

F8-deficiency in mice is associated with increased von Willebrand Factor (VWF) content in the hepatic endothelium and with increased VWF plasma levels

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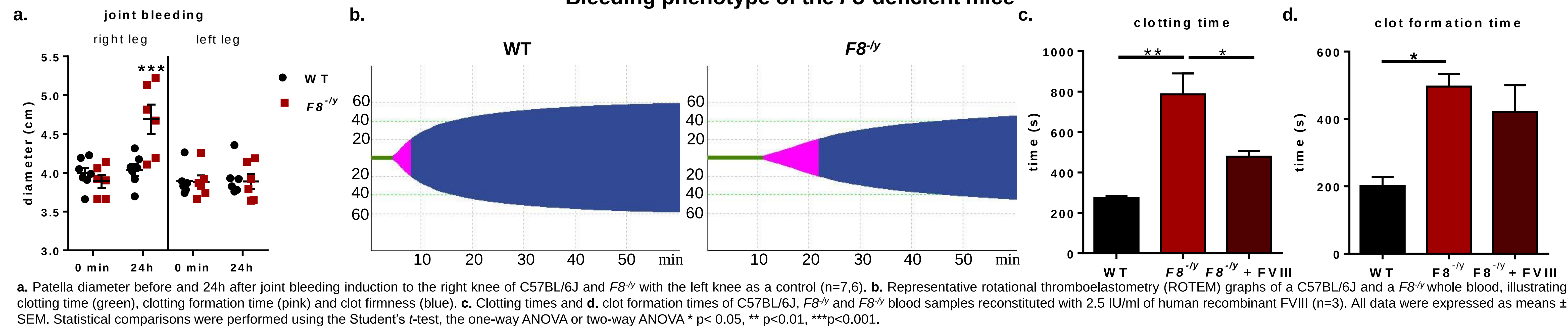
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Background

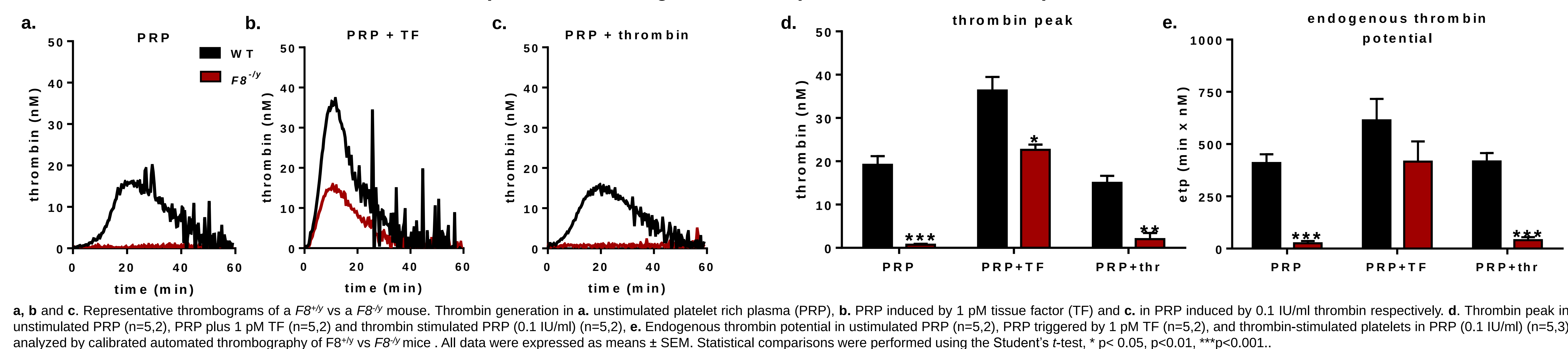
The anti-hemophilic coagulation factor FVIII is synthesized in the liver sinusoidal endothelium and co-stored together with von Willebrand Factor (VWF) in Weibel-Palade bodies of endothelial cells. While VWF is recognized as the carrier molecule of FVIII in plasma, stabilizing FVIII activity by preventing proteolytic degradation¹, the possible impact of *F8*-deficiency on VWF plasma levels is unresolved. The *F8*-deficient mouse model is a useful tool to study hemophilia A, avoiding the confounding variables deriving from the heterogeneity of the disease. Therefore, we used a hemophilia A mouse model with disrupted exon 16 of the *F8* gene², which we back-crossed onto a pure C57BL/6J genetic background. In addition to the hemostatic, bleeding, and coagulation characteristics, we analyzed littermates from heterozygous breedings for their hepatic endothelial VWF content, VWF plasma levels, VWF multimer size and quantified the expression of the VWF modifier gene, CMP-N-acetylneuraminate-beta-galactosamide-alpha-2,3-sialyltransferase 4 (ST3GAL4).

Results

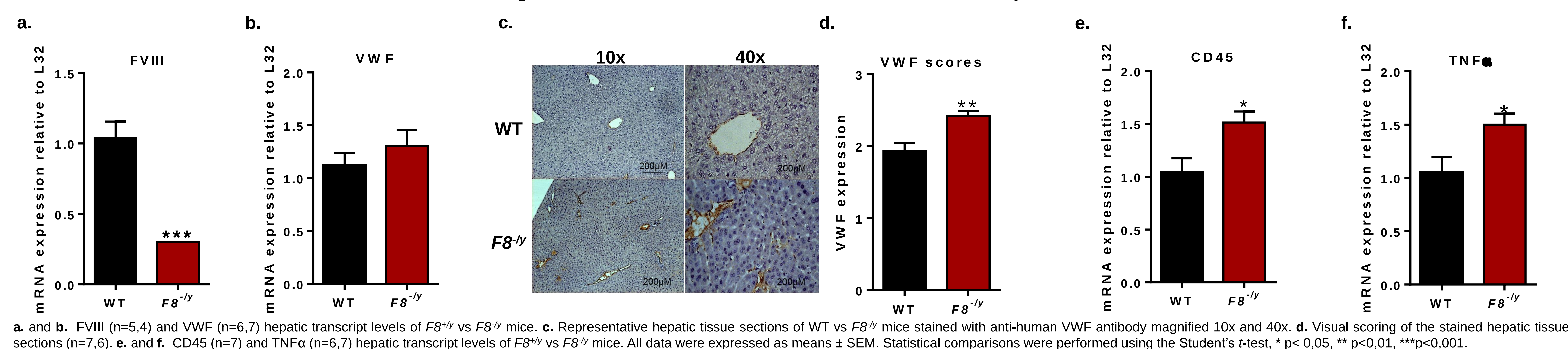
Bleeding phenotype of the *F8*-deficient mice



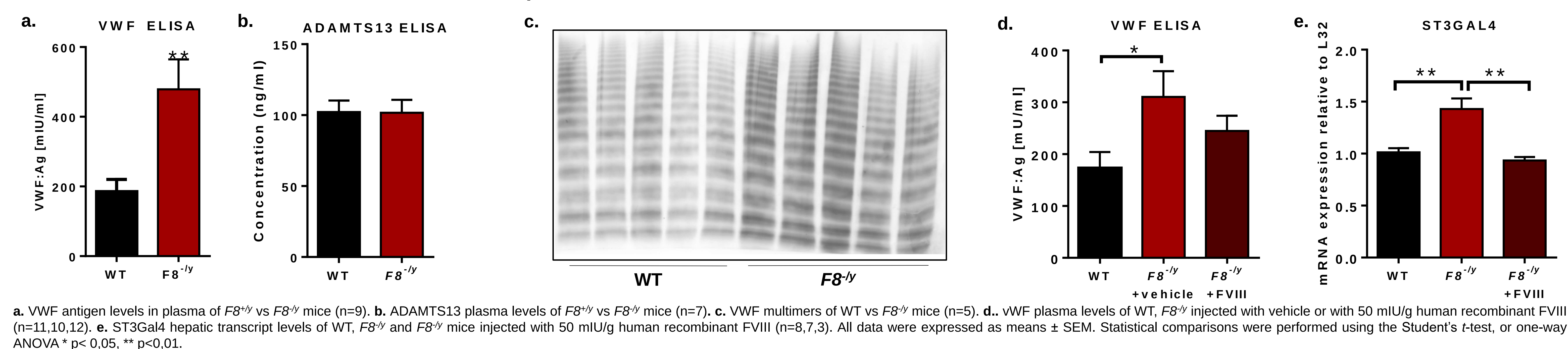
Impaired thrombin generation of platelets in *F8*-deficient plasma



F8-deficient mice show signs of inflammation in the liver and increased hepatic endothelial VWF content



VWF plasma levels are elevated in *F8*-deficient C57BL/6J mice



Conclusion

F8^{-/-} mice on the C57BL/6J background show the expected bleeding phenotype, but also an increased VWF expression in the liver endothelium together with increased VWF plasma levels and hepatic inflammation. This increase could potentially be explained by the increased hepatic ST3Gal4 expression. Reconstitution of human recombinant FVIII rescues the bleedind phenotype as well as the increased VWF plasma levels and reduces the hepatic ST3Gal4 transcript levels.

References:

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- Bi L, Lawler AM, Antonarakis SE, High KA, Gearhart JD, Kazazian HH Jr. Targeted disruption of the mouse factor VIII gene produces a model of haemophilia. *Nat Genet.* 1995;10:119-21.

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