

# The MAPT H1 Haplotype Is Associated with an Increased Clinical and Neuropathological Severity of Chronic Traumatic Encephalopathy

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Post-mortem examination of brains from patients with chronic traumatic encephalopathy (CTE) reveals massive accumulation of neurofibrillary tangles (NFTs) throughout the brain. Mild yet repetitive traumatic brain injury, in the form of concussive or subconcussive blows, currently stands as the primary factor linked to CTE. The microtubule associated protein tau (MAPT) gene encompasses two haplotypes, H1 and H2, resulting from a ~900 kb ancestral genomic inversion. Despite numerous genetic associations between the MAPT gene and other tauopathies, extensive exploration of the role of MAPT in the onset or severity of CTE has yet to be conducted. This study examined the possible association between the MAPT gene and the severity of clinical and neuropathological features of CTE. MAPT genotyping was conducted on 39 CTE brain samples from professional football players, professional hockey players, professional wrestlers, military Veterans, and 52 controls. The MAPT H2 haplotype was found to be associated with increased disease duration amongst CTE patients in this study ( $p=0.015$ ). Age of death of the CTE patients in this study was found to be lower amongst MAPT H1 homozygotes than MAPT H2 carriers by approximately 9.2 years, but this was not a statistically significant difference ( $p=0.137$ ). The stage/age ratio of MAPT H2 carriers was found to be significantly lower than that of the homo-zygous H1 carriers, indicating a much slower progression of neurodegeneration amongst MAPT H2 carriers ( $p=0.0184$ ). Caucasian ancestry was not associated with increased CTE severity or onset. Thus, the MAPT H1 haplotype seems to lead to a more severe and faster progression of CTE and highlights a potential role for genetic factors in the development of CTE.