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ORIGINAL ARTICLE

Molecular insights and risk estimating computational database for Parkinson's disease (PDASD)

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Abstract

Parkinson's disease (PD) is a more prevalent neurological disorder that typically manifests in adults. It is primarily caused by the death of dopaminergic neurons in the substantia nigra, which leads to the degeneration of cardinal motor symptoms. Several epigenetic elements are linked to the development of PD. The Parkin, PINK1, DJ-1, UCHL1, LRRK2, NURR1, ATP13A2, GSK3B, and SNCA are important genes that are involved in the regulatory processes and development of PD. The objective of the study is to develop a knowledge-based database for PD. "Parkinson Disease Associated SNP Database (PDASD)" has been created to establish connections between PD-associated SNPs, related pathways, proteins, risk assessment, and molecular mechanisms, available FDA drugs for PD, nutrition involvement of PD and available PD literature through the utilization of HTML and Java programming languages. This PDASD database has been amalgamated with 13 distinct databases to improve the accessibility of SNP data. The implementation of PDASD is anticipated to expedite the process and facilitate the identification of innovative drug candidates for PD through the application of computational drug design techniques in PD therapeutics. The PDASD database serves as a secondary resource that enhances the existing data from various tools to predict the status of SNPs, specifically missense variant risk factors. This platform consolidates the effects of all identified SNPs, facilitating easier access to their positional information and thereby optimizing time efficiency for users. A novelty of this database is its capacity to inform common people about the progression of PD through accessible molecular mechanisms and information regarding nutritional benefits. It will be useful to understand the interconnection of signaling pathways, molecular mechanisms, and risk-associated SNPs of PD, which may contribute to improving human health, especially for the community with PD. The PDASD is an open and accessed database connected via the following URL: https://www.generisk.in/PDASD/

Keywords Database · Knowledge base · nsSNPs · Parkinson's disease · PD molecular mechanism · PD signal pathway

1 Introduction

Parkinson's disease (PD) is the second most prevalent neurological disorder after Alzheimer's disease (Thenganatt and Jankovic 2014; Deng et al. 2017). This PD is the degeneration of cells in the substantia nigra, with a specific impact on the ventral part of the pars compacta. At the point of death, there is a marked reduction of 50–70% in the number of neurons within this particular brain region compared to unaffected individuals (Davie 2008). There are various symptoms and signs associated with PD, with the most common motor features being rest tremor, bradykinesia, rigidity, and postural instability. Additionally, non-motor features such as olfactory dysfunction, cognitive impairment, psychiatric symptoms, and autonomic dysfunction (Deng et al. 2017;

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Poewe et al. 2017). In this disease, around 1% of the population is affected at the age of 65 years, with the rate rising to 4–5% among individuals aged 85 years. The average age at which features typically appear is 70 years of age, although 4% of people experience early-onset disease before reaching the age of 50 (Trinh and Farrer 2013). The development of neuroconditions in PD was found to be affected by a range of epigenetic factors and single nucleotide polymorphisms (SNPs) present in certain coexisting genes that were actively expressed (Subramaniyan et al. 2023). There are several genes that have been associated with significantly increasing the susceptibility to PD in a predominantly Mendelian manner. Through various genetic and functional analyses, mutations in SNCA, Parkin, UCHL1 (Ubiquitin Carboxyl-Terminal Hydrolase L1), DJ-1, PINK-1(PTEN Induced Kinase 1), LRRK2 (Leucine-rich repeat kinase 2), ATP13A2 (ATPase Cation Transporting 13A2), GSK3B (Glycogen Synthase Kinase-3 Beta) and NURR1 have been validated as more influential factors in the improvement of the disease within an individual or a familial context (Mouradian 2002; Pankratz and Foroud 2007; Hardy 2010; Domingo and Klein 2018). Despite these genetic variations, they contribute to a minority of PD cases, representing less than 10% of the majority of the populations. Therefore, the investigation of genetic predisposition risk factors in the majority of PD cases remains a topic of significant interest for numerous researchers (Tan 2007).

Many sources of information are available in the public domain and open-source databases, which has a significant influence on pathway-based drug development using in silico methods. Knowledge about signaling and metabolic pathways is essential for understanding how proteins are involved in the development of PD and how nutritional supplements involve reducing PD. This understanding is crucial for identifying potential targets for therapeutic interventions and validating the efficacy of these targets (Loganathan et al. 2023). The dispersed information on PD-associated proteins and pathways in biological databases and literature made data collection more difficult. Although the researchers were gathering relevant information on a certain target protein from multiple sources, this process gradually required a significant of time to establish a comprehensive understanding. Therefore, having access to relevant information on involved proteins, genes SNPs, and biochemical pathways on a single open-access webpage is anticipated to speed up molecular diagnosis and enable the development of more honest strategies for individualized PD patient management (Gopinath et al. 2014). Currently, there exists a limited number of online databases dedicated to PD, including ParkDB (Taccioli et al. 2011), PDGene (Lill et al. 2012), and Gene4PD (Li et al. 2021). However, these databases primarily concentrate on only two or three gene expressions. In contrast, the objective of the PDASD database is to identify early predisposed SNPs associated with PD through the application of a computational evolutionary algorithm and proprietary software developed by our team. While three databases are accessible to the public concerning Parkinson's disease, they predominantly focus on gene expression and genomics, lacking comprehensive information on the role of nutritional supplements in PD, available FDA-approved medications, and the listing of highly deleterious SNPs. The PDASD database specifically targets the identification of highly deleterious SNPs across nine genes relevant to PD patients. We utilized a range of bioinformatics tools, including SIFT, Polypen 2, PMut, and PANTHER, to systematically evaluate and calculate the risk levels associated with SNPs across nine genes implicated in PD. By integrating and consolidating the outputs generated by these computational analyses, we developed a comprehensive database that catalogs and organizes the potential genetic risk factors contributing to PD susceptibility. Furthermore, this database aims to elucidate the impact of PD on the human body and to explore the involvement of specific nutritional supplements about the identified genes and the pathways associated with PD. This in-silico prediction software to computationally elucidate the disease-causing SNPs of nine genes was selected based on pathways to analyze how these SNPs affected the structure, regulation, and function of the corresponding proteins (Gopinath et al. 2014; Loganathan et al. 2023). This database will prove to be useful in PD research, as it facilitates the identification of gaps in the SNPs of genes associated with the pathogenesis of PD. Furthermore, it aids in the identification of high-risk SNPs related to PD, thereby enabling targeted interventions to mitigate these risk factors. Such efforts have the potential to decrease the risk among individuals. Additionally, this resource will assist researchers, clinicians, and individuals affected by PD in comprehending the underlying causes of the condition and the therapeutic benefits of various nutrients.

2 Materials and methods

2.1 The incorporation of pathway and gene information with PD proteins

The PD-associated genes and protein information were collected from the KEGG pathway database. This database contains pathways associated with various human diseases, including neurodegenerative, cancer, immune, cardiovascular, endocrine, metabolic, and infectious diseases (Kanehisa et al. 2011; Gopinath et al. 2014). The neurodegenerative pathways for PD, Ferroptosis, Amyotrophic Lateral Sclerosis, Huntington's disease, Spinocerebellar Ataxia, and Prion disease are available in the KEGG PATHWAYS and KEGG DISEASE databases. All proteins related to Parkinson's

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disease were obtained from the KEGG pathway database (Loganathan et al. 2023). The genes associated with PD pathways were linked to KEGG GeneIDs and then correlated with their respective UniProt IDs through an identifier mapping tool (Jain et al. 2009; Magrane & Consortium, 2011).

2.2 Acquisition of data

The PD-associated details, genes, and protein-related information were collected from the literature and the KEGG pathway database. For literature, we utilized PubMed, Google Scholar search, and other search engines to identify the most pertinent articles related to our specified keywords. Additional reviews and articles were refined through the application of several keywords, such as PD, proteins, SNPs, PD pathways, and PD mechanisms and nutrition supplements involved in PD. Eventually, articles and information were carefully collected by excluding those that lacked pertinent information (Johansson et al. 1996). After gathering information, we identified nine genes (SNCA, UCHL1, DJ1, NURR1, LRRK2, ATP13A2, GSK3B, Parkin, and PINK1) and utilized ensemble, dpSNPs, and DisGeNET databases to compile the SNPs associated with PD (Yasmin 2022). Subsequently, the identified SNPs underwent structural and functional analysis using 13 tools to assess missense variants, culminating in the integration of these findings into the PDASD interactive database (Choudhury et al. 2021; Loganathan et al. 2021). The functions of those 13 tools are as follows:

2.3 SIFT (Sift (Sorting Intolerant From Tolerant)

SIFT (https://sift.bii.a-star.edu.sg/) is a computational tool utilized for predicting the functional consequences of amino acid substitutions based on sequence homology. It differentiates between intolerant and tolerant substitutions and assesses the potential impact of SNPs on protein function. A SIFT score of less than 0.05 suggests that a missense variant is likely to be deleterious, whereas a score of 0.05 or higher indicates that the variant is likely to be benign (Ng 2003).

2.4 PANTHER (Protein Analysis Through Evolutionary Relationships)

PANTHER (http://www.pantherdb.org/) serves as a resource for the analysis of genetic variants. SNPs that receive a score below -3 are categorized as deleterious, whereas those with a score exceeding -3 are regarded as neutral (Mi et al. 2019).

2.5 PolyPhen-2 (Polymorphism phenotyping v2)

PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) is an online resource developed to evaluate the impact of amino acid substitutions on the structure and function of human proteins. Scores within the range of 0.96 to 1 are classified as 'Probably damaging,' scores from 0.71 to 0.95 are deemed 'Possibly damaging,' and scores between 0.31 and 0.70 are categorized as 'benign' (Adzhubei et al. 2013).

2.6 PhD-SNP (Predictor of human deleterious single nucleotide polymorphisms)

PhD-SNP (http://snps.biofold.org/phd-snp/phd-snp.html) is a computational tool developed to predict the effects of amino acid substitutions or insertions/deletions on the biological function of proteins (Gb et al. 2022).

2.7 SNPs&GO (Single nucleotide polymorphism database and gene ontology)

SNPs&GO (http://snps.biofold.org/snps-and-go/snps-and-go.html) is a computational method that employs support vector machine (SVM) algorithms to predict mutations associated with diseases in protein sequences. The accuracy of the predicted variant scores is reported to be 82%, accompanied by a Matthews' correlation coefficient of 0.63. Variants that receive a score exceeding 0.5 are categorized as 'disease' variants (Capriotti et al. 2013a, b).

2.8 MutPred2

The MutPred2 tool (http://mutpred.mutdb.org) classifies amino acid substitutions as either pathogenic or neutral. Utilizing a machine learning algorithm, it predicts the pathogenicity of mutations and offers an understanding of the molecular mechanisms that contribute to their disease-causing potential (Pejaver et al. 2017).

2.9 SNAP2 (screening for non-acceptable polymorphisms)

SNAP2 (https://www.rostlab.org/services/snap/) employs exclusively sequence-based computational data to classify all nsSNPs across various proteins as either deleterious (impacting functionality) or neutral (having no effect). This tool facilitates the swift assessment of functionally significant sites in novel proteins and provides dependable predictions regarding the effects of genetic variants (Hecht et al. 2015).

2.10 Predict Snp2

PredictSNP (https://loschmidt.chemi.muni.cz/predictsnp/) functions as a consensus classifier. The scores generated by PredictSNP are situated within a continuous range of $< -1, +1 >$. Mutations are classified as neutral if their

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scores fall between -1 and 0, while those with scores in the interval $(0, +1>$ are considered deleterious (Bendl et al. 2016; Akhtar et al. 2021).

2.11 MAPP (Multivariate Analysis of Protein Polymorphism)

MAPP predicts the functional consequences of modified amino acids by assessing the physicochemical properties identified through protein sequence alignment. The interpretability of MAPP's impact ratings, which provide a clear rationale for predictions based on these physicochemical characteristics, enhances its capacity for accurate outcome forecasting (Dash et al. 2020).

2.12 PMUT

PMUT (http://mmb.irbbarcelona.org/PMut/analyses/new/) facilitates the rapid and accurate prediction of the pathogenicity of single-point amino acid alterations, achieving an 80% success rate in human applications, through the utilization of neural networks. The pathogenicity score is quantified on a scale from 0 to 1, with scores exceeding 0.5 indicating the presence of pathogenic mutations (Ferrer-Costa et al. 2005; Wang et al. 2019).

2.13 Meta-SNP

Meta-SNP is a meta-predictor tool designed to integrate the outcomes of various SNP effect prediction tools. The reported overall accuracy of Meta-SNP is 73.02% (Capriotti et al. 2013a, b).

2.14 Suspect

The Suspect webserver (http://www.sbg.bio.ic.ac.uk/~suspect/), which focuses on predicting phenotypes of single amino acid variants based on disease susceptibility, demonstrates an accuracy rate of 82% in its predictions (Yates et al. 2014).

2.15 Pon-P2

The PON-P2 (http://structure.bmc.lu.se/PON-P2/) method employs machine learning to forecast pathogenic missense mutations. It classifies the missense variants of a protein into three categories: unknown, neutral, and pathogenic (Niroula et al. 2015).

This formation of a risk assessment panel is intended to improve the comprehension of genetic determinants and associated information concerning PD (Cherian and Divya 2020; Day and Mullin 2021). Simultaneously, the section dedicated to molecular mechanisms facilitates the examination of the processes that contribute to the pathogenesis of PD. The sixth panel provides accessible information regarding medications for PD that have received approval from the Food and Drug Administration (FDA). Additionally, in the seventh panel, we present a comparative table detailing the binding affinity scores of nine wild-type and mutant targets about FDA drugs for PD. The binding affinity scores were derived from molecular docking studies conducted using the PyRx version 0.8 software package. Both the wild-type and mutant variants of all target molecules underwent optimization and energy minimization processes utilizing PyRx 0.8. Following energy minimization, the optimized structures were selected for subsequent docking investigations. Before initiating the docking studies, we selected FDA-approved medications from the Drug Bank for PD. Additionally, all compounds underwent energy minimization before being subjected to docking analysis. For each target, the dimensions of the active site were defined as the grid size (Roy et al. 2021; Abraham et al. 2022; Ss et al. 2024). The docking process was enhanced using the AutoDock Vina plugin within PyRx version 0.8. The scoring function employed in this study, AutoDock Vina, is essential for predicting the efficacy of the ligands about the protein targets. Finally, the Discovery Studio visualizer was utilized to construct, visualize, and analyze the interactions between the ligands and proteins (D. Iqbal et al. 2023; Zulfat et al. 2024). Furthermore, an additional panel addresses the formulation of nutritional supplements that are employed in conjunction with the management of PD (Glatzle et al. 2008; Kocot et al. 2017; Zhao et al. 2019; Iqbal et al. 2022; Turton et al. 2021).

2.16 Fabrication of database

Following the completion of the computational effect of SNPs on the protein regulation was predicted and regulations were analyzed using risk estimation tools developed by Python and Java programming languages, which are written in CSS, HTML, and JSON-like formats. The front-end development employs HTML, CSS, and JSON, while the back-end utilizes Python and Java. HTML is responsible for generating tables, images, and videos, whereas CSS is utilized to establish the structural presentation of data, encompassing aspects such as color, background, font style, font size, and the formatting of tables. JSON is implemented for data tables, leveraging the Bootstrap framework. In turn, Java and Python serve as the back-end technologies for the development of a database tailored to specific parameters related to SNPs. Libraries like jQuery and AJAX (load and alert) in JavaScript were used for mouse- clicking and scrolling the content in our database (Fig. 1). AJAX load was as used as a method to load the data from a server and return to the selected elements and AJAX alert is used to callback function as requested by the user in the first parameter which shows the alert if the mandatory field are not filled in the

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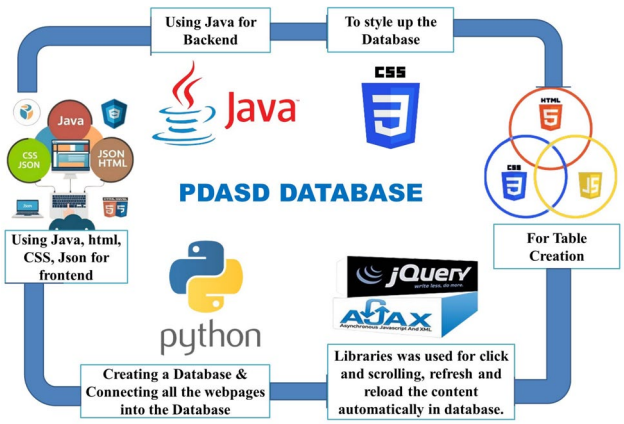

Fig. 1 The methods used to estimate the computational database of PD

second parameter. The risk estimation panel classifies the effect values of SNPs into specific parameters, employing programming languages such as Python and Java. In the realm of risk estimation, SNPs have been systematically classified into four distinct categories based on their associated effects. A comprehensive analysis utilizing 13 analytical tools was conducted to identify high-risk deleterious SNPs pertinent to PD. The findings indicated that SNPs yielding results from 0 to 3 tools classified as deleterious were associated with no risk, whereas those with results from 4 to 6 tools indicated a moderate risk. SNPs that received results ranging from 7 to 9 tools were considered to present a risk, while those classified with results from 10 to 13 tools were categorized as high-risk SNPs. Thus, the potential severity of harm is systematically organized within this database according to these four defined scoring thresholds. The effects of SNPs on target function have been confirmed through experimental data. These SNPs have been compared with patient information or earlier published research (Supplementary Table 1). This database encompasses the identified SNPs of nine genes that have been linked to PD. The PDASD database as an interactive risk estimation tool, multiple allelic interactions, molecular mechanism of PD, risk associated factors for PD and pathway analysis, scoring matrices for PD risk calculations, and relevant articles were in the database. The workflow of the database is explained in Fig. 2 and the front end's various interactive tools and images are shown in Figs. 3 and 4. Through this database, if any individual wants to know the risk estimation for PD feeding, the right information and risk estimation can be taken as an outcome (Gopinath et al. 2014; Loganathan et al.

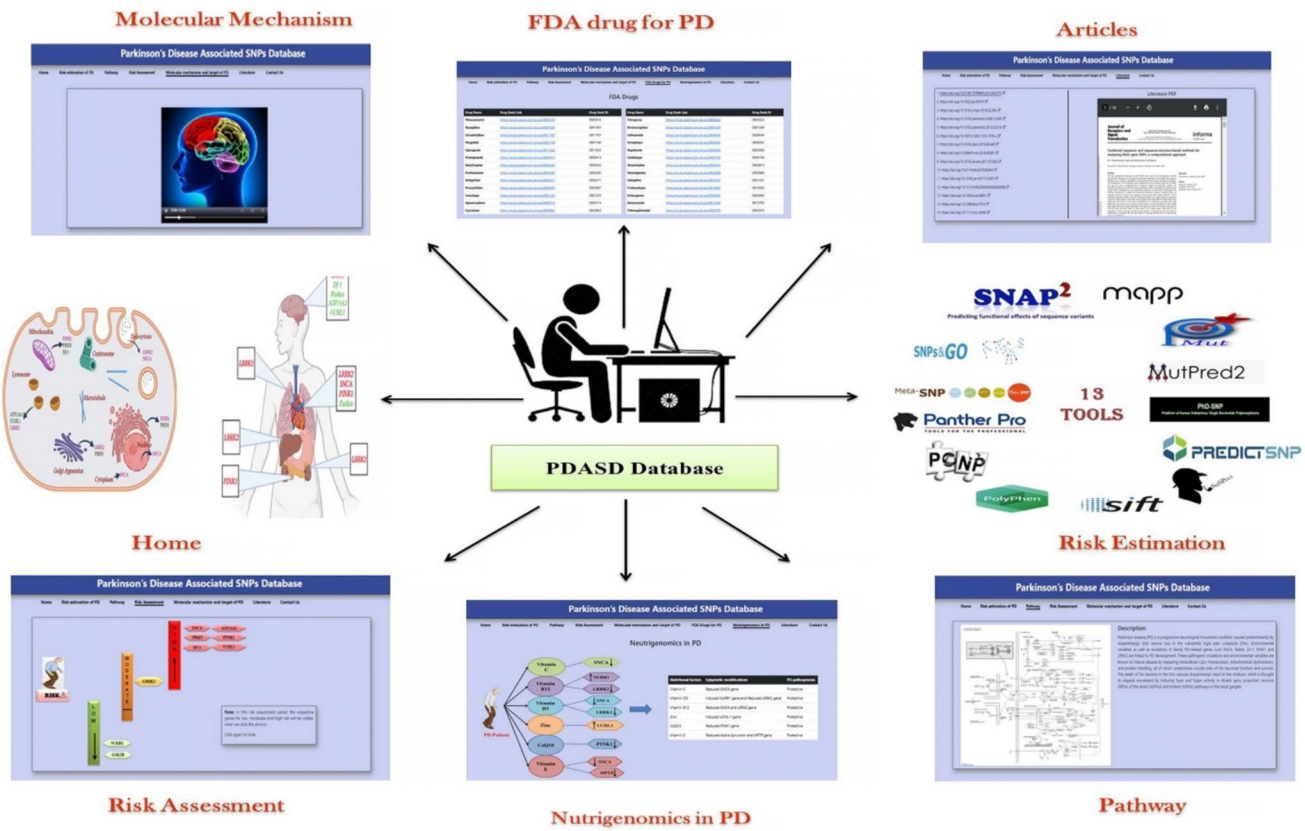

Fig. 2 The Workflow of the PDASD Database in PD

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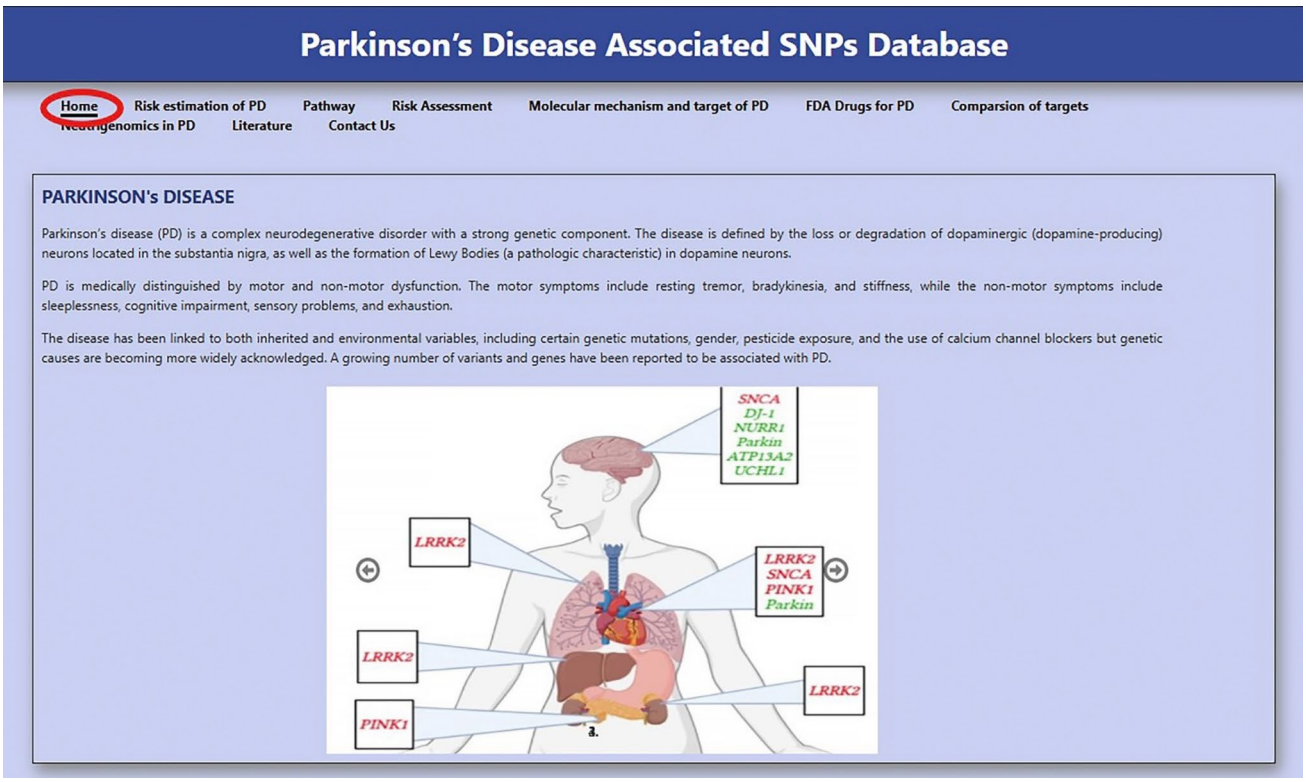

Fig. 3 Homepage of the PDASD knowledgebase

2023). The PDASD database is designed with a user-friendly interface, facilitating ease of access for users. It allows for straightforward searching and prediction of SNP risk levels, as well as providing relevant literature on PD. This database is freely accessible online to researchers, scientists, medical professionals, and the general public.

3 Result and discussion

3.1 Integration of data

The open-source biological database plays a significant role in supporting life science researchers by providing them with access to the latest information compiled from diverse sources of literature and databases in a concise and comprehensible format**.** Our database connects the user to various knowledge bases through connections of hyperlinks. The database uses a centric filter which allows the user to search the information according to their needs. It is widely recognized that variations in gene expression and its proteins can lead to dysfunction in the biochemical pathway associated with the structural and functional integrity of proteins such as SNCA, LRRK2, DJ1, NURR1, PINK1, ATP13A2, Parkin, UCHL1, and GSK3B, eventually contributing to the improvement of PD. There is currently a notable endeavor underway to identify the pathophysiological pathway, employing detailed mapping and functional methodologies. Therefore, it is essential to comprehend the pathogenic mechanism involved with protein is essential for managing and treating patients by emphasizing pathway regulation. The exploration of novel PD targets and SNPs in the investigation of associated missense variants is a current focus of research. Databases and the literature both include updates on proteins linked to PD; these sources may not encompass all relevant data. Establishing connections between PD-related pathways, genes, and proteins has the potential to establish a robust basis for the management of PD.

The PDASD database encompasses a collection of PD-related proteins, SNPs, pathway, risk assessment data, FDA drugs for PD, Nutrigenomics in PD, and insights into the molecular mechanisms underlying PD. This data is collected from various databases including KEGG, Google Scholar, PubMed, Ensemble, dpSNPs, and DisGeNET. According to the currently available literature, all SNPs (missense variants) have been clinically validated in the context of PD. In Supplementary Table 1 we included references to all clinically validated SNPs. All collections of SNPs were comprehensively analysed for structural and functional information from multiple databases such as sift, panther, polypen 2, mutpred 2, predict Snp2, Mapp, Pmut, meta SNP, suspect, Pon-P2, PHD-SNP, SNPs&GO, and SNAP2. Subsequently,

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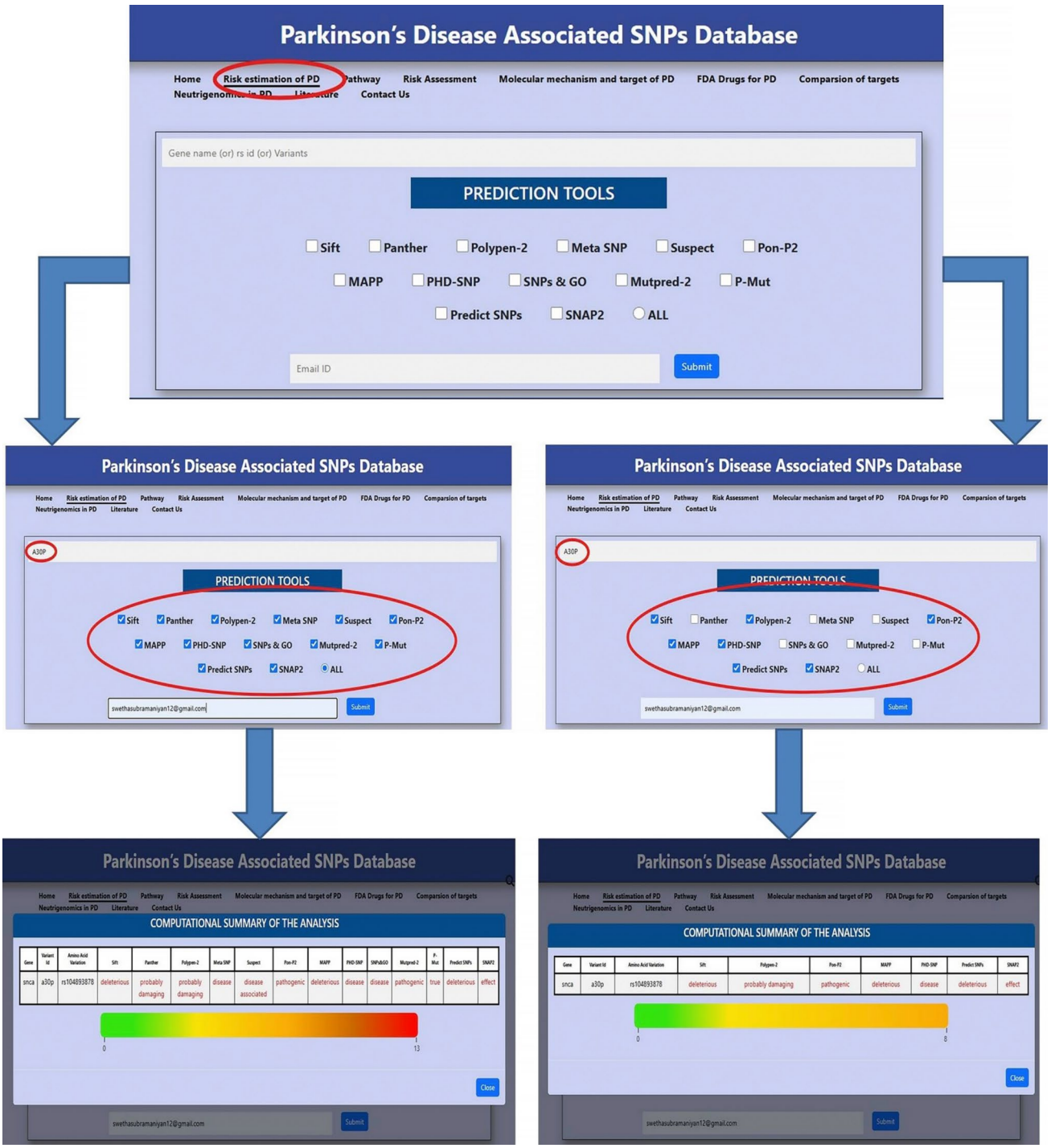

Fig. 4 Screenshot of PD risk estimation panel for the query related to vulnerable SNPs associated with PD and the result outcome page of the Database (In the risk estimation panel, a systematic approach has been implemented to determine the probability of genetic mutations or rs id associated with PD)

we conducted a comparative analysis of existing databases, such as ParkDB, Gene4PD, and PDGene, within the context of our database. The currently available societal databases do not encompass information regarding the molecular mechanisms of PD, nutritional supplements, FDA-approved medications for PD, or clinically validated SNPs associated with the condition. In contrast, the PDASD database incorporates all of these data, thereby serving as a valuable knowledge resource for researchers, healthcare professionals, and individuals affected by PD. This database contains

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information about the characteristics of SNPs, which can be utilized to categorize proteins with similar properties for further insights. PDASD provides users with access to various databases and knowledge bases via connections, where they may find out more details about SNPs and molecular mechanisms.

3.2 User interface

The PDASD database, PD proteins, pathway molecular mechanism, and SNPs were linked. It was implemented using HTML and JavaScript.

3.3 Programming languages for developing the database

HTML was used for structured and semantic meaning content in our database including images, tables, video, and other graphical representations. It was also used for organizing the contents, headings, table structure and alignments according to the database view. CSS is used for styling our database features like how content is presented, including aspects like background color, font, layout and animations of our database. Bootstrap was developed using JavaScript for our database which allows the users to view as per their requirements. Python was used as a backend for developing our database which involves user interaction between the frontend (what users interact with) and backend (database and server).

To consolidate and present the analysed results and also estimate the genetic basis of possible risk factor estimation, this interactive database (PDASD) was developed. The PDASD database (https://www.generisk.in/PDASD/) provides information on the targets of PD as well as the single nucleotide polymorphisms (SNPs) that may be associated with them. Additionally, the PDASD database offers a comprehensive pathway and visual representation of how genes impact individuals affected by PD, as well as the presence and absence of predisposed markers (SNPs) in the population (Fig. 2). The homepage of the PDASD database provides a comprehensive overview of PD symptoms, molecular mechanisms, pathway, genomic information, and FDA drugs for PD, Nutrition supplements for PD and literature.

3.4 Implementation

The PDASD database is hosted on Windows 10 and can be accessed globally through the internet. The entire webpage can be reached at the following URL: https://www.generisk.in/PDASD/

3.5 How can PDASD help?

3.5.1 Home page

Figure 3 presents an overview of the PDASD database, which facilitates an understanding of PD and its associated symptoms. The homepage features a visual representation that effectively illustrates the number of genes linked to PD, as well as the specific organelles with which these genes are associated, thereby enhancing comprehension of the disease. This homepage description provides an overview of PD, detailing its symptoms, which include resting tremor, bradykinesia, rigidity, and postural instability, as well as olfactory dysfunction, cognitive impairment, and psychiatric symptoms. Additionally, it discusses the various factors contributing to the onset of PD, including environmental variables, genetic factors, gene mutations, and exposure to pesticides. Specifically, the homepage presents a singular figure that elucidates the specific genes associated with PD and their expression in various organs of PD patients. In this figure, nine genes are highlighted, with those represented in pink indicating upregulation, while those depicted in green signify downregulation within the context of PD pathology.

3.6 Risk estimation of PD section

Figure 4 illustrates the risk estimation calculations for nine genes associated with missense variants in PD. This panel aims to predict the risk levels of missense variants in PD-related genes utilizing thirteen computational tools, including SIFT, PANTHER, PolyPhen-2, MutPred2, PredictSNP2, MAPP, PMut, MetaSNP, Suspect, PON-P2, PHD-SNP, SNPs&GO, and SNAP2. The search engine allows users to input the missense variants, select the desired tool results, and submit the analysis. Upon submission, the results are displayed in the database, indicating the number of deleterious levels associated with each missense variant. This information aids in understanding the risk levels of missense variants in genes related to PD.

The PDASD database currently includes results for nine genes (SNCA, ATP13A2, LRRK2, NURR1, PINK1, UCHL1, GSK3B, DJ1, and Parkin) with missense variants linked to PD (Supplementary Table 1). This risk estimation panel enables users to identify the SNPs most closely associated with nine PD risky specific genes. By determining which SNPs are associated with high, moderate, or low risk, this resource can facilitate the computational diagnosis of PD. Users can ascertain the risk profiles of SNPs related to PD through the risk estimation features of this database. Such insights allow researchers and clinicians to identify high-risk patients, thereby potentially decreasing the incidence of the disease in future populations and enabling timely medical interventions to mitigate risk. In the future,

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this database will be expanded to include all genes with missense variants associated with PD. This computational analysis serves as a valuable resource for researchers and scientists in identifying genes that pose a risk for PD.

3.7 Pathway

The third panel focuses on elucidating the pathway associated with PD (Fig. 5). This pathway aims to enhance the understanding of the number of genes implicated in PD, as well as the interactions among these genes, including gene-to-gene interactions. Additionally, it addresses the role of mitochondrial dysfunction and oxidative stress in the context of PD. The comprehensive pathway encompasses the mitochondrial pathway, calcium signaling pathway, and ubiquitin pathway, all of which contribute to the interactions of PD-related genes in cellular death processes.

3.8 The panel of risk assessment

The risk assessment panel is designed to identify genes associated with varying levels of risk specifically high, moderate, and low pertaining to PD. The involvement of various genes in PD we categorized into three levels of significance. At a high level, the genes SNCA, ATP13A2, UCHL1, PINK1, PRKN, and DJ-1 are prominently associated with PD. LRRK2 is considered to have a moderate level of involvement, while NURR1 and GSK3B are classified as having a low level of association with the disease. These classifications were derived from a comprehensive review of the literature, including sources such as Google Scholar and PubMed articles. Additionally, it elucidates the relationship between these genes and PD. Environmental factors have been recognized as significant contributors to PD for an extended period. Heavy metals, particularly manganese and iron, have been associated with Parkinsonian conditions for decades. More recently, a broader range of environmental agents, including pesticides, herbicides, fungicides, and additional heavy metals, have been correlated with the onset of PD and PD-like syndromes. These environmental factors, such as pesticides and heavy metals, exert detrimental effects that may exacerbate the risk of developing PD by inducing genetic variations associated with familial forms of the disease (e.g., SNCA, LRRK2, PINK1). This, in turn, leads to mechanisms associated with PD, including mitochondrial dysfunction, oxidative stress, and impaired protein degradation. Consequently, this section provides comprehensive information regarding the relevant genes, including details about missense variants associated with the corresponding

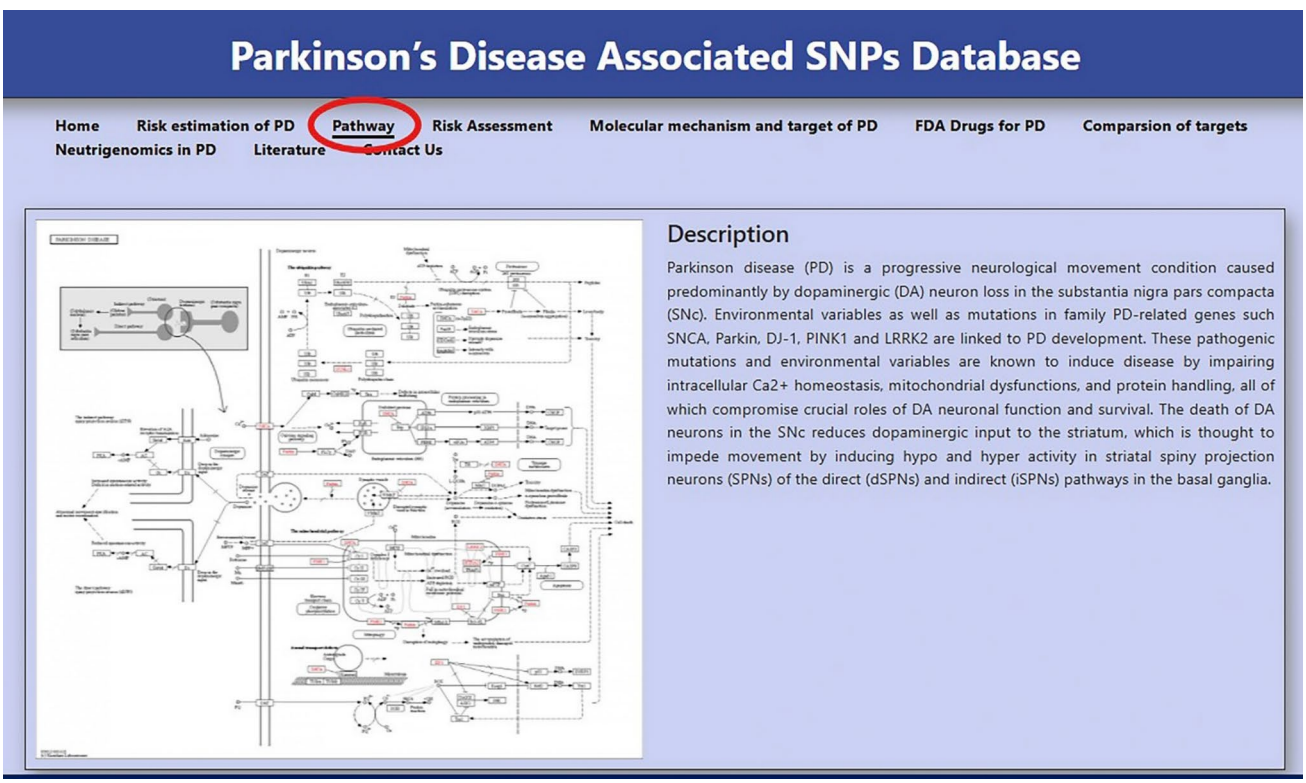

Fig. 5 Screenshot view of the signaling pathway involved in the PD (The pathway section pertaining to PD has been selected and integrated into the database from the KEGG pathway server)

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proteins, the length of the sequences, and their specific locations (Fig. 6).

3.9 Molecular mechanism

The fifth panel illustrating the molecular mechanisms is visually effective in elucidating the process by which PD develops within the human body. This section is particularly beneficial for the general population. It details the role of the midbrain's substantia nigra in dopamine production, the impact of cell death, and the specific genes implicated in these processes, including those that are up regulated and down regulated. This panel provides a comprehensive understanding of these complex interactions. This indicates that optimal dopamine production occurs without causing harm to nerve cells, thereby reflecting a state of good physical health in the individual. In the context of SNCA, LRRK2, and PINK1, there is an upregulation (overexpression) of these genes, while ATP13A2, NURR1, DJ1, PRKN, GSK3B, and UCHL1 exhibit downregulation (reduced expression). Various environmental, genetic factors, and mutations, contribute to the regulation of genes associated with PD. These regulatory changes are implicated in the pathogenesis of PD. Notably, mutations in the LRRK2 gene lead to its overexpression, which subsequently triggers the release of cytochrome c (CYTC). Additionally, the down

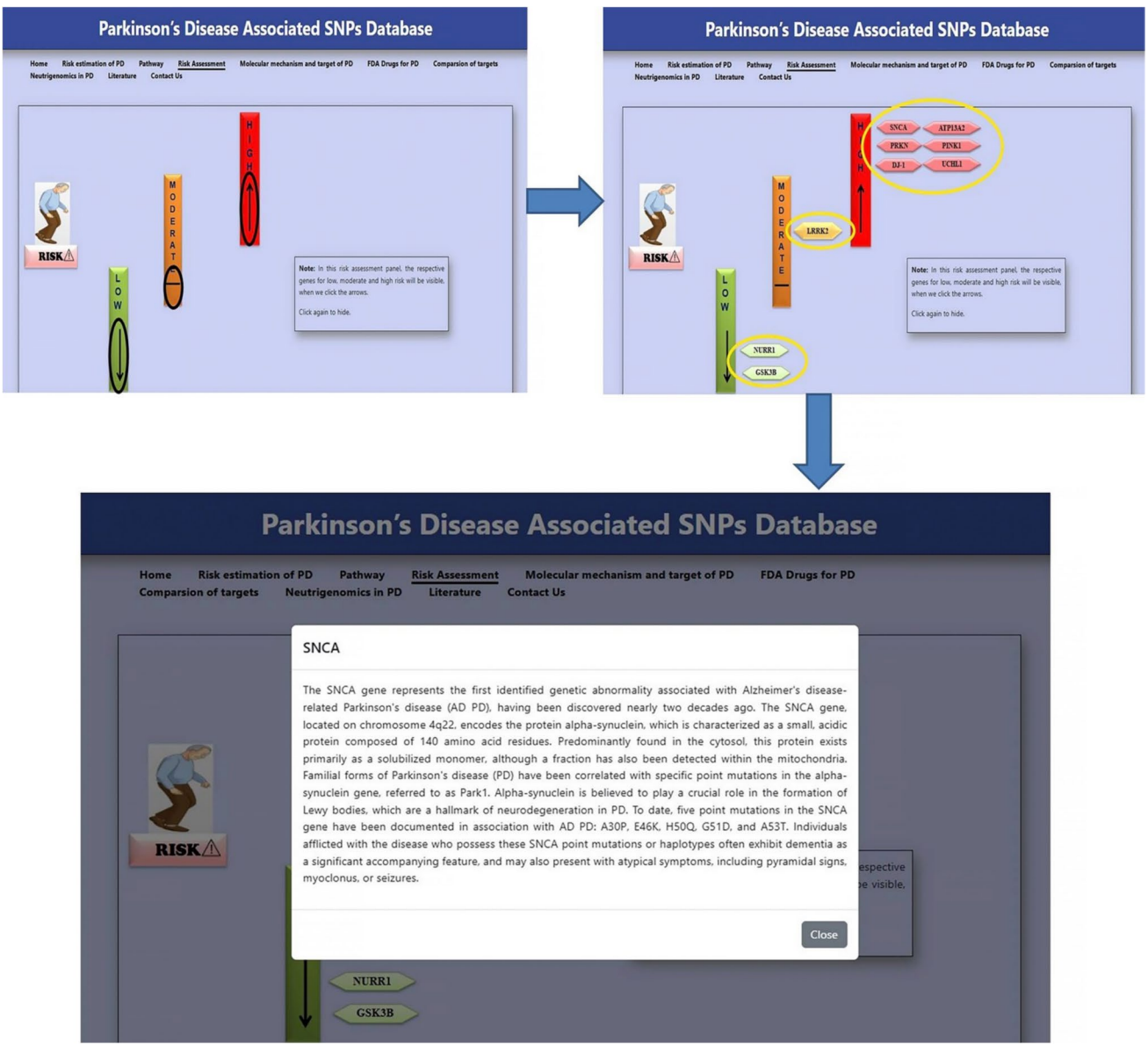

Fig. 6 Risk assesment based on the gene associated with PD in the PDASD Database (In the field of risk assessment, the database was incorporated to the extent to which genes linked to PD contribute to a vulnerability to developing PD)

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regulation of ATP13A2 facilitates the accumulation of alpha-synuclein (SNCA), resulting in oxidative stress due to the aggregation of this protein. This oxidative stress ultimately leads to neuronal cell death. Furthermore, the down regulation of DJ-1 and Parkin, alongside the upregulation of PINK1, disrupts mitochondrial function, which is critical for neuroprotection and neurogenesis. The downregulation of Parkin and UCH-L1, in conjunction with the ubiquitin–proteasome system (UPS), contributes to the degeneration of misfolded SNCA, which is a significant factor in the induction of cell death. This alteration leads to a decrease in dopamine hormone production, resulting in dopamine deficiency, which subsequently contributes to neuronal cell death. Such cell death is associated with the pathophysiology of PD (Fig. 7).

3.10 FDA drugs for PD

The PDASD database has been enhanced to incorporate 26 medications approved by the FDA for the treatment of Parkinson's disease (PD). These medications include Pimavanserin, Rasagiline, Pergolide, Opicapone, Pramipexole, Benztropine, Profenamine, Trihexyphenidyl, Selegiline, Entacapone, Foslevodopa, Benserazide, Droxidopa, Rivastigmine, Ropinirole, Amantadine, Carbidopa, Rotigotine, Procyclidine, Levodopa, Safinamide, Bromocriptine, Tolcapone, Apomorphine, Cycrimine, and Istradefylline. Presently, the FDA-approved drugs are linked to the DrugBank database, thereby facilitating their accessibility within this platform. The pharmacological agents discussed herein are specifically designed to target certain biological pathways. The **HTR** target is activated by the drugs Pimavanserin, Pergolide, Pramipexole, Rotigotine, Apomorphine, and Bromocriptine. The **MAOB** gene is engaged by Rasagiline, Safinamide, and Selegiline. The **DRD** target is influenced by Pergolide, Pramipexole, Levodopa, Apomorphine, Bromocriptine, Ropinirole, and Amantadine. Additionally, the **ADRA** and **CHRM** targets are activated by Istradefylline, Benztropine, Profenamine, Rotigotine, Procyclidine, Apomorphine, Cycrimine, Bromocriptine, Droxidopa, and Trihexyphenidyl. The **COMT** gene is activated by Opicapone, Tolcapone, Foslevodopa, and Entacapone. Furthermore, the **DDC** target is engaged by Carbidopa and Benserazide. Lastly, the **ACHE, BCHE**, and **MAOA** targets are activated by Rivastigmine and Selegiline. This section is designed to assist patients, scientists, researchers, and healthcare professionals in their analyses. The panel provides information on the number of available drugs and includes links to the DrugBank, which offers detailed descriptions of each medication. This linkage facilitates direct access to comprehensive drug information (Fig. 8).

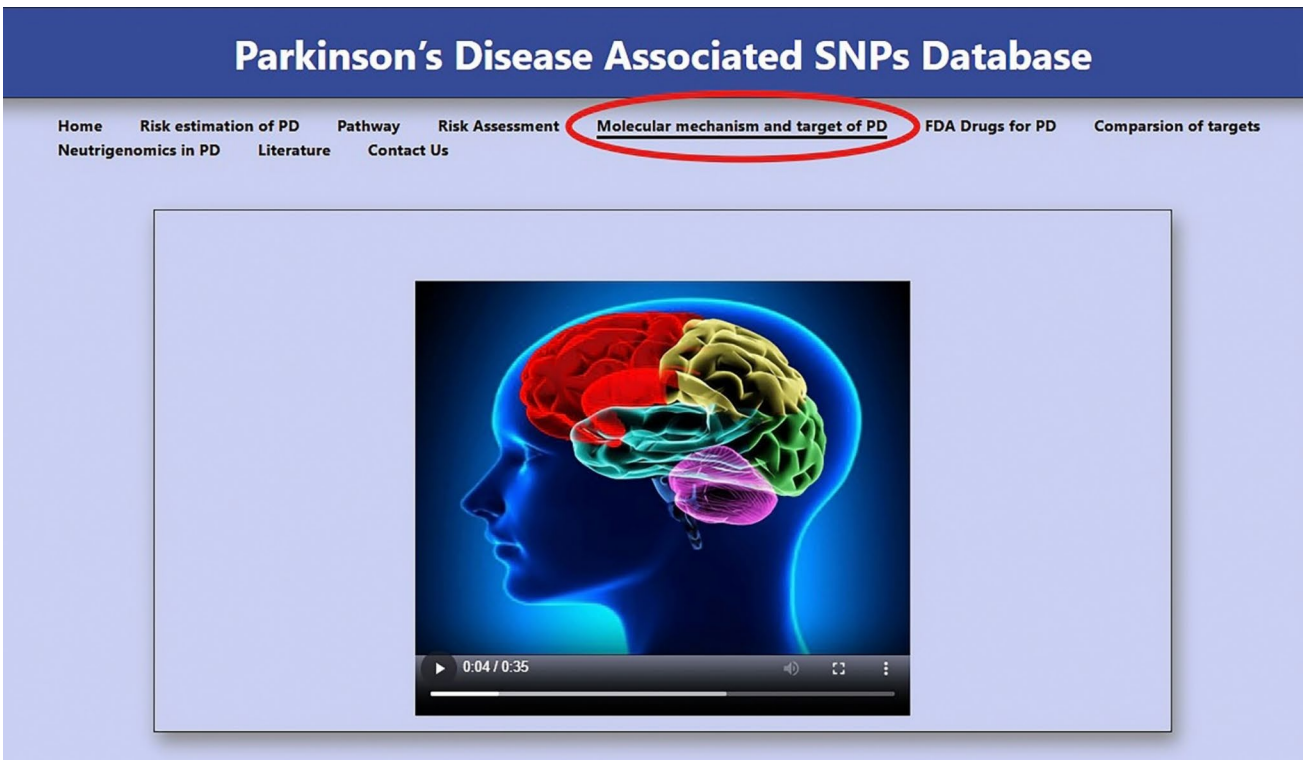

Fig. 7 Short-view presentation about the molecular mechanism of the PD targets (In this database, a concise video is presented to illustrate the impact of PD on an individual)

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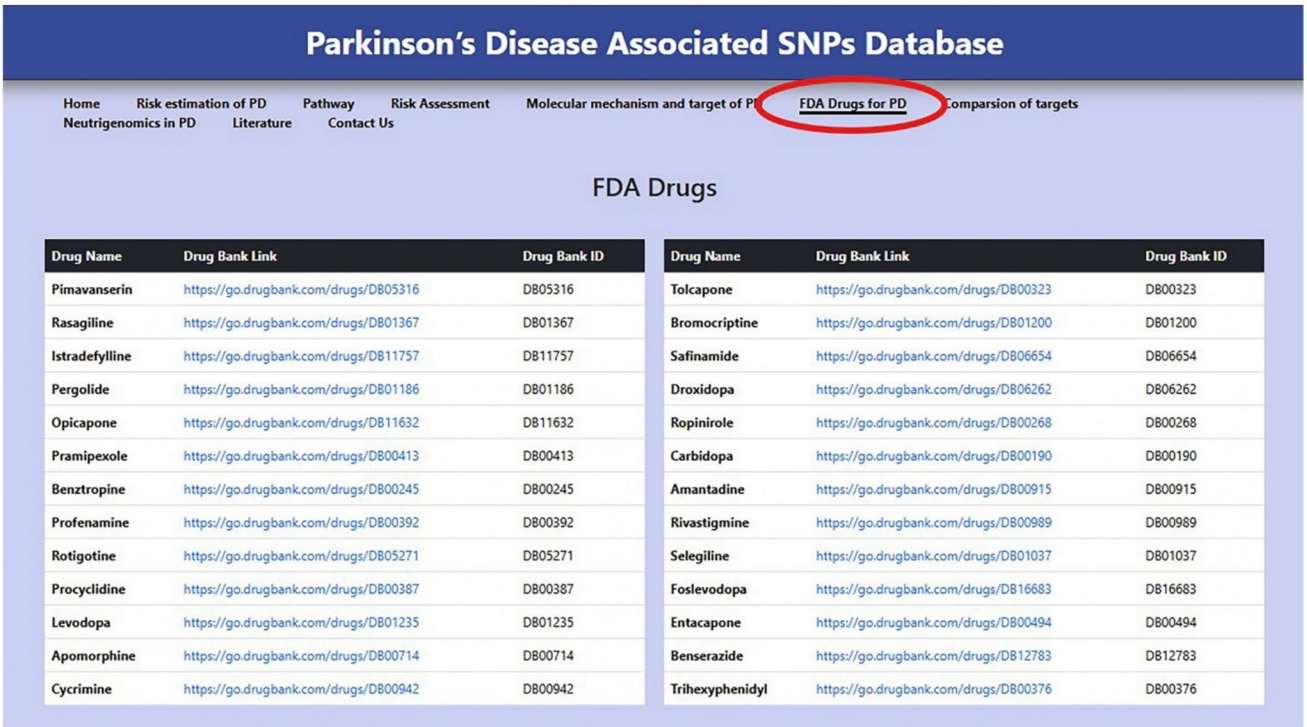

Drug Name	Drug Bank Link	Drug Bank ID
Pimavanserin	https://go.drugbank.com/drugs/DB05316	DB05316
Rasagiline	https://go.drugbank.com/drugs/DB01367	DB01367
Istradefylline	https://go.drugbank.com/drugs/DB11757	DB11757
Pergolide	https://go.drugbank.com/drugs/DB01186	DB01186
Opicapone	https://go.drugbank.com/drugs/DB11632	DB11632
Pramipexole	https://go.drugbank.com/drugs/DB00413	DB00413
Benztropine	https://go.drugbank.com/drugs/DB00245	DB00245
Profenamine	https://go.drugbank.com/drugs/DB00392	DB00392
Rotigotine	https://go.drugbank.com/drugs/DB05271	DB05271
Procyclidine	https://go.drugbank.com/drugs/DB00387	DB00387
Levodopa	https://go.drugbank.com/drugs/DB01235	DB01235
Apomorphine	https://go.drugbank.com/drugs/DB00714	DB00714
Cycrimine	https://go.drugbank.com/drugs/DB00942	DB00942

Drug Name	Drug Bank Link	Drug Bank ID
Tolcapone	https://go.drugbank.com/drugs/DB00323	DB00323
Bromocriptine	https://go.drugbank.com/drugs/DB01200	DB01200
Safinamide	https://go.drugbank.com/drugs/DB06654	DB06654
Droxidopa	https://go.drugbank.com/drugs/DB06262	DB06262
Ropinirole	https://go.drugbank.com/drugs/DB00268	DB00268
Carbidopa	https://go.drugbank.com/drugs/DB00190	DB00190
Amantadine	https://go.drugbank.com/drugs/DB00915	DB00915
Rivastigmine	https://go.drugbank.com/drugs/DB00989	DB00989
Selegiline	https://go.drugbank.com/drugs/DB01037	DB01037
Foslevodopa	https://go.drugbank.com/drugs/DB16683	DB16683
Entacapone	https://go.drugbank.com/drugs/DB00494	DB00494
Benserazide	https://go.drugbank.com/drugs/DB12783	DB12783
Trihexyphenidyl	https://go.drugbank.com/drugs/DB00376	DB00376

Fig. 8 The Screenshot view of the FDA drugs for PD

3.11 The panel of comparison of targets

Furthermore this section, we present a comparison table that includes nine wild-type and mutant targets along with their binding affinities for FDA-approved drugs. In Fig. 9 illustrates this comparison, highlighting the differences in binding affinity scores between the wild-type and mutant targets. The data indicate that some FDA drugs exhibit a higher binding affinity for wild-type targets compared to their mutant counterparts. Certain FDA-approved pharmaceuticals demonstrate a greater binding affinity for mutant-type targets in comparison to their wild-type equivalents. The binding affinity predictions were generated using the PyRx version 0.8 software package. Additionally, the table includes two-dimensional interaction images that depict the binding interactions of FDA drugs with both wild-type and mutant targets.

3.12 The section of nutrigenomics in PD

The section on Nutrigenomics in PD elucidates the role of nutritional supplements in the context of PD. It discusses how certain nutrients can downregulate specific genes, while others may activate particular targets. An understanding of PD necessitates the consideration of various vitamins, minerals, and nutrients. It is conceivable that specific molecules derived from vitamins, minerals, and nutrient-rich sources, such as plants, animals, or seaweeds, may hold potential for the development of therapeutic interventions for PD in the future. Consequently, a medicinal solution may be formulated based on these findings. Thereby contributing to the pathophysiology of PD. This section further explores the pathogenic mechanisms of PD, the epigenetic modifications associated with the disease, and the nutritional factors that play a significant role in these processes.

Epigenetic modifications encompass processes such as DNA methylation and histone modifications. In the context of PD, the regulation of DNA methylation is disrupted; leading to a diminished capacity for methylation and consequently altered expression of genes associated with PD. DNA methylation involves the addition of a methyl group to a DNA strand, a reaction facilitated by DNA methyltransferases (DNMTs). In addition to folate, various other nutrients are recognized for their significant roles in one-carbon metabolism and DNA methylation. Specifically, vitamins B6, B9, and B12 serve as essential cofactors in the modification of DNA methylation. For instance, in cases of vitamin B deficiency, the methylation status of dopaminergic neurons is altered, rendering these neurons more vulnerable to stress. Furthermore, the expression of α-synuclein (α-SYN) is subject to epigenetic regulation through histone modifications that interact with the SNCA promoter. These modifications include H3K27ac, H3K4me1/3, H3K9me1/2, H3K14ac, H3K18ac, and H2AK119ub, which can enhance

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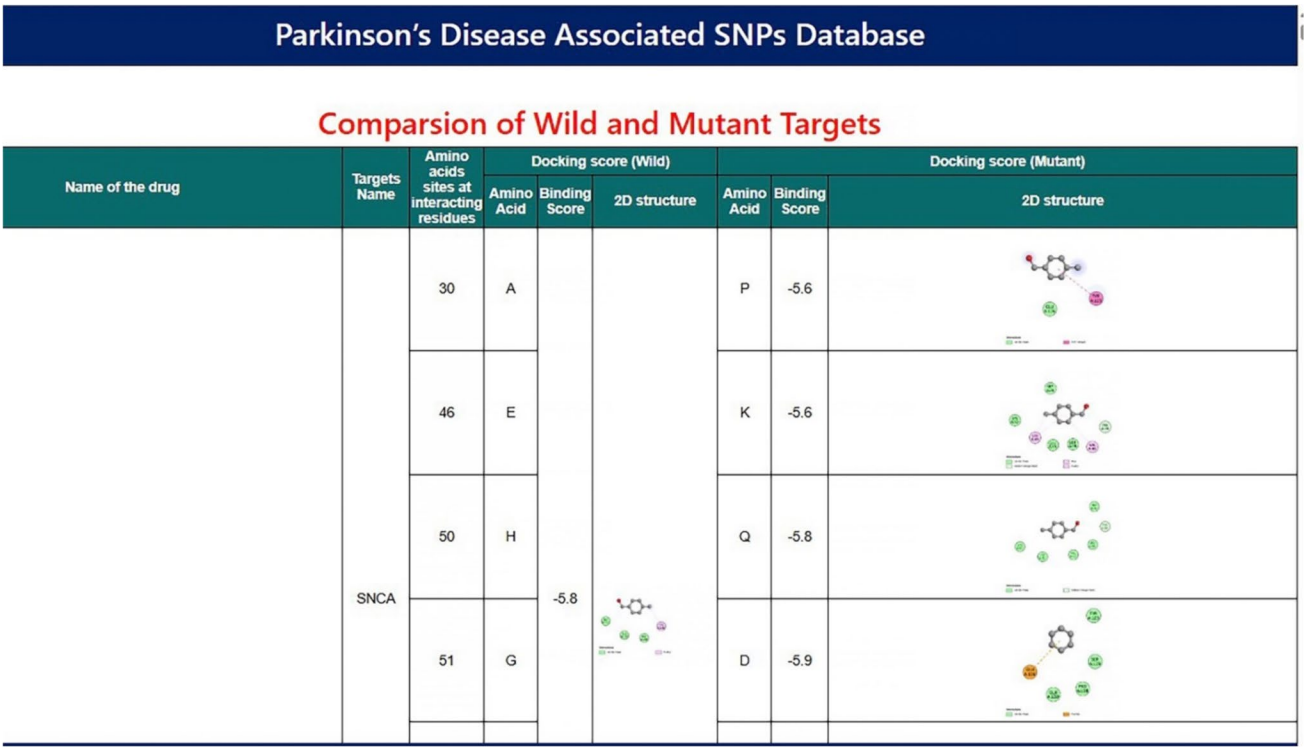

Name of the drug	Targets Name	Amino acids sites at interacting residues	Docking score (Wild)			Docking score (Mutant)		
			Amino Acid	Binding Score	2D structure	Amino Acid	Binding Score	2D structure
	SNCA	30	A	-5.8		P	-5.6	
		46	E			K	-5.6	
		50	H			Q	-5.8	
		51	G			D	-5.9	

Fig. 9 The Screenshot view of the Comparison of wild and mutant targets in PD

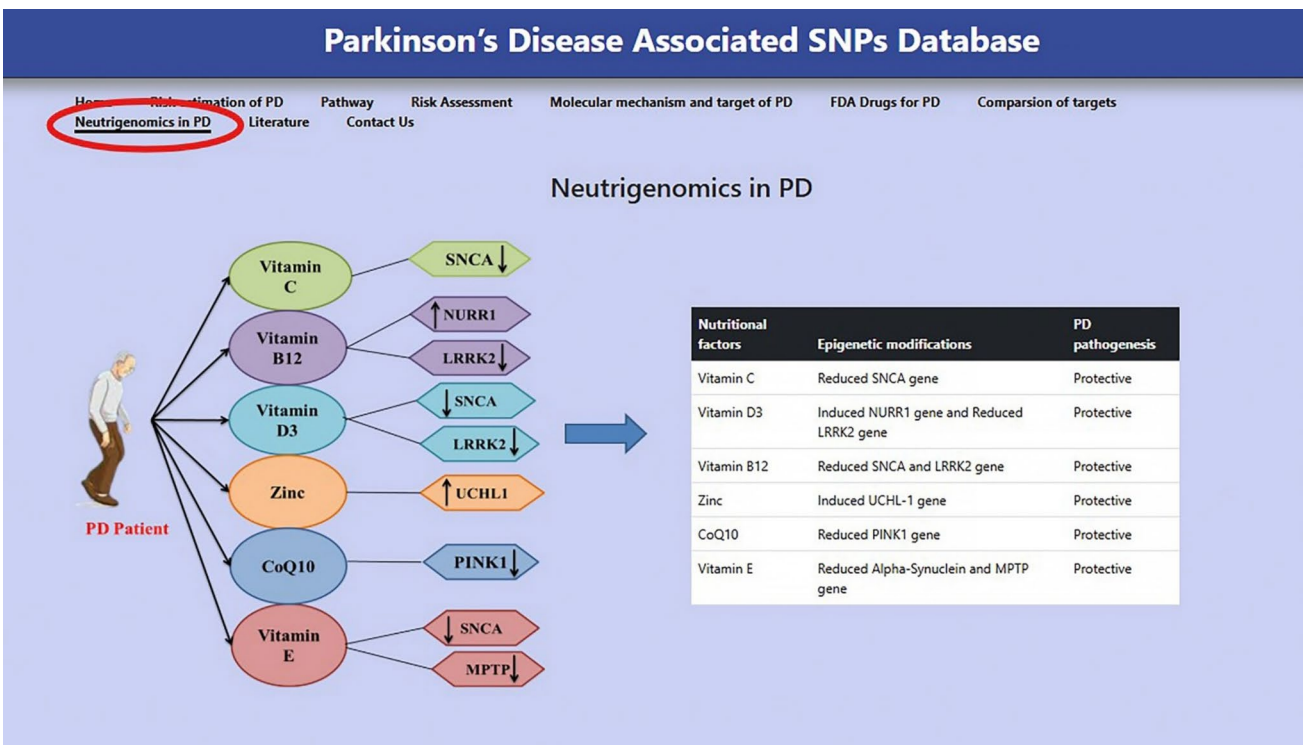

Fig. 10 The Nutrigenomics based on the gene associated with PD in the PDASD Database

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SNCA expression and subsequently increase α-SYN levels, thereby elevating the risk of developing PD (Fig. 10).

The final section comprises a literature review that encompasses research and review articles pertinent to PD (Fig. 11). Identifying potential targets is a crucial aspect of the drug discovery process for PD; the world needs novel therapeutic approaches in PD, which makes target identification important in the drug discovery process. It is a significant challenge to connect structurally and functionally characterized targets to the disease. Therefore, the focus of PDASD is to identify therapeutic targets for the management and therapy of PD. Aggregating pertinent data across various levels really aids in focusing and improving comprehension of the therapeutic targets. In addition to helping new users understand the current molecular targets, this might aid in the identification of therapeutic targets that have not previously been focused on PD treatment.

4 Conclusion

PD is a common neurological disorder that predominantly presents in adults. Key genes implicated in the regulatory mechanisms and pathogenesis of PD include Parkin, PINK1, DJ-1, UCHL1, LRRK2, NURR1, ATP13A2, GSK3B, and SNCA. The PDASD database encompasses proteins associated with PD, along with their nsSNPs, relevant pathway, risk assessments, and molecular mechanisms. Additionally, it includes information on FDA-approved medications for PD, the role of nutrition in the disease, and a compilation of existing literature related to PD. The creation of the web-based PDASD database, which is provided on a single open-access webpage utilizing HTML and Java, The PDASD database has been integrated with various external databases to enhance accessibility to SNP data. Utilizing tools such as SIFT, PANTHER, PolyPhen-2, MutPred 2, PredictSNP2, MAPP, PMut, MetaSNP, Suspect, PON-P2, PHD-SNP, SNPs&GO, and SNAP2, along with literature sources, enables a comprehensive SNP pathogenic analysis. This approach offers a robust foundation for the formulation of treatment and management approaches for PD by establishing connections between therapeutic targets and SNPs linked to the condition. Finally, the PDASD Database (interactive database) was created to assess the influence of specific nucleotide variations SNPs on the disease progression of PD in the early-onset predisposed stage of the disease among the population. The assigned risk values were determined or obtained from the risk estimation database. It will be useful for early identification, interpretation of NGS reports of PD and the genetic basics of PD confirmation and treatment. This database serves as a valuable resource for researchers, scientists, clinicians, and the general public, enabling them to grasp the implications of PD. It provides insights into the diverse factors related to PD and their associated effects. Furthermore, the database underscores the importance of nutritional supplements in the context of PD.

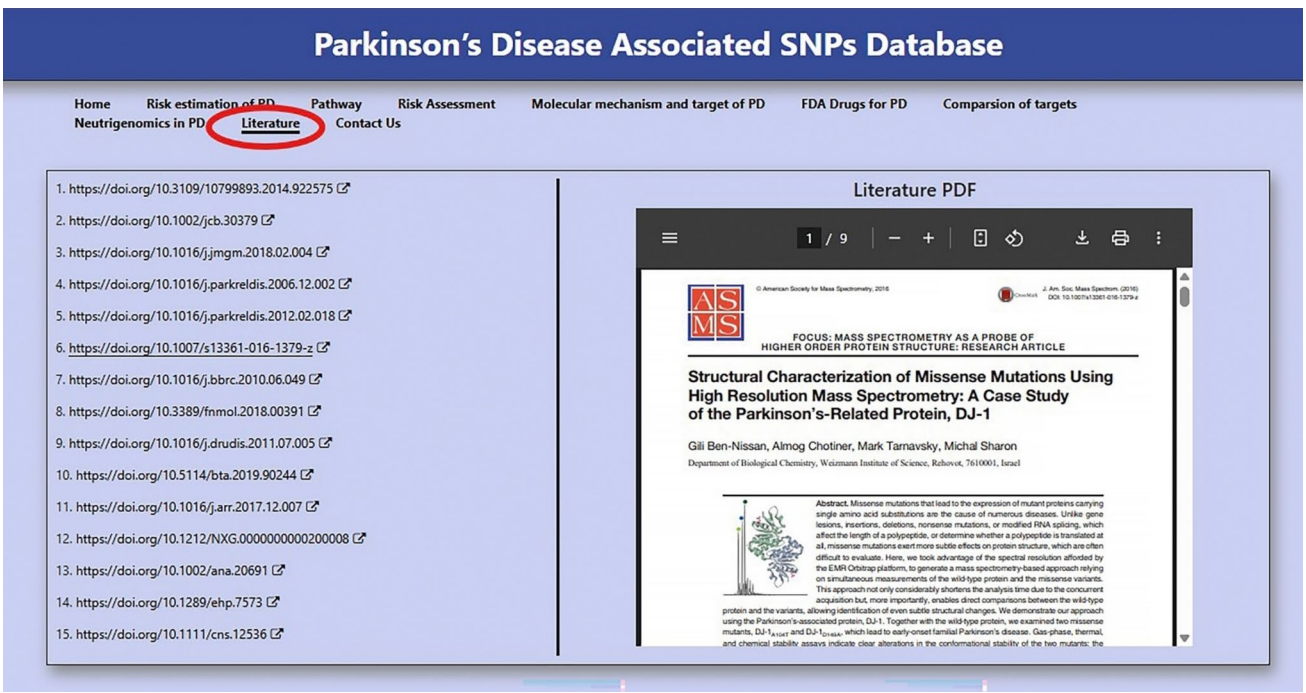

Fig. 11 Fetching literature connected with PD in the PDASD Database (Further literature is also given, from which further knowledge can be obtained)

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Ultimately, it may prove beneficial for researchers, scientists, and clinicians by supporting future drug discovery initiatives aimed at improving outcomes for patients with PD.

5 Limitations

Our database has some gaps and limitations. This study specifically examined SNPs associated with only nine genes as risk factors for Parkinson's disease (PD). However, the database lacks prevalence data. In future research, we aim to incorporate additional genes and prevalence data related to PD.

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Data availability The data may be made available to readers upon request to the corresponding author.

Declarations

Conflict of interests The authors have declared no competing interests.

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