Variants in the Mitochondrial Intermediate Peptidase (MIPEP) Gene are Associated with Gray Matter Density in the Alzheimer's Disease Neuroimaging Initiative Cohort

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Cancer and Alzheimer's disease (AD) incidence is inversely correlated, but the genetic underpinnings of this relationship remain to be elucidated. Recent findings identified lower gray matter density in frontal regions of participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI) with cancer history compared to those without such history, across diagnostic groups (Nudelman et al., 2014). Pathways proposed to impact cancer and AD, including metabolism and survival, may play an important role in the observed difference. To test this hypothesis, a genome-wide association study (GWAS) using mean frontal gray matter cluster values was performed for all Caucasian participants in this cohort with neuroimaging and genetic data (n=1405). Analysis covaried for age, sex, AD, and cancer history. Of the two genes with the most significant SNPs ($p<10^{-5}$), WD repeat domain 5B (WDR5B) and mitochondrial intermediate peptidase (MIPEP), MIPEP was selected for further analysis given the hypothesis focus on metabolism. ANOVA analysis of MIPEP top SNP rs8181878 with frontal gray matter cluster values in SPSS indicated that while this SNP is significantly associated with gray matter density ($p=2x10^{-6}$), no interaction was observed with cancer history or AD diagnosis. Furthermore, whole brain gray matter voxel-wise analysis of this SNP using Statistical Parametric Mapping 8 software showed that minor allele(s) of this SNP were significantly ($P_{FWE}<0.05$) associated with higher gray matter density. These results suggest that the minor allele of MIPEP SNP rs8181878 may be protective against gray matter density loss, highlighting the importance of metabolic processes in aging and disease.