MedicalXpress

New approach to link genome-wide association signals to biological function

June 30 2011

Researchers have developed a new strategy to improve the outcome of genome-wide association (GWA) studies.

GWA studies involve rapidly scanning markers across the genomes of many people. By doing this, scientists can look for the association between certain genetic markers or variants within the population, and a particular trait, including disease. However, the challenge is to take these initial association signals and identify the functional DNA changes and their molecular consequences. This is an important step in translating these findings into clinical benefits.

The researchers validated a generic framework to streamline discovery of functional DNA variants underlying GWA signals. The team sought to understand the complexity of genomes and sequence variation leading to a better understanding of the affected gene function and biological pathways involved at the cellular level.

As a result, this will benefit many scientists around the world who are currently applying GWA studies to search for genes that affect countless common traits and diseases. It is estimated this new strategy could shed light on around one in four GWA signals for a given trait, but this will depend heavily on the knowledge of the relevant cell types.

The collaborative study was led by Dirk Paul, a Marie Curie PhD Fellow at the Wellcome Trust Sanger Institute, and Dr Panos Deloukas, who leads the Institute's Genetics of Complex Traits in Humans Group. Their

approach was based on a technique to map regions of the genome that are 'open for business', in an open conformation that allows it to be easily activated. DNA in cells is packed tightly with proteins into a structure called chromatin. The team used a method called FAIRE (formaldehyde-assisted isolation of regulatory elements) to find the open chromatin regions and study variants picked up by GWA studies.

With the knowledge that many associated variants are not located inside protein-coding regions, but outside – possibly at regions that are involved in gene regulation – the researchers studied variants by screening genetic regions associated with blood traits in two blood cell types.

"GWA studies have been very successful in allowing us to home in on the biologically relevant parts of the genome, but we need to build functional data sets in all human cell types to convert initial findings into biological mechanisms," said Dr Deloukas. "This study is one such example and shows the power of integrating genomic and biological data."

The scientists investigated one region on chromosome 7 that was 'open for business' and contained a variant associated with platelet characteristics. This region was open in cells that form the platelets found in blood (megakaryocytes), but not in cells that form red blood cells themselves (erythroblasts).

The scientists showed that this variant is functional by affecting the binding affinity of EVI1, a transcription factor controlling gene activity. The regulatory variant influences the expression of PIK3CG, a gene involved in platelet biology. Mice depleted of PIK3CG showed expression differences in several key platelet genes including Von Willebrand factor (VWF), mutations which cause the most common bleeding disorder called Von Willebrand disease1. The researchers found candidate functional variants at a further six GWA regions,

providing opportunities for further discoveries with biological consequences.

"The initial success of our strategy has given us confidence that we can apply it to uncover genetic variants associated with different cardiometabolic traits, in particular coronary artery disease, which we are currently studying," said Dirk Paul. "We are finding many associations and we need a pathway to identify the functional variants and understand their biological meaning. We have shown this is one promising route towards that goal."

More information: Paul DS et al. (2011) Maps of Open Chromatin Guide the Functional Follow-Up of Genome-Wide Association Signals: Application to Hematological Traits. *PLoS Genetics*, published online 30 June 2011.

Related Research
Soranzo N, et al. A novel variant on chromosome 7q22.3 associated with mean platelet volume, counts, and function. Blood (2009); 113(16):3831-7. bloodjournal.hematologylibrary … ent/full/113/16/3831

Provided by Wellcome Trust Sanger Institute