Von Willebrand's Disease (vWD)

Among women with unexplained menorrhagia

vWD Prevalence

- The commonest congenital bleeding disorder at 1 to 2/100
- Autosomal inheritance, mostly dominant
- Multiple different types comprising **quantitative** or **qualitative** defects of von Willebrand Factor (vWF)
- Considerable heterogeneity in clinical phenotype and in genotype

vWD Clinical Perspective 1

- Commonest signs: epistaxes; **menorrhagia**; post-operative bleeds; oral and GI bleeding (angiodysplasia)
- Both genders affected equally, **but** menses, pregnancy & childbirth mean women are more vulnerable. Over 60% of vWD patients are women (Cabrera, 1989)
- Menorrhagia (>80 ml/cycle) and iron deficiency in >65%. Begins at menarche.

vWD Clinically 2

- Morbidity in a **critical** sector of society, when demands of family and work are greatest
- Lack of awareness of medical community
- No objective criteria for estimating blood loss
- Cultural barriers exist in Iran, preventing discussion. In affected families, menorrhagia may be considered normal
- Pregnancy usually well tolerated

vWD Clinically 3

- Prevalence of vWD in women with menorrhagia is greater than perceived:

11 studies of 998 women with menorrhagia showed 13% had some form of vWD (Kadir, 2004)

Average time to diagnosis in US: 16 years due to unawareness.

In UK & US, only 2% and 4% of specialists considered vWD screening for menorrhagia

Unawareness may lead to early hysterectomy

vWD Clinically 4

- US College of Obst/Gynae (2001) recommended vWD screening for:

1. Adolescents with severe menorrhagia
2. Women before hysterectomy for menorrhagia
3. Adults where no cause for menorrhagia found

Kirtava, 2003, reports other gynae. problems in vWD: dysmenorrhea (in 50%); ovarian cyst; endometriosis; even haemoperitoneum

Diagnosis of vWD

- Laboratory investigation complex and not widely available:

Template Bleeding Time; PFA-100 closure time; Platelet count; FVIII:C; vWF:Ag; vWF: RiCoF; vWF: CB; vWF: FVIIIB; RIPA; HMW Multimer Analysis; Molecular Genetic studies; MCMDM-1vWD Questionnaire (70% sensitive; 98% specific)

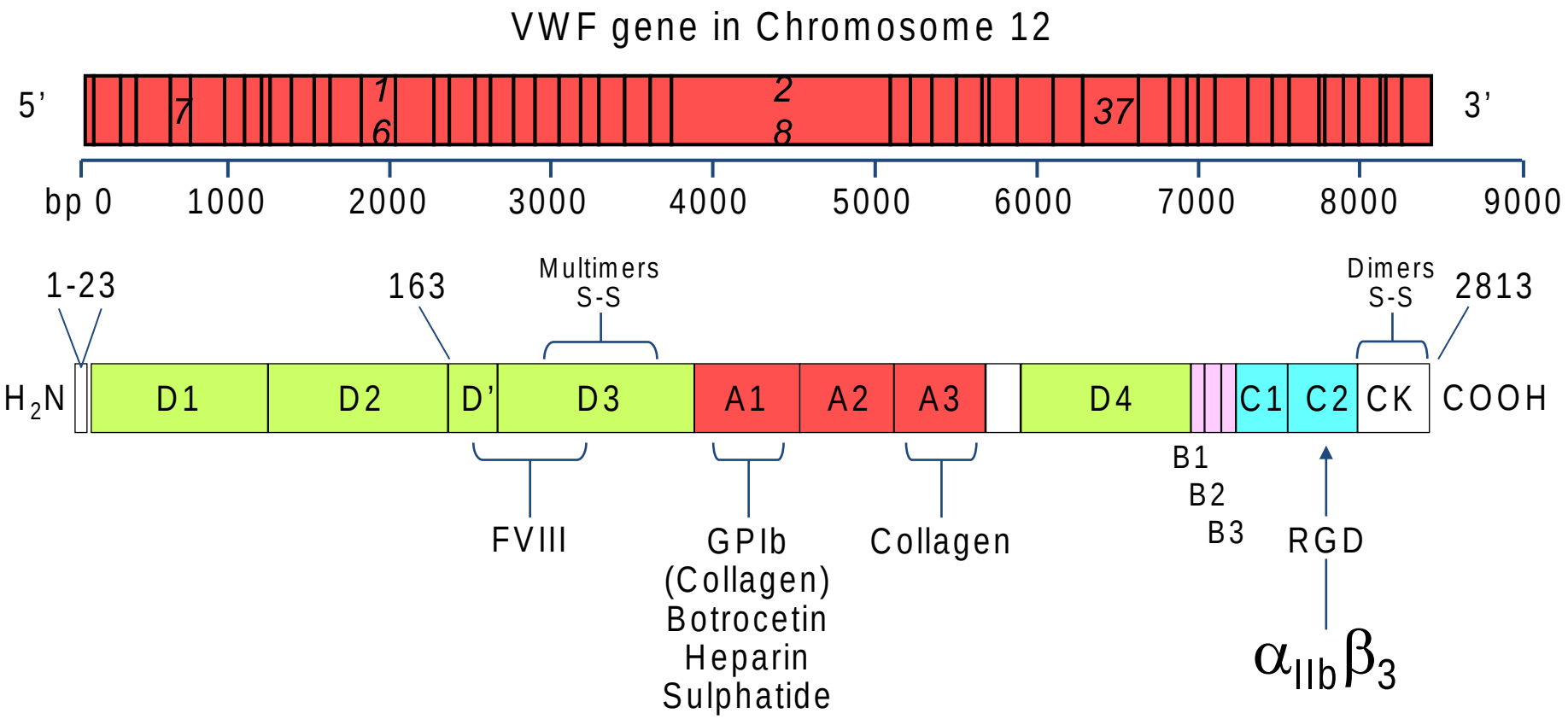
vWD type 2 Diagnosis

- vWD type 2: a variety of Functional & Structural Defects causing:
- Defective vWF-dependent platelet function in vWD types 2A, 2B and 2M, and abnormally low Ristocetin co-Factor or defective vWF:Ag/Collagen binding
- Defective vWFactor/ FVIII binding in vWD 2N

vWD type 2 Diagnosis

- Abnormal platelet-dependent function is often associated with **absence** of HMW Multimers – i.e in vWD 2A and 2B, or
- **Presence** of HMW Multimers, which are **dysfunctional** – i.e in vWD 2M, or
- HMW Multimers are **supranormal** as in vWD Vicenza

ENCODING REGIONS OF VWF AND FUNCTIONAL DOMAINS



Molecular Genetics of vWD type 2

- Identifying mutations helps classify variants; provides insights into structure/function, and enables pre-natal diagnosis & counselling.
- Mutations in the D3 Domain – vWD Vicenza
  Mutations in the A1 Domain – modify GP1b platelet binding – **increased** affinity =vWD 2B or **decreased** affinity in vWD 2M or 2A/2M
  Mutations in A2 Domain – vWD 2A
  Mutations in D' Domain – vWD 2N

vWD type 2 Mutations Identified

- So far, we have carried out genetic analysis of 168 cases from 32 unrelated families, initially screening Exon 28; Exons 17 to 21 for vWD 2N, or Exon 27 for Vicenza type.
- Our results: 53 vWD type 2A; 27 vWD type 2B; 36 vWD 2M; 26 vWD type 2N; 24 vWD Vicenza type and 2 Platelet-type vWD cases.