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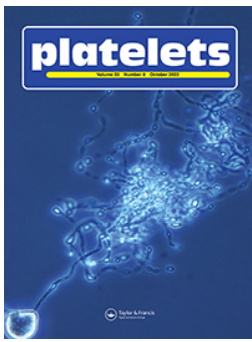
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## GENE OF THE ISSUE



# Inherited ADAMTS13 mutations associated with Thrombotic Thrombocytopenic Purpura: a short review and update

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## Abstract

ADAMTS13 is a plasma metalloprotease with the primary function of cleaving VWF to maintain hemostasis. Circulating ADAMTS13 is in the closed conformation until blood vessel injury triggers a VWF-dependant activation to the open active form of the protein. ADAMTS13 is a multi-domain protein with the domains broadly functioning to interact and cleave VWF or maintain global latency of ADAMTS13. Thrombotic Thrombocytopenic Purpura is a disease characterized by excessive thrombi formation in the microvasculature, diagnosis is made when ADAMTS13 activity is <10%. In the hereditary form, a variety of mutations are found throughout all domains of ADAMTS13, examples are given alongside details of each domain in this article. ADAMTS13 mutations can inhibit the binding and cleavage of VWF directly or indirectly through reduced secretion, leading to increased size of VWF multimers and platelet recruitment. Molecular characterization of ADAMTS13 may provide insight into the mechanisms of TTP to aid in both scientific and clinical research.

## Keywords

ADAMTS13, Thrombotic Thrombocytopenic Purpura, VWF

## History

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## Introduction

The *ADAMTS13* (a disintegrin and metalloprotease with thrombospondin type 1 motif 13) gene encodes a plasma metalloprotease, crucial to the regulation of blood coagulation via cleavage of large Von Willebrand factor (VWF) multimers. VWF is a large glycoprotein central to coagulation, mainly through recruitment of platelets and formation of a hemostatic plug at sites of vessel damage [1]. Through cleavage of VWF at the scissile bond (Tyr1605-Met1606), ADAMTS13 prevents accumulation of ultra-large VWF multimers in circulation and therefore perturbs excessive aggregation of platelets to maintain the delicate haemostatic thrombotic balance [2].

## Clinical features of TTP

Thrombotic Thrombocytopenic Purpura (TTP) is a rare blood disorder, associated with excessive thrombus formation in the microvasculature. This leads to a variety of symptoms ranging dramatically in their severity. Mild clinical manifestations include headaches and lethargy, through to potentially fatal manifestations of transient ischemic attack, stroke, myocardial

damage or renal failure. In total, 75% of patients were female and 25% male according to the regional UK TTP registry (2008) [3]. Diagnosis of TTP relies foremost on ADAMTS13 activity (threshold of <10%), due to lack of uniformity in symptoms and respective severity across patients. The congenital form of disease (cTTP) is associated with biallelic mutations (autosomal recessive inheritance) in the *ADAMTS13* gene, whilst the immune-mediated form (iTTP) involves autoantibody targeting of the ADAMTS13 protein; the acquired form is more prevalent (95% of cases). cTTP is confirmed by direct sequence analysis of the *ADAMTS13* gene; defects may be homozygous or compound heterozygous [3].

A plethora of mutations are found throughout all domains of the *ADAMTS13* gene, including missense, frameshift, insertions, deletions and splice site alterations. The effects of these mutations on ADAMTS13 differ both within and between domains. Investigation into the effects of mutations on the structure and activity of ADAMTS13 could provide a more robust link with disease severity and onset, to build on the information currently available linking mutational data to patient phenotype.

Whilst in some cases immediate treatment for TTP may be required from birth, symptoms may first arise in adulthood, for example, after trauma such as infection or pregnancy. Stroke is an often-fatal manifestation of the disease in infants (frequency is 25–31% of patients with cTTP) [4]. Treatment of cTTP involves ADAMTS13 replacement either as fresh frozen plasma infusion or using an intermediate purity FVIII concentrate (8Y), pending licensing of recombinant ADAMTS13. Currently other, less invasive treatment options are still limited [5,6]. Immediate intervention dramatically decreases mortality rates and provides reduction of some symptoms such as headaches and abdominal pain in the majority of patients; as well as 80% reduction in TIA [7,8].

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However, relapse is still common (40% in TTP and 69% in cTTP specifically) even when receiving treatment [8,9]. This suggests the treatment for acute disease is adequate but a search for long-term treatment would be beneficial.

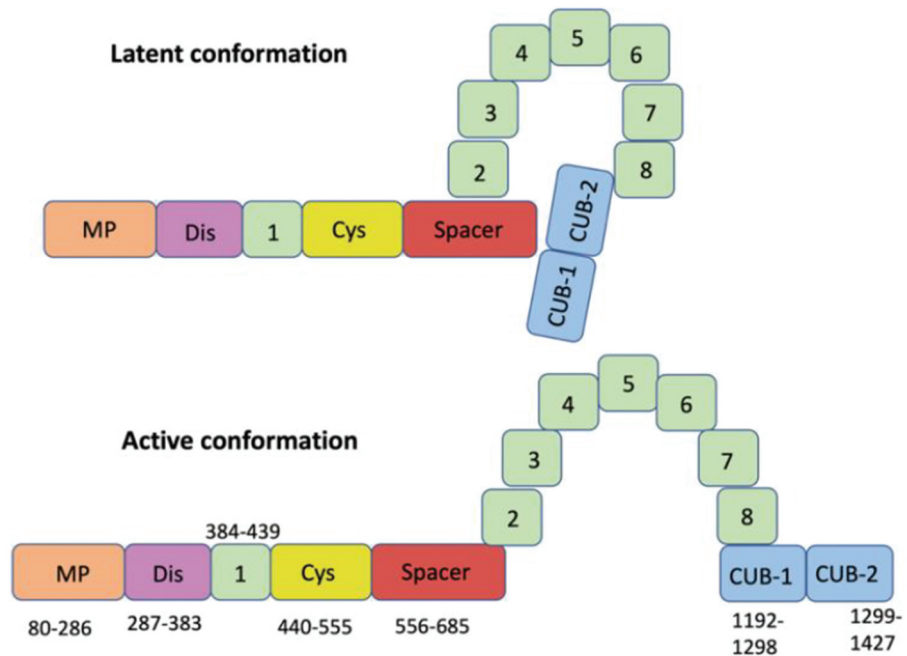
### ADAMTS13 and mutations

The *ADAMTS13* gene consists of 29 exons at chromosome location 9q34.2. The start of the gene encodes for a signal peptide and short propeptide at the *N*-terminus, however this propeptide bears no regulatory control over folding or activity, differing to other

ADAMTS family proteins [10]. ADAMTS13 consists of a multi-domain structure with the *N*-terminal domains (MDTCS) responsible for proteolysis through a series of exosites for VWF binding and cleavage, whilst the C-terminal domains regulate protein latency. The circulating form of ADAMTS13 is the closed form with latency achieved both on the domain level, within the metalloprotease (MP) domain, and at the protein level through the interaction between the Spacer-CUB domains preventing access to exosites (Figure 1A).

Figure 1B illustrates the distribution of mutations across the ADAMTS13 MDTCS domains. A summary of mutations

**A**



**B**

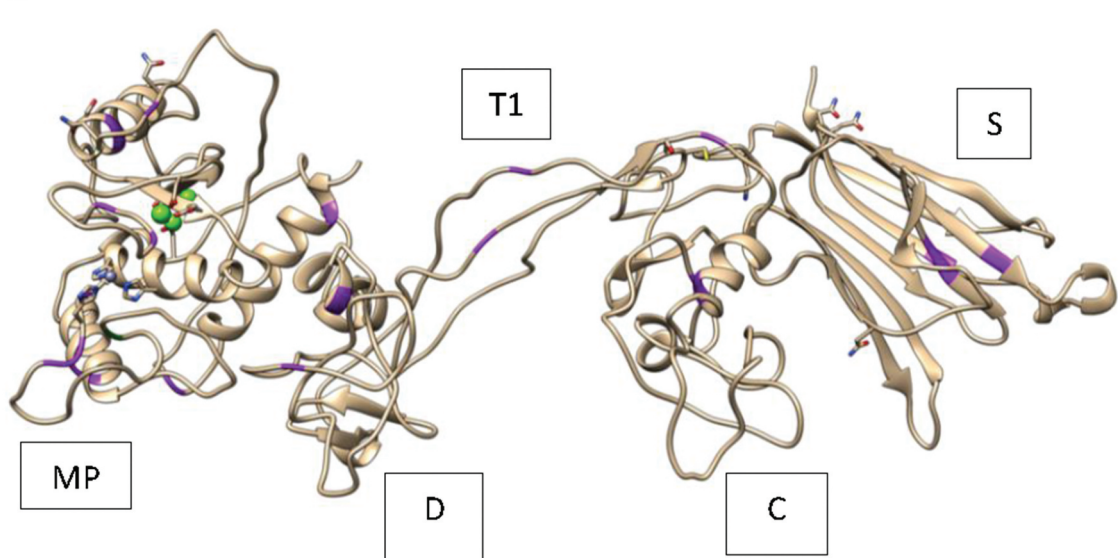


Figure 1. (A) Schematic diagram of domain structure of ADAMTS13 in open and closed conformation. Domains are as follows: Metalloprotease, Disintegrin, Thrombospondin-repeat (numbered 1–8), Cysteine rich, Spacer and CUB 1 and 2; amino acid numbers are given for each domain. In the latent closed conformation, the binding sites for VWF are inaccessible with the spacer–CUB interaction present facilitated by the TSP repeats. In the active open conformation this interaction is disrupted so all binding sites for VWF are accessible. (B) ADAMTS13 MDTCS structure (PDB:6QIG) with mutations highlighted purple, depicts the spread of mutations across the *N*-terminal domains (MP: metalloprotease, D: Disintegrin, T1: Thrombospondin repeat 1, C: Cysteine-rich, S: Spacer).

Table 1. ADAMTS13 mutations in TTP patients. Selection of mutations was based on available phenotype data as well as cited evidence to give examples across domains. Where in vitro work has been carried out this has been included to help understand the effect of the specific mutation on the protein, especially in the case of heterozygous mutations.

Affected domain	DNA Change	Amino acid change	Homozygous or heterozygous	Patient characteristics (onset, ADAMTS13 activity and disease course)	Patient characteristics induced	Predicted structural effect on the protein	Other supporting evidence	References
MP	305G>A	R102H	Homozygous	Pregnancy induced	Pregnancy induced	Disruption of active site either directly or indirectly	In vitro partially reduced secretion	Hing et al. (2013) and Underwood (2015)
	356C>T	S119F	Homozygous	Diagnosis at 17yo, severe complications	Diagnosis at 17yo, severe complications	Potential disruption of active site either directly or indirectly	Reduced secretion with reduced catalytic efficiency	Meyer et al. [29] and Hing et al. (2013)
	414 +IG>A	Splice variant	Homozygous	Neonatal onset <3% activity	Neonatal onset <3% activity	Abolished splicing at the exon 4-intron 4 boundary	Improper splicing at exon/intron 4.	[25]
	428T>C	I143T	Homozygous	Recurring relapse	Recurring relapse	Potential disruption of active site either directly or indirectly	Intracellular retention and proteasome degradation	Underwood (2015) and Hing et al. (2013)
	448T>C	S150P	Homozygous	Neonatal onset	Neonatal onset	Potential disruption of active site either directly or indirectly	NA	Hing et al. (2013)
	577C>T	R193W	Homozygous	Pregnancy induced	Pregnancy induced	Disruption of active site	Reduced secretion with no detectable activity	Hing et al. (2013) and Matsumoto et al. (2004)
	587C>T	T196I	Patient 1: Homozygous Patient 2: Heterozygous	P1: Infant diagnosis, P2: infant diagnosis and activity at <5%.	P1: Infant diagnosis, P2: infant diagnosis and activity at <5%.	Disruption of S1 subsite and therefore VWF interaction	<25% activity reported in vitro	Levy et al. [14], Pimanda et al. (2004) and Camilleri (2012)
	695T>A	L232Q	Homozygous	Neonatal onset	Neonatal onset	Disruption of active site either directly or indirectly	NA	Hing et al. (2013)
	703G>C	D235H	Homozygous	Neonatal onset	Neonatal onset	Disruption of active site either directly or indirectly	NA	Hing et al. (2013)
	706G>T	G236C	Homozygous	Pregnancy induced	Pregnancy induced	Disruption of active site either directly or indirectly	NA	Hing et al. (2013)
Dis	749C>T	A250V	Heterozygous	Recurring relapses, activity <3%	Recurring relapses, activity <3%	Close proximity to Zn <sup>2+</sup> ion may compromise proteolytic activity	Markedly reduced activity	Uchida et al. [15] and Shelat et al. (2005)
	803G>C	R268P	Heterozygous	Neonatal onset and frequent relapses	Neonatal onset and frequent relapses	Disrupted protein folding	Abolished secretion and reduced activity	Kokame et al. [19] and Hommais et al. (2007)
	932G>A	C311Y	Homozygous	Neonatal onset	Neonatal onset	Disulphide bond formation affected	NA	Hing et al. (2013) and Assink et al. (2003)
	1045C > T	R349C	Heterozygous	Pregnancy induced, activity <1%	Pregnancy induced, activity <1%	Dis domain exosite is altered affecting VWF interaction	NA (but R349D has complete loss of activity)	[16,17]
TSP-1	1177C > T	A393*	Heterozygous	Neonatal onset and severe disease course, activity <4%	Neonatal onset and severe disease course, activity <4%	Severely truncated protein	NA- hypothesized as inactive	Hassenpflug et al. (2018)
	1225C>T	R409W	Homozygous	Neonatal onset, <5% activity	Neonatal onset, <5% activity	Hydrophobic substitution of residue may cause destabilisation	Reduced secretion	Camilleri et al. (2012)
	1308G>C	Q436H	Homozygous	Neonatal onset	Neonatal onset	May affect the local environment around disulfide bonds.	NA	Hing et al. (2013)
-	1331G>A	splice variant	Heterozygous	Acute episodes, <3% activity	Acute episodes, <3% activity	Improper mRNA formation due to splice variation	improper mRNA formation	[15]

(Continued)

Table I. (Continued).

Affected domain	DNA Change	Amino acid change	Homozygous or heterozygous	Patient characteristics (onset, ADAMTS13 activity and disease course)	Predicted structural effect on the protein	Other supporting evidence	References
Cys	1345C>T	Q449*	Homozygous, (heterozygous parents)	<3% activity in homozygous patient and 45–60% in heterozygous parents.	Loss of C-terminal domains	Normal secretion but very low activity detected	[19]
	1523G>A	C508Y	Heterozygous	<3% activity	Affects proper protein folding	In vitro secretion is abolished	[25]
Spacer	1783–1784delTT	L595fs	homozygous	Very low activity (<0.1 U/mL)	Truncated protein due to frameshift	NA	Savasan et al. (2003)
	1787C>T	A596 V	Two unrelated families, both homo/heterozygous	2 unrelated patients both with <5% activity and neonatal onset	A larger residue substitution may alter tertiary structure	Greatly reduced secretion and activity	Veyradier et al. (2004) and Camilleri et al. (2012)
	1973A>G	Y658C	Homozygous	Pregnancy induced, <5% activity	Introduction of cysteine may affect disulfide bond formation	NA	Ho Lee et al. (2011)
TSP-repeats	2017A>T	I673F	Heterozygous	Neonatal onset	Affects protein folding	Abolished secretion	[25]
	Not stated	W688X	Homozygous	Neonatal onset, ADAMTS13 activity <1%	Prematurely truncated protein	Severely reduced activity under shear stress.	[29]
	2074C>T	R692C	Homozygous	Neonatal onset, ADAMTS13 activity <1%	Disulphide bond formation may be affected	Severely reduced secretion	Meyer et al. [29] and Hing et al. (2013)
	Not stated	C804 R	Homozygous	Neonatal onset, ADAMTS13 activity <1%	Disulphide bond formation maybe affected	Severely reduced secretion	[29]
	2723 G>A	C908Y	Heterozygous	neonatal onset, <3% activity	Disruption of disulfide bond	Abolished secretion	[25]
	2930–2935del	R979delmsW	Homozygous	<20% activity reported	Truncated protein	NA	Peyvandi et al. (2004)
	3178C>T	R1060W	Both homo/heterozygous	Very low ADAMTS13 activity, asymptomatic until pregnancy, patients have milder courses of disease generally	Localized misfolding within ADAMTS13 due to change in charge	Severe intracellular retention, <5% secretion	Savasan et al. (2003), Scully et al. (2014) and Lotta et al. (2010)
	3367C>T	R1123C	Heterozygous	Neonatal onset, <3% activity, recurrent episodes	Creation of mixed disulfide bond	Abolished secretion	[25]
CUB-1	3716 G>T	G1239 V	Homozygous	Infant onset, recurring relapse, activity was <1%	Affecting protein structure through folding	Severely reduced secretion and reduced activity	[20,30]
	c.3923 G>A	G1308D	Heterozygous	Pregnancy induced, <3% activity	Affects protein folding and stability	Severely reduced secretion	Jiang et al. (2020)
CUB-2	4143dupA	E1382Rfs	Both homo/heterozygous.	Homozygous with neonatal onset and more severe clinical course than heterozygous patients	Truncated protein	Severely reduced secretion and activity	Hassenpflug et al. (2018) and Peyvandi et al. (2004)



associated with TTP in different ADAMTS13 domains are shown in Table I (mutations were selected if both clinical data and literature was available). Findings from *In vitro* experiments have also been included, where available. This data can help give a clearer association between phenotype and specific mutations found in heterozygous patients. Yang et al. 2022 reported that more than 150 mutations in ADAMTS13 have been reported worldwide. These mutations are diverse in both type and location in the gene, but broadly affect either activity or secretion of ADAMTS13 [11]. Therefore, although TTP mutations can be private to each patient, a link between mutations and disease characteristics may be uncovered with more evidence through increased understanding of protein structure and function, and how this is altered in cTTP.

The Metalloprotease domain is responsible for the cleavage of VWF. In the latent state, VWF is not accommodated as Ca<sup>2+</sup> binding loops can occlude the active site. Allosteric activation of ADAMTS13 is achieved by a series of complementary exosite interactions with VWF, which therefore acts as both a substrate and an allosteric activator of ADAMTS13 [12,13]. VWF is also required to undergo a conformational change to expose the A2 domain where cleavage takes place at the scissile bond. TTP causative mutations reported in the MP domain can disrupt the interaction with VWF for example, p.T196I (c.587C>T) missense mutation (reported in cTTP) has <5% activity, likely due to disruption of subsite S1 interactions [14]. Alternatively, the p.A250V (c.749C>T) mutation led to activity <5%, as proteolytic activity may be comprised due to the proximity of the mutation to the Zn<sup>2+</sup> ion [15].

The ADAMTS13 disintegrin (Dis) domain plays a pivotal role in enhancement of substrate VWF binding and conformational activation of the MP domain. R349 is engaged (binds D1614 in VWF A2 domain), this removes the local latency within the MP domain, allowing presentation of the active site. This interaction is essential, supported by p.R349C (c.1045C > T) a TTP-causing mutation affecting this exosite with <1% activity. Furthermore, R349D resulted in almost complete loss of proteolytic activity *in vitro* [16,17].

The cysteine-Rich domain (CRD) of ADAMTS13 contains 10 cysteine residues which are paired to form disulfide bonds [16]. This domain is homologous with others in the ADAMTS family; however, the non-conserved V-loop forms a hydrophobic pocket to favor interactions with the VWF A2 domain [18]. TTP patient with heterozygous mutation p.C508Y (c. 1523G>A) had <3% activity, which also showed abolished secretion *in vitro*, potentially due to changes in protein folding and stability. However, p.Q449\* (c. 1345C>T) results in normal secretion but very low activity [18]. The absence of some domains may explain differing severity of disease or dictate the neonatal onset of the disease [19]. Incorrect folding or structure alteration of ADAMTS13 leads to issues with secretion as found through *in vitro* mutagenesis studies [20].

The spacer domain is of functional importance for the interaction with VWF, with the spacer exosite important for VWF recognition [20–22]. If ADAMTS13 residue R660 is mutated (positive charge is essential at this residue) proteolytic activity is abolished suggesting this residue, and therefore the spacer domain exosite, is essential for activity and recognition of VWF [23,24]. This is supported by the low activity as reported in the CRD mutant previously (p.Q449\*), where this essential residue is lacking. The mutation p.I673F (c. 2017A>T) *in vitro*, shows no detectable secretion; reported in a heterozygous patient with severe neonatal onset TTP [25]. Under normal conditions ADAMTS13 has an inbuilt mechanism to maintain “global” latency and prevent activation until required. This is provided by the interaction of the C-terminal CUB domains with the spacer domain.

ADAMTS13 contains eight Thrombospondin type-1 repeat domains (TSPs), the first within the N-terminal domains between the Dis and CRD. TSP-1 is thought to function in facilitating ligand interaction. TTP causative mutation R398H was reported in a patient (no data available) which alters a conserved residue among ADAMTS family members [14]. TSPs 2–8 link the spacer domain to the C-terminal CUB-domains, with three linker regions between 2/3, 4/5 and 8/CUB-1 [13,26]. These repeats have no available crystal structure; they are required largely for flexibility and supporting the CUB–Spacer interaction which maintains latency; deletion of TSP7 and TSP8 disrupted this allosteric regulation [27]. Mutations may lead to reduced secretion due to abnormal folding of the protein evidenced by the mutation p.R1060W (c. 3178C>T), one of the most observed in TTP [28].

There are 2 CUB domains at the C-terminus, unique to ADAMTS13 within the ADAMTS family. The CUB domains are involved in the initial binding between ADAMTS13 and the D4CK domain of VWF. This results in conformational changes in both proteins, resulting in linearizing VWF and unfolding of ADAMTS13 through disruption of the Spacer–CUB interaction [26]. Previous work has revealed that ADAMTS13 folds its distal CUB domains to the proximal spacer domain to limit exposure of the N-terminal exosites until required for interaction with VWF [13]. Mutations in both CUB1–2 affect protein secretion rather than protease activity directly. Mutation p.G1239V (c. 3716G>T) affecting CUB-1 was reported in a homozygous patient with reduced plasma ADAMTS13 levels and recurring relapse [29,30]. E1382Rfs6 (c. 4143dupA) in CUB2 causes loss of 49 AAs with subsequent negligible secretion and protease activity. There is association with neonatal-childhood onset TTP [31].

## Treatment and concluding remarks

Due to the advances in ADAMTS13 structural studies as well as secretion and activity assays, new treatments are emerging for cTTP. Investigation into MDTCS constructs to partially restore some of the abolished proteolytic activity in ADAMTS13-/- murine models is in its early stages but provides proof of concept for potential TTP treatment in the future [32]. The first clinical trial with recombinant ADAMTS13 to test pharmacokinetics and safety has been published, providing another avenue to explore potential cTTP treatments [33]. There is also potential for wider uses in organ dysfunction such as myocardial ischemia due to the downstream effect on hemostasis the UL-VWF multimers cause. Furthermore, identification of important residues in disease through use of patient mutation data alongside 3D structures from further crystallography studies, may provide a scaffold to rationally modify ADAMTS13 for use as a thrombolytic therapeutic agent or in replacement therapy.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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