NEWS AND VIEWS

# Haplotyping by force

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If DNA is the instruction manual for life, then our understanding of life has been greatly hindered by the fact that the text of the manual is too small to read. For all the remarkable technologies that have been developed for sequencing the human genome, obtaining detailed DNA sequence information is still a chore. This task would be much easier if scientists could interrogate and image a DNA strand directly, on the nanometer or even Ångstrom scale. On page 760, Woolley et al.[1] have provided such a tool by adapting a single carbon nanotube as an atomic force microscope (AFM) probe, which they used to locate hybridized DNA sequence tags with a spatial resolution of 3 nm. In doing so, the authors have demonstrated the remarkable potential that nanotechnology holds for defining the nanoscopic biological world.

Conceptually, the physical mapping technique developed by Woolley et al. resembles optical mapping[2] and high-resolution in situ hybridization[3], in which chromosome lengths and distances can be imaged directly by fluorescence microscopy. The resolution of these latter methods, however, is inherently limited to tens of kilobase pairs by the wavelength of light. By using an analytical tool on par with the nanometer scale of DNA, the authors have achieved resolution higher than 100 bp in their "force mapping" of polymorphisms in the UGT1A7 gene. Just as one might choose fluorescent dyes with distinct emissive properties as *optical* tags for fluorescence microscopy, Woolley et al. use objects that differ in size as orthogonal *force* tags for AFM. These tags were attached to oligonucleotide probes, hybridized to the single-stranded DNA target, and directly correlated to specific haplotypes.

From a biotechnological standpoint, Woolley et al. have provided a useful way of determining the phase of single-nucleotide polymorphisms (SNPs). Current methods of scoring SNPs (such as hybridization to microarrays or direct gel sequencing) can accurately type individual SNPs, but cannot determine which chromosome of a diploid pair is associated with each polymorphism. Force mapping, on the other hand, obtains this haplotype information by directly imaging the probes hybridized to the gene of interest (Fig. 1). The expanding catalogue of SNPs, coupled with recent upward revisions of the number of SNPs required to adequately characterize genetic variation in humans[4], make it more likely that single genes will contain multiple SNPs and that accurate haplotyping will be necessary to correlate these SNPs with gene function. The technique described by Woolley et al., as a result, has important implications for the growing field of functional genomics.

Moreover, the article offers an elegant demonstration of the utility of nanotechnology to study nanoscale biological phenomena. The resolution and sensitivity of scanning probe microscopies, and particularly of atomic force microscopy with carbon nanotube-modified tips, have allowed scientists to observe individual DNA molecules, proteins[5], and the interactions between these biological molecules[6] in breathtaking detail. At the same time, scientists are learning to design novel materials to interact with biological structures on the same nanometer scale[7]. Eventually, this integration of nanotechnology and biotechnology will yield methods for the synthesis of hybrid biomaterials with desired physical properties[8], improved medical diagnostics[9,10], and nanoscale biomachines and devices[11] that might someday be capable of performing programmed tasks in vivo.

Although it remains to be seen whether the novel approach to haplotyping developed by Woolley et al. can be used in a clinical setting, the technology nonetheless represents an important step toward capitalizing on the promise of nanotechnology and, in particular, scanning-probe microscopies, in the biological and medical arenas.

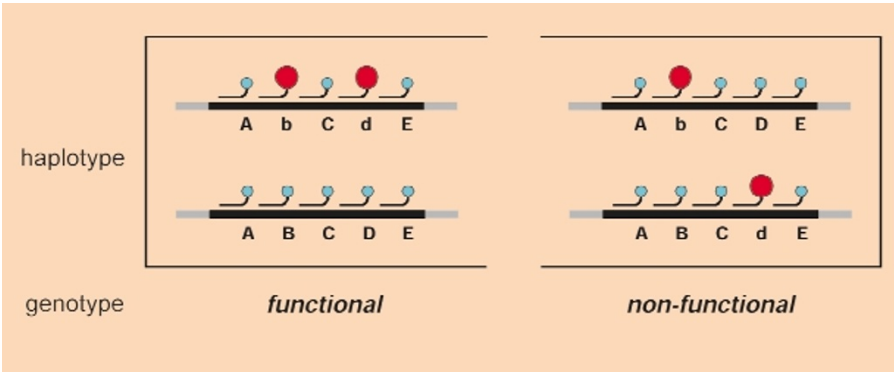


**Figure 1. Haplotypes of two individuals for a gene bearing multiple SNPs, with each polymorphism probed with different-sized force tags for AFM imaging. In this case, the phase of the coding polymorphisms determines the genotype; even though the individuals are both heterozygous at alleles B and D, the individual on the left expresses the gene correctly and the one on the right does not. Typical SNP scoring methods would fail to distinguish the two individuals, but the haplotyping method described by Woolley et al. characterizes their genotypes correctly.**

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