

Clinical Deep Phenotyping of *ABCA7* Mutation Carriers

Alana S. Campbell, DO, Charlotte C.G. Ho, BS, Merve Atik, MD, Mariet Allen, PhD, Sarah Lincoln, BS, Kimberly Malphrus, BS, Thuy Nguyen, BS, Stephanie R. Oatman, BS, Morgane Corda, MS, Olivia Conway, MS, Samantha Strickland, PhD, Ronald C. Petersen, MD, Dennis W. Dickson, MD, Neill R. Graff-Radford, MD, and Nilüfer Ertekin-Taner, MD, PhD

Correspondence
Dr. Ertekin-Taner
taner.nilufer@mayo.edu

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Abstract

Background and Objectives

Putative loss-of-function (pLOF) *ABCA7* variants that increase Alzheimer disease (AD) risk were identified; however, deep phenotypic characterization of these variants in mutation carriers is limited. We aimed to obtain deep clinical phenotypes of *ABCA7* pLOF mutation carriers from a large retrospectively reviewed series.

Methods

Genotypes were determined for 5,353 individuals evaluated at Mayo Clinic for 6 reported *ABCA7* pLOF variants (p.E709fs, p.Trp1214X, p.L1403fs, c.4416+2T>G, p.E1679X, and c.5570+5G>C). Medical records of 100 mutation carriers were reviewed for demographics, clinical phenotypes, and diagnoses. Eleven mutation carriers had autopsy-based neuropathologic diagnoses.

Results

We confirmed that *ABCA7* pLOF mutations confer AD risk in our series of 2,495 participants with AD and 2,858 cognitively unaffected participants. Clinical review of 100 mutation carriers demonstrated phenotypic variability of clinical presentations with both memory and non-memory cognitive impairment and a subset presenting with motor symptoms. There was a wide range of age at onset of cognitive symptoms (ages 56–92 years, mean = 75.6). Ten of the 11 autopsied mutation carriers had AD neuropathology. *ABCA7* pLOF mutation carriers had higher rates of depression (41.6%) and first-degree relatives with cognitive impairment (38.1%) compared with the general population.

Discussion

Our study provides a deep clinical review of phenotypic characteristics of mutation carriers for 6 *ABCA7* pLOF mutations. Although memory impairment was the most common initial symptom, nonmemory cognitive and/or motor symptoms were present in a substantial number of mutation carriers, highlighting the heterogeneity of clinical features associated with these mutations. Likewise, although AD neuropathology is the most common, it is not the only autopsy-based diagnosis. Presence of earlier ages at onset, higher rates of depression, and first-degree relatives with cognitive impairment among mutation carriers suggest that these genetic variants may have more aggressive clinical features than AD in the general population. This deep phenotyping study of *ABCA7* pLOF mutation carriers provides essential genotype-phenotype correlations for future precision medicine approaches in the clinical setting.

From the Department of Neurology (A.S.C., S.R.O., N.R.G.-R., N.E.-T.), and Department of Neuroscience (C.C.G.H., M. Atik, M. Allen, S.L., K.M., T.N., S.R.O., M.C., O.C., S.S., D.W.D., N.E.-T.), Mayo Clinic, Jacksonville, FL; and Department of Neurology (R.C.P.), Mayo Clinic, Rochester, MN.

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Glossary

ABCA7 = ATP-binding cassette, subfamily A, member 7; **AD** = Alzheimer disease; **AGD** = argyrophilic grain disease; **APP** = amyloid precursor protein; **AUT** = autopsy-confirmed participants; **CBS** = corticobasal syndrome; **DLBD** = diffuse Lewy body disease; **FTD** = frontotemporal dementia; **JS** = clinical participants from Mayo Clinic, Jacksonville, FL; **MCI** = mild cognitive impairment; **mRNA** = messenger RNA; **OR** = odds ratio; **PA** = pathologic aging; **PD** = Parkinson disease; **pLOF** = putative loss of function; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **QC** = quality control; **RS** = clinical participants from Mayo Clinic, Rochester, MN.

In the past decade, genome-wide association studies have led to the discovery of over 25 susceptibility loci for late-onset Alzheimer disease (AD).^{1,2} Rare, putative loss-of-function (pLOF) mutations that confer AD risk were observed in *ABCA7*^{3–12} and common AD risk variants.^{1,2,13} ATP-binding cassette, subfamily A, member 7 (*ABCA7*) is a transporter protein coded by the *ABCA7* gene on chromosome 19p13.3 with high expression both peripherally and centrally in hippocampal CA1 neurons and glial cells in the brain. *ABCA7* plays an important role in brain lipid homeostasis, amyloid precursor protein (APP) processing, and macrophage-mediated phagocytosis, and it is believed to have a protective role against AD.^{14,15} Although exact pathogenic mechanisms of *ABCA7* mutations in AD are not entirely clear, experimental models have shown that deficiency of *ABCA7* can trigger the amyloid cascade through multiple mechanisms including defective lipid metabolism, promoting APP processing thereby accelerating amyloid-beta deposition, and disrupting the phagocytic clearance roles of the microglial network.¹⁶

A genetic study in an Icelandic population of 3,419 individuals with AD and 151,805 controls discovered that rare *ABCA7* variants, predicted to introduce a premature stop codon and result in reduced protein levels, were associated with AD risk independent of *APOE*.¹⁰ Follow-up studies confirmed these risk associations across multiple cohorts from Europe and the United States.^{5,8,10,11} Our group investigated the downstream effects of 3 of the most common *ABCA7* pLOF mutations (E709fs, L1403fs, and c.5570+5G>C) to determine whether lower messenger RNA (mRNA) and protein levels were indeed observed as predicted. The results demonstrated a lack of correlation between brain *ABCA7* mRNA and protein levels, challenging the theory of loss of mRNA and protein as the primary pathogenic mechanism for all pLOF variants.¹¹ Another study also identified transcribed mRNA for 7 pLOF mutations,⁷ including the 3 we reported,¹¹ and the presence of alternative transcripts for some mutation carriers, raising the possibility of a rescue from potential nonsense-mediated decay due to these mutations.

Despite numerous genetic studies on *ABCA7* mutations and their role in AD, there remains a gap in the literature of in-depth clinical reviews of mutation carriers. To our knowledge, the largest series of *ABCA7* mutation carriers with clinical phenotyping comprised 22 individuals from a Belgian Alzheimer disease patient cohort,¹⁷ 4 of whom also had autopsy evaluation.

This study described onset age, presenting symptoms, clinical diagnosis, and, where available, imaging data from carriers of 7 types of mutations, where 15 individuals with p.E709fs and 2 with c.67-1G>A (p.0) were evaluated, with the remaining mutations described each in 1 patient (p.V541fs, p.W1214*, p.Q1401fs, p.R1564*, and p.A2045fs). This¹⁷ and other smaller studies of *ABCA7* mutation carriers^{5,18} revealed variability in phenotypes, with clinical AD being the most common diagnosis, in addition to Parkinson disease (PD).¹⁸ We reported the identification of 12 carriers for 5 *ABCA7* pLOF mutation types in an autopsy cohort of 381 patients with non-AD pathologies.¹¹ These non-AD mutation carriers had pathologic diagnoses of progressive supranuclear palsy (PSP), vascular dementia (VaD), diffuse Lewy body disease (DLBD), and pathologic aging (PA) with argyrophilic grain disease (AGD), in addition to 45 mutation carriers with AD assessed in the same study.¹¹

Collectively, these studies suggest clinical and pathologic phenotypic variability for *ABCA7* mutation carriers; however, deep phenotyping of *ABCA7* mutation carriers in sizable cohorts is lacking due to the rarity of these mutations in well-characterized clinical cohorts. In this study, we aimed to bridge this knowledge gap: first, by the discovery of mutation carriers through genotyping of 5,353 participants to screen 6 *ABCA7* pLOF variants^{3,5,10,11} (p.Trp1214X [rs201060968], p.L1403fs, c.4416+2T>G [rs113809142], p.E1679X, p.E709fs, and c.5570+5G>C [rs200538373]), followed by a retrospective chart review of 100 identified mutation carriers for deep clinical phenotyping. Our study provides in-depth clinical phenotyping in this large series of clinical participants that is expected to guide current care and future precision medicine approaches in the clinical setting.

Methods

Participants

This study included 5,375 individuals, 2,889 of whom had been included in our prior study,¹¹ and 2,486 new participants were genotyped to expand the cohort. These 5,375 individuals were recruited through Mayo Clinic, Jacksonville, FL (JS), Rochester, MN (RS), or from the Mayo Clinic Brain Bank (AUT) and genotyped for the 6 *ABCA7* pLOF variants (p.Trp1214X [rs201060968], p.L1403fs, c.4416+2T>G [rs113809142], p.E1679X, p.E709fs, and c.5570+5G>C [rs200538373]) previously evaluated by us¹¹ and others.^{3,5,10}

Table 1 Genetic Association Study Participant Demographics

Series	Diagnosis	N	Age, mean ± SD	Female, n (%)	APOE ε4+, n (%)
AUT	AD	1,179	81.47 ± 8.70	689 (58)	724 (61)
JS	AD	761	75.83 ± 6.29	477 (63)	506 (66)
	Control	869	80.05 ± 6.74	492 (57)	219 (25)
	All	1,630	78.08 ± 6.86	969 (59)	725 (44)
RS	AD	555	80.95 ± 7.90	325 (59)	277 (50)
	Control	1,989	82.20 ± 5.91	1,075 (54)	453 (23)
	All	2,544	81.92 ± 6.41	1,400 (55)	730 (29)
Combined	AD	2,495	79.63 ± 8.25	1,491 (60)	1,507 (60)
	Control	2,858	81.54 ± 6.25	1,567 (55)	672 (24)
	All	5,353	80.65 ± 7.31	3,058 (57)	2,179 (41)

Abbreviations: AD = Alzheimer disease; AUT = autopsy-confirmed participants; control = cognitively unimpaired controls; JS = clinical participants from Mayo Clinic Jacksonville, FL; RS = clinical participants from Mayo Clinic Rochester, MN; N = number of participants.

Sample demographics for 5,353 postquality control participants included in the genetic association analyses. Mean age (SD) was calculated based on the age at death for AUT, age at first AD diagnosis for RS and JS AD patients, and age at last diagnosis for JS and RS controls.

Following genotype quality control (QC), a total of 5,353 participants were retained for genetic analysis comprising 1,179 participants with autopsy-confirmed AD, 1,316 participants with clinically diagnosed AD, and 2,858 clinically diagnosed control participants. Clinical or neuropathologic diagnosis of possible/probable or definite AD, respectively, was given according to NINCDS-ADRDA criteria.¹⁹ One hundred individuals who were mutation carriers and who also had clinical records were evaluated further for their clinical characteristics by retrospective chart review. Informed consent and approval by the Mayo Clinic Institutional Review Board were obtained for all participants.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed patient consent and approval by the Mayo Clinic Institutional Review Board were obtained.

Genotyping

Genotyping of *ABCA7* pLOF mutations examined in our prior study was performed as previously described¹¹ using Custom TaqMan SNP assays (Applied Biosystems, Foster City, CA) for 5 of the variants. Genotypes were analyzed on ABI Prism 7900 Detection System using SDS version 2.2.2 software (Applied Biosystems). For p.E709fs, the presence of the 7bp deletion was identified by generation of fluorescently labeled PCR products and assessed using the ABI3730xl Genetic Analyzer (Applied Biosystems) and GeneMapper Software 5.0 (Applied Biosystems). All *ABCA7* pLOF mutations identified were validated by sequence analysis as described previously¹¹ with the exception of rs20053873 (c.5570+5G>C), in which confirmation used PCR primer sequences for exon 41 (forward sequence: ctgggcctcactgagacc; reverse sequence: gggcctgtccgcgtgtggg). PCR products and sequencing reactions were purified and ran using the Agencourt AMPure system (Beckman Coulter, Brea,

CA) and BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) and Agencourt CleanSEQ (Beckman Coulter) and ABI3730xl Genetic Analyzer (Applied Biosystems), respectively. Sequence analysis was performed using Sequencher 4.8 software (Gene Codes Corporation, Ann Arbor, MI).

Genetic Quality Control and Association Analyses

Following genotyping, additional QC steps were performed. Individuals who were (1) not of non-Hispanic White descent or of unknown race, (2) not diagnosed as AD or control, or (3) have an age of death (autopsy AD), age at first AD diagnosis (clinical AD), or age at last diagnosis (clinical control) that was less than 60 years were excluded from the genetic association analyses for late-onset AD risk. For the purposes of the clinical review described in next section, we included such participants to capture the full spectrum of race, age, and diagnoses for clinical phenotyping. Any individuals with missing *APOE* genotypes or sex were excluded from further genetic or clinical analyses. The resulting cohort comprising 2,495 participants with AD and 2,858 control participants was used for genetic association analyses. AD risk associations were tested for each of the 6 *ABCA7* pLOF mutation individually and also in aggregate, within each series (JS, RS, and AUT) and in all series combined, using 2-sided Fisher exact tests or in an *APOEε4* adjusted or unadjusted logistic regression models. All statistical analyses were performed using StatsDirect (version 3.3.4) or R statistical software (version 4.0.2).

Clinical Review

The medical records of 100 *ABCA7* mutation carriers were retrospectively reviewed while blinded to the mutation variant of participants. Of these, 62 were seen by neurologists and 29 by internal or family medicine physicians at Mayo Clinic in Rochester, MN, or Jacksonville, FL. Nine patients, who did not have detailed clinical records, but had sex, age at first visit, and

Table 2 Association of *ABCA7* pLOF Mutations With Alzheimer Disease Risk

Variant	Maj/Min	Chr19 position (hg19)	rs number	All AD (N = 2,495)			All CON (N = 2,858)			AUT AD (N = 1,179)			JS AD (N = 761)			JS CON (N = 869)			RS AD (N = 555)			RS CON (N = 1,989)		
				N	n	% MAF	N	n	% MAF	N	n	% MAF	N	n	% MAF	N	n	% MAF	N	n	% MAF	N	n	% MAF
p.E1679X	G/T	1,058,154	NA	2,443	1	0.020	2,813	0	0.000	1,163	1	0.043	734	0	0.000	858	0	0.000	546	0	0.000	1,955	0	0.000
p.L1403fs	T/del	1,055,907	NA	2,487	14	0.281	2,846	7	0.123	1,177	6	0.255	758	4	0.264	864	1	0.058	552	4	0.362	1,982	6	0.151
c.4416+2T>G	T/G	1,056,244	rs113809142	2,483	3	0.060	2,845	1	0.018	1,172	1	0.043	759	2	0.132	864	1	0.058	552	0	0.000	1,981	0	0.000
c.5570+5G>C	G/C	1,061,892	rs200538373	2,463	40	0.812	2,823	20	0.354	1,170	15	0.641	746	13	0.871	848	5	0.295	547	12	1.097	1,975	15	0.380
p.Trp1214X	A/G	1,054,256	rs201060968	2,454	2	0.041	2,826	1	0.018	1,168	1	0.043	741	1	0.067	851	0	0.000	545	0	0.000	1,975	1	0.025
p.E709fs	GGAGCAG/del	1,047,508–1,047,514	NA	2,303	18	0.391	2,641	9	0.170	1,170	12	0.513	588	3	0.255	736	3	0.204	545	3	0.275	1,905	6	0.157
Collapsed				2,495	78	1.563	2,858	38	0.665	1,179	36	1.527	761	23	1.511	869	10	0.575	555	19	1.712	1,989	28	0.704
Fisher exact							OR = 2.34 (1.43–3.81) $p = 4.13E-04^a$			OR = 2.68 (1.22–6.34) $p = 8.05E-03^b$			OR = 2.48 (1.30–4.65) $p = 3.70E-03^c$											
							OR = 2.39 (1.60–3.64) $p = 7.60E-06^d$			OR = 2.45 (1.53–3.92) $p = 8.55E-05^e$														

Abbreviations: AD = Alzheimer disease; AUT = autopsy-confirmed participants; Chr19 position (hg19) = position in chromosome 19 based off hg19 build; CON = cognitively unimpaired controls; JS = clinical participants from Mayo Clinic, Jacksonville, FL; MAF = minor allele frequency; Maj/Min = major/minor allele; n = number of mutation carriers; N = number of participants; NA = not available; OR = odds ratio; pLOF = putative loss of function; RS = clinical participants from Mayo Clinic, Rochester, MN.

Mutation annotation and frequencies split by diagnosis and recruitment site are described. Fisher exact 2-sided tests showing AD association for the collapsed mutation counts between groups are displayed. Difference in N across variants is due to failed genotyping. Results are shown for the analyses as follows: ^aAUT AD vs all controls; ^bJS AD vs JS controls; ^cRS AD vs RS controls; ^dall AD vs all controls; and ^eJS + RS AD vs JS + RS controls.

Table 3 *ABCA7* pLOF Mutation Carrier Demographics

	All (N = 100)	Cognitively impaired (N = 67)	Cognitively unimpaired (N = 33)	p.Trp1214X (N = 4)	p.E1679X (N = 1)	c.4416+2T>G (N = 4)	c.5570+5G>C (N = 48)	p.E709fs (N = 24)	p.L1403fs (N = 19)
Female, N (%)	62 (62)	43 (64.2)	19 (57.6)	2 (50)	—	2 (50)	29 (60.4)	18 (75)	11 (57.9)
Age, mean ± SD (range)									
First visit	76.78 ± 7.92 (56–95)	75.63 ± 8.23 (56–92)	79.12 ± 6.77 (62–95)	75.75 ± 11.18 (59–82)	76	78.75 ± 6.18 (72–87)	76.81 ± 7.71 (57–92)	76.63 ± 7.28 (59–86)	76.74 ± 9.65 (56–95)
Last visit	81.04 ± 8.68 (56–98) ^a	80.48 ± 9.04 (56–96) ^a	82.15 ± 7.93 (62–98)	79.5 ± 11.70 (62–86)	78	81.75 ± 6.18 (75–87)	81.04 ± 8.19 (62–94)	81.57 ± 7.59 (67–96) ^a	80.74 ± 11.58 (56–98)
Duration of follow-up, mean ± SD (range)^b	4.89 ± 4.77 (0–23)	5.26 ± 5.33 (0–23)	4.00 ± 2.99 (0–9)	4.00 ± 1.41 (2–5)	2	1.00 ± 1.41 (0–3)	4.84 ± 4.37 (0–17)	6.67 ± 6.53 (0–23)	4.41 ± 4.21 (0–15)
APOE ε4 positive, N (%)	33 (33)	26 (38.8)	7 (21.2)	1 (25)	1 (100)	—	16 (33.3)	6 (25)	9 (47.4)
Depression, n/N (%)^c	37/89 (41.6)	29/63 (46.0)	8/26 (30.8)	3/4 (75)	1/1 (100)	2/4 (50)	16/45 (35.6)	8/20 (40)	7/15 (46.7)
First-degree relative, n/N (%)^d	24/63 (38.1)	22/52 (42.3)	2/11 (18.2)	1/4 (25)	1/1 (100)	2/3 (66.7)	10/34 (29.4)	4/11 (36.4)	6/10 (60)

Abbreviations: N = number of participants; pLOF = putative loss of function.

Demographics for the 100 carriers of *ABCA7* pLOF mutations who are included in the clinical chart review. Data are split by cognitively impaired and unimpaired participants, as well as by mutation type.

^a Excludes 1 individual with missing data.

^b Includes individuals with known follow-up durations.

^c n = number of individuals with a history of depression, N = all individuals where depression history, whether present or absent, is available.

^d n = number of individuals with a first-degree relative who is cognitively impaired, N = all individuals where first-degree relative history, whether present or absent, is available.

Table 4 ABCA7 pLOF Cognitively Impaired Mutation Carrier Clinical Features

	All (N = 67)	p.Trp1214X (N = 3)	p.E1679X (N = 1)	c.4416+2T>G (N = 3)	c.5570+5G>C (N = 33)	p.E709fs (N = 15)	p.L1403fs (N = 12)
Diagnosis, N (%)							
AD	43 (64.2)	1 (33.3)	—	2 (66.7)	26 (78.8)	9 (60)	5 (41.7)
MCI	10 (14.9)	1 (33.3)	—	—	3 (9.1)	4 (26.7)	2 (16.7)
Other	14 (20.9)	1 (33.3)	1 (100)	1 (33.3)	4 (12.1)	2 (13.3)	5 (41.7)
Presenting symptom, N (%)							
Amnestic	51 (76.1)	1 (33.3)	—	2 (66.7)	27 (81.8)	12 (80)	9 (75)
Unknown ^d	9 (13.4)	1 (33.3)	—	—	5 (15.2)	2 (13.3)	1 (8.3)
Behavioral	3 (4.5)	1 (33.3)	—	—	—	1 (6.7)	1 (8.3)
Parkinsonism	3 (4.5)	—	—	1 (100)	1 (3.0)	—	1 (8.3)
Language	1 (1.5)	—	1 (100)	—	—	—	—
Nonmemory symptom, N (%)							
None	36 (53.7)	2 (66.7)	—	2 (66.7)	22 (66.7)	6 (40)	4 (33.3)
Unknown	11 (16.4)	—	—	—	5 (15.2)	3 (20)	3 (25)
Behavioral	6 (9) ^{a,b}	—	—	—	2 (6.1) ^a	2 (13.3)	2 (16.7) ^b
Language	5 (7.5) ^c	—	1 (100)	—	—	3 (20)	1 (8.3) ^c
Parkinsonism	5 (7.5) ^b	—	—	1 (100)	2 (6.1)	—	2 (16.7) ^b
Gait abnormalities	4 (6) ^c	—	—	—	2 (6.1)	—	2 (16.7) ^c
Visuospatial	3 (4.5) ^{a,b}	—	—	—	1 (3) ^a	1 (6.7)	1 (8.3) ^b
Alien limb	1 (1.5)	1 (33.3)	—	—	—	—	—

Abbreviations: AD = Alzheimer disease; MCI = mild cognitive impairment; N = number of participants; pLOF = putative loss of function. ABCA7 pLOF mutation carrier clinical features are shown for 67 cognitively impaired participants included in the clinical chart review. Data are shown for all mutations combined and also for each mutation type. Three individuals with >1 nonmemory symptoms were included in counts for each corresponding symptom: ^avisuospatial and behavioral; ^bvisuospatial, parkinsonism, and behavioral; ^clanguage and gait abnormalities; and ^dincludes 2 individuals clinically diagnosed with nonamnestic mild cognitive impairment.

APOE genotype data, were also included in the clinical review. Ages at first and last visits with the neurologist were used for mutation carriers diagnosed by a neurologist, and otherwise, ages at first/last visits with the internal/family medicine physician were used. Where available, presenting neurologic symptoms were broadly categorized (amnestic, language, behavioral, parkinsonism, and unknown), and any nonmemory symptoms were further cataloged (language, behavioral, parkinsonism, gait abnormalities, visuospatial, alien limb, unknown, or none).

Depression was noted for an individual if it was documented in the medical record during any visit; however, it was not specified if this diagnosis preceded or followed onset of neurologic symptoms. A first-degree relative was defined as a parent, sibling, or child. Clinical impairment was documented by such phrases: “history of memory problems,” “cognitive impairment,” “Alzheimer disease,” or “dementia.” Family history of other neurodegenerative disorders, such as PD, was not recorded.

After clinical data were collected from the participants’ medical records, their mutation group was subsequently revealed for analyses to determine descriptive statistics for the 6 mutations and to perform comparisons with findings from the literature.

Data Availability

All data generated during this study are included in this published article and its supplementary information files (links.lww.com/NXG/A508). Original raw deidentified data may be made available after a reasonable and well-justified request to the corresponding author.

Results

Genetic Analysis

A total of 5,353 individuals were genotyped for 6 previously reported ABCA7 pLOF variants and passed QC (Table 1 and eTable 1, links.lww.com/NXG/A508)¹¹ to conduct AD risk associations. We previously assessed these 6 variants for

Table 5 ABCA7 pLOF Mutation Carrier Neuropathologic Features

Mutation	Ethnicity	Sex	APOE	Age				Duration of follow-up	Clinical				Pathology		
				Onset	First visit	Last visit	Death		Diagnosis	Cognitively impaired	Presenting features	Nonmemory symptoms	Depression	Diagnosis	Braak
p.Trp1214X	NHW	M	33	54	59	62	64	4	CBS	Yes	Behavioral	Alien limb	Yes	AD and LBD	6
c.5570+5G>C	NHW	M	33	N/A	83	83	84	0	NCI	No	Unknown	Tremor	No	AD	4.5
c.5570+5G>C	NHW	M	33	57	60	65	65	5	AD	Yes	Amnestic	None	No	AD and VaDis	6
c.5570+5G>C	NHW	F	33	73	75	82	84	7	AD	Yes	Amnestic	Gait	Yes	AD, Fahr, and VaDis	5.5
c.5570+5G>C	AA	F	34	73	77	77	78	0	AD	Yes	Amnestic	None	No	AD, Fahr, and VaDis	5
c.5570+5G>C	NHW	F	33	87	84	88	92	4	AD	Yes	Amnestic	None	No	AD	5
p.E709fs	NHW	F	23	86	81	86	89	5	MCI	Yes	Amnestic	None	Yes	AD and AGD	5
p.E709fs	NHW	M	33	70	78	83	84	5	PPA	Yes	Behavioral	Language	Yes	AD and VaDis	5
p.E1679X	NHW	M	44	66	76	78	80	2	FTD	Yes	Language	Language	Yes	AD and CVA	6
p.L1403fs	NHW	F	34	53	56	56	64	0	AD	Yes	Amnestic	Behavioral	Yes	AD	6
c.4416+2T>G	NHW	F	33	78	78	87	87	1	PD; MCI	Yes	Parkinsonism	Parkinsonism	Yes	VaDis	2.5

Abbreviations: AA = African American; AD = Alzheimer disease; AGD = argyrophilic grain disease; CBS = cortical basal syndrome; FTD = frontotemporal dementia; LBD = Lewy body disease; MCI = mild cognitive impairment; NCI = no cognitive impairment; NHW = non-Hispanic White; PD = Parkinson disease; pLOF = putative loss of function; PPA = primary progressive aphasia; UNK = unknown; VaDis = vascular disease.

association with risk for AD and other neurodegenerative diseases in a cohort of 2,889 participants and explored their impact on mRNA and protein levels in the brain.¹¹ Here, we have expanded the cohort to include an additional 2,486 participants and performed deep clinical phenotyping of minor allele carriers. Of these 5,353 participants, 116 (2.17%) were carriers of at least 1 *ABCA7* mutation. The presence of at least 1 of these mutations was significantly associated with AD risk (odds ratio [OR] = 2.39, $p = 7.60E-06$), with 78 carriers of 2,495 participants with AD compared with 38 of 2,858 controls (Table 2). This association persisted even when the combined mutation counts for AD and control participants were further split by recruitment site, clinical and autopsy diagnosis (Table 2), and analysis was adjusted for *APOE* $\epsilon 4$ tagging variant (rs429358) presence in a logistic regression model (OR = 2.65, $p = 4.11E-06$).

Each mutation was also analyzed separately to elucidate the underlying mutation driving AD association (eTable 2, links.lww.com/NXG/A508). *ABCA7* c.5570+5G>C mutation conferred significant AD risk in the overall series (OR = 2.3, $p = 2.5 E-03$) and in the subset of all clinically diagnosed participants (OR = 2.8, $p = 9.7 E-04$), whether they were recruited at Mayo Clinic in Jacksonville, FL (JS) (OR = 3.0, $p = 3.4 E-02$), or Rochester, MN (RS) (OR = 2.9, $p = 7.9 E-03$). Despite a trend for increased risk in participants with autopsy-confirmed AD, the AD risk association for c.5570+5G>C did not achieve statistical significance (OR = 1.8, $p = 9.2 E-02$). *ABCA7* p.E709fs was also significantly associated with risk in the participants with autopsy-confirmed AD (OR = 3.0, $p = 1.5 E-02$). No other mutations had statistically significant association with AD risk when tested individually.

Demographics and Clinical Characteristics

There were 100 mutation carriers with available clinical data. Demographics and clinical characteristics are described in Table 3. All participants were non-Hispanic White with the exception of 3 individuals who were African American (c.5570+5G>C), Asian (p.L1403fs), or Hispanic White (p.E709fs). The majority of mutation carriers were female (62%). Based on clinical review, 67 individuals were cognitively impaired, and 33 were cognitively unimpaired. The mean age at first visit was 76.8 years, with a wide age range of 56–95 years. Cognitively impaired mutation carriers had a mean age at first visit of 75.6 (range: 56–92) years, and cognitively unimpaired had a mean age at first visit at a later age of 79.1 (range: 62–95) years. Of 100 mutation carriers, 87 had known duration of follow-up, and 63 of these had greater than or equal to 2 years of follow-up (Table 3). *APOE* $\epsilon 4$ was present in 26/67 (39%) of cognitively impaired individuals compared with 7/33 (21%) of cognitively unimpaired.

There was information on history of memory problems in first-degree relatives for 63 mutation carriers (Table 3). A total of 38.1% (24/63) mutation carriers had a first-degree relative with memory problems. The cognitively impaired group had a substantially higher frequency of first-degree relative with reported memory problems, 22/67 (42%),

compared with that for cognitively unimpaired mutation carriers, 2/33 (18%). Frequency and age at onset of memory problems are provided for the first-degree relative of each type of mutation for the 63 carriers where these data were available (eTable 3, links.lww.com/NXG/A508). As expected, the highest numbers of first-degree relatives with memory problems were observed for carriers of the most common *ABCA7* c.5570+5G>C mutation (10 first-degree relatives of 34 carriers with these data), followed by p.L1403fs (6 first-degree relatives/10 carriers) and p.E709fs (4 first-degree relatives/11 carriers) mutations.

Information on depression was available for 89 of 100 mutation carriers. Of these, 42% were diagnosed with depression. Of the cognitively impaired group, 29/63 (46%) had depression compared with 8/26 (31%) in the cognitively unimpaired group.

The clinical phenotypic descriptions of cognitively impaired mutation carriers are presented in Table 4. The clinical diagnoses of mutation carriers ($n = 100$) fell into the broad categories of Alzheimer disease ($n = 43$), mild cognitive impairment (MCI) ($n = 10$), cognitively unimpaired ($n = 33$), and other ($n = 14$). The other category included 1 corticobasal syndrome (CBS), 1 frontotemporal dementia (FTD), 1 primary progressive aphasia (PPA), 2 posterior cortical atrophy, 1 PD with MCI, 3 dementia with Lewy bodies, 2 unspecified dementia, and 3 VaD.

Of the 67 cognitively impaired mutation carriers, the majority presented with amnesic symptoms 51/67 (76%), whereas 3/67 (4.5%) presented with parkinsonism, 3/67 (4.5%) behavioral disturbance, 1/67 (1.5%) language difficulty, and 9/67 (13%) were unknown. There were 36/67 (54%) who displayed purely amnesic symptoms; however, 24/67 (36%) had additional nonmemory symptoms, including 6/67 (9%) behavioral disturbances, 5/67 (7.5%) language deficits, 5/67 (7.5%) parkinsonism, 4/67 (6%) gait abnormalities, 3/67 (4.5%) visuospatial, and 1/67 (1.5%) alien limb phenomenon. The remaining 11/67 (16.4%) were unknown due to no further descriptive characteristics noted in the medical record.

Mutation-specific demographics and phenotypes are presented in eTable 4 (links.lww.com/NXG/A508). Of the 6 mutations genotyped, observed carrier counts ranged from 1 to 48 in the individuals with available medical records, with c.5570+5G>C ($n = 48$), p.E709fs ($n = 24$), and p.L1403fs ($n = 19$) being the most common among these variants, as noted in our previous cohort, and p.Trp1214X ($n = 4$), E1679X ($n = 1$), and c.4416+2T>G ($n = 4$) being rare. Across all 6 variants, *APOE* $\epsilon 4$ positivity, depression history and a positive first-degree relative were higher among the cognitively impaired individuals compared with the cognitively unimpaired.

There were 11 autopsies of mutation carriers, of whom 10 had AD pathology and 1 had vascular PD (Table 5). Five of these

had c.5570+5G>C, 2 had p.E709fs, and 1 each had p.Trp1214X, p.E1679X, p.L1403fs, and c.4416+2T>G mutations. The patient with *ABCA7* c.4416+2T>G had vascular parkinsonism with Braak of 2.5 and clinical diagnosis of PD and MCI. This was a woman with age at onset of neurological symptoms of 78 years, *APOE* $\epsilon 3/\epsilon 3$ genotype who died at age 87 years. All other mutation carriers had Braak of 4.5 or above and AD pathology, although most also had other pathologies, including vascular disease (n = 5), Lewy bodies (n = 1), AGD (n = 1), and Fahr disease (n = 2).

The most common clinical diagnosis for these autopsied patients was AD (n = 5). These patients included 4 with *ABCA7* c.5570+5G>C and 1 with p.L1403fs mutation. These 5 patients and a patient with MCI and p.E709fs mutation had amnesic presentations. One *ABCA7* c.5570+5G>C mutation carrier, who died at age 84 years, had no cognitive impairment and only tremors. This patient had *APOE* $\epsilon 3/\epsilon 3$ genotype and early AD pathology with Braak of 4.5.

Of the 10 autopsy-confirmed mutation carriers with AD, 3 had atypical clinical presentations. One patient with the *ABCA7* p.Trp1214X mutation and *APOE* $\epsilon 3/\epsilon 3$ genotype was a man with clinical diagnosis of CBS. He presented with left alien limb phenomenon and behavioral problems at age 54 years. He had no family history of neurodegenerative disease. His first clinical visit was at age 59 years and death occurred at age 64 years. His diagnoses at autopsy were AD (Braak Stage VI) and transitional LBD. Another patient with autopsy-confirmed AD was a man with the *ABCA7* p.E1679X mutation and *APOE* $\epsilon 4/\epsilon 4$ genotype who presented with FTD. He had word-finding difficulty, semantic aphasia, and memory loss at age 66 years, as well as a family history of late-life dementia in his mother. His first clinical visit was at age 76 years, and he died at age 80 years. His pathologic diagnoses were AD (Braak Stage VI) with concurrent vascular disease. The third patient with autopsy-confirmed AD with an atypical clinical presentation had *ABCA7* p.E709fs mutation and *APOE* $\epsilon 3/\epsilon 3$ genotype. This man with a clinical diagnosis of PPA presented at age 70 years with progressive memory loss, severe fluent aphasia, disinhibition, and myoclonus. There was a family history of dementia in his mother, diagnosed at age 74 years. He had his first clinical visit at age 78 years, and he died at age 84 years. His diagnoses at autopsy were AD (Braak Stage V) and concurrent arteriosclerotic leukoencephalopathy, most marked in the parietal lobe.

There was variability in the ages at onset of symptoms (53–87 years) and death (64–92 years). The youngest age at onset was observed for the *ABCA7* p.L1403fs carrier (age at onset/death = 53/64) who also had *APOE* $\epsilon 3/\epsilon 4$ genotype. This was followed by the *ABCA7* p.Trp1214X carrier (age at onset/death = 54/64 years) who had *APOE* $\epsilon 3/\epsilon 3$ genotype. One of the *ABCA7* c.5570+5G>C carriers, who had *APOE* $\epsilon 3/\epsilon 3$, had the third youngest age at onset/death (57/65 years). Of interest, there was a wide range for age at onset and age at death, even for the same *ABCA7* c.5570+5G>C mutation.

Discussion

In this study, we expanded the cohort from our previous study of 2,889 individuals to 5,353 individuals genotyped for 6 rare *ABCA7* pLOF variants (p.E709fs, p.Trp1214X, p.L1403fs, c.4416+2T>G, p.E1679X, and c.5570+5G>C).¹¹ Our findings validate the significant association of *ABCA7* pLOF mutations as risk variants for AD both collectively and also for the relatively more common c.5570+5G>C and p.E709fs variants, individually.

In addition, we performed a medical record review of 100 individuals with these rare variants to characterize their clinical and where available also neuropathologic phenotypes. We hypothesized that there would be clinical and neuropathologic heterogeneity among the *ABCA7* pLOF mutation carriers. Of these 100 deeply phenotyped mutation carriers, 67 had cognitive impairment, the majority of whom had clinical AD and memory impairment as their clinical diagnosis and presenting symptom, respectively. Nevertheless, other clinical diagnoses (20%) and nonmemory presenting symptoms (10%) were noted supporting clinical heterogeneity in clinical presentation and diagnoses for *ABCA7* pLOF mutation carriers.

Importantly, our study included 11 mutation carriers who had postmortem evaluation, 10 of whom had AD neuropathology and 1 *ABCA7* c.4416+2T>G carrier with vascular pathology and clinical PD. Many of those with AD neuropathology had additional neuropathologies, the most common of which was vascular disease. The copathologies observed in the *ABCA7* mutation carriers likely reflect the well-known pathologic heterogeneity of AD, which is often mixed with vascular and other neurodegenerative pathologies.²⁰ Our findings on autopsied patients in this and our prior study¹¹ suggest that deleterious effects of *ABCA7* pLOF mutations may not be specific to AD neuropathology, but that it may also pose risk for other neuropathologies. In a prior study, we identified 12 autopsied individuals who were carriers of *ABCA7* pLOF mutations (p.E709fs, p.L1403fs, c.4416+2T>G, p.E1679X, and c.5570+5G>C), who did not meet the neuropathologic criteria for AD, but had non-AD pathologic diagnoses, including PSP, VaD, DLBD, PA, and AGD.¹¹ It is plausible that pLOF mutations in *ABCA7*, a lipid transporter, have broad effects on AD, other neurodegenerative diseases, and VaD through disruptions in lipid metabolism and/or its interactions with *APOE*.²¹

Given the rarity of *ABCA7* pLOF variants, deep clinical and neuropathologic phenotyping studies in mutation carriers are limited. A retrospective review in a Belgian cohort characterized the phenotypes of 22 rare *ABCA7* pLOF mutation carriers, 15 of whom had the p.E709fs variant¹⁷ and the remaining patients had 6 other mutation types. All 22 individuals presented with memory impairment, except 1 patient who presented with dopamine-responsive parkinsonism. Seventeen of these patients had neuropsychological testing

and imaging studies. Additional clinical findings in these 17 mutation carriers included behavioral disturbance (13/17), language difficulties (10/17), visual hallucinations (3/17), and delusions (4/17). Although all patients had a typical AD phenotype, 4 had an initial differential diagnosis of VaD, frontotemporal dementia, or dementia with Lewy bodies due to the other clinical features present. Four patients from this Belgian cohort who underwent autopsy had AD neuropathology.

Another study conducted in patients with clinical PD identified 4 *ABCA7* variants (p.E709fs, p.Trp1214X, p.L1403fs, and rs113809142) previously described in AD and 3 others not previously reported in AD (p.R1754X, p.L737CfsX60, and p.P1205fsX12).¹⁸ Two patients from this study who carried either p.Trp1214X or p.L1403fs mutation came to autopsy, and both had PD and AD pathologies.

Collectively, our current study and prior work by our group¹¹ and others^{17,18} underscore the clinical and neuropathologic heterogeneity of *ABCA7* pLOF mutation carriers. Our deep phenotyping of 100 mutation carriers provides a detailed account of presenting and accompanying clinical symptoms, as well as neuropathologic findings in this cohort. Although memory symptoms, as well as clinical and pathologic AD diagnosis are the predominant features of *ABCA7* pLOF mutation carriers, non-memory presentations and non-AD pathologies, including parkinsonian and vascular copathologies, respectively, were also present. These findings have implications for both research and clinical purposes. The role of *ABCA7* dysfunction should be studied not only in AD models, but also in α -synucleinopathy and vascular disease. In addition, non-AD clinical diagnoses or non-memory symptoms should not rule out the presence of *ABCA7* pLOF mutations.

Our study also provides information on other clinical aspects of *ABCA7* pLOF mutation carriers, including age of patients, history of depression, and frequency of cognitive impairment in first-degree relatives. In our study, we also observed a wide range for age at first visit (56–92 years) and symptom onset (53–92 years) for the cognitively impaired mutation carriers. Notably, 18% of those had symptom onset before age 65 years. Of interest, there was an enrichment for *ABCA7* pLOF mutations in a European cohort of 928 patients with early-onset AD (3%) compared with 980 controls (0.6%).⁷ Likewise, in a French study of 484 patients with early-onset AD, there was an excess of *ABCA7* pLOF mutations compared with controls.⁹ Although these findings suggest a potential role for screening patients with early onset of cognitive impairment for *ABCA7* pLOF mutations, the wide age range underscores caution against excluding these mutations as potential risk factors. Another conclusion from our study is the likely presence of other factors that modify disease onset or progression in *ABCA7* pLOF mutation carriers. For example, among our autopsy-confirmed patients, 5 had the same c.5570+5G>C mutation with ages at onset and death ranges of 57–87 and 65–92 years, respectively. *APOE* could not explain the differences in the ages because both the oldest and

youngest patient had the *APOE* ϵ 3/ ϵ 3 genotype. Furthermore, one of the c.5570+5G>C mutation carriers was cognitively normal at death and had only mild AD neuropathology. Studying specific *ABCA7* pLOF mutation carriers with variable clinical and pathologic phenotypes offers an opportunity to uncover disease-modifying factors in AD.

In our study, we had information on cognitive impairment in first-degree relatives for 63 mutation carriers. There was a history of cognitive impairment in 22/52 (42%) of relatives of mutation carriers and 2/11 (18%) without cognitive impairment. These findings are in agreement with a positive family history identified in 10/22 *ABCA7* pLOF mutation carriers (45.5%) in a Belgian study¹⁷ and with higher than the estimated cumulative AD risk by age 85 years in non-Hispanic Whites who had a first-degree relative with AD (26.9%).²² Of interest, available paternal (4/24) vs maternal (17/24) first-degree relative in our study showed a higher percentage for the latter (71%), consistent with prior reports on stronger AD risk with a positive maternal history.^{23,24} These findings should be pursued in prospective studies by performing genetic screens of *ABCA7* pLOF mutations and obtaining detailed family history.

Another observation in our study was the high rate of depression among mutation carriers in both the cognitively impaired (29/63, 46%) and unimpaired groups (8/26, 31%). Depression has been described frequently in patients with AD. The prevalence of depression in adults over age 65 years ranges between 1 and 15%.²⁵ In a longitudinal study of 27,776 individuals with dementia, MCI, or normal cognition, rates of depression rates were significantly higher among those with dementia (25%) and MCI (22%) compared with those with normal cognition (10%).²⁶ Depression affects approximately 20%–30% of patients with AD.²⁷ In our study, it is interesting to note that both cognitively impaired and unimpaired individuals had a high frequency of depression, suggesting a possible deleterious role of *ABCA7* pLOF mutation for this debilitating condition.

With 5,353 participants screened for 6 *ABCA7* pLOF mutations, and 100 mutation carriers who underwent clinical and neuropathologic phenotyping, our study provides in-depth characterization of these variants with both clinical and research implications. Nevertheless, there are several limitations to this study. First, the clinical phenotyping is based on retrospective medical record review, which could have introduced bias in the collection of clinical data. Although 63 of the mutation carriers had greater than or equal to 2 years of follow-up, clinical data for some patients were based on only 1 visit. Mutation carriers were not evaluated by a neurologist unless they had symptoms, which could have led to underdiagnosis of subtle cognitive problems in those deemed to be cognitively unimpaired. To date, the largest published deep clinical phenotyping study of *ABCA7* pLOF mutations included 22 patients.¹⁷ A more recent mutation screen identified 67 AD and 18 control *ABCA7* mutation carriers.¹² Both of these studies were in the Belgian population. Although our study is the largest to date investigating deep clinical

phenotyping of *ABCA7* pLOF mutations, there is still limited power given the rarity of mutation carriers. We focused on 6 *ABCA7* mutations previously reported,¹¹ and future phenotyping studies on other rare and common variants implicated in AD at this locus are needed. Moreover, although we found that adjustment for *APOEε4* presence did not affect the association of *ABCA7* pLOF mutations with AD, it will be important for future studies to investigate this association in the context of other known neurodegenerative disease mutations and their impact on the clinical and phenotypic heterogeneity. In addition, future studies in large population-based cohorts will be needed to estimate the penetrance of these rare *ABCA7* pLOF variants in AD. Finally, although we included *ABCA7* pLOF mutation carriers of any race/ethnicity in the phenotyping, all but 3 of these were non-Hispanic Whites. We previously identified *ABCA7* missense AD risk variants in a whole-exome sequencing study of African Americans.²⁸ Future studies on different ethnic groups are necessary to understand the full spectrum of phenotypes for *ABCA7* pLOF mutations.

In conclusion, our study confirms *ABCA7* pLOF for their risk on AD in 5,353 individuals, provides deep clinical phenotyping on 100 mutation carriers, including 11 autopsied patients, and identifies features that are important for future research studies and in the clinical setting. Future studies on prospective cohorts of AD and non-AD patient populations, as well as model systems, are necessary to elucidate the role of *ABCA7* in various neurodegenerative disease processes.

Although earlier age at onset of symptoms was more common, there was a broad age range for *ABCA7* pLOF mutation carriers, which should stimulate research on genetic and environmental modifiers in these patients. Our findings on higher frequency of first-degree relatives with cognitive impairment, more commonly for mothers of mutation carriers, early age at onset, and higher rates of depression support a role for genetic screening of *ABCA7* in the research setting, especially for patients with these clinical features. Such screens with careful genetic counseling are expected to be useful in the clinical setting in the near future when greater information on longitudinal outcomes of mutation carriers or targeted therapies is available. In conclusion, our deep phenotyping study on *ABCA7* pLOF mutation carriers represents an essential step for future precision medicine approaches in the clinical setting.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Alana S. Campbell, DO	Department of Neurology, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Charlotte C.G. Ho, BS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Merve Atik, MD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Mariet Allen, PhD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Sarah Lincoln, BS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Kimberly Malphrus, BS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Thuy Nguyen, BS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
Stephanie R. Oatman, BS	Department of Neurology, and Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Morgane Corda, MS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Olivia Conway, MS	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Samantha Strickland, PhD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data and analysis or interpretation of data
Ronald C. Petersen, MD	Department of Neurology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Dennis W. Dickson, MD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Neill R. Graff-Radford, MD	Department of Neurology, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Nilüfer Ertekin-Taner, MD, PhD	Department of Neurology, and Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Clinical Deep Phenotyping of ABCA7 Mutation Carriers

Alana S. Campbell, Charlotte C.G. Ho, Merve Atik, et al.

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