ASSOCIATION OF ALZHEIMER'S DISEASE WITH POLYMORPHISMS IN THE PON GENE CLUSTER ON CHROMOSOME 7.
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The genetic component in the etiology of late-onset Alzheimer’s disease (AD) arises from a combination of distinct effects of an unknown number of genomic loci. Mapping these loci could provide clues that would help the study of the pathophysiological pathways leading to the development of AD, and could open possibilities for treatment. At present, only the well known polymorphism in the APOE gene had been implicated in AD in a consistently replicable manner, although data exist to support the involvement of several additional loci. There is a growing body of evidence from pathological, clinical and genetic studies implicating the cerebrovascular pathway in AD. The human PON genes (PON1, PON2 and PON3,) clustered in tandem on chromosome 7q21-q22, encode three variants of the enzyme paraoxonase, which is a widely expressed arylesterase present in serum. Serum paraoxonase activity is associated with HDL. Polymorphisms in PON1 and PON2 are associated with increased risk of coronary heart disease in Caucasian and Asian populations, respectively. PON1-deficient knockout mice show increased susceptibility to atherosclerosis relative to their wildtype littermates when fed on a high-fat, high-cholesterol diet. We used gene mapping techniques to assess the potential involvement of PON genes in the etiology of late onset AD. In a sample of African American families comprising of 236 AD cases and 168 unaffected siblings, using an association test which takes the family structure into account (GEE,) we found a significant association of AD with several Single Nucleotide Polymorphisms (SNPs) in PON2 (most significant p =0.0002.) Using a transmission disequilibrium test, which is robust to population admixture, we also found disease associated haplotypes spanning the PON2 region, in a sample of 73 African American and Caucasian families (p= 0.0026.) These results support an involvement of paraoxonase in the etiology of late onset AD.