## ThromboGenomics

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Hemostasis is organised by interplays between platelets, coagulation, and fibrinolysis. DNA variants in genes that encode for regulators of these three processes are known to cause inherited forms of bleeding or thrombosis. Over the last decade, next generation sequencing (NGS) has been applied for the clinical diagnostics of these conditions. To date, nearly 100 curated disease-causing genes have been identified to cause inherited bleeding, platelet, or thrombotic disorders (the full gene list can be downloaded from www.isth.org/page/GinTh_GeneLists).[1] This gene list is dynamic and receives yearly updates during the meeting of the ISTH SSC Subcommittee on Genomics in Thrombosis and Hemostasis (SSC-GinTH). This list is epically useful for clinical labs that implemented (virtual or targeted) multigene panel tests to diagnose inherited bleeding or thrombotic disorders. Such NGS-based panel is a cost-effective approach to rapidly screen patients. The international study ThromboGenomics has shown that diagnostic rates obtained for thrombocytopenia, platelet function, coagulation and thrombotic disorders are 47.8%, 26.1%, 63.6% and 48.9%, respectively, while this rate dropped to 3.2% for patients with unexplained bleeding disorders (having normal laboratory test parameters) using a targeted multigene panel test.[2] High diagnostic rates were obtained for patients with abnormal laboratory test data for (anti-)coagulation parameters or with low platelet counts while patients with the platelet function disorder 'storage pool disease' or having an unexplained bleeding disorder are typically associated with very low diagnostic rates as the causative genes for these conditions are still unknown. Of interest, is also the unexpected finding of oligogenic inheritance where patients have variants in more than one gene.

Though multigene panel tests have been proven successful, there are still many potential pitfalls when interpreting the role of novel rare variants and it is important to apply rigorous standards when assigning 'variant pathogenicity'. Providing a molecular diagnosis to patients is highly desirable as this might alter clinical management and provides important information for counseling, however making incorrect assumptions about variants could be harmful. For that reason, guidelines for variant interpretation have been developed that are similar for all rare diseases based on the criteria developed by American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) that proposed a variant classification system using five levels: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, and pathogenic. Examples will be given for variant interpretation and tools to score variant pathogenicity. We will also touch on ethics, consenting and incidental findings with specific examples taken for bleeding and thrombotic disorders. Today, this field still struggles with the detection of numerous VUS that can't be used in clinical practice. These VUS require further functional and genetic studies to proof pathogenicity. Rapid screening models and data exchange with the community could improve the variant classification. The GoldVariants database[3] was developed by the SSC-GinTH to capture variants related to bleeding and thrombosis.

**References**

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