FAST MOVING FRONTS - 2009

September 2009

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J. Evan Sadler talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Clinical Medicine. The author has also sent along images of their work.

Article: Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor
Authors: Sadler, JE, *et. al*
J THROMB HAEMOST, 4 (10): 2103-2114 OCT 2006
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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

I think our paper is highly cited because it provides a relatively simple and useful framework to organize a complex mass of biochemical and clinical data. von Willebrand disease (VWD) is a bleeding disorder caused by inherited defects in von Willebrand factor (VWF), which is an enormous multimeric blood protein that is necessary for hemostasis.

VWF is assembled (Figure 1) within endothelial cells from identical subunits that first form dimers in the endoplasmic reticulum "tail-to-tail" through disulfide bonds between C-terminal domains. These dimers are transported to the Golgi, where they form multimers that are linked "head-to-head" by disulfide bonds between N-terminal D3 domains.

The finished multimers are stored in densely packed tubular arrays within morphologically unusual vesicles called Weibel-Palade bodies, from which they are secreted into the blood. VWF multimers perform their hemostatic function by binding to exposed connective tissue and to certain platelet membrane glycoproteins, thereby facilitating the adhesion of platelets at sites of vascular injury. VWF also binds blood clotting factor VIII and stabilizes it in the circulation.

The complicated biosynthesis and multiple binding functions of VWF can be disrupted by mutations to yield many disease phenotypes that can be challenging to diagnose and treat appropriately. The classification of VWD that we proposed (Figure 2) condenses this variety into a manageable set of categories, providing a common language to describe and analyze what we know.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

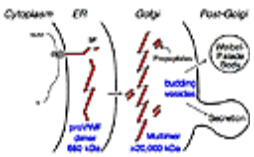
The classification recognizes a small number of different pathophysiologic mechanisms which disrupt VWF biosynthesis, structure, or function. It's intended to be simple, to rely on widely available laboratory tests, and to correlate with important clinical characteristics.

There is a reasonably good relationship between VWF genotype and VWD phenotype, especially for the qualitative or type 2 variants of VWD (Figure 3). For example, multimer assembly requires the C-terminal CK domains for dimerization in the endoplasmic reticulum, and both the propeptide and D3 domains for final assembly in the Golgi.

Mutations in any of these regions cause the loss of hemostatically effective large VWF multimers, which is characteristic of VWD type 2A. Gain-of-function mutations in the A1 domain that cause spontaneous binding of VWF to platelets also cause VWD type 2B, which is usually associated with thrombocytopenia. Loss-of-function mutations that impair platelet or collagen binding cause VWD type 2M.

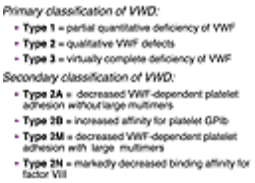
One of my favorite variants is VWD type 2N, which is caused by mutations in or near the factor VIII binding site. These patients have very low factor VIII levels and sometimes are misdiagnosed as having hemophilia A. In fact, their factor VIII gene is normal and they simply clear their endogenous factor VIII too quickly. Distinguishing hemophilia from VWD type 2N has important implications for treatment. Genetic counseling also differs because hemophilia A is an X-linked disorder, whereas VWD type 2N is autosomal recessive.

Figure 1 [+] details



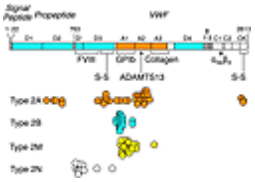
Biosynthesis of VWF. The VWF precursor is translocated... ⇢

Figure 2 [+] details



Classification of VWD... ⇢

Figure 3 [+] details



Mutations in VWD type 2. The VWF precursor consists of a sig... ⇢

SW: Would you summarize the significance of your paper in layman's terms?

VWD appears to be the most common inherited bleeding disorder, and it is caused by many different kinds of defects in VWF. As a consequence of this variability, patients with different types of VWD vary considerably in the severity of bleeding symptoms and require different treatments. The paper describes a way to distinguish several types of VWD so that, in most cases, we can choose the best treatment to stop or prevent bleeding for our patients.

SW: How did you become involved in this research and were any particular problems encountered along the way?

About 25 years ago, several research groups around the world, including mine, cloned the VWF gene and began characterizing the mutations that cause VWD. Within a few years I think we all realized that the wealth of new molecular data offered an opportunity to take a fresh look at how VWD was diagnosed and classified, which we did first in 1994 and, most recently, in 2006.

The Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis has provided a perfect organizational structure to accomplish this task through their Subcommittee on von Willebrand Factor, which includes active basic and clinical investigators with broad international representation.

I would say that our major problem was simply sorting through the vast literature on VWD and distilling it into a relatively concise framework that did not unintentionally misrepresent the state of the science. I have been very impressed by the world community of researchers that study bleeding disorders, which has been unfailingly collegial, dedicated, and willing to work. Achieving consensus was relatively easy, although coordinating authors from so many countries was a challenge and our manuscript required approximately two years to write.

SW: Where do you see your research leading in the future?

Clearly there are gaps in our knowledge, and no classification we can devise today will be perfect. For example, patients with any particular mutation don't necessarily have the same severity of bleeding symptoms. There must be other factors in a person's genetic makeup, environment, or life history that influences how they respond to mutations in the VWF gene.

One of our biggest challenges is to understand these factors and the interplay between them, so that we

can understand the relationship between VWF genotype and disease phenotype. Many of my coauthors are actively engaged in translational or clinical research to address this problem.

My laboratory is focusing on biochemical studies of how VWF multimers are assembled and how they function. Together, these approaches should lead to better diagnostic tests and treatments that are tailored for the unique needs of each patient.

SW: Do you foresee any social or political implications for your research?

I can give an example that relates to women's health, which is a social and political issue worldwide. Excessive menstrual bleeding is especially common in VWD, and is a significant cause of disability and iron-deficiency anemia. In fact, most patients with symptomatic VWD are women. Research summarized in our classification paper has led to an increased awareness of VWD as a significant medical problem, particularly for women, which I hope will result in the wider availability of treatments to improve their quality of life.

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KEYWORDS: ADAMTS-13; CLASSIFICATION; PATHOPHYSIOLOGY; VON WILLEBRAND DISEASE.

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Figures and descriptions:

Figure 1:

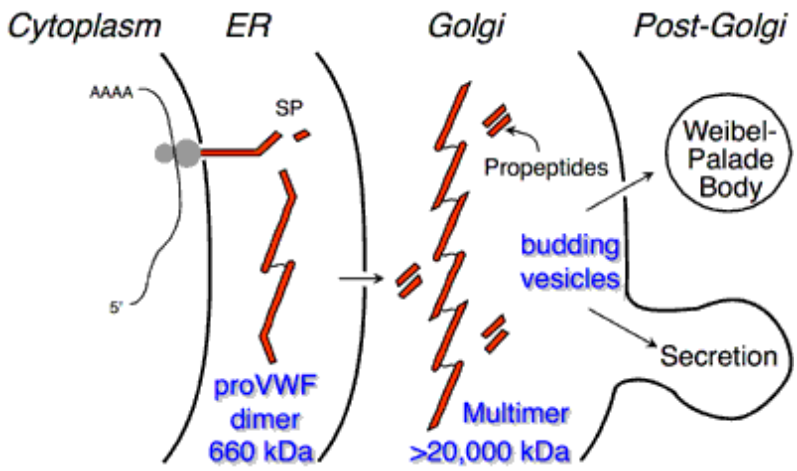

Figure 1: Biosynthesis of VWF. The VWF precursor is translocated into the ER, where the signal peptide (SP) is cleaved and disulfide bonds form between C-terminal domains to yield proVWF dimers. In the Golgi, disulfide bonds form between N-terminal domains to yield multimers, and the propeptide is cleaved. Multimers are secreted or packaged into Weibel-Palade bodies for later secretion.

Figure 2:

Primary classification of VWD:

- **Type 1** = partial quantitative deficiency of VWF
- **Type 2** = qualitative VWF defects
- **Type 3** = virtually complete deficiency of VWF

Secondary classification of VWD:

- **Type 2A** = decreased VWF-dependent platelet adhesion *without* large multimers
- **Type 2B** = increased affinity for platelet GPIb
- **Type 2M** = decreased VWF-dependent platelet adhesion *with* large multimers
- **Type 2N** = markedly decreased binding affinity for factor VIII

Figure 2: Classification of VWD.

Figure 3:

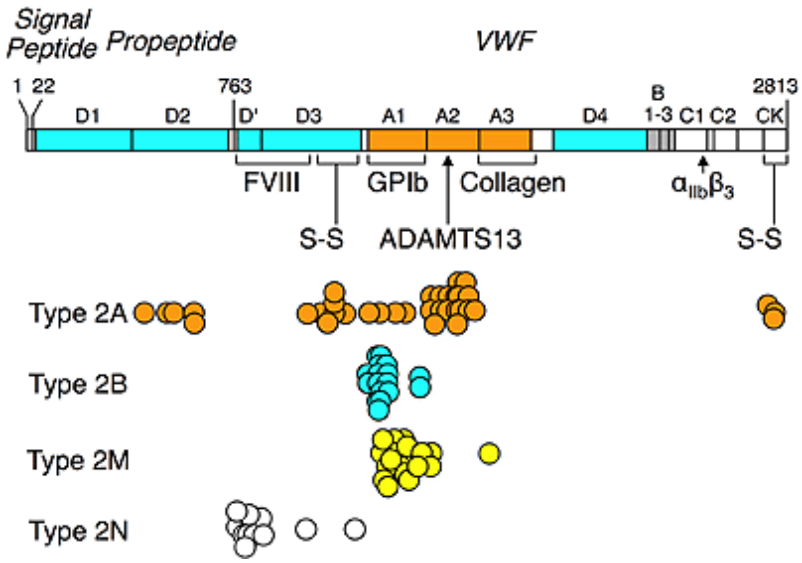

Figure 3: Mutations in VWD type 2. The VWF precursor consists of a signal peptide (residues 1-22), propeptide (residues 23-763), and mature subunit residues 764-2813. Structural motifs are labeled. Locations are indicated for intersubunit disulfide bonds (S-S); binding sites for factor VIII, platelet GPIb, fibrillar collagen, platelet integrin aIIbß3; and the site cleaved by the metalloprotease ADAMTS13. Circles show the location of mutations known to cause VWD type 2A (orange), 2B (blue), 2M (yellow), and 2N (white).

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