VON WILLEBRAND DISEASE

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VON WILLEBRAND DISEASE

- Von Willebrand Disease is the commonest heritable bleeding disorder.
- Autosomal Inheritance.
- Affects both sexes but presents more frequently in females because of menorrhagia.
- The abnormality may be quantitative or qualitative

Dr Erik von Willebrand

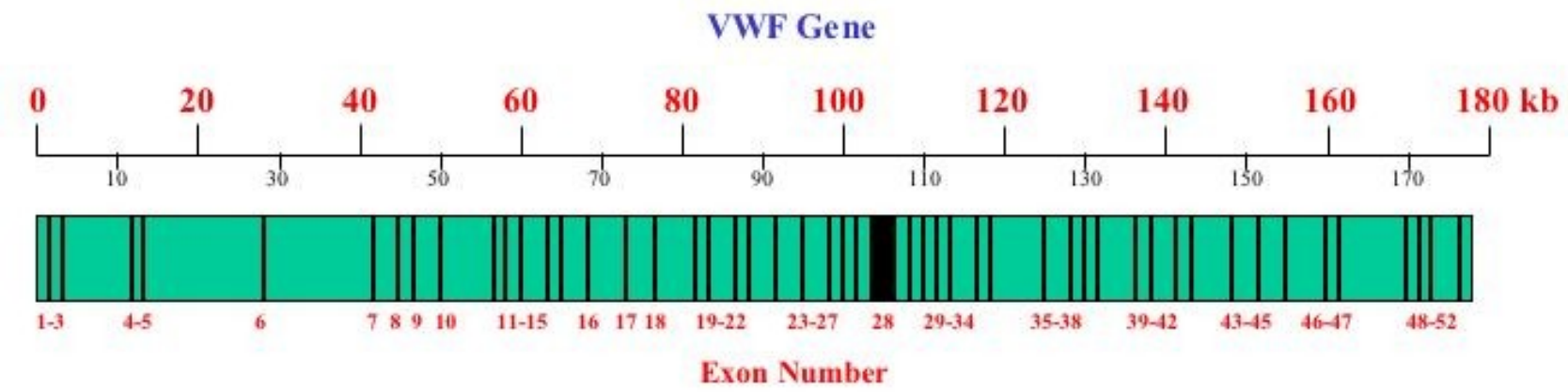
1870-1949

von Willebrand Disease

- Disorder was first described by Erik von Willebrand in 1926 in persons living off the coast of Finland
- Although described in 1926, our understanding of this complex and variable bleeding disorder remains far from complete.
- VWF encoded by a gene on chromosome 12p13 was cloned simultaneously by several groups in 1986.
- Marked heterogeneity in phenotype, autosomal Dominant or Recessive Inheritance
- Affects 1% of general population

vWF Genetics

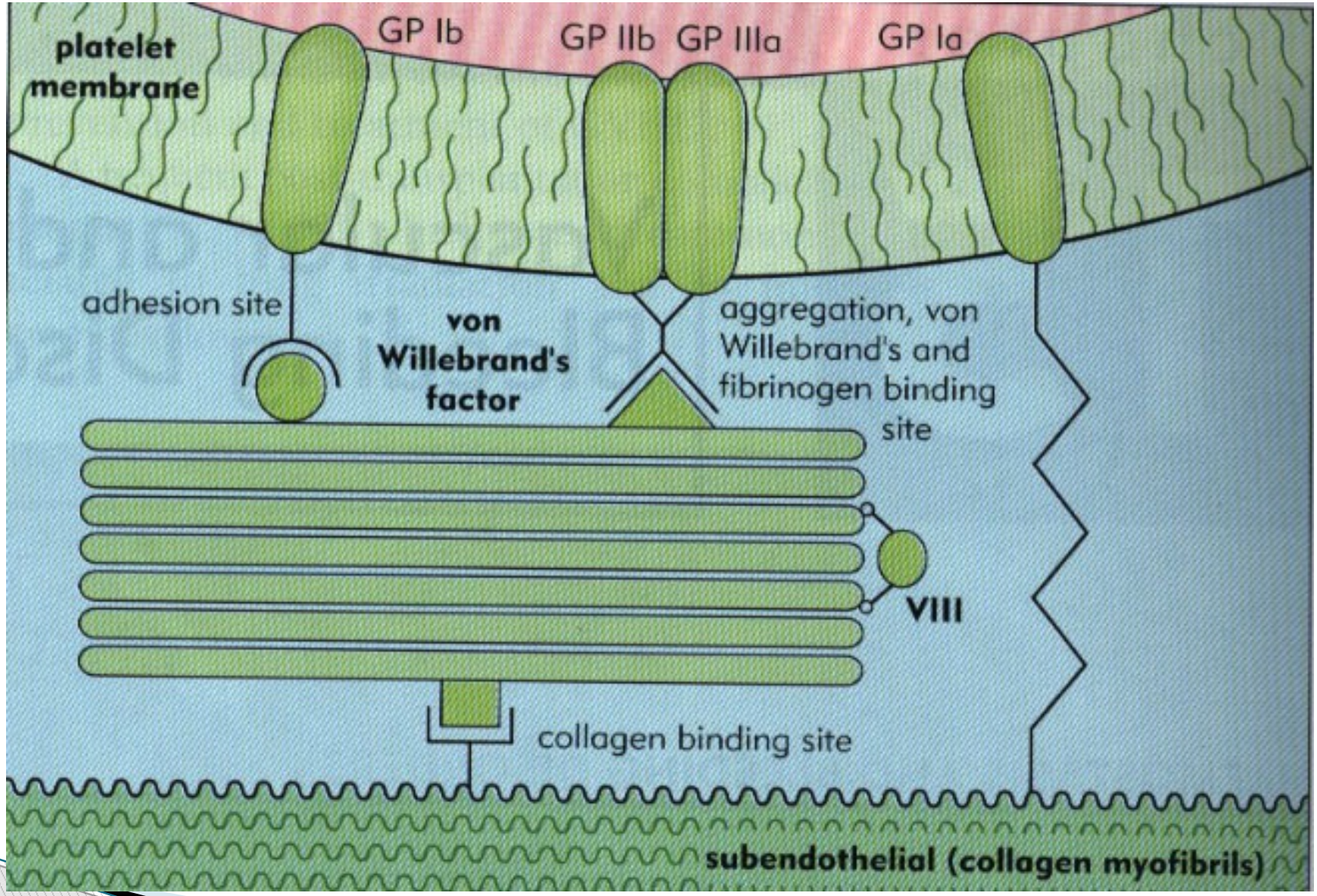
Location of Gene: chromosome 12 (p13.3)



- http://www.vwf.group.shef.ac.uk/pictures.html

von Willebrand Factor (vWF)

- vWF is the protein that makes the platelets stick together to form a platelet plug.
- VWF is a carrier protein for factor VIII.
- VWF ensures that there is enough factor VIII in the blood stream, and carries it to the site of injury, and protects it from being broken down in the blood stream.


platelet membrane
GP Ib
GP IIb
GP IIIa
GP Ia
adhesion site
von Willebrand's factor
aggregation, von Willebrand's and fibrinogen binding site
VIII
collagen binding site
subendothelial (collagen myofibrils)

- VWF is produced predominantly in Vascular endothelial cells.
  - Stored in secretory granules (Weibel-Palade bodies)
  - Released by stress or DDAVP

- Also produced in bone marrow megakaryocytes.
  - Stored in alpha-granules
  - Released by platelet activation.
  - DDAVP does not release platelet vWF

- Endoplasmic Reticulum
  - Dimerization

- Golgi Apparatus
  - Multimerization

- Plasma vWF has a half-life of approximately 12 hours (range 9–15 hours)
- vWF is present in the form of ultra-large multimers, which are subsequently cleaved into smaller forms by plasma metalloprotease ADAMTS13

CLINICAL FEATURES

- Vary according to the severity of the deficiency.
- Mild to moderately severe bleeding tendency
- Bruising, epistaxes
- Prolonged bleeding from minor cuts
- Bleeding after trauma or surgery
- Menorrhagia (20% of women with menorrhagia have VWD)

LABORATORY DIAGNOSIS
Preliminary Diagnosis

For the laboratory diagnosis of VWD assess both the amount of VWF present(VWF:Ag) and its functional capacity.

At present , it is generally possible to assess three important functions:

1)FVIII binding (VWF:FVIIIB)

2)Platelet-dependent function (VWF:Rco)

3)Collagen-binding function (VWF:CB)

Secondary tests for classification of VWD

- If a deficiency suggestive of VWD is detected then further tests, particularly multimer analysis and ristocetin-induced platelet aggregation(RIPA) should be performed to allow accurate classification.

Types of von Willebrand Disease

- **Type 1** – von Willebrand levels are lower than normal
- **Type 2** – there is a defect in the structure of the von Willebrand protein that causes lower than normal VWF protein activity
- **Type 3** – there is very little or no von Willebrand protein produced at all.

Degrees of Severity

Type of vWD	Severity
Type 1	Symptoms are usually mild
Type 2	Symptoms are usually moderate
Type 3	Symptoms are usually severe

Classification

Type 1 WVD

- Level of vWF in plasma is low.
- vWF mediates platelet adhesion and binding FVIII normally.
- FVIII is normal or mildly decreased.
- vWF multimer analysis is normal.

Classification

Type 2 A

- Platelet adhesion is decreased because the proportion of large vWF multimers is decreased.
- Levels of vWF:Ag and FVIII may be normal or modestly decreased.
- vWF:Rco is markedly decreased.

Classification

Type 2 B

- Mutations increase platelet–vWF binding and leads to the proteolytic degradation and depletion of large vWF multimers.
- Patients have thrombocytopenia that is exacerbated by surgery, pregnancy, or other stress.
- RIPA is increased at low concentrations of ristocetin.

Classification

Type 2 M

- Reduced interaction of vWF with platelet GPIb or with connective tissue.

- Screening laboratory results are similar with type 2A vWD and the distinction between them depends on multimer gel electrophoresis.

Classification

Type 2 N

- Impaired binding to FVIII, lowering FVIII levels.
- Type 2 N : Autosomal recessive
- The FVIII level is low but vWF:Ag and vWF:RCo are normal.
- Discrimination from hemophilia A needs FVIII–vWF binding assay.

Classification

Type 3

- Type 3 vWD is characterized by undetectable vWF protein and activity.
- FVIII levels are usually very low.

MANAGEMENT

- The FIRST-LINE TREATMENT for minor bleeding after local measures have failed in TYPE 1VWD is Desmopressin.
- This will produce a brisk rise in VWF and FVIII levels(30 minutes after I/V Infusion) and a shortening of bleeding time.
- Tranexamic acid may be effective on its own in some circumstances such as menorrhagia or as a mouthwash for oral cavity bleeding.

- In patients in whom Desmopressin is ineffective or contraindicated, the NEXT LINE of treatment is:
- Concentrate containing adequate amounts of functionally active VWF with preservation of the high molecular weight multimers.
- Cryoprecipitate CAN be used in these circumstances.

Cryoprecipitate

- Each bag contains about 100 IU vWF
- Volume overload
- Not always available
- Immunological reaction
- Not reliable response

- Factor concentrates will always be required for treatment of Type 3 VWD, most Type 2 and those Type1 variants with inadequate desmopressin response.
- In situations where concentrates fail to stop bleeding, cryoprecipitate and platelet concentrates may prove effective.

Clinical Course and Complications In Type1 VWD

- Patients with Type1 VWD lead relatively normal lives, with normal life expectancy.
- Menstruation is seldom a cause of severe blood loss, although menorrhagia is common. This can usually be managed satisfactory with antifibrinolytics or by hormonal therapy.
- If these are not effective,then self-administeration at home of desmopressin by intranasal or subcutaneous routes can be useful.
- During pregnancy,the VWF levels rise spontaneously to the normal or low-normal range in most patients with type1 VWD.


THANK
YOU