DEMENTIA WITH LEWY BODIES: A ROLE FOR MUTATIONS IN DEMENTIA AND PARKINSON’S DISEASE GENES?

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Dementia with Lewy bodies (DLB) represents a neurodegenerative disorder characterized by clinicopathological features that overlap with those of Alzheimer dementia (AD) and Parkinson’s disease (PD). Therefore, genetic commonalities between these diseases can be anticipated. Although genetic studies have discovered few genetic determinants associated with DLB that are known to be implicated in classic forms of AD or PD, a comprehensive mutation analysis of all major dementia and PD genes in an extended DLB population is still lacking.

With this study, we aimed to unravel the contribution of \textit{APP}, \textit{PSEN1}, \textit{PSEN2}, \textit{MAPT}, \textit{PGRN}, \textit{TARDBP}, \textit{PRNP}, \textit{SNCA}, \textit{LRRK2}, \textit{PINK1}, \textit{DJ-1}, \textit{PARK2} and \textit{GBA} to the genetic etiology of DLB in a Flanders-Belgian cohort consisting of 99 patients. We performed a gene-based mutation analysis by direct sequencing of all coding exons, exon-intron boundaries, and regulatory regions reported to contain pathogenic variants. Moreover, we developed qPCR assays to allow the detection of dosage effects due to CNVs in \textit{APP}, \textit{MAPT}, \textit{PGRN}, \textit{TARDBP}, \textit{SNCA}, \textit{LRRK2}, \textit{PINK1}, \textit{DJ-1} and \textit{PARK2}.

We detected in the dementia genes one proven pathogenic missense mutation in \textit{PSEN1} and \textit{PSEN2}, three known possible pathogenic missense variants in \textit{GRN}, and one novel missense variant of unclear pathogenic nature in \textit{MAPT}. In the PD genes we identified 5 novel missense variants (2 in \textit{PARK2}, 2 in \textit{PINK1} and 1 \textit{GBA}) with unknown pathogenic character.

Our results indicate an important contribution of well established dementia and PD genes to the genetic background of DLB and confirm a genetic overlap between DLB, AD and PD.