Mapping project moves forward despite controversy

On October 29, an international consortium announced the start of a $100 million, three-year project to construct a new type of map of the human genome. According to its proponents, the International Haplotype Mapping Project, or 'HapMap', will speed the discovery of genetic factors that contribute to such common conditions as diabetes and heart disease. However, many population geneticists outside the project contend that it rests on a series of dubious scientific assumptions and is unlikely to benefit public health or research.

The HapMap is an outgrowth of efforts to map single-nucleotide polymorphisms (SNPs), single-base differences between human DNA sequences. Because an estimated 10 million SNPs are spread throughout the genome, some researchers see them as the key to mapping multiple genes associated with complex disease traits.

Recent work has shown that SNPs in some regions are inherited in clusters, raising the possibility that the clusters, or haplotypes, could be used as markers to reduce the number of SNPs that must be identified in mapping a gene. Labs participating in the HapMap, which are located in the US, UK, Canada, Japan and China, will now try to create a genome-wide map of these clusters based on DNA samples from different human populations.

Traditionally, human geneticists have relied on family-based studies to find genes. The HapMap is a tool for association studies, which compare genetic markers in unrelated people who have a disease with markers in a control population. "All the HapMap is doing is making association studies more efficient by taking advantage of the natural block structure of the genome. You don't have to look at every single SNP, so you're just making a very intelligent choice of SNPs to study," says Lisa Brooks, a program director at the National Human Genome Research Institute, one of the organizations funding the project. Brooks says that the HapMap hopes to establish its standards for quality control and data formatting within the next few months, and that map will be released in a public database as the project progresses.

But Joe Terwilliger, a population geneticist at Columbia University, says, "There's almost nobody who's not intimately involved with [the HapMap] who thinks it's a good idea. I can't believe they're spending that much money on something so silly. It's just a waste." Kenneth Kidd, professor of genetics and psychiatry at Yale University, is also skeptical, arguing that the HapMap relies on the assumption that common diseases are caused by common genetic variants: "There are lots of complex diseases where that has pretty much already been excluded ... and to me that basic hypothesis simply counters almost everything we know."

The project also assumes that the block structure found in a few genetic loci will be a general feature of the genome, and although Kidd concedes that "there's no question there are hotspots ... there's no evidence that's the general rule." HapMap participant Charles Rotimi, director of genetic epidemiology at the National Human Genome Center at Howard University in Washington, says, "The only way you can know is to do the work on the scale proposed, then there is no opportunity to say 'well, maybe we didn't study a large enough population to actually know this.'"

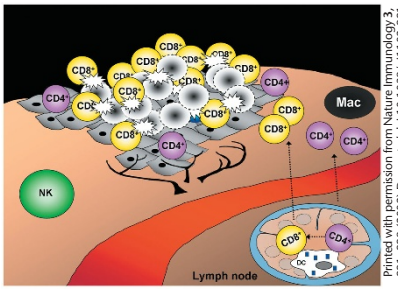
Terwilliger finds this logic unpersuasive: "It's just wishful thinking that the association methods will work in humans when they don't work in mice or *Drosophila*. Nobody has anything to say besides, 'we can't prove that it won't work.' I just find it absolutely amazing that I'm being asked to prove that it won't work when these are the guys who want $100 million."

But HapMap researchers are equally adamant about the usefulness of the new approach. "I think that the family-based approaches that we've been using will at best identify two or three genes," says Thomas Hudson, leader of the HapMap group at McGill University in Montreal, who adds that a SNP- or haplotype-based approach is "the only systematic way to go and test the genome for these common variants."

Alan Dove, Philadelphia

Review reopens old disagreements

Last month's publication of a review on the role of the immune system in tumor development has revealed a persistent divide between some groups of the cancer research community. The long-standing disagreement centers on the ability of the immune system to intercept tumors of non-viral origin.



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Model of elimination phase of cancer immunoediting process

Several animal studies in the 1970s failed to show that immunosurveillance protects against the effects of non-viral carcinogens, and the immune system lost much of its status as a protector against tumor formation. But Robert Schreiber, whose review in *Nature Immunology* (**3**, 991; 2002) combines data from his laboratory with other evidence from around the world, says that the mice in those studies were not truly immunodeficient. "Experiments were done with mice that had spontaneous mutations affecting the immune system, but which did not delete it," says Schreiber. "That could not have been known back then."

Using knockout mice, Schreiber, professor of pathology at Washington University School of Medicine, and his colleagues have now shown that cancers occur more frequently in immunodeficient animals than in those with a largely intact immune system. Moreover, it seems that the immune system actually plays a role in shaping the type of tumor formed, because tumorigenic cells undergo natural selection to develop proteins that evade immunosurveillance, a process that Schreiber calls 'immuno-editing'.

Not everyone is convinced. Although cancer expert Robert Weinberg of the Whitehead Institute agrees that immunosurveillance protects against cancers with a viral etiology—such as non-Hodgkin lymphoma, Kaposi sarcoma and cancers of the genitourinary system—he doubts that other tumors are recognized as foreign by the immune system. "Virtually all the proteins made by cancer cells are normal proteins," he says. "Whereas viruses are invaders."

Schreiber hopes his findings will stimulate new research into the phenomenon. "We have to realize that when we try to attack tumors, we should understand that they have already undergone shaping by the immune system," he says. "We need to boost our immunity very strongly in order to react against tumors with reduced immunogenicity."

Chris Dickey, New York