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Disease-causing regions of the genome that affect gene expression levels are mapped with a new method

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The researchers discovered dozens of DNA variants linked to mechanisms of autoimmune disease. Credit: Sergey Nivens/iStock/Thinkstock

A new technique for pinpointing the exact DNA regions that impact gene regulation lays the groundwork for identifying new drug targets and for developing diagnostics to predict disease risk, A*STAR scientists report.

"Once you know the actual causal variant, it's easy to link it to a gene. That's a key missing link in current drug target identification," says Shyam Prabhakar, from the Genome Institute of Singapore, who led the work.

In trying to find the genetic underpinnings of disease, researchers often scan hundreds of thousands of markers across the genomes of thousands of people in search of specific variations associated with a particular health problem. However, the genetic associations they find are rarely the mutations that actually spur disease. The identified variants are usually only linked to the true causative mutations in DNA, and existing methods have struggled to identify those genetic drivers of disease, especially because the mutations often fall in regulatory regions, not in coding genes themselves.

Prabhakar and his colleagues decided to develop a new approach focusing on the parts of the genome that are associated with chemical markers known as acetyl groups. These chemical tags affect how tightly DNA is wound around its packing proteins. Looser chromosomes mean more gene expression. So the level of acetylation acts as an indicator or regulatory signal to indicate the activity of nearby genes.

The researchers used a method known as ChIP-seq in a novel fashion to identify DNA mutations at all acetylated regions in the genome—what Prabhakar calls 'regulome sequencing'. He and his team created a statistical test to correlate differences in acetylation levels (and, by extension, gene regulation) with single-letter differences in the genome. They called it the genotype-independent signal correlation and imbalance (G-SCI) test.

By analyzing data from 57 cell lines, all derived from human B-cells, a type of cell involved in immunity, the researchers discovered dozens of DNA variants linked to mechanisms of autoimmune disease. "The beauty of our method is it does everything in one shot," says Prabhakar. "It's a really cheap and easy method. You don't need any prior information."

Prabhakar's group is now applying the same method, and the G-SCI test,

to post-mortem brain tissue in an effort to understand diseases such as autism and schizophrenia. The researchers are also looking at various kinds of blood cells to probe the genetics of susceptibility to infectious disease.

More information: Ricardo Cruz-Herrera del Rosario et al. Sensitive detection of chromatin-altering polymorphisms reveals autoimmune disease mechanisms, *Nature Methods* (2015). DOI: 10.1038/nmeth.3326

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