A powerful mouse resource for mapping genetic traits, identifying modifying genes and unravelling gene networks

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Mapping genetic traits, especially complex ones, can be difficult in human populations for a variety of reasons. These include hurdles to multiple sampling of different tissues and at multiple time points, as well as controlling for environmental effects. However many of the associated difficulties can be mitigated by using mice. A powerful mouse resource with a greatly improved genetic diversity than those previously available is the Collaborative Cross. One of only 3 international nodes exists in Perth, Australia.

The Collaborative Cross is derived from eight genetically diverse founder mouse strains. The genome of each descendent strain is a mosaic of chromosomal segments inherited randomly from the founders. As the genomes of all founder lines have been sequenced, a virtual genome assembly of each offspring strain can be established after high-density single nucleotide polymorphism arrays. The Complex Trait Consortium's aim was to create 1000 Collaborative Cross descendent strains worldwide.

We have analysed approximately 60 Western Australian Collaborative Cross strains for a variety of traits, in particular those relevant to skeletal muscle. We have performed measurements of young (~6 weeks of age) and older (6 to 9 months of age) mice, both male and female.

As a proxy measure of skeletal muscle function we have measured voluntary running wheel activity (distance run per day, maximum speed, average speed, time spent running per day, real-time activity levels). We have also analysed body weight and investigated further select strains by magnetic resonance imaging. Tissue RNA microarrays are being performed on *soleus*, *extensor digitorum longus* and heart muscles.

Our results show marked phenotypic variation across all traits, including comparisons from the same mouse strains at two time points. We have identified quantitative trait loci (QTL) for several traits. In addition significant expression QTL (eQTL) for various muscle-related genes have been established, implicating the genomic region/s influencing expression of those genes.

Haplotype analysis can reveal the founder mouse strain/s contributing to the trait being investigated. Subsequent comparison of the whole genome sequence data for all founder strains can then reveal likely sequence variant candidates within the linkage region as targets for further interrogation.

Associated bioinformatics resources allow mining of gene correlations and networks, helping to unravel gene functions and associations. Additionally, correlations between traits can be determined by cross-referencing different phenotypic datasets (*e.g.* voluntary exercise and skeletal muscle gene expression).

We are also attempting to map genetic modifiers of disease, such as skeletal muscle actin disease, and dystrophin-deficient muscular dystrophy (*mdx*), by breeding mouse models with multiple Collaborative Cross strains. Once genetic modifier/s for improved skeletal muscle disease phenotypes are identified, they could be targeted for modulation as potential therapeutic avenues.