

ERN-EuroBloodNet Topic on Focus on Thrombotic Thrombocytopenic Purpura (TTP)



PATIENTS

What is TTP?

Explanation of the disease in simple terms
Types: congenital (cTTP) vs. acquired (iTTP)

Prof. Flora PEYVANDI



**Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico**



Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario



Regione
Lombardia

Flora PEYVANDI

email : flora.peyvandi@unimi.it

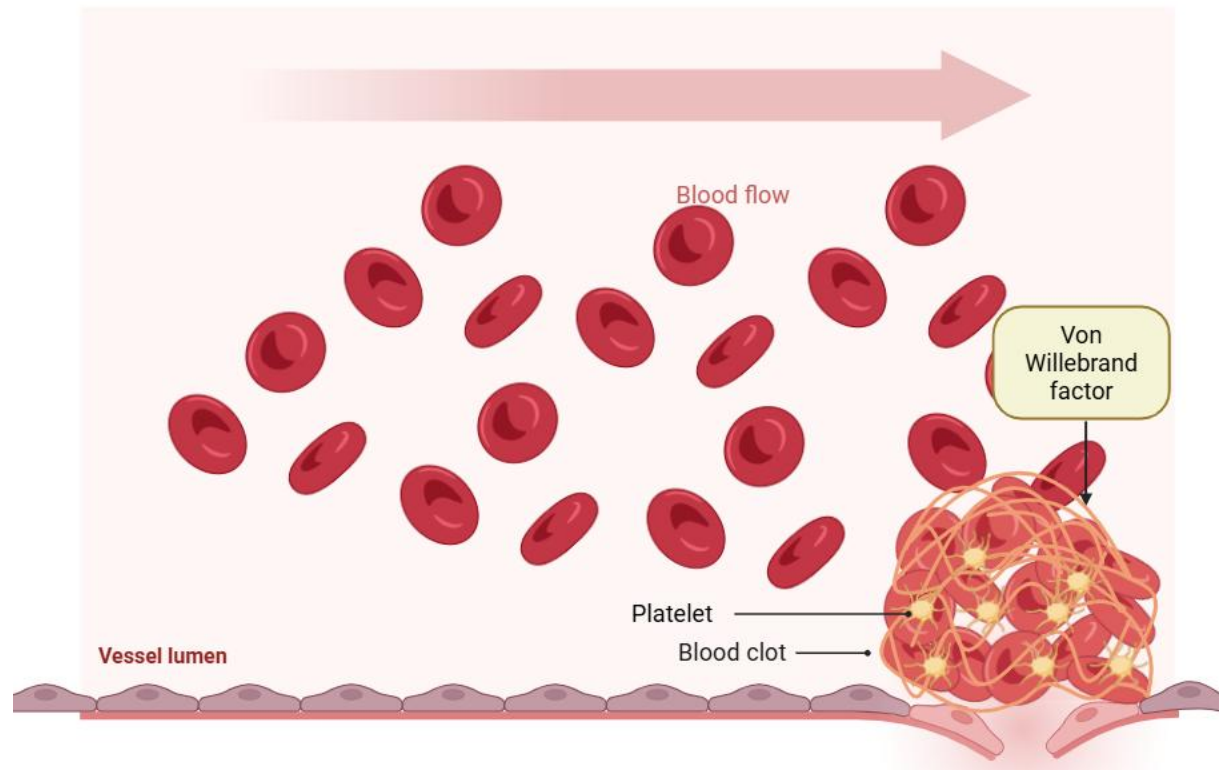


 | Disclosure for conflict of interest goes here...

Educational symposia	Sanofi, Sobi, Biomarin, Kedrion, Bayer, Roche
Advisory Comitee member	Sanofi, Sobi, Roche, CSL Behring, Novo Nordisk, Biomarin, Regeneron, Metagenomi, Star-Therapeutics, Bayer, Pfizer, Takeda, TargED.



First: why do we need platelets?

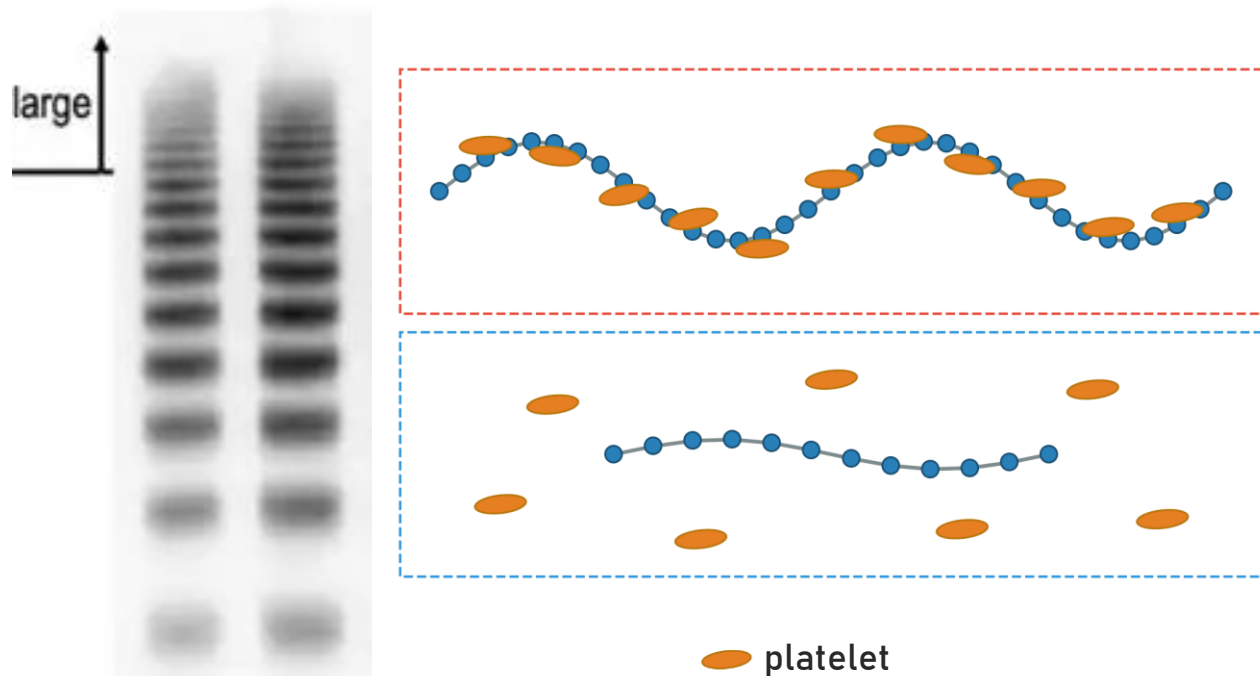


**Platelets help seal an injured blood vessel
VWF help them to stick**



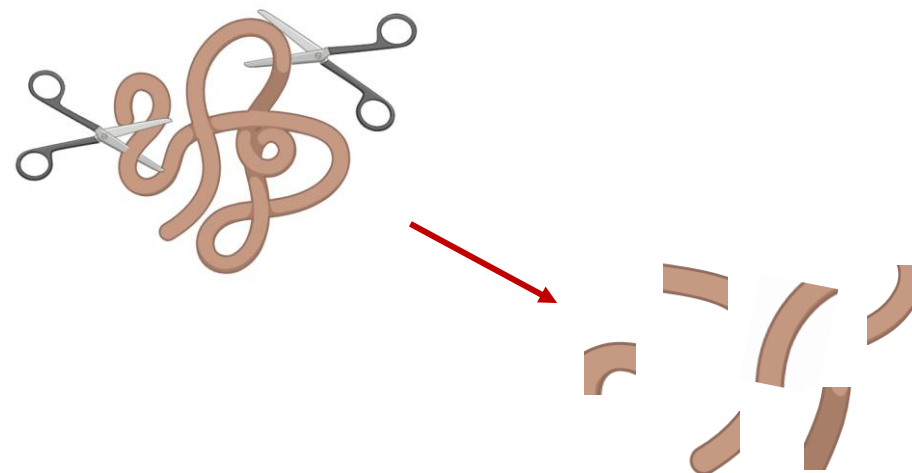
Meet ADAMTS13: the molecular scissors

VWF structure



Multimers: Sakatsume K et al. ASAJO 2002

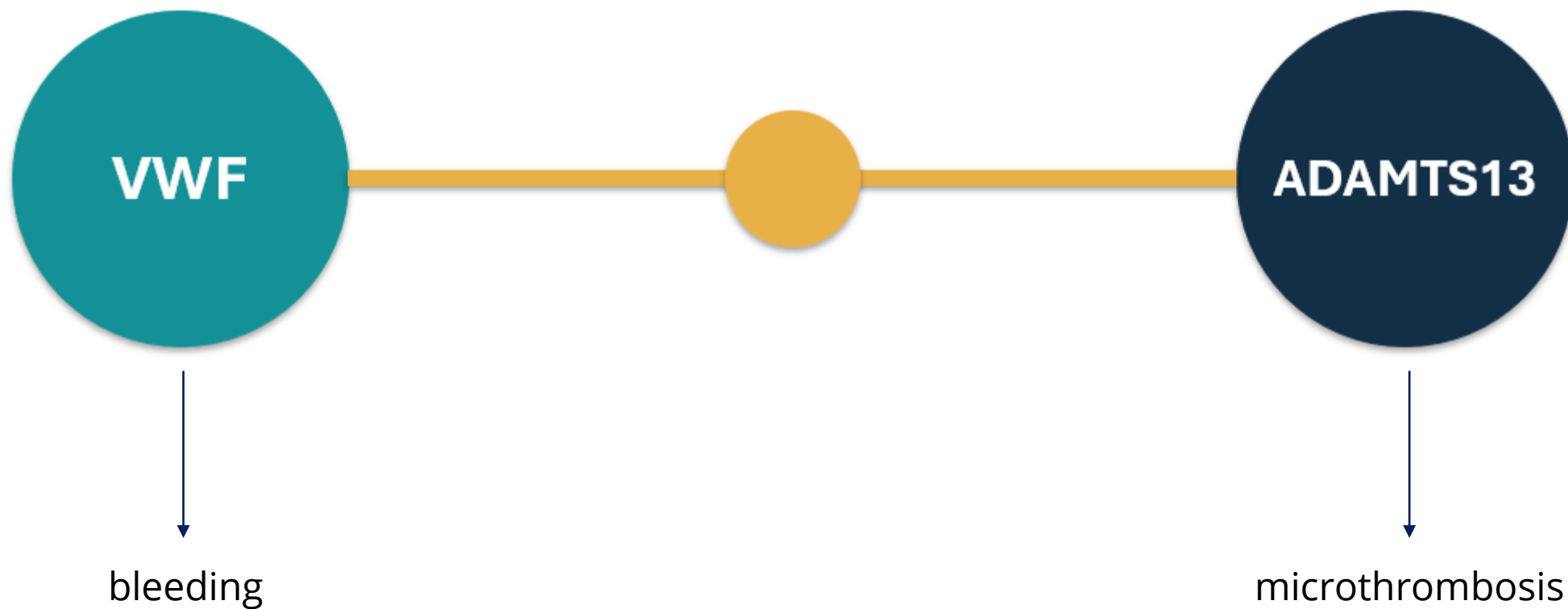
Ultra large VWF strand needs to be cut by ADAMTS13



Otherwise these large multimers attach platelets and form thrombi in microvessels



Healthy circulation depends on balance





What changes in TTP?

1

**Very low
ADAMTS13**

2

**Ultra-large VWF
persists**

3

**Platelets stick
inappropriately**

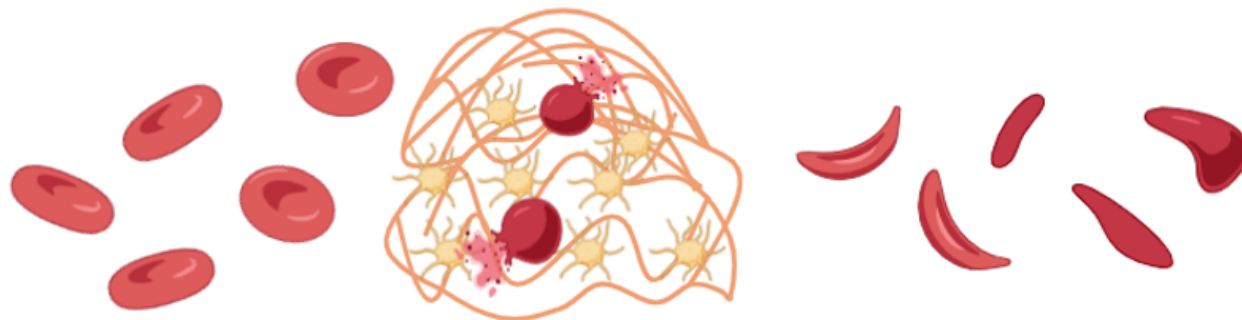
4

**Microclots form
in small vessels**

In vital organs
such as brain,
kidney, heart



What happens to platelets and red blood cells in TTP?



Platelets become trapped in microclots

Red cells passing through partially blocked small vessels can be mechanically damaged

THROMBOCYTOPENIA

[low platelets]

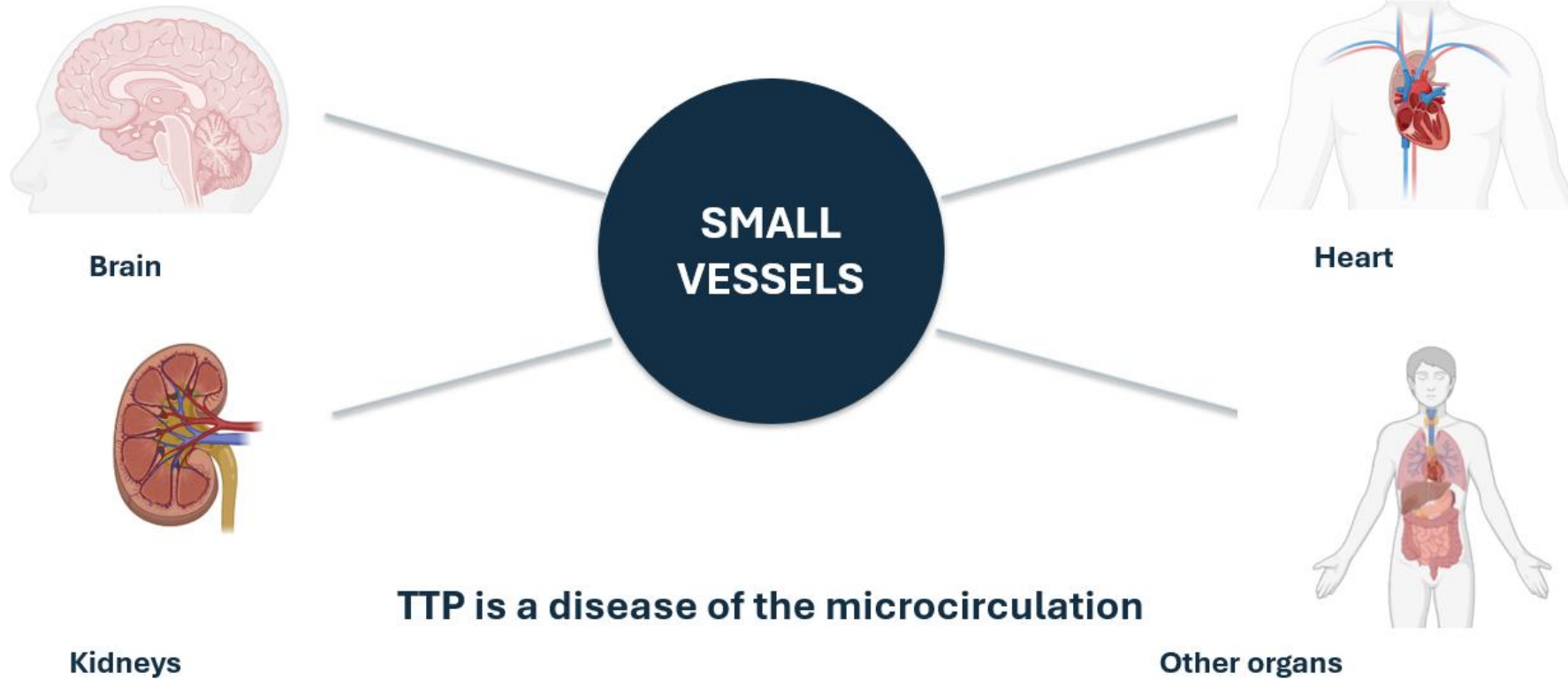
HAEMOLYTIC ANEMIA

[low hemoglobin]

Zheng XL et al. J Thromb Haemost. 2020;18:2486–2495.



Why can TTP affect different organs?



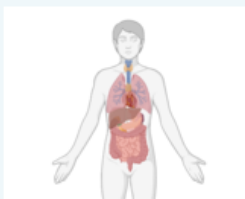


Symptoms can look very different from person to person



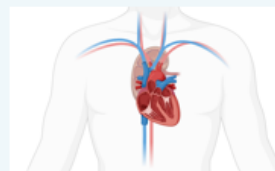
Neurological

Headache
Confusion
Weakness
Seizures



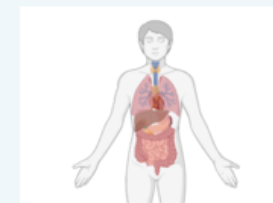
General

Extreme fatigue
Fever
Feeling unwell



Cardiac

Chest discomfort
Shortness of breath



Other

Abdominal
symptoms
Kidney involvement

Not every patient has all symptoms

Kremer Hovinga JA, George JN. N Engl J Med. 2019;381:1653–1662; Zheng XL et al. JTH. 2020;18:2486–2495.



TTP is an emergency, and it is treatable

Treatment should start as soon the diagnosis is made



Without treatment the
mortality rate is high



Modern treatments has
transformed the outcome
of patients with TTP



TTP:

IMMUNE TTP

Cause

**The immune system targets
ADAMTS13**

How common?

The large majority (>95%)

Can relapse?

Yes More than 50%

CONGENITAL TTP

Cause

**Inherited changes in the
ADAMTS13 gene**

How common?

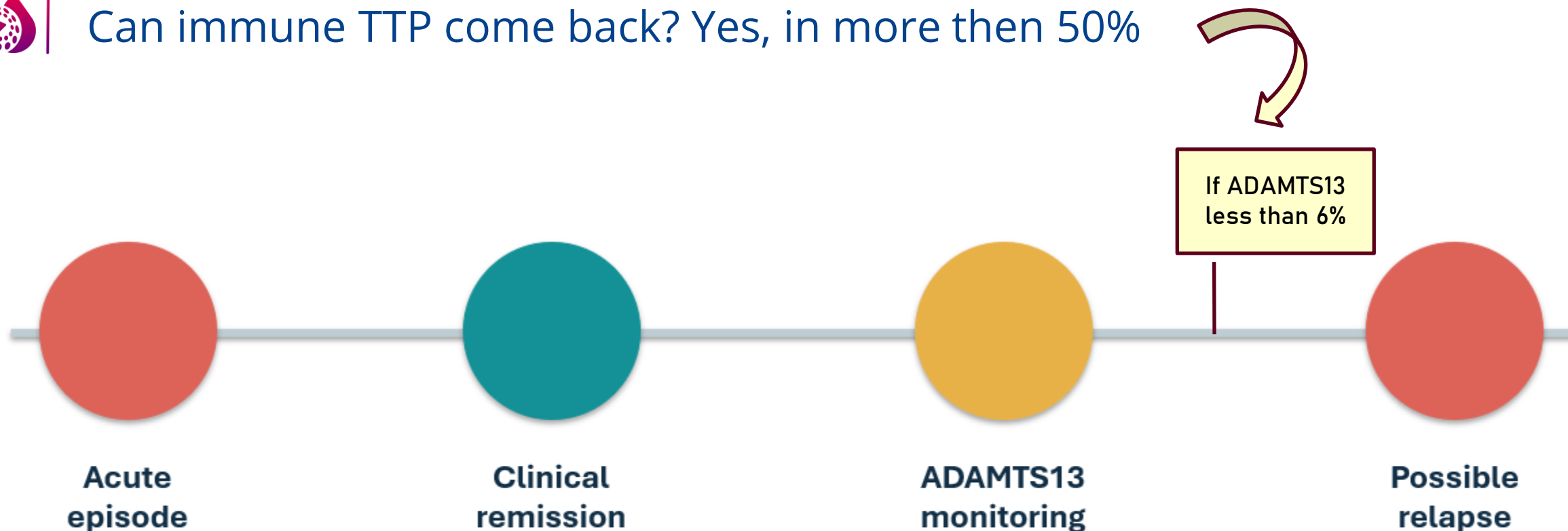
Rare (<5%)

Lifelong condition?

Yes

Kremer Hovinga JA, George JN. *N Engl J Med.* 2019;381:1653–1662; Zheng XL et al. *JTH.* 2020;18:2486–2495.

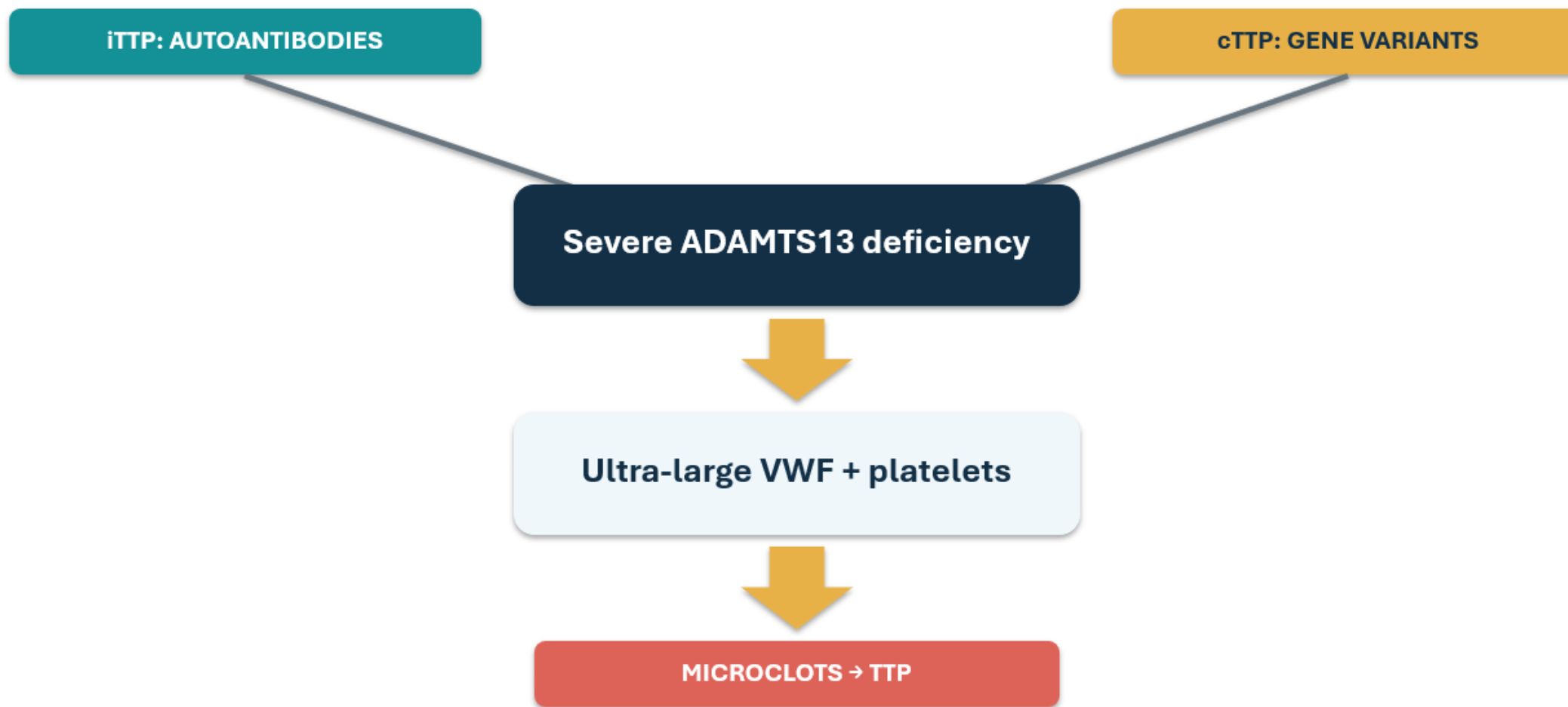
 Can immune TTP come back? Yes, in more than 50%



Follow-up continues even when you feel completely well.



Different cause, same final pathway



[event with low platelets and low hemoglobin]

THE CLOSING MESSAGE

- **TTP is a serious disease and, once diagnosed, should be treated immediately**
- **Once the patient has recovered, they should be followed regularly at a centre with expertise in this field**

ERN-EuroBloodNet Topic on Focus on Thrombotic Thrombocytopenic Purpura (TTP)



PATIENTS

Understanding the disease

Causes and Risk Factors

Barbara FERRARI, MD

03 October 2026



**Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico
Milan, ITALY**



Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario



Regione
Lombardia

Barbara FERRARI, MD
Specialist in Internal Medicine

Email: barbara.ferrari@policlinico.mi.it





Disclosure for conflict of interest

No conflicts of interest



01

Genetic VS Immune-mediated Causes



TTP pathway: everything starts from ADAMTS13 deficiency

1

**Very low
ADAMTS13**

2

**Ultra-large VWF
persists**

3

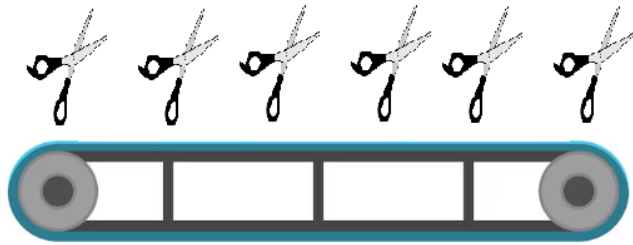
**Platelets stick
inappropriately**

4

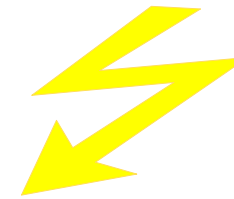
**Microclots form
in small vessels**



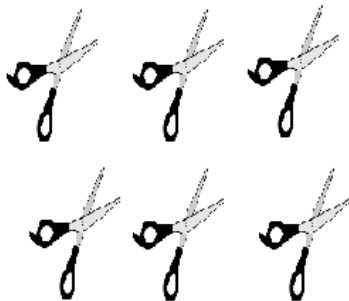
ADAMTS13 deficiency may be caused by problems at two different levels:



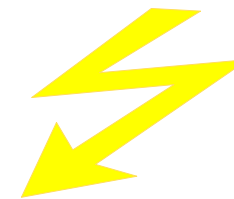
ADAMTS13
production



**GENETIC
CAUSES**



ADAMTS13
circulation in the blood

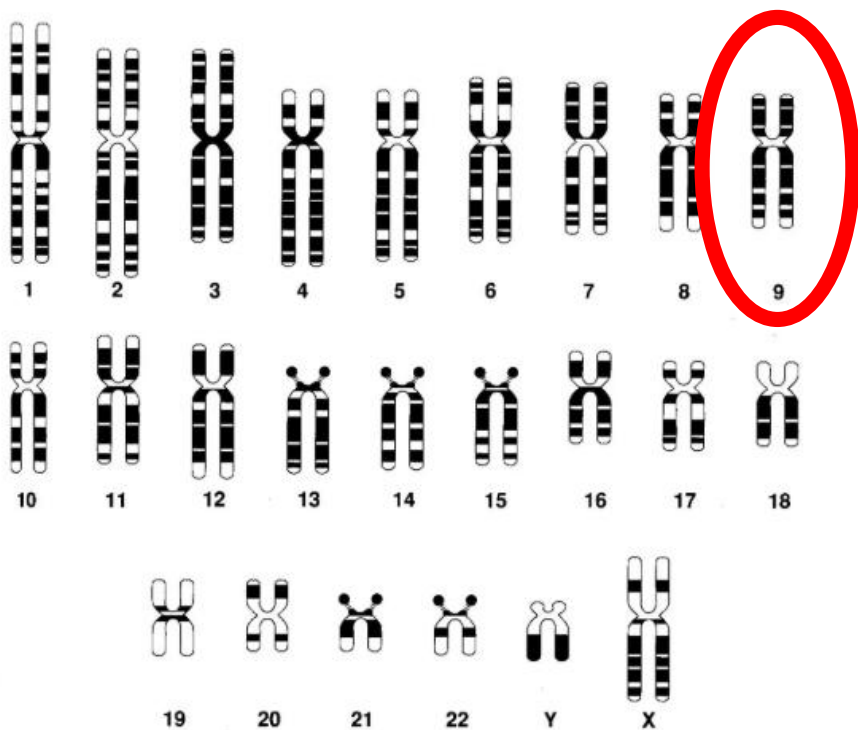


**IMMUNE-
MEDIATED
CAUSES**

Zheng XL, Sadler JE. Pathogenesis of thrombotic microangiopathies. Annu Rev Pathol. 2008;3:249-77



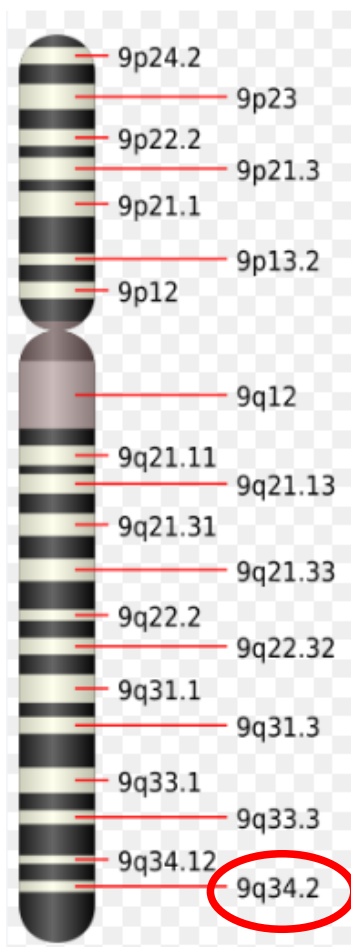
ADAMTS13 production depends on genetic information on chromosome 9



- The instructions to produce everything in our body are written as a code (sequences of DNA) in the **genes**, located in the **chromosomes**
- Under normal conditions, we all have 23 pairs of chromosomes, with one chromosome inherited from each parent (maternal and paternal)
- ADAMTS13 production depends on a gene located on **chromosome 9**



Congenital TTP (cTTP) depends on mutations in the *ADAMTS13* gene



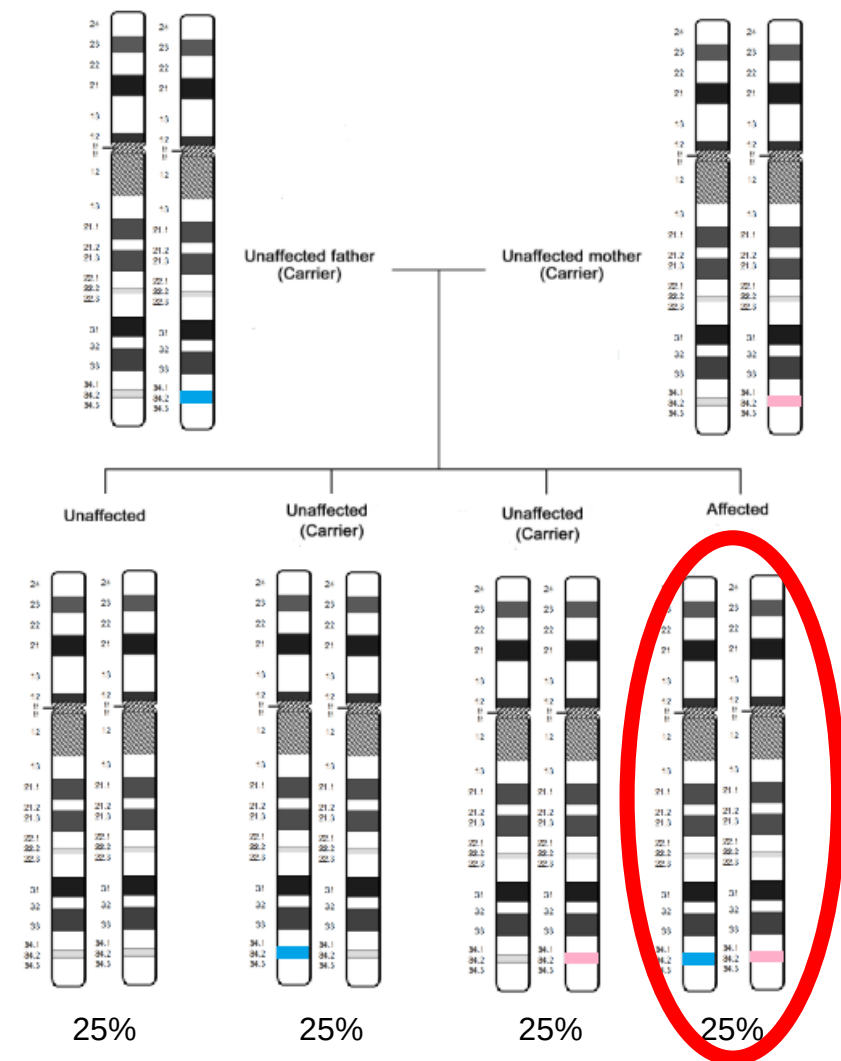
- A **mutation** is a change in the code (DNA) of a gene, leading to an error in the instructions
- If the *ADAMTS13* gene on one chromosome (maternal or paternal) is mutated, the patient is a **carrier** of the mutation, but does not develop the disease (the code on the other chromosome is correct → ADAMTS13 role is preserved)
- If the *ADAMTS13* gene on both chromosomes (maternal and paternal) is mutated, the patient is affected by the disease, **congenital or inherited TTP** (both codes are wrong → ADAMTS13 role is not preserved)

Levy GG, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001 Oct 4;413(6855):488-94.



How is **cTTP** inherited?

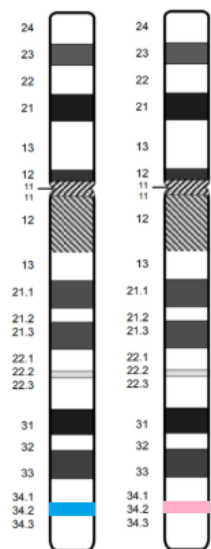
- Both parents must be carriers of a mutation (usually the same in consanguineous relatives)
- The baby has a 25% risk of being affected (and a 50% risk of being a carrier). There is also a 25% probability of being totally unaffected
- This type of inheritance is called **recessive**
- > 350 different mutations described so far



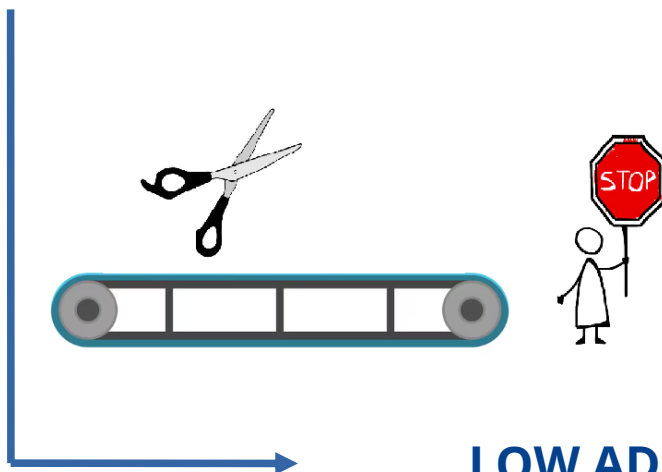
Carter MA, Scully M. Genetics of Thrombotic Thrombocytopenic Purpura: systematic review in immune and congenital TTP. JTH 2026;24(5): 1575-1586



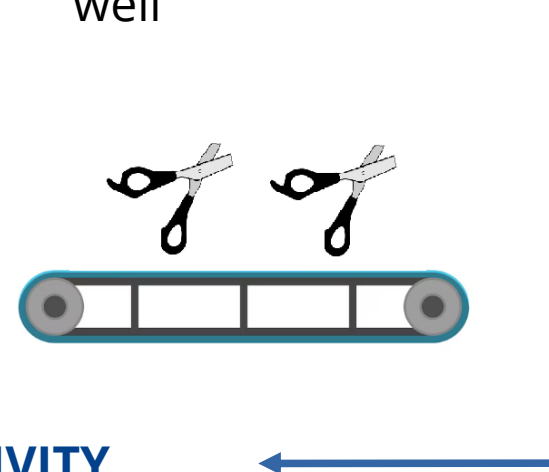
Mutations of *ADAMTS13* gene on both chromosomes lead to wrong production of ADAMTS13 since birth



● low production of the enzyme



● production of a “wrong” enzyme, which doesn’t work well



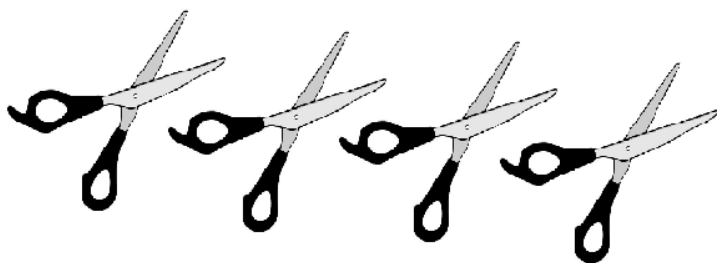
**LOW ADAMTS13 ACTIVITY
in the circulation**

NOTE: irreversible condition



In immune-mediated TTP (iTTP) ADAMTS13 becomes an immune target

ADAMTS13 is normally produced BUT is wrongly recognized as an "enemy" by the immune system



Circulating ADAMTS13

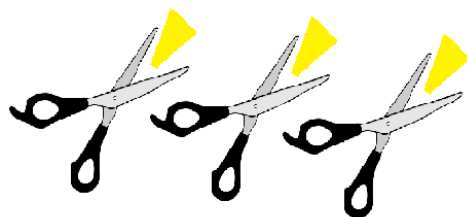
The immune system produces "wrong" antibodies against "normal" ADAMTS13 (**auto-antibodies**)



Anti-ADAMTS13 Abs



Anti-ADAMTS13 Abs block or remove circulating ADAMTS13



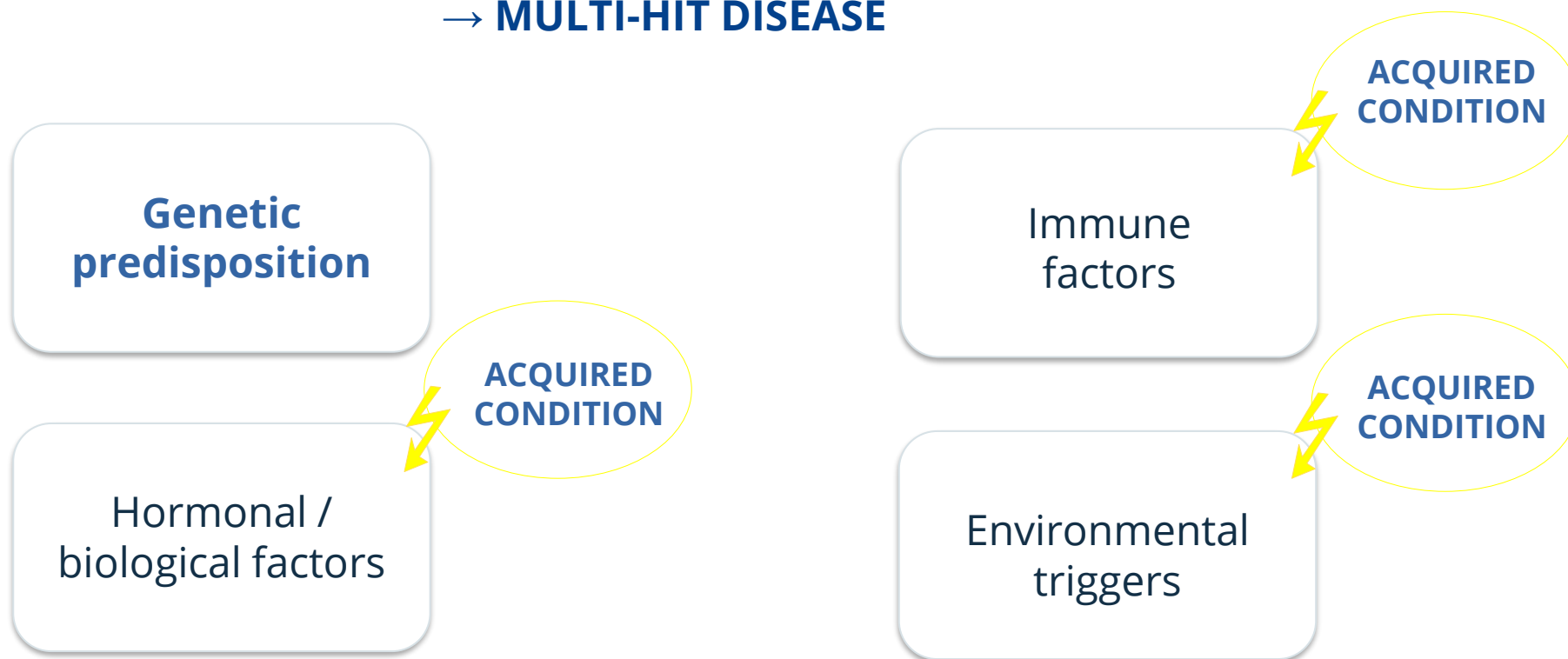
**LOW ADAMTS13 ACTIVITY
in the circulation**

NOTE: potentially reversible condition



Why does the immune system make wrong anti-ADAMTS13 Abs?

**In most cases, there is no clear single cause
→ MULTI-HIT DISEASE**



How do doctors distinguish the two types apart?

1

ADAMTS13 activity

Is it severely reduced?

2

ADAMTS13 antibodies

Is the immune system involved?

3

Genetic testing

Are inherited ADAMTS13 variants present?

NOTE: absence of anti-ADAMTS13 Ab alone does not prove congenital TTP → **genetic testing** is needed to confirm cTTP

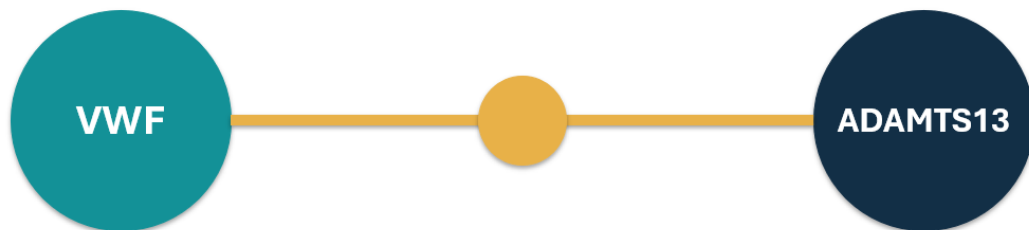
Zheng XL, et al. 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. JTH 2025, 23(11): 3711-3732

02

Common Triggers

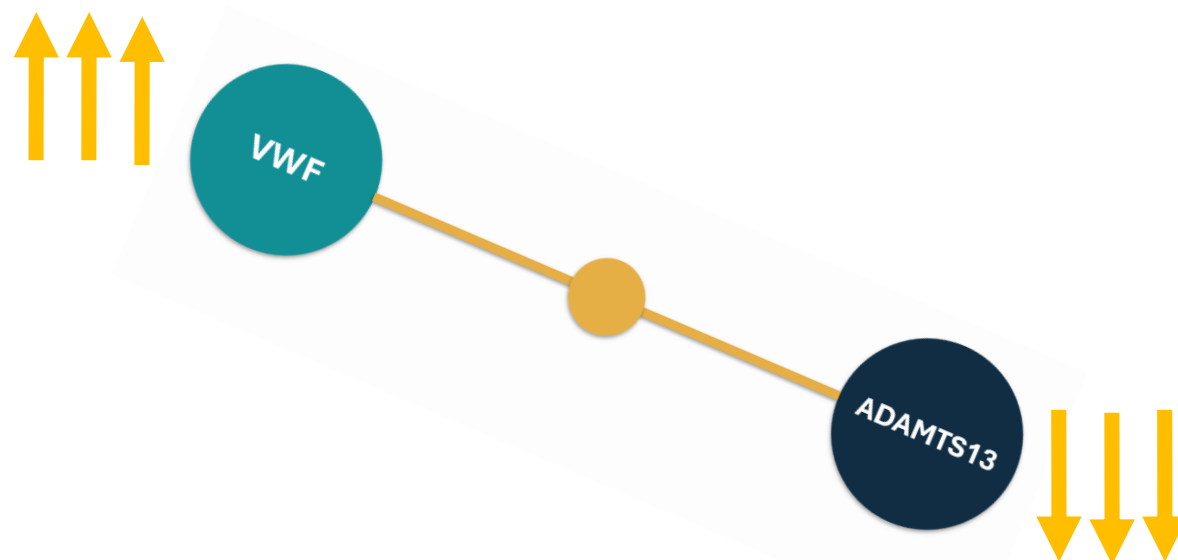


Even in cTTP, despite absent ADAMTS13, patients do not relapse all the time...why?



Healthy circulation depends on a balance between VWF and ADAMTS13

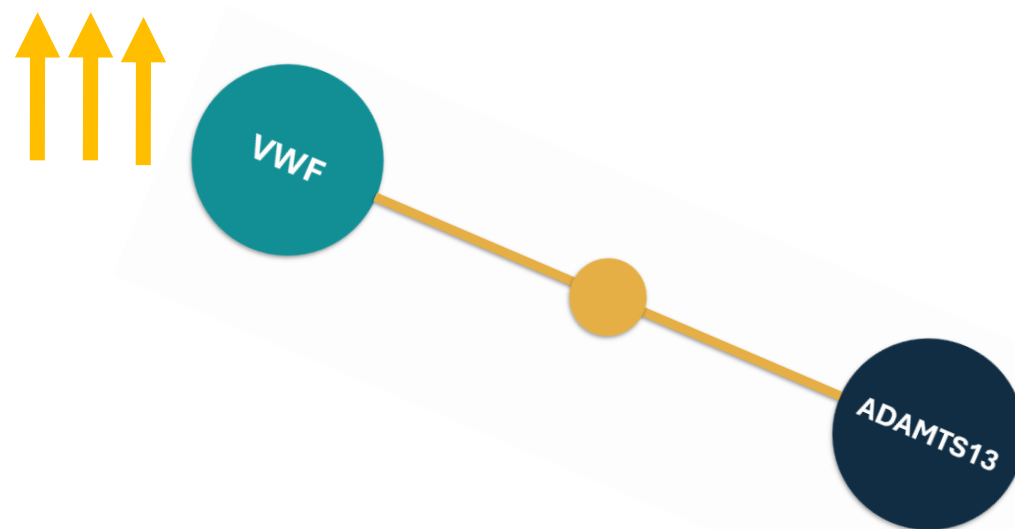
Conditions that increase VWF and/or decrease ADAMTS13 may **trigger** an acute TTP event





Conditions which increase VWF may act as trigger of both **cTTP** and **iTTP**

- Pregnancy
- Infections (e.g. HIV)
- Major surgery (mainly vascular, cardiac, orthopaedic)
- Cancer (mainly gastrointestinal)
- Certain drugs (i.e. estrogens, chemotherapeutic agents)

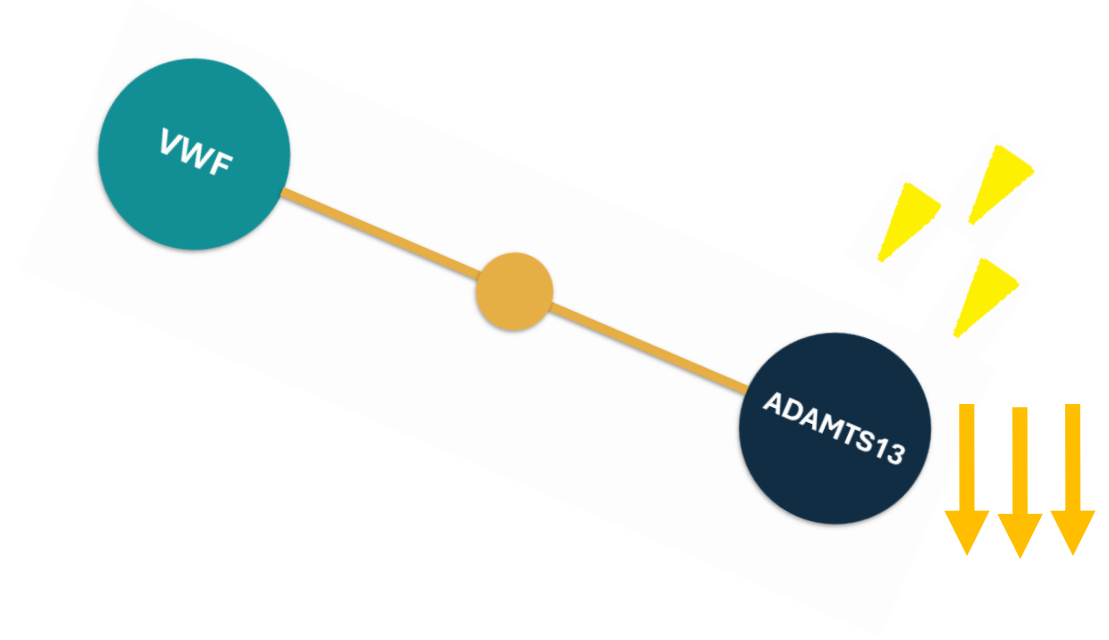


...mainly through endothelial release of VWF...



Conditions which induce autoantibodies production may trigger **iTTP**

- Infections
- Concomitant autoimmune disorders (e.g. Systemic Lupus Erythematosus, Sjogren)
- Certain drugs (e.g. thienopyridines)



...mainly through molecular mimicry or loss of immune tolerance...

Pregnancy is a major issue in TTP

Specific focus on
“TTP and Pregnancy”
on January 13th

CLOSING MESSAGES

- Low ADAMTS13 activity is the key element in TTP
- ADAMTS13 deficiency is *necessary* but not *sufficient*
 - to develop acute TTP
- Recognizing (and treating) trigger conditions is crucial in managing TTP

ERN-EuroBloodNet Topic on Focus on Thrombotic Thrombocytopenic Purpura (TTP)



webinar

PATIENTS

Symptoms and early warning signs

What to notice. When to act.

Andrea ARTONI, MD PhD



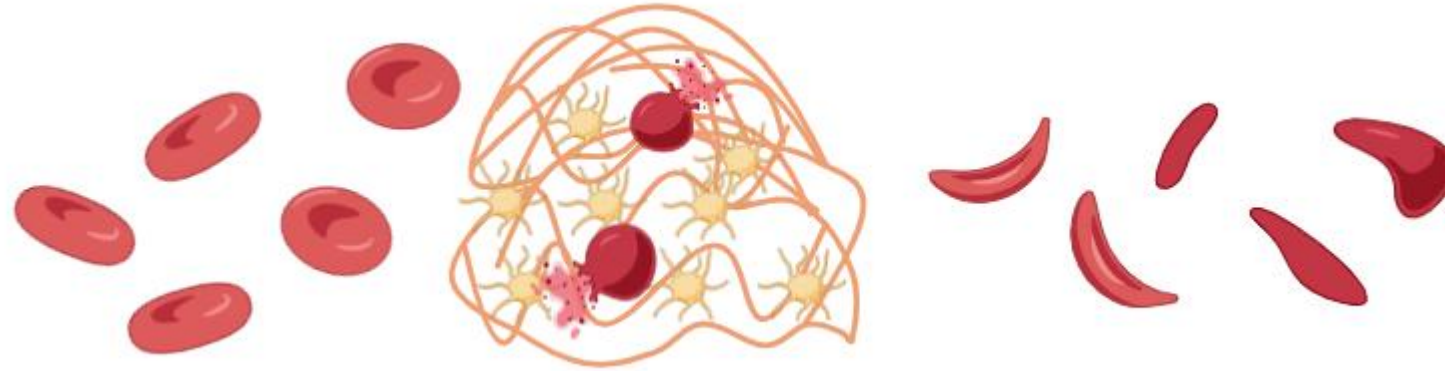


COI for Andrea Artoni

Consultancy	Name of Institutes/Companies
Conference fees	None
Advisory Comitee member	Sanofi, Takeda
Travel support	SOBI Novo Nordisk



What happens to platelets and red blood cells in TTP?



Platelets become trapped in microclots

Red cells passing through partially blocked small vessels can be mechanically damaged

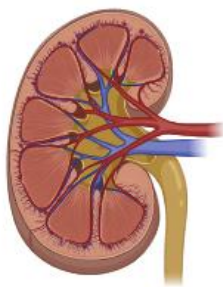
THROMBOCYTOPENIA

HAEMOLYTIC ANEMIA

TTP affects different organs

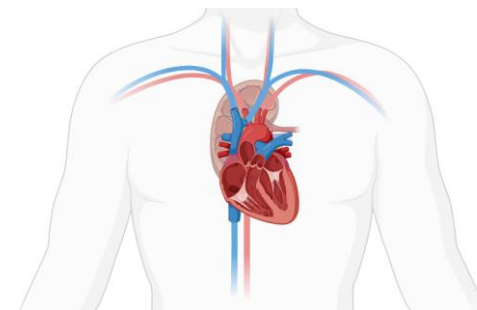


Brain

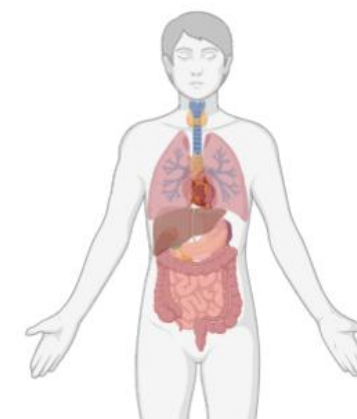


Kidneys

**SMALL
VESSELS**



Heart



Other organs



Why symptoms occur

In TTP, tiny clots can affect blood flow through small vessels.



Platelet levels fall

BLEEDING

Red blood cells break apart

ANEMIA

Organs may receive less blood

ISCHEMIA

Symptoms may appear suddenly and worsen quickly.

Zheng XL et al. J Thromb Haemost. 2020;18:2486–2495.



Possible early symptoms

- Unusual or extreme tiredness
- Headache
- Fever or flu-like symptoms
- Nausea, vomiting or diarrhoea
- Shortness of breath or a fast heartbeat



Notice what feels new, unexplained or different for you.

Zheng XL et al. *J Thromb Haemost.* 2020;18:2486–2495.



Skin changes and bleeding



Unexplained bruising

Tiny red or purple spots *petechiae*

Nose or gum bleeding

Bleeding that takes longer to stop

Heavier menstrual bleeding

TTP can occur without obvious bruising or bleeding.

Signs of red blood cell damage

When red blood cells break down faster than the body can replace them, you may notice:

- Pale skin
- Yellow skin or eyes
- Dark urine
- Marked weakness
- Shortness of breath or a fast heartbeat



Report new changes promptly

URGENT



Seek emergency help for any new neurological symptom

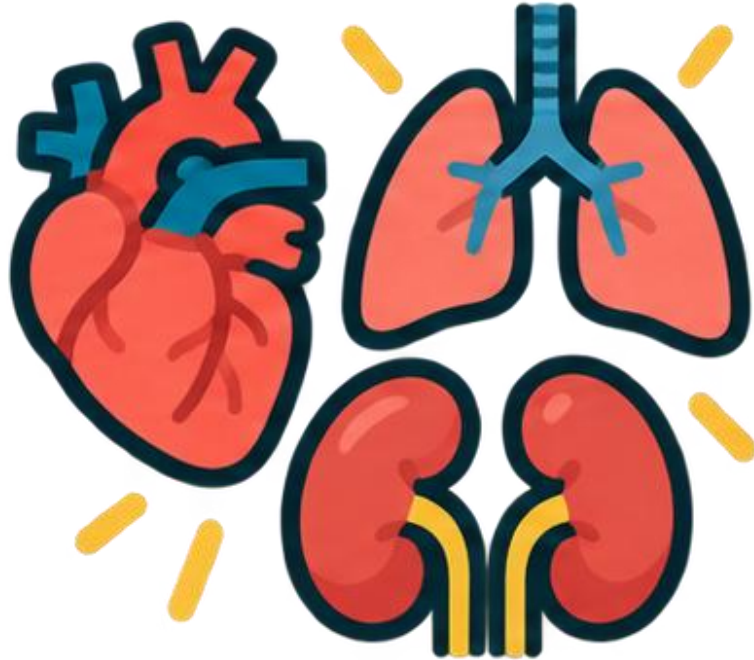
- Confusion or unusual drowsiness
- Difficulty speaking or understanding
- Weakness, numbness or facial drooping
- New vision problems
- A seizure or loss of consciousness
- A sudden severe or unusual headache



Treat stroke-like symptoms as an emergency



Other urgent warning signs



Chest pain

Severe shortness of breath

Very little urine or blood in the urine

Severe abdominal symptoms

Symptoms that worsen rapidly

You do not need to have every symptom before seeking help.

Zheng XL et al. J Thromb Haemost. 2020;18:2486–2495.

Your action plan- if you know you have TTP

- 1** Contact your TTP team immediately
- 2** Follow your personal emergency plan
- 3** Seek emergency care for severe or neurological symptoms
- 4** Tell the emergency team that you have TTP
- 5** Ask whether you need an urgent blood test



YOUR TTP TEAM

Add phone number here

Keep follow-up appointments even when you feel well.

Zheng XL et al. J Thromb Haemost. 2020;18:2486–2495.

Key message

Symptoms can be non-specific.

TTP can still become serious quickly.

NEW, UNUSUAL OR WORSENING SYMPTOMS

Contact your TTP team as soon as possible.

SEVERE OR NEUROLOGICAL SYMPTOMS

Seek emergency medical care immediately.



When in doubt, ask for medical advice.



www.eurobloodnet.eu



@ERNEuroBloodNet



eurobloodnet-european-reference-
network-on-rare-hematological-diseases



Eurobloodnet - European Reference
Network on Rare Hematological Diseases



ERN-EuroBloodNet's EDUcational
Youtube channel



Funded by the European Union.
Views and opinions expressed
are however those of the
author(s) only and do not
necessarily reflect those of the
European Union or European
Health and Digital Executive
Agency (HaDEA). Neither the
European Union nor the
granting authority can be held
responsible for them.



Funded by
the European Union

THANK YOU



Funded by the European Union.
Views and opinions expressed are
however those of the author(s) only
and do not necessarily reflect those of
the European Union or European
Health and Digital Executive Agency
(HaDEA). Neither the European Union
nor the granting authority can be held
responsible for them.



Funded by
the European Union