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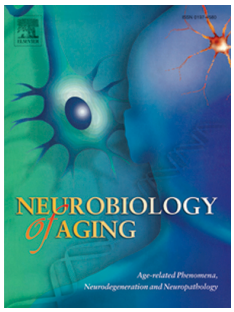

RAB39B gene is not a common cause of Parkinson's disease or dementia with Lewy bodies

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RAB39B gene is not a common cause of Parkinson's disease or dementia with Lewy bodies

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Abstract

Mutations in *RAB39B* gene have been linked to X-linked early onset Parkinsonism with intellectual disabilities. The aim of this study was to address the genetic contribution of *RAB39B* to Parkinson disease (PD), Dementia with Lewy Bodies (DLB), and pathologically-confirmed Lewy Body Dementia (pLBD) cases. A cohort of 884 PD, 399 DLB and 379 pLBD patients were screened for *RAB39B* mutations, but no coding variants were found, suggesting *RAB39B* is not a common cause of PD, DLB or pLBD in Caucasian population.

Keywords: Dementia with Lewy Bodies, Lewy Body Dementia, *RAB39B,* Parkinson's disease

Disclosure: The authors declare that they have no conflicts of interest to report.

Introduction

Ras-Related Protein Rab-39B (RAB39B) belongs to the RabGTPase family, which regulates intracellular vesicular trafficking, and acts in synapse formation and maintenance (Giannandrea, et al., 2010). Loss-of-function mutations including a premature stop codon and a variant in the 5' splice site of *RAB39B* exon 1 have been reported to cause an X-linked mental retardation syndrome (Giannandrea, et al., 2010). However, a recent study also linked *RAB39B* mutations with early onset Parkinsonism and intellectual disability (ID) (Wilson, et al., 2014). A whole gene deletion was identified in an Australian family and a missense mutation (c.503C>A; p.T168K) co-segregated in a Wisconsin family with 13 affected males (Wilson, et al., 2014). Interestingly, the authors observed wide-spread α-synuclein pathology (diffuse Lewy body disease) in one autopsy from the Australian family, carrying the gene deletion. Therefore, we decided to assess the frequency of *RAB39B* mutations in a series of PD, DLB and pLBD patients.

Materials and methods

A total of 1652 samples were collected from the Mayo Clinic, split into 884 PD (145 early onset PD (≤ 50 ages) and 739 late onset PD), 399 DLB and 379 pLBD patients. Clinical diagnosis of PD and DLB was established according to consensus criteria for PD (Hughes, et al., 1992) and DLB (McKeith, et al., 2005). The pLBD cases are a pathologically series that was categorized according to the consortium on Dementia with Lewy Bodies (McKeith, et al., 1996). All subjects were unrelated Caucasians individuals. The Mayo Clinic Institutional Review Board approved the study, and all subjects provided written informed consent. Characteristics of the PD, DLB and pLBD cohorts are summarized in Supplementary Table 1. See Supplementary Material for additional information.

Results

Sequencing of 884 PD, 399 DLB and 369 pLBD samples patients identified no coding variants. We identified a c.215+3G>A variant two nucleotides away from the previously reported c.215+1G>A mutation (Giannandrea, et al., 2010) in a late onset sporadic PD patient. However, neither splicing algorithms, nor exonic splicing enhancer (ESE) analyses predicted a damaging effect or a modification in ESE motifs for this variant.

Discussion

Previous studies have shown that loss of function mutations in *RAB39B* lead to PD and ID possibly due to dysregulation of α-synuclein homeostasis (Wilson, et al., 2014) and mislocalization of mutant RAB39B (Mata, et al., 2015). In our study, we checked if mutations in *RAB39B* caused PD, DLB or LBD pathology. However, no coding variants were found.

Although *RAB39B* c.215+3G>A variant is only 2 nucleotides away from c.215+1G>A mutation, which is considered to be pathogenic (Giannandrea, et al., 2010), the bioinformatic analyses did not predict any potential effect for our variant. Further studies have implicated *RAB39B* mutations (c.574G>A; p.G192R and c.557G>A; W186stop) in more typical late-onset PD clinical phenotypes (Lesage, et al., 2015,Mata, et al., 2015). Our data supports previous papers that suggested that mutations in *RAB39B* are not a common cause of PD (Lesage, et al., 2015,Lochte, et al., 2016). Additionally, our results suggest that they are not a common cause of DLB or pLBD in the US Caucasian population.

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Peter R. Rapp
Neurobiology of Aging
Editor-in Chief
Baltimore, Maryland

Dear Editor,

RE: *RAB39B* gene is not a risk factor for Parkinson's disease, or dementia with Lewy bodies in Caucasian population – Highlights

Below you will find our recommended highlights for this paper:

- *RAB39B* mutations have been involved in X-linked parkinsonian disorder with intellectual disabilities.
- We screened 884 Parkinson's disease (PD), 399 Dementia with Lewy bodies (DLB) and 379 pathologically-confirmed Lewy body disease (pLBD) patients and found no coding mutations in *RAB39B* gene.
- *RAB39B* c.215+3G>A splicing variant does not seem to be a pathogenic variant.
- *RAB39B* is not a common cause of PD, DLB or pLBD in Caucasian population.