GENETIC DEFECTS IN VON WILLEBRAND DISEASE

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Introduction

Von Willebrand disease (VWD) is the most common congenital bleeding disease. Its diagnosis is based on clinical and laboratory aspects. However, in many cases is complex, due to the possible variability in analytical testing for the influence of environmental factors and acquired. In these cases of uncertain diagnosis, genetic analysis plays an important role. Nevertheless, molecular diagnosis of VWD is hampered by three factors: the large size of VWF gene which is comprised of 52 exons; the presence of a highly homologous partial pseudogene in chromosome 22; and the fact that VWF is highly polymorphic. The aim of this study was to determine genetic variations in 11 families with VWD.

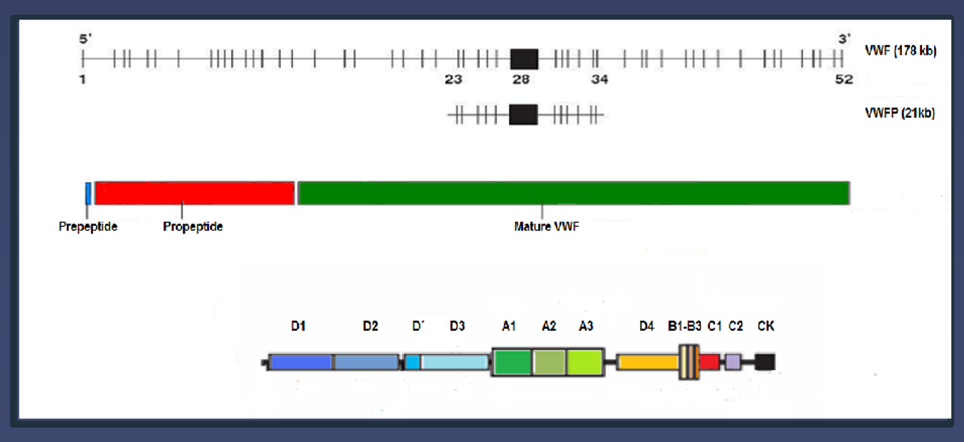

Figure 2: VWF Structure.

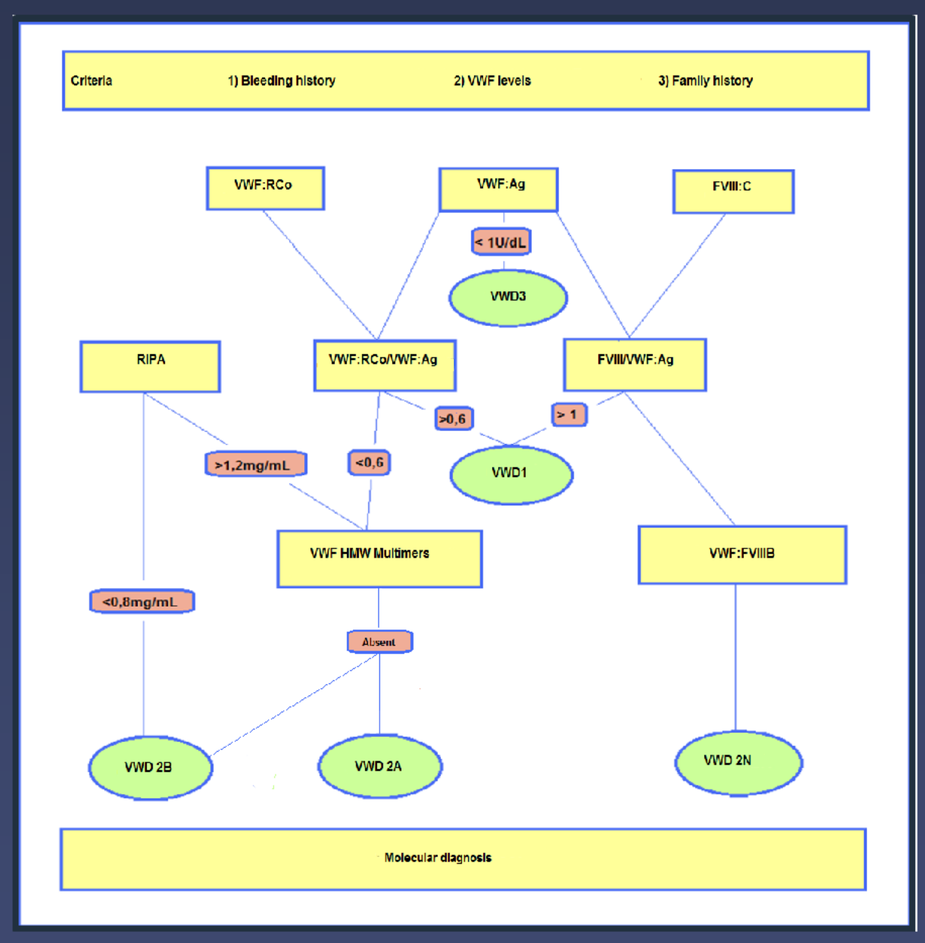

Figure 1: Flow-chart for the correct diagnosis and classification of different VWD types.

Material and methods

We studied 11 unrelated families previously diagnosticated with VWD: 3 families with VWD type 3, 5 with VWD type 2B, 2 families with VWD type 2A and a family with VWD type 1. Mutation screening was done by PCR and direct sequencing of the coding VWF exons 2-52 including flanking intron sequences.

Figure 3: Automatic Sequencer CEQ 8000 (Beckman-Coulter).

Results

Two families with VWD type 2B presented simultaneously R1315H and R1341Q mutations. This is the first study found mutations (R1341Q) and (R1315H) in the same family. The others families with VWD type 2B presented R1306Q mutation in homozygosis and R1306W, R1308W mutations in heterozygosis. Two families with VWD type 2A were heterozygous for R1374H and C1272G mutations. The family with VWD type 1 presented simultaneously P1266L and V1279I mutations in heterozygosis. The three families with VWD type 3 were heterozygous for Q1311X. All this mutations were located in exon 28 and were previously described in the ISTH-SSC VWF Online Database.

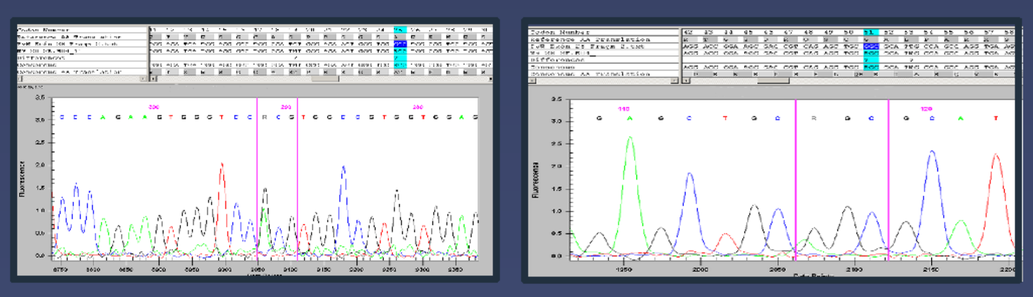

Figure 4: R1315H and R1341Q mutations.

Mutation	Exon	Type of vWD	Nº of families
R1315H R1341Q	28	VWD 2B	2
R1306W	28	VWD 2B	1
R1308W	28	VWD 2B	1
R1306Q	28	VWD 2B	1
R1374H	28	VWD 2A	1
C1272G	28	VWD 2A	1
P1266L V1279I	28	VWD 1	1
Q1311X	28	VWD 3	3

Table 1: vWD Mutations.

Discussion

Starting the genetic analysis of the vWF gene by exon 28 is useful in patients with VWD type 2A, 2B and 3. This rapid genetic diagnosis in these patients will increasingly inform patient management and genetic counselling decisions.

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