NOVEL SUSCEPTIBILITY LOCI IDENTIFIED FOR ALZHEIMER’S DISEASE

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Introduction: Alzheimer’s disease (AD) is genetically complex and shows heritability up to 79%. Until recently, APOE was the only unequivocal susceptibility gene for late-onset AD. A number of genome-wide association studies (GWAS) have now been performed and additional AD susceptibility genes have been identified including CLU, PICALM, CR1 and BIN1. Larger studies are now required to identify remaining susceptibility variants for Alzheimer’s disease.

Aims: To identify novel susceptibility loci for AD.

Methods: We sought to identify new susceptibility loci for AD through a 3-stage association study. The first stage of the study comprised a meta-analysis of four GWAS datasets (up to 6688 cases and 13685 controls). SNPs that remained significant at P<1x10⁻⁵ were tested for replication in the second stage of the study, comprising 4896 cases and 4903 controls. In Stage 3, SNPs showing significant evidence of replication in Stage 2 were tested for association in an independent sample comprising up to 8286 cases and 21258 controls.

Results: In Stage 1 we identified 61 SNPs associated with AD at P≤1x10⁻⁵ following meta-analysis of four GWAS datasets. Of ten SNPs at novel loci selected for further analysis, three variants (at two loci) showed significant evidence for replication both in Stage 2 and in Stage 3. A meta-analysis of all data (>50000 individuals) provided strong evidence that these two novel loci influence AD susceptibility (Meta-P<5x10⁻¹⁴).

Conclusions: The identification of novel AD susceptibility loci provides new insight and impetus for focused studies aimed at understanding the pathogenesis of AD.