

Genetic Determinants of von Willebrand Disease Type I

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Synopsis:

Von Willebrand Disease (vWD) type 1 is the most common form of vWD, accounting for as much as 80% of reported cases. With prevalence estimates as high as 1.6% in the general population, upwards of 4.5 million Americans may be affected. Unfortunately vWD type 1 is also the most difficult type to diagnose, leading to greater patient distress and increased cost. The goal of the proposed study is to identify and characterize common polymorphisms within the von Willebrand factor (vWF) gene that account for a sufficient portion of variation in vWF levels to be clinically useful in the diagnosis and management of von Willebrand disease (VWD) type I.

Successful execution of this project will advance the understanding of vWD by providing a strong foundation to direct future studies, and an experimental paradigm that can be used to accelerate the dissection of complex traits. The long-term goal is to understand the manner in which these common variations affect variation in coagulation and predispose to disordered bleeding, ultimately leading to new therapies and preventative interventions. Moreover, the methodology can be applied to any gene locus in the search for genetic causes of vWD.

The primary function of the hemostatic system is to balance the body's dynamic requirements for clotting and bleeding. An imbalance, either acquired or inherited, in any of the many factors that contribute to hemostasis often leads to hemorrhage or thrombosis (Harmening, 2002).

An essential procoagulant molecule is von Willebrand factor (vWF), which is responsible for the adherence of platelets to damaged endothelium. VWF performs two major roles in hemostasis: it mediates the adhesion of platelets to sites of vascular injury, making it vital for platelet plug formation (Goodnight, 2001; Montgomery, 2001), and it serves as a carrier protein to stabilize coagulation factor VIII. (Castaman, 2003) A deficiency of this protein results in mucocutaneous bleeding and posttraumatic or post surgical bleeding, causing vWD.

In order to minimize the risk of misdiagnosis, it is often recommended that the laboratory evaluation be performed on a least two different occasions, and in spite of this, considerable variability can occur when the tests are repeated in a given patient over time. The need for molecular studies to improve the current diagnostic approach is apparent.

The identification of susceptibility genes for vWD is both desirable and tenable, and would lead to a clearer distinction of type 1 sub-groups and their risk of bleeding, improved treatment and efficacy, and more accurate and appropriate genetic counseling. Identification of genetic polymorphisms is also likely to lead to further understanding of mechanisms involved in vWD and directed pharmacologic intervention.