Table S1 Clinical severity score. Assignment of the Bygum score based on the age at disease onset, number of organs ever affected, and need for long-term prophylaxis (1). Clinical severity score cumulated, 0–10 points. The Ferraro classification included the frequency of symptoms and their intensity based on averaged data since disease onset (for patients with long-term histories, the mean values for the past five years were taken into account) (2). * The sum of the frequency and intensity scores was used to classify the severity of the disease as follows: severe (≥7 points), moderate (5 or 6 points), mild (≤4 points), and asymptomatic (0 points).

	Bygum points	Ferraro points*
Age at onset: 0–5 years	3	n/a
Age at onset: 6–10 years	2	n/a
Age at onset: 11–20 years	1	n/a
Age at onset: >20 years	0	n/a
Skin edema	1	n/a
Painful abdominal edema	2	n/a
Laryngeal edema	2	n/a
Other clinical manifestations	1	n/a
Long-term prophylaxis	1	n/a
Frequency: >one episode a month	n/a	3
Frequency: between 6 and 11 episodes a year	n/a	2
Frequency: <6 episodes a year	n/a	1
no symptoms of angioedema	n/a	0
Intensity: presence of discomfort but no disruption in daily activity	n/a	2
Intensity: discomfort reducing normal daily activity	n/a	4
Intensity: inability to work or perform daily activity and/or necessity of hospital care	n/a	5

Table S2. Variants in the *SERPING1* gene identified in homozygous probands as well as two dominant variants that affect codon 322 but result in a different amino acid substitution.

				Predictive algorithm							
Region	**DNA change**	**Predicted protein change (immature)**	**C1-INH domain**	**EVE Score[1]**	**SIFT[2]**	**Poly Phen2[3]**	**CADD PHRED[4]**	**Mutation Taster[5]**	**MAF[6]**	**Existing variant**	**Reference**
exon 1	c.-161A>G	5'UTR		-	-	-	20.7	-	n.d.	rs1291031675	(3, 4)
exon 3	c.440T>A	p.Val147Glu	helix A'	*0.262*	0.01	0.458	16.53	Benign	n.d.	n.d.	(5)
exon 4	c.668A>C	p.Gln223Pro	s2A	0.823	0.01	0.694	25.1	Deleterious	n.d.	n.d.	(6)
exon 6	c.964G>A	p.Val322Met	s3C	0.689	0.00	0.99	26.7	Benign	n.d.	n.d.	present study
exon 6	c.965T>G‡	p.Val322Gly	s3C	0.562	0.00	0.996	24.7	Benign	n.d.	n.d.	(7)
exon 6	c.965T>A‡	p.Val322Glu	s3C	0.793	0.00	0.973	24.7	Benign	n.d.	n.d.	(6)
exon 6	c.965_967delTGC‡	p.Val322_323delinsAla	s3C	-	-	-	-	Deleterious	n.d.	n.d.	(6)
exon 7	c.1045C>T	p.Leu349Phe	s2B	0.548	0.03	*0.234*	23.4	Deleterious	6.36E-05	rs141075266	(6, 8)
exon 7	c.1198C>T⊥	p.Arg400Cys	loop s2C/s6A	0.708	0.00	0.99	23.0	Deleterious	4.77E-05	rs201363394	(9-13)
exon 7	c.1202T>C	p.Ile401Thr	s6A gate	0.535	0.00	0.909	24.7	Deleterious	n.d.	rs1263371770	(14, 15)
exon 8	c.1379C>T⊥	p.Ser460Phe	RCL[7] P7	0.658	0.00	0.993	22.8	Deleterious	n.d.	n.d.	(14, 15)
exon 8	c.1385T>G	p.Ile462Ser	RCL[7] P5	0.394	0.00	*0.029*	17.2	Deleterious	n.d.	rs763451792	(16)

[1]EVE (evolutionary model of variant effect) is an algorithm predicting the clinical significance of human variants based on sequences of divers organism across evolution (17). Score ranges from 1, most pathogenic, to 0, most benign. EVE class variants are categorized as pathogenic (underlined), uncertain (black), or benign (italics). No prediction possible is indicated with a minus.

[2]SIFT (Sorting Intolerant from Tolerant) is an algorithm predicting the effect of amino acid substitutions on protein function, with their negative results being more trusty than the positive ones (18). Scores <0.05 suggesting a deleterious change are underlined.

[3]PolyPhen-2 (polymorphism phenotyping 2) is a tool that predicts the possible impact of an amino acid substitution on the structure and function of a human protein (19). Protein transcript ENST00000278407 was used for the calculation. Score values <0.700 indicate a benign variant (shown in italics), including those with the variability of a possibly damaging effect (black). Likely damaging variants are underlined.

[4]CADD (combined annotation dependent depletion) is a tool that integrates diverse genome annotations to score the deleteriousness of single nucleotide variants as well as insertion/deletions variants in the human genome (20). The PHRED-like scaled CAAD score simplifies the interpretation of the raw CAAD score by

ranking it relative to all possible substitutions in the human reference genome (e.g., a score of 20 or greater indicates a raw score in the top 1% of all possible reference genome SNVs). The higher the score, the higher the probability of a deleterious effect of a variant.

[5]MutationTaster2021 is a tool predicting the effects of DNA variants, integrating publicly available sources of data, e.g., gnomAD, ExAC pLI scores, and ClinVar. It provides a binary prediction (deleterious or benign).

[6]Data of the minor allele frequency (MAF) of a variant originates from gnomADv2; variants not listed are indicated as n.d.

[7]RCL (reactive center loop), a sequence motif that is specifically recognized by target proteases.

‡This dominant variant affects the codon present in homozygous carriers but results in a different amino acid substitution.

⊥This variant has been described as likely pathogenic in several heterozygous carriers.

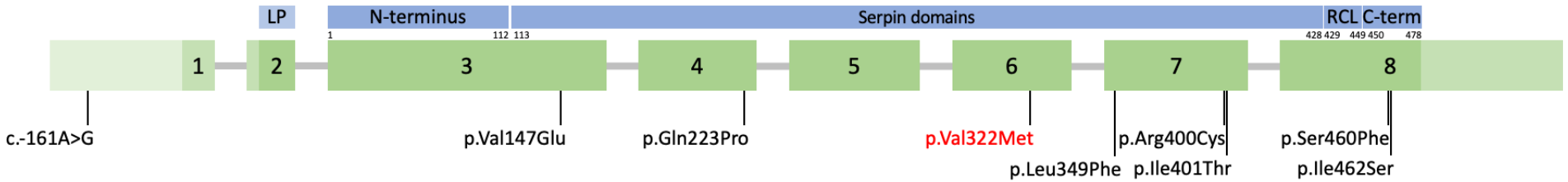

Figure S1. Distribution of the reported recessive variants in the *SERPING1* gene according to their mature protein numbering. The present variant is highlighted in red. Green boxes represent exons 1–8 with the CDS in dark green, light green boxes represent untranslated regions (UTRs). The main protein domains are depicted in blue. RCL, reactive centre loop; LP, leader peptide; serpin, serine protease inhibitor.

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