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So, why is it that a minority of patients develops inhibitors and that the majority of patients is seemingly tolerant to the foreign FVIII protein? What we know is that inhibitor development is caused by an intricate interplay of both genetic and environmental factors (see figure).6,8 Astermark and colleagues have demonstrated that the F8 genotype and other markers in immune response genes are major players in the field.6 These genetic markers of inhibitor development include HLA class II alleles and several single nucleotide polymorphisms (SNPs) in immune response genes.7,9

Still, further insight into the etiology of inhibitor development is urgently needed. If it is possible to predict a specific patient’s individual risk of developing inhibitors, individualized treatment regimens or modification of immunologic factors in high-risk patients could possibly prevent inhibitors. Moreover, identification of immunologic pathways to inhibitor development may provide novel therapeutic targets to prevent inhibitors. So, how to push forward in the quest toward the prediction and prevention of inhibitor development?

In the current study, Astermark et al endeavored to unravel the genetic susceptibility for inhibitor development. This enormous challenge required a substantial number of patients. The authors joined hemophilia researchers worldwide and succeeded in studying 833 patients by combining cohorts from 3 different studies. An evaluation of 13 331 SNPs in primarily immune response and immune modifier genes yielded 53 SNPs that predicted inhibitor status in all cohorts. Of these, 13 markers were statistically significantly associated with inhibitor development in the combined cohort (meta P values < .001). In addition, 8 of the 53 SNPs were significant predictors among the discordant brother pairs. The identified genetic markers are known to be involved in various B and
ultimately not only benefit those with hemophilia, but possibly also a wider group of patients with auto-immune diseases.

Conflict-of-interest disclosure: S.C.G. has reported receiving unrestricted research support from ZLB Behring, Novo Nordisk, Wyeth, Baxter, and Bayer. K.F. is a member of the European Hemophilia Treatment and Standardization Board sponsored by Baxter, has received unrestricted research grants from CSL Behring and Bayer, and has given lectures at educational symposiums organized by Pfizer and Bayer.

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Comment on Hategan et al, page 1455

Counting 1 fibrin molecule at a time

Robert A. S. Ariëns1 | UNIVERSITY OF LEEDS

In this issue of Blood, Hategan et al report on the development of a novel method to study single molecule kinetics of fibrin polymerization.1

Each fibrin fiber is composed of thousands of fibrin molecules in width (diameter). For example, a fiber with a thickness of 400 nm consists of around 5000 fibrin molecules in diameter, and a fiber with a diameter of 900 nm consists of 25 000 molecules. Data based on Hategan et al.1 Schematic representation; not drawn to scale. Fiber is only part filled.

Using total internal reflection fluorescence microscopy (TIRFM), Hategan and colleagues are able to follow in real time the addition of individual fibrin molecules to growing fibrin fibers during clot formation. In essence, the authors base their calculations on steps of

COMMENT THROMBOSIS & HEMOSTASIS

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Unraveling the genetics of inhibitors in hemophilia

Samantha C. Gouw and Karin Fijnvandraat