Table S1: individual clinical and genetic information on study participants.

Part 1: *ADAMTS13* mutations and genotype score.

Cohort	Patient number	Family number	Mutation	Mutation classification N-/C-terminal	Mutation severity score (=1 for N-terminal and =0 for C-terminal)	Genotype severity score (sum of mutation severity scores)
Bergamo	1	1	p.E1382Rfs*6	C	0	0
			p.E1382Rfs*6	C	0	
Bergamo	2	2	p.R1123C	C	0	0
			p.R1123C	C	0	
Bergamo	3	3	p.W1016*	C	0	1
			p.G236C	N	1	
Bergamo	4	4	p.W28Lfs*111	Not classified	NA	NA
			p.R1060W	C	1	
Bergamo	5	4	p.W28Lfs*111	Not classified	NA	NA
			p.R1060W	C	1	
UK	6	5	p.R1060W	C	0	0
			p.R1060W	C	0	
UK	7	6	p.R1206*	C	0	0
			p.R1060W	C	0	
UK	8	7	p.R1060W	C	0	0
			p.R1060W	C	0	
UK	9	8	p.R1060W	C	0	0
			p.R1060W	C	0	
UK	10	9	p.S240Afs*7	Not classified	NA	NA
			p.R910*	C	0	
UK	11	9	p.S240Afs*7	Not classified	NA	NA
			p.R910*	C	0	
UK	12	9	p.S240Afs*7	Not classified	NA	NA
			p.R910*	C	0	
France	13	10	p.R507Q	N	1	2
			p.A596V	N	1	
France	14	11	c.825-?_?del	Not classified	NA	NA
			p.C758R	N	0	
France	15	12	p.I79M	N	1	2
			p.R268P	N	1	
France	16	13	p.A596V	N	1	2
			p.A596V	N	1	
France	17	14	p.S1085Cfs*12	C	0	1
			p.S203P	N	1	
Milan	18	15	p.V88M	N	1	1
			p.G1239V	C	0	

Milan	19	16	p.E98Pfs*31	Not classified	NA	NA
			p.E1382Rfs*6	C	0	
Milan	20	17	p.C977_R979delinsW	C	0	0
			p.C977_R979delinsW	C	0	
Milan	21	18	p.I143T	N	1	2
			p.I143T	N	1	
Milan	22	19	p.Q436H	N	1	2
			p.Q436H	N	1	
Milan	23	20	p.R1060W	C	0	0
			p.R1060W	C	0	
Milan	24	21	p.R102C	N	1	2
			p. D235Y	N	1	
Milan	25	17	p.C977_R979delinsW	C	0	0
			p.C977_R979delinsW	C	0	
Milan	26	22	p.R193Q	N	1	1
			p.R1095W	C	0	
Milan	27	23	p.(S36_C37delfs*102)	Not classified	NA	NA
			p.(S36_C37delfs*102)	Not classified	NA	
Milan	28	24	p.S150P	N	1	2
			p.S150P	N	1	
Milan	29	25	p.A596V	N	1	1
			p.C1084Y	C	0	

Part 2: ADAMTS13 measurement by SELDI-TOF mass spectrometry.

Cohort	Patient Number	ADAMTS13 Activity°, %	A13:Act Replicate 1, %	A13:Act Replicate 2, %	A13:Act Difference in the two replicates, %
Bergamo	1	4.46	4.00	4.91	0.91
Bergamo	2	6.77	6.04	7.49	1.45
Bergamo	3	1.01	0.97	1.04	0.07
Bergamo	4	3.47	3.73	3.20	0.53
Bergamo	5	3.89	3.64	4.14	0.50
UK	6	4.73	4.66	4.79	0.13
UK	7	3.83	3.82	3.84	0.02
UK	8	6.37	5.82	6.93	1.11
UK	9	5.98	5.82	6.14	0.32
UK	10	0.54	0.52	0.56	0.04
UK	11	0.57	0.57	0.56	0.01
UK	12	1.42	1.45	1.39	0.06
France	13	3.49	3.34	3.65	0.31
France	14	6.67	6.27	7.07	0.80
France	15	2.39	2.16	2.61	0.45
France	16	4.97	4.71	5.23	0.52
France	17	2.39	2.47	2.31	0.16
Milan	18	5.14	5.27	5.02	0.25
Milan	19	1.96	1.96	1.96	0.00

Milan	20	3.08	3.07	3.08	0.01
Milan	21	0.25	0.25	0.25	0.00
Milan	22	0.25	0.25	0.25	0.00
Milan	23	5.94	5.89	5.98	0.09
Milan	24	1	0.94	1.06	0.12
Milan	25	1.79	1.71	1.87	0.16
Milan	26	5.53	5.69	5.38	0.31
Milan	27	0.67	0.65	0.70	0.05
Milan	28	1.28	1.27	1.29	0.02
Milan	29	0.25	0.25	0.25	0.00

°Measured by SELDI-TOF mass spectrometry

Part 3: Clinical phenotype.

Gender	Age at last follow-up	Total number of TTP episodes	Annual Rate of TTP episodes	FFP prophylaxis	Age at first TTP episode requiring treatment with FFP
M	36	26	0.72	1	18
M	36	Na*	Na*	0	21
M	29	5	0.17	0	5
F	38	4	0.11	0	20
F	36	1	0.03	0	28
F	25	1	0.04	0	24
F	32	3	0.09	0	30
F	30	1	0.03	0	29
F	42	2	0.05	0	32
M	6	23	3.83	1	0.16
M	13	30	2.31	1	0.16
M	15	56	4	1	0.16
F	27	10	0.37	1	0.16
M	18	6	0.33	1	0.16
F	13	10	0.77	1	0.16
F	14	8	0.57	0	0.16
F	16	2	0.33	0	0.16
M	66	10	0.37	0	23
F	27	6	0.09	1	15

M	29	4	0.14	0	22
M	22	5	0.23	0	11
M	9	30	3.33	1	0.16
F	28	2	0.07	0	18
F	9	5	0.56	0	2
M	34	1	0.03	0	29
F	36	1	0.03	0	32
F	4	3	0.75	1	0.16
F	8	1	0.13	Na**	5
M	3	8	2.57	1	1

*Chronic jaundice and thrombocytopenia

**Current prophylaxis status unknown

Part 3: Clinical phenotype (continued).

Cohort	Patient Number	Persistent renal or neurological damage	History of neonatal jaundice or thrombocytopenia
Bergamo	1	1	0
Bergamo	2	1	1
Bergamo	3	0	0
Bergamo	4	0	0
Bergamo	5	0	0
UK	6	0	0
UK	7	0	0
UK	8	0	0
UK	9	0	0
UK	10	0	1
UK	11	0	1
UK	12	0	1
France	13	0	1
France	14	0	1
France	15	0	1
France	16	1	1
France	17	0	1
Milan	18	0	0
Milan	19	0	0

Milan	20	0	0
Milan	21	0	0
Milan	22	0	1
Milan	23	0	0
Milan	24	0	0
Milan	25	0	0
Milan	26	0	0
Milan	27	0	1
Milan	28	0	0
Milan	29	0	0

Table S2. List of protein sequences, functionally related with ADAMTS13, used by SIFT to predict the weighted probability of aminoacid substitutions.

GI identifier	**Protein**	**Organism**
gi16306598	von Willebrand factor-cleaving protease	Homo sapiens
gi355567362	hypothetical protein EGK_07235	Macaca mulatta
gi296191110	A disintegrin and metalloproteinase with thrombospondin motifs 13	Callithrix jacchus
gi332833255	A disintegrin and metalloproteinase with thrombospondin motifs 13	Pan troglodytes
gi355752956	hypothetical protein EGM_06555	Macaca fascicularis
gi332255397	A disintegrin and metalloproteinase with thrombospondin motifs 13	Nomascus leucogenys
gi335281186	A disintegrin and metalloproteinase with thrombospondin motifs 13	Sus scrofa
gi354499351	A disintegrin and metalloproteinase with thrombospondin motifs 13	Cricetulus griseus
gi301770673	A disintegrin and metalloproteinase with thrombospondin motifs 13	Ailuropoda melanoleuca
gi47076321	vWF-cleaving protease	Mus musculus
gi76671947	A disintegrin and metalloproteinase with thrombospondin motifs 13	Bos taurus
gi348574536	A disintegrin and metalloproteinase with thrombospondin motifs 13	Cavia porcellus
gi334311967	A disintegrin and metalloproteinase with thrombospondin motifs 13	Monodelphis domestica
gi351702668	A disintegrin and metalloproteinase with thrombospondin motifs 14	Heterocephalus glaber
gi291416170	ADAM metallopeptidase with thrombospondin type 1 motif, 13	Oryctolagus cuniculus
gi337298368	ADAM metallopeptidase with thrombospondin type 1 motif, 13	Canis lupus familiaris
gi301627601	A disintegrin and metalloproteinase with thrombospondin motifs 13-like	Xenopus (Silurana) tropicalis
gi47214646	Unnamed protein product	Tetraodon nigroviridis
gi170587999	ADAM-TS Spacer 1 family protein	Brugia malayi
gi327277760	A disintegrin and metalloproteinase with thrombospondin motifs 9-like	Anolis carolinensis
gi324499880	A disintegrin and metalloproteinase with thrombospondin motifs gon-1	Ascaris suum
gi312073463	hypothetical protein	Loa loa
gi341881902	CBN-GON-1 protein	Caenorhabditis brenneri

gi187036667	CBR-GON-1 protein	Caenorhabditis briggsae AF16
gi189310657	Protein GON-1, isoform a	Caenorhabditis elegans
gi308481215	CRE-GON-1 protein	Caenorhabditis remanei
gi194225985	A disintegrin and metalloproteinase with thrombospondin motifs 13	Equus caballus
gi344276566	A disintegrin and metalloproteinase with thrombospondin motifs 9	Loxodonta africana
gi224073646	ADAM metallopeptidase with thrombospondin type 1 motif, 13	Taeniopygia guttata
gi326930462	A disintegrin and metalloproteinase with thrombospondin motifs 13-like	Meleagris gallopavo
gi345305489	A disintegrin and metalloproteinase with thrombospondin motifs 20-like	Ornithorhynchus anatinus
gi363740569	A disintegrin and metalloproteinase with thrombospondin motifs 13	Gallus gallus
gi291233410	A disintegrin-like and metalloprotease with thrombospondin type 1 motifs 9B-like	Saccoglossus kowalevskii
gi293348901	A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 20	Rattus norvegicus
gi156554461	A disintegrin and metalloproteinase with thrombospondin motifs 9-like	Nasonia vitripennis
gi307177515	A disintegrin and metalloproteinase with thrombospondin motifs 9	Camponotus floridanus
gi242016083	ADAMTS-15 precursor, putative	Pediculus humanus corporis
gi326670284	A disintegrin and metalloproteinase with thrombospondin motifs 13	Danio rerio
gi317419046	A disintegrin and metalloproteinase with thrombospondin motifs 9	Dicentrarchus labrax
gi156393647	Predicted protein, partial	Nematostella vectensis
gi348516300	A disintegrin and metalloproteinase with thrombospondin motifs 13-like	Oreochromis niloticus
gi115961217	Similar to ADAM metallopeptidase with thrombospondin type 1 motif, 16 preproprotein	Strongylocentrotus purpuratus
gi297674911	a disintegrin and metalloproteinase with thrombospondin motifs 16-like	Pongo abelii
gi328712328	A disintegrin and metalloproteinase with thrombospondin motifs 9	Acyrthosiphon pisum
gi332022171	A disintegrin and metalloproteinase with thrombospondin motifs 7	Acromyrmex echinatior
gi340729183	A disintegrin and metalloproteinase with thrombospondin motifs 7-like	Bombus terrestris

gi350417726	A disintegrin and metalloproteinase with thrombospondin motifs 7-like	Bombus impatiens
gi221130399	similar to abnormal GONad development family member (gon-1)	Hydra magnipapillata
gi328791471	A disintegrin and metalloproteinase with thrombospondin motifs 7-like	Apis mellifera
gi307204909	A disintegrin and metalloproteinase with thrombospondin motifs 7	Harpegnathos saltator
gi157110122	Adamts-7	Aedes aegypti
gi198434768	similar to ADAMTS-18 precursor (A disintegrin and metalloproteinase with thrombospondin motifs 18)	Ciona intestinalis
gi241752359	Thrombospondin-like protein, putative	Ixodes scapularis
gi229286595	Hypothetical protein BRAFLDRAFT_81341	Branchiostoma floridae
gi125980875	GA17954 - gene product from transcript GA17954-RA	Drosophila pseudoobscura pseudoobscura
gi195162497	GL14460 gene product from transcript GL14460-RA	Drosophila persimilis
gi270002066	Hypothetical protein TcasGA2_TC001014	Tribolium castaneum
gi347965338	AGAP001113-PA, partial	Anopheles gambiae str. PEST
gi321479334	Hypothetical protein	Daphnia pulex
gi195043400	GH12754 gene product from transcript GH12754-RA	Drosophila grimshawi
gi195131919	GI15899 gene product from transcript GI15899-RA	Drosophila mojavensis
gi195340560	GM12429 gene product from transcript GM12429-RA	Drosophila sechellia
gi281359911	CG4096 gene product from transcript CG4096-RB	Drosophila melanogaster
gi195396533	GJ16647 gene product from transcript GJ16647-RA	Drosophila virilis
gi194888962	GG18778 gene product from transcript GG18778-RA	Drosophila erecta
gi194764322	GF20800 gene product from transcript GF20800-RA	Drosophila ananassae
gi195448967	GK24921 gene product from transcript GK24921-RA	Drosophila willistoni
gi55249587	Adamts1 protein	Xenopus laevis
gi195501264	GE26372 gene product from transcript GE26372-RA	Drosophila yakuba
gi357614481	Hypothetical protein	Danaus plexippus
gi157278173	ADAMTS-1 protein precursor	Oryzias latipes
gi313245795	Unnamed protein product	Oikopleura dioica

gi34452244	Egg bindin receptor protein 1 precursor	Strongylocentrotus franciscanus
gi170069658	Adamts-7	Culex quinquefasciatus
gi195996845	Hypothetical protein	Trichoplax adhaerens
gi112983432	A disintegrin and metalloproteinase with thrombospondin motifs 1 precursor	Bombyx mori
gi268580489	C. briggsae CBR-ADT-1 protein	Caenorhabditis briggsae
gi195574509	GD18032 gene product from transcript GD18032-RA	Drosophila simulans
gi6164595	Lacunin - large multidomain extracellular matrix protein	Manduca sexta
gi290886119	ADAM metallopeptidase with thrombospondin type 1 motif 1	Ovis aries
gi13346812	Thrombospondin	Haemonchus contortus
gi256071138	ADAMTS5 peptidase (M12 family)"	Schistosoma mansoni
gi170791244	Thrombospondin-like protein	Dictyocaulus viviparus
gi358338697	A disintegrin and metalloproteinase with thrombospondin motifs 3	Clonorchis sinensis
gi339237895	Papilin	Trichinella spiralis
gi312373041	Hypothetical protein	Anopheles darlingi
gi301130834	Papilin	Rhipicephalus microplus
gi322787488	Hypothetical protein	Solenopsis invicta
gi218780434	Thrombospondin, type 1 repeat-containing protein	Desulfatibacillum alkenivorans AK-01
gi320169775	Thrombospondin	Capsaspora owczarzaki ATCC 30864
gi307111205	Hypothetical protein	Chlorella variabilis
gi340378441	Hypothetical protein	Amphimedon queenslandica
gi323650036	A disintegrin and metalloproteinase with thrombospondin motifs 16	Perca flavescens
gi226457552	Predicted protein	Micromonas pusilla CCMP1545
gi146271971	HyTSR1 protein	Hydra vulgaris
gi110735379	Rhamnospondin	Hydractinia symbiolongicarpus
gi139689701	Hypothetical protein	marine metagenome
gi339521865	Thrombospondin 1	Capra hircus
gi13928546	Complement component C6	Branchiostoma belcheri

Table S3. Multiple measurements in the same patients on different samples. Similar residual activity was measured in samples collected months apart from the same patients.

Patient NO (see Supplementary Material S1)	ADAMTS13 activity*	A13:Act Replicate 1	A13:Act Replicate 2
9	5.98	5.82	6.14
	5.19	4.97	5.41
26	5.53	5.69	5.38
	6.57	6.81	6.33
27	0.67	0.65	0.70
	0.58	0.58	0.59

*****Measured by SELDI-TOF mass spectrometry

Tables S4. ADAMTS13 missense mutations and polymorphisms and their functional annotation.

Protein	SIFT	Polyphen 2	PMut	Align GVGD
TTP associated mutations				
p.I79M	T	BEN	NEUTRAL	C0
p.V88M	A	PROD	NEUTRAL	C15
p.H96D	A	PROD	NEUTRAL	C65
p.R102C	T	PROD	NEUTRAL	C65
p.S119F	A	PROD	NEUTRAL	C65
p.I178T	A	PROD	NEUTRAL	C65
p.R193W	A	PROD	PATHOLOGICAL	C65
p.T196I	A	PROD	NEUTRAL	C65
p.S203P	T	PROD	PATHOLOGICAL	C65
p.L232Q	A	PROD	NEUTRAL	C65
p.H234Q	A	PROD	NEUTRAL	C15
p.D235H	A	PROD	NEUTRAL	C65
p.G236C	A	PROD	NEUTRAL	N/D
p.A250V	A	PROD	NEUTRAL	C65
p.S263C	A	PROD	NEUTRAL	C65
p.R268P	T	BEN	NEUTRAL	C65
p.Y304C	T	PROD	NEUTRAL	C65
p.C311Y	A	PROD	PATHOLOGICAL	C65
p.R312Q	T	PROD	NEUTRAL	C35
p.C322G	A	PROD	NEUTRAL	C65
p.T323R	T	PROD	PATHOLOGICAL	C65
p.F324L	T	PROD	NEUTRAL	C15
p.C347S	A	PROD	NEUTRAL	C65
p.R349C	A	PROD	NEUTRAL	C65
p.P353L	A	PROD	NEUTRAL	C65
p.G385E	A	PROD	PATHOLOGICAL	C65
p.W390C	A	PROD	PATHOLOGICAL	C65
p.R398C	A	PROD	NEUTRAL	C35
p.R398H	A	PROD	PATHOLOGICAL	C25
p.C438S	A	PROD	NEUTRAL	C65
p.R507Q	T	PROD	PATHOLOGICAL	C35
p.C508Y	A	PROD	PATHOLOGICAL	C65
p.G525D	A	PROD	PATHOLOGICAL	C65

Table S4. *(continued).*

Protein	SIFT	Polyphen 2	PMut	Align GVGD
TTP associated mutations				
p.R528G	T	PROD	PATHOLOGICAL	C65
p.G550R	A	PROD	PATHOLOGICAL	C65
p.A596V	T	PROD	NEUTRAL	C65
p.A606P	T	PROD	PATHOLOGICAL	C25
p.P671L	T	PROD	PATHOLOGICAL	C65
p.I673F	T	PROD	NEUTRAL	C15
p.R692C	T	PROD	NEUTRAL	C65
p.Q723K	T	BEN	PATHOLOGICAL	C45
p.C758R	A	PROD	PATHOLOGICAL	C65
p.C908S	A	PROD	PATHOLOGICAL	C65
p.C908Y	A	PROD	PATHOLOGICAL	C65
p.G909R	A	PROD	PATHOLOGICAL	C65
p.C951G	A	PROD	PATHOLOGICAL	C65
p.C1024R	A	PROD	PATHOLOGICAL	C65
p.C1024G	A	PROD	PATHOLOGICAL	C65
p.R1060W	A	PROD	PATHOLOGICAL	C65
p.R1123C	A	PROD	PATHOLOGICAL	C65
p.C1213Y	A	PROD	PATHOLOGICAL	N/D
p.I1217T	A	PROD	PATHOLOGICAL	N/D
p.R1219W	A	PROD	PATHOLOGICAL	N/D
p.G1239V	A	PROD	PATHOLOGICAL	N/D
p.R1336W	A	PROD	PATHOLOGICAL	N/D
ADAMTS13 polymorphisms				
p.R7W	T	BEN	PATHOLOGICAL	C65
p.T339R	T	PROD	NEUTRAL	C65
p.Q448E	T	BEN	NEUTRAL	C25
p.Q456H	A	BEN	NEUTRAL	C15
p.P457L	T	PROD	NEUTRAL	C65
p.P475S	T	BEN	PATHOLOGICAL	C65

Table S4. *(continued).*

Protein	**SIFT**	**Polyphen 2**	**PMut**	**Align GVGD**
ADAMTS13 polymorphisms				
p.R484K	T	BEN	NEUTRAL	C25
p.V604I	T	BEN	NEUTRAL	C25
p.P618A	T	PROD	NEUTRAL	C25
p.R625H	T	PROD	PATHOLOGICAL	C25
p.E634K	T	BEN	NEUTRAL	C55
p.A732V	T	PROD	NEUTRAL	C65
p.E740K	T	BEN	NEUTRAL	C55
p.V832M	T	PROD	NEUTRAL	C15
p.A900V	T	BEN	NEUTRAL	C65
p.S903L	T	BEN	PATHOLOGICAL	C65
p.G982R	T	PROD	PATHOLOGICAL	C65
p.A1033T	T	PROD	NEUTRAL	C55
p.R1096H	T	BEN	PATHOLOGICAL	C25
p.T1226I	T	BEN	PATHOLOGICAL	N/D

T, tolerated; A, affects protein function; BEN, benign; PROD, probably damaging; N/D, not determinable with Align GVGD software.

For Align GVGD the reported number reflects the severity of the effect of the mutation on the protein, with C0 being the least severe and C65 being the most severe.