Cholesterol metabolism pathway: Cognitive change and Alzheimer's disease risk

Chandra A. Reynolds, PI
Jonathan A. Prince, Co-PI

Project Description: The etiologies of normative cognitive change and Alzheimer's disease (AD) in late adulthood are not fully understood. Outside of the gene encoding apoE, consistent candidate gene associations are relatively scant. Established effects of genetic variation in *APOE*, the primary cholesterol transporter in the brain, upon lipid levels, cognitive change, and AD risk suggest the cholesterol pathway may be centrally important. We propose to target genes integral to cholesterol homeostasis and perform multi-tiered association studies to investigate the possible existence and impact of functional genomic sequence variation on plasma lipid parameters, CSF $A\beta$ and tau, measures of longitudinal cognitive performance, and Alzheimer's disease (AD). We have prioritized numerous genetic markers, focusing on HapMap based markers as well as potential functional polymorphisms within multiple cholesterol genes. We hypothesize that functional genetic polymorphism occurs in the selected candidate genes and will explain variance in a variety of cholesterol related phenotypes, with stronger effects upon proximal phenotypes (e.g. cholesterol and $A\beta$ levels) than for cognitive phenotypes and AD risk. Several related longitudinal Swedish twin studies will be combined to test association with serum lipid biomarkers, cognitive decline, total dementia and AD risk. Additionally, we will use a large established Swedish AD case-control sample for testing additional biomarkers (CSF $A\beta$, tau) and AD risk. Across twin and case-control studies there are 3,858 of individuals (59% female) available for analysis of DNA markers, 1,227 with AD diagnoses. Of those with DNA, there are 676 twin pairs with available lipid biomarkers and 729 twin pairs with available cognitive data. Our goals are to move stepwise from anonymous variance components to measured genes in the cholesterol pathway, intermediate biomarkers, and ultimate behavioral and clinical phenotypes. Of principal interest is to: (1) test the association of cholesterol gene markers with serum lipid and CSF biomarkers; (2) test the association of lipid biomarkers and cholesterol gene markers with cognitive decline across verbal,

spatial, memory and perceptual speed domains, using longitudinal growth models to quantify change; and (3) test the association of cholesterol gene markers, total dementia and AD risk. We will apply haplotype and multi-locus regression approaches to determine association. Strengths of the study include multiple levels of replication and rich longitudinal data, both for lipid and cognitive traits. The examination of multiple candidate genes in the cholesterol pathway, using both twin-based and case-control methods, will lead to an increased understanding of factors that contribute to cognitive changes, total dementia and AD risk in late-life.

Questions or requests regarding the project can be directed to:
Chandra A. Reynolds, PhD
Associate Professor
Department of Psychology
1344 Olmsted Hall
University of California - Riverside
Riverside, CA 92521
e-mail: chandra.reynolds@ucr.edu