A sensitized ENU mutagenesis screen for dominant genetic modifiers of thrombosis in the factor V Leiden mouse

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Venous thrombosis affects approximately one in a thousand individuals per year. A gain-of-function in the factor V gene, factor V Leiden (FVL) is the most common known inherited risk factor for venous thrombosis. Penetrance is incomplete, with only ~10% of FVL individuals experiencing clinically significant thrombosis in their lifetimes. We are performing a whole genome mutagenesis screen to identify candidates for the modifier genes responsible for the incomplete penetrance and variable expressivity of FVL in humans. Previously, we demonstrated synthetic lethality between FVL and genetic deficiency of a key coagulation pathway regulatory factor, tissue factor pathway inhibitor (TFPI). Complete TFPI deficiency in mice is embryonic lethal, whereas heterozygosity is compatible with normal survival. However, homozygosity for FVL (FvQ/Q) in the context of heterozygosity for TFPI (Tfpi+/-) is uniformly lethal due to disseminated perinatal thrombosis. This synthetic lethal interaction was utilized as a phenotyping tool for a sensitized ENU mutagenesis screen. We aim to uncover novel dominant mutations that improve hemostatic balance leading to survival of FvQ/Q Tfpi+/- mice. Male FvQ/Q mice were mutagenized with a single ENU dose of 150 mg/kg, bred to FvQ/+ Tfpi+/- double heterozygous females. Surviving G1 offspring were analyzed to identify rescued mice with the FvQ/Q Tfpi+/- genotype. Analysis of 284 G1 offspring to date has identified six mice that survived to weaning, with two rescued animals surviving to >5 months of age. Based on these results, an expanded screen is underway, along with efforts to map the currently identified rescuing mutation.

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