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Genome-wide study into new gene functions in the formation of platelets

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In a study into the genetics of blood cell formation, researchers have identified 68 regions of the genome that affect the size and number of platelets. Platelets are small cells that circulate in the blood and are key to the processes of blood clotting and wound healing.

In this genome-wide study, the team used a multidisciplinary approach to successfully identify new genetic variants involved in the formation of platelets and more importantly, defined the function of genes near these variants using a series of biological analyses.

Abnormally high or low platelet counts can lead to disease. An increase in the number of platelets, or an increase in their size can lead to an increased risk for thrombotic events, like heart attacks and strokes. A very low number of platelets or platelets that do not function well, increases the risk of bleeding.

"This is a detective story starting with the initial genetic discovery, allowing us to identify new genes that could contribute to platelet associated diseases," says Professor Willem H Ouwehand, senior co-author at the University of Cambridge and NHS Blood and Transplant. "Our aim of this genome-wide meta-analysis study was to discover which genes control the size and number of platelets, to understand how these genes instruct blood stem cells to orchestrate every day the formation of billions of platelets and finally to investigate whether genes associated with heart attacks and strokes overlap with the genes that affect platelet formation."

In this collaborative study, the team first developed a prioritisation strategy that allowed them to identify and pinpoint the genes underlying the formation of platelets through biological annotations of these genes. This effort laid the foundation for the construction of a protein-protein interaction network that shows how the different genetic players interact. Finally, they analysed the role of the genes in model organisms and found their function to be conserved in evolution.

The researchers found the newly identified genes associated with platelet characteristics overlap with other genes implicated in inherited bleeding disorders. This genetic overlap suggests that this study may help discover new genes implicated in severe forms of bleeding disorders, providing evidence that the new findings will be significant in clinical research for improvements in the care of patients.

This study involved about 68,000 individuals from different ancestries (European, South & East Asian) making it the largest genome-wide meta-analysis study to be conducted globally on platelet number and volume.

"This is the largest dataset of this type ever produced, and yields a wealth of new exciting biological discoveries and insights into the genetic control of blood cell formation," says Dr Nicole Soranzo, senior co-author from the Wellcome Trust Sanger Institute. "Our findings will be relevant not only to better understand the mechanisms leading to the formation of blood cells, but also to pinpoint new genes involved in diseases with altered blood clotting."

The team examined the role of the genes they identified in the fruit fly and zebrafish. They found that reducing the activity of one of these genes, arhgef3, in fish abrogates not only the production of platelets but also of red blood cells because the blood forming cells cannot capture iron. The study has shown that the human equivalent, ARHGEF3 gene is an important new regulator of the uptake of iron from the diet.

Tropomyosin 1 is a member of a family of genes already known to be involved in the regulation of muscle contraction and plays a role in an inherited form of heart disease. This study found a novel role for this well-known protein in platelet formation.

"This study provides a paradigm for how to successfully translate genome-wide association studies into function" says Dr Christian Gieger, senior co-author from the Institute of Genetic Epidemiology at the Helmholtz Center Munich. "We have shown that biologic and functional annotation can greatly enhance our ability to interpret genetic data."

"These genes could be used in the future as new targets to develop better and safer platelet inhibitors for treatments of patients with heart attacks or strokes."

More information: Gieger et al 'New gene functions in megakaryopoiesis and platelet formation' DOI: 10.1038/nature10659

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