Plenary Lecture

Mapping and Sequencing the Human Genome: Status, strategies, prospects, and implications

Dr. Victor A. McKusick

The NRC/NAS committee on mapping and sequencing the human genome, in recommending that a special project be mounted, concluded that we should "map first, sequence later." The reasons were at least 2: sequencing technology required improved for maximum efficiency, and mapping information including ordered clones of DNA segments was desirable, even necessary, for sequencing. Several types of maps include high resolution genetic maps based on RFLPs, the map of expressed genes, and the "contig map" constructed, for example, from YAC (yeast artificial chromosome) clones. In addition, maps of cDNAs (created from mRNAs at different stages of development and different tissues) could be useful. It would also be useful to determine which of the 4,000 or more anonymous DNA segments now mapped are expressed. Presently over 1,700 expressed genes have been mapped to specific chromosomes and chromosome regions. The rate of mapping has accelerated progressively in the last 15 years and shows no tendency to slow. Of course some sequencing is going on at the same time as mapping, but mounting of an all-out effort at sequencing will await improved technology. While awaiting technologic improvements, sequencing of simpler genomes concerning which there is much genetic information provides useful experience.

The development of a progressively more saturated map of RFLPs and VNTRs has increased greatly the ease with which diseases of unknown biochemical nature have been mapped, thus opening up the possibility of their elucidation by "reverse genetics" and diagnosis by the linkage principle and direct DNA methods.

Already the mapping and sequencing information has proved highly useful, not only in relation to Mendelian disorders, but also in a remarkable way in relation to the category of somatic cell genetic diseases, which all neoplasms represent.

The sequencing and then mapping of the complete mitochondrial chromosome is a paradigm for the nuclear genome.

Already societal, ethical, legal and commercial issues raised by the Genome Project are being addressed. Issues of confidentiality must be kept in mind.

The organization of the Human Genome Project will probably be chromosome by chromosome and in the case of large chromosomes, chromosome arm by chromosome arm, following the pattern of the Human Gene Mapping workshops. Various groups and individuals will constitute consortia to take the lead in collating the data as it is generated, assuring open access to biomaterials and technology

for the research, and seeing that the job is completed for each part of the genome. It is foreseen that the Human Genome Organization (HUGO) will serve a coordinating role.