ABC7 frameshift deletion associated with Alzheimer disease in African Americans

ABSTRACT

Objective: To identify a causative variant(s) that may contribute to Alzheimer disease (AD) in African Americans (AA) in the ATP-binding cassette, subfamily A (ABC1), member 7 (ABC7) gene, a known risk factor for late-onset AD.

Methods: Custom capture sequencing was performed on ~150 kb encompassing ABC7 in 40 AA cases and 37 AA controls carrying the AA risk allele (rs115550680). Association testing was performed for an ABC7 deletion identified in large AA data sets (discovery n = 1,068; replication n = 1,749) and whole exome sequencing of Caribbean Hispanic (CH) AD families.

Results: A 44-base pair deletion (rs142076058) was identified in all 77 risk genotype carriers, which shows that the deletion is in high linkage disequilibrium with the risk allele. The deletion was assessed in a large data set (531 cases and 527 controls) and, after adjustments for age, sex, and APOE status, was significantly associated with disease (p = 0.0002, odds ratio [OR] = 2.13 [95% confidence interval (CI): 1.42-3.20]). An independent data set replicated the association (447 cases and 880 controls, p = 0.0117, OR = 1.65 [95% CI: 1.12-2.44]), and joint analysis increased the significance (p = 1.414 × 10^-5, OR = 1.81 [95% CI: 1.38-2.37]). The deletion is common in AA cases (15.2%) and AA controls (9.74%), but in only 0.12% of our non-Hispanic white cohort. Whole exome sequencing of multiplex, CH families identified the deletion cosegregating with disease in a large sibship. The deleted allele produces a stable, detectable RNA strand and is predicted to result in a frameshift mutation (p.Arg578Alafs) that could interfere with protein function.

Conclusions: This common ABC7 deletion could represent an ethnic-specific pathogenic alteration in AD. Neurology Genet 2016;2:e79; doi: 10.1212/NXG.0000000000000079

GLOSSARY

AA = African Americans; ABC = ATP-binding cassette; AD = Alzheimer disease; CH = Caribbean Hispanic; CI = confidence interval; GATK = Genome Analysis Toolkit; GWAS = genome-wide association study; OR = odds ratio; SNV = single-nucleotide variant.

Alzheimer disease (AD) is the leading cause of dementia in the elderly. AD occurs at a higher frequency in minority populations, with estimates of AD being twice as frequent in African Americans (AA) compared with non-Hispanic white (NHW) populations. APOE was the first gene associated with AD and the ε4 allele confers an increased risk across populations. Although APOE ε4 occurs more frequently in AA than NHW, paradoxically, it has a lower effect

*These authors contributed equally to the manuscript.

From the John P. Hussman Institute for Human Genomics (H.N.C., B.W.K., S.R., K.L.H.-N., M.A.K., P.I.W., D.V.B., D.M.D., M.L.C., J.M.V., J.R.G., G.W.B., E.R.M., R.M.C.), Department of Neurology (H.N.C., J.M.V., M.A.P.-V.), Dr. John T. Macdonald Foundation Department of Human Genetics (D.M.D., M.L.C., J.M.V., J.R.G., G.W.B., E.R.M., R.M.C.), Miller School of Medicine, University of Miami, FL; The Taub Institute for Research on Alzheimer’s Disease and the Aging Brain (B.N.V., R.M.), Gertrude H. Segaliesky Center, Departments of Neurology, Psychology, and Epidemiology, College of Physicians and Surgeons, Columbia University, New York, NY; Department of Pathology and Laboratory Medicine (B.A.D., G.D.S.), University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; Department of Biology (R.L., G.S.B., M.A.P.-V.), North Carolina A&T State University, Greensboro, NC; Departments of Medicine, Neurology, Ophthalmology, Genetics & Genomics, Epidemiology, and Biostatistics (I.L.H.), Boston University, MA; and Department of Epidemiology and Biostatistics (J.L.H.), Institute for Computational Biology, Case Western Reserve University School of Medicine, Cleveland, OH. Coinvestigators are listed at Neurology.org/ng.

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size in AA.⁵⁻⁷ Therefore, while differing ethnicities share risk genes and alleles, the consequences may be different in distinct populations.

Recent studies have identified >20 additional loci associated with late-onset AD, including ABCA7.⁸⁻¹⁰ Although ABCA7 was first implicated in NHW, a genome-wide significant signal was also detected in AA individuals at rs115550680, a position in linkage disequilibrium with the NHW genome-wide association study (GWAS) hits.⁸⁻¹¹ The AA allele confers a higher risk ($\rho = 2.21 \times 10^{-9}$, odds ratio [OR] = 1.79 [95% confidence interval (CI): 1.47–2.12]) than the most significantly associated alleles in NHW.⁶⁻⁹,¹¹ The effect size of the AA ABCA7 allele is comparable to APOE ε4 in AA ($\rho = 5.5 \times 10^{-47}$, OR = 2.31 [95% CI: 2.19–2.42]).¹² To date, there is no evidence of a functional consequence of the AA ABCA7 risk allele.¹²⁻¹⁵ Therefore, targeted sequencing of ABCA7 was performed to identify potential causative variants. A frameshift deletion was found associated with AD in AA, but was virtually absent in NHW. Thus, this deletion potentially represents a common, ethnic-specific, and likely pathogenic alteration that confers risk to AD.

**METHODS** Standard protocol approvals, registrations, and patient consents. All the individuals ascertained for this study provided written informed consent prior to their inclusion. If a study participant was not competent to provide consent, the immediate next of kin or a legal representative provided written consent on the behalf of the participant. All participants were ascertained using a protocol that was approved by the appropriate Institutional Review Board. Oversight of this study falls under the University of Miami Institutional Review Board #20070307.

Sample collection. African Americans. Individuals were ascertained for this study after they provided informed consent at the John P. Hussman Institute for Human Genomics (HIHG) at the University of Miami Miller School of Medicine (Miami, FL), North Carolina A&T State University (Greensboro, NC), and Case Western Reserve University (Cleveland, OH) for the HIHG data set. Each of the participants was ascertained using a protocol that was approved by the appropriate Institutional Review Board. Oversight of this study falls under the University of Miami Institutional Review Board #20070307.

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following primers (rs115550680-F: GCCAATATGGCCAAA CCATC, rs115550680-R: TCCAAAACCTGTGATAGCC) to generate a 245-bp amplicon. PCR reactions were set up with 2 mM MgCl₂ and touchdown PCR was performed. Sequencing reactions were performed using the Big Dye Terminator v3.1 (Life Technologies, Carlsbad, CA), reactions were run on a 3730xl DNA Analyzer (Life Technologies), and results were evaluated using the Sequencer v4.10.1 program (Gene Codes Corporation, Ann Arbor, MI).

**TaqMan SNP genotyping analysis.** Both the ABCA7 deletion (rs142076058) and the AA ABCA7 risk allele (rs115550680) were evaluated using the TaqMan single-nucleotide polymorphism (SNP) Genotyping Assays (Life Technologies). The ABCA7 deletion was evaluated by a custom-designed TaqMan SNP Genotyping Assays designed to recognize the presence or absence of the deletion. This assay had to be ordered as a “non-Human Assay” (forward primer: GCCTGGATCTACTCCGTGAC, reverse primer: GAGGCAGCTGAGGAACCA, FAM probe: GAGACGCGGCTGG—identifies when the sequence is deleted, VIC probe: CGCCATGGGGCT—wild-type allele). Samples were amplified for 40 cycles and, when amplification was low, an additional 20 cycles was added. The plates were read on the 7900HT Fast Real-Time PCR machine (Applied Biosystems, Foster City, CA), and data were analyzed with the SDS v2.4 software.

**RNA isolation and real-time PCR.** RNA was isolated from blood collected in PAXgene blood RNA tubes (PreAnalytiX, Hombrechtikon, Switzerland) from 10 samples with and 10 samples without the ABCA7 deletion and extracted following the manufacturer’s standard protocol. RNA was quantified on the 2100 BioAnalyzer (Agilent Technologies) and was required to have an RIN ≥6. Complementary DNA (cDNA) libraries were generated using the iScript Reverse Transcriptase Supermix for RT-qPCR kit (BIO-RAD). PCR primers were designed to amplify the cDNA across the deletion (cDNA-F: TGTTCCTGCGTGTGCTGA, cDNA-R: AGCAGGAAGCTCTGGGTCAC) and the resulting PCR products resolved on a 2% agarose gel. The wild-type allele results in an amplicon of 316 bp, whereas the allele with the deletion produces a 272-bp amplicon.

**Statistical analysis.** The GENMOD program, as part of the SAS/STAT software, was used to perform the association tests under a logistic regression model. Association tests were performed with adjustments for age, sex, APOE status, and relatedness between samples (SAS Institute, Cary, NC). Conditional analysis was performed in PLINK.26 The Fisher exact test was used to evaluate the differences in the alleles frequency of the deletion between African and European populations reported in the ExAC database.

**RESULTS** We selected 40 AA AD cases and 37 AA controls (aged >65 years) carrying the AA risk allele, rs115550680, to perform custom massively parallel sequencing of a 150-kb region that includes ABCA7 and 8 flanking genes and a small nuclear RNA. Samples were sequenced to an average depth of over 1,000× and evaluated for single-nucleotide variants (SNVs) and insertions and deletions. One thousand one hundred twenty SNVs were detected by sequencing with 11 variants showing different frequencies in cases and controls ($p < 0.1$, table e-1 at Neurology.org/ng). In addition, a 44-base pair (bp) deletion (rs142076058, p.Arg578Alafs) located ~3.5 kb upstream of the AA risk allele was identified in all 77 individuals, which suggests that it is in high linkage disequilibrium with the risk allele (figure 1).

To further evaluate the rs142076058 deletion, a custom TaqMan genotyping assay was designed to evaluate the deletion in our larger AA cohort,
Table 1  Association testing of the deletion in African American cohorts

<table>
<thead>
<tr>
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<th>Samples with deletion/ total samples (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>Pr &gt; Z:</th>
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<tr>
<td>HIHG</td>
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<td>Cases</td>
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<td>1.42-3.20</td>
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<td>Controls</td>
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<tr>
<td>ADGC</td>
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<td></td>
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<tr>
<td>Cases</td>
<td>63/447 (14.9)</td>
<td>1.65</td>
<td>1.12-2.44</td>
<td>0.0117</td>
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<tr>
<td>Controls</td>
<td>88/880 (10.0)</td>
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<tr>
<td>Cases</td>
<td>149/978 (15.2)</td>
<td>1.81</td>
<td>1.38-2.37</td>
<td>1.414 × 10^{-5}</td>
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<tr>
<td>Controls</td>
<td>137/1,407 (9.7)</td>
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</table>

Abbreviations: ADGC = Alzheimer’s Disease Genetics Consortium; CI = confidence interval; HIHG = John P. Hussman Institute for Human Genomics, University of Miami.

designated as HIHG. After adjustments for age, sex, and APOE status, the deletion was found to be significantly associated with AD (p = 0.0002, OR = 2.13 [95% CI: 1.42–3.20], table 1) in 531 cases and 527 controls. The deletion occurred in 9.3% of control individuals but in 16.2% of AD cases. A subset of 8 individuals were pathologically confirmed cases of AD; 2 were found to carry the deletion whereas the remaining 6 did not. The AA risk allele was also genotyped in this data set. The risk allele was significantly associated with AD (p = 0.0005, OR = 2.07 [95% CI: 1.38–3.13]) and in linkage disequilibrium with the deletion (D’ = 1.000, r² = 0.995, tables e-2 and e-3). The top SNPs in ABCA7 reported previously in NHW studies were also found to be in linkage disequilibrium with the deletion (table e-4). Genotyping was also performed on our NHW AD samples (n = 3,275), but only 4 individuals were identified with the deletion (0.12%), all of whom carried the AA risk allele, which indicates that the genomic fragment carrying the deletion in these individuals may be of African descent.

An independent AA data set from the Alzheimer’s Disease Genetics Consortium (ADGC) was evaluated in the same manner, and the deletion was again associated with AD (p = 0.0117, OR = 1.65 [95% CI: 1.12–2.44], table 1), occurring in 10.0% of control individuals and 14.9% of AD cases. Joint analysis of the 2 cohorts increased the strength of the association (p = 1.414 × 10^{-5}, OR = 1.81 [95% CI: 1.38–2.37], table 1). Association testing was also performed for each data set without APOE adjustment; more significant results were obtained with APOE adjustment, demonstrating that APOE did not influence the association (table e-5). Examination of the ages of cases and controls with and without the deletion did not find a significant difference between any of these groups (table e-6).

To examine the association with AD in another ethnic group with a high level of African ancestry (~42%), we evaluated whole exome sequencing data on 19 CH families from the Dominican Republic with multiple affected AD participants. In addition to a relatively high level of African ancestry, CHs are highly inbred and have a high incidence of AD, and are thus enriched for AD genetic risk factors. We independently identified the same 44-bp deletion from whole exome sequencing of 3 affected individuals from a large CH family. Subsequent examination of the family revealed that the deletion segregated in a large sibship in the family (figure 2). Both the deletion and AA risk allele were isolated in all 7 siblings who clinically presented in a range from AD (individuals 5, 6, 8, 12, and 99) to milder stages of dementia (individuals 7 and 11). Haplotype analysis around the ABCA7 deletion using SNP data in the 1-Mb flanking region on the family revealed that an affected aunt who does not carry the deletion, individual 3 (figure 2), has distinct ancestral haplotypes from the family members in the large sibship with the deletion (table e-7). This finding suggests that individual 3’s AD phenotype can be attributed to other genetic factors and that the ABCA7 deletion is highly penetrant in the sibship. Because several members of this CH family were known to have early-onset AD (age at onset <65 years), we examined the entire AA AD cohort (both HIHG and ADGC) to determine whether there was an effect of the deletion on age at onset in AD. We found no
difference in the age at onset in cases with the deletion (75.6 years [SD 9.6]) compared with cases absent for the deletion (76.8 years [SD 8.7], $p = 0.09$).

To determine whether the $ABCA7$ allele with the deletion was being transcribed, RNA was isolated from the blood of AA individuals both with and without the $ABCA7$ deletion. Reverse transcription PCR across the deletion region demonstrated that the allele carrying the deletion is transcribed and produces a stable detectable RNA strand (figure 3).

This deletion was reported previously in the Exome Aggregation Consortium (ExAC: http://exac.broadinstitute.org) [June 2015], a repository of 60,706 unrelated individuals from 6 distinct ethnic groups. In the ExAC data set, the deletion was found in 7.77% of individuals of African ancestry and 0.95% of Latino individuals, but was absent from individuals of European ancestry. This difference in population frequencies between the African and European populations was highly significant ($p < 1 \times 10^{-10}$).

**DISCUSSION** We identified a 44-bp deletion in $ABCA7$ that is associated with AD in individuals of African ancestry. Although the deletion did occur in unaffected individuals, it was found at a higher frequency in individuals with AD (15.2% of cases vs 9.74% of controls), implicating it as a risk factor for disease. This reaffirms that the deletion is likely to be of African ancestry. Furthermore, the combined cases from the HIHG and ADGC data sets had the deletion at a frequency of 15.2%, approximately twice as high as that identified with through ExAC African populations (7.8%), lending additional evidence of a relationship to disease. The deletion was also independently identified in an AD family from the Dominican Republic, a population that has a relatively high level of African ancestry, 41.8%.27 Examination of the linkage disequilibrium

![Figure 3](image.png)

(A) Real-time PCR from cDNA of 3 samples without the $ABCA7$ deletion (+/+ ) and 3 samples heterozygous for the $ABCA7$ deletion (deletion/+). All samples produce an amplicon of 316 base pairs, but only the samples with deletion generate a lower, 272-base pair amplicon (arrow). (B) Sanger sequencing from the 5′ end of the deletion in an African American control lacking the deletion and Alzheimer disease (AD)-specific line heterozygous for the deletion. The arrow denotes where the deleted allele begins to be out of frame with the wild-type allele C. Sanger sequencing from the 3′ end of the deletion from the same control and AD individuals.
of the deletion with the top 3 previously reported SNPs found a high $r^2$ across all locations, but only a large $r^2$ with the African-specific risk allele (table e-4), further supporting that distinct alleles confer AD risk in different ethnicities.39,11

The deletion is predicted to cause a frameshift at amino acid 578, encoding for 168 incorrect amino acids before stopping prematurely compared with the largest isoform that generates a protein of 2,146 amino acids (figure 1B). However, both AAA domains and 9 additional transmembrane domains would be predicted to be lost in this truncated protein, and thereby interfere with the protein’s function of exporting the lipid phosphatidylserine.29 Alternatively, the shortened transcript may be subjected to nonsense-mediated decay (NMD), as was seen following NMD, and the c.5570+5G>C alteration led to aberrant splicing30,31 (figure 1B). Therefore, this study may be the first to connect a potentially pathogenic and common alteration with a GWAS signal in ABCA7.

ABCA7 is a member of the ATP-binding cassette (ABC) transporter family, a large group of 49 genes that encode for membrane proteins that facilitate the movement of substrates across cell membranes.33,34 ABCA7 is expressed in the brain in neurons and microglia.35,36 There is evidence both in patients and animal models demonstrating that inadequate levels of ABCA7 may be directly correlated with Alzheimer pathogenesis.37-39 The ABCA7 protein is involved in the processing of amyloid precursor protein.40 In addition, evidence has shown that ABCA7 acts in the phagocytic pathway through extracellular signal-regulated kinase signaling.41,42 ABCA7 is not the only ABC transporter gene linked to AD; ABCA1, ABCB1, ABCC1, ABCCG1, ABCCG2, and ABCC4 are all implicated in Aβ regulation.43-48 Furthermore, a study identified rare loss-of-function alterations in NHW patients diagnosed with Parkinson disease, including specific variants previously reported in AD individuals, which demonstrates that this gene may contribute to the risk of multiple neurodegenerative disorders.49

Therefore, the results of this study demonstrate that there is a 44-bp deletion in ABCA7 that is associated with AD and in linkage disequilibrium with the previously identified AA risk allele. The deletion was relatively frequent in our large AA AD cohorts, independently identified in 1 of 19 CH AD families, and virtually absent from our large NHW AD cohort. Thus, the deletion could represent a common, ethnicity-specific alteration that confers risk of AD in populations with African ancestry.
American Journal of Alzheimer’s Disease & Other Dementias and Clinical Genetics holds a patent for Use of PLXNA4 as a drug target and biomarker for Alzheimer disease; has been a consultant for Novartis Pharmaceuticals, Gerson Lerman, and Guidepoint Global; has received research support from NIH, the Fidelity Foundation, and the Thorne Memorial Foundation; and has been a consultant for Finnegan & Associates LLP regarding legal proceedings. Dr. Cuccaro has served on the editorial board of Child Psychiatry & Human Development. Dr. Vance has received honoraria from the University of Alaska (served on an NIH grant’s internal review), and NEPTR, Department of Defense; has served on the editorial boards of the American Journal of Neurodegenerative Diseases and Neurology Genetics; holds patents for Method of detecting Charcot-Marie-Tooth disease type 2A, TRPC6 involved in glomerulonephritis, and Methods for identifying an individual at increased risk of developing coronary artery disease; has received research support from NIH/NINDS and the Hussman Foundation; and has received royalty payments from Duke University. Dr. Gilbert has been a consultant for Glenview NGLG; and has received research support from the Alzheimer’s Association. Dr. Beecham has received research support from NIH and the Department of Defense. Dr. Martin has served on the editorial board of Frontiers in Statistical Genetics and Methodology; and holds US Patent No. 6607759—Test for Linkage and Association in General Pedigrees: The Pedigree Disequilibrium Test. Dr. Carney reports no disclosures. Dr. Mayeux has received research support through government grants RO1 AG037212 and RFI AG015473. Dr. Schellenberg has served on the Alzheimer’s Association Medical Advisory Board, Society of Progressive Supranuclear Palsy Scientific Advisory Board, Alzheimer Research Consortium Peplher PSP Research Foundation Medical and Scientific Advisory Committee, the Alzheimer’s Association External Scientific Advisory Board, the scientific advisory board of the United Kingdom Parkinson Disease Center, the steering committee of the University College London, the Alzheimer’s Disease Sequence Project, Structural Variant Work Group, the advisory committee of the Alzheimer’s Disease Sequence Project, the Mayo Clinic Rochester Udall Center External Advisory Committee, the Discovery Assessment Panel of the University of Miami Alzheimer’s Disease Center; has received travel funding/speaker honoraria from the Alzheimer’s Disease Center, CurePSP, the University of California, the 25th Annual Southern California Alzheimer’s Disease Research Conference, the University of California Institute for Memory Impairment and Neurological Disorders, Biomarkers in Neuropsychiatric Disorders (Toronto, Canada), NIH, Novartis, the McKnight Brain Institute, the University of Florida, the Florida Alzheimer’s Disease Center, the Lou Ruvo Center for Brain Health, the Accelerated Medicines Program Alzheimer’s Disease, the University of Virginia, and Columbia University; has served on the editorial boards of the Journal of NeuroTransmission, the American Journal of Alzheimer’s Disease and Other Dementias, Neurodegenerative Diseases, Current Alzheimer Research, and Pathology and Laboratory Medicine International; is an employee of the University of Pennsylvania; and has received research support from NIA/NIH, CurePSP, and CBD Solutions. Dr. Byrd reports no disclosures. Dr. Haines has received travel funding/speaker honoraria from Novartis; has served on the editorial boards of Neurogenetics, Current Protocols in Human Genetics, and Human Molecular Genetics; has received royalties from John Wiley & Sons; has received research support from the NIH/NIA Consortium for Alzheimer’s Sequence Analysis (CASA) and NIH/NEI; and has received royalty payments from Athena Diagnostics. Dr. Pericak-Vance reports no disclosures. Go to Neurology.org/ng for full disclosure forms.

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