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

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Abstract

Mutations in Ras-related protein Rab-39B (*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's 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* mutations are not a common cause of PD, DLB, or pLBD in Caucasian population.

Keywords

Dementia with Lewy bodies; Lewy body dementia; RAB39B; Parkinson's disease

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Disclosure statement

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

1. Introduction

Ras-related protein Rab-39B (RAB39B) belongs to the Rab GTPase 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 (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 1 brain 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 pathologically confirmed Lewy body dementia (pLBD) patients.

2. 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 and DLB. The pLBD cases are a pathologic series that was categorized according to the consortium on dementia with Lewy bodies. 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.

3. Results

Sequencing of 884 PD, 399 DLB, and 369 pLBD patients identified no coding variants. We identified a c.215+3G>A variant 2 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 analyses predicted a damaging effect or a modification in exonic splicing enhancer motifs for this variant.

4. Discussion

Previous studies have shown that loss-of-function mutations in *RAB39B* lead to PD and intellectual disability possibly due to dys-regulation 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 pLBD 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 support previous articles that suggested that mutations in *RAB39B* are

not a common cause of PD (Lesage et al., 2015; Lochte et al., 2016). In addition, our results suggest that they are not a common cause of DLB or pLBD in the US Caucasian population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.03.021.