Background: Butyrylcholinesterase K-variant (BChE-K) is associated with ~30% less active enzyme in serum, while apolipoprotein E4 allele (ApoE4) is related to high ApoE level. Intriguingly, risk of developing Alzheimer’s disease (AD) increases in subjects carrying both ApoE4 and BChE-K, but in ApoE4-non-carriers, BChE-K appears protective.

Objectives: We sought mechanistic explanations in these regards by investigating whether ApoE4 genotype and protein could modify BChE phenotype.

Methods: Patients with AD were BCHE-K genotyped (n=179). Proteomic/enzymatic analysis were performed on plasma, CSF or both.

Results: Plasma-BChE activity was 26±5% (p< 0.002) less in K-carriers than non-K-carriers. CSF-BChE activity was merely 17±5% less in the K-carriers (n=50) compared to non-carriers (n=78, p< 0.03). CSF-BuChE protein level did not differ between the K-carriers and non-carriers. ApoE4 genotype was related to different phenotypes of BChE and to its protein level (p< 0.013, n=128), particularly in K-heterozygotes. In absence of ApoE4, carriers (n=16) and non-carriers (n=16) of BChE-K had remarkably similar CSF-BChE activity (p=0.82, n=32), although K-carriers had 24-39% less BChE protein. In contrast in presence of ApoE4, BChE-K genotype was associated with a phenotype with 14-46% reduced activity (p< 0.02, n=94), despite an essentially identical circulating BChE protein compared with non-K-carriers (1±4%, p=0.79). Hence in ApoE4-carriers, the specific BChE activity was 24±5% less in the K-carriers (n=34) than non-carriers (p< 0.001, n=60). BChE-K was gene-dose dependently associated with reduced levels of glial markers, GFAP and S100β, but increased TNF-α, IL-1β and ApoE levels.

Conclusion: ApoE4 modulates phenotypic BChE activity, which may lead to functional abnormalities in acetylcholinoceptive cells, such as microglia.