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

Hendrika A. van Dorland, Magnus Mansouri Taleghani, Kazuya Sakai, Kenneth D. Friedman, James N. George, Ingrid Hrachovinova, Paul N. Knöbl, Anne Sophie von Krogh, Reinhard Schneppenheim, Isabella Aebi-Huber, Lukas Bütikofer, Carlo R. Largiadèr, Zuzana Cermakova, Koichi Kokame, Toshiyuki Miyata, Hideo Yagi, Deirdra R. Terrell, Sara K. Vesely, Masanori Matsumoto, Bernhard Lämmlle, Yoshihiro Fujimura and Johanna A. Kremers-Hovinga

© 2019 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2019.216796

Received: January 16, 2019.
Accepted: February 20, 2019.
Pre-published: February 21, 2019.
Correspondence: JOHANNA A. KREMER HOVINGA - johanna.krem@insel.ch
The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: Key findings at enrolment until 2017

Supplemental Material

Supplementary Appendix A

Collaborators of the Hereditary TTP Registry by country:

**AUSTRIA:** Paul N. Knöbl (Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna); **CANADA:** MacGregor Steele (Section of Pediatric Hematology, Alberta Children’s Hospital, Calgary); **COLOMBIA:** Agustin Dario Contreras Acosta (Pediatric Hematology and Oncology Hospital La Misericordia, Bogotá D.C.); **CZECH REPUBLIC:** Šárka Blahutová, Radomíra Hrdličková, Tereza Sulaková, Tomáš Záral (Fakultní nemocnice Ostrava, Ostrava Poruba); Zuzana Cermaková (Blood Center, University Hospital Ostrava, Ostrava); Ingrid Hrachovinova (NRL for Hemostasis, Institute of Hematology and Blood Transfusion, Prague); **DENMARK:** Ove Juul Nielsen (Department of Hematology, Rigshospitalet University Hospital, Copenhagen); **GERMANY:** Holger Kleemann, Hohenfels; **HUNGARY:** Zoltán Prohászka, György Sinkovits (Research Laboratory, 3rd Department of Internal Medicine and MTA-SE Research Group of Immunology and Hematology, Budapest); Marienn Réti (Department of Hematology and Stem Cell Transplantation, Central Hospital of Southern Pest, National Institute of Hematology and Infectious Diseases, Budapest); Zsolt Klucsk (Hospital of Bács-Kiskun County, Kecskemét); **INDIA:** Sangeetha Geminiganesan (Department of Pediatrics and Division of Ped. Nephrology Sri Ramachandra Medical college and Research Institute, Porur Chennai); **ISRAEL:** Maya Koren-Michowitz (Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv & Department of Hematology, Assaf Harofeh Medical Center, Zerifin); Odit Gutwein (Institute of Hematology, Assaf Harofeh Medical Center, Zerifin); **JAPAN:** Shin Imamura (Department of Internal Medicine, Japanese Red Cross Fukui Hospital, Fukui); Masatake Ishimura, Shouichi Ohga (Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka); Motoaki Shiratsuchi (Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka); Tomohiro Yagyu (Department of Hematology, Seirei Hamamatsu General Hospital, Hamamatsu); Seiji Kinoshita (Department of Pediatrics, Higashiho Saka City Medical Center, Higashiosaka); Etsoo Itoh (Department of Pediatrics, Hirotsuki University, Hirotsuki); Fumihiro Taguchi (Department of hematology, lizuka Hospital, lizuka); Mitsuo Takahashi (Newtown Nephro Medical Clinic, Iwaki); Yasutaka Aoyama (Department of Hematology, Fuchu Hospital, Izumi); Rie Kanai (Department of Pediatrics, Shimane University School of Medicine, Izumo); Masanori Matsumoto, Kazuya Sakai (Department of Blood Transfusion Medicine, Nara Medical University, Kashihara); Yosifumi Ubara (Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki); Daichiro Hasegawa (Department of Hematology, Hyogo Prefectural Kobe Children's Hospital, Kobe); Ryojiro Tanaka (Department of Nephrology, Hyogo Prefectural Kobe Children's Hospital, Kobe); Toshi Imai (Department of Hematology, Kochi Health Science Center, Kochi); Masahiro Migita (Department of Pediatrics, Japanese Red Cross Kumamoto Hospital, Kumamoto); Yutaka Imamura (Department of Hematology, St.Mary's Hospital, Kurume); Yoshiyuki Ogawa (Department of Hematology, Gunma University Graduate School of Medicine, Maebashi); Teruhiko Kozuka (Department of Hematology, Ehime Prefectural Central Hospital, Matsuyama); Hiroyasu Tanaka (Department of Perinatology and Gynecology, Kagawa University School of Medicine, Miki); Shinichi Hisanaga (Department of Internal Medicine, Koga General Hospital, Miyazaki); Hikaru Kobayashi (Department of Hematology, Japanese Red Cross Nagano Hospital, Nagano); Masatoshi Moriyama (Department of Medical Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata); Satoshi Higasa (Division of Hematology, Hyogo College of Medicine, Nishinomiya); Nobumasa Inoue (Department of Hematology, National Hospital Organization...
Osaka National Hospital, Osaka); Yoshihiro Fujimura (Japanese Red Cross Kinki Block Blood Center, Osaka); Hiroshi Miyabayashi (Division of Neonatology, Saitama Children's Medical Center, Saitama); Shinsuke Ohtaki, Saori Tanabe (Department of Pediatrics, Nihonkai General Hospital, Sakata); Mutsuko Konno (Department of Pediatrics, Sapporo-Kosei General Hospital, Sapporo); Masanobu Moriya (Department of Hematology, Aiku Hospital, Sapporo); Youji Sasahara (Department of Pediatrics, Tohoku University, Sendai); Nobu Akiyama (Department of Hematology, Tokyo Metropolitan Bokutoh Hospital, Tokyo); Michiko Kajiwara (Department of Transfusion Medicine, Tokyo Medical and Dental University, Tokyo); Azusa Nagao (Department of Hematology, Oogikubo Hospital, Tokyo); Kazuhiiko Natori (Division of Hematology and Oncology, Toho University Medical Center, Tokyo); Shigeyoshi Ohba (Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Tokyo); Hideo Wada (Department of Molecular and Laboratory Medicine, Mie University, Tsu); Yasuhiro Fujii (Department of Blood Transfusion, Yamaguchi University of Medicine, Ube); Maiko Shimomura (Department of Pediatrics, Shikoku Medical Center for Children and Adults, Zentsuji);

NORWAY: Elisabeth Siebke (Barne- og ungdomsavdelinga, Aalesund Sykehus, Aalesund); Astrid Dale (Medical department, Førde Central hospital, Førde); Nina Haagenrud Schulz (Department of Hematology, Akershus University Hospital, Lørenskog); Anne Sophie von Krogh, Petter Quist-Paulsen (Department of Hematology, St Olavs Hospital Trondheim University Hospital, Trondheim);

PAKISTAN: Moiz Bushra (Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital, Karachi, Pakistan); Fadoo Zehra (Department of oncology, The Aga Khan University Hospital, Karachi, Pakistan); Safia Jalal, Gulab Fatima Rani (Department of Haematology/Oncology, North West General Hospital, Peshawar, KPK, Pakistan);

POLAND: Grazyna Kucharska (Zespół Szpitali Miejskich Hospital, Chorzów); Lidia Hyla –Kleot (Department of Pediatric Surgery and Urology, Medical University of Silesia in Katowice, Katowice); Magdalena Górska-Kosicka, Jerzy Windyga (Department of Disorders of Haemostasis and Internal Medicine Institute of Hematology and Transfusion Medicine, Warsaw); Piotr Adamczyk, Maria Szczepanska, Renata Tomaszewska (Department of Pediatric Hematology and Oncology, School of Medicine with the Division of Dentistry in Zabrze, Zabrze);

SAUDI ARABIA: Saleh Al Shanbari (Pediatric Hematology Oncology, Childrens Hospital, Makkah); Safiah Ghazzawi (Pediatric Maternity and children Hospital, Makkah, Saudi Arabia);

SPAIN: Sandra Ortega Sanchez (Blood and Tissue Bank, Barcelona); Xavier Solanich (Feixa Llarga s/n Bellvitge Hospital Barcelona and Hospital Universitari de Bellvitge - IDI ELL Barcelona); Maria Fernanda Lopez-Fernandez (Hospital Materno Infantil, INIBIC-C.H.U. A Coruña, Coruña);

SWITZERLAND: Florian Buchkremer (Nephrology, Dialysis & Transplantation, Kantonsspital Aarau, Aarau, Switzerland); Thomas Braschler (Hematology Luzerner Kantonsspital, Lucerne, Switzerland); Johanna A. Kremer Hovinga, Bernhard Lämmlle (Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, Bern); Pierre-Yves Lovey (Service d'hématologie Hôpital du Valais-Institut Central, Sion, Switzerland); Stefan Farese (Department of Nephrology, Burgerspital, Solothurn, Switzerland);

USA: Christine L. Kempton (Hematology and Medical Oncology, Emory University, Atlanta); Chris Holmes (Hematology and Oncology, University of Vermont Medical Center Burlington, Vermont); Rinah Shopnick (Division of Hematology/Oncology, Ralph H. Johnson VA Medical Center, Charleston); Spero R. Cataland (Division of Hematology, Wexner Medical Center at the Ohio State University, Columbus, Ohio); Zora R. Rogers, The University of Texas Southwestern Medical Center Dallas, and The Pauline Allen Gill Center for Cancer and Blood Disorders Children's Medical Center Dallas, Texas); Andrea Orsey (Pediatric hematology/oncology, Connecticut Children's Medical Center, Hartford); Gary Jones (Department of Hematology/Oncology, Children's Mercy Hospital, Kansas City); Rachel Cameron (Kingfisher, Oklahoma); Matthew Fletcher (Pediatric Hematology/Oncology, Ochsner Medical Center, New Orleans); Samuel Milanovich (Pediatric Hematology/Oncology, Sanford Children's Hospital, Sioux Falls).

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

1. Antoine G, Zimmermann K, Plaimauer B, Grillowitzer M, Studt JD, Lämmle B, Scheiflinger F. ADAMTS13 gene defect in two brothers with constitutional thrombotic thrombocytopenic purpura and normalization of von Willebrand factor-cleaving protease activity by recombinant human ADAMTS13. Br J Haematol. 2003; 120(5): 821-4.

2. Assink K, Schiphorst R, Allford S, Karpman D, Etzioni A, Bricht B, van de Kar N, Monnens L, van den Heuvel L. Mutation analysis and clinical implications of the von Willebrand factor cleaving protease deficiency. Kidney international 2003; 63 (6): 1995-1999.

3. Borgi A, Khemiri M, Veyradier A, Kazdaghi K, Barsaoui S. Congenital Thrombotic Thrombocytopenic Purpura: Atypical Presentation and New ADAMTS 13 Mutation in a Tunisian Child. Mediterr J Hematol Infect Dis. 2013, 5(1): e2013041.

4. Čermáková Z, Hrdliková R, Suláková T, Koristka M, Kovárová P, Hrachovinová I. Thrombotic thrombocytopenic purpura: incidence of congenital form of disease in north Moravia (region Moravia-Silesia). Prague Med Rep. 2009; 110(3): 239-44

5. Eura Y, Kokame K, Takafuta T, Tanaka R, Kobayashi H, Ishida F, Hisanaga S, Matsumoto M, Fujimura Y, Miyata T. Candidate gene analysis using genomic quantitative PCR: identification of ADAMTS13 large deletions in two patients with Upshaw-Schulman syndrome. Mol Genet Genomic Med. 2014; 2(3): 240-4.

6. Fujimura Y, Matsumoto M, Isonishi A, Yagi H, Kokame K, Soejima K, Murata M, Miyata T. Natural history of Upshaw-Schulman syndrome based on ADAMTS13 gene analysis in Japan. J Thromb Haemost. 2011; 9 Suppl 1:283-301.

7. Hura T, Kitano A, Kajiwara T, Kondo T, Sakai K, Hamasaki Y. Factor VIII concentrate-responsive thrombocytopenia, hemolytic anemia, and nephropathy. Evidence that factor VIII:von Willebrand factor is involved in its pathogenesis. Am J Pediatr Hematol Oncol. 1986; 8(4): 324-8.

8. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

9. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

10. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

11. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

12. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

13. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.

14. Hyla-Klekot L, Kucharska G, Słonka K. Variety of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol. 2001; 14(2):437-54.
18. Kovarova P, Hrdlickova R, Blahutova S, Cermakova Z. ADAMTS13 kinetics after therapeutic plasma exchange and plasma infusion in patients with Upshaw-Schulman syndrome. J Clin Apher. 2019; 34(1):13-20.
19. Matsumoto M, Kokame K, Soejima K, Miura M, Hayashi S, Fujii Y, Iwai A, Ito E, Tsuji Y, Takeda-Shitaka M, Iwadate M, Umeyama H, Yagi H, Ishizashi H, Banno F, Nakagaki T, Miyata T, Fujimura Y. Molecular characterization of ADAMTS13 gene mutations in Japanese patients with Upshaw-Schulman syndrome. Blood. 2004; 103(4):1305-10.
20. Meyer SC, Jedd R, Meddeb B, Gouider E, Lämmlle B, Kremer Hovinga JA. A first case of congenital TTP on the African continent due to a new homozygous mutation in the catalytic domain of ADAMTS13. Ann Hematol. 2008; 87(8):663-6.
21. Mise K, Ubara Y, Matsumoto M, Sumida K, Hiramatsu R, Hasegawa E, Yamanouchi M, Hayami N, Suwabe T, Hoshino J, Sawa N, Ohashi K, Kokame K, Miyata T, Fujimura Y, Takaichi K. Long term follow up of congenital thrombotic thrombocytopenic purpura (Upshaw-Schulman syndrome) on hemodialysis for 19 years: a case report. BMC Nephrol. 2013; 14: 156.
22. Miura M, Koizumi S, Nakamura K, Ohno T, Tachinami T, Yamagami M, Taniguchi N, Komishita S, Abildgaard CF. Efficacy of several plasma components in a young boy with chronic thrombocytopenia and hemolytic anemia who responds repeatedly to normal plasma infusions. Am J Hematol. 1984; 17(3): 307-19.
23. Ogawa Y, Matsumoto M, Sadakata H, Isonishi A, Kato S, Nojima Y, Fujimura Y. A Unique Case Involving a Female Patient with Upshaw-Schulman Syndrome: Low Titers of Antibodies against ADAMTS13 prior to Pregnancy Disappeared after Successful Delivery. Transfus Med Hemother. 2015; 42(1): 59-63.
24. Pérez-Rodríguez A, Battle-López A, Blanco R, Varela I, León J, Delgado MD, Lourès E, Rodríguez-Trillo A, García-Rivero A, Costa-Pinto J, Batlle J, López-Fernández MF. A novel mutation in ADAMTS13 of a child with Upshaw-Schulman syndrome. Thromb Haemost. 2014;112(5):1065-1068.
25. Rank CU, Kremer Hovinga J, Mansouri Taleghani M, Lämmlle B, Getze JP, Nielsen OJ. Congenital thrombotic thrombocytopenic purpura caused by new compound heterozygote mutations of the ADAMTS13 gene. Eur J Haematol. 2014; 92(2):168-71.
26. Saitoh H, Murakami H, Mori C. Upshaw-Schulman syndrome in two siblings. Acta Paediatr Jpn. 1990; 32(4): 373-6.
27. Sasahara Y, Kumaki S, Ohashi Y, Minegishi M, Kano H, Bessho F, Tsuchiya S. Deficient activity of von Willebrand factor-cleaving protease in patients with Upshaw-Schulman syndrome. Int J Hematol 2001; 74: 109-114.
28. Schnepfenreich R, Kremer Hovinga JA, Becker T, Budde U, Karpmann D, Brockhaus W, Hrchovínová I, Korczowski B, Oyen F, Rittich S, von Rosen J, Tjønnfjord GE, Pimpana JE, Wienker TF, Lämmlle B. A common origin of the 4143insA ADAMTS13 mutation. Thromb Haemost. 2006; 96(1): 3-6.
29. Shibagaki Y, Matsumoto M, Kokame K, Ohba S, Miyata T, Fujimura Y, Fujita T. Novel compound heterozygote mutations (H234Q/R1206X) of the ADAMTS13 gene in an adult patient with Upshaw-Schulman syndrome showing predominant episodes of repeated acute renal failure. Nephrol Dial Transplant 2006; 21: 1289-1292.
30. Studt JD, Kremer Hovinga JA, Antoine G, Herrmann M, Rieger M, Scheffinger F, Lämmlle B. Fatal congenital thrombotic thrombocytopenic purpura with apparent ADAMTS13 inhibitor: in vitro inhibition of ADAMTS13 activity by hemoglobin. Blood. 2005; 105(2):542-4.
31. Tanaka H, Tenkumo C, Mori N, Kokame K, Fujimura Y, Hata T. Case of maternal and fetal deaths due to severe congenital thrombotic thrombocytopenic purpura (Upshaw-Schulman syndrome) during pregnancy. J Obstet Gynaecol Res. 2014; 40(1): 247-9.
32. Tapia JE, Hauser GA, Riedler GF. Rezidivierendes, histologisch gesichertes Moschcowitz-Syndrom während der Schwangerschaft. Schweizerisch medizinische Wochenschrift 1981; 111: 1287-1292.
33. Tsuda M, Shiratsuchi M, Nakashima Y, Ikeda M, Muta H, Narazaki T, Masuda T, Kimura D, Takamatsu A, Matsumoto M, Fujimura Y, Kokame K, Matsushima T, Ogawa Y. Upshaw-Schulman syndrome diagnosed during pregnancy complicated by reversible cerebral vasogenic oclusive syndrome. Transfus Apher Sci. 2018; 57(6): 790-792.
34. Uchida T, Wada H, Mizutani M, Iwashi M, Ishihara H, Shibano T, Suzuki M, Matsubara Y, Soejima K, Matsumoto M, Fujimura Y, Ikeda Y, Murata M; Research Project on Genetics of Thrombosis.
Identification of novel mutations in ADAMTS13 in an adult patient with congenital thrombotic thrombocytopenic purpura. Blood 2004; 104: 2081-2083.

35. von Krogh AS, Kremer Hovinga JA, Tjønnfjord GE, Ringen IM, Lämmle B, Waage A, Quist-Paulsen P. The impact of congenital thrombotic thrombocytopenic purpura on pregnancy complications. Thromb Haemost. 2014; 111(6): 1180-3.

36. von Krogh AS, Quist-Paulsen P, Waage A, Langseth ØO, Thorstensen K, Brudevold R, Tjønnfjord GE, Largiadèr CR, Lämmle B, Kremer Hovinga JA. High prevalence of hereditary thrombotic thrombocytopenic purpura in central Norway: from clinical observation to evidence. J Thromb Haemost. 2016 Jan; 14(1):73-82.

37. Yagi H, Konno M, Kinoshita S, Matsumoto M, Ishizashi H, Matsui T, Titani K, Fujimura Y. Plasma of patients with Upshaw-Schulman syndrome, a congenital deficiency of von Willebrand factor-cleaving protease activity, enhances the aggregation of normal platelets under high shear stress. Br J Haematol 2001; 115: 991-997.
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.

**Supplemental References**

1. Furlan M, Robles R, Morselli B, Sandoz P, Lämmle B. Recovery and half-life of von Willebrand factor-cleaving protease after plasma therapy in patients with thrombotic thrombocytopenic purpura. Thromb Haemost. 1999;81(1):8-13.

2. Fujimura Y, Kokame K, Yagi H, Isonishi A, Matsumoto M, Miyata T. Hereditary Deficiency of ADAMTS13 Activity: Upshaw–Schulman Syndrome. In: Rodgers GM, ed. ADAMTS13: Biology and Disease. Cham: Springer International Publishing; 2015:73-90.

3. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017;15(2):312-322.

4. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158(3):323-335.

5. Vesely SK, George JN, Lämmle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood. 2003;102(1):60-68.
Supplementary Figure S1.
Flow chart of patient enrolment into the Hereditary TTP Registry until the end of 2017

Assessed patients with suspected or confirmed diagnosis of cTTP (n=149)

Excluded (n=7)
Patients not having cTTP (n=7)

Eligible patients (n=142)
from 136 families

Confirmed patients (n=123)
from 117 families

Suspected patients (n=19)
from 19 families
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.
B

![Histogram showing ADAMTS13 activity distribution]

- **Homozygous carriers (n=20)**
- **Compound Heterozygous carriers (n=14)**

C

![Scatter plot showing age at disease onset]

- **Homozygous carriers**
- **Compound heterozygous carriers**

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

* 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                                             | Value          |
|-------------------------------------------------------|----------------|
| 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
| 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.Gln44fs*                        | 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  | p.Thr435Serfs*                    | Deletion      | Metalloprotease | Colombia            | 1 (0.41%)            |
| 4    | c.356C>T    | p.Ser119Phe                       | Missense      | Metalloprotease | Tunisia             | 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 | Norway              | 1 (0.41%)            |
| 6    | c.686+1G>A  | -                                 | Splice site   | Metalloprotease | Japan               | 1 (0.41%)            |
| 6    | c.687-2A>G  | -                                 | Splice site   | Metalloprotease | Austria             | 2 (0.81%)            |
| 6    | c.681G>C    | p.Gly227Arg                       | Missense      | Metalloprotease | Japan               | 2 (0.81%)            |
| 7    | c.688-8C>G  | p.Leu232Gln                       | Missense      | Metalloprotease | USA                 | 1 (0.41%)            |
| 7    | c.695T>AA   | 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.749G>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.1056C>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.1193G>T   | p.Arg398Cys                       | Missense      | TSP1-1        | Japan               | 1 (0.41%)            |
| 10   | c.1313G>C   | p.Cys438Ser                       | Missense      | TSP1-1        | Japan               | 2 (0.81%)            |
| 10   | c.1313G>T   | p.Cys438Phe                       | Missense      | TSP1-1        | Hungary             | 2 (0.81%)            |
| cDNA Position | Amino Acid | Missense/Deletion/Insertion | Functional Effect | Country/Region |
|---------------|------------|-----------------------------|------------------|---------------|
| c.1345G>A     | p.Glu449*  | Nonsense                     | Cysteine-rich    | Japan         |
| c.1856delG    |            | Deletion                     | Cysteine-rich    | Japan         |
| c.1520G>A     | p.Arg507Gln| Missense                    | Cysteine-rich    | Czech Republic, Hungary, Norway |
| c.1523G>A     | p.Cys508Tyr| Missense                    | Cysteine-rich    | Japan         |
| c.1574G>A     | p.Gly525Asp| Missense                    | Cysteine-rich    | Japan         |
| c.1648G>A     | p.Gly550Arg| Missense                    | Cysteine-rich    | Japan         |
| c.1816G>A     | p.Ala606Pro| Missense                    | Cysteine-rich    | Japan         |
| c.1885delT    | p.Arg629Glufs*69| Deletion                      | Spacer          | Japan         |
| c.2017A>T     | p.Ile673Phe| Missense                    | Spacer          | Japan         |
| c.2042delA    | p.Lys681Cysfs*16| Deletion                      | Spacer          | Denmark       |
| c.2074C>T     | p.Arg692Cys| Missense                    | TSP1-2           | USA           |
| c.2105G>T1    | p.Gly702Val| Missense                    | TSP1-2           | Israel        |
| c.2167C>A     | p.Gln723Lys| Nonsense                    | TSP1-2           | Japan         |
| c.2203G>T     | p.Glu735*  | Nonsense                    | TSP1-2           | Tunisia       |
| c.2259delA    | p.Cys754Alafs*| Deletion                      | TSP1-3           | Japan         |
| c.2272T>C     | p.Cys758Arg| Deletion                    | TSP1-3           | Poland        |
| c.2279delG    | p.Gly760Alafs*18| Deletion                    | TSP1-3           | Switzerland   |
| c.2281G>A     | p.Gly761Ser| Missense                    | TSP1-3           | Poland        |
| c.2410T>C     | p.Gly894Arg| Missense                    | TSP1-3           | Norway        |
| c.2434_2441delinsC1| p.Glu812Pro*| Deletion                      | TSP1-4           | Japan         |
| c.2455delG    | p.Glu819Leufs*24| Deletion                    | TSP1-4           | Poland        |
| c.2674C>T     | p.Gln892*  | Nonsense                    | TSP1-4           | Japan         |
| c.2723G>A     | p.Cys908Tyr| Missense                    | TSP1-5           | Japan         |
| c.2724C>G     | p.Cys908Trp| Missense                    | TSP1-5           | Japan         |
| c.2725G>C     | p.Gly909Arg| Missense                    | TSP1-5           | Japan         |
| c.2726C>T     | p.Arg910*  | Nonsense                    | TSP1-5           | Japan         |
| c.2731+1G>T1  |            | Splice site                 | TSP1-5           | Austria       |
| c.2785C>T     | p.Gln929*  | Missense                    | TSP1-5           | Japan         |
| c.2836C>T     | p.Cys964Arg| Missense                    | TSP1-5           | Austria, Czech Republic |
| c.3070T>C     | p.Cys1024Arg| Missense                    | TSP1-7           | Japan         |
| c.3070T>G     | p.Cys1024Gly| Missense                    | TSP1-7           | Japan         |
| c.3100A>T     | p.Arg1034* | Missense                    | TSP1-7           | Japan         |
| c.3178C>T     | p.Arg1060Trp| Missense                    | TSP1-7           | Austria, Switzerland, Hungary, Norway, Poland, USA |

| cDNA Position | Amino Acid | Missense/Deletion/Insertion | Functional Effect | Country/Region |
|---------------|------------|-----------------------------|------------------|---------------|
| c.3198_3199delCT| p.Cys1067Valfs*17| Deletion                      | TSP1-7           | Japan, Saudi Arabia |
| c.3220_3224del| p.Tyr1074Alafs*46| Deletion                      | TSP1-7           | Japan         |
| c.3242G>A     | p.Trp1081* | Nonse                        | TSP1-7           | Japan         |
| c.3367C>T     | p.Arg1123Cys| Missense                    | TSP1-8           | India, Japan   |
| c.3368G>A     | p.Arg1123His| Missense                    | TSP1-8           | Denmark       |
| c.3421delC1   | p.His1141Thrfs*85| Deletion                      | TSP1-8           | Japan         |
| c.3616C>T     | p.Arg1206* | Nonse                        | TSP1-8           | Japan         |
| c.3628C>T1    | p.His1210* | Nonse                        | TSP1-8           | Japan         |
| c.3850T>C     | p.Ile1217Thr| Insertion                   | TSP1-8           | Japan         |
| c.3857_3658insT| p.Pro1220Serfs*| Deletion                      | TSP1-8           | USA           |
| c.3862delC1   | p.Arg1228Alafs*48| Deletion                      | TSP1-8           | Switzerland   |
| c.3716G>T     | p.Gly1239Val| Missense                    | TSP1-9           | America       |
| c.3725T>C1    | p.Leu1242Ser| Missense                    | TSP1-9           | Austria       |
|   | SNP | Mutation Type | Proteins | Location | Frequency |
|---|-----|---------------|----------|----------|-----------|
| 27 | c.3751_3892+587del729 | Deletion | CUB-1 | Japan | 1 (0.41%) |
| 27 | c.3904C>T | Nonsense | CUB-2 | Japan | 2 (0.81%) |
| 28 | c.4006C>T | Missense | CUB-2 | Switzerland, Japan | 4 (1.63%) |
| 29 | c.4091_4092insA | Insertion | CUB-2 | Czech Republic | 1 (0.41%) |
| 29 | c.4119delG | Deletion | CUB-2 | Japan | 1 (0.41%) |
| 29 | c.4135T>C | Missense | CUB-2 | USA | 1 (0.41%) |
| 29 | c.4143_4144dupA | 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.