news

could entail introducing a TRIM5α gene encoding the HIV-resistant protein, with the aim of repopulating a generation of cells capable of resisting infection, thereby preventing progression to AIDS, he explains.

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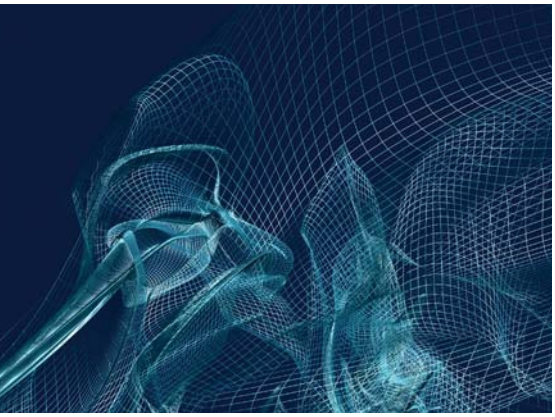
Untangling the patterns of genetic variation

Martina Habeck, m.habeck@gmx.net

Scientists involved in the international HapMap project have completed a map of 1 million common markers of genetic variation across five human populations. Efforts are now underway to create an even denser map, with one single-nucleotide polymorphism (SNP) signpost every 600 bases. The data provide scientists with an essential tool for the development of more effective, individualized treatments.

An embarrassment of riches

The HapMap is a follow-on from the Human Genome Project. 'It grew out of the realization that there was an embarrassment of riches in the SNP databases,' says bioinformaticist Lincoln Stein at the Cold Spring Harbor Laboratory (Cold Spring Harbor, NY, USA), who is a principal participant in the HapMap project. 'The public projects had been so successful in finding SNPs that there were now over 8 million SNPs in the public databases.' However, information was lacking on the frequency of these variants and how the frequencies vary between different populations. Moreover, recent studies found a lot of redundancy in SNP databases [1]. Therefore, the International HapMap Consortium – a public–private partnership of scientists and funding agencies from the USA, the UK, Canada, China, Japan and Nigeria – was formed in October 2002 to define a structure of all this variation.



The human genome can be parsed into DNA regions within which little recombination has occurred – the so-called haplotype blocks. The SNPs in such a haplotype block are strongly associated with each other, whereas the association with other SNPs is relatively weak. Looking for these patterns, which are highly conserved across populations, the International HapMap Consortium began genotyping sequence variants of 270 DNA samples from populations with Northern and Western European, Chinese, Nigerian and Japanese ancestry. The resulting haplotype map tells researchers which SNPs describe the variation in a specific genomic region.

Customized medicine

'The primary goal is to make disease-gene finding faster and to help develop genetic-based tests that will indicate the best therapy for different individuals, in order to make possible this idea of customizing medicine to a person's genetic background,' notes Stein.

The $130 million project, designed to provide 1 million markers of common variation, was due to be completed in September this year, but thanks to technological advances during its course, it was completed half a year before schedule. The Affymetrix spin-off company Perlegen Sciences (Mountain View, CA, USA) now received $3.3 million funding to genotype another 4.6 million SNPs from publicly available databases. By September this year, they aim to add information on 2.25 million additional SNP signposts to the freely accessible HapMap databases (www.hapmap.org; www.ncbi.nlm.nih.gov/SNP; http://snp.ims.u tokyo.ac.jp). 'We are delighted that we get to triple the size of the HapMap without tripling the cost,' says Stein. 'It is typical of the genome project, that the science drives the technology and the technology drives the science.'

The HapMap set that has been done so far clearly has gaps in it, says Douglas Easton, a Cancer-Research-UK-funded epidemiologist at the University of Cambridge (Cambridge, UK). 'The new set [will be] much denser. The idea is to try and get to the point where one is as confident as possible that all the common variants have been identified.' This could help our understanding of the molecular basis of common diseases, like cardiovascular disease and diabetes. However, Easton adds that there might be a lot more rare variants to look for; they are much harder to approach and are not evaluated in the HapMap project.

New targets

Researchers worldwide are already using the current data by comparing the haplotype patterns of different groups of people. Much of that research focuses on the study of genes that have been linked to disease or drug metabolism. But scientists have also begun to design experiments that look at the whole genome. If an association study finds a certain haplotype more often in people with a given disease or drug response, researchers will narrow down their search to that genomic region to find the specific genetic variant involved in the disease or drug response, with the tag SNPs serving as signposts indicating that the culprit variant lies nearby. Easton predicts that these association studies will be going on over the next 2–3 years. 'Hopefully, out of that will come new targets for new therapies,' he concludes.

References

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