Exome Array Finds Rare Variants Associated with Blood Traits

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Hematological traits such as hemoglobin concentration and white blood cell count are important clinical measurements, and are used as biomarkers in medicine to inform diagnosis and prognosis. Previous genetic association studies have identified hundreds of loci that impact quantitative blood cell traits, but have not yet fully characterized the heritable component of variation between individuals. In a recent report in *Nature Genetics*, Drs. Paul Auer and Alexander Reiner and colleagues in the Public Health Sciences Division used new genotyping arrays to identify several rare mutations in protein-coding regions of the genome that affect blood cell traits. These findings demonstrate how performing exome-wide genotyping on large numbers of individuals is an effective approach for identifying novel variants that contribute to complex traits, and can complement genome-wide association studies.

To investigate the impact of rare variants on blood traits, the researchers used an exome array to genotype roughly 31,000 participants from three collaborating studies. These new assays target protein-coding variants in the genome that are rare (minor allele frequency < 0.1%) or low-frequency (minor allele frequency between 0.1 and 1%), rather than the more common variants targeted by other genotyping platforms. These genotypes were then analyzed for their association with four blood cell phenotypes: hemoglobin concentration, hematocrit levels, white blood cell count, and platelet count.

Using this approach, the authors were also able to identify missense or splice-site variants in several key hematopoiesis regulators associated with blood cell traits. These gene variants were associated with platelet count (*TUBB1*, *SH2B3*, and *JAK2*), hematocrit levels and hemoglobin concentration (*EPO* and *HBB*), and white blood cell count (*CXCR2*). Said co-senior author Reiner, "our findings highlight the contribution of rare and low-frequency coding variants of key genes involved in the regulation of hematopoiesis in contributing to the inter-individual differences in circulating blood cell counts in large cohorts of apparently hematologically healthy individuals."

Of these findings, the novel association between the *CXCR2* gene and white blood cell count is of particular interest because it required the use of gene-based tests in order to be identified. As the association is driven mainly by three independent low-frequency missense variants, this relationship

had not been detected in previous genome-wide studies. This emphasizes the relevance of gene-based tests as a tool to evaluate rare variants for their contribution to phenotypic variation.

To further support this new relationship, the researchers also looked at sequence data from families with rare, Mendelian congenital hematologic disorders. In doing so, they identified a *CXCR2* frameshift mutation that abolished ligand-induced CXCR2 signal transduction and chemotaxis in a pedigree with congenital neutropenia. By converging these two lines of evidence, said co-senior author Reiner, "we were able to identify causal missense variants in the chemokine receptor *CXCR2* which lead to lower circulating white blood cell and neutrophil counts by inhibiting neutrophil release from the bone marrow."

To follow-up these findings, the authors are planning to continue bringing together and leveraging multiple lines of evidence. Said Reiner, "an important next step will be to integrate the new blood cell count-associated genetic loci with available blood cell lineage-specific human transcriptomic, functional genomic, and epigenomic datasets." Utilizing these multiple resources should then allow the authors "to functionally characterize the mechanism by which specific variants regulate hematopoiesis in humans, which should improve the clinical translatability of these findings." For example, identifying such variants could have potential implications for diagnostic screening and drug development for a variety of hematological and inflammatory disorders, such as lung disease and stroke.

Other PHS investigators contributing to this project were Drs. Chris Carlson, Charles Kooperberg, Ulrike Peters, and Li Hsu, as well as Ms. Ursula Schick and Mr. Jeff Haessler.

Citation:

Auer PL, Teumer A, Schick U, O'Shaughnessy A, Lo KS, Chami N, Carlson C, de Denus S, Dubé MP, Haessler J, Jackson RD, Kooperberg C, Perreault LP, Nauck M, Peters U, Rioux JD, Schmidt F, Turcot V, Völker U, Völzke H, Greinacher A, Hsu L, Tardif JC, Diaz GA, Reiner AP*, Lettre G*. 2014. Rare and low-frequency coding variants in CXCR2 and other genes are associated with hematological traits. *Nat Genet*. 46(6):629-34.

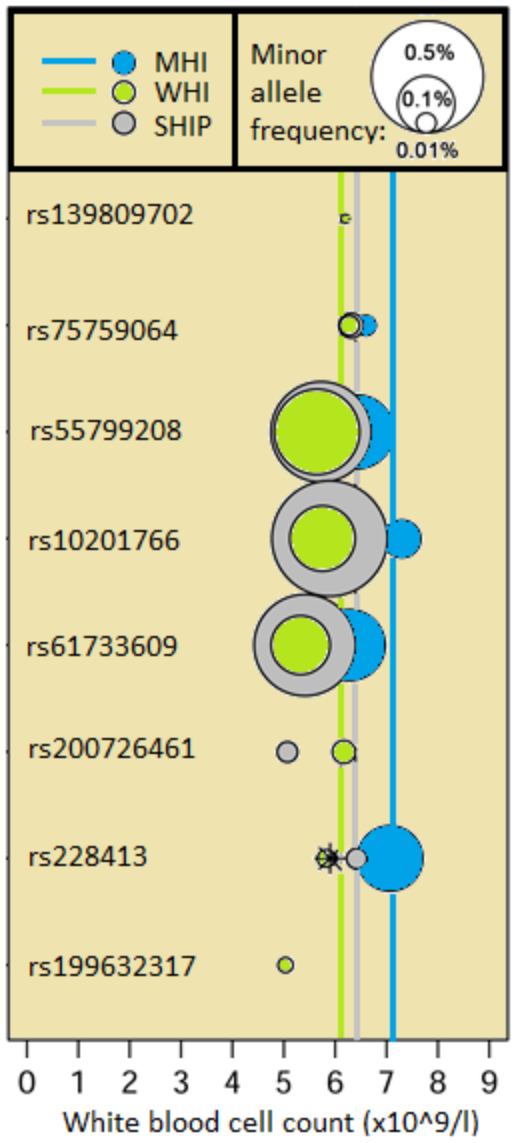

Image provided by Dr. Alex Reiner

Rare and low-frequency missense variants in the CXCR2 gene are associated with lower white blood cell count. The vertical lines represent the mean white blood cell count in each of the three participating studies, while the color-coded circles provide the white blood cell count for participants that carry the variants. Circles are sized according to their minor allele frequency within that study. For one variant (rs228413), there was one MHI participant that is homozygous for the rare allele (represented by a star). Participating in the study were the Montreal Heart Institute Biobank (MHI), the Women's Health Initiative (WHI), and the Study of Health in Pomerania (SHIP).