Overlap between Parkinson disease and Alzheimer disease in \textit{ABCA7} functional variants

\textbf{ABSTRACT}

\textbf{Objective:} Given their reported function in phagocytosis and clearance of protein aggregates in Alzheimer disease (AD), we hypothesized that variants in ATP-binding cassette transporter A7 (\textit{ABCA7}) might be involved in Parkinson disease (PD).

\textbf{Methods:} \textit{ABCA7} variants were identified using whole-exome sequencing (WES) on 396 unrelated patients with PD and 222 healthy controls. In addition, we used the publicly available WES data from the Parkinson’s Progression Markers Initiative (444 patients and 153 healthy controls) as a second, independent data set.

\textbf{Results:} We observed a higher frequency of loss-of-function (LOF) variants and rare putative highly functional variants (Combined Annotation Dependent Depletion [CADD] >20) in clinically diagnosed patients with PD than in healthy controls in both data sets. Overall, we identified LOF variants in 11 patients and 1 healthy control (odds ratio [OR] 4.94, Fisher exact \(p = 0.07\)). Four of these variants have been previously implicated in AD risk (p.E709AfsX86, p.W1214X, p.L1403RfsX7, and rs113809142). In addition, rare variants with CADD >20 were observed in 19 patients vs 3 healthy controls (OR 2.85, Fisher exact \(p = 0.06\)).

\textbf{Conclusion:} The presence of \textit{ABCA7} LOF variants in clinically defined PD suggests that they might be risk factors for neurodegeneration in general, especially those variants hallmarked by protein aggregation. More studies will be needed to evaluate the overall impact of this transporter in neurodegenerative disease. \textit{Neurol Genet} 2016;2:e44; doi: 10.1212/NXG.0000000000000044

\textbf{GLOSSARY}

AAE: age at examination; AD: Alzheimer disease; CADD: Combined Annotation Dependent Depletion; GATK: Genome Analysis Tool Kit; LOF: loss-of-function; MAF: minor allele frequency; OR: odds ratio; PCA: principal component analysis; PD: Parkinson disease; PL: Phred-scaled likelihood; PPMI: Parkinson’s Progression Markers Initiative; VQS: variant quality score; WES: whole-exome sequencing.

Parkinson disease (PD) and Alzheimer disease (AD), the 2 most common neurodegenerative diseases, have substantial overlap in pathologic and clinical representation. Both present with protein aggregates on autopsy, indicating potentially similar mechanisms of aberrant protein clearance. Clinically, \(\sim 30\%\) to 40\% of patients with PD present with dementia during their disease course,\(^1,2\) whereas approximately 30\% of patients with AD develop parkinsonism,\(^3\) with a relatively higher percentage of these in patients with AD with Lewy bodies.\(^4\) Evidence for genetic overlap has also been reported for risk factors and age-at-onset modifiers,\(^5,6\) again supporting a hypothesis of shared mechanisms in these common disorders. Specifically, \textit{APOE} status was originally discovered to be a strong risk factor and modifier of onset age for AD (odds ratio [OR] \(\approx 3.5\)), but subsequent studies indicated that \textit{APOE} exerted similar, although less pronounced, effects in PD (OR \(\approx 1.8\)).\(^5,6\) In contrast, association of the microtubule-associated protein tau (\textit{MAPT}) haplotype H1 has been identified in many parkinsonian disorders, including PD (OR \(\approx 0.65\)), for decades. More recently, it was shown that this haplotype also contributes to AD risk (OR \(\approx 0.85–0.96\)).\(^3,9\)
Recent studies have identified \textit{ABCA7} (ATP-binding cassette transporter A7) as a risk factor for AD through genome-wide association studies in large case-control data sets.\textsuperscript{10,11} Subsequent sequencing efforts have identified multiple rare loss-of-function (LOF) variants associated with AD risk (OR $\approx 2$).\textsuperscript{12–14} \textit{ABCA7} is reported to be involved in the transport of phospholipid and cholesterol across membranes to ApoE.\textsuperscript{15} Alternatively, \textit{ABCA7} has been implicated in the activation of phagocytosis to clear amyloid plaques or even apoptotic cells.\textsuperscript{16,17}

Overall, ABC transporters are functional throughout the brain, although most are at the blood-brain barrier.\textsuperscript{18} These transporters have been reported to be involved in several disorders, including PD (e.g., \textit{ABCB1} or multidrug resistance gene [\textit{MDR1}], PD\textsuperscript{19}, \textit{ABCC7} or cystic fibrosis transmembrane conductance regulator [\textit{CFTR}], cystic fibrosis\textsuperscript{20}; \textit{ABCA1}, Tangier disease\textsuperscript{21} and AD\textsuperscript{22}; \textit{ABCA13}, bipolar disorder\textsuperscript{23}). Given \textit{ABCA7}'s potential function in protein clearance through the phagocytic pathway and the overlap between AD and PD, we hypothesized that \textit{ABCA7} is a likely candidate gene for PD. We present a report of \textit{ABCA7} LOF variants in 2 large sequencing data sets of patients with PD and healthy controls.

**METHODS Sample selection.** Patients included in this study were collected by the University of Miami Morris K. Udall Parkinson Disease Research Center of Excellence (J.M.V., principal investigator) and 13 centers of the Parkinson Disease Genetics Collaboration.\textsuperscript{24} Neurologists, most of whom were movement disorder specialists, examined all the patients and healthy controls. A standard neurologic examination including the Unified Parkinson's Disease Rating Scale was performed and has been described previously.\textsuperscript{25} Unaffected individuals demonstrated no signs of the disease at age at examination (AAE). A total of 411 unrelated patients with PD and 231 unrelated control individuals were included for whole-exome sequencing (WES). Principal component analyses (PCAs) were performed twice using either common or rare variants detected through the WES (threshold minor allele frequency [MAF] 5\% in both Exome Variant Server and 1000 Genomes Project). We identified 24 outliers (15 patients and 9 healthy controls) due to either population substructure (not clustering with white, non-Hispanic HapMap reference samples in common variant PCA) or excessive sequence errors/contamination (in rare variant PCA). The remaining 396 patients and 222 healthy control individuals are all of white, non-Hispanic/Latino descent.

**Standard protocol approvals, registrations, and patient consents.** All participants of the collaboration were collected after approval by each contributing center’s institutional review board and provided written informed consent.

**Variant annotation.** Variants were annotated using Seattle-Seq including function within the gene and Combined Annotation Dependent Depletion (CADD) scores. Variants with CADD scores $\geq$ 20 were included in the analysis, as these are among the 1\% highest ranked positions genome-wide in terms of potential functionality.\textsuperscript{27}

**Variants in known PD genes.** Only 1 individual with an \textit{ABCA7} LOF variant had a single heterozygous variant of unclear status in \textit{PARK2} (R275W in individual 3593 of PPMI WES). No further known mutations or variants of unclear status were identified in \textit{SNCA}, \textit{PARK2, PINK1, PARK7, LRRK2, EIF4G1, HTRA2, VPS35, FBXO7}, and \textit{PLA2G6} in the LOF or CADD $\geq$ 20 variant carriers.

**Statistical analysis.** The cumulative association of functional variants with PD was assessed by a 2 × 2 contingency table analysis. The association of PD with the frequency of functional variants in cases and controls from both data sets combined was evaluated by calculating the OR and statistical significance using a 1-tailed Fisher exact test. Two parallel analyses were used: one for all LOF variants and a second for those rare variants (MAF < 5\% in 1000 Genomes) with CADD $\geq$ 20.
## Table 1
Putative highly functional variants identified in the Udall and PPMI whole-exome sequencing data sets

<table>
<thead>
<tr>
<th>Variant</th>
<th>rsID</th>
<th>Change</th>
<th>AD*</th>
<th>Protein domain</th>
<th>CADD</th>
<th>PolyPhen-2</th>
<th>Udall (alleles)</th>
<th>PPMI (alleles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>A. LOF variants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chr19:1047507 AGGAGCAG&gt;A</td>
<td>—</td>
<td>E709AfsX86</td>
<td>Ca-O, Ca-Co</td>
<td>Loss of ABC-I, ABC-II, TM-II domain</td>
<td>35</td>
<td>—</td>
<td>0/360</td>
<td>0/210</td>
</tr>
<tr>
<td>chr19:1047590 CT&gt;C</td>
<td>—</td>
<td>L737CfsX60</td>
<td>No</td>
<td>Loss of ABC-I, ABC-II, TM-II domain</td>
<td>29.8</td>
<td>—</td>
<td>0/550</td>
<td>0/326</td>
</tr>
<tr>
<td>chr19:1054223 TG&gt;T</td>
<td>—</td>
<td>P1205QfsX12</td>
<td>No</td>
<td>Loss of ABC-II, TM-II domain</td>
<td>24.5</td>
<td>—</td>
<td>0/652</td>
<td>0/372</td>
</tr>
<tr>
<td>chr19:1054255 G&gt;A</td>
<td>201060968 W1214X</td>
<td>Ca-O</td>
<td>Loss of ABC-II, TM-II domain</td>
<td>43</td>
<td>—</td>
<td>1/624 (0.2)</td>
<td>0/356</td>
<td>1/856 (0.1)</td>
</tr>
<tr>
<td>chr19:1055907 CT&gt;C</td>
<td>—</td>
<td>L1403RfsX7</td>
<td>Ca-Co</td>
<td>Loss of ABC-II, most of TM-II domain</td>
<td>34</td>
<td>—</td>
<td>2/790 (0.3)</td>
<td>0/444</td>
</tr>
<tr>
<td>chr19:1056244 T&gt;G</td>
<td>113809142 IVS32+2T&gt;G</td>
<td>Ca-Co</td>
<td>Loss of ABC-II, most of TM-II domain</td>
<td>16.72</td>
<td>—</td>
<td>1/768 (0.1)</td>
<td>0/428</td>
<td>0/876</td>
</tr>
<tr>
<td>chr19:1058727 C&gt;T</td>
<td>—</td>
<td>R1754X</td>
<td>No</td>
<td>Loss of ABC-II domain</td>
<td>40</td>
<td>—</td>
<td>1/792 (0.1)</td>
<td>0/444</td>
</tr>
<tr>
<td>B. Rare variants with CADD &gt;20b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chr19:1045108 G&gt;C</td>
<td>—</td>
<td>L441F</td>
<td>No</td>
<td>Extracellular loop-I</td>
<td>24.4</td>
<td>Probably damaging</td>
<td>0/748</td>
<td>0/424</td>
</tr>
<tr>
<td>chr19:1045173 G&gt;C</td>
<td>3752233 R463P</td>
<td>No</td>
<td>Extracellular loop-I</td>
<td>28.8</td>
<td>Probably damaging</td>
<td>1/770 (0.1)</td>
<td>0/434</td>
<td>0/878</td>
</tr>
<tr>
<td>chr19:1047169 T&gt;C</td>
<td>144852598 L620P</td>
<td>Ca-Co</td>
<td>—</td>
<td>23.8</td>
<td>Probably damaging</td>
<td>1/604 (0.2)</td>
<td>0/360</td>
<td>1/840 (0.1)</td>
</tr>
<tr>
<td>chr19:1048950 G&gt;A</td>
<td>149949633 G776R</td>
<td>No</td>
<td>—</td>
<td>20.9</td>
<td>Probably damaging</td>
<td>0/602</td>
<td>0/334</td>
<td>1/888 (0.1)</td>
</tr>
<tr>
<td>chr19:1051006 G&gt;A</td>
<td>143718918 R880Q</td>
<td>Ca-Co, Ca-Co</td>
<td>ABC-I domain</td>
<td>33</td>
<td>Probably damaging</td>
<td>1/784 (0.1)</td>
<td>0/438</td>
<td>0/886</td>
</tr>
<tr>
<td>chr19:1051944 G&gt;A</td>
<td>139214131 R989H</td>
<td>Ca-O</td>
<td>ABC-I domain</td>
<td>25.1</td>
<td>Probably damaging</td>
<td>0/654</td>
<td>0/392</td>
<td>0/844</td>
</tr>
<tr>
<td>chr19:1052072 G&gt;A</td>
<td>200951390 G1032S</td>
<td>No</td>
<td>ABC-II domain</td>
<td>24.8</td>
<td>Probably damaging</td>
<td>0/582</td>
<td>0/354</td>
<td>1/880 (0.1)</td>
</tr>
<tr>
<td>chr19:1061803 A&gt;G</td>
<td>—</td>
<td>N1829S</td>
<td>No</td>
<td>ABC-II domain</td>
<td>21.9</td>
<td>Probably damaging</td>
<td>1/726 (0.1)</td>
<td>0/424</td>
</tr>
<tr>
<td>chr19:1062254 G&gt;A</td>
<td>368864109 R1885H</td>
<td>No</td>
<td>ABC-II domain</td>
<td>22.4</td>
<td>Probably damaging</td>
<td>0/752</td>
<td>0/410</td>
<td>1/882 (0.1)</td>
</tr>
<tr>
<td>chr19:1063546 G&gt;A</td>
<td>375389773 A1906T</td>
<td>No</td>
<td>ABC-II domain</td>
<td>22.8</td>
<td>Probably damaging</td>
<td>0/728</td>
<td>1/408 (0.3)</td>
<td>0/868</td>
</tr>
</tbody>
</table>

Abbreviations: ABC = ATP-binding cassette; CADD = Combined Annotation Dependent Depletion; Ca-O = case only; Ca-Co = cases and controls; Co-O = control only; LOF = loss-of-function; PPMI = Parkinson’s Progression Markers Initiative; TM = transmembrane.

Genomic positions are relative to hg19; protein positions to NP_061985.2. Counts are depicted as affected alleles/total covered alleles (frequency in %).

*Reported in Alzheimer disease (AD).

Minor allele frequency <5% in 1000 Genomes.
Table 2: Clinical characteristics of loss-of-function carriers in Udall whole-exome sequencing data set

<table>
<thead>
<tr>
<th>Individual</th>
<th>Variant</th>
<th>AAO/ AAE, y</th>
<th>Reported family history</th>
<th>Cognitive impairmenta</th>
<th>Pathology</th>
<th>Segregation analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>W1214X</td>
<td>NA/76</td>
<td>Yes</td>
<td>No</td>
<td>PD Braak V, AD Braak V (AAD 81)</td>
<td>No other DNA available</td>
</tr>
<tr>
<td>2</td>
<td>L1403RfsX7</td>
<td>63/71</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>Variant present in other affected (AAO 50) and unaffected (AAE 61)</td>
</tr>
<tr>
<td>3</td>
<td>L1403RfsX7</td>
<td>64/73</td>
<td>No</td>
<td>No</td>
<td>PD Braak V, AD Braak III (AAD 74)</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>IVS32+2T&gt;G</td>
<td>68/71</td>
<td>Yes</td>
<td>NA</td>
<td>—</td>
<td>Variant present in other affected (AAO 66)</td>
</tr>
<tr>
<td>5</td>
<td>R1754X</td>
<td>56/59</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>Family with 2 potential sources of PD; variant absent in other affected</td>
</tr>
</tbody>
</table>

Abbreviations: AAO = age at onset; AAE = age at last examination; AAD = age at death; AD = Alzheimer disease; NA = not applicable; PD = Parkinson disease.

RESULTS In-house WES (Udall) data set. As in AD, we observed 4 LOF (nonsense, frameshift, splice) variants in 396 unrelated patients with PD from the in-house WES data set (table 1A: p.W1214X, p.R1754X, p.L1403RfsX7, and IVS32+2T>G or rs113809142). No nonsense, frameshift, or splice variants were observed in the 222 healthy controls. All but p.R1754X have been previously reported in patients with AD as well.12,14 In addition, many rare (MAF <5% in 1000 Genomes) missense variants (table 1 and table e-2) and common coding variants (table e-3) were observed in both patients and healthy controls. Information on the clinical symptoms of the LOF carriers presented here can be found in table 2. None of the LOF carrier patients in this data set presented with dementia or cognitive impairment at ascertainment or last examination. Two of the LOF patients underwent autopsy examination. Both demonstrated signs of AD pathology (AD Braak stage III and V) in addition to their PD pathology (both PD Braak stage V). Family members were available for testing genetic segregation for only the p.L1403RfsX7 and IVS32+2T>G variant carriers, and cosegregation of the LOF variant with disease was observed in both families (table 2). Eight of 39 rare variants observed in this data set have a CADD score >20 (table 1B); these include the 3 LOF variants and 5 missense variants (in 4 patients and 1 control), of which 3 affect the ATP-binding cassette domain (p.R880Q, p.N1829S, and p.A1906T).

PPMI WES data set. In this data set of 444 patients and 153 healthy controls, we observed 1 nonsense variant (p.W1214X, 1 patient and 1 control) and 4 frameshift variants (p.E709AfsX86, 2 patients; p.L737CfsX60, 1 patient; p.P1205fsX12, 1 patient; p.L1403RfsX7, 1 patient), as well as many missense variants (table 1 and table e-2). Besides p.W1214X and p.L1403RfsX7, frameshift p.E709AfsX86 was previously observed in patients with AD.12,14 Relevant clinical information on the PPMI carriers can be found in table 3. More information can be found on PPMI’s Web site. All patients carrying an LOF variant presented with at least 2 of 3 cardinal symptoms; only 2 are reported to have signs of cognitive decline. The control individual carrying p.L1403RfsX7 (AAE 56) reportedly displayed some rigidity in the right arm upon activity but had no further symptoms diagnostic of PD. Of the 47 rare variants (including missense), 11 had CADD scores >20 (table 1B), including 6 missense variants (in 5 patients and 1 healthy control), of which 3 are located in the ATP-binding cassette domains (p.R989H, p.G1032S, and p.R1885H).

Burden tests. When examining the LOF variants across both data sets, a strong but not quite statistically significant association with PD risk was observed (11 in 1,680 case alleles vs 1 in 750 control alleles; OR = 4.94, p = 0.07). A moderate but not quite significant association was observed when comparing the burden of all rare variants with CADD >20,
which includes all LOF except for IVS32+2T>G (19 in 1,680 case alleles vs 3 in 750 control alleles; OR = 2.85, p = 0.06).

**DISCUSSION** This study expands the growing clinical, pathologic, and genetic overlap between PD and AD. We were able to identify known LOF ABCA7 variations in patients with PD and demonstrate a strong association of PD with ABCA7 LOF (OR = 4.94) and putative highly functional variants (OR = 2.85), although the observed enrichment was not quite statistically significant (p = 0.07 LOF variants or p = 0.06 CADD >20 rare variants). The rare frequency of these variants and the relatively small sample size (particularly for the controls) limited our power to detect significant association with rare variants.

Three of the 7 described LOF variants have not been previously reported in patients with AD (p.R1754X, p.L737CfsX60, and p.P1205fsX12). All are very rare in the Exome Aggregation Consortium database (allele frequency of p.R1754X and p.1205fsX12 <5 × 10⁻⁵ and p.L737CfsX60 was not seen). In addition, we identified the variant p.L1403RfsX7 in only 3 patients and not in controls, which supports the original observed enrichment of this variant in only patients with AD.¹²,¹⁴ Both p.E709AfsX86 and p.W1214X have been reported as strong AD risk factors and shown to reduce ABCA7 expression.¹²,¹⁴ Although the onset age of PD in the latter 2 LOF carriers (tables 2 and 3) is earlier than that reported for AD carriers (range 54–90 years and 84 years, respectively),¹² it is within the range expected for classical PD. We observed an additional 10 putative highly functional non-LOF variants with CADD >20. Prior knowledge of the LOF variants that contribute to AD risk and the rarity of all functional variants strongly suggests that ABCA7 also contributes to PD risk.

One control with an LOF variant was identified (p. W1214X in PPMI data set). However, the individual is relatively young, with AAE of 56 years and presented with signs of arm rigidity upon activity. Therefore, disease status appears unclear for this individual.

The presence of cognitive changes in some of the LOF carrier patients (tables 2 and 3) is of obvious interest. On average, the LOF cases in the Udall WES were followed for ~6 years without any indication of cognitive changes. The autos pied LOF cases (in the Udall WES) presented with pathologic signs of AD along with obvious PD changes confirming PD diagnosis. The patients with the p.W1214X (AD Braak stage III) and p.L1403RfsX7 variants (AD Braak stage V) still presented with no cognitive changes at their last clinical examination (table 2; individual 1 5 years before death and individual 3 1 year before death). In contrast, the PPMI patients carrying p.W1214X and p.P1205QfsX12 are reported to present with some signs of cognitive decline on clinical examination (table 3, individuals 3278 and 3866). As some cognitive decline was reported and AD has a later onset age than that of PD in general, we cannot exclude concomitant disease in these individuals with reported cognitive decline or AD pathology. However, dementia is common in patients with PD,¹,² and AD pathology is observed in a relatively high proportion of both patients with PD and healthy individuals upon death,²⁹ placing these observations in line with the expected PD process and commonalities of the 2 disorders. Additional autopsy studies will be needed to further investigate the AD pathologic features in PD ABCA7 variant carriers.

Overall, our data suggest that ABCA7 functional variants (LOF or variants with CADD >20) represent rare variant risk factors for clinical PD. The identification of LOF variants in both patients with AD and patients with PD implies that ABCA7 is involved in both disorders. Given ABCA7’s reported function in phagocytosis and clearance of protein aggregates, a likely mechanism for ABCA7 variants would be the decreased clearance of β-amyloid and α-synuclein in AD and PD. It would be interesting to investigate the presence of ABCA7 variants in other protein accumulation disorders.

This and other studies have now implicated several ABC transporters in neurologic, specifically neurodegenerative, diseases,¹⁹–²³ which implies that ABC transporters (and ABCA7 specifically) are interesting candidate genes for neurodegeneration in general.

**AUTHOR CONTRIBUTIONS** K.N. and J.M.V. conceived and designed the experiments. W.K.S. was responsible for sample collection. G.W.B., E.M., and L.M. performed initial QC and analyzed the exome sequencing data. A.A. and K.J.-W. performed the preliminary variant analysis and Sanger sequencing validation. K.N., W.K.S., G.W.B., and J.M.V. performed the statistical analysis and interpreted the data. K.N. and J.M.V. wrote the manuscript. K.N., W.K.S., E.M., and J.M.V. edited the manuscript. The authors jointly discussed the experimental results throughout the duration of the study. All authors read and approved the final manuscript.

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DISCLOSURE
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REFERENCES
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