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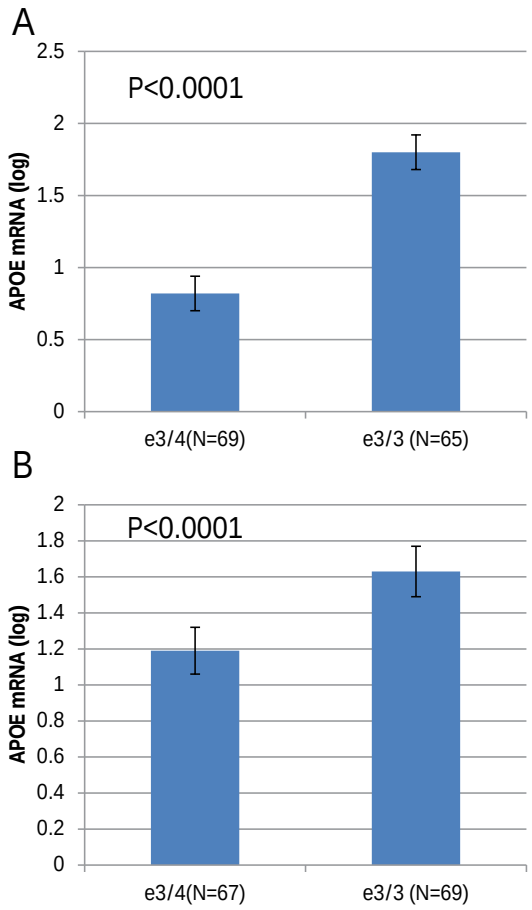

Figure 1: The effect of *APOE* haplotypes on *APOE*-mRNAs expression levels in human brain tissues from LOAD donors. The study cohort consisted of brain (temporal and occipital cortex) tissues from Caucasian donors with LOAD. Subjects were genotyped for rs429358 and rs7412 SNPs to determine *APOE* status. Fold levels of human *APOE* mRNA were assayed in (**A**) temporal and (**B**

variants act as a repressor of luciferase gene expression in reporter gene constructs, whereas expression was reduced to approximately half of that observed for the 'VL' variant [39].

Collectively the studies reviewed here suggest that up-regulated function of *A* due to either enhanced protein activity or increased *A* expression levels may contribute, in part, to the etiology of LOAD. Figure 3 summarizes our proposed model. While this model suggests the triggering event, the biochemical and cell biological pathways that mediate the consequences of this event are still being determined. Our perception of increased *A* e3 protein levels as a LOAD-pathogenic mechanism agrees with the concept that changes in expression levels of 'normal' protein in the brain can lead to neurodegenerative diseases. In conclusion, genetic heterogeneity across the *A* -LD region may lead, through di erent molecular mechanisms, to elevated ('pathogenic') *A* function and possibly explains the extremely strong genetic association of the *A* -LD region with increased LOAD-risk and related phenotypes.

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