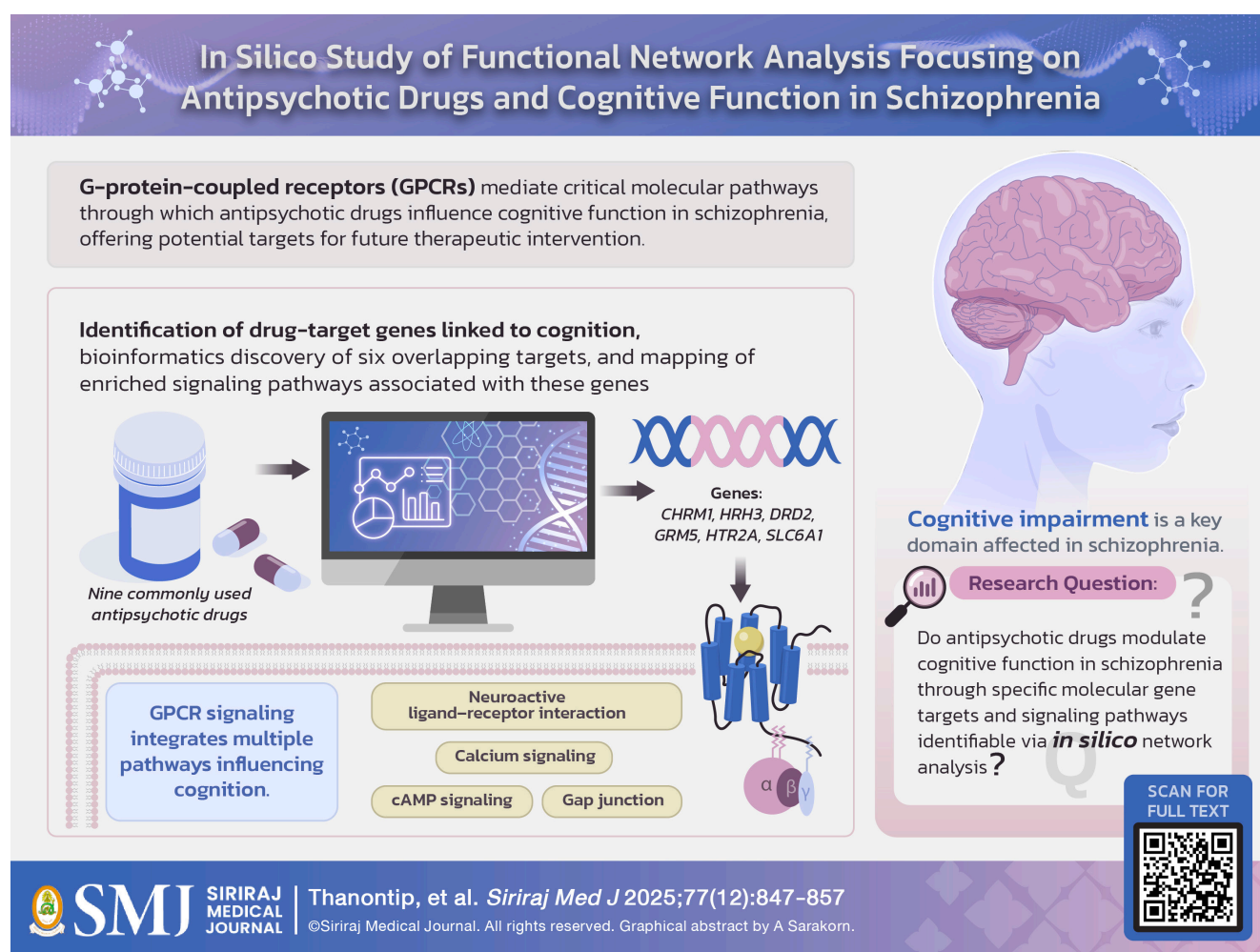


In Silico Study of Functional Network Analysis Focusing on Antipsychotic Drugs and Cognitive Function in Schizophrenia

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ABSTRACT

Objective: Recent evidence has emphasized cognitive dysfunction in psychiatric disorders. This study explores bioinformatics analysis aimed at investigating gene targets and pathways related to antipsychotic drug effects on cognitive function in schizophrenia. The main purpose of conventional antipsychotics is to treat the positive symptoms, but they have limited evidence for the involvement of these drugs in cognitive function. Therefore, this study aimed to explore the pathway for the antipsychotic signaling in the cognitive function of schizophrenia.

Materials and Methods: Nine frequently used antipsychotics were included from the literature review. The GeneCards database was utilized to identify the drug target genes associated with cognitive function in schizophrenia. The gene lists were analyzed with two different tools, WebGestalt and STRING. The overlapping genes that result from the two previous steps may play an essential role in cognitive function. These genes were analyzed to find out the related pathway using the KEGG database.

Results: The potential gene list consists of CHRM1, HRH3, DRD2, GRM5, HTR2A, and SLC6A1. The functional enrichment in KEGG reveals six target proteins involved in several pathways, which play an essential role in cognitive function, including the neuroactive ligand-receptor interaction, the gap junction, the calcium signaling pathway, and the cAMP signaling pathway.

Conclusion: The results reveal that G-protein-coupled receptors (GPCRs) are the main target site of potential mechanisms or processes related to antipsychotics and cognitive function. Therefore, GPCRs might be a promising candidate for future research on potential therapeutic targets for intervention in neurological dysfunction-associated cognitive deficits in schizophrenia.

Keywords: In silico study; functional network analysis; antipsychotic drugs; cognitive function; schizophrenia (Siriraj Med J 2025; 77: 847-857)

INTRODUCTION

Schizophrenia is a psychiatric illness characterized by psychotic symptoms, including positive symptoms and negative symptoms.^{1,2} Cognitive deficit is a neurological dysfunction that occurs in schizophrenia.³⁻⁶ The cognitive domains that show differential impairment in schizophrenia include attention, executive function, language skills, working memory, and cognitive flexibility.^{7,8} These determine the functional impairment characteristic of schizophrenia, which disturbs their daily life activity and quality of life.⁹ Therefore, the most concerning clinical target in the treatment of schizophrenia is not only to reduce the psychotic symptoms but also to improve cognitive function.¹⁰

Cognitive impairment may develop from the pathology of the disease itself in some schizophrenia patients.¹¹ It has been implicated that conventional antipsychotics are effective in treating psychological symptoms; however, they cannot improve cognitive function.¹² The effects of antipsychotics on cognition are complex, which might depend on the stage of illness and the doses of antipsychotics. It has been reported that a dose reduction in a patient who is clinically in an advanced phase of remission, causing cognitive decline associated with antipsychotic drugs. On the other hand, dose reduction or discontinuation after reaching stable remission might

improve cognitive function.¹³ Several lines of evidence revealed that the usage of antipsychotics in high doses impairs cognitive function in schizophrenia patients.^{14,15} On the contrary, a low dose of conventional medications such as haloperidol improves cognitive functions.¹⁶

According to the heterogeneity of antipsychotics in their pharmacologic properties, they have differential profiles of cognitive efficacy in patients with schizophrenia. Therefore, understanding the molecular mechanisms and mode of action of each antipsychotic related to cognitive processes is needed to address the gap in knowledge. Computational network analysis is a potential tool that may answer these knowledge gaps by providing a biological explanation for antipsychotic targets and insights for the putative molecular mechanism of antipsychotic agents, focusing on cognitive function. Therefore, this study aimed to explore the interaction of the target protein, which is related to the action of antipsychotic drugs and cognitive functions related to schizophrenia. The results of this study could be explored to discover more effective novel target treatment of neurological dysfunction involving neuropsychological-associated cognitive deficit.

MATERIALS AND METHODS

The conceptual framework was designed to gain

insight into the pathway of the potential protein involved in antipsychotics and cognitive function in schizophrenia. The framework starts to identify the commonly used antipsychotics for schizophrenia using a literature review and then using bioinformatics tools to identify gene targets for selected antipsychotics and genes associated with cognitive function in schizophrenia. Next step, the gene associated with antipsychotics and cognitive function in schizophrenia was identified. Then, protein-protein interaction network analysis and network clustering were performed, followed by the identification of a common gene that is associated with antipsychotics and cognitive function in schizophrenia from two different methods. Finally, the pathway that contains potential protein involves antipsychotics and cognitive function in schizophrenia was identified (Fig 1).

Identification of commonly used antipsychotics

In silico study of network analysis focusing on antipsychotic drugs and cognitive function in people with schizophrenia was started to identify commonly used antipsychotics for schizophrenia (step 1 of Fig 1) by reviewing published articles and textbooks.¹⁷⁻²⁰

Identification of gene targets for selected antipsychotics

GeneCards (<https://genecards.org>) and a database for searching genes of interest (step 2 of Fig 1) were used to identify gene targets for selected antipsychotics. Target genes of selected antipsychotics were identified using the names of 9 antipsychotics as a keyword. The keyword for searching in this step is "[compounds] (Aripiprazole) OR [compounds] (Chlorpromazine) OR [compounds] (Fluphenazine) OR [compounds] (Haloperidol) OR [compounds] (Olanzapine) OR [compounds] (Quetiapine) OR [compounds] (Risperidone) OR [compounds] (Thiothixene) OR [compounds] (Ziprasidone)".

Identification of genes associated with cognitive function in schizophrenia by GeneCards Database

The GeneCards database²¹ was used to identify genes associated with cognitive function in schizophrenia (step 3 of Fig 1). [publications] (schizophrenia) AND [disorders] (Schizophrenia AND [publications] (cognitive) AND [disorders] (cognitive) OR [functions] (cognitive) OR [pathways] (cognitive) is the keyword for searching in this step.

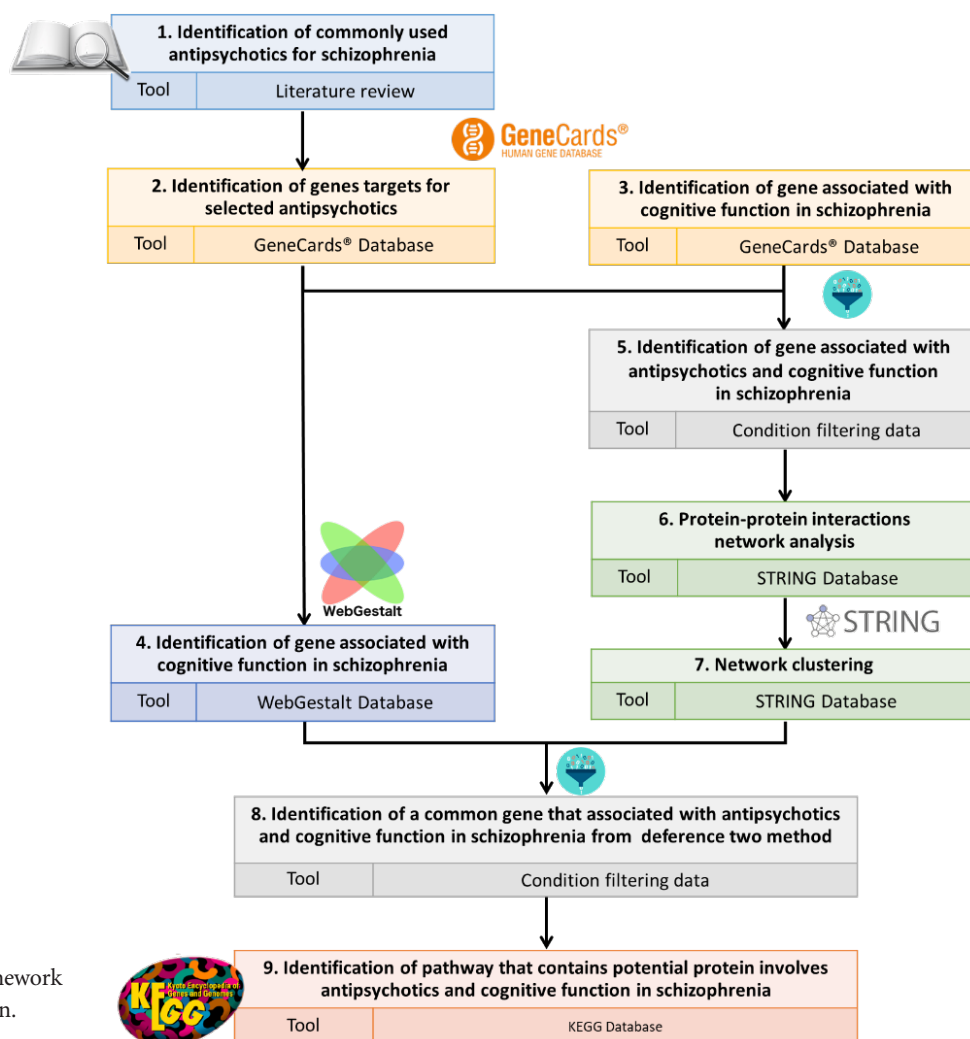


Fig 1. Conceptual framework of experimental design.

Identification of genes associated with cognitive function in schizophrenia by WebGestalt Database

The gene associated with cognitive function in schizophrenia was identified by the WebGestalt Database (<http://www.webgestalt.org/>) (step 4 of Fig 1), which stands for WEB-based GEne SeT AnaLysis Toolkit.²² Over-representation analysis (ORA) is a method used in this study. The upload gene list is collected from the previous step (step 2 of Fig 1), which is the identification of gene targets for antipsychotics.

Identification of genes associated with antipsychotics and cognitive function in schizophrenia

This step is a consequence of step 2 (identification of gene targets for selected antipsychotics) and step 3 (identification of genes associated with cognitive function in schizophrenia by GeneCards Database). Gene findings from the previous step were condition formatting, then filtered by matching in both terms of antipsychotics and cognitive function in schizophrenia. The step-by-step data condition formatting and filtering data in Microsoft Excel is used to find common genes between two gene lists. The gene identification starts by selecting the data column > Conditional formatting in the Home ribbon > Highlight cell rule > Duplicate Values, and then pressing OK. Then, select the data column > Sort & Filter in the home ribbon > Filter to apply the filter dropdown icon to selected columns.

Protein-protein interactions network analysis

The gene list from the previous step (step 5 of Fig 1) was further analyzed to identify protein-protein interactions and construct a protein-protein interactions network using the STRING database. The step to identify protein-protein interactions of the gene of interest starts with inputting the name of the gene of interest into the multiple proteins search box and then selecting auto-detect organism and search. The input of the Gene list might appear in several organisms. The Homo sapiens organism was selected from the list. Many proteins in Homo sapiens might similar to the input data. The matching protein was selected. A protein-protein interactions network was generated and visualized only connected nodes in interaction evidence mode, using three interaction sources: experiment, database and co-expression. The default setting was applied for the minimum required interaction score and the maximum number of interactions to show in the network display mode.

Network clustering

The network was clustered using the Markov Clustering

method (MCL), with three inflation parameters to establish the most interconnected cluster of the protein-protein interaction (PPI) network.²³

Identification of a common gene associated with antipsychotics and cognitive function in schizophrenia from deference two methods

Gene findings from the WebGestalt and network clustering were condition formatting, then filtered by matching genes from the two lists. The condition formatting and filtering data settings in Microsoft Excel were used to find common genes between two gene lists.

Identification pathway of potential proteins involved in antipsychotics and cognitive function in schizophrenia

The results from the previous step of deference two methods, which involved the identification of a common gene associated with antipsychotics and cognitive function in schizophrenia, were used to identify the related pathway by the STRING database. The results of the related pathway were shown in functional enrichment in the analysis section.²⁴

Comprehensive graphical user interface snapshots, input datasets, parameter configurations, filtering criteria, threshold values, and detailed procedural steps for each analysis are provided in the Supplemental Data.

RESULTS

The nine commonly used antipsychotics were chosen, including Aripiprazole, Chlorpromazine, Fluphenazine, Haloperidol, Olanzapine, Quetiapine, Risperidone, Thiothixene, and Ziprasidone.^{17-20,24}

The results of gene targets for antipsychotics showed a total of 223 target genes (Fig 2). The results obtained from the GeneCards Database showed that 122 genes were associated with cognitive function in schizophrenia (Fig 2). The results from WebGestalt database analysis showed that 223 gene targets for nine selected antipsychotics were characterized into three main categories, including biological process, cellular component, and molecular function. Apart from 223 genes, the results showed that 31 genes were found to be associated with cognitive function in schizophrenia (Fig 2).

The 28 candidate genes associated with antipsychotics and cognitive function in schizophrenia were constructed into protein-protein interaction networks analysis using the STRING database. The results showed 28 Nodes of protein and 33 Edges, representing interactions between pairs of proteins. The protein-protein interaction was identified based on experimental, database, or coexpression evidence. Moreover, nine proteins, including CHAT,

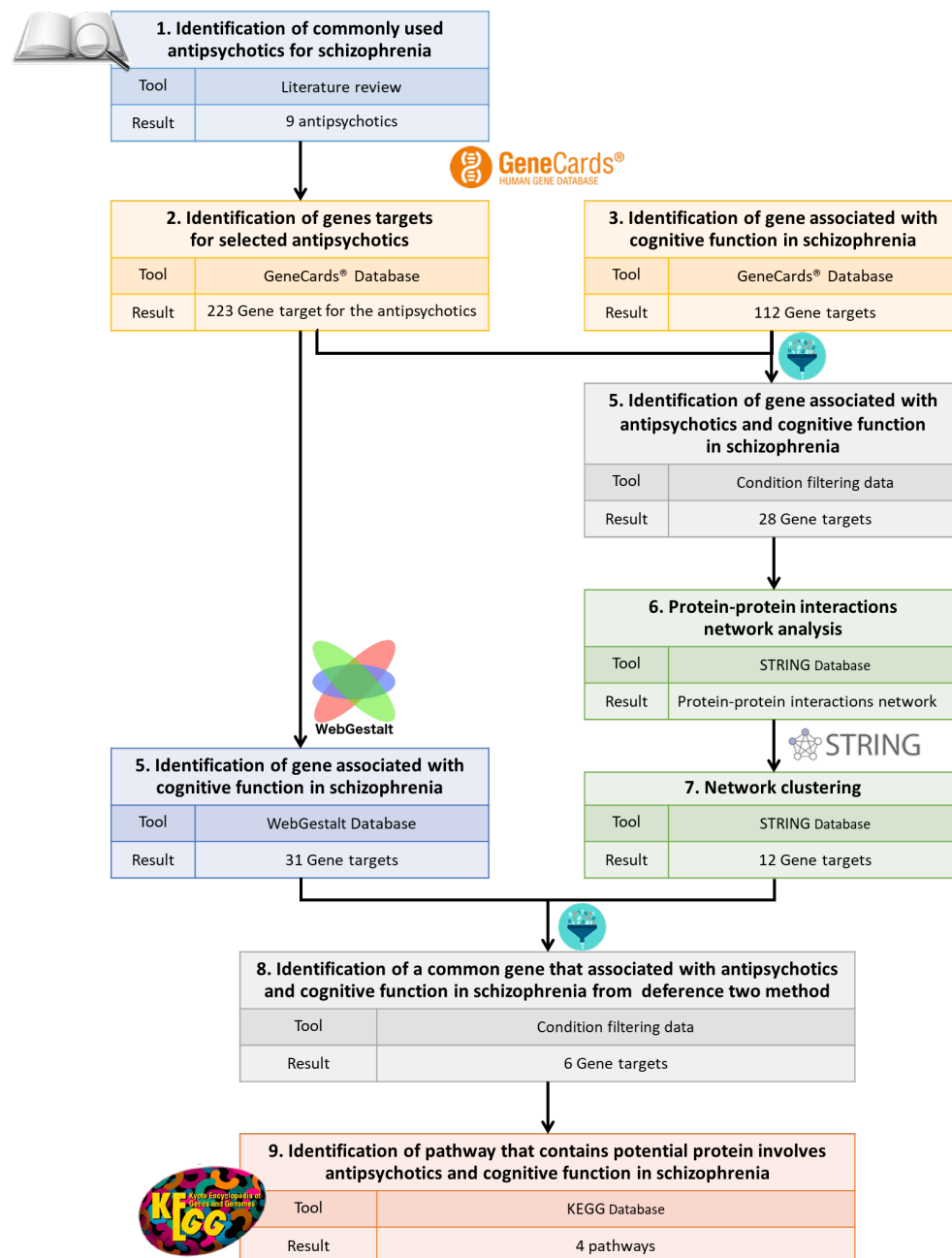


Fig 2. Flow diagram illustrating the summary of results.

APOE, GAD1, PLA2G6, SLC18A2, IL10, MTHFR, COMT, and TH, have no interaction with any protein (Fig 3A).

The network clustering of 28 candidate genes associated with antipsychotics and cognitive function in schizophrenia was constructed using the STRING database. The results exhibited four network clusters, and the largest cluster comprises 12 proteins. The 7 more proteins were clustered in one cluster of 3 proteins and two clusters of 2 proteins, respectively. The nine disconnected nodes were hidden from the network clustering (Fig 3B). The 12 proteins of the large clustering were selected for analysis in the next experiment.

The target gene associated with antipsychotics and cognitive function in schizophrenia, collected from 31

genes of the WebGestalt database analysis and 12 genes of network clustering, was taken into consideration using deference two methods. The six common genes associated with antipsychotics and cognitive function in schizophrenia were obtained from deference two methods, which include CHRM1, HRH3, DRD2, GRM5, HTR2A and SLC6A1. The gene symbol, description and antipsychotics interact with the 6 candidate genes are shown in Table 1.

The six common genes associated with antipsychotics and cognitive function in schizophrenia were further analyzed using KEGG (Kyoto Encyclopedia of Genes and Genomes) analysis. The KEGG analysis results in 4 pathways, including neuroactive ligand-receptor

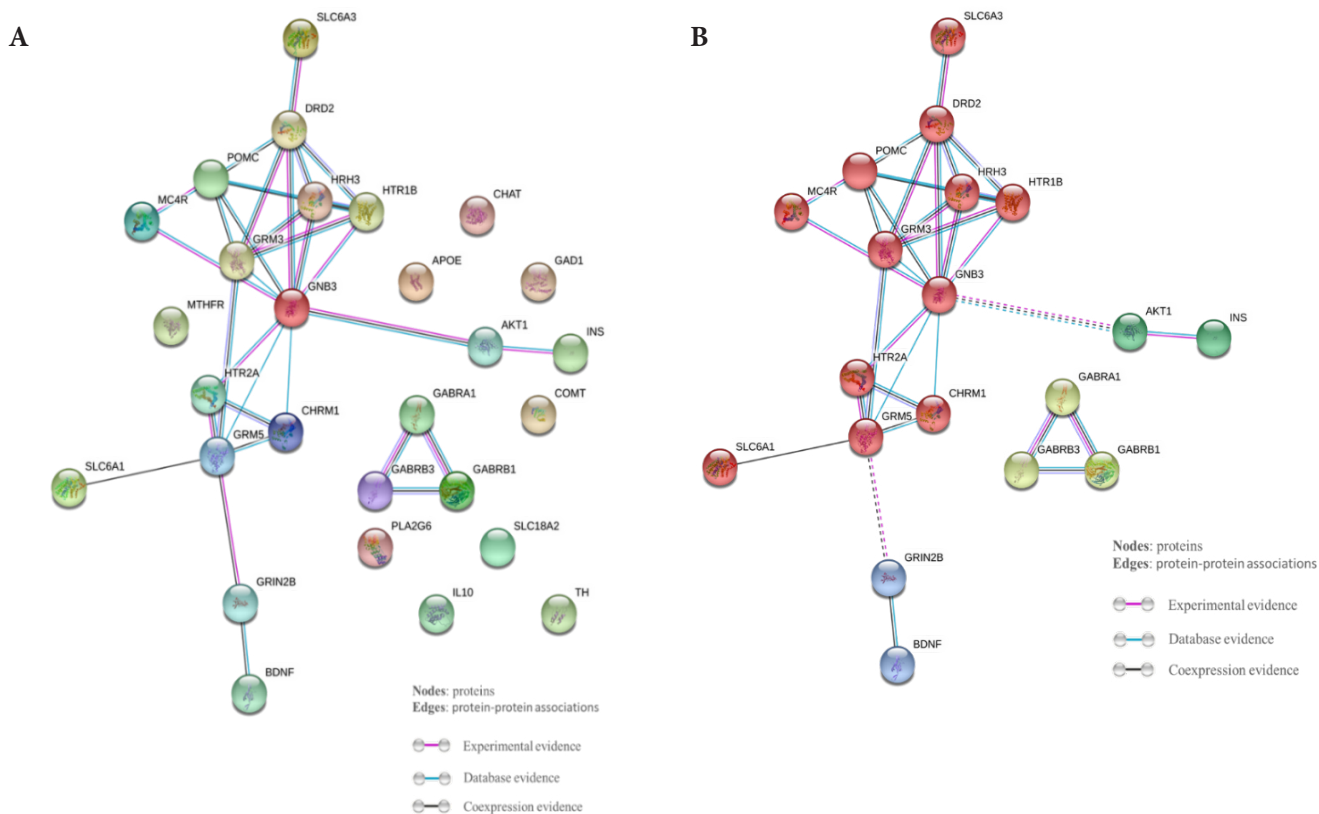


Fig 3. (A) Protein-protein interactions (PPI) network of proteins associated with antipsychotics and cognitive function in schizophrenia. The protein-protein interaction is characterized by three different types of evidence, including experimental, database, or coexpression. Each evidence of protein-protein interaction is shown in a different color of the connecting line. The experimental, database or coexpression evidence is indicated in purple, blue and black lines, respectively. (B) Protein-protein interactions network of proteins associated with antipsychotics and cognitive function in schizophrenia after network clustering and hiding disconnected nodes. The network clustering is indicated in color.
(A larger version of this figure is available in the Supplemental Data file.)

TABLE 1. Gene symbol, description, and list of antipsychotics interact with the common gene associated with antipsychotics and cognitive function in schizophrenia from deference two methods.

No.	Gene Symbol	Description	Antipsychotics interact with the gene
1	CHRM1	cholinergic receptor muscarinic 1	Aripiprazole, Chlorpromazine, Olanzapine, Quetiapine, Ziprasidone
2	HRH3	histamine receptor H3	Aripiprazole, Risperidone
3	DRD2	dopamine receptor D2	Aripiprazole, Chlorpromazine, Fluphenazine, Haloperidol, Olanzapine, Quetiapine, Risperidone, Thiothixene, Ziprasidone
4	GRM5	Glutamate metabotropic receptor 5	Haloperidol
5	HTR2A	5-hydroxytryptamine receptor 2A	Aripiprazole, Chlorpromazine, Fluphenazine, Haloperidol, Olanzapine, Quetiapine, Risperidone, Thiothixene, Ziprasidone
6	SLC6A1	solute carrier family 6 member 1	Haloperidol

interaction, gap junction, calcium signaling pathway, and cAMP signaling pathway (Table 2). The observed gene count, background gene count, false discovery rate and matching proteins in the network of each pathway are shown in Table 2.

DISCUSSION

Recently, several lines of evidence emphasized the functional role of antipsychotic drugs in the cognitive function of psychiatric disorders, including schizophrenia.^{25-30,61-63} However, the mode of action and molecular mechanisms of antipsychotic drug-related cognitive function are not clearly understood. Bioinformatics is one of the tools that reduces the costs and time to study drugs and target-specific drugs.^{28,29} Moreover, network analysis is a bioinformatics approach that is employed to gain a broad and in-depth picture of protein-protein interaction (PPI) networks and signaling pathways.³⁰

In the present study, nine frequently used antipsychotics were selected from the literature review. The GeneCards database was used to identify the drug target gene and gene of interest involved in cognitive function in schizophrenia. The next step was to analyze the gene lists with two different tools: WebGestalt Database, a functional enrichment analysis web tool, and STRING database, a web tool for studying protein-protein interactions. The overlapping six genes from the two previous steps may play an essential role in cognitive function. The potential gene list consists of 6 genes including CHRM1 (cholinergic receptor muscarinic 1), HRH3 (histamine receptor H3), DRD2 (dopamine receptor D2), GRM5 (glutamate metabotropic receptor 5), HTR2A (5-hydroxytryptamine receptor 2A) and SLC6A1 (solute carrier family 6 member 1). These genes were analyzed to find the related pathway using the KEGG database. Functional enrichment in KEGG

reveals 6 target proteins involved in several pathways, which play an important role in cognitive function, including neuroactive ligand-receptor interaction³¹⁻³⁶, gap junction³⁷, calcium signaling pathway³⁸⁻⁴⁰, and the cAMP signaling pathway.⁴¹

CHRM1 (Cholinergic Receptor Muscarinic 1) is a G protein-coupled receptor involved in acetylcholine binding and is implicated in cognitive function. Reduced cortical CHRM1 levels have been linked to cognitive decline and executive dysfunction in schizophrenia.⁴²⁻⁴⁵ HRH3 (Histamine Receptor H3) modulates histamine signaling in the CNS and regulates neurotransmitter release; H3 receptor antagonists show potential in treating cognitive impairment in schizophrenia without extrapyramidal side effects.^{42,46,47} DRD2 (Dopamine Receptor D2) participates in locomotion, reward, memory, and learning; mutations and polymorphisms in DRD2 are associated with schizophrenia risk and cognitive deficits.^{42,48,49} GRM5 (Glutamate Metabotropic Receptor 5), a glutamate receptor modulating synaptic plasticity, is linked to cognitive impairments in schizophrenia and may be a promising target to reverse these deficits.^{42,50,51} HTR2A (5-Hydroxytryptamine Receptor 2A) regulates neural activity and cognition; serotonergic modulation via 5-HT receptors contributes to cognitive and motor function improvements in schizophrenia treatment.^{42,52,53} SLC6A1 (Solute Carrier Family 6 Member 1) encodes a GABA transporter affecting synaptic inhibition, with impairments contributing to working memory deficits in schizophrenia.^{42,54}

Nine antipsychotics bind to their protein target with different action mechanisms, and most of them are receptor antagonists. It has been noted that the large group of proteins involves antipsychotics and cognitive function in schizophrenia are receptors of the

TABLE 2. List of pathways that contain potential proteins involved in antipsychotics and cognitive function in schizophrenia

No.	#Term ID	Term description	Observed gene count	Background gene count	False discovery rate	Matching proteins in the pathway
1	hsa04080	Neuroactive ligand-receptor interaction	5	272	0.000000065	CHRM1, DRD2, GRM5, HRH3, HTR2A
2	hsa04540	Gap junction	3	87	0.0000186	DRD2, GRM5, HTR2A
3	hsa04020	Calcium signaling pathway	3	179	0.0001	CHRM1, GRM5, HTR2A
4	hsa04024	cAMP signaling pathway	2	195	0.0074	CHRM1, DRD2

neuroactive ligand-receptor interaction pathway, including CHRM1 (Cholinergic Receptor Muscarinic 1), DRD2 (Dopamine Receptor D2), GRM5 (Glutamate Metabotropic Receptor 5), HRH3 (Histamine Receptor H3), and HTR2A (5-Hydroxytryptamine Receptor 2A). These receptors are G-protein-coupled receptors (GPCRs).^{55,56} (Fig 4) The downstream cascade of DRD2, HRH3, and CHRM1 is adenylate cyclase (AD), which activates Cyclic AMP (cAMP) and protein kinase A (PKA) in a cAMP signaling pathway.^{57,58} PKA-mediated molecule that connects the cAMP signaling pathway and the gap junction. PKA might act on a gap junction as an inhibitor.⁵⁹ Gap junctions hold intercellular channels that allow direct communication and direct transfer of small molecules between the cytosolic of neighboring cells. The communication of these channels is essential for many biological processes, such as apoptosis and differentiation. Taken together, a cAMP-PKA signaling pathway is a crucial mediator of long-term memory formation.⁴¹ The finding of new targets of antipsychotics in the present study is consistent with the recent evidence that glutamate metabotropic receptor modulators and serotonin agonists have the potential to improve cognitive impairments in schizophrenia.⁶⁰

The involvement of GPCRs and their associated signaling pathways, such as neuroactive ligand-receptor interaction, calcium signaling, and cAMP signaling, in cognitive processes and antipsychotic drug action is well-established in schizophrenia research.⁶⁴ This study

confirms these known mechanisms; however, the scientific contribution lies in the integrative identification of six overlapping target genes (CHRM1, HRH3, DRD2, GRM5, HTR2A, and SLC6A1) through dual bioinformatics approaches, refining specific drug-gene interaction candidates relevant to cognitive dysfunction.

Distinctly, the analysis highlights potential unique drug-gene interactions by mapping commonly prescribed antipsychotics to specific gene targets, some of which have been underexplored in population-specific contexts. For example, the inclusion of HRH3 and SLC6A1 as candidate genes suggests avenues beyond the classical dopaminergic and serotonergic targets, aligning with emerging therapeutic efforts to modulate histaminergic and GABAergic systems in schizophrenia cognition.⁶⁵

Regarding the broad nature of the enriched pathways identified, this study advances understanding by contextualizing the role of these pathways specifically in cognitive impairment among schizophrenia patients. For instance, the cAMP-PKA signaling cascade identified here is crucial for synaptic plasticity and long-term memory formation, directly linking molecular targets to known cognitive deficits in schizophrenia.⁶⁶ Furthermore, the neuroactive ligand-receptor pathway's multiple GPCR targets illustrate how antipsychotics modulate neurotransmission collectively affecting cognitive domains.

Comparatively, prior bioinformatics and network pharmacology studies in schizophrenia have predominantly

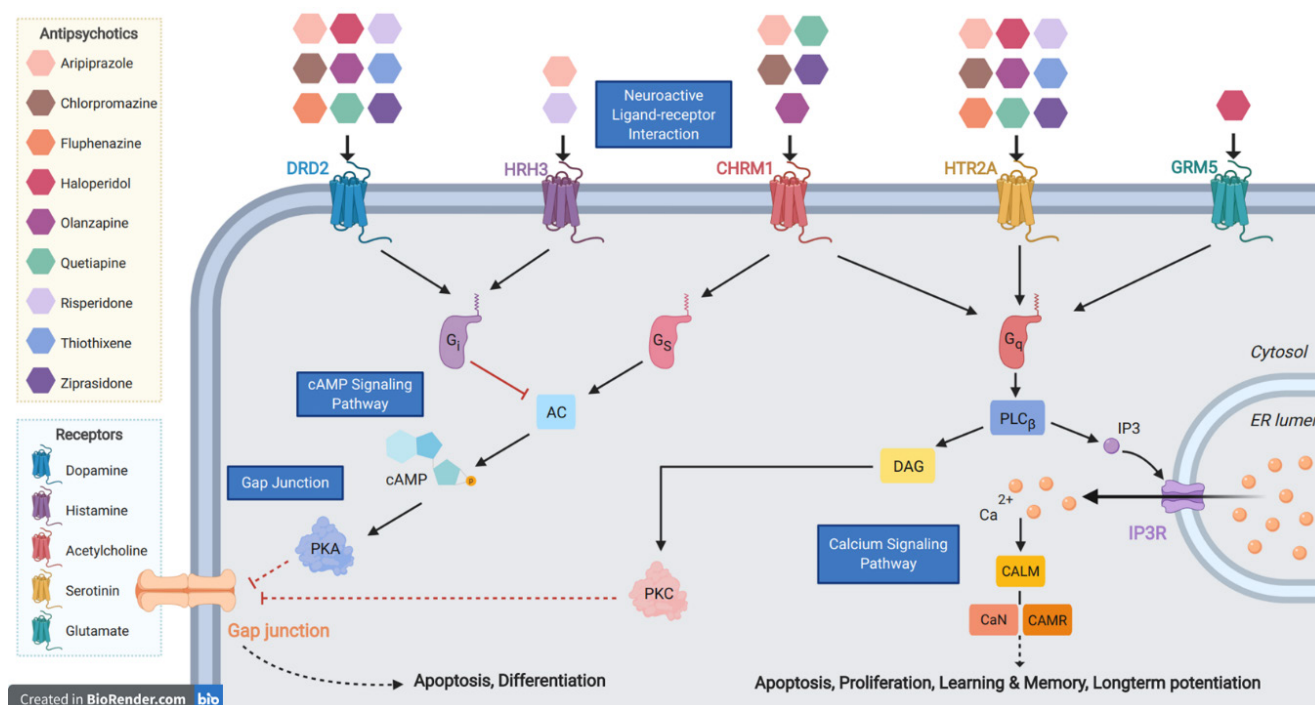


Fig 4. Schematic representation of antipsychotics' action on receptors and signal transduction pathways.

focused on genetic susceptibility or broad molecular networks without integration of specific antipsychotic drug targets.⁶⁷ This study contributes by bridging drug pharmacology and cognitive genomics, utilizing a combinatorial approach of gene target overlap, protein interaction networks, and pathway enrichment. Therefore, it provides a more targeted framework for identifying therapeutic candidates that could be further investigated in population-specific and pharmacogenetic contexts.⁶⁴

Current evidence mostly reveals the role of antipsychotic action on psychotic symptoms and cognitive functions in schizophrenia patients.^{63,68,69} However, the mechanism of action of antipsychotic drugs on GPCRs related to the neurological processes of cognitive function is limited. The results of this study highlight the interaction of the molecular mechanisms of antipsychotic drugs on the neurological processes associated with psychosis and cognitive function. Therefore, this crucial evidence might suggest the conceptual framework for further study on pharmacological and clinical applications of novel antipsychotic drugs with dual effects on psychotic symptoms and cognitive functions in schizophrenia.

CONCLUSION

The findings of this study support existing evidence that G-protein-coupled receptors (GPCRs) are critical targets through which antipsychotics exert their effects on cognitive function in schizophrenia. While the identification of enriched pathways such as neuroactive ligand-receptor interaction, calcium signaling, and cAMP signaling aligns with well-established biological mechanisms, this study refines these pathways by linking specific gene targets implicated in cognitive dysfunction in schizophrenia. Such integrative bioinformatics analyses enhance understanding of molecular interactions underlying cognitive deficits and provide a more precise molecular framework that connects antipsychotic pharmacodynamics with cognition-related genetic factors. This may facilitate the identification of candidate targets for future research aiming at developing therapies to address cognitive impairments in schizophrenia.

Data Availability Statement

Data will be made available on request.

DECLARATIONS

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Conflict of Interest

The authors declare no conflicts of interest related to this article.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, K.T., B.C., V.C., J.C.; Investigation, K.T.; Formal analysis, K.T., B.C., V.C.; Visualization and writing-original draft, B.C., J.C.; Writing-review and editing, B.C., J.C.; Supervision, B.C., V.C., V.S., J.C. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

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