VON WILLEBRAND DISEASE (VWD)

TERM DEFINITION

An inherited bleeding disorder caused by quantitative deficiency or qualitative dysfunction of **von Willebrand factor**, resulting in impaired platelet adhesion and, in some patients, reduced FVIII levels.

CLASSIFICATION

von Willebrand disease

Quantitative defect

- Type 1
- Type 3

Qualitative defect

- Type 2A
- Type 2B
- Type 2M
- Type 2N

At a Glance

- Most common inherited bleeding disorder
- Defects may be:
  - Quantitative (Type 1, 3)
  - Qualitative (Type 2) defect
- Impaired platelet adhesion in most patients
- Reduced FVIII levels in some patients

The central concept

Too little vWF (Type 1, Type 3) ●●●●○○○○

VWF present but defective (Type 2) ●●✗●✗●●●

Type	Hallmark	Inheritance	Frequency
1	Partial quantitative deficiency	AD	70-80%
2A	Loss of HMW multimers	AD	10-15%
2B	↑ Platelet binding, loss of HMW multimers	AD	5%
2M	Defective platelet or collagen binding (preserved multimers)	AD	<5%
2N	↓ FVIII binding	AR	Rare
3	Near-complete deficiency	AR	<1%

AD, autosomal dominant, AR autosomal recessive,

CLINICAL PEARLS

- **Type 2N represents *Normandy***
- **Typically normal physical exam unless recent bleeding**
- **PT is normal; aPTT may be mildly prolonged**
- **Activity < Antigen → Think Type 2**
- **Presents presenting primarily with mucocutaneous bleeding**
- **Blood group O is associated with lower baseline VWF levels**
- **DDAVP is generally avoided in type 2B**
- **A low VWF level (30–50 IU/dL) is not always diagnostic for vWD**
- **VWF levels fluctuate with physiology**

PATHOPHYSIOLOGY

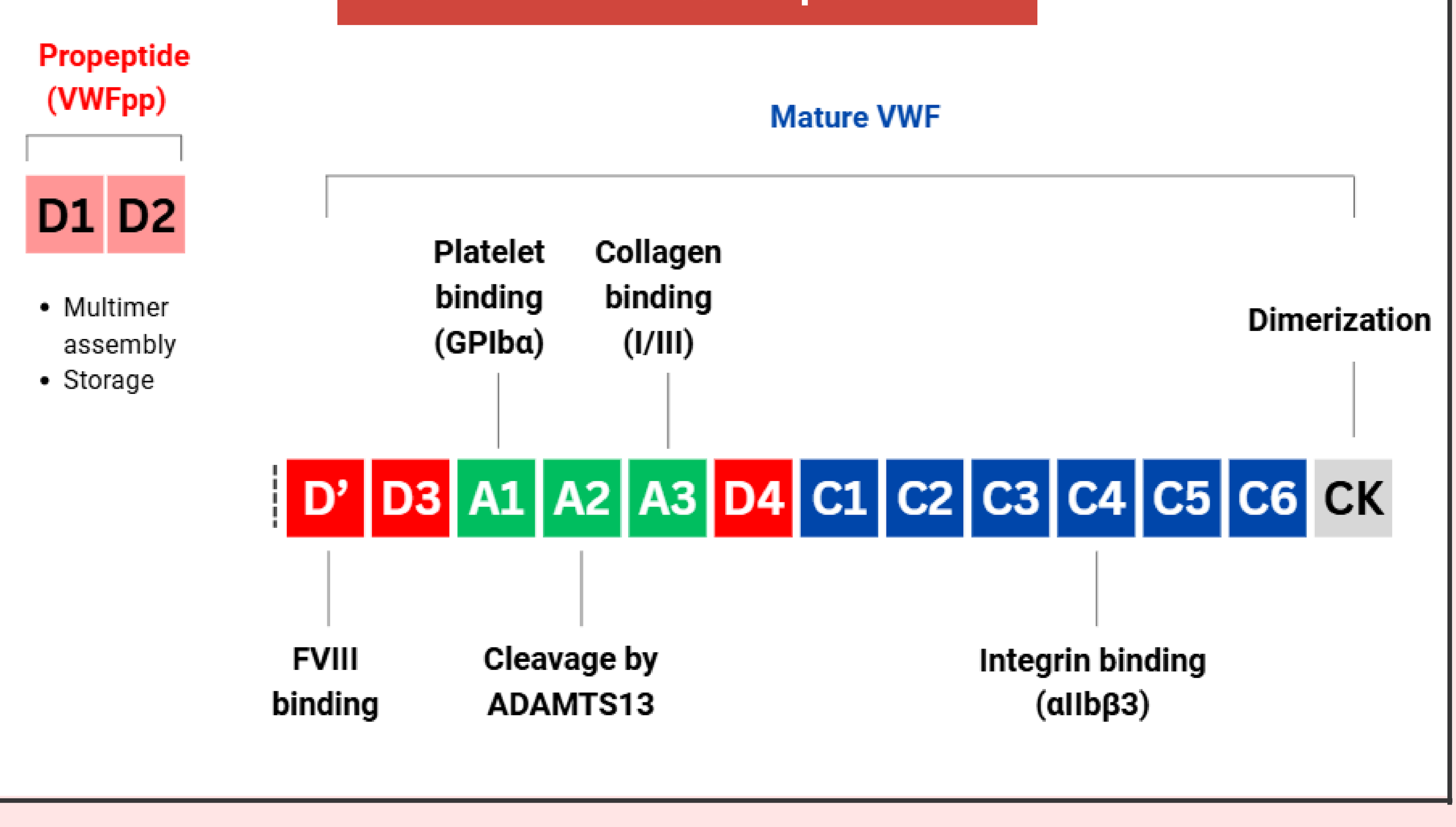
Normal vWF function

- Produced by endothelial cells and megakaryocytes
- Stored in Weibel–Palade bodies and platelet α-granules
- Mediates platelet adhesion via GPIbα
- Carries and stabilizes FVIII

vWF deficiency or dysfunction

- ↓ Platelet adhesion → defective primary hemostasis (mucocutaneous bleeding)
- ↓ FVIII protection → secondary hemostatic defect
- Clinical phenotype depends on quantitative or qualitative VWF abnormalities

Structure–function map of VWF



DIAGNOSIS

EACH ASSAY INTERROGATES A DIFFERENT FUNCTION OF VWF

CONSIDER

Consider the diagnosis in a patient with:

- A personal and/or family history of mucocutaneous bleeding, and
- Laboratory evidence of abnormal von Willebrand factor (VWF) and/or FVIII levels or function

STEP 1 TESTING

Initial laboratory evaluation:

- VWF antigen (VWF:Ag)
- Platelet-dependent VWF activity*
- FVIII

Interpretation:

- Normal → VWD less likely
- Activity proportional to antigen → quantitative deficiency
- Activity disproportionately reduced → qualitative defect
- Proceed to Step 2 if needed

Platelet-dependent VWF activity is measured by VWF:GPIbM, VWF:GPIbR, or VWF:RCo, depending on the laboratory.

STEP 2 TESTING

Assay	Key finding	Subtype indicated
Multimers	Loss of HMW multimers	2A or 2B
Low-dose RIPA	Enhanced platelet binding	2B
VWF:CB	↓ Collagen binding	2M
VWF:FVIIIB	↓ FVIII binding	2N
Genetics	Selected subtype confirmation	Selected cases

THERAPEUTIC PRINCIPLES

TREATMENT OPTIONS

- Desmopressin (DDAVP)
- VWF replacement therapy
- Antifibrinolytics
- Local hemostatic measures

TREATMENT SELECTION

- Based on VWD subtype
- Bleeding severity
- Procedure planned
- Individual DDAVP responsiveness

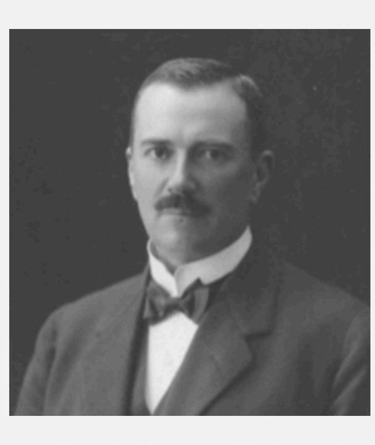
Treatment depends on the VWD subtype, bleeding severity, and clinical context.

EVOLUTIONARY MECHANISMS

- Origins and Function — VWF first appeared with early vertebrates, coinciding with the rise of a closed, high-pressure circulation and thrombocytes. Its primordial role was to link platelets to injured vessel walls under shear flow.
- Co-evolution and Modular Design — VWF's D-, A-, C-, and CK-domains arose stepwise through domain duplication and specialization, creating a multifunctional adhesive protein—a molecular Swiss-army knife for hemostasis.
- Balancing Act — Natural selection tuned VWF expression and cleavage by ADAMTS13 to balance bleeding and thrombosis; too little causes hemorrhage, too much fosters microvascular clotting.

HISTORY OF MEDICINE

- 1920s: Erik von Willebrand describes Finnish family disorder.
- 1950s–80s: FVIII complex separated; VWF identified.
- 1990s–present: Molecular subtypes, targeted therapy, refined care.



Erik Adolf von Willebrand (1870 - 1949)

Take-home message

Understanding VWD means connecting structure, function, and clinical reasoning

ATTRIBUTIONS
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The Blood Project
ENCYCLOPEDIA OF BLOOD