

AHCDC von Willebrand Disease Scientific Sub-Committee

Annual Report 2006-2007

Members

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Activities:

- a) The molecular basis of Type 1 VWD
- b) Quality of life assessment in VWD
- c) Observational study of DDAVP in VWD
- d) Von Willebrand disease in pregnancy
- e) The genetics of type 3 VWD
- f) Type 2B/Platelet type VWD Registry
- g) Prophylactic therapy for VWD

A. The molecular basis of type 1 VWD (PI. David Lillicrap)

The results of the mutation analysis performed as part of the Canadian type 1 VWD study has recently been published in *Blood* (*Blood* 109:145-54, 2007). This study has shown that in the 123 index type 1 VWD cases investigated, 37% showed no evidence of a candidate *VWF* gene mutation. The analysis identified 50 different putative *VWF* mutations; 31 (62%) missense mutations, 8 (16%) changes involving the *VWF* transcriptional regulatory region, 5 (10%) small deletions/insertions, 5 (10%) splicing consensus sequence mutations, and 1 nonsense mutation. Twenty-one of the index cases had more than one putative *VWF* mutation identified but these cases did not show more severe VWD phenotypes. We were more likely to identify putative mutations in cases with lower VWF levels, and the contribution of other factors, such as ABO blood group seems more important in milder cases. Taken as a whole, the results of the study support a complex spectrum of molecular pathology resulting in the quantitative trait, Type 1 VWD. In more severe cases, genetic changes are common within the *VWF* gene and are highly penetrant. In milder cases, the genetic determinants are more complex and more likely to involve factors outside of the *VWF* gene. Our understanding of the molecular pathogenesis of type 1 VWD is still in its infancy, and further mechanistic studies are now in progress as part of a NIH-funded program project grant with investigators in Milwaukee (Drs Montgomery and Haberlichter) and Sheffield (Drs Goodeve and Peake).

B. Quality of life assessment in VWD (PI Ronnie Barr)

This multicenter study evaluating the influence of VWD on QoL will close enrollment in 2007. Standardized and validated QoL questionnaires have been completed by a large VWD population and correlated with the patients' Hb and serum ferritin levels. An abstract describing preliminary results from the project were presented at the 2006 WFH meeting in Vancouver.

C. Observational studies of DDAVP in VWD (PI Augusto Federici)

This study has been organized by the VWF Scientific Subcommittee of the ISTH. Two Canadian centers, Toronto (HSC) and Kingston, have enrolled VWD 15 patients into the study which has now recruited >220 VWD patients worldwide to evaluate their response to DDAVP.

D. Von Willebrand Disease in Pregnancy (PI Christine Demers)

This study is co-sponsored with the Women's bleeding disorder sub-committee. The aim of the study is to characterize the levels of VWF and FVIII in normal women and women with VWD during and immediately after pregnancy. Post-partum blood loss is also being quantified through validated methods. This study is now being supported by the Canadian Hemophilia Society.

E. The Genetics of type 3 VWD (PI Paula James)

This CHS-sponsored study has begun to enroll "nuclear trios" from families with type 3 VWD. The causative mutations in these families are being investigated in the reference laboratory in Kingston and the pattern of these mutations compared to the spectrum of mutations already documented in the Canadian type 1 VWD population. The study hypothesis is that the type 3 and type 1 mutations will show little overlap and that many more null mutations will be documented in the type 3 population.

F. Type 2B-Platelet type VWD Registry (PI Maha Othman)

The differentiation between type 2B VWD and platelet type VWD (PT-VWD) is notoriously difficult with standard phenotypic studies. However, the treatment of the two conditions is distinct (VWF concentrates in type 2B VWD and platelet concentrates in PT-VWD). All cases of PT-VWD have, to date, been associated with heterozygous mutations in the Glycoprotein Iba gene which has a single coding exon. In contrast, all type 2B VWD mutations localize to exon 28 of the VWF gene. Thus, differentiation of these very similar disorders can readily be

established by genetic testing using a stable and easily transportable substrate (genomic DNA). The Kingston mutation testing laboratory has now received additional supplementary funding to evaluate cases of phenotypically-defined type 2B VWD to see how many of these cases are in fact PT-VWD. This study will be enrolling subjects from the international VWD community and is sponsored by the ISTH VWF SSC.

G. Prophylactic treatment of VWD (PIs Berntorp and Abshire)

A protocol for a new international multicenter study of prophylactic therapy in patients with VWD that experience recurrent mucocutaneous or musculoskeletal bleeding is being developed. The AHCDC has been represented in these discussions by Drs Carcao and Winikoff.