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Abstracts

Papers appearing in the August 2019 issue

Genome-wide brain DNA methylation analysis suggests epigenetic reprogramming in Parkinson disease

Objective Given the known strong relationship of DNA methylation with environmental exposure, we investigated whether brain regions affected in Parkinson disease (PD) were differentially methylated between PD cases and controls.

Methods DNA chip arrays were used to perform a genome-wide screen of DNA methylation on the dorsal motor nucleus of the vagus (DMV), substantia nigra (SN), and cingulate gyrus (CG) of pathologically confirmed PD cases and controls selected using the criteria of Beecham et al. Analysis examined differentially methylated regions (DMRs) between cases and controls for each brain area. RNA sequencing and pathway analysis were also performed for each brain area.

Results Thirty-eight PD cases and 41 controls were included in the analysis. Methylation studies revealed 234 significant DMR in the DMV, 44 in the SN, and 141 in the CG between cases and controls (Sidak $p < 0.05$). Pathway analysis of these genes showed significant enrichment for the Wnt signaling pathway (FDR < 0.01).

Conclusions Our data suggest that significant DNA methylation changes exist between cases and controls in PD, especially in the DMV, one of the areas affected earliest in PD. The etiology of these methylation changes is not yet known, but the predominance of methylation changes occurring in the DMV supports the hypothesis that vagus nerve function, perhaps involving the gastrointestinal system, is important in PD pathogenesis. These data also give independent support that genes involved in Wnt signaling are a likely factor in the neurodegenerative processes of PD.

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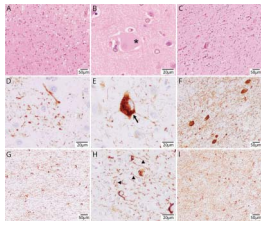
MAPT p.V363I mutation: A rare cause of corticobasal degeneration



Objective Patients with corticobasal syndrome (CBS) present with heterogeneous clinical features, including asymmetric parkinsonism, dyspraxia, aphasia, and cognitive impairment; to better understand the genetic etiology of this rare disease, we undertook a genetic analysis of microtubule-associated protein tau (*MAPT*).

Methods We performed a genetic evaluation of *MAPT* mutations in 826 neurologically healthy controls and 173 cases with CBS using the Illumina NeuroChip genotyping array.

Results We identified 2 patients with CBS heterozygous for a rare mutation in *MAPT* (p.V363I) that is located in the highly conserved microtubule-binding domain. One patient was pathologically confirmed and demonstrated extensive 4-repeat-tau-positive thread pathology, achromatic neurons, and astrocytic plaques consistent with corticobasal degeneration (CBD).

Conclusions We report 2 CBS cases carrying the rare p.V363I *MAPT* mutation, one of which was pathologically confirmed as CBD. Our findings support the notion that this rare coding change is pathogenic.

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