TECHNOLOGY

DNase I assay gets a face lift

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For the past 25 years, the access we have had to active chromatin has been predominantly afforded by DNase I — an enzyme that preferentially snips accessible and presumably active promoters and enhancers. This traditional approach has now been given a makeover — by marrying it to microarrays two groups have now come up with related ways of turning the DNase I assay into a high-resolution genome-scale effort.

The conventional way of detecting active chromatin involves digesting DNA with DNase I and then separating the fragments on a Southern blot: a probe to the region of interest will reveal whether it has been cleaved by the enzyme. The technique works well, but the need for individual gels and probes makes it feasible and affordable only for a region-by-region approach. This method therefore

does not meet modern ambitions to build gene regulatory networks, and to understand how changes in gene regulation affect normal and disease states. Two papers have now devised ways of using DNase I to assay many genes sensitively and efficiently in a single experiment: in both techniques the DNase I-digested fragments are isolated, labelled and then hybridized to a microarray of tiled DNA fragments (see diagram).

In both methods, DNA is digested by DNase I in the conventional manner. Then, in the DNase-chip method of Crawford *et al.*, the cut ends of the DNA are each ligated to a biotinylated tag: these are then captured by a streptavidin column, washed off, labelled and then hybridized to the microarray. The technique devised by Peter Sabo and co-workers, called DNase-array, rests on the assumption that short stretches of open chromatin are likely to be cut not just once, but twice by DNase I in close proximity. This time the short fragments are separated by size on a sucrose gradi-

ent, and then isolated, labelled and hybridized to the microarray.

The results reported by the two groups are qualitatively similar; as expected, most accessible DNA regions map to gene-rich regions, in the vicinity of predicted transcription sites, or otherwise at known regulatory sites. But the methods also threw up some surprises, such as the fact that DNase I hypersensitive sites tend to be clustered, and can also frequently be found at the transcription termination site of genes.

The microarrays cover only 30 Mb of human genome, that is, the portion chosen by the **ENCODE** project. Although this region corresponds to only 1% of the genome, the authors see no reason why, given time and money, their methods cannot be extended to the entire genome and, for that matter, to any other species — by simply varying the representation on the chips.

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ORIGINAL RESEARCH PAPERS Crawford, G. E. *et al.* DNase-chip: a high-resolution method to identify DNase I hypersensitive sites using tiled microarrays. *Nature Methods* 3, 503–509 (2006) | Sabo, P. J. *et al.* Genome-scale mapping of DNase I sensitivity in vivo using tiling DNA microarrays. *Nature Methods* 3, 511–518 (2006)

WEB SITE

Encyclopedia of DNA elements (ENCODE) project: <http://www.genome.gov/10005107>