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***ADORA1* mutations are not a common cause of Parkinson's disease and dementia with Lewy bodies**

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Letter to the Editor

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are two common neurodegenerative diseases characterized by alpha-synuclein inclusions (Lewy bodies) present in the midbrain (PD) or spread throughout the limbic system and neocortex (DLB). A recent study identified a homozygous missense mutation (p.G279S) in the adenosine A1 receptor gene (*ADORA1*) in an autosomal recessive, early-onset, L-DOPA-responsive, consanguineous Iranian family with parkinsonism with cognitive decline¹. The authors of this study made two claims. First, they proposed that *ADORA1* mutations cause parkinsonism with cognitive impairment. Second, they suggested that *ADORA1* is positioned within PARK16 locus, which has been robustly associated with increased risk for

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PD in several populations². We investigated whether *ADORA1* pathogenic mutations are present in the European population and we scrutinized the relationship between *ADORA1* and PARK16. Interestingly, both adenosine and its receptors have been linked to neurodegeneration³. Further, there is evidence for an interaction between the adenosine receptors and dopamine receptors⁴. These findings make *ADORA1* an interesting candidate gene for PD as well as DLB.

Whole-exome sequencing data was obtained from the International Parkinson's Disease Genomics Consortium (IPDGC), including a total of 1,214 PD cases and 4,911 controls and we analyzed 111 pathologically confirmed North American DLB cases that have been described elsewhere⁵. Identified missense variants were annotated, compared with European individuals from the Exome Aggregation Consortium database (ExAC, <http://exac.broadinstitute.org/>) and assessed for pathogenicity. We did not identify the proposed pathogenic p.G279S variant or any other homozygous or compound heterozygous coding variants in our whole-exome sequencing data. In total, we detected 59 heterozygous missense variants, 46 in the controls, 12 in PD cases and one in DLB cases (allele frequencies 0.0047, 0.0049 and 0.0045 respectively, 0.0036 in ExAC, Supplementary Table 1). Eight were novel variants (not present in ExAC and dbSNP) and the majority had low or moderate pathogenicity scores. Additionally, none of the gene burden tests for PD or age of onset demonstrated significant associations. In total out of the >66,000 investigated individuals (ExAC and included exomes) only one individual with a homozygous missense variant was identified (South Asian ExAC individual with p.V166M) suggesting that homozygous variants in *ADORA1* are extremely rare.

Genome-wide association (GWA) summary statistics of PD were downloaded from the IPDGC generated meta-analysis (<http://pdgene.org/>). *ADORA1* is located 2.5 Mb upstream of the PARK16 GWA signal (Figure 1). Variants surrounding *ADORA1* are not significantly associated with PD according to the latest meta-analysis, and conditional analyses of variants surrounding the *ADORA1* gene had no effect on the PARK16 association signal.

In conclusion, *ADORA1* is not a common risk factor or causal gene for PD or DLB in the European population, and our data show that *ADORA1* mutations are not driving the PARK16 association signal. Importantly, the lack of pathogenic variants in *ADORA1* in Europeans does not invalidate the results reported by Jaber et al¹, but further work is needed to clarify the role of *ADORA1* in the pathogenesis of parkinsonism with cognitive decline in non-European ancestry populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AUTHORS' ROLES

- 1) Research project: A. Conception (SWS, JSS), B. Organization (CB, SWS), C. Execution (CB)
- 2) Data generation: A. Experimental (CL, DGH, MF, SWS, JTG) B. DLB samples (OP, JT)
- 3) Statistical Analysis: A. Design (SWS, CB, JSS, MN, JRG, JD), B. Execution (CB, JSS, MN)
- 4) Manuscript Preparation: A. Writing of the first draft (CB), B. Review and Critique (all authors)

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Figure1.

ADORA1 is not located within the Parkinson's disease PARK16 locus. Shown here are the association signals at the PARK16 locus using summary statistics from the most recent genome-wide association study in Parkinson disease (obtained from <http://pdgene.org/>) relative to the position of ADORA1 (underlined red), which is located 2.5 Mb upstream of the PARK16 locus. Due to lack of linkage disequilibrium, several interspersed recombination points and the long distance between PARK16 and ADORA1 it is not likely that ADORA1 is part of the PARK16 locus.