

AHCDC von Willebrand Disease Scientific Sub-Committee

Annual Report 2009

Members

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Activities:

- a) The molecular basis of Type 1 VWD
- b) Quality of life assessment in VWD
- c) Von Willebrand disease in pregnancy
- d) The genetics of type 3 VWD
- e) Evaluation of a validated bleeding score in children
- f) Type 2B/Platelet type VWD Registry
- g) Prophylactic therapy for VWD
- h) Genome-wide association study for mucocutaneous bleeding

A. The molecular basis of type 1 VWD (Investigators: Drs Lillicrap, James, Blanchette, Rand)

Studies to better understand the molecular pathogenesis of type 1 VWD continue in the Kingston laboratory. Current activities are focused in three main areas: several of the putative transcriptional mutants are in the process of being characterized to determine their functional significance. A manuscript describing the detailed characterization of one of these mutants is currently undergoing revision for Blood. Second, several putative splicing mutants are being assessed to determine the role of aberrant RNA processing in type 1 VWD. Finally, studies are also underway to evaluate alternative pathogenetic mechanisms in the patients in whom a VWF mutation has yet to be identified. An extension of the initial Type 1 VWD study has also been completed in a pediatric patient cohort from Sick Kids in Toronto (23 index cases and 62 family members). A manuscript describing these results will be submitted to JTH later this year.

B. Quality of life assessment in VWD (Investigator: Dr Barr)

This multicenter study evaluating the influence of VWD on QoL closed enrollment in 2007. Further financial support to enable analysis of the collated data has been obtained from the CHS. This analysis has now been completed and a manuscript is due to be submitted to Haemophilia.

C. Von Willebrand Disease in Pregnancy (Investigator: Dr. 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 using pictorial charts. This study has now been completed, and the results are in the process of being compiled into a manuscript.

D. The Genetics of type 3 VWD (Investigator: Dr. James)

This study is enrolling “nuclear trios” from families with type 3 VWD. Enrollment has now been completed for 37 type 3 VWD families comprising 136 family members (75 affected and 61 unaffected/status unknown). The causative mutations in these families are being determined and the pattern of these mutations compared to the spectrum of mutations already documented in the Canadian type 1 VWD population.

E. Evaluation of a validated bleeding score in children (Investigators: Drs James, Silva, Blanchette, Rand)

Using a modified version of the previously validated MCMDM-1 (“Vicenza”) bleeding questionnaire, a study has been completed to evaluate the potential utility of this score in a pediatric population. This study has added new pediatric-specific bleeding questions to the previously utilized abbreviated MCMDM-1 questionnaire. The study has evaluated a population of 142 healthy children (in collaboration with Jim Riddell, Nurse Coordinator at the Oakland Children’s Hospital Hemophilia Program) and children with previously diagnosed mucocutaneous bleeding disorders. A bleeding score of >2 was found to be positive in this study. A manuscript reporting this study is in press in the Journal of Thrombosis and Hemostasis.

F. Type 2B-Platelet type VWD Registry (Investigators: Drs Othman and Lillicrap)

The differentiation between type 2B VWD and platelet type VWD (PT-VWD) is notoriously difficult with standard phenotypic studies. The Kingston mutation testing laboratory has now received additional supplementary funding from the CHS to evaluate cases of phenotypically-defined type 2B VWD to see how many of these cases are in fact PT-VWD. This study is enrolling subjects from the international VWD community and is sponsored by the ISTH VWF SSC. There is also an internet registry site containing detailed information about this disease (<http://www.pt-vwd.org/>).

G. Prophylactic treatment of VWD (Investigators: Drs Carcao and Winikoff)

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

H. Determinants of novel genetic influences of mucocutaneous bleeding – GWAS project (Investigators: Drs James and Lillicrap)

The pathogenetic basis of many cases of mucocutaneous bleeding remains unresolved. With this in mind, there are plans to perform a large multicenter and multinational genome wide association study correlating the phenotype of bleeding (evaluated with a validated bleeding score) with genetic variation (SNPs) throughout the genome. Dr. James has been funded through the BChERP grant competition to undertake this study.