RESEARCH HIGHLIGHTS

GENOMICS

A structural map of the human genome

Pursuing a great promise of the human genome project, a plethora of studies is being carried out to find single-nucleotide polymorphisms (SNPs) associated with disease susceptibility. But these are not the only source of variation between individuals.

Researchers have long suspected the importance of other variations such as insertions, deletions and inversions in our genome. These so-called structural variations, however, are more difficult to detect than SNPs. Convinced that crucial information is being overlooked, Evan Eichler and his group at the University of Washington in Seattle, set out to discover structural variations in the genome of one individual, using the human genome sequence as a reference.

They used a large fosmid library, built from the DNA of a test individual, and mapped where the two ends of each clone appear in the human genome reference. Because the size of the clones in a fosmid library is very consistent (about 40 kilobases; kb), the two paired ends most often map to sequences separated by the same distance-but the interest is in the exceptions. A pair of fosmid ends aligning to a pair of sequences separated by more than 40 kb in the reference reveals a deletion in the test individual. Conversely, a separation of less than 40 kb signals an insertion, and an inconsistency in their orientation indicates an inversion.

The study, published in *Nature Genetics*, revealed about 300 sites of structural variation. Once a structural variation has been identified, sequencing the corresponding clone is easy; this reveals the exact nature of the underlying structural change, and permits the design of genotyping tests to evaluate its frequency in a population.

The problem is the price tag. Analysis of each individual amounts to sequencing about one million paired ends, "a mini-genome project" as Eichler calls it. But this is not a onetime shot. His laboratory, in collaboration with Agencourt, University of Washington Genome Center and US National Human Genome Research Institute, is embarking on the analysis of another eight to ten individuals, selected from the HapMap collection to represent extremes of genetic diversity, with the goal of building a more global structural map of the human genome. Undoubtedly, these data will broaden the human genome consensus and drive new genetic studies. "The key will be moving forward with the development of robust genotyping assays to do association studies with diseases," says Eichler. Although his lab has established PCR-based genotyping tests for some of the variation sites, he is not convinced that this is the way to go. Instead, he insists, "we need new technology development to be able to detect inversions in a highthroughput and robust fashion."

"Think about where SNPs were 10 years ago," says Eichler, "in discovery phase; this

CHEMICAL TOOLS

An attractive alternative

Tiny magnetic tubes could provide an unconventional solution for several research problems, and a useful vehicle for imaging and drug delivery applications.

The trusty sphere remains the preferred form for nanoparticles but this shape leaves only one surface for modification, complicating the generation of multifunctional particles. In 2002, Charles Martin's laboratory at the University of Florida decided to try a different approach. "We needed a technology that could be modified differentially between the inner and outer surface," explains Sang Bok Lee, a former postdoc in Martin's lab. The solution they arrived at was to use silica nanotubes—easy to synthesize, soluble in aqueous solutions, and offering two easy-tomodify surfaces (Mitchell *et al.*, 2002).

Lee, now at the University of Maryland, has recently expanded on this work, demonstrating a modification that allows the generation of magnetic versions of these nanotubes (Son *et al.*, 2005). By simply layering the inner surface of the tubes with magnetite, the tubes become much more useful for *in vivo* applications. "The magnetic properties will give you imaging capabilities using MRI, so that you can simply trace the nanoparticles inside the body," says Lee. "And one more potential advantage with using these magnetic nanotubes is with magnetically assisted biointeraction... If you can use magnetic fields, then you may be able to hold those nanoparticles is where we are now with structural variations". Eichler is confident in the power of the method, in part because it relies on a skill that genome centers already have mastered: sequencing libraries of millions of clones. In his view, "combining lots of sequencing in a random fashion with structural information is the way of the future."

Veronique Kiermer

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Tuzun, E. *et al.* Fine-scale structural variation of the human genome. *Nat. Genet.*; published online 15 May 2005.

at specific spots inside the body, to give enough time for those particles to interact with cancer cells or [other targets]."

They also have promise for *in vitro* applications. In one experiment, Lee's group functionalized the inner surfaces with molecules capable of binding a specific dye; when the tubes were added to a dye solution and then magnetically isolated, nearly 95% of the dye was removed. Likewise, nanotubes with inner surfaces coated with antigen proved capable of highly specific magnetic separation of antibodies recognizing that protein.

Lee's primary interest, however, remains in optimizing these magnetic nanotubes for use in drug delivery. Although drugs can readily be loaded into the tubes, preventing early drug release remains an obstacle, and the group is investigating potential solutions. "Ideally," says Lee, "we are hoping to modify the inner surface with drug molecules through strong chemical interactions such as ionic or chemical bonds... [after which] we can use enzymatic activity or another treatment to cleave those chemical bonds so that drug molecules can easily be released after a short time." **Michael Eisenstein**

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Son, S.J. *et al.* Magnetic nanotubes for magnetic field–assisted bioseparation, biointeraction, and drug delivery. *J. Am. Chem. Soc.* **127**, 7316–7317 (2005). Mitchell, D.T. *et al.* Smart nanotubes for bioseparations and biocatalysis. *J. Am. Chem. Soc.* **124**, 11864–11865 (2002).