COMPUTATIONAL INVESTIGATIONS ON STRUCTURAL AND FUNCTIONAL IMPACT OF SNP IN PARKINSON'S DISEASE ASSOCIATED WITH HUMAN MONOAMINE OXIDASE-B (MAO-B)

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Abstract

Single nucleotide polymorphism (SNP) is type of mutation and one of the major factor in determining susceptibility of an individual to a particular disease and response to the action of a drug. Thus mapping the structural and functional effects of SNP is the most important step in drug research and development in the context of personalized medicine. Parkinson's disease is a neurodegenerative disorder affecting central nervous system (CNS) usually associated with aging. The symptoms of this disease includes nervous coordination problems like difficulty in walking, swallowing, chewing, slowness of movement and speaking along with other emotional problems like depression. The inhibition of metabolic enzyme monoamine oxidase B (MAO-B) is a key step to suppress the progression of the disease. The three dimensional crystal structure of the MAO-B was taken from Protein Data Bank (PDB ID: 4CRT). Gene name of the enzyme were selected using Kyoto encyclopedia of genes and genomes (KEGG) database. Single Nucleotide Polymorphism (SNP) data were retrieved from dbSNP database. SIFT and Polyphen-2 were used complementary for selecting 'high confidence non synonymous SNP (nsSNP) based on sequence based and structure based approaches respectively. The nsSNP which were found to be damaging using both SIFT and PolyPhen-2 score analysis were further evaluated for their stability using IMutant-2.0. The functional impact of deleterious and damaging SNP were studied by modelling the homology modelling the protein using SWISS MODEL. The effect of the standard drug Zelapar was analysed in both mutated and native proteins using molecular docking studies. Results revealed that almost all the mutated proteins had a significantly lesser interaction with the drug compared to the native protein.

Keywords: Homology modeling, Parkinson's disease, MAO-B, Single nucleotide polymorphism

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Introduction

Single nucleotide polymorphism(SNP) is a type of mutation and has attained significant research interest in the field of personalized medicine(Wong et al.,2018). They are caused by alteration of structural stability in the protein and these alterations cause distortions in drug interaction sites through variation in amino acid residues by mutation (Syvänen,2001). To reveal the extent of SNP and its effect on drug-protein interaction, it is very much essential to probe the details of damaging(deleterious) SNPs by constructing the 3D models of protein framework through homology modeling methods.

Parkinson's disease (PD) is a neurodegenerative disorder that adversely affects nervous coordination activities and causes usually in aged individuals. During the initial stage of PD the symptoms are usually mild and insignificant motor disability. As the disease progresses the symptoms become more prevalent and affect the ambulation and coordination ability of individual affecting the quality of living (Fox et al.,2018). Thus with the advancement of the disease the affected individual lose ability to do locomotive activity and finally may leads to death. According to WHO statistics, the availability of drugs against PD is varying in different WHO regions. The global drug availability is around 60.6% where Africa has the least around 12.5% and Europe scores maximum of 79.1%.

Implementation of *Insilico* methods in drug discovery for PD is a novel approach on the last decade (Uenaka et al., 2018; Lemos et al.,2018). The exploration of mechanism of PD is a breakthrough for designing effective target based drugs and thereby improving the treatment options. Human monoamine oxidase-B(MAO-B) is a potential target for anti-PD and anti-alzheimer's drugs. MAO A and MAO B are two mitochondrial transmembrane isozymes which are bound through C-terminal transmembrane polypeptide segment(Binda et al.,2002). They acts as catalysts for the oxidative deamination of primary, secondary and tertiary amines and also play an important role in controlling the concentration of Serotonin, Dopamine, Adrenaline and Noradrenaline. Both the MAOs differ significantly in their substrate specificity, physiological distribution and sensitivity to respective inhibitors which helps to develop selective drug molecules for inhibition. For long time these isozymes have been attained pharmacological research interest owing to the focus on reversible and irreversible inhibitors that used for the clinical treatment in neurological disorders. MAO B is mostly observed in *substantia nigra* and periventricular region of the hypothalamus and also in areas which are having Dopamine rich neurons(Carradori et al.,2014). The substrates of MAO B include small amine molecules like benzylamine and phenethylamine. Extent of MAO B expression is observed to be increased three times in the case of aged neurons (Fowler et al.,1980). Literature reports that increased MAO B level would also associated with induced apoptosis in neurons (Boulton et al., 1998). According to Saura (Saura et al.,1994) patients having Alzheimer's are also observed to have elevated MAO B levels in plaque associated brain cells(astrocytes). For these reasons MAO B inhibitors gained significant research interest for the design and development of novel neuroprotective and antidepressant classes of drugs.

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Recent literature reports a complimentary approach for identifying SNP for minimizing errors associated with *insilico* prediction (Dakal et al.,2017). This strategy includes both structure based and sequence based prediction of non synonymous SNPs(nsSNP). Based on the available sequence data obtained from the database the mutated protein chains can be modeled using homology modeling technique. Moleccular modeling studies can be further use to confirm the binding of standard drug against both native and modeled protein sequences. This gives a more clear idea about the effectiveness of drug against the SNP mutated protein targets and the demand for identifying novel and effective drugs that binds to the these targets for effective treatment in PD. We propose that this is a very effective and useful strategy for personalized medicine in the treatment of PD.

Materials and Methods

1. Retrieval of SNP data: Structural data of proteins and other biological macromolecules are readily available in Protein data bank(Berman et al.,2000). The three dimensional structure of human monoamine oxidase-B enzyme was collected from Protein Data Bank (PDB ID: 4CRT) as shown in Figure 2. MAO B is attached on the outside of mitochondrial membrane. The crystal structure shows the formation of polypeptide chains by the C-terminal amino acids which is extended by alpha-helix which originates on the amino acid residue Val 489 to form a transmembrane helical segment(Esteban et al.,2014). Details of genes were retrieved from Kyoto encyclopedia of Genes and Genomes (KEGG) database and the list of rsIDs were downloaded from NCBI repository.

The overall workflow protocol used in our study is represented in Figure 1.

2. Identification of damaging nsSNP using SIFT and PolyPhen-2: This is a combined step where we used a hybrid approach of structure and sequence based prediction of nsSNP to screen the 'high confidence' nsSNP using SIFT and PolyPhen-2 respectively(Dakal et al.,2017). SIFT can predict 90% of the damaging SNPs through *in-silico* approach. It predicts deleterious(damaging) and tolerated (non-damaging) substitutions based on a sequence homology and physical properties of sequence submitted to the database. The functional consequences of amino acid substitutions caused due to nsSNPs were predicted and ascertained using the respective SIFT score. Ng and Henikof (Ng et al., 2003) reports the criteria in which amino acid substitutions at a given position with normalized probabilities of ≤ 0.05 in a tolerance index are predicted to be damaging; whereas those with normalized probabilities ≥ 0.05 are predicted to be tolerated. The results were further screened using PolyPhen-2. PolyPhen-2 having score >0.96 was identified as 'probably damaging' and selected as 'high confidence' nsSNPs for further studies.

3. Analysing stability using IMutant-2: The effects of nsSNP on the stability was analysed using IMutant-2. It is an online tool for analyzing the change in stability of the macromolecular target after the mutation by comparison with the original protein. This tool can be used as a

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Protein stability predictor on single point mutation from protein sequence and structure.The stability is analysed regarding to the difference in free energy between native protein and the mutated protein using IMutant-2 (Galea et al.,2016). This analysis gives significant information about the effect of SNP on the stability of the target under consideration.

4. Homology Modeling: When an experimental structure of target protein is absent in the database, it is a standalone option to use *Insilico* methods for creating three dimensional structures using tools like SWISS MODEL. SWISS-MODEL presently build approximately 3000 models per day making it one of the most widely used structure modelling servers in the world.

In homology modelling, a three dimensional model of a target sequence (macromolecule) is generated by correlating experimental data from an evolutionary related protein structure which serves as a template for the modeled structure as shown in Figure 3. The default modelling protocol of SWISS MODEL consists of the following five major steps (Waterhouse et al.,2018).

4.1. **Input data**: The target structure can be introduced as amino acid sequence, either in FASTA, FASTA CANONICAL format or as plain text. This sequence data can be retrieved from Uniprot database (Apweiler et al.,2004). If the target protein consists of different protein chains as subunits(Heteromer), amino acid sequences or UniProtKB accession codes must be specifed for each subunit in the structure.

4.2. **Template search**: Sequence data provided as the input serve as a query to search for evolutionary related protein structures against the SWISS-MODEL template library SMTL. BLAST and HHblits search methods are performed in this process(Remmert et al.,2012).

4.3. **Template selection**: templates are ranked according to Global Model Quality Estimate (GMQE) (Biasini et al.,2014) and Quaternary Structure Quality Estimate (QSQE) (Bertoni et al.,2017). Top ranked templates and alignments are compared to verify whether they represent alternative conformational states or cover different regions of the target protein. multiple templates are selected automatically and different models are built accordingly. Interactive graphical views facilitate the analysis and comparison of available templates through three-dimensional structures, sequence similarity and quaternary structure features (Waterhouse et al.,2018).

4.4. **Model building**: For each selected template, a 3D protein model is automatically generated by transferring conserved atom coordinates as defned by the target template alignment. Residue coordinates corresponding to insertions/deletions in the alignment are generated by loop modelling and a full-atom protein model is obtained by constructing the non-conserved amino acid side chains.

5. **Model quality estimation**: The quality of the built models were estimated according to their GMQE and QMEAN scoring values. The outcome of SWISSMODEL results relies on the

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QMEAN scoring function to quantify modelling errors and give estimates on expected model accuracy(Benkert et al.,2010). SWISS MODEL workspace is used for homology modeling of mutated protein based on BLAST method of sequence alignment against a template. For the different structures obtained, XRD structures with maximum coverage and identity was selected. Ramachandran plots and statistical analysis of the modeled protein structures were verified to confirm the stability and existence of modeled protein.

The sequence of SNP mutated protein were collected from Uniprot databse and used for modeling using SWISS MODEL. From the results, the protein with maximum coverage, Identity, GMQE score and based on X ray diffraction(XRD) method was selected and verified using Ramachandran Plot along with the local quality estimate of the component chains and acceptable Z-score value.

5. Docking analysis: The binding ability of standard drug Zelapar(Selegiline) which is used in Parkinson's disease is analysed with different protein structures obtained using Homology modeling method and the results were compared with binding of the drug with native protein using Autodock Vina (Trott et al.,2010). Zelapar is recommended in patients who don't have significant improvement on treatment with the drug leavodopa (Chaudhuri et al.,2016). The three dimensional structure of Zelapar is retrieved from PUBCHEM database (Figure 4) and it is converted to PDB format for docking using Openbabel online tool. The PDB structure was initially prepared by removal of ligands that present in the binding site (FAD and ASS), detergents and other atoms like chlorine. Hydrogen is added to the prepared protein. Both the target and ligand is imported to the Autodock workspace and it is then docked with appropriate grid space (Platania et al.,2012). This procedure is repeated for all the modeled structures of MAO B obtained from SWISS MODEL.

Various online tools used in this study are summarized below:

Method	Database	Website Link
Collection of 3D structure of protein	Protein Data Bank	http://www.pdb.org
Retrieval of SNP data	Kyoto encyclopedia of Genes and Genomes (KEGG)	https://www.genome.jp/kegg/kegg2.html
Screening of damaging SNPs	SIFT PolyPhen-2	https://sift.bii.a-star.edu.sg/www/SIFT_dbSNP.html http://genetics.bwh.harvard.edu/pph2/index.s

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		html
Stability analysis of SNPs	IMutant-2	http://folding.biofold.org/i-mutant/i-mutant2.0.html
Conversion of SDF to PDB format	Openbabel	http://www.cheminfo.org/Chemistry/Cheminformatics/FormatConverter/index.html
Homology modeling	SWISS MODEL	http://swissmodel.expasy.org/SWISS-MODEL.html
Chemical structures	PUBCHEM	https://pubchem.ncbi.nlm.nih.gov/

Results and Discussion

1. Prediction and screening of damaging nsSNP based on sequence and structure homology methods:

Identification and collection of damaging nsSNP of a protein using only a single approach is not sufficient and effective. Each tool has specific threshold cut-off value for predicting damaging nsSNP and results in irrelevant predictions. Thus we used two tools as a complementary approach where sequence homology based prediction using PolyPhen-2 works on a genetic approach and structural homology based prediction using SIFT works on a functional approach. This hybrid approach for nsSNP prediction is already reported in literature.

Gene name of the target protein human MAO-B were identified using Kegg database and nsSNPs corresponding to the gene MAOB were further retrieved from NCBI database.

121 SNPs which were identified as 'Tolerated' using SIFT score prediction were not included in further *in-silico* analysis since these do not influence any change in amino acid in protein sequence(Figure 5). PolyPhen-2 is used for screening the damaging SNPs which was identified

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using SIFT score prediction. PolyPhen-2 having score >0.96 was identified as 'probably damaging' and selected as 'high confidence' nsSNPs for further studies. Prediction using PolyPhen-2 ruled out five amino acid substitutions (A56T , T505M, T489M, G390S, G389R) from total 24 SNPs as 'benign' based on the PolyPhen score.

2. Stability analysis: IMutant-2 is used to analyse the effect of nsSNP on the stability of native protein. It is based on the free energy difference between the original and mutated proteins. All the SNPs were found to have less stability after mutation than before mutation.

The results of above analysis were summarized in Table 1.

SL.No	Amino acid change	PROTEIN ID	Uniprot ID	SIFT Prediction	Polyphen-2		Stability
1	P130Q	ENSP00000367309	P27338	DELETERIOUS	0.999	Damaging	Decrease
2	P114Q	ENSP00000441613	B7Z242	DELETERIOUS	0.998	Damaging	Decrease
3	R38H	ENSP00000367309	P27338	DELETERIOUS	0.999	Damaging	Decrease
4	R22H	ENSP00000441613	B7Z242	DELETERIOUS	0.980	Damaging	Decrease
5	P304L	ENSP00000367309	P27338	DELETERIOUS	0.976	Damaging	Decrease
6	P288L	ENSP00000441613	B7Z242	DELETERIOUS	0.999	Damaging	Decrease
7	A72T	ENSP00000367309	P27338	DELETERIOUS	0.948	Damaging	Decrease
8	A56T	ENSP00000441613	B7Z242	DELETERIOUS	0.429	Benign	Decrease
9	I272T	ENSP00000367309	P27338	DELETERIOUS	0.999	Damaging	Decrease
10	I256T	ENSP00000441613	B7Z242	DELETERIOUS	0.999	Damaging	Decrease
11	I256T	ENSP00000442240	B7Z242	DELETERIOUS	0.999	Damaging	Decrease
12	P109L	ENSP00000367309	P27338	DELETERIOUS	0.996	Damaging	Decrease
13	P93L	ENSP00000441613	B7Z242	DELETERIOUS	0.728	Damaging	Decrease
14	P93L	ENSP00000442240	B7Z5H3	DELETERIOUS	0.995	Damaging	Decrease
15	R399P	ENSP00000441613	B7Z242	DELETERIOUS	1	Damaging	Decrease
16	R415P	ENSP00000367309	P27338	DELETERIOUS	1	Damaging	Decrease
17	T505M	ENSP00000367309	P27338	DELETERIOUS	0.048	Benign	Decrease
18	T489M	ENSP00000441613	B7Z242	DELETERIOUS	0.048	Benign	Decrease
19	G393V	ENSP00000442240	B7Z5H3	DELETERIOUS	0.891	Damaging	Decrease
20	G390S	ENSP00000442240	B7Z5H3	DELETERIOUS	0.001	Benign	Decrease
21	Y60C	ENSP00000367309	P27338	DELETERIOUS	1	Damaging	Decrease
22	Y44C	ENSP00000441613	B7Z242	DELETERIOUS	1	Damaging	Decrease
23	Y44C	ENSP00000442240	B7Z5H3	DELETERIOUS	1	Damaging	Decrease
24	G389R	ENSP00000442240	B7Z5H3	DELETERIOUS	0.018	Benign	Decrease

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3. Homology Modeling:

The SWISS MODEL created three dimensional structure models of the mutated enzyme chains according to the input sequences given. The workspace will show details like structure, GMQE , QMEAN scores along with sequence identity as shown in Figure 6. The nsSNP P130Q got modeled structure at resolution of 2.4 Ǻ based on template protein 2vrl.1 (chain A) with Global Model quality estimate(GMQE) score of 0.98. Ramachandran plot gives idea about the existence of a given biological macromolecule through the correlation of their Phi and Psi angles.The ramachandran plot analysis showed very good estimate that 97.07% of the residues are in favored and additional allowed regions as shown in Figure 7. Similarly other nsSNPs P304L, A72T and P109L have Ramachandran favored regions 96.97%, 97.07% and 97.17% respectively. All are having GMQE score of 0.98 which is a very good value. Statistical analysis also gives good QMEAN values for all the modeled structures using SWISS MODEL(Figure 8). Data are summarized in the table below.

Sl.No	Amino acid change	GMQE	QMEAN	Ramachandran plot Favored regions
1	P130Q	0.98	0.68	97.07%
2	P304L	0.98	0.32	96.97%
3	A72T	0.98	0.61	97.07%
4	P109L	0.98	0.75	97.17%

3. Docking analysis: Autodock Vina is used to analyze the binding modes between the standard drug used for Parkinson's disease and the original and mutated proteins of human monoamine oxidase-B obtained using homology modeling technique. The SDF format of the file is converted to PDB format using Openbabel tool for docking study. Results revealed that almost all the mutated proteins had a significantly lesser interaction with the drug compared to the native protein. Most of the modeled structures got low binding score than the native MAO B which is having -7.2Kcal/mol. The lowest scoring SNPs are tabulated in the following table.

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Sl.No	Amino acid change	Docking score (Kcal/mol)
	Native MAO B	**-7.2**
1	P130Q	-5.4
2	P304L	-5.3
3	A72T	-5.2
4	P109L	-5.4

The images showing interaction of MAO B with Standard drug and the least scoring SNP (A72T) with the same drug is given as Figure 9 and Figure 10 respectively. Analysis of binding energy revealed that the binding affinity of the standard drug reduced considerably in all the mutant forms compared to the native protein. The weak binding affinity of the mutant forms could be due to least number of protein ligand interactions such as Electrostatic energy, Van der waals energy and hydrogen bonding. Such weak interactions would lead to lowered binding of drugs with the target proteins subsequently affecting the catalytic function of the protein. The present analysis reveals that the loss of effective binding affinity could lead to decrease in catalytic affinity through decrease in stability of mutants and reduced binding affinity towards the essential residues in the protein

Conclusion

We have done an in silico analysis for the identification and analysis of non synonymous Single nucleotide polymorphism(nsSNP) associated with Human monoamine oxidase B which is a vital target for the drugs in neurological disorders like Parkinson's disease. The data obtained were used to build new SNP mutated structures through homology modeling technique. Autodock Vina software is used to obtain the binding affinity of Zelapar against the modeled structures and the study showed the importance and necessity of developing a new drug which is having a good binding ability in the mutated structures. The data obtained in this study is very relevant in the scenario of personalized medicine due to the significance of the disease and for identifying a novel candidate for the treatment of Parkinson's disease through MAO B inhibition.

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References

Apweiler R, Bairoch A, Wu CH, Barker WC, Boeckmann B, Ferro S, Gasteiger E, Huang H, Lopez R, Magrane M, Martin MJ. UniProt: the universal protein knowledgebase. Nucleic acids research. 2004 Jan 1;32(suppl_1):D115-9.

Benkert,P., Biasini,M. and Schwede,T. (2011) Toward the estimation of the absolute quality of individual protein structure models. *Bioinformatics*, **27**, 343–350.

Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The protein data bank. Nucleic acids research. 2000 Jan 1;28(1):235-42.

Bertoni M, Kiefer F, Biasini M, Bordoli L, Schwede T. Modeling protein quaternary structure of homo-and hetero-oligomers beyond binary interactions by homology. Scientific reports. 2017 Sep 5;7(1):10480.

Biasini M, Bienert S, Waterhouse A, Arnold K, Studer G, Schmidt T, Kiefer F, Cassarino TG, Bertoni M, Bordoli L, Schwede T. SWISS-MODEL: modelling protein tertiary and quaternary structure using evolutionary information. Nucleic acids research. 2014 Apr 29;42(W1):W252-8.

Binda C, Newton-Vinson P, Hubálek F, Edmondson DE, Mattevi A. Structure of human monoamine oxidase B, a drug target for the treatment of neurological disorders. Nature structural & molecular biology. 2002 Jan;9(1):22.

Boulton AA, Eisenhofer G. Catecholamines: bridging basic science with clinical medicine. by Goldstein DS, Eisenhofer G., McCarty R., Academic Press, New York. 1998:273-92.

Carradori S, D'Ascenzio M, Chimenti P, Secci D, Bolasco A. Selective MAO-B inhibitors: a lesson from natural products. Molecular diversity. 2014 Feb 1;18(1):219-43.

Chaudhuri KR, Qamar MA, Rajah T, Loehrer P, Sauerbier A, Odin P, Jenner P. Non-oral dopaminergic therapies for Parkinson's disease: current treatments and the future. npj Parkinson's Disease. 2016 Dec 1;2:16023.

Dakal TC, Kala D, Dhiman G, Yadav V, Krokhotin A, Dokholyan NV. Predicting the functional consequences of non-synonymous single nucleotide polymorphisms in IL8 gene. Scientific reports. 2017 Jul 26;7(1):6525.

Esteban G, Allan J, Samadi A, Mattevi A, Unzeta M, Marco-Contelles J, Binda C, Ramsay RR. Kinetic and structural analysis of the irreversible inhibition of human monoamine oxidases by ASS234, a multi-target compound designed for use in Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. 2014 Jun 1;1844(6):1104-10.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3370116

Fowler CJ, Wiberg Å, Oreland L, Marcusson J, Winblad B. The effect of age on the activity and molecular properties of human brain monoamine oxidase. Journal of neural transmission. 1980 Mar 1;49(1-2):1-20.

Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RM, Seppi K, Coelho M, Sampaio C, Movement Disorder Society Evidence-Based Medicine Committee. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Movement Disorders. 2018 Aug;33(8):1248-66.

Galea CA, Huq A, Lockhart PJ, Tai G, Corben LA, Yiu EM, Gurrin LC, Lynch DR, Gelbard S, Durr A, Pousset F. Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia. Annals of neurology. 2016 Mar;79(3):485-95.

Lemos A, Melo R, Preto AJ, Almeida JG, Moreira IS, Dias Soeiro Cordeiro MN. In Silico Studies Targeting G-protein Coupled Receptors for Drug Research Against Parkinson's Disease. Current neuropharmacology. 2018 Jul 1;16(6):786-848.

Ng PC, Henikoff S. SIFT: Predicting amino acid changes that affect protein function. Nucleic acids research. 2003 Jul 1;31(13):3812-4.

Platania CB, Salomone S, Leggio GM, Drago F, Bucolo C. Homology modeling of dopamine D2 and D3 receptors: molecular dynamics refinement and docking evaluation. PloS one. 2012 Sep 6;7(9):e44316.

Remmert M, Biegert A, Hauser A, Söding J. HHblits: lightning-fast iterative protein sequence searching by HMM-HMM alignment. Nature methods. 2012 Feb;9(2):173.

Saura JL, Luque JM, Cesura AM, Da Prada M, Chan-Palay V, Huber G, Löffler J, Richards JG. Increased monoamine oxidase B activity in plaque-associated astrocytes of Alzheimer brains revealed by quantitative enzyme radioautography. Neuroscience. 1994 Sep 1;62(1):15-30.

Syvänen AC. Accessing genetic variation: genotyping single nucleotide polymorphisms. Nature Reviews Genetics. 2001 Dec;2(12):930. Syvänen AC. Accessing genetic variation: genotyping single nucleotide polymorphisms. Nature Reviews Genetics. 2001 Dec;2(12):930.

Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry. 2010 Jan 30;31(2):455-61.

Uenaka T, Satake W, Cha PC, Hayakawa H, Baba K, Jiang S, Kobayashi K, Kanagawa M, Okada Y, Mochizuki H, Toda T. In silico drug screening by using genome-wide association study data repurposed dabrafenib, an anti-melanoma drug, for Parkinson's disease. Human molecular genetics. 2018 Aug 22;27(22):3974-85.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3370116

Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, Heer FT, de Beer TA, Rempfer C, Bordoli L, Lepore R. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic acids research. 2018 May 21;46(W1):W296-303.

Wong XY, Groothuis-Oudshoorn CG, Tan CS, van Til JA, Hartman M, Chong KJ, IJzerman MJ, Wee HL. Women's preferences, willingness-to-pay, and predicted uptake for single-nucleotide polymorphism gene testing to guide personalized breast cancer screening strategies: a discrete choice experiment. Patient preference and adherence. 2018;12:1837.

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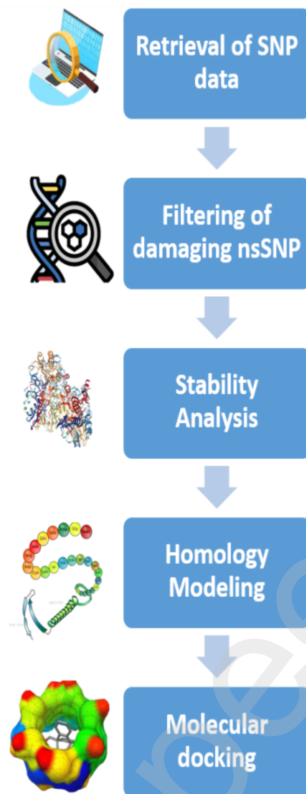

Figure 1: Overall workflow protocol

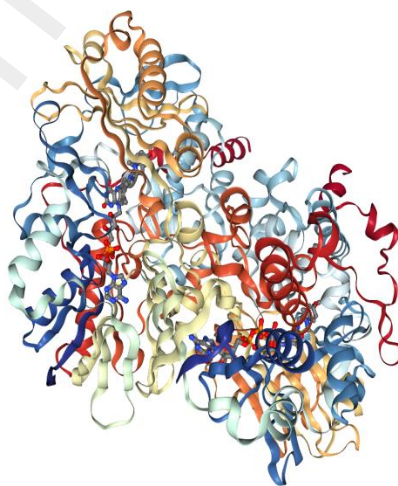

Figure 2: 3D view of Human MAO B (PDB ID: 4CRT)

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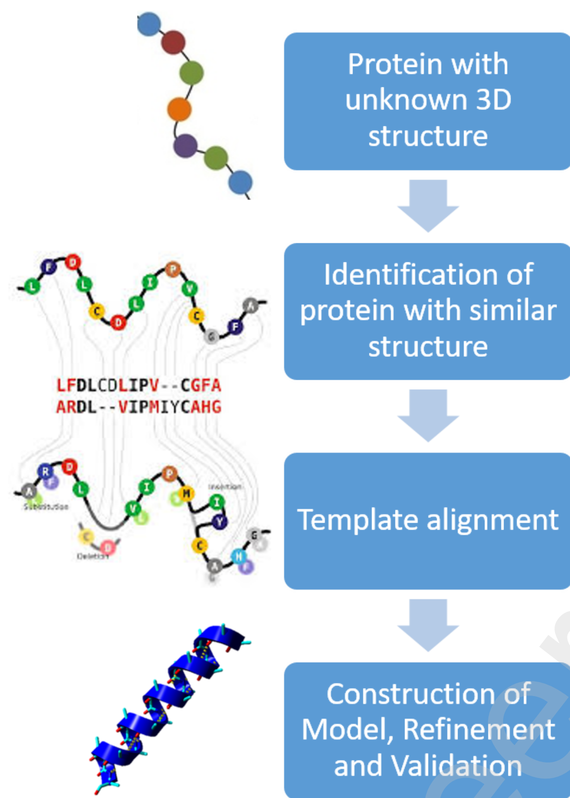

Figure 3: Homology modeling process

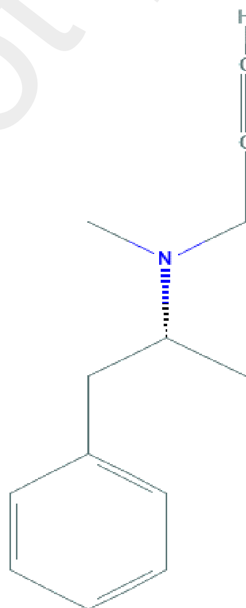

Figure 4: Structure of Zelapar(Selegiline)

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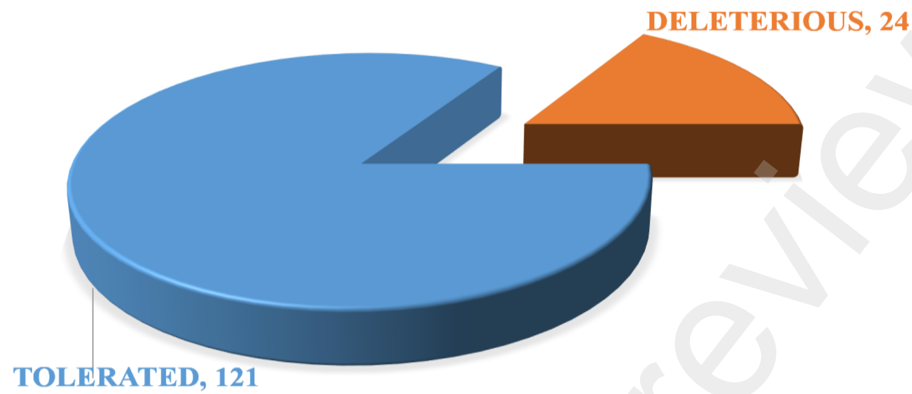

Figure 5: SIFT prediction of Damaging SNPs

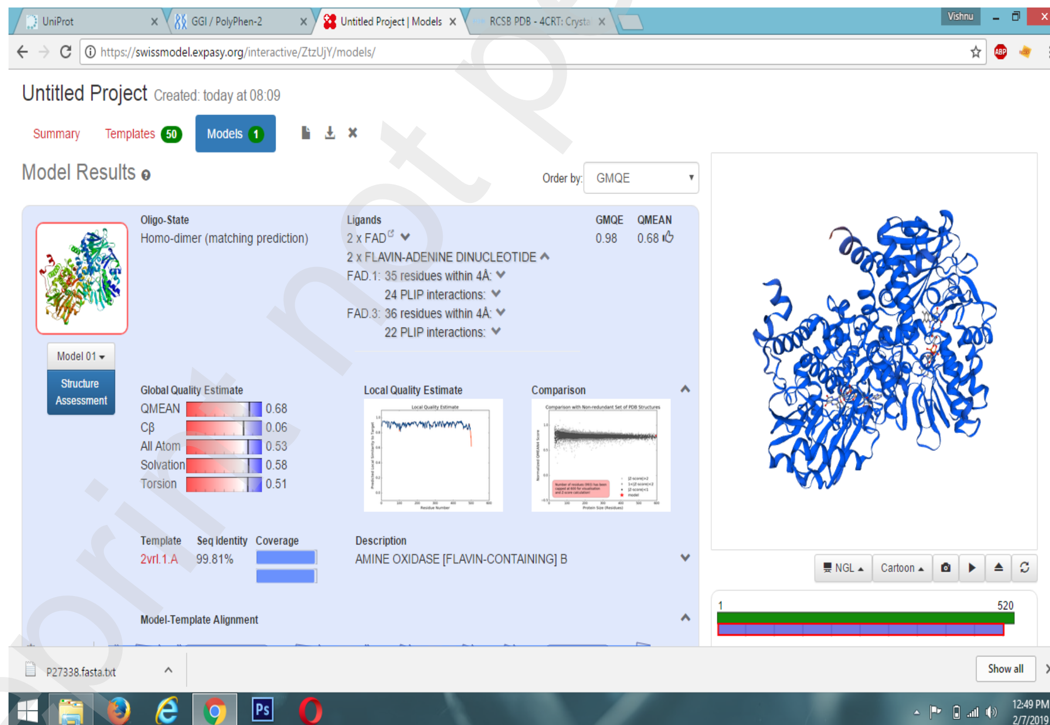

Figure 6: Results of Homology modeling in SWISS MODEL workspace

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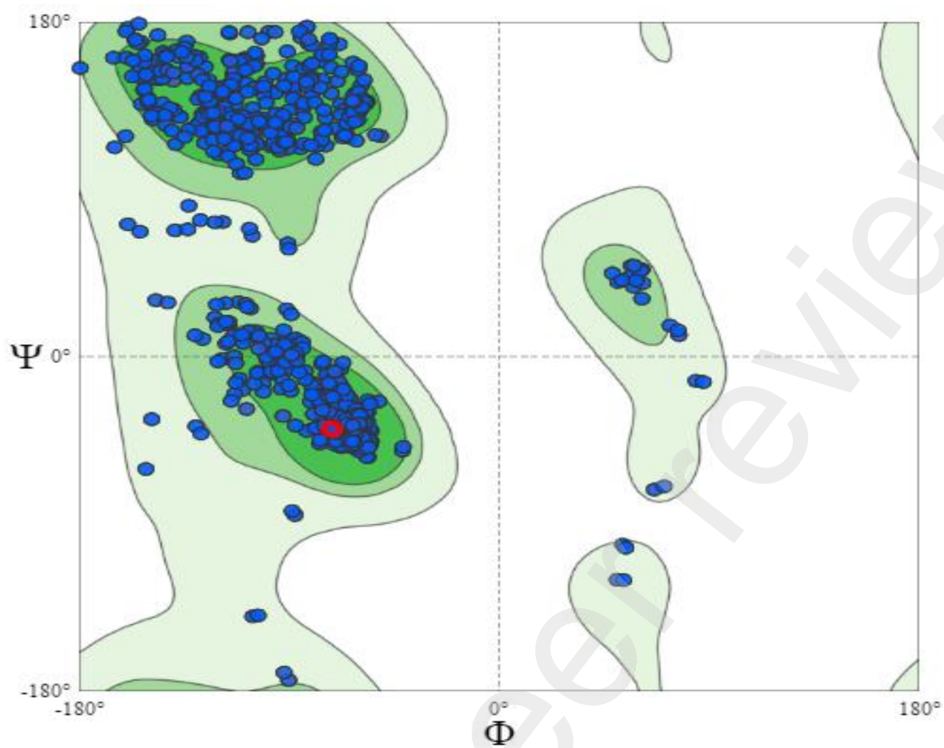

Figure 7: Ramachandran plot of P130Q

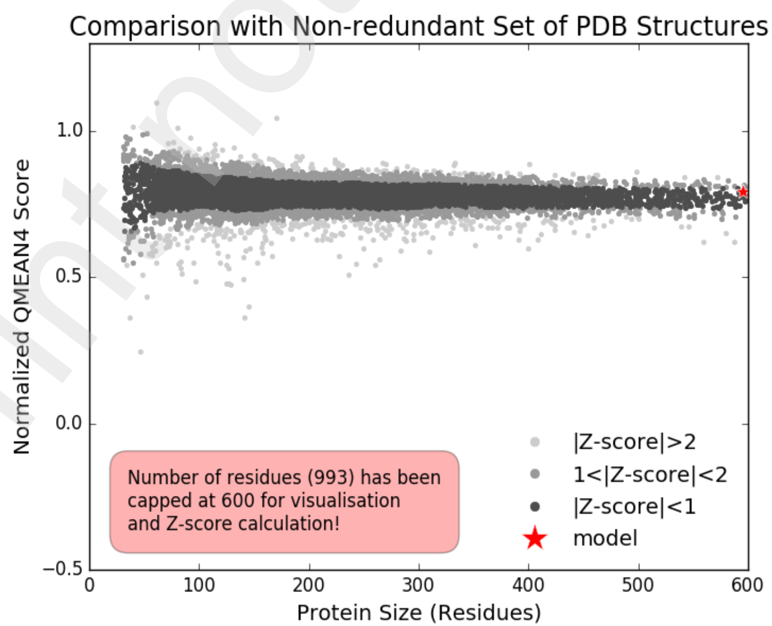

Figure 8: QMEAN score analysis of P130Q

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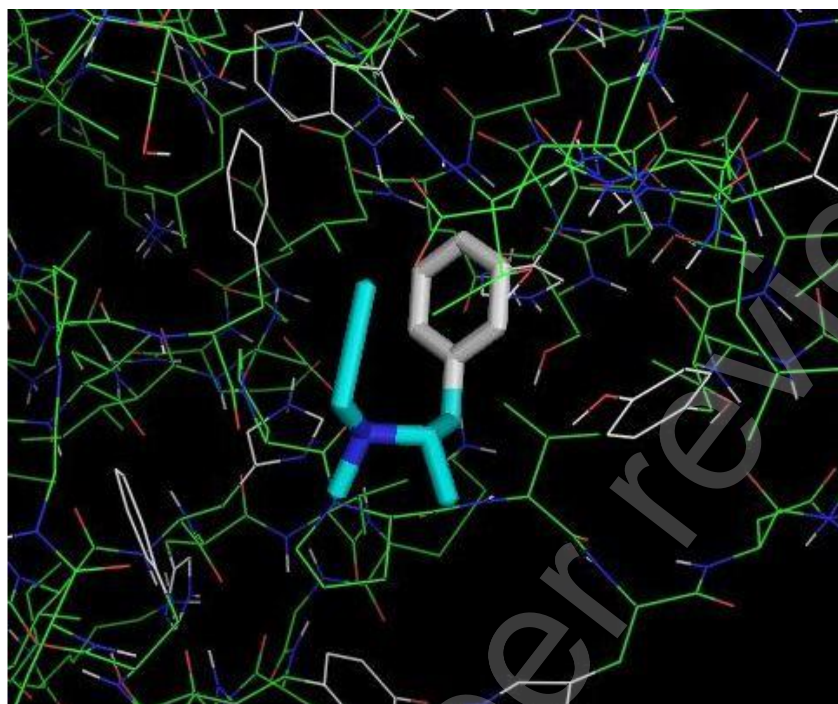

Figure 9: Binding interaction of Zelapar with native protein

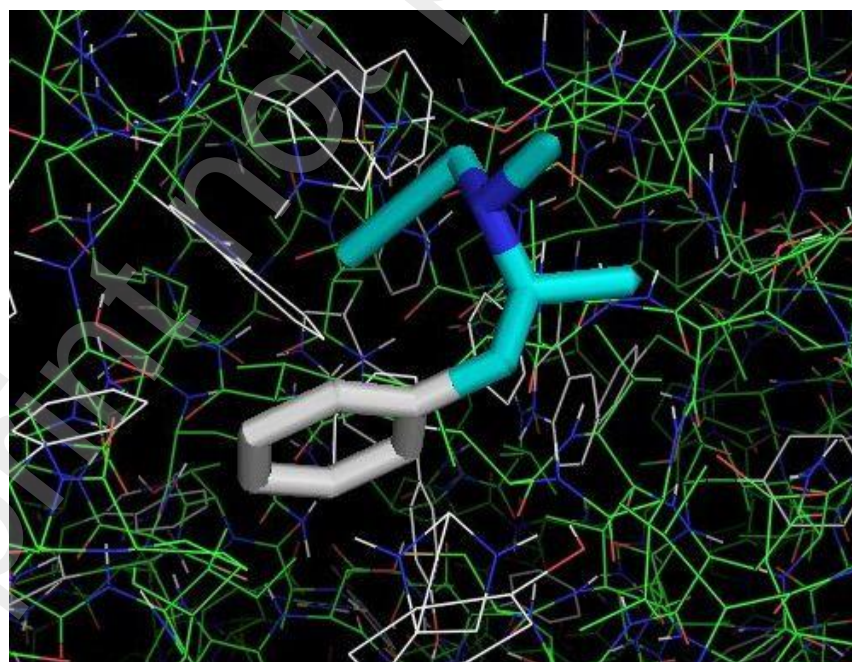

Figure 10: Binding interaction of Zelapar with P130Q

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