A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease

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OBJECTIVE: While the apolipoprotein E (APOE) epsilon allele is a well-established risk factor for late-onset Alzheimer's disease (AD), initial genome scans using microsatellite markers in late-onset AD failed to identify this locus on chromosome 19. Recently developed methods for the simultaneous assessment of hundreds of thousands of single nucleotide polymorphisms (SNPs) promise to help more precisely identify loci that contribute to the risk of AD and other common multigenic conditions. We sought here to demonstrate that more precise identification of loci that are associated with complex, multi-genic genetic disorders can be achieved using ultra-high-density whole-genome associations by demonstrating their ability to identify the APOE locus as a major susceptibility gene for late-onset AD, despite the absence of SNPs within the APOE locus itself, as well as to refine odds ratios (ORs) based on gold-standard phenotyping of the study population. METHOD: An individualized genome-wide association study using 502,627 SNPs was performed in 1086 his-topathologically verified AD cases and controls to determine the OR associated with genes predisposing to Alzheimer's disease. RESULTS: As predicted, ultra-high-density SNP genotyping, in contrast to traditional microsatellite-based genome screening approaches, precisely identified the APOE locus as having a significant association with late-onset AD. SNP rs4420638 on chromosome 19, located 14 kilobase pairs distal to the APOE epsilon variant, significantly distinguished between AD cases and controls (Bonferroni corrected p value = 5.30 x 10(-34), OR = 4.01) and was far more strongly associated with the risk of AD than any other SNP of the 502,627 tested. CONCLUSION: This study provides empirical support for the suggestion that the APOE locus is the major susceptibility gene for late-onset AD in the human genome, with an OR significantly greater than any other locus in the human genome. It also supports the feasibility of the ultra-high-density whole-genome association approach to the study of AD and other heritable phenotypes. These whole-genome association studies show great promise to identify additional genes that contribute to the risk of AD.

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