Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

L. C. DUNN AND MOUSE GENETIC MAPPING

THE year 1990 marks the 70th anniversary of the beginning of systematic mapping of the mouse genome. The first detection of linkage between two genes in the mouse, and also the first in any vertebrate, had occurred five years earlier, when HALDANE and his colleagues (1915) described the linkage of the coat color genes for *albinism* and *pink-eyed dilution*. However, it was not till 1920 that L. C. DUNN (1920a) published a paper on a systematic search for linkage among various coat color genes.

This was just one of many major contributions made by DUNN which laid foundations for the present highly detailed knowledge of the mouse genetic map. This map in turn makes the mouse now one of the key experimental organisms in genetics, particularly in relation to present efforts to elucidate the structure and function of the human genome. In the same year, DUNN (1920b) published what must have been the first paper on comparative mapping, in which he compared the linkage of *albinism* and *pink-eye* in mice and rats and investigated in detail factors, such as age and sex, which affect recombination between these genes in the mouse. Later, DUNN was involved in the development of inbred strains of mice, which are now very important in the mapping of DNA and protein variants. He was also one of the founders of the mouse Nomenclature Committee and of *Mouse News Letter*, which have provided the underlying framework for the databases which are now essential to successful mapping. In yet another contribution, DUNN was one of the first to use wild mice in genetic research (WAELSCH 1989). The wealth of genetic variation in wild mice, including species and subspecies closely related to laboratory mice, has led to the present most widely used mapping method, the interspecific backcross (AVNER *et al.* 1988). DUNN'S particular interest in wild mice was the insight they provided into understanding the *t*-complex on mouse chromosome *17* (WAELSCH 1989). The pioneering work of DUNN and his colleagues on this fascinating genetic variant has led to much recent molecular mapping, to the proximal half of chromosome *17* being now the most intensively mapped region of the mouse genome, and to the cloning of a gene of major importance in vertebrate development (HERRMANN *et al.* 1990).

Progress in mouse genetic mapping has always been exponential (EICHER 1981), with the number of mapped genes doubling approximately every seven years. Thus, from our present vantage, the pace of advance in the early years appears slow. The first 50 years were spent in defining linkage groups. New genes were tested against all known genes or linkage groups, as in DUNN'S (1920a) paper on independent genes. GRÜNEBERG'S (1943, 1952) reference work of this time included tables showing which of these "tests for independent segregation" had already been completed. Also during this time, the statistical and theoretical backgrounds for the estimation of linkage or independence were much improved. In his 1920 papers DUNN used no statistics, but later FISHER (1946) published the maximum likelihood method for estimating recombination fractions, now the standard method. The detection of linkage between genes was put on a more rational basis by CARTER and FALCONER (1951), who put forward the concept of the "swept radius" or length of the genetic maps scanned in any given test for linkage, and thereby enabled the development of more rationally designed stocks for detecting linkage.

During the first 40 years or so, the genes mapped were mainly those producing some visible phenotypic effect, such as changes in coat color or texture, or in the skeleton or behavior. The work used "linkage testing stocks" of the type developed by CARTER and FALCONER. In the 1920s and 1930s much work went into the development of inbred strains (FESTING 1979; MORSE 1978, 1981). DUNN was the founder of the 129 strain, now widely used, but the great value of inbred strains in mapping studies was to emerge much later. The first biochemical genetic variant in inbred strains was found in 1941 (F. H. J. FIGGE and L. C. STRONG, quoted by MORSE 1981) and in the 1960s and 1970s emphasis shifted to the mapping of enzyme and other protein variants. It was then that the immense value of the inbred strains as a source of genetic variation became clear. Strains were typed for a wealth

of variants and RODERICK and his colleagues (RODERICK, STAATS and WOMACK 1981; RODERICK and GUIDI 1989) developed an extensive database of the alleles carried at particular loci in inbred strains. RODERICK and GUIDI (1989) provide a table of data on 338 loci in 246 strains, derived from a larger database at The Jackson Laboratory containing information on 426 loci in 569 strains. A breakthrough occurred when BAILEY (1971) developed the concept of recombinant inbred strains, subsequently developed further by TAYLOR (1978) for use in genetic mapping. In this method, two inbred strains with known genetic characteristics are crossed. The F_2 offspring are then paired at random and their offspring are mated brother × sister for 20 or more generations to form a new set of strains, the recombinant inbred or RI strains. In the formation of the new strains, genetically linked characters will tend to stay together and the number of cases of separation of two linked traits will depend on the recombination between them. Hence, if the set of recombinant inbred strains is typed, one can detect which traits are linked and the approximate recombination frequency between them. As a database of typed traits builds up, a given set of RI strains becomes steadily more powerful for linkage detection (TAYLOR 1989).

The study of biochemical variants led to increasing interest not only in inbred strains but also in wild mice. DUNN (DUNN and MORGAN 1952) had first used wild mice to search for new forms of the *t*-complex. He indeed found a range of different *t*-haplotypes and concluded that they are maintained as polymorphisms in the wild as a result of their abnormally high transmission from heterozygous males (DUNN and MORGAN 1952; DUNN 1957, 1964). Wild mice were then found to provide a rich source of biochemical genetic variation (CHAPMAN 1978) and numerous inbred strains were developed from various subspecies and species (BONHOMME and GUÉNET 1989). Another type of variation found among wild mice, and of key importance in genetic mapping, was karyotypic variation. For the first 50 years of mapping, mouse linkage groups could not be assigned to chromosomes. Many induced chromosome aberrations, mainly reciprocal translocations, had been studied (SEARLE 1989) and, following the pioneering work of SNELL (1946), had been shown to involve particular linkage groups. However, mouse chromosomes were not cytogenetically distinguishable until, in 1971, techniques for chromosome banding made possible the identification of individual chromosomes (MILLER and MILLER 1975). Knowledge of which linkage groups were associated with particular chromosome aberrations then enabled the assignment of linkage groups to chromosomes. The aberrations used included not only the induced reciprocal translocations, but also Robertsonian translocations found in wild mice, especially in *Mus poschiavinus* in certain alpine valleys where some populations had up to nine pairs of Robertsonians (GROPP and WINKING 1981).

Thus, in 1972 the linkage map appeared for the first time with the linkage groups assigned to chromosomes (GREEN 1972). Mapping then entered a new phase involving the precise location of genes, both in terms of their recombination with other genes and in their physical location with respect to chromosome G-bands. A recent advance in methodology has again involved the use of wild mice. GUÉNET and his colleagues (AVNER *et al.* 1988) showed that, if subspecies or closely related species of mice are compared, restriction fragment length variants (RFLVs) can be found for nearly all probes with the use of only one or two retriction enzymes. Thus, if laboratory mice are crossed with a wild species, usually *Mus spretus*, and the F_1 female is backcrossed to the laboratory strain (in a so-called interspecific backcross), all genes or other DNA markers can be mapped by their RFLVs. If DNA from individual backcross animals is stored, successive markers can be mapped, so that a panel of DNA from backcross animals becomes a resource which yields more detailed information as time progresses. DNA from animals with recombination within a certain interval can be used for further and finer mapping within that interval, thus enabling "homing in" on a region of interest as, for instance, in attempts to clone a gene. DUNN's interest in the *t*-complex has led to recent work which provides an interesting example of the use that can be made of a collection of rare recombinants in the region of interest. The *t*-complex is now known to involve a variant region of chromosome *17* (SILVER 1985; FRISCHAUF 1989; LYON 1990), which was first recognized by an interaction with the mutant gene for *brachyury, T*. Heterozygotes of *T* with wild type are short-tailed, whereas *T/t* heterozygotes are tailless. In mice heterozygous for a *t*-complex and a wild-type chromosome *17*, recombination is suppressed over the region occupied by the *t*-complex as a result of four inversions carried in the *t*-complex (HAMMER, SCHIMENTI and SILVER 1989). However, rare recombinants are found. These recombinants have been kept and used to provide evidence for the genetic basis of the transmission ratio distortion and male sterility which are other features of the *t*-complex (LYON 1984, 1986). Further use of these rare recombinants has enabled the ordering on the chromosome of numerous DNA markers derived by microdissection of the proximal region of chromosome *17* (FOX *et al.* 1985; FRISCHAUF 1989). Together with cloned genes and DNA markers from other sources, there are now over 100 markers on chromosome *17*, mainly in the proximal region (VINCEK *et al.* 1989). About 20 megabase pairs in three segments have been mapped by pulsed-field gel electrophoresis (BARLOW and LEHRACH 1989). In turn

this has facilitated the detection of candidate genes for the *distorter* and *responder* genes (RAPPOLD *et al.* 1987; SCHIMENTI *et al.* 1988) thought to be responsible for the transmission ratio distortion and male sterility, and also has led to the cloning of the *brachyury* gene (HERRMANN *et al.* 1990). The cloning of this gene is a major step forward because it plays a crutical role in the development of vertebrates. It is thought to be important in mesoderm formation and homozygotes fail to develop the notochord and the entire posterior part of the body.

With the detailed knowledge of comparative mapping now available, it should be possible to map the human homolog of *brachyury* very quickly. Although comparative mapping began at the same time as systematic mapping of the mouse itself with DUNN's paper on linkage in mice and rats, progress was relatively slow during the subsequent 50 years. Mapping was then largely restricted to markers with visible phenotypes and it was difficult to be sure of the homologies of particular syndromes. For instance, the mouse has many known genes for short tail or for polydactyly. Which of these might be the homolog of a gene with a similar effect in another species? With the use of protein variants, and even more when DNA markers became a standard tool for mapping, the determination of homologies could be made with much more confidence. Comparative mapping has since proceeded very rapidly, particularly in the comparison of mouse and human gene maps. The human homologies of nearly half the length of the mouse recombination map are now known (NADEAU 1989; SEARLE *et al.* 1989; LALLEY *et al.* 1989). Each mouse chromosome has homologies with from two to seven human chromosomes, and the known length of conserved segments ranges from <1 cM to >30 cM. Similarly, each human chromosome has homologies with up to six mouse chromosomes. So far, for instance, all known homologs of genes on human *17* are on mouse chromosome *11*, but mouse *11* has homologies with five other human chromosomes (BUCHBERG *et al.* 1989). Knowledge of homologies is not only valuable in making chromosome assignments in other species, it is also important in identifying mouse homologs of human syndromes. Many such homologs of human syndromes are now known, particularly for those diseases in which the underlying protein or DNA defect is known. Some syndromes are clearly similar in man and mouse. Examples include the testicular feminization syndrome, due to a mutation in the androgen receptor (LYON, CATTANACH and CHARLTON 1981), and the hemoglobin mutants, in which comparable molecular changes produce comparable physiological effects (PETERS *et al.* 1985). In other cases the phenotypes of homologous mouse and human genetic defects may be rather different. The mouse mutant *mdx*, with a lesion in the dystrophin gene *Dmd* (RYDER-COOK *et al.* 1988), has a much milder syndrome than is seen in Duchenne muscular dystrophy resulting from dystrophin defects in man. Similarly, the mouse gene *small-eye* (*Sey*) is apparently homologous with the aniridia defect of the Wilms-aniridia syndrome in man, but has a rather different effect (GLASER and HOUSMAN 1989; HOGAN *et al.* 1986). In these cases, knowledge that the mouse gene was appropriately located was important in finding the homology, and further homologous syndromes will no doubt be identified in this way in the future.

With the wealth of information now available on the mouse map, the importance of coordinated and widely available databases becomes clear. Here DUNN was once again a pioneer. Fifty years ago, in 1939, with GRÜNBERG and SNELL, DUNN founded the first Nomenclature Committee for the mouse, and produced the first gene list (DUNN, GRÜNEBERG and SNELL 1940). Ten years later, in 1949, DUNN, together with SALOME GLUECKSOHN-SCHOENHEIMER (now WAELSCH), edited the first edition of *Mouse News Letter* (now *Mouse Genome*) (SEARLE 1974). Both the Nomenclature Committee and *Mouse News Letter* have continued ever since. The Nomenclature Committee not only promulgates rules for genetic nomenclature but also promotes the dissemination of gene lists and maps with *Mouse News Letter* as its main organ of publication, and has sponsored the production of works of reference giving not only mapping data but also data on the necessary resources such as inbred strains, RI strains and wild strains (GREEN 1981; LYON and SEARLE 1989). The database underlying the mouse map was for many years maintained by M. C. GREEN (1966) and more recently by DAVISSON and RODERICK and their colleagues (DAVISSON, RODERICK and DOOLITTLE 1989). With the exponential growth of information, in the near future the maps are likely to become too detailed to be published regularly on paper, and there will be a move toward electronic publication. Already The Jackson Laboratory makes available on-line the set of databases known as Gbase, including a list of loci, mapping data, and lists of inbred strains and their variants (DAVISSON *et al.* 1989).

Indeed, in the future the previously exponential rate of increase in mapped genes may be surpassed. With the use of interspecific backcrosses, suitable RFLVs for mapping will be available for almost all genes. In addition, there will be anonymous DNA markers generated by microdissection, chromosome sorting and other means. However, in view of the wealth of RFLVs for known genes, anonymous DNAs will be relatively less important than in human genetic mapping. Other variants for mapping will be generated by induced mutagenesis. This may either use conventional agents such as chemicals or radiation, with mutants being collected from known loci or

regions (RINCHIK *et al.* 1986, 1990; RINCHIK, CARPENTER and SELBY 1990; RUSSELL, MONTGOMERY and RAYNER 1982; RUSSELL *et al.* 1979; HITOTSUMACHI, CARPENTER and RUSSELL 1985; SHEDLOVSKY *et al.* 1986; KING *et al.* 1989), or may involve insertional mutagenesis, with the advantage that the mutations will be tagged and thus cloning will be facilitated (GRIDLEY, SORIANO and JAENISCH 1987). Directed mutagenesis by homologous recombination will obviously be an important tool (CAPECCHI 1989). It is probable that the wheel will come full circle and that mutants with visible phenotypes will again become important, either as homologs of human syndromes or as genes with major roles in development.

For the first time, the true length in centimorgans of the mouse genome should become known. For this, convenient markers of centromeres and telomeres are needed and will surely become available. A problem is that this length may well be that, not of the laboratory mouse genome but of the F_1 between *Mus spretus* and the laboratory mouse. Already, one small inversion has been found which differentiates these two genomes (HAMMER, SCHIMENTI and SILVER 1989) and there may well be others. Indeed, there may be differences among strains in small inversions or recombination hot spots, so that details of map lengths may vary from strain to strain. Insight will also be gained into chromosome structure and the genetic content of light and dark G-bands (BICKMORE and SUMNER 1989). At present there is strong variation in the density of markers on the map, from about 20 markers per 10 cM in some regions to fewer than one per 20 cM in others. Does this reflect real differences in the density of genes in different regions or variations in chiasma frequency, or is it merely an artifact of incomplete knowledge?

Thus, it is clear that the mouse has a key role in relation to the human genome mapping project. On the one hand it is by far the best mapped experimental vertebrate, and indeed ranks among the best mapped higher organisms. On the other hand there is detailed knowledge of the comparative mapping of the mouse and human genomes. The mouse is also an excellent organism, in both techniques and resources, for experimental manipulation and analysis of the genome. This means that the mouse will be of fundamental importance in elucidating the genetic basis of mammalian development and will be equally valuable in understanding the genetic basis of human disease.

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