A bioinformatics driven map of pharmacogenomic variation and genetic variants in Alzheimer's disease therapy

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia globally. First-line AD therapy using cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine shows interindividual variation in effectiveness, indicating the involvement of genetic factors. This study aims to identify genetic variants that influence response to AD therapy through bioinformatics and pharmacogenomic approaches. Data were retrieved from PharmGKB and analyzed based on therapy efficacy, allele frequencies across populations (1000 Genomes), and gene expression (GTEx). Four SNP variants were found to be relevant: rs6494223 (CHRNA7), rs3793790 and rs2177370 (CHAT), and rs1803274 (BCHE). Specific genotypes such as CC (rs6494223), GG and AA (CHAT), and TT (rs1803274) showed better therapy response. Expression analysis showed that the CHAT gene is highly expressed in the brain, reinforcing its pharmacogenetic relevance. In contrast, CHRNA7 and BCHE showed high expression in non-neuronal tissues, yet still play a systemic role in acetylcholine metabolism. Variations in allele frequencies between populations were also identified, underscoring the importance of population-based therapeutic approaches. These results support the importance of simple genetic screening in the development of precision therapies for Alzheimer's. This study demonstrates that integrating pharmacogenomic and gene expression data can provide a better understanding of the heterogeneity of AD therapy response and open the possibility of personalized treatment based on the patient's genetic profile.

Keywords: *Alzheimer's disease; SNP; pharmacogenomics; CHRNA7; CHAT; BCHE.*
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Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder and accounts for over 60% of dementia cases worldwide. It is characterized by the accumulation of β-amyloid plaques and neurofibrillary tangles in the brain, leading to synaptic damage and gradual neuronal death [1, 2]. The main clinical symptoms of AD include memory loss, cognitive impairment, disorientation, and impaired executive function, ultimately significantly impacting patients' quality of life [3]. With increasing global life expectancy, the prevalence of AD is expected to continue to rise, making it a major challenge facing 21st-century healthcare systems. In an effort to control symptoms and slow disease progression, cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine have become first-line pharmacological therapies for AD [4, 5]. These drugs work by increasing the concentration of acetylcholine in the synaptic cleft, which is believed to decrease due to damage to cholinergic neurons. Although the widespread use of cholinesterase inhibitors has demonstrated beneficial clinical effects in some patients, the response to these therapies is highly heterogeneous [6]. Some patients experience improvements in cognitive function, while others show no significant changes or even experience side effects. This phenomenon indicates deeper biological determinants, one of which is genetic factors [6].

As the fields of pharmacogenomics and bioinformatics have advanced, a number of genetic variants have been identified as being associated with response to AD therapy [7]. Genes such as *CHRNA7 (cholinergic receptor nicotinic alpha 7 subunit)*, *CHAT (choline O-acetyltransferase)*, and *BCHE (butyrylcholinesterase)* plays a crucial role in the cholinergic neurotransmission pathway, which is the primary target of cholinesterase inhibitors [8]. Single nucleotide polymorphisms (SNPs) in these genes are thought to influence drug pharmacodynamics and pharmacokinetics, thus impacting therapeutic efficacy [9]. However, existing research findings remain inconsistent across studies, and a comprehensive understanding of gene-drug interactions in Alzheimer's patients remains limited. This creates an urgent need for the integration of genetic and pharmacological data to optimize individualized therapies [10].

This study aims to conduct an integrative bioinformatics and pharmacogenomics analysis of genetic variants associated with cholinesterase inhibitor efficacy in AD patients [7]. Utilizing evidence-based data from PharmGKB and a bioinformatics approach to allele frequencies, genomic locations, and clinical relevance, this study seeks to identify genetic profiles that can predict response to therapy [10, 11]. The results of this study are expected to contribute to the development of precision medicine strategies in neurology, particularly in personalizing Alzheimer's treatment based on patient genetic characteristics. A deeper understanding of the relationship between genetics and drug response will also broaden insights into disease mechanisms and open up opportunities for more effective and safe therapies.

Material and methods. ***Research Design and Strategy.*** This exploratory descriptive study, using a bioinformatics approach, aimed to evaluate the influence of genetic variants on the response to cholinesterase inhibitor therapy in Alzheimer's disease patients [12]. The analysis was based on secondary data using validated open sources, focusing on two main approaches: population analysis (allele frequency) and genetic expression.

Data Sources and Variant Selection. Genetic variant data were obtained from the Pharmacogenomics Knowledgebase (PharmGKB) using the keywords "Alzheimer's disease", "donepezil", "galantamine", and "rivastigmine". Variants included in the study were selected based on the following criteria:

1. Associated with effectiveness or response to Alzheimer's therapy.
2. Having information on SNP ID, gene name, relevant drug, and reported phenotype.
3. Accompanied by a minimum level of evidence of Level 3 from PharmGKB.

Population Frequency Analysis. Population Frequency Analysis An allele frequency analysis was performed from the 1000 Genomes Project (Phase1) database, which includes major world populations: Africa (AFR), America (AMR), Asia (ASN), and Europe (EUR). The frequency data were used to identify potential differences in therapy response based on the genetic background of the populations [13].

Genetic Expression Analysis. Gene expression data were obtained through searches of relevant literature and public gene expression databases, such as GTEx (Genotype-Tissue Expression) or expression references available at PharmGKB. The focus of the analysis was to determine whether genes containing selected variants (such as *CHRNA7, CHAT, BCHE*) have significant expression in brain tissues, particularly the cerebral cortex and hippocampus, relevant to Alzheimer's pathophysiology [14].

Data Presentation and Interpretation. Data are presented in descriptive tables that include information on SNPs, genes, associated drugs, phenotypes, allele frequencies in the population, and gene expression. Interpretation is narrative, emphasizing the biological and clinical relevance of each variant to the potential therapeutic response of Alzheimer's patients.

Table 1. *List of genetic variants (SNPs) associated with cholinesterase inhibitor therapy response in Alzheimer's disease patients based on data from PharmGKB*

Variant	Gene	Drugs	Phenotype Categories	Phenotype	Pediatric	Level	PharmGKB ID
rs6494223	*CHRNA7*	donepezil; galantamine; rivastigmine	Efficacy	Alzheimer's disease	FALSE	3	1444686893
rs3793790	*CHAT*	donepezil; galantamine; rivastigmine	Efficacy	Alzheimer's disease	FALSE	3	1447814424
rs2177370	*CHAT*	donepezil	Efficacy	Alzheimer's disease	FALSE	3	1447943640
rs1803274	*BCHE*	donepezil	Efficacy	Alzheimer's disease; Cognitive disorders	FALSE	3	1449564963

Results. Bioinformatics analysis of data from PharmGKB identified four genetic variants (SNPs) relevant to the effectiveness of cholinesterase inhibitor therapy in Alzheimer's disease patients. All variants were classified as efficacy phenotypes and had Level of Evidence 3, indicating support from the scientific literature but not yet reaching a high level of clinical validation. The rs6494223 variant is located in the *CHRNA7* gene, which plays a key role in the cholinergic neurotransmission pathway in the brain. This SNP is known to be associated with response to three types of cholinesterase inhibitors donepezil, galantamine, and rivastigmine [15]. Although there is no strong correlation between studies, the data suggest that certain genotypes, such as CC or CT, may be associated with a better response than TT. Furthermore, two important variants were identified in the *CHAT* gene: rs3793790 and rs2177370 [16]. The rs3793790 variant is associated with response to donepezil, galantamine, and rivastigmine, while rs2177370 is associated only with donepezil. Early studies suggest that individuals with the GG genotype for rs3793790 or AA for rs2177370 may exhibit a better response to therapy compared to those with the other genotypes. A fourth variant, rs1803274, is found in the *BCHE* gene, which affects acetylcholine metabolism in the central nervous system. This SNP has been associated with the effectiveness of donepezil therapy, as well as with cognitive impairment associated with Alzheimer's. The TT genotype for this variant has been reported to have a better response to therapy than CC, which tends to indicate resistance to treatment [17]. The four variants identified in this study are all non-pediatric (pediatric category: FALSE), confirming the relevance of this pharmacogenetic study to the adult population. These findings provide an initial insight into the genetic contribution to variation in response to cholinesterase inhibitor therapy and open the possibility of developing more personalized therapies for Alzheimer's patients based on their genetic profile.

Variant Analysis of rs6494223 in Genes CHRNA7. Variants rs6494223 is an SNP located in the gene *CHRNA7* (cholinergic receptor nicotinic alpha 7 subunit), which plays a key role in the cholinergic neurotransmission pathway in the brain [18]. This gene encodes the alpha-7 nicotinic acetylcholine receptor subunit, which is known to be involved in modulating neurotransmitter release, synaptic plasticity, and cognitive function processes highly relevant in the pathophysiology of Alzheimer's disease. According to PharmGKB data, the allele CC on rs6494223 is associated with better response to donepezil therapy, indicated by slower decline in cognitive decline compared to genotype CT and TT. However, the literature shows inconsistencies: several other studies have reported conflicting results or even found no significant association between genotype and response to donepezil. This suggests that in addition to genetic factors, other clinical and environmental aspects may influence the effectiveness of therapy. Genotype CT showed a moderate response to donepezil therapy, with better clinical outcomes compared to TT, but worse than CC. Meanwhile, patients with genotype TT tend to experience the low-

est response to therapy, with a more rapid progression of cognitive decline. However, as with other genotypes, these data still require further study because existing studies have produced inconsistent results. Overall, the presence of the SNP rs6494223 in *CHRNA7* showed potential as a predictive biomarker in Alzheimer's therapy, particularly for donepezil. However, clinical interpretation should be approached with caution given the variability of findings across populations and the need for further validation studies with prospective designs and large sample sizes [19].

Variant Analysis of rs3793790 in Genes CHAT. Variants rs3793790 is an SNP in a gene *CHAT* (choline O-acetyltransferase), a key enzyme involved in acetylcholine biosynthesis in the central nervous system. Changes in the expression or function of this gene may affect the effectiveness of cholinesterase inhibitor therapy, which works by increasing acetylcholine levels in the synaptic cleft [20]. According to data from PharmGKB, individuals with the genotype GG show best therapeutic response to donepezil, galantamine, and rivastigmine compared with genotype AA And AG. The more optimal therapeutic effect in the GG genotype is likely related to increased efficiency of the cholinergic pathway through activity Undisturbed *CHAT*. In contrast, the genotype AA associated with the lowest therapeutic response, which can potentially lead to suboptimal clinical outcomes. Patients with the genotype AG showed an intermediate response, better than AA but not as good as GG. However, as with other variants, therapeutic response can also be influenced by non-genetic factors, such as age, comorbid conditions, and drug interactions. These findings support the potential *CHAT-rs3793790* as a candidate pharmacogenetic biomarker in personalized Alzheimer's therapy. Identification of patient genotypes for this SNP may aid in optimizing cholinesterase inhibitor drug selection and dosage [21].

Variant Analysis of rs2177370 in Genes CHAT. Variants rs2177370 also found in genes *CHAT*, which is a key enzyme in the synthesis of the important neurotransmitter acetylcholine, is drastically reduced in patients with Alzheimer's disease [22]. This SNP is specifically associated with response to donepezil, one of the first-line drugs in cholinesterase inhibitor therapy. The analysis results showed that patients with the genotype AA own the best response to donepezil therapy, compared with genotype AG and GG. This increased effectiveness is likely due to higher efficiency of acetylcholine production through enzyme expression or activity. *CHAT* optimal. Patients with genotype AG also showed an increased response compared to GG, although not as large as that observed in genotype AA. On the other hand, the genotype GG associated with the lowest therapeutic response, which may be associated with more rapid symptom progression or lack of clinical improvement. This variation indicates that rs2177370 has the

Table 2. *The relationship between the rs6494223 genotype in the CHRNA7 gene and the response to donepezil therapy in Alzheimer's disease patients*

Variant	Allele	Phenotype	PharmGKB ID
rs6494223	CC	Patients with the CC genotype and Alzheimer's disease may have an improved response to donepezil (slower cognitive decline) as compared to patients with the CT and TT genotypes, although this is contradicted by another study which showed the opposite, and another which showed no association between genotype and response to donepezil in patients with Alzheimer's disease. Other clinical and genetic factors may also influence response to donepezil in patients with Alzheimer's disease	1444686893
	CT	Patients with the CT genotype and Alzheimer's disease may have an improved response to donepezil (slower cognitive decline) as compared to patients with the TT genotype, and a worse response as compared to the CC genotype. This is contradicted by another study which showed the opposite, and another which showed no association between genotype and response to donepezil in patients with Alzheimer's disease. Other clinical and genetic factors may also influence response to donepezil in patients with alzheimer's Disease	
	TT	Patients with the TT genotype and and Alzheimer's disease may have a worse response to donepezil (faster cognitive decline) as compared to patients with the CT and CC genotypes, although this is contradicted by another study which showed the opposite, and another which showed no association between genotype and response to donepezil in patients with Alzheimer's disease. Other clinical and genetic factors may also influence response to donepezil in patients with Alzheimer's disease	

Table 3. *The relationship between the rs3793790 genotype in the CHAT gene and the response to donepezil, galantamine, and rivastigmine therapy in Alzheimer's disease patients*

Variant	Allele	Phenotype	PharmGKB ID
rs3793790	AA	Patients with the AA genotype and Alzheimer's disease may have a decreased response to donepezil, galantamine, or rivastigmine as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patient's response to donepezil, galantamine, and rivastigmine	1447814424
	AG	Patients with the AG genotype and Alzheimer's disease may have a decreased response to donepezil, galantamine, or rivastigmine as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's response to donepezil, galantamine, and rivastigmine	
	GG	Patients with the GG genotype and Alzheimer's disease may have increased response to donepezil, galantamine, or rivastigmine as compared to patients with the AA or AG genotype. Other genetic and clinical factors may also influence a patient's response to donepezil, galantamine, and rivastigmine	

potential to be an important pharmacogenetic marker in predicting donepezil effectiveness. However, it should be noted that drug metabolism and effectiveness are also influenced by other genetic factors beyond *CHAT*, as well as by clinical and environmental factors [22].

Variant Analysis of rs1803274 in Genes BCHE. Variants rs1803274 is one of the important SNPs in the gene *BCHE* namely an enzyme that plays a role in the degradation of acetylcholine and works as an alternative metabolic pathway when acetylcholinesterase (AChE) activity is disrupted [23]. Changes in function *BCHE* can affect the availability of acetylcholine in the synaptic cleft and the effectiveness of therapy with cholinesterase inhibitors, particularly donepezil and rivastigmine. Data from PharmGKB show that patients with the genotype TT own best therapeutic response to cholinesterase inhibitors, with the possibility of more significant improvement in cognitive symptoms compared to genotype CT and CC. This higher efficacy may be due to lower BCHE enzyme activity in the TT genotype, thus prolonging the cholinergic effect of the drug. In contrast, the TT genotype CC associated with the lowest therapeutic response, thought to be due to higher BCHE enzymatic activity, which accelerates acetylcholine degradation and reduces drug effectiveness. Genotype CT showed variable responses: some patients performed better than CC but not as well as TT, indicating a partial heterozygote effect. These findings strengthen the role of rs1803274 as a potential pharmacogenetic biomarker in tailoring Alzheimer's therapy. However, as with other variants, clinical response is also strongly influenced by external factors and individual patient characteristics, so interpretation of the results must be carried out comprehensively [24].

Population Frequency Analysis and Functional Annotation of Variants. Allele frequency analysis based on data 1000 Genomes Project Phase 1 indicates variations in the distribution of alleles for each genetic variant across populations [25, 26]. These differences are important to consider because they may influence the potential for different therapeutic responses in certain ethnic groups. rs6494223 on genes *CHRNA7* have allele frequencies T relatively high in Asian (ASN=0.59) and American (AMR=0.43) populations, but lower in European (EUR=0.38) populations. This variant is intronic and showed no evolutionary constraint based on GERP and SiPhy scores, indicating that this position is not very evolutionarily conservative. Two other variants, rs3793790 And rs2177370, both located in the gene *CHAT* and also has a nature intronic without evidence of evolutionary constraint. However, both show high allele frequencies in Asian (ASN=0.82 and 0.79) and American (AMR=0.73 and 0.53) populations, which may have implications for differences in treatment response across ethnicities [14]. In contrast, the variant rs1803274 on genes *BCHE* is the only variant that is missense and show positive evolutionary constraints, both based on scores GERP and SiPhy. This suggests that mutations at this position are more likely to have a significant biological impact. Allele frequency T in this variant was quite low across all populations (between 0.13P0.19), which may indicate that the risk genotype is relatively rare but has the potential to strongly influence the response to cholinesterase inhibitors [25].

Table 4. *The relationship between the rs2177370 genotype in the CHAT gene and the response to donepezil therapy in Alzheimer's disease patients*

Variant	Allele	Phenotype	PharmGKB ID
rs2177370	AA	Patients with the AA genotype and Alzheimer's disease may have an increased response to donepezil compared to patients with the AG or GG genotype. Other genetic and clinical factors may also impact the metabolism of donepezil	1447943640
	AG	Patients with the AG genotype and Alzheimer's disease may have increased response to donepezil compared to patients with the GG genotype. Other genetic and clinical factors may also impact the metabolism of donepezil	
	GG	Patients with the GG genotype and Alzheimer's disease may have a decreased response to donepezil compared to patients with the AA or AG genotype. Other genetic and clinical factors may also impact the metabolism of donepezil	

Table 5. *The relationship between the rs1803274 genotype in the BCHE gene and the response to cholinesterase inhibitor therapy in Alzheimer's disease patients*

Variant	Allele	Phenotype	PharmGKB ID
rs1803274	CC	Patients with the CC genotype and Alzheimer's disease may be less likely to respond to treatment with cholinesterase inhibitors as compared to patients with the TT genotype. Other genetic and clinical factors may also influence response to cholinesterase inhibitors	1449564963
	CT	Patients with the CT genotype and Alzheimer's disease may be less likely to respond to treatment with cholinesterase inhibitors as compared to patients with the TT genotype, or more likely to respond as compared to patients with the CC genotype. Other genetic and clinical factors may also influence response to cholinesterase inhibitors	
	TT	Patients with the TT genotype and Alzheimer's disease may be more likely to respond to treatment with cholinesterase inhibitors as compared to patients with the CC genotype. Other genetic and clinical factors may also influence response to cholinesterase inhibitors	

Table 6. *Genomic characteristics, allele frequencies across populations, and functional annotation of variants associated with Alzheimer's disease therapy*

Variant	Gene	chr	post (hg38)	Reference	Alternate	1000 Genomes Phase 1 Frequencies				Sequence constraint		dbSNP functional annotation
						AFR	AMR	ASN	EUR	by GERP	by SiPhy	
rs6494223	*CHRNA7*	chr15	32104256	C	T	0.44	0.43	0.59	0.38	No	No	intronic
rs3793790	*CHAT*	chr10	49632690	G	A	0.58	0.73	0.82	0.71	No	No	intronic
rs2177370	*CHAT*	chr10	49630828	A	G	0.47	0.53	0.79	0.36	No	No	intronic
rs1803274	*BCHE*	chr3	165773492	C	T	0.14	0.13	0.16	0.19	Yes	Yes	missense

Genetic Expression Analysis of CHRNA7, CHAT, and BCHE. As part of the bioinformatics approach, genetic expression analysis was performed to evaluate whether genes containing associated SNP variants have significant expression in brain tissues, particularly in tissues relevant to the pathophysiology of Alzheimer's disease such as the cerebral cortex, hippocampus, and basal forebrain. Fig. 1 shows the gene expression profile. *CHRNA7* in various body tissues based on RNA-seq data. Contrary to initial expectations that the highest expression would appear in brain tissue, the analysis results actually showed that *CHRNA7* is most highly expressed in testicles And thyroid gland. Although this gene is functionally known as a nicotinic acetylcholine receptor that plays a role in synaptic transmission and cognitive modulation, its expression in brain tissues such as the cortex and hippocampus is relatively low compared to these peripheral tissues [27]. This finding suggests a functional role *CHRNA7* in the central nervous system is likely not fully reflected by total expression levels, and may be influenced by local factors such as specific cell types or post-transcriptional regulation [28]. Therefore, pharmacogenetic interpretation of the rs6494223 variant remains relevant despite the expression *CHRNA7* more dominant in non-neural networks.

Fig. 2 shows gene expression *CHAT*, which is key in acetylcholine biosynthesis through the activity of the enzyme choline acetyltransferase. Expression *CHAT* it is also highly expressed in brain tissue, including subcortical areas rich in cholinergic neurons. This variation in expression reinforces the importance of the rs3793790 and rs2177370 variants in influencing cholinesterase inhibitor efficacy, especially since high gene expression in target tissues may increase its pharmacogenetic relevance [29]. Fig. 3 presents the gene expression profile. *BCHE*, which shows a wide distribution of expression in various body tissues. The results of the analysis showed that the highest expression *BCHE* detected on the network fallopian tube, esophagus, and colon, not in brain tissue as previously assumed. Although the expression *BCHE* in the central nervous system is relatively low, this gene still has biological relevance to acetylcholine metabolism, because it can function as an alternative pathway of the enzyme acetylcholinesterase (AChE) [30]. High expression in peripheral tissues suggests that its role *BCHE* may be more significant in the systemic regulation of acetylcholine than at the local brain level. Therefore, the rs1803274 variant in this gene, although not brain-specific, still has the potential to modulate response to cholinesterase

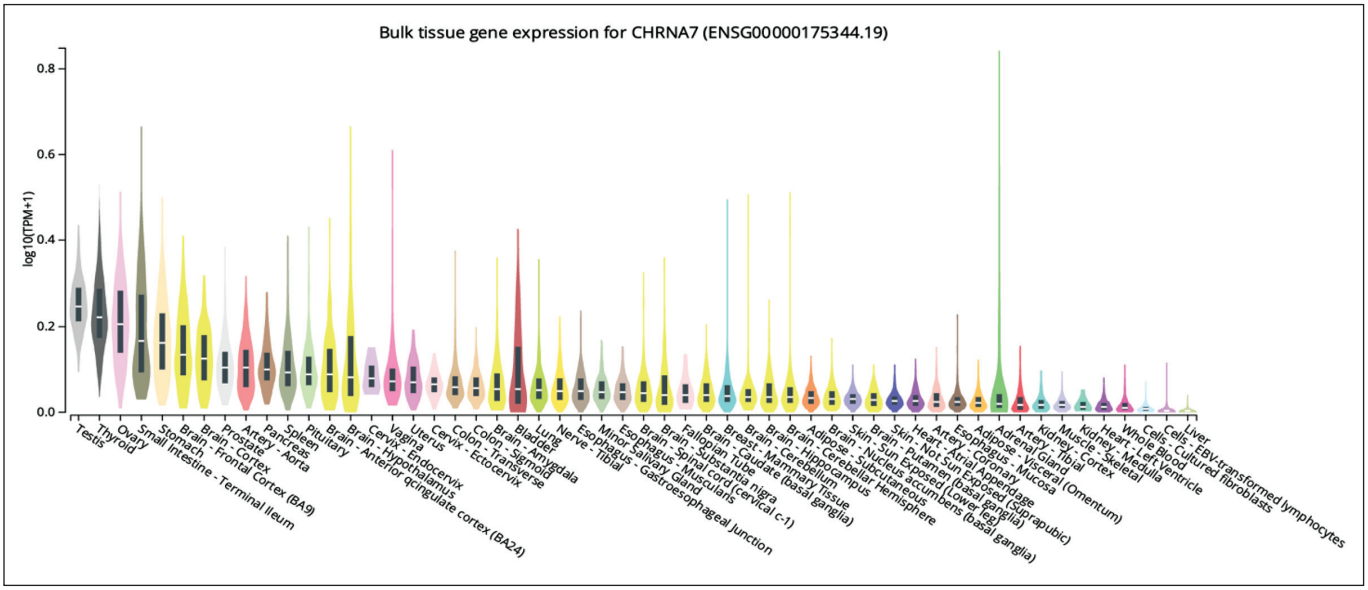

Fig. 1. *Gene expression profile CHRNA7 in various human body tissues*[1]

[1]Цветные рисунки к этой статье представлены на сайте журнала: nnp.ima-press.net

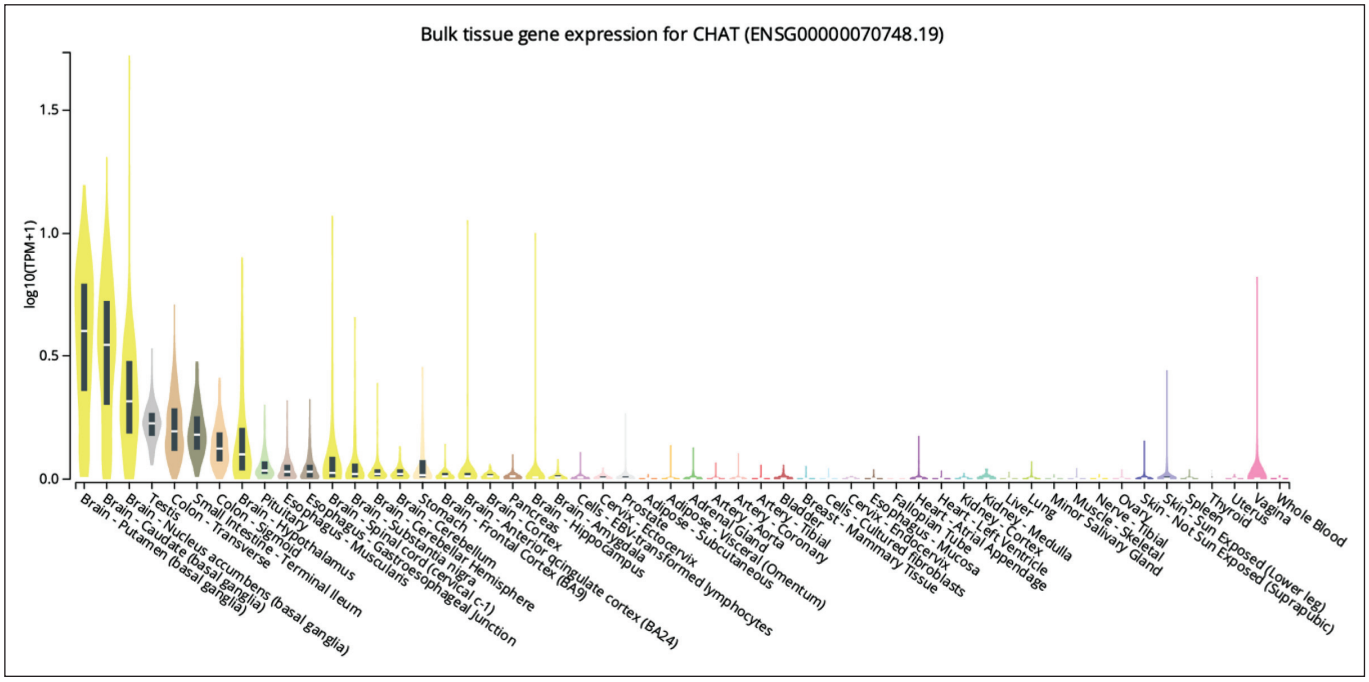

Fig. 2. *Gene expression profile CHAT in various human body tissues*

inhibitors systemically, particularly related to drug metabolism and bioavailability. These findings support the importance of considering non-neuronal tissue expression in the pharmacogenetic interpretation of Alzheimer's treatment [31].

Discussion. This study revealed that four genetic variants rs6494223 *(CHRNA7)*, rs3793790 and rs2177370 *(CHAT)*, and rs1803274 *(BCHE)* have the potential to modulate the response to cholinesterase inhibitor therapy in Alzheimer's disease patients. These three genes have a crucial role in the cholinergic pathway, which is the primary target of AD treatment, namely by increasing acetylcholine levels in the synapse. Genetic variations in these genes can impact pharmacological efficacy through complex mechanisms, including differences in enzymatic activity, receptor number, and mRNA stability. The analysis results showed that certain alleles of the SNP rs6494223 *(CHRNA7)*, especially the genotype CC correlated with a better clinical response to donepezil. This finding is consistent with the hypothesis that this variant may increase the efficiency of the α7 nicotinic receptor, which plays a key role in regulating cognitive function [8]. However, expression data suggest that *CHRNA7* is highly

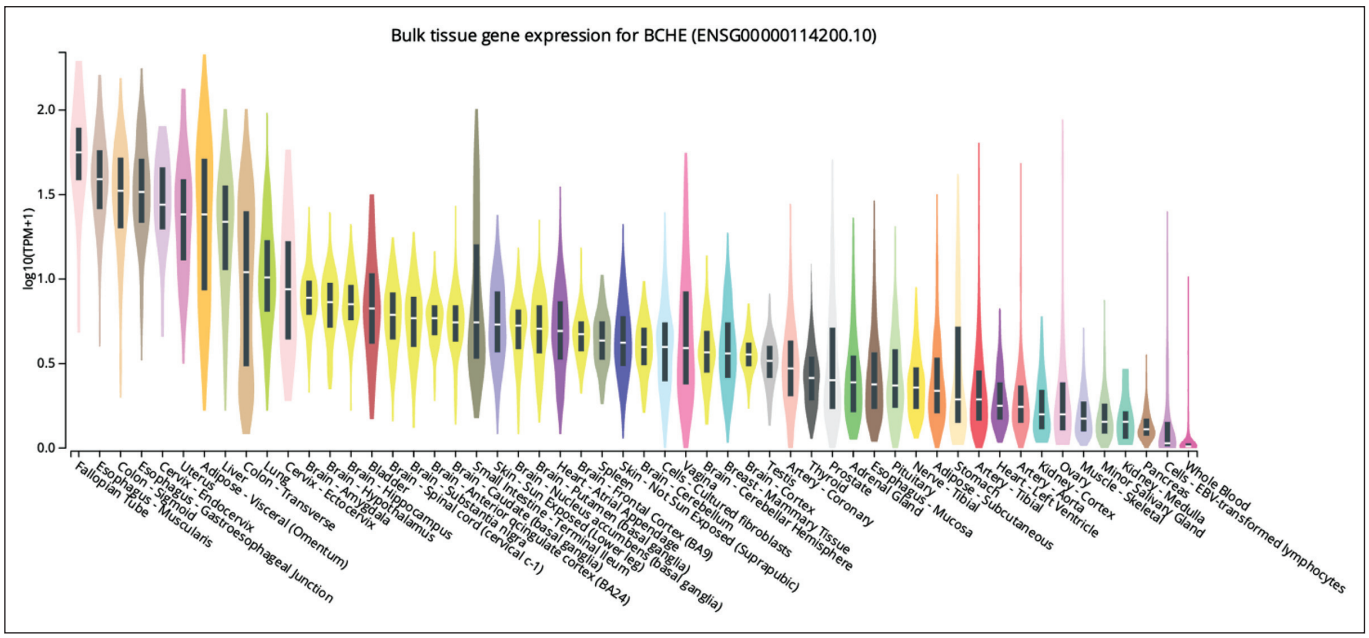

Fig. 3. *Gene expression profile BCHE in various human body tissues*

expressed in non-neuronal tissues such as the testis and thyroid, rather than the cortex or hippocampus [32]. This raises the possibility that its effects on the brain may be mediated through systemic or tissue-specific regulatory mechanisms not represented in bulk RNA-seq analysis. Therefore, further studies using single-cell transcriptomics or proteomics approaches are needed to more precisely evaluate its functional contribution [32].

Two other variants on *CHAT*, namely rs3793790 and rs2177370, each indicating that the genotype GG And AA is associated with an increased response to donepezil, galantamine, or rivastigmine. This is consistent with the role of *CHAT* in the synthesis of acetylcholine a major pathway in cholinergic function. Interestingly, the expression *CHAT* was found to be highly expressed in brain tissue, particularly in areas rich in cholinergic neurons, strengthening the biological validity of these pharmacogenetic findings [33]. From a precision medicine perspective, patients with a low-risk genotype may be optimal candidates for cholinesterase inhibitor therapy, while those with a high-risk genotype may require alternative therapies or dose adjustments. Meanwhile, the rs1803274 variant in the *BCHE* highlighting the potential interactions between drug pharmacodynamics and pharmacokinetics. Genotype TT showed a higher therapeutic response, most likely due to decreased *BCHE* activity, thereby reducing acetylcholine degradation. Although the expression *BCHE* higher in peripheral tissues such as the fallopian tube, esophagus, and colon, its role as a systemic metabolic enzyme remains relevant because it can indirectly influence circulating acetylcholine. Thus, although not a brain-specific gene, *BCHE* remains important in the context of the overall metabolism of AD therapy [33].

Differences in allele frequencies between populations, such as the high prevalence of minor alleles for rs3793790 and rs2177370 in Asian populations, suggest that response to Alzheimer's therapy may be significantly influenced by ethnic genetic background [34]. This is important considering that most clinical trials are conducted in Caucasian (EUR) populations, which have a different allele distribution than Southeast Asian populations. Therefore, a local, population-based pharmacogenetic approach needs to be developed to avoid therapeutic bias and improve treatment efficacy at the regional level. However, this study has several limitations. First, all data were sourced from secondary databases and have not been functionally validated at the experimental or clinical level. Second, interactions between SNPs and non-genetic factors such as age, gender, comorbidity status, or drug interactions were not analyzed in this study [7]. Third, the gene expression analysis was based solely on bulk-tissue RNA-seq, thus not capturing heterogeneity across brain cell types. Therefore, further validation through prospective studies using multi-omics and individual-level data approaches is urgently needed. Overall, these findings highlight the importance of integrating bioinformatics and pharmacogenomic approaches in understanding the heterogeneity of Alzheimer's therapy response. Identification of biologically and clinically relevant candidate SNPs could underpin strategies of precision medicine – a more efficient, safer, and genetically profiled approach. Applying simple genetic screening to these variants could be a valuable tool in clinical decision-making for optimizing future Alzheimer's therapies.

Conclusion. This study shows that the genetic variants rs6494223 *(CHRNA7)*, rs3793790 and rs2177370 *(CHAT)*, and rs1803274 *(BCHE)* are associated with the response to cholinesterase inhibitor therapy in Alzheimer's disease patients. Certain genotypes such as CC, GG, AA, and TT were found to be associated with increased therapy efficacy. Allele frequency analysis showed variations in distribution between populations, while genetic expression showed differences in expression levels between clinically and biologically relevant tissues. Overall, these findings support the potential integration of genetic and bioinformatics data in the development of individualized therapeutic approaches in Alzheimer's disease.

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