APOE LOCUS HAPLOTYPES MODULATE EXPRESSION

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Introduction: Genetic variation within the APOE gene locus is strongly associated with late onset Alzheimer's disease (LOAD) risk. Multiple regulatory elements outside of APOE have been reported to influence apoE expression. In this investigation we hypothesized that genetic variation within the regulatory elements and promoters of the APOE locus contain unique haplotypes that influence the expression of multiple APOE locus genes.

Aims: The first aim was to demonstrate that previously described regulatory elements (ME1, BCR) influence reporter gene expression differentially according to haplotype context. The second aim was to explore the haplotype effect of putative regulatory elements (IVS2-4 of TOMM40 and Ex4 of APOE) on reporter gene expression.

Methods: Luciferease reporter constructs containing haplotypes of both a core promoter region (APOE or TOMM40) and ME1, BCR or putative regulatory elements (IVS2-4 of TOMM40APOE) were evaluated for their impact on luciferase activity in human neuronal and astrocyte cell lines.

Results: The results of this investigation suggest that the APOE promoter interacts with the BCR and TOMM40 IVS2-4 whereas the TOMM40 promoter interacts with ME1, BCR, TOMM40 IVS2-4 and APOE Ex4 to influence expression differentially according to haplotype and cell type.

Conclusion: Functional characterization of genetic variation in the APOE locus suggests that a complex transcriptional regulatory structure is modulated by the presence or absence of specific and sometimes distantly located regulatory element haplotypes.