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DNA dysmethylation of various genes contributes to disease risk in progressive supranuclear palsy

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Statement of the Problem: Progressive Supranuclear Palsy (PSP) is a neurodegenerative tauopathy. The etiology of this complex disorder is poorly understood. An accumulation of multiple environmental, genetic, and possibly epigenetic factors is thought to eventually cause disease. Thus, advanced age contributes to risk as do certain polymorphisms of the genes MAPT, STX6, EIF2AK3, and MOBP. A possible role of epigenetic changes in PSP is currently under investigation and dys-regulation of several miRNAs has been reported. This study was performed to investigate whether DNA dys-methylation might also contribute to disease.

Methods: DNA was extracted from forebrains of 94 PSP patients (age at death 72±5.3 years) and 72 controls (76±7.9 years). Methylation was studied using the Infinium 450k array of Illumina that includes more than 485,000 potentially methylated CpG sites distributed over the entire genome. 200 ng of bisulfite-converted DNA were hybridized to the array. Arrays were scanned and GenomeStudio software (version 2011.1; Illumina Inc., San Diego, CA) was used to measure the intensity of DNA methylation signals on the arrays. DAVID Bioinformatics resources 6.7 were used for functional analysis of hyper- and hypo-methylated genes. Highly significant ($P<0.01$) methylation differences of >1% were compiled and the location of these differentially methylated sites was analyzed. Functional annotation clustering was performed and enrichment scores >1.3 were considered significant.

Findings: Significant ($p<0.01$) methylation differences of >1% were detected at 621 sites amounting to 383 protein-coding genes. At high stringency ($p<0.01$, methylation difference >5%), dys-methylated CpGs were found associated with 30 genes. 142 of the dysmethylated sites were also detected in age- and gender-matched cohorts (difference >1%, $p<0.01$). Disease-specific changes were found at 59 and age-dependent methylation differences were detected at 16 CpG sites. Of the genes dys-methylated by >5% ($p<0.01$) differences were disease-specific in 8 and age-dependent in 3 genes. While dysmethylation of >5% affected one or a few CpG sites in most genes, in one, i.e. DLX1 hyper-methylation was found at multiple sites including a CpG island in the 3´-untranslated region (UTR) of the gene. This and flanking genes (DLX2, METAP1D) are methylated in an age-dependent manner. Among the disease-specifically dys-methylated genes, HDAC4, which might serve as a therapeutic target, was hypo-methylated. Conclusion: The data suggest that both disease-specific and age-dependent, i.e. premature dysmethylation of various genes contribute to PSP.