"Complex Traits and Normal Variation: Partnership Between Mice and Humans"
Genetic Epidemiology / Genetics Session
2005 National Oral Health Conference
Pittsburgh, PA, May 4, 2005

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Mouse Facts:
A strain of mouse is considered inbred following a minimum of 20 consecutive generations of sister x brother mating. At this point ~98% of the strain's loci are homozygous. Many current mouse strains have been inbred more than 150 generations and are essentially homozygous at all loci. Each inbred strain is also isogenic (genetically identical) because all individuals trace back to a common ancestor in the twentieth or a subsequent generation.

Contemporary laboratory mice owe their origin to a limited number of founder stocks once held by mouse enthusiasts (mouse fanciers) who treated these animals as pets. Over time more that 400 inbred strains have emerged. Today approximately 10% of these inbred strains are used in biomedical research. The following nine inbred strains: 129S1/SvImJ; A/J; AKR/J; BALBcbyJ; C3H/HeJ' DBA/2J; FVB/NJ; NOD/LtJ; and C57BL/6J account for 85% of all inbred strain usage in biomedical research.

An inbred strain has a unique set of characteristics that sets it apart from all other inbred strains. Many traits do not vary from generation to generation. Other traits are easily influenced by diet and environmental conditions and may vary from one generation to the next.

Humans and mice are ten times more closely related to each other than either is to flies (D. melanogaster) or nematodes (C. elegans).

Taxonomic breakdown of homologues of mouse proteins according to taxonomic range. Only a small fraction of genes are possibly rodent-specific (<1%) as compared with those shared with other mammals (14%, not rodent-specific); shared with chordates (6%, not mammalian-specific); shared with metazoans (27%, not chordate-specific); shared with eukaryotes (29%, not metazoan-specific); and shared with prokaryotes and other organisms (23%, not eukaryotic-specific). Dozens of local gene family expansions have occurred in the mouse lineage. Most of these seem to involve genes related to reproduction, immunity and olfaction, suggesting that these physiological systems have been the focus of extensive lineage-specific innovation in rodents.

There is considerable conservation of gene order (synteny) between mice and humans. Synteny means "same thread" (or ribbon), a state of being together in location, as synchrony would be together in time. This translates into the ability to localize the human orthologue knowing the location of the mouse gene and vice versa. Other useful definitions, 'paralogous' for genes that arose from a common ancestor gene within one species and 'orthologous' for the same gene in different species.

Mouse Phenome Project:
The goal is to establish a collection of baseline phenotypic data on commonly used and genetically diverse inbred mouse strains through a coordinated international effort."

This has been an international effort coordinated through The Jackson Laboratory in Bar Harbor, ME. The Mouse Phenome Database Website is freely accessed at (http://aretha.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home)

A core of 41 strains has been selected to provide the foundation for normal variation among a number of quantitative traits.

The MPD website will enable investigators to identify appropriate strains for:

- physiological testing
- drug discovery
- toxicology studies
- mutagenesis
- disease onset and susceptibility
- new models of human disease
- QTL analyses and identification of new genes
- unraveling the influence of environment on genotype

Complex Traits:

Many traits that are present in populations of humans and other organisms are determined by multiple factors. Many common diseases that have genetic components and can be considered complex traits. The complexity arises because individual factors contribute to the total variation in the trait observed in the entire population. Complex traits can be continuous in distribution (e.g. height), or they may be dichotomous (e.g. cleft lip). Multiple genetic and environmental factors may interact with each other and their interaction can be unpredictable. The genetic components of a complex trait can be identified through quantitative trait loci (QTL) mapping. The example used today is the mandible. When the environment is superimposed upon the genotype, QTL mapping can also be utilized. Mice offer many opportunities and advantages to dissect the contributions of environment and genotype for a particular complex trait.

There are various stages of QTL analysis:

- QTL detection
- QTL mapping
- Fine mapping
- Gene cloning

When considering a genetic study in mice the degree of genetic contribution must be determined first. A survey of a panel of strains can lead to indications of heritability. It is common to find a pair of strains that display extremes of the trait (e.g. big vs. small, resistant vs. susceptible). Furthermore, the model of gene action should be determined through reciprocal intercrossing of two candidate strains. F1 (hybrid) progeny can be investigated for the complex trait. Based upon those observations it is possible to determine if the trait fits a dominant, recessive, or additive model of gene action. It is also possible to determine if bias towards one sex exists. Completion of these preliminary steps will allow construction of appropriate breeding schemes (F2 vs. backcross) and to perform power calculations to estimate the total number of animals needed as well as the appropriate degree of coverage for a genome scan.