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ORIGINAL RESEARCH

Biomarker Variants of Dopamine Receptor Genes Influence the Binding Interaction Between Dopamine Receptor and Risperidone

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Introduction: Risperidone is atypical antipsychotic medication commonly used to control behavioral symptoms in children with autism and widely considered a first-line treatment for acute and maintenance treatment of schizophrenia and bipolar mania. However, the response to risperidone is varied between patients due to genetic factors such as dopamine receptor genes.

Methods: Using state-of-the-art tools, the current study designed to predict the most deleterious SNPs of the five (*DRD1, DRD2, DRD3, DRD4* and *DRD5*) dopamine receptors genes, and their impact on the function and structure of dopamine receptor protein and the binding with risperidone. In-silico tools such as SIFT, PolyPhen2, PANTHER, PROVEAN, SNPs & GO, CRAVAT-VEST score, Mutation Assessor, FannsDB-CONDEL score, predict SNP and SNAP2 were subjected to predicting the deleterious nature of 1581 non-synonymous SNPs (nsSNP) of dopamine receptors genes.

Results: The analysis predicted the most deleterious nsSNPs in each dopamine receptor: rs759268810 in *DRD1*, rs866976053 in *DRD2*, rs1274871399 in *DRD3*, rs745604469 in *DRD4*, and rs778635010 in *DRD5*. Significant reduction in the binding free energy in the mutant (F198C: S score = −7.29 kcal/mol) in the D2 subtype of the dopamine receptor compared to the wild (F198: S score = −8.73 kcal/mol) at the interaction analysis with risperidone. Cumulative analysis of the interaction between risperidone and dopamine receptor protein revealed the rs866976053 as the most deleterious nsSNP among the 1581 nsSNPs of the dopamine receptor genes.

Conclusion: The observation of the state-of-the-art tools-based analysis and observations of MD simulations prioritized the F198C of *DRD2* as a candidate variant for wet lab studies to find its impact on drug efficacy for managing autism, schizophrenia and bipolar mania.

Keywords: autism, risperidone, schizophrenia, bipolar mania, dopamine receptor, mutation, DRD2, docking

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with childhood onset, while schizophrenia and bipolar mania typically manifest in late adolescence or early adulthood. ASD, schizophrenia and bipolar mania are considered common multifactorial disorders influenced by complex genetic and environmental factors.[1–3] The prevalence is increasing worldwide and over the last decade, there was around 50% to 2000% increase in autism cases.[4] It has a variety of symptoms that range from mild to severe which include deficits in social interaction, communication, language impairment and repetitive disorder.[5,6] Currently, there are behavioral and educational interventions, but an effective curative therapy has not been found yet.[1]

Atypical antipsychotics are a class of medications that are used in many psychiatric disorders including bipolar, schizophrenia and maladaptive behaviors of autism patients.[7,8] One of the most used medications is risperidone which

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shows favorable outcomes compared to other antipsychotics such as olanzapine. However, atypical antipsychotics are associated with harmful side effects like metabolic disorders and weight gain that may lead to noncompliance with therapy.[9] Moreover, there are inter-individual variations in response between patients taking atypical antipsychotics[5,10–12] due to the heterogeneity of ASD, one medication cannot be used as a universal treatment for all patients.[13,14]

Genetic diversity particularly through Single Nucleotide Polymorphisms (SNP), contributes to the variability of drug response.[1] Non-synonymous single nucleotide polymorphisms (nsSNPs) are predominantly associated with inherited diseases and are positioned in protein-coding regions as well as have neutral or deleterious effects on protein function and structure.[15] Risperidone works by an antagonistic mechanism on dopamine D2 and serotonin (5-HT [5-hydroxytryptamine]) 2A receptor.[16–18] It is typically used to treat Schizophrenia. In 2006, risperidone was approved by the Food and Drug Association (FDA) for the management of aggressiveness and irritability in children with ASD.[19]

The selection of autism spectrum disorder, schizophrenia and bipolar disorder as the focus of this study is rooted in their shared pathophysiological foundation involving dopaminergic system dysfunction. These disorders exhibit significant overlap in the dysregulation of dopamine signalling within the mesolimbic and mesocortical pathways, which are critical for social cognition, motor control and emotional regulation.[20,21] While risperidone is a primary therapeutic agent for these conditions, previous clinical studies on *DRD2* gene polymorphisms, such as −141C Ins/Del and Taq1A, have shown inconsistent results regarding treatment response and side-effect profiles like weight gain.[22] This inconsistency highlights a critical knowledge gap and the structural and functional mechanisms by which specific non-synonymous SNPs (nsSNPs) alter receptor-ligand binding remain poorly understood.

Studying the effect of nsSNPs on the function and structure of the protein using wet lab studies is costly, time-consuming and difficult. Therefore, utilizing in-silico analysis by modern bioinformatics tools instead of wet lab studies to determine the effect of nsSNPs on protein structure and function will be more reliable and cost-effective.[15,19,23–25] This study aims to predict the most deleterious SNPs and their pathogenic effect on the function and structure of five dopamine receptor genes and their impact on the binding with risperidone.

Materials and Methods

Datasets and SNPs Retrieval

Gene sequences of the five dopamine receptors (*DRD1, DRD2, DRD3, DRD4*, and *DRD5*) in build 37 were downloaded from the NCBI database in April 2019. The NCBI -dbSNPs (Single Nucleotide Polymorphism) of the dopamine receptors genes were retrieved by limiting the search only to missense, nonsense, frameshift, and 3′ and 5′ translated regions in homo sapiens. The non-synonymous SNP was subjected to find the deleterious effects.

SIFT Blink for Sequence Homology

Sort Intolerant From Tolerant (SIFT) is a program that can be used to anticipate if the protein function will be affected by amino acid substitution by using sequence homology.[26–28] In polymorphisms or mutagenesis studies, it will differentiate between functionally deleterious or neutral amino acid changes. SIFT scores are classified as follows; a score value equal to or less than 0.05 represents tolerated nsSNP, and a score value equal to or more than 0.05 corresponds to deleterious nsSNP.[26,29]

Impact of Amino Acid Substitution Predicted by PolyPhen 2

Polymorphism Phenotyping v2 (PolyPhen 2) is a tool used to predict the impact of an amino acid substitution on human protein function and structure using straightforward physical and comparative considerations. The input query was submitted in FASTA sequence format with the position of the native substitution amino acid and the substituted mutant amino acid, specificity, sensitivity estimation and calculation of PSIC score (position- specific independent count) all can be done using PolyPhen 2. Position- specific independent count score classifies nsSNP as damaging, probably damaging and benign.[24,28]

PANTHER for Protein Stability and Function Evaluation

PANTHER-PSEP (Protein Annotation through Evolutionary Relationship) is a classification system which integrates gene ontology, function and statistical analysis which allows biologists to perform gene expression experiments and

analyze gene data from sequencing. Around 82 complete genomes are classified into gene families and subfamilies and in the phylogenetic trees their evolutionary relationships are captured.[29,30] Based on substitution position-specific evolutionary conservation (subPSEC) score the probability of deleterious (p deleterious) nsSNP can be determined, nsSNP labeled as deleterious if the score is ≥0.5.[31]

PROVEAN

Protein Variation Effect Analyzer (PROVEAN) is a prediction tool that is used to determine if insertions, deletions, and substitutions of single or multiple amino acids will have functional effects.[32] If the PROVEAN score is equal to or less than (−2.5) then the protein variant will have a deleterious effect. However, if the score is above (−2.5) it will have a neutral effect.[33]

SNPs & GO and PhD-SNP

SNPs & GO (Single Nucleotide Polymorphism & Genetic Ontology) is a tool that uses protein functional annotation to predict single amino acid polymorphism (SAPs). The server input includes sequence and/or its 3D structure if available, a target variation and its functional Gene Ontology (GO) terms. The output gives the probability of protein variation to cause disease. A nsSNP associated with disease is indicated if the probability value is more than 0.5 for each variant.[27] PhD-SNP (Predictor of human Deleterious Single Nucleotide Polymorphisms) classifies SNP as neutral or disease-related. Protein sequence, position, new residue, prediction and Multi SVM (Support Vector Machine) are the required input. The results will provide several mutated positions, new residue, wild-type residue, and the prediction of neutral or disease-related polymorphism (Snps.biofold.org, 2020).

CRAVAT- VEST Score

CRAVAT (Custom Ranked Analysis of Variants Toolkit) is a bioinformatics tool for genomic variant interpretation. VEST score is a tool to predict protein functional impact. The VEST training set is a positive class of disease-causing germline variants from the Human Gene Mutation Database (HGMD Professional 2012v2) and a negative class of common variants from the Exome Sequencing Project dataset (ESP6500 accessed July 2012).

Mutation Assessor

This online server predicts the impact of amino acid mutation observed in cancer or missense polymorphism on protein function. Functional impact is assessed based on an evolutionary conservation of the mutated amino acid in protein homologs. The input format includes a list of the human genomic variants. Results categories based on FI score as high (>3.5), medium (>2-3.4), low (>1-1.9), and neutral (<1) impact.[34,35]

FannsDB-CONDEL Score

FannsDB (Functional Annotations Data Base) used for non-synonymous SNVs (single nucleotide variants) is a database that has pre-calculated scores for several predictors. CONDEL (Consensus Deleteriousness) score is used to evaluate the outcome of non-synonymous SNVs. The input was as a list of the human genomic variants and the result was classified as disease (>0.5) or neutral (<0.5).[36]

Predict SNPs

An online tool works as a consensus classifier that predicts mutation associated with disease. Input submitted as FASTA sequence format with the substitution of the native and mutant amino acid change. Results are considered to be neutral (<−1, 0>) and deleterious (0, +1>) (Loschmidt.chemi.muni.cz, 2020).

SNAP2

SNAP2 (Screening for Non-Acceptable Polymorphisms 2) is an online classifier tool that predicts changes in protein structure, solvent accessibility, and pathogenicity as a result of nsSNP. The result classified as +100, have an effect; −100 neutral <-1.[37]

Cumulative Score

The Cumulative Score represents a consensus-based filtering approach used to determine the pathogenicity of each non-synonymous Single Nucleotide Polymorphism (nsSNP). It is calculated by aggregating the binary predictions (Damaging/Deleterious vs Neutral/Tolerated) from the ten independent bioinformatics algorithms utilized in this study (SIFT, PolyPhen-2, PANTHER, PROVEAN, SNAP2, SNPs&GO, PhD-SNP, VEST, Mutation Assessor, and CONDEL). For each SNP, a score of "1" was assigned if a tool predicted the variant to be Damaging (D), Probably Damaging (PD), Disease, Effect (E), or High (H) impact based on the specific numerical thresholds of that tool. Conversely, a score of "0" was assigned for neutral or tolerated predictions. The cumulative score is the total number of tools that reached a consensus on the deleterious nature of the. This rigorous multi-tool validation ensures that only the most robustly predicted deleterious variants are selected for subsequent structural homology modeling and molecular docking analysis.

Protein-Protein Complex Interaction

We used the STRING database (Version 12.0) to analyse the physical and functional interactions between the five dopamine receptors (DRD1, DRD2, DRD3, DRD4 and DRD5). Functional enrichment analysis was conducted against a whole-genome background to ensure statistical accuracy. All reported p-values were multiple-testing adjusted using the False Discovery Rate (FDR) method. The significance threshold for enrichment was set at FDR < 0.05.[38]

Homology Modeling and Molecular Docking

The 3D Structures of all dopamine receptors are not available in the protein data bank (PDB). Therefore, to get the 3D structure FASTA sequence of all dopamine receptors (UniProt IDs: DRD1: P21728; DRD2: P14416 isoforms P14416-1; DRD3: P35462 isoforms P35462-1; DRD4: P21917 and DRD5: P21918) was downloaded from UniProt (The Universal Protein Resource (UniProt), 2007) and submitted to the SWISS model to get the template with the highest coverage and build a protein model.[39,40] The quality of the modeled proteins was maintained as described earlier.[15] Then PYMOL software was used to generate the normal, mutant, and superimpose protein (ver.1, Schrodinger). Root mean square deviation (RMSD) was measured by SOFTBERRY software.[41] For energy minimization, an active site selection and docking molecular operating environment (MOE) program was used (Chemical Computing Group Inc., MOE).

Molecular Dynamic Simulations

Molecular dynamic simulations of the interaction between DRD2 wild protein (F198) and mutant F198C variants and risperidone were analyzed using Desmond (Schrodinger, LLC, NY, USA). Protein-Ligand Root Mean Square Deviation (RMSD) of DRD2 wild protein (F198) with risperidone was calculated. Types of protein-ligand interactions (or "contacts") of DRD2 wild protein (F198) and mutant (F198C) risperidone were studied.

While the primary MD simulations were performed as single 100 ns production trajectories per system, we cross-validated the results using an independent simulation engines, GROMACS (with the CHARMM36 force field) to ensure the robustness of our findings. Both platforms independently converged on similar stability profiles, lending confidence to the descriptive conclusions regarding the impact of the F198C mutation on risperidone binding.

Statistical Analysis

The study tested the null hypothesis (H_0) that there is no significant difference in the binding free energy of risperidone between the wild-type and mutated (F198C) dopamine D2 receptors. The alternative hypothesis (H_1) posits that the F198C mutation significantly alters the binding affinity, as measured by the score of GBVI/WSA binding free energy (kcal/ mol). Initial sata analysis was performed using descriptive statistics beyond automated platform outputs. Descriptive outputs include total SNP counts per gene and variant pathogenicity scores from 10 bioinformatics tools (SIFT, PolyPhen-2, PANTHER, PROVEAN, SNPs&GO, PhD-SNP, CRAVAT, Mutation Assessor, CONDEL and PredictSNP). Results were categorized as "deleterious" or "neutral" based on tool-specific thresholds (eg., SIFT ≤ 0.05, PROVEAN ≤ -2.5). Protein-ligand interactions, RMSD values, and binding free energies (kcal/mol) were generated via MOE and Desmond (Schrodinger LLC, NY). STRING functional enrichment p-values were reported as false discovery rate adjusted values.

Results

SNP Datasets and Retrieval for Dopamine Receptors

The results of SNP from the NCBI of the five-dopamine receptor (*DRD1, DRD2, DRD3, DRD4* and *DRD5*) genes give a total of 1017 SNPs sequence of *DRD1* in chromosome 5 (970 dbSNP, 200 nsSNP), no-nonsense, frameshift, 5′ UTR variant, and 3′ variant was observed. A total of 17,882 genomic variants on the sequence of *DRD2* in chromosome 11 (17,738 dbSNP, 229 nsSNP, 1 nonsense, 2 frameshifts, 75 5′ UTR variant, 275 3′ variant). A total of 18,182 SNP sequences of *DRD3* in chromosome 3 (17889 dbSNP, 245 nsSNP, 8 nonsenses, 9 frameshifts, 209 5′ UTR variant, 21 3′ variant). A total of 2,424 SNP sequences of *DRD4* in chromosome 11 (2,234 dbSNP, 487 nsSNP, 9 nonsense, 80 frameshift, 4 5′ UTR variant, 52 3′ variant). A total of 1,227 SNP sequences of *DRD5* in chromosome 4 (1080 dbSNP, 420 nsSNP, 28 nonsense, 34 frameshift, 135 5′ UTR variant, 146 3′ variant) (Table 1). *DRD2* and *DRD3* have reported with maximum number of SNPs among all the dopamine receptor genes (Table 1).

The initial retrieval from the NCBI dbSNP database for the five dopamine receptor genes (*DRD1, DRD2, DRD3, DRD4* and *DRD5*) yielded a vast array of genomic variants. For *DRD2*, a total of 17,882 genomic variants were identified. Following the methodology described in Datasets and SNPs Retrieval, these were filtered to focus on functional regions. This resulted in a refined dataset of 606 specific variants (including missense, nonsense, and UTR variants) that were subjected to further deleterious prediction analysis.

Protein Interactions Using STRING

The protein-protein interaction analysis on the functional involvement of dopamine receptor genes revealed that they are significantly involved in dopamine binding (FDR-adjusted p-value = 9.32×10^{-15}), dopamine receptor signaling pathway (FDR-adjusted p-value = 1.62×10^{-11}) and dopamine synapse (FDR-adjusted p-value = 1.48×10^{-10}). They are members of the rhodopsin-like G-protein coupled receptor family (FDR-adjusted p-value = 3.16×10^{-17}).

Deleterious nsSNPs Among Dopamine Receptor Genes

The deleterious nature of the amino acid substitutions was predicted using 10 (SIFT, Poly-Phen, PANTHER, PROVEAN, SNAP, SNPs & GO, phD-SNP, mutation assessor, VEST and CONDEL) different tools described in the methodology (Figures 1 and 2A–E). The total number of SNPs in the *DRD1* gene is 671, total number of deleterious SNPs in each tool: is 77 in SIFT, 65 in Poly-Phen, 69 in PANTHER, 53 in PROVEAN, 66 in SNAP, 36 in SNPs & GO, 48 In phD-SNP, 76 IN mutation assessor, 145 in VEST P value and 41 in CONDEL. Total number of SNPs in *DRD2* 606, total deleterious SNPs in each tool: 92 in SIFT, 81 in PolyPhen, 89 in PANTHER, 64 in PROVEAN, 81 in SNAP, 45 in SNPs & GO, 56 in phD-SNP, 91 in mutation assessor, 49 in VEST P value and 59 in CONDEL. Total SNPs in *DRD3* 167. Total deleterious SNPs in each tool: 43 in SIFT, 37 in Poly-Phen, 38 in PANTEHR, 37 IN PROVEAN, 41 in SNAP, 29 in SNPs & GO, 33 in phD-SNP, 41 in mutation assessor, 26 in VEST P value and 28 in CONDEL. The total SNPs in *DRD4* is 654 total deleterious SNPs in each tool: 270 in SIFT, 251 in Poly-Phen, 192 in PANTHER, 186 in PROVEAN, 244 in SNAP, 149 in SNPs & GO, 186 IN phD-SNP, 0 in mutation assessor, 34 in VEST P value and 8 in CONDEL. The total SNPs in *DRD5* is 560. Total deleterious SNPs in each tool: 227 in SIFT, 207 in Poly-Phen, 181 in PANTHER, 189 in PROVEAN, 202 in SNAP, 138 in SNPs & GO, 168 in phD-SNP, 0 in mutation assessor, 105 in VEST P value and 165 in CONDEL (Figure 1). The cumulative score was calculated to detect the highest deleterious SNPs for each dopamine receptor gene. There were 3, 3, 6, 1, and 2 SNPs found to be deleterious

Table 1 Distribution of the SNPs in Dopamine Receptor Genes in NCBI Viewer

Gene	Total Number of SNP	Chromosome	dbSNP	nsSNP	Nonsense	Frameshift	5′ URT Variant	3′ Variant
DRD1	1017	5	970	200	0	0	0	0
DRD2	17882	11	17738	229	1	2	75	275
DRD3	18182	3	17889	245	8	9	209	21
DRD4	2424	11	2234	487	9	80	4	52
DRD5	1227	4	1080	420	28	34	135	146

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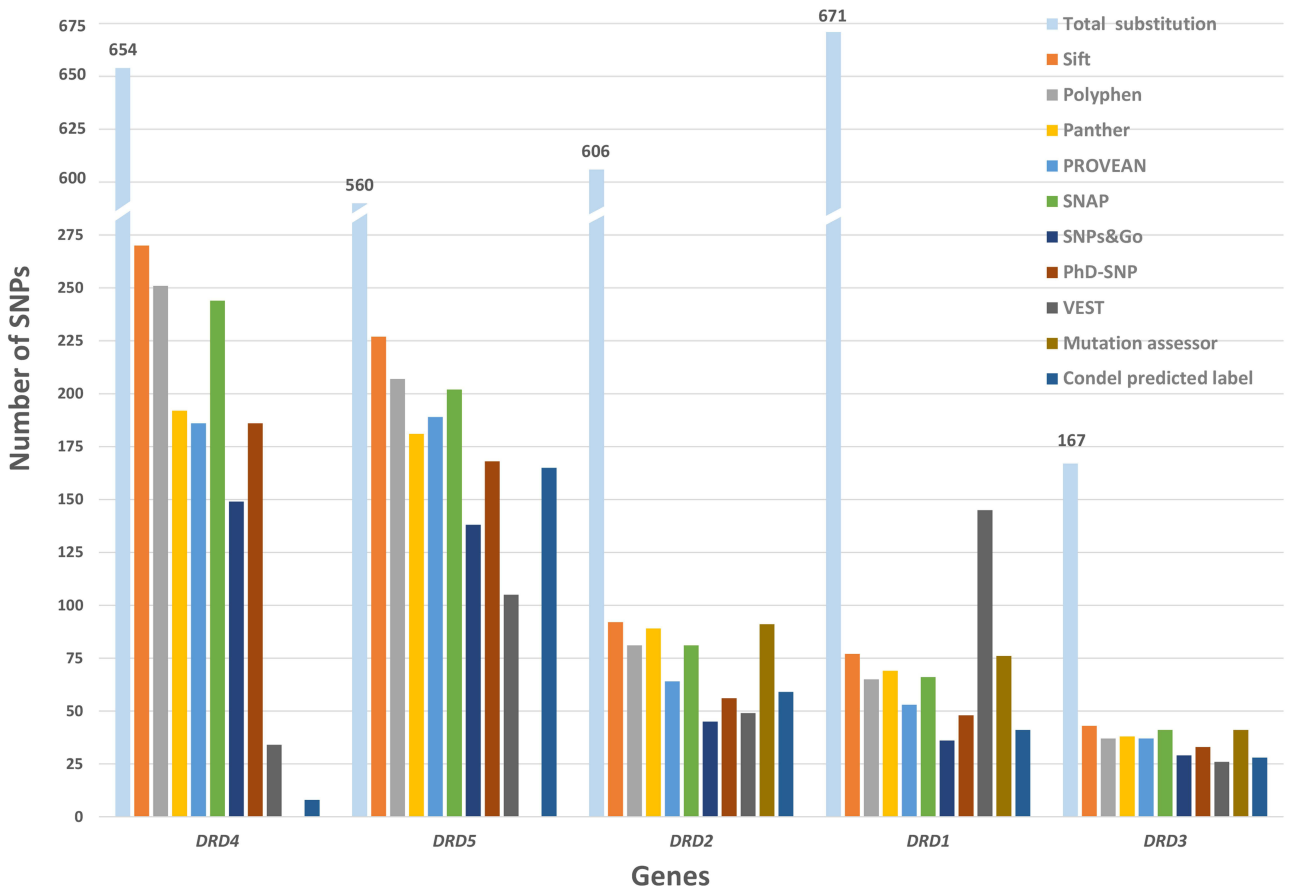

Figure 1 Screening and prediction of deleterious nsSNPs in dopamine receptors genes by 9 different computational tools.

in *DRD1, DRD2, DRD3, DRD4*, and *DRD5* respectively in all the tested tools (Table 2). The highest deleterious SNPs for each dopamine receptor gene were selected for further analysis (Table 2; Figure 2A–E).

Homology Modeling of Dopamine Receptors Proteins and Docking

The most significant deleterious SNPs in each dopamine receptor gene were selected to identify their structural impact on DRD1, DRD2, DRD3, DRD4, and DRD5 proteins. The SWISS-MODEL server was used to model the 3D structure of dopamine receptor proteins. The best template for each dopamine receptor (PDB ID, 6CM4 for DRD2) was selected depending on the highest quality. Then all templates were mutated and superimposed to identify the structural changes (Table 3, Figure 3). The most prominent changes observed due to the mutation F198C (Mutation percentage = 64.5%) were taken for the effect of mutation in the DRD2 protein- risperidone binding analysis (Table 4; Figure 4A–D). The molecular docking analysis revealed an increase in final score of GBVI/WSA binding free energy in the mutant (F198C: S score = −7.0234 to −7.5559 kcal/mol) than wild (F198: S score = −8.5542 to −8.91 kcal/mol), affinity also showed similar behavior, also observed with changes in the hydrogen bonds. The results revealed a statistically significant difference ($p = 0.001485$), with the mutant F198C showing a significantly higher (less favorable) binding energy (Mean = −7.29 kcal/mol) compared to the wild-type F198 (Mean = −8.73 kcal/mol). The analysis of Lipinski's Rule parameters confirmed that risperidone maintained its drug-like properties and bioavailability throughout the docking simulations (Table 4). The stability of these ligand-based parameters indicates that the statistically significant reduction in binding affinity observed in the mutant complex is attributable exclusively to the structural reorganization and loss of hydrophobic contacts within the DRD2 receptor caused by the F198C substitution, rather than any alteration in the physicochemical profile of ligand.

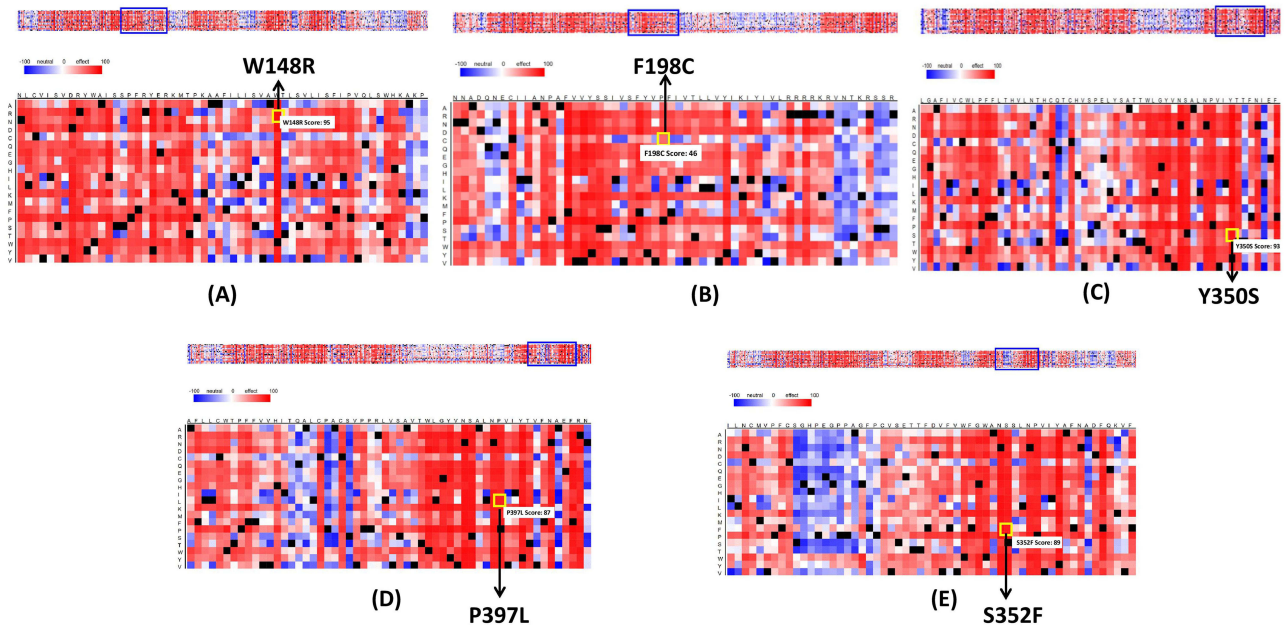

Figure 2 Heatmap analysis of deleterious single nucleotide polymorphisms (SNPs) across the five dopamine receptor genes (DRD1–DRD5). Panels A–E represent the functional impact of amino acid substitutions: (**A**) Pathogenic amino acid substitution, W148R in DRD1 gene with score: 95; (**B**) Pathogenic amino acid substitution, F198C in DRD2 gene with score: 78; (**C**) Pathogenic amino acid substitution, Y350S in DRD3 gene with score: 93; (**D**) Pathogenic amino acid substitution, P397L in DRD4 gene with score: 87; (**E**) Pathogenic amino acid substitution, S352F in DRD5 with score: 89. The color-coded scale indicates the predicted functional effect, where blue/white boxes signify neutral or tolerated variations and red/darker highlighted boxes indicate increasingly deleterious or pathogenic impacts on the biological function of the protein. The yellow boxes specifically highlight the location of the pathogenic substitutions analysed in each panel (A–E). The arrow symbols within the heatmap specifically denote the position of the wild-type residue and the resulting pathogenic substitution analysed in this study.

Molecular Dynamic Simulations

The docked complexes of risperidone with DRD2 wild protein F198 and mutant F198C variants were analyzed by 100 ns MD simulation for the DRD2-F198-risperidone and DRD2-F198C-risperidone complex intermolecular interaction and stability concerning time. The final poses for the interacting DRD2-F198-risperidone and DRD2-F198C-risperidone complexes were obtained at the end of the MD simulation. The molecular dynamic simulations of the interaction between risperidone and DRD2 wild protein F198 (Figure 5A, C, E, G and I) and mutant F198C (Figure 5B, D, F, J and H) variants confirm the docking results of prominent impact by the amino acid substitution F198C (Figure 5). Root mean square deviation (RMSD) data were used to assess how the overall DRD2 wild protein F198 and mutant F198C protein stability changed because of the mutation. The stability and convergence of the 100 ns MD trajectories were confirmed by the RMSD profiles, which stabilized for both the wild-type and mutant complexes, suggesting that the simulation time was more than sufficient to sample the relevant conformational space. Ligand fit on protein for the DRD2-F198-risperidone and DRD2-F198C-risperidone complexes showed prominent deviation after 40 ns. Also, the DRD2-F198-risperidone and DRD2-F198C-risperidone interaction profiling revealed the development of hydrogen bonds, ionic, hydrophobic, and water bridges concerning time in the 100 ns simulated trajectories. However, a noticeable shift was observed in the hydrogen bonds in the DRD2-F198-risperidone complex to ionic bonds in the DRD2-F198C-risperidone complex. This variation in the deviation range in the mutant DRD2-F198C-risperidone complex represents the effect of the substituted amino acid (F198C) on the protein structure and explains the stability change. Figure 5G and Figure 5H display the RMSF values for DRD2-F198-risperidone and DRD2-F198C-risperidone complex. Throughout the course of the whole simulation period, the RMSFs of the entire DRD2-F198C-risperidone complex dramatically diverged (at atom index 5 to 9) from the DRD2-F198-risperidone. Changes in the RMSFs represent the effects of deleterious amino acid substitutions (F198C) in the DRD2 protein and identify the flexibility alterations. This 100 ns window provides a reliable statistical ensemble for evaluating the impact of the F198C substitution on risperidone binding.

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Table 2 The Highest Deleterious SNPs for Each Dopamine Receptors Gene

Gene	SNP	CHR	BPP	ALLELES	Amino Acid Change	SIFT		Poly Phen2		PANTHER	PROVEAN		SNAP2		SNPs&GO		PhD-SNP		VEST	Mutation Assessor		CONDEL		Cumulative Score
						Pre	Score	Pre	Score	Pre	Pre	Score	Pre	Score	Pre	Probability	Pre	Probability	*p*-value	Pre	Fi Score	Condel	Pre	
DRD1	rs759268810	5	174869661	A, G	W148R	D	0	PD	1	PD	D	−12.97	E	95	D	0.765	D	0.942	0.00293	H	4.605	0.8304	D	14/14
	rs767856135	5	174869774	G, A	S110F	D	0	PD	1	PD	D	−5.57	E	88	D	0.8	D	0.904	0.00253	H	4.405	0.7996	D	14/14
	rs774846844	5	174869816	C, T	C96Y	D	0	PD	1	PD	D	−9.16	E	81	D	0.844	D	0.95	0.00374	H	3.63	0.7522	D	14/14
DRD2	rs748707296	11	113281570	G, C	P404R	D	0.009	PD	0.991	PD	D	−3.2	E	78	D	0.513	D	0.795	0.00486	H	3.64	0.6408	D	14/14
	rs866976053	11	113286273	A, C	F198C	D	0	PD	1	PD	D	−7.22	E	46	D	0.575	D	0.841	0.00253	H	3.95	0.8690	D	14/14
	rs549053606	11	113288753	C, T	D131N	D	0.004	PD	0.988	PD	D	−4.82	E	78	D	0.75	D	0.862	0.00071	H	3.885	0.8439	D	14/14
DRD3	rs200007633	3	113847595	G, A	R358W	D	0	PD	1	PD	D	−6.56	E	92	D	0.768	D	0.922	0.00182	H	4.28	0.7279	D	14/14
	rs1274871399	3	113847618	T, G	Y350S	D	0	PD	1	PD	D	−7.54	E	93	D	0.789	D	0.893	0.00253	H	4.71	0.7775	D	14/14
	rs148428613	3	113847643	T, C	N342D	D	0	PD	1	PD	D	−4.19	E	91	D	0.79	D	0.748	0.00162	H	4.66	0.7515	D	14/14
	rs868709956	3	113847736	G, A	P311S	D	0	PD	1	PD	D	−6.86	E	75	D	0.721	D	0.869	0.00374	H	4.725	0.8328	D	14/14
	rs868709956	3	113847736	G, T	P311T	D	0	PD	1	PD	D	−6.88	E	75	D	0.724	D	0.86	0.00314	H	4.38	0.8331	D	14/14
	rs1339649517	3	113866288	G, C	P167R	D	0	PD	1	PD	D	−8.69	E	49	D	0.808	D	0.92	0.00091	H	3.775	0.7041	D	14/14
DRD4	rs745604469	11	640533	C, T	P397L	D	0	PD	1	PD	D	−8.17	E	87	D	0.768	D	0.904	0.00374	N/A	N/A	0.5834	D	12/12
DRD5	rs778635010	4	9784707	T, C	S352P	D	0	PD	1	PD	D	−3.94	E	91	D	0.784	D	0.87	0.00314	N/A	N/A	0.8668	D	12/12
	rs748400899	4	9784708	C, T	S352F	D	0	PD	1	PD	D	−4.73	E	89	D	0.854	D	0.937	0.00223	N/A	N/A	0.8642	D	12/12

Abbreviations: CHR, Chromosome; BPP, Base pair position in the chromosome; PRE, Prediction by the state-of-art-tool; D, Damaging, Deleterious or Disease; PD, Probably Damaging; E, Effect; H, High; N/A, Data Not Available.

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Table 3 Mutation Percentage of Superimposed (Wild/Mutant) DRD Receptors

Protein	Superimposed (Wild/Mutant)	Mutation Percentage	RMSD
DRD1	W148R	14.2%	0.043
DRD2	F198C	64.5%	0.026
DRD3	Y350S*	42.9%	0.020
DRD4	P397L	47.8%	0.056
DRD5	S352P	58.9%	0.071

Notes: * Residue numbering system based on NP_387512.3:p.Tyr350Ser.

To validate the structural findings, an independent 100 ns MD simulation was conducted using the GROMACS with the CHARMM36 force field (Figure 6A–C). The protein–backbone RMSD achieved rapid thermodynamic equilibrium, mirroring the stability observed in the Desmond trajectory. Critical descriptors of global integrity, including the Radius of Gyration (Rg) and Solvent Accessible Surface Area (SASA) remained remarkably constant throughout the production run. These metrics confirm that the DRD2-risperidone complex maintains a compact, native-like fold without evidence of unfolding or significant surface remodelling. Furthermore, per-residue RMSF and persistent hydrogen-bond networks corroborated the stability of the binding pocket, providing cross-platform reinforcement of the simulation results.

Discussion

Gene variants can play a prominent role in how they interact with drugs but remains underestimated how much influence it withholds on various diseases. This study demonstrates the important role of genetic variants of dopamine receptor proteins that can affect the interaction affinity of risperidone drug investigated by using molecular docking studies. Variations in response to treatment with risperidone which is a mostly widely used atypical antipsychotic that has been observed for several psychiatric illnesses such as mixed bipolar disease, schizophrenia, and irritability in autistic patients. The primary target for typical and atypical antipsychotics is the D2 dopamine receptor.[42,43] However, medications that promiscuously work against the related receptor could lead to life-threatening adverse effects.[44] Therefore, understanding the structure and function of the DRD2 receptor at the molecular level would provide benefits for medication design.[45,46] Risperidone is one of the atypical antipsychotics that works by blocking dopamine D2 receptor (DRD2) and serotonin (5-HT[5-hydroxytryptamine]) 2A receptors.[47] It shows favorable outcomes and improvement in symptoms when used in the management of patients with ASD.[48] Even though there is treatment variation in the treatment efficacy of risperidone, no predictable marker has been identified yet.[49] Risperidone produces its therapeutic and adverse effects by antagonist mechanism on the dopamine receptor, DRD2. Therapeutic response variations may result from genetic variants of the DRD2 receptor and it could be useful as a predictable marker.[50] This study used state-of-the-art in-silico tools to examine the effect of SNPs on the five-dopamine receptor (DRD1, DRD2, DRD3, DRD4 and DRD5) by obtaining the sequence from these tools to identify the most pathogenic polymorphisms, those methodologies were elaborated for various protein and proved for its applications.[51,52] After using 10 different computational tools for screening and prediction of the most deleterious nsSNP among the five-dopamine receptor; they revealed all the nsSNPs in *DRD1* (671), *DRD2* (606), *DRD3* (167), *DRD4* (654) and *DRD5* (560), and they were subjected for cumulative analysis as described earlier.[51] Then few nsSNP were shortlisted as highly pathogenic and the highest for each dopamine receptor; rs759268810 in *DRD1*, rs866976053 in *DRD2*, rs1274871399 in *DRD3*, rs745604469 in *DRD4*, rs778635010 in *DRD5* as the most pathogenic. This finding helps to eliminate a tremendous amount of laboratory work that is needed to identify the pathogenic nsSNP. Among the five DRD receptors the most deleterious SNP rs866976053 and pathogenic amino acid substitution, F198C in the DRD2 receptor was taken for drug-protein interaction analysis. The findings of the study may help to improve the clinical use of risperidone since *DRD2* and some other genes have been found in association at least twice with some adverse reactions (ie. increased prolactin, metabolic changes and extrapyramidal symptoms).[52] The molecular docking of risperidone and the most pathogenic amino-acid substitution in DRD2 revealed noticeable changes in the interaction analysis. The docked complexes of risperidone with DRD2 proteins, wild F198 and mutant F198C were studied using MD simulation for 100 ns revealing the influence of amino acid substitution on the DRD2-F198C-risperidone complex

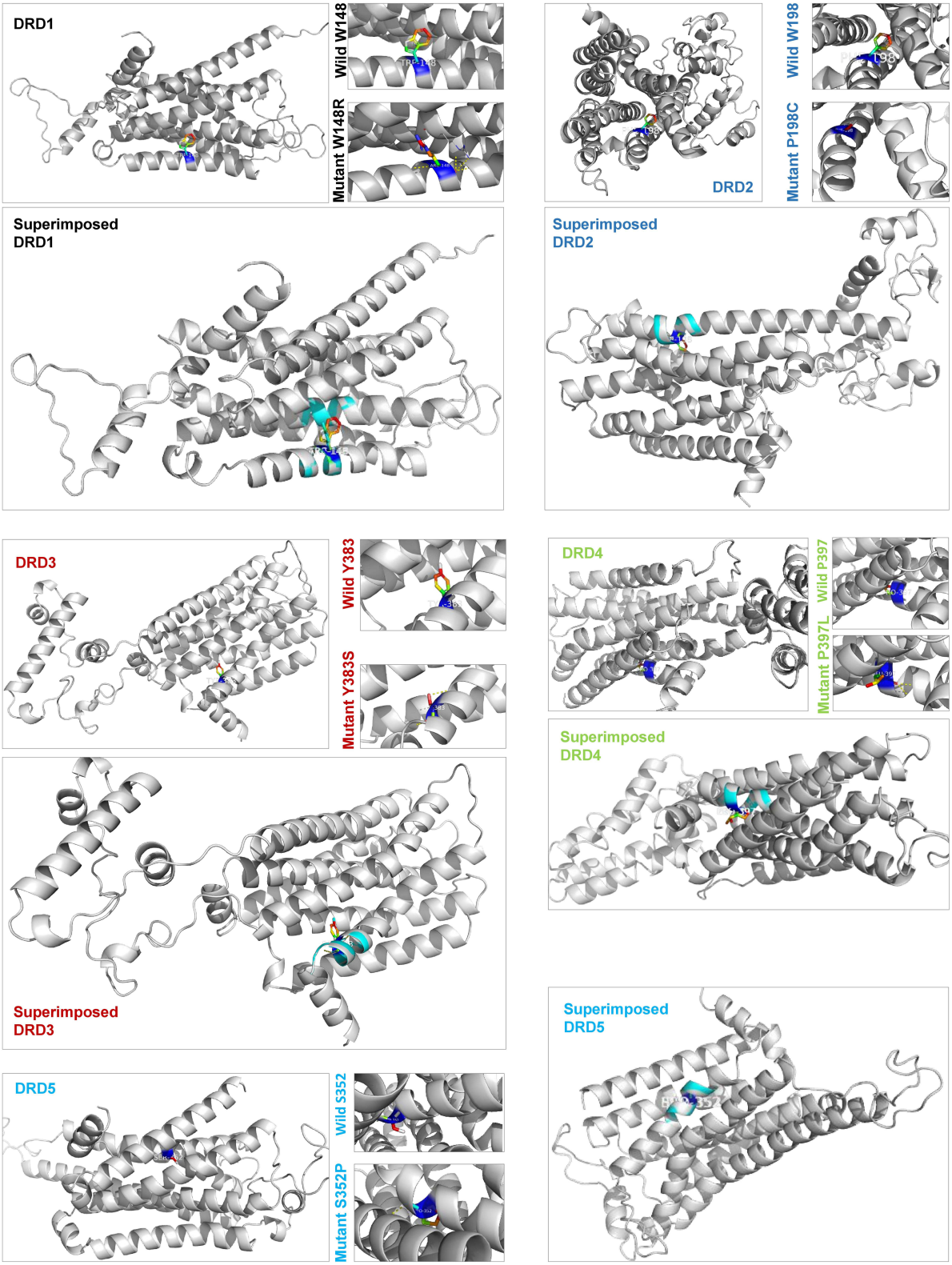

Figure 3 Structural comparison and superimposition of wild-type and mutant dopamine receptors (DRD1–DRD5). The figure displays the secondary ribbon structures of dopamine receptors DRD1 through DRD5 in both their wild-type and mutant states. Superimposed: Large panels titled demonstrate the spatial alignment of the wild and mutant protein backbones. These overlays highlight the structural deviations resulting from the mutations. In all superimposed close-up views, the stick representation corresponds to the wild-type amino acid residue.

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Table 4 The Properties of the Risperidone with Wild and Mutated DRD2 Receptors

DRD2	Lipinski's rule					Strain	Solvation	Affinity	rseq	mseq	S	rmsd_ refine	E_ conf	E_ place	E_ score1	E_ refine
	ΔG	Log P	NoB	HbA	HbD											
Normal F198	−4.29	4.24	1	1	0	12.72	−51.2	−9.94	1	1	−8.7152	1.96	−16.32	−92.59	−11.38	−48.08
Mutant F198C	−4.29	4.24	0	0	0	21.84	−50.75	−8.13	1	1	−7.2929	1.11	0.23	−82.93	−9.46	−39.28

Abbreviations: Risperidone obeyed Lipinski's rule (ΔG kcal/ mol; NoB, Number of hydrogen bond; HbA, Hydrogen bond acceptor; HbD, Hydrogen bond donors; Log P, The log octanol/water partition coefficient); S, MOE Score, the final score of GBVI/WSA binding free energy (kcal/ mol); RMSD_refine, the mean square deviation after refinement; E_place, score of the placement phase; E_conf, energy conformer; E_refine, score refinement; E_scor1, score the first step of notation.

by the noticeable shift on the hydrogen bonds in the wild-risperidone complex to ionic bonds in the mutant protein-risperidone complex. Hence, the effect of risperidone might change in autistic patients with F198C in DRD2 protein. This observation can improve the management strategies in autistic patients. Complete studies are mandatory for all the deleterious amino acid substitutions in the risperidone-interacting protein. Furthermore, the development of best management strategies can change the attitude of parents with autistic patients.[51]

At the structural level, the substitution of Phenylalanine (F) at position 198 with Cysteine (C) represents a significant physicochemical shift. F198 is a bulky, aromatic residue located within the transmembrane helix, contributing to the hydrophobic core and aromatic "cage" that stabilizes risperidone. The mutation to a smaller, polar thiol-containing

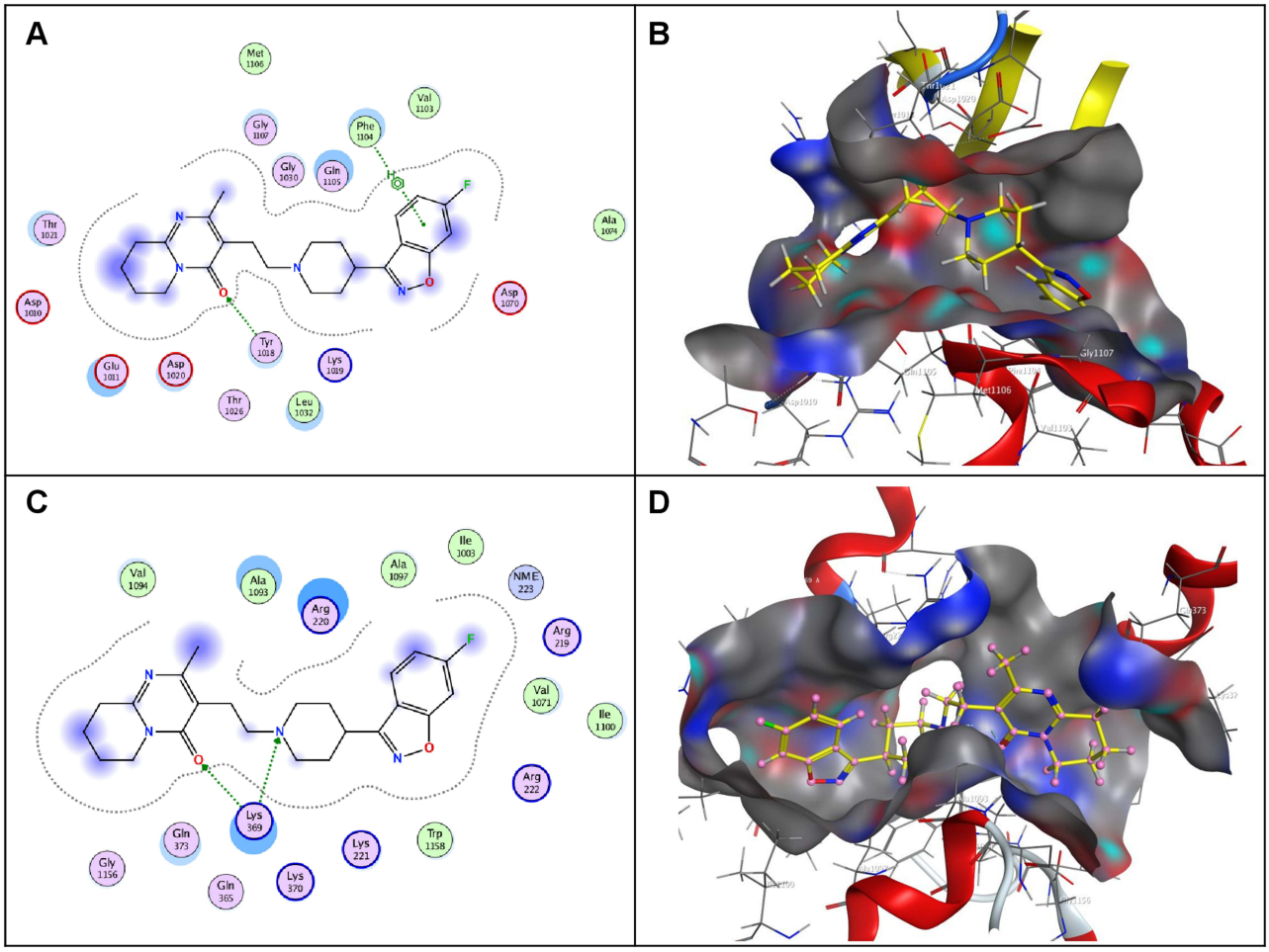

Figure 4 Interaction of risperidone with wild F198 ((**A**) 2D, (**B**) 3D) and mutant F198C ((**C**) 2D, (**D**) 3D) DRD2 protein.

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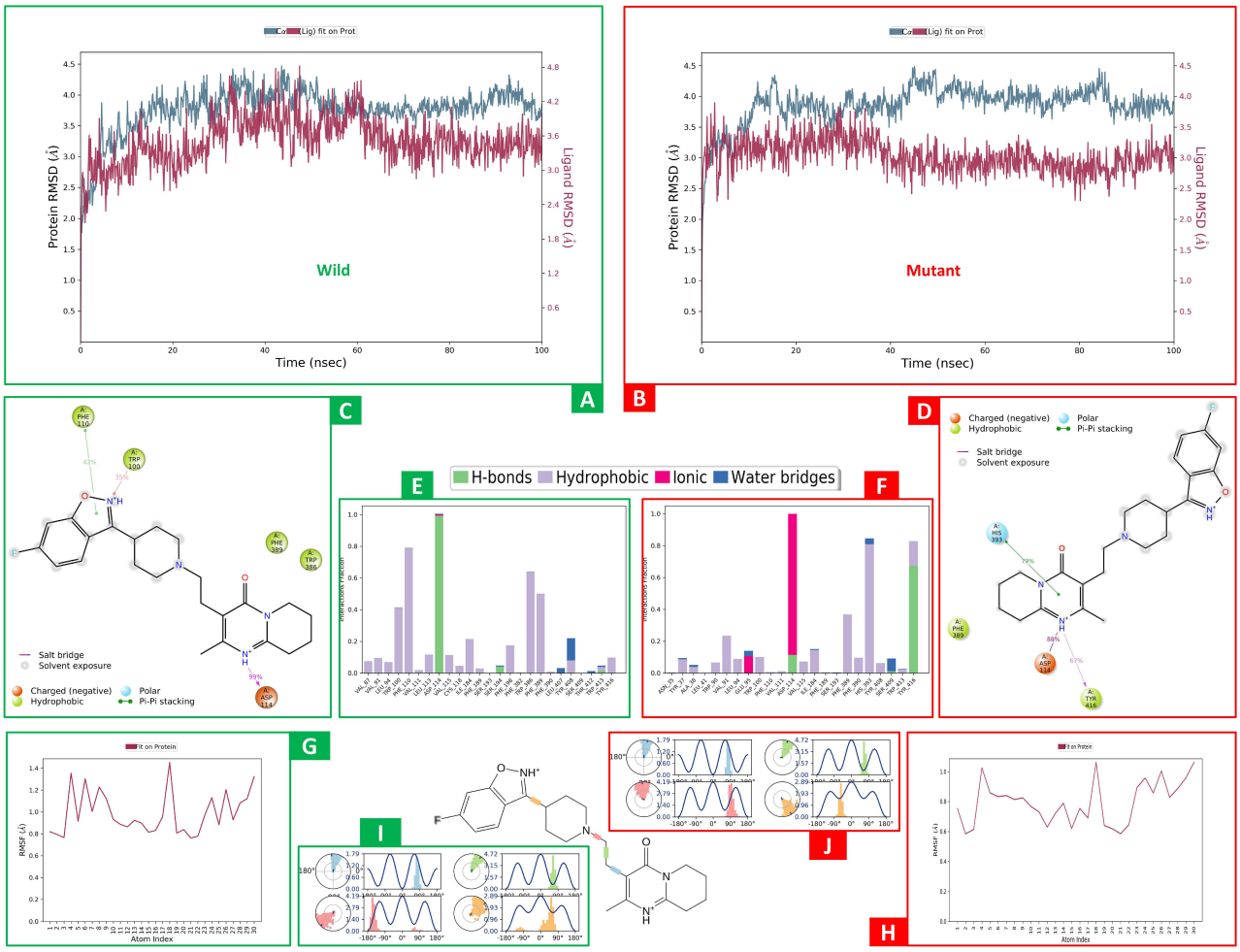

Figure 5 Molecular dynamic simulations of the interaction between DRD2 wild protein (F198) (Boarded green colour) and mutant F198C (Boarded red colour) variants and risperidone. (**A**) Protein-Ligand Root Mean Square Deviation (RMSD) of DRD2 wild protein (F198) and risperidone. (**B**) A: Protein-Ligand RMSD of DRD2 mutant F198C and risperidone. (**C**) Risperidone atom interactions with the DRD2 wild protein (F198) and risperidone. (**D**) Risperidone atom interactions with the DRD2 mutant F198C and risperidone. (**E**) Types of protein-ligand interactions (or "contacts") of DRD2 wild protein (F198) and risperidone. (**F**) Types of protein-ligand interactions (or "contacts") of DRD2 mutant F198C and risperidone. (**G**) Ligand risperidone fluctuations, with respect to DRD2 wild protein (F198). (**H**) Ligand risperidone fluctuations, with respect to DRD2 mutant F198C. (**I** and **J**) The risperidone torsions plot of the conformational evolution of every rotatable bond in the risperidone throughout the simulation trajectory (0.00 through 100.00 nsec). The embedded structure of risperidone shows color-coded rotatable bonds and supported by a dial plot and bar plots of the same color. Histogram shows the conformational strain the risperidone undergoes to maintain DRD2 (I: F198) (J- F198C)-bound conformation.

Cysteine reduces crucial pi-pi and hydrophobic interactions, which likely increases the flexibility of the binding pocket of the receptor. The substitution of the bulky, aromatic Phenylalanine (F198) with the smaller, polar Cysteine (C198) in the transmembrane helix 5 (TM5) region induces a critical conformational shift in the orthosteric binding pocket (Figure 4). F198 typically provides a stabilizing hydrophobic roof over the aromatic rings of risperidone. Its removal not only reduces binding affinity (GBVI/WSA dG) but also likely alters the relative orientation of TM5 and TM6. Mechanistically, such structural instability in TM5 is known to impede the transition of the receptor to its active state, potentially hindering the G-protein recruitment. This suggests that the F198C variant may act as a partial loss-of-function mutation, resulting in attenuated downstream signal transduction, specifically the inhibition of adenylyl cyclase and the regulation of Dopamine-mediated cAMP levels. Consequently, patients carrying this variant may exhibit a diminished therapeutic response to risperidone due to suboptimal receptor-ligand complex stability. The clinical utility of the F198C variant (rs866976053) as a biomarker depends on its distribution across diverse populations. Current data from genomic databases indicate that rs866976053 is a rare variant. While its rarity limits its use as a universal screening tool, its high predicted pathogenicity suggests that individuals carrying this variant would likely exhibit profound resistance or heightened sensitivity to risperidone, making it a critical target for personalized psychiatric medicine. Despite the

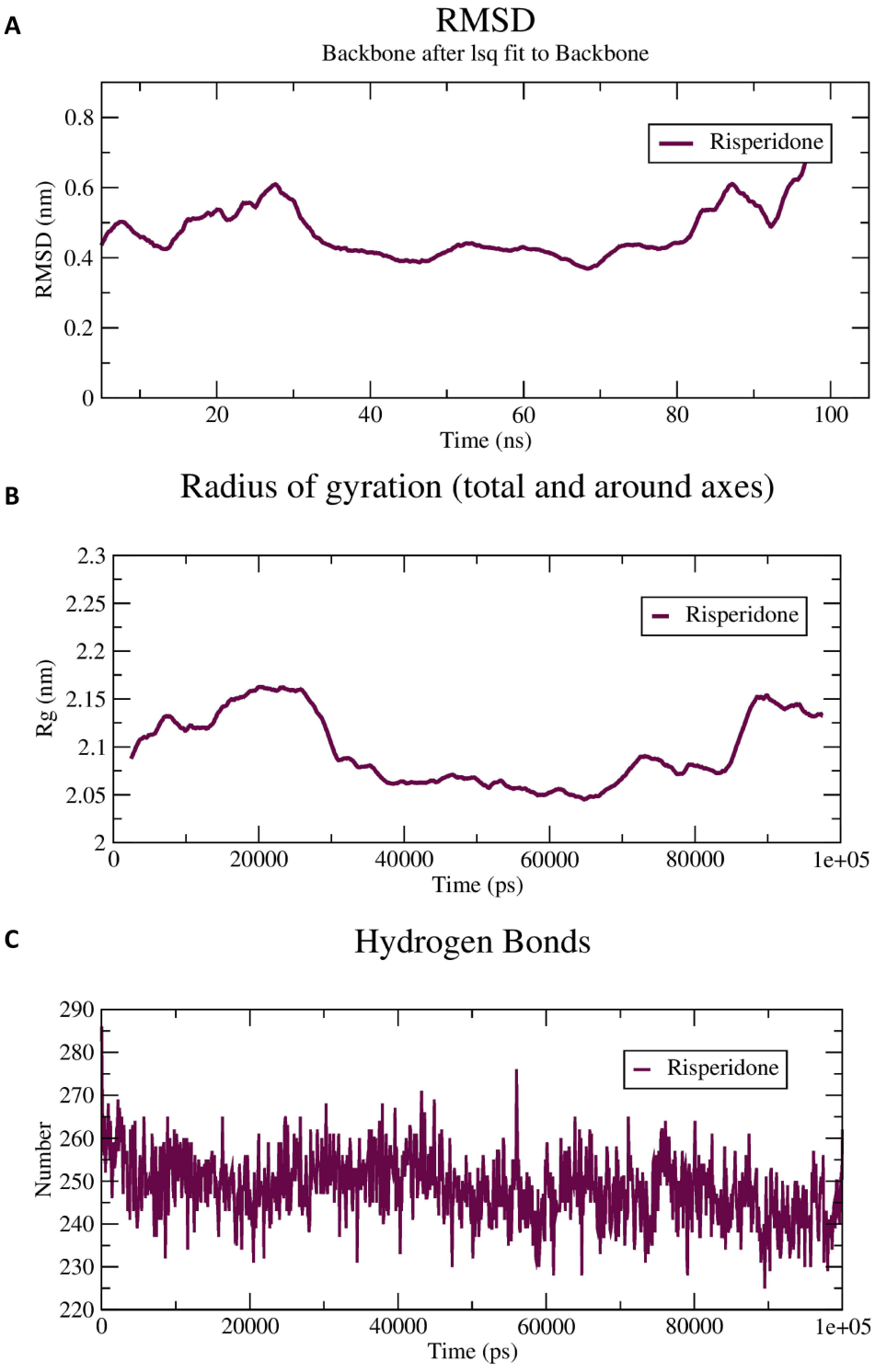

Figure 6 Cross-validation of DRD2-risperidone complex stability using GROMACS (CHARMM36). (**A**) RMSD of protein backbone atoms showing equilibration; (**B**) Radius of Gyration (Rg) maintaining global protein compactness; (**C**) Intermolecular hydrogen bond persistence between DRD2 and risperidone throughout the 100 ns trajectory. These results independently replicate the stability profiles observed in the Desmond simulations.

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robustness of the 10-tool consensus and MD simulation approach, this study has limitations. As a purely computational predictive investigation, the functional impacts described remain theoretical. The lack of in vitro experimental validation and the absence of clinical cohort data are significant constraints. Future research utilizing CRISPR-Cas9 engineered cell lines or retrospective analysis of clinical trial datasets is required to confirm the generalizability of these findings. Detailed clinical trial studies are needed to reveal the pathogenic amino acid substitution, F198C in DRD2 receptor in patients with ASD, schizophrenia and bipolar mania for the management approaches.

While the in silico data strongly suggests a functional impact for the rs866976053 (F198C) variant, several limitations must be considered. Analysis of the dbSNP and Variation Viewer data reveals that rs866976053 is a highly rare variant with no reported frequency data in major global population projects such as 1000 Genomes, ExAC, or gnomAD. The variant was originally submitted to dbSNP (SS1849899874) as part of a whole-exome sequencing study (Batch: Samuels 09 08 2015) with an extremely small ascertainment sample size (n=2). Consequently, its prevalence in different ethnic populations remains entirely unknown. This limits the generalisation of our findings to the broader population of patients experiencing risperidone resistance. This rarity suggests that while the mutation is highly impactful, it does not explain risperidone resistance on a broad population level. Future in vitro functional assays are required to validate these findings.

Conclusion

The present study confirms and supports the influence of genetic variants of DRD2 protein on neuropsychiatric response to risperidone that is explained by various degrees of binding affinity. The nsSNP rs866976053 that corresponds to F198C amino acid change was found to be the most deleterious among 229 nsSNP in the DRD2 receptor, as confirmed by the computational tools used including the MD simulations. The structural stability and binding profiles of the DRD2-risperidone complex were independently cross-validated using both Desmond and GROMACS (CHARMM36) simulation tools, which yielded consistent results regarding the impact of the F198C mutation on protein-ligand dynamics.The most deleterious nsSNP affects the binding between mutated DRD2 with risperidone. Clinical-level in-depth studies can reveal the effects of deleterious amino acid substitution on the treatment with risperidone. This study contributes to the existing literature by identifying the rare rs866976053 (F198C) variant as a high-priority candidate for understanding inter-individual variability in antipsychotic response. By bridging the gap between genomic data and molecular-level protein-ligand dynamics, we provide an initial idea on the structural basis for why certain patients may exhibit poor therapeutic outcomes. Future research should prioritize clinical cohort validation and in vitro functional assays to determine if this variant can serve as a reliable pharmacogenetic biomarker. These findings explored the way for more precise management strategies, potentially allowing clinicians to tailor risperidone dosages or select alternative atypical antipsychotics based on a unique genetic profile of patients.

Institutional Review Board Approval and Informed Consent

The study was approved by the Institutional Review Board of Imam Abdulrahman Bin Faisal University (IRB-2025-13-0353).

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Disclosure

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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