

**Combined factors V and VIII deficiency climbs onto the map.**

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Editorial

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Inherited bleeding diseases have lit the path to our current understanding of hemostasis. An affected patient usually has a defect in one gene that causes deficiency of one blood clotting factor, simultaneously proving the existence of the factor and demonstrating its biological importance. Combined Factors V and VIII deficiency deviates from this pattern because a single autosomal recessive defect reduces the blood levels of two proteins encoded by unlinked genes on chromosomes 1 (Factor V) and X (Factor VIII). This rare disorder has substantial theoretical importance because it exposes an uncharacterized metabolic connection between these critical factors. In this issue of *The Journal*, Nichols et al. (1) make progress toward understanding this connection by mapping combined Factors V and VIII deficiency to the long arm of chromosome 18.

Combined Factors V and VIII deficiency was recognized first in 1954, when Oeri et al. (2) studied two young brothers, born of a consanguineous mating, with bruising, nosebleeds, gum bleeding, and intramuscular hematomas; both had decreased plasma Factor V and Factor VIII. Since then, at least 91 homozygous patients belonging to 60 unrelated families have been reported (3). About 40% of the families live in the Mediterranean basin, and consanguinity is present in two-thirds. The populations with the highest disease frequency are Oriental and Sephardic Jews in Israel. Almost all heterozygous carriers are asymptomatic and have normal levels of Factor V and Factor VIII. Affected homozygotes commonly have excessive bleeding after surgical procedures, deliveries, and menorrhagia. They have approximately equal decreases of Factors V and VIII, usually 5–25% of normal, and the residual Factor V and Factor VIII molecules appear to be normal (3).

Many mechanisms have been proposed to explain this mysterious dual deficiency. The most intriguing recent model was based on the observation that four unrelated patients with combined Factors V and VIII deficiency had no protein C inhibitor (PCI) in their blood (4). A little background explains the appeal of this finding. Protein C is a protease zymogen that is cleaved and activated by thrombin. Activated protein C degrades Factors V and VIII, thereby acting as a physiologic anticoagulant. Activated protein C is neutralized by PCI, so that absence of PCI could result in unopposed destruction of Factors V and VIII, causing deficiency of both. Unfortunately, as Thomas Huxley said of another attractive scenario, “the great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact—was played, almost immediately.” The clearance of transfused Factor V and Factor VIII was found to be normal, and the endogenous Factor VIII released by a dose of 1-desamino-[8-D-arginine]-vasopressin (DDAVP) also had normal survival; thus, accelerated catabolism of Factors V and VIII is not the problem. Other patients were shown to have normal

PCI levels. After reexamination of the original patients also showed normal PCI levels, the initial finding of PCI deficiency was attributed to lability of PCI upon repeated freezing and thawing of plasma samples.

Against this background, mapping the locus of combined Factors V and VIII deficiency to a small interval on chromosome 18q is a major advance that would have been impossible even a few years ago. Traditional family studies were never practical because the disease is so rare. In principle, mapping by homozygosity and linkage disequilibrium methods would be ideal because consanguinity is common in affected families, and combined Factors V and VIII deficiency has a high prevalence in populations with relatively well-defined founding dates. In fact, only eight families were needed to place the disease locus in a 2.5-cM interval (1). However, these approaches require a densely spaced genetic map that has become available only recently, as a product of the human genome project. Approximately 30 additional inbred families throughout the world constitute untapped resources for further mapping. Yeast artificial chromosomes spanning the region will speed the identification of more genetic markers. These approaches should shrink the candidate interval and transform the problem into a straightforward, if tedious, search among candidate genes.

When the gene is found, what will it be? Even at the present stage, its location on chromosome 18q excludes all known hemostatic proteins, including PCI. The clearance of Factors V and VIII is normal in the combined deficiency, so the defect probably affects a process common to their biosynthesis. Consideration of Factors V and VIII structure and function suggests several possibilities, some of them exotic.

Factors V and VIII are homologous and perform similar cofactor functions in membrane-bound enzyme complexes. Both proteins are made in the liver as single chain precursors and are composed of three types of domains arranged in the order A1-A2-B-A3-C1-C2. The A domains are homologous to ceruloplasmin and the C domains are homologous to discoidin, a slime mold protein; the B domains are dissimilar. Both proteins contain free cysteine residues. They undergo similar post-translational modifications including N-linked and O-linked glycosylation, sulfation on tyrosine residues, and incorporation of a divalent copper ion, probably into a site also conserved in ceruloplasmin (5, 6). Several of these steps could be targets in combined Factors V and VIII deficiency. For example, the two homologous genes could require a specific transcription factor. A particular protein “chaperone” might be necessary for efficient folding of a conserved structural domain, or for the handling of unpaired cysteines. The presence of copper ions in Factors V and VIII is especially unusual, and mistakes in the incorporation of copper ions might impair the synthesis of both proteins. There are many other possibilities. Of course, defects in any such mechanism might not be completely selective for Factors V and VIII. In that case, combined Factors V and VIII deficiency could prove to be more pleiotropic, when one learns how to look.

The world's literature on combined Factors V and VIII deficiency (including abstracts and letters) comprises less than 100 items, but this disease has a special status in our field as an enigma that has resisted all but the crudest level of understanding. Its map location is a signpost marking the first step toward the molecular characterization of the disease, which may involve a truly novel biosynthetic pathway. Given the past history of combined Factors V and VIII deficiency, the final answer may be a surprise.

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