[O-T-066] REGULATION OF PLASMA VON WILLEBRAND FACTOR (VWF) BY MODIFIER GENES

J.A. Shavit, H.L. Lemmerhirt, D. Ginsburg. Pediatrics; Human Genetics; Internal Medicine and Human Genetics, University of Michigan, Ann Arbor, United States

Introduction: Plasma VWF levels are highly variable in the normal human population, and two-thirds of this variability is due to heritable factors (modifier genes). These modifiers contribute to the wide variability in bleeding among patients with VWD (von Willebrand disease), as well as the difficulty in establishing this diagnosis. We previously mapped four loci responsible for variable VWF levels among several inbred mouse strains, which we termed *Mvwf1-4* (modifier of *Vwf*).
Methods: We chose inbred strains with 3.5-fold divergent VWF plasma levels, C57BL/6J and WSB/EiJ, neither of which carries the *Mvwf1* or *Mvwf2* alleles. F1 hybrid mice were backcrossed onto C57BL/6J to generate 200 N2 progeny. Plasma VWF levels were determined by ELISA and each mouse was genotyped with 149 markers spanning the genome.
Results: We identified two major candidate loci with linkage to VWF levels. The first locus (*Mvwf5*) mapped to the *Vwf* gene itself on chromosome 6, with a logarithm of the odds (LOD) score of 12.1. Analysis of *Vwf* mRNA from F1 mice showed that *Mvwf5* exerts its effect at the level of mRNA transcription or stability. A second potential modifier (*Mvwf6*) localized to chromosome 10 with a LOD score of 4.6, and displayed additive effects with *Mvwf5*. Two additional loci mapped to chromosomes 4 and 5, with LOD scores of 2.4 and 3.4, respectively. The former locus maps to the same region of chromosome 4 as *Mvwf3*, a candidate modifier from mouse strains A/J and CASA/RkJ.
Conclusions: We have identified a 2nd natural *Vwf* gene variant among inbred mice (*Mvwf5*), a novel VWF regulatory locus on murine chromosome 10 (*Mvwf6*), and 2 other possible VWF modifiers on chromosomes 4 and 5. Surprisingly, two of six *Mvwf* loci characterized to date correspond to hypomorphic mutations at the *Vwf* gene itself and appear to interact with modifier loci on other chromosomes. Similar interactions are likely to explain the extensive variability in plasma VWF levels observed in the general human population as well as among patients with VWD.
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