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EDITORIAL

Genomic momentum for hemostasis and thrombosis

As biomedical scientists and clinicians, we are fortunate to live at a time when the potential translational benefits of genetic knowledge have never been better. When Francis Crick wrote to his son Michael in 1953, informing him that, "Jim Watson and I have probably made a most important discovery…Our structure is very beautiful", one suspects that not even he could have predicted the advances that would derive from this revelation over the next 65 years.

Since the initial publication of the Human Genome Project results in 2001 and the subsequent utility of next generation sequencing approaches in the past decade, the speed of genomic knowledge advancement has been remarkable. The field of hemostasis and thrombosis has remained at the forefront of these advances since the early 1980s when the genes implicated in the most common inherited bleeding disorders, *F8*, *F9* and *VWF*, were among the first human genes to be cloned and characterized. Soon after these discoveries, initial molecular genetic testing became available for the hemophilias and von Willebrand disease, and recombinant clotting factor concentrates were first used as replacement therapies in hemophilia in 1989.

Against this background of enthusiastic engagement in genomic science of the thrombosis and hemostasis community, a new Scientific and Standardisation subcommittee of ISTH was proposed in 2011. This initiative was led by Willem Ouwehand, who subsequently became the first chairperson of the SSC on Genomics in Thrombosis and Hemostasis. In this issue of the journal, this Subcommittee reports their progress in curating a list of disease-causing genes for bleeding, thrombosis, and platelet disorders (BTPD).

The SSC initiative to generate a list of curated genes causing BTPDs began in 2014 and the current list includes 91 genes that are inherited as germline mutations (the PIGA gene that acquires somatic mutations in paroxysmal nocturnal hemoglobinuria is the single non-germline association). Of this list of 91 disease-causing genes, 21 result in coagulation factor deficiencies and bleeding, 9 in thrombotic disease and 61 in disorders of platelet number and/or function. This list only includes Tier 1 or diagnostic grade genes that have been identified through the application of the following criteria: evidence of supportive genotype-phenotype co-segregation in at least three genetically independent families, robust support from functional studies and/or a mouse model that recapitulates the human phenotype where less than three affected families are known.

Tier 2 and 3 genes represent loci for which peer-reviewed literature support is limited often to single kindreds, and for which functional studies and/or mouse models have yet to provide conclusive evidence to be linked to a human disease resulting in bleeding or thrombosis. While the current list of 91 curated Tier 1 genes provides the thrombosis and hemostasis community with a substantial foundation to initiate molecular diagnostic testing in patients and their families, a sustained effort will be required to review the status of current Tier 2 and 3 genes, and other newly identified loci with possible hemostatic associations. This effort has recently been aided by the establishment, in 2017, of a Clinical Domain Working Group for Thrombosis and Hemostasis within the Clinical Genome Resource, ClinGen. This Working Group has a substantial ISTH connection.

In 2019, the molecular testing for patients with inherited BTPDs is increasingly likely to involve a next generation sequencing gene panel strategy, with the simultaneous evaluation of all 91 candidate Tier 1 genes. The information derived from these studies can be applied to personal and family counseling, optimization of therapy and disease prognostication.

Overall, over the past decade, enormous progress has been made in advancing our genomic knowledge of BTPD causing genes. However, as is often the case with genetic advances, caution must be maintained where the possibility of incidental findings may have long-term consequences such as the association of premalignant genetic variants in some genes causing inherited thrombocytopenia. Nevertheless, in aggregate, the advances in genomic science in our field have undoubtedly been beneficial, both in terms of increasing scientific knowledge and in its application to clinical care. The ISTH SSC on Genomics in Thrombosis and Hemostasis is playing a key role in this process.

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