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The evolution of genetic maps

This special issue of *Nature Genetics* contains two unique contributions that demonstrate the rapidly increasing pace of genetic mapping in humans and mice. These two papers — from Dr Jean Weissenbach and his colleagues at Généthon in Paris (on page 246)[1], and Dr Eric Lander's team at the Whitehead Insitute/MIT Center for Genome Research in Cambridge, Massachusetts (page 220)[2] — provide the most detailed and informative genetic maps compiled so far of the human and mouse genomes respectively. Although mapping is continuing in earnest and is not yet complete, these latest snapshots of the human and mouse genomes convey a wealth of information: the final all-out effort to complete the maps (to a sufficiently dense level of resolution) will be concluded within the next couple of years.

The Généthon human genetic map incorporates more than 2,000 microsatellite markers, interspersed with some familiar human genes, and thereby more than doubles the number of landmarks presented in Généthon's first comprehensive genetic map, published in October 1992 (ref. 3). Full details of the markers that constituted the first map were made available electronically, and in a printed catalogue distributed by the authors. The presentation of their data in this issue is essentially the same, and (by popular demand) retains the full primer sequences for the microsatellites.

At an average spacing of just 2.9 cM, the current Généthon map essentially fulfils one of the main goals set in the latest five-year plan for the genome project[4], namely to have a 2–5 cM linkage map by 1995. By then, the map will be better still. Weissenbach estimates that his group will have identified nearly 5,000 markers, although it will take many more months to place them precisely on the evolving genetic map. The tricky and time-consuming part of compiling these comprehensive

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4,000 and counting — Equipment put to good use at the Whitehead Institute/MIT Genome Center includes a robotic workstation to set up PCR in microtitre plates (left) and the "waffle iron" for the reactions themselves (right) (courtesy E. Lander).

Listing of principal genetic maps in humans and mouse

Group	Year	Spacing (cM)[a]	Features
Human			
Collaborative Research	1987	10	403 loci (incl. 393 RFLPs)
NIH/CEPH	1992	<5	1416 loci (incl. 279 genes)
Généthon	1992	4.4	814 microsatellites
Pittsburgh	1994	6.2	655 loci[b]
CHLC	1994	4.9	1,123 loci
Généthon	1994	2.9	2,066 microsatellites
Mouse			
MIT	1992	4.3	317 SSLPs
Frederick/MIT	1993	0.6	1,098 genes + 1,518 SSLPs
MIT Genome Center	1994	0.35	4,006 SSLPs

[a]Average spacing varies with parameters such as lack of telomere coverage and proportion of markers positioned uniquely, and does not necessarily correlate with total number of mapped loci.
[b]Localized uniquely (odds >1,000:1). Total number of loci = 1,663.
CHLC, Cooperative Human Linkage Center; SSLP, simple sequence length polymorphisms

genetic maps, he says, is not so much establishing the markers and generating the primary data, but more in performing the calculations and checking for errors as the maps are assembled.

The mouse genetic map from Lander and coworkers includes more than 4,000 microsatellite markers. This represents more than twelve times as many as the first incarnation of the map exactly two years ago[5] and more than twice as many as the integrated map of microsatellites and gene loci presented last year[6], in which 250 microsatellite markers were positioned on the gene map. The first version of the map was constructed by just two researchers in 18 months. With considerably more resources (of the automated and human variety) now available, the MIT Genome Center is poised to build a final version of the map consisting of 6,000 markers. Given that it is already more than two-thirds of the way there, Lander believes that the complete map will be delivered ahead of schedule, perhaps as soon as the end of 1995. Of course, both human and mouse maps are continuing to evolve. Full details can be obtained via electronic mail, as described in the papers.

Swift progress: It was only seven years ago that workers at Collaborative Research (a Massachusetts-based biotechnology company) published the first linkage map of the entire human genome, consisting of some 400 polymorphic markers providing coverage of an estimated 95% of the genome[7]. Their announcement drew a mixed reception, for many large holes in the coverage still existed, notably on some of the smaller chromosomes. But as the number of linked markers has grown (see Table), these gaps have shrunk considerably; the new Généthon collection, for example, leaves only one gap greater than 20 cM (on chromosome 19). Furthermore, the maps made up of random DNA polymorphisms are slowly being integrated with the positions of known gene loci[8]. The drawback to begin with was that most of the random markers were relatively uninformative, but this has been solved by building integrated human genetic linkage maps[9,10].

The improving coverage of the genome may not have a dramatic impact on the early stages of 'shotgun linkage' attempts to localize new disease genes: already several groups and private companies have compiled and distribute evenly spaced sets of markers, and newly developed automated methods using specially designed, fluorescently labelled primers may speed things up still more[11]. But once a tentative linkage is found, it can be pinpointed with great precision, and in some cases the chromosomal region of interest may already exist as a contig of yeast artificial chromosomes[12].

The Genome Project still faces severe difficulties in meeting its long-term goal of sequencing the human genome in the next 11 years or so, largely because of lack of progress in devising improved technologies for large-scale DNA sequencing[4] (recent successes for *Caenorhabditis elegans*[13] and *Saccharomyces cerevisiae*[14] notwithstanding). But there are no complaints about the pace at which the human and mouse genetic maps are being built. The next task is to sustain this momentum into the next phase of the project — the construction of detailed physical maps for the whole genome. □

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