"Genome-wide Association Study Confirms SNPs in *SNCA* and the *MAPT* Region as Common Risk Factors for Parkinson Disease"

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ABSTRACT

Parkinson disease (PD) is a chronic neurodegenerative disorder with a cumulative prevalence of greater than one per thousand. While several rare Mendelian forms of PD have been described, these do not contribute to the genetic susceptibility for a majority of PD cases. Candidate gene studies have suggested associations for several genes, although not without inconsistent findings in some studies. With the availability of high-throughput genotyping, to date three independent genome-wide association studies (GWAS) have investigated the genetic susceptibility to PD using various study designs and genotyping platforms. These studies have also implicated several genes as PD risk loci with strong, but not genome-wide significant, associations. In this study, we combined data from two previously published GWAS of Caucasian subjects with our GWAS of 604 cases and 619 controls for a joint analysis with a combined sample size of 1752 cases and 1745 controls. SNPs in *SNCA* (rs2736990, p-value = 6.7×10^{-8}; genome-wide adjusted p = 0.0109, odds ratio (OR) = 1.29 [95% CI: 1.17-1.42] G vs. A allele, population attributable risk percent (PAR%) = 12%) and the *MAPT* region (rs11012, p-value = 5.6×10^{-8}; genome-wide adjusted p = 0.0079, OR = 0.70 [95% CI: 0.62-0.79] T vs. C allele, PAR% = 8%) were genome-wide significant. No other SNPs were genome-wide significant in this analysis, though several biologically plausible genes (*RORA*, *NPAS3*, *WIPF1*, *DBC1*, *GFPT2*) were associated with PD in at least two of three data sets ($p<0.05$) with consistent direction of effects across samples. This study confirms that *SNCA* and the *MAPT* region are major genes whose common variants are influencing risk of PD. These genes have thus become uncontroversial PD risk factors, and thorough follow-up with resequencing and functional experiments to determine the mechanism by which these genes associate with PD are necessary.