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RESEARCH

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In silico analysis of missense SNPs in *GABRA1*, *GABRB1*, and *GABRB3* genes associated with some diseases in neurodevelopmental disorders

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Abstract

Background Neurodevelopmental disorders are disorders that are generally seen in the early developmental period of an individual's life and involve more than one disease that causes disruptions in the central nervous system. These disorders can be given as examples of diseases such as autism, mental retardation, some epileptic disorders, communication disorders, and mental retardation. The aim of this study is to determine the possible harmful effects of missense single nucleotide polymorphisms (SNPs) in the *GABRA1*, *GABRB1*, and *GABRB3* genes, which are associated with neurodevelopmental disorders, on the structure and stabilization of the protein, using in silico methods. Software tools SIFT, PolyPhen-2 HumVar, PolyPhen-2 HumDiv, PROVEAN, SNAP2, PHD-SNP, SNP&GO, PANTHER, and MetaSNP were used to predict harmful SNPs. I-Mutant and MUpro software tools were used to predict the effects of predicted harmful SNPs on protein stabilization. The STRING software tool was used for protein–protein interactions, the GeneMANIA software tool for gene–gene interactions, and the Project HOPE software tool for three-dimensional modeling examples.

Results As a result of the bioinformatics analysis, rs121434579, rs139163545, and rs267600530 in the *GABRA1* gene; rs74608570, rs75612351, rs78815529 in the *GABRB1* gene, and rs7819600779, rs1719850690, rs7819600779, rs171985060690, rs7819600779, rs1719850600779, rs149963014 in the *GABRB3* gene were predicted as harmful SNPs.

Conclusions In this study, protein structure, function, and stabilization of SNPs known to cause amino acid substitutions in *GABRA1*, *GABRB1*, and *GABRB3* genes associated with some diseases in neurodevelopmental disorders were investigated using bioinformatics tools. As a result of the results obtained in our study, it is thought that it will benefit experimental studies and bioinformatics studies.

Keywords *GABRA1*, *GABRB1*, *GABRB3*, Single nucleotide polymorphism (SNP), In silico, Neurodevelopmental disorders

Background

Neurodevelopmental disorders (NDD) are defined by delayed and abnormal development of the brain, especially early in development. Neurodevelopmental disorders lead to deficiencies in cognitive, verbal, and motor behaviors and other functions, especially accompanied by somatic findings [1]. In particular, various environmental and genetic factors cause diseases such as autism, Down Syndrome, Rett Syndrome, neurofibromatosis, and

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epilepsy which are examined among neurodevelopmental disorders. Neurodevelopmental disorders are seen in approximately 1–2% of the population compared to the general population [2]. Different genetic mutations and environmental factors are effective in the emergence of neurodevelopmental disorders. Examples of these environmental factors are various infections, immune dysfunction, endocrine and metabolic dysfunction, trauma, and nutritional differences [3]. Another factor that genetically affects neurodevelopmental disorders can be given as an example of single nucleotide polymorphism (SNP).

GABRA1 encodes the alpha (a) subunit of the gamma-aminobutyric acid receptor (GABAAR) which is located in chromosome 5 [4]. This gene encodes the (GABA) gamma-aminobutyric receptor. GABA, a neurotransmitter in the mammalian brain, acts on the GABAA receptor with ligand-closed chloride channels. The chloride conductivity through which these channels act can be modified and regulated by agents that bind to the GABAA receptor, such as benzodiapenes (GeneCards n.d.). *GABRB1*, also known as Gamma-Aminobutyric Acid Type A Receptor Subunit Beta 1, is located between 46,995,740–47,428,461 base pairs on chromosome 4 (GeneCards n.d.). The *GABRB1* gene is a good candidate gene among the specific genes participating in the structure and function of the thalamus. This gene acts on the beta subunit of the GABAA receptor, which specifically affects fast synaptic transmission in the mammalian brain. The domain of this gene has been found to affect postsynaptic current, a fast inhibitory site in the thalamus. Several clinical trials have been proposed, including studies between *GABRB1* and the thalamus and patients with bipolar disorder, autism, schizophrenia, neuropathic pain, and alcohol dependence [5]. The *GABRB3* gene is a gene located on chromosome 15q12 that encodes beta-3 protein, a GABAA receptor-linked gamma-aminobutyric acid (GABA) receptor subunit. The *GABRB3* gene is thought to have possible effects on histamine-directed effects, GABA iron-gated ion channel function, and inhibitory GABAergic synapses. The beta-3 subunit is expressed in structures such as the thalamus, cerebellum, cerebral grey matter, and hippocampi. Dysfunction of the *GABRB3* gene has been associated with neurodevelopmental disorders [6]. In this study, protein structure, function and stabilization of SNPs known to cause amino acid changes in *GABRA1*, *GABRB1,* and *GABRB3* genes associated with some diseases investigated in neurodevelopmental disorders were investigated using bioinformatics tools.

With the identification of quantitative trait loci as a result of genome-wide association studies (GWAS) for the detection of sequence variation in humans, interest in large-scale high-density SNP studies has increased significantly [7]. SNP is defined as single base sequence variations encountered in a particular region of the genome. As a result of human genome studies, SNPs are quite common in the human genome and SNPs can be used especially in the mapping of genetic diseases. There may be millions of SNPs in an individual, and these millions of SNPs are an important type of DNA polymorphism in the emergence of genetic and morphological differences between individuals. SNPs can be used in different fields. For example, it can be used for individual identification and identification, for ancestry, for phenotype determination, and for pathological and toxicological studies [8].

In silico, in its most general sense, means the determination of chemical substances and the calculation and scientific analysis of their effects using computer and computer simulation technologies. In silico methods have recently gained momentum in the field of toxicology and pharmacology. With these methods, the body's properties, effects, and response to these effects can be predicted through computer-based chemical and drug programs. Considering the benefits of in silico methods, data can be determined in a short time with this method, it is cheap and fast, and it allows the evaluation of more than one data at the same time. It also provides an alternative to animal experiments and in vitro testing [9].

The purpose of this study is to predict deleterious SNPs in the *GABRA1*, *GABRB1,* and *GABRB3* genes associated with neurodevelopmental disorders and to analyze three-dimensional models of proteins encoded by those genes, gene–gene interactions, and protein–protein interactions using various online software tools to provide data for further experimental and bioinformatic studies.

Methods

Data collecting

The SFARI database was used to select genes to be studied in our study (https://gene.sfari.org/). NCBI (https://www.ncbi.nlm.nih.gov/snp/) and NCBI dbSNP (https://www.ncbi.nlm.nih.gov/snp/), were used to determine the SNP ID, position, nucleotide change, and amino acid changes of the SNPs within those genes. UniProt database (http://www.uniprot.org/) was used to obtain FASTA format amino acid sequence and UniProtKB entry numbers of proteins.

Gene–gene interactions

The gene–gene interactions were examined by using the GeneMANIA software tool (https://genemania.org/). GeneMANIA is a website for making assumptions about the function of genes, constructing gene sequences, analyzing gene sequences, and identifying genes for functional analysis. This software tool can be used for

single-gene queries, multi-gene queries, and network scanning. When a gene is scanned to this website, it finds its possible interaction with other genes [10].

Protein–protein interactions

Protein–protein interaction was determined using the STRING software tool (https://string-db.org/). The STRING database aims to collect and integrate this information by bringing together data involved in known or probable protein–protein interactions for more than one organism [11].

In silico analysis of SNPs

SIFT, PolyPhen-2 (HumVar and HumDiv), PROVEAN, SNAP2, PHD-SNP, SNP&GO, PANTHER, and Meta-SNP software tools were used to predict the possible effects of SNPs in the *GABRA1*, *GABRB1* and *GABRB3* genes on the protein structure and function. In the results obtained from these software tools, SNPs that have predicted common deleterious or disease-related results have been determined in all of them.

Sorting Intolerant From Tolerant (SIFT) is a publicly available software tool that estimates if an amino acid change causes impaired protein function based on physical features and sequence homology of amino acids [12] (https://sift.bii.a-star.edu.sg/). Polymorphism Phenotyping v2 (PolyPhen-2) is a publicly available software tool that estimates the stability and effect of amino acid changes on human proteins by evaluating based on functional and physical evolution [13] (http://genetics.bwh.harvard.edu/pph2/). PROVEAN (Protein Variation Effect Analyzer) is a publicly available software tool that evaluates if an amino acid substitution or indel (small genetic variation) has an effect on the functionality of a protein. Harmful and neutral results can be achieved with PROVEAN (http://provean.jcvi.org/index.php). SNAP2 is a neural network-based software tool to discriminate between various neutral and non-neutral variants, reveal biochemical differences of input, and reveal functional and structural features of the predicted protein sequence [14] (https://rostlab.org/services/snap2web/). PHD-SNP is a publicly available software tool for predicting whether single point protein mutations in a given region will be disease-causing or neutral polymorphisms. Two different results can be obtained "disease" or "neutral" by this software tool (https://snps.biofold.org/phd-snp/pages/PhD-SNP_Help.html). SNP&GO is a publicly available software tool for predicting single-point protein mutations in human diseases. SNP&GO is a support vector machine-based tool that estimates disease-causing mutations in the protein (https://snps.biofold.org/snps-and-go/snps-and-go.html). PANTHER (Protein Analysis Through Evolutionary Relationships) is a public database designed to facilitate gene and protein classes. In this software tool, proteins are classified according to their various functions (http://www.pantherdb.org/). In the Meta-SNP software tool, results can be obtained with the help of the SIFT, PHD-SNP, PANTHER, and SNAP2 software tools to distinguish between disease-related non-synonymous SNVs (nsSNV) (https://snps.biofold.org/meta-snp/).

Effects of predicted harmful SNPs on protein stabilization

I-Mutant 3.0 and MUpro software tools based on support vector machines were used to predict the impacts of predicted harmful SNPs on protein stabilization. The I-Mutant 3.0 and MUpro are publicly available software tools that predict the effects of mutations at a single location on the stabilization of proteins. (http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi), (http://mupro.proteomics.ics.uci.edu/).

Creating three-dimensional models of predicted deleterious variations

The 3D modeling of the proteins was obtained via the Project HOPE software tool. Project HOPE is a public website that analyzes the point mutation in the protein sequence. In this software tool, 3D shapes and animations are reported by searching and integrating the information in the system by entering protein mutation and sequence information. In addition, results of amino acids in terms of size, charge, hydrophobicity, and conservation were obtained with the Project HOPE software tool. (https://www3.cmbi.umcn.nl/hope/).

Results

Prediction results of harmful SNPs by in silico methods

A total of 21,956 SNPs of which 263 were missense SNPs were found in the *GABRA1* gene. 299 amino acid substitutions for 263 SNPs were examined. 399 missense SNPs were determined in the *GABRB1* gene among a total of 170,637 SNPs and 335 amino acid changes were analyzed for those missense SNPs. *GABRB3* gene contained 338 missense SNPs among 86,129 SNPs and 357 amino acid substitutions were determined for those missense ones.

Using all software tools, it was determined that there were three harmful SNPs (rs121434579, rs139163545, rs267600530) in the *GABRA1* gene (Table 1), three SNPs (rs74608570,rs75612351, rs78815529) in the *GABRB1* gene (Table 2) and six SNPs (rs78196007,rs78196007, rs17850679, rs72708067, rs111596597, rs149963014) in the *GABRB3* gene (Table 3).

Table 1 Possible prediction results of SNPs using software tools in the GABRA1 gene

SNP Number	rs121434579	rs139163545	rs267600530
Nucleotide change	C > A	C > A/C > T	C > T
Amino acid change	A322D	R147W	S303F
SIFT result	Damaging	Damaging	Damaging
SIFT score	0.027	2.45	0.001
PolyPhen-2 HumDiv result	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 HumDiv score	0.999	1.000	1.000
PolyPhen-2 HumVar results	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 HumVar score	0.992	1.000	0.092
PROVEAN results	Deleterious	Deleterious	Deleterious
PROVEAN score	− 4.785	− 7.295	− 5.469
SNP&GO results	Disease	Disease	Disease
SNP&GO score	8	8	7
SNAP2 results	Effect	Effect	Effect
SNAP2 score	64	86	38
SNAP2 accuracy rate	%80	%91	%66
PHD-SNP results	Disease	Disease	Disease
PHD-SNP RI score	8	9	7
PANTHER results	Probably damaging	Probably damaging	Probably damaging
META-SNP results	Disease	Disease	Disease
META-SNP score	0.85	0.85	0.74
META-SNP confidence value	6	6	5
I-Mutant result	Decrease	Decrease	Increase
I-Mutant Reliability Index	4	4	5
I-Mutant DDG value	− 0.75	− 0.32	0.21
MUpro result	Decrease	Decrease	Increase
MUpro score	− 0.76389212	− 10.569.948	0.22722624

Table 2 Possible prediction results of SNPs using software tools in the GABRB1 gene

SNP number	rs74608570	rs75612351	rs78815529
Nucleotide change	A > G	C > T	G > T
Amino acid change	D450G	P458L	W469C
SIFT results	Damaging	Damaging	Damaging
SIFT score	0.013	0.001	0
PolyPhen-2 HumDiv results	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 HumDiv score	0.999	0.998	1.000
PolyPhen-2 HumVar results	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 HumVar score	0.997	0.998	0.999
PROVEAN results	Deleterious	Deleterious	Deleterious
PROVEAN score	− 5.553	− 8.026	− 10.504
SNP&GO results	Disease	Disease	Disease
SNP&GO score	8	8	7
SNAP2 results	Effect	Effect	Effect
SNAP2 score	84	62	77
SNAP2 accuracy rate	91%	80%	85%
PHD-SNP results	Disease	Disease	Disease
PHD-SNP RI score	8	8	5
PANTHER results	Probably damaging	Probably damaging	Probably damaging

Table 2 (continued)

SNP number	rs74608570	rs75612351	rs78815529
META-SNP results	Disease	Disease	Disease
META-SNP score	0.85	0.85	0.85
META-SNP confidence value	9	9	8
I-Mutant result	Decrease	Decrease	Decrease
I-Mutant Reliability Index	2	1	9
I-Mutant DDG value	− 1.44	− 0.70	− 1.67
MUpro result	Decrease	Increase	Decrease
MUpro score	− 203.199	0.025153447	− 0.82275225

Table 3 Possible prediction results of SNPs using software tools in the GABRB3 gene

SNP number	rs78196007	rs78196007	rs17850679	rs72708067	rs111596597	rs149963014
Nucleotide change	G > A/G > T	G > A/G > T	T > A	T > C	A > G	T > C
Amino acid change	T156I	T85I	Q173L	M80V	I213T	Y324C
SIFT results	Damaging	Damaging	Damaging	Damaging	Damaging	Damaging
SIFT score	0	0.001	0	0.004	0.001	0
PolyPhen-2 Hum-Div Results	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 Hum-Div Score	1.000	1.000	1.000	1.000	0.998	1.000
PolyPhen-2 Hum-Var Results	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging
PolyPhen-2 HumVar Score	0.990	0.998	0.999	0.984	0.989	0.998
PROVEAN results	Deleterious	Deleterious	Deleterious	Deleterious	Deleterious	Deleterious
PROVEAN score	− 5.254	− 5.403	− 6.396	− 3.004	− 4.234	− 8.181
SNP&GO results	Disease	Disease	Disease	Disease	Disease	Disease
SNP&GO score	7	9	9	8	4	6
SNAP2 results	Effect	Effect	Effect	Effect	Effect	Effect
SNAP2 score	61	69	53	50	57	47
SNAP2 Accuracy rate	80%	80%	75%	75%	75%	71%
PHD-SNP results	Disease	Disease	Disease	Disease	Disease	Disease
PHD-SNP RI score	1	3	9	7	2	8
PANTHER results	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Probably damaging
META-SNP results	Disease	Disease	Disease	Disease	Disease	Disease
META-SNP score	0.85	0.78	0.85	0.85	0.74	0.85
META-SNP confidence value	5	6	7	7	3	7
I-Mutant result	Decrease	Decrease	Increase	Decrease	Decrease	Decrease
I-Mutant Reliability Index	5	0	1	8	9	4
I-Mutant DDG value	− 0.11	− 0.12	− 0.06	− 1.00	− 2.25	− 1.16
MUpro result	Decrease	Increase	Decrease	Decrease	Decrease	Decrease
MUpro score	− 0.20622366	0.030569622	− 0.34506944	− 1.487.868	− 19.379.582	− 11.142.667

Results of the protein stabilization

The effects of high-risk SNPs in the *GABRA1*, *GABRB1,* and *GABRB3* genes on the protein stabilization were investigated using software tools I-Mutant 3.0 and MuPro. The results are shown in Tables 1, 2, and 3, respectively.

Gene–gene interactions

The GeneMANIA software tool was used to examine the interaction of the *GABRA1*, *GABRB1*, and *GABRB3* genes with other genes, respectively. The gene–gene interactions within the three genes are shown in Fig. 1. Co-expression/localization, genetic/physical interactions, predicted, pathway, and shared protein domains were also shown in Fig. 1.

Protein–protein interaction

The STRING database shows the relationship to 10 proteins encoded by the *GABRA1*, *GABRB1,* and *GABRB3* (Fig. 2) genes.

Creating three-dimensional models of predicted harmful variations

The possible effects of amino acid substitution because of by SNPs in the *GABRA1*, *GABRB1,* and *GABRB3* genes were investigated using the Project HOPE and the three-dimensional modeling of the proteins was obtained (Table 4). Also, the differences in hydrophobicity, charge, and size between wild and mutant-type amino acid residues at polymorphism positions were investigated with Project HOPE. The results are summarized in Table 5.

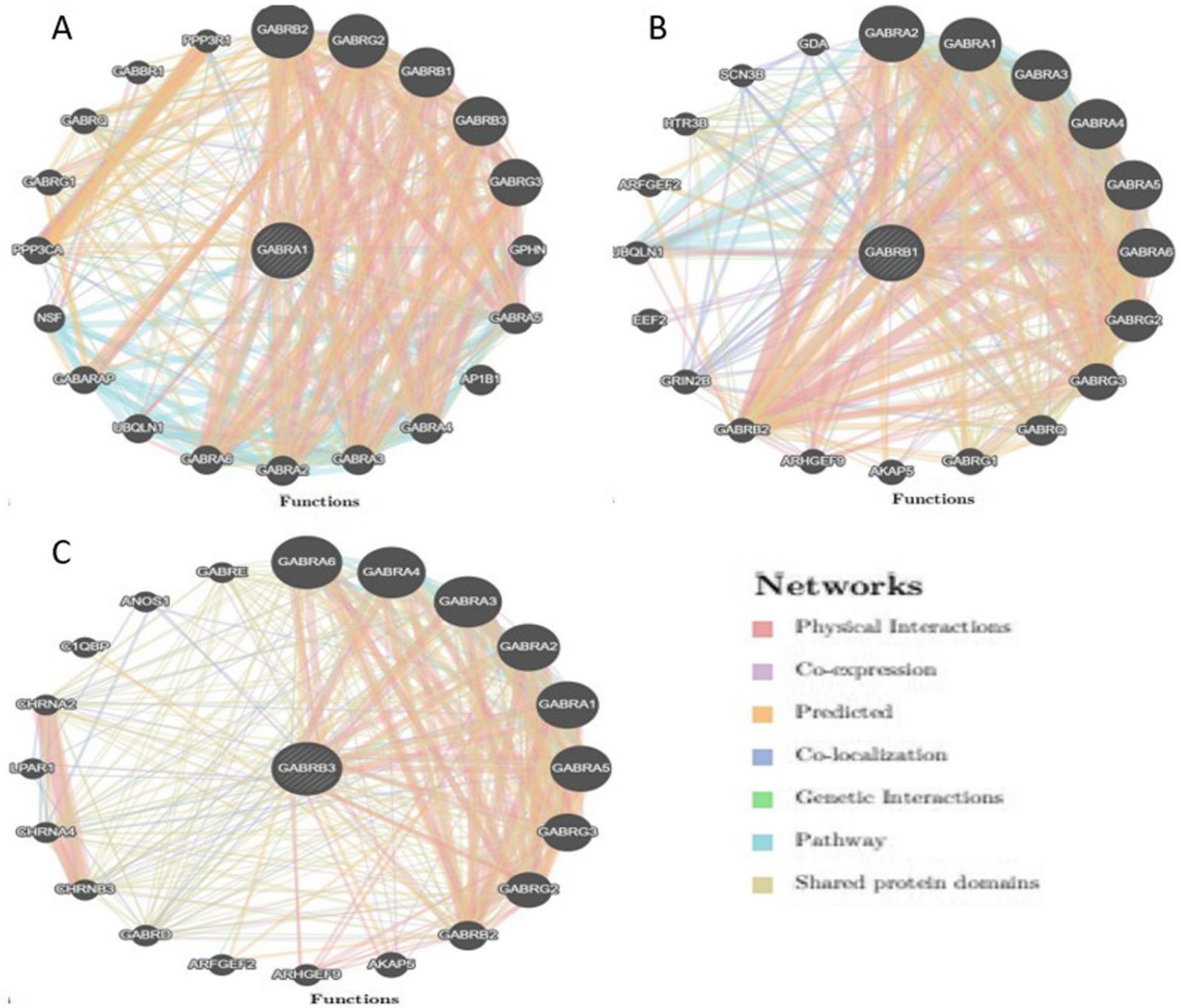


Fig. 1 **A** *GABRA1*, **B** *GABRB1* and **C** *GABRB3* gene–gene interaction network (GeneMANIA n.d.)

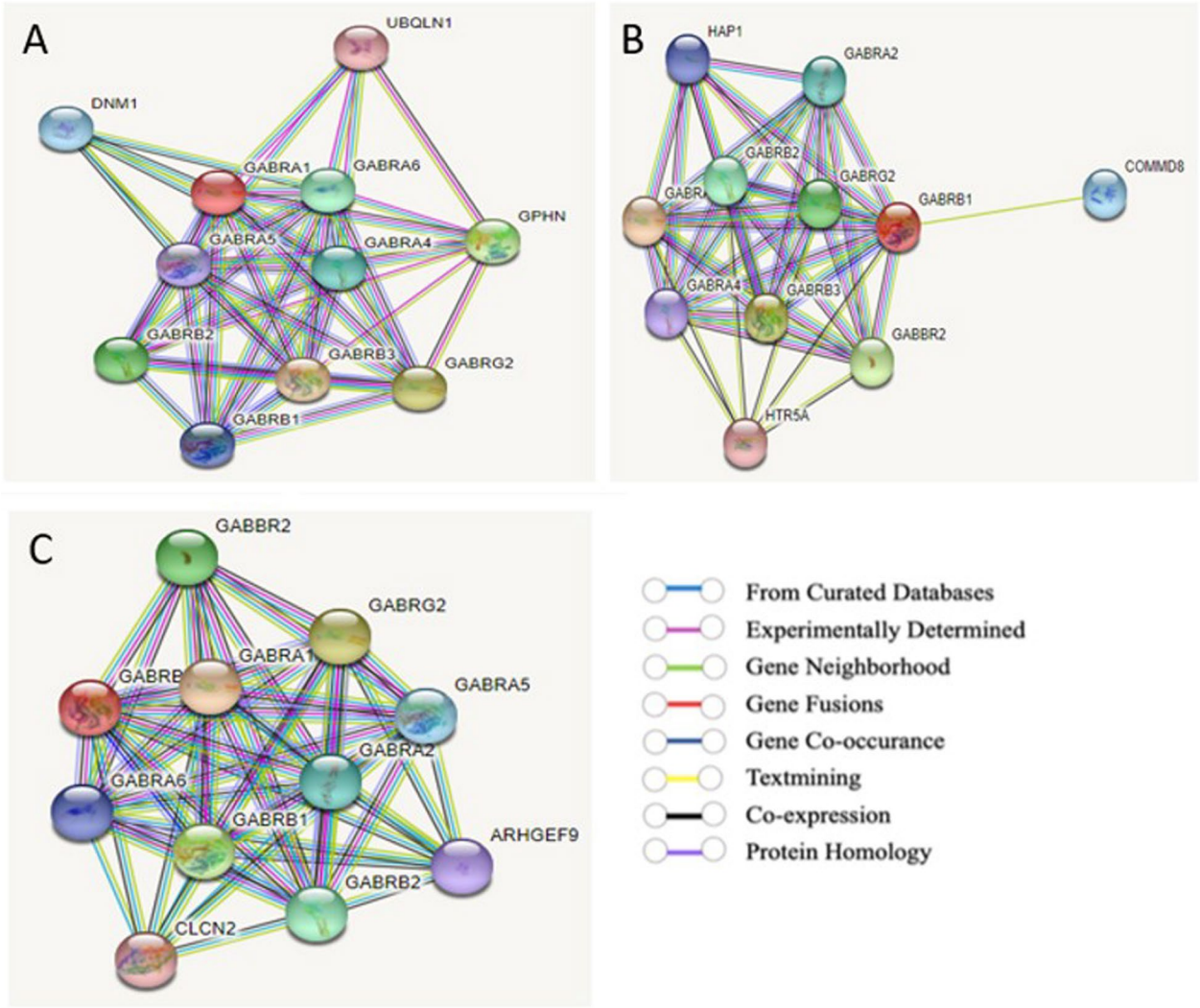


Fig. 2 Interaction network of proteins associated with the **A** GABRA1, **B** GABRB1 and **C** GABRB3 protein (STRING n.d.)

In addition, according to the evolutionary conservation analysis scores of the Project HOPE software tool, it is estimated that the mutation is likely to be damaging to the protein due to mutant residues in the S303F, R147W, and A322D substitutions in the GABRA1; D450G and P458L substitutions in the GABRB1; I213T, Q173L, T85I, and T156I substitutions in the GABRB3 are near a conserved region. In addition, W469C amino acid change in the GABRB1 is estimated to be probably damaging to the protein because of wild-type residue is very conserved. Although the wild-type residue is very conserved in the M80V substitution in GABRB3, the mutation might not be damaging in some rare cases due to the properties of mutant residue which is near to a highly conserved position. Due to the characteristics of the Y324C mutant residue in the GABRB3, this mutation is acceptable even though the mutant residue is near a conserved region [18].

Discussion

SNPs can alter the effects of the encoded protein and disease outcome. Due to differences in genetic sequences and their effects on protein structure and stabilization, in silico studies of SNPs have accelerated the understanding of this relationship. Experimentally investigating the effect of multiple SNPs can be very costly. It is also a laborious process and takes a lot of time. Consequently, in silico methods can be a preliminary platform to investigate the function of SNPs [15]. In our study, possible harmful effects of SNPs in *GABRA1*, *GABRB1,* and *GABRB3* genes associated with neurodevelopmental

Table 4 Project HOPE software tool modeling results of *GABRA1*, *GABRB1*, *GABRB3*

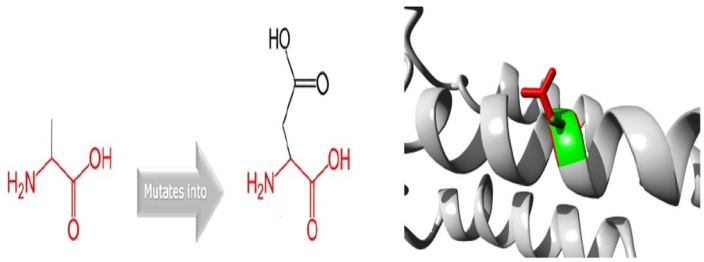
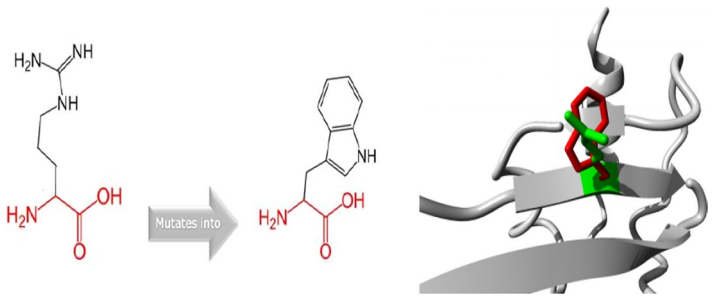
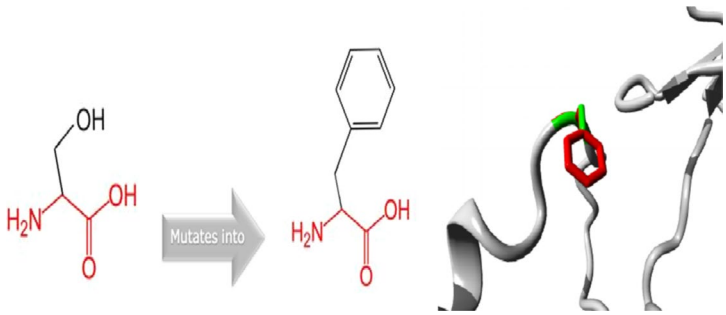
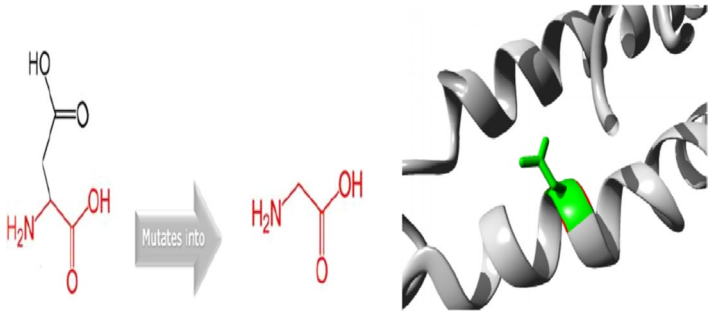
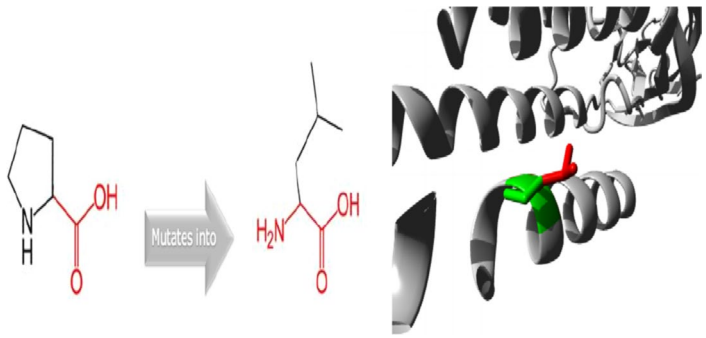
SNP number	Modeling	Explanation
rs121434579		Conversion of Alanine to Aspartic acid at position 322 as a result of the rs121434579 polymorphism
rs139163545		Conversion of Arginine to Tryptophan at position 147 as a result of the rs139163545 polymorphism
rs267600530		Conversion of Serine to Phenylalanine at position 303 as a result of the rs267600530 polymorphism
rs74608570		Conversion of Aspartic acid to Glycine at position 450 as a result of the rs74608570 polymorphism
rs75612351		Conversion of Leucine to Proline at position 458 as a result of the rs75612351 polymorphism

Table 4 (continued)

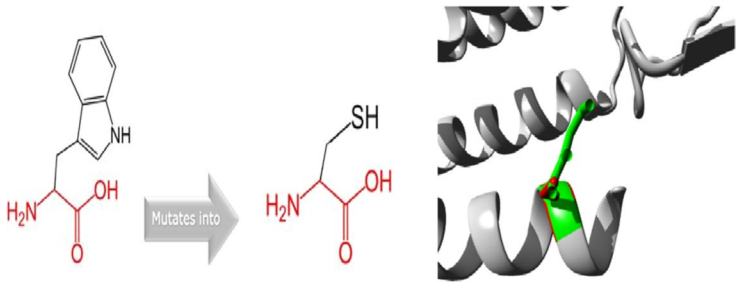
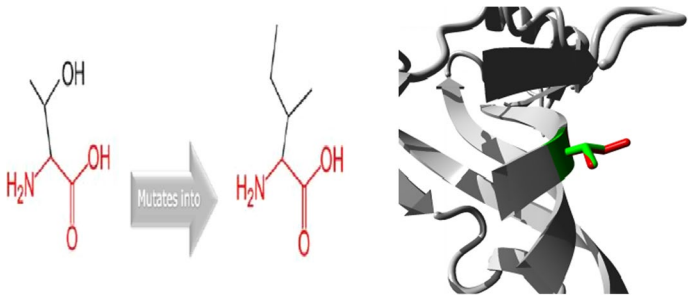
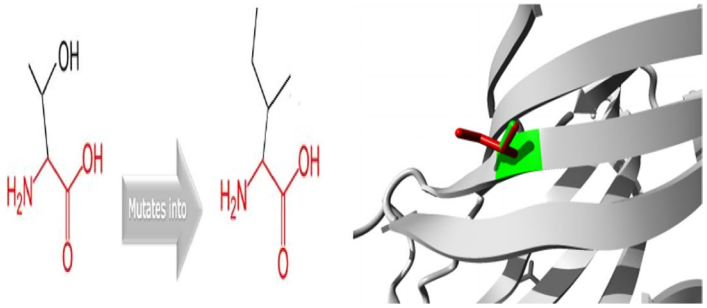
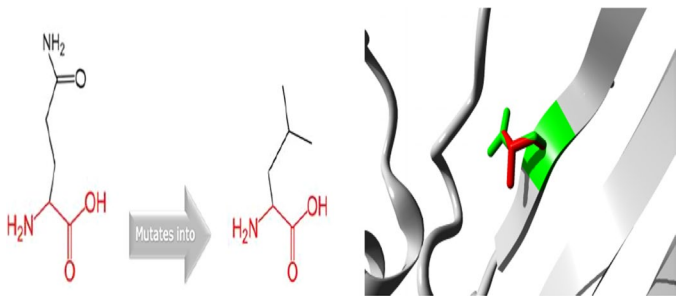
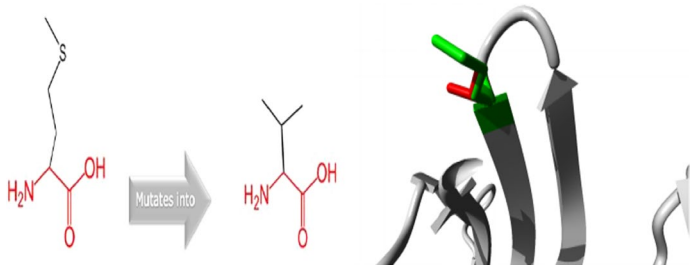
SNP number	Modeling	Explanation
rs78815529		Conversion of Tryptophan to Cysteine at position 469 as a result of the rs78815529 polymorphism
rs78196007		Conversion of Threonine to Isoleucine at position 85 as a result of the rs78196007 polymorphism
rs78196007		Conversion of Threonine to Isoleucine at position 156 as a result of the rs78196007 polymorphism
rs17850679		Conversion of Leucine to Glutamine at position 173 as a result of the rs17850679 polymorphism
rs72708067		Conversion of Methionine to Valine at position 80 as a result of the rs72708067 polymorphism

Table 4 (continued)

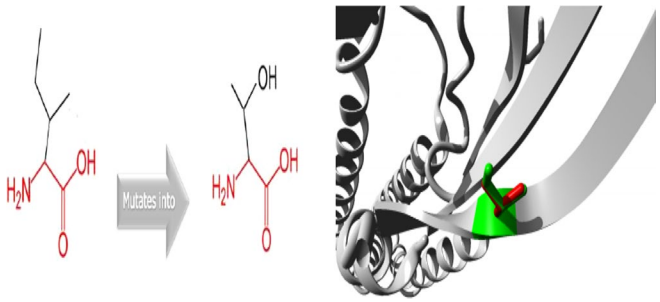
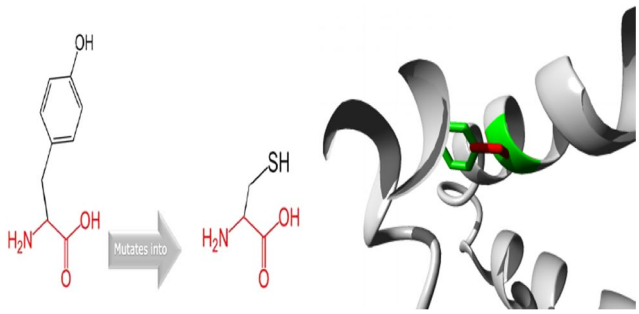
SNP number	Modeling	Explanation
rs111596597		Conversion of Isoleucine to Threonine at position 213 as a result of the rs111596597 polymorphism
rs149963014		Conversion of Tyrosine to Cysteine at position 324 as a result of the rs149963014 polymorphism

Table 5 Results of differences between wild and mutant variants from the Project HOPE software tool

SNP number	Amino acid change	Wild type feature			Mutant type feature		
		Size	Charge	Hydrophobic	Size	Charge	Hydrophobic
rs121434579	A322D	<	Neutral	>	>	–	<
rs139163545	R147W	**<**	+	**<**	**>**	**–**	**>**
rs267600530	S303F	<	No result	<	>	No result	>
rs74608570	D450G	>	–	>	<	Neutral	<
rs75612351	P458L	<	No result	No result	>	No result	No result
rs78815529	W469C	>	No result	No result	<	No result	No result
rs78196007	T156I	<	No result	<	>	No result	>
rs78196007	T85I	<	No result	<	>	No result	>
rs17850679	Q173L	>	No result	<	<	No result	>
rs72708067	M80V	>	No result	No result	<	No result	No result
rs111596597	I213T	>	No result	>	<	No result	<
rs149963014	Y324C	>	No result	<	<	No result	>

disorders were investigated with SIFT, PolyPhen-2, PROVEAN, SNAP2, PHD-SNP, SNP&Go, PANTHER, and META-SNP. The effects of amino acid change caused by SNPs on protein stabilization were investigated using I-Mutant 3.0 and MuPro software tools (Tables 1, 2, and 3). The differences in hydrophobicity, charge, and size between wild and mutant type amino acids as well as three-dimensional modeling of protein and polymorphism sites were investigated using the Project HOPE software tool (Tables 4, 5). Gene–gene and protein–protein interactions were determined via GeneMANIA and STRING software tools, respectively (Figs. 1, 2).

In our study, there was no study other than the A322D and R147W variants in the GABRA1 gene in

the literature on SNPs, which we found to be potentially harmful in common with all software tools. Biterge Süt et al. (2021) investigated nsSNPs of ion channel-related genes in epilepsy and they reported that A322D in the GABRA1 gene was pathogenic and decreased protein stability via in silico methods [16]. Hernandez et al. (2016) investigated variants in *GABR* genes in cases of genetic epilepsy 2016. The R147W variant is one of the variants identified by exon sequencing. Also, the R147W variant was scored as deleterious via with PolyPhen-2 software tool [17].

The size differences between wild and mutant type amino acids can affect the contacts with the lipid-membrane, can disturb the multimeric interactions, or can cause an empty space in the core of the protein (Table 5). These disruptions differ according to the position of the amino acid, whether the residue is embedded or surface, and whether the mutant residue is larger or smaller than the wild. If one of the wild or mutant residues is glycine or proline, the flexibility and rigidity properties of these amino acids, respectively, may be affected by the mutation, thus locally affecting the conformation [18]. The charge differences between wild and mutant type amino acids are shown in Table 5. Differences in charge between wild and mutant residues, such as being oppositely charged, having a charged residue when uncharged, or vice versa, can lead to different results. For example, the mutation can cause repulsion between the mutant residue and neighboring residues or loss of the charge of a buried residue [18]. The differences in hydrophobicity between residues are shown in Table 5. If the hydrophobicity of the residues differs this can cause various situations such as loss of hydrophobic interactions with other molecules on the surface of the protein, affecting the hydrogen bond formation or the multimeric contacts [18]. The hydrophobicity value of amino acids is related to the side chains. In particular, it is a scale of how strongly the side chains are pushed out. If the hydrophobicity is positive, it indicates that this amino acid is not present in the aqueous medium. The negative value of hydrophobicity indicates a higher affinity of the amino acid toward water [19]. Finally, changes in the structure of the protein can be observed due to the decrease in the stabilization of the proteins. In addition, its solubility may be affected and protein activity may decrease or disappear completely [20]. Furthermore, the increase in stability may reduce unfolding rates which results in the formation of aggregates [21].

Conclusions

In conclusion, the protein structure, function, and stabilization of SNPs known to cause amino acid substitutions in the *GABRA1*, *GABRB1,* and *GABRB3* genes, which are associated with some diseases processed in neurodevelopmental disorders, using bioinformatics tools in this study. As a result of the results obtained in our study, it is thought that it will benefit experimental studies and bioinformatics studies.

Abbreviations

SNPs	Single nucleotide polymorphisms
NDD	Neurodevelopmental disorders
GABA	Gamma-aminobutyric receptor
GABAAR	Gamma-aminobutyric acid receptor
GWAS	Genome-wide association studies
SIFT	Sorting Intolerant From Tolerant
PROVEAN	Protein Variation Effect Analyzer
PANTHER	Protein Analysis Through Evolutionary Relationships
nsSNV	Non-synonymous SNVs

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Author contributions
MM: Data collection, in silico analysis, writing—original draft preparation. KÖF: Organizing the research, designing the research and methodology, writing (review and editing). ÖOE: Writing (review and editing), contributed with comments on methodology. KM Writing (review and editing) contributed with comments on methodology.

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Declarations

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There is no need for ethics committee approval.

Consent for publication
Not applicable.

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The authors declare that they have no competing interests.

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