diagnosis of undefined primary hemostatic disorder. Only highly qualified centers where more specific tests are available may take on the task of further evaluation. The platelet physiology subcommittee of the International Society of Thrombosis and Haemostasis (ISTH) has dedicated its work during recent years to searching for ways to improve and standardize platelet function testing, applying platelet aggregometry, the PFA-100 device, and a proteomics approach.2-4

This report also raises the issue of the gap between genotype and phenotypic expression in hereditary diseases. The D304N substitution was observed in the index patient, who presented with mild bleeding symptoms, and in his father, who had no history of bleeding. As in other cases, a search for modifier genes and for other factors might shed light on this differential phenotypic expression. Thus, the genetic background of a disease does not always explain all phenotypes, and a search for genetic and environmental modifiers should be considered for a more comprehensive understanding of this entity.

Improved understanding of the complex, multiple pathways of platelet activation is significantly contributing to the development of new antiplatelet drugs. Antiplatelet drug therapy is currently undergoing a dramatic revolution, including novel observations on platelet drug resistance, more refined dose adjustment, and development of more potent and safer new drugs. One such example is the development of new TxA2 R inhibitors. Such inhibitors are potentially more effective than aspirin because of their inhibitory effect on endothelial cell TxA2 R as well.

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Computed 3-dimensional structure of the human TxA2 receptor. Adapted from Chou.6
anti–factor H (anti-fH) autoantibodies and that these autoantibodies have functional consequences similar to those caused by the prototypical mutations in the C-terminal region of factor H.2,3 On the basis of these genetic and functional data, it is well established that aHUS is a disease of complement dysregulation. Accordingly, it is believed that in persons carrying the aHUS-associated mutations or developing anti-fH autoantibodies, conditions that trigger complement activation, resulting in deposition and amplification of C3b on the kidney microvasculature endothelial cells, cannot be controlled. This culminates in tissue damage and destruction.

Moore et al in this issue of Blood provide clinical data from 13 cases with anti-fH autoantibodies in the Newcastle cohort that further support their relevance in aHUS pathogenesis.1 Most importantly, they show for the first time that some of these aHUS patients also carry mutations (or polymorphisms) in other complement genes previously associated with increased risk for aHUS. Occurrence of multiple different risk factors is relatively common among aHUS patients and has been invoked as an explanation for the incomplete penetrance of aHUS (close to 50%) in carriers of mutations in the complement AP proteins.5 The concurrence of genetic defects and autoantibodies, therefore, reinforces the idea that multiple hits in complement components are necessary for the development of aHUS in some patients. In addition, it indicates that autoantibodies and mutations may contribute in a similar way to aHUS pathogenicity.

Why do some persons develop anti-fH autoantibodies that mimic the aHUS-associated CFH mutations? The available data suggest that there may be a genetic component to the origin of the anti-fH autoantibodies. In fact, it is well documented that they often concur with homozygosity for a 80-kb-long genomic deletion encompassing the CFHR1 and CFHR3 genes.6 Moore et al in this issue of Blood and Abarrategui Garrido and colleagues in a previous one analyzed this question in detail and established a specific relationship between the deficiency of the complement factor H–related 1 (CFHR1) protein and the generation of anti-fH antibodies associated with aHUS. This is an intriguing association for which there is now no clear explanation. Interestingly, these autoantibodies recognize the C-terminus of factor H, a region critical for the development of aHUS that is nearly identical in CFHR1, and not surprisingly, they cross-react with CFHR1. Moore et al suggest that deficiency of CFHR1 may result in a failure of central and/or peripheral tolerance to the homologous region in factor H, but there are other possibilities including cross-reactivity with microbial antigens. Answering these questions may require a better understanding of the role of CFHR1. Moreover, searches for additional genetic and environmental factors associated with these autoantibodies may help to explain why despite being the CFHR1 deficiency so frequent in the normal population (~ 4%), only a few persons develop them.

The available evidence from aHUS patients associates the presence of the anti-fH antibodies with the onset or disease recurrences. The data also suggest that the titer of autoantibodies may spontaneously decline with time. This may explain retrospectively a significant number of aHUS cases for whom no genetic defect in the complement genes has been found and argues for implementing a standardized routine autoantibody screening at the aHUS onset.

Understanding aHUS risk factors is of high potential interest, given the current promises of therapies for aHUS patients. In this respect, it is encouraging that behind the apparent complexity of many different risk factors associated with aHUS, the “autolesion” by complement is envisioned as the single pathogenic mechanism underlying this disorder. This is good news because, in addition to the potential for individual aHUS patients benefiting from specific therapies, inhibitors blocking activation of the complement AP may represent a universal therapy for all of them.

There is still much more to be learned about autoantibodies against complement pathways.
components. Future studies warrant novel and exciting data that will improve our knowledge of aHUS and other human disorders.

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aHUS: a disorder with many risk factors

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