Overlap between Parkinson disease and Alzheimer disease in *ABCA7* functional variants

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ABSTRACT

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 (*ABCA7*) might be involved in Parkinson disease (PD).

Methods: *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.

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 $p = 0.06$).

Conclusion: The presence of *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. ***Neurol Genet* 2016;2:e44; doi: 10.1212/NXG.0000000000000044**

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, ~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,[5–9] again supporting a hypothesis of shared mechanisms in these common disorders. Specifically, *APOE* status was originally discovered to be a strong risk factor and modifier of onset age for AD (odds ratio [OR] ≈ 3.5), but subsequent studies indicated that *APOE* exerted similar, although less pronounced, effects in PD (OR ≈ 1.8).[5,6] In contrast, association of the microtubule-associated protein tau (*MAPT*) haplotype H1 has been identified in many parkinsonian disorders, including PD (OR ≈ 0.65), for decades. More recently, it was shown that this haplotype also contributes to AD risk (OR ≈ 0.85–0.96).[8,9]

Supplemental data at Neurology.org/ng

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Recent studies have identified *ABCA7* (ATP-binding cassette transporter A7) as a risk factor for AD through genome-wide association studies in large case-control data sets.[10,11] Subsequent sequencing efforts have identified multiple rare loss-of-function (LOF) variants associated with AD risk (OR ≈ 2).[12–14] *ABCA7* is reported to be involved in the transport of phospholipid and cholesterol across membranes to ApoE.[15] Alternatively, *ABCA7* has been implicated in the activation of phagocytosis to clear amyloid plaques or even apoptotic cells.[16,17]

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

Sequence capture, sequencing, alignment, and variant calling. Fragmented DNA was captured using the Agilent SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, CA), designed to cover 38 Mb or 50 Mb of human genomic sequences. We used the 38 Mb capture kit in the initial 15 individuals (all patients); the remaining samples (N = 603) were processed using the 50 Mb version 3 kit. The libraries were loaded onto an Illumina cBot for cluster generation (Illumina, San Diego, CA). The primer-hybridized flow cells were then transferred to HiSeq2000 sequencers and paired-end sequencing was performed in a 2 × 101b mode (Illumina). The base calling was performed by Illumina CASAVA 1.6 pipeline and aligned to hg19 using Genome Analysis Tool Kit (GATK) v1.1. The Unified Genotyper from GATK performs variant quality score (VQS) recalibration and genotype refinement to make accurate variant calls.[26] In addition, the Unified Genotyper generates normalized Phred-scaled likelihood (PL) scores without priors for each alternate genotype. Variants with VQSLOD <-3, depth <6, and alternate PL scores <99 are excluded from the rest of the analysis presented here. Missing genotypes in table 1 reflect low depth of sequencing reads in certain coding regions, not low quality of the called genotypes and are consistent across patient and control data sets.

Sanger sequencing. Bidirectional Sanger sequencing (BigDye Terminator Cycle sequencing Kit; Life Technologies, Grand Island, NY) on a 3130 Genetic Analyzer (Life Technologies) was used to confirm and perform segregation analyses in the families with LOF variants. Primer sequences are available in table e-1 at Neurology.org/ng.

Parkinson's Progression Markers Initiative data. We used the WES data available through the Parkinson's Progression Markers Initiative (PPMI) as a comparison data set. More detailed information on this data set can be found on the PPMI Web site (http://www.ppmi-info.org/). In short, the exome was captured using the Illumina Nextera Rapid Capture Expanded Exome Kit (62 Mb), sequenced on Hiseq2500, and aligned to hg19. Variants were called using GATK's Haplotype Caller. The available data set comprises 462 patients with PD and 183 healthy controls. We excluded healthy controls with AAE <50 years and samples not clustering with the in-house Udall WES data set on common and rare variant PCAs. This reduced the number of samples for analysis to 444 patients and 153 healthy controls. The same filters on VQSLOD, depth, and PL score were applied for this data set.

Variant annotation. Variants were annotated using SeattleSeq including function within the gene and Combined Annotation Dependent Depletion (CADD) scores. Variants with CADD scores >20 were included in the analysis, as these are among the 1% highest ranked positions genome-wide in terms of potential functionality.[27]

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

Table 1 Putative highly functional variants identified in the Udall and PPMI whole-exome sequencing data sets

Variant	rsID	Change	AD[a]	Protein domain	CADD	PolyPhen-2	Udall (alleles)		PPMI (alleles)	
							Cases	Controls	Cases	Controls
A. LOF variants										
chr19:1047507 AGGAGCAG>A	—	E709AfsX86	Ca-O[12], Ca-Co[14]	Loss of ABC-I, ABC-II, TM-II domain	35	—	0/360	0/210	2/802 (0.3)	0/262
chr19:1047590 CT>C	—	L737CfsX60	No	Loss of ABC-I, ABC-II, TM-II domain	29.8	—	0/550	0/326	1/880 (0.1)	0/298
chr19:1054223 TG>T	—	P1205QfsX12	No	Loss of ABC-II, TM-II domain	24.5	—	0/652	0/372	1/836 (0.1)	0/272
chr19:1054255 G>A	201060968	W1214X	Ca-O[12]	Loss of ABC-II, TM-II domain	43	—	1/624 (0.2)	0/356	1/856 (0.1)	1/290 (0.3)
chr19:1055907 CT>C	—	L1403RfsX7	Ca-Co[14]	Loss of ABC-II, most of TM-II domain	34	—	2/790 (0.3)	0/444	1/888 (0.1)	0/306
chr19:1056244 T>G	113809142	IVS32+2T>G	Ca-Co[14]	Loss of ABC-II, most of TM-II domain	16.72	—	1/768 (0.1)	0/428	0/876	0/296
chr19:1058727 C>T	—	R1754X	No	Loss of ABC-II domain	40	—	1/792 (0.1)	0/444	0/888	0/306
B. Rare variants with CADD >20[b]										
chr19:1045108 G>C	—	L441F	No	Extracellular loop-I	24.4	Probably damaging	0/748	0/424	1/888 (0.1)	0/306
chr19:1045173 G>C	3752233	R463P	No	Extracellular loop-I	28.8	Probably damaging	1/770 (0.1)	0/434	0/878	0/300
chr19:1047169 T>C	144852598	L620P	Ca-Co[12]	—	23.8	Probably damaging	1/604 (0.2)	0/360	1/840 (0.1)	0/270
chr19:1048950 G>A	149949633	G776R	No	—	20.9	Probably damaging	0/602	0/334	1/888 (0.1)	0/306
chr19:1051006 G>A	143718918	R880Q	Ca-Co[12] Ca-Co[13]	ABC-I domain	33	Probably damaging	1/784 (0.1)	0/438	0/886	0/306
chr19:1051944 G>A	139214131	R989H	Ca-O[12]	ABC-I domain	25.1	Probably damaging	0/654	0/392	0/844	1/278 (0.4)
chr19:1052072 G>A	200951390	G1032S	No	ABC-II domain	24.8	Probably damaging	0/582	0/354	1/880 (0.1)	0/298
chr19:1061803 A>G	—	N1829S	No	ABC-II domain	21.9	Probably damaging	1/726 (0.1)	0/424	0/888	0/306
chr19:1062254 G>A	368864109	R1885H	No	ABC-II domain	22.4	Probably damaging	0/752	0/410	1/882 (0.1)	0/304
chr19:1063546 G>A	375389773	A1906T	No	ABC-II domain	22.8	Probably damaging	0/728	1/408 (0.3)	0/868	0/290

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 %).
[a] Reported in Alzheimer disease (AD).
[b] Minor allele frequency <5% in 1000 Genomes.

Table 2 Clinical characteristics of loss-of-function carriers in Udall whole-exome sequencing data set

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

Abbreviations: AAO = age at onset; AAE = age at last examination; AAD = age at death; AD = Alzheimer disease; NA = not applicable; PD = Parkinson disease.
Protein positions are relative to NP_061985.2.
[a] Cognitive impairment on last examination.

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).

Table 3 Clinical characteristics of loss-of-function carriers in Parkinson's Progression Markers Initiative whole-exome sequencing data set

Individual	Variant	AAO/ AAE, y	Reported family history	Cognitive decline	Notes
4115	E709AfsX86	65/67	No	No	
3593	E709AfsX86	55/56	No	No	
3530	L737CfsX60	63/65	No	No	
3866	P1205QfsX12	52/53	No	Yes	
3278	W1214X	64/65	No	Yes	
3613 (control(?))	W1214X	—/56	No	No	Rigidity in the right arm with activity only
3504	L1403RfsX7	60/61	No	No	

Abbreviations: AAO = age at onset; AAE = age at examination.
Protein positions are relative to NP_061985.2.

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.L1403Rfs7, 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 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 $<5 \times 10^{-5}$ 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 autopsied 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[28] 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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