Qualitative Platelet Disorders

Hematology Online Review Series

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Disclosures

Advisory board member for Octapharma, Dova, Principia, Argenx, Sanofi, Janssen and Shionogi

Consultant for Novartis, Shionogi, Dova, Principia, Argenx, Rigel, Janssen, Sobi, and Bayer

Research funding from Sysmex, Novartis, Rigel, Principia, Argenx, Dova, Octapharma, Janssen, Sobi and Astra Zeneca

Coag Lab Research Funds from Rocket Pharmaceuticals and Werfen

Medical Advisory Board Member for PDSA, CdLS foundation, 22q Society FWG+BD

Co-Chair of Hemostasis/Thrombosis GCEP and member Platelet Disorder VCEP for ClinGen

Coagulation Laboratory Research Funding: Rocket Pharmaceuticals; Werfen

Learning Objectives

- Identify the common clinical presentations of qualitative platelet disorders (platelet function disorders: PFD)
- Understand the clinical manifestations of PFD and the impact on patients and families
- Describe the limitations of currently available clinical testing
- Demonstrate the potential impact of novel therapeutics on patients with inherited platelet disorders
- List potential acquired causes of platelet dysfunction



Why should we care?

Platelet disorders are common (even though the individual disorders may be rare)

Prevalence of inherited platelet disorders is between 1:1M and 3:1000 individuals.

Up to 20% of women with heavy menstrual bleeding have platelet function disorders

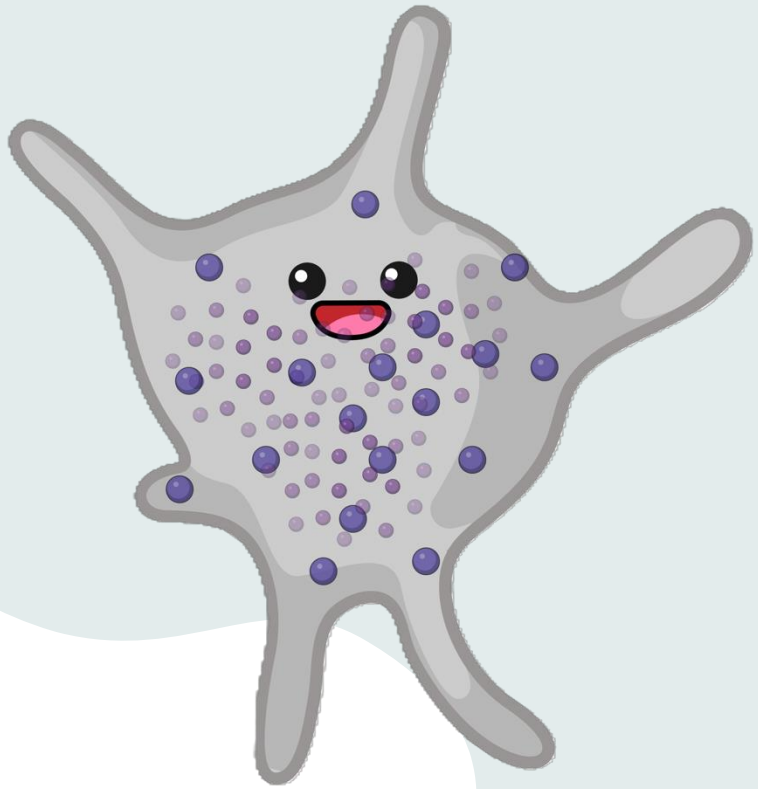
Frequency of surgical bleeding in PFD is high (19-54% of procedures)

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What do platelet disorders look like?

- Common signs and symptoms
- General categories

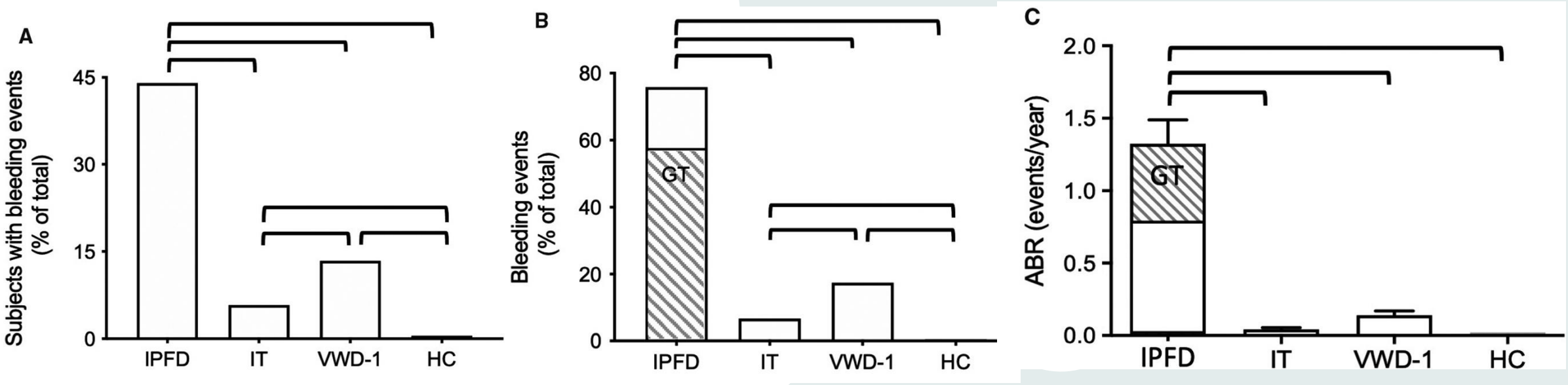
- Important note:
  - the prevalence of vWD is 0.6-1.3% with 1:1000 with clinically significant bleeding
  - gnomAD database review suggests the prevalence of LOF variants in platelet disorder genes is 0.329% of the population (Oved, JTH 2021)



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What do platelet disorders look like?

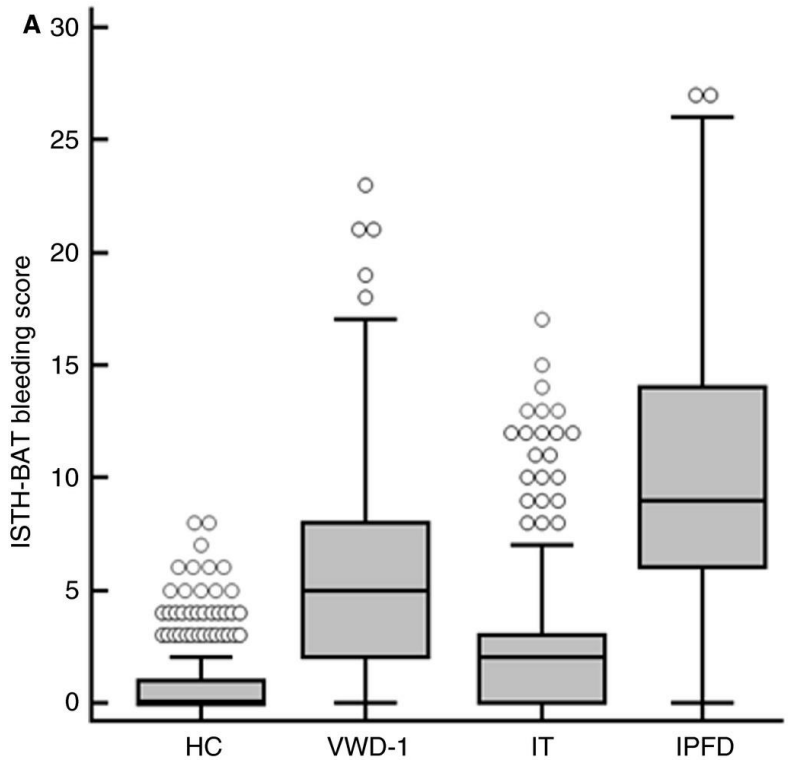
Bleeding phenotypes are highly variable (with severe and frequent bleeding in some types of platelet disorders)

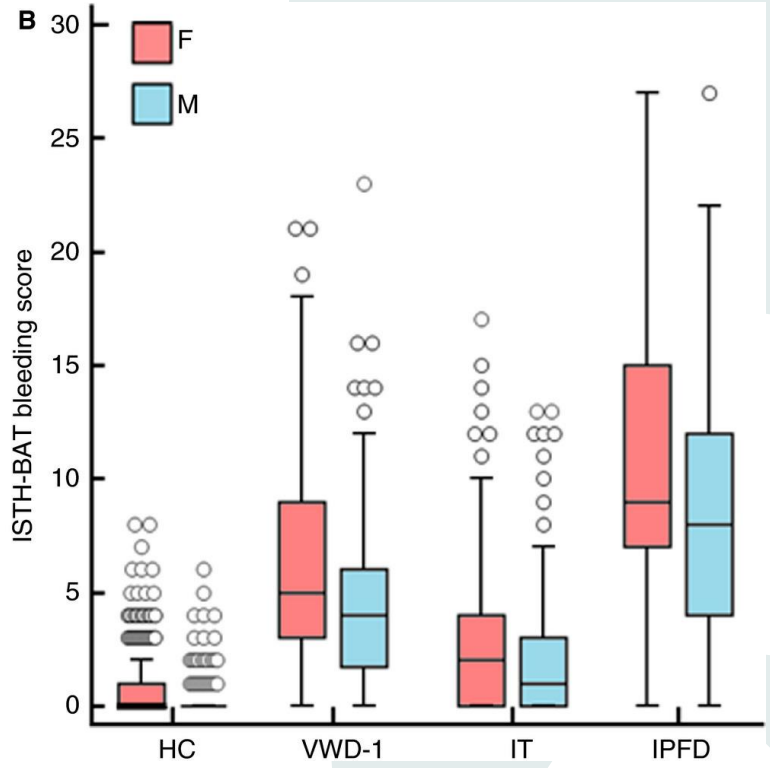


1.Gresele P, Falcinelli E, Bury L …
The ISTH bleeding assessment tool as predictor of bleeding events in inherited platelet disorders: Communication from the ISTH SSC Subcommittee on Platelet Physiology
Journal of Thrombosis and Haemostasis, 19, 1364-1371

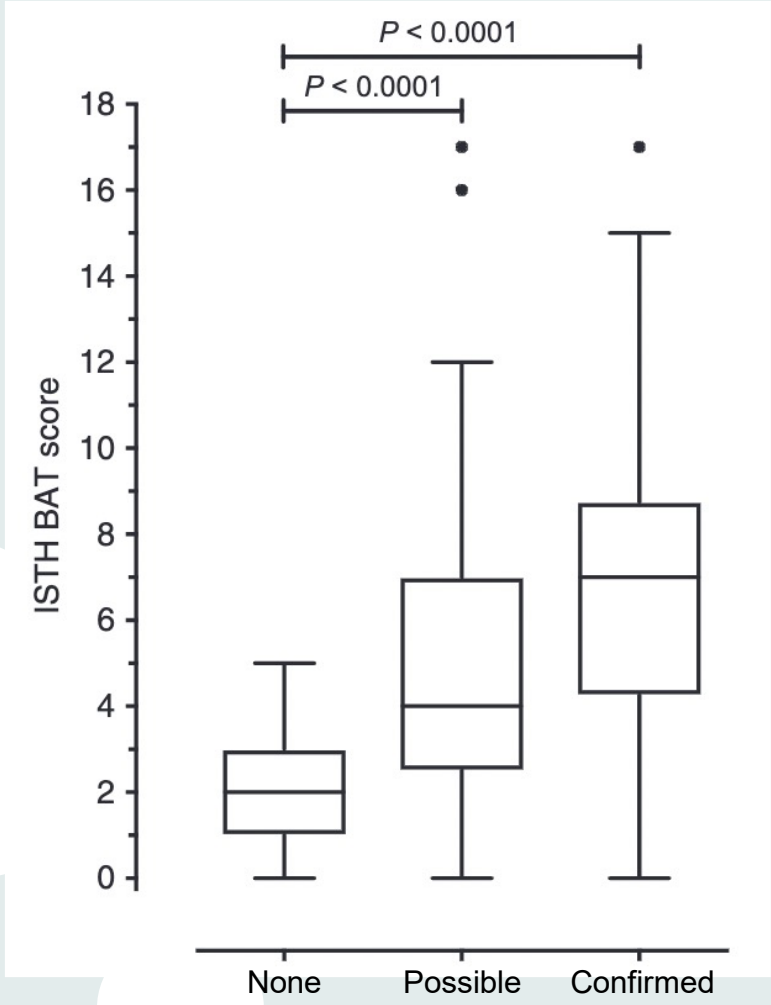
What do platelet disorders look like?

Bleeding scores are elevated (esp in adults)





Gresele et al JTH 2020



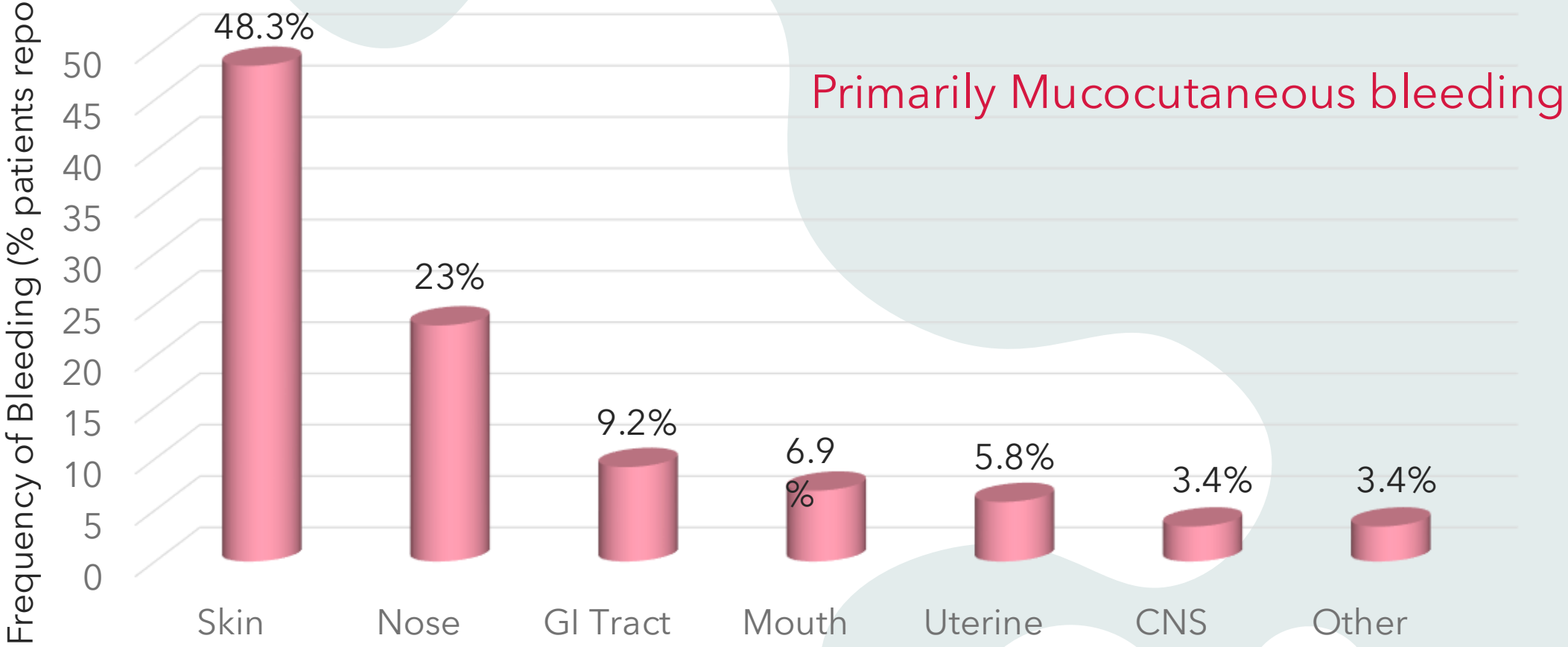
Adler et al JTH 2019;

Bleeding scores in Pediatrics

Pediatric	WHO median (IQR)			ISTH-BAT median (IQR)		
	All	Female	Males	All	Female	Males
IPFD	3 (2-3)	3 (2-3)	2.5 (1.75-3)	8 (6.5-14)	8 (8-13)	8 (4-11)
IT	1 (0-2)	1 (0-2)	1 (0-1.5)	1 (0-3)	1.5 (0-4.2)	1 (0-2.5)
VWD-1	1 (1-2)	1 (0-2)	1 (0.25-2)	3 (1-6)	6 (0-12.5)	3 (1-5)
HC	0 (0-0)	0 (0-0.5)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)

Gresele et al JTH 2020

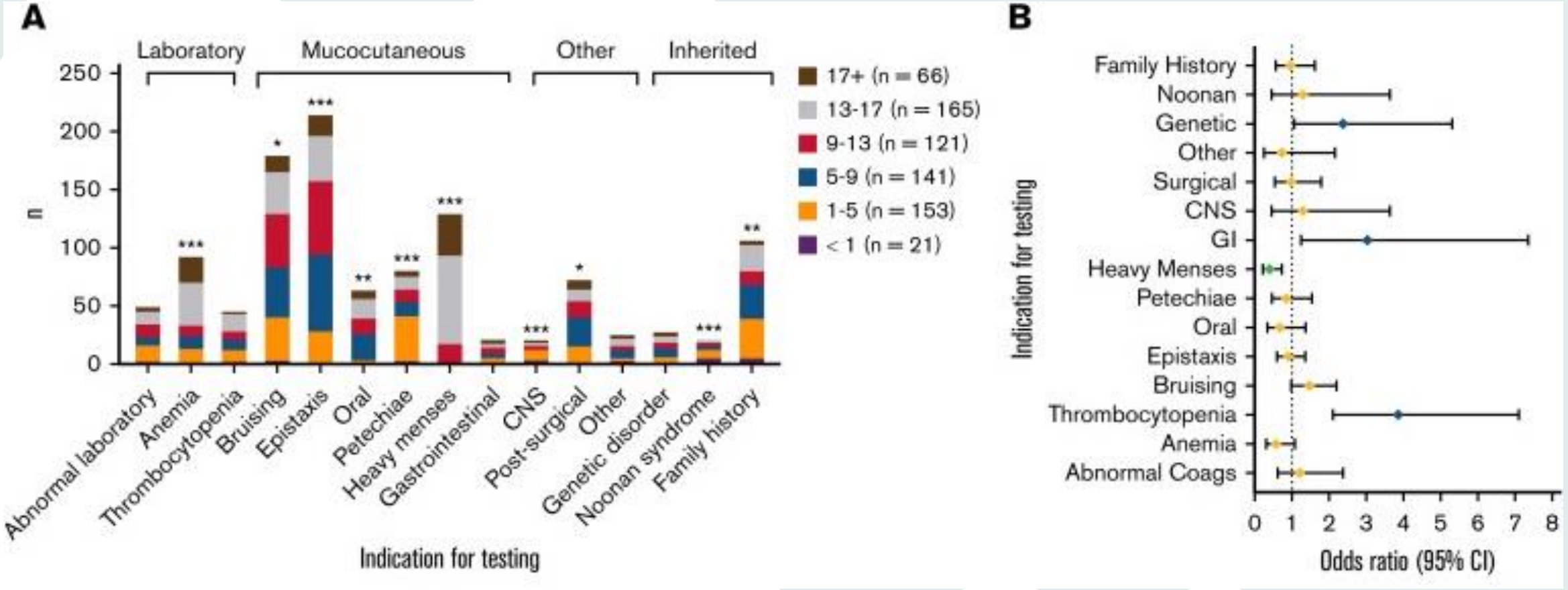
Signs and Symptoms of Platelet Disorders



Primarily Mucocutaneous bleeding

Gok et al, RPTH, 2025

Signs and Symptoms of Platelet Disorders



Doshi et al, blood VTH 2026

Severe Hemorrhage in Platelet Disorders

Risk varies by disease

Some patients have high lifetime risk of significant hemorrhage (GT, WAS, BSS)

- Recent Natural History Study in GT showed 88% pts have weekly bleeding with >50% bleeding 3x per week or more and 80% missing school or work due to bleeding
- 30% alloimmunization to platelets

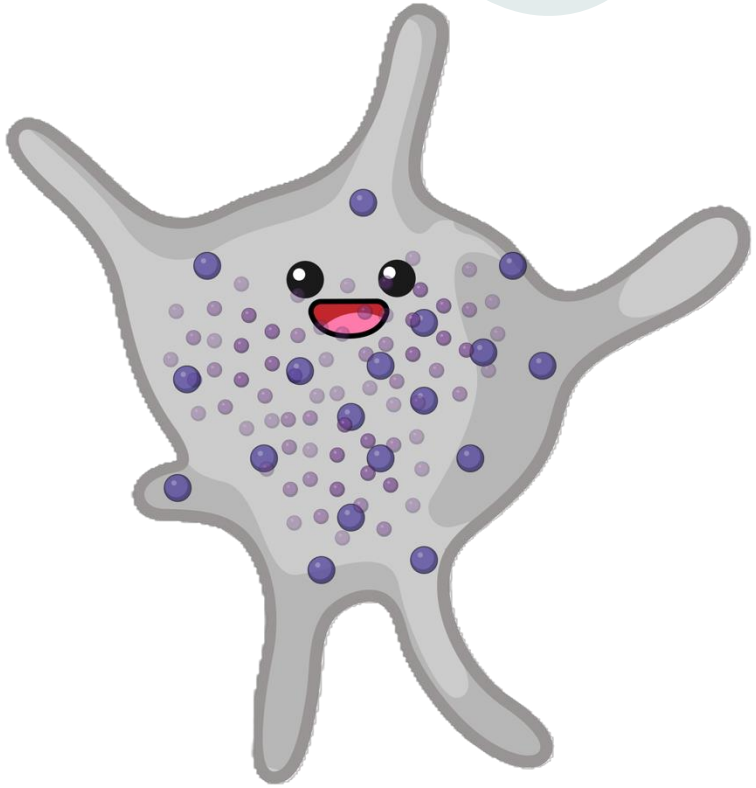
Some patients have minimal bleeding (MYH9, TUBB1, ACTN1)

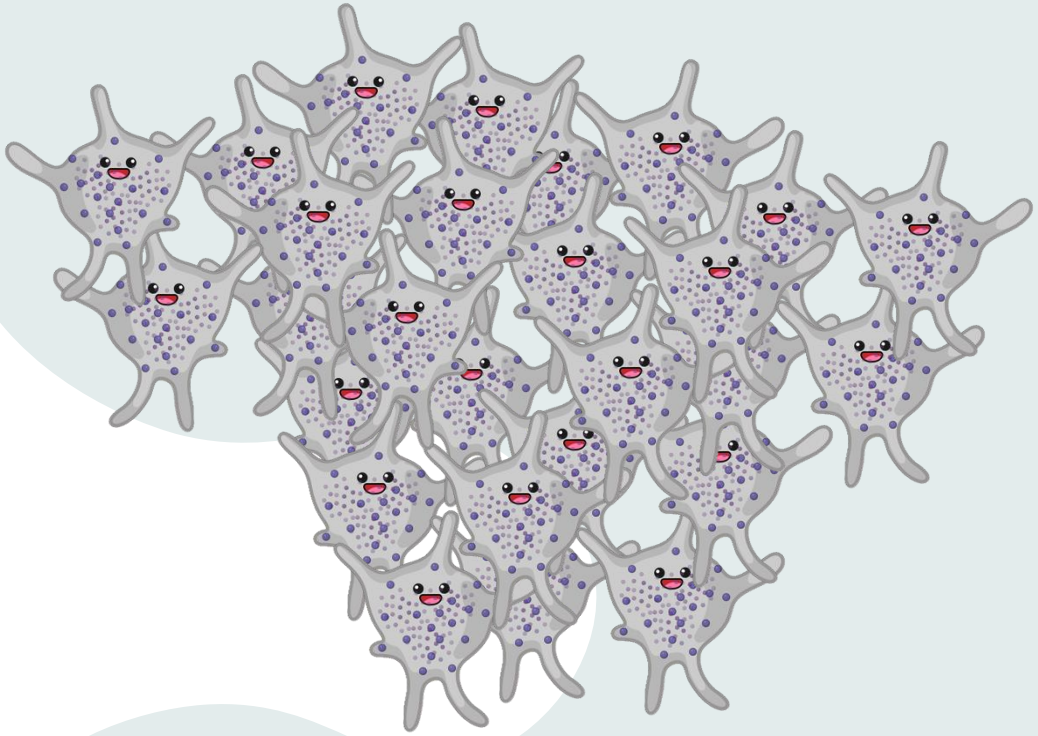
Others are moderate (RUNX1, HPS)

Types of Platelet Disorders



Types of Platelet Disorders

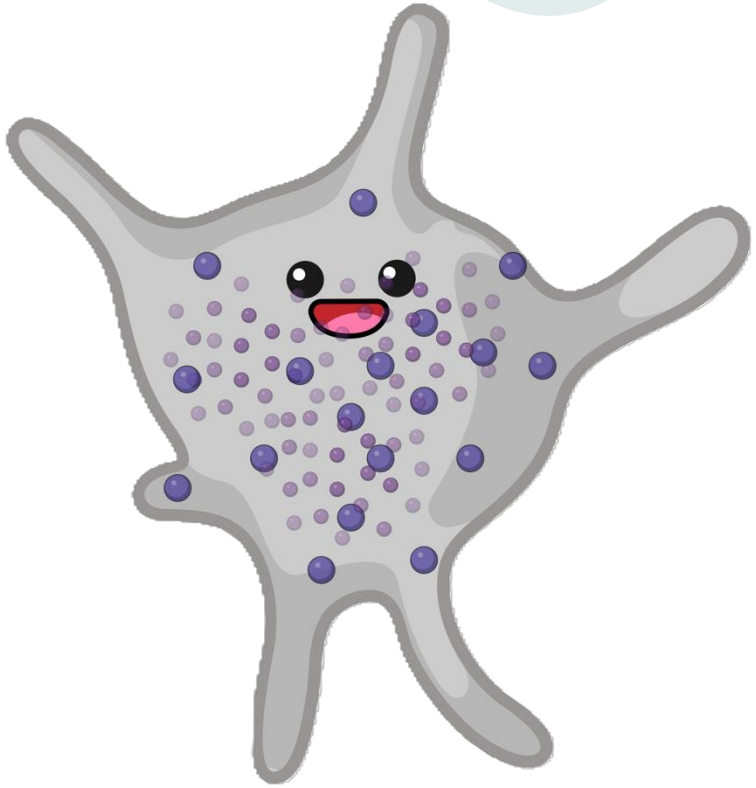


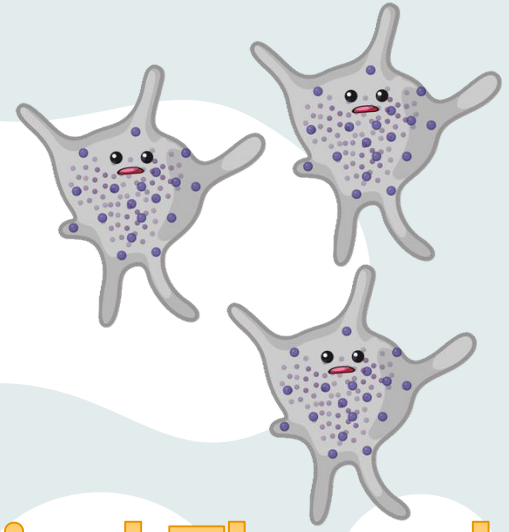


Platelet Party

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Types of Platelet Disorders

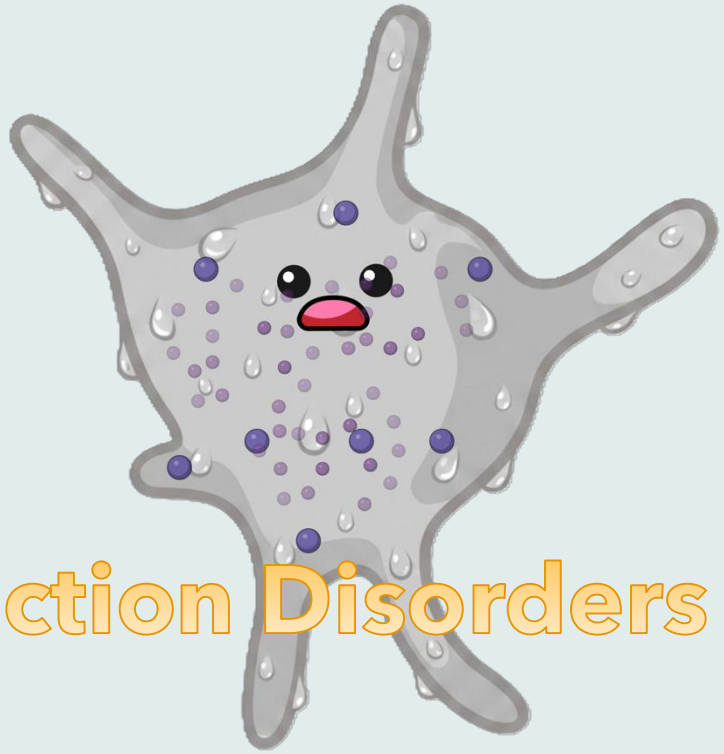


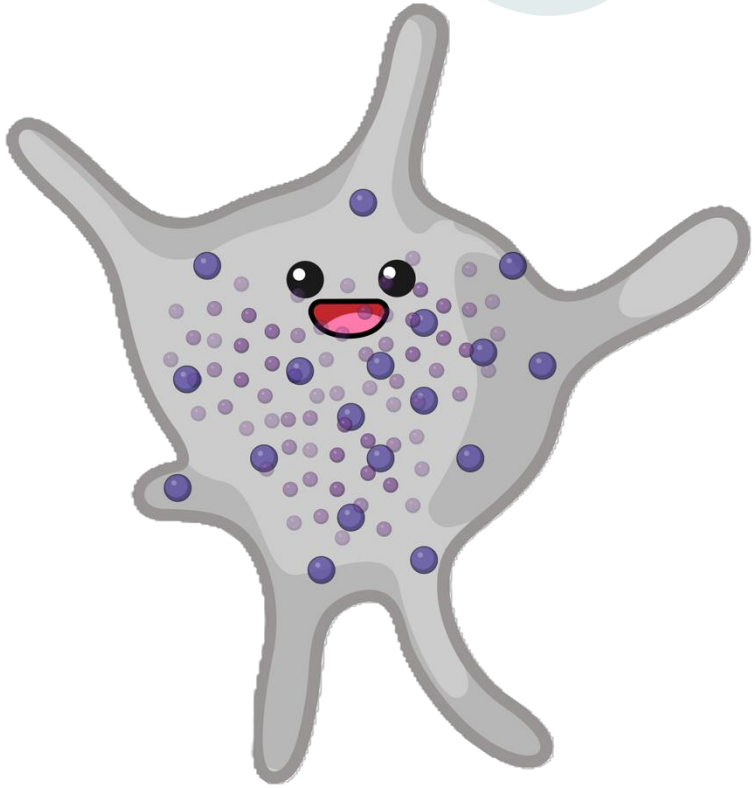


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Congenital Thrombocytopenia

Types of Platelet Disorders

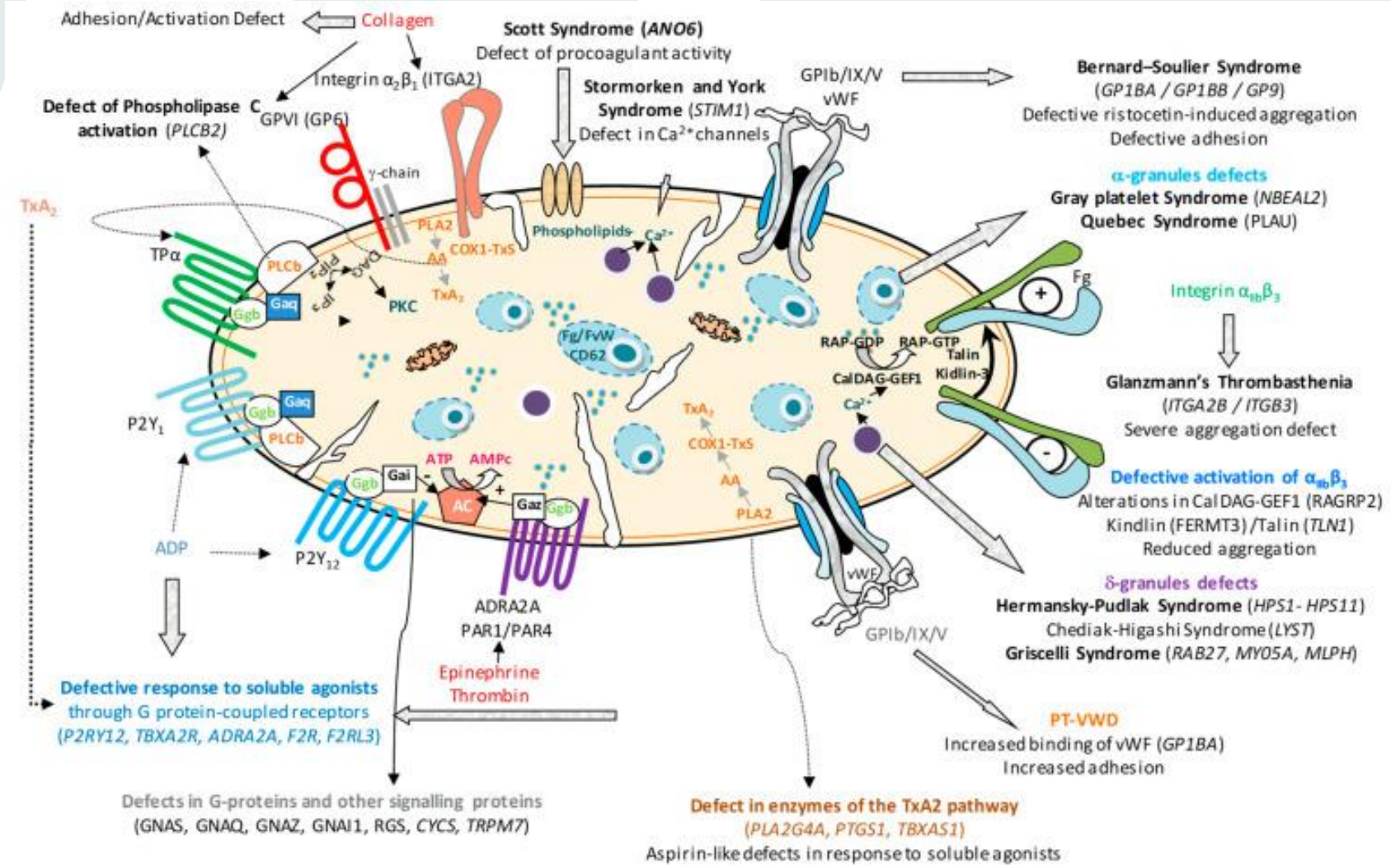




Platelet Function Disorders

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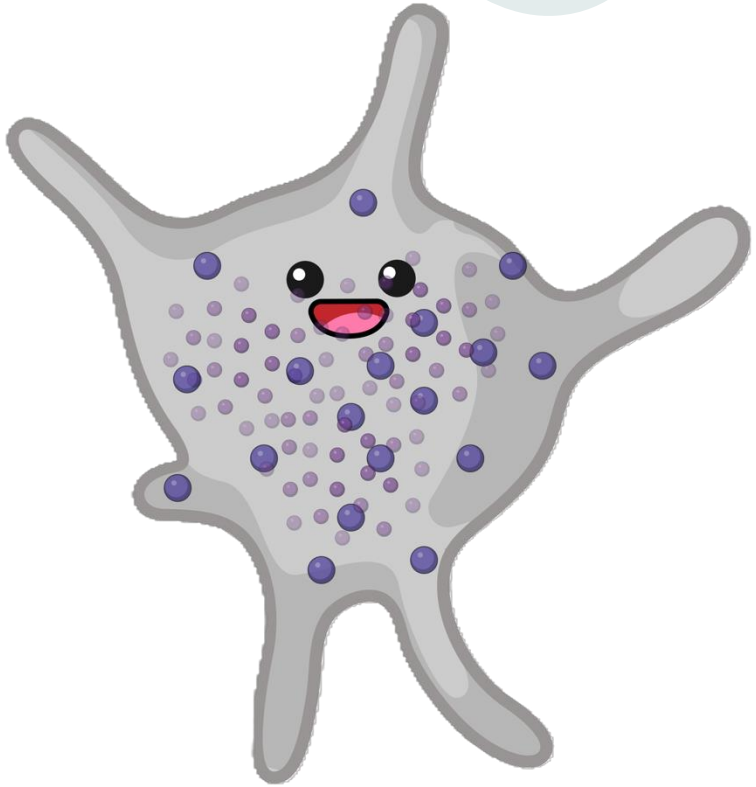
Platelet Function Disorders

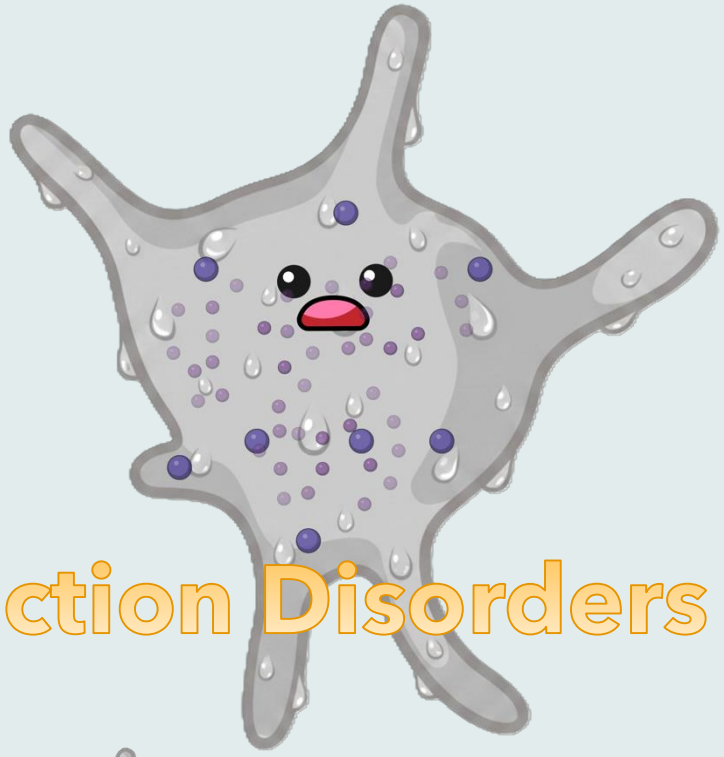


- Receptors for adhesive proteins
- G-Protein Coupled Receptors
- Granules
- Signal Transduction Proteins
- Membrane Phospholipids
- Transcription Factors
- Cytoskeletal Proteins
- Enhanced Fibrinolytic Activity

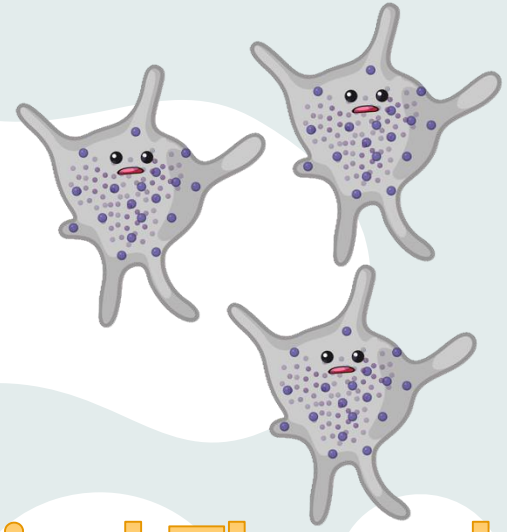
Biomolecules. 2025 Oct 30;15(11):1528. doi: 10.3390/biom15111528

Types of Platelet Disorders





Platelet Function Disorders



Congenital Thrombocytopenia

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Types of Platelet Disorders



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n Disorders

Congenital Thrombocytopenia

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How can we diagnose a platelet disorder?

Differentiate normal from abnormal platelet count

And normal from abnormal platelet function

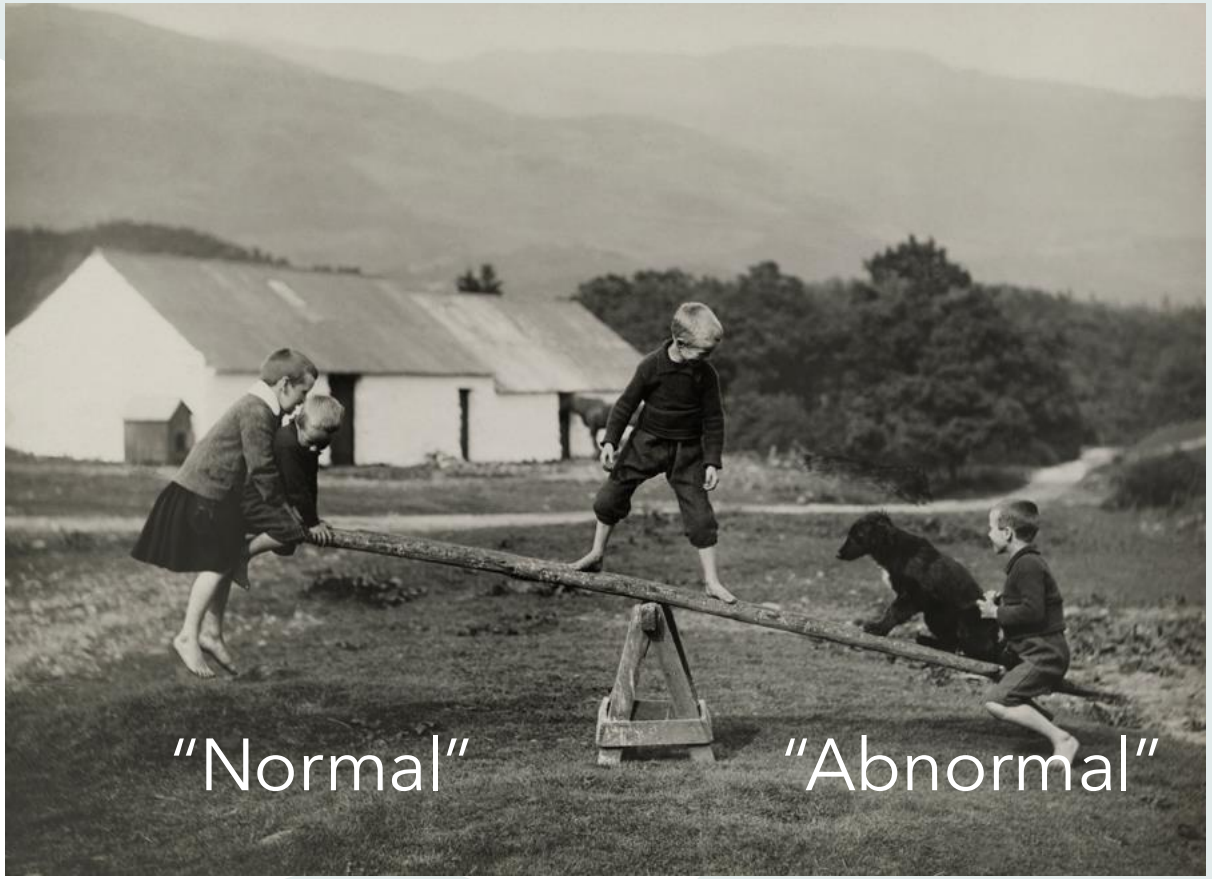


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How can we diagnose a platelet disorder?

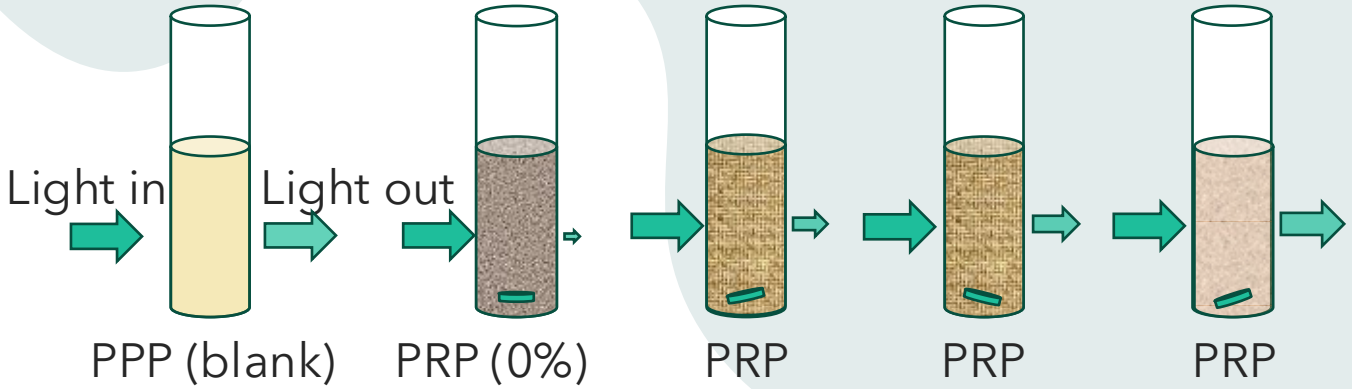
Differentiate normal from abnormal platelet count

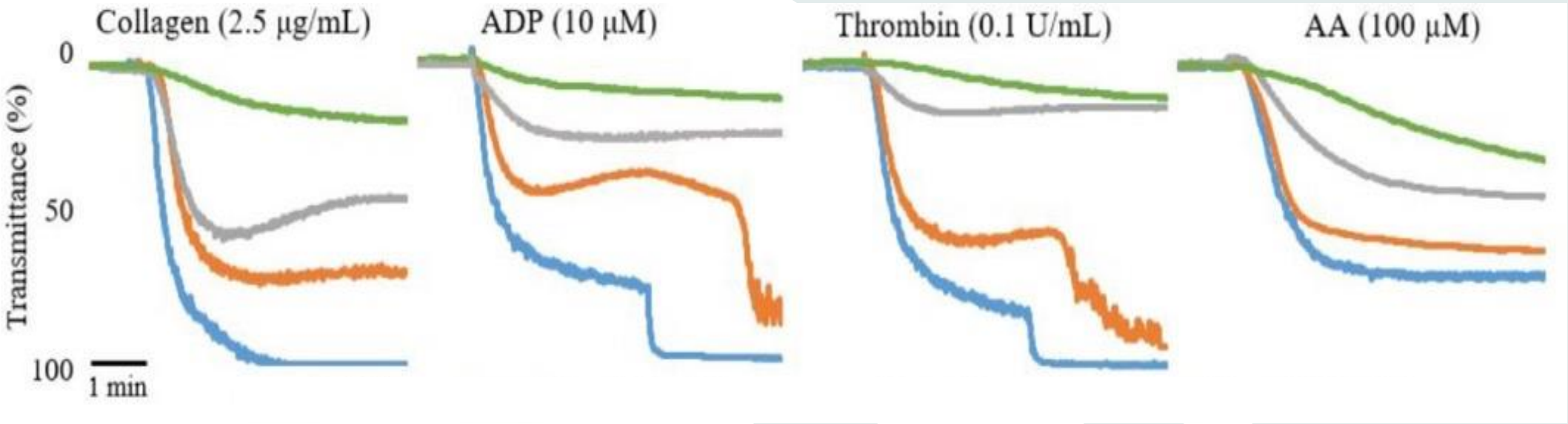
And normal from abnormal platelet function



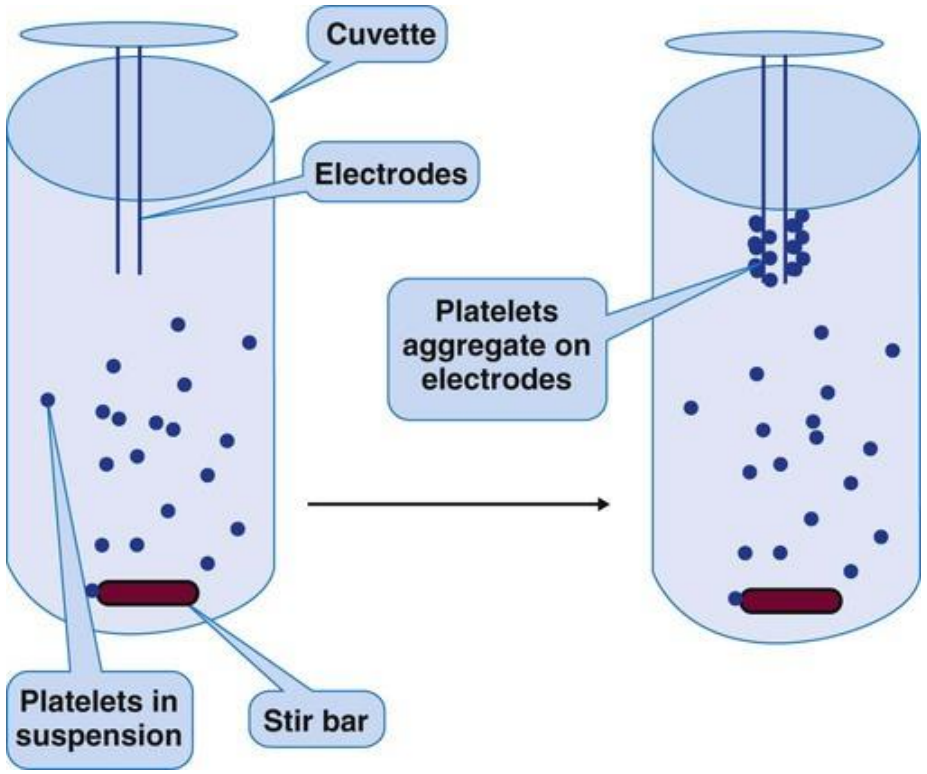
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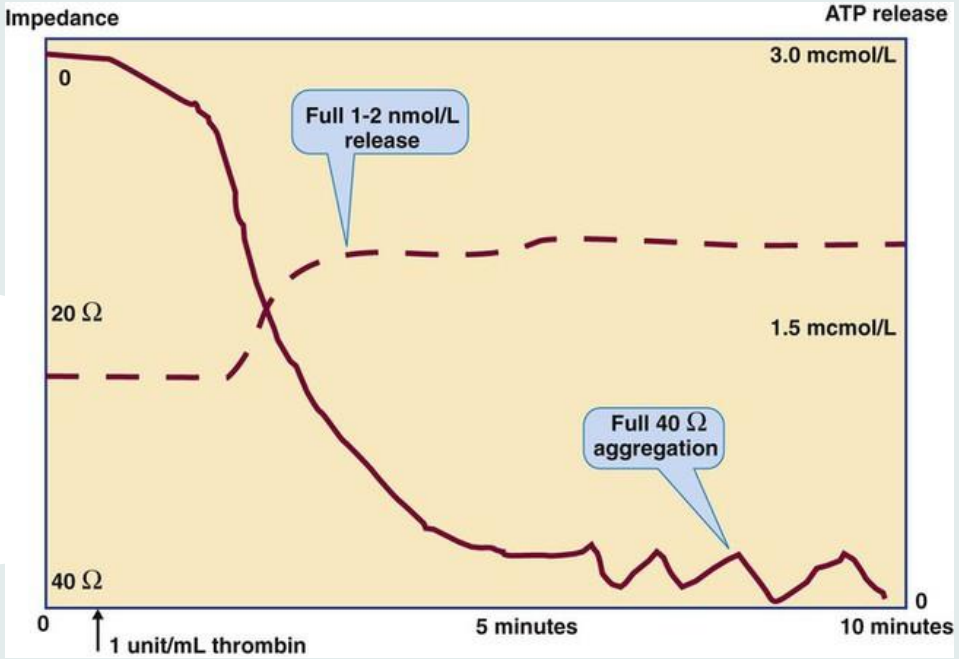
Light Transmission Aggregometry





Whole Blood Impedence Lumiaggregometry





Platelet Aggregation

Agonist	Tests
Arachidonic acid and U46619	Thromboxane Pathway (aspirin)
Thrombin	Multiple receptors to test full aggregation independent of ADP and prostaglandin pathways (sledgehammer)
ADP	Specific receptor, weak agonist
Epinephrine	Specific receptor to cause release of dense granules
Collagen	Depends on intact membrane receptors, thromboxane pathway AND membrane phospholipase
Ristocetin	Requires only functional GP1b/IX complex

Platelet Aggregation

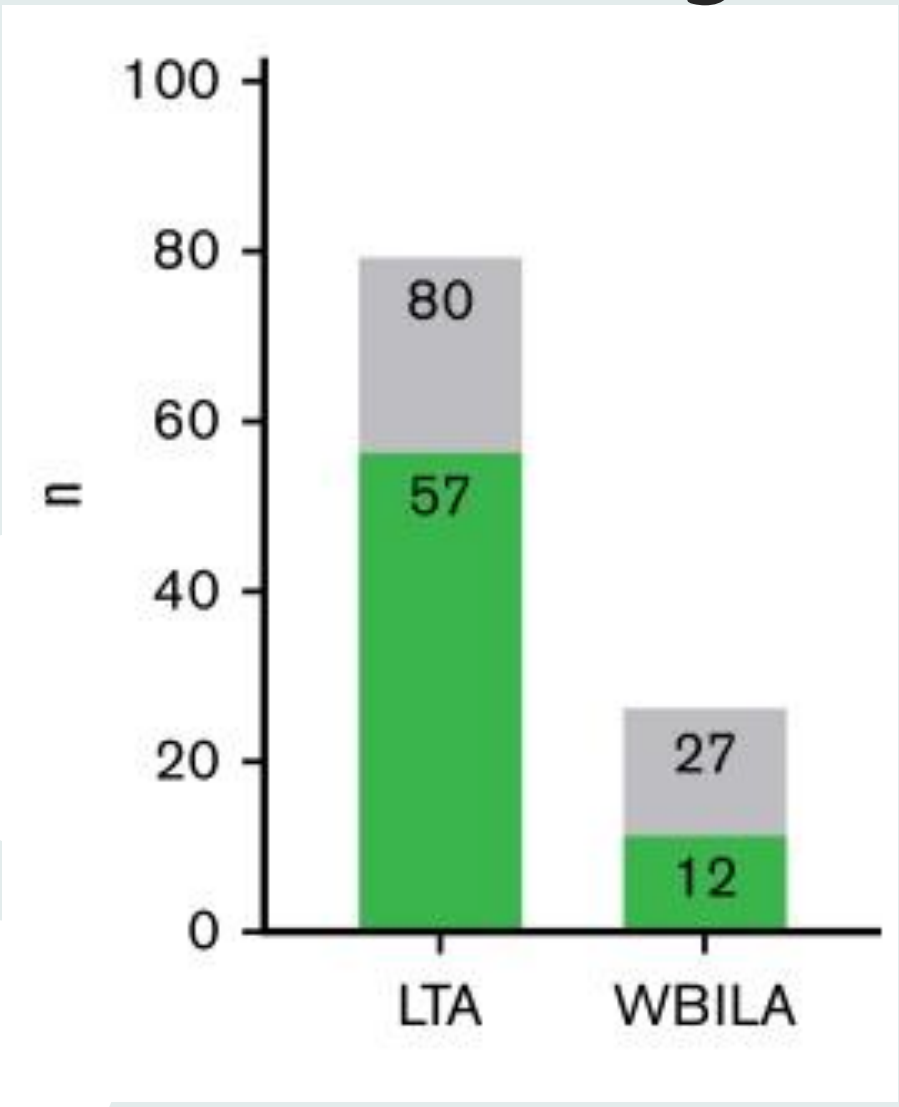
Disorder	Agonist			
	ADP	Epinephrine	Collagen	Ristocetin
Storage Pool Deficiency	0	Absent 2nd wave	0 to +	++++
Glanzmann Thrombasthenia	0	0	0	++++
Bernard-Soulier Syndrome	++++	++++	++++	0
Signaling Defect	0 to +	0 to +	0 to +	++++

Important Considerations for Testing

Recommendation to verify abnormal on repeat testing

>25% of LTA and ~50% of of WBILA were normal on repeat in our cohort

WBILA and LTA display good sensitivity (91.1% and 92.4%) and specificity (87.2% and 84.5%) for clinical diagnosis of plt disorder



Blood VTH 2025 Dec 15;3(1):100135. doi: 10.1016/j.bvth.2025.100135

Platelet Function Primer

Other tests you'll hear about:

PFA 100

Bleeding Time

Thromboelastography

Platelet Mapping

Verify Now

PFA-100

In vitro test of platelet ability to close a membrane

Uses whole blood; affected by hemoglobin and WBC count

Supposed to be simple and less user dependent

Closure time to ADP-Collagen and EPI-Collagen

May be useful to look at aspirin effect

Needs to be confirmed with formal aggregometry

As a screening test for platelet disorders it is INADEQUATE: sensitivity is LOW (6%)



Bleeding time

Leaves scars

Operator dependent

Easily done wrong resulting in prolongation of bleeding time

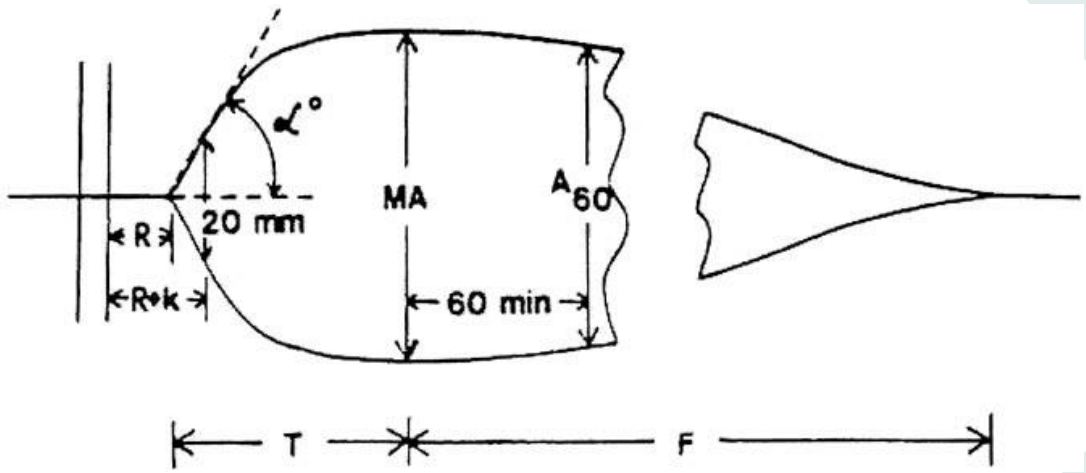
Affected by anemia; probably by WBC as well

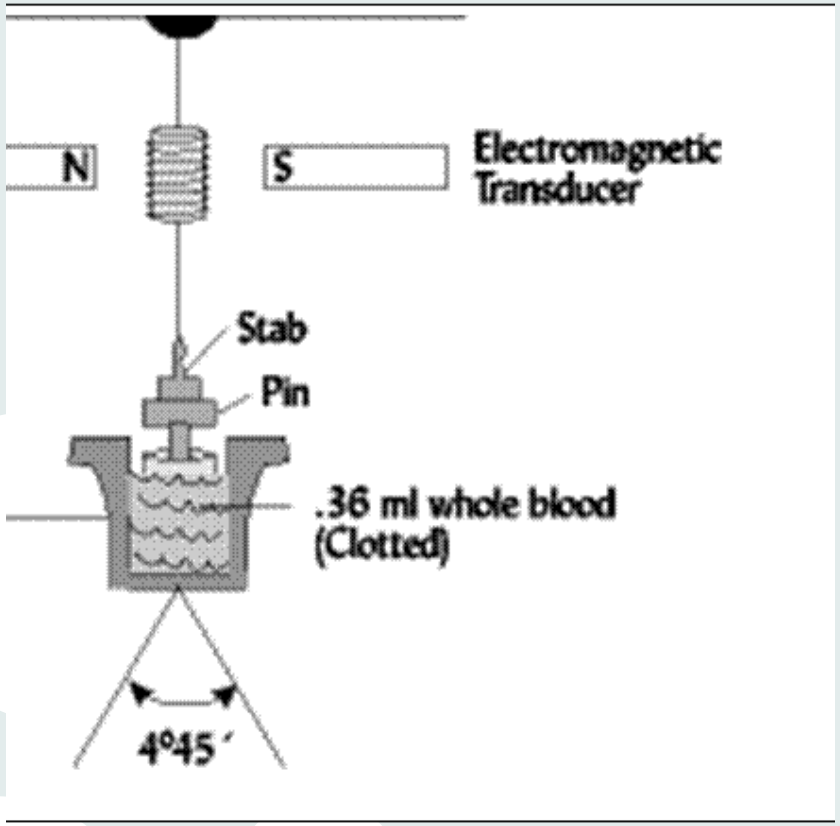


Thromboelastography (TEG)

Looks at whole blood clotting (evaluates coagulation and platelet function)

Can also look at fibrinolysis





Evaluation of a suspected platelet disorder

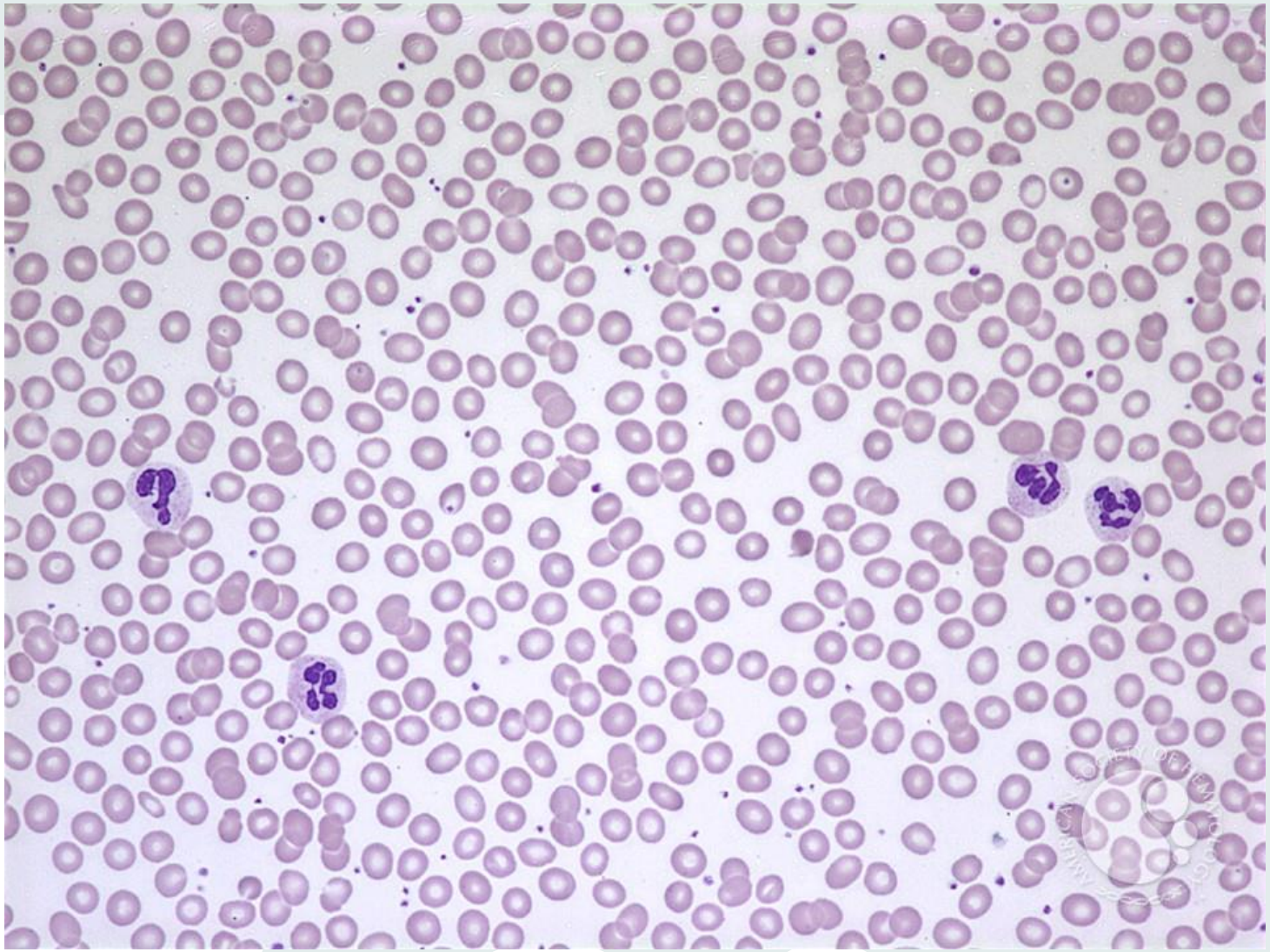
- CBC
  - Size
  - Number
  - Associated changes in Neutrophil or RBC morphology
- Platelet function
  - Platelet aggregation
  - Measure of granule function:
  - Seratonin release, ATP/ADP ratio, mepacrine, lumiaggregometry
- Surface receptors by flow, platelet EM, other testing

Evaluating the Smear

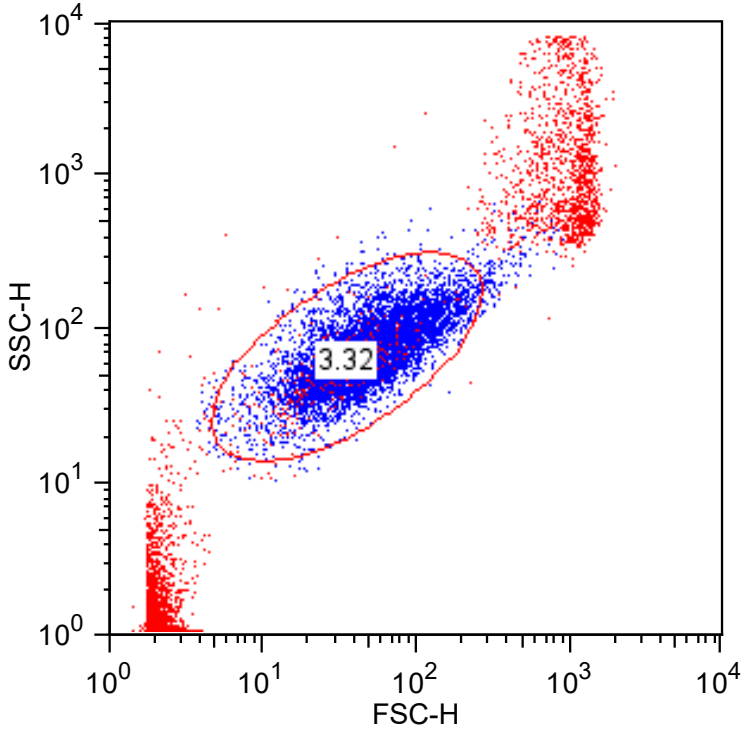
Look at platelet morphology

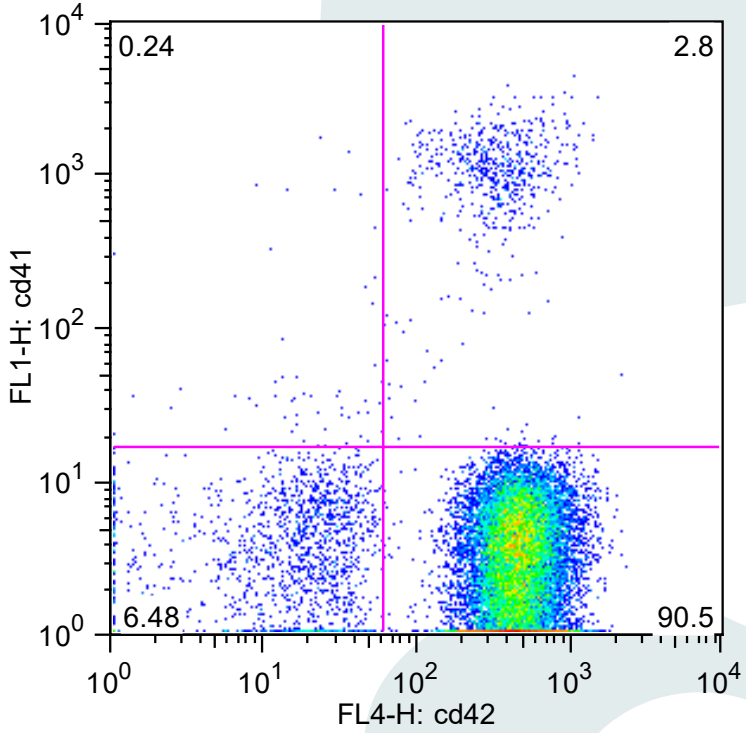
WBC

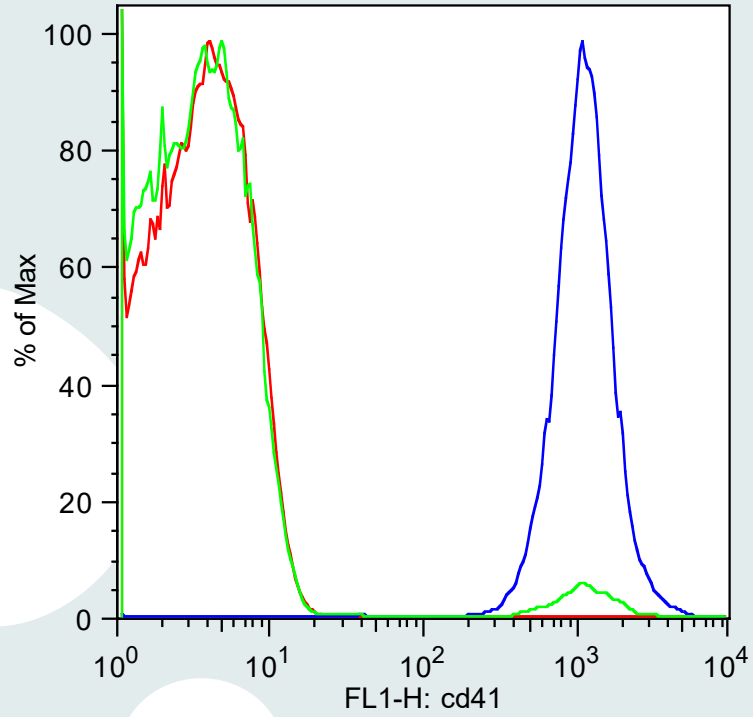
RBC



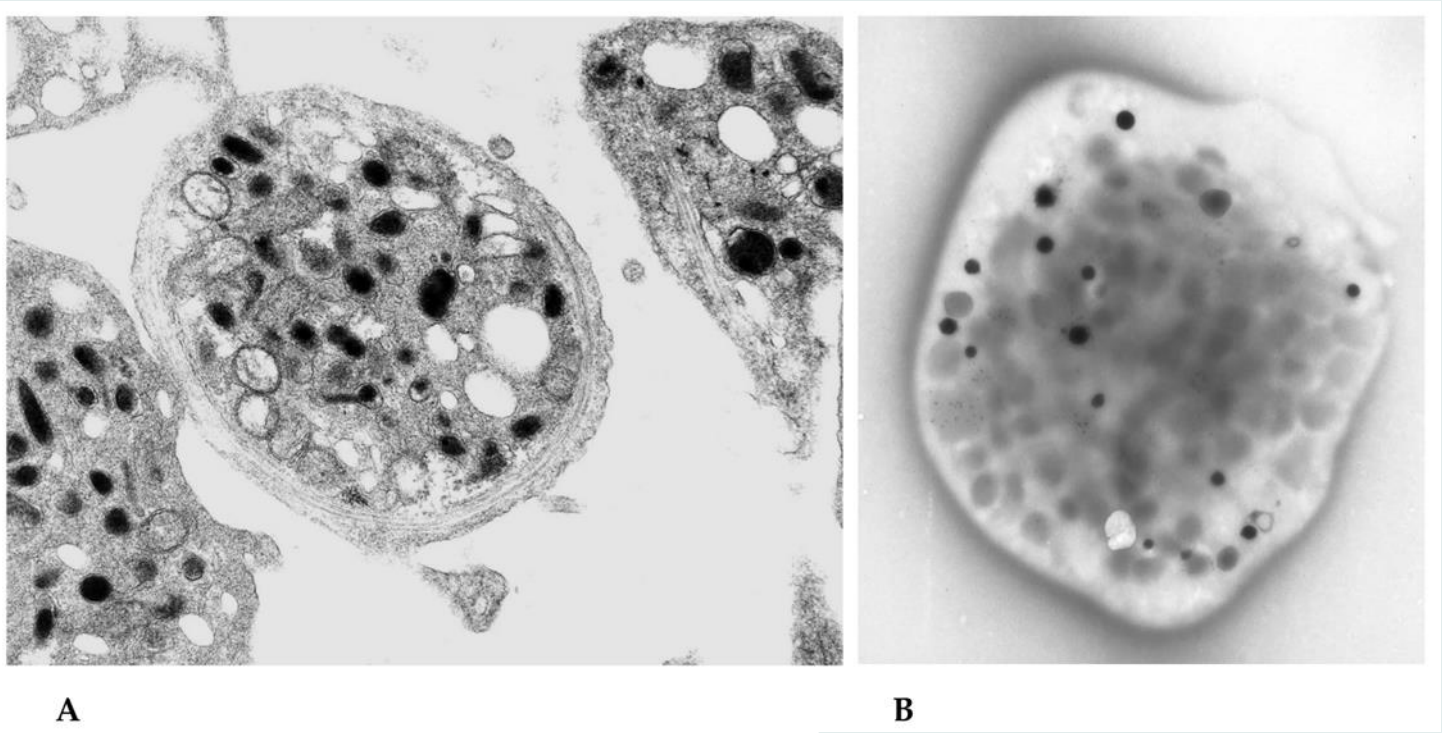
Surface receptors







Electron microscopy



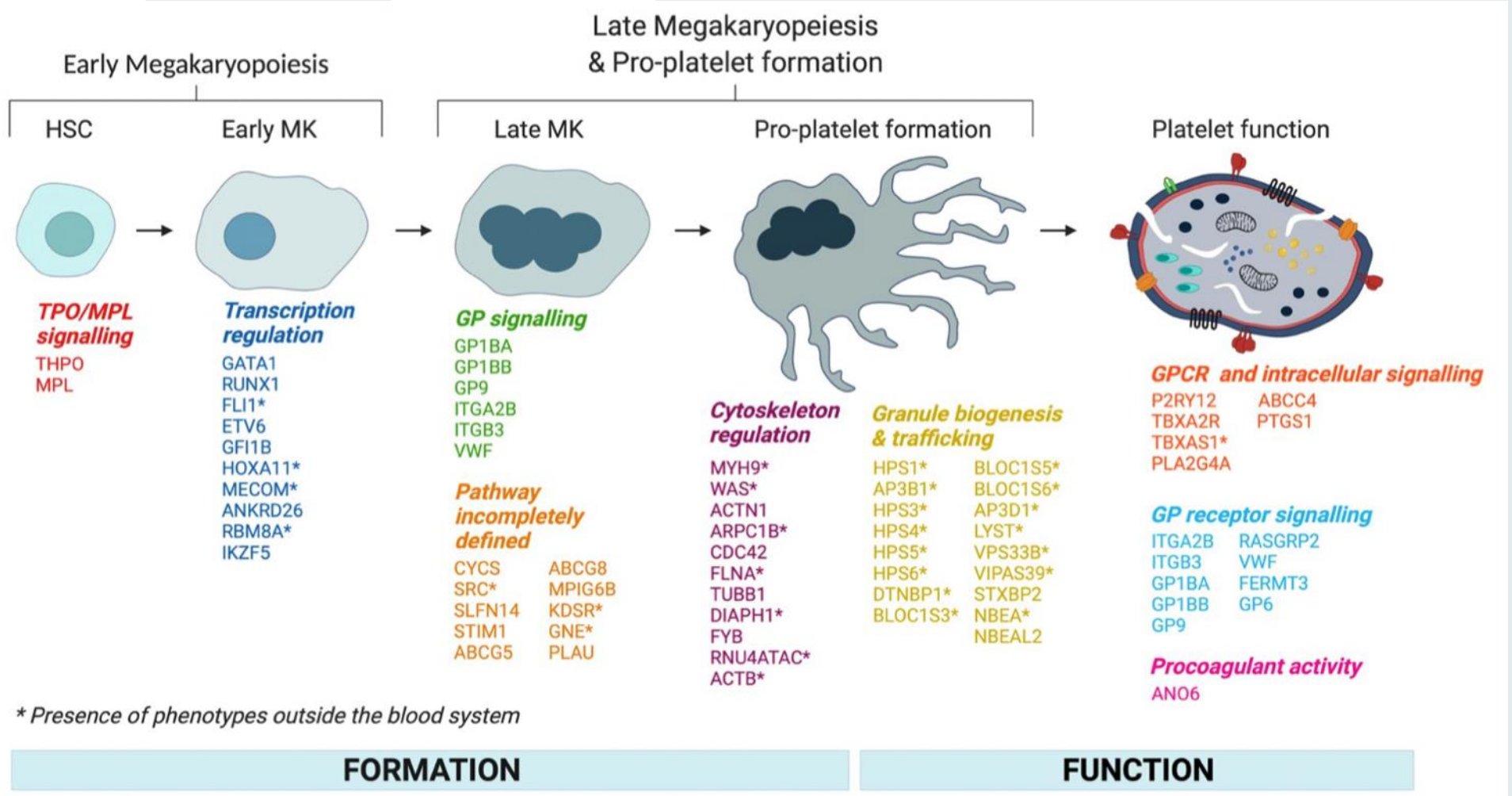
We are looking for the chips in a chocolate chip cookie

Evaluation of a suspected platelet disorder

- CBC
  - Size
  - Number
  - Associated changes in Neutrophil or RBC morphology
- Platelet function
  - Platelet aggregation
  - Measure of granule function:
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- Surface receptors by flow, platelet EM, other testing

Genetic Testing

Genes Implicated in Platelet Disorders



Genetics and Platelet Disorders

Inherited Thrombocytopenias: Confirm molecular basis in >60% of patients

Inherited Platelet Function Disorders: Confirm molecular basis in <30% of patients

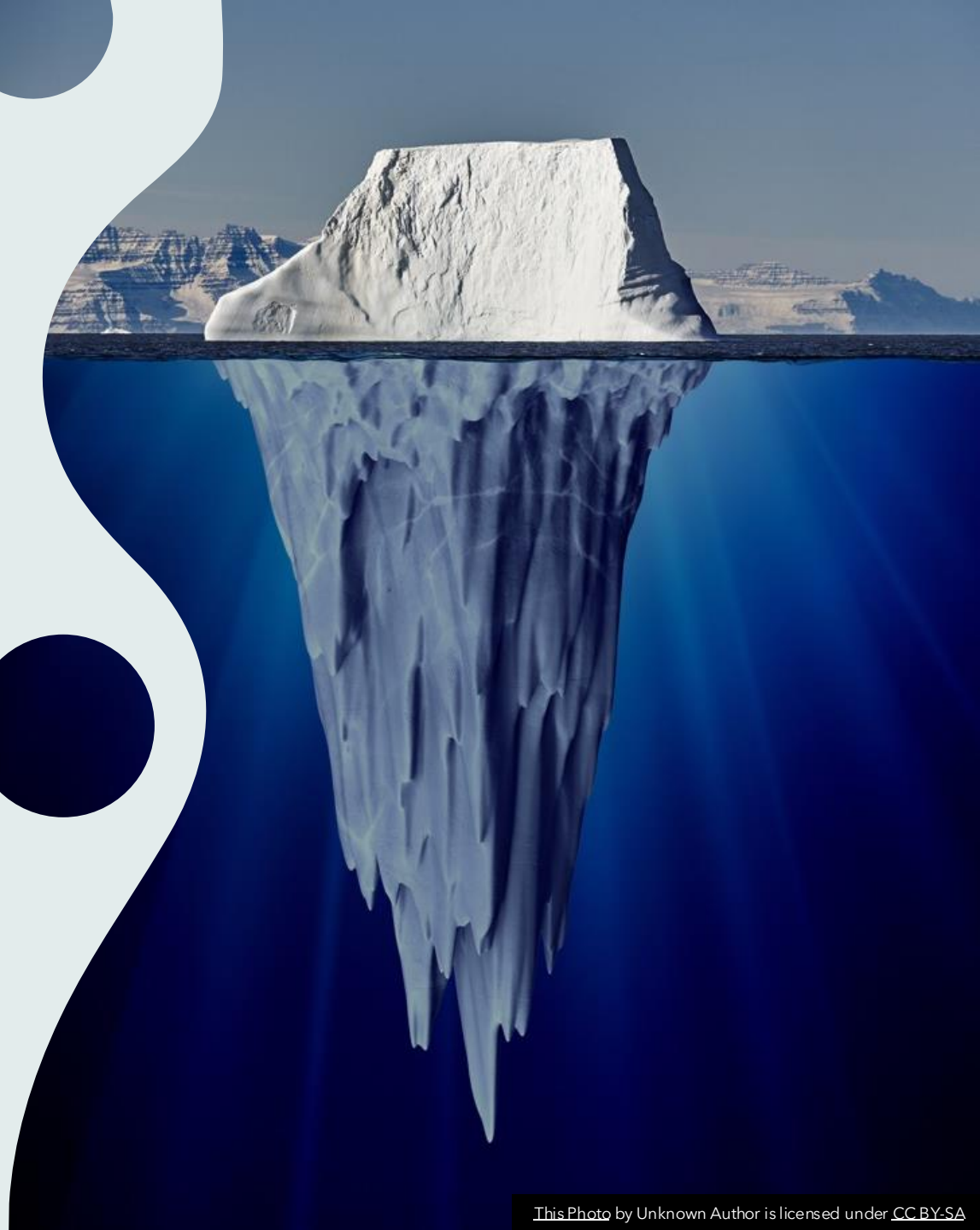


Genetics and Platelet Disorders

Prevalence of inherited platelet disorders is between 1:1M and 3:1000 individuals.

Platelet count is a very easy thing to measure but platelet function is much more nebulous

The difference between normal and abnormal for platelet function is more a matter of degrees than an easily determined “line in the sand”



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Challenges in diagnosis

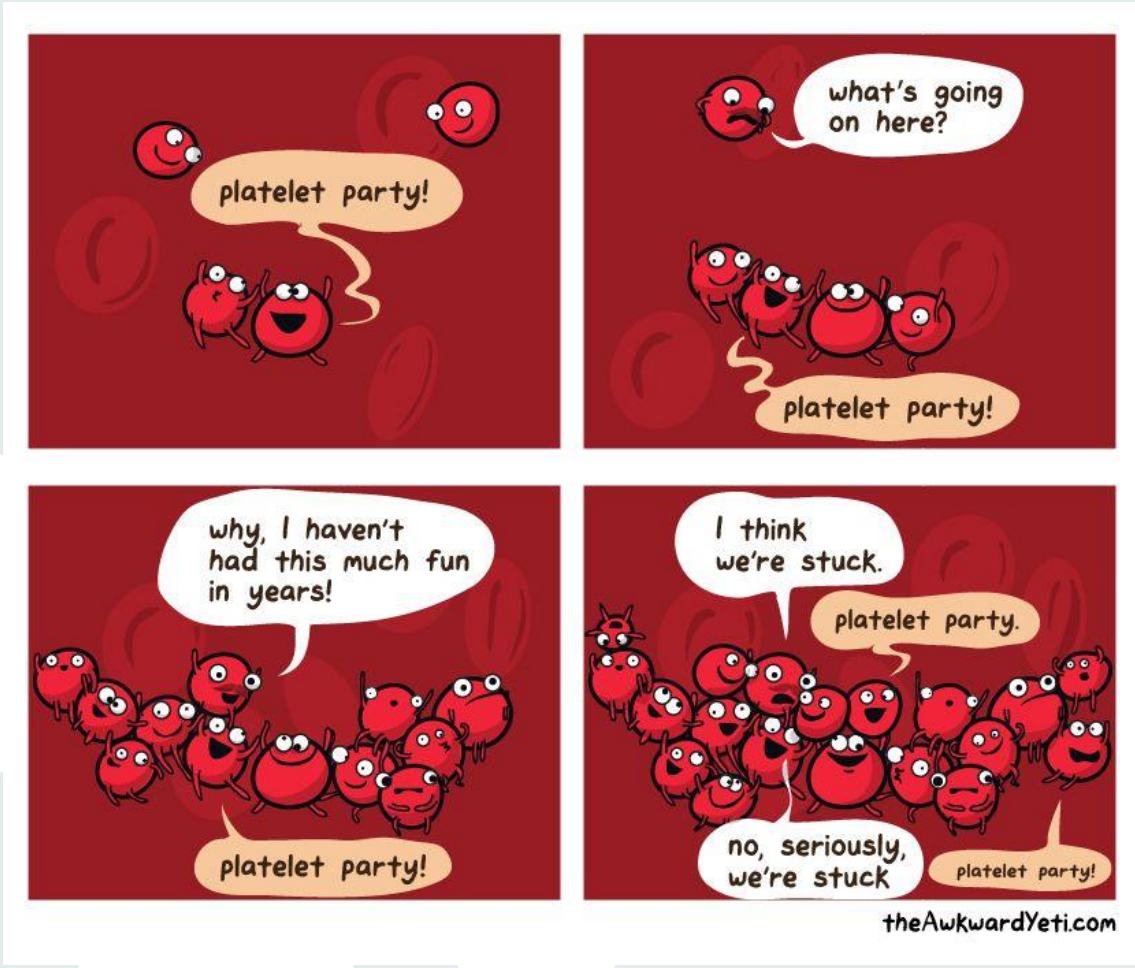
Large blood volumes (for LTA, especially)

Platelets are easily excited

Challenges in diagnosis

Large blood volumes (for LTA, especially)

Platelets are easily excited



Challenges in diagnosis

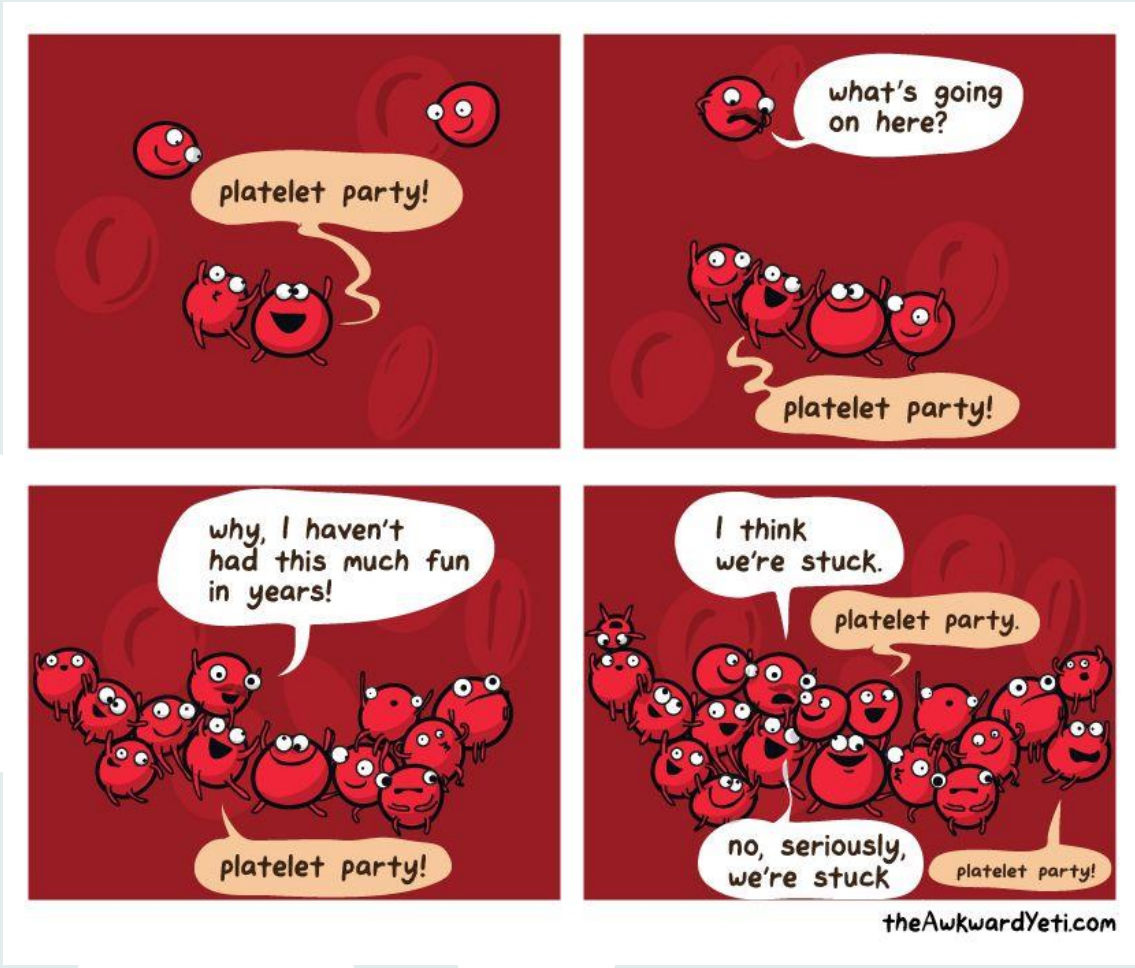
Large blood volumes (for LTA, especially)

Platelets are easily excited

Many theoretical and actual ways to interfere

- NSAIDs
- SSRIs
- Exercise
- Caffeine
- Nicotine (Vaping)

Acquired platelet disorders are more common



Acquired Disorders of Platelet Function

Medications

Chronic renal disease

Liver disease

Bone marrow disease

Cardiopulmonary bypass

Antiplatelet antibodies

Acquired storage pool disorders

Acquired Disorders of Platelet Function

- Statistically, probably more common
  - Congenital disorders are underdiagnosed and often missed
  - Mild congenital function disorders combined with inhibitory drugs may produce significantly more symptoms
- Most often medication related

Acquired Platelet Dysfunction - Drugs

NSAIDS
Antibiotics
Cardiovascular Drugs
β-Adrenergic Blockers (propranolol)
Vasodilators (Nitroprusside, nitroglycerin)
Calcium Channel Blockers (Verapamil)
Quinidine

Psychotropic Drugs
Selective serotonin reuptake inhibitors (SSRIs)
Tricyclic Antidepressants (Imipramine)
Phenothiazines (Chlorpromazine)
Anesthetics
Local (e.g., Dibucaine); General (e.g., Halothane)
Chemotherapeutic Agents
Mithramycin, BCNU, Daunorubicin, MEK inhibitors
Dextrans
Ethanol
Vitamin E
Radiographic Contrast Media

NSAIDS and Bleeding

Reversibly inhibit cyclooxygenase

Variable binding to COX-1/COX-2 depending on drug so relative risk of bleeding varies

Combined with other drugs may worsen bleeding – eg SSRIs

Because binding is reversible, but same site as aspirin, can interfere with antithrombotic effect

Selective Serotonin Re-uptake Inhibitors (SSRIs)

Platelets incorporate serotonin into dense granules – by uptake from plasma

SSRIs inhibit platelet function – prolong BT, inhibit aggregation - secretion, prolong PFA CT.

Associated with increased risk of GI bleeds, transfusions following orthopedic surgery, and hospital admissions for bleeding

Platelet dysfunction in renal disease

Uremia classically associated with platelet dysfunction

- Independent of platelet count
- Platelet adhesion defect
  - Perhaps why DDAVP helps in bleeding
- Decreased platelet secretion
  - Impaired arachidonic acid and prostaglandin metabolism
- Storage pool defect
  - Decreased ADP, serotonin and TxA2
- Defect in GPIIb/IIIa signaling
  - Impaired fibrinogen binding

Altered levels of endothelial NO and PGI2?

Due to platelet activation during dialysis?

Due to circulating Arg-Gly-Arg containing peptides?

Can not forget importance of anemia in altering vascular rheology

Chronic Renal Failure: Therapeutic Approaches

Increase in Hct by RBC transfusions and erythropoietin is associated with correction of BT and diminished clinical bleeding

- Dialysis (hemodialysis and peritoneal) effective in correcting the BT and platelet aggregation defect

Platelet transfusions

DDAVP shortens BT in 50-75% patients

Cryoprecipitate shortens the BT in some studies

Conjugated estrogens (IV or oral) reported to shorten prolonged BT

Platelets in Liver Disease

6% thrombocytopenia in chronic, non-cirrhotic liver disease

76% mild-moderate thrombocytopenia in cirrhosis

13% severe thrombocytopenia (<50K/mcL platelet count)

Platelet dysfunction

10-20% portal vein thrombosis; DVT and embolic disease

Platelet Dysfunction in Liver Disease

Defects in thromboxane A2 synthesis

Storage pool deficiency

GP1b abnormalities

?role of anemia similar to renal disease

Summary – Acquired Platelet Defects

Common cause of platelet dysfunction

Suspect in a patient with new onset bleeding symptoms

Careful medication history is important (any medication could be culprit, but most not associated with clinical bleeding)

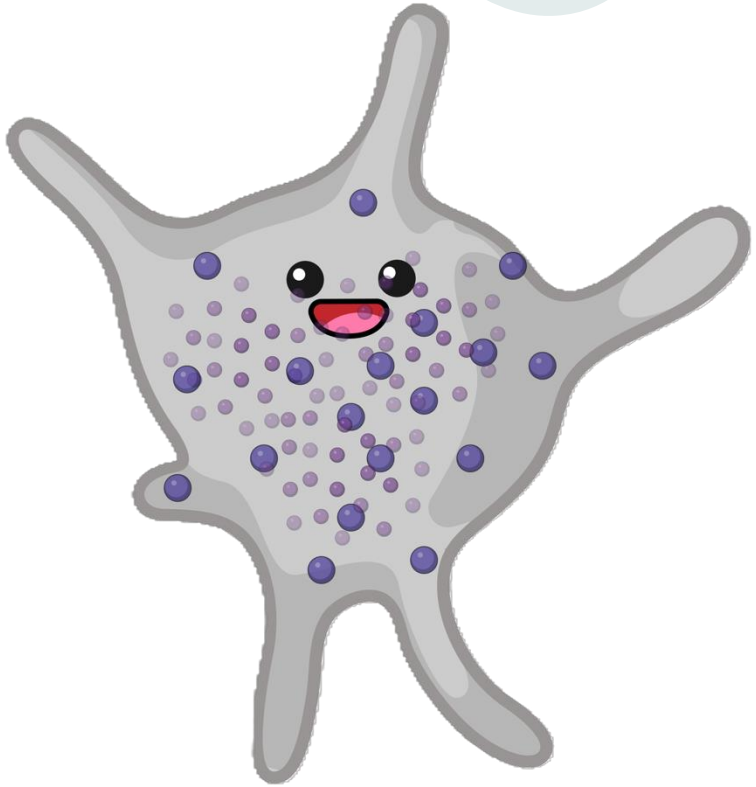
Not always ***unintended*** effect of therapy (although bleeding is not generally the goal)

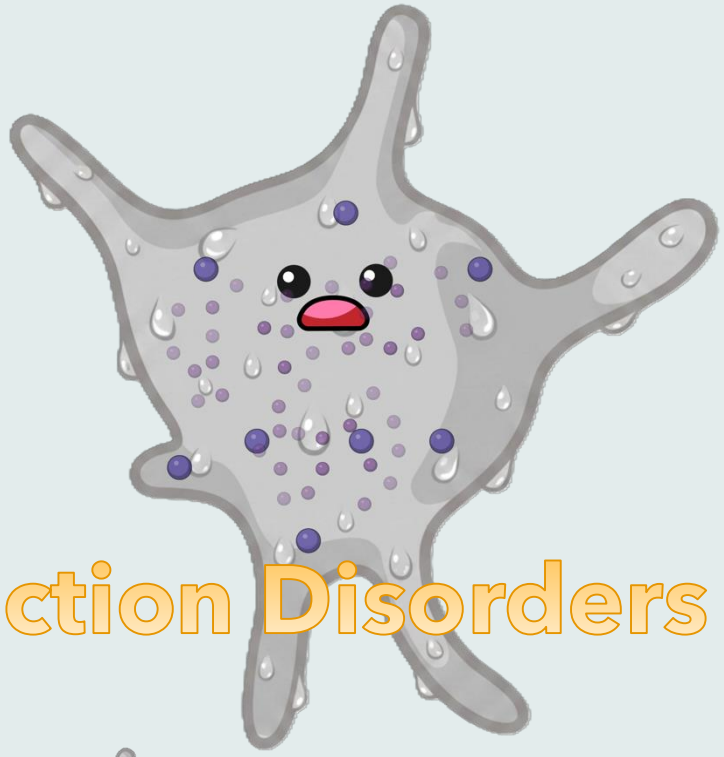
Liver and renal disease are potentially associated with platelet dysfunction

Acquired platelet dysfunction with cardiopulmonary bypass beyond thrombocytopenia

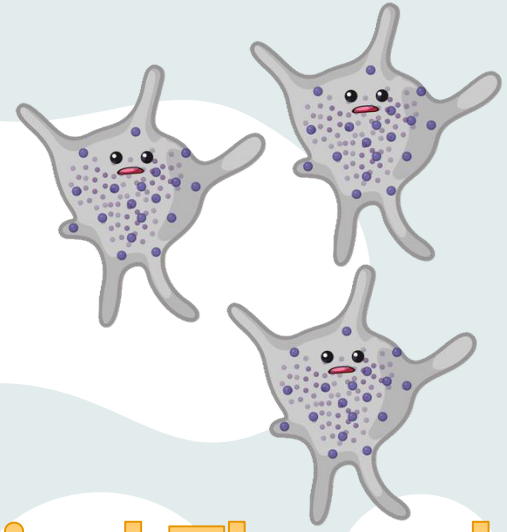
Bone marrow disease associated with acquired storage pool disease

Types of Platelet Disorders





Platelet Function Disorders



Congenital Thrombocytopenia

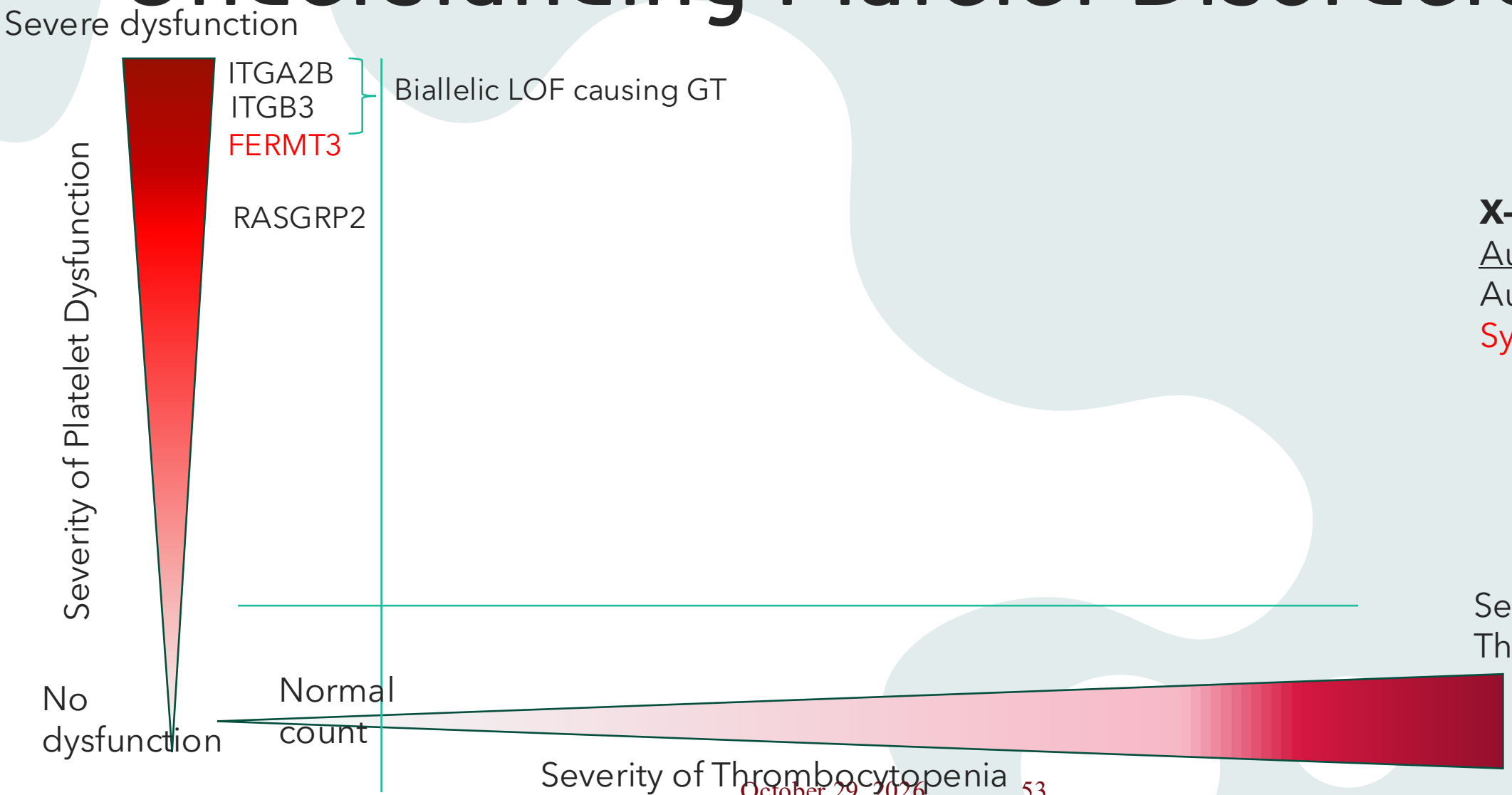
Created in
https://BioRender.com

Understanding Platelet Disorders



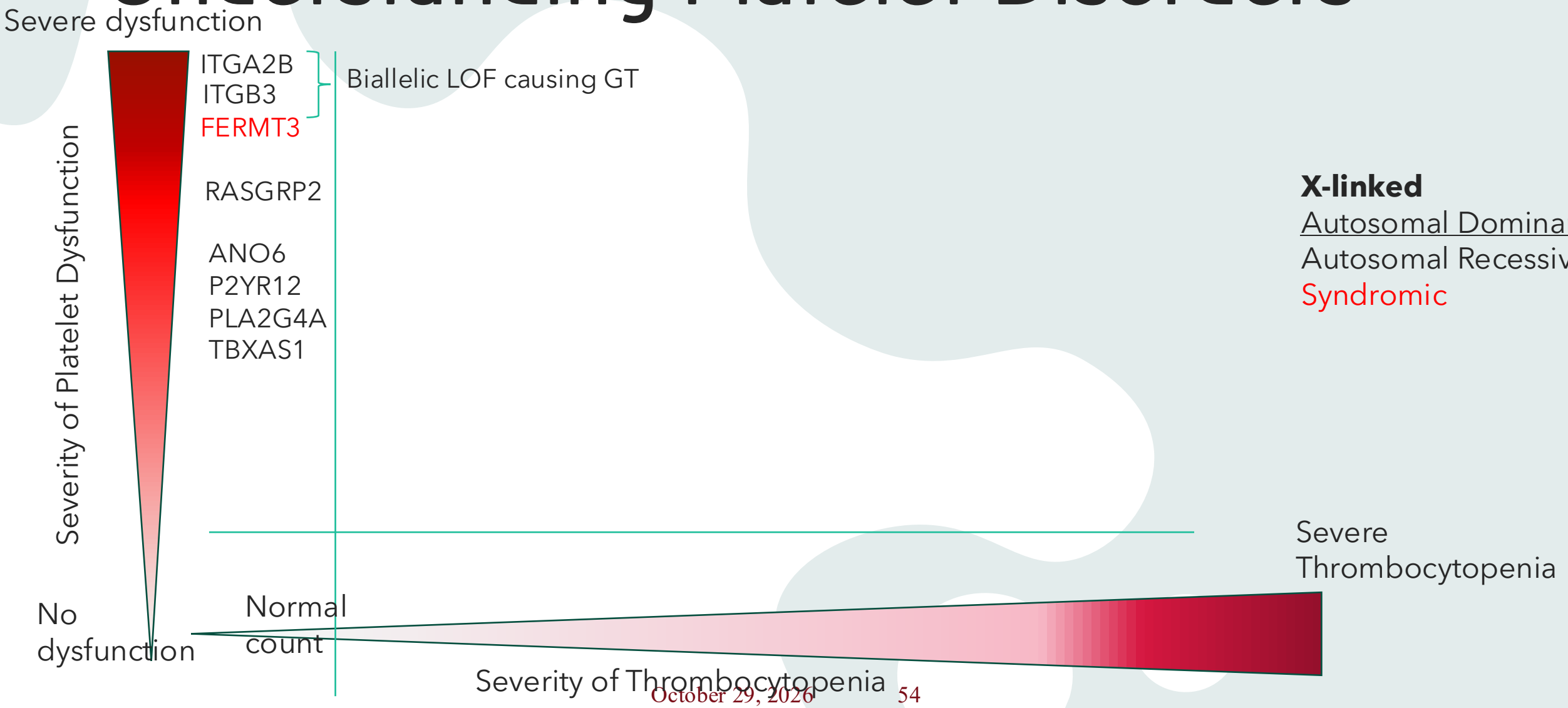
X-linked
Autosomal Dominant
Autosomal Recessive
Syndromic

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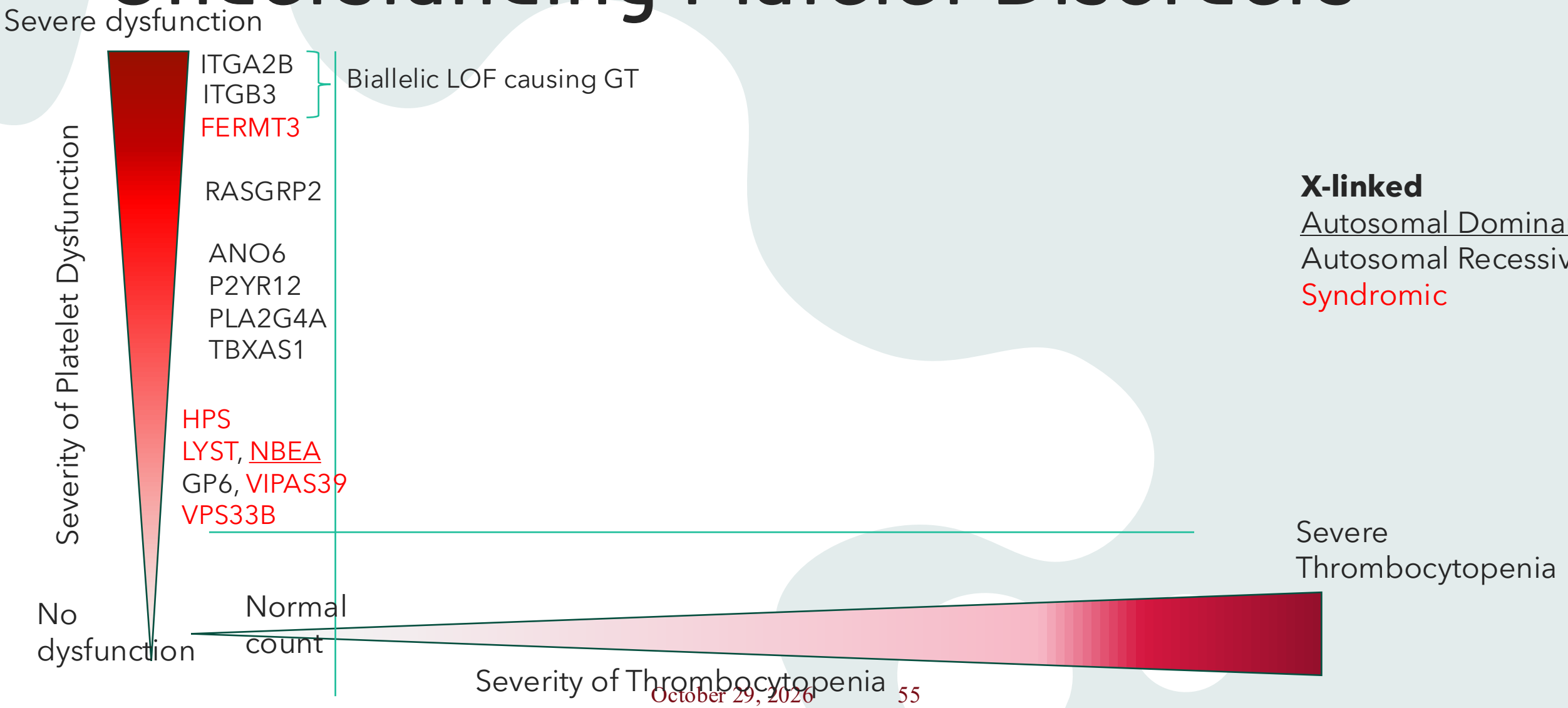


X-linked
Autosomal Dominant
Autosomal Recessive
Syndromic

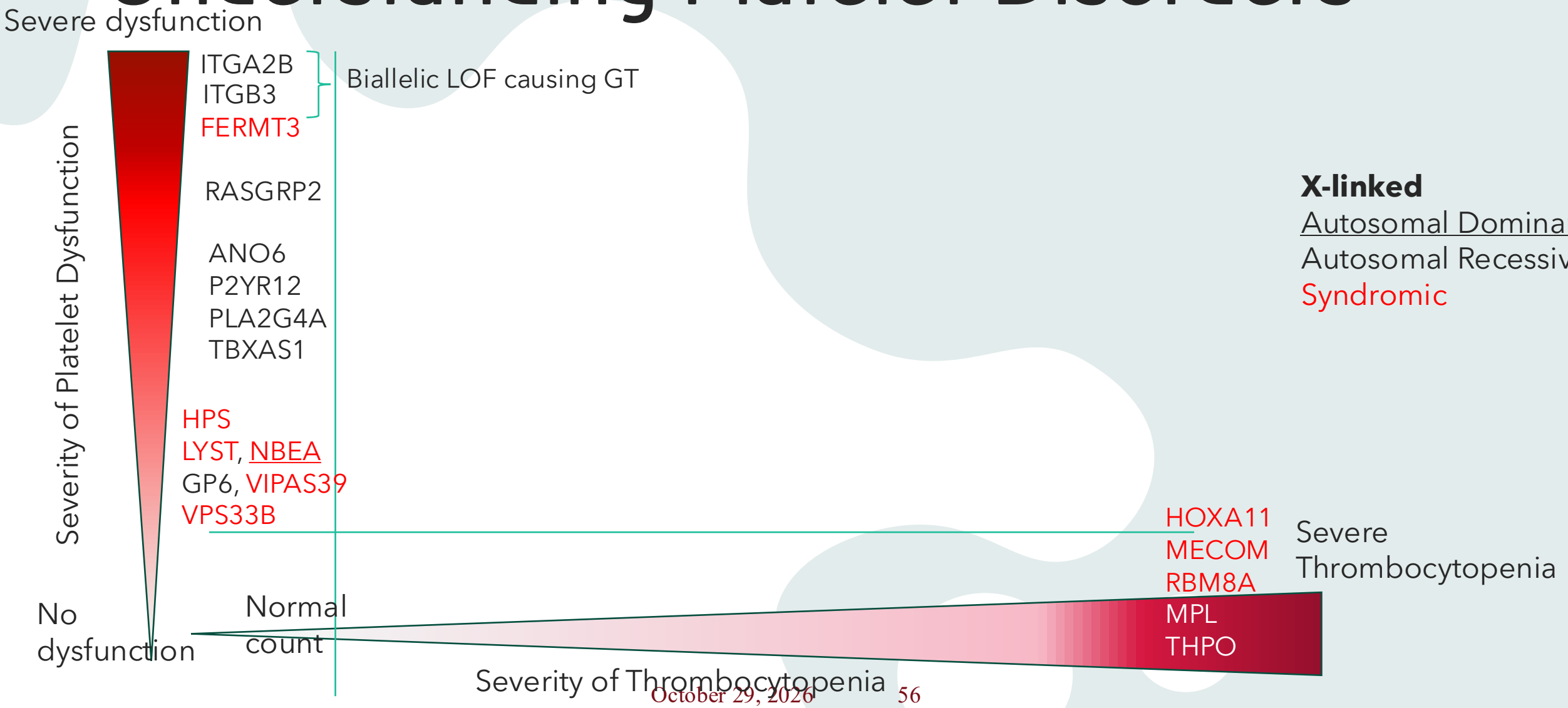
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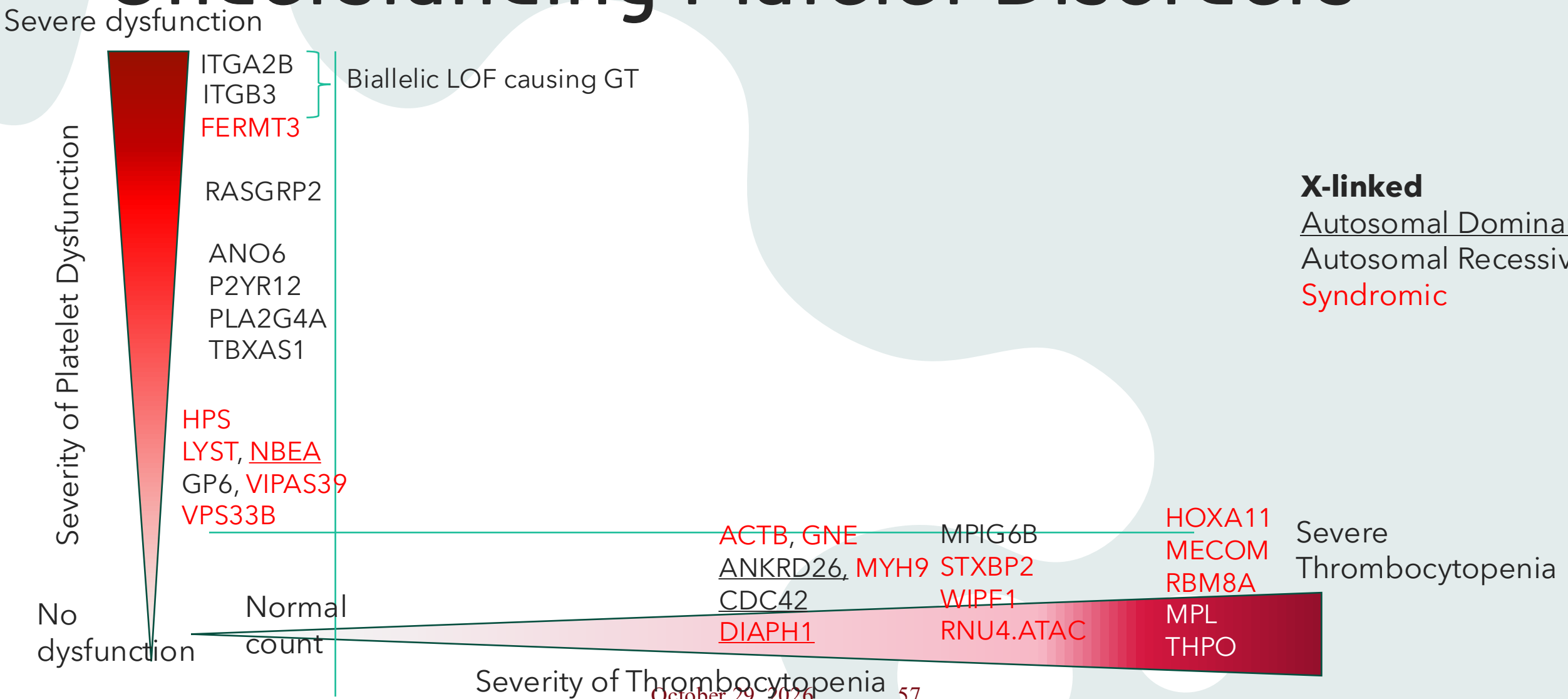
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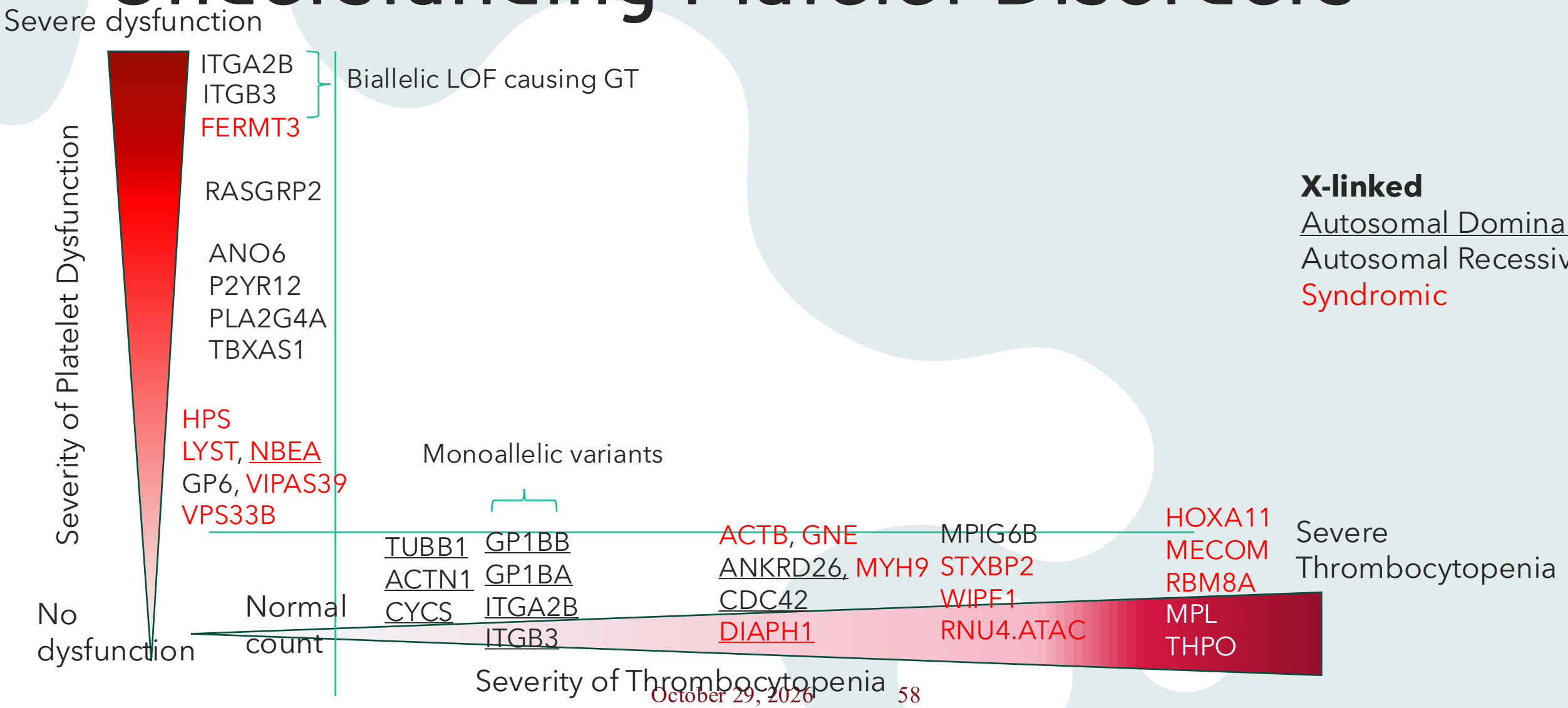
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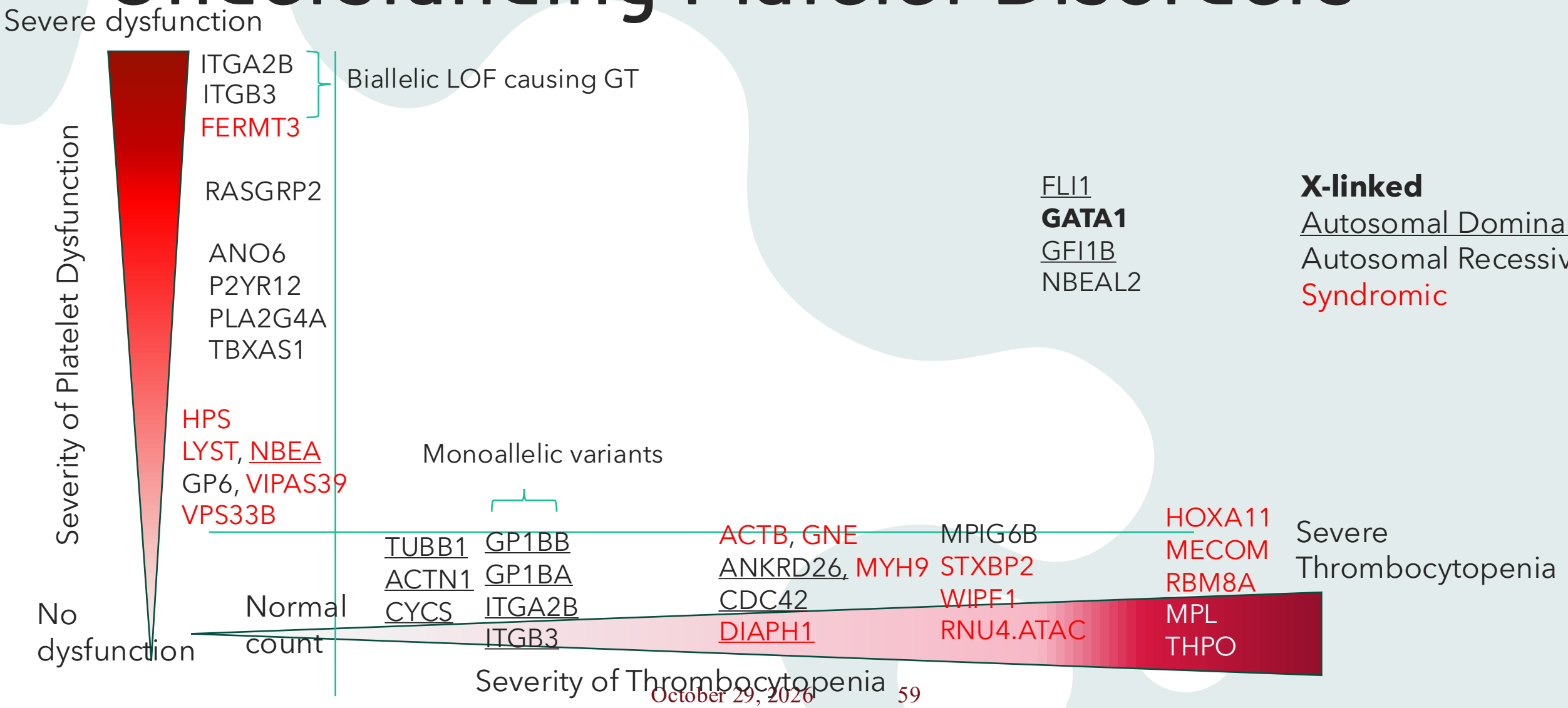
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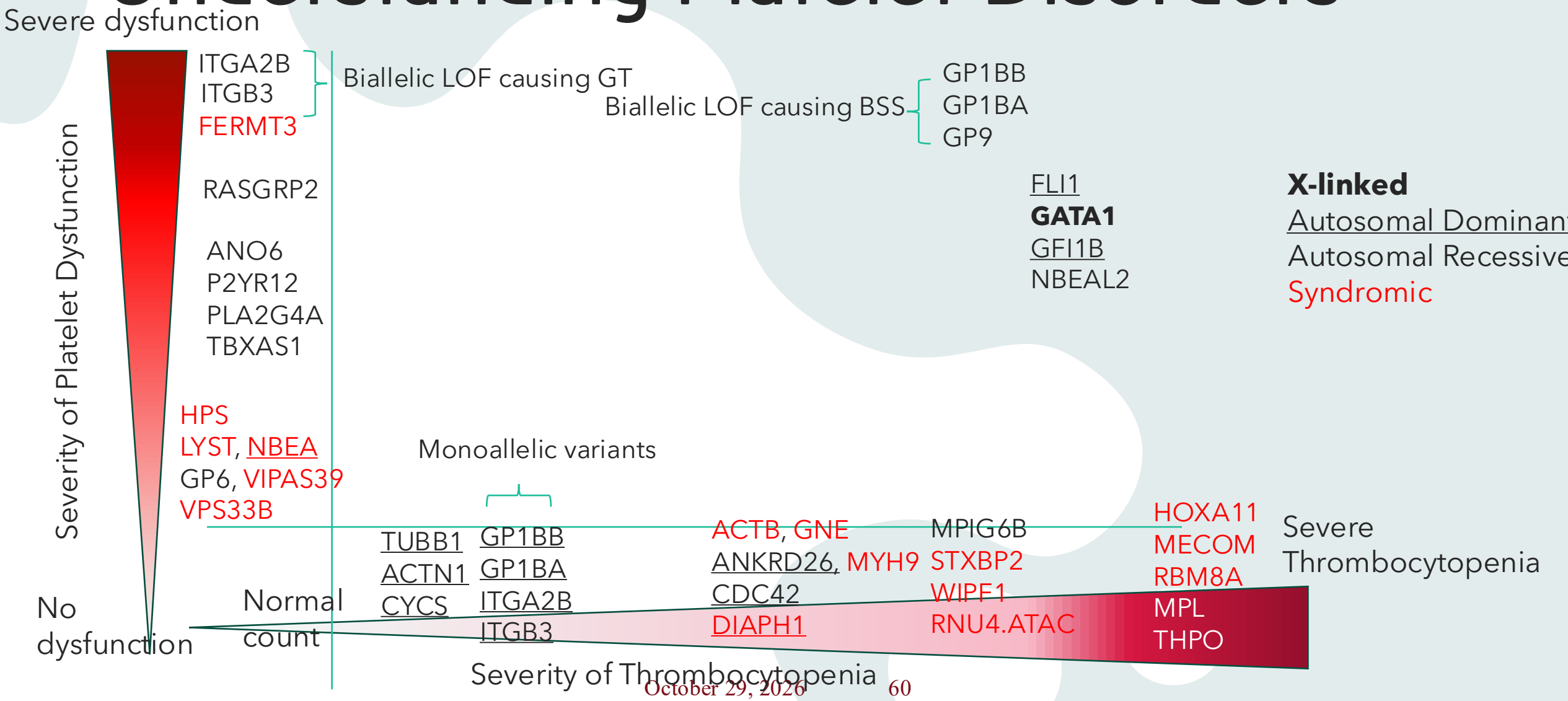
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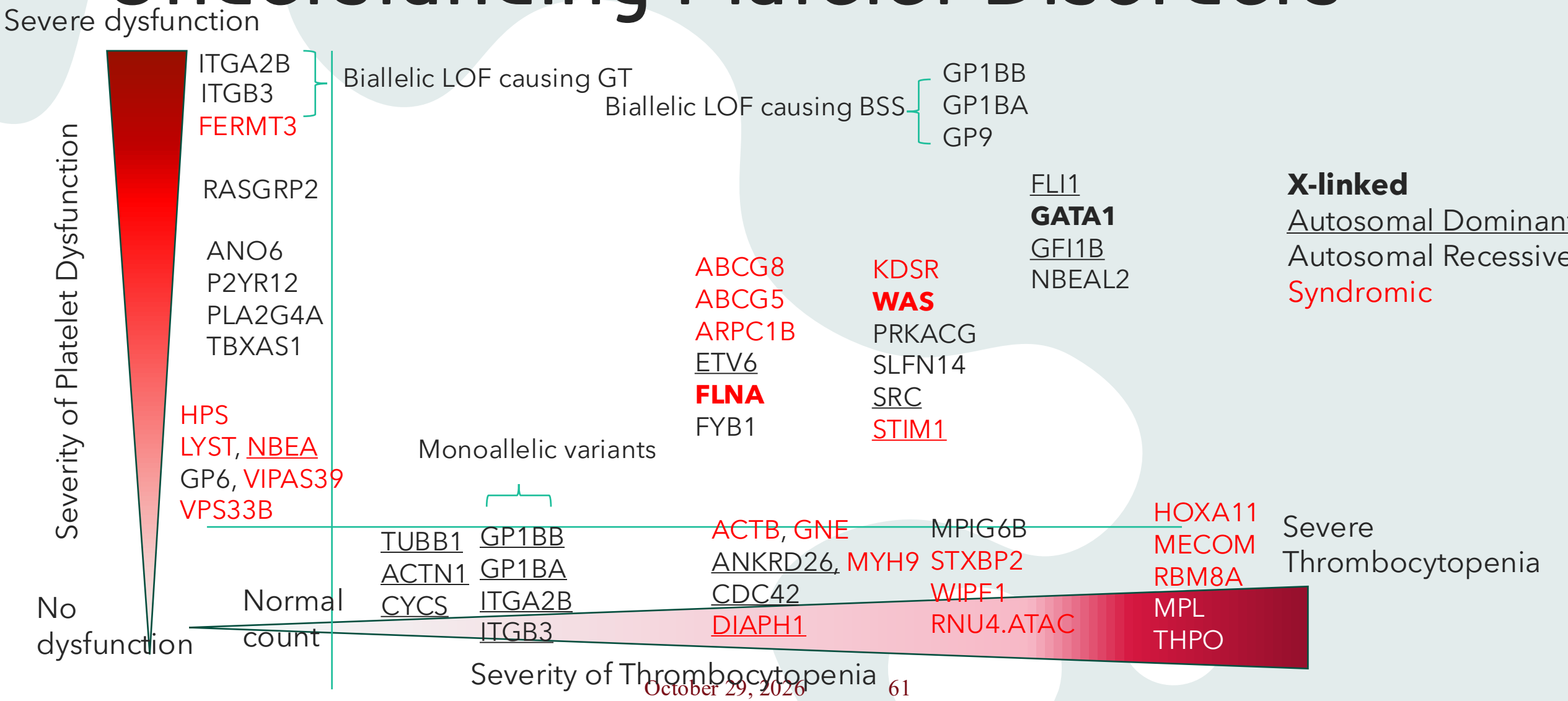
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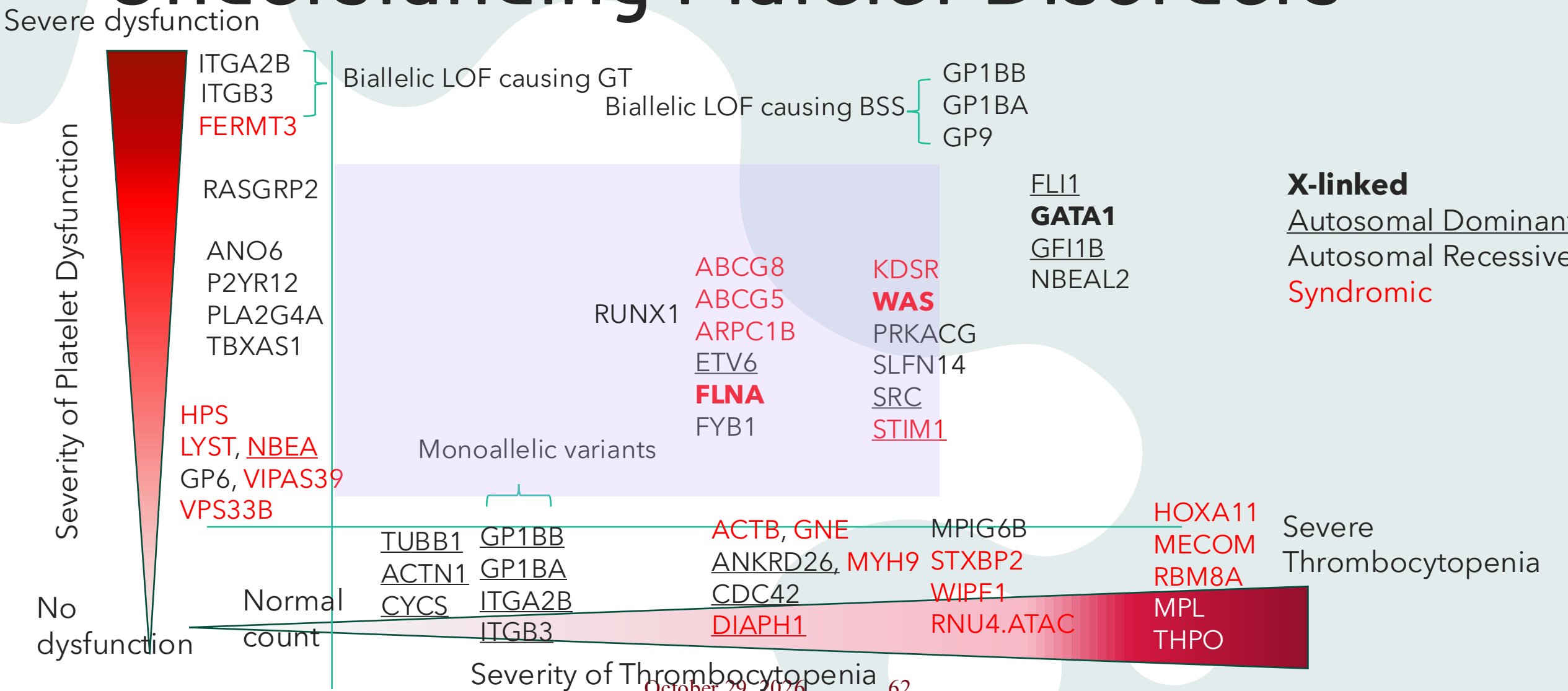
Understanding Platelet Disorders



Understanding Platelet Disorders



Understanding Platelet Disorders



Management

Management of Platelet Disorders

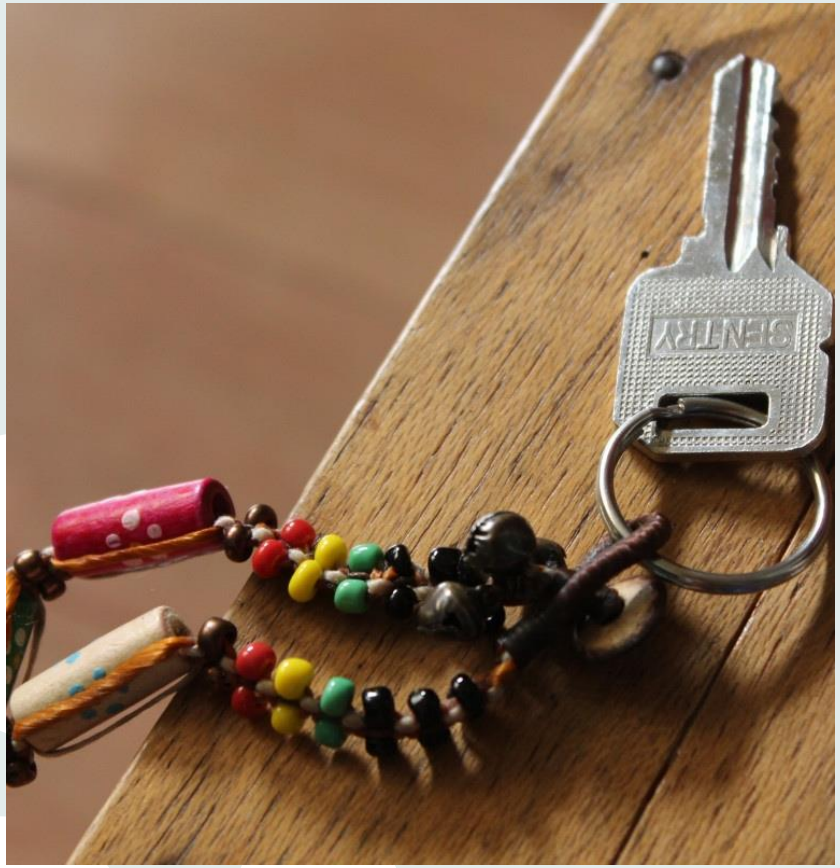
Prevention of bleeding is key

Prevent nosebleeds by managing nasal allergies/dryness

- Inhaled corticosteroids
- Cool mist humidifier
- Bactroban or Vaseline in the nares
- Treat aggressively at the start of a nosebleed

Good dental hygiene and regular dental cleaning (prevent gingivitis)

Hormonal therapies or IUD for menstrual bleeding



Management of Platelet Disorders

- Platelet transfusion is the mainstay for significant bleeding symptoms
  - Need to use HLA match platelets whenever possible
- Antifibrinolytics (ε-aminocaproic acid; tranexamic acid)
- DDAVP
- Recombinant activated factor 7



Novel Therapies in Platelet Disorders

Sutacimig

Rebalancing agents

TPO-RA for thrombocytopenias

Hematopoietic Stem Cell Transplant

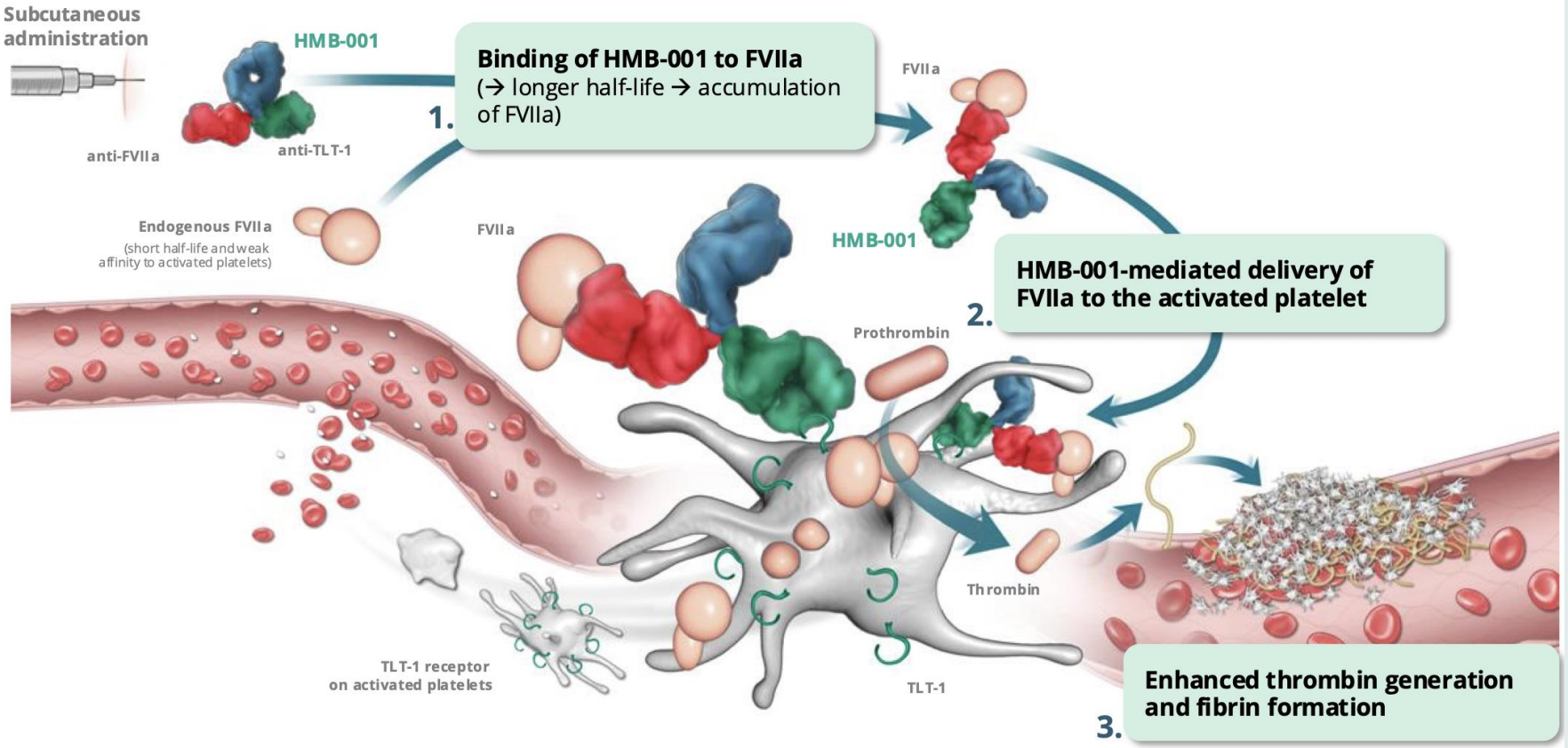
CRISPER/CAS9 or other gene therapy?

Sutacimig

Bispecific antibody

Low-volume (<1 ml) SQ dose

TLT-1 potentiated FVIIa-mediated thrombin generation



HMB-001 binds and accumulates endogenous FVIIa and, following vessel lesion, localizes FVIIa to the surface of activated platelets via TLT-1 potentiation[1]

Sutacimig

Phase 2 preliminary data presented at ASH

34 adult patients; 6 week run in (document baseline bleeding)

12 week treatment and then up to 20 months LTE with 4 dosing levels

Weekly dosing with 87% reduction in ATBR

Currently designing phase 3 trial which will include patients age 12 yo and up

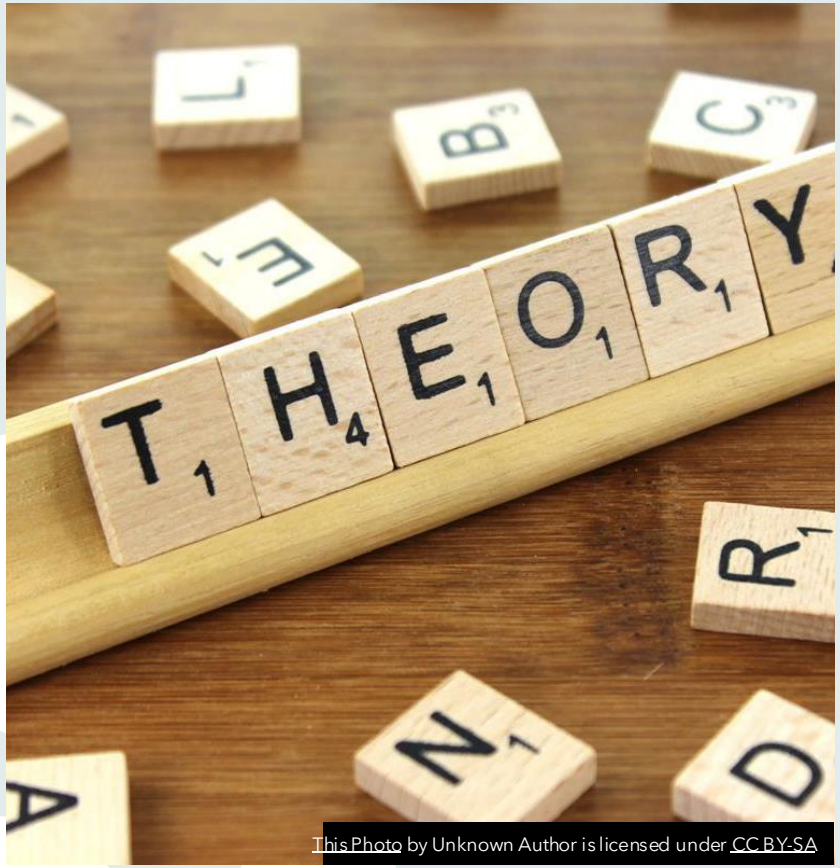
Rebalancing agents

Concizumab has been evaluated *in vitro* in blood from patients with GT looking at Thrombin Generation

Patients with GT have impaired Tissue factor induced thrombin generation due to the critical role of platelet membranes in coagulation

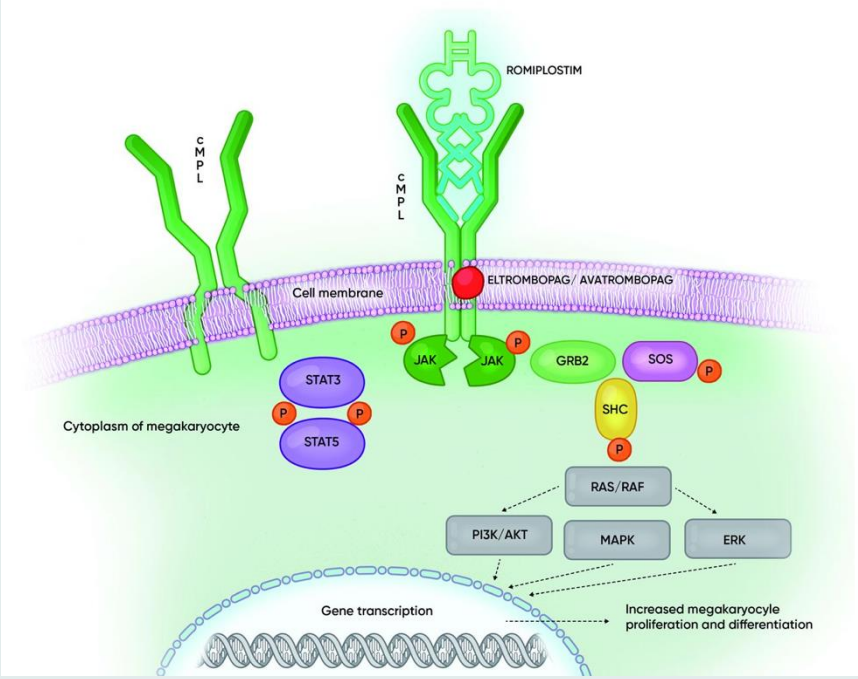
Without normal integrin signaling, platelet membranes are not appropriately "scrambled" and there is less thrombin generated

Concizumab reduced TF induced inhibition of thrombin generation, balancing the incomplete role of platelets



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TPO-RA



IPD	Patients (n)	TPO-RA/Dose	OR (%)	Major response (>100 x 10^9/L)(%)	Clinical Efficacy
MYH9	34	Elt/50-75 mg/d	92	~70	Uniformly robust response; excellent for surgical bridging
WAS	81	Elt/Romi	~60	33-50	Slower, variable response. Marked reduction in bleeding not relate to count change
ANKRD26-RD	10	Elt/50-75 mg/d	87	25	Mostly minor response but doubling so maybe good for surgery
Monoallelic BSS	2	Elt/50-75 mg/d	100	100	Rapid response akin to MYH9
THPO-RT	5	Romi/4-9 mcg/kg	100	100 (trilineage)	Reverses BMF

Summary – inherited platelet disorders

Our understanding of the mechanisms of platelet disorders is growing

Our ability to appropriately diagnose patients is still very limited

Genetic Testing plays an important role for diagnosis

Management focuses on preventing bleeding

Novel therapies are available/in development, and the future of treatment may include prophylaxis

Questions?

Email: lambertm@chop.edu

Acknowledgements

Children's Hospital of Philadelphia
Special Coagulation Lab

ThromboGenomics

Pump It Up For Platelets!

ICON
PEDIATRIC ITP CONSORTIUM OF NORTH AMERICA



Platelet Disorder Team



Immune Dysregulation Team

ClinGen
Clinical Genome Resource

American Society of Hematology

ISTH

SSC: GENOMICS IN THROMBOSIS AND HEMOSTASIS

Foundation for Women & Girls with Blood Disorders

Platelet Disorder Support Association
Empowering ITP Patients