The importance of gene regulation for common human disease

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A new study published in *Nature Genetics* on Sunday 16 September 2007 show that common, complex diseases are more likely to be due to genetic variation in regions that control activity of genes, rather than in the regions that specify the protein code.

This surprising result comes from a study at the Wellcome Trust Sanger Institute of the activity of almost 14,000 genes in 270 DNA samples collected for the HapMap Project. The authors looked at 2.2 million DNA sequence variants (SNPs) to determine which affected gene activity.

They found that activity of more than 1300 genes was affected by DNA sequence changes in regions predicted to be involved in regulating gene activity, which often lie close to, but outside, the protein-coding regions.

"We predict that variants in regulatory regions make a greater contribution to complex disease than do variants that affect protein sequence," explained Dr Manolis Dermitzakis, senior author from the Wellcome Trust Sanger Institute. "This is the first study on this scale and these results are confirming our intuition about the nature of natural variation in complex traits.

"One of the challenges of large-scale studies that link a DNA variant to a disease is to determine how the variant causes the disease: our analysis will help to develop that understanding, a vital step on the path from genetics to improvements in healthcare."

Past studies of rare, monogenic disease, such as cystic fibrosis and sickle-cell anaemia, have focused on changes to the protein-coding regions of genes because they have been visible to the tools of human genetics. With the HapMap and large-scale research methods, researchers can inspect the role of regions that regulate activity of many thousands of genes.

The HapMap Project established cell cultures from participants from four populations as well as, for some samples, information from families, which can help to understand inheritance of genetic variation. The team used these resources to study gene activity in the cell cultures and tie that to DNA sequence variation

‘We have generated an information resource readily available to investigators working in the mapping of variants underlying complex traits. Regions of association can be correlated with signatures of regulatory regions affecting gene expression' explained Dr Panos Deloukas, Senior Investigator at the Wellcome Trust Sanger Institute

"We found strong evidence that SNP variation close to genes - where most regulatory regions lie - could have a dramatic effect on gene activity," said Dr Barbara Stranger, post-doctoral fellow at WT Sanger Institute. "Although many effects were shared among all four HapMap populations, we have also shown that a significant number were restricted to one population."

They also showed that genes required for the basic functions of the cell - so-called housekeeping genes - were less likely to be subject to genetic variation. "This was exactly as we would expect: you can't mess too much with the fundamental life processes and we predicted we would find reduced effects on these genes," said Dr Dermitzakis.

The study also detected SNP variants that affect the activity of genes

located a great distance away. Genetic regulation in the human genome is complex and highly variable: a tool to detect such distant effects will expand the search for causative variants. The authors note, however, that the small sample size of 270 HapMap individuals is sensitive enough to detect only the strongest effects.

The results of this study are becoming available in public databases such as Ensembl for researchers to use.

The paper is accompanied by two others examining effects of changes to regulatory DNA in samples from asthma and from heart study patients.

Source: Wellcome Trust Sanger Institute

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