



Press release

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Finding variants in the human genome

HapMap 3 points the way forward for human genetics studies


New findings show the value of genetic studies across human populations and the value of the latest DNA sequencing technologies to interrogate genetic variation. The results, from the latest phase of the international HapMap Project, are reported today in *Nature*. The researchers' extensive study of genetic variation in multiple populations will form a framework for future genetic studies of variation and disease: their findings highlight the need to examine various populations in order to tease out the widest collection of genetic variants, as well as the requirement to deploy sequencing technologies to find as many variants as possible.

The HapMap Project seeks to identify signposts on the human genome that will simplify the search for important genetic variants. In the latest phase – HapMap 3 – the researchers looked for variants across the genome in 1184 samples from 11 populations. The large sample set and the wide range of populations were chosen to maximize the variation captured. The project includes both single-letter differences, called SNPs, as well as large differences from the loss, gain or duplication of regions, called CNPs.

“Despite the remarkable achievements following from the Human Genome Project, our knowledge of human genetic variation remains limited,” says Richard Gibbs, one of the Principal Investigators of the project from Baylor College of Medicine. “Here we have studied more populations and were able to include CNPs in genomewide studies. These refined results tell us more about human genetic variation and about how to study variation successfully.”

The results show that rarer variants are distributed more unevenly between populations. This might be expected – evolutionary theory implies that the common variants are generally the older ones, having had greater time to spread through a population – but also cautions that genetic studies should include a wide range of population groups to maximize discovery of more recent, population-specific variants.

“The closer we look at human genetic variation, the greater the granularity,” underlines Emmanouil Dermitzakis, the Project Coordinator from the University of Geneva. “An important task in genetics is to discriminate between the variants that



are important for health and those that are part of the background. This new version of the HapMap will help us design ways to do that – to sort the wheat from the chaff.” In addition to the genotyping discussed above, HapMap 3 also sequenced ten segments of 100,000 bases from well-characterized regions. Unlike discovery using DNA chips – as used in most studies to date – direct sequencing is not biased towards more common variants, but is blind to their frequencies, giving a direct estimate of the frequencies of variants.

The researchers found that most variants were relatively uncommon (found in less than 1 person in 10), and they also found a large number of rare variants (each found in less than 1 in 200 people) or ‘private’ variants (found in only one person). Almost eight of ten variants were new and almost four of ten of those seen in less than 1 in 100 people were found in only one population.

From the results, the researchers suggest that variants in some genes, including genes involved in the immune system, wound healing and sense of smell, are under selection in different populations. These genes can now be studied to learn about how these systems work and about disease resistance. These findings show the value of having large studies that include many populations and samples to achieve comprehensive understanding of human variation.

“Some have talked about how little has come from the Human Genome Project over the past ten years, but perhaps they forget how little we knew then,” says David Altshuler, one of the Principal Investigators of the study from the Broad Institute. “It is amazing that we have gone from a genome less than 90% completed to looking at genetic changes in one in 200 people or rarer. A few years ago, we had no idea of the extent of structural variation or how we might sample variants present at low frequency. The HapMap and other large-scale projects have transformed our understanding of the human genome and its relation to health and disease.”

The HapMap 3/ENCODE 3 data set is publicly available at <http://www.hapmap.org>. The study was funded by the *Wellcome Trust* (UK), the National Institute of Health (USA), as well as the University of Geneva, the *Fondation Louis-Jeantet* and the *NCCR Frontiers in Genetics* (Switzerland).

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