# ABCA7 genotype altered Aβ levels in cerebrospinal fluid in Alzheimer's disease without dementia

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**Background:** ATP-binding cassette transporter A7 (ABCA7) rs3764650 has been identified to be a susceptibility locus for Alzheimer's disease (AD), but its role in cerebrospinal fluid (CSF) proteins was still unclear.

**Methods:** The associations of rs3764650 with CSF $A\beta_{1-42}$, t-tau and p-tau were analyzed in non-dementia AD, including preclinical and prodromal AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

**Results:** Finally, GG + GT genotypes significantly decreased CSF $A\beta_{1-42}$ level, but did not alter CSF t-tau and p-tau levels in non-dementia AD at baseline, which was further confirmed in longitudinal studies.

**Conclusions:** Our findings supported that ABCA7 modified AD risk by altering Aβ deposition rather than tau pathology.

**Keywords:** Alzheimer's disease (AD); ATP-binding cassette transporter A7 (ABCA7); cerebrospinal fluid biomarkers (CSF biomarkers); β-amyloid (Aβ)

Submitted May 15, 2018. Accepted for publication Jun 21, 2018.
doi: 10.21037/atm.2018.07.04
**View this article at:** http://dx.doi.org/10.21037/atm.2018.07.04

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by early short-term memory loss progressing into dementia. It has been documented that clinical symptoms result from the deposition of β-amyloid (Aβ) and tau pathology in brain, and Aβ has been observed to mainly aggregate and accumulate in the brain in non-dementia AD until a critical threshold is reached in AD, which exhibits a sigmoidal trajectory characterized by a rapid progression and finally a plateau. Aβ deposition can be measured by cortical amyloid positron emission tomography (PET) ligand binding (1,2) or low cerebrospinal fluid (CSF) $A\beta_{1-42}$ (3-5).

ATP-binding cassette, subfamily A, member 7 (ABCA7) has been found to be expressed abundantly in brain microglia, implying a role of ABCA7 in amyloid clearance and fibril

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

formation (1-5). ABCA7 loss-of-function (LOF) was reported to contribute to AD by promoting Aβ processing and pathology in cell culture and mouse models (1). In addition, our group identified that ABCA7 variants were associated with Aβ deposition on amyloid imaging but were not related to Aβ levels in CSF test (6). Recently, ABCA7 variable number tandem repeat (VNTR) length was observed to correlate with CSF $A\beta_{1-42}$ (5). Therefore, the relation between ABCA7 polymorphisms and CSF $A\beta_{1-42}$ was still inconsistent across these studies, and it's necessary to further identify the association, especially in the non-dementia AD stage in which Aβ is mostly deposited.

To date, ABCA7 rs3764650 has been identified to be significantly associated with AD susceptibility in genome-wide association studies (GWAS) and following studies (7-18). To explore the functional consequences of the rs3764650 in ABCA7 and its possible effect on AD pathogenesis, we attempted to analyze its associations with CSF proteins ($A\beta_{1-42}$, t-tau, and p-tau) in non-dementia AD subjects.

## Methods

### *ADNI dataset*

ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and nonprofit organizations (http://adni.loni.usc.edu). ADNI, with Michael W. Weiner, MD as the principal investigator, was approved by the regional ethical committees of all participating institutions and written informed consent was obtained from all participants.

### *Subject classification*

Subjects were classified into preclinical and prodromal AD by CSF $A\beta_{1-42}$ or 18FAV-45-PET according to the National Institute on Aging and Alzheimer's Association (NIA-AA) research criteria in 2011. The cutoff value for abnormal CSF $A\beta_{1-42}$ levels was ≤192 pg/mL or 18FAV-45-PET ≥1.11. The application of a normal/abnormal cut point for each amyloidosis biomarker divided the non-dementia subjects into amyloid group (non-dementia Aβ+) and non-amyloid group (non-dementia Aβ–) and subdivided the former into preclinical AD and prodromal AD from CN and mild cognitive impairment (MCI) group respectively.

### *Genotyping*

ADNI samples were genotyped using the Illumina Human 610-Quad Bead Chip array (Illumina, Inc., San Diego, CA, USA), including 620,901 SNP and CNV markers which were employed for genotyping. Here we extracted the genetic data of ABCA7 (rs3764650) from the ADNI PLINK data format.

### *CSF proteins*

Methods for the collection, extraction, and examination of CSF proteins, including $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau), have been described previously (19,20). Finally, a total of 410 non-dementia Aβ+ subjects (104 preclinical AD subjects and 306 prodromal AD subjects) were included in CSF analysis from the ADNI sites.

### *Data analysis*

All statistical analyses were conducted using R. We used a multiple linear regression model to analyze the effects of ABCA7 rs3764650 on CSF biomarkers at baseline with corrections for age, gender, educational level, and APOE ε4 genotype; and we used a linear mixed effects model (including age, gender, educational level, and APOE ε4 genotype as covariates) with random intercepts and slope for time to test the association of rs3764650 with the levels of CSF biomarkers from longitudinal data (21). For all the tests, we claim that ABCA7 rs3764650 is significantly associated with the levels of CSF biomarkers when P values are below 0.05. Moreover, our subjects were restricted to non-Hispanic and white people to avoid genetic stratification across ethnicities.

## Results

Finally, 410 non-dementia Aβ+ subjects (231 male *vs.* 179 female) consisted of 104 preclinical AD subjects (47 male *vs.* 57 female) and 306 prodromal AD subjects (184 male *vs.* 122 female). The demographic characteristics and distributions of the genotypes are shown in *Table 1*. Prodromal AD had the higher frequency for the APOE ε4 allele and performed worse than did preclinical AD on MMSE. As expected, the levels of CSF $A\beta_{1-42}$, t-tau and p-tau were different between the two groups, and prodromal AD had lower CSF $A\beta_{1-42}$, higher t-tau

 

**Table 1** The demographics for the independent dataset

| Characteristics | Non-dementia Aβ+ | | Preclinical AD | | Prodromal AD | | P* |
|---|---|---|---|---|---|---|---|
| | Sample size | Data | Sample size | Data | Sample size | Data | |
| Age, mean years (SD) | 410 | 74.01 (6.89) | 104 | 75.77 (5.57) | 306 | 73.41 (7.19) | <0.01 |
| Gender (male/female) | 410 | 231/179 | 104 | 47/57 | 306 | 184/122 | <0.01 |
| Education, mean years (SD) | 410 | 15.92 (2.80) | 104 | 15.94 (2.65) | 306 | 15.91 (2.85) | 0.953 |
| APOE ε4 (0/1/2) | 410 | 178/182/50 | 104 | 63/34/7 | 306 | 115/148/43 | <0.01 |
| MMSE scores, mean (SD) | 410 | 27.85 (1.83) | 104 | 29.06 (1.15) | 306 | 27.44 (1.83) | <0.01 |
| ABCA7 rs3764650, T/G | 410 | 735/85 | 104 | 191/17 | 306 | 544/68 | 0.305 |
| CSF Aβ (pg/mL), mean (SD) | 410 | 142.58 (28.91) | 104 | 149.12 (29.41) | 306 | 140.36 (28.44) | <0.01 |
| CSF t-tau (pg/mL), mean (SD) | 407 | 99.31 (52.86) | 104 | 79.9 (38.74) | 303 | 105.98 (55.41) | <0.01 |
| CSF p-tau (pg/mL), mean (SD) | 410 | 43.78 (22.95) | 104 | 37.03 (19.13) | 306 | 46.08 (23.70) | <0.01 |

Data are given as sample size and mean followed by (SD) unless otherwise indicate. P*, preclinical AD *vs.* prodromal AD. MMSE, mini-mental state exam; SD, standard deviation.

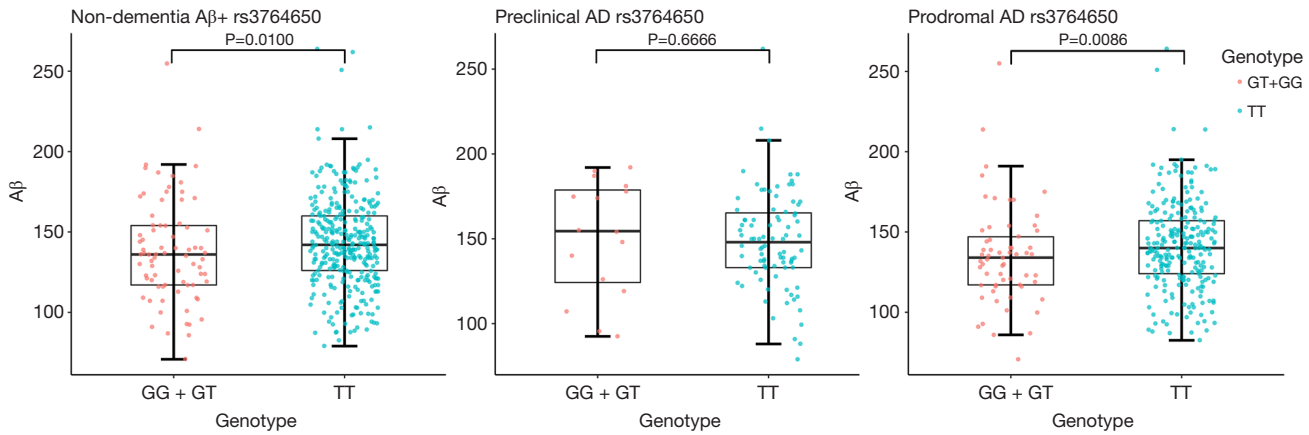


**Figure 1** ABCA7 rs3764650 and CSF $A\beta_{1-42}$ at baseline in the non-dementia AD. AD, Alzheimer's disease; CSF, cerebrospinal fluid.

and p-tau levels than did preclinical AD. We used the dominant model in our analysis because the number of homozygotes (GG) was too small.

Finally, GG + GT genotypes (77, 138.38±31.95 pg/mL) showed lower $A\beta_{1-42}$ level when compared to TT genotype (333, 143.55±28.12 pg/mL) in the non-dementia Aβ+ group. Moreover, GG + GT genotypes (61, 135.11±30.81 pg/mL) had lower $A\beta_{1-42}$ level than did TT genotypes (245, 141.66±27.73 pg/mL) in the prodromal AD group, while they did not differ in CSF $A\beta_{1-42}$ level in the preclinical AD group. In the multiple linear regression model, GG + GT genotypes significantly decreased the level of CSF $A\beta_{1-42}$ in non-dementia Aβ+ group (β=−8.8043, P<0.05), and a negative correlation between rs3764650 polymorphisms and CSF $A\beta_{1-42}$ was also found in the prodromal AD group (β=−9.9756, P<0.01) (*Figure 1*). No significant relationships between the levels of CSF t-tau and p-tau and ABCA7 rs3764650 were observed at baseline in all diagnostic groups (P>0.05) (*Table 2*).

Furthermore, we used a linear mixed effects model to test this association in longitudinal studies. The significant negative association of the rs3764650 polymorphism with CSF $A\beta_{1-42}$ was also present within non-dementia Aβ+ group (β=−0.3328, P<0.005) and within prodromal AD group (β=−0.3567, P<0.01) (*Figure 2*). However, the associations of rs3764650 with other CSF proteins (t-tau and p-tau) were

**Table 2** Correlations between ABCA7 rs3764650 and CSF biomarkers at baseline in the non-dementia AD

| Biomarker | Non-dementia Aβ+ | | Preclinical AD | | Prodromal AD | |
|---|---|---|---|---|---|---|
| | β coefficient | P value | β coefficient | P value | β coefficient | P value |
| CSF Aβ | −8.804 | 0.010 | −3.505 | 0.667 | −9.976 | 0.009 |
| CSF t-tau | 4.677 | 0.478 | −4.049 | 0.703 | 6.048 | 0.437 |
| CSF p-tau | 0.432 | 0.882 | −3.939 | 0.458 | 1.473 | 0.664 |

AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

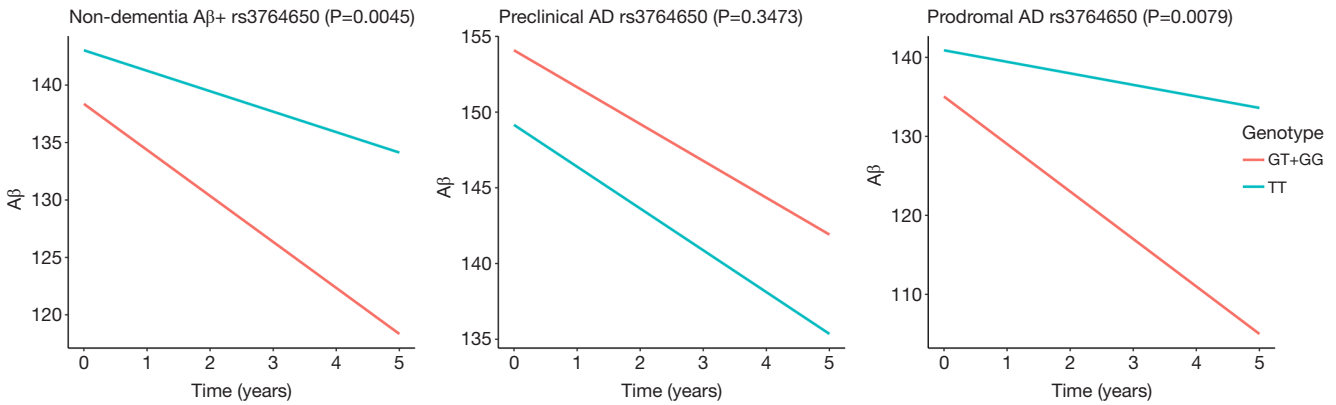


**Figure 2** ABCA7 rs3764650 and CSF $A\beta_{1-42}$ in longitudinal studies in non-dementia AD. AD, Alzheimer's disease; CSF, cerebrospinal fluid.

**Table 3** Correlations between ABCA7 rs3764650 and CSF biomarkers in longitudinal studies in the non-dementia AD

| Biomarker | Non-dementia Aβ+ | | Preclinical AD | | Prodromal AD | |
|---|---|---|---|---|---|---|
| | β coefficient | P value | β coefficient | P value | β coefficient | P value |
| CSF Aβ | −0.333 | 0.005 | −0.251 | 0.347 | −0.357 | 0.008 |
| CSF t-tau | 0.082 | 0.517 | −0.100 | 0.715 | 0.106 | 0.455 |
| CSF p-tau | −0.018 | 0.881 | −0.245 | 0.336 | 0.037 | 0.793 |

AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

also not detected in longitudinal studies (P>0.05) (*Table 3*).

## Discussion

This study provided a comprehensive evaluation of the impact of ABCA7 SNP rs3764650 on CSF proteins ($A\beta_{1-42}$, t-tau and p-tau) in non-dementia AD, including preclinical AD and prodromal AD. In non-dementia AD, rs3764650 was detected to correlate with low CSF $A\beta_{1-42}$ level rather than CSF tau proteins (t-tau and p-tau) at baseline, and the correlation between ABCA7 and CSF $A\beta_{1-42}$ was further verified in the prodromal AD group. As we further extended these findings in longitudinal studies, the significant associations still existed in non-dementia AD and prodromal AD. Therefore, our study detected that ABCA7 increased AD risk through involving in Aβ deposition but not in tau pathology, which was consistent with the previous findings.

ABCA7 was identified as a known risk factor for AD in genetic analyses. Former studies have found that ABCA7 variants contributed to AD by altering the clearance of

 

microglia or the phagocytosis of macrophages, resulting in Aβ accumulation (22-27). In addition, ABCA7 variants have been observed to be associated with Aβ deposition on amyloid imaging, but not associated with the level of $A\beta_{1-42}$ in CSF (6). Different from previous studies, our study explored the correlation between ABCA7 and the CSF $A\beta_{1-42}$ level in the non-dementia AD stage (from preclinical AD to prodromal AD), which may explain the inconsistency between our result and those of other studies.

## Conclusions

In summary, our study showed that ABCA7 genetic variants altered CSF $A\beta_{1-42}$ level in non-dementia AD to modify the AD risk, which provided new evidence for the hypothesis that ABCA7 may contribute to the AD risk by altering Aβ deposition rather than tau pathology.

## Acknowledgements

*Funding*: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This work was also supported by grants from the National Key R&D Program of China (2016YFC1305803), the National Natural Science Foundation of China (81701253), Qingdao Key Health Discipline Development Fund, Qingdao Outstanding Health Professional Development Fund, and Shandong Provincial Collaborative Innovation Center for Neurodegenerative Disorders.

## Footnotes

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* ADNI, with Michael W. Weiner, MD as the principal investigator, was approved by the regional ethical committees of all participating institutions and written informed consent was obtained from all participants.

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**Cite this article as:** Ma FC, Zong Y, Wang HF, Li JQ, Cao XP, Tan L; Alzheimer's Disease Neuroimaging Initiative. ABCA7 genotype altered Aβ levels in cerebrospinal fluid in Alzheimer's disease without dementia. Ann Transl Med 2018;6(22):437. doi: 10.21037/atm.2018.07.04

 