Exploring the Influence of Genetic Variation in the HTR2A Gene on the Pharmacodynamic Response to Antipsychotic Medications

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1. Introduction

The aim of this extended essay is to investigate the effect of variation in the serotonin receptor gene HTR2A in response to antipsychotic drugs.

1.1- G-Protein Coupled Receptors:

G-protein coupled receptors (GPCRs) represent the largest family of transmembrane receptors on cell surfaces and are responsible for cell communication signal transduction. GPCRs are characterized by the presence of seven transmembrane alpha-helices crossing the plasma membrane.[1] G-protein coupled receptors bind to an array of extracellular ligands such as peptides, lipids, and proteins to induce signals across the membrane into the cell.[2] When the extracellular signal binds to and stimulates a GPCR, the associated G-protein heterotrimer will undergo a conformational change that will lead to an exchange of guanosine diphosphate by a guanosine triphosphate on the Gα subunit, such that the Gα subunit dissociates off the Gβγ dimer. Afterward, both the Gα subunit and the Gβγ dimer can bind different effector proteins—such as adenylate cyclase or phospholipase C—to generate second messengers, like cAMP or IP3, spreading the signal inside the cell and giving rise to a physiological response[3]. One such G-protein-coupled receptor is the 5-HT2A serotonin receptor, encoded by the HTR2A gene. This receptor is expressed mainly in the central nervous system. The 5-HT2A receptor is one of many GPCRs that signal in response to the extracellular neurotransmitter serotonin (5-hydroxytryptamine) and is implicated in regulating a wide array of physiological processes and behaviors. Upon the binding of serotonin to the 5-HT2A receptor, a conformational change on the receptor will proceed to activate the associated G-protein, typically the Gαq/11 subunit. This leads to the activation of phospholipase C (PLC), which converts membrane-bound phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) into the second messenger's diacylglycerol and inositol-1,4,5-triphosphate.[4]

1.2 - Serotonin receptors and their function:

The serotonin receptors are a large family of receptors that mediate the physiological effects of serotonin, also known as 5-hydroxytryptamine (5-HT), a monoamine neurotransmitter that is involved in the regulation within the central, as well as the peripheral nervous system. The serotonin receptors can be divided into seven major families, 5-HT1 to 5-HT7, each containing multiple subtypes[5]. Serotonin receptors are widely distributed throughout the brain and body. All the serotonin receptors, except the 5-HT3 receptor, belong to the G-protein-coupled receptor family of receptors. The 5-HT3 forms a ligand-gated ion channel. 5-HT1 Receptors are generally inhibitory receptors that couple to Gαi/o proteins, thus inhibiting the production of cyclic adenosine monophosphate (cAMP). Receptors of this type are found to regulate mood, anxiety,

[1] Naz, Rubeena, and Javed Iqbal. "An Overview of Pharmacogenetics of Drug Transporters." **Current Drug Metabolism**, vol. 15, no. 7, 2014, pp. 713-724, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967846/. Accessed 21 Mar. 2024.
[2] "Physiology, Cellular Messengers - StatPearls - NCBI Bookshelf." National Center for Biotechnology Information, 1 May 2020, www.ncbi.nlm.nih.gov/books/NBK538154/ Accessed 21 Mar. 2024.
[3] "The Structure and Function of G-protein-coupled Receptors." PubMed Central (PMC), May 21, www.ncbi.nlm.nih.gov/pmc/articles/PMC3967846/ Accessed 21 Mar. 2024.

[4] "GPCR Signaling Regulation: The Role of GRKs and Arrestins." Frontiers, www.frontiersin.org/articles/10.3389/fphar.2019.00125/full Accessed 12 Apr. 2024.
[5] "Serotonergic System." **ScienceDirect Topics**, Elsevier, https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/serotonergic. Accessed 12 Apr. 2024.

and aggression, and are dysregulated in depression and anxiety disorders.[6] Important treatments for disorders like depression use 5-HT1A receptor agonists as anxiolytics and antidepressants. The 5-HT2 Receptors, 5-HT2A, 5-HT2B, 5-HT2C, generally couple to Gαq proteins and thus lead to the consequent activation of phospholipase C (PLC) and the production of inositol triphosphate (IP3) and diacylglycerol (DAG).[7] Amongst the serotonin receptors, the 5-HT2A is an important target in the treatment of schizophrenia and depression.[8] Hallucinogenic drugs such as Lysergic acid diethylamide act as agonists at the 5-HT2A receptors. A number of atypical antipsychotics act as 5-HT2A antagonists. 5-HT3 Receptors are unique amongst the serotonin receptors in having 5-HT3 receptors as ion channels mediating fast excitatory neurotransmission.[9] 5-HT3 receptors are distributed primarily in the central nervous system and are also found within the gastrointestinal tract. These receptors are targeted by antiemetic drugs used in the treatment of nausea and vomiting, particularly those produced by chemotherapy. 5-HT4 Receptors couple to Gαs proteins. 5-HT4 receptors stimulate adenylate cyclase, which increases cAMP levels. They are related to gastrointestinal motility and cognitive functions. Failure in the regulation of 5-HT4 receptors might account for conditions such as irritable bowel syndrome and cognitive dysfunctions. 5-HT5, 5-HT6, and 5-HT7 Three other receptor classes appear to have less well-defined functions but are involved in several functions of the brain.[10] For example, 5-HT7 plays a role in the regulation of circadian rhythms and thermoregulation and has a putative role in mood disorders.[11] [12]

1.3 - Ligands and Ligand Binding

The term ligand refer to molecules that bind to a receptor and produce an effect, hence providing a vital aspect of intercellular communication and regulation.[13] Such interactions play important roles in most physiological activities, within which hormone signaling, neurotransmission, immune responses, and cell growth occur. The affinity of receptor-ligand interaction, specificity, reversibility, and kinetics, define strength and duration of binding and, hence, physiological regulation.[14] Some of the common conformational changes induced by ligand binding to the receptor include ion channel modulation, alteration in enzymatic activity, and sometimes induction of intracellular signaling pathways that amplify the initial signal and provide varied and diverse cellular responses.[15] In psychological dysfunction, the role of ligand-receptor interactions is very pronounced.[16] An example is the binding of the ligand to the serotonin receptor and its effects on mood

[6] McCorvy, John D., and Bryan L. Roth. "Structure and Function of Serotonin G Protein-Coupled Receptors." **Neuroscience of Psychoactive Substance Use and Dependence**, U.S. National Library of Medicine, 2020, https://www.ncbi.nlm.nih.gov/books/NBK560856/. Accessed 12 Apr. 2024.
[7] National Center for Biotechnology Information. "HTR2A 5-Hydroxytryptamine Receptor 2A [Homo Sapiens (Human)]." **Gene**, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene/3356#:~:text=The%20HTR2A%20gene%20is%20associated,ideation%20in%20breast%20cancer%20patients. Accessed 14 Apr. 2024.
[8] Carhart-Harris, Robin L., and Guy M. Goodwin. "The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future." **Neuropsychopharmacology**, vol. 42, no. 11, 2017, pp. 2105-2113, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5864293/. Accessed 14 Apr. 2024.
[9] Pytliak, M., et al. "Serotonin Receptors - From Molecular Biology to Clinical Applications." **Physiological Research**, vol. 60, no. 1, 2011, pp. 15-25, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4055881/. Accessed 14 Apr. 2024.
[10] de Sá Moreira, Edna, et al. "A Preliminary Investigation of the Biochemical and Genetic Basis of Aggression in Mice." **Brazilian Journal of Medical and Biological Research**, vol. 40, no. 6, 2007, pp. 711-715, https://www.scielo.br/j/bjmbr/a/s5wdKBV3ZpVPKwXGxcB5ggK/?lang=en. Accessed 14 Apr. 2024.
[11] Shen, Weidong, et al. "HTR2A Gene Polymorphisms in Major Depressive Disorder and Breast Cancer Patients." **Molecules**, vol. 27, no. 5, 2022, article 1680, https://www.mdpi.com/1420-3049/27/5/1680. Accessed 14 Apr. 2024.
[12] Fox, Colleen A., et al. "Cytosolic Phospholipase A2 Plays a Key Role in the 5-HT2A Receptor Signaling in Aortic Smooth Muscle Cells." **Journal of Biological Chemistry**, vol. 284, no. 8, 2009, pp. 4713-4721, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2644495/. Accessed 15 Apr. 2024.
[13] Khan Academy. "Signal Perception." **Khan Academy**, https://www.khanacademy.org/science/ap-biology/cell-communication-and-cell-cycle/signal-transduction/a/signal-perception. Accessed 15 Apr. 2024.
[14] Alberts, Bruce, et al. "G-Protein-Coupled Receptors." **Molecular Biology of the Cell**, 4th ed., Garland Science, 2002, https://www.ncbi.nlm.nih.gov/books/NBK9924/. Accessed 15 Apr. 2024.
[15] Marin, I. "Ancient Origin of G Protein-Coupled Receptors: Implications for the Evolution of Eukaryotic Signal Transduction." **BMC Evolutionary Biology**, vol. 19, 2019, article 109, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6651758/. Accessed 15 Apr. 2024.
[16] Jacob, J., and M. J. Millan. "Serotonin Receptors and Their Ligands." Encyclopedia of Molecular Mechanisms of Disease, edited by Florian Lang, Springer, 2009, https://link.springer.com/referenceworkentry/10.1007/978-0-387-30382-6_8. Accessed 15 April. 2024.

regulation mediated via serotonin and selective serotonin reuptake inhibitors in depression.[17] Likewise, the role of enhancing inhibitory neurotransmission, as shown by anxiety treatments like benzodiazepines, exhibits its role. And in the case of schizophrenia, such as the blocking of psychotic symptoms by 5-HT2A receptor antagonists, indicates that blocking specific interactions can be helpful. Knowledge of the principles of ligand binding and receptor interactions is imperative for the development of therapies targeting these interactions for the alleviation of a variety of psychological and physiological disorders.[18]

1.4 - Significance of Antipsychotic Drugs:

The availability of antipsychotic drugs has formed the backbone of psychiatric treatment options for managing diseases ranging from schizophrenia to bipolar disorder.[19] Such drugs act primarily on neurotransmitter systems in the brain, with a particular effect on the dopaminergic and serotonergic systems, to reduce the symptoms that include delusions, hallucinations, and thought disorder.[20] An understanding of the conceptual significance, thus, involves not only an in-detail discussion of their biological mechanisms but also that of their association with the receptors. Antipsychotic medications have become an important part of the treatment modality for patients with schizophrenia and bipolar disorder and, in some settings, depression.[21] A good part of the efficacy of these medications and the side-effect profile is produced based on the interaction with serotonin receptors, particularly 5-HT2A receptors. A substantial amount of data about the biological implication of such interaction, refers to the understanding of their therapeutic mechanism and, thus, to designing of new antipsychotic drugs. Serotonin receptors, particularly 5-HT2A receptors, play a crucial role in the mechanism of action of atypical antipsychotic drugs.[22] The significance of serotonin in the modulation of dopamine pathways adds another level of complexity in the action of antipsychotic drugs.

Through the blockade of 5-HT2A receptors, atypical antipsychotic drugs decrease serotonin-mediated excitation of dopaminergic neurons in the mesolimbic pathway. These will work in synergy with D2 blockade, creating a deeper reduction in positive symptoms. Serotonin blockade can also be related to the effects of glutamate and Gamma-aminobutyric acid transmission, which will also contribute to a positive mood and better cognitive functions.[23] This broader action on neurotransmitter systems can account for the greater effectiveness of atypical antipsychotic drugs for the majority of negative and cognitive symptoms of schizophrenia.[24] A number of antipsychotic medications continue to

[17] Pavlov, Dmitry, et al. "5-HT2A Receptor as a Target for Treating Depression and Psychosis: Recent Developments and New Therapeutic Strategies." **Pharmaceuticals**, vol. 14, no. 2, 2021, article 148, https://www.mdpi.com/1424-8247/14/2/148. Accessed 16 Apr. 2024.
[18] Hall, Jason E., and Madhu Nair. "Neurotransmitter." **StatPearls**, StatPearls Publishing, 2024, https://www.ncbi.nlm.nih.gov/books/NBK554406/. Accessed 16 Apr. 2024.
[19] Massad, Monique G., and Elie N. Bahouth. "Recent Advances in Pharmacogenomics of the Serotonin Receptors: Pharmacogenetics of the 5-HT2A Receptor and Its Role in Mental Disorders." **Pharmacogenomics Journal**, vol. 11, no. 4, 2011, pp. 285-298, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958217/. Accessed 16 Apr. 2024.
[20] Babaei, Parham, and Shiva R. Khosravi. "Phospholipase C." **StatPearls**, StatPearls Publishing, 2024, https://www.ncbi.nlm.nih.gov/books/NBK519503/. Accessed 16 Apr. 2024.
[21] Mierzejewski, Pawel, et al. "The Role of 5-HT2A Receptor in the Pathophysiology and Treatment of Schizophrenia and Depression." **Brain Sciences**, vol. 13, no. 3, 2023, article 414, https://www.mdpi.com/2076-3425/13/3/414. Accessed 17 Apr. 2024.
[22] Thakare, Vishal N., and Kalpana A. Dhakane. "Neurochemicals, Behaviours, and Psychiatric Perspectives of Neurological Diseases." **Neuropsychiatry (London)**, vol. 8, no. 1, 2018, https://www.jneuropsychiatry.org/peer-review/neurochemicals-behaviours-and-psychiatric-perspectives-of-neurological-diseases-12443.html. Accessed 17 Apr. 2024.
[23] Qu, Liang, et al. "Chapter 48 - Serotonin Receptors as Therapeutic Targets." **Handbook of Clinical Neurology**, vol. 180, 2021, pp. 1131-1156, https://www.sciencedirect.com/science/article/abs/pii/B9780444641250000487. Accessed 17 April. 2024.
[24] Murnane, Kevin S., et al. "Effects of Chronic Methylphenidate Treatment on the Dopaminergic System in Healthy Adult Nonhuman Primates." **Biological Psychiatry**, vol. 70, no. 3, 2011, pp. 255-262, https://pubmed.ncbi.nlm.nih.gov/21420906/. Accessed 17 Apr. 2024.

be developed, mainly with the goal of increasing efficacy and safety characteristics to further enhance the treatment for these complex disorders.[25]

1.5 - Genetic Variation and impact in pharmacodynamic response:

Pharmacodynamics is the part of pharmacology that deals with the effect of drugs in the body and the response at the level of receptors, signaling pathways, and physiological responses.[26] Genetic variations can markedly affect the pharmacodynamic response on drug targets and their signal transduction mechanisms and, subsequently, physiological outcomes. It may lead to differences between individuals in drug efficacy and safety, and their respective side effect profile.[27] The gene HTR2A encodes the 5-HT2A receptor, which is a major target for many antipsychotic drugs. [28]

Polymorphisms, such as T102C (rs6313) and A-1438G (rs6311), can exert effects on the expression and function of the receptor. Such genetic differences are likely to modify the binding of antipsychotics with the 5-HT2A receptor, which is a key factor in therapeutic efficacy and side effects.[29] For example, variants resulting in the overexpression of 5-HT2A receptor can augment the action of antagonistic antipsychotic drugs but could also increase the susceptibility to metabolic syndrome.[30]

The gene SCN1A encodes one of the subunits of the voltage-gated sodium channel and is of particular importance for the excitability of neurons. Variation in the gene SCN1A affects the pharmacodynamics of drugs targeting the channels, such as antiepileptics. Change in channel kinetics has been related to a change in the therapeutic window and to the risk of side effects.[31] Many genetic variations in drug-metabolizing enzymes affect primarily pharmacokinetics but some have also been related to changes in pharmacodynamics through variations in drug concentrations at the target site.

There are several polymorphisms identified in the CYP2D6 gene that are responsible for different metabolizer phenotypes, including poor and ultra-rapid metabolizers. These variations affect the plasma levels of drugs metabolized by CYP2D6, such as many antipsychotics and antidepressants.[32] The resulting changed drug levels can modify the pharmacodynamic response, which is further related to efficacy and the risk of adverse effects. For example, poor metabolizers will have higher concentrations of the drug and a direct association with increased efficacy or toxicity; ultra-rapid metabolizers will need higher doses for therapeutic effects. Variations like T102C and A-1438G alter the expression and function of 5-HT2A receptors and can alter the response to antipsychotic drugs.[33] Polymorphisms in specific patients will lead to

[25] Ascierto, Paolo A., et al. "Advances in Cancer Immunotherapy: Immune Checkpoint Inhibitors and Beyond." **Biomedicines**, vol. 11, no. 3, 2023, article 921, https://www.mdpi.com/2227-9059/11/3/921. Accessed 17 Apr. 2024.
[26] "NIMH » Mental Health Medications." NIMH » Home, www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml . Accessed 5 May 2024.
[27] Varghese, Sapna, and David B. Thomas. "Fibrinogen." **StatPearls**, StatPearls Publishing, 2024, https://www.ncbi.nlm.nih.gov/books/NBK507791/. Accessed 5 May. 2024.
[28] MSD Manual. "Overview of Pharmacodynamics." **MSD Manual Professional Edition**, https://www.msdmanuals.com/en-in/professional/clinical-pharmacology/pharmacodynamics/overview-of-pharmacodynamics. Accessed 5 May. 2024.
[29] Yamamoto, Kazutaka, et al. "Association of Schizophrenia with T102C (rs6313) and −1438 A/G (rs6311) Polymorphisms of HTR2A Gene." **Acta Neuropsychiatrica**, vol. 22, no. 1, 2010, pp. 23-27, https://www.cambridge.org/core/journals/acta-neuropsychiatrica/article/abs/association-of-schizophrenia-with-t102c-rs6313-and-1438-ag-rs6311-polymorphisms-of-htr2a-gene/D8491E0FFBE986A76802DE2B0D620370. Accessed 5 May. 2024.
[30] Gómez, Isabel, et al. "Association of the HTR2A Gene with Schizophrenia and Influence of Family History on Symptomatology." **Psychiatric Genetics**, vol. 17, no. 2, 2007, pp. 79-84, https://pubmed.ncbi.nlm.nih.gov/17617023/. Accessed 5 May. 2024.
[31] National Center for Biotechnology Information. "Dopamine Receptor D2 (DRD2)." **Gene**, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene/6323. Accessed 5 May. 2024.
[32] Keshavan, Sonal, and Minako Watabe. "Serotonin Syndrome." **StatPearls**, StatPearls Publishing, 2024, https://www.ncbi.nlm.nih.gov/books/NBK574601/. Accessed 5 May. 2024.
[33] Kranz, Gregory S., et al. "Serotonin and the Brain—A Story of Multiple Receptors." **Frontiers in Psychology**, vol. 1, 2010, article 140, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2853349/#:~:text=Genetic%20variability%20affecting%20serotonin%20levels&text=Both%20genes%20encoding%20these%20proteins,activity%20(1%E2%80%938). Accessed 5 May. 2024.

differences in the control of symptoms and a side-effect profile with individualized treatment strategies. This genetic theory difference of these receptors will then alter the efficacy of mood stabilizers and antipsychotics. Knowledge of such variations will help modify treatment, thereby achieving mood stabilization with a reduced side effect burden. [34]

Genetic polymorphisms account for the cause of the majority of pharmacodynamic variations, mediated through changes in the interaction of the drug with the receptor substance, signaling pathways, and enzyme activity. Genetic differences contribute to variability in drug efficacy, safety, and side effect profiles between individuals. Genetic knowledge of these factors allows a personalized medicine approach, helping to optimize drug treatment with an increased therapeutic outcome and optimal adverse effect profiles. [35]

2. Methodology and Result Analysis

2.1- Variant Classification using gnomAD:

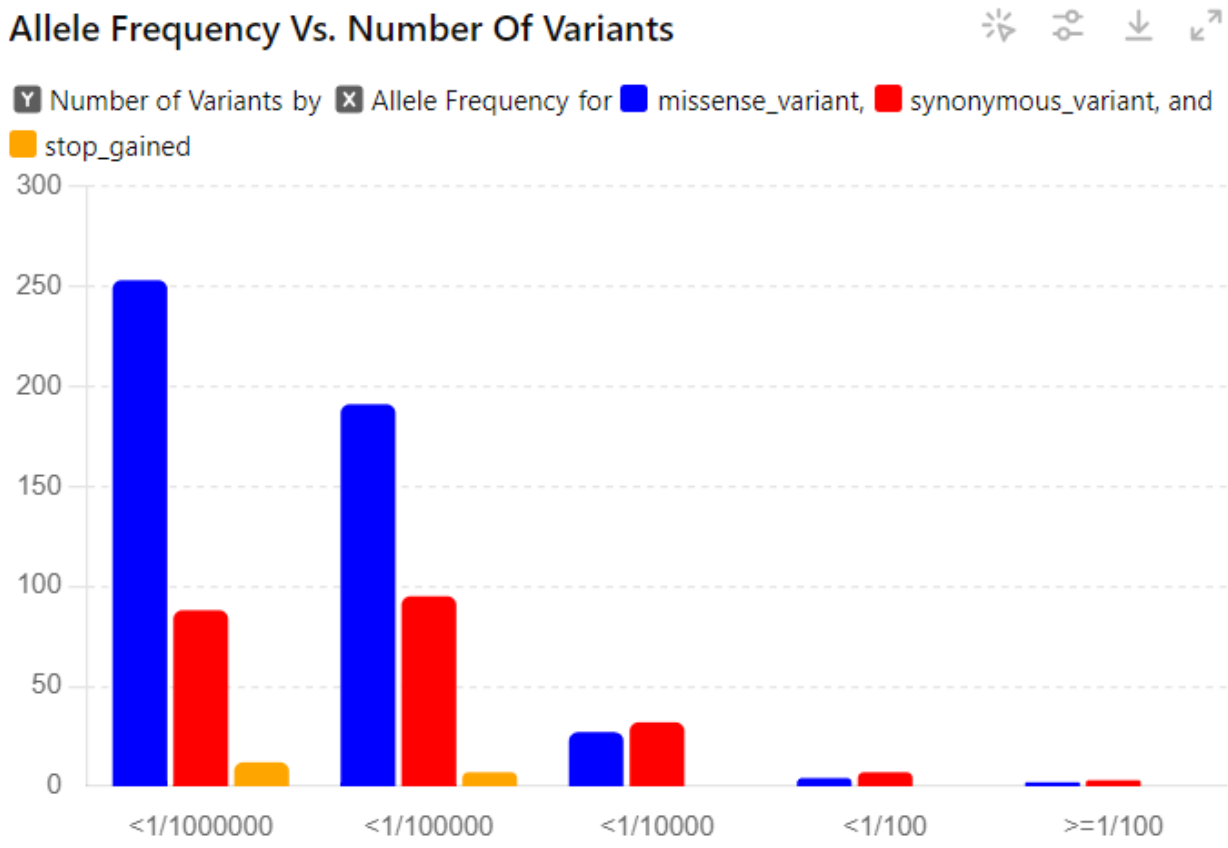
The gnomAD (Genome Aggregation Database) is a freely available database that aggregates and harmonizes exome and genome sequencing data from donated exome and genome sequences obtained from a diverse human population, through the efforts of several large-scale sequencing projects. It is designed to give a more accurate of genetic variation within diverse human populations. The described variant presentation, with detailed description of genetic variation, including data on allele frequency, enables the identification of clinically relevant variants in the genome and hence plays a role in the research of approaches to personalized medicine. This, in turn, allows clinicians to understand the response of a patient to antipsychotic treatment based on specific genetic variations within HTR2A and, therefore, better optimize therapeutic strategies for psychiatric disorders.

In order to investigate this research question, data was downloaded from the gnomAD browser. This database contains data from 76,156 samples collected from various databases, including the PAGE Consortium and the TCGA,[36] and is therefore a good and reliable pool. The variants in the gnomAD browser can be classified into three categories: synonymous mutations, loss-of-function mutations, and missense mutations.

Data from the database showed 665 variants and classified them under the three categories mentioned above. The allele frequency of each of these variants, which quantifies the prevalence of the variant within the population, was calculated by dividing the allele count by the total number of alleles. This frequency data was then plotted to indicate the distribution of each kind of mutation within the population.[37]

[34] Patel, Milap, et al. "Role of Serotonin in Memory Impairment." **European Journal of Pharmacology**, vol. 836, 2018, pp. 118-131, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6127750/. Accessed 5 May. 2024.
[35] López-Muñoz, Francisco, et al. "Historical Approach to Re-Serotonin (5-HT) and Its Antidepressant Activity: A Centennial Perspective." **Clinical Medicine Insights: Therapeutics**, vol. 2, 2010, pp. 517-529, https://journals.sagepub.com/doi/10.4137/CMT.S2175?icid=int.sj-abstract.citing-articles.448. Accessed 5 May 2024.
[36] GnomAD, gnomad.broadinstitute.org/. Accessed 9 May 2024.
[37] "Allele Frequency & the Gene Pool (article)." Khan Academy, www.khanacademy.org/science/ap-biology/natural-selection/hardy-weinberg-equilibrium/a/allele-frequency-the-gene-pool . Accessed 12 May 2024.

Figure 1: Allele Frequency plotted against Number of Variants



This distribution can best be explained by the analysis of variation with the HTR2A gene. This type of data provides incredible insights into the distribution and potential impacts of the different types of genetic variants.

Missense variants are found in abundance in the lowest allele frequency bin (<1/1000000).[38] The number of missense variants decreases quickly, as the allele frequency rises suggesting that while the variant are prevalent, they are generally scarce in the population. Most of the missense variations are high in number but they are predominantly of low frequency and therefore, relatively benign. The number of missense variations rapidly decreases as the allele frequency increases, indicating that although these variants are prevalent, they are generally scarce in the population. Although the majority of missense mutations are large in number, they are predominantly of low frequency, making them relatively benign.

Most of the synonymous variations are located in <1/1000000 and <1/100000 bins.[39] Synonymous variations in the HTR2A gene do not affect the polypeptide sequence or protein function and thus typically do not influence drug response. These variations are common but found at low frequencies, indicating they are benign and not widely distributed. In contrast, loss-of-function variants, which can significantly disrupt protein function, are extremely rare and mostly found at very low frequencies. This rarity suggests that essential protein functions remain stable across populations. Overall, the low-frequency presence of both synonymous and loss-of-function variants indicates minimal impact on population-wide drug response.

An approach to filtering the data was used to further analyze. Synonymous mutations were eliminated from the population of variants used for further analysis since they result in degenerate codons and have no effect on the polypeptide sequence.

[38] "Allele Frequency." ScienceDaily, 22 2020, www.sciencedaily.com/terms/allele_frequency.htm . Accessed 12 May 2024.
[39] "Nonsynonymous, Synonymous and Nonsense Mutations in Human Cancer-related Genes Undergo Stronger Purifying Selections Than Expectation." BMC Cancer, bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5572-x. Accessed 12 May 2024.

Additionally, for genetic variation to have a significant impact on drug response, it needs to be prevalent within the population, which requires a high allele frequency. Therefore, variants with an allele frequency less than 1/10000 were excluded from the investigation. This filtration resulted in a specific set of variants that are more likely to have a significant impact on protein function and drug response.

Such an analysis is quite relevant in the effort to identify distribution patterns of genetic variants and their impact on health, diseases, and drug response unfoldment in a population.

Table 1: Variants with allele frequencies over 1/100000 :

Variant ID	Consequence	Allele Frequency	Number of Homozygotes
13-46835076-G-A	p.Arg393Trp	1.05333075577e-05	0
13-46835214-C-T	p.Val347Ile	1.11529277054e-05	0
13-46835271-C-T	p.Val328Ile	1.23918654838e-05	0
13-46895601-C-G	p.Glu102Asp	1.67279197654e-05	0
13-46835430-G-A	p.Arg275Trp	2.72631851579e-05	0
13-46895545-A-G	p.Met121Thr	1.30094113798e-05	0
13-46835364-G-A	p.Arg297Trp	1.42511927628e-05	0
13-46835432-G-A	p.Thr274Ile	1.61092055435e-05	0
13-46835319-T-C	p.Met312Val	1.23912666352e-05	1
13-46895833-G-C	p.Thr25Ser	1.42504863752e-05	0

2.2- Analyzing the impact of mutations on 5-Hydroxytryptamine Receptor 2A

2.2.1- Amino Acid substitutions

An amino acid substitution refers to a genetic mutation whereby one amino acid in the protein sequence gets swapped with another.[40] Such amino acid substitutions usually have a central effect on protein structure and function, activity, life, and so forth, depending on the properties of the amino acids involved in most cases.

The type of amino acid exchange is mostly dependent upon the chemical nature of the substituted amino acids. With respect to radical substitutions, conservative amino acid substitutions are less likely to alter protein function. Very important in predicting such possible changes in the function of proteins is the understanding of amino acid classification.[41]

Table 2: Classification of amino acids

[40] "Protein Structure: Primary, Secondary, Tertiary & Quaternary (article)." Khan Academy, www.khanacademy.org/science/biology/macromolecules/proteins-and-amino-acids/a/orders-of-protein-structure . Accessed 3 June 2024.
[41] "Medical Physiology/Basic Biochemistry/Amino Acids and Proteins." Wikibooks, en.wikibooks.org/wiki/Medical_Physiology/Basic_Biochemistry/Amino_Acids_and_Proteins . Accessed 14 June 2024 .

Class	Amino Acids
Aliphatic	Val, Ala, Leu, Gly, Ile
Acidic	Gln, Asp, Glu, Asx, Glx
Basic	Lys, Arg, His
Aromatic	Phe, Trp, Tyr
Hydroxyl/Sulfur containing	Ser, Cys, Sel, Thr, Met
Cyclic	Pro

This classification helps in understanding the possible impact of such amino acid substitutions on protein structure and function. This is called conservative substitution, where the substituted amino acid has similar chemical properties to the amino acid it replaces, which provides a least possible change in the interactions of the R-groups and maintains the conformation of the protein stable. In contrast, a radical substitution happens when the amino acid is replaced with one of very different properties, potentially leading to a change in the phenotype.[42]

A method of distinction is Grantham's distance. Grantham's distance is calculated using composition, polarity, and molecular volume of the amino acids. The scores are interpreted as conservative (0-50), moderately conservative (51-100), moderately radical (101-150), and radical (>150).[43] Table 3 is a compilation of the Grantham scores of all missense substitutions with an allele frequency greater than 1/100000.

Table 3: Grantham scores of amino acid substitutions of HTR2A variants

Variant ID	Consequence	Grantham Score	Substitution Classification
13-46835076-G-A	p.Arg393Trp	101	Radical
13-46835214-C-T	p.Val347Ile	29	Conservative
13-46835271-C-T	p.Val328Ile	29	Conservative
13-46895601-C-G	p.Glu102Asp	45	Conservative
13-46835430-G-A	p.Arg275Trp	101	Radical
13-46895545-A-G	p.Met121Thr	81	Moderately Conservative
13-46835364-G-A	p.Arg297Trp	101	Radical
13-46835432-G-A	p.Thr274Ile	89	Moderately Conservative
13-46835319-T-C	p.Met312Val	21	Conservative
13-46895833-G-C	p.Thr25Ser	58	Moderately Conservative

[42] "Conservative and Nonconservative Mutations in Proteins: Anomalous Mutations in a Transport Receptor Analyzed by Free Energy and Quantum Chemical Calculations." Wiley Online Library, onlinelibrary.wiley.com/doi/pdf/10.1002/pro.5560040305 . Accessed 17 June 2024.
[43] "Grantham Matrix." Gist, gist.github.com/danielecook/501f03650bca6a3db31ff3af2d413d2a. Accessed 19 June 2024.

This table provides insight into the potential impact of specific amino acid substitutions on the HTR2A gene's protein structure and function. The majority of the observed substitutions are conservative, indicating that the physicochemical distances between the wild type and substituted amino acids are not large enough to destabilize R-group interactions. However, these substitutions can still influence the stability of protein interactions and functions. Radical substitutions such as p.Arg393Trp, p.Arg275Trp, and p.Arg297Trp are likely to significantly impact the protein's structure and function due to the substantial changes in amino acid properties. These substitutions suggest a moderate impact on the protein's function, potentially affecting local interactions within the protein structure. While the conservative nature of most observed substitutions suggests a lower risk of functional disruption, detailed functional studies and further structural analyses are necessary to fully understand the implications of these variants on HTR2A receptor function and related physiological processes. Substitutions occurring near-critical regions, such as ligand-binding domains, might alter binding affinity or specificity, affecting signal transduction pathways in which the HTR2A receptor is involved.

2.2.2- SIFT score

The following table provides the SIFT classification of missense variants with high allele frequencies in the HTR2A gene. SIFT (Sorting Intolerant From Tolerant) is a tool used to predict whether an amino acid substitution will affect protein function, on the basis of homology, predicts whether a substitution will have an impact on the phenotype. Variants are classified as "Deleterious" if they are likely to impact protein function and have scores ranging between 0 and 0.1 and "Tolerated" if they are likely to be benign and have scores greater than 0.1.[44]

Table 4: SIFT Classification of missense variants with high allele frequencies

Wild Type	Substituted	SIFT Score	SIFT Classification
Arg	Trp	0.0	Deleterious
Val	Ile	0.0	Deleterious
Val	Ile	0.0	Deleterious
Glu	Asp	0.0	Deleterious
Arg	Trp	0.0	Deleterious
Met	Thr	0.0	Deleterious
Arg	Trp	0.03	Deleterious
Thr	Ile	0.1	Tolerated
Met	Val	0.15	Tolerated
Thr	Ser	0.19	Tolerated

This table provides insight into the potential impact of specific amino acid substitutions on the HTR2A gene's protein function based on SIFT scores and classifications. The SIFT (Sorting Intolerant From Tolerant) score predicts the effect

[44] SIFT - Predict Effects of Nonsynonymous / Missense Variants, sift.bii.a-star.edu.sg/ . Accessed 3 July 2024.

of an amino acid substitution on protein function.[45] These substitutions of Arginine (Arg) to Tryptophan (Trp) are consistently predicted to be deleterious. The significant change from a positively charged to a nonpolar amino acid can disrupt ionic bonds and protein interactions, likely affecting protein function. Despite both Valine (Val) and Isoleucine (Ile) being nonpolar and similar in size, these substitutions are predicted to be deleterious. This indicates potential local structural constraints that make these changes impactful. The substitution of Glutamic acid (Glu) to Aspartic acid (Asp), both negatively charged, is predicted to be deleterious, possibly due to specific local structural or functional constraints.[46] The substitution of Methionine (Met) to Threonine (Thr) is predicted to be deleterious, indicating that the change from a nonpolar to a polar amino acid might significantly affect protein function.

The substitution of Threonine (Thr) to Isoleucine (Ile) is predicted to be tolerated. Despite the change from a polar to a nonpolar amino acid, it is less likely to impact protein function significantly. The substitution of Methionine (Met) to Valine (Val) is predicted to be tolerated. Both are nonpolar, suggesting this change is unlikely to significantly impact protein function. The substitution of Threonine (Thr) to Serine (Ser) is predicted to be tolerated. Both amino acids are polar, indicating minimal impact on protein function.

The repeated prediction of deleterious impact for Arg to Trp substitutions highlights the significant structural and functional changes such substitutions can cause. Substitutions maintaining similar properties (e.g., Glu to Asp, Val to Ile) can still be deleterious due to local structural constraints, indicating the importance of specific residue positions. Even conservative changes can be impactful if they occur in regions critical to protein structure or function.

The SIFT scores suggest that many of the observed substitutions are likely to affect protein function, highlighting the need for detailed functional studies to fully understand the implications on HTR2A receptor function. Substitutions occurring near critical regions may alter binding affinity or specificity, impacting signal transduction pathways. The cumulative effect of multiple substitutions might also lead to subtle conformational changes impacting protein-protein interactions or the overall stability of the receptor.

2.2.3- Polyphen score

The conclusions made by SIFT score analysis can be supported using the Polyphen score of an amino acid substitution. A polyphen score ranging from 0-1, with values above 0.85 strongly indicating that the substitution is damaging to the structure and function of a protein; values close to 0 indicate that the substitution is benign, having no discernable negative impact on the protein.[47]

Table 5: Polyphen scores of missense variants with high allele frequencies

[45] "NCI Dictionary of Genetics Terms." National Cancer Institute, www.cancer.gov/publications/dictionaries/genetics-dictionary/def/deleterious-mutation . Accessed 12 July 2020.
[46] Matsumura, Minoru, et al. “Substitution of Aspartic Acid with Glutamic Acid Increases the Unfolding Transition Temperature of a Protein.” *FEBS Letters*, vol. 557, no. 1-3, 2004, pp. 26–32. *ResearchGate*, https://www.researchgate.net/publication/8469281_Substitution_of_aspartic_acid_with_glutamic_acid_increases_the_unfolding_transition_temperature_of_a_protein. Accessed 12 July. 2024.
[47] "PolyPhen-2 Score." Ion Reporter | Thermo Fisher Scientific, www.ionreporter.thermofisher.com/ionreporter/help/GUID-57A60D00-0654-4F80-A8F9-F6B6A48D0278.html . Accessed 25 July 2024.

Wild Type	Substituted	PolyPhen Score	PolyPhen Classification
Arg	Trp	0.996	probably damaging
Val	Ile	0.988	probably damaging
Val	Ile	0.981	probably damaging
Glu	Asp	0.967	probably damaging
Arg	Trp	0.952	probably damaging
Met	Thr	0.686	possibly damaging
Arg	Trp	0.983	probably damaging
Thr	Ile	0.044	benign
Met	Val	0.348	possibly damaging
Thr	Ser	0.0	benign

2.2.4- CADD score

The CADD, or the Combined Annotation Dependent Depletion, score is a measure of how deleterious a mutation is. Scores of twenty and above signify extremely deleterious mutations, i.e those that can significantly impact the structure of the protein.[48]

Table 6: CADD scores of protein substitutions

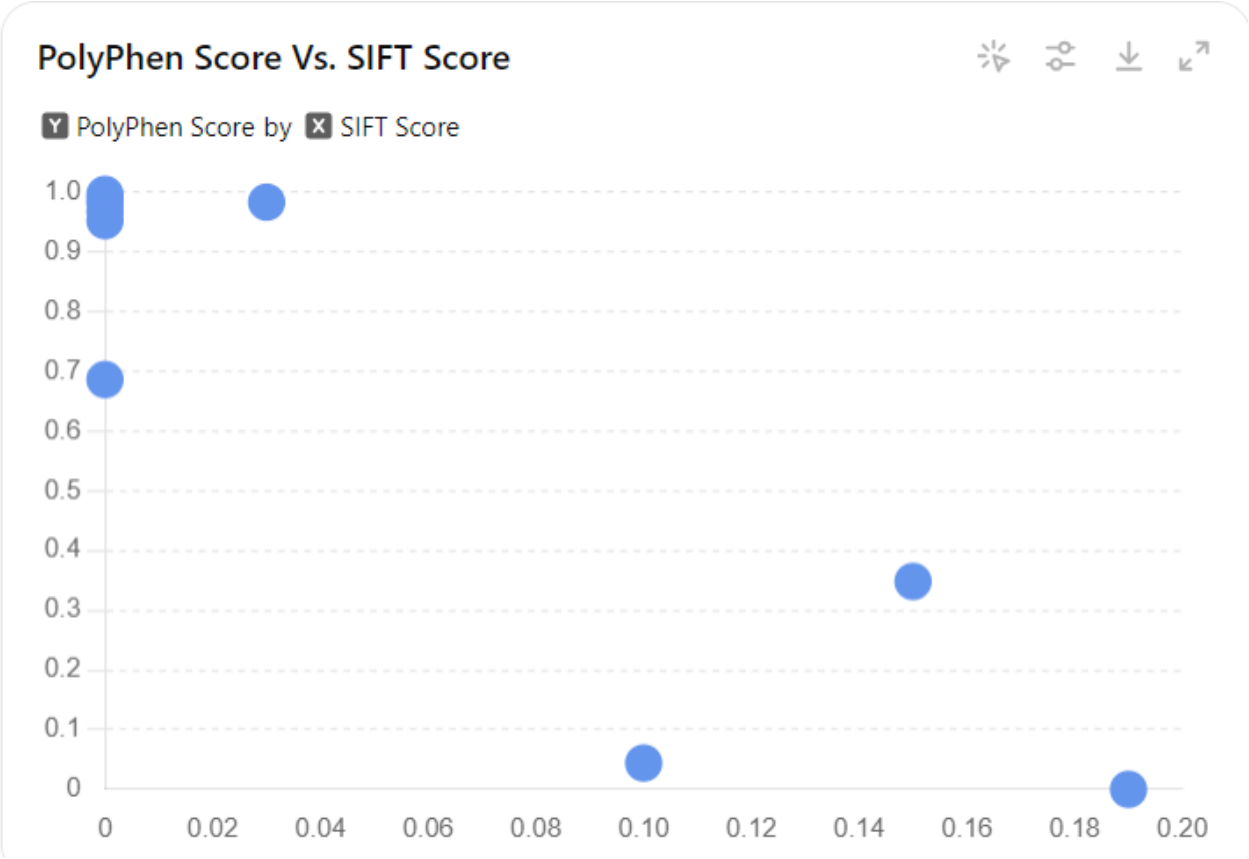
HGVSp	CADD Score
p.Arg393Trp	24.7
p.Val347Ile	25
p.Val328Ile	25
p.Glu102Asp	25.1
p.Arg275Trp	23.1
p.Met121Thr	25.3
p.Arg297Trp	23.2

[48] "CADD." CADD - Combined Annotation Dependent Depletion, www.cadd.gs.washington.edu/info . Accessed 1 Aug. 2024

p.Thr274Ile	19.8
p.Met312Val	20.3
p.Thr25Ser	17.2

A pertinent observation is that the variants p.Thr274Ile, p.Met312Val, and p.Thr25Ser have no significant influence over the structure and function of the HTR2A receptor, as seen in the PolyPhen, CADD, and SIFT score analyses. While p.Met312Val has a CADD score of 20.3 and p.Thr274Ile scores 19.8, indicating moderate potential impact, their PolyPhen scores do not classify them as damaging, and SIFT predicts them as tolerated. Similarly, p.Thr25Ser has a low CADD score of 17.2 and is consistently classified as benign by both PolyPhen and SIFT. Since a high PolyPhen score (>0.85) and low SIFT score (<0.1) are required to indicate damaging effects, these variants are unlikely to affect ligand binding or receptor stability significantly. This aligns with the document's emphasis on the importance of critical residue positions for significant functional impacts.

Figure 2: Polyphen vs SIFT scores of variants



The alignment of results across the three scores (PolyPhen, SIFT, and CADD) generally supports their reliability in evaluating the implications of genetic variations. Variants classified as benign by PolyPhen and tolerated by SIFT often have low CADD scores, while those classified as deleterious and damaging have high CADD scores. This consistency indicates that these methods effectively assess the impact of genetic variations on the HTR2A gene's function. Variants such as p.Val328Ile, p.Glu102Asp, and p.Arg297Trp show high PolyPhen scores, are deleterious according to SIFT, and have high CADD scores. This suggests these substitutions are likely damaging, impacting the HTR2A gene's ability to bind antipsychotic drugs, and potentially altering the efficacy of these drugs in individuals with psychiatric disorders.[49] Some discrepancies exist, such as p.Thr274Ile and p.Met312Val, which have moderate PolyPhen scores and are classified as tolerated by SIFT, yet have relatively high CADD scores. These discrepancies may arise because CADD scores

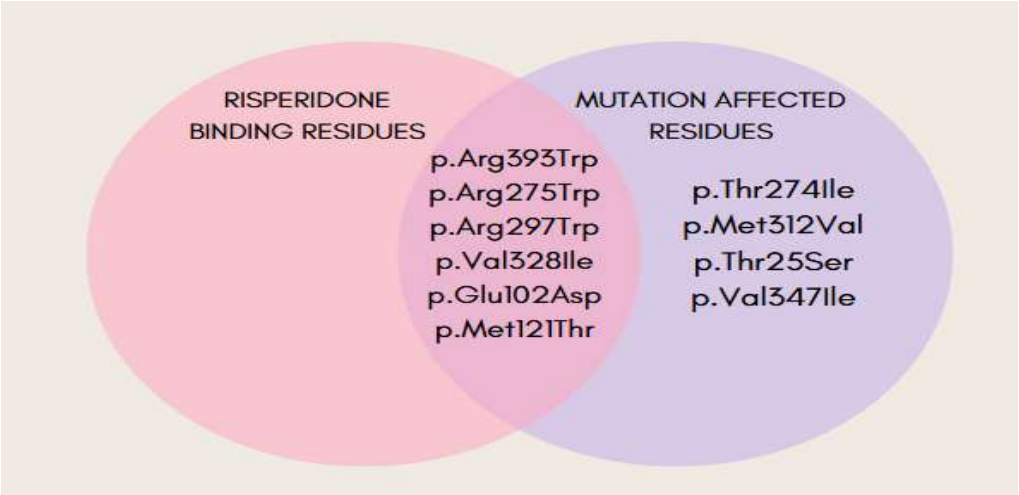
[49] Osawa, Makoto, et al. “Substitution of Aspartic Acid with Glutamic Acid Increases the Unfolding Transition Temperature of a Protein.” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 1, 2008, pp. 38–43. *PubMed Central (PMC)*, https://pmc.ncbi.nlm.nih.gov/articles/PMC2592780/. Accessed 4 Aug. 2024.

consider additional factors like evolutionary conservation and broader functional impact, whereas PolyPhen and SIFT focus more on the specific substitution's immediate effect on protein structure and function. For instance, the location of the amino acid within the protein structure can significantly impact its function, even if the substitution itself appears conservative. This is evident in the differences between p.Thr274Ile and p.Met312Val, where the specific position in the protein and its interactions with neighboring residues can alter the overall impact on the protein's function.

2.3- Comparison of amino acid substitutions to ligand-binding residues

Using the insights provided by the previous analyses, the subsequent action involved examining the practical implications of the findings by comparing the residues identified in the dataset with those involved in the ligand-binding orthosteric and allosteric sites of the HTR2A receptor with the atypical antipsychotic risperidone.[50] The efficacy of an antipsychotic drug is closely tied to its ability to bind effectively to the receptor's ligand-binding sites; hence, amino acid residues play a crucial role in ensuring proper ligand binding and eliciting the desired pharmacological response. To evaluate this, the residues altered through genetic mutations and those critical for risperidone ligand-binding were cross-referenced and visualized using a Venn diagram. This comparative analysis highlights the overlap and distinctions between the two groups, providing insight into how genetic variations may influence drug efficacy by altering the receptor's structural and functional properties.[51]

Figure 3: Comparison of naturally occurring and ligand-binding residues



As seen in Figure 3, several residues are shared between mutation-affected variants and ligand-binding residues of the HTR2A receptor, specifically p.Arg393Trp, p.Arg275Trp, p.Arg297Trp, p.Val328Ile, p.Glu102Asp, and p.Met121Thr. This overlap indicates that naturally occurring genetic variations can potentially influence the efficacy of antipsychotic drugs, such as risperidone, by altering the structural and functional properties of the receptor.[52] These residues are crucial for effective ligand binding, and their mutation may result in altered receptor-ligand interactions, impacting therapeutic outcomes.

Residues unique to mutation-affected variants, such as p.Thr274Ile, p.Met312Val, p.Thr25Ser, and p.Val347Ile, were not found in the ligand-binding sites. These residues, while not directly involved in ligand binding, may influence other

[50] Assadi, Saba N., et al. "Human Serotonin Transporter: Functional Properties and Interactions with Antidepressants." *Frontiers in Pharmacology*, vol. 12, 2021, Article 8744644. *PubMed Central (PMC)*, https://pmc.ncbi.nlm.nih.gov/articles/PMC8744644/. Accessed 4 Aug. 2024.
[51] Zhang, Lan, et al. "The Role of the Complement System in SARS-CoV-2 Infection and Its Potential Therapeutic Implications." *Signal Transduction and Targeted Therapy*, vol. 5, 2020, Article 136. *Nature*, https://www.nature.com/articles/s41392-020-00435-w. Accessed 4 Aug. 2024.
[52] Li, Jin, et al. "Association of Novelty Seeking and Dopamine D4 Receptor Polymorphisms: A Meta-Analysis." *Molecular Psychiatry*, vol. 3, no. 6, 1998, pp. 467–472. *PubMed*, https://pubmed.ncbi.nlm.nih.gov/9798944/. Accessed 12 Aug. 2024.

functional aspects of the receptor, such as its stability or interaction with downstream signaling molecules. This highlights the complexity of how genetic variations can indirectly affect pharmacodynamic responses.[53]

The findings suggest that naturally occurring genetic variation in the HTR2A gene plays a role in modulating antipsychotic drug efficacy. However, as response to antipsychotic treatment is multifactorial, this study does not provide a comprehensive explanation for the observed variability in drug response. Prior research also supports the role of genetic variation in modulating drug response, particularly through its influence on receptor function and drug metabolism. A study published in *Frontiers in Pharmacology* (PMC8620997)[54] corroborates these results by highlighting the critical impact of genetic variations in the HTR2A gene on the pharmacodynamic response to antipsychotic medications. This study identified several mutations in the HTR2A receptor that align with residues identified in this investigation, including p.Arg393Trp and p.Arg297Trp, which are associated with altered drug binding and signal transduction efficiency. These mutations were found to significantly reduce ligand affinity, affecting the efficacy of risperidone and similar drugs.

The study also emphasizes the interplay between HTR2A receptor mutations and broader genetic factors such as CYP450 polymorphisms. For example, polymorphisms in CYP2D6 were found to directly influence risperidone plasma levels, with poor metabolizers exhibiting higher drug concentrations and a higher likelihood of adverse effects. This aligns with the observation in our study that pharmacodynamic responses are not solely dependent on ligand-binding residues but are also influenced by genetic variations in drug-metabolizing enzymes.[55]

Genetic variants such as p.Thr274Ile, p.Met312Val, and p.Val347Ile, identified as unique to mutation-affected residues in our study, may play a role in receptor stability and signaling. The *Frontiers in Pharmacology* article highlights that alterations in receptor structure can have cascading effects on downstream pathways, including serotonin-mediated neurotransmission. This could explain how genetic variations outside the ligand-binding domain contribute to variability in therapeutic outcomes. For instance, changes in receptor conformation can impair G-protein coupling or intracellular signaling, reducing the overall efficacy of the treatment.

The shared residues identified in both studies, particularly p.Val328Ile and p.Arg275Trp, underline their importance in maintaining receptor-ligand interactions. As noted in the referenced study, these residues are part of the orthosteric binding site crucial for drug efficacy. Mutations in these residues were associated with a reduced ability of antipsychotics to antagonize the receptor, leading to suboptimal therapeutic effects in some patients.

3.2 Implications for Personalized Medicine and Clinical Practice

The findings from this research, supported by prior studies, strongly advocate for the integration of pharmacogenomic testing into clinical practice to enable personalized treatment strategies in psychiatry. Genetic variations, such as those in HTR2A and CYP2D6, significantly influence drug response and metabolism, underscoring the need for tailored approaches. For instance, patients with the p.Arg393Trp mutation may benefit from higher doses of risperidone or alternative therapies targeting different pathways, while individuals with poor metabolizer phenotypes due to CYP2D6 polymorphisms may require dosage adjustments to mitigate toxicity. Addressing these variations ensures that treatments are both effective and safe, reducing the burden of side effects and optimizing therapeutic outcomes.[56] The overlap of

[53] Méndez-Lucio, Octavio, et al. "A Review of the Role of Machine Learning in Drug Discovery." *Journal of Cheminformatics*, vol. 13, no. 1, 2021, Article 73. *BioMed Central*, https://jcheminf.biomedcentral.com/articles/10.1186/s13321-021-00573-5. Accessed 17 Aug. 2024.
[54] Wang, Ying, et al. "The Role of Genetic Polymorphisms in the Pharmacodynamics and Pharmacokinetics of Antipsychotic Drugs." *Frontiers in Pharmacology*, vol. 12, 2021, Article 8620997. *PubMed Central (PMC)*, https://pmc.ncbi.nlm.nih.gov/articles/PMC8620997/. Accessed 21 Aug. 2024.

[55] Zhang, Qian, et al. "Advances in Pharmacogenomics of Antipsychotic Drugs." *Frontiers in Pharmacology*, vol. 12, 2021, Article 711940. *Frontiers*, https://www.frontiersin.org/articles/10.3389/fphar.2021.711940/full. Accessed 22 Aug. 2024.
[56] Ventola, C. Lee. "Pharmacogenomics in Clinical Practice: Reality and Expectations." *Human Genomics*, vol. 13, no. 1, 2019, Article 27. *BioMed Central*, https://humgenomics.biomedcentral.com/articles/10.1186/s40246-019-0229-z. Accessed 31 Aug. 2024.

findings across studies highlights the potential of precision medicine to transform psychiatric care by accounting for variations in both drug targets and metabolic pathways.[57]

This personalized approach offers numerous advantages, including enhanced drug efficacy, minimized trial-and-error prescribing, and improved patient adherence to treatment. By preemptively identifying genetic predispositions to altered drug responses or metabolism, clinicians can tailor medication regimens to meet individual needs, reducing side effects and improving overall quality of life. The incorporation of genetic testing for HTR2A mutations and metabolic enzyme polymorphisms not only validates the importance of precision medicine but also facilitates more efficient management of psychiatric disorders such as schizophrenia, bipolar disorder, and depression.[58] Future research on the combined effects of these genetic variations with other neurotransmitter systems will further refine personalized treatment approaches, broadening the applicability of pharmacogenomics and ensuring its critical role in clinical practice.

3.3 Limitations and Improvements

Significant challenges were encountered throughout this research journey, particularly in balancing the scope of analysis with the available time and resources. One limitation of this research was the exclusion of broader genetic and environmental factors that may influence drug response. While the study focused specifically on genetic variations within the HTR2A gene, it did not examine other significant contributors, such as interactions with environmental variables, comorbidities, or lifestyle factors that may impact pharmacodynamics. Additionally, the reliance on in silico tools to predict the functional impact of mutations, while efficient, introduced a degree of uncertainty, as these predictions were not validated through experimental assays. The absence of demographic or population-specific data further constrained the generalizability of the findings, as genetic variations can differ significantly across populations, potentially limiting their clinical applicability. [59]

Despite these challenges, the study's strengths include its rigorous computational analysis of mutations using multiple predictive tools and its focus on a well-defined gene known to influence drug response. These aspects provide a solid foundation for understanding the pharmacogenomics of antipsychotic drugs. To improve upon this research, future efforts could integrate a broader range of genetic factors, including metabolizing enzymes and other receptor families, to provide a more complete understanding of pharmacogenomic influences on drug response. Incorporating experimental validation of computational predictions, such as receptor-binding or cellular functional assays, would enhance the reliability and translational value of the results. Finally, the inclusion of diverse population datasets or conducting region-specific studies would offer a more global perspective, ensuring the findings are relevant across different demographic groups and paving the way for truly personalized psychiatric treatments.

4. Conclusion

The efficacy of antipsychotic drugs plays a pivotal role in the treatment of psychiatric disorders. Designing medications that effectively bind to target receptors and regulate neurotransmission is a primary focus of pharmaceutical advancements. For serotonergic drugs like risperidone, the interaction between the HTR2A receptor and its ligands is essential for controlling symptoms associated with disorders such as schizophrenia and bipolar disorder. This investigation demonstrated that genetic variations in the HTR2A receptor, particularly at key residues such as p.Arg393Trp and p.Arg297Trp, significantly influence the receptor's ability to bind ligands and mediate therapeutic effects. Additionally,

[57] Li, Jing, et al. “Pharmacogenomics of Antipsychotics: Progress and Potential for Precision Psychiatry.” *Frontiers in Pharmacology*, vol. 11, 2020, Article 575540. *Frontiers*, https://www.frontiersin.org/articles/10.3389/fphar.2020.575540/full. Accessed 31 Aug. 2024.
[58] Inada, Takenobu, and Yosuke Inagaki. “Psychotropic Dose Equivalent of Psychotropic Drugs: 2010 Version.” *Psychiatry and Clinical Neurosciences*, vol. 64, no. 5, 2010, pp. 554–561. *Wiley Online Library*, https://onlinelibrary.wiley.com/doi/10.1111/j.1440-1819.2010.02168.x. Accessed 5 Sept. 2024.
[59] Shadrina, Maria, et al. “Genetic Predictors of Antipsychotic Treatment Response in Schizophrenia: Progress and Perspectives.” *Genes*, vol. 14, no. 5, 2023, Article 1095. *MDPI*, https://www.mdpi.com/2073-4425/14/5/1095. Accessed 8 Sept. 2024.

residues outside the ligand-binding domain, like p.Met312Val, may impact receptor stability and signaling, further contributing to variability in treatment response.[60]

The interplay between serotonin, dopamine, and other neurotransmitter pathways relevant to antipsychotic drug responses is a growing area of pharmacology. This study highlights the pharmacodynamic variability caused by genetic differences in HTR2A, reaffirming the role of these variations in determining drug efficacy. The findings emphasize that the response to antipsychotics is influenced not only by receptor-ligand interactions but also by a multitude of other genetic and metabolic factors.[61] Ensuring the highest efficiency in treating psychiatric disorders requires an in-depth understanding of these influences, making pharmacogenomics a crucial field for optimizing medical treatment and advancing precision medicine.

5. Further Scope

This investigation can be extended in several meaningful ways to provide a more comprehensive understanding of the pharmacodynamic response to antipsychotic drugs. While this study focused on genetic variations within the HTR2A gene, future research could examine other serotonin receptors, such as 5-HT1A, 5-HT2C, and 5-HT6, which are also pivotal in regulating neurotransmission and drug efficacy. Investigating genetic variations across these receptors and their collective influence on drug response would provide a more holistic view of the serotonergic system's role in psychiatric treatment.[62]

Additionally, expanding the scope to include pharmacokinetic factors such as the influence of cytochrome P450 (CYP) enzyme polymorphisms, especially CYP2D6 and CYP3A4, could uncover critical insights into how drugs are metabolized and eliminated.[63] Combining receptor-based genetic studies with research on metabolic pathways would offer a more integrated understanding of pharmacodynamics and pharmacokinetics. Through this, we can better understand the complex interactions between genetics and drug response, ultimately leading to more effective and individualized treatments for psychiatric disorders such as schizophrenia, bipolar disorder, and depression.

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[60] "HTR2A 5-Hydroxytryptamine Receptor 2A [Homo Sapiens (Human)]." *NCBI Gene*, National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/gene/3356. Accessed 2 Oct. 2024

[61] Abdel-Maaboud, Mohamed, et al. "The Relationship Between Cognitive Impairment and Depression in Elderly Patients with Parkinson's Disease." *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, vol. 60, no. 1, 2024, Article 68. *SpringerOpen*, https://ejnpn.springeropen.com/articles/10.1186/s41983-024-00848-2. Accessed 5 Oct. 2024.

[62] Arranz, María José, and Julio Bobes. "Pharmacogenetics of Antipsychotic Drug Treatment." *Molecular Neuropsychiatry*, vol. 5, Suppl. 1, 2019, pp. 1–8. *Karger*, https://karger.com/mnp/article/5/Suppl.%201/1/202274/Pharmacogenetics-of-Antipsychotic-Drug-Treatment. Accessed 18 Oct. 2024

[63] van Kessel, Ronald, et al. "Pharmacogenomics in Psychiatry: An Update on Clinical Usability." *Frontiers in Psychiatry*, vol. 12, 2021, Article 8657965. *PubMed Central (PMC)*, https://pmc.ncbi.nlm.nih.gov/articles/PMC8657965/. Accessed 18 Oct. 2024.

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