Phenotype of ischemic stroke and stroke outcomes in high risk pedigrees.

Research Plan

SPECIFIC AIMS:

Stroke is a high morbidity, high mortality disease, with heterogeneous subtypes and unclear heritability. Since stroke primarily affects the aged and has a high case fatality, family history data are often limited and survivors are few. Molecular genetic studies have typically been limited to a case-control methodology. Association studies, both candidate-gene and genome wide association studies, have looked for specific polymorphisms associated with increased stroke risk or stroke mortality but most have not been replicated.[1] [2] Frequently-cited reasons for the lack of consistency in results includes small sample sizes, phenotyping errors, and poor (or no) differentiation of subtypes.[3] [1] Regarding subtypes, most studies have not differentiated even the most basic stroke subtypes (hemorrhagic stroke vs. ischemic stroke) and even fewer have differentiated ischemic stroke subtypes (cardioembolic stroke, small vessel stroke, atherosclerotic stroke, other known types (e.g. dissection), and cryptogenic), despite these subtypes having clear and separate pathophysiologies. Recently, due to failures of association studies and lack of knowledge of genetic epidemiology, there has been a call for high quality, large, genetic epidemiologic studies of stroke.[4]

In this study, Dr. Cannon-Albright, PhD, Genetic Epidemiology, and I propose to utilize a pedigree methodology to find families at high risk for stroke and stroke mortality and then determine their excess heritable risk, i.e. the risk beyond that expected from traditional vascular risk factors. We will then deeply phenotype the families to determine what stroke subtypes are highlyheritable. We will be able to use results from this preliminary study to form the basis for an external grant application aimed at determining the genetic causes of the excess heritable risk. Though we currently plan to perform high density single nucleotide polymorphism (SNP) analysis followed by exome sequencing of highly linked regions,[5, 6] we will take advantage of any advances in genetic analytic technology at the time of analysis.

AIM 1: Determine heritability of ischemic stroke incidence, prevalence, and mortality. Identify families at high risk of ischemic stroke, utilizing the Utah Population Database (UPDB) and linking with known, high quality cases by using the University of Utah Stroke Center quality database. My preliminary work with Dr. Cannon-Albright has identified 23,448 persons in the UPDB with death coded as ischemic stroke and >300 families with 3-87 cases per pedigree at high risk for ischemic stroke mortality.[7] This work will be expanded by querying the Enterprise Data Warehouse for incident and prevalent stroke cases, cross-referencing families with the Stroke Center database, expanding the pedigrees to include published pedigree information (such as found in obituaries), and conducting family member interviews.

AIM 2: Deeply phenotype representative, available families at high risk, to determine 1) if heritability is attributed to traditional risk factors of intermediate phenotypes rather than a pure stroke phenotype and 2) which ischemic stroke subtype is highly inherited. This is critical as no current stroke studies of stroke genetics have focused on specific stroke subtypes. We will utilize both record review and in-person interviews to phenotype the ischemic stroke cases into the classic subtypes, utilizing the Causative Classification of Stroke system.[8]