# Detection of Dynamic Effects of Rare Haplotypes and Their Interaction with Environmental Factor on Complex Disease

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Two important contributors to missing heritability are believed to be rare variants and gene-environment interaction (GXE). Thus, detecting GXE where G is a rare haplotype variant (rHTV) is a pressing problem. Haplotype analysis is usually the natural second step to follow up on a genomic region that is implicated to be associated through single nucleotide polymorphism (SNP) analysis. Further, the behavior of a gene can be dynamic, thus it is important to focus on gene-environment interactions and study the dynamic effects of genes on a trait over time if longitudinal data are available. In this work, we model the effects of both rare and common haplotypes over time using longitudinal data through time-varying coefficients (tvc) using B-spline and incorporate environmental factors and their interacting effects using the Logistic Bayesian LASSO (LBL) framework, leading to the LBL-tvc methodology. Since longitudinal data are collected forward in time over a certain period in a cohort of individuals, we formulate the likelihood of our model prospectively. We cast the problem into a Bayesian framework for more precise estimations of effect sizes of rare haplotypes and adopt the Markov chain Monte Carlo

(MCMC) methods for sampling from the posterior distribution for statistical inferences. We carry out extensive simulations to evaluate the properties of LBL-tvc and to assess its robustness to model mis-specification. We also apply LBL-tvc to analyze the MAP4 gene on chromosome 3 and smoking on their effects on hypertension based on data from a Mexican American population, and have identified several haplotypes, including a rare one, that are associated with hypertension with varying effect sizes in the range of 55-85 years of age.