

RESEARCH PAPER

A Theoretical Examination of Structure-Function Disruptions by nsSNPs in the SNCA Gene: Towards Nano-Therapeutic Design

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ARTICLE INFO

Article History:

Received 08 March 2026

Accepted 26 June 2026

Published 01 July 2026

Keywords:

Missense

Nano-technology Single

Nucleotide Polymorphisms

SNCA gene

STRING

ABSTRACT

This study investigates the role of non-synonymous single nucleotide polymorphisms (nsSNPs) in the SNCA gene in Parkinson's disease (PD) using a multidisciplinary approach. By combining bioinformatics, computational biology, structural biology, and experimental assays, the research identifies nsSNPs, assesses their functional consequences, and explores their impact on α -synuclein, a protein associated with PD. Special attention is given to the A53T nsSNP, which is linked to increased PD risk and severity. The study sheds light on therapeutic strategies to mitigate nsSNP effects, offering insights into the genetic basis of PD and personalized therapeutic interventions. Additionally, three mutations (E46K, A30P, and Y133K) are examined for their potential influence on α -synuclein protein stability and function, highlighting the need for further research to confirm these findings. Furthermore, future studies could expand this investigation by incorporating nanotechnology-based approaches to develop potential therapeutic strategies. Nanoparticle-based drug delivery systems, nano-biosensors for early detection of α -synuclein aggregation, and molecular dynamics simulations of nanoparticle-protein interactions are explored as promising avenues for Parkinson's disease treatment and diagnosis.

How to cite this article

Mohammed D., Hanna D., Baqer S. et al. A Theoretical Examination of Structure-Function Disruptions by nsSNPs in the SNCA Gene: Towards Nano-therapeutic Design. J Nanostruct, 2026; 16(3):4135-4143. DOI: 10.22052/JNS.2026.03.096

INTRODUCTION

The human genome, containing 3 billion base pairs, is a vast genetic landscape with 23 pairs of chromosomes. Single Nucleotide Polymorphisms (SNPs) are fundamental genetic

variants, representing the most common form of genetic diversity among individuals. SNPs occur one in every 300 base pairs and serve as key markers of genetic variation, influencing traits, disease susceptibility, and environmental

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responses [1]. Protein structure, function, and phenotype can be impacted by genetic variants known as nonsynonymous Single Nucleotide Polymorphisms (nsSNPs). These variants directly change the sequence of amino acids in encoded proteins. These genetic variants have been linked to various human diseases, from rare monogenic disorders to complex multifactorial conditions like neurodegenerative diseases, highlighting the importance of understanding and managing these genetic variations [2]. Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor symptoms, including tremor, rigidity, and bradykinesia, as well as non-motor symptoms, such as cognitive impairment and psychotic disturbances. The disease is associated with the progressive degeneration of dopaminergic neurons in the substantia nigra of the brain. According to Poewe W. et al. [3], genetic factors play a significant role in susceptibility to the disease. One important contributor to PD pathogenesis is the SNCA gene, which encodes alpha-Synuclein. Alpha-Synuclein plays essential roles in synaptic function, neurotransmitter release, and synaptic vesicle trafficking. However, the abnormal aggregation of α -Synuclein into Lewy bodies, a pathological hallmark of PD and other Synucleinopathies, is observed in affected brains [4]. Genetic studies have established an association between SNCA gene variations and the risk of developing PD. Several nonsynonymous single-nucleotide polymorphisms (nsSNPs) in the SNCA coding region may alter α -Synuclein expression, aggregation propensity, and cellular interactions, thereby influencing susceptibility to PD. Understanding the structural and functional consequences of these nsSNPs is crucial for elucidating PD pathogenesis and developing targeted therapeutic interventions [5]. This research aims to investigate the structural and functional implications of nsSNPs within the SNCA gene using a multidisciplinary approach that includes bioinformatics, computational biology, structural biology, and functional assays. The study will analyze large-scale genomic datasets to identify nsSNPs and evaluate their evolutionary conservation, predicted functional effects, and population frequencies. Using advanced computational modeling techniques, high-resolution structural models of wild-type and variant α -Synuclein proteins will be generated. Comparative analyses will be conducted to

understand how nsSNPs affect alpha-Synuclein's native conformation and dynamics, potentially altering its interactions with cellular components and pathways involved in protein homeostasis, synaptic function, and neuronal viability. The research will also bridge the genotype-phenotype gap by integrating computational predictions with experimental validation. The study will use in vitro protein expression, biophysical characterization, and cellular assays to investigate the functional consequences of selecting nsSNPs on α -Synuclein biology. This research aims to deepen our understanding of neurodegenerative disorders and inform the development of personalized therapeutic strategies to mitigate the harmful effects of specific nsSNPs in affected individuals.

Nanotechnology has emerged as a revolutionary approach in the diagnosis and treatment of neurodegenerative diseases, including Parkinson's disease. The unique physicochemical properties of nanomaterials, such as their high surface-to-volume ratio, tunable size, and ability to cross the blood-brain barrier (BBB), make them ideal candidates for targeted drug delivery and early disease detection. Although certain nanocarrier systems can facilitate drug transport across the blood-brain barrier (BBB), this capability depends on their composition, surface functionalization, physicochemical characteristics, and administration route [6]. Recent advances in nanomedicine have demonstrated the potential of nanoparticle-based systems to deliver therapeutic agents directly to affected brain regions, minimize systemic toxicity, and enhance drug bioavailability [7].

Several types of nanoparticles have been investigated for potential applications in Parkinson's disease, including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), polymeric nanoparticles (PLGA and chitosan), liposomes, and carbon-based nanomaterials. Targeting ligands, such as transferrin and lactoferrin, have been used for surface functionalization to enhance interactions with blood-brain barrier transport pathways and improve drug delivery to the central nervous system [8]. Nanobiosensors have also been investigated for their ability to detect α -Synuclein and its aggregated forms, suggesting their potential to improve the sensitivity of diagnostic methods [9]. However, further validation is required before these technologies can be considered reliable for presymptomatic

diagnosis or routine clinical use.

Integrating nanotechnology with computational analyses of SNCA variants may provide a framework for identifying potential mutation-specific therapeutic strategies. By characterizing the predicted effects of nonsynonymous single-nucleotide polymorphisms (nsSNPs) on α -Synuclein structure, stability, and aggregation propensity, computational investigations may help identify molecular features relevant to the future design of nanoparticle-based therapeutic systems. Such systems could potentially be engineered to interact with disease-associated protein conformations or to deliver agents that modulate pathological aggregation pathways.

MATERIALS AND METHODS

The α -Synuclein (SNCA) gene sequence and protein sequence (P37840) were analyzed using NCBI dbSNP and Uniprot Knowledgebase databases. The coding area contains 173 single nucleotide polymorphisms (SNPs), 13 of which are nonsynonymous (nsSNPs). The protein's structure and function can be affected by these mutations, which can lead to missense or nonsense modifications [10]. The research used seven methods to predict the deleterious effects of nsSNPs. SIFT (Sorting Intolerant From Tolerant) predicts whether amino acid substitutions are tolerated or deleterious. The article "Predictor of Human Deleterious Single Nucleotide Polymorphisms" [11] describes PhD-SNP. Capriotti and Fariselli in 2017 [12] discuss several resources in the literature, including Polymorphism Phenotyping v2 (PolyPhen-2), PMut, Protein Analysis Through Evolutionary Relationships (PANTHER) [13], and SNPs and GO [14]. SIFT assesses the impact of an amino acid substitution on protein function by analyzing sequence homology and the physical properties of the substituted amino acids [15]. The PolyPhen-2 tool forecasts the impact of substituted amino acids on the structure and function of a protein, utilizing physical and comparative features [16]. PROVEAN is a support vector machine (SVM) service that predicts the functional impact of a substituted amino acid on a specific protein. Tools such as PANTHER, SNPs and GO, PhD-SNP, and PMut were employed to anticipate the potential involvement of single nucleotide polymorphisms in illness onset by functional protein annotation [17, 18]. High-risk nsSNPs were defined as those

predicted to be deleterious by four or more of the aforementioned in silico methods. To assess the effects of point mutations on the stability of the α -Synuclein (SNCA) protein, the following tools were utilized: INPS-MD, Mupro, and I-Mutant 3.0. The $\Delta\Delta G$ value (kcal/mol) and the level of protein instability can be predicted by I-Mutant 3.0, a support vector machine (SVM) based predictor. The $\Delta\Delta G$ value, which stands for delta delta G, is the disparity between the Gibbs free energy values of the wild-type protein and the mutant protein. The protein's stability is reduced when the $\Delta\Delta G$ value is less than 0, while improved stability is indicated when the $\Delta\Delta G$ value is greater than 0, according to Capriotti E et al. [19]. Mutation datasets used by MUpro, on the other hand, are based on a combination of support vector machines (SVMs) and neural networks [20]. The $\Delta\Delta G$ value is computed using the third technique, INPS-MD, which stands for Impact of nonsynonymous mutations on Protein Stability Multi-Dimension and is based on sequence descriptors and Support Vector Regression (SVR). According to Zhang et al. [21] and Adiba et al. [22], the $\Delta\Delta G$ is measured by both MUpro and INPS-MD to estimate protein stability, and the $\Delta\Delta G$ cut-off value is also the same as in I-Mutant 3.0. To anticipate the effect of mutations on protein stability, the aforementioned methods were fed the α -Synuclein (SNCA) protein sequence together with wild-type and substituted amino acids at their appropriate positions [19]. The MutPred2 web service was used to further analyze the frequently predicted mutations in order to separate out neutral or disease-associated amino acid alterations in protein sequences. This machine learning method predicts the pathogenicity of substituted amino acids by combining genetic and molecular data. Additionally, it forecasts the disease's molecular cause [23]. Project HOPE is an automated tool for analyzing the structural and biochemical consequences of point mutations in protein sequences [24]. We entered the seven SNPs (rs IDs) from the Protein Data Bank that contained the IL-4 protein's main structure into HOPE. By compiling structural data from multiple sources, HOPE forecasts the three-dimensional structure of the altered protein and explains the change (in both the protein's configuration and function). Research on protein-protein interactions aims to identify and categorize all of the functional relationships between cell proteins. Protein interaction predictions were made using the

online database STRING [25]. Using information on relapse-free and overall survival (OS) from the Gene Expression Omnibus (GEO), the European Genome-Phenome Atlas (EGA), and the Cancer Genome Atlas (TCGA) datasets, the Kaplan-Meier plotter database offers biomarker evaluation and discovery based on meta-analysis in cancer patients. The analysis's goal is to determine the average remaining life expectancy because, at some point, everyone will face a crisis that may significantly alter their approach to resource management, clinical decision-making, and health

policy formulation [26, 27]. With this approach, the possible impacts of genes (mRNA, miRNA, and protein) on cancer patient survival (including gastric, ovarian, lung, and breast cancer) might potentially be studied by aggregating microarray data on gene expression from 21 distinct cancer types [28]. The Affymetrix ID for the α -Synuclein (SNCA) gene was used to do an overall survival study on all cancer patients. The graphic was used to depict the hazard ratio (HR) together with the log-rank P-value and 95% confidence intervals [29, 30].

Table. 1. Analysis of the SNCA gene response to amino acid substitutions using SIFT, PolyPhen-2, SNPs, GO, PhD-SNP, and PANTHER.

rsID	Amino Acid Change	SIFT Prediction	PolyPhen-2	PhD-SNP	PANTHER	SNPs and GO
rs104893875	E46K	Tolerated	Probably Damaging	Disease	Natural	Natural
rs104893877	A53T	Tolerated	Benign	Natural	Natural	Natural
rs104893878	A30P	Deleterious	Probably Damaging	Disease	Disease	Disease
rs138969470	L100I	Tolerated	-	-	-	-
	L86I	Tolerated	-	-	-	-
rs145138372	P103T	Tolerated	Error	-	-	-
	P117T	Tolerated	Benign	Natural	Natural	Natural
rs201106962	H50Q	Tolerated	Possibly Damaging	Natural	Natural	Natural
	M113I	Deleterious	Error	-	-	-
rs191055637	M127I	Deleterious	Possibly damaging	Natural	Natural	Natural
	E109K	Tolerated	Error	-	-	-
rs200056149	E123K	Tolerated	Probably Damaging	Natural	Natural	Natural
	M102V	Tolerated	Error	-	-	--
rs372101729	M116V	Tolerated	Benign	Natural	Natural	Natural
	T54A	Tolerated	Probably Damaging	Natural	Natural	Natural
rs375682339	P138S	Deleterious	Probably Damaging	Natural	-	Natural
	P124S	Deleterious	Error	-	-	-
	P110S	Deleterious	Error	-	-	-
	Y133C	Tolerated	Benign	Natural	Disease	Natural
rs377006107	Y119C	Tolerated	Error	-	-	-
	Y105C	Tolerated	Error	-	-	-

Table. 3. Investigating the Molecular Mechanisms of Pathogenicity.

Amino Acid Changes	G-value	MutPred2	
		Molecular mechanisms with p-values <= 0.05	
E46K	0.646	Altered Disordered interface	0.28
		Gain of Methylation at E46	0.28
		Altered Transmembrane Protein	0.13
		Loss of helix	0.3
		Loss of Methylation at K32	0.29
A30P	0.901	Gain of Loop	0.27
		Altered Metal binding	0.17
		Loss of Ubiquitylation at K32	0.15
Y133k	0.196	-	-

RESULTS AND DISCUSSION

The DbSNP database identified a total of 42272 SNPs in the α -Synuclein (SNCA) gene, of which 173 were classified as missense SNPs. The analysis focused exclusively on these missense SNPs, excluding the remaining 41292 intrinsic SNPs, 77 synonymous SNPs, and 5407 non-coding SNPs. A total of 13 polymorphisms were further investigated, and their potential functional effects on the SNCA protein were evaluated using various computational tools to assess their structural and functional impacts (Table 1).

Three nsSNPs were specifically selected for in-depth investigation from the original pool of SNCA. The SIFT, PhD-SNP, PolyPhen-2, PANTHER_PSEP, and SNPs and GO tools were used to predict the potential deleterious effects of nsSNPs. Altogether, these tools identified nsSNPs as harmful or linked to diseases. Notably, as shown in Table 2, a consensus of at least three tools identified these nsSNPs as potentially harmful, likely harmful, or detrimental, indicating the need for additional research.

The MutPred2 web server was employed to further investigate the three previously identified nsSNPs predicted to be potentially deleterious. The probability scores (g and p values) obtained from the analysis are presented in Table 3. MutPred2 is used to predict molecular changes that may affect biological processes. The results of the MutPred2 analysis suggest that two mutations, E46K and A30P, may cause structural changes in the protein.

Some of the changes identified in this

study include alterations in methylation and ubiquitylation, loss of a helix at residue K32, gain of a loop and methylation at residue E46, alterations at the disordered interface, changes in metal binding, and modifications affecting transmembrane protein properties. The MutPred2 prediction for the Y133K variant suggests that its effects on protein function are likely to be neutral (Table 3).

Using a threshold of 0.50, the general score (g-score) generated by MutPred2 represents the overall predicted probability of pathogenicity. A g-score higher than 0.50 ($g > 0.50$) suggests that a mutation may be pathogenic. Furthermore, confident hypotheses are defined as those with $g > 0.75$ and $p \leq 0.05$, whereas actionable hypotheses are defined as those with $g > 0.50$ and $p \leq 0.05$. Notably, the MutPred2 predictions for E46K and A30P yielded g-scores greater than 0.50 and p-values below 0.05 (Table 3). These findings provide evidence that certain nsSNPs may be responsible for structural and functional changes in the protein α -Synuclein (SNCA).

The predicted nonsynonymous single-nucleotide polymorphisms (nsSNPs) were subjected to additional analysis using free energy comparison techniques in I-Mutant 2.0, INPS-MD, and Mupro to assess their potential effects on protein stability. Both INPS and MuPro consistent results, suggesting that all three nsSNPs are predicted to reduce protein stability. In contrast, I-Mutant 2 predicted that the two nsSNPs, E46K and A30P, would decrease protein stability,

Table. 2. Investigation of disease-related nonsynonymous single nucleotide polymorphisms (nsSNPs) in the SNCA gene.

rsID	Amino Acid Change	SIFT Prediction	PolyPhen-2	PhD-SNP	PANTHER	SNPs and GO
rs104893875	E46K	Tolerated	Probably Damaging	Disease	Natural	Natural
rs104893878	A30P	Deleterious	Probably Damaging	Disease	Disease	Disease
rs377006107	Y133C	Tolerated	Benign	Natural	Disease	Natural

Table. 4. The impact of single nucleotide polymorphisms on α -Synuclein stability.

I-Mutant2.0		INPS		Mupro	
DDG	Δ DDG	DDG	Δ DDG	DDG	Δ DDG
-0.44	Decrease stability	-1.37472	Decrease stability	-0.49213515	Decrease stability
-1.86	Decrease stability	-0.612178	Decrease stability	-1.374655	Decrease stability
1.02	Increase stability	-0.351841	Decrease stability	-0.70944411	Decrease stability

whereas Y133K would increase it (Table 4). The predictions consistently yielded $\Delta\Delta G$ values below zero. This finding suggests a potential alteration in protein stability, which may effect its structure and function, as shown in Table 4.

As outlined in Table 5, the HOPE project was used to analyze the structural effects of amino acid substitutions in the native protein. The results showed that the mutant amino acids differed from their wild-type counterparts in terms of size, charge, and hydrophobicity, as summarized in Table 5. Specifically, the three selected nonsynonymous single-nucleotide polymorphisms (nsSNPs) resulted in the amino acid substitutions E46K, A30P, and Y133K.

Further analysis using the HOPE project

indicated that these mutations were located within the domain region. Notably, all three mutations were found in highly conserved regions. According to the HOPE predictions, the wild-type residues of E46K and A30P were smaller than their corresponding mutant residues, whereas the wild-type residue of Y133K was larger than its mutant counterpart. Regarding charge, the wild-type residue of E46K was negatively charged, while its mutant form was positively charged. Similarly, the wild-type residue of Y133K was neutral, whereas its mutant form was positively charged. Furthermore, the hydrophobicity of Y133K was lower in the mutant form than in the wild-type form (Table 5). Overall, this analysis provides information about the locations of these mutations and their

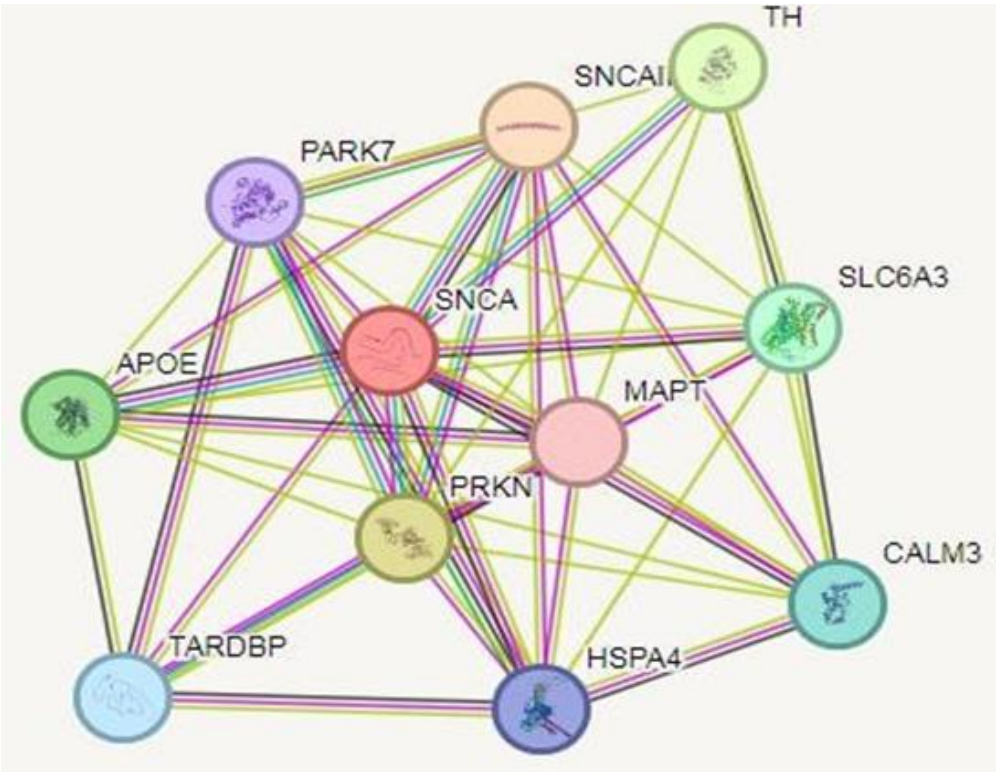


Fig. 1. Protein–protein interaction network of SNCA generated using the STRING database.

Table. 5. Analysis of three distinct SNCA gene mutations, summarizing their HOPE results.

Amino Acid		Size		Charge		Hydrophobicity-Value	
Variant	Wild-Type	Mutant		Wild-Type	Mutant	Wild-Type	Mutant
E46K	Smaller	Bigger		Negative	Positive	-	-
A30P	Smaller	Bigger		-	-	-	-
Y133K	Bigger	Smaller		Neutral	Positive	More Hydrophobic	Less Hydrophobic

potential effects on the structure and function of the α -Synuclein (SNCA) gene.

The STRING server results indicate that the protein α -Synuclein (SNCA) interacts with TH, SNCAII, PARK7, APOE, SLC6A3, MAPT, PRKN, TARDBP, HSPA4, and CALM3 (Fig. 1).

Using clinical data, we investigated the association between dysregulation of the α -Synuclein (SNCA) gene and clinical outcomes. The Kaplan–Meier Plotter was used to evaluate the prognostic significance of SNCA expression. Specifically, the survival outcomes of patients with gastric malignancies of the lungs, breast, pancreas, colon, and ovaries were analyzed. The graphical analysis revealed associations between SNCA expression levels and survival outcomes across different cancer types. For ovarian cancer, patients were divided into high- and low-SNCA-expression groups based on the median expression level. SNCA expression abnormalities were linked to a poor

outcome for ovarian cancer patients. Individuals who have higher levels of SNCA expression lived longer than those with lower levels. $P = 0.00047$, and the Hazard Ratio (HR) and P value for ovarian cancer were 0.0005 (HR: 1.11 – 1.44). On the other hand, high SNCA expression was associated with a higher risk and a lower survival rate for gastric cancer (HR 1.46 (1.23-1.73)), pancreatic cancer (HR 0.83(0.82-0.97)), lung cancer (HR 1.15(1.02-1.29)), breast cancer (HR 0.79 (0.71 – 0.87, $P = 3.3 \times 10^{-6}$)), and colon cancer (HR 1.47(1.18-1.84)). Because many forms of cancer can result from transcription mistakes, health needs to maintain appropriate expression levels of α -Synuclein genes Fig. 2.

The SNCA gene's coding and noncoding regions contain thousands of known polymorphisms. Identifying functionally significant SNPs among variants that may be either neutral or damaging through molecular methods is time-consuming and expensive. Therefore, computational

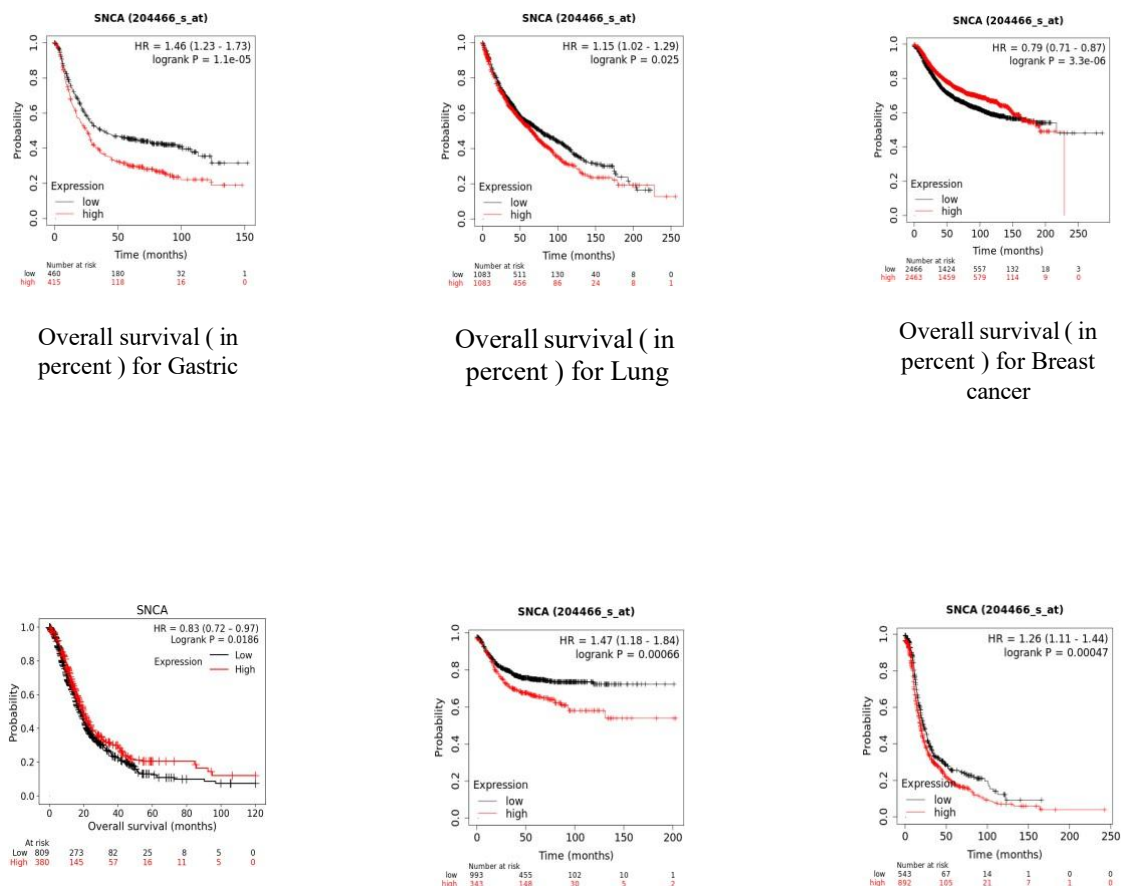


Fig. 2. Overall survival rates (%) across different cancer types.

techniques are crucial in anticipating and spotting significant alterations that negatively impact protein function [31-33]. However, because different algorithms use different parameters, this in silico approach has limitations in predicting dangerous nsSNPs. As a result, singular algorithms are not required to accurately forecast dangerous nsSNPs. It is necessary to use many algorithms with varying parameters and features in order to forecast dangerous nsSNPs. Reliability can be assured by obtaining a consensus decision from the majority of tools. We examined genetic variations in the SNCA locus. In addition to the 21 reported SNPs, (5) tools, namely SIFT prediction, polyphen-2, PhD-SNP, PANTHER, and SNPs and GO, have identified seven high-risk SNPs. The seven filtered nsSNPs were analyzed with I- Mutant2.0, MuPro, and IPNS-MD to study the protein stability effect. It was found that all three nsSNPs cause a decrease in stability, while it is expected that the rigidity of the SNCA protein will increase (Table 4). We used the MutPred20web site to look for molecular changes that could change the SNCA protein annotation (Table 3). The change in protein stability affects the conformational structure and thus determines the function of the protein [34]. The most significant impacts on protein annotation are caused by nonsynonymous single nucleotide polymorphisms (nsSNPs), which can also affect protein stability. A decrease in protein stability can alter how proteins fold, potentially leading to protein degradation or abnormal aggregation [35, 36]. The Project HOPE software has provided important insights into the potential effects of missense SNPs in the SNCA gene. Specifically, the polymorphisms rs104893875, rs104893878, and rs377006107 correspond to the amino acid changes Y133C, A30P, and E46K, respectively. The structure of SNCA proteins may be disrupted by these substituted amino acids due to their distinct physiological and chemical characteristics. The residues of wild-type amino acids are more hydrophobic than those of the substituted amino acids. The Y133K mutation results in the loss of the protein's hydrophobic interactions with other molecules. Furthermore, all mutations were located within a region that UniProt has designated as an intrinsically disordered region. Variations in amino acid properties may disrupt this region and interfere with its function. However, our findings indicate that these mutations are predominantly located in binding-site regions. The functional

consequences of this SNP for downstream signaling and interactions with the SNCA receptor complex have been investigated in several studies. Ford et al. (2009) demonstrated that this SNP increased MAPT stability and affected receptor binding [37]. Theoretically, mutations in binding-site regions may interfere with SNCA interactions with receptors, potentially impairing downstream signaling. According to the STRING analysis, the interaction network includes TH, SNCAI1, PARK7, APOE, SLC6A3, MAPT, PRKN, TARDBP, HSPA4, and CALM3 (Fig. 1). Additionally, SNCA may play both tumor-promoting and tumor-suppressive roles. Elevated SNCA expression has been associated with increased tumor growth, poor prognosis, and drug resistance.

CONCLUSION

The present study used several computational approaches to investigate the association between nonsynonymous single-nucleotide polymorphisms (nsSNPs) in the SNCA gene and Parkinson's disease. The SNCA gene encodes the α -Synuclein protein, whose stability and function may be affected by three variants (E46K, A30P, and Y133K). These variants were predicted to reduce protein stability, suggesting that they may contribute to structural and functional alterations in α -Synuclein. The mutant proteins carrying these nsSNPs exhibited structural differences compared with the wild-type α -Synuclein protein. These findings may have implications for future research into the potential role of genetic testing in risk assessment and treatment strategies for Parkinson's disease and other Synucleinopathies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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