

A comparative study on psychiatric disorders: Identification of shared pathways and common agents

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Abstract— Distinct but closely related diseases generally present shared symptoms, which address possible overlaps among their pathogenic mechanisms. Identification of significantly impacted shared pathways and other common agents are expected to elucidate etiology of these disorders and to help design better intervention strategies. In this research effort, we studied six psychiatric disorders including schizophrenia (SCZ), anorexia (AN), bipolar disorder (BD), depressive disorder (DD), autism (AU) and attention deficit hyperactivity disorder (ADHD). Our methodology can be classified into the following two parts: In Part I, common susceptibility genes; and in Part II, genome-wide association studies (GWAS) data were used to find enriched pathways of psychiatric disorders. 59 KEGG pathways were commonly identified in both parts. 31 of these pathways are disease pathways. Pathways related to cancer and infectious diseases were predominant compared to others. Most of the acquired pathways were in accordance with previous studies in literature. A combination of susceptibility genes and GWAS data is an effective approach to identify significantly impacted pathways in multifactorial diseases. In this respect, shared modules were determined after applying hierarchical clustering of the enriched pathways. These identified modules may tell us the association of psychiatric disorders with the enriched pathways. Taken all together, common pathways and shared modules are expected to highlight the causative factors and important mechanisms behind complex psychiatric diseases, leading to effective drug discovery.

Keywords—psychiatric disorders, shared pathways, functional enrichment, pathway clustering

I. INTRODUCTION

Psychiatric disorders are incomprehensible morbidities in medicine and generally characterized by a combination of atypical perceptions, thoughts, moods, behaviour and relation with others. They are considered as one of the main contributors in global disease burden [1]. Despite their recognition for many decades and well-documentation of their impact on public health, the etiology of these disorders is largely unknown and classification of them is based on their symptoms and ongoing signs. However, there is significant evidence that these disorders have strong heritability, and a substantial proportion of this heritability has been shown to be due to shared genetic variants [2]. Also, it was suggested that explicit evidence of common genetic risk at individual loci exists among these disorders [3].

Further progress should be made in order to elucidate the factors and identify the biological mechanisms and pathways

underlying these disorders. However, studies focusing on single disorders are challenged and not very effective in many cases, especially regarding multi-factorial diseases [4,5], one of which is psychiatric disorders. Multiple targets or pathways should be taken into consideration to get successful treatment outcomes.

There are phenotypic overlaps in the pathogenic mechanisms underlying different psychiatric disorders (for example, between bipolar disorder and ADHD [6], and between autism and schizophrenia [7]). Compared to studying diseases individually, identification and analysis of common pathways across multiple related disorders could be a much more powerful approach to determine their pathogenic processes. Once the common pathogenic processes are well understood, novel insights into the etiology of diseases could be provided and more effective drug combinations and treatment strategies can be discovered.

Differentially expressed genes (DEG) and genome-wide association studies (GWAS) are generally used to focus on a single disease; however, for multifactorial diseases, their shared pathways and common factors should be considered. In this study, we propose a comparative approach where **Part I** is based on the method proposed in [8] using susceptibility genes of multiple diseases (Figure 1). In **Part II**, PANOGA [9] is performed on GWAS data of these diseases (Figure 2). This two-step approach is applied across the six psychiatric disorders: schizophrenia (SCZ), anorexia (AN), bipolar disorder (BD), depressive disorder (DD), autism (AU) and attention deficit hyperactivity disorder (ADHD). In Part I, susceptibility genes for these disorders were collected from online public databases. The common susceptibility genes among these disorders were determined and subsequently, their neighbouring genes with significant connectivity were obtained utilizing DIAMOnD algorithm [10]. Together with the common susceptibility genes, neighbouring genes in the human protein-protein interaction network (PPI), called as (CNN), were extracted and put into pathway enrichment analysis to identify pathways related with psychiatric disorders. Enriched pathways were clustered and common modules were acquired from clusters. In Part II, subnetworks for each disease were obtained and subsequently pathway enrichment analysis were performed for each subnetwork group. Common pathways were obtained and then the same steps as in Part I were applied. Both results from two sections

were compared and analyzed to elucidate the factors and mechanisms behind these disorders.

II. MATERIALS AND METHODS

Protein-protein interaction network (PPI) was acquired from supporting information of [10] and interactions belonging to other species were removed. Our extensive protein-protein interaction network comprises 13,450 human genes and 141,280 edges (interactions).

The susceptibility genes for all diseases were collected from DisGeNET. This public data source is one of the wide and comprehensive databases that store human gene-disease associations available at present [11]. After fetching related records, we determined 411, 182, 572, 850, 1031 and 1954 unique susceptibility genes for ADHD, AN, AU, BD, DD and SCZ, respectively. GWAS data for psychiatric disorders were provided by [12], where GWAS data produced for 37 different traits were analyzed by grouping related diseases.

A. Part I: Pathway Identification Using Susceptibility Genes

In this Part, we followed the method proposed in [8] via modifying the first neighbours extracting step with DIAMOnD algorithm. Firstly, we found the intersection of gene sets for six psychiatric disorders and defined it as the common susceptibility genes of related diseases. These common genes were in turn fed into the DIAMOnD algorithm as seed genes. Genes in close association with common susceptibility genes in terms of connectivity were detected in the PPI by setting the maximum number of added nodes to 1000 in the algorithm. Next, all interactions including common susceptibility genes and/or genes closely related with them were extracted from PPI and the network comprising common genes and genes in close association with them constituted Common gene Neighbour Network (CNN) including 982 genes.

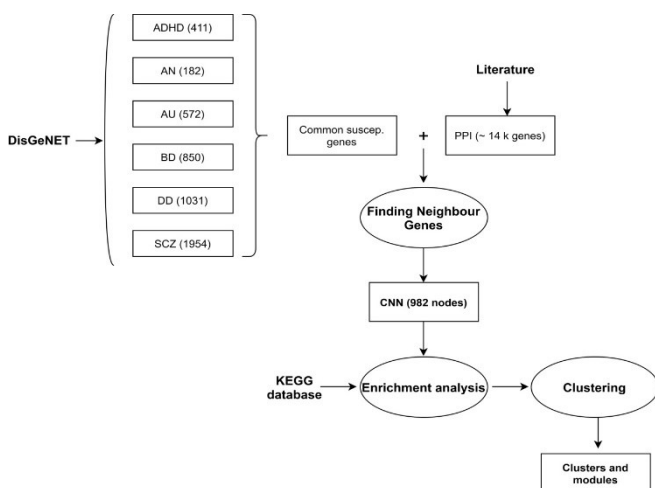


Figure 1. Workflow of the approach in Part I

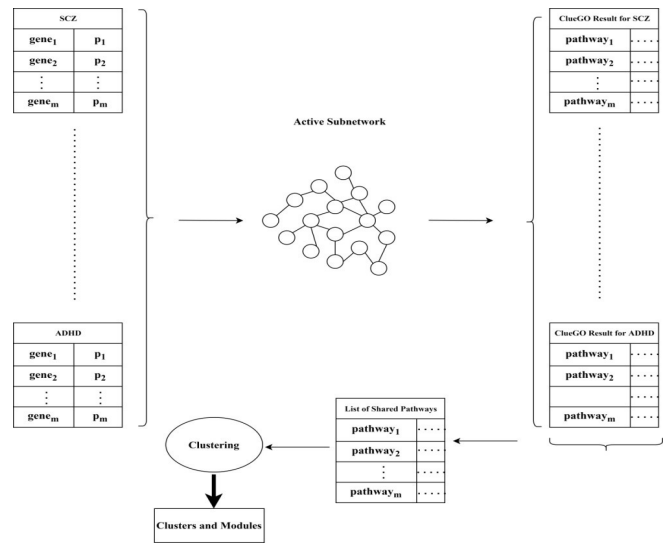


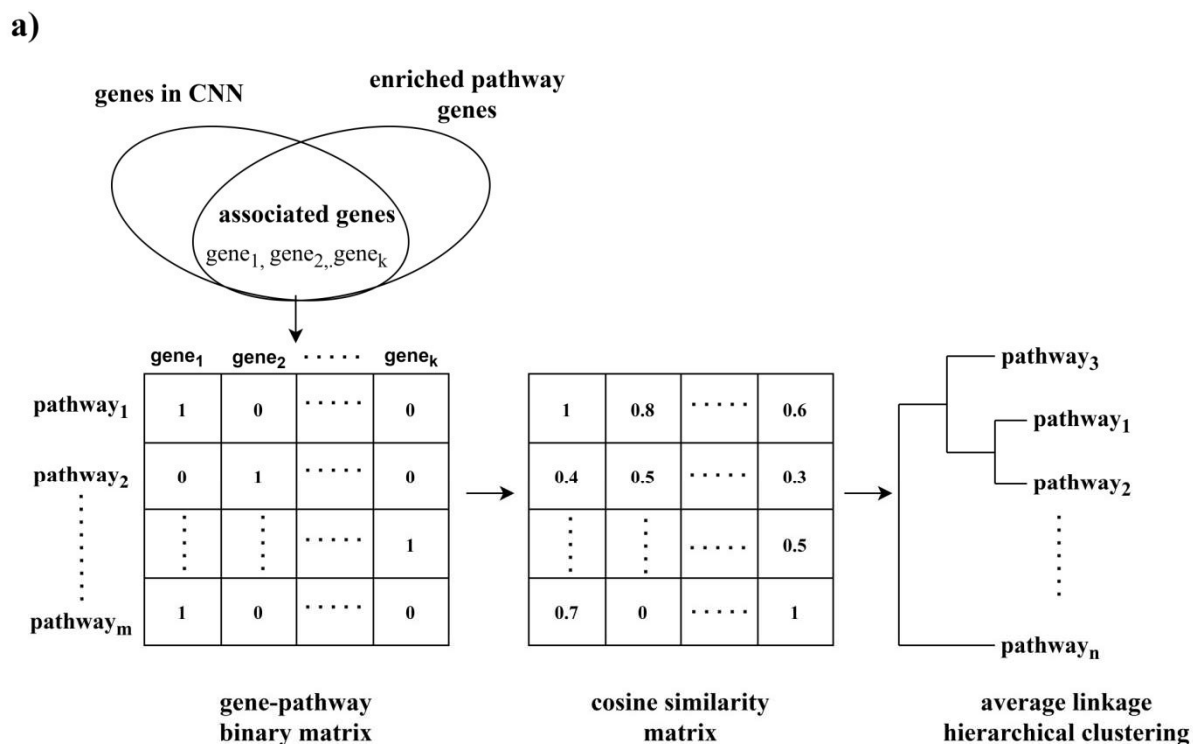
Figure 2. Workflow of the technique in Part II

CNN consists of the common susceptibility genes and their closely related neighbouring genes in PPI. Pathway enrichment with genes in CNN possibly gives shared pathways of psychiatric disorders. We utilized ClueGO v2.5.6 [13] to perform KEGG [14] pathway enrichment analysis for all distinct genes in CNN. ClueGO is a Cytoscape [15] application that can be used to find enriched pathways for a given list of genes. As for statistical choices, two-sided hypergeometric test (enrichment/depletion) was applied and p-values were corrected using Bonferroni correction [16]. Pathways with corrected p-value < 0.05 were considered associated biological pathways with CNN genes and reserved for further analysis.

Genes in enriched pathways and CNN genes were intersected to obtain **associated genes** available in both gene sets. Then, a binary matrix of pathway-associated gene was formed in which a value of 0 in a cell in the matrix indicates the absence of the gene of interest and a value of 1 shows the presence of related gene in the respective pathway. A cosine similarity matrix of pathways was derived using this binary matrix. Next, pathways were clustered as groups by applying average-linkage hierarchical clustering method (Figure 3a). Common associated genes in each pathway cluster were identified and then matched to CNN to get their connected subnetwork, called shared module (Figure 3b). Both clustering result and acquired modules in this method were compared and analyzed with clustering and module results obtained in Part II, which is discussed next.

B. Part II: Pathway Identification Using GWAS Data

GWAS data enabled us to have gene-p values peculiar to each psychiatric disorder. We took advantage of network-oriented steps of PANOGA to determine active subnetworks for each disease using PPI and GWAS data. jActiveModules [17], another Cytoscape plugin, was applied to uncover active subnetworks in PPI specific to each disease. An active subnetwork is actually a subnetwork in a PPI including genes,



b)

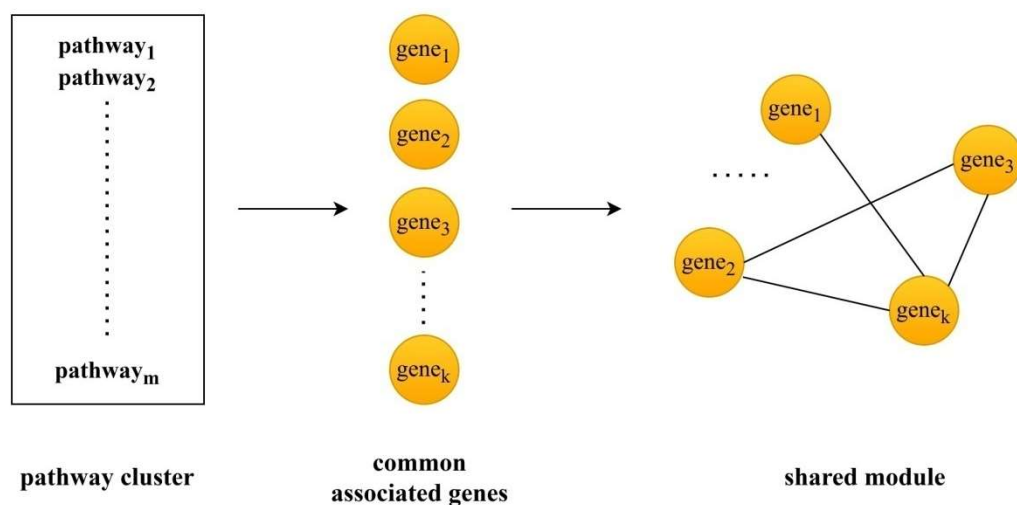


Figure 3. Pathway clustering and module determination

most of which are associated with a disease [18]. These subnetworks were then inputted into ClueGO to find enriched pathways and next shared pathways among psychiatric disorders were identified. Our final pathway list contained shared pathways whose corresponding genes were unified in the end (Figure 2).

Genes in CNN were intersected with shared pathway genes so associated genes for GWAS data were identified. Following steps are identical to Part I where a

binary matrix was created and a cosine similarity matrix based on this similarity matrix was constructed. Then shared pathways were clustered using hierarchical clustering approach. Subsequently, common associated genes were extracted from each shared pathway cluster and shared modules were found (Figure 3b).

III. RESULTS AND DISCUSSION

A. Affected Pathways

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