Bleeding disorders - Section 2

Genetic basis of platelet disorders

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Inherited platelet disorders (IPD) are characterized by marked genetic heterogeneity, far greater than previously appreciated.[1] The list of genes involved in the regulation of megakaryopoiesis, platelet formation and function is rapidly growing since the introduction of next generation sequencing (NGS) approaches[2-14] to improve genetic diagnosis of IPD patients with or without bleeding problems and often other clinical symptoms that are not related to the blood system.[15] Based on studies in patients with inherited thrombocytopenia, it became obvious that in addition to thrombopoietin, the transcriptional regulation and cytoskeletal organization of megakaryocytes is essential for normal platelet production.[1] Though most IPD with abnormal granules have a normal platelet count, granule biogenesis takes place during megakaryopoiesis and some molecular players have been discovered but this process is not well studied. Finally, some gene defects only affect platelet function and also in this group, different pathways are important. Figure 1 shows the different IPD genes and their mode of inheritance, grouped

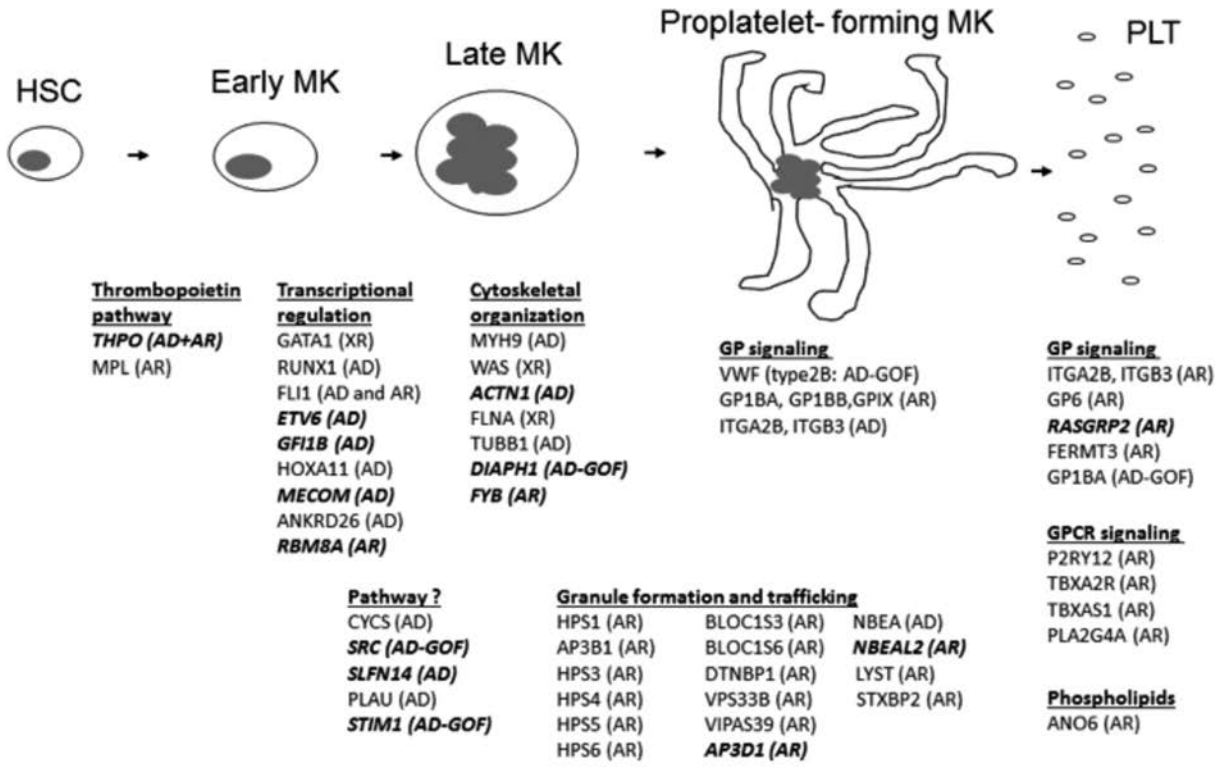

Figure 1. Simplified schematic presentation of the genetic regulation of megakaryopoiesis and platelet formation and function. Megakaryocytes (MK) differentiate from hematopoietic stem cells (HSC) in the bone marrow and undergo dramatic changes in content (e.g. granule formation) and morphology to form platelets. The most important regulators of megakaryopoeisis are the thrombopoietin pathway and some lineage-specific transcription factors. Cytoskeletal reorganizations in the MK are essential to form platelets. The glycoproteins (GP) and G protein-coupled receptors (GPCR) are mainly known be important for platelet formation. For some genes, the biological pathways are not really well defined. The IPD genes known to cause a defect in platelet count and/or function have been added to this overview and the mode of inheritance was mentioned (autosomal recessive; AR, autosomal dominant; AD or X-linked; AR). Different IPDs are caused by a gain-of-function (GOF) mutation.

according to their expected function in platelet biology. Interestingly, NGS studies have not only introduced a new era in the fields of molecular medicine but have also identified completely unexpected players that now deserve further detailed functional characterization. Alongside the scientific interest, genetic diagnosis is important for patients. There is increasing recognition that some IPDs are associated with severe pathologies, including an increased risk of malignancy and a definitive diagnosis can inform prognosis and care. Still many IPD patients do not receive a genetic diagnosis.[15] This would mean that much more genes will be discovered, defects are also present in the non-coding gene regions or oligogenetic inheritance is playing a role in IPDs. Bioinformatics, statistics and functional genetics will be essential for future research in this field. A next generation sequencing targeted approach has very recently been developed for platelet, thrombosis and bleeding disorders that includes the screening of these genes (www.thrombogenomics.org.uk).

References

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First application of NGS in the field of IPD with the discovery of NBEAL2 as causative gene for the Gray platelet syndrome.

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WGS that showed the first germ line SRC mutation in a syndrome for thrombocytopenia, myelofibrosis and bleeding.

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Detailed patient phenotyping using the Human Phenotype Ontology (HPO) system in combination with NGS will be used to identify novel genes for IPD.