The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: key findings at enrollment until 2017

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Supplemental Material

Supplementary Appendix A

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Collaborative Institute:

Versiti Wisconsin, Inc. (d/b/a BloodCenter of Wisconsin), Milwaukee, WI, USA

Supplementary Appendix B

Publications in which confirmed patients of the Hereditary TTP Registry have been reported

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Supplemental Methods

Eligibility

The diagnosis of congenital TTP is established through the following diagnostic criteria:

1. An available suitable patient or family history.
2. A severe ADAMTS13 deficiency (ADAMTS13 activity ≤10% of normal) in the absence of an ADAMTS13 inhibitor, documented in plasma samples withdrawn at two different time points with an interval of more than 14 days.

3a. Identified homozygous or compound heterozygous *ADAMTS13* gene mutations, or

3b. A plasma infusion trial with a full ADAMTS13 recovery and plasma half-life of 2-4 days.[1,2]

Patients fulfilling criteria 1, 2, and either 3a or 3b are enrolled as *confirmed patients.* Patients are enrolled as *suspected patients* when criteria 1 and 2 are met with no or only one *ADAMTS13* mutation identified and no testing for ADAMTS13 recovery and half-life has been performed.

Data collection at enrolment

Data were collected through a web-based electronic database, consisting of case report forms (webspirit®, 2mt software, Ulm, Germany), with secure access via the study's website www.ttpregistry.net.

The following data were captured in collaboration with the treating physicians at enrolment: biochemical and clinical data on the course of cTTP up to enrolment; possible triggers of acute episodes (i.e. pregnancy, infections); past and current treatment provided, including plasma therapy.

Overt disease onset and acute episode definitions

To determine "probable" overt disease onset for each patient, entered data were individually evaluated from the neonatal period until age at enrolment, including the earliest reported acute episode and time-point of clinical diagnosis. Overt disease onset was defined as the first reported occurrence of thrombocytopenia in combination with 2 or more other features such as prolonged hyperbilirubinemia, petechiae, anemia, hemolysis, schistocytes, or other disorders (e.g. epileptic seizures, mental impairment) for which the patient had received therapeutic intervention, e.g. exchange blood transfusion, blood or platelet transfusion, plasma infusion, plasmapheresis, etc.

Reported TTP episodes represent acute illnesses for which the patient had sought medical care and had received various treatments. Remission was defined as no (new) clinical signs, no laboratory abnormalities, achieved usually by plasma therapy and maintained for ≥ 30 days after stopping plasma therapy. A relapse is defined as an acute TTP episode after achieving remission, as defined for immune-mediated TTP.[3-5]

Statistical analysis

Data of confirmed cTTP patients enrolled in the Hereditary TTP Registry until 2017 were evaluated. Categorical variables are reported as numbers and percentages and compared between groups with Fisher's exact test. Continuous data are reported as median and range (and 25th and 75th percentiles for certain variables), and compared by Wilcoxon rank-sum test. To check for equal distribution of patients in two groups (compound heterozygotes vs homozygotes), an exact binomial probability test

with a reference probability of 50% was used. Spearman's rank correlation was used to compare age at overt disease onset with residual ADAMTS13 activity level. All analyses were done with Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX). A level of significance of $\alpha = 0.05$ was assumed.

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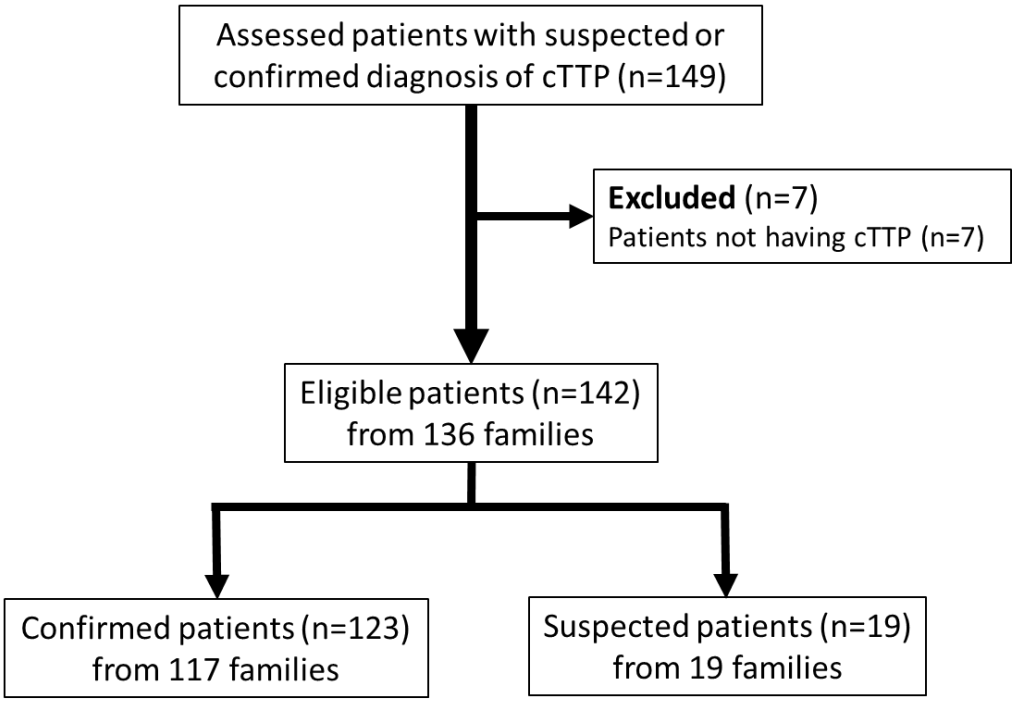
Supplementary Figure S1.

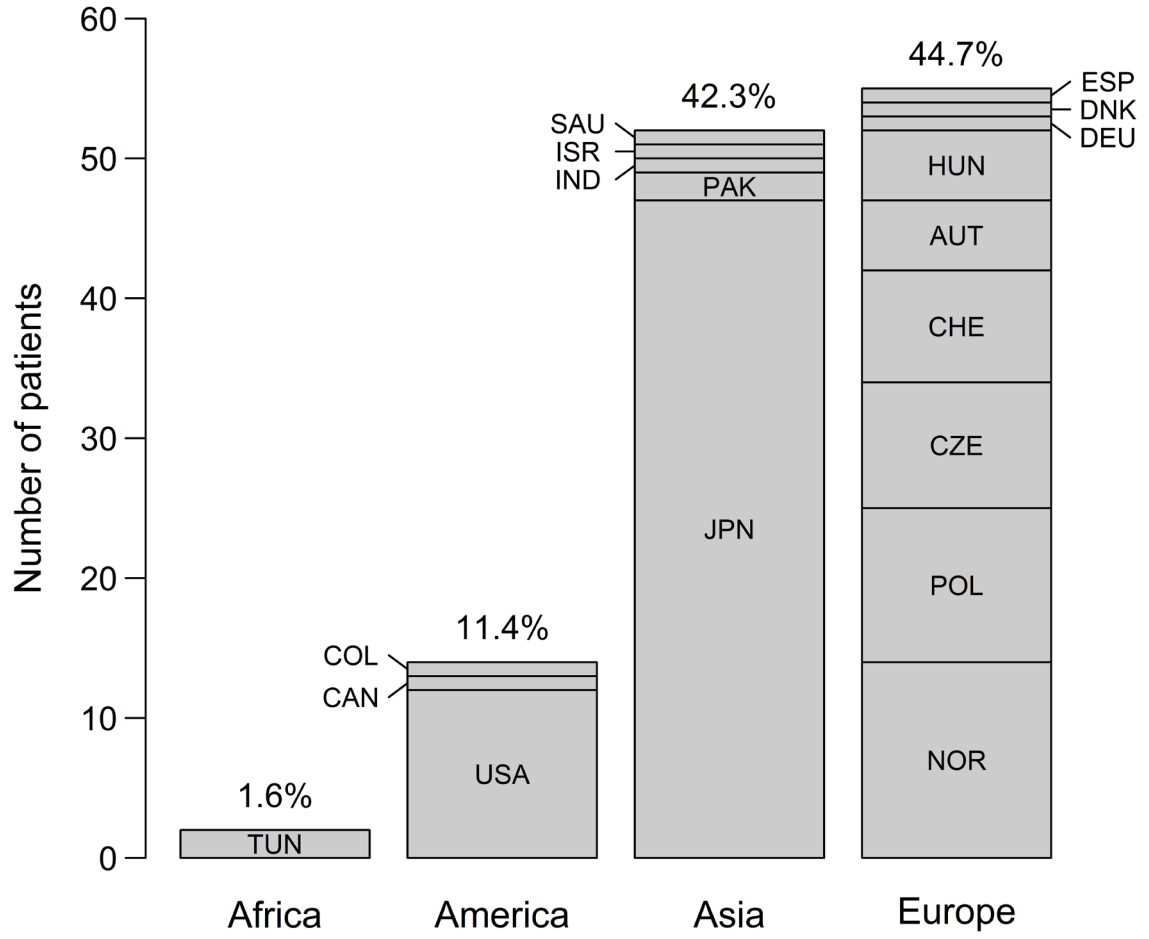
Flow chart of patient enrolment into the Hereditary TTP Registry until the end of 2017



Supplementary Figure S2.

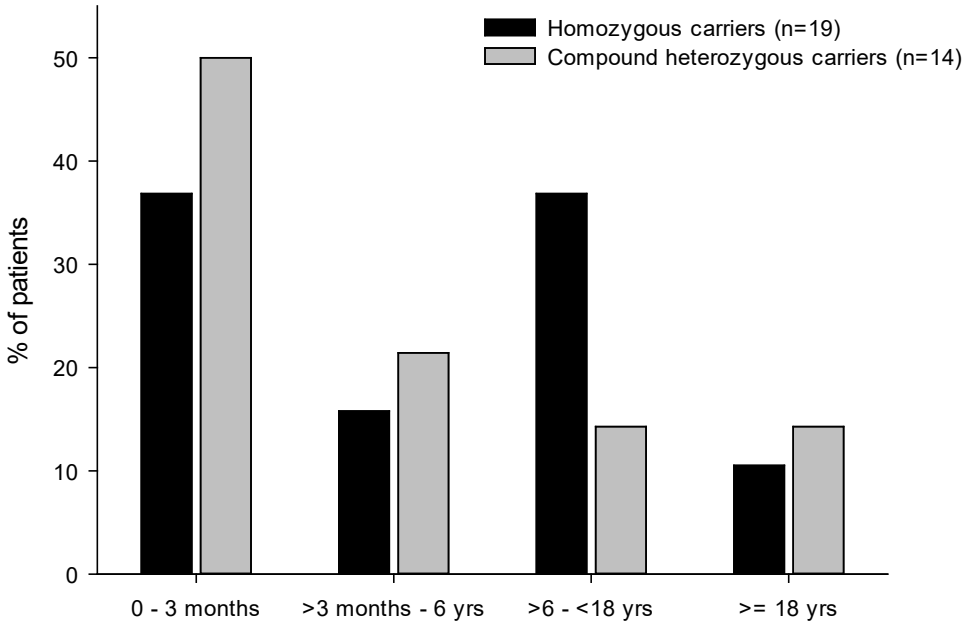
Enrolment of 123 confirmed cTTP patients through the different international sites.

The following number of patients were enrolled from different countries in Europe (total n=55): 14 patients from Norway (NOR), 11 from Poland (POL), 9 from the Czech Republic (CZE), 8 from Switzerland (CHE), 5 from Austria (AUT), 5 from Hungary (HUN), and 1 each from Germany (DEU), Denmark (DNK), and Spain (ESP). In Asia (n=52), 47 patients were enrolled from Japan, 2 patients from Pakistan (PAK), and 1 patient each from India (IND), Israel (ISR), and Saudi Arabia (SAU). From the American continents, 12 patients were enrolled from the United States of America (USA), and 1 patient each from Canada (CAN), and Colombia (COL). From Africa, 2 patients were enrolled from Tunisia (TUN)



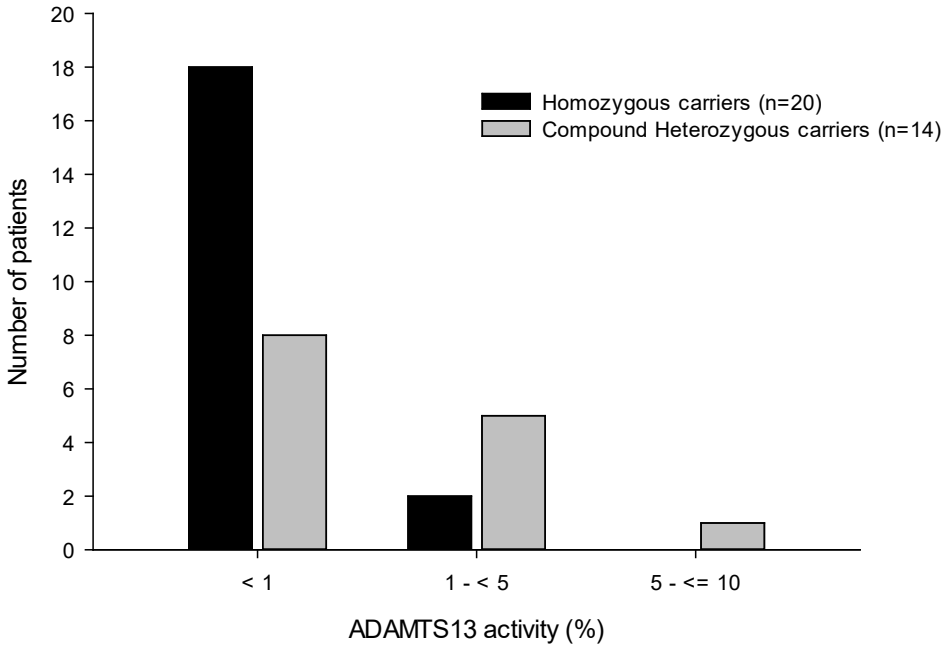
Supplementary Figure S3.
Disease onset and ADAMTS13 activity in carriers of the ADAMTS13 c.4143_4144dupA mutation

Panel **A**. Proportion of homozygous and compound heterozygous carriers of the *ADAMTS13* c.4143_4144dupA mutation by different age ranges at disease onset. Median age at disease onset for homozygous carriers is 5.0 (0-22.3) and for compound heterozygous carriers 1.1 years (0-35.0) (P = 0.6). Panel **B.** Homozygous and compound heterozygous carriers by ADAMTS13 activity. Panel **C.** Individual disease onset in all *ADAMTS13* c.4143_4144dupA mutation carriers having an ADAMTS13 activity <1%. Information available for 15 homozygous (H) and 7 compound heterozygous (CH) carriers. Median age of disease onset is represented by a horizontal line.

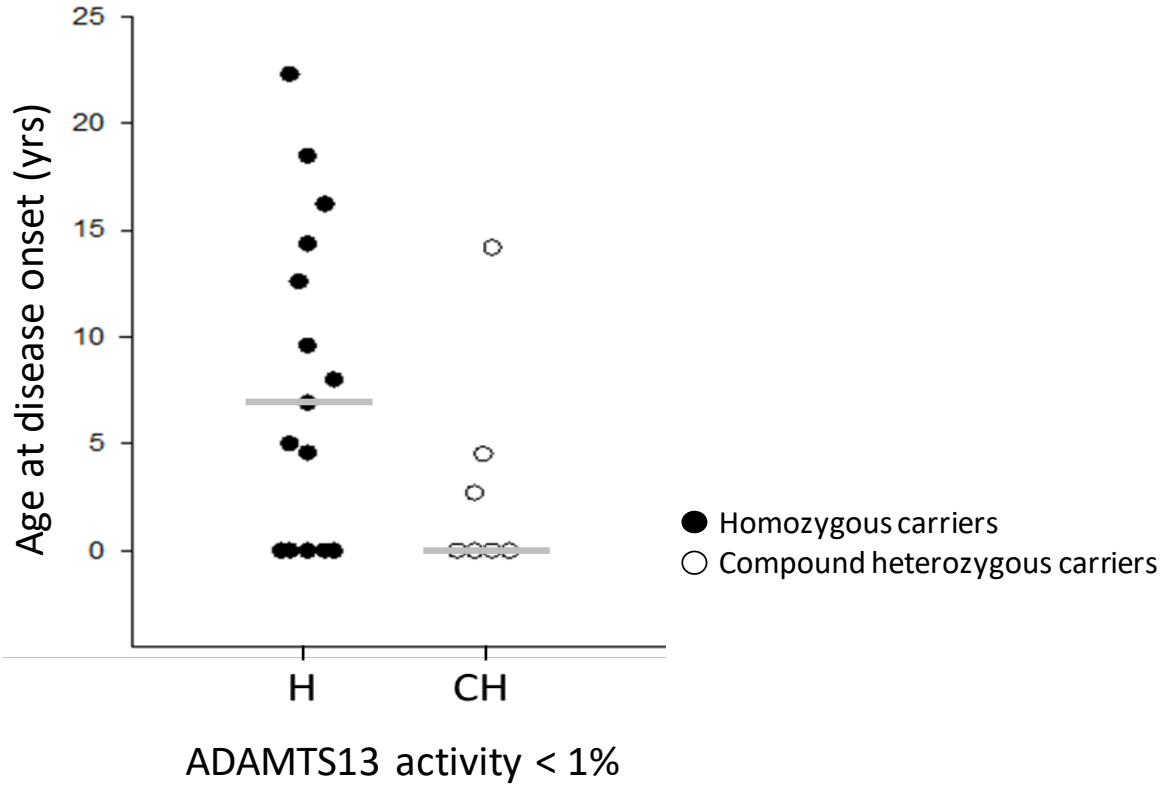


A

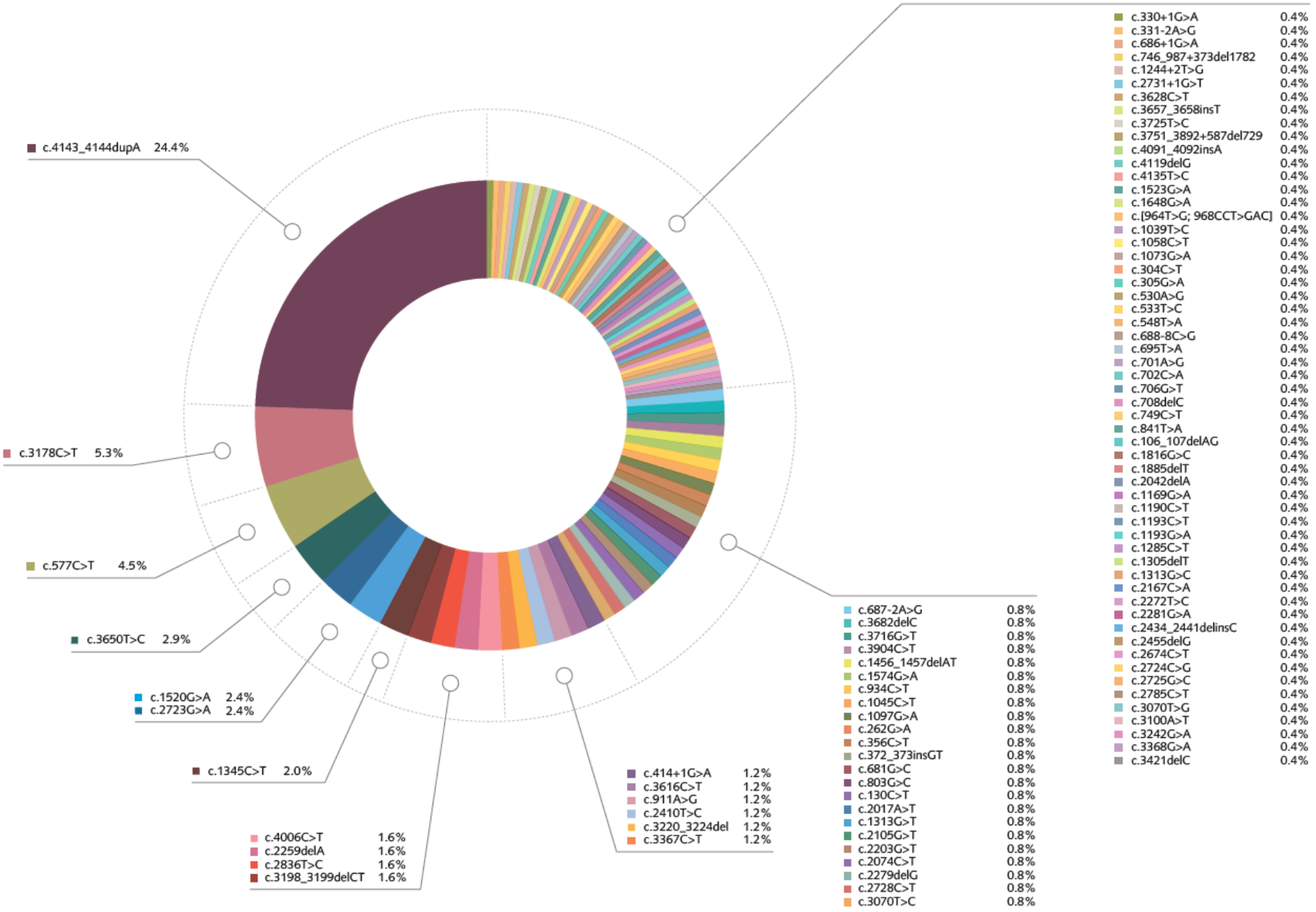
B


Homozygous carriers (n=20)
Compound Heterozygous carriers (n=14)
Number of patients
0
2
4
6
8
10
12
14
16
18
20
< 1
1 - < 5
5 - <= 10
ADAMTS13 activity (%)

C


Age at disease onset (yrs)
0
5
10
15
20
25
H
CH
ADAMTS13 activity < 1%
Homozygous carriers
Compound heterozygous carriers

Supplementary Figure S4. **Allelic frequency of the different *ADAMTS13* mutations (n=97) found in 123 confirmed cTTP patients.**



Supplementary Table S1. Comparison of ADAMTS13 activity assays using plasma samples of 41 confirmed cTTP patients

ADAMTS13 activities between assays correlated well (r=0.7) and were concordant in 33/41 samples (of the concordant samples 22/33 had an ADAMTS13 activity ≤ 1% by both assays, and a measurable ADAMTS13 activity between 1.1-11.9% in 11/33 samples). In an additional five samples, ADAMTS13 activity was <LLQ by one and 1.1-1.8% by the other assay. Mean paired difference ± SD was 0.81% ± 2.3%.

Patient number*	Date sample withdrawn	*ADAMTS13* mutation		modified FRETS-VWF73 assay** (%)	chromogenic ADAMTS13-ACT ELISA*** (%)
		Mutation 1	Mutation 2		
1	29.03.2004	p.H234Q	p.R1206X	<1	<0.5
2	16.06.2004	c.4143_4144dupA	c.4143_4144dupA	<1	0.7
3	06.08.2004	p.R1060W	p.R1060W	5.4	6.7
4	28.10.2004	c.4143_4144dupA	c.4143_4144dupA	<1	1.6
5	13.04.2005	c.1885delT	p.C908Y	<1	<0.5
6	13.07.2005	p.C946R	c.3198delCT	1.1	1.1
7	27.09.2005	c.2000delA	p.R1219Q	6.7	2.8
8	18.10.2005	p.G385E	p.R1206X	1.0	<0.5
9	06.01.2006	c.4143_4144dupA	c.4143_4144dupA	<1	0.9
10	13.04.2006	c.4143_4144dupA	c.4143_4144dupA	1.4	<0.5
11	24.04.2006	p.W688X	p.W688X	<1	<0.5
12	29.05.2006	p.R193W	p.R193W	<1	<0.5
13	31.08.2006	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
14	11.09.2006	p.Y177C	p.R1060W	6.2	5.9
15	06.10.2006	p.R1060W	p.R1060W	1.8	0.9
16	29.06.2007	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
17	29.07.2007†	c.4143_4144dupA	c.4143_4144dupA	5.1	3.4
18	06.09.2007	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
19	23.10.2007	p.S119F	p.S119F	1.6	<0.5
20	16.03.2008	c.2259delA	c.2259delA	<1	<0.5
21	30.09.2008†	c.4143_4144dupA	c.4143_4144dupA	3.7	3.1
22	13.11.2008	c.717delC	p.R1219W	<1	<0.5
23	14.11.2008	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
24	26.11.2008	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
25	12.12.2008	c.717delC	p.R1219W	<1	<0.5
26	20.01.2009	p.Q723K	p.R398C	<1	<0.5
27	25.02.2009	p.R193W	p.W1081X	<1	<0.5
28	26.02.2009	c.3220_3224del	c.3220_3224del	<1	<0.5
29	01.04.2009	p.R268P	p.Y304C	<1	<0.5
30	19.06.2009	c.4143_4144dupA	c.4143_4144dupA	<1	<0.5
31	21.07.2009	p.C946R	p.C946R	<1	3.3
32	22.01.2010	p.I1217T	c.4143_4144dupA	2.8	1.2
33	02.02.2010	p.V88M	p.V88M	11.9	2.4
34	11.03.2010	c.3892+1A	c.3892+1A	<1	0.7
35	14.05.2010	c.2042delA	p.R1123H	<1	0.7
36	21.07.2010	p.L232Q	p.R1060W	5.3	2.6
37	22.07.2010	p.S336P	p.W390X	11.4	4.1
38	18.09.2010	p.A690T	p.R915C	7.7	5.5
39	22.04.2011	p.R398H	c.2434_2441delinsC	6.0	0.7
40¶	05.07.2011	p.R1095Q	Not found	<1	1.6
41¶	20.09.2011	p.R1034X	Not found	3.0	<0.5

***** Not all listed patients were enrolled in the Registry ****** Analyses were performed at the Department of Hematology and Central Hematology Laboratory, Bern University Hospital, University of Bern, Switzerland, and at *** the Department of Blood Transfusion Medicine, Nara Medical University, Japan, respectively, in Q4/2011 and Q1/2012.

† Sample withdrawn during plasma infusion treatment cycle

¶ Diagnosis was confirmed by a plasma infusion trial.

Supplementary Table S2. Occurrence of acute TTP episodes and their duration in cTTP patients up to enrolment

Variables	
Total reported number of episodes at enrolment*	291
Median number of episodes per patient	2.00 [1.0, 22.0]
Median number of episodes per patient-year	0.10 [0.02, 8.91]
Median duration of an episode (d)**	7.00 [0.00, 4.00, 13.0, 128]

Continuous variables are presented as median [minimum, maximum] or as median [minimum, 25th percentile, 75th percentile, maximum]

* Detailed information available from 81 patients

**Duration missing for 74 episodes; 0 means acute situation was under control within less than one day

Supplementary Table S3. Mutations of *ADAMTS13* analyzed in 123 confirmed cTTP patients enrolled in the Hereditary TTP Registry between 2006 and 2017

Exon	DNA	Predicted effect (Protein if mRNA)	Mutation type	Domain	Patient enrolled in	All alleles (N = 246[†])
2	c.106_107delAG	p.Ser36fs*102	Deletion	Propeptide	Spain	1 (0.41%)
2	c.130C>T	p.Gln44*	Nonsense	Propeptide	Switzerland	2 (0.81%)
3	c.262G>A	p.Val88Met	Missense	Metalloprotease	Norway	2 (0.81%)
3	c.304C>T	p.Arg102Cys	Missense	Metalloprotease	USA	1 (0.41%)
3	c.305G>A	p.Arg102His	Missense	Metalloprotease	USA	1 (0.41%)
3	c.330+1G>A	-	Splice site	Metalloprotease	Japan	1 (0.41%)
3	**c.331-2A>G[§]**	**-**	**Splice site**	**Metalloprotease**	**Colombia**	1 (0.41%)
4	c.356C>T	p.Ser119Phe	Missense	Metalloprotease	Tunesia	2 (0.81%)
4	c.372_373insGT	p.Arg125Valfs*	Insertion	Metalloprotease	Japan	2 (0.81%)
4	c.414+1G>A[†]	-	Splice site	Metalloprotease	Japan	3 (1.22%)
5	c.530A>G	p.Tyr177Cys	Missense	Metalloprotease	Switzerland	1 (0.41%)
5	c.533T>C	p.Ile178Thr	Missense	Metalloprotease	Japan	1 (0.41%)
6	**c.548T>A[§]**	**p.Leu183Gln**	**Missense**	**Metalloprotease**	**Canada**	1 (0.41%)
6	c.577C>T	p.Arg193Trp	Missense	Metalloprotease	Japan	11 (4.47%)
6	c.686+1G>A	-	Splice site	Metalloprotease	Japan	1 (0.41%)
6	c.687-2A>G	-	Splice site	Metalloprotease	Austria	2 (0.81%)
7	c.681G>C	p.Gly227Arg	Missense	Metalloprotease	Japan	2 (0.81%)
7	**c.688-8C>G[§]**	**-**	**Splice site**	**Metalloprotease**	**USA**	1 (0.41%)
7	c.695T>A	p.Leu232Gln	Missense	Metalloprotease	Norway	1 (0.41%)
7	c.701A>G	p.His234Arg	Missense	Metalloprotease	Japan	1 (0.41%)
7	c.702C>A	p.His234Gln	Missense	Metalloprotease	Japan	1 (0.41%)
7	c.706G>T	p.Gly236Cys	Missense	Metalloprotease	Colombia	1 (0.41%)
7	**c.708delC[§]**	**p.Ala237Argfs*12**	**Deletion**	**Metalloprotease**	**USA**	1 (0.41%)
7	c.746_987+373del1782	-	Deletion	Metalloprotease	Japan	1 (0.41%)
7	c.749C>T	p.Ala250Val	Missense	Metalloprotease	Japan	1 (0.41%)
7	c.803G>C	p.Arg268Pro	Missense	Metalloprotease	Japan	2 (0.81%)
8	c.841T>A	p.Cys281Ser	Missense	Metalloprotease	Japan	1 (0.41%)
8	c.911A>G	p.Tyr304Cys	Missense	Disintegrin	Japan	3 (1.22%)
8	c.934C>T	p.Arg312Cys	Missense	Disintegrin	Japan	2 (0.81%)
8	c.[964T>G; 968CCT>GAC]	p.Cys322Gly/ Thr323Arg/ Phe324Leu	Missense	Disintegrin	Japan	1 (0.41%)
9	**c.1039T>C[§]**	**p.Cys347Arg**	**Missense**	**Disintegrin**	**USA**	1 (0.41%)
9	c.1045C>T	p.Arg349Cys	Missense	Disintegrin	Japan	2 (0.81%)
9	c.1058C>T	p.Pro353Leu	Missense	Disintegrin	USA	1 (0.41%)
10	c.1073G>A	p.Gly385Glu	Missense	Disintegrin	Japan	1 (0.41%)
10	**c.1097G>A[§]**	**p.Cys366Tyr**	**Missense**	**Disintegrin**	**Japan**	2 (0.81%)
10	C.1169G>A	p.Trp390Stop	Missense	TSP1-1	Canada	1 (0.41%)
10	**c.1190C>T[§]**	**p.Ser397Phe**	**Missense**	**TSP1-1**	**Japan**	1 (0.41%)
10	c.1193C>T	p.Arg398Cys	Missense	TSP1-1	Japan	1 (0.41%)
10	c.1193G>A	p.Arg398His	Missense	TSP1-1	Japan	1 (0.41%)
10	c.1244+2T>G	-	Splice site	TSP1-1	Japan	1 (0.41%)
11	c.1285C>T	p.Gln429*	Nonsense	TSP1-1	Switzerland	1 (0.41%)
11	**c.1305delT[§]**	**p.Thr435Serfs***	**Deletion**	**TSP1-1**	**USA**	**1 (0.41%)**
12	c.1313G>C	p.Cys438Ser	Missense	TSP1-1	Japan	1 (0.41%)
12	**c.1313G>T[§]**	**p.Cys438Phe**	**Missense**	**TSP1-1**	**Hungary**	2 (0.81%)

12	c.1345C>T	p.Gln449*	Nonsense	Cysteine-rich	Japan	5 (2.03%)
13	**c.1456_1457delAT[§]**	**p.Met486Valfs*47**	**Deletion**	**Cysteine-rich**	**Pakistan**	**2 (0.81%)**
13	c.1520G>A	p.Arg507Gln	Missense	Cysteine-rich	Czech Republic, Hungary, Norway	6 (2.44%)
13	c.1523G>A	p.Cys508Tyr	Missense	Cysteine-rich	Japan	1 (0.41%)
13	c.1574G>A	p.Gly525Asp	Missense	Cysteine-rich	Japan	2 (0.81%)
14	c.1648G>A	p.Gly550Arg	Missense	Cysteine-rich	Japan	1 (0.41%)
16	c.1816G>C	p.Ala606Pro	Missense	Spacer	Japan	1 (0.41%)
16	c.1885delT	p.Arg629Glufs*69	Deletion	Spacer	Japan	1 (0.41%)
17	c.2017A>T	p.Ile673Phe	Missense	Spacer	Japan	2 (0.81%)
17	c.2042delA	p.Lys681Cysfs*16	Deletion	Spacer	Denmark	1 (0.41%)
17	c.2074C>T	p.Arg692Cys	Missense	TSP1-2	USA	2 (0.81%)
18	**c.2105G>T[§]**	**p.Gly702Val**	**Missense**	**TSP1-2**	**Israel**	2 (0.81%)
18	c.2167C>A	p.Gln723Lys	Missense	TSP1-2	Japan	1 (0.41%)
18	c.2203G>T	p.Glu735*	Nonsense	TSP1-2	Tunesia	2 (0.81%)
19	c.2259delA	p.Cys754Alafs*	Deletion	TSP1-3	Japan	4 (1.63%)
19	c.2272T>C	p.Cys758Arg	Missense	TSP1-3	Poland	1 (0.41%)
19	c.2279delG	p.Gly760Alafs*18	Deletion	TSP1-3	Switzerland	2 (0.81%)
19	c.2281G>A	p.Gly761Ser	Missense	TSP1-3	Poland	1 (0.41%)
19	c.2410T>C	p.Cys804Arg	Missense	TSP1-3	Norway	3 (1.22%)
20	**c.2434_2441delinsC[§]**	**p.Glu812Pro***	**Deletion**	**TSP1-4**	**Japan**	**1 (0.41%)**
20	c.2455delG	p.Ala819Leufs*24	Deletion	TSP1-4	Poland	1 (0.41%)
21	**c.2674C>T**	**p.Gln892***	**Nonsense**	**TSP1-4**	**Japan**	**1 (0.41%)**
21	c.2723G>A	p.Cys908Tyr	Missense	TSP1-5	Japan	6 (2.44%)
21	c.2724C>G	p.Cys908Trp	Missense	TSP1-5	USA	1 (0.41%)
21	c.2725G>C	p.Gly909Arg	Missense	TSP1-5	Japan	1 (0.41%)
21	c.2728C>T	p.Arg910*	Nonsense	TSP1-5	Pakistan	2 (0.81%)
21	**c.2731+1G>T[§]**	**-**	**Splice site**	**TSP1-5**	**Austria**	**1 (0.41%)**
22	c.2785C>T	p.Gln929*	Nonsense	TSP1-5	Japan	1 (0.41%)
22	c.2836T>C	p.Cys946Arg	Missense	TSP1-5	Austria, Czech Republic	4 (1.63%)
24	c.3070T>C	p.Cys1024Arg	Missense	TSP1-7	Japan	2 (0.81%)
24	c.3070T>G	p.Cys1024Gly	Missense	TSP1-7	USA	1 (0.41%)
24	c.3100A>T	p.Arg1034*	Nonsense	TSP1-7	Japan	1 (0.41%)
24	c.3178C>T	p.Arg1060Trp	Missense	TSP1-7	Austria, Switzerland, Hungary, Norway, Poland, USA	13 (5.28%)
24	c.3198_3199delCT	p.Cys1067Valfs*17	Deletion	TSP1-7	Japan, Saudi Arabia	4 (1.63%)
24	c.3220_3224del	p.Tyr1074Alafs*46	Deletion	TSP1-7	Japan	3 (1.22%)
24	c.3242G>A	p.Trp1081*	Nonsense	TSP1-8	Japan	1 (0.41%)
25	c.3367C>T	p.Arg1123Cys	Missense	TSP1-8	India, Japan	3 (1.22%)
25	c.3368G>A	p.Arg1123His	Missense	TSP1-8	Denmark	1 (0.41%)
25	**c.3421delC[§]**	**p.His1141Thrfs*85**	**Deletion**	**TSP1-8**	**Japan**	**1 (0.41%)**
26	c.3616C>T	p.Arg1206*	Nonsense	CUB-1	Switzerland, Japan	3 (1.22%)
26	**c.3628C>T[§]**	**p.Gln1210***	**Nonsense**	**CUB-1**	**Austria**	**1 (0.41%)**
26	c.3650T>C	p.Ile1217Thr	Missense	CUB-1	Spain, Japan, USA	7 (2.85%)
26	c.3657_3658insT	p.Pro1220Serfs*	Insertion	CUB-1	Japan	1 (0.41%)
26	**c.3682delC[§]**	**p.Arg1228Alafs*48**	**Deletion**	**CUB-1**	**USA**	2 (0.81%)
27	c.3716G>T	p.Gly1239Val	Missense	CUB-1	Switzerland	2 (0.81%)
27	**c.3725T>C[§]**	**p.Leu1242Ser**	**Missense**	**CUB-1**	**Austria**	**1 (0.41%)**

27	c.3751_3892+587del729	-	Deletion	CUB-1	Japan	1 (0.41%)
28	c.3904C>T	p.Gln1302*	Nonsense	CUB-2	Japan	2 (0.81%)
28	c.4006C>T	p.Arg1336Trp	Missense	CUB-2	Switzerland, Japan	4 (1.63%)
29	c.4091_4092insA	p.His1364Glnfs*	Insertion	CUB-2	Czech Republic	1 (0.41%)
29	c.4119delG	p.Gln1374Serfs*22	Deletion	CUB-2	Japan	1 (0.41%)
29	**c.4135T>C[§]**	**p.Thr1379Arg**	**Missense**	**CUB-2**	**USA**	1 (0.41%)
29	c.4143_4144dupA	p.Glu1382Argfs*6	Insertion	CUB-2	Austria, Czech Republic, Germany, Hungary, Norway, Poland, USA	60 (24.39%)

[§] Mutations in bold have not been reported before

[†] In one patient, only one mutation was found, cTTP diagnosis was confirmed by a plasma infusion trial as described in Furlan *et al.*, Thromb Haemost. 1999; 81(1):8-13, and in Meyer *et al.*, Ann Hematol. 2008; 87(8):663-6.