

# Effect of genetic polymorphisms on Alzheimer's disease treatment outcomes: an update

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**Abstract:** Genetic variations in individuals may cause differences in the response to cholinesterase inhibitor drugs used in the treatment of Alzheimer's disease (AD). Through this review, we aimed to understand the potential relationship between genetic polymorphisms and treatment response in AD. We conducted a systematic review of the studies published from 2006 to 2018 that assessed the relationship between genetic polymorphisms and the pharmacotherapeutic outcomes of patients with AD. Via several possible mechanisms, genetic polymorphisms of many genes, including *ABCA1*, *ApoE3*, *CYP2D6*, *CHAT*, *CHRNA7*, and *ESR1*, appear to have strong correlations with the treatment response of patients with AD. Indeed, these genetic polymorphisms, either in the form of single nucleotide polymorphisms or direct changes to one or more amino acids, have been shown to cause differences in the therapeutic response. In summary, our findings indicate that genetic polymorphisms should be considered in the management of AD to achieve both effective and efficient treatment outcomes in terms of cost and prognosis.

**Keywords:** Alzheimer's disease, genetic polymorphisms, treatment response

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive dementia. AD suggests distinctive neuropathology and/or neurochemical deficiency in selective brain regions. It is considered the most common cause of dementia and accounts for 60%–70% of all cases of dementia. Approximately 4.6 million cases of dementia have been reported annually worldwide, and by 2050, 100 million people are projected to have dementia. On the contrary, ~20% of the world's population aged >80 years has AD.<sup>1</sup>

AD is characterized by a reduced memory capacity (or dementia), decreased numbers of cholinergic neurons, accumulation of amyloid- $\beta$ , and neurofibrillary neuronal formation.<sup>2</sup> The pathogenesis of AD is considered complex. Although there are several hypotheses involving genetic factors, the precise etiology has not yet been identified.<sup>3</sup> AD causes synaptic dysfunction in the early phase of the disease, thereby disrupting the communication of important nerves involved in memory as well as other cognitive functions. Degeneration in AD begins in the medial temporal lobe, particularly in the entorhinal cortex and hippocampus. Damage to these regions may result in memory deficits and is observed as an initial clinical manifestation.<sup>4</sup>

AD itself is pathologically defined as extracellular accumulation of amyloid- $\beta$ , intracellular accumulation of tau proteins, loss of neurons and synapses, brain atrophy, and general inflammation. Some genetic mutations have been identified as risk factors and are believed to be involved in the pathological development of AD.<sup>3</sup> Several types

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of genetic mutations or disturbances have been identified in patients with AD, including the presence of dysfunctional mutations, single nucleotide polymorphisms (SNPs),<sup>5</sup> mitochondrial mutations, and epigenetic changes.<sup>6</sup> A recent study by Jiang et al showed the tendency of genetic variation as a factor responsible for AD development. Furthermore, the same study also suggested that AD genetic variations are significantly enriched in the pathways of the immune system.<sup>7</sup>

Effective pharmacological treatments of AD are currently lacking. The first-line treatment for mild-to-moderate AD involves acetylcholinesterase inhibitors (AChEI) as well as non-pharmacological therapies, including multidimensional stimulation therapy (MST), to prevent and slow the cognitive impairment often observed in patients with AD. However, the outcomes of those therapies may be influenced by differences in genetic polymorphisms among individuals. For example, polymorphisms of *ABCA1* and *CYP2D6* can affect AChEI therapy, whereas those of *ApoE-4* and *SNAP-25* can affect MST.<sup>3</sup> In this study, we discuss recent findings on the association of genetic polymorphisms with the outcomes of AD treatment. This association has not been comprehensively reviewed, as previous review studies mainly focused on the association of genetic polymorphism with the development of AD.

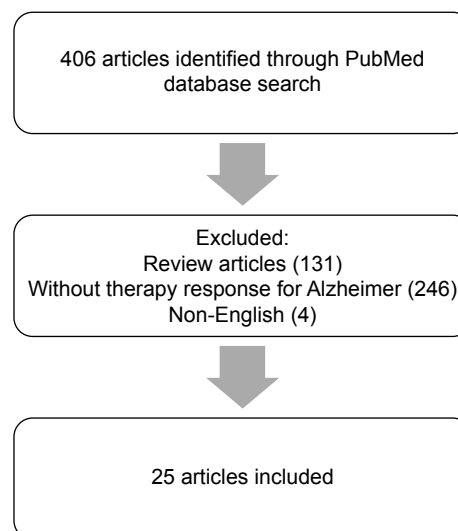
## Methodology

This review included studies published in the PubMed database obtained using the keywords “polymorphism” and “Alzheimer’s therapy.” Reviews, non-English studies, and unrelated studies, such as those reporting the lack of therapeutic outcomes for AD and genetic polymorphisms, were excluded. The flowchart of the literature search is shown in Figure 1.

Of the total 405 articles obtained in July 2018, we included 24 studies<sup>3,5,8–29</sup> that particularly focused on the association between genetic polymorphisms and the outcomes of the treatment of AD (Table 1).

## Effect of genetic polymorphisms on the pharmacotherapeutic outcomes of AD

Because an effective pharmacotherapeutic management strategy for AD has not yet been established, AChEI therapy is currently used as the first-line drug therapy for AD management. However, genetic polymorphisms reportedly affect the outcomes of AChEI therapy. Indeed, several genes have been studied in this regard, including *ABCA1*, *ApoE*, *PON-1*, *CHRNA7*, *CHAT*, *ESRI1*, and *CYP2D6*.



**Figure 1** Flowchart depicting the literature search process.

## ABCA1

*ABCA1* is located on chromosome 9 and is reportedly associated with late-onset AD. ATP-binding cassette transporter A1 (*ABCA1*) is a membrane transporter protein that stimulates cholesterol and phospholipid efflux to apolipoproteins.<sup>30</sup> In addition, *ABCA1* plays a role in cholesterol transport by neutralizing the capacity of A $\beta$  aggregation in an ApoE-dependent manner; this in turn facilitates the elimination of A $\beta$  from the brain, thereby directly transporting it into the blood.<sup>31</sup>

Lu et al<sup>25</sup> reported that patients with AD who have the *ABCA1* gene (rs2230806, GG genotype) exhibited considerably better therapeutic outcomes than patients who have the AA or AG genotype. Indeed, patients with the GG genotype were shown to exhibit the best response to donepezil (DNP) therapy (21 of 49 responders) and the lowest frequency as non-responders (4 of 39 non-responders). The authors also tested the *ABCA1* gene, rs2230808 base G>A, and reported that it does not considerably affect the therapeutic outcomes.<sup>25</sup>

## ApoE

*ApoE* is a protein carrier for cholesterol transport in the brain. *ApoE* is presented as three isoforms as follows: *ApoE2*, *ApoE3*, and *ApoE4*. *ApoE2* has been shown to reduce amyloid- $\beta$  buildup, thus considered a protective factor against AD pathology.<sup>26</sup>

In 2016, Lu et al<sup>26</sup> studied the Han Chinese population and reported that compared with the *ApoE3* carriers, the *ApoE3* non-carriers in that population responded considerably better to DNP therapy. The authors also reported that compared with *ApoE3* carriers, patients with AD who were

**Table I** Association of gene polymorphism with therapy response

Genes	Subjects	Location	Therapy	Results	Ref no
<b>CHRNA7</b>					
rs8024987 (C→G)	204	Taiwan	ChEI	Improvement MMSE score in G allele carrier	7
rs8024987 (C→G)	177	Brazil	ChEI	No improvement MMSE score in G allele carrier	8
rs6494223	177	Brazil	ChEI	No association between polymorphism and therapy response	9
rs6494223	177	Brazil	ChEI	No association between polymorphism and therapy response	8
<b>CHAT</b>					
rs2177370	158	Korea	ChEI	Association between polymorphism and therapy response	10
rs3793790	158	Korea	ChEI	Association between polymorphism and therapy response	10
Haplotype rs11101187–rs2177370	158	Korea	ChEI	Allele CC and CT result in different Ach synthesis rates, which is associated with therapy response	10
rs733722	121	Northern Ireland	ChEI	Each copy of C allele result decline MMSE points/year relative to the T allele, which reflected the response to therapy	5
rs 3810950 (2384G>A) in the +4 position	135	Korea	ChEI	No improvement in first 12 weeks of treatment and significant difference in therapy response in A allele carrier at week 26 of therapy	11
rs2177369 (A→G)	171	Italy	ChEI (rivastigmine and DNP)	No association between polymorphism and therapy response	12
<b>CYP2D6</b>					
rs1080985	208	China	ChEI (DNP)	No significant difference in polymorphism between responder and non-responder of DNP treatment	13
rs1080985	88	Poland	ChEI (DNP)	No significant difference in polymorphism between responder and non-responder of DNP treatment	14
rs1080985 Allele G	127	Italy	ChEI (DNP)	Significantly higher frequencies of G allele in non-responder patients	15
rs1080985	77	China	ChEI (DNP)	Combination of S-DNP plasma concentrations and genotype was useful for monitoring DNP treatment outcomes	16
CYP2D6*4	38	India	ChEI (DNP) and DNP + memantine	Association between polymorphism and DNP monotherapy response	17
CYP2D6*10	110	China	ChEI (DNP)	Significantly higher frequency of CYP2D6*1/*10 and CYP2D6*10/*10 genotypes of responders	18
rs1080985	415	Italy	ChEI (DNP)	Association between polymorphism and DNP therapy response	19
CYP2D6	57	Italy	ChEI (DNP)	Significant association of gene variation and clinical response with DNP	20
CYP2D6*3	18	India	ChEI (rivastigmine and memantine)	Significant correlation with improvement of MMSE score	21
CYP2D6	42	Italy	ChEI (DNP)	Improvement of MMSE score and value showed significant correlation	22
<b>PON-1</b>					
PON gene 7q21.3	73	Italy	ChEI	R allozyme (Arg) has better therapy response than Q allozyme (Gly)	23
<b>ABCA1</b>					
rs2230806 and rs2230808	88	China	ChEI	MMSE score significantly increases in rs2230806 GG allele carrier	24
<b>ApoE</b>					
E3 and E4 carrier/non-carrier	85	China	ChEI	Response to DNP influenced by ApoE E3 allele	25
Combined E3 carrier/non-carrier and rs2230806	88	China	ChEI	E3 carrier and rs2230806 GG allele carrier showed best therapeutic response	24
E3 and E4 carrier/non-carrier	208	China	ChEI	The ApoE polymorphisms did not influence 6 months of DNP treatment	13
E3 and E4 carrier/non-carrier	97	Brazil	ChEI	No association between ApoE polymorphisms and DNP response	26
E4 carrier/non-carrier	177	Brazil	ChEI	The presence of the E4 allele showed worst response to ChEI response	9
E4 carrier/non-carrier	110	China	ChEI	No association between ApoE E4 status and efficacy of DNP	18
E4 carrier/non-carrier	167	Spain	ChEI	No association between ApoE4 and rivastigmine efficacy	27

(Continued)

Table 1 (Continued)

Genes	Subjects	Location	Therapy	Results	Ref no
<i>E4</i>	58	–	MST	Subjects with negative ApoE4 alleles (ApoE4–) responded better to MST therapy	3
<b>ESRI</b> <i>P and X allele carrier/ non-carrier</i>	184	Italy	ChEI	At least one copy of P or X allele carrier showed better response significantly than non-carrier	28
<b>SNAP-25</b> <i>rs363050</i>	58	–	MST	G allele carrier has better MST therapy response	3
<i>rs363039</i>	58	–	MST	A allele carrier has better MST therapy response	3

**Abbreviations:** ChEI, cholinesterase inhibitor; DNP, donepezil; MMSE, Mini Mental State of Examination; MST, multidimensional stimulation therapy; PON-1, paraoxonase-I.

*ApoE3* non-carriers exhibited better therapeutic responses to DNP. In addition, compared with *ApoE3* carriers who had the *ABCA1* gene rs2230806 AG/AA genotype, patients with AD who were *ApoE3* non-carriers and had the *ABCA1* gene rs2230806 GG genotype exhibited the best therapeutic responses to DNP.<sup>25</sup>

Another study reported that compared with *ApoE4* carriers, *ApoE4* non-carriers exhibited a considerably better response to DNP treatment.<sup>10</sup> Another study that observed the association between *ApoE4* and AD reported that >80% of the *ApoE4*-negative patients with AD exhibited marked improvement after 30 weeks as assessed via the AD scores Alzheimer's Disease Assessment Scale (ADAS), whereas 60% of the *ApoE4* carriers had lower ADAS scores compared with baseline. These results indicate that *ApoE4* plays a role in AD-related cholinergic dysfunction and may be useful in the prognosis of patients with AD who poorly respond to AChEI therapy.<sup>32</sup> In contrast, Miranda et al<sup>27</sup> and Zhong et al<sup>19</sup> reported no association between *ApoE4* polymorphisms and the clinical response to DNP after 6–12 months of follow-up.

## Paraoxonase-I (PON-I)

PON-1 is an arylesterase; it has multiple biological activities, including acetylcholinesterase inhibition. PON-1 can hydrolyze paraoxon, the active metabolite of parathion having toxic acetylcholinesterase properties, to provide protection against exogenous organophosphates.<sup>33</sup>

The serum level and activity of PON-1 considerably vary in humans and are determined by polymorphisms in related genes.<sup>34</sup> The basis of the genetic polymorphism of *PON-1* is the change in Gln to Arg at residue 192, which produces the following three possible genotypes: QQ, QR, and RR. The Q allozyme with a Gln at residue 192 has low paraoxon hydrolysis activity, whereas the R allozyme with an Arg at residue 192 exhibits higher activity.<sup>35</sup>

Pola et al<sup>24</sup> reported that compared with patients carrying the Q allele, those carrying the R allele on the *PON-1* gene

responded better to therapy. This may be due to the mutations that occur, thereby causing differences in the synthesis of PON-1 with different hydrolysis activities. Thus, the R allele is associated with higher enzyme activity. Apart from its role as an endogenous cholinesterase inhibitor, the PON-1 protein has been hypothesized to synergistically interact with drugs that act as AChEIs.<sup>24</sup>

## CHRNA7

The loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChRs) is a major pathological hallmark of AD.<sup>36,37</sup> nAChRs are ligand-gated ion channels that mediate the effects of the neurotransmitter acetylcholine. Alpha-7 nAChRs, which are encoded by *CHRNA7* on chromosome 15q14, are one of the major nAChR subunits in the central nervous system. Weng et al<sup>8</sup> suggested an association between SNPs in *CHRNA7* and the response to cholinesterase inhibitors in the treatment of AD. The polymorphism that occurs at rs8024987, which is located in an intron of *CHRNA7* in the form of a homozygous or heterozygous C→G transversion, results in better outcomes for cholinesterase inhibitor therapy, with the GG allele providing a better response than the GC allele. However, a further analysis showed that this association was not found in male responders, thereby indicating considerable interaction between gender and SNPs at rs8024987.<sup>8</sup> Moreover, Weng et al<sup>8</sup> reported that women, particularly those carrying the GG or GC allele, compared with those who are non-carriers or non-galantamine-treated, tend to exhibit better responses to galantamine therapy.

However, conflicting results of the association of *CHRNA7* with the outcomes of the treatment of AD have also been reported. In their study, Clarelli et al failed to establish an association between the polymorphism in rs8024987 and cognitive therapy response using cholinesterase inhibitors.<sup>9</sup> Studies concerning the polymorphism in rs6494223 also failed to establish an association with the response to AChEI therapy.<sup>9,10</sup>

Subsequent haplotype analyses have demonstrated that of the four haplotype blocks obtained, one comprising the SNPs at rs885071 (T→G) and rs8024987 (C→G) was associated with therapeutic outcomes. The tendency to respond to the therapy was better when the GG haplotype was observed. However, although the SNPs at rs885071 and rs8024987 are strong in linkage disequilibrium, the pairwise correlations between them are low.<sup>8</sup>

As described in Figure 2, the correlation between the polymorphisms in *CHRNA7* and the cognitive therapy response of ChEI may be associated with multiple pathways. The SNP at rs8024987 occurs in the intron part that might affect the expression of the alpha-7 nAChR via a pre-mRNA splicing mechanism, which leads to changes in protein production. ChEI directly enhances cognition by reducing acetylcholine breakdown, which binds the alpha-7 nAChR, subsequently increasing cholinergic neurotransmission.<sup>38</sup> In vitro studies have reported that the alpha-7 nAChR plays a vital role in mediating the neuroprotective effects of ChEI against the toxicity of amyloid-β.<sup>39,40</sup> The alpha-7 nAChR can also modulate neurotransmitter release in presynaptic neurons.<sup>41</sup> On the contrary, chronic treatment with ChEI also helps increase the alpha-7 nAChR, which induces a positive feedback loop to amplify the effects of ChEI.<sup>42</sup> The possible mechanism of polymorphisms in *CHRNA7* affects ChEI cognitive response.

## Choline acetyltransferase (ChAT)

AD is associated with the widespread degeneration of cholinergic neurons; AChEIs have been approved for treating symptoms with the ultimate goal of restoring cholinergic deficits.<sup>43</sup> Thus, the cholinergic system is considered a reasonable target in terms of pharmacogenomic studies. Moreover, numerous studies have established an association between genetic polymorphisms in cholinergic genes and the therapeutic effects of AChEIs.<sup>5,13</sup> However, the therapeutic response rate of AChEIs varies from 40% to 70%.<sup>44</sup>

ChAT is an enzyme encoded by *ChAT*, which plays a role in acetylcholine synthesis by using choline and acetyl-CoA as substrates. ChAT activity is known to be reduced in patients with AD, and this reduction appears to be related to the severity of dementia.<sup>13,45</sup>

Yoon et al investigated 25 points of SNPs in the ChAT-encoding gene and reported that the two SNPs, rs 2177370 and rs3793790, located in the introns of *ChAT*, were associated with AChEI drug response. The haplotype analysis demonstrated four haplotype blocks comprising 13 haplotype alleles; in particular, one haplotype block was significantly

associated with the AChEI drug response and included two haplotype alleles, with one comprising rs2177370.<sup>11</sup>

The association of *ChAT* polymorphisms with AChEI therapy response is associated with the function of AChEIs as an inhibitor of acetylcholinesterase that breaks down acetylcholine. The efficacy of AChEIs depends on the synthesis of acetylcholine itself; thus, when acetylcholine synthesis is impaired owing to the degeneration of cholinergic neurons in patients with AD, the synthesis capacity of the remaining neurons is expected to support the response of the AChEI drug. The CC haplotype itself is reportedly associated with a decrease in the synthesis of ACh, whereas the CT haplotype is associated with a higher rate of ACh synthesis.<sup>11</sup>

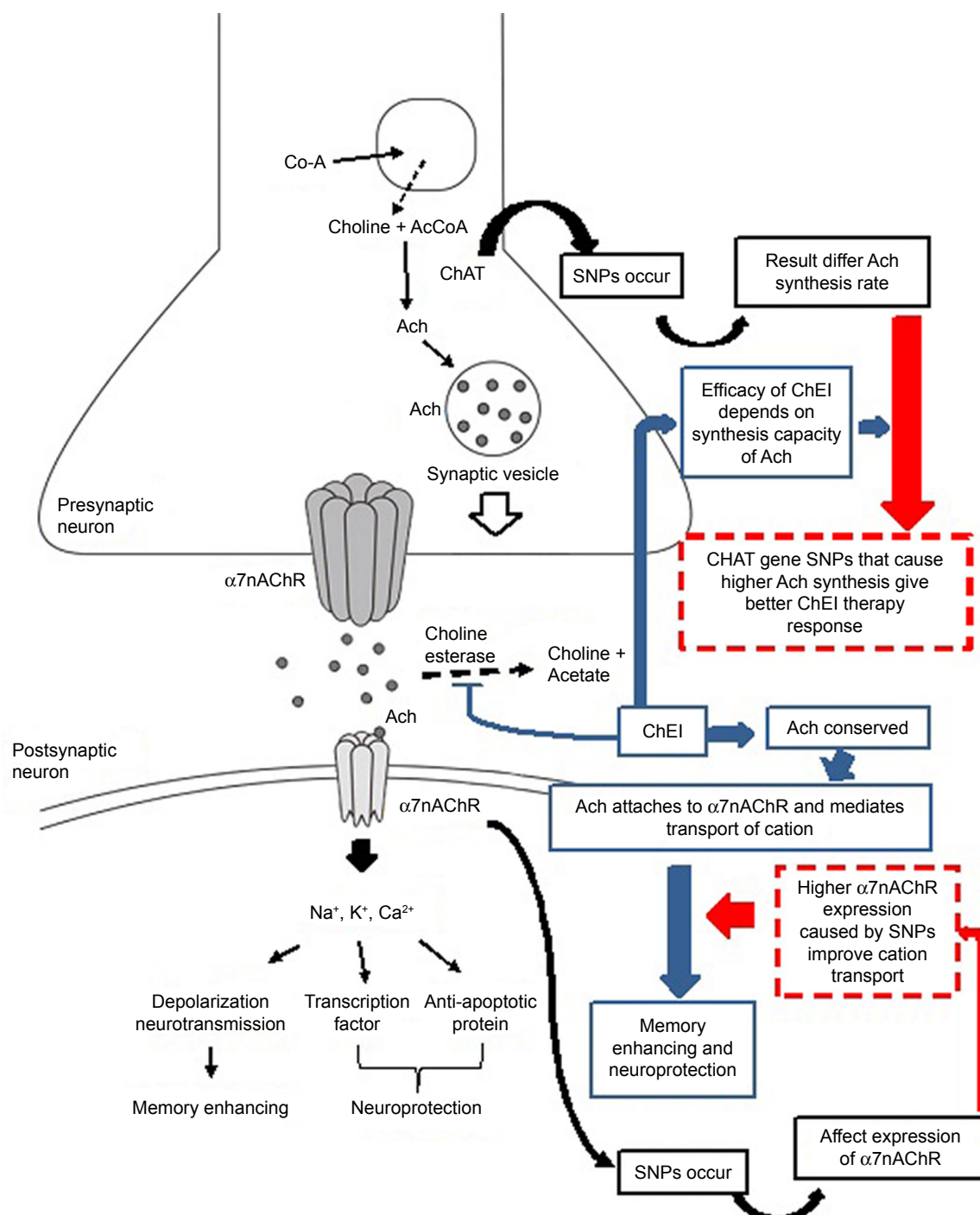
Several studies have investigated SNPs occurring in *ChAT*. Scacchi et al<sup>13</sup> reported that the polymorphism at rs2177369, with G/G with respect to the G/A+A/A genotypes, is considered a risk factor for AD but the authors did not observe an association with the response to ChEI therapy. However, Harold et al<sup>5</sup> reported that the occurrence of the C allele results in considerable decline in the Mini Mental State of Examination (MMSE) score, which is associated with the therapeutic response.

In 2015, Lee et al<sup>12</sup> reported that they did not observe an association between *ChAT* A carriers (alleles and non-carriers) and the outcomes of 12 weeks of DNP treatment. However, after 26 weeks of treatment, a considerable difference was observed in the therapeutic outcomes between A *ChAT* carrier alleles and non-carriers. The mean MMSE score in the Korean version of the Consortium to Establish a Registry for AD assessment battery MMSE-KC increased after 26 weeks of therapy with DNP in the *ChAT* A carriers.<sup>12</sup> The difference in the outcomes of these treatments is associated with the possible efficiency of *ChAT* translation, which occurs when there is a change (2384 G→A), and the recognition of the initiator codon is improved. Although this is not a rate-limiting enzyme, the substitution of the A allele for G may decrease the production of ChAT, which may be related to the therapeutic effects of DNP.<sup>46</sup>

## ESR1

ESR1 is an estrogen receptor located on chromosome 6q25. ESR1-mediated estrogen activity in the brain occurs via the activation of transmembrane, intracellular, and membrane-bound proteins.<sup>47</sup> Scacchi et al<sup>29</sup> reported that compared with non-carriers, patients with at least one P and X allele of the two ESR1 SNPs rs2234693 and rs9340799 exhibited a better treatment response. This is likely due to the presence of the P and X alleles, which increase acetylcholine biosynthesis, thereby increasing acetylcholinesterase inhibition.





**Figure 2** Possible mechanism of polymorphisms in *ChAT* and *CHRNA7* affecting ChEI cognitive response.

**Notes:** ChEI increases the levels of acetylcholine, which binds the  $\alpha$ -7 nAChR encoded by *CHRNA7*. The effect of polymorphisms in *ChAT* with AChEI therapy response is associated with the synthesis capacity of the remaining cholinergic neurons to favor the response to AChEIs. The polymorphism effect of *CHRNA7* on the therapeutic response may be through 1) modulation of the release of the neurotransmitters in presynaptic neurons, 2) memory enhancement by modulation of cholinergic neurotransmission, 3) neuroprotection through the  $\alpha$ -7 nAChR, 4) regulation enhancement of  $\alpha$ -7 nAChR by ChEI, and 5) positive allosteric modulation of galantamine-mediated at the  $\alpha$ -7 nAChR.

**Abbreviations:** ChAT, choline acetyltransferase; ChEI, cholinesterase inhibitor; SNP, single nucleotide polymorphism.

## CYP2D6

*CYP2D6* is responsible for the hydroxylation or demethylation of approximately 25% of all clinically important drugs, including antiarrhythmics, antipsychotics, antihistamines,

and antidepressants.<sup>48</sup> *CYP2D6* plays a role in the metabolism of central nervous system agents with narrow therapeutic indexes in which its treatment and accumulation can produce symptoms similar to those of the disease. Substrates and

inhibitors metabolized by CYP2D6 have basic and oxidized nitrogen molecules. They also tend to have flat lipophilic regions and functional groups that are capable of electrostatic interactions or forming hydrogen bonds.<sup>48</sup>

Pilotto et al<sup>16</sup> conducted a study during a 6-month follow-up period after DNP therapy in 115 patients (60% responders and 40% non-responders) and reported considerably higher frequencies of patients with G allele at rs1080985 in non-responders than in responders. Further analysis showed that patients with the G allele had a higher risk accompanied with poor response to DNP treatment. This study also suggested that the SNP at rs1080985 in *CYP2D6* may influence the clinical efficacy of DNP therapy in patients with mild-to-moderate AD; furthermore, *CYP2D6* genotype analysis may be useful in identifying subgroups of patients with AD who exhibit different clinical responses to DNP.<sup>16</sup> The results of this study were later confirmed via a follow-up study conducted by Albani et al in 2012.<sup>20</sup>

In 2013, Zhong et al<sup>19</sup> reported a higher frequency of the CYP2D6\*1/\*10 and CYP2D6\*10/\*10 genotypes in responders than in non-responders after 6 months of DNP therapy. CYP2D6\*1 is a wild-type form of CYP2D6, whereas CYP2D6\*10 is mutant allele and the last one exhibits reduction in catalytic activity thus retard metabolism. Furthermore, those with the genotypes CYP2D6\*1/\*10 and CYP2D6\*10/\*10 also had higher DNP plasma concentrations and better cognitive scores than those with the CYP2D6\*1/\*1 genotype. Thus, the authors suggested that patients with AD with mutant alleles (\*10) in *CYP2D6* may respond better to DNP than those with wild-type alleles (\*1).<sup>19</sup>

Sonali et al<sup>22</sup> assessed patients undergoing rivastigmine therapy and reported a considerable allele frequency of CYP2D6\*3 polymorphisms, where there is a frameshift mutation in the fifth exon and resulted an inactive enzyme. In addition, a study conducted by the same group in 2014 reported that the frequency of the CYP2D6\*3 alleles was considerably associated with the results of DNP monotherapy. The authors also suggested that the CYP2D6 polymorphism may play a role in regulating the plasma concentrations of AD drugs.<sup>18</sup> These results were supported by the findings of Lu et al<sup>17</sup> who attempted to determine the steady-state plasma concentrations of S-DNP in patients by combining their CYP2D6 genotypes and reported it to be useful to monitor the effectiveness of clinical DNP therapy in patients with AD.

Other studies have also reported that the CYP2D6 genotype analysis is useful for identifying subgroups of patients with AD who had different clinical responses to DNP therapy.<sup>21,23</sup> Conflicting results, however, were also reported.

Klimkowicz-Mrowiec et al<sup>15</sup> and Liu et al<sup>14</sup> reported that the CYP2D6 polymorphism did not influence the response to DNP therapy in either the Polish or Chinese population, respectively.

## Association of genetic polymorphisms with the outcome of non-pharmacological therapies of AD

The symptoms of AD, including cognitive impairment, function, and behavior, vary greatly among individuals and may depend on the patient's age at the onset of AD, location of the affected region of the brain that controls cognition, prevalence of behavioral symptoms, and speed of progression.<sup>49</sup> Genetic factors themselves are known to play an important role in this variability, because disease progression and functional restoration are highly dependent on the neuroplastic capacity of the remaining neural tissue.<sup>50</sup> Synaptosomal-associated protein of 25 kDa (SNAP-25) is one protein in addition to ApoE4 that plays a role in regulating the plasticity of neurons in neural tissues.<sup>51</sup> Both genes have been reported to affect the outcomes of non-pharmacological treatments of AD, including MST, which aims to prevent and slow cognitive impairment in patients.<sup>3</sup>

## SNAP-25

SNAP-25 is a vesicular protein composed of 206 amino acids encoded by a gene located on chromosome 20 and is a SNARE target molecule located at the terminal of presynaptic neurons.<sup>52</sup> Binding occurs in one of the SNARE domains of SNAP-25 with the syntaxin 1A plasma membrane and in another domain with a vesicle-associated membrane protein (VAMP). Interactions also occur between SNAP-25 and synaptotagmin, in which it is essential to promote the fusion of calcium-mediated membranes as well as control the fusion pore at the final stage of exocytosis, which is the release phase of neurotransmitters.<sup>53</sup> In addition to regulating the release of neurotransmitters through exocytosis, SNAP-25 also plays a role in modulating various types of voltage-gated calcium channels (VGCCs), including types N, P/Q, and L, in which the overexpression of SNAP-25 considerably inhibits the function of these channels and lowers the response to depolarization.<sup>54</sup>

Polymorphisms of SNAP-25 itself are known to be associated with the risk of developing AD. The intron with the alleles rs363050 (A) and rs363043 (T) and the haplotype rs363050/rs363043 A→T are more commonly present in individuals with AD and are associated with pathological values of the fMRI parameter. Guerini et al<sup>3</sup> reported that

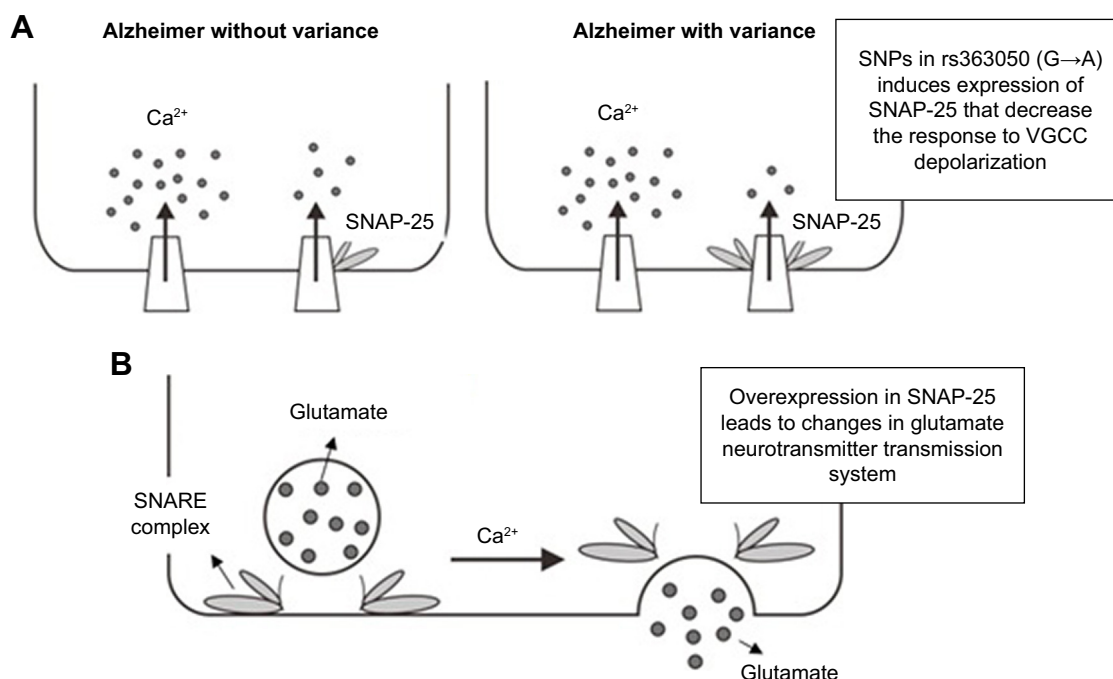
a polymorphism (SNP) in the SNAP-25-encoding gene not only increases the risk of AD but also affects the outcomes of MST therapy. MST therapy is a cognitive stimulation therapy related to recreational and psychomotor therapy that is not only capable of improving cognitive disorders but also serves to increase activity in the temporal region of the thalamus and right insular cortex.<sup>55</sup> Indeed, test results have shown that subjects carrying the rs363050 (G) and rs363039 (A) alleles are characterized as having a lower Neuropsychiatric Inventory (NPI) score, reflecting an increase in post-therapy behavioral function using the MST method.<sup>3</sup>

On the contrary, the type of allele carried, either homozygous or heterozygous, also influences the therapeutic outcomes. Patients with the rs363050 homozygous (GG) allele, who represent a minor population of the overall sample patient population, have been shown to exhibit better improvement in therapeutic outcomes than those with the homozygous (AA) allele, who represent the major population. Patients with heterozygous alleles (AG) also showed better therapeutic outcomes compared with homozygous patients. In rs363039, the patients who were homozygous for the minor allele (AA) exhibited improved behavioral function when compared with those who were homozygous for the major allele (GG). Guerini et al<sup>3</sup> also suggested a possible link between the genotype dose effects and NPI scores.

The effect of the polymorphisms (SNPs) of the rs363050 allele on the efficacy of therapy is also associated with the SNAP-25 gene transcription function, in which the allele rs363050(A) has a much higher expression of SNAP-25 than the allele rs363050(G) (Figure 3A).<sup>56</sup> The overexpression of SNAP-25 encountered in individuals with the rs363050(A) allele considerably inhibits the function of the VGCC channel and decreases the response to depolarization.<sup>54</sup> Calcium influx of nerve terminals is negatively regulated by complex formation between SNAP-25 and VGCC.<sup>57</sup> On the contrary, the overexpression of SNAP-25 in adulthood generates deficits in the memory formation process via the role of SNAP-25 in glutamate-dependent excitatory transmission (Figure 3B). The core of the fusion molecule (SNARE Complex) consists of synaptobrevin/VAMP2, syntaxin-1, and SNAP-25.<sup>57</sup> The expression of SNAP-25 in the adult dorsal hippocampus also leads to the deregulation of memory consolidation in that region of the brain.<sup>58</sup> Furthermore, the overexpression of SNAP-25 in hippocampal neuron cultures is also reportedly associated with synaptic transmission disorders.<sup>59</sup>

## ApoE

The ApoE protein is a glycoprotein composed of 299 amino acids with varying levels of post-translation stabilization via O-glycosylation of threonine residues.<sup>60</sup> Although neurons can produce ApoE under some conditions, even in smaller



**Figure 3** The role of SNAP-25 in presynapse.

**Note:** (A) Presynaptic effect of SNAP-25 on VGCCs and (B) the role of SNAP-25 in  $\text{Ca}^{2+}$ -mediated vesicle fusion.

**Abbreviations:** SNAP-25, synaptosomal-associated protein of 25 kDa; SNP, single nucleotide polymorphism; VGCCs, voltage-gated calcium channels.



amounts compared with that produced by astrocytes,<sup>61</sup> non-neuron astrocytes and some microglia are the main cell types that express ApoE in the brain.<sup>62,63</sup> ApoE4 is one of the isoforms resulting from polymorphisms found in *ApoE*, with the others being ApoE2 and ApoE3. The three isoforms of ApoE differ by only one or two amino acids at the residues 112 and 158; however, these differences are capable of altering the structure and function of ApoE.<sup>64</sup> All three ApoE isoforms promote the occurrence of A $\beta$ 42 fibrillation; however, the highest effect is shown by ApoE4.<sup>65</sup> On the contrary, ApoE4 increases A $\beta$ 40 aggregation more effectively than ApoE3.<sup>66</sup> However, some studies have reported that A $\beta$ 40 and A $\beta$ 42 have opposite effects on the aggregation of A $\beta$  in vivo.<sup>67</sup> The aggregation of A $\beta$ 40 is known to be more common in patients with AD and exhibits a dose-dependent model with the ApoE4 gene.

Previous studies have shown that patients with AD who carry positive ApoE4 alleles (ApoE4+) exhibit more rapid cognitive impairment; thus, the status of ApoE4 in recent studies may serve to predict the outcomes of cognitive stimulation in visuospatial memory.<sup>68</sup> Furthermore, Guerini

et al<sup>3</sup> also reported that patients with negative ApoE4 alleles (ApoE4-) responded better to MST therapy than those with positive alleles (ApoE4+). The effect of the gene dose on the MMSE score also indicated that compared with patients with the ApoE4+/E4+ allele, those with the ApoE4+/E4- allele exhibited better response to MST therapy, although not better than patients with the E4-/E4- allele did.<sup>3</sup> The low response of MST therapy in patients with the E4+/E4+ allele was determined by decreased ApoE lipoprotein function in stimulating synaptic development,<sup>69</sup> lipid debris clearance,<sup>70</sup> and promotion of growth in the fibers of cellular granules.<sup>71</sup>

## Prevalence of genetic polymorphisms in genes associated with the outcomes of treatment of AD

Interestingly, the phenomenon of genetic polymorphisms that occur in various genes discussed in the review is not rare. As presented in Table 2, various studies have reported on the genotype distribution of these genes.<sup>10,11,14,16,19,25–27,29,72–77</sup> Therefore, the consideration of genetic polymorphisms as part of a therapeutic strategy cannot be underestimated and

**Table 2** Illustration of occurrence of polymorphism in healthy individuals

Area (ethnicity)	Number of health subjects included in the study	Genotype (%)				References
<b>CHAT (rs3810950)</b>		<b>G/G</b>	<b>G/A</b>	<b>A/A</b>		
China (Asian)	271	66.05	30.62	3.32		71
Austria (Caucasian)	456	58.77	35.96	5.26		72
Denmark (Caucasian)	1,308	4.20	34.78	61		73
Korea (Asia)	1,386	73.80	24.67	1.51		74
<b>CHAT (2177370)</b>		<b>C/C</b>	<b>T/C</b>	<b>T/T</b>		
Korea (Asian)	55	80	12.72	7.27		10
<b>CHAT (rs3793790)</b>		<b>A/A</b>	<b>G/A</b>	<b>G/G</b>		
China (Asian)	405	70.12	26.67	3.20		75
Korea (Asian)	55	76.36	18.18	5.45		10
<b>CHRNA7</b>		<b>CC</b>	<b>CG</b>	<b>GG</b>		
Taiwan (Asian)	432	80.56	19.44	–		76
<b>CYP2D6</b>		<b>GG</b>				
Italy	127	36.22				15
<b>ABCA1 (rs2230806)</b>		<b>GG</b>	<b>GA</b>	<b>AA</b>		
China (Asian)	88	28.40	47.72	23.86		24
<b>ABCA1 (rs2230808)</b>		<b>GG</b>	<b>GA</b>	<b>AA</b>		
China (Asian)	88	39.77	53.40	6.81		24
<b>ApoE</b>		<b>E3+</b>	<b>E3–</b>	<b>E4+</b>	<b>E4–</b>	
China (Asian)	88	89.77	10.22	–	–	24
China (Asian)	85	89.41	10.58	38.8	61.1	25
China (Asian)	206	–	–	48.05	51.94	13
Brazil	97	38.14	5.15	22.68	20.61	26
Brazil	177	–	–	50.28	42.93	9
China (Asian)	110	–	–	23.63	63.63	18
<b>ESR1 (rs2234693 and rs9340799)</b>		<b>PX+</b>	<b>PX–</b>			
Italy (Caucasian)	184	36.41	27.17			29

**Note:** This shows that polymorphism is a very probable problem in normal humans though.

is believed to have a considerable impact. On the contrary, the genotype distribution that occurs in several genes appears to depend on certain geographies and races.

## Conclusion and future prospects

Polymorphisms occurring in patients with AD, either in the form of SNPs or direct changes to one or more amino acids in a protein, have been shown to be capable of causing differences in the therapeutic responses in individuals using the same drug. Thus, genetic polymorphisms should be considered to achieve effective and efficient treatment outcomes both in terms of prognosis and cost. A therapeutic guideline based on genetic polymorphisms has actually been established,<sup>78–82</sup> therefore, a therapeutic guideline that considers genetic polymorphisms for patients with AD is required to determine effective and efficient therapies for AD.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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