inversions, are clustered together at two sites; our data suggest that the rearrangements occurred in a coincident fashion, or were commonly associated with unstable DNA sequences at those sites. Interestingly, both rearranged regions are occupied by large tandemly clustered gene families, suggesting that these locally repeated sequences may have contributed to their evolutionary instability. The structure and conserved functions of genes within these and other clustered gene families located on H19 also represent an active line of interest to our group. More recently, we have extended mapping studies to include clustered gene families located in other chromosomal regions, and are working to define the borders of mouse-human syntenic segments on a broader, genome-wide scale.

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Positional Cloning of Murine Genes

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Chromosome rearrangements, notably deletions and translocations, have proved invaluable as tools in the mapping and molecular cloning of a acquired and inherited human diseases. Because balanced translocations are cytologically visible, and generally produce profound disturbances in both gene expression and DNA structure without necessarily disturbing the structure of multiple genes, this type of mutation provides an especially valuable "tag" that greatly simplifies mapping, cloning, and assessment of candidate genes associated with a disease. Although balanced translocations are relatively rare in human populations, they are readily induced in the mouse. Using various mutagenesis protocols, we have generated numerous translocation-bearing mutant mouse strains that display an impressive variety of health-related anomalies, including obesity, polycystic kidneys, gastrointestinal disorders, limb and skeletal deformities, neural tube defects, ataxias, tremors, hereditary deafness and blindness, reproductive dysfunction, and complex behavioral defects. The ability to map the genes associated with translocation breakpoints cytogenetically, first crudely through straightforward banding techniques and then to a higher level of resolution using fluorescence in situ hybridization methods, allows us to avoid the costly and time-consuming crosses that are required for the mapping of most mutant genes. With this rapidly-obtained, crude-level mapping information available, we can readily assess possible relationships between newly arising mutant phenotypes and linked candidate genes or related diseases that map to homologous regions of the human genome. Using this approach, we have recently begun to define the map positions of several mutations. Mapping results have led us to the identification of candidate genes for two mutations: one associated with congenital deafness and predisposition to severe gastric ulcers, and another associated with late-onset obesity. So far, we have characterized only a fraction of the mouse strains that comprise this valuable, recently-generated mutant collection in detail. As a integral part of this program, we are actively exploring new strategies and integrating information, technology and resources derived from the Human Genome research effort, that promise to increase the efficiency of breakpoint mapping and cloning dramatically. The mutations are scattered widely throughout the mouse genome corresponding to a broad selection of human homology regions. As new breakpoints are mapped, and large numbers of newly-sequenced cDNA clones are assigned to the mouse and human maps, the potential for rapid association between cloned gene and mapped mutation will increase dramatically. This large collection of murine translocation mutants therefore represents a powerful resource for linking mapped cDNA clones to health-related phenotypes throughout the genome.

In addition to the analysis of translocation mutants, we have also characterized other types of mouse mutations, including: (1) *tottering* and *leaner*, allelic mutations associated with ataxia and epilepsy in mice, and representing murine models for human diseases, familial hemiplaegic migraine and episodic ataxia, respectively; and (2) *jdf2*, a locus associated with mutations causing runting, neuromuscular tremors and male sterility which is located in a mouse region related to the Prader Willi-Angleman syndrome gene interval of human 15q11-q13. Both sets of mutations affect large, complex, and highly conserved genes, and provide important animal models for the exploration of the diverse roles their human counterparts may play in human disease. In concert with these gene cloning studies, we have been involved in exploring new means of exploiting mouse-human genomic conservation in the isolation of functionally-significant sequences from large cloned regions of human DNA. The methods we have developed hold great promise as an efficient tool for gene discovery in cloned genomic regions.

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