

The Role of Phosphodiesterase 4D in Genetic Susceptibility to Ischemic Stroke

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Introduction: Cerebrovascular disease causes over 200,000 deaths in the United States each year. Additionally, it is the leading cause of disability and is responsible for \$53.6 billion in costs annually. Genetic susceptibility to ischemic stroke, accounting for over 80% of all strokes, has been long established, but the exact genetic determinants have remained elusive. However, recent studies of an Icelandic population have identified the gene phosphodiesterase 4D (*PDE4D*) to be significantly associated with ischemic stroke. We examined whether a similar association exists within the diverse population of The Greater Cincinnati / Northern Kentucky area. **Methods:** A sample of 384 patients with ischemic stroke were identified along with an equal number of controls matched for age, race, and gender. Each individual was interviewed for risk factor exposure and blood or buccal samples were obtained. DNA was extracted and amplified using a standardized whole genome amplification (WGA) protocol. Six single nucleotide polymorphisms (SNPs) within the *PDE4D* gene, which were previously reported to be associated with ischemic stroke, were genotyped using the TaqMan assay after optimization for each primer set. Haplotypes were inferred using PHASE.ver 2.1. **Results:** One SNP was non-segregating while the remaining were found to be in Hardy-Weinberg equilibrium. Individual SNP genotypes were not significantly associated with the ischemic stroke outcome after race stratification, although a trend was observed for marker rs152312 among whites ($p=0.13$). A significant association was observed between haplotypes of the *PDE4D* gene and ischemic stroke among whites ($p=0.0001$) and blacks ($p=0.009$). Differences between cases and controls were found primarily in rare haplotypes (<5% frequency among controls) while the most common haplotypes were not significantly different between cases and controls. **Conclusion:** We found that haplotypes based on 5 SNPs of the *PDE4D* gene are significantly associated with ischemic stroke in individuals of the Greater Cincinnati / Northern Kentucky area. This and future studies will bring us closer to providing individualized and more effective stroke therapy and prevention options to our patients.