

Genetic Architecture of Obesity Predisposition Expression Studies

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Abstract:

Obesity is a multifactorial trait controlled by complex contributions of genetics and environment. Genetic predisposition results from combinations of relatively small effects of DNA variations within a large number of genes, known as quantitative trait loci (QTL). Well over 200 QTL have been reported for growth and body composition traits in the mouse, likely representing at least 50 to 100 distinct predisposition genes. Molecular biology has yielded significant advancements in understanding these traits at the metabolic and physiological levels. However, little has been learned regarding the identity and nature of the underlying polygenes. The wide gap between our knowledge of physiological mechanisms underlying complex traits, and the nature of genetic predisposition, significantly impairs discovery of genes underlying QTL controlling obesity.

Identification and genetic mapping of key transcriptional, proteomic and metabolomic events will uncover large lists of significant positional candidate genes for obesity predisposition. Integration of experimental approaches to jointly evaluate predisposition and physiology will increase success of QTL identification by merging the power of recombination with functional analysis. Measuring physiologically relevant sub-phenotypes within structured QTL mapping populations will not only facilitate pathway-specific prioritization among candidate genes, but may also directly identify genes underlying QTL. This would advance our understanding of the genetic architecture of complex traits by testing the hypothesis that genes controlling predisposition to obesity are predominantly involved in trans-regulation of primary physiological pathways regulating energy balance