Original Article

In silico Evaluation of Single-Nucleotide Polymorphisms in *CHRNA7* and *GRIN1* Genes Related to Alzheimer's Disease

Arash Rezaeirad[1], Ömer Faruk Karasakal[2], Ebru Özkan Oktay[3], Mesut Karahan[4]

[1]Molecular Biology Master's Degree, Institute of Science, Üsküdar University, [2]Medical Laboratory Techniques, [3]Laboratory Technology, [4]Biomedical Device Technology, Vocational School of Health Services, Üsküdar University, Istanbul, Türkiye

Abstract

Aim: The purpose of this study is to predict the possible impact of missense single-nucleotide polymorphisms (SNPs) in *CHRNA7* and *GRIN1* genes associated with AD on protein structure, function, and stabilization and to analyze gene–gene interactions via *in silico* methods. **Materials and Methods:** SIFT, PolyPhen-2, SNPsandGO, PROVEAN, SNAP2, PhD-SNP, and Meta-SNP were used to estimate high-risk SNPs. The impact of SNPs on protein stabilization was evaluated with I-Mutant 3.0 and MUpro software. Three-dimensional models of amino acid changes were determined with the Project HOPE software. Furthermore, the gene–gene interactions were analyzed via GeneMANIA. **Results:** According to the results of 603 missense SNPs in the *CHRNA7* gene, rs142728508 (Y233C), rs12899798 (W77G), rs138222088 (R227H), rs140316734 (R227C), rs199633275 (P322R), rs199819119 (L29F), rs200147286 (Q49P), rs200908085 (Y115C), rs201094833 (Q61R), rs201473594 (N69D), rs201210785 (E195K), and rs368352998 (S48W) polymorphisms were predicted as deleterious. Similarly, rs193920837 (P117 L), rs3181457 (I540M), and rs201764643 (R217P) polymorphisms in the *GRIN1* were estimated as deleterious. **Conclusion:** It is thought that the results of this study will provide useful information to guide future diagnostic and experimental strategies for AD.

Keywords: *Alzheimer's disease, CHRNA7, GRIN1, in silico, single-nucleotide polymorphism*

Introduction

Alzheimer's disease (AD) is known as a neurodegenerative disease (ND) that causes neurochemical deficiency in some parts of the brain, accumulation of amyloid-β, decreased cholinergic neurons, and formation of neurofibrillary tangles. Furthermore, pathologically, it causes amyloid-β accumulation outside the cell, while accumulation of tau proteins is observed inside the cell.[1-3] Lately, a range of research has reported that the amyloid-β peptide binds to the alpha 7 nicotinic acetylcholine receptor (α7nAChR) on neuronal cell surfaces, which results in the precipitate of amyloid plaque formation in AD.[4,5] *CHRNA7* gene encodes α7nAChR which are ligand-gated ion channels and substantially expressed in neuronal tissues.[6,7] Furthermore, the N-methyl-D-aspartate (NMDA) receptor is a subtype of glutamate receptors and has been reported to be closely related to neuronal activities. *GRIN1* (glutamate ionotropic receptor NMDA type subunit 1) gene encodes the GluN1 of NMDA receptors.[8]

Single-nucleotide polymorphisms (SNPs) are significant in investigating the risk of susceptibility to diseases and in detecting drug responses. Therefore, SNPs have a key role in the detection of ND.[9,10] Among the SNP types, missense SNPs cause amino acid substitution. Depending on its location, this change can have significant impacts on protein structure, function, and stabilization. The possible deleterious effects of missense SNPs in *CHRNA7* and *GRIN1* genes that lead to amino acid changes on protein function and structure can be estimated with the help of *in silico* analysis software with different algorithms, and the results can further guide diagnostic and experimental strategies.

The aim of this study is to predict the possible impact of missense SNPs in *CHRNA7* ve *GRIN1* genes associated with

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Orcid
Arash Rezaeirad {ORCID: 0000-0001-9006-200X}
Ömer Faruk Karasakal {ORCID: 0000-0001-7803-3249}
Ebru Özkan Oktay {ORCID: 0000-0002-0395-9845}
Mesut Karahan {ORCID: 0000-0002-8971-678X}

Address for correspondence:
Dr. Ömer Faruk Karasakal, Mimar Sinan Mah. Selman-I Pak Cad, Üsküdar Üniversitesi Çarşı, Yerleşkesi, PK: 34664, Istanbul, Turkey.
E-mail: omerfaruk.karasakal@uskudar.edu.tr

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AD on protein structure, function, and stabilization and to analyze gene–gene interactions using *in silico* methods.

Materials and Methods

There is no need for ethics committee approval.

First, the SNPs in the CHRNA7 and GRIN1 genes were obtained from the NCBI dbSNP (https://www.ncbi.nlm.nih.gov/snp/). The sequences of the protein encoded by the CHRNA7 and GRIN1 genes were obtained from the UniProt (https://www.uniprot.org/). Second, publicly available software such as SIFT, PolyPhen-2 (HumDiv-HumVar), SNPs and GO, PROVEAN, SNAP2, PHD-SNP, and Meta-SNP were used to predict potentially harmful SNPs in CHRNA7 and GRIN1 genes. After, I-Mutant 3.0 and MuPro were used to estimate its effect on protein stabilization. Furthermore, three-dimensional (3D) modeling of proteins was created by the Project HOPE. Finally, the gene–gene interactions were determined with the GeneMANIA (https://genemania.org/) [Figure 1].

SIFT (Sorting Intolerant From Tolerant) predicts the impact of an amino acid substitution on the function of a protein according to the sequence similarity and physical features of amino acids.[11] PolyPhen-2 (HumDiv, HumVar) is a software that estimates the effects of an amino acid replacement on the structure and function of a given protein based on physical and comparative features.[12] SNPsandGO predicts whether a SNP is associated with diseases based on protein functional annotation.[13] PROVEAN is a software that makes a prediction on the impact of an amino acid change on the protein function.[14] SNAP2 predicts the functional effects of amino acid substitution based on a "neural network."[15] PhD-SNP (Predictor of human Deleterious SNP) is defined as a predictor of harmful SNPs in humans. The PhD-SNP algorithm was used for estimating the effect of human SNPs in both coding and noncoding sites.[16] The Meta-SNP was used to estimate whether a particular protein variation can be identified as disease-associated.[17]

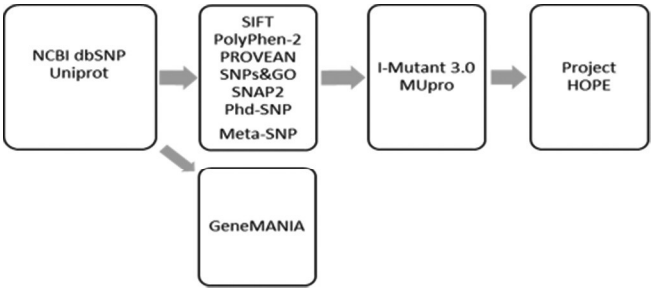


Figure 1: *In silico* analyses tools

MUpro[18] and I-Mutant 3.0[19] are support vector machine-based tools that estimate protein stability alterations due to SNPs. 3D modeling of proteins is created by Project HOPE. It also reports data on features of residues at polymorphism sites.[20] The interactions of *CHRNA7* and *GRIN1* genes with other genes were determined with the GeneMANIA software tool.[21]

Results

Results of gene–gene interaction

It was determined that there were 161 links between them when the interaction of the *CHRNA7* gene with 20 genes was examined. The maximum associated five genes with *CHRNA7* were *MAPK15, ADCY6, MAPKAPK5, MAPK4,* and *MAPK6*. Similarly, 624 links were determined between *GRIN1* and 20 genes examined. *GRIN2A, GRIN2B, FBXO2, GRIN3A,* and *DRD1* genes were determined as the top five genes which have the maximum association with *GRIN1* [Figure 2] (GeneMANIA).

Results of *in silico* analysis of *CHRNA7* and *GRIN1* genes

SNPs information for the CHRNA7 and GRIN1 genes was accessed from the NCBI dbSNP in September 2021. The total number of SNPs belonging to the CHRNA7 gene was 51693 and the number of missense SNPs was 603. A total of 913 different amino acid changes of these missense SNPs were determined. Among them, twelve missense SNPs were determined to be possibly harmful and the results of the analysis are showed in Table 1. For the GRIN1 gene, 591 missense SNPs were determined

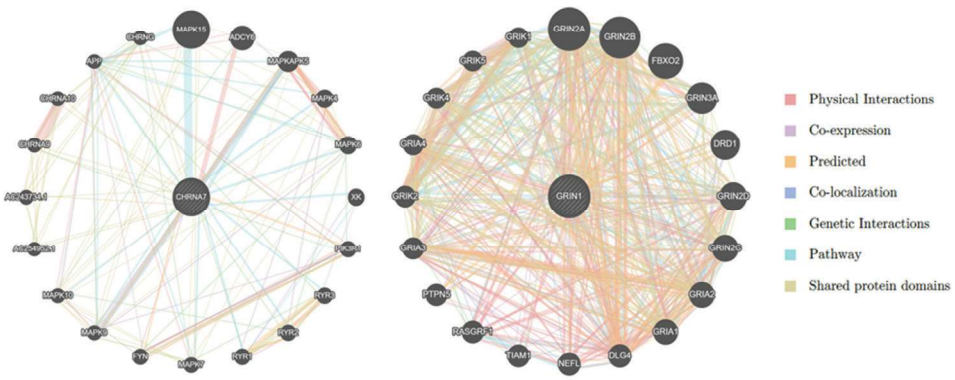


Figure 2: Gene–gene interaction of *CHRNA7* and *GRIN1* genes

Table 1: Prediction results of SNPs in the *CHRNA7* and *GRIN1* genes

Gene name	SNP number	Amino acid change	SIFT	Score	PolyPhen-2 HumDiv	Score	PolyPhen-2 HumVar	Score	PROVEAN score
CHRNA7	rs142728508	Y233C	Dlt	0	PD	1.000	PD	1.000	Dlt
	rs12899798	W77G	Dlt	0	PD	1.000	PD	1.000	Dlt
	rs138222088	R227H	Dlt	0.001	PD	1.000	PD	0.998	Dlt
	rs140316734	R227C	Dlt	0	PD	1.000	PD	1.000	Dlt
	rs199633275	P322R	Dlt	0.001	PD	1.000	PD	0.992	Dlt
	rs199819119	L29F	Dlt	0.002	PD	1.000	PD	1.000	Dlt
	rs200147286	Q49P	Dlt	0.024	PD	0.986	PD	0.983	Dlt
	rs200908085	Y115C	Dlt	0.022	PD	1.000	PD	0.997	Dlt
	rs201094833	Q61R	Dlt	0	PD	0.996	PD	0.977	Dlt
	rs201210785	E195K	Dlt	0	PD	0.999	PD	0.986	Dlt
	rs368352998	S48W	Dlt	0	PD	1.000	PD	0.999	Dlt
	rs201473594	N69D	Dlt	0.044	PD	0.982	PD	0.950	Dlt
GRIN1	rs193920837	P117L	Dlt	0	PD	1.000	PD	1.000	Dlt
	rs3181457	I540M	Dlt	0.002	PD	0.999	PD	0.996	Dlt
	rs201764643	R217P	Dlt	0	PD	1.000	PD	0.998	Dlt

Gene name	Score	SNPs and GO	Score	Meta-SNP results	Meta-SNP score	SNAP2	Score	Expected accuracy	PhD-SNP	RI
CHRNA7	-8.472	Disease	10	Disease	0.853	Effect	65	80%	Disease	8
	-10.612	Disease	10	Disease	0.885	Effect	90	95%	Disease	7
	-4.574	Disease	10	Disease	0.625	Effect	66	80%	Disease	7
	-7.398	Disease	10	Disease	0.761	Effect	61	80%	Disease	6
	-5.409	Disease	10	Disease	0.635	Effect	78	85%	Disease	3
	-3.293	Disease	10	Disease	0.720	Effect	2	53%	Disease	4
	-2.540	Disease	10	Disease	0.519	Effect	24	63%	Disease	1
	-7.538	Disease	10	Disease	0.883	Effect	30	66%	Disease	8
	-3.362	Disease	10	Disease	0.759	Effect	76	85%	Disease	7
	-3.675	Disease	10	Disease	0.792	Effect	57	75%	Disease	5
	-5.724	Disease	10	Disease	0.778	Effect	7	53%	Disease	5
	-4.235	Disease	10	Disease	0.763	Effect	18	59%	Disease	5
GRIN1	-7.801	Disease	10	Disease	0.773	Effect	64	80%	Disease	9
	-2.582	Disease	7	Disease	0.506	Effect	17	59%	Disease	8
	-5.362	Disease	9	Disease	0.634	Effect	80	91%	Disease	6

RI: Reliability index, PD: Probably damaging, Dlt: Deleterious, SIFT: Sorting Intolerant From Tolerant, SNPs: Single-nucleotide polymorphisms

among 13914 SNPs and 751 different amino acid changes were detected. Among them, three missense SNPs were determined to be harmful, and the analysis results are given in Table 1.

Table 2: Stability results of *CHRNA7* and *GRIN1*

Gene name	SNP ID	Amino Acid change	I-Mutant 3.0	DDG (Kcal/mol)	RI	MUpro	DDG
CHRNA7	rs142728508	Y233C	Decrease	0.00	7	Decrease	−0.95518426
	rs12899798	W77G	Decrease	−2.74	9	Decrease	−1.8496217
	rs138222088	R227H	Decrease	−1.22	8	Decrease	−1.198904
	rs140316734	R227C	Decrease	−1.49	3	Decrease	−0.60266667
	rs199633275	P322R	Decrease	−0.24	3	Decrease	−1.1710044
	rs199819119	L29F	Decrease	0.72	4	Decrease	−1.3135187
	rs200147286	Q49P	Decrease	−0.60	1	Decrease	−1.5366824
	rs200908085	Y115C	Decrease	0.85	1	Decrease	−0.77705861
	rs201094833	Q61R	Decrease	−1.02	3	Decrease	−0.91951906
	rs201210785	E195K	Decrease	−1.06	4	Decrease	−1.2298417
	rs368352998	S48W	Increase	−0.32	0	Decrease	−0.38466246
	rs201473594	N69D	Decrease	−1.20	8	Decrease	−0.43114591
GRIN1	rs193920837	P117L	Decrease	−1.43	6	Decrease	−0.33774896
	rs3181457	I540M	Decrease	−0.79	8	Decrease	−1.0170584
	rs201764643	R217P	Decrease	−1.28	4	Decrease	−1.6345586

DDG: Delta Delta G, RI: Reliability index, SNP: Single-nucleotide polymorphism

Table 3: Features of amino acids at polymorphism sites

Gene	SNP ID	Amino acid substitution	Size	Charge	Hydrophobicity
CHRNA7	rs142728508	Y233C	Wild type >Mutant type	-	Wild type <Mutant type
	rs12899798	W77G	Wild type >Mutant type	-	Wild type >Mutant type
	rs138222088	R227H	Wild type >Mutant type	Wild type: Positive Mutant type: Neutral	-
	rs140316734	R227C	Wild type >Mutant type	Wild type: Positive Mutant type: Neutral	Wild type <Mutant type
	rs199633275	P322R	Wild type <Mutant type	Wild type: Neutral Mutant type: Positive	Wild type >Mutant type
	rs199819119	L29F	Wild type <Mutant type	-	-
	rs200147286	Q49P	Wild type >Mutant type	-	Wild type <Mutant type
	rs200908085	Y115C	Wild type >Mutant type	-	Wild type <Mutant type
	rs201094833	Q61R	Wild type <Mutant type	Wild type: Neutral Mutant type: Positive	-
	rs201210785	E195K	Wild type <Mutant type	Wild type: Negative Mutant type: Positive	-
	rs368352998	S48W	Wild type <Mutant type	-	Wild type <Mutant type
GRIN1	rs193920837	P117L	Wild type <Mutant type	-	-
	rs3181457	I540M	Wild type <Mutant type	-	-
	rs201764643	R217P	Wild type >Mutant type	Wild type: Positive Mutant type: Neutral	Wild type <Mutant type

SNP: Single-nucleotide polymorphism

Results of protein stability

Stability analysis of proteins was performed with the I-Mutant 3.0 and MUpro software tools for variants that all online software tools predicted to be functionally harmful. The prediction results of are shown in Table 2.

Results of amino acids at polymorphism sites and three-dimensional models

The features of amino acid changes caused by variants in CHRNA7 and GRIN1 genes on protein structure and function were obtained with Project HOPE. The size, hydrophobicity, and charge differences between wild and variant amino acids as well as 3D structures of the protein were estimated. The results are given in Tables 3 and 4, respectively.

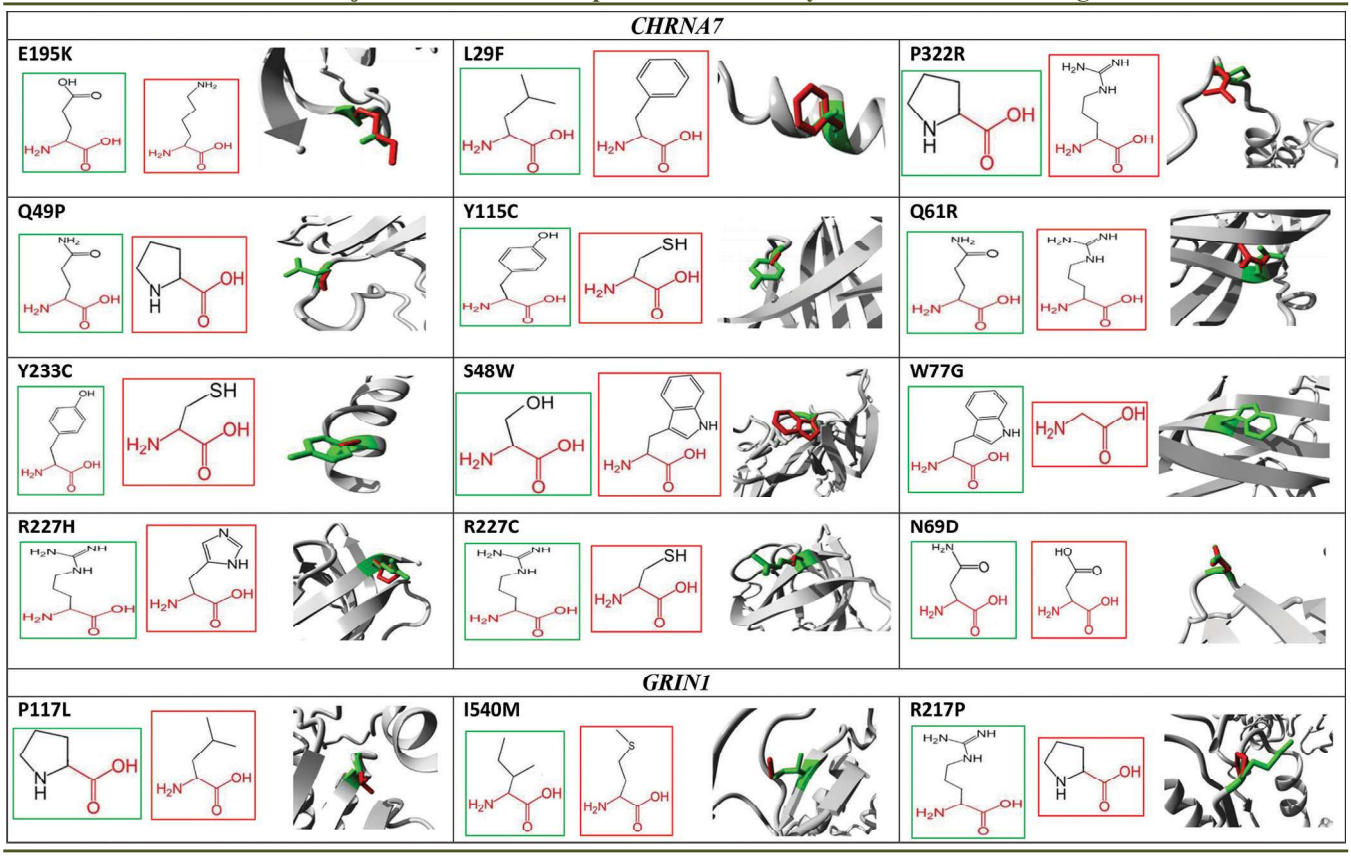
Discussion

In recent years, polymorphisms in the *CHRNA7* and *GRIN1* genes, which are associated with AD, have been the focus of attention. For example, the roles of polymorphisms in the *CHRNA7* gene in response to inhibitors in AD[22,23] and polymorphisms in the *CHRNA7* gene in AD[24] have been reported. Furthermore, the association studies between variations in the *GRIN1* gene and in various diseases such as type 2 diabetes mellitus,[25] paranoid schizophrenia,[26] and Parkinson's disease[27] have been reported. In this study, the possible effects of polymorphisms in these genes were determined by bioinformatics approach based on their roles on various diseases. The high-risk SNPs predicted using bioinformatics tools are rs142728508 (Y233C), rs12899798 (W77G), rs138222088 (R227H), rs140316734 (R227C), rs199633275 (P322R), rs199819119 (L29F) rs200147286 (Q49P), rs200908085 (Y115C), rs201094833 (Q61R), rs201210785 (E195K), and rs368352998 (S48W) in the *CHRNA7* gene and rs193920837 (P117 L), rs3181457 (I540M), and rs201764643 (R217P) in the *GRIN1* gene in this study.

The differences of features between wild and variant type amino acids of amino acid substitutions were investigated via Project HOPE [Table 3]. The protein stability changes caused by amino acid substitutions were estimated via I-Mutant and MUpro [Table 2]. Amino acid changes can affect the folding rate of a protein and depend mainly on the location and type of mutations.[28] Amino acid substitutions can alter the function of a protein with disruption of hydrogen bonds or salt bridges, changing of the physicochemical effects, and geometric constraint changes. These changes may cause destabilization of protein or some abnormal biological functions.[29]

The investigation of gene–gene interactions is significant in the etiology of some diseases such as cancer, cardiovascular, and immune system.[30] For this reason,

Table 4: Project HOPE results of proteins encoded by *CHRNA7* and *GRIN1* genes



gene–gene interaction map was determined in terms of genetic interaction, physical interaction, coexpression, colocalization, shared protein domains, pathways, and predicted interaction in *CHRNA7* and *GRIN1* genes [Figure 2].[31]

Conclusion

Consequently, it is recommended that SNPs, which are predicted to be high risk in *CHRNA7* and *GRIN1* genes as a result of bioinformatic analyses carried out, should be primarily evaluated and investigated in experimental and clinical studies related to AD. For this reason, it is thought that the findings obtained from the study will provide important data for future experimental studies.

Patient informed consent

There is no need for patient informed consent

Ethics committee approval

There is no need for ethics committee approval.

Financial support and sponsorship

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Arash Rezaeirad (40%): Data collection, in silico analysis, writing—original draft preparation
- Ömer Faruk Karasakal (30%): Organizing the research, designing the research and methodology, writing (review and editing).
- Ebru Özkan Oktay (15%): Writing (review and editing), contributed with comments on methodology.
- Mesut Karahan (15%): Writing (review and editing), contributed with comments on methodology.

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