Network-Assisted Investigation of Antipsychotic Drugs and Their Targets

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Antipsychotic drugs are tranquilizing psychiatric medications primarily used in the treatment of schizophrenia and similar severe mental disorders. So far, most of these drugs have been discovered without knowing much on the molecular mechanisms of their actions. The available large amount of pharmacogenetics, pharmacometabolomics, and pharmacoproteomics data for many drugs makes it possible to systematically explore the molecular mechanisms underlying drug actions. In this study, we applied a unique network-based approach to investigate antipsychotic drugs and their targets. We first retrieved 43 antipsychotic drugs, 42 unique target genes, and 46 adverse drug interactions from the DrugBank database and then generated a drug–gene network and a drug–drug interaction network. Through drug–gene network analysis, we found that seven atypical antipsychotic drugs tended to form two clusters that could be defined by drugs with different target receptor profiles. In the drug–drug interaction network, we found that three drugs (zuclopenthixol, ziprasidone, and thiothixene) tended to have more adverse drug interactions than others, while clozapine had fewer adverse drug interactions. This investigation indicated that these antipsychotics might have different molecular mechanisms underlying the drug actions. This pilot network-assisted investigation of antipsychotics demonstrates that network-based analysis is useful for uncovering the molecular actions of antipsychotics.

Introduction. – Antipsychotics are tranquilizing psychiatric medications primarily used in the treatment of schizophrenia and similar severe mental disorders [1]. Although antipsychotics are efficient in the treatment of schizophrenia and related disorders, they have a range of adverse side effects, of which the most common side effects include extrapyramidal symptoms (EPS), sedation, and weight gain [1–3]. These adverse side effects cause a major hindrance of concordance among antipsychotics. In the past decade, through numerous studies at multiple levels, a number of important advances have been made in our understanding of the molecular mechanism underlying these drugs' actions. These studies are in the genetics [4][5], molecular biology [6–8], and neuroreceptor imaging [9–11] areas. Additionally, recent genetic studies have indicated that the etiology of central nervous system (CNS) disorders like schizophrenia involves many genes interacting with each other or with environmental risk factors, but each of which contributes a small-risk on its own [12–19]. The polygenic theory suggests that the most effective medications should interact with several molecular targets, not just one target [20][21]. Therefore, we hypothesized that a network-based investigation of antipsychotics and their targets might provide us a

high level view of drugs' underlying mechanisms that otherwise would have been missed in typical single drug studies.

Recent network-based investigations in pharmacology provide one novel approach to facilitate efforts in drug discovery [22]. Advances in this area have led to the proposal of a new concept, 'network pharmacology' [23], as well as the application in multiple fields of pharmacology of numerous network-based studies such as target identification, prediction of side effects, and investigation of general patterns of drug actions [22–24]. In pharmacology networks, nodes can be drugs, targets, diseases, and proteins connected by physical interactions found in literature, and edges represent direct physical interactions, activation, inhabitation, coregulation, or any other relationship between the nodes. Analysis of these networks has been demonstrated to greatly increase our understanding of the mechanisms underlying drug actions [24] and identify novel drug targets [25][26]. Although these studies provide good illustrations for network pharmacology, one major problem is the lack of a complete and error-free set of antipsychotics and their targets. This issue has been largely eased thanks to a comprehensive and publicly available database, DrugBank, which is a unique bioinformatics and cheminformatics resource with comprehensive drug target information [27–29]. Although the data collected in DrugBank are still incomplete or not error-free, they offer us an opportunity to study multiple drugs and their targets at one time, so that the molecular mechanism underlying an antipsychotics' action can be explored at the systems level.

In this study, we performed a systematic investigation of antipsychotics at the network level. We first retrieved 43 antipsychotic drugs from DrugBank (version 3.0) [27], and then we extracted their targets and adverse drug interactions from DrugBank as well. After mapping target proteins to genes and filtering redundancy of these interactions, we generated drug–gene and drug–drug networks. Finally, we explored how strongly these antipsychotic drugs and/or target genes interact within the drug–gene or drug–drug network, respectively. This network-assisted investigation provides us with novel insights into the relationships among antipsychotics and/or targets, which may provide valuable information for further understanding antipsychotics and the development of more effective drugs.

Results and Discussion. – *An Overview of 43 Antipsychotic Drugs, Their Targets, and Interactions.* We retrieved 43 antipsychotic drugs by searching the keyword 'antipsychotic' in the field of 'Category' from DrugBank (version 3.0) and then manually checked them before the follow-up analyses. The details of the 43 drugs, including DrugBank IDs, their names, approval status by at least one country, number of targets, and number of drugs having adverse drug interactions with them are compiled in *Table 1*. Of the 43 antipsychotic drugs, most have been used to treat schizophrenia and related psychotic disorders' symptoms based on indications defined by DrugBank.

These drugs have 41 proteins as targets in the format of UniProtKB IDs [30]. After mapping the UniProtKB IDs to NCBI gene symbols, we obtained 42 unique human genes as target genes. Among these, 30 belong to G-protein coupled receptors, including adrenergic receptors, cholinergic receptors, dopamine receptors, glutamate receptors, histamine receptors, and serotonin receptors. To further assess the function

Table 1. *Summary of Antipsychotic Drugs and Their Targets and Interaction Drugs*

DrugBank ID	Name	Status	No. of targets	No. of interaction drugs
DB01614	Acepromazine	Approved	6	2
DB01063	Acetophenazine[a])	Approved	2	15
DB06288	Amisulpride[a])	Approved	4	0
DB01238	Aripiprazole[a])	Approved	25	12
DB00767	Benzquinamide[a])	Approved	6	0
DB01038	Carphenazine[a])	Approved	3	0
DB01178	Chlormezanone	Approved, withdrawn	1	0
DB00477	Chlorpromazine[a])	Approved	6	49
DB01239	Chlorprothixene[a])	Approved	12	4
DB00363	Clozapine[a])	Approved	26	55
DB00298	Dapiprazole	Approved	3	1
DB00450	Droperidol	Approved	2	22
DB01463	Fencamfamine[a])	Illicit, approved, withdrawn	1	0
DB00875	Flupenthixol[a])	Approved	5	18
DB00623	Fluphenazine[a])	Approved	3	28
DB04842	Fluspirilene[a])	Approved	3	0
DB00502	Haloperidol[a])	Approved	5	56
DB00408	Loxapine[a])	Approved	4	18
DB00933	Mesoridazine[a])	Approved	2	73
DB01403	Methotrimeprazine[a])	Approved	19	46
DB01618	Molindone[a])	Approved	4	7
DB00334	Olanzapine[a])	Approved	25	10
DB00904	Ondansetron	Approved	5	0
DB01267	Paliperidone[a])	Approved	14	12
DB00850	Perphenazine[a])	Approved	3	31
DB01100	Pimozide[a])	Approved	4	45
DB01621	Pipotiazine[a])	Approved	4	6
DB00433	Prochlorperazine[a])	Approved	1	29
DB00420	Promazine[a])	Approved	14	15
DB01608	Propericiazine[a])	Approved	3	18
DB01224	Quetiapine[a])	Approved	26	27
DB00409	Remoxipride[a])	Approved, withdrawn	5	0
DB00206	Reserpine	Approved	1	24
DB00734	Risperidone[a])	Approved	14	25
DB06144	Sertindole[a])	Approved, withdrawn	8	2
DB00391	Sulpiride[a])	Approved	2	0
DB01622	Thioproperazine[a])	Approved	6	3
DB00679	Thioridazine[a])	Approved	6	85
DB01623	Thiothixene[a])	Approved	3	93
DB00831	Trifluoperazine[a])	Approved	6	30
DB00508	Triflupromazine[a])	Approved	5	15
DB00246	Ziprasidone[a])	Approved	25	93
DB01624	Zuclopenthixol[a])	Approved	6	101

[a]) These drugs have been used in the treatment of schizophrenia and related psychotic disorders based on DrugBank indication annotation.

of these genes, we conducted pathway-enrichment analyses through WebGestalt [31] and Ingenuity Pathway Analysis (IPA, *Ingenuity System Inc.*, USA). We found five KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways and six IPA canonical pathways significantly enriched in these 42 genes (*Benjamini–Hochberg* [32] adjusted p value $< 1.0 \times 10^{-5}$; *Table 2*). As expected, among the 42 genes, 31 belong to the pathway 'neuroactive ligand–receptor interaction', which is the top pathway among the significant pathways (adjusted p value: 8.84×10^{-62}). Furthermore, serotonin receptor-signaling and dopamine receptor-signaling pathways existed in the enriched pathways, which confirmed that serotonin and dopamine receptors play important roles in the efficacy of antipsychotic drugs [9][33–35]. Among these targets, 36 have been reported to be associated with psychological disorders such as schizophrenia and bipolar disorder according to Ingenuity Systems Biological Functions, indicating that mutations of these target genes are critical in the affinity and potency of antipsychotic drugs [4][36].

Table 2. *Pathways Enriched in the Target Genes of Antipsychotic Drugs*

Pathway	No. of genes	Adjusted p value[a])
Neuroactive ligand–receptor interaction[b])	31	8.84×10^{-62}
G-Protein coupled receptor signaling[c])	29	1.26×10^{-33}
cAMP-Mediated signaling[c])	22	2.51×10^{-30}
Serotonin receptor signaling[c])	12	3.98×10^{-23}
Dopamine receptor signaling[c])	8	1.00×10^{-10}
Calcium signaling pathway[b])	18	1.17×10^{-8}
Gap junction[b])	5	6.31×10^{-8}
Regulation of actin cytoskeleton[b])	5	3.71×10^{-6}
AMPK Signaling[c])	6	7.08×10^{-6}
Vascular smooth muscle contraction[b])	4	7.35×10^{-6}
Cardiac hypertrophy signaling[c])	7	8.13×10^{-6}

[a]) Adjusted p values were estimated by *Benjamini–Hochberg* method [32] for multiple testing between drug target genes and whole genome genes. [b]) Enriched pathways identified by WebGestalt using the KEGG database. [c]) Enriched pathways identified by Ingenuity Pathway Analysis (IPA).

Among 43 drugs, 34 have been reported previously with interactions, totaling 999 unique interactions with 212 other drugs. These interactions were compiled from several public drug-related databases and textbooks based on the adverse side effects that occur when two of the drugs were administered together [27]. To examine the characteristics of these drug classifications, we grouped these drugs by using Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc_ddd_index/). ATC System divides the active drugs into different groups according to the organ or system on which they act, and/or their therapeutic and chemical characteristics at five different levels and 14 main groups at the first level. Here, we used the first level to examine the classification of all drugs in the interactions (246 drugs). According to the number of drugs in each group, the CNS system was the top group, which included 93 drugs (37.8%) from the total of 246 drugs. The cardiovascular system was ranked as the second group and included 30 drugs (12.2%).

Additionally, systemic anti-infectives was the third ranking group and included 28 drugs (11.4%). These observations indicate that most antipsychotics tend to cause side effects with drugs belonging to these groups.

An Antipsychotic Drug–Gene Interaction Network. We constructed a drug–gene interaction network in which a drug and a target gene are connected to each other, if the protein encoded by the gene is a known target of the drug. The drug–gene interaction network consists of 85 nodes (43 antipsychotic drugs and 42 target genes) and 336 edges (*Fig. 1*). For drugs, the average number of their targets is 7.8, and for target genes, the average number of targeting drugs is 8.0. The number of genes targeted by antipsychotic drugs ranges from 1 to 26, indicating a wide range (*Table 1*).

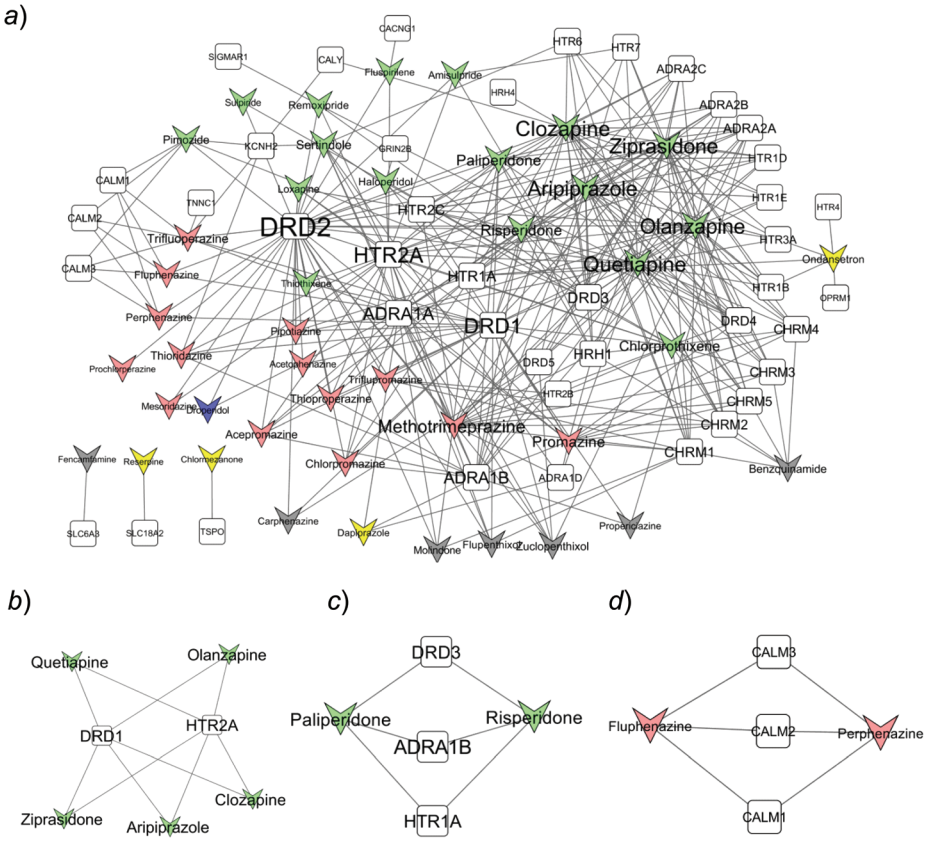

Fig. 1. *Drug–gene network.* a) *Drug–gene global network.* b)–d) *Drug–gene subnetworks generated by software MCODE.* The nodes with *Vee* shapes represent drugs, and the nodes with rounded rectangles represent target genes. The size of each node is proportional to its connectivity: for drugs, the number of target genes; for target genes, the number of targeting drugs. Drug groups are annotated by Anatomical Therapeutic Chemical (ATC) classification system and they are labeled by following color code. *Red:* antipsychotic drugs derived from phenothiazine. *Green:* antipsychotic drugs derived from non-phenothiazine. *Blue:* anesthetics drugs. *Yellow:* other types of drugs in ATC system. *Grey:* drugs without ATC code.

Among them, ten drugs have more than ten targets: clozapine (26 target genes), quetiapine (26), aripiprazole (25), olanzapine (25), ziprasidone (25), methotrimeprazine (19), paliperidone (14), promazine (14), risperidone (14), and chlorprothixene (12). Among the 42 targets, ten genes have more than ten drugs targeting them: *DRD2* (36 drugs), *HTR2A* (26), *DRD1* (26), *ADRA1B* (16), *DRD3* (14), *HTR1A* (13), *HTR2C* (12), *HRH1* (12), and *CHRM1* (12).

These 43 drugs could be organized in five groups according to drug classification at the fourth level in the ATC system: 14 antipsychotic drugs derived from phenothiazine, 17 antipsychotic drugs derived from non-phenothiazine, one anesthetics drug, four other drug types, and seven drugs without ATC codes. *Fig. 1* showes that five types of drugs could be roughly separated from each other based on their targets. Applying the MCODE clustering algorithm implemented in Cytoscape [37][38], we could identify three subnetworks. The first one included five antipsychotic drugs (aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone), the second one included two antipsychotic drugs (risperidone and paliperidone), and the last one included two drugs (fluphenazine and perphenazine). All the drugs in clusters 1 and 2 belong to the class of atypical antipsychotic drugs. Generally, antipsychotic drugs are classified into first-generation antipsychotics (FGAs; typical or conventional antipsychotics) and secondary-generation antipsychotics (SGAs; atypical antipsychotics) [2][39][40]. They are different because the SGAs have important advantages over FGAs, such as better efficacy for positive and negative symptoms, mood symptoms, improved tolerability, and apparent reduction of the risk of extrapyramidal side effects (EPSEs) [41]. We extracted all targets of these drugs to construct an atypical antipsychotic drug subnetwork (*Fig. 2*). The five drugs (aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone) in the first cluster are mainly connected with four types of receptors (adrenergic receptors, cholinergic receptors, dopamine receptors, and serotonin receptors), while the two drugs (risperidone and paliperidone) in the second cluster mainly have connections with adrenergic receptors, dopamine receptors, and specific serotonin receptors. This observation might suggest different mechanisms of drug actions between these two clusters. Additionally, compared to other drugs, clozapine has two unique target genes, *CALY* and *HRH4*. Gene *CALY* encodes a calcyon neurospecific vesicular protein, which does not belong to any receptors mentioned above. This gene has been consistently observed to be up-regulated in brains from schizophrenic patients [42][43]. *CALY* has also been reported to be associated with attention-deficit hyperactivity disorder [44]. Furthermore, thr protein encoded by *CALY* has been reported to have interaction with DRD1, a common target of antipsychotic drugs [45]. Taking all of this information into account, *CALY* might play a critical role in the mechanism of action of clozapine. For *HRH4*, no report has been found on its association with antipsychotics or schizophrenia based on our PubMed literature searches.

An Antipsychotic Drug–Drug Association Network. To obtain a general view of the adverse drug interactions that occur between antipsychotic drugs, we collected the adverse drug interactions from DrugBank only among these antipsychotics. From the 43 drugs, 17 have been reported to have 46 unique adverse drug interactions. This means that some of these drugs, when taken together, could cause multiple adverse effect events. The observed number, 46, accounts for 33.8% of all possible pairs (136 =

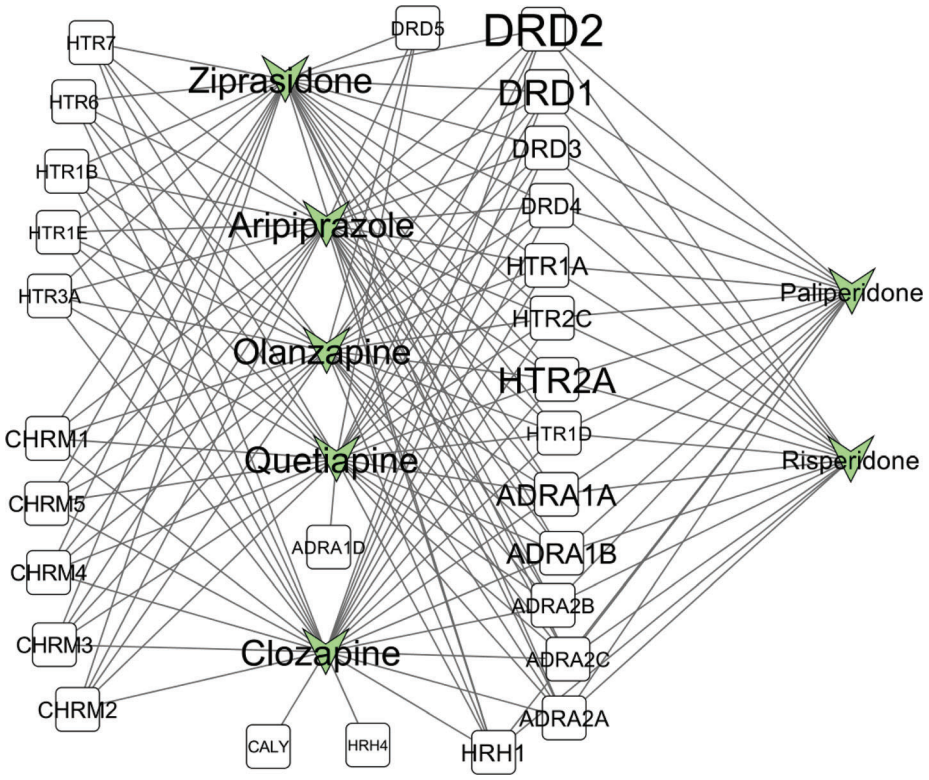

Fig. 2. *Network of seven atypical antipsychotic drugs and their target genes.* Definition of colors and shapes for nodes is the same as in *Fig. 1*.

$17 \cdot 16/2$), indicating that these antipsychotic drugs are more likely to have adverse drug interactions. This speculation is consistent with previous results [46][47].

We constructed a drug–drug interaction network by assigning these adverse drug interactions as edges and drugs as nodes (*Fig. 3*). The average connectivity (number of linked drugs) of this network is 5.4. Among the 17 drugs, three (zuclopenthixol, ziprasidone, and thiothixene) have more interactions than other drugs. Their connectivities are 13, 13, and 12, respectively. This observation suggests that these three drugs should not be administered with other drugs at the same time. Interestingly, clozapine has only one interaction – it interacts with haloperidol.

Among the 46 adverse drug interactions, 41 are related to cardiovascular diseases. In the psychiatric research community, the association between cardiovascular events and antipsychotics has been investigated for a long time. The results of these investigations indicated that patients with schizophrenia have a higher prevalence of a cardiovascular disease than the general population [48–50]. Interestingly, gene *CMYA5*, which encodes cardiomyopathy-associated 5, was recently found to be significantly associated with schizophrenia based on a meta-analysis of 23 replication samples, one of largest efforts on meta-analysis of schizophrenia risk genes or markers [51].

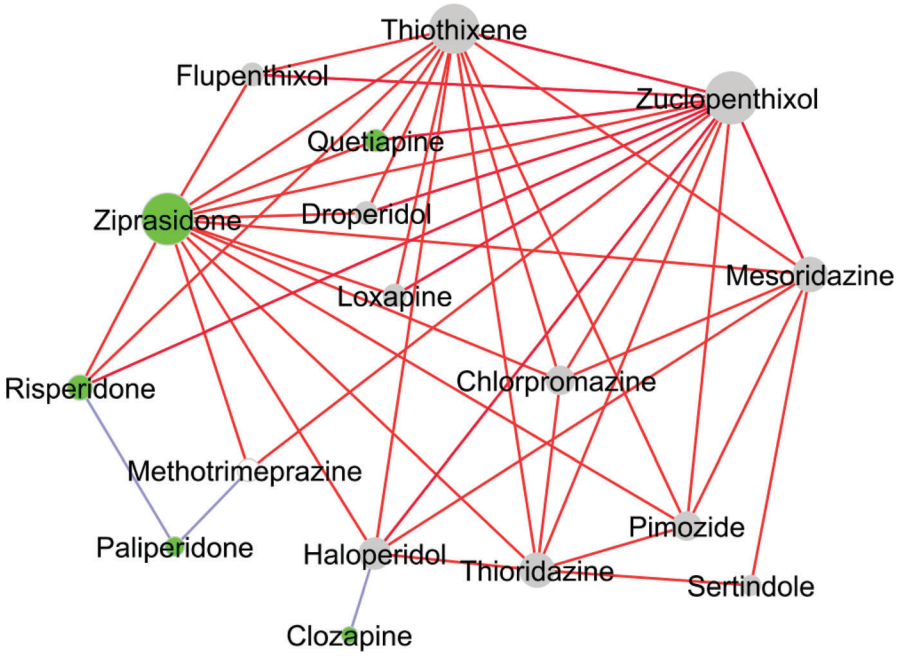

Fig. 3. *Antipsychotic drug–drug interaction network*. In this network, each node represents one antipsychotic drug, and each edge represents the co-occurrence of two drugs in one adverse-effect event. Nodes in *green* correspond to atypical antipsychotic drugs, and nodes in *grey* correspond to other antipsychotic drugs. Edge colors represent different types of adverse side effects: *blue* is for the side effect related to the central nervous system (CNS), and *red* is for the side effect related to heart disease risk.

Conclusions. – In this study, we collected and annotated 43 antipsychotic drugs, 42 targets, and 46 adverse drug interactions from DrugBank. We hypothesized that a network-based investigation of these drugs may provide important insights for understanding the actions of these drugs and for generating results for future validation. We tested this hypothesis by examining target functional and network features, including pathway-enrichment tests, drug–gene and drug–drug network analysis. The enrichment test results consistently indicated that antipsychotics' targets are over-represented in G-protein coupled receptors and neurotransmitter systems. In our network analysis, we found that antipsychotic drugs tend to cluster together based on the ATC classifications. Of specific note, atypical drugs cluster together strongly. We also found that the drug clozapine has two unique targets, CLAY and HRH4, which might provide novel clues for further investigation of molecular mechanisms of this drug. Our analysis supports the scenario that antipsychotic consumption is related to cardiovascular disease. Overall, these results indicated that the network-based method is effective, and biological processes of antipsychotics might be involved in many pathways and diseases.

We acknowledge the financial support of this project from a *2009 NARSAD Maltz Investigator Award* to *Z. Z.* and a *2010 NARSAD Young Investigator Award* to *J. S.*

Experimental Part

Antipsychotic Drugs, Target Genes, and Adverse Drug Interactions. The DrugBank database (http://www.drugbank.ca/) is a unique bioinformatics and cheminformatics resource that provides detailed biochemical specifications and target information for each drug [27–29]. It is one of the most comprehensive drug databases, and offers an opportunity to study drugs and their targets at the systems level. To identify the drugs related to psychoses, we collected drugs whose categories include keywords 'antipsychotic' on June 2011. Accordingly, we retrieved 43 specific drugs, each of which was checked manually before we retrieved other drug relation information.

Most of drug entries in the database contain targets, which can include a protein, macromolecule, nucleic acid, or small molecule to which a given drug binds, resulting in an alteration of the normal function of the bound molecule and a desirable therapeutic effect. Drug targets are mostly the common proteins such as enzymes, ion channels, and receptors. In this study, we focused on proteins because we can investigate their interactions too. A target gene is defined as a gene that encodes for a protein to which a given drug binds. We first extracted the UniProtKB ID number from DrugBank for each of the corresponding targets identified above into a text file and then mapped them to a gene ID through ID Mapping in UniProt database (http://www.uniprot.org/).

DrugBank also provides adverse drug interaction information mainly based on known adverse side effects which occur when two or more drugs are taken together. These interactions are compiled through a variety of web and textbook resources and checked by an accredited pharmacist, and thus this compilation represents the most complete publicly accessible collection of its kind (DrugBank, 2008). In this study, we mainly extracted these interactions occurred between antipsychotic drugs.

Pathway-Enrichment Analysis of Drug Target Genes. To gain overall insight of functional characteristics of these drug targets, we performed pathway-enrichment analyses using WebGestalt [31] and Ingenuity Pathway Analysis (IPA). After we obtained drug target genes, we imported them into WebGestalt for KEGG pathway analysis or Ingenuity Systems for core analysis. These analyses are applied to identify the enriched pathways within the given gene set by comparing them to the whole human genome through statistical test application. WebGestalt analysis implemented the hypergeometric test while IPA used *Fisher*'s exact test. To reduce the type I errors, we applied *Benjamini–Hochberg* method (1995) to adjust *p* values for multiple testing [32].

Network Analysis and Visualization. In this work, we constructed two major networks: drug–gene network and drug–drug network. The first network consists of the antipsychotic drugs and their target genes, which was generated by compiling the relationship between drugs and their targets. The drug–drug interaction network was generated by compiling the drug pairs with adverse effect events. For the purpose of simplifying the two networks, we only checked the node connectivity (the number of edges linked to a given node), which is the network's most elementary characteristic [52]. To generate tightly connected subnetworks, we used software MCODE [37] with the default parameters implemented in software Cytoscape (version 2.8) [38]. All networks were visualized using Cytoscape (version 2.8).

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Received September 15, 2011