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SPECIAL MOUSE STRAINS REPOSITORY: GENETIC TOOLS FOR QUANTITATIVE TRAIT ANALYSIS

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Genetic analysis of complex traits is facilitated with model systems in which genetic manipulations, e.g. linkage crosses or construction of congenic strains makes it possible to associate phenotype with quantitative trait loci (QTL) that map to one or more regions on particular chromosomes. Identification of QTL is the first step in the process of associating a gene to a phenotype.

Although powerful methods exist for complex trait analysis in mice, they usually are time consuming and expensive, requiring large genetic crosses and expensive genotyping. The Special Mouse Strains Repository (SMSR) at The Jackson Laboratory maintains and distributes genetic tools for QTL analysis, including 5 recombinant inbred strain sets (total of 89 strains) and the first complete mouse consomic (chromosome substitution) strain set, consisting of 21 strains. The consomic set, C57BL/6J-Chr #^{A}/NaJ, was made by replacing individual chromosomes from the A/J donor strain in the C57BL/6J host strain. Both the RI and the chromosome substitution strain sets improve the efficiency of identifying genes in mouse models of human multigenic diseases.

A set of RI strains is generated by mating mice of two genetically diverse inbred strains, randomly mating F1 mice to produce F2 mice, and then brother-sister inbreeding multiple lines for at least 20 generations. Individual RI strains generated from the same initial cross each have a unique combination of loci derived by recombination of the alleles present in the original parental strains. RI strains have a number of advantages over F2 or backcross mouse populations as tools for mapping genes or identifying quantitative trait loci (QTL). Unlike linkage cross progeny, a set of RI strains is a perpetually renewable resource. Genetic and phenotypic data acquired for an RI strain set are cumulative, enhancing the value of the strain set for further studies. In addition, as extensive genetic data and maps exist for most RI strain sets, in many cases no additional genotyping is necessary to map a newly characterized trait.

Chromosome substitution (CS), or consomic strains, can accelerate QTL identification and mapping. CS strains are produced by transferring a single, full-length chromosome from one inbred strain onto the genetic background of a second strain by repeated backcrossing. A set of 21 strains, each derived from the same donor and host strains, but having a different host strain chromosome (Chromosome 1-19, X or Y) replaced by its counterpart from the donor strain, comprises a complete panel of CS strains.

Detection of a QTL associated with a phenotypic trait that differs between the donor and the host of a CS panel is accomplished simply by phenotyping mice from each member of the set. The presence of the trait of interest in a particular CS strain indicates that there must be at least one QTL on that chromosome. The advantages of QTL analysis using CS strains are that (1) initial linkage crosses are unnecessary, (2) genotyping is not required, (3) fewer mice need to be phenotyped, and (4) QTL with weaker phenotypic affects can be detected compared to linkage crosses. Mice of the CS strain exhibiting the trait of interest can be used to generate, within a few generations, a series of congenic strains that subdivide the chromosome into segments and thus refine the position of the QTL of interest.