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GENERAL INFORMATION

von Willebrand disease, molecular biology and diagnosis☆

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KEYWORDS
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Abstract
Background: von Willebrand disease is the most common inherited disorder of the coagulation proteins in humans. There are three types: 1, 2A, 2B, 2N, 2M and 3. It is associated with mutations on chromosome 12 in the region p13.2, encoding the von Willebrand factor (VWF), which is synthesised in endothelial cells and megakaryocytes.
Discussion: The VWF gene has been characterised using molecular biology techniques, which have acquired an important role in diagnosis of von Willebrand disease, as well as in the investigation of alterations in other genes, which may be involved in regulating the synthesis, processing, and secretion of VWF. However, there are still no strategies to integrate the molecular biology diagnostic tests available.
Analysis of VWF multimers is a methodology that meets the characteristics for diagnosis, but it is not easy to standardise. Considering that even in tertiary centres in our country, von Willebrand patients do not have a definitive diagnosis, it is necessary to implement these methodologies to study and improve diagnosis.
Conclusions: von Willebrand disease is highly heterogeneous due to the molecular mechanisms that produce the various clinical and laboratory phenotypes. In Mexico there are few studies

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related to this disease; therefore it is essential to conduct a comprehensive study including clinical, basic, and special testing laboratory tests, in order to establish a correct diagnosis, develop new therapeutic approaches, and offer the appropriate medical care and genetic counselling.

PALABRAS CLAVE
Enfermedad de von Willebrand;
Factor de von Willebrand

Enfermedad de von Willebrand, biología molecular y diagnóstico

Resumen
Antecedentes: La enfermedad de von Willebrand es el trastorno hereditario más frecuente de las proteínas de la coagulación en los seres humanos. Existen 3 tipos: 1, 2A, 2B, 2N, 2M, y 3. Está asociada a mutaciones en el cromosoma 12, en la región p13.2, que codifica para el factor de von Willebrand (VWF), el cual se sintetiza en las células endoteliales y megacariocitos.
Discusión: La biología molecular ha permitido la caracterización del gen del VWF, adquiriendo un papel importante en el diagnóstico la enfermedad de von Willebrand así como en la investigación de alteraciones en otros genes, que pueden estar involucrados en la regulación de la síntesis, procesamiento y secreción del VWF. Sin embargo, aún no se han integrado las estrategias de biología molecular entre las pruebas de diagnóstico disponibles.
El análisis de los multímeros del VWF es una metodología que cumple con las características para el diagnóstico, pero no es fácil de estandarizar. Tomando en consideración que aún en los centros de tercer nivel en nuestro país los enfermos de von Willebrand no cuentan con un diagnóstico definitivo, es necesario implementar estas metodologías para su estudio y mejorar su diagnóstico.
Conclusiones: La enfermedad de von Willebrand es heterogénea debido a los mecanismos moleculares que producen los distintos fenotipos clínicos y de laboratorio. En México existen pocos trabajos relacionados con esta enfermedad, por ello es fundamental realizar un estudio integral que incluya aspectos clínicos, pruebas de laboratorio básicas y especiales, para establecer el diagnóstico correcto, desarrollar nuevos enfoques terapéuticos, y así ofrecer atención médica y asesoramiento genético adecuados.

Background

Coagulation disorders are hereditary haemostatic abnormalities, and some may present considerable diagnosis and treatment difficulties. The von Willebrand disease is a hereditary disorder characterised by mucocutaneous haemorrhages of variable intensity, mainly affecting the primary haemostasis in platelet interaction, von Willebrand factor (VWF) and endothelium. It implies changes in the structure, function or concentration of the VWF, a plasmatic protein secreted by endothelial cells circulating in plasma.[1]

According to Vischer and de Moerloose, in 1926 Erik Adolf von Willebrand described a serious haemorrhagic disorder called pseudo haemophilia in a family with prolonged bleeding times despite having normal platelet counts.[1,2] Later it was shown that this disorder is it related to a decrease in procoagulant activity in factor VIII of coagulation (FVIII), which may be compensated through an infusion of plasma or fractions of plasma, which evidences that the disease is caused by the lack of a plasma factor.[3] In 1971, it was determined that FVIII and VWF were different proteins, and in 1975 Gralnick and Coller[4] characterised the VWF. This discovery was accompanied by a new laboratory test using ristocetin to evaluate platelet function in this disease[4,5] and, in 1985, the different nature of the VWF was definitely proved when describing the sequence of the VWF gene.[5,6]

von Willebrand factor

The VWF is a multimeric protein synthetised in cells of the vascular endothelium, megakaryocytes and platelets with 12 h average life, codified in a gene of 52 exons (178 kb) localised in 12p13.2, and transcribes an mRNA of 8.8 kb (2813 amino acids [aa]). Currently, more than 160 normal variants of the gene structure are known. Its transcription is regulated by specific cell-type transcription factors (GATA and ETS proteins), and there are also several repressive transcriptional elements in the ascending sequence of the gene (Fig. 1).[7–9] On the other hand, there is a partial copy in chromosome 22 (pseudo gene) of exons 23–34 of the sequence of chromosome 12; this non-functional evolutional remnant shows a 3% sequence divergence in relation to the gene of chromosome 12 and seems to have been