states in patients with atresia of IVC.

## 1 | INTRODUCTION

The development of the venous system in the human fetus takes place during gestational weeks 6–8. The formation of the inferior vena cava (IVC) in the human embryo is a complex process that results from the fusion and regression of three paired veins: the posterior cardinal, subcardinal, and supracardinal veins. This complex origin explains the possibilities of multiple congenital IVC malformations.<sup>1</sup>

Failure of the development of the IVC is a rare disorder,<sup>2</sup> often used to describe two distinct entities.<sup>3</sup>

First, interruption of the IVC, the failure of the hepatic-subcardinal anastomosis to form, results in suprarenal/intrahepatic interruption of the IVC with azygos continuation. The infrarenal IVC is normal, and blood from the renal segment of the IVC is shunted into the azygos system and right atrium through the superior vena cava. This occurs in approximately 0.6%–2% of patients with other cardiovascular defects and in 0.3% of otherwise healthy individuals. It is often seen in conjunction with transposed abdominal viscera, polysplenia or asplenia, renal hypoplasia or agenesis, and dysgenesis of the lungs. Dextrocardia, atrial septal defects, atrioventricular canal and pulmonary artery stenosis are also associated with infrahepatic interruption of the IVC.<sup>2</sup> Usually, those patients are diagnosed at an early stage.

Second, isolated absence of the infrarenal segment of the IVC is an extremely rare anomaly.<sup>2</sup> Except for renal hypoplasia/aplasia, no other associated congenital anomalies have been reported in these patients, who may remain asymptomatic if a venous collateral system is developed, returning blood from the iliac veins to the heart through the azygos and hemiazygos veins (azygos continuation). Thus, absence of the infrarenal IVC segment is usually diagnosed by fortuitous finding on advanced imaging.<sup>2</sup> As a single embryonic event does not fully explain this type of IVC abnormality, some authors suggest that it may be an acquired defect.<sup>4</sup> In 1980 Milner and Marchan<sup>5</sup> were the first authors to suggest that infrarenal absence of the IVC is not of embryonic origin but is the result of intrauterine or perinatal thrombosis of the IVC, a hypothesis supported thereafter by other authors.<sup>1,6–8</sup> Twenty years were

required to get the first clinical report showing infrarenal IVC absence following perinatal IVC thrombosis, supporting the possibility that infrarenal IVC absence is a solitary finding and may be associated with perinatal IVC thrombosis.<sup>9</sup>

The relationship between atresia of IVC and thrombosis is not only restricted to the potential pathogenic mechanism. A significant increased risk of adulthood venous thrombosis has been described among patients with this malformation. Patients with atresia of IVC have a 10-fold risk of venous thrombosis.<sup>10</sup> Bianchi et al.<sup>11</sup> suggest that this malformation increased the risk of deep venous thrombosis (DVT) by diminishing cardiac return and promoting abdominal and lower extremity venous stasis. Therefore, the acronym “KILT” has been proposed to designate the clinical association of kidney and IVC abnormalities with leg thrombosis.<sup>12</sup>

As far as we know, only one study questions whether agenesis of IVC might be hereditary, based on two cases from a cohort of 163 cases with this vascular malformation.<sup>13</sup> In one family, father and son—the latter with DVT—had IVC atresia in the same segment. The second remarkable case was a couple of twins with agenesis of IVC. Unfortunately, no genetic defect was reported in any of these two interesting cases.<sup>13</sup>

The identification of IVC atresia in a case with early idiopathic DVT and antithrombin deficiency caused by the homozygous *SERPINC1* c.391C > T variant (*p.Leu131Phe*; antithrombin Budapest 3) encouraged us to evaluate the penetrance of this vascular abnormality in this severe thrombophilia.

## 2 | MATERIAL AND METHODS

### 2.1 | Ethics

All included subjects gave their informed consent to enter the study, which was approved by the Ethics Committee of Morales Meseguer Hospital and by the Committee of the Hungarian Scientific Council on Health, and performed in accordance with the 1964 Declaration of Helsinki and their later amendments.

## 2.2 | Patients

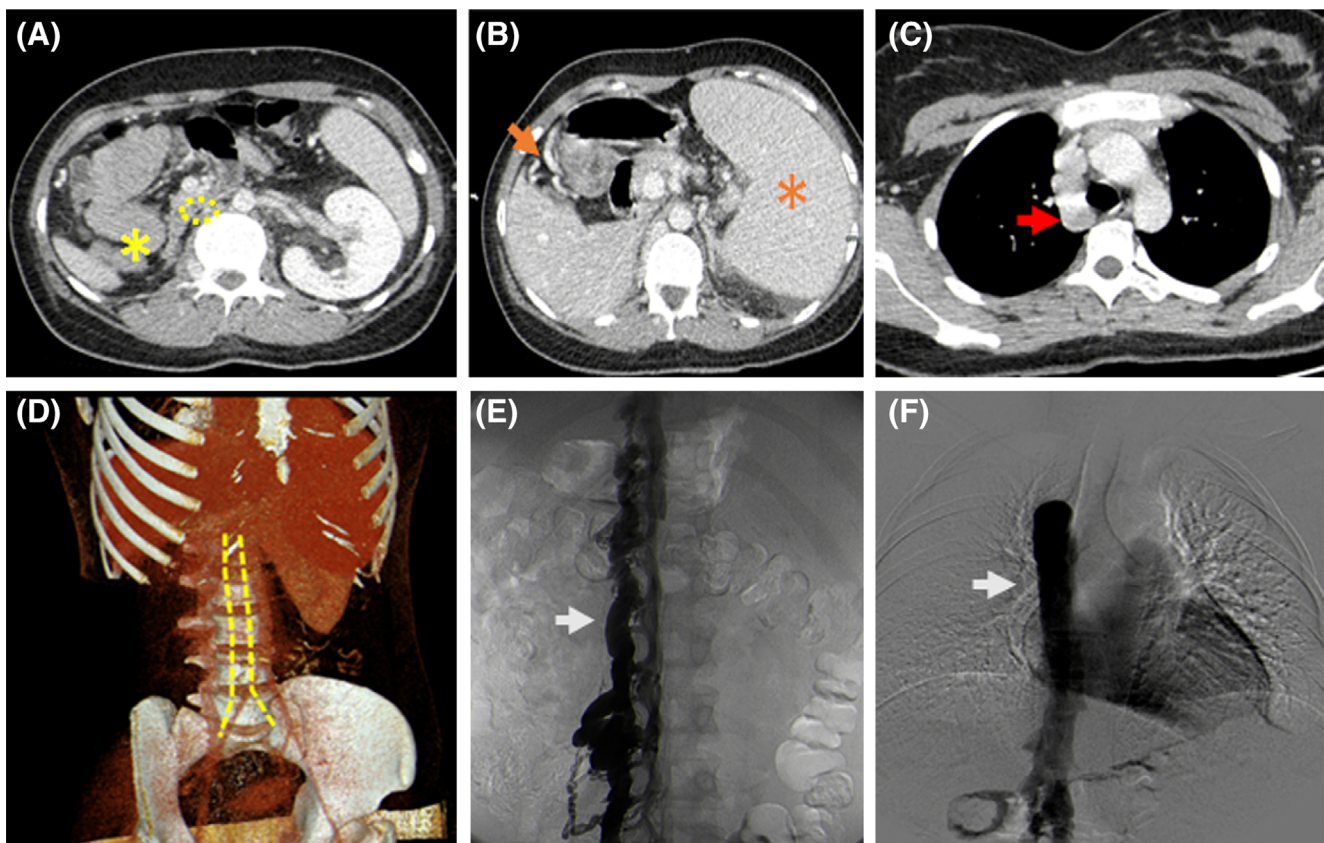
The study was done in 61 homozygous carriers of antithrombin Budapest 3 (*SERPINC1* p.Leu131Phe) selected from a cohort of 1118 subjects with congenital antithrombin deficiency recruited during 24 years (1997–2021) in two national reference centers for antithrombin deficiency from Spain and Hungary. Briefly, 640 unrelated patients were consecutively diagnosed with antithrombin deficiency in their local healthcare centers within a thrombophilia screening performed after discontinuation of oral anticoagulation in symptomatic patients. In all cases, antithrombin deficiency was confirmed in one of the two reference centers by measurement of antithrombin activity, antigen levels and genetic analysis. Family studies were done in available first- and second-degree affected relatives, to recruit the final cohort of 1118 cases with congenital antithrombin deficiency. Available cases homozygous for the Budapest 3 variant were approached during their outpatient visits or by telephone call to inform them of this study. We included patients who gave their informed consent to evaluate abdominal vascular malformations by reviewing imaging records or by a new computed tomography (CT) (Figure S1, supplementary material). Additional thrombophilic parameters (protein C activity, free protein S antigen, resistance to

activated protein C, factor V Leiden, prothrombin c.\*97G > A [G20210A] and antiphospholipid antibodies) were collected when available. Patients' medical records were retrospectively evaluated in search of thrombotic events and possible risk factors. Venous thrombotic events were objectively diagnosed and confirmed through routine imaging procedures, such as Doppler ultrasonography, phlebography, CT or magnetic resonance imaging for DVT and CT pulmonary angiography or lung perfusion scintigraphy for pulmonary embolism.

## 2.3 | Genetic analysis

Genetic variants in *SERPINC1* were identified by different sequencing methods (i.e., sequencing the seven exons and flanking intronic regions and whole gene sequencing by next-generation sequencing) and multiplex ligation-dependent probe amplification (MLPA), as described previously.<sup>14</sup>

Short tandem repeat (STR) analysis of 14 polymorphic markers flanking *SERPINC1* and covering 14 MB around *SERPINC1* (Figure S2) was done following standard procedures in our cohort of patients with CT data.



**FIGURE 1** Radiologic findings supporting agenesis of inferior vena cava (IVC) and compensatory mechanisms in the proband. (A–C) Axial computed tomography sections showing agenesis of IVC (yellow-dashed circumference) and associated vascular and abdominal anomalies: right renal agenesis (yellow star), gastric varices (orange arrow), splenomegaly (orange star) and azygos enlargement (red arrow). (D) Reformatted three-dimensional scan images evidencing agenesis of IVC (projection of absent IVC position is shown). (E, F) Cavography and phlebography confirming collateral circulation and enlarged hemiazygos (E) and azygos (F) (white arrows)

TABLE 1 Characteristics of cases homozygous for the Budapest 3 variant evaluated by computed tomography analysis

Patient	Cohort	Sex	Age (years)	Anti-FXa (%)	Ag (%)	Age of first thrombosis (years)	Recurrent thrombosis	IVC atresia (segment)	Other anatomic disorder	Other thrombophilia	Anticoagulant treatment
1	Spain	F	29	18%	70%	DVT (24)	Yes	Yes (infrarenal)	Absence of right kidney and right adrenal gland (KILT triad)	No	AVK
2	Spain	F	48	24%	70%	DVT (30)	No	No	No	No	AVK
3 <sup>a</sup>	Spain	F	44	17%	69%	DVT (39)	No	No	No	FV Leiden +/-	Dabigatran 150 mg BID
4 <sup>a</sup>	Spain	M	50	9%	69%	DVT (50)	No	No	No	FV Leiden +/-	Dabigatran 150 mg BID
5	Spain	M	40	15%	81%	DVT (16)	No	Yes (infrarenal)	No	FV Leiden +/-	AVK
6	Spain	M	35	8%	75%	DVT (30)	No	No	LCIV, double IVC	No	AVK
7	Spain	M	87	28%	ND	DVT (67)	Yes	Yes (infrarenal)	No	No	AVK
8	Spain	M	32	18%	95%	DVT (21)	Yes (2x)	Yes (infrarenal)	Bilateral agenesis of common iliac veins and left renal atrophy (KILT triad)	No	Dabigatran 150 mg BID
9	Hungary	F	55	12%	80%	DVT (15)	No	Yes (infrarenal)	Hypoplasia of common iliac veins	No	AVK
10 <sup>a</sup>	Hungary	F	27	14%	84%	DVT (16)	Yes	Yes (infrarenal)	Hypoplasia of common iliac veins	No	Apixaban 5 mg BID
11	Hungary	M	26	23%	84%	DVT (16 days)	Yes (3x)	Yes <sup>b</sup> (infrarenal)	Hypoplasia of common iliac veins	FV Leiden +/-	AVK
12	Hungary	M	12	16%	80%	No thrombosis	-	Yes (infrarenal)	No	No	None
13	Hungary	F	32	ND	ND	DVT (29)	No	Yes (infrarenal)	No	FV Leiden +/-	Rivaroxaban 20 mg OD
14	Hungary	F	27	25%	70%	DVT (25)	No	Yes (infrarenal)	No	No	AVK
15	Hungary	F	75	15%	76%	DVT (20)	No	Yes (infrarenal)	No	No	Rivaroxaban 20 mg OD
16	Hungary	M	34	16%	84%	DVT (25)	No	Yes (infrarenal)	No	No	AVK
17	Hungary	M	30	14%	ND	DVT (24)	Yes	No	No	No	Rivaroxaban 15 mg BID
18 <sup>a</sup>	Hungary	F	28	17%	76%	DVT (22)	Yes	No	No	No	Rivaroxaban 20 mg OD
19	Hungary	M	61	12%	ND	DVT (35)	Yes	No	No	No	Rivaroxaban 20 mg OD
20	Hungary	F	27	16%	88%	DVT (10)	Yes	No	No	No	Apixaban 5 mg BID
21	Hungary	M	22	16%	80%	DVT (14)	No	Yes (infrarenal)	No	No	AVK



TABLE 1 (Continued)

Patient	Cohort	Sex	Age (years)	Anti-FXa (%)	Ag (%)	Age of first thrombosis (years)	Recurrent thrombosis	IVC atresia (segment)	Other anatomic disorder	Other thrombophilia	Anticoagulant treatment
22 <sup>a</sup>	Hungary	M	28	17%	90%	DVT (21)	Yes	Yes (infrarenal)	No	No	Apixaban 5 mg BID
23 <sup>a</sup>	Hungary	F	27	17%	ND	DVT (24)	No	Yes (infrarenal)	No	No	Apixaban 5 mg BID
24	Hungary	M	30	22%	88%	DVT (13)	Yes	Yes (infrarenal)	Hypoplasia of common iliac veins	FV Leiden +/-	AVK

Abbreviations: Ag, antithrombin antigen, reference interval, 80%–120%; anti-FXa, antithrombin anti-FXa activity, reference interval, 80%–120%; AVK, anti-vitamin K treatment; BID, twice daily; DVT, deep venous thrombosis; IVC, inferior vena cava; LCIV, left common iliac vein; ND, no data.

<sup>a</sup>P3 is the sister of P4, P10 is the sister of P18, and P23 is the sister of P22.

<sup>b</sup>Confirmed by lower limb venography and cavography.

## 2.4 | Biochemical and functional characterization of antithrombin deficiency

These methods have been described elsewhere.<sup>15,16</sup> Briefly, anti-thrombin activity (anti-FXa and anti-FIIa, progressive and heparin cofactor activity) was determined in citrated plasma by chromogenic methods. Antigen levels were measured by rocket immunoelectrophoresis, enzyme-linked immunosorbent assay, or immunonephelometry. Analysis of plasma antithrombin forms included crossed immunoelectrophoresis and polyacrylamide gel electrophoresis. Western blot immunostaining was done using a specific anti-human antithrombin polyclonal antibody (A9522; Sigma-Aldrich, Saint Louis, MO).

Peripheral blood was collected at least 3 months after the acute thrombotic event and patients were not anticoagulated with heparin or direct oral anticoagulants before blood sampling.

## 2.5 | Image analysis

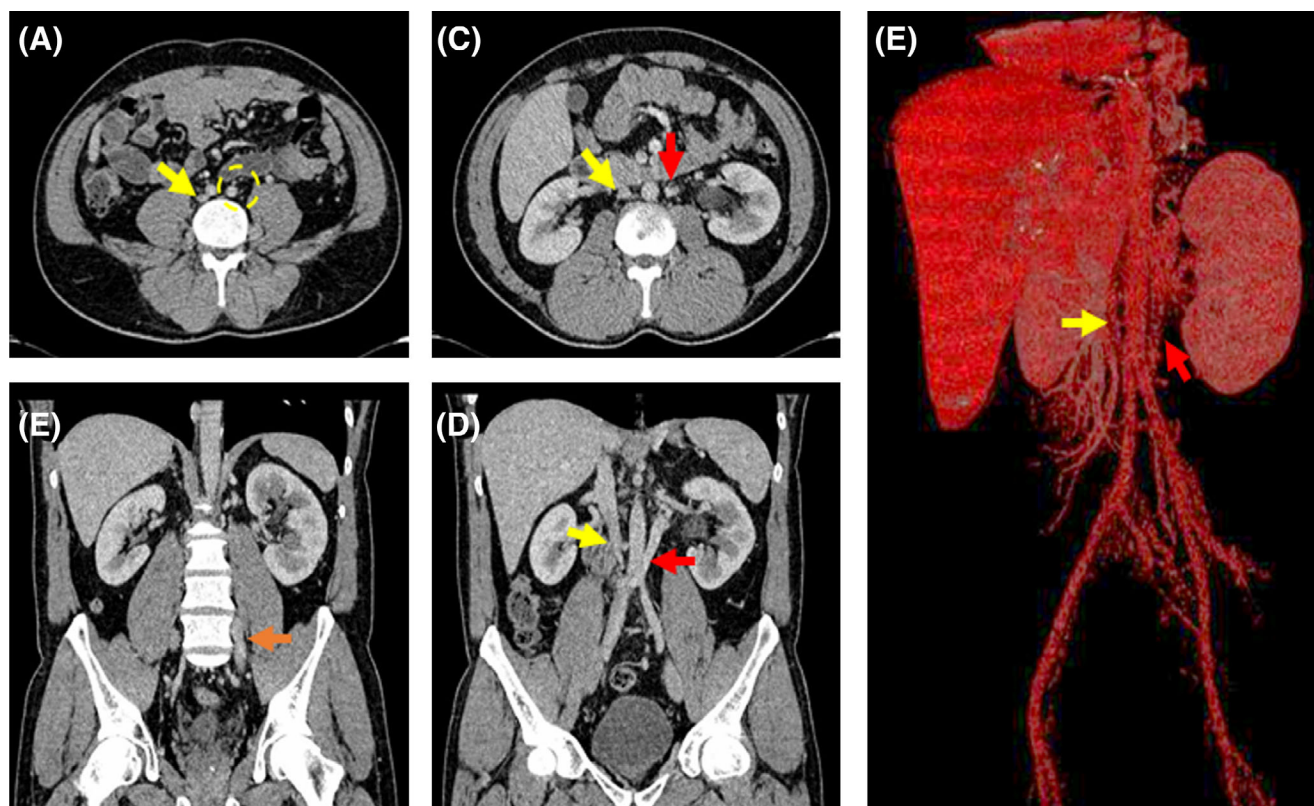
Identification of vascular and other abdominal malformations was done in all cases by experienced radiologists using routine CT with administration of intravenous contrast. Standard technical procedures were performed.<sup>17</sup> Basically, the IVC system was evaluated at 60–90 s after intravenous administration of 120–150 mL of contrast material at a rate of 3–5 mL/s. Generation of multiplanar reformatted CT images was available in order to appreciate complex anomalies. Additionally, in selected cases, collateral circulation and hemodynamic implications generated by the absence of the vena cava were explored by cavography and phlebography. The type of IVC atresia was established according to a previously published classification.<sup>3</sup>

## 3 | RESULTS

### 3.1 | Identification of the first homozygous case with antithrombin Budapest 3 and IVC atresia

Our study was initiated from a 26-year-old woman of Roma origin anticoagulated with acenocoumarol due to an idiopathic DVT 2 years previously, who presented with severe upper gastrointestinal bleeding under supratherapeutic levels of anticoagulation (international normalized ratio [INR] = 5.21). Upper endoscopy revealed variceal bleeding. Subsequent CT scan showed gastric varices, together with an enlarged hemiazygos vein, hepatosplenomegaly and the absence of infrarenal IVC, right renal vein and ipsilateral kidney/suprarenal gland (Figure 1A–D). Cavography and phlebography of hepatic veins confirmed collateral circulation (Figure 1E,F).

During hospitalization, the patient received prothrombin complex concentrates (1000 IU) and vitamin K (10 mg), and developed a new event of DVT in the contralateral limb that was initially treated with low-molecular-weight heparin (enoxaparin 1 mg/kg BID) but with poor clinical response. Heparin resistance was suspected, as FXa



**FIGURE 2** Radiologic findings supporting left common iliac vein agenesis and compensatory mechanisms in P6. (A) Axial computed tomography section in which iliac pedicles are surrounded (yellow-dashed circumferences). Unlike the right iliac pedicle (where the vein is pointed with a yellow arrow), the left one lacks common iliac vein. (B) Coronal computed tomography section showing collateral circulation via lumbar veins (orange arrow), which drains blood from left lower limb and bypasses venous atresia. (C–E) Computed tomography sections and reformatted three-dimensional scan images evidencing compensatory double inferior vena cava (IVC) (normal IVC and left IVC are highlighted with yellow and red arrows, respectively)

inhibitory activity was undetectable. Retrospective analysis of thrombophilia screening at the first thrombotic event revealed low plasma antithrombin activity (anti-FXa heparin cofactor activity: 18%). These findings prompted further studies evaluating antithrombin deficiency by molecular methods. *SERPINC1* sequencing revealed a homozygous *c.391C > T* variant responsible for the Budapest 3 variant (*p.Leu131Phe*), a type II deficiency affecting the heparin binding site of antithrombin (type II HBS).<sup>18</sup> This encouraged the use of antithrombin concentrates (Kyberlin P 3000 IU), which rendered excellent results with no thrombotic/bleeding recurrence.

A complete characterization of her antithrombin deficiency including functional analysis using both progressive and heparin cofactor assays, antigen assays, and crossed immunoelectrophoresis in the presence of heparin was done 1 month after she was discharged (Figure S3).

### 3.2 | Identification of Budapest 3 variant in homozygous state within two large cohorts and search for vascular defects

This case encouraged us to test for atresia of IVC among cases of this specific severe thrombophilia. The screening of our cohorts of

patients with antithrombin deficiency and family studies identified 61 cases homozygous for the Budapest 3 variant, 11 in Spain (from eight unrelated families) and 50 in Hungary (from 41 unrelated families) (Figure S1). Forty-six out of 61 cases homozygous for the Budapest 3 variant were successfully contacted to be informed of this study. Fifteen patients were lost during follow-up and could not be contacted, and one additional patient was dead at the time of study enrollment. Twenty-four patients (eight from Spain and 16 from Hungary) gave their informed consent to evaluate abdominal vascular malformations by reviewing imaging records ( $N = 14$ ) or by a new CT ( $N = 10$ ) (Figure S1). Table 1 shows the clinical characteristics of these patients, as well as the radiologic findings. The vast majority of patients declared themselves as of Roma origin.

Sixteen cases homozygous for the Budapest 3 variant out of the 24 evaluated had atresia of IVC (66.7%, 95% confidence interval [CI]: 44.7%–84.4%), and all of them had absence of the infrarenal segment of IVC. Seven subjects with IVC atresia had additional hypoplastic anomalies. The index case (P1) had absence of right renal vein and ipsilateral renal/suprarenal agenesis, another subject (P8) had left renal atrophy and bilateral agenesis of common iliac veins, and four patients (P9, P10, P11 and P24) also showed hypoplasia of the common iliac veins. One additional case with no IVC atresia (P6) had left

**TABLE 2** Short tandem repeat (STR) number variations in gene regions proximal and distal to SERPINC1 in antithrombin Budapest 3 homozygous patients

No.	C	Atresia	STR: D1S															
			460	196	431	452	2815	1165	2790	2814	218	2691	2659	2791	212	2751		
1	S	IVC	ND	ND	17/19	9/10	ND	ND	ND	20/20	SERPINC1	11/11	ND	20/20	ND	15/15	ND	18/18
2	S	No	ND	ND	18/18	8/10	ND	ND	ND	20/21		11/11	ND	20/20	ND	17/17	ND	18/18
3	S	No	ND	ND	15/23	9/10	ND	ND	ND	20/20		11/11	ND	20/20	ND	15/15	ND	18/18
4	S	No	ND	ND	15/18	10/13	ND	ND	ND	20/20		11/11	ND	20/20	ND	15/15	ND	18/18
5	S	IVC	ND	ND	15/23	9/10	ND	ND	ND	20/20		11/11	ND	20/20	ND	15/15	ND	18/18
6	S	LIV	ND	ND	17/21	8/11	ND	ND	ND	20/22		11/11	ND	20/20	ND	15/17	ND	18/18
7	S	IVC	ND	ND	18/21	8/10	ND	ND	ND	20/21		11/11	ND	20/20	ND	17/17	ND	18/18
8	S	IVC	ND	ND	18/18	8/8	ND	ND	ND	20/20		11/11	ND	20/20	ND	17/17	ND	18/18
9	H	IVC	ND	ND	ND	ND	ND	ND	ND	ND		ND	ND	ND	ND	ND	ND	ND
10	H	IVC	6/7	12/15	ND	ND	18/18	13/13	13/13	20/20		ND	24/25	ND	11/15	ND	11/20	ND
11	H	IVC	7/7	12/18	ND	ND	18/18	13/13	13/13	20/20		ND	24/25	ND	11/15	ND	11/20	ND
12	H	IVC	7/7	17/17	ND	ND	18/18	4/22	4/22	20/20		ND	24/25	ND	14/15	ND	11/20	ND
13	H	IVC	6/7	12/17	ND	ND	18/24	13/13	13/13	20/20		ND	24/25	ND	11/15	ND	12/20	ND
14	H	IVC	6/7	12/17	ND	ND	18/24	14/14	14/14	20/20		ND	24/25	ND	11/11	ND	12/20	ND
15	H	IVC	7/7	12/17	ND	ND	12/18	13/25	13/25	20/20		ND	24/25	ND	11/15	ND	11/20	ND
16	H	IVC	6/6	12/17	ND	ND	18/22	13/13	13/13	20/20		ND	24/25	ND	11/11	ND	13/20	ND
17	H	No	6/7	12/15	ND	ND	12/18	13/13	13/13	20/20		ND	24/25	ND	11/11	ND	13/20	ND
18	H	No	6/7	12/15	ND	ND	18/18	13/13	13/13	20/20		ND	24/25	ND	11/15	ND	12/20	ND
19	H	No	6/6	12/17	ND	ND	16/18	13/22	13/22	20/20		ND	25/25	ND	12/16	ND	11/19	ND
20	H	No	ND	ND	ND	ND	ND	ND	ND	ND		ND	ND	ND	ND	ND	ND	ND
21	H	IVC	6/6	12/16	ND	ND	18/18	13/13	13/13	20/20		ND	24/25	ND	11/11	ND	11/20	ND
22	H	IVC	7/7	15/17	ND	ND	18/18	13/22	13/22	20/20		ND	24/25	ND	15/18	ND	12/20	ND
23	H	IVC	7/7	15/17	ND	ND	18/18	13/22	13/22	20/20		ND	24/25	ND	15/18	ND	13/20	ND
24	H	IVC	5/6	12/12	ND	ND	18/21	13/20	13/20	20/22		ND	24/25	ND	15/15	ND	20/22	ND

Abbreviations: C, Cohort; H, Hungary; S, Spain.

common iliac vein atresia, a different hypoplastic defect of the IVC system, with compensatory double IVC (Figure 2).

Overall, the prevalence of IVC system (IVC and/ or iliac vein) atresia among homozygous carriers of the Budapest 3 variant was 70.8% (95% CI: 48.9%–87.3%). This frequency was similarly high in both populations: 5/8 (62.5%, 95% CI: 24.5%–91.5%) in the Spanish cohort and 12/16 (75.0%, 95% CI: 47.6%–92.7%) in the Hungarian cohort.

### 3.3 | Laboratory and clinical characteristics of patients with and without IVC system atresia

Consistent with previous reports, homozygosity for the Budapest 3 variant was associated with severe type II antithrombin deficiency with very low anti-FXa activity (mean anti-FXa: 16.9%, 95% CI: 14.8%–19.0%) and nearly normal antigen levels (mean antigen: 79.4%, 95% CI: 75.6%–83.2%). Similar values were measured in patients with IVC system atresia (anti-FXa: 18.1%, 95% CI: 15.7%–20.6%; antigen: 81.7%, 95% CI: 77.4%–86.0%) and in those without (anti-FXa: 14.6%, 95% CI: 10.3%–18.9%; antigen: 74.5%, 95% CI: 66.9%–82.1%).

Clinically, all homozygous antithrombin Budapest 3 subjects included in the study, except for a 12-year-old child, had developed a thrombotic event at the time of enrollment. Seven subjects suffered from the first thrombotic episode during the pediatric/pubertal period, five of them (71.4%) with IVC atresia, and three (42.9%) were also carriers of the FV Leiden prothrombotic polymorphism. Sixteen homozygous carriers of the Budapest 3 variant had thrombosis in the adulthood, 10 of them (62.5%) with IVC system atresia, and three (18.8%) were also heterozygous for the FV Leiden polymorphism (Table 1).

Overall, median age at the first thrombotic episode was 24 years (95% CI: 18.0–30.0 years). Individuals with IVC system atresia were younger when they developed their first thrombotic event (median age = 21 years, 95% CI: 16.3–25.7) than patients without IVC atresia (median age = 30 years, 95% CI: 20.8–39.2).

All symptomatic carriers were on lifelong oral anticoagulant therapy after the first thrombotic episode, 11 with anti-vitamin K treatments and 12 with direct oral anticoagulants (DOACs). The rate of thrombosis recurrence was 10/24 (41.7%, 95% CI: 22.1%–63.3%), with no differences between patients with and without IVC system atresia: 7/16 (43.7%, 95% CI: 19.8%–70.1%) and 3/7 (42.9%, 95% CI: 10.0%–81.6%), respectively (Table 1). In both groups, the recurrences developed under oral anticoagulation except for two cases, the index case, who suffered the recurrence when the anticoagulation was removed due to the bleeding event and the case P11, who discontinued AVK (anti-vitamin K) treatment due to bad compliance. P10, P19, and P20 suffered recurrence under anticoagulation with AVK (INR in the therapeutic range), and therefore lifelong DOACs were introduced instead. Patient P20 suffered recurrent thrombosis during pregnancy, while on low-molecular-weight heparin treatment without antithrombin concentrate supplementation.

Regarding the type of thrombosis, all thrombotic episodes and their recurrences in patients with IVC system atresia were DVT of the lower extremities, except for three recurrent episodes in two patients, P8 and P11, that had unusual locations (splanchnic and stroke). No single case had pulmonary embolism (Table 1). The fact that in patients with IVC atresia pulmonary return is via the azygos circulation, making a more circuitous route to the lung, might explain this finding.

Finally, the vena cava was the localization of the thrombotic event in one patient with DVT who had no IVC agenesis (P2).

### 3.4 | Association of the IVC system atresia with SERPINC1 defects

As Spanish and Hungarian patients with antithrombin Budapest 3 shared the same haplotype and this genetic defect has been reported to be a founder defect,<sup>19</sup> it could be speculated that a recessive genetic variant affecting a neighboring gene and linked to the *SERPINC1* variant could be the real cause of the congenital malformation identified in carriers of this severe thrombophilia. To rule out this hypothesis, we evaluated 14 STRs. As shown in Table 2, genetic rearrangements, also affecting STRs close to *SERPINC1*, were detected in patients both with and without IVC system agenesis. The genes not covered by this analysis are shown in Table S1, but none of them has been previously directly or indirectly associated with a vascular disorder.

## 4 | DISCUSSION

We demonstrate a high prevalence of IVC atresia in patients carrying the antithrombin Budapest 3 variant in homozygous state. Antithrombin is probably the most important endogenous anticoagulant. The efficient inhibitory mechanism and the broad range of procoagulant proteases that this anticoagulant serpin inhibits (not only thrombin and FXa, but also FVIIa, FIXa, FXIa and FXIIa) explain why antithrombin deficiency was the first and so far the strongest thrombophilia that significantly increases the risk of thrombosis.<sup>20</sup> Antithrombin Budapest 3 (*p.Leu131Phe*) is a recurrent mutation that is relatively prevalent in central Europe, particularly in Hungary, according to its founder effect and suggested ancient origin,<sup>19</sup> which affects the heparin binding domain of antithrombin (type II HBS).<sup>18</sup> The intact progressive activity of this variant together with the negligible effect of the mutation in the beta antithrombin—a physiological glycoform with higher heparin affinity resulting from the inefficient glycosylation of Asn167—explains the mild risk of thrombosis associated with a heterozygous defect.<sup>21</sup> This also explains why antithrombin Budapest 3 is the only variant together with antithrombin Toyama (*p.Arg79Cys*, another type II HBS deficiency) that has been identified in homozygous state.<sup>20</sup> However, homozygous antithrombin Budapest 3 causes a severe hypercoagulable state that often leads to the development of premature, recurrent, and life-threatening thrombotic events.<sup>16,20</sup>



Thus, homozygous antithrombin Budapest 3 has been considered as one of the most severe viable thrombophilias.<sup>20</sup> Antithrombin deficiency is also crucial during embryo development. Complete absence of antithrombin causes embryonic lethality in animal models. In mice, until 14.5 gestational days, the frequency of living antithrombin<sup>-/-</sup> embryos matched the Mendelian rate, and their appearance was indistinguishable from that of antithrombin<sup>+/-</sup> or antithrombin<sup>+/+</sup> embryos. However, at 15.5 and 16.5 gestational days, approximately 70% and 100% of the antithrombin<sup>-/-</sup> embryos had died, respectively, showing extensive subcutaneous hemorrhage and fibrin(ogen) deposition in the degenerated myocardium and liver, suggestive of intravascular coagulation.<sup>22</sup> Additionally, disruption of the zebrafish antithrombin locus results in spontaneous venous thrombosis in larvae, and although homozygous mutants survive into early adulthood, they eventually succumb to massive intracardiac thrombosis.<sup>23</sup> Recently, we identified the first compound antithrombin deficiency in a human dead embryo.<sup>24</sup> Antithrombin deficiency is also prevalent in perinatal thrombosis, and pediatric thromboses are relatively common among patients homozygous for the Budapest 3 variant.<sup>16,25,26</sup> Particularly interesting to this study was the extensive thrombosis involving the IVC and the renal vein described by our group in a newborn homozygous for the Budapest 3 variant.<sup>27</sup> Thus, severe antithrombin deficiency states might also be involved in intrauterine or perinatal thrombosis.

Despite the fact that anomalies of the IVC and its variations were first described more than 200 years ago,<sup>28</sup> the molecular basis and pathological mechanism of this congenital disorder have been elusive so far. The identification in our study of IVC system atresia in 70.8% of patients homozygous for the *c.391C > T* variant in *SERPINC1* (*p.Leu131Phe*; antithrombin Budapest 3) and the STR data suggesting a minor, if any, effect of other linked genetic defect support an important role for this rare genetic defect in this rare vascular disorder. The fact that this finding was observed in two different populations (Spain and Hungary) reinforces this association, although the underlying mechanism remains to be determined. The signaling functions of antithrombin<sup>29</sup> may suggest that an impaired binding of this variant antithrombin to glyocalix/glycosaminoglycans could be important to the complex sequential remodeling of the abdominal venous system in the embryo. Alternatively, the inhibition of serine proteases involved in the signaling of the embryonic venous endothelium, smooth muscle cells, or other pericytes might be inefficient in carriers of the Budapest 3 variant. However, the gestational age timing between cava formation (4–8 gestational weeks) and the time when the expression of antithrombin mRNA and plasma levels can be initially detected in fetuses (5–10 gestational weeks)<sup>30</sup> strongly support an alternative hypothesis to explain the association between antithrombin Budapest 3 in homozygosis and IVC system atresia. The clues pointing to a thrombotic event in IVC during the embryonic development to explain the agenesis of this vein,<sup>5–9</sup> together with the severe hypercoagulable state of homozygous carriers of this *SERPINC1* variant, led us to speculate that an impaired control of thrombin during the development and perinatal life of Budapest 3 homozygous carriers might favor an

early thrombotic event affecting the IVC system. This thrombotic event might cause vein agenesis, and potentially atresia of other related organs (kidney or suprarenal glands). This malformation is totally or partially compensated by collateral circulation (azygos continuation) or even by additional countervailing malformations (such as double IVC in the case of iliac vein atresia). The identification of isolated cases with thrombophilias and agenesis of IVC, protein C deficiency,<sup>31</sup> protein S deficiency,<sup>32</sup> and other antithrombin deficiencies,<sup>10,33</sup> supports the association found in this study and encourages the search for congenital thrombophilia in cases with IVC atresia.

Why in utero thrombosis occurs in the IVC system over other vascular territories remains intriguing. The stepwise-pattern establishment of the early embryo vasculature,<sup>34</sup> coupled with the intrinsic complexity of IVC formation<sup>1</sup> and fetal circulation rheological factors,<sup>35</sup> might lead to more pronounced hypoxia and blood stasis in this vascular system. The combination of these factors with the severe hypercoagulable state associated with homozygous antithrombin Budapest 3 may be critical.

Further studies are required to validate the strong association between the severe thrombophilia (homozygous antithrombin Budapest 3) and IVC system atresia found in this study. Animal models might be an option, although we should be aware that these models do not always simulate human conditions. Indeed, previous studies and our own experience showed that no heterozygous type I antithrombin-deficient mice developed idiopathic thrombosis throughout their life.<sup>22</sup> Interestingly, a mouse model homozygous for the Toyama variant *p.Arg79Cys* had lethal consequences. Moreover, homozygosity for the Toyama variant was associated with spontaneous, often massive, thrombosis in the heart and, less frequently, in the lungs. Additionally, severe degeneration of the eyes was registered, often with disruption of the retina and occasionally perforation of the cornea, probably due to ocular vein occlusion. Signs of portal hypertension were also observed. Finally, an enlarged spleen was seen in homozygous mice, but no vascular malformation was reported.<sup>36</sup> Thus, we think that the best way to confirm the role of this and other congenital thrombophilias in this vascular malformation is the systematic screening of congenital thrombophilias among patients with IVC agenesis.

It also remains to be clarified why penetrance is not complete for IVC system defects in homozygous carriers of the Budapest 3 variant. Thrombosis is a complex multifactorial disease involving multiple factors, which include risk but also protective elements.<sup>37</sup> Thus, new studies are required to identify the factor(s) protecting from IVC system agenesis in a few homozygous carriers of antithrombin Budapest 3, who also had later thrombotic events in the adulthood.

Finally, our study also draws attention to the high thrombotic risk of patients with atresia of IVC during pediatric age or adulthood.<sup>13</sup> Certainly, the stasis and the collateral circulation induced by IVC absence will contribute to the increased risk of thrombosis of these patients; but if our hypothesis is confirmed by new studies, the presence of a severe thrombophilia in cases with IVC system atresia might support not only the role of a severe hypercoagulable state in the development of the first thrombotic event during embryogenesis but

also the recurrence during pediatric age/adulthood. In these cases, the benefits of prophylactic antithrombotic procedures under risk situations are expected according to the results observed in previous studies with carriers of severe thrombophilias.<sup>38,39</sup> Finally, as heparin is not effective in homozygous patients for the Budapest 3 variant, other antithrombotic prophylaxis and treatments for a highly possible thrombotic event, such as antithrombin concentrates,<sup>40</sup> must be used in patients with IVC system atresia homozygous for the Budapest 3 variant. Further studies are required to validate these findings.

In conclusion, although our study has the inherent limitations of a retrospective chart review design and some missing data, the small sample size, and complete data available only for 24/61 participants, we consider that our results show a strong association, supporting the finding of the first molecular defect involved in the agenesis of the IVC system, which sustains a role for severe thrombophilias in this vascular defect. These hypothesis-generating results should lead on to further research aimed at screening thrombophilic defects, not only homozygous antithrombin Budapest 3, in patients with IVC atresia, and probably with other similar vascular malformations.

#### ACKNOWLEDGMENTS

We sincerely appreciate the collaboration of Dr. F. López-Andreu (Hospital Reina Sofia, Murcia); C. Pascual (Hospital Gregorio Marañón, Madrid); A. Palomo (Hospital Materno Infantil, Málaga); S. Asenjo and P. Simal (Hospital San Carlos, Madrid), I. Bajusz, N. Sebő, and E. Varga (County Hospital Miskolc); and A. Róna-Tas and A. Selmezi (Health Centre of Hungarian Military Force, Budapest) for recruiting patients homozygous for the Budapest 3 variant. We also recognize the technical assistance of Nuria García-Barberá and Zsuzsanna Szabó. The study was supported by grants from the Hungarian National Research Development and Innovation Office (OTKA K116228), the Ministry of National Economy, Hungary (GINOP-2.3.2-15-2016-00039); the Instituto de Salud Carlos III and FEDER (PI18/00598); and the Fundación Séneca (19 873/GERM/15). MEM-B has a postdoctoral contract from University of Murcia, Spain. CB-P has a Río Hortega fellowship. BM-B has a postdoctoral fellowship from Fundación Séneca.

#### CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

#### AUTHOR CONTRIBUTIONS

MEM-B, RG, MS, CB-P, AM, BM-B, AM-C, RC-R and JP recruited the samples and performed experimental analysis. PI, IZ, ZO, JJ R-S, LE, MSI, JMG, ÁS, and AM-C recruited patients and clinical outcomes and designed the research. ME M-B, CB-P, VV, JC and ZB designed the research and wrote the paper. All authors read and approved the final manuscript.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

#### ORCID

María E. de la Morena-Barrio  <https://orcid.org/0000-0001-7426-4947>

Carlos Bravo-Pérez  <https://orcid.org/0000-0001-9794-7847>

Juan J. Rodríguez-Sevilla  <https://orcid.org/0000-0002-4741-7925>

María S. Infante  <https://orcid.org/0000-0003-0096-9359>

Belén de la Morena-Barrio  <https://orcid.org/0000-0002-6696-7762>

#### REFERENCES

- Bass JE, Redwine MD, Kramer LA, Huynh PT, Harris JH Jr. Spectrum of congenital anomalies of the inferior vena cava: cross-sectional imaging findings. *Radiographics*. 2000;20:639-652. <https://doi.org/10.1148/radiographics.20.3.g00ma09639>
- Oliveira JD, Martins I. Congenital systemic venous return anomalies to the right atrium review. *Insights Imaging*. 2019;10:115. <https://doi.org/10.1016/s13244-019-0802-y>
- Ghandour A, Partovi S, Karupphasamy K, Rajiah P. Congenital anomalies of the IVC—embryological perspective and clinical relevance. *Cardiovasc Diagn Ther*. 2016;6:482-492. <https://doi.org/10.21037/cdt.2016.11.18>
- Bass JE, Redwine MD, Kramer LA, Harris JH. Absence of the infrarenal inferior vena cava with preservation of the suprarenal segment as revealed by CT and MR venography. *Am J Roentgenol*. 1999; 172:1610-1612. <https://doi.org/10.2214/ajr.172.6.10350299>
- Milner LB, Marchan R. Complete absence of the inferior vena cava presenting as a paraspinous mass. *Thorax*. 1980;35:798-800. <https://doi.org/10.1136/thx.35.10.798>
- d'Archembeau O, Verguts L, Myle J. Congenital absence of inferior vena cava. *J Belge Radiol*. 1990;73:516-517.
- Haswell DM, Berrigan TJ. Anomalous inferior vena cava with accessory Hemiazygos continuation. *Radiology*. 1976;119:51-54. <https://doi.org/10.1148/119.1.51>
- Dougherty MJ, Calligaro KD, DeLaurentis DA. Congenitally absent inferior vena cava presenting in adulthood with venous stasis and ulceration: a surgically treated case. *J Vasc Surg*. 1996;23:141-146. [https://doi.org/10.1016/S0741-5214\(05\)80044-8](https://doi.org/10.1016/S0741-5214(05)80044-8)
- Ramanathan T, Michael T, Hughes D, Richardson AJ. Perinatal inferior vena cava thrombosis and absence of the infrarenal inferior vena cava. *J Vasc Surg*. 2001;33:1097-1099. <https://doi.org/10.1067/mva.2001.114205>
- Bianchi M, Giannini D, Balbarini A, Castiglioni MG. Congenital hypoplasia of the inferior vena cava and inherited thrombophilia: rare associated risk factors for idiopathic deep vein thrombosis. A Case Report. *J Cardiovasc Med*. 2008;9:101-104. <https://doi.org/10.2459/JCM.0b013e328014a8a4>
- Ruggeri M, Tosetto A, Castaman G, Rodeghiero F. Congenital absence of the inferior vena cava: a rare risk factor for idiopathic deep-vein thrombosis. *Lancet*. 2001;357:441. [https://doi.org/10.1016/S0140-6736\(00\)04010-1](https://doi.org/10.1016/S0140-6736(00)04010-1)
- Van Veen J, Hampton KK, Makris M. Kilt syndrome? *Br J Haematol*. 2002;118:1199-1200. <https://doi.org/10.1046/j.1365-2141.2002.370311.x>
- Sagban T, Scharf RE, Wagenhäuser MU, et al. Elevated risk of thrombophilia in agenesis of the vena cava as a factor for deep vein thrombosis. *Orphanet J Rare Dis*. 2015;10:3. <https://doi.org/10.1186/s13023-014-0223-4>
- De la Morena-Barrio B, Borràs N, Rodríguez-Alén A, et al. Identification of the first large intronic deletion responsible of type I antithrombin deficiency not detected by routine molecular diagnostic methods. *Br J Haematol*. 2019;186:e82-e86. <https://doi.org/10.1111/bjh.15913>
- de la Morena-Barrio M, Sandoval E, Llamas P, et al. High levels of latent antithrombin in plasma from patients with antithrombin

- deficiency. *Thromb Haemost.* 2017;117:880-888. <https://doi.org/10.1160/TH16-11-0866>
16. Gindele R, Selmezi A, Oláh Z, et al. Clinical and laboratory characteristics of antithrombin deficiencies: a large cohort study from a single diagnostic center. *Thromb Res.* 2017;160:119-128. <https://doi.org/10.1016/j.thromres.2017.10.023>
  17. Smillie RP, Shetty M, Boyer AC, Madrazo B, Jafri SZ. Imaging evaluation of the inferior vena cava. *Radiographics.* 2015;35:578-592. <https://doi.org/10.1148/rg.352140136>
  18. Olds RJ, Lane DA, Boisclair M, Sas G, Bock SC, Thein SL. Antithrombin Budapest 3 an antithrombin variant with reduced heparin affinity resulting from the substitution L99F. *FEBS Lett.* 1992;300:241-246. [https://doi.org/10.1016/0014-5793\(92\)80854-A](https://doi.org/10.1016/0014-5793(92)80854-A)
  19. Gindele R, Oláh Z, Ilonczai P, et al. Founder effect is responsible for the p.Leu131Phe heparin-binding-site antithrombin mutation common in Hungary: phenotype analysis in a large cohort. *J Thromb Haemost.* 2016;14:704-715. <https://doi.org/10.1111/jth.13252>
  20. Corral J, de la Morena-Barrio ME, Vicente V. The genetics of antithrombin. *Thromb Res.* 2018;169:23-29. <https://doi.org/10.1016/j.thromres.2018.07.008>
  21. Martínez-Martínez I, Navarro-Fernández J, Østergaard A, et al. Amelioration of the severity of heparin-binding antithrombin mutations by posttranslational mosaicism. *Blood.* 2012;120:900-904. <https://doi.org/10.1182/blood-2012-01-406207>
  22. Ishiguro K, Kojima T, Kadomatsu K, et al. Complete antithrombin deficiency in mice results in embryonic lethality. *J Clin Invest.* 2000;106:873-878. <https://doi.org/10.1172/JCI10489>
  23. Liu Y, Kretz CA, Maeder ML, et al. Targeted mutagenesis of zebrafish antithrombin III triggers disseminated intravascular coagulation and thrombosis, revealing insight into function. *Blood.* 2014;124:142-150. <https://doi.org/10.1182/blood-2014-03-561027>
  24. Bravo-Pérez C, Morena-Barrio ME, Palomo A, et al. Genotype-phenotype gradient of SERPINC1 variants in a single family reveals a severe compound antithrombin deficiency in a dead embryo. *Br J Haematol.* 2020;191:e32-e35. <https://doi.org/10.1111/bjh.16963>
  25. de la Morena-Barrio B, Orlando C, de la Morena-Barrio ME, Vicente V, Jochmans K, Corral J. Incidence and features of thrombosis in children with inherited antithrombin deficiency. *Haematologica.* 2019;104:2512-2518. <https://doi.org/10.3324/haematol.2018.210666>
  26. Kovac M, Mitic G, Djilas I, et al. Genotype phenotype correlation in a pediatric population with antithrombin deficiency. *Eur J Pediatr.* 2019;178:1471-1478. <https://doi.org/10.1007/s00431-019-03433-5>
  27. Kovac M, Mitic G, Jesic M, Djordjevic V, Muszbek L, Bereczky Z. Early onset of abdominal venous thrombosis in a newborn with homozygous type II heparin-binding site antithrombin deficiency. *Blood Coagul Fibrinolysis.* 2017;28:264-266. <https://doi.org/10.1097/MBC.0000000000000570>
  28. Abernethy J, Banks J. IX. Account of two instances of uncommon formation, in the viscera of the human body. *Philos Trans R Soc London.* 1793;83:59-66. <https://doi.org/10.1098/rstl.1793.0010>
  29. Rezaie AR, Giri H. Anticoagulant and signaling functions of antithrombin. *J Thromb Haemost.* 2020;18:3142-3153. <https://doi.org/10.1111/jth.15052>
  30. Hassan HJ, Leonardi A, Chelucci C, et al. Blood coagulation factors in human embryonic-fetal development: preferential expression of the FVII/tissue factor pathway. *Blood.* 1990;76:1158-1164.
  31. Tribe H, Borgstein R. Dysgenesis of the inferior vena cava associated with deep venous thrombosis and a partial protein C deficiency. *J Radiol Case Rep.* 2013;7:46-52. <https://doi.org/10.3941/jrcr.v7i11.1485>
  32. Liao W-L, Shih M-Y, Wang J. Venous thromboembolism in a young girl with duplication of the inferior vena cava and protein S deficiency. *Turk J Haematol.* 2019;36:133-135. <https://doi.org/10.4274/tjh.galenos.2019.2018.0332>
  33. Muscianese L, Seese RR, Graham W, Williams JH. Congenital atresia of the inferior vena cava and antithrombin III deficiency in a young adult: compounding risk factors for deep vein thrombosis. *BMJ Case Rep.* 2015;2015:bcr2014205729. <https://doi.org/10.1136/bcr-2014-205729>
  34. McGrath KE, Koniski AD, Malik J, Palis J. Circulation is established in a stepwise pattern in the mammalian embryo. *Blood.* 2003;101:1669-1675. <https://doi.org/10.1182/blood-2002-08-2531>
  35. Kiserud T, Acharya G. The fetal circulation. *Prenat Diagn.* 2004;24:1049-1059. <https://doi.org/10.1002/pd.1062>
  36. Dewerchin M, Héroult J-P, Wallays G, et al. Life-threatening thrombosis in mice with targeted Arg48-to-Cys mutation of the heparin-binding domain of antithrombin. *Circ Res.* 2003;93:1120-1126. <https://doi.org/10.1161/01.RES.0000103634.69868.4F>
  37. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. *Blood Transfus.* 2011;9:120-138. <https://doi.org/10.2450/2010.0066-10>
  38. Mahmoodi BK, Brouwer J-LP, Ten Kate MK, et al. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. *J Thromb Haemost.* 2010;8:1193-1200. <https://doi.org/10.1111/j.1538-7836.2010.03840.x>
  39. De Stefano V, Rossi E, Paciaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. *Haematologica.* 2002;87:1095-1108.
  40. Brown SA, Mitchell M, Cutler JA, Moore G, Smith MP, Savidge GF. Rapid genetic diagnosis in neonatal pulmonary artery thrombosis caused by homozygous antithrombin Budapest 3. *Clin Appl Thromb Hemost.* 2000;6:181-183. <https://doi.org/10.1177/10760296000600312>

## SUPPORTING INFORMATION

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

**How to cite this article:** de la Morena-Barrio ME, Gindele R, Bravo-Pérez C, et al. High penetrance of inferior vena cava system atresia in severe thrombophilia caused by homozygous antithrombin Budapest 3 variant: Description of a new syndrome. *Am J Hematol.* 2021;96(11):1363-1373. <https://doi.org/10.1002/ajh.26304>