TITLE

Altered expression of a unique set of genes reveals complex etiology of Schizophrenia

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Abstract

Purpose: The etiology of schizophrenia is extensively debated, and multiple factors have been contended to be involved. A panoramic view of the contributing factors in a genome-wide study can be an effective strategy to provide a comprehensive understanding of its causality.

Materials and Methods: GSE53987 dataset downloaded from GEO-database, which comprised mRNA expression data of post-mortem brain tissue across three regions from control and age-matched subjects of schizophrenia (N= Hippocampus (HIP): C-15, T-18, Prefrontal cortex (PFC): C-15, T-19, Associative striatum (STR): C-18, T-18). Bio-conductor 'affy' package used to compute mRNA expression, and further t-test applied to investigate differential gene expression. The functional and disease association analyses of the derived genes performed using PANTHER Classification System, GeneCards and NCBI database.

Results: A set of 40 genes showed significantly altered ($p<0.01$) expression across all three brain regions (38 protein coding, 2 noncoding). The functional analysis revealed, genes involved in maintaining basic housekeeping functions as catalysis (44.7%), binding (34.2%), and nucleic acid binding transcription factor activity (13.2%), transporter activity (10.50%), enzyme regulation (7.90%), and structural molecule activity (5.3%), and implicated in biological processes and events, and molecular pathways relating basic neuronal functions. The gene set found associated with neoplasm, inflammatory/immune cell, and immunodeficiency/virus-mediated, neurodegenerative and neurological, metabolic, and congenital diseases respectively.

Conclusions: The functional analysis of the gene set unravels gross components of the multi-factorial etiology of schizophrenia. The deviant expression of genes maintaining basic cell machinery explains compromised neuronal processing, and associated pathology may involve intricate mechanisms shared with various other diseases.

Keywords: Genome-wide expression study, Genetic signature, Etiology, Hippocampus, Associative striatum, Prefrontal cortex

Abbreviations: Schizophrenia (SCZ), Hippocampus (HIP), Associative striatum (STR), Prefrontal cortex (PFC), International Classification of Diseases (ICD)

1. Introduction

The etiology of Schizophrenia (SCZ) is extensively debated (Rubeša, Gudelj, & Kubinska, 2011; Tandon, Keshavan, & Nasrallah, 2008) and no single way appears enough to explain the causality of the disease. An uncertainty of the etiology has greatly impeded the treatment of the disease, and neither of the therapeutic approaches (Rubeša et al., 2011) is proving much helpful in halting its progression.

Many candidate genes have been reported (Gogos & Gerber, 2006) but none of them actually got validated in population-based studies for persistent association (Crow, 2008; Farrell et al., 2015). A disease signature derived from genome-wide expression patterns was highly desirable that would not only help to reach to accurate diagnosis of the disease but also in developing optimal therapeutic approaches aimed at maximum relief of the patients. Plentiful is now known on structural and functional changes in the brain in the schizophrenic patients but a comprehensive genome-wide exploration of its pathogenesis in the affected brain regions is still a leftover task.

1.1. SCZ pathology may be reflected in expression analysis of neural genes

SCZ has been noted to cause significant architectural changes in many brain regions, the hippocampal, prefrontal cortex, and basal nuclei regions have been chief among them (Kegeles et al., 2010; Manoach, 2003; Tamminga, Stan, & Wagner, 2010).

The architectural changes in the brain varied from the changes in the total size and volume of specific brain regions (Haijma et al., 2012; Ward, Friedman, Wise, & Schulz, 1996) to neural connection between different brain regions (Arnedo et al., 2015; Harrison, 1999; Stephan, Baldeweg, & Friston, 2006), pruning of dendritic spines (Glausier & Lewis, 2013) and synapses (Sekar et al., 2016; Whalley, 2016), synaptic dysfunction (Yin, Chen, Sathyamurthy, Xiong, & Mei, 2012), and also functional changes as oscillatory coupling (Uhlhaas & Singer, 2013) and neuronal firing patterns (Krabbe et al., 2015). Each SCZ brain may have a few or more of such architectural defects. The recent study by Sekar et al (2016) in mice models reported a variant allelic form of complement C4A (which is involved into the pruning of synapses) may cause excessive synaptic pruning in developing neural circuits and may put the individuals at risk of developing SCZ.

How the neural architectural changes are instructed by the changes in the neural genes has also been shown by some recent studies. Piskorowski et al (2016) have shown in the mouse model that deletion of 22q11 locus may involve the genes making synaptic proteins and that may produce SCZ like symptoms. Fromer and colleagues (2016) have identified over 100 of

genetic loci harbouring SCZ associated variants which together involve scores of genes supporting polygenic etiology of SCZ, and also altering the expression or knock down of some of such genes in animal or human stem cell models has shown to compromise neural functions effectively.

1.2. Genetic basis of SCZ: much is now known but connecting mechanism is missing

SCZ gives a life time risk of ~1 % and shows high heritability (~ 69-81%) (Lichtenstein et al., 2009; Sullivan, Kendler, & Neale, 2003; Wray & Gottesman, 2012). The SCZ heritability is derived from CNVs, SNPs, de novo mutations, and structural modifications at gene promoter regions without involving gene sequences as have been revealed in the genome-wide studies (Akbarian, 2010; Gejman, Sanders, & Duan, 2010; Kavanagh, Tansey, O'Donovan, & Owen, 2015; Rees, O'Donovan, & Owen, 2015). Plenty of CNVs and SNP variants have been reported till (Gejman, Sanders, & Duan, 2010) yet but none of these appear to be present as a constant association, and also none of them ensures a causal association or contributing alone significantly to the genetic liability for the disease. The de novo rare mutations and gene promoter region non-sequence involving changes are also not able to explain the high heritability of SCZ in isolation. Emerging evidence suggest the genetic etiology of SCZ may be deriving from accumulative effect of all such gene structure changes (Freedman et al., 2001; Fromer et al., 2016). But how these entire factors act together to produce an accumulative effect is little understood yet; there may be a possibility that they act through influencing expression of neuronal genes by altering gene promoter regions, which is technically permitted with all such genetic factors (Bray, 2008; Fromer et al., 2016). Evidence suggests, all the above said factors together may implicate thousands of the genes, an indication for the polygenic etiology of the SCZ (Freedman et al., 2001; Fromer et al., 2016; Gottesman & Shields, 1967; Purcell et al., 2014).

Contrary to the factors contributing to the heritability of SCZ which may show vertical transfer from the parents to offspring and infer susceptibility for the disease influencing the expression of neural genes, expression derangement of the genes may arise of the gene-environment interactions during foetal development and in the lifetime of the individuals (Akbarian, 2010; Caspi & Moffitt, 2006; Champagne, 2013). The gene expression changes resulting from environmental interactions theoretically may involve de novo mutations, and epigenetic modifications at the gene promoter sites (Akbarian, 2010; Kavanagh et al., 2015; Purcell et al., 2014).

The biological contribution to the disease etiology is ascertained by the adoption studies which showed that offspring of the diseased mothers although adopted by normal families, bear high risk for developing the disease (Ingraham & Kety, 2000). Conversely, an essential environmental contribution to the disease etiology is indicated by the findings in the twin-based studies that the siblings of the monozygotic twins who although share almost same genome but differ in heritability for SCZ (Dempster et al., 2011). A gene-environmental interaction necessary for the disease etiology was further indicated by the observation in the adoption studies that siblings of the mothers with schizophrenia showed more prevalence of the disease in harsher rearing conditions in adopter families in comparison to the controls whose original parents had no disease (Ingraham & Kety, 2000). But the extent of the contribution by each in gene-environment interactions may be varying with cases (considering numerous variables which may interact), and studies which may explain this precisely, are lacking.

Prenatal and perinatal environments have been also evidenced to influence initiation of the disease in the adult (Meli, Öttl, Paladini, & Cataldi, 2012). Prenatal maternal infections and psychological stress, and also obstetric conditions have been found to put permanent influence on the foetal brain and are considered risk factors for schizophrenia (Børglum et al., 2014; D Malaspina et al., 2008; Mittal, Ellman, & Cannon, 2008). Evidence supports the view that insults to the developing brain get hardwired which creates susceptibility for developing SCZ in adulthood if faced with stressful life conditions (Feigenson, Kusnecov, & Silverstein, 2014; Giovanoli et al., 2013; Mednick et al., 1998).

Furthermore, even the maternal depression or severe stress in perinatal and/or in childhood period have been found to raise chances of SCZ in the offspring during adulthood (Khashan et al., 2008; Mäki et al., 2010).

The ‘two-hit’ hypothesis for etiogenesis of SCZ (Feigenson et al., 2014; Giovanoli et al., 2013; Mednick et al., 1998) has got wide acceptance among scholars and now a ‘multiple hit’ hypothesis is also being suggested by some authors (Davis et al., 2016). Although a primary insult to the developing brain would be must, both of these hypotheses state that a second or successive environmental hit on the genetically or environmentally primed brain may be necessary for the genesis of SCZ. The ‘first hit’ probably decreases the threshold for the ‘second or subsequent hits’ and in this way primes brain susceptible for developing SCZ during adulthood. Literature evidence suggest that CNVs and SNPs, specific mutations and also intergenerational epigenetic influences create a primarily genetically susceptible brain which if gets further hit by adverse environmental conditions during adulthood, may be

leading to SCZ (Giusti-Rodríguez & Sullivan, 2013; Helbig, 2014; Rutten & Mill, 2009; Xu et al., 2011). Similarly, a significant environmental insult during development may also prime the brain for developing SCZ with further environmental hits (Giovanoli et al., 2013).

The challenging environmental conditions during pre and perinatal period (Bandelow et al., 2004; Feinberg, 1983; Meli et al., 2012), childhood rearing up, and adolescence which found associated with increased risk of SCZ, all may be involved in SCZ etiogenesis by influencing the expression of neuronal genes (Bray, 2008).

Social environmental conditions during adulthood like unemployment, urban living, geographical migration, and prolonged war have been also reported to be associated with increased chances of getting SCZ (Dean & Murray, 2005; Yaktin & Labban, 1992). The mediating mechanism for such social environment induced SCZ is not clear yet, but the logical conclusion from the available evidence indicate that underlying mechanism of social environment induced SCZ may be chronic psychological stress acting on the neural genes mediated by different complex biological methods as intergenic interactions (epistasis), epigenetic reprogramming, or microRNA (Brami-Cherrier et al., 2014; Caputo, Ciolfi, Macri, & Pizzuti, 2015; Tandon, Keshavan, & Nasrallah, 2008) or splicing quantitative trait loci (sQTLs) mediated regulations (Takata, Matsumoto, & Kato, 2017). The psychological stress may also have been mediating the increased chances of SCZ following personal issues as early life bereavement, social defeats (Khashan et al., 2008; Selten & Cantor-Graae, 2005; Selten, van der Ven, Rutten, & Cantor-Graae, 2013).

Whatever be the organizing mechanism, the resultant up and down regulation of the neuronal genes may be the chief etiological mechanism in SCZ (Bray, 2008). Plausibly, the dysregulation of the neuronal genes, especially which are involved in maintaining basic cell architecture and machinery, may compromise the information processing in neurons in affected brain regions which manifests as disorganized and deficient behaviour evident in SCZ (Hemby et al., 2002; Maycox et al., 2009).

1.3. Ontological and disease association analysis of altered neural genes may reflect SCZ etiology

Based on the mounting body of evidence (what we discussed above), we hypothesized that the altered expression of neuronal genes may be the connecting link between all genetic and environmental factors involved in the etiogenesis of SCZ, hence an ontological analysis of the genes showing altered expression in various brain regions may unravel the components of the complex etiology of SCZ. Although polygenic hence multifactorial etiology of the SCZ

is now a well accepted fact, the involved individual factors are still scarcely identified. This has been a visible lacuna in the literature, so we have targeted this in the present study. We have also tried to derive a genetic signature for SCZ which would comprise of significantly altered genes in most commonly affected brain regions and may be used for screening or monitoring of disease progression.

2. Materials & Methods

2.1. Data Resources

The mRNA expression data were retrieved from the GEO (Genome Expression Omnibus) (http://www.ncbi.nlm.nih.gov/geo/), a public repository for high-throughput microarray. The RNA was originally isolated from post-mortem brain tissue across three specific regions (Hippocampus (HIP), Prefrontal cortex (PFC): Brodmann Area 46, and Associative striatum (STR)) of control {N=18 (HIP), 19 (PFC), 18(STR)} and age-matched subjects with schizophrenia {N=15 (HIP), 15 (PFC), 18 (STR)}. Equal numbers of male and female (except for odd number samples) diagnosed SCZ cases and controls of adult age (range 22-68 years). The controls were matched for the age and sex and were free of any neurological or psychiatric illness during their life course.

2.2. Data retrieval and analysis

The RNA was isolated from HIP, PFC (Brodmann Area 46), and associative STR and hybridized to U133_Plus2 Affymetrix chips for m-RNA expression study. Expression analysis of mRNA was done by using "affy" package (http://www.bioconductor.org/packages/release/bioc/html/affy.html), which was deposited at Bioconductor and developed in R statistical software program and scripting language. It used three steps to calculate the expression intensities: (i) background correction; (ii) normalization (data were normalized by RMA, subjected to pair wise comparison followed by Benjamini and Hochberg False Discovery rate correction (FDR)), and (iii) expression calculation. After calculation of mRNA expression intensity a simple unpaired two tailed t-test (significance set at $p \leq 0.01$) was applied to the data to filter out the set of genes expressed significantly in all three brain regions.

To categorize the derived significantly altered genes on the basis of their involvement in molecular functions, molecular pathways, and biological events, PANTHER (Protein ANalysis THrough Evolutionary Relationships) Classification System (http://www.pantherdb.org/) and NCBI gene database (http://www.ncbi.nlm.nih.gov/gene/)

were exploited. Further, gene-disease association analysis was done on the basis of GeneCards database (http://www.genecards.org/cgi-bin/listdiseasecards.pl), and marked diseases were classified using International Classification of Diseases (ICD) (http://www.who.int/classifications/icd/en/).

3. Results

A set of 40 genes (Protein coding-38; RNA-gene-2) was identified showing statistically significant ($p \leq 0.01$) altered mRNA expression in schizophrenic patients in the all three brain regions studied (Table 1). Interestingly, it was observed that most of the genes were down-regulated in all three brain regions (32/40). Also, the same genes in all three brain regions have shown the similar direction of expression changes.

These genes were classified into six categories on the basis of their molecular functions (Fig. 1). Further; the genes were classified into fourteen categories on the basis of involvement in biological processes and events (Table 2). However, some genes belong to more than one category.

Furthermore, in pathway linkage analysis, the gene set was found to link with 36 molecular pathways (Fig. 2) that broadly could be placed in seven categories based on their commonality (Table 3).

The gene-disease association analysis resulted in long list of various diseases associated with gene set which were further classified on the basis of International Classification of Diseases (ICD) in six categories (Fig. 3). Many of the diseases in a class had shown association with more than one genes so we took account of total number of hits pertaining to each class (outer ring, Fig. 3), and also the actual number of diseases in each class (inner ring, Fig. 3).

The highest number of hits and implicated diseases were obtained for the class Neoplasm (340/40) and the inflammatory/immune cell mediated diseases (149/40) followed by other classes (Immuno-deficiency diseases: 27/19, neurodegenerative diseases: 41/27, metabolic diseases: 20/15, congenital malformations (26/14) (Fig. 3).

4. Discussion

The structural and functional brain abnormalities have been repeatedly reported in patients with SCZ (Antonova et al., 2004). The brain regions chosen for this study are noted to be predominantly affected in SCZ (Kegeles et al., 2010; Manoach, 2003; Tamminga et al., 2010). Hence, the study of genome expression status in these brain regions was expected to

unravel mysterious disease etiology which may be conclusive in deciding suitable therapeutic strategies to the disease. Also, as none of the genes revealed in this study had been reported earlier as the candidate gene, the new set appeals for fresh attention for the etiology of SCZ.

4.1. Involvement of the gene set in molecular functions

The functional analysis of the gene-set (Fig. 1) elucidated the genes being involved in the regulation of basic machinery and housekeeping functions of the neurons viz. receptor-ligand binding (Muguruza et al., 2013), catalysis (Mabrouk et al., 2010), enzymatic regulation (Enriquez-Barreto & Morales, 2016), nucleic acid binding transcription factor activity (Boyajyan, Atshemyan, & Zakharyan, 2015), structural molecule activity (Föcking et al., 2015) and transport activities (Wiesel et al., 2002). It is well evident that dysregulation of all these basic functions of neurons will certainly manifest in compromised neuronal physiology and hence information processing which has been a hallmark of the progressed SCZ (Giersch et al., 2015). The molecular function analysis also showed the hierarchy of the functions compromised in SCZ (Fig. 1) (the catalysis and receptor-ligand binding being most affected functions), and that knowledge can be exploited in prioritizing therapeutic targets.

4.2. Involvement of the gene set in biological processes and events

The comprehensive influence of the dysregulation of these genes in pathogenesis of SCZ gets further clarified in the analysis for the involvement in the biological processes and cellular events (Table 2). The implication of genes involved in ubiquitination (Table 2a), enzyme activity (Table 2b) and energy production mechanisms (Table 2c) may point towards a generalized failure of the basic functions in neurons; as ubiquitination is known to regulate the diverse spectrum of cellular functions (Hershko & Ciechanover, 1998) and same should be true for the genes encoding enzymes , especially those necessary for mitochondrial functions (ATP5D, PDK4) (Bubber et al., 2004), regulating specific signalling pathways (MAPK9) (Enriquez-Barreto & Morales, 2016) and involved in phosphorylation (ATP5D, PDK4) or dephosphorylation (PPM1E) (Emamian, Karayiorgou, & Gogos, 2004; Vaughan, 2004). The dysregulation of genes involved in energy production (Table 2c) also confirms prevailed view in the literature that energy production mechanisms get compromised in SCZ (Prabakaran et al., 2004; Robicsek et al., 2013; Verge et al., 2011).

Again, down-regulation of genes which function as regulator of the cell growth mechanisms (Table 2d) explains reduced neuronal cell sizes, synaptic connection and brain volume in specific brain regions noted in schizophrenia (Rais et al., 2012; Ward et al., 1996) (Rais et al.,

2012; Ward et al., 1996), and significant upregulation of genes involved in the programmed death (Table 2e) may indicate pro-apoptotic mechanisms prevailing in particular brain regions in schizophrenia, and this inference also gets supported by some earlier studies (Jarskog, Glantz, Gilmore, & Lieberman, 2005; Jarskog, Selinger, Lieberman, & Gilmore, 2004; Rapoport, Addington, Frangou, & Psych, 2005) but that may not be a generalised feature in SCZ, as we also noted an evidence contrary to the claim also that an anti-apoptotic gene MCL-1 (Perciavalle et al., 2012) was found significantly upregulated in all three brain regions, but there is literature evidence that although MCL-1 is an anti-apoptotic gene, it regulates cell cycle negatively hence limiting the mitosis (Fujise, Zhang, Liu, & Yeh, 2000).

Also, the significantly altered expression of the genes involved in cytoplasmic vesicular transport and exocytosis (Table 2f), dynamic regulation of actin and tubulin cytoskeleton (Table 2g), and ion channel homeostasis (Table 2h) (Lidow, 2003), lipid-binding (PITPNA) and synthesis (CADPS) (Table 2i) may hint of compromised neuronal information processing in SCZ.

4.3. Involvement of the gene set in molecular pathways

In pathway linkage analysis (Fig. 2, Table 3), the category involving largest number of molecular pathways has been that of neurotransmitters /modulators and neurohormones (Table 3a) which fits with clinical manifestations of the disease and also gets support from existing theories that the etiology of SCZ majorly may be based on dysregulation of this category of molecules (Gill & Grace, 2016; Matthysse & Sugarman, 1978).

Various neurotransmitters based hypotheses have been proposed for the etiology of SCZ (Iqbal, Goldsamt, Wetzler, Schwartz, & Praag, 1993; Jentsch & Roth, 1999; Matthysse & Sugarman, 1978; Toda & Abi-Dargham, 2007; Wassef, Baker, & Kochan, 2003) but none of them are primarily explaining causality of the diseases. The result of this study (Fig. 3, Table 3) indicates that disease etiology is not implicating any single transmitter but many of them together, although literature gives evidence on involvement of the many transmitters or peptides in SCZ pathology independently, an evidence on group involvement is lacking, and an integrative study aimed at an unifying mechanism for involvement of more than one neurotransmitter and or modulators at a time, may be warranted (Bencherif, Stachowiak, Kucinski, & Lippiello, 2012). The misexpression of the genes for neurotransmitters and modulators may have the greatest impact on the synaptic transmission (Frankle, Lerma, & Laruelle, 2003; K. Mirnics, Middleton, Lewis, & Levitt, 2001) and oscillation coupling of the

neural wave bands (Carlén et al., 2012; McNally, McCarley, & Brown, 2013; Uhlhaas & Singer, 2010) hence consequently may compromise neural communications severely.

The linkage of the immune cell/chemokine mediated pathways (Table 3b) is strongly supported by literature (Jones, Mowry, Pender, & Greer, 2005; Müller & Schwarz, 2010; Reale et al., 2011). An immunogenic basis of SCZ etiogenesis had also been brought forward (Jones et al., 2005; Malavia et al., 2017) although counter to this hypothesis has also been placed which limits the role of immune function related genes as a solo or major factor in SCZ etiology (Pouget et al., 2016) (further discussed in subsections 4.5.2 and 4.6.3). Also, the involvement of growth, differentiation and survival of neurons in the specific brain regions (Table 3c) (A. S. Lee et al., 2016; Maschietto et al., 2015) (further discussed in subsection 4.2) and pathways related to apoptosis (Table 3d) (Jarskog et al., 2005, 2004; Lin et al., 2016) (also discussed in subsection 4.2), and related to protein synthesis (Table 3e) and degradation (Table 3f) (English et al., 2015; Rubio, Wood, Haroutunian, & Meador-Woodruff, 2013) has been well documented in the literature (also discussed in subsection 4.2). The linkage of FGF signalling pathway (Table 3c) under neuronal growth, differentiation and survival to SCZ etiology has been corroborated by a freshly published study by Narla et al (2017) who regarded it as a central pathway commanding all other pathways in developing brain strengthening the view that SCZ has a neurodevelopmental etiology.

The linking of the pathways involved in the pathogenesis of major neurodegenerative diseases (Table 3g) such as Alzheimer (Aoki, Mizuki, & Terashima, 2005; Horesh, Katsel, Haroutunian, & Domany, 2011), Parkinson (Nalls et al., 2014), and Huntington's disease (Boxall, Porteous, & Thomson, 2011; Tsuang, DiGiacomo, Lipe, & Bird, 1998) indicates neurodegenerative nature of SCZ and may help in understanding the disease pathogenesis as well as developing new drug targets (further discussed in 4.5.3).

4.4. Non-protein-coding genes: Unknown functions

The neuronal functions associated with 2 non-coding genes (LOC100507534, LOC100507534) couldn't be ascertained from the literature but it's interesting to find the significant alteration of these long non-coding RNAs in SCZ which has never been reported before. There are now strong indications that non-coding genes are implicated in SCZ pathology (Roussos et al., 2014; X. Xiao, Chang, & Li, 2017)

4.5. Association of the gene-set with diseases other than SCZ

Association of the gene-set with other diseases indicates the commonality of their pathogenic mechanisms with SCZ and also provides greater insight on its etiogenesis. Almost all classes of disease identified in this study have been extensively supported by the literature and ranking of the associated disease classes may be also indicating the dominance of the particular pathogenesis mechanism in SCZ (Neoplasms> Inflammatory/Immune cell mediated> Immunodeficiency> Neurodegenerative and neurological disorders> Metabolic diseases> Congenital malformations, Fig. 3).

4.5.1. Neoplasm

The unravelled association of the gene-set with neoplasm in gene-disease association study is unique, and gets further confirmed in individual appreciation of the genes. The genes for lymphoma (BCL6, NCBI Gene ID: 604) and acute leukemia (MCL-1, NCBI Gene ID: 4170) or causing risk of both (ANPEP, NCBI Gene ID: 290) were found significantly altered in SCZ (Table 1). The BCL6, MCL-1 and ANPEP are also known to be implicated in many other cancers (Akgul, 2009; Sørensen et al., 2013; Walker et al., 2015). A specific gene for the breast cancer (SAFB2, NCBI Gene ID: 9667, lost in 20% of the breast cancer cases (Oesterreich, 2003), and also few genes which are associated with specific functions in the body and depleted in various tumors/cancers as genes specific for chondrogenesis (CHSY1, NCBI Gene ID: 22856) (Fernandes, 2014; Kalathas et al., 2010) and connective tissue formation (HAPLN1, NCBI Gene ID: 1404) (Ivanova et al., 2009; Sim, Hu, & Viapiano, 2009) were also found significantly altered in SCZ (Table 1).

Certain genes in our reported list are involved in DNA repair (Table 2j), m-RNA transcription (Table 2k), post-transcriptional gene modifications (Table 2l), protein translation (Table 2m), and cell cycle regulation (Table 2n), and involvement of these biological processes and cellular events also can be well marked in cancers. Thus, altered expressions of these genes present strong evidence in favour of the logic that basic molecular repertory and regulatory mechanisms involved in schizophrenia and neoplasm may be common.

4.5.2. Inflammatory/immune cell mediated and immunodeficiency diseases

The genes linked with various acute and chronic inflammatory diseases (Kirkpatrick & Miller, 2013; Malavia et al., 2017; Müller, Myint, & Schwarz, 2012) (Fig. 3) hint for an inflammatory component involved in pathogenesis of SCZ (Hope et al., 2011; Kirkpatrick & Miller, 2013; Saetre et al., 2007). Many reports have been found implicating inflammation as a culprit in the development of SCZ (Kirkpatrick & Miller, 2013; Saetre et al., 2007; Trépanier, Hopperton, Mizrahi, Mechawar, & Bazinet, 2016). It's possible that a persistent state of neuroinflammation could be working as a trigger for the genesis of the disease (Trépanier et al., 2016). The dysregulation of lymphoblastic (BCL6) and myelocytic lineage (MCL-1) in SCZ revealed in this study provides a reason for the association of the gene- set with immunodeficiency diseases (Fig. 3). Few other genes indicated in study were also found associated with specific immunodeficiency diseases (SAMD5-HIV) or viral infections (CXADR-coxsackie or group C adenoviruses) making the claim stronger, and various reports from the literature also supported increased susceptibility for immunodeficiency diseases in SCZ (Carey, Carey, & Kalichman, 1997; Cournos, McKinnon, & Sullivan, 2005; Seeman, Lang, & Rector, 1990).

4.5.3. Neuro-degenerative/neurological diseases and congenital malformations

This had been a long time puzzle (Dolores Malaspina, 2006) that schizophrenia is a pure neurodevelopmental (Narla et al., 2017; Rapoport et al., 2005) disease or neurodegenerative disorder (Christopoulos, Massouri, Fotopoulos, & Hamogeorgakis, 2006; Lieberman, 1999), although advocacy in favour of neurodevelopmental etiology is getting upper hand with fresh research (also discussed in subsection 4.3) (Narla et al., 2017), evidence has been presented in favour of both (Pino et al., 2014), and our study also comes to support this notion (Fig. 2). The evident association of the gene set with neurodegenerative diseases and congenital malformations indicates neurodegenerative as well as neurodevelopmental mechanisms operating in SCZ. The involvement of molecular pathways related to brain development and neurogenesis (Table 3c) and neurodegeneration (Table 3g) unravelled in our study supports a mixed etiology of SCZ. A mixed hypothesis which describes a neurodevelopmental genesis of the disease, and also explains associated neurodegenerative changes as an essential consequence in the later course of the disease, could be more justifying for the pathological basis of SCZ (Ashe, Berry, & Boulton, 2001; Lieberman, 1999).

4.5.4. Metabolic diseases

A range of metabolic problems (McEvoy et al., 2013; Xiaolin Xiao et al., 2011) have been reported to be linked with SCZ, and the gene expression studies are also available to support alteration of the various metabolic pathways in SCZ (Middleton, Mirnics, Pierri, Lewis, & Levitt, 2002; Károly Mirnics, Middleton, Marquez, Lewis, & Levitt, 2000; Narayan, Head, Gilmartin, Dean, & Thomas, 2009). The set of genes identified in this study showed direct association with different metabolic diseases and syndromes (Fig. 3) which warranted for a metabolic derangement in the disease. Such metabolic derangement arises as a by product of SCZ or inducing genesis of the disease itself, further needs to be investigated.

4.6. Further insights

4.6.1. Massive protein derangement

The set revealed in this study mostly contained protein-coding genes (38 out of 40), and their significantly altered expression provides a clue for massive derangement of the proteome in schizophrenia which has been also suggested by a proteome-based study (Palmowski et al., 2014). After all, protein based etiology of SCZ still remains conflicting whether it is the derangement of protein production that gives rise to symptoms of schizophrenia or an upset of the proteome is a by product of the disease process itself. A recent study has indicted abnormal metabolism of some proneural proteins involved in formation of synapses as a probable etiological factor in SCZ (D'Rozario et al., 2016).

4.6.2. Evidence for associated male infertility in schizophrenia

Two of the altered genes, SOX9 and SPAG7 (Table 1), are known to regulate selective germ cell development, and spermatogenesis which may be an explanation for the associated infertility in male SCZ patients (Bundy, Stahl, & MacCabe, 2011; Haukka, Suvisaari, & Lönnqvist, 2003). Also, the implication of gonadotrophin releasing hormone (GNRH) pathway (Table 3a) with the gene set provides a reason for the associated infertility in SCZ (Cantalamessa et al., 1985) The noted linking of the schizophrenia with sex-selective genes, and also to the fertility regulating pathway are unique findings, to our knowledge never noticed before hence deserves curious attention. Although abnormal response to exogenous GNRH administration is known in acute SCZ. However, an elevated secretion of prolactin which is a GNRH suppressor has also been noted in SCZ which may be an usual side effect of many anti-psychotic drugs (Halbreich, Kinon, Gilmore, & Kahn, 2003).

4.6.3. Immune genes may be crucial but not a major contributor to SCZ etiology

The increasing number of studies has advocated an immune basis of SCZ (Hope et al., 2011; Jenkins, 2013; Jones et al., 2005; Müller & Schwarz, 2010). The recent study by Sekar et al (2016) implicated variant allelic form of complement C4A, and also an association of the major histocompatibility complex (MHC) to SCZ etiology has been successively supported by many studies (Mokhtari & Lachman, 2016; Walters et al., 2013). A recent large-scale genome-wide study has implicated genes involved in immunological regulation to SCZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Very recently, Malavia et al (2017) reported 8 genes related to extended human leukocyte antigen (HLA) region expressed inversely in SCZ and rheumatoid arthritis, a severe inflammatory disease of autoimmune origin, suggesting shared pathology between the two diseases. Contrary to these, another recent study has identified only limited enrichment of immune function related genes in SCZ when has been compared to five autoimmune diseases, and bears a view that rather than a solo immune basis, SCZ etiology may be incorporating pleiotropic effects (variants of a single nucleotide polymorphism that would influence more than one phenotypic traits) of a small number of immune genes that also regulate brain development and plasticity (Pouget et al., 2016). Our study has also noted contribution of immune genes (BCL6, MCL1, SAMD5, CXADR, Table.1, also discussed in subsection 4.5.2) to SCZ etiology along with many other contributory factors.

4.6.4. Genetic basis of schizophrenia: indications from this study

Although great heritability (Freedman et al., 2001; Tsuang et al., 1998) accounted for SCZ which advocates a predominantly genetic determination of its etiology, it's still too much difficult to ascertain the exact genetic basis for it. In fact, a longitudinal germ line transfer of the disease has never been proved. Even known mutations (Freedman et al., 2001) or SNPs and CNVs (Need et al., 2009) are not sure enough to cause SCZ, and the currently prevailed view on etiology of the disease suggests, it is polygenic and hence multifactorial (Purcell et al., 2014) in origin (accumulates small effects of many genes), and carries remarkable influence of epigenetic mechanisms (Akbarian, 2010; Deng, Sobell, & Knowles, 2010; S.-A. Lee & Huang, 2016) in disease pathogenesis which can induce the disease in the individuals who were genetically susceptible to it. Role of epigenetics in etiology of SCZ

gets a small hint in our study also (histone acetyltransferase gene KAT5, NCBI Gene ID: 10524, Table 2l).

Our study confirms the view that SCZ etiology is polygenic and multifactorial, and also identifies the probable contributory factors (Fig. 1, Table 2). Although, this study has implicated the genes representing many ontological categories as we discussed above, neither of the category has been large enough to contain more than few genes, which suggests a multifactorial etiology of SCZ where all factors will add some effects rather than being a solo actor. Further, how the change in genomic architecture is translated in to the behavioural features of SCZ can be explained by the altered expression of the genes related to specific neuronal functions (further elaborated in subsection 4.6.5).

4.6.5. Detuning of the normal neuronal gene expression may be etiomechanism of SCZ

Massive gene expression changes in three important regions of the brain which regulate different cognitive and stereotype functions (Kegeles et al., 2010; Manoach, 2003; Tamminga et al., 2010) indicate that SCZ may be arising from interactions of all such individual genetic changes hence consequent accumulated effect on neural functions of the affected brain regions. As we discussed above, the ontological analysis of the gene set in our study provides the basis for comprehensive loss of neural functions in SCZ. An altered neural functionary of these brain regions which are nodal points for the neural network involved in neurocognitive functions plausibly may manifest in SCZ like symptoms. It seems that normalized expressions of these genes are necessary for optimum neural functioning and detuning of their expressions is reflected in characteristic disorganization of the behavior marked by the disease. Further, how detuning of the expression of neuronal genes lead to change of behavior may implicate the dysregulation of the usually ongoing synaptic and other neuroplastic changes in the brain. If we elaborate this theory further, it also hints that schizophrenia pathology can be reverted to the unmeasured extent with plausible normalization of the altered expression of the genes with rehabilitative or therapeutic approaches.

The gene set revealed in this study provides a better representation of the brain pathology developing in schizophrenia as it included major brain regions affected in the disease hence can be used as a genetic signature for diagnosing and monitoring the disease progression as well as therapeutic effects of the drugs, and also benefits of rehabilitative practices.

5. Conclusions

The significant changes in the expression of large set of genes associated with diverse functions maintaining basic machinery of the cells noted in the study is in confirmation to the literature that etiology of SCZ is multifactorial and polygenic and provides explanation for the compromised neural functions characteristically evident in the disease. The detuning of the normal gene expression in different brain regions may severely affect the neural functions in diseased individuals, and may be the actual reason for the observed disorganized behaviour which has been regarded as a hallmark for the progressed SCZ. The misexpression of spermatogenesis related genes noted in our study is a unique finding indicating a possible reason behind predominant male infertility in SCZ, hence needs to be further investigated. The revealed association of the gene set with various categories of other diseases may be an indication that SCZ shared pathogenic mechanisms with each of them. The revealed gene set may also be used as a biomarker for SCZ to screen and predict individuals at risk or to monitor progression of the disease in affected individuals, and also may be exploited therapeutically to monitor influence of drugs and rehabilitative approaches on gene expression, and normalization of the gene set expression may be aimed for a successful therapeutic approach.

6. Further research

The present study has focused on the most commonly involved three brain regions in SCZ, and the genes which were significantly altered in only one or two and not in all three brain regions selected for study have not been included in analysis and they might carry some value in disease etiology; so we suggest further region-specific gene analysis for the all three affected brain regions individually. Moreover, the gene expression changes in many other brain regions which are known to be implicated may be also hiding the part of the story on etiogenesis of SCZ which needs to be investigated. A neural circuit specific analysis of the changes in gene expressions targeted to the individual neurocognitive domains may further augment the etiological clarity on SCZ. Although we used a robust study design to keep away the biases by randomized sampling of the test and control, a more personalised study taking more care of possible confounding factors as age, sex, progression of disease and drug intake history of each sample etc., which will also require a much larger sample size, and also the validation of the analysed data with more than one gene expression analysis techniques and methods may further augment the value of this research. Also, the feasibility of normalization

of altered expressions of genes with rehabilitative or therapeutic approaches may be investigated through appropriate study designs in the biological models of SCZ.

7. References

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Table1. Genome wide m-RNA expression (statistical significance set at p ≤0.01) in three brain regions of schizophrenic patients and healthy controls (data represented as mean).

	Hippocampus			Prefrontal Cortex			Associative striatum		
Gene Symbol	**Control (n=15)**	**SCZ (n=18)**	**p-value**	**Control (n=15)**	**SCZ (n=19)**	**p-value**	**Control (n=18)**	**SCZ (n=18)**	**p-value**
MSANTD3	8.33	8.03	0.001	8.71	8.50	0.003	8.15	8.03	0.006
CXADR	5.52	5.00	0.001	5.46	5.10	0.003	5.83	5.44	0.004
ZNF385B	6.27	5.47	0.000	8.30	8.06	0.005	8.44	7.61	0.008
SAFB2	7.12	7.46	0.005	6.88	7.13	0.002	7.49	7.74	0.006
FBXO9 1559094_at	9.49	8.71	0.000	10.19	9.70	0.002	8.78	8.28	0.002
FBXO9 1559096_x_at	10.68	10.07	<0.001	11.25	10.92	0.004	10.27	9.95	0.003
MCL1	9.74	10.23	0.002	9.76	10.10	0.002	9.83	10.25	0.002
PITPNA	10.74	10.39	0.000	11.18	11.04	0.006	10.31	10.16	0.008
PSMC3	9.64	9.17	<0.001	9.92	9.72	0.008	10.15	9.80	0.008
IFITM2	9.77	10.46	0.001	9.29	9.83	0.003	10.04	10.47	0.008
ICMT	8.09	7.93	0.008	8.22	8.00	0.001	8.83	8.43	0.000
UQCRC1	10.70	10.29	<0.001	11.06	10.92	0.003	10.69	10.46	0.008
ASNA1	9.30	8.99	0.000	9.42	9.29	0.006	9.19	8.99	0.008
TIAL1	7.97	7.70	0.000	7.94	7.79	0.003	7.89	7.67	0.003
GTF2H1	7.59	7.02	0.000	8.04	7.77	0.002	7.38	6.96	0.003
ANPEP	9.22	10.26	<0.001	8.81	9.61	0.004	9.36	10.11	0.005
SOX9	9.39	9.70	0.008	9.07	9.55	0.001	9.41	9.70	0.002
CHSY1	8.18	8.64	0.001	8.29	8.60	0.002	8.20	8.49	0.007
BCL6	9.78	10.48	0.000	10.18	10.48	0.002	9.52	10.00	0.009

PDCD6	10.11	9.65	<0.001	10.29	10.11	0.004	10.01	9.73	0.005
ERCC1	9.13	8.84	0.000	9.09	8.95	0.008	8.85	8.65	0.000
MYO5A	8.70	8.30	0.003	9.24	8.90	0.004	7.69	7.35	0.002
KCNK1	10.73	10.40	0.003	10.90	10.70	0.003	10.08	9.78	0.008
GNAO1	10.58	10.23	0.006	10.61	10.32	0.001	10.37	10.03	0.005
HAPLN1	5.84	5.14	0.002	5.88	5.53	0.002	4.77	4.49	0.007
PPM1E	9.12	8.26	0.007	7.62	7.33	0.008	6.37	6.08	0.001
KAT5	8.46	8.29	0.001	8.70	8.59	0.008	8.68	8.56	0.008
MAPK9	8.13	7.50	<0.001	8.74	8.40	0.001	8.03	7.63	0.003
SPAG7	9.90	9.65	0.000	9.92	9.80	0.001	9.52	9.37	0.001
ANAPC5	11.02	10.84	<0.001	10.95	10.81	0.001	11.02	10.80	0.009
ATP5D	10.71	10.40	<0.001	10.76	10.60	0.005	10.66	10.46	0.008
UBE4B	7.76	7.50	0.006	8.03	7.87	0.010	7.71	7.45	0.004
SCRN3	8.12	7.65	0.001	8.18	7.98	0.008	7.64	7.27	0.002
SMIM7	9.13	8.77	0.001	9.35	9.14	0.005	9.38	9.05	0.002
PDK4	8.24	9.15	0.001	7.98	8.85	0.000	8.60	9.27	0.003
RBM18	9.31	8.99	0.001	9.60	9.47	0.006	9.18	8.96	0.003
SAMD5	6.76	6.38	0.006	6.85	6.60	0.001	7.47	6.85	0.000
CADPS	6.43	6.20	0.004	6.40	6.16	0.005	6.10	5.89	0.004
LOC100506538 /// NDUFAF6	8.13	7.57	0.001	8.50	8.28	0.004	8.11	7.69	0.008
LOC100507534	6.38	5.28	0.002	6.29	5.51	<0.001	4.42	4.19	0.007

Table 2. Involvement of the gene set in biological processes and events.

a	**Ubiquitination**	FBXO9, ANAPC5, UBE4B , SMIM7
b	**Enzyme activity**	PPM1E, MAPK9, ATP5D, ICMT, PDK4, PSMC3
c	**Energy production mechanisms**	UQCRC1, ASNA1, ATPD5, PDK4
d	**Cell growth**	MAPK9, ANAPC5, CHSY1
e	**Programmed cell death**	IFITM2[a], TIAL1[a], PDCD6[a], MCL-1[b]
f	**Cytoplasmic vesicular transport and exocytosis**	MYO5A,PITPNA, ASNA1,CADPS, SCRN3
g	**Dynamic regulation of cytoskeleton**	MYO5A
h	**Ion channel homeostasis**	KCNK1, PDCD6
i	**Lipid binding and synthesis**	PITPNA, CAPDS
j	**DNA repair**	ERCC1, KAT5
k	**m-RNA transcription**	MSANTD3,GTF2H1, GNAO1, MAPK9
l	**Post transcriptional gene modifications**	KAT5
m	**Protein translation**	TIAL1
n	**Cell cycle regulation**	ANAPC5, MAPK9

Reference: NCBI gene database (http://www.ncbi.nlm.nih.gov/gene/). a=Pro-apoptotic, b=Anti-apoptotic

Table 3. Involvement of the gene set in molecular pathways

Neurotransmitters/ modulators/neuro-hormones (a)	**Immune cell/chemokine mediated (b)**	**Growth, differentiation and cell survival (c)**	**Apoptosis (d)**	**Protein synthesis (e)**	**Protein degradation (f)**	**Pathogenesis of neurodegenerative diseases (g)**
(i)Metabotropic glutamate receptor group II pathway (P00040)	(i) B cell activation (P00010)	(i) EGF receptor signaling pathway (P00018)	(i) Apoptosis signaling pathway (P00006)	(i) General transcription regulation (P00023)	(i) Ubiquitin proteasome pathway (P00060)	(i) Alzheimer disease-amyloid secretase pathway (P00003)
(ii) GABA-B receptor II signaling (P05731)	(ii) T cell activation (P00053)	(ii) FGF signaling pathway (P00021)				(ii) Alzheimer disease-presenilin pathway (P00004)
(iii) Muscarinic acetylcholine receptor 2 and 4 signaling pathway (P00043)	(iii) Toll receptor signaling pathway (P00054)	(iii) TGF-beta signaling pathway (P00052)				(iii) Huntington disease (P00029)
(iv) Nicotinic acetylcholine receptor signaling pathway (P00044)	(iv) Inflammation mediated by chemokine and cytokine signaling pathway (P00031)	(iv) FAS signaling pathway (P00020)				(iv) Parkinson disease (P00049)
(v) 5HT1 type receptor mediated signaling pathway (P04373)	(v) Integrin signalling pathway (P00034)	(v) Heterotrimeric G-protein signaling pathway-Gq				

		alpha and Go alpha mediated pathway (P00027)
(vi) Endogenous cannabinoid signaling (P05730)	(vi) Interferon-gamma signaling pathway (P00035)	(vi) Oxidative stress response (P00046)
(vii) Enkephalin release (P05913)		(vii) Ras Pathway (P04393)
(viii) Opioid prodynorphin pathway (P05916)		
(ix) Opioid proopiomelanocortin pathway (P05917)		
(x) CCKR signaling map (P06959)		
(xi) Gonadotropin-releasing hormone receptor pathway (P06664)		

Figure Legends:

Fig. 1. Involvement of the gene set in molecular functions

(Catalysis (n=17, p=44.7%), binding (n=13, p=34.2%), and nucleic acid binding transcription factor activity (n=5, p=13.2%), transporter activity (n=4, p=10.50%), enzyme regulation (n=3, p=7.90%), and structural molecule activity (n=2, p=5.3%), n=number of genes, p=percentage Source: Panther Classification System)

Cross-references in Text: Sections 3 (Result) and 4 (Discussion, subsections 4.1 and 4.6.4).

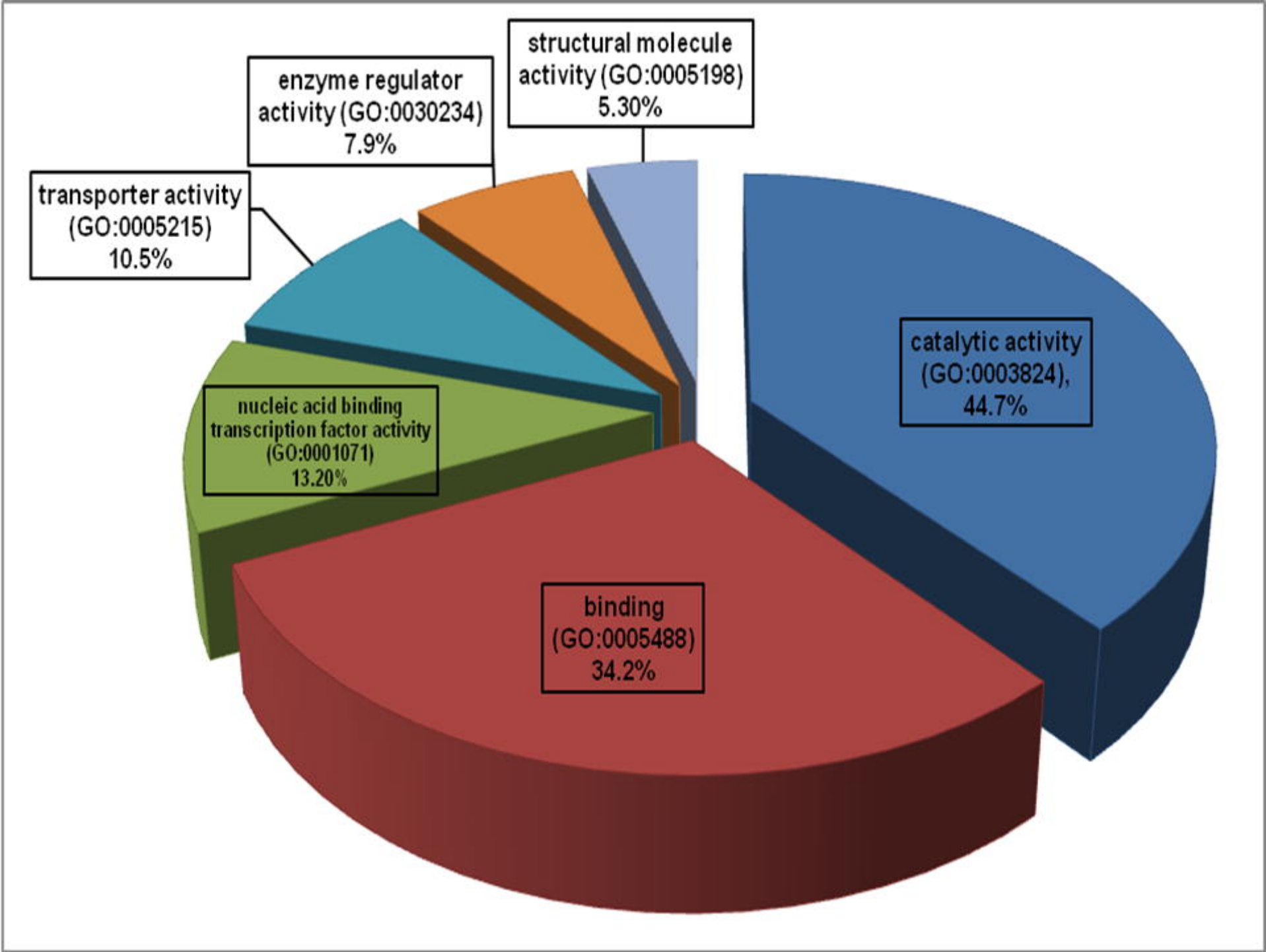
Fig. 2. Involvement of the gene set in molecular pathways

Cross-references in Text: Sections 3 (Result) and 4 (Discussion, subsections 4.3 and 4.5.3).

Fig. 3. Gene-disease association for the revealed gene set

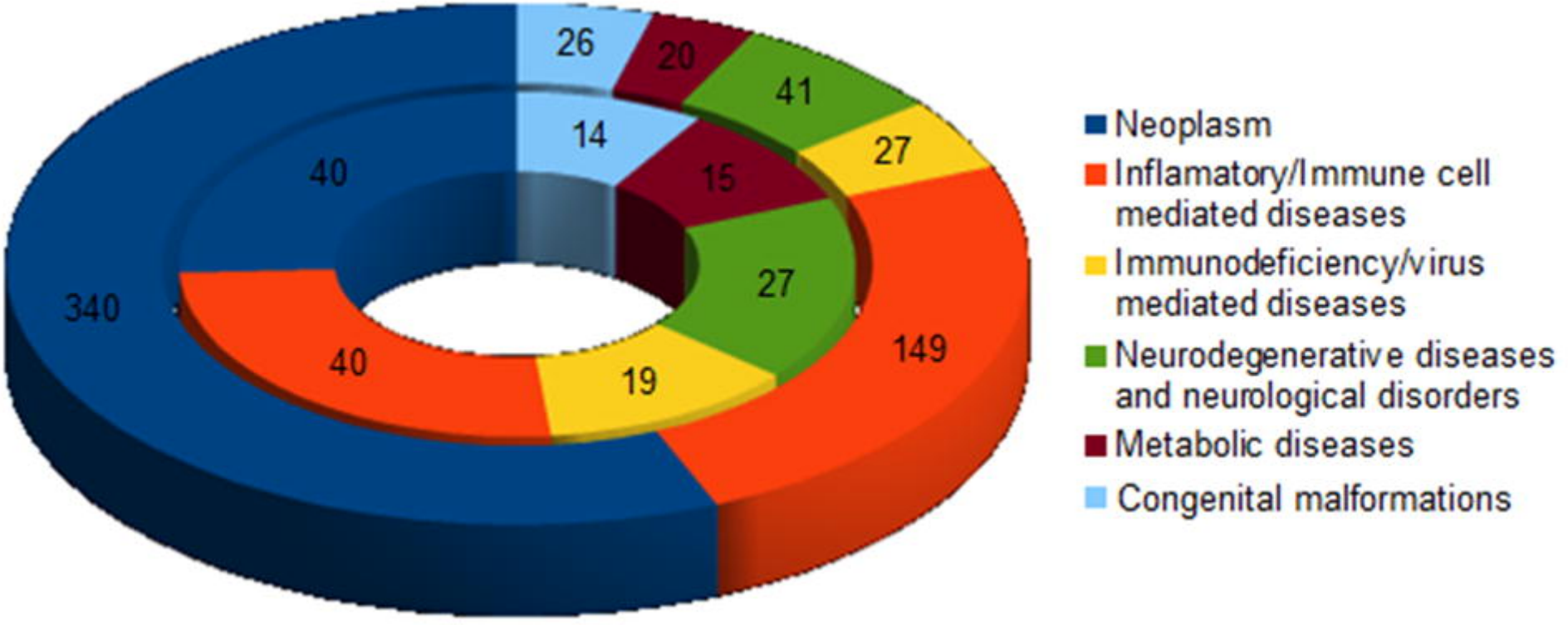
(Outer ring and inner ring show total number of hits for the diseases in each class and actual number of the diseases in each class respectively)

Cross-references in Text: Sections 3 (Result) and 4 (Discussion, subsections 4.5, 4.5.2 and 4.5.4).


structural molecule activity (GO:0005198) 5.30%
enzyme regulator activity (GO:0030234) 7.9%
transporter activity (GO:0005215) 10.5%
nucleic acid binding transcription factor activity (GO:0001071) 13.20%
catalytic activity (GO:0003824), 44.7%
binding (GO:0005488) 34.2%

Number of genes: 40
Total pathway hits: 36
Source: PANTHER pathway

- 5HT1 type receptor mediated signaling pathway (P04373)
- Alzheimer disease-amyloid secretase pathway (P00003)
- Alzheimer disease-presenilin pathway (P00004)
- Apoptosis signaling pathway (P00006)
- B cell activation (P00010)
- CCKR signaling map (P06959)
- EGF receptor signaling pathway (P00018)
- Endogenous cannabinoid signaling (P05730)
- Enkephalin release (P05913)
- FAS signaling pathway (P00020)
- FGF signaling pathway (P00021)
- GABA-B receptor II signaling (P05731)
- General transcription regulation (P00023)
- Gonadotropin-releasing hormone receptor pathway (P06664)
- Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027)
- Huntington disease (P00029)
- Inflammation mediated by chemokine and cytokine signaling pathway (P00031)
- Integrin signalling pathway (P00034)
- Interferon-gamma signaling pathway (P00035)
- Metabotropic glutamate receptor group II pathway (P00040)
- Muscarinic acetylcholine receptor 2 and 4 signaling pathway (P00043)
- Nicotinic acetylcholine receptor signaling pathway (P00044)
- Opioid prodynorphin pathway (P05916)
- Opioid proopiomelanocortin pathway (P05917)
- Oxidative stress response (P00046)
- Parkinson disease (P00049)
- Ras Pathway (P04393)
- T cell activation (P00053)
- TGF-beta signaling pathway (P00052
- Toll receptor signaling pathway (P00054)
- Transcription regulation by bZIP transcription factor (P00055)
- Ubiquitin proteasome pathway (P00060)


26
20
41
14
15
27
40
27
340
40
19
149
Neoplasm
Inflamatory/Immune cell mediated diseases
Immunodeficiency/virus mediated diseases
Neurodegenerative diseases and neurological disorders
Metabolic diseases
Congenital malformations