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**Original Research Article**

# Influence of the rs1080985 Single Nucleotide Polymorphism of the *CYP2D6* Gene and *APOE* Polymorphism on the Response to Donepezil Treatment in Patients with Alzheimer's Disease in China

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**Key Words**

CYP2D6 · APOE · Donepezil · Polymorphism · Alzheimer's disease · Chinese population

**Abstract**

***Background/Aim:*** Recent data have indicated that the rs1080985 single nucleotide polymorphism (SNP) of the *cytochrome P450 (CYP) 2D6* and the common *apolipoprotein E (APOE)* gene may affect the response to donepezil in patients with Alzheimer's disease (AD). We investigated this association in Chinese patients with mild-to-moderate AD. ***Methods:*** In this prospective cohort study, analyses of CYP2D6 and APOE were conducted in 208 native Chinese patients with mild-to-moderate AD. All patients were treated with donepezil 5 mg/day for 6 months, and the response to treatment was assessed using the Mini-Mental State Examination. ***Results:*** No significant differences between responders (68.9%) and nonresponders (31.1%) to donepezil treatment (6 months' duration) were observed in the distribution of the *CYP2D6* rs1080985 SNP, common *APOE* polymorphism or a combination of the two. ***Conclusions:*** Our results suggest that neither the *CYP2D6* nor the *APOE* polymorphism influences the 6-month response to donepezil treatment in a Chinese population with AD.



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## Introduction

Donepezil is a specific piperidine-based inhibitor of acetylcholinesterase and the most commonly prescribed treatment for mild-to-moderate Alzheimer's disease (AD) [1]. Donepezil yields significant benefits on cognitive function, activities of daily living (ADL), and behavior [2, 3]. However, the degree of this benefit varies between individuals, with studies reporting only 45–47% of treated individuals demonstrating an improvement in cognition [4, 5]. Interindividual genetic variations in the *cytochrome P450* (*CYP*) *2D6* and *apolipoprotein E (APOE)* gene have been found to influence which individuals respond to donepezil [6]. Predicting nonresponders to donepezil would allow immediate initiation of alternate antidementia drugs such as *N*-methyl-D-aspartate receptor antagonists.

Currently, in clinical settings, the norm is to trial the treatment and change it if it proved to be ineffective. However, an audit conducted in Leeds (UK) revealed that 33% of AD patients were prescribed donepezil without any documented benefit in cognition as assessed by the Mini-Mental State Examination (MMSE) or ADL [4]. Hence, identification of specific genetic polymorphisms associated with a good response to donepezil treatment would allow an individually designed approach to therapy for patients with AD, thus minimizing the societal costs associated with ineffective therapy.

The *CYP2D6* enzyme plays a key role in the first-pass metabolism of donepezil [7]. The gene located on chromosome 22q13.1–13.2 is highly polymorphic, with the G allele of the single nucleotide polymorphism (SNP) rs1080985 ($C^{-1584} \rightarrow G$) in the promoter region of the *CYP2D6* gene associated with higher gene expression and greater enzymatic activity in vivo [8]. This SNP has also been associated with a poorer response to donepezil in Italian patients with AD [9–11], yet found to play no effect in 88 Polish patients [12]. To our knowledge, there are no current published findings examining this association in the Chinese population.

Another enzyme found to influence the *CYP2D6*-related enzyme, as well as liver metabolism, is *APOE*. *APOE* may influence liver function and drug metabolism by modifying hepatic steatosis and transaminase activity [13].The relationship between response to donepezil and the common *APOE* polymorphism in patients with AD has been investigated in several studies, but the results remain controversial [6, 14–16]. However, when the *APOE* and *CYP2D6* genotypes are integrated into bigenic clusters, it becomes clear that the presence of the *APOE*-Ɛ4/Ɛ4 genotype is able to convert pure *CYP2D6**1/*1 extensive metabolizers into full poor metabolizers, indicating the existence of a powerful influence of the *APOE*-Ɛ4 homogenous genotype on the drug-metabolizing capacity of pure *CYP2D6*-extensive metabolizers [17]. Whether this remains true for donepezil and the rs1080985 polymorphism remains to be clarified.

The aim of our study was to evaluate the association between response to donepezil with the rs1080985 SNP of the *CYP2D6* gene and the *APOE* polymorphism in a Chinese population with mild-to-moderate AD.

## Methods

Consecutive patients admitted to the Dementia Clinic at Huanhu Neurological Hospital, Tianjin, China, were screened for enrolment in the study. Exclusion criteria were: (i) previous or current treatment with memantine or cholinergic drugs; (ii) presence of psychiatric disorder, and (iii) significant brain damage (Hachinski Ischemic Score <4). In total, we collected 206 mild-to-moderate probable AD subjects diagnosed according to the NINCDS-ADRDA international criteria [18]. Further evaluation included medical, neurologic and neuropsychological examinations, interviews with a close informant, laboratory testing,

brain magnetic resonance imaging or computed tomography, and if indicated, positron emission computed tomography. Dementia severity was assessed by MMSE. The study patients were treated with donepezil 5 mg/day for 6 months. Follow-up was performed at 6 months of treatment. A patient who showed improvement or no deterioration in cognition as evaluated by MMSE at the 6-month follow-up was defined as responder. All participants were of Asian descent. The study was approved by the local Ethical Committee of Tianjin Huanhu Hospital. All participants (or caregivers) gave written informed consent for study inclusion.

*DNA Extraction and Genotyping*

Genomic DNA of every subject was isolated from peripheral nuclear blood cells using the Omega Blood DNA Kit according to the manufacturer's instructions (Omega Bio-Tek, Inc.). Polymerase chain reaction (PCR) was performed at a total volume of 25 μl containing 1 μl of DNA template (30–60 ng/μl), 2.5 μl of 10× Taq buffer, 2 μl of dNTP mixture (2.5 mM), 0.5 μl of Taq DNA polymerase (2.5 U/μl; Takara Biotech), 2 μl of each primer (10 μM) and $ddH_2O$. The PCRs were done using a thermal cycler system (Bioer). Then, the PCR products were exposed to direct nucleotide sequencing using an ABI 3730 DNA analyze (Invitrogen). APOE was genotyped by the RFLP method as previously described [19].

*Statistical Analysis*

Univariate and multivariate logistic regression analyses were performed using SPSS version 22 (SPSS Inc., Chicago, Ill., USA). Starting from the data by Pilotto et al. [10], we hypothesized to find an effect size (w = 0.48) for the allelic frequency of rs1080985. Accordingly, a priori power analysis showed that we had to compare 93AD, equally divided into responders and nonresponders, to replicate the association (α = 0.05, power: 0.99).

## Results

Table 1 reports the baseline characteristics of our sample as well as the genotypic and allelic distributions of rs1080985 and APOE. In our population, there were 68.9% responders and 31.1% nonresponders. Responders and nonresponders showed no differences in baseline MMSE score or gender. Analysis of the rs1080985 SNP showed that 150 (72.8%) patients were CC homozygotes, 50 (24.3%) were CG heterozygotes, and 6 (2.9%) were GG homozygotes. No differences were found between these observed frequencies and the expected Hardy-Weinberg equilibrium frequencies for responders and nonresponders (p = 0.11 and p = 0.16, respectively).

Analysis of the APOE polymorphism showed that there were in total 6 (2.9%) patients who were Ɛ2/Ɛ3 heterozygotes, 101 (49.0%) were Ɛ3/Ɛ3 homozygotes, 7 (3.4%) were Ɛ2/Ɛ4 heterozygotes, 35 (40.3%) were Ɛ3/34 heterozygotes, and 8 (4.4%) were Ɛ4/Ɛ4 homozygotes.

Univariate analysis which assessed the association between rs1080985 and response to donepezil did not find a significant effect by applying a dominant allelic model [Odds ratio (OR) 1.494, 95% confidence interval (CI) 0.677–3.299, p = 0.319]. To correct for possible confounders, a multivariate analysis was performed considering age, gender, MMSE score at baseline and *APOE*-Ɛ4 status. The results remained insignificant using the same allelic model as above (OR 1.584, 95% CI 0.677–3.71, p = 0.29).

Finally, we performed a stratification analysis to test for interaction between rs1080985 and *APOE*-Ɛ4 status in responders and nonresponders. The results are shown in table 2. We found a nonsignificant increase of frequency in nonresponders bearing both the *APOE*-Ɛ4 variant and the rs1080985 G allele.

**Table 1.** Response to 6 months of donepezil treatment according to rs1080985 and *APOE* genotypes

| | Female | Age, years | MMSE baseline | MMSE at the 6-month follow-up |
|---|---|---|---|---|
| R (n = 142) | 76 (53.5%) | 68.127±8.89 | 16.521±5.616 | 18.0282±5.78 |
| NR (n = 64) | 36 (56.2%) | 72.91±8.83 | 16.875±6.215 | 14.656±6.80 (p = 0.011)[a] |

| | Genotype count | | | Allele count | | |
|---|---|---|---|---|---|---|
| rs1080985 | C/C | C/G | G/G | C | G | p |
| R (n = 142) | 108 (76.1%) | 30 (21.1%) | 4 (2.8%) | 246 (86.6%) | 38 (13.4%) | |
| NR (n = 64) | 42 (65.6%) | 20 (31.3%) | 2 (3.1%) | 104 (81.1%) | 19 (19.0%) | 0.254[b] |

| | Genotype count | | | | | | Allele count | | |
|---|---|---|---|---|---|---|---|---|---|
| *APOE* | Ɛ2 Ɛ2 | Ɛ2 Ɛ3 | Ɛ2 Ɛ4 | Ɛ3 Ɛ3 | Ɛ3 Ɛ4 | Ɛ4 Ɛ4 | Ɛ2 | Ɛ3 | Ɛ4 |
| R (n = 142) | 0 | 4 (2.8%) | 5 (3.5%) | 69 (48.6%) | 58 (40.8%) | 6 (4.2%) | 9 (3.2%) | 200 (70.4%) | 75 (26.4%) |
| NR (n = 64) | 0 | 2 (3.1%) | 2 (3.1%) | 32 (50.0%) | 25 (39.1%) | 3 (4.7%) | 4 (3.1%) | 91 (71.1%) | 33 (25.8%) |

Values are n (%) or means ± SD. R = Responder; NR = nonresponder.
[a] Versus responders, the Student's t test was used. [b] p value for multivariate logistic regression correcting for age, gender, and MMSE score at baseline.

**Table 2.** Proportion of responders and nonresponders to donepezil stratified by *APOE*-Ɛ4 and rs1080985 genotypes, respectively

| | | | |
|---|---|---|---|
| *Responders (n = 142)* | | | |
| (4) *APOE*-Ɛ4 (–) rs1080985 G-allele (–) 59 (41.4%) | (3) *APOE*-Ɛ4 (–) rs1080985 G-allele (+) 20 (14.1%) | (2) *APOE*-Ɛ4 (+) rs1080985 G-allele (–) 50 (35.2%) | (1) *APOE*-Ɛ4 (+) rs1080985 G-allele (+) 12 (8.5%) |
| *Nonresponders (n = 64)* | | | |
| *APOE*-Ɛ4 (–) rs1080985 G-allele (–) 25 (38.7%) | *APOE*-Ɛ4 (–) rs1080985 G-allele (+) 12 (18.8%) | *APOE*-Ɛ4 (+) rs1080985 G-allele (–) 18 (28.1%) | *APOE*-Ɛ4 (+) rs1080985 G-allele (+) 8 (12.5%) |
| *OR (95% CI)* | | | |
| Reference | 1.450 (0.430–4.888); p = 0.548 | 0.87 (0.315–2.404); p = 0.788 | 1.611 (0.384–6.752); p = 0.705 |

## Discussion

The main aim of this study was to assess whether the significant association between rs1080985 minor allele and a response to donepezil, found in Italian patients by Pilotto et al. [10] and Albani et al. [11], was present in Chinese patients with AD. Hence, we replicated the grouping criteria for the response to treatment and duration of follow-up (6 months). Our study did not find donepezil to be associated with rs1080985 or APOE-Ɛ4 in a Chinese population.

Previous studies in Italian patients found that the rs1080985 minor allele (G) reduced the responsiveness to donepezil treatment in patients with AD [10, 11]. However, the effect was found to be small to moderate. Similar to a study in Polish individuals [12], findings did not show a significant role of the minor allele in improving the clinical response to donepezil. These contrasting findings suggest that there are additional factors, probably genetic factors that are correlated with ethnicity which are involved in the response to donepezil treatment.

In a post hoc analysis, our sample size had 99% power to determine an effect size (w = 0.48) found by Pilotti et al. [10] and 80% power to determine a weaker effect size (w = 0.28); however, none were found. Thus, the findings of this study may be considered quite solid. Moreover, the rate of responders to donepezil is in agreement with a meta-analysis of randomized clinical trials of donepezil 5–10 mg/day reporting a treatment response of 30–68% after 6 months [2, 3].

With such controversial findings across different ethnicities, it remains unclear as to whether rs1080985 may be a useful predictor for response to cholinergic therapy. Furthermore, the functional actions of the minor allele of rs1080985 remains controversial, as it has been associated with increased *CYP2D6* expression in human livers [20, 21] and greater *CYP2D6* hydroxylation capacity [22]. Nevertheless, gene assays did not support a transcriptional effect of rs1080985 [23, 24]. The latter study suggested that the observed association with increases *CYP2D6* protein levels results from linkage disequilibrium with upstream enhancer SNP [25]. Hence, a better prediction of donepezil response should take into account other *CYP2D6* genetic variants. In fact, it has been recently described that a genetic analysis of 16 polymorphisms in *CYP2D6* was effective to discriminate between responders and nonresponders to therapy, so rs1080985 genotyping might be complementary to this more inclusive method [10].

Recent studies have suggested that the Ɛ4 allele of the *APOE* polymorphism seems to improve the responsiveness to donepezil treatment in patients with AD; however, this improvement is only marginal and unclear as to whether it is clinically significant (Ɛ4 has a 0.13 worsening of ADL while non-Ɛ4 had a 0.17 worsening) [6, 26]. In agreement with other studies [11, 16], our study did not find a significant role of the Ɛ4 allele in improving the clinical response to donepezil. Important to highlight is that the studies which showed a response had a longer observational period (12–36 months) than those which did not find an association (3–12 months). Taking into consideration these results, it is possible that there is no relationship between *APOE*-Ɛ4 and response to donepezil, or that there is a small association that only becomes measureable after 12 months of cholinergic treatment. Considering that recent open-label extension trials showed donepezil to have cognitive and functional benefits for treatment durations of >12 months [27], future prospective long-term studies are needed to assess the effect of *APOE-Ɛ4* on cholinergic therapy.

Three studies that have analyzed the interaction between *APOE* status and rs1080985 did not find a direct interaction between *APOE* and *CYP2D6* polymorphisms [11–13]. In one of these studies, a marginal significance (p = 0.05) for frequency of the *APOE*-Ɛ4 and rs1080985 G allele was found, but an independent effect of *APOE*-Ɛ4 on response to donepezil was not found [12]. In our study, *APOE*-Ɛ4 was not significantly associated with the therapeutic response to donepezil. None of the three studies supported the hypothesis of a direct interaction between *APOE* and *CYP2D6* polymorphisms on response to donepezil treatment.

An important limitation of our study is the lack of a placebo group to control for cognitive decline or improvement. Thus, future controlled clinical trials are warranted. Furthermore, due to the number of exclusion criteria set in selecting patients, there is a possible genetic bias in patient enrolment. However, analyses of the genotype frequencies of the SNP rs1080985 in the study cohort were comparable to the *CYP2D6* genotype distribution reported in Asian individuals [28]. Moreover, the observed genotype frequencies at the *CYP2D6* and *APOE* loci did not differ from the expected Hardy-Weinberg frequencies, also after categorizing patients according to response or nonresponse to donepezil treatment.

Although data regarding the *CYP2D6* polymorphism are inconclusive, the results of published studies encourage a continued evaluation of the role of rs1080985 polymorphism in response to donepezil treatment in different ethnicities, and to assess other genetic variants

of *CYP2D6* that may be in linkage disequilibrium. Further placebo-controlled studies are also required. Until further confirmation is established, it is recommended that medical practitioners closely monitor for improvements in MMSE and ADL in treated AD patients, whereby the lack of improvement or maintenance in cognitive function over 6 months necessitates a change in medication.

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