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A computational network analysis based on targets of antipsychotic agents

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ABSTRACT

Currently, numerous antipsychotic agents have been developed in the area of pharmacological treatment of schizophrenia. However, the molecular mechanism underlying multi targets of antipsychotics were yet to be explored. In this study we performed a computational network analysis based on targets of antipsychotic agents. We retrieved a total of 96 targets from 56 antipsychotic agents. By expression enrichment analysis, we identified that the expressions of antipsychotic target genes were significantly enriched in liver, brain, blood and corpus striatum. By protein-protein interaction (PPI) network analysis, a PPI network with 77 significantly interconnected target genes was generated. By historeceptomics analysis, significant brain region specific target-drug interactions were identified in targets of dopamine receptors (*DRD1*-Olanzapine in caudate nucleus and pons (P-value < 0.005), *DRD2*-Bifeprunox in caudate nucleus and pituitary (P-value < 0.0005), *DRD4*-Loxapine in Pineal (P-value < 0.00001)) and 5-hydroxytryptamine receptor (*HTR2A*-Risperidone in occipital lobe, prefrontal cortex and subthalamic nucleus (P-value < 0.0001)). By pathway grouped network analysis, 34 significant pathways were identified and significantly grouped into 6 sub networks related with drug metabolism, Calcium signaling, GABA receptors, dopamine receptors, Bile secretion and Gap junction. Our results may provide biological explanation for antipsychotic targets and insights for molecular mechanism of antipsychotic agents.

1. Introduction

During the past half century, numerous antipsychotic agents were developed and dramatic growth of research in the area of pharmacological treatment of schizophrenia has advanced our understanding of the neurobiology and neuropharmacology of the illness (Miyamoto et al., 2012). Meanwhile, genetic studies demonstrated a polygenic risk of psychiatric disorders such as schizophrenia, indicating a multi-gene effect on genetic basis of these diseases (Purcell et al., 2009), (Purcell et al., 2014), thus suggesting multi targets for the pharmacological treatment of schizophrenia (Stahl, 2009).

Recent network-based investigations in pharmacology provide a novel approach to facilitate drug discovery (Arrell and Terzic, 2010). Analyses of these networks had been demonstrated to be able to greatly advance our understanding of the mechanisms underlying drug actions (Berger and Iyengar, 2009) and identify novel drug targets (Hwang et al., 2008). Previous studies had revealed adverse drug interactions in the course of schizophrenia treatment *via* this approach (Sun et al., 2013). During these years, antipsychotic agents have been designed based on a variety of targets. However, whether these targets would biologically interact in the perspective of system biology, as well as the molecular mechanism underlying multi targets of antipsychotics were yet to be explored.

In this study, we performed a computational network analysis based on targets of antipsychotic agents. Our results from expression enrichment analysis, PPI based network analysis, historeceptomics analysis and pathway grouped network analysis may provide a biological explanation for antipsychotic targets and insights for molecular mechanism of antipsychotic agents.

2. Materials and methods

2.1. Identification of antipsychotic targets

To obtain target genes of antipsychotic agents, we searched Drugbank database (Version 5.0) (http://www.drugbank.ca/) with the searching term "antipsychotic agents". As Drugbank was a

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bioinformatics and cheminformatics resource that provided detailed biochemical specifications and target information for each drug, we collected information including the antipsychotic agents, Drugbank ID, target genes and target type in our study.

2.2. Expression enrichment analysis of antipsychotic targets

As psychiatry disorders are associated with abnormal brain functions, the expression condition of antipsychotic target genes in brain tissues is worthy of investigation. Therefore, to detect whether antipsychotic target genes were expressed in brain tissues, we performed expression enrichment analysis of target genes in different tissues by DAVID (Huang da et al., 2009a), (Huang da et al., 2009b), the P-value of enrichment was calculated by Fisher's Exact test, with P-value < 0.05 as significance.

2.3. Construction and analysis of protein-protein interaction (PPI) network of antipsychotic targets

To investigate whether antipsychotic targets were biologically interacted with each other, we constructed a PPI network by using of protein–protein interaction data from STRING (Search Tool for the Retrieval of Interacting Genes) v10 database (Szklarczyk et al., 2015), which provided data of protein-protein interactions with high-confidence from varied sources based on their neighborhood, gene fusions, co-occurrence, co-expression, experiments, curated databases and literature mining. Target genes of antipsychotic agents were considered as the nodes of PPI network, and known interactions from co-expression, experiments and curated databases were selected to construct the PPI network. To evaluate whether target genes in PPI networks were significantly connected, we calculated edge-count probabilities in random graphs with given degrees (Pradines et al., 2005). Shortly, for a PPI network with N nodes, the number of edges (protein-protein interactions) in this network X_N was considered as a Poisson–Binomial variable. Then the significance of our PPI network was then assessed by calculating the significance of observed edge-count compared with expected edge-count, with P-value of 0.05 as the threshold of significance.

The network was then analyzed based on topological parameters including betweenness centrality (BC) and node degree using a Cytoscape plug-in called "Network Analyzer" (Assenov et al., 2008). Nodes carrying high degrees (>10) and betweenness centrality (BC > 0.1) were considered as nodes that were densely interconnected with others, indicating these genes might play significant roles in network (Nair et al., 2014). The final network was visualized by Cytoscape software (Version 3.1.1) based on these parameters wherein we mapped the node degree to the node color and betweenness centrality to the node size in the network view.

2.4. Historeceptomics analysis

To evaluate whether targets identified from network analysis could significantly interacted with related antipsychotic drugs in central nervous system, the top five targets with the largest number of interacted antipsychotic drugs in Table 1, as well as top targets with prioritized parameters in the PPI network were analyzed by a historeceptomics approach (Shmelkov et al., 2015). First, drug-target bioactivity data of *in vitro* binding affinities of a drug to a target protein was obtained from ChEMBL (https://www.ebi.ac.uk/chembl/). For each target, we compared the binding affinities (displayed as *Ki* (nm)) of its interacted antipsychotic drugs and obtained the drug with the highest affinity. Second, tissue-specific gene expression data were obtained through the BioGPS web tool (http://biogps.org/), using the data set 'GeneAtlas U133A, gcrma', which included a genome-wide expression data in 77 different tissues of human. The expression level of each target gene in each tissue was obtained and normalized into "Z-value". Then, we integrated drug-target bioactivity data (displayed in *Ki*) and tissue-specific gene expression data (displayed in Z-value), and calculated drug-specific-tissue-target scores (historeceptomics score, H-score) as H-score $= -\log_{10} Ki \times$ Z-value. To identify targets with significant historeceptomics scores, we performed the generalized extreme Studentized deviate test.

2.5. Pathway grouped network analysis of antipsychotic targets

To investigate whether antipsychotic targets were enriched in functional pathways, we performed pathway enrichment analysis. Information from Kyoto encyclopedia of genes and genomes (KEGG) database (Ogata et al., 1999) was used to annotate related pathways. The pathway enrichment test was based on hypergeometric test, the P-value was corrected by Benjamini–Hochberg methods and the significance was set as 0.05.

To investigate whether identified pathways were biologically interconnected, we constructed a pathway grouped network of antipsychotic targets by using a Cytoscape plug-in called "ClueGO" (Bindea et al., 2009). The relationship between pathways was defined based on their shared genes and calculated by chance corrected kappa statistics. Then the created network represented the pathways as nodes which were linked based on a predefined kappa score level. In our pathway grouped network analysis, we set the kappa score level as "0.3" as ClueGo referenced. The group P-value was determined by hypergeometric test, the P-value was corrected by Benjamini–Hochberg methods and the significance was set as 0.05. The final network was visualized by Cytoscape software (Version 3.1.1).

3. Results

3.1. Identification of antipsychotic targets

After searching in DrugBank, we retrieved a total of 56 antipsychotic agents, which are used to treat schizophrenia and related psychotic disorders, the details of these drugs including drug name, drug ID, target genes were displayed in Table S1. Then a total of 96 target genes were obtained from 51 antipsychotic agents (there were 5 antipsychotic agents without any target identified), details of target genes including gene name, gene title, target type and numbers of interacted antipsychotic agents were displayed in Table 1. In the target list, *DRD2*, *HTR2A*, *DRD1*, *CYP2D6*, and *ADRA1A* were top five targets interacted with the largest number of antipsychotic agents.

3.2. Expression enrichment analysis of antipsychotic targets

By expression enrichment analysis, we identified the expression of antipsychotic target genes were significantly enriched in four tissues: liver tissue with 21 target genes involved (P-value = 1.90E−03), brain tissue with 53 target genes involved (P-value = 2.92E−03), blood with 9 target genes involved (P-value = 1.71E−02) and corpus striatum with 2 target genes involved (P-value = 2.45E−02). Results of expression enrichment analysis were shown in Table 2.

3.3. Construction and analysis of protein-protein interaction (PPI) network of antipsychotic targets

By using 96 target genes as nodes and investigating high-confidence PPIs from the STRING databases, a PPI network with 77 interconnected target genes was generated. This PPI network was shown in Fig. 1. To evaluate whether genes in PPI networks were significantly connected, by statistical analysis, we found the observed number of network edges (protein-protein interactions) was significantly larger than random chance (366 edges *vs.* 46 edges, P-value < 1.00E−20), indicating target genes in the PPI network were closely interconnected, rather than randomly interacted with each other.

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