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

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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 feeded 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.

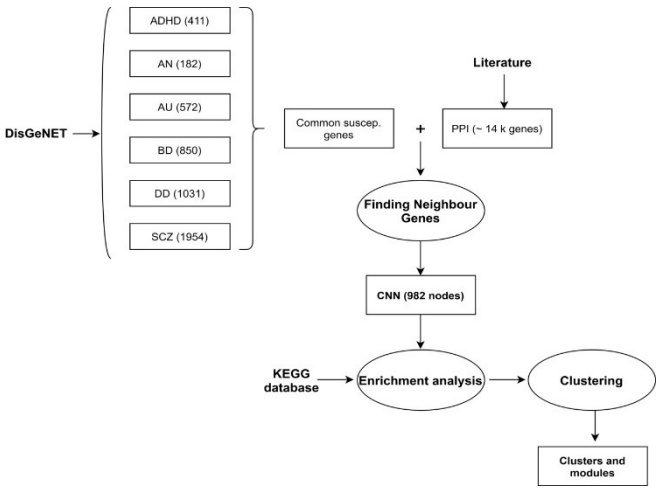

Figure 1. Workflow of the approach in Part I

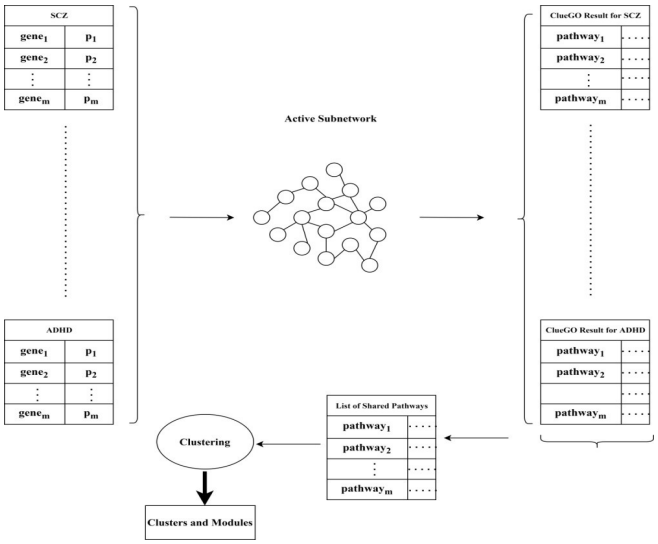

Figure 2. Workflow of the technique in Part II

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,

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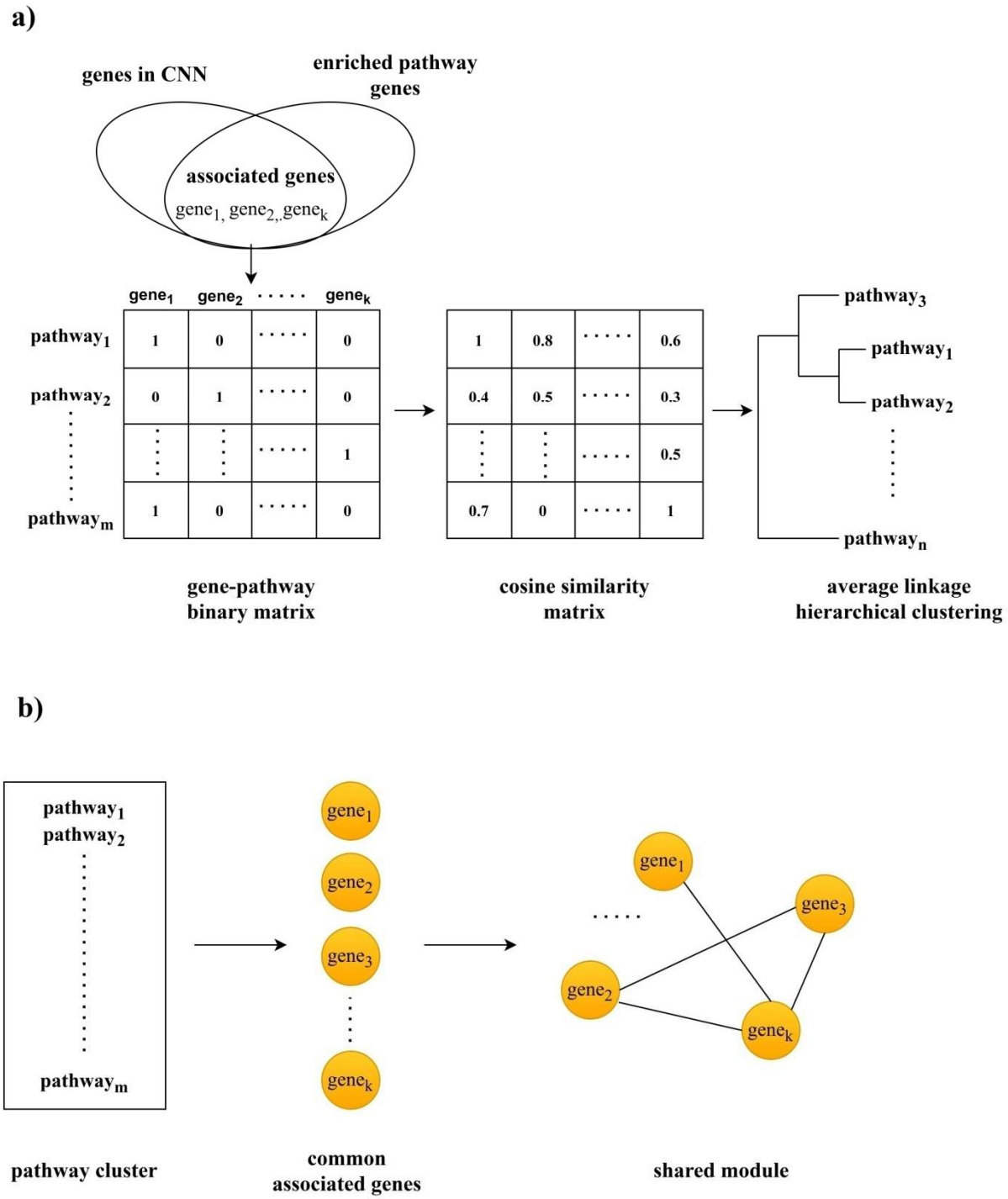

Figure 3. Pathway clustering and module determination

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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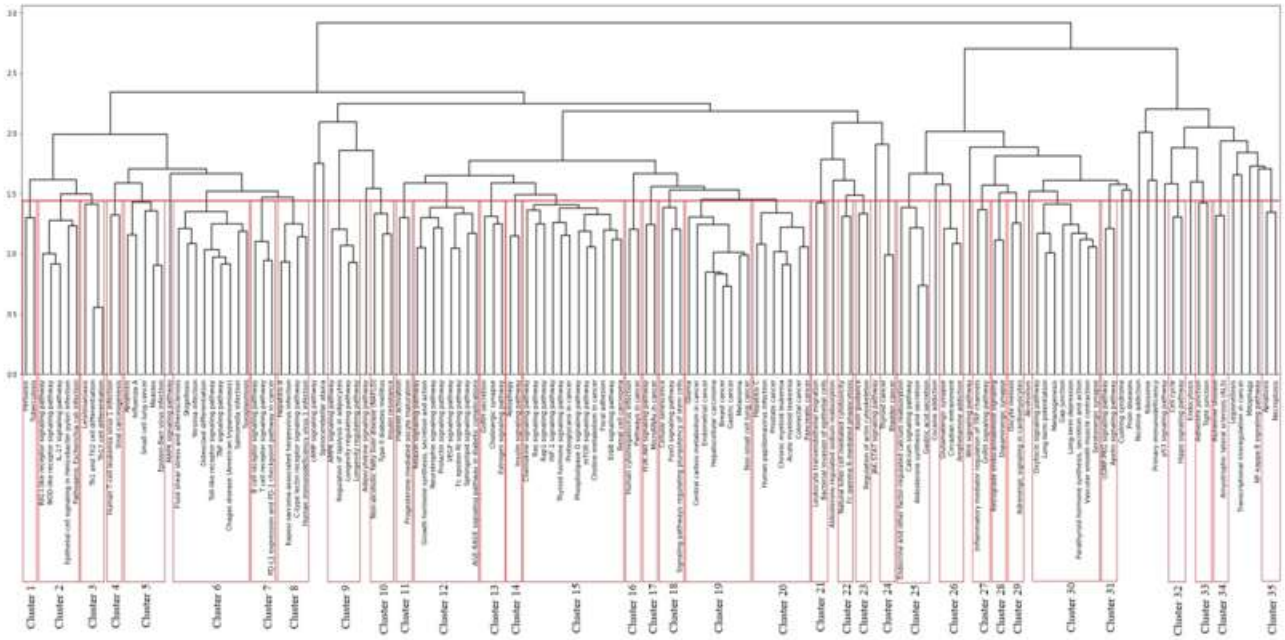

Figure 4. Hierarchical clustering result for Part I

We obtained 13 common susceptibility genes for SCZ, AN, BD, DD, AU and ADHD in Part I. The CNN, built in Part I, was used in Part II, too to take the intersection of it with shared pathways determined in Part II. Recorded number of enriched pathways, genes in enriched pathways and associated genes in both methods are shown in Table I.

Among two sections, we observed 59 common pathways, most of which are involved in formed clusters determined in Part II (thirteen pathways were excluded since they don't include any associated genes as mentioned in the next section). These common enriched pathways can be divided into two categories: functional pathways and disease pathways. 31 pathways were human disease pathways and related to five kind of human diseases: cancers, infectious diseases, neurodegenerative diseases, endocrine and metabolic diseases, and substance dependence. Among them, cancers and infectious diseases include the largest number of pathways (14 and 12, respectively). Actually, the fact that these two types of diseases come to the fore is not a surprising result. Psychiatric disorders were found to be involved in patients at different stages of cancer and cancer survivors [19-21]. It is also well established that multiple infectious diseases can provoke the development of psychiatric disorders and these disorders were often associated with physical illnesses [22]. Drugs used for treatment of infectious diseases, and serious infections such as HIV can lead to trigger miscellaneous psychiatric syndromes [23]. Studies suggest that neurodegenerative diseases and psychiatric disorders can be associated with each other and a recent study showed this correlation among patients with amyotrophic lateral sclerosis (ALS) and their families [24].

Section Name	No. Of. Enr. Pathways	No. Of. Enr. Pathway Genes	No. Of. Assoc. Genes
Part I	148	693	693
Part II	109	2873	601

Table I. Common items in both sections

The remaining 28 functional pathways were classified as: cell growth and death, cellular community – eukaryotes, development and regeneration, endocrine system, excretory system, immune system, nervous system, signal transduction, and translation. Many patients with psychiatric disorders involve immune dysfunction, immune abnormalities or inflammation in central nervous system [25]. Mentally ill were found to be more susceptible to dysregulation of their immune systems, especially patients with SCZ have been associated with an altered immune system [26]. Dysregulation of some endocrine systems, such as the thyroid system or the parathyroid system, can affect behaviours and some symptoms of psychiatric disorders are widespread in endocrinological disorders. The evidence for the correlation between endocrine dysfunctions and psychiatric disorders was presented earlier, which was generally result of the examination of hypothalamic-pituitary axis [27].

Although apoptosis is specifically related to neurodegenerative diseases, it is also associated with psychiatric diseases. Apoptosis, which is also referred to as programmed cell death, is a mechanism of cell death that occurs in a programmed fashion. This important biological phenomenon is a required part of body development, for nervous system in particular. Excess or loss of neurons, a consequent of abnormalities in apoptosis, is encountered symptoms for particular psychiatric disorders, too [28-29].

Many studies reported association of osteoporosis or osteopenia with SCZ [30-32] and BD [33-35] but quite recently, Cui et al. [36] suggested that there is no association with these disorders. This topic remains controversial and needs further study. Previous studies demonstrated that

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psychiatric disorders are related to focal adhesion [37], adherens junction [38] and gap junction [39-40].

B. Clustering of Affected Pathways

Pathway Analysis section showed that pathways could be associated with each other, such as neurodegenerative disease and nervous system. Searching the molecular connections between these pathways can enable us to define their relation with psychiatric disorders and this may make a major contribution to understanding the etiology of these disorders and to developing effective treatment strategies. We clustered enriched pathways found in both Part I and Part II to inquire the underlying connections among them. Output of hierarchical clustering for Part I is depicted in Figure 4 and 35 clusters were determined as shown. The shared modules were extracted from clusters and kept for analysis with modules in Part II. Hierarchical clustering has been performed in Part II in the same way and this time 21 clusters were identified. Shared modules from generated clusters were obtained similarly as in Part I. Thirteen pathways in Part II were found to involve no associated genes during clustering and therefore removed from analysis and weren't taken into consideration any more. It was realized that clusters 24, 28 and 34 from Part I were the same as clusters 7, 2 and 12 from Part II, respectively (clustering result in Part II is not shown due to space limitations). Shared modules, consisting of common associated genes within each cluster, were detached from clusters in Part I and Part II. These modules are, in fact, part of CNN because the associated genes were determined by intersecting CNN genes with genes in enriched pathways (Figure 3a). Extracted modules might be the core subnetworks in CNN and could give an idea about the relationship between pathways in a cluster and psychiatric disorders. Once the operating mechanism and interconnectivity of these modules with related pathways are unraveled, progress can be made in insight into pathological processes of psychiatric disorders.

The shared modules from two sections were compared and identical or similiar modules were noted. To illustrate with an example, Figure 6 shows a shared module found in both methods. Connections of genes within the module with common susceptibility genes were presented too. This common module was extracted from the cluster, a common cluster found in both sections, including Dopaminergic synapse and Retrograde endocannabinoid signaling. These two pathways are included in nervous system so dysregulation of common susceptibility genes may give rise to the dysfunction of the module and this might be a fundamental causative factor for the impairment of the nervous system in psychiatric patients. These shared modules, obtained and analyzed using common susceptibility genes and GWAS data, thus are worthy to be examined.

IV. CONCLUSION

Multifactorial diseases (also called complex diseases) are difficult to treat because they can be caused by a combination of genetic variations and environmental effects. In multifactorial diseases a certain variant on a gene may be concealed or confounded by other contributing factors but the combination of multiple variants with small effects can be the key contributing factor for the complex disease. Observable similarities between interrelated diseases imply potential overlaps in their underlying mechanisms. Delineating the common pathways and network modules for groups of closely related diseases can provide an in-depth insight into the etiologies or pathogenesis of these disorders. Elucidation of common factors for related diseases will also facilitate drug repositioning, which is related to determination of new indications from available drugs or of alternative uses for a newly identified drug.

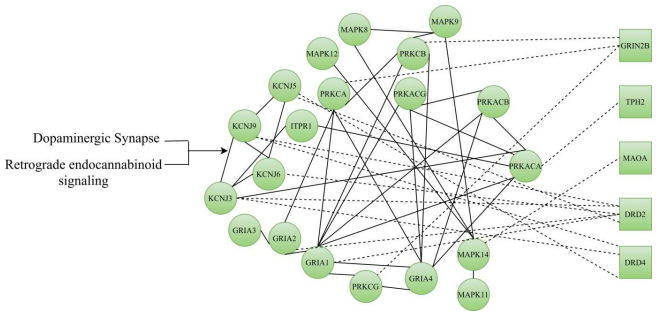

Figure 5. One common shared module

In this research effort, we have studied six psychiatric disorders including SCZ, AN, BD, DD, AU and ADHD. Our methodology consists of two parts which were named as Part I and Part II. Common susceptibility genes and GWAS data were used separately to find enriched pathways in Part I and Part II, respectively. Thirteen pathways were omitted from analysis in Part II since no associated genes were found within them. 59 KEGG pathways were commonly found in both methods. Those pathways were present in cancers, infectious diseases, neurodegenerative diseases, immune system, endocrine system, apoptosis, osteoclast differentiation, focal adhesion, adherens junction, and gap junction. Our findings agree with the previous studies and in literature enough evidence for the correlation of psychiatric disorders with aforesaid pathways is available. The methodology presented in this paper can be applied to any group of related complex diseases. Our comparative approach integrates both susceptibility genes and GWAS data for a specific disease and offers efficient results by obtaining common pathways and modules. Analyzing common pathways and modules using two different types of related data can help us gain a better understanding of intrinsic biological processes of multifactorial diseases.

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