

# **Genetic Approaches for Identifying Genes for Complex Diseases**

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The identification of genes contributing to common disorders, such as diabetes and coronary artery disease (CAD), has proven difficult due to their genetic complexity and the influence of environmental factors. While positional cloning has led to the identification of numerous genes for rare Mendelian disorders, the application of this tedious process to complex diseases has been disappointing.

As an example of this approach, we performed genetic crosses between strains of mice that had differential susceptibility to cardiovascular and metabolic traits. The culmination of this work resulted in the identification of 5-lipoxygenase (5-LO) as a gene conferring dramatic resistance to atherosclerotic lesion development in mice, even in the presence of markedly elevated cholesterol levels. Interestingly, 5-LO was also associated with other metabolic traits such as body fat and insulin metabolism. 5-LO is the rate-limiting enzyme in leukotriene biosynthesis, a class of inflammatory molecules derived from arachidonic acid, which have been known for many years to be involved in the pathogenesis of asthma. Thus, 5-LO may be involved in the atherosclerotic process through its inflammatory properties and the effects of its byproducts. The mechanisms by which 5-LO influences the metabolic traits associated with diabetes and obesity remains unknown.

Given these results in mice, we tested whether 5-LO affects cardiovascular phenotypes in humans as well. Previous studies had demonstrated that various alleles of a 5-LO promoter polymorphism exhibited functional differences *in vitro* and were associated with a pharmacogenetic response in asthma patients. Therefore, this polymorphism was genotyped in a cohort of individuals characterized for carotid intima-media thickness (IMT), an accepted surrogate marker for atherosclerosis. Interestingly, individuals who were homozygous for the “deleted” alleles of the polymorphism had significantly greater IMT than individuals in the other genotype groups. This effect was observed even after adjustment for a number of covariates, including ethnicity, lipids levels, diabetes, smoking, and medication use. Current studies are focusing on extending these initial findings to large case-control cohorts consisting of myocardial infarction patients or individuals who have undergone coronary angiography, which are more formal assessments of cardiovascular disease. In addition to 5-LO, the other major genes of the 5-LO/leukotriene pathway are also being investigated for their genetic contribution to atherosclerosis.

These studies demonstrate that using a combination of mouse and human genetics can lead to genes underlying complex diseases. The development of novel genomics and bioinformatics tools, such as the creation of whole genome congenic strains, microarray technologies, and the availability of the genomic sequence from different mouse strains, will accelerate this process.

### **Selected References:**

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