need to be designed against highly conserved parts of the viral genome.

Kay and colleagues went beyond the *in vitro* systems and genetically engineered mice that express siRNAs against hepatitis C RNA to show that this technique also works well *in vivo* to prevent viral replication.

After this bumper crop of promising results, it remains to be seen how close we are to RNAi-mediated antiviral therapy. Because siRNAs tap into natural gene-silencing pathways, a new form of intracellular immunization against viral infection might be just around the corner.

Magdalena Skipper

References and links

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humans affected with asthma, we need all the targets we can find.

Chris Gunter, Associate Editor, Nature

References and links

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WEB SITES
Asthma Gene Database: http://cooke.gsf.de/asthmagen/main.cfm
NCBI "Genes and Disease" on asthma: http://www.ncbi.nlm.nih.gov/disease/asthma.html

HAPLOTYPE MAPPING

Shortcut around the block

Until now, gene mappers have had to take the long road to finding disease genes, as combing the whole genome can be a lengthy and expensive undertaking. However, a shortcut could be opened up if, as some propose, the human genome turns out to be 'block-like', that is, consisting of DNA regions in which recombination is rare, bordered by recombination hot spots. The theory goes that disease genes could be tracked to one of several haplotypes (combinations of alleles) that define each block. If each haplotype can be identified by a small number of markers, mapping would become quicker and cheaper. However, some groundwork needs to be done before the 'haplotype mapping' approach can take off: the first is to assess properly the block-like structure of the genome. Two papers have done just that by empirically delineating the haplotype blocks in our genome. On the basis of the success of these two reports, the second step — using the haplotype map, or HapMap, to map disease genes of the human genome — should soon follow.

In the first study, Stacey Gabriel and colleagues used ~4,000 publicly available SNPs (single-nucleotide polymorphisms) to identify blocks in 51 autosomal regions — selected on the basis of having closely spaced SNPs and totalling 13 Mb, or ~0.4%, of the genome — and then compared them among four populations: Europeans, Asians, Africans and African Americans. The authors found 928 blocks, which, as expected, were shorter in the older, African populations, consistent with the view that blocks become eroded over time by recombination. The fact that few (3–5) common haplotypes were identified for each block, and that they could be uniquely identified with as few as 6–8 random markers was very reassuring, as was the fact that half of the haplotypes were shared by all four populations. Perhaps less encouraging was the finding that the average size of the blocks is quite small (11–22 kb), meaning that, to be useful, the HapMap might need to be built from up to a million SNPs.

A similar pattern was seen in a second study, by Dawson *et al.*, who used 1,500 publicly available SNPs and insertion/deletion polymorphisms to derive 59 haplotypes across the whole of chromosome 22. The size of blocks across this chromosome is quite variable: small stretches are interspersed with large (up to 800-kb) blocks in which recombination is low. As in the previous study, common haplotypes could be distinguished by genotyping very few (in this case, three) SNPs. A strength of this study was the use of family-based samples, which the authors show are a more informative source of haplotype information than are unrelated individuals.

Constructing a HapMap might therefore be technically feasible, but will it work? The arguments against using haplotype mapping to locate complex trait genes have been well rehearsed. The emphasis on common haplotyes (captured using common SNPs) presupposes that common diseases are caused by common variants and precludes the identification of rarer, and perhaps population-specific, alleles. Believers and non-believers alike will just have to await the formal test to see who is right.

Tanita Casci

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WEB SITES
The SNP Consortium Ltd: http://brie2.cshl.org
The Centre d'Etude du Polymorphisme Humain (CEPH) genotype database: http://www.cephb.fr/cephdb