Using Growth Curves to Model Triglyceride Responses to Fenofibrate Therapy: Associations of Response with Candidate Genes

Andrew Van Brunnt

Mentor: Ingrid Borecki, Ph.D.

Abstract

Coronary heart disease (CHD) is the single largest killer of both men and women in America. It is estimated that CHD caused 1 of every 5 deaths in the United States in 2003. There is ample evidence that cholesterol levels predict atherosclerosis, and therefore, CHD. Recent studies also support the importance of serum triglyceride (TG) levels as independent predictors of CHD risk. Triglycerides are particularly important for risk management because of their responsiveness to various interventions. The goal of the GOLDN study is to identify genes involved in TG response to two strong environmental interventions, one to raise TG (dietary intake of a high-fat shake) and the other to lower TG (a 3-week trial of fenofibrate). In the present study, we focus on polygenic modeling of SNP effects on variability in fenofibrate response in extended families that previously had participated in the NHLBI Family Heart Study. A response phenotype was developed using growth curve modeling techniques in which several variations on generating the phenotype were explored, and the resulting phenotypes were judged by their heritability estimates. A model simultaneously accounting for multiple measurements, family correlations, and the effects of covariates yielded a response phenotype that was 39% heritable. Subsequently, 100 pre-selected SNPs in 25 candidate genes were tested for their ability to explain variability in response. Several methods were employed to detect SNP associations with the phenotype. First, the SNPs were screened for marginal effects. Next, multivariate regression methods were used to develop a polygenic model. To determine which combination of SNPs best explained the response, several selection methods were tested including forward stepwise, backwards elimination and regression by leaps and bounds. A model including 18 of the SNPs was developed which accounted for a maximum of 37% of the genetic variation of the response, allowing for dominance effects. This model could be used to adjust the phenotype for these known effects in future efforts to identify novel relevant genes by whole genome linkage and association studies.