



Title: Genetic Moderators of the Relationship of Obstructive Sleep Apnea to the Development of Alzheimer's Disease

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The serotonin transporter polymorphism (5-HTTLPR) is implicated in neural systems subserving complex emotional and cognitive processing. Studies suggest the *s* allele variant of 5-HTTLPR moderates the relationship of stress to a range of outcomes, including anxiety, cognition and sleep quality, although findings are mixed in older adults. Apolipoprotein E4 allele is a well documented risk factor for cognitive impairment, decline and Alzheimer's Disease (AD). Increased prevalence of the APOE E4 allele also has been found in patients with obstructive sleep apnea (OSA). 5-HTTLPR consists of a short (*s*) allele, and long (*l*) allele, and the *s* allele appears to be a stress vulnerability factor. The *l* allele has previously been related to upper airway pathology, and OSA.

We investigated the potential interactive relationship of 5-HTTLPR and APOE E4 allele to obstructive sleep apnea (OSA) and cognitive function in 140 community-dwelling older adults, with thirty percent suffering from Mild Cognitive Impairment (MCI). All participants underwent full ambulatory polysomnography in their homes, and parameters such as hypoxia, sleep fragmentation, and self-reported sleep quality were assessed.

The 5-HTT *l* allele was significantly associated with increased levels of OSA ($p=0.01$). The 5-HTT *s* allele was associated with poorer memory ($p=.001$), however the *s* allele was significantly associated with poorer subjective sleep quality. We did not observe any independent association of the E4 allele with prevalence or level of OSA, but there was a significant additive effect of the 5HTTLPR and APOE on memory function, with those with the *l* allele and E4 allele having higher levels of OSA, but those with the *s* and E4 alleles having the worst memory function associated with increased severity of OSA.

These findings suggest the 5-HTT *l* allele may be an important risk factor for OSA in older adults. Further, the interaction of *s* allele and APOE E4 allele on the relationship of sleep apnea to impaired memory and risk for AD may account for the mixed findings in this literature. The findings further underscore the highly complex relationship between genetic risk factors, sleep apnea and endophenotypes associated with increased risk of developing AD.