The factor V Leiden mutation results in the *in vivo* loss of a critical FV anticoagulant function

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The Factor V Leiden (FVL) mutation is the commonest thrombotic risk factor in humans. Heterozygous carriers have an approximately 10% lifetime incidence of venous thrombosis, compared to 80% in homozygotes. FVL is resistant to degradation by Activated Protein C (APC), resulting in prolonged factor V (FV) prothrombinase cofactor activity. *In vitro* studies suggest that FV can serve as a cofactor for APC in the inactivation of Factor VIIIa, with FVL demonstrating a reduced cofactor activity. To address the relative *in vivo* contributions of these mechanisms to thrombosis associated with FVL, we examined crosses among genetically engineered mice heterozygous deficient for FV (Fv+/-) or tissue factor pathway inhibitor (TFPI, Tfpi+/-), homozygous or heterozygous for the FVL mutation (FvQ/Q or FvQ/+), or carrying either a liver specific (MalbFvTg+) or platelet specific (Pf4FvTg+) FV transgene. Analysis of offspring from an intercross between FvQ/- and FvQ/Q mice demonstrated a reduction in the survival of FvQ/- mice compared to FvQ/Q (49 vs. 113 out of 162 total offspring, expected ratio is 1 : 1, $p < 0.05$). We recently reported synthetic thrombotic lethality of the FvQ/Q and Tfpi+/- genotypes. Analysis of FvQ/- mice in the setting of reduced TFPI demonstrated a similar uniform lethality for the FvQ/- Tfpi+/- genotype, in contrast to the normal survival of FvQ/+Tfpi+/- mice. Introduction of either the MalbFv or Pf4Fv transgenes into this cross resulted in partial rescue of the lethal FvQ/- Tfpi+/- phenotype. These data confirm the association of homozygous FVL with a more severe thrombotic phenotype than in heterozygotes. These findings identify the critical mechanism for this enhanced thrombosis as loss of a wild-type-specific activity, rather than increased APC resistance. This critical wild type FV function can be provided by either the platelet or plasma FV pool. These findings have important implications for the role of FV in the regulation of hemostatic balance.

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