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ORIGINAL RESEARCH

Association of CHAT Gene Polymorphism rs3793790 and rs2177370 with Donepezil Response and the Risk of Alzheimer's Disease Continuum

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Background: Genetic variation plays an important role in drug response, there are few relevant studies on patients with Alzheimer's disease continuum (ADC).

Objective: This study focused on the associations between two single nucleotide polymorphisms (SNPs) (rs3793790 and rs2177370) located in the CHAT gene and donepezil response in ADC patients, and further evaluated the associations between the two SNPs and ADC.

Material and Methods: According to 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) standard, amyloid β-protein positive (Aβ+) and negative (Aβ-) patients were recruited according to the Aβ-PET/CT standard. rs3793790 and rs2177370 were genotyped in buccal swab samples by using the MassARRAY system. We used the Mini Mental State Examination (MMSE) in Chinese version, caregiver evaluation, and prescribing behavior to assess therapeutic response during the 9-month period. Using logistic regression models, we analyzed the relationship between the two SNPs and donepezil response in 58 Aβ+ patients treated with donepezil alone at the initial diagnosis of ADC. We also explored a probable link between the two SNPs and ADC in 147 Aβ+ and 73 Aβ– patients using a logistic regression analysis.

Results: The chance of donepezil response was higher in patients with the G allele of rs3793790 and/or the A allele of rs2177370 than in those without (odds ratio (OR) 6.83, 95% confidence interval (CI): 1.64–28.49). Additionally, the rs3793790 variant was not associated with ADC, whereas the A allele in rs2177370 increased 1.51-fold the ADC risk (OR 2.51, 95% CI: 1.28–4.95).

Conclusion: The genetic variants of rs3793790 and rs2177370 were associated with the donepezil response, and rs2177370 may have a moderate relationship with the risk of ADC.

Keywords: Alzheimer's disease, pharmacogenomics, variant, gene, donepezil

Introduction

Alzheimer's disease (AD), the main type of dementia, is characterized by a progressive deterioration in cognition with varying degrees of psycho-behavioural symptoms, eventually leading to damage in the basic bodily functions.[1] Characteristic pathological changes have occurred in the brain before the patient has clinical symptoms, and amyloid β-protein (Aβ) deposition and hyperphosphorylated tau protein are key links of AD pathogenesis.[2] As pathological changes such as Aβ and tau continue to worsen, the appearance and progression of clinical symptoms are eventually elicited.[3] Therefore, it is considered to be an Alzheimer's disease continuum (ADC) rather than an entity.[3] However, therapeutic options are limited, with two main categories of drugs in clinical practice, including acetylcholinesterase inhibitors (AChEIs) represented by donepezil and N-methyl-D-aspartic acid (NMDA) receptor blockers represented by

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memantine.[4] In the new era of advocating the concept of precision medicine, the development of pharmacogenomics (PGx) has provided new strategies for ADC treatment and helped optimize treatment using existing drugs.[5]

PGx focuses on the action of genetic variation in mediating pharmacokinetics and pharmacodynamics, ultimately achieving improved drug action and reducing adverse effects in clinical practice.[6] Furthermore, a comprehensive insight into the genetic mechanisms of different drug responses can facilitate the development of new drugs.[7] Currently, a multitude of retrospective analyses and prospective trials have been conducted on cardiovascular, oncological, and psychiatric disorders to confirm the hypothesis that pharmacogenomically guided treatment may optimize drug outcomes in clinical practice. However, few relevant studies are available on ADC pharmacogenomics.[8]

Heterogeneity of drug response is an almost inevitable topic in contemporary medicine, and genetic variations have been shown to play an important role in individual disparities in drug response.[9] Donepezil, an acetylcholinesterase inhibitor, was approved by the FDA in 1996 as a commonly used drug for the treatment of AD with therapeutic efficacy rates ranging from 20–60%.[10] Several studies have evaluated the relationship of genetic polymorphisms with the donepezil response in ADC patients. A study in a Canada population indicated that the single nucleotide polymorphism (SNP)-rs733722 in CHAT gene may represent a potential marker of AChEIs response, and patients carrying T allele in the SNP were more likely to be effective than those carrying C allele.[11] Lee et al[12] suggested that A allele at the +4 position of CHAT gene may have a positive impact on donepezil response in ADC patients. Scacchi et al[13] in an Italian population reported that a significant association of BCHE gene polymorphism rs1355534 with the efficacy of donepezil and rivastigmine was present. Braga et al[14] observed that the variants of rs6494223 in CHRNA7 gene were helpful for understanding the AChEIs response in ADC patients in Brazil. As the roles of inflammatory mediators, immune factors, and oxidative stress in the pathogenesis of ADC have been described, genetic polymorphisms in IL-6 and FOXO1 have been gradually explored as potential factors influencing donepezil response in ADC patients.[15,16] However, genomic research is highly Eurocentric, with 97% of the participants being European and approximately 2.2% Asian, lacking ethnic diversity.[7] Therefore, it is necessary to conduct ADC-related pharmacogenomic analyses of East Asian populations.

Using the Pharmacogenetics and pharmacogenomics knowledge base (PharmGKB, https://www.pharmgkb.org/) and Clinical pharmacogenetics implementation consortium (CPIC, https://cpicpgx.org/) databases, we searched for SNPs with a minimum allele frequency of ≥1% in East Asian populations, which may be associated with the donepezil response to ADC therapies. The search showed that two SNPs located in the CHAT gene, rs3793790 (chr10:49,632,690 (GRCh38.p14), Alleles G>A / G>C, Frequency G=0.325) and rs2177370 (chr10:49,630,828 (GRCh38.p14), Alleles A>G, Frequency G=0.470), were found to be associated with donepezil response only in a Korean population.[17] Analyses of these two SNPs in other East Asian populations are lacking, and the clear advantages of pharmacogenomically guided treatment remain to be validated in future studies.

Furthermore, a decline in the level of acetylcholine (ACh) in the brain is a feature in ADC patients linking to cognitive decline.[18] Although cholinergic dysfunction and ADC are not explicit causations, numerous studies have demonstrated a role for cholinergic deficits in the development of ADC, which is related to memory and cognitive processes.[19] Choline acetyltransferase (ChAT) is a key enzyme that catalyzes ACh synthesis. ACh is involved in AD pathogenesis. ChAT activity is markedly reduced in the brains of ADC patients, which may be related to disease severity and can be inhibited by Aβ oligomers.[20] CHAT is the gene encoding ChAT, and its polymorphism seems to influence ChAT activity, which indirectly affects the risk of ADC.[21] Previous studies have found a certain relationship between CHAT gene polymorphism rs3810950 and ADC.[22] Tang et al[23] indicated that A-allele carriers of rs3810950 have an earlier onset of ADC than those G-allele carriers in Chinese population. Scacchi et al[13] observed that CHAT gene polymorphism rs2177369 may play a relevant role in ADC risk. However, the relationship between the polymorphisms rs3793790 and rs2177370 in the CHAT gene and ADC in the Chinese population has not been explored.

Therefore, our study aimed to evaluate the association of the rs3793790 and rs2177370 variants with the therapeutic response to donepezil in Chinese patients with ADC and to further analyze the potential link between the two SNPs and the risk of ADC.

Material and Methods

Study Patients

We recruited patients between January 2022 and August 2023 at the Chinese PLA General Hospital.

Donepezil response analyses were performed in 58 Aβ+ patients treated with donepezil alone at the initial ADC diagnosis. We assembled and recorded demographic information, clinical manifestations, comorbidities, family history, APOE genotype, Clinical Dementia Rating (CDR) scores,[24] Mini Mental State Examination (MMSE) scores in Chinese version[25,26] before and after treatment, and information on the subjects' drugs. Inclusion criteria: Aβ+ patients with ADC meeting 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) standard by the Aβ-Positron Emission Tomography-Computed Tomography (PET/CT) examination, and CDR scores 0.5–2, and with a caregiver who can provide relevant information and sign an informed consent form. Exclusion criteria: Patients with other disorders that cause cognitive impairment, such as thyroid dysfunction, severe hepatic and renal insufficiency, or severe systemic or psychiatric illnesses that prevent them from completing the clinical assessment.

Correlation analyses between the rs3793790 and rs2177370 variants and the risk of ADC were performed in 147 Aβ+ and 73 Aβ– patients by Aβ-PET/CT examination. We collected the demographic information, comorbidities, family history, and APOE genotype of the subjects.

This study was approved by the Ethics Committee of the Chinese PLA General Hospital (S2021-640-02), and written informed consent was obtained from all the patients. It conformed to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Genetic Analysis

rs3793790 and rs2177370 of CHAT were genotyped from buccal swab samples using the MassARRAY system.

Genomic DNA extraction: DNA was extracted from buccal swab samples using a Purifier 32 Nucleic Acid Extractor (Jifan Biotechnology Co., Ltd.).

PCR system configuration: Multiplex PCR primers were included in the approved clinical test kit (Zhejiang Hangzhou Machinery No. 20,210,448, Zhejiang Digena Diagnostic Technology Co., Ltd.). Specific sequence information of the primers is still under intellectual property protection.

Nucleic acid mass spectrometry flight detection: PCR amplification was performed using the Xi'an Tianlong Gentier96E PCR instrument, purification using shrimp alkaline enzyme, and extension products using a single base. Mass spectrometry was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), and target region sequences were identified using mass spectrometry software.

Measures

The donepezil response was assessed after 9 months of treatment. Donepezil was considered effective when ΔMMSE (difference in MMSE scores in Chinese version between after 9 months and before applying donepezil) was ≥ -1[27,28] and the caregiver indicated that the patient's symptoms had improved or not significantly changed while donepezil was applied consistently and regularly. Donepezil was defined as ineffective when $\Delta MMSE < -1$, and the caregiver indicated that the patient's symptoms had worsened to discontinue or change donepezil or add other drugs to improve cognition.

Statistical Analyses

SPSS software (version 27.0) was used for statistical analyses. Comparisons between groups: *t*-test for normally distributed measures, otherwise Wilcoxon test; $\chi 2$ test or Fisher's exact test for count data. Logistic regression models were used to analyze factors associated with donepezil response and ADC. Statistical significance was set at $P<0.05$.

Results

Gene Frequencies

A total of 58 patients with ADC were included in the donepezil response analyses (27 males, 31 females), aged 70.84 ±8.30 years. The genotype results showed that ε3 was the most common allele (58.62%) of APOE, followed by ε4

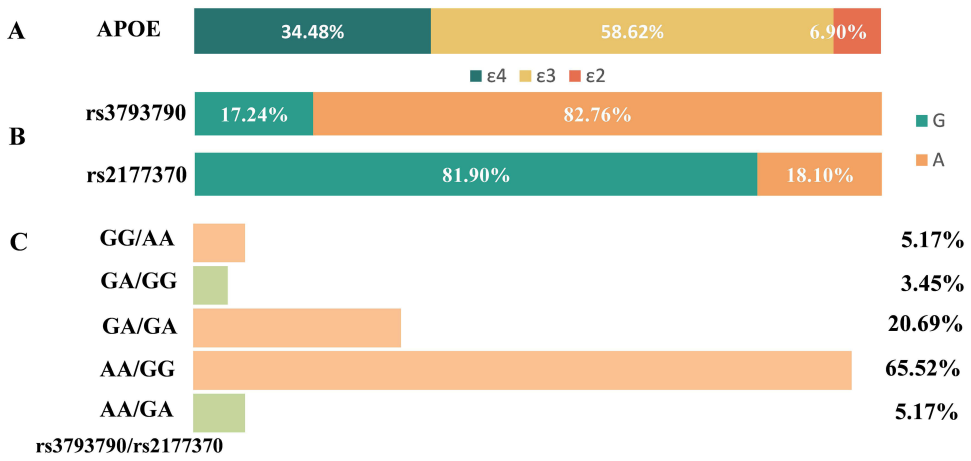

Figure 1 Gene frequencies of APOE and CHAT in patients with Alzheimer's disease continuum. (**A**) APOE alleles frequency. (**B**) The rs3793790 and rs2177370 alleles frequency. (**C**) CHAT genotypes frequency.

(34.48%). (Figure 1A) In the CHAT gene, the frequency of G allele in rs3793790 was 17.24% and the frequency of A allele in rs2177370 was 18.10%. (Figure 1B) Interestingly, we found that when rs3793790 carried the G allele, rs2177370 carried the A allele simultaneously, and when rs3793790 carried the A allele, rs2177370 often carried the G allele, with a concordance rate of 91.38% (GG/AA, GA/GA, AA/GG). (Figure 1C)

Association of rs3793790 and rs2177370 Variants with Donepezil Response

Of the 58 patients, donepezil was effective in 33 (56.90%) and ineffective in 25 (43.10%) patients with ADC. Compared to the ineffective group, the frequency of carrying the G allele in rs3793790 and the A allele in rs2177370 was significantly higher in the effective group (P<0.05, Table 1). Univariate logistic regression analysis showed that baseline MMSE scores, dementia severity, and the rs3793790 and rs2177370 variants were associated with donepezil therapeutic response (P<0.05, Table 2). Further multifactorial regression analysis showed that donepezil was more likely to be

Table 1 Comparisons Between Effective Group and Ineffective Group of Donepezil Response

Factors	Ineffective group (n=25)	Effective group (n=33)	P
Age[a]	70.68±7.74	70.97±8.81	0.897
Gender[b]			0.847
Male	12 (48.00)	15 (45.45)	
Female	13 (52.00)	18 (54.55)	
Baseline MMSE scores[a]	19.12±4.42	22.36±4.37	0.002
Dementia severity[b]			0.052
MCI	2 (8.00)	10 (30.30)	
Mild AD	19 (76.00)	22 (66.67)	
Moderate AD	4 (16.00)	1 (3.03)	
Comorbidities[b]			
Hypertension	11 (44.00)	8 (24.24)	0.112
Hyperlipidemia	13 (52.00)	12 (36.36)	0.234
Diabetes	4 (16.00)	8 (24.24)	0.443
Coronary artery disease	6 (24.00)	6 (18.18)	0.588
Cerebrovascular disease	3 (12.00)	2 (6.06)	0.643
Anxiety-depression state	10 (40.00)	7 (21.21)	0.120

(*Continued*)

Table 1 (Continued).

Factors	Ineffective group (n=25)	Effective group (n=33)	P
Family history of dementia[b]	4 (16.00)	5 (15.15)	0.930
Donepezil dose[b]			0.300
5mg/d	17 (68.00)	18 (54.55)	
10mg/d	8 (32.00)	15 (45.45)	
APOE-ε4[b]	14 (56.00)	23 (69.70)	0.282
rs3793790-G[b]	3 (12.00)	14 (42.42)	0.012
rs2177370-A[b]	2 (8.00)	16 (48.48)	<0.001
rs3793790-G and/or rs2177370-A[b]	4 (16.00)	16 (48.48)	0.010

Notes: a expressed as "$\bar{x} \pm s$". b expressed as "n (%)".
Abbreviations: MMSE, Mini Mental State Examination; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Table 2 Univariate Logistic Regression Analysis of Factors Associated with Donepezil Response

Factors	OR (95% CI)	P
Age	1.00 (0.94–1.07)	0.894
Gender (Ref: male)	1.11 (0.39–3.14)	0.847
Baseline MMSE scores	1.19 (1.04–1.36)	0.014
Dementia severity		
MCI	Ref	0.070
Mild AD	0.23 (0.05–1.19)	0.080
Moderate AD	0.05 (0.003–0.72)	0.028
Comorbidities		
Hypertension	0.41 (0.13–1.25)	0.116
Hyperlipidemia	0.53 (0.18–1.52)	0.236
Diabetes	1.68 (0.44–6.37)	0.446
Coronary artery disease	0.70 (0.20–2.52)	0.589
Cerebrovascular disease	0.47 (0.07–3.07)	0.433
Anxiety-depression state	0.40 (0.13–1.28)	0.124
Family history of dementia	0.94 (0.22–3.92)	0.930
Donepezil dose (Ref: 5mg/d)	1.77 (0.60–5.24)	0.302
APOE-ε4	1.81 (0.61–5.34)	0.285
rs3793790-G	5.40 (1.35–21.69)	0.017
rs2177370-A	10.82 (2.19–53.51)	0.003
rs3793790-G and/or rs2177370-A	4.94 (1.39–17.57)	0.014

Abbreviations: MMSE, Mini Mental State Examination; MCI, mild cognitive impairment; AD, Alzheimer's disease; OR, odds ratio; 95% CI, 95% confidence interval.

effective in patients carrying the G allele in rs3793790 and/or the A allele in rs2177370 than in those who carried neither allele (OR 6.83, 95% CI: 1.64–28.49, P=0.008, Table 3).

Association of rs3793790 and rs2177370 Variants with ADC

The analyses included 147 patients with Aβ+ and 73 patients with Aβ–. There were significant differences in the genotype and allele distributions of APOE and rs2177370 between ADC and control groups (P<0.05, Table 4), whereas

Table 3 Multivariate Logistic Regression Analysis of Factors Associated with Donepezil Response

Factors	OR (95% CI)	P
Dementia severity[a]		
MCI	Ref	0.040
Mild AD	0.19 (0.04–1.06)	0.059
Moderate AD	0.03 (0.001–0.499)	0.015
rs3793790-G and/or rs2177370-A[b]	6.83 (1.64–28.49)	0.008

Notes: a. Considering the association between MMSE scores and dementia severity, only dementia severity was included in multivariate logistic regression analysis. b. Considering the association between rs3793790 and rs2177370, rs3793790-G and/or rs2177370-A were included in the multivariate logistic regression analysis.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4 Comparisons the Polymorphism of APOE and CHAT Gene Between Alzheimer's Disease Continuum Group and Control Group

Groups	Genotypes or allele (n)			χ^2	P
APOE	**ε4/ε4**	**ε4/non-ε4**	**Non-ε4/non-ε4**		
ADC	10	76	61	12.562	0.002
Control	5	20	48		
	ε4	Non-ε4			
ADC	96	198		6.995	0.008
Control	30	116			
CHAT-rs3793790	GG	GA	AA		
ADC	10	42	95	1.526	0.483
Control	2	20	51		
	G	A			
ADC	62	232		1.341	0.247
Control	24	122			
CHAT-rs2177370	GG	GA	AA		
ADC	84	53	10	7.768	0.019
Control	55	17	1		
	G	A			
ADC	221	73		8.237	0.004
Control	127	19			

Abbreviation: ADC, Alzheimer's disease continuum.

the variances of rs3793790 between groups were not statistically significant (P>0.05, Table 4). Univariate logistic regression analysis showed that APOE and rs2177370 variants were associated with ADC (P<0.05, Table 5).

Further multifactorial regression analysis indicated that carriers of the APOE-ε4 allele were related to the risk of ADC (OR 2.85, 95% CI: 1.50–5.42, P=0.001, Figure 2), and carriers of the rs2177370-A allele were associated with a 2.51 times higher risk of ADC than non-carriers (OR 2.51, 95% CI: 1.28–4.95, P=0.008, Figure 2). A combination of rs2177370 and APOE gene analyses showed that carriers of the A/ε4 allele had a 6.10-fold increased ADC risk compared to carriers of the G/non-ε4 allele (OR 7.10, 95% CI: 2.60–19.38, P<0.001, Figure 2).

Table 5 Univariate Logistic Regression Analysis of Factors Associated with Alzheimer's Disease Continuum

Factors	OR (95% CI)	P
Age	1.06 (1.03–1.10)	<0.001
Gender (Ref: male)	0.75 (0.43–1.32)	0.315
Years of education	1.00 (0.94–1.07)	0.963
Comorbidities		
Hypertension	1.29 (0.72–2.33)	0.394
Hyperlipidemia	1.31 (0.72–2.39)	0.384
Diabetes	0.99 (0.49–2.02)	0.982
Coronary artery disease	4.06 (1.37–12.06)	0.012
Cerebrovascular disease	1.32 (0.45–3.85)	0.612
Anxiety-depression state	0.68 (0.35–1.31)	0.246
Family history of dementia	0.56 (0.28–1.10)	0.090
APOE-ε4	3.07 (1.69–5.55)	<0.001
CHAT		
rs3793790-G	1.27 (0.69–2.32)	0.439
rs2177370-A	2.29 (1.23–4.28)	0.009

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

The use of genetic background as a predictor of drug response is an emerging and exploratory area of research in ADC. We found that polymorphism of the CHAT gene was associated with donepezil response in ADC patients, and CHAT genetic variants play a role in the risk of ADC. These findings support the use of PGx in ADC.

Efficient and rapid multi-locus testing using the MassARRAY nucleic acid mass spectrometry platform suggested that the frequency of the G allele in rs3793790 was 17.24% and that of the A allele in rs2177370 was 18.10% in patients with ADC, which was similar to the findings of a previous study.[17] Additionally, we found that when rs3793790 carried the G allele, rs2177370 often carried the A allele and vice versa, with a concordance rate of 91.38%. However, this mechanism requires further investigation.

The results of this study imply that donepezil was more effective in patients carrying the G allele of rs3793790 and/or the A allele of rs2177370 than in those who did not. Yoon et al[17] assessed 21 SNPs of the CHAT gene for their relationship with donepezil response and concluded that rs3793790 and rs2177370 were related to donepezil therapeutic

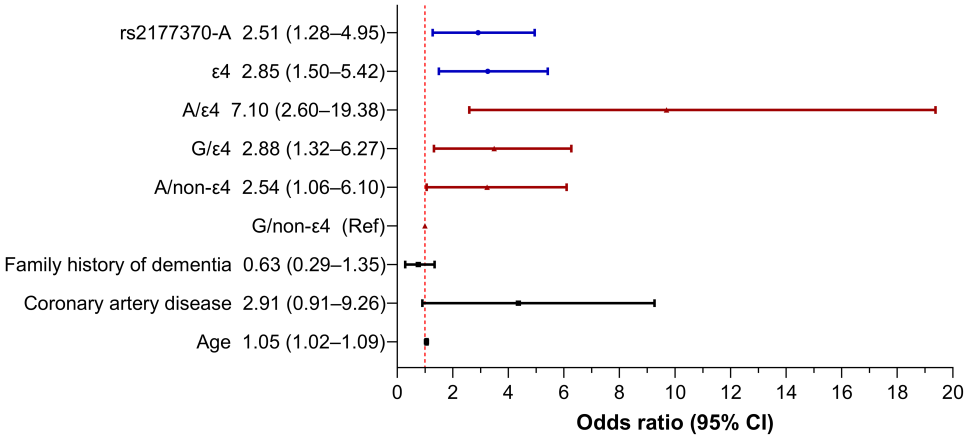

Figure 2 Multivariate logistic regression analysis of factors associated with Alzheimer's disease continuum. Blue: the rs2177370 and APOE gene analyses in multivariate logistic regression analysis. Red: a combination of rs2177370 and APOE gene analyses in multivariate logistic regression analysis. Black: adjusted factors in multivariate logistic regression analysis.

response in patients with AD from Korea. Enhancing levels of ACh is an important therapeutic target in patients with AD, providing a basis for the development of AChEIs.[18] Donepezil, an AChEI, alleviates AD symptoms by inhibiting degradation of ACh. ChAT is a critical enzyme for ACh synthesis and is encoded by CHAT. Thus, the levels of ACh synthesis may vary for each individual with CHAT gene polymorphisms, which may indirectly influence donepezil response.[10]

The G allele of rs3793790 and A allele of rs2177370 in CHAT may be effective alleles for donepezil treatment. Patients carrying effective alleles may acquire greater benefits from donepezil in ADC therapy. In addition, based on the findings of previous studies, pharmacogenomic effects are significantly greater in homozygotic genotypes than in heterozygotic genotypes.[7] Consequently, we propose that the chance of a good donepezil response increases in patients with the GG genotype of rs3793790 and AA genotype of rs2177370. Although these findings highlight the potential benefits of testing the rs3793790 and rs2177370 genotypes in the heterogeneity of donepezil response in ADC therapy, heavy challenges remain for clinical application, such as the lack of better alternative treatments and evidence of cost-effectiveness in testing genetic variants.[29]

The human APOE gene has three alleles, ε2, ε3 and ε4, encoding three protein isoforms, APOE2, APOE3 and APOE4, respectively. The ε4 allele is the strongest risk gene and the ε2 allele is the strongest protective gene for sporadic AD.[30] It also has been found to a higher rate of hemorrhage of amyloid associated imaging abnormality (ARIA-H) after treatment with anti-Aβ monoclonal antibodies such as aducanumab in APOE ε4 carriers compared with APOE ε2 or ε3 carriers.[31] Some studies have also suggested that the APOE gene may be associated with donepezil response, but current studies have mixed findings. The results of two recent meta-analyses have not found an independent impact of the APOE gene on donepezil therapeutic response in AD patients.[32,33] Based on the data from this study, we did not consider the association between APOE gene and donepezil response.

The impact of cholinergic deficits on the course of AD has been elaborated in a multitude of studies.[34] Some studies have indicated that other SNPs in CHAT are associated with the risk of AD. Ahn et al[35] supposed that the rs3810950 and rs1880676 variants in the CHAT gene had an impact on AD, depending on APOE genotypes; the impact was only apparent in patients not carrying the APOE-ε4 allele. Hálová et al[22] using an in silico approach and pointed out that the distinct structure of ChAT protein provided the molecular basis for ChAT activity related to the rs3810950 variant, facilitating the revisiting of the cholinergic hypothesis.

Further analysis suggested that the A allele in rs2177370 increased 1.51-fold the ADC risk, while the rs3793790 variant and ADC may not be relevant. When rs2177370-A is combined with APOE-ε4, there is a 7.1 times the risk of ADC. These findings indicate that rs2177370 might be a potential susceptibility gene for ADC with pharmacogenomic properties, which are reasonable and existent due to the role of the cholinergic system in the course of ADC. The favourable response to donepezil seems to indirectly support the diagnosis of ADC to some extent. However, the mechanisms by which genetic variants of the CHAT gene affect donepezil response and ADC risk are unknown.[17] Alternative splicing CHAT gene can produce various mRNA transcripts causing the appearance of different ChAT isoforms such as 82-,74- and 69-kDa ChAT.[36] A recent study has elucidated that older 82-kDa ChAT-expressing mice may be related to memory impairment and neuroinflammation.[37] Therefore, we speculate that the rs2177370 variants located in the intronic region may influence the regulation of the CHAT gene, causing the abnormal ChAT protein isoforms, which affects their roles in specific cholinergic pathways. The mechanisms remain to be further verified by fundamental researches.

Strengths and Limitations

This study explored the use of PGx in ADC and supported the association of rs3793790 and rs2177370 variants with inter-individual differences in response to donepezil in ADC patients. In addition, we concluded that the rs2177370 variant has a moderate relationship with the risk of ADC. Significantly, the diagnosis of the subjects in our study was supported by Aβ-PET/CT examination, which enhanced the reliability of the results.

However, our study had some limitations. First, the measures of donepezil response need to be enriched, such as adding the assessment of different cognitive domains.[38] Second, the risk factors for ADC were evaluated using cross-sectional analyses, and patients were not followed over the natural course of the disease. In addition to rs3793790 and rs2177370, other loci associated with the mechanism of action of donepezil require further exploration, and functional predictions and clinical guidance may evolve with new evidence.[39]

Conclusions

CHAT genetic variations are linked to the donepezil response. The chance of donepezil response increases in patients with the G allele of rs3793790 and/or A allele of rs2177370. In addition, rs2177370 may be a potential susceptibility gene loci for ADC with pharmacogenomic properties. These results further support the important role of PGx in ADC.

Acknowledgments

An unauthorized version of the Chinese MMSE was used by the study team without permission, this issue was rectified between the authors and PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR. This work was supported by the Chinese PLA General Hospital, Beijing, China (XYZ-202108). We sincerely appreciate all participants for their contributions to this study.

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Disclosure

All authors declare no conflicts of interest in this work.

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