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COMMON VARIANT IN *GRN* IS A GENETIC RISK FACTOR FOR HIPPOCAMPAL SCLEROSIS IN THE ELDERLY

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Hippocampal sclerosis (HpScl) is common in elderly subjects with dementia, either alone or accompanied by other pathologic processes. It is found in over 70% of cases of frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U) for which TAR DNA binding protein (TDP-43) is a specific marker. In previous studies of pathologically confirmed Alzheimer disease (AD) cases with and without HpScl, TDP-43 immunoreactivity was detected in 23% of AD and 71% of HpScl cases. One of the most common genetic causes of FTLD-U is mutations in the progranulin gene (*GRN*) on chromosome 17. Recently, a common genetic variant in the 3´UTR of *GRN* (rs5848; c.*78C>T) was shown to be located in a microRNA binding site that regulated progranulin expression. In a Mayo Clinic FTLD series, there was selective increase in the TT genotype of rs5848 (p=0.002) compared to controls. Results of a *GRN* genetic screening in 644 cases of pathologically confirmed AD showed a trend (p=0.06) for TDP-43 immunoreactivity to associate with the rs5848 variant. Of 50 cases of AD with HpScl, 82% carried a T-allele, while only 39% of AD cases without HpScl had a T-allele. The difference in the frequency of the *GRN* rs5848 T allele in HpScl was greater than chance (p=0.005). The results suggest that a genetic variant in *GRN* may lead to decreased levels of progranulin and that this may be a risk factor for HpScl in the elderly.