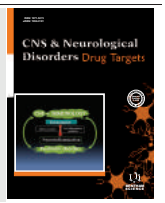
CNS & Neurological Disorders - Drug Targets, 2016, *15*, 477-488

Global Expression Studies of Schizophrenic Brain: A Meta-Analysis Study Linking Neurological Immune System with Psychological Disorders

Sajjad Karim[1], Mohammad A. Kamal[2,4], Zafar Iqbal[3], Shakeel A. Ansari[1], Mahmood Rasool[1], Mohammed H. Al-Qahtani[1], Gazi Damanhouri[2] and Zeenat Mirza[*,2]



[1]*Center of Excellence in Genomic Medicine Research, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia*

[2]*King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia*

[3]*College of Applied Medical Sciences, King Saud Bin Abdulaziz University for Health Sciences, National Guards Health Affairs, Riyadh, Saudi Arabia*

[4]*Enzymoics, Hebersham, NSW 2770, Australia*

Abstract: Schizophrenia, a psychological disorder with enormous societal impact, is a result of abnormalities in gene expression and dysregulation of the immune response in the brain. Few studies have been conducted to understand its etiology, however, the exact molecular mechanism largely remains unknown, though some poorly understood theories abound. Present meta-study links the role of central nervous system, immunological system and psychological disorders by using global expression approach and pathway analysis.

We retrieved genome-wide mRNA expression data and clinico-pathological information from five independent studies of schizophrenic patients from Gene Expression Omnibus database. We continued further with three studies having common platform. Our result showed a total of 527 differentially expressed genes of which 314 are up regulated and 213 are down regulated. After adjusting the sources of variation, we carried out pathway and gene ontology analysis, and observed alteration of 14-3-3-mediated signaling, γ-aminobutyric acid receptor signaling, role of nuclear factor of activated T-cells in regulation of the immune response, G beta gamma signaling, dopamine- and cyclic AMP-regulated phosphoprotein of relative molecular mass 32,000 feedback in cAMP signaling, complement system, axonal guidance signaling, dendritic cell maturation, cAMP response element-binding protein signaling in neurons and interleukin-1 signaling pathways and networks.

Conclusively, our global gene expression pathway and gene set enrichment analysis studies suggest disruption of many common pathways and processes, which links schizophrenia to immune and central nervous system. Present meta-study links the role of central nervous system, immunological system and psychological disorders by using global expression approach and pathway analysis.

Keywords: Schizophrenia, psychological disorder, gene expression, immune system, DNA microarray, central nervous system.

INTRODUCTION

'Schizophrenia' literally means 'splitting of the mind', is a severe psychiatric disorder with abnormal patterns of behavioral or psychological symptoms [1]. Schizophrenic patients suffer from multiple categories of psychological disorders and affects ~1% of world population [2]. It involves complex interactions between genetic and environmental factors [3] and also is associated with myelination, synaptic transmission, metabolism, immune function and ubiquitination [4-8]. Symptoms vary in type and severity whereas etiological reasons include genetic predisposition [9], developmental [10] or neurodegenerative processes [11], neurotransmitter abnormalities [12, 13], viral infection [14] and immune dysfunction or autoimmune mechanisms [15-18].

The transcriptomic meta-analysis is a commonly used strategy to explore the molecular basis of the disease and has recently gained popularity in neuropsychiatry and neuroimmunology as well [19-22]. Differential gene expression studies of schizophrenia have reported varied inconsistent gene list with altered expression [23, 24]. The differences can be attributed to many factors: difference of sample cohort, methodologies, platform choice, and data analysis and besides them batch effect can also add variability [25-29]. We attempt to combine high-throughput genomics studies and re-analyze the data to reduce variability and therefore identify the consistent gene expression changes.

Previous studies have reported the common gene loci for susceptibility genes for schizophrenia and human leukocyte antigen (HLA) complex which are involved in immune function [30]. Key mediator role of cytokines in immune and central nervous system has also been reported [30, 31]. An increased level of interleukin (IL) -1, IL-6 and tumor necrosis factor has been reported in schizophrenia patients

*Address correspondence to this author at the King Fahd Medical Research Center, PO Box-80216, King Abdulaziz University, Jeddah -21589, Saudi Arabia; Tel: +966-12-6401000, Ext. 72074;
E-mails: zmirza1@kau.edu.sa; zeenat_mirza@rediffmail.com

1996-3181/16 $58.00+.00

amid loss of central nervous system volume and microglial activation [32]. It has also been shown that increased IL-8 levels in pregnancy are associated with risk of schizophrenia in the offspring [33, 34].

Although studies have been conducted to link mental disorders (schizophrenia) with immune dysfunction and alterations in central nervous systems, the pathophysiology and molecular mechanism of the illness is still not well understood, indicating a strong genetic component that lie as the base for the disease. In an attempt to gain deeper insight into disease mechanism, we applied comprehensive microarray analysis on publicly available data to determine the common molecular features of the disease.

MATERIALS AND METHODS

Patients and Samples

Global expression studies of schizophrenia were performed with expression dataset retrieved from NCBI's GEO database (Table **1**). Provided sample information was used to classify case and control. We initially assembled a dataset of 114 schizophrenic and 99 healthy control individuals from five independent studies from different microarray platforms; GSE21935 [35], GSE17612 [36], GSE21138 [37], GSE62333 [38], GSE18312 [39], however, we continued further finally with 81 schizophrenic and 71 healthy controls from three studies (GSE17612::28:23; GSE21138::30:29; GSE21935::23:19) having common platform (GPL570, HG-U133_Plus_2 array chip) to minimize the variations and to obtain bigger cohort size for present meta-analysis study. We also unified the data coming from different sources using integrated bioinformatics approach.

Gene Expression Analysis

Partek Genomics Suite version 6.6 (Partek Inc., MO, USA) was used to import affymetrix .CEL files which were normalized using RMA (robust multiarray average) algorithm. Analysis of variance (ANOVA) was applied on the grouped data set to analyze mean expression level on a gene-by-gene basis and differentially expressed genes were generated using a Benjamini Hochberg's FDR (false discovery rate) of 0.05 with 2 and 1.5 fold change cut off. Disease and tissue type were two factors in ANOVA model and equal variance were assumed. Spearman's correlation similarity matrix was used for 2-dimensional unsupervised average linkage hierarchical clustering and classification.

Functional and Pathway Analysis

The principal microarray data analysis was done to detect biological pathways to demonstrate the utilities of more robust biomarker discovery methods for complex diseases like schizophrenia. Ingenuity Pathways Analysis (IPA) software (Ingenuity Systems, Redwood City, CA) was used to define biological networks, interaction and functional analysis among the differentially regulated genes in schizophrenia. We uploaded 527 differentially expressed genes of schizophrenia, along with their p-values and fold changes, into the IPA tool for core analysis revealing associated genetic network, canonical pathway, and biofunctions.

Gene Set Enrichment Analysis

A broader understanding of global expression results is possible by grouping the genes of interest into biological processes, cellular component and molecular functions of the genes. Gene ontology enrichment study was done to functionally categorize schizophrenia's significant genes and to identify specific genes linked with immunological response and process. The implication of this relationship amid transcriptomic data and canonical pathways was calculated by Fisher's exact test and a cutoff enrichment score >3 (p-value <0.05) was used to identify major over expression of functional categories.

RESULTS

This study was focused to find common connections between psychological disorders (schizophrenia) with CNS and immunological processes using transcriptional profiling of nearly 28,000 annotated genes. We analyzed gene expression data retrieved from GEO database and identified genes linked to different biological pathways and networks. Principal component analysis was done to make sure that the samples from the same tissue type clustered tightly together and outliers were removed from study accordingly.

Identification of Differentially Expressed Genes

To understand the molecular link among psychological disorders (schizophrenia), CNS and immunology, we did genome-wide transcriptomic analysis and identified 527 differentially expressed genes, 314 up and 213 down regulated (1.5 fold change, $p < 0.05$) while when the cutoff was made more stringent that is 2 fold FDR, the number of significant genes were reduced to 51 with 27 up and 24 down regulated (Table **2**, Fig. **1**). Of the genes that were

Table 1. Gene Expression Dataset of Schizophrenia retrieved for GEO database.

Dataset	Reference	Microarray Platform	Brain Regions	No. of Subjects (Scz:control)
GSE21935	[35]	HG-U133 Plus 2.0	Superior temporal cortex (BA22)	23:19
GSE17612	[36]	HG-U133 Plus 2.0	Anterior Prefrontal cortex (BA46)	28:23
GSE21138	[37]	HG-U133 Plus 2.0	Frontal (BA46)	30:29
GSE62333	[38]	HuGene-1_1-st	Fibroblast	20:20
GSE18312	[39]	HuEx-1_0-st	Blood	13:8

Table 2. Differentially expressed upregulated and downregulated genes (FDR >0.05, Fold change >2) of psychological disorders (Schizophrenia *vs* controls).

Gene Symbol	Gene Title	Fold-Change (Upregulated)	p-Value/FDR
S100A8	S100 calcium binding protein A8	6.03527	0.000437201
C1QB	complement component 1, q subcomponent, B chain	2.77543	0.000771172
C1QC	complement component 1, q subcomponent, C chain	2.62656	0.000543679
MT1M	metallothionein 1M	2.56029	3.78E-05
SCIN	scinderin	2.53803	0.000503976
BAG3	BCL2-associated athanogene 3	2.52431	6.69E-06
FCGR3A///FCGR3B	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)///Fc fragment of IgG, low aff	2.4807	0.000377411
CP	ceruloplasmin (ferroxidase)	2.46205	0.000257121
YBX3	Y box binding protein 3	2.29616	0.000418019
CD14	CD14 molecule	2.22078	0.00135428
FCGR1B	Fc fragment of IgG, high affinity Ib, receptor (CD64)	2.16093	0.00038466
PDK4	pyruvate dehydrogenase kinase, isozyme 4	2.15486	0.00129401
C10orf10	chromosome 10 open reading frame 10	2.15203	0.00164335
PLSCR4	phospholipid scramblase 4	2.15148	6.47E-07
SERPINA1	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	2.13441	0.000444364
C1QA	complement component 1, q subcomponent, A chain	2.1291	0.000984387
MT1X	metallothionein 1X	2.11952	0.000517547
MGST1	microsomal glutathione S-transferase 1	2.11244	9.70E-05
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	2.09413	0.00157553
AQP1	aquaporin 1 (Colton blood group)	2.08546	0.000524451
IFITM1///IFITM2	interferon induced transmembrane protein 1///interferon induced transmembrane protein	2.05941	0.000214366
RFX4	regulatory factor X, 4 (influences HLA class II expression)	2.03979	4.53E-06
SLCO4A1	solute carrier organic anion transporter family, member 4A1	2.03534	0.000768198
IFITM2	interferon induced transmembrane protein 2	2.03097	0.00020738
SLC39A12	solute carrier family 39 (zinc transporter), member 12	2.01999	2.90E-06
AQP4	aquaporin 4	2.01523	4.67E-05
DTNA	dystrobrevin, alpha	2.00358	0.00326206
Gene Symbol	Gene Title	Fold-Change (Downregulated)	p-value/FDR
RGS4	regulator of G-protein signaling 4	-3.10433	0.000335282
PVALB	parvalbumin	-2.95709	1.14E-05
NDRG3	NDRG family member 3	-2.60441	2.24E-06
GAD1	glutamate decarboxylase 1 (brain, 67kDa)	-2.44832	2.71E-05
RAB3C	RAB3C, member RAS oncogene family	-2.37211	0.00075108
NEFH	neurofilament, heavy polypeptide	-2.2927	0.000214867
GABRA1	gamma-aminobutyric acid A receptor, alpha 1	-2.24225	0.000109665
TAC1	tachykinin, precursor 1	-2.22834	0.00103168
C11orf87	chromosome 11 open reading frame 87	-2.17618	0.000726334
CADPS	Ca++-dependent secretion activator	-2.14635	0.00323668

(Table 2) contd…..

Gene Symbol	Gene Title	Fold-Change (Upregulated)	p-Value/FDR
CBLN4	cerebellin 4 precursor	-2.14357	5.26E-07
RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	-2.09706	0.000118709
ATP2B2	ATPase, Ca++ transporting, plasma membrane 2	-2.08439	8.67E-06
MFSD4	major facilitator superfamily domain containing 4	-2.07121	0.000166348
VSNL1	visinin-like 1	-2.06718	0.00188539
PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	-2.06697	0.00109483
MYT1L	myelin transcription factor 1-like	-2.06303	0.00249397
NEFL	neurofilament, light polypeptide	-2.05627	0.0006315
SST	somatostatin	-2.03488	0.00311891
SNAP25	synaptosomal-associated protein, 25kDa	-2.0244	0.000626538
PCSK1	proprotein convertase subtilisin/kexin type 1	-2.02398	0.00260887
ATP6V1A	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	-2.00755	0.00395464
SCAMP1	secretory carrier membrane protein 1	-2.00147	0.000712588

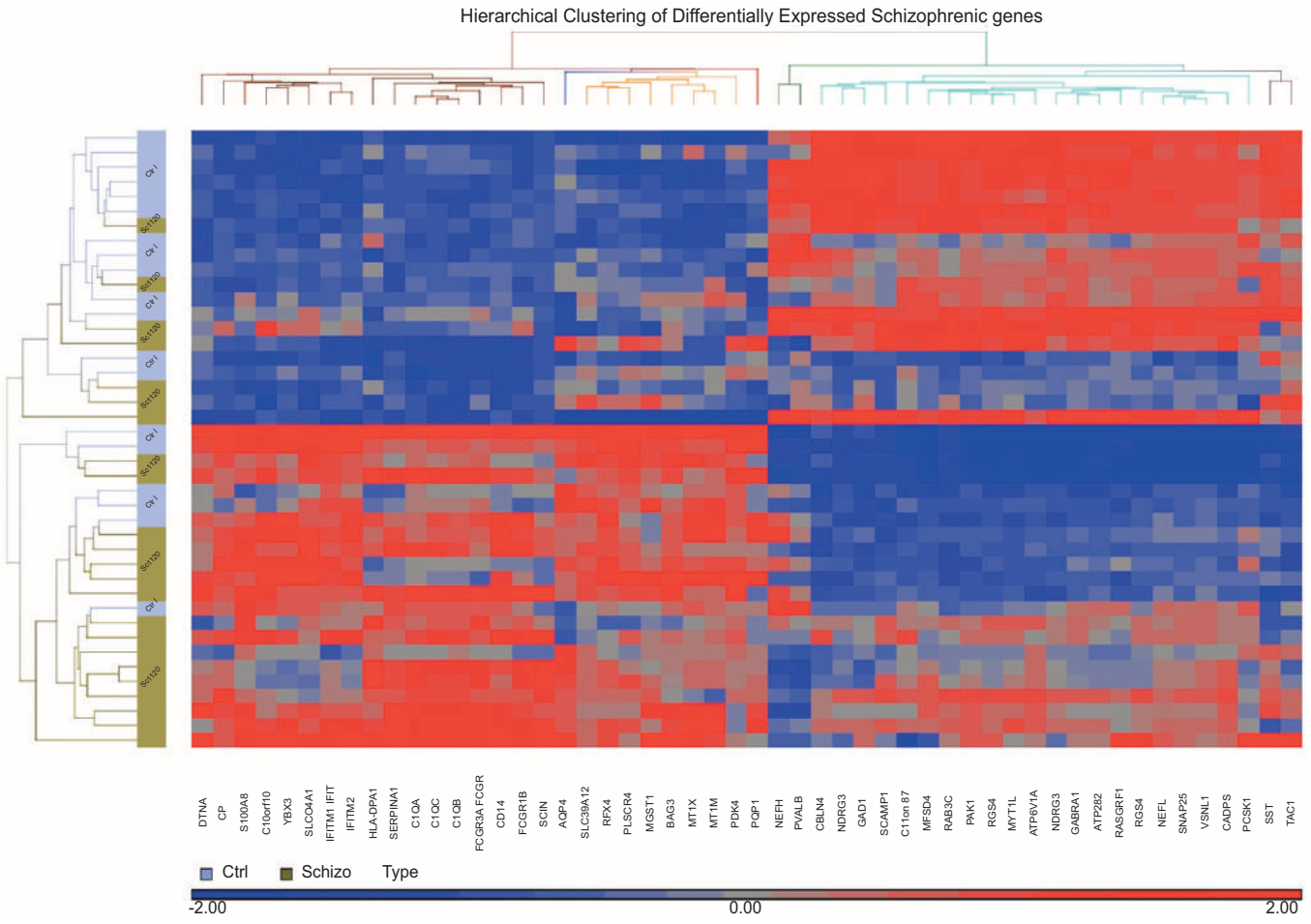


Fig. (1). Hierarchical clustering of differentially expressed schizophrenic genes. Description: dendrogram shows the specific pattern of change in expression in red-blue picture where red denotes upregulation and blue denotes downregulation according the color scale at the bottom. Each column and row represents single gene and experiment respectively.

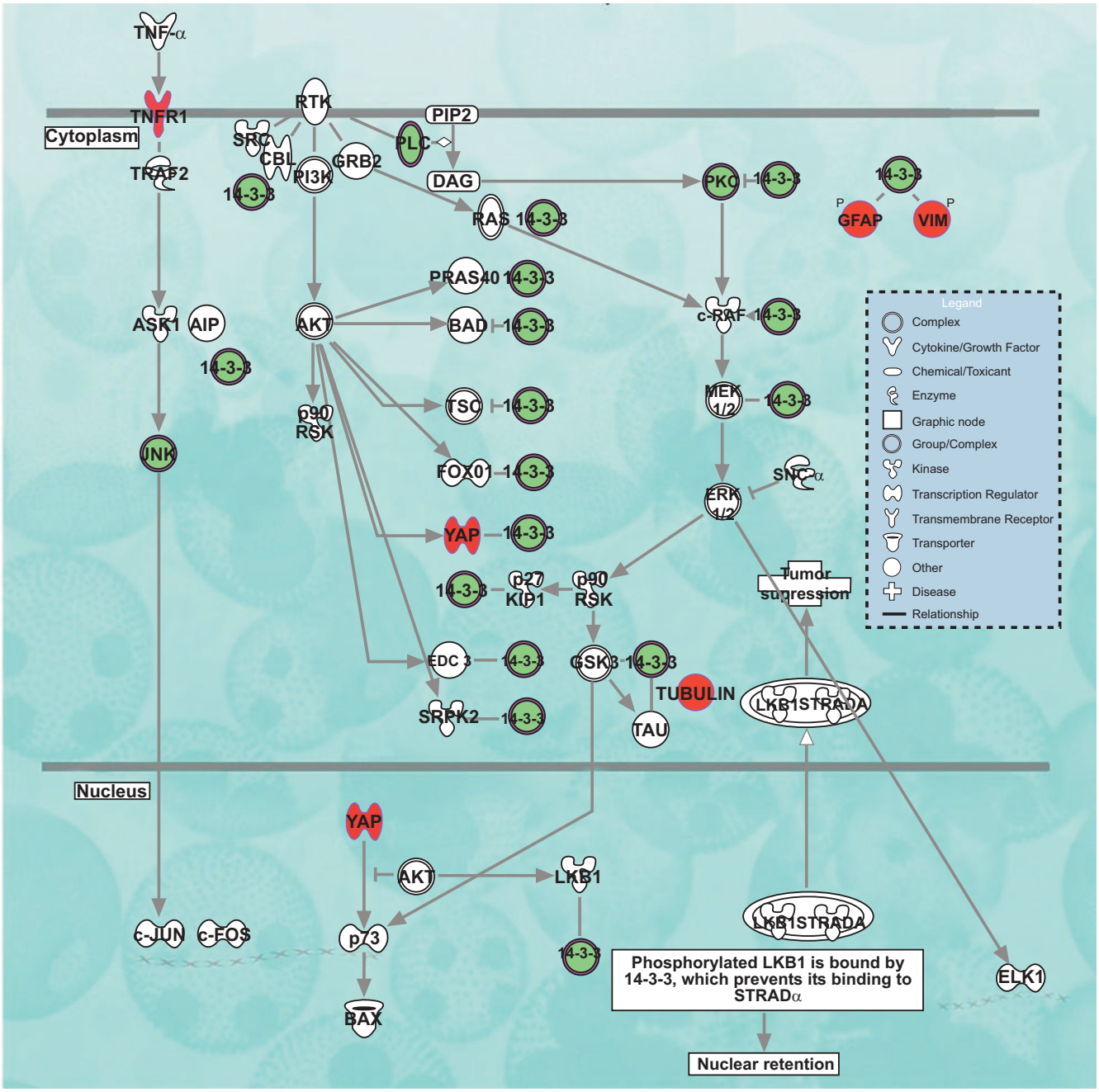


Fig. (2). 14-3-3-mediated Signaling pathway overlaid with significant genes of schizophrenia. Red donates up regulation (TNFRSF1A, TUBB6, VIM, YAP1) and green denotes down regulation (GFAP, MAP2K4, PRCL2, PRKCB, YWHAB/E/Z).

upregulated, the most significant were S100 calcium binding protein A8 (S100A8), complement component 1, q subcomponent, B chain and C chain (C1QC and C1QC), metallothionein 1M and 1X (MT1M and MT1X), scinderin (SICN), Fc fragment of IgG IIIa, receptor (FCGR3A), and BCL2-associated athanogene 3 (BAG3), while the most downregulated genes were: regulator of G-protein signaling 4 (RGS4), parvalbumin (PVALB), NDRG family member 3 (NDRG3), glutamate decarboxylase 1 (GAD1), neurofilament, heavy polypeptide (NEFH) Ca^{2+}-dependent secretion activator (CADPS), cerebellin 4 precursor (CBLN4) and gamma-aminobutyric acid A receptor, alpha 1 (GABRA1). Gene ontology enrichment method shows the connection of schizophrenia with immune and CNS, and we found following -major histocompatibility complex, class II genes such as; DM alpha (HLA-DMA), DP alpha 1 (HLA-DPA1), DQ beta 1 (HLA-DQB1) and DR beta 1 (HLA-DRB1) to be up regulated.

Pathways and Networks Underlying Immune Dysfunction in Schizophrenia

We examined molecular networks of schizophrenia associated genes using Ingenuity Pathway Analysis tool to decipher the underlying molecular mechanisms and physiological processes which may be involved in the

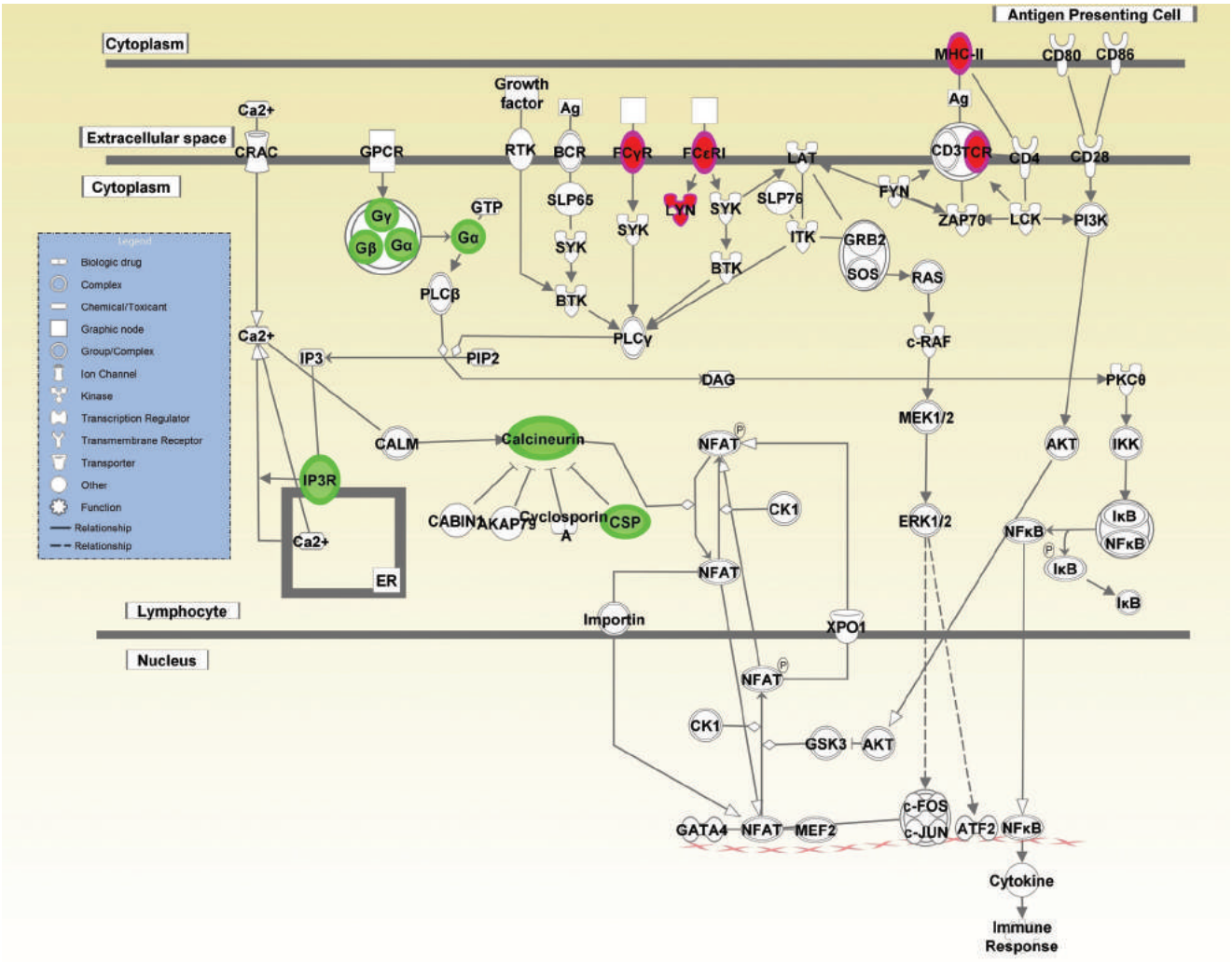


Fig. (3). Role of NFAT in regulation of the immune response pathway overlaid with significant genes of schizophrenia showed immune effect. Red donates up regulation (TNFRSF1A, TUBB6, VIM, YAP1) and green denotes down regulation (GFAP, MAP2K4, PRCL2, PRKCB, YWHAB/E/Z).

disease pathophysiology. Transcriptomic signatures of schizophrenia displayed noteworthy disturbances in signaling pathways like 14-3-3-mediated Signaling (Fig.**2**), role of nuclear factor of activated T-cells (NFATs) in regulation of the immune response (Fig. **3**), γ-aminobutyric acid (GABA) receptor signaling (Fig. **4**), G beta gamma signaling, dopamine- and cyclic AMP-regulated phosphoprotein of relative molecular mass 32,000 (dopamine-DARPP32) feedback in cAMP signaling, complement system, axonal guidance signaling, dendritic cell maturation, cAMP response element-binding protein (CREB) signaling in neurons and IL-1 signaling (Table **3**). This analysis helped us to conclude a strong correlation amongst schizophrenia, immune dysfunction and CNS.

Functional analysis has predicted the following pathways to be significantly affected (considering the cut off, Z score > 2) - calcium signaling (Z score -2.64), Liver X receptor-retinoid X receptor activation (Z score -2.45), neuropathic pain signaling in dorsal horn neurons (Z score -2.44), gonadotropin-releasing hormone signaling (Z score -2.24), renin-angiotensin signaling (Z score -2.23), CREB signaling in neurons (Z score -2.23), and aryl hydrocarbon receptor signaling (Z score +2.00). We also found increased level in role of NFAT in regulation of the immune response (Z score +1.667), Gαi signaling (Z score +1.63), and integrin-linked kinase signaling (Z score +1.667) pathways.

Further gene ontology enrichment method identified various immunological responses to be affected in schizophrenia and also found alteration in the expression of the genes such as: complement component 1, q subcomponent, A, B and C chain (C1QA, C1QB, C1QC), complement component 3 (C3), complement component 4A and 4B (C4A, C4B), CD14 molecule (CD14), Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide (FCER1G), fibroblast growth factor 2 and 9 (FGF2 and FGF9), interferon, gamma-inducible protein 16 (IF16), integrin, beta 2 (ITGB2), v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN), mitogen-activated protein kinase kinase 4 (MAP2K4), p21 protein (Cdc42/Rac)-activated kinase 1 (PAK1), S100 calcium binding protein A8, A9, A11 and A12 (S100A8, S100A9, S100A11 and S100A12), Thy-1 cell surface antigen (THY1), transforming

Table 3. Top ingenuity canonical pathways identified in pathway and network analysis.

Canonical Pathways	-log (p-Value)	Molecules
14-3-3-mediated Signaling	4.52E00	VIM, MAP2K4, TNFRSF1A, TUBB6, PRKCB, YAP1, PLCL2, YWHAE, YWHAZ, YWHAB, GFAP
Role of NFAT in Regulation of the Immune Response	4.26E00	FCGR1B, GNA13, FCER1G, RCAN2, GNAL, FCGR2A, PPP3R1, GNB5, GNG3, HLA-DMA, ITPR1, LYN, FCGR3A/FCGR3B
GABA Receptor Signaling	3.97E00	SLC32A1, GABBR2, GAD1, GABRG2, UBQLN1, GABRA1, NSF, GABRD
G Beta Gamma Signaling	3.75E00	KCNJ9, KCNJ3, GNA13, GNB5, GNG3, PAK1, PRKCB, GNAL, PRKAR1A
Tec Kinase Signaling	3.36E00	GNA13, MAP2K4, GNB5, GNG3, PAK1, TNFRSF21, PRKCB, FCER1G, RHOJ, GNAL, LYN
CXCR4 Signaling	2.79E00	GNA13, MAP2K4, GNB5, GNG3, PAK1, PRKCB, ITPR1, RHOJ, GNAL, LYN
Calcium-induced T Lymphocyte Apoptosis	2.79E00	PPP3R1, HLA-DMA, PRKCB, ITPR1, FCER1G, ATP2A2
Clathrin-mediated Endocytosis Signaling	2.78E00	STON2, FGF12, S100A8, PPP3R1, SERPINA1, AMPH, ITGB8, ITGB2, FGF2, SYNJ1, FGF9
Dopamine-DARPP32 Feedback in cAMP Signaling	2.56E00	KCNJ9, KCNJ3, PPP3R1, PRKCB, ITPR1, PLCL2, ATP2A2, CAMKK2, CALY, PRKAR1A
Synaptic Long Term Depression	2.53E00	CRH, GNA13, RARRES3, PRKCB, ITPR1, PLCL2, GRIA4, GNAL, LYN
Phospholipase C Signaling	2.42E00	GNA13, PPP3R1, GNB5, GNG3, PRKCB, ITPR1, FCER1G, RHOJ, TGM2, FCGR2A, AHNAK, LYN
Complement System	2.18E00	C1QC, C1QB, ITGB2, C1QA
Axonal Guidance Signaling	2.1E00	GNA13, ADAM23, PAK1, TUBB6, NGEF, EFNA5, EPHA4, RTN4, GNAL, PRKAR1A, SLIT2, PPP3R1, GNB5, GNG3, KLC1, PRKCB, PLCL2
Dendritic Cell Maturation	2.1E00	FCGR1B, MAP2K4, HLA-DMA, TNFRSF1A, TYROBP, FCER1G, PLCL2, FCGR2A, FCGR3A/FCGR3B
B Cell Receptor Signaling	1.99E00	BCL6, PPP3R1, MAP2K4, PRKCB, APBB1IP, PTPRC, SYNJ1, FCGR2A, LYN
CD28 Signaling in T Helper Cells	1.97E00	PPP3R1, MAP2K4, HLA-DMA, PAK1, ITPR1, PTPRC, FCER1G
CREB Signaling in Neurons	1.97E00	GNA13, GNB5, GNG3, PRKCB, ITPR1, PLCL2, GRIA4, GNAL, PRKAR1A
IL-1 Signaling	1.9E00	GNA13, MAP2K4, GNB5, GNG3, GNAL, PRKAR1A

growth factor, beta 2 (TGFB2), transforming growth factor, beta receptor 1 (TGFBR1), tumor necrotic factor receptor superfamily, member 1A and member 21 (TNFRSF1A and TNFRSF21), and V-set and immunoglobulin domain containing 4 (VSIG4) (Table **4**, Fig. **5**).

DISCUSSION

Although central nervous systems, mental disorders (schizophrenia) and immune dysfunction are discussed since couple of decades, the field has never come into the mainstream of research. To understand the complexity of schizophrenia, recent research on pathogenesis has shifted its focus on meta-analysis of high throughput data of neurotransmitter systems in the brain and the present study is a humble step in this direction. Genome wide approaches have been applied several times for the human gene expression analysis focusing on specific diseases as a route to gain an insight into aetiology and understand the underlying pathogenic mechanisms. The up and downregulation of various genes are being increasingly reported as biomarkers for prognosis as well as diagnosis of complex diseases like cancer, autoimmune and neurodegenerative disorders [40-43].

For long genetic studies have shown that the most probable schizophrenia's susceptibility genes are on chromosome 6p22.1 [44] while this region also includes many genes of the HLA complex which are shown to have a direct relation to the immune function [30, 45]. In addition, other studies have shown the mutual regulatory relationship of immune and central nervous systems in which inflammatory marker plays the key role of mediator in the brain-immune system relay during the acute phase immune response [30, 31]. In the present study, we have reported many new genes and pathways showing strong association in between schizophrenia, immune system and central nervous system. We hereby, discuss the role of the most associated canonical pathways.

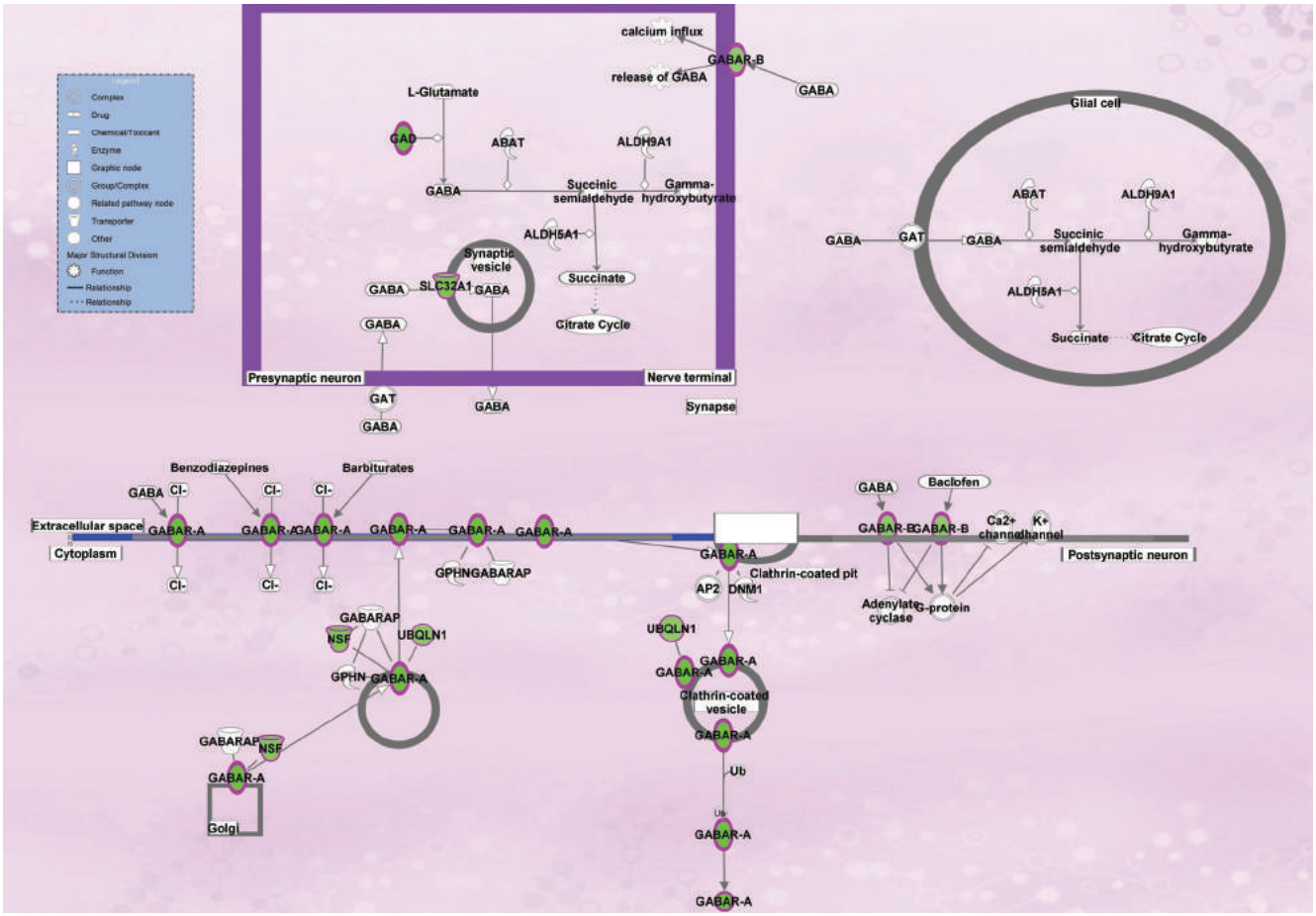


Fig. (4). GABA Receptor Signaling pathway overlaid with significant genes of schizophrenia showed under expression. All overlaid genes were down regulated (GABBR2, GABRA1, GABRD, GABRG2, GAD1, NSF, SLC32A1, UBQLN1) and shown in green color.

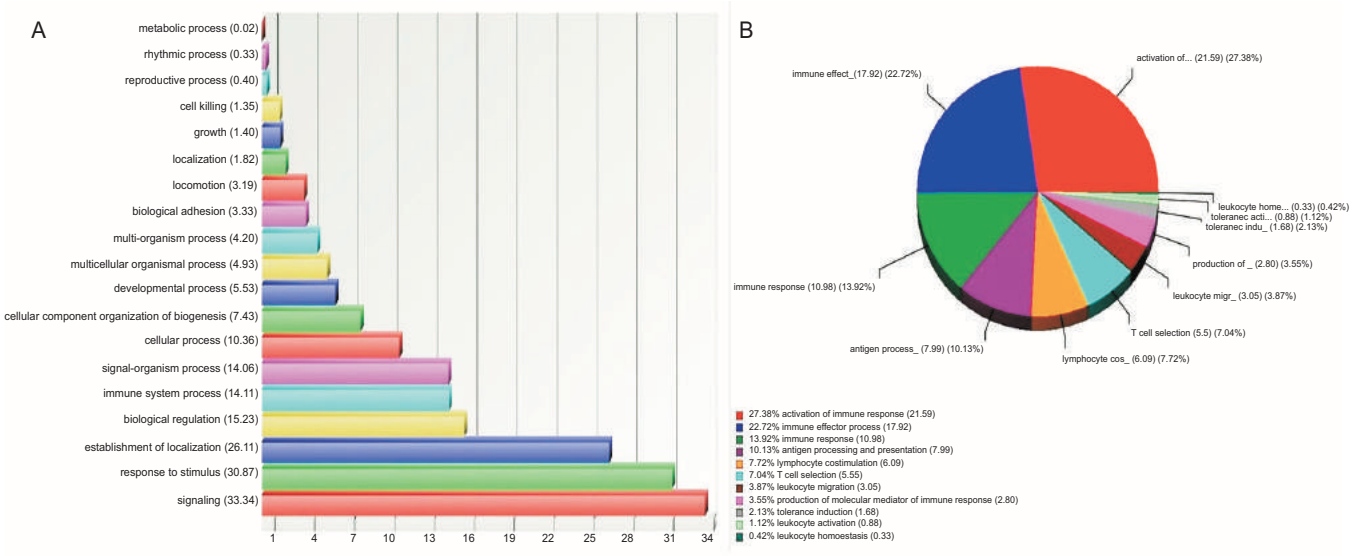


Fig. (5). Functional analysis and Gene Ontology analysis: (**A**) Gene set enrichment analysis study showing strong association of schizophrenia with "signaling, response to stimulus, establishment of localization, biological regulation and immune response process" as represented by enrichment score (14.11). (**B**) Pie chart diagram showing percentage distribution of sub-function under immune response process.

Table 4. Gene ontology enrichment study identified genes linking schizophrenia with Immunological process.

Immunological Functions	Genes
Activation of Immune response	C1QA, C1QB, C1QC, C3, C4A///C4B///C4B_2, CACNB4, CD14, CFH///CFHR1, FCER1G, FCGR1A///FCGR1B, FCGR2A, FCGR3A///FCGR3B, HLA-DPA1, HLA-DQB1, HLA-DRB1///HLA-DRB4, HSP90AB1, IFI16, ITGB2, ITPR1, LYN, MAP2K4, PAK1, PRKCB, PTPRC, THEMIS, THY1, TNFRSF21, VSIG4
Immune effector process	C1QA, C1QB, C1QC, C3, C4A///C4B///C4B_2, CADM1, CFH///CFHR1, DDIT4, FCER1G, FCGR1A///FCGR1B, FCGR2A, FCGR3A///FCGR3B, HLA-DMA, HLA-DQB1, HLA-DRB1///HLA-DRB4, HSP90AB1, IFI16, IFITM1, IFITM2, IFITM3, ITPR1, LYN, PAK1, PLSCR1, PTPRC, TRIM22, VSIG4, ZC3HAV1
Immune response (Innate, humoral, adaptive)	ARHGDIB, BCL6, C1QA, C1QB, C3, C4A///C4B///C4B_2, CADM1, CALM1///CALM2, CD14, CFH///CFHR1, FCER1G, FCGR1B, FCGR2A, FCGR3A///FCGR3B, FGF2, FGF9, GEM, HLA-DMA, HLA-DPA1, IFI16, IFITM1///IFITM2///IFITM3, ITGB2, ITPR1, LGALS3, LOC101060503, LYN, MAP2K4, PAK1, PPP3R1, PRKAR1A, S100A12, S100A8, TNFRSF21, TRIM22, TYROBP, VSIG4, YWHAB, ZC3HAV1.
Antigen processing and presentation	AP1S1, DYNC1I1, FCER1G, FCGR1A///FCGR1B, HLA-DMA, HLA-DPA1, HLA-DRB1///HLA-DRB4, KIFAP3, KLC1, RAB3C, RAB6A
Lymphocyte co-stimulation	HLA-DPA1, HLA-DQB1, LYN, PAK1
T-cell Selection	HLA-DMA, ITPKB, PTPRC, THEMIS
Leukocyte migration	FCER1G, ITGB2, LGALS3, LYN, MSN, PECAM1, S100A8, S100A9, TGFB2
Production of Molecular mediator of immune response	HLA-DQB1, HLA-DRB1///HLA-DRB4
Tolerance Induction and Leukocyte homeostasis	LYN
Leukocyte activation	BCL6, CADM1, FCER1G, MT1G, PRKCB, PTPRC, S100A12, TYROBP, ZFP36L1, ZFP36L2

14-3-3 Mediated Signaling Pathway

The 14-3-3 proteins are a family of neuroprotective proteins abundantly expressed in the brain [46] existing as homodimers or heterodimers in following isoforms: β, γ, ε, η, σ, τ/θ and ζ [47, 48]. They are functionally involved in the neurite outgrowth, synaptic transmission and plasticity regulation, neuronal differentiation, migration and survival, and ion channel regulation [47, 49-51]. Dysregulation of 14-3-3 proteins have been implicated in schizophrenia [52, 53]. Foote *et al*, 2015 exhibited synaptic alterations, and schizophrenia-associated behavioral deficits mainly impairments in associative learning and memory in 14-3-3 functional knockout transgenic mice [54]. The underlying cause can be attributed to alterations in multiple neurotransmission systems due to reduction of dendritic complexity and spine density in forebrain excitatory neurons, which alter synaptic connectivity in the prefrontal cortical synapse of the 14-3-3 functional knock-out mice. The dendritic spine defect stems at molecular level from dysregulated actin dynamics secondary to a disruption of the 14-3-3-dependent regulation of phosphorylated cofilin.

We list out reasons to suggest that the 14-3-3 family of proteins may be candidate risk genes for schizophrenia [55]: i. linkage analysis reports single nucleotide polymorphisms of individual 14-3-3 isoforms in schizophrenia patients [56]; ii. *Ywhah*, encoding the 14-3-3η isoform, is located within the established 22q12-13 candidate risk chromosomal region [57]; iii. postmortem studies detected decreased neuronal expression of 14-3-3 at the protein and the mRNA levels in the brains of schizophrenia patients [52, 58]; and iv. exome sequencing revealed that *de novo* mutations of *Ywhag* and *Ywhaz* are among a group of postsynaptic proteins overrepresented in schizophrenia populations [59, 60]. Besides these reasons, 14-3-3 mediated signaling was also recently reported as one of the most prominent pathway in an elaborate hippocampal difference-in-gel electrophoresis (2-D DIGE) proteomics study coupled with IPA [53].

Role of NFAT in Regulation of the Immune Response Pathway

NFATs are a family of calcium-dependent transcription factors expressed in a variety of immune cells and critically involved in immune response, prime regulators of T-cell development and function [61]. NFAT is specifically activated by stimulation of receptors coupled to calcium - calcineurin (CaN) signals. Both common genetic variation and rare mutations in genes encoding Ca^{2+} channel subunits, have pleiotropic effects on risk for multiple neuropsychiatric disorders, like schizophrenia [62]. The assembly of varied NFAT complexes functions simultaneously as coincidence detectors as well as signal integrators [63]. CaN is linked to receptors for neurotransmitters like NMDA, dopamine and GABA [64]. NFAT and Fos-Jun complex is required for productive immune responses.

CaN, along with transcription factor NFAT, is regulator of neurons and plays an important role in circuit development and refinement through axonal outgrowth, synaptogenesis, memory formation and neuronal response [65, 66]. Extracellular Ca^{2+} stimulus activates CaN phosphatase and quickly dephosphorylates NFATc proteins which on reaching the nucleus, get assembled on DNA with nuclear proteins [65, 66]. Nuclear import of dephosphorylated NFATs is facilitated by importins; however, dephosphorylated NFATs are rapidly exported

from nucleus and rephosphorylation is carried by glycogen synthase kinase 3 to critically regulate the NFAT transcription from transient Ca^{2+} influxes and to decode the Ca^{2+} signals is to be exhibited. Other kinases including CK1, p38 and c-Jun NH2-terminal kinases, also phosphorylate NFAT proteins and control their nuclear shuttling [63]. T-Cell anergy is induced by NFAT1, if its interaction with transcriptional partners (c-Fos and c-Jun) is prevented. Possible role of NFAT signaling in schizophrenia pathogenesis has been suggested in genetic studies conducted on mice and humans [63].

Mutant CaN-Aγ gene knockout mice displayed characteristic symptoms of schizophrenia like increased random movement, attention deficits, less social interaction, and deficits in sensorimotor gating by impaired prepulse inhibition [67]. This indicates insufficiency of CaN to be one of the causes for schizophrenia. NFAT signaling pathway is a well known target for immunosuppressive drugs (cyclosporines and FK506) wherein they bind to immunophilins that potentially block interaction between CaN and NAFT and effectively suppressing the immune response [68].

GABA Receptor Signaling Pathway

GABA is the chief inhibitory neurotransmitter regulating numerous processes all through the brain development of a child [69]. During adulthood, GABA signaling mainly regulates hippocampal neurogenesis [70]. Alterations in GABAA receptor (GABAAR) expression levels disturbs neural synchrony and play vital role in the pathogenesis of CNS disorders including schizophrenia [71, 72], anxiety [73] and inflammatory responses [74]. Deregulated inflammatory mediators have an impact on downstream pathways involved in neuronal inflammation, damage and degeneration, leading to pathogenesis of neuropsychiatric disorders like schizophrenia [75]. GABA-mediated synaptic transmission produces synchronized neural network oscillations that controls the processing and flow of neural information required for normal cognitive function of brain [76, 77]. A study conducted on postmortem brain suggests an association of deficits of GABA-mediated synaptic transmission [71].

Several gene association studies had linked GABA receptor subunits to schizophrenia [78-80]. Decreased protein expression of $GABA_B$ receptor subunits 1 and 2 (GABBR1 and GABBR2) has been reported [81]. Recently, proteomic pathway analysis of the hippocampus in schizophrenia highlighted GABAergic interneuron pathology [53]. Considerable decline of GABRβ1 protein in schizophrenia patient's brains has been reported [69]. Novel therapeutics based on neurosteroids that can promote GABA modulation and lessen GABAergic dysfunction seems promising.

Interestingly, high-throughput genome-wide study has reported that NFATc4 along with GABA receptor signaling modulates hippocampal neurogenesis of progenitor cells and plays key role in the regulation of GABA signaling. GABA receptor signaling further regulates the expression of GABRA2 and GABRA4 subunit, suggesting that the GABAAR/calcineurin/NFATc4 axis is a potential selective druggable target for the emotional mental disorders treatment [82].

CONCLUSION

Present study shows that several of the differentially expressed genes and canonical pathways recognized in schizophrenia have already been found to be involved in immune function and central nervous systems. Gene ontology enrichment studies further strengthens the association between schizophrenia with immunological responses. In conclusion, our global gene expression and pathway analysis suggests disruption of many common pathways and processes linking schizophrenia with immune and central nervous system. Our findings warrant further study of the molecular mechanisms underlying the identified canonical metabolic networks responsible for the complex etiology of the multi-factorial disease. More such studies targeting significantly associated pathway might open the opportunities for pathway-specific therapeutic and diagnostic biomarker discoveries.

AUTHORS CONTRIBUTION

Study design (Sajjad Karim, Mohammad A. Kamal and Zeenat Mirza); Data retrieval and compilation (Zafar Iqbal, Shakeel A. Ansari and Mahmood Rasool); Data analysis (Sajjad Karim, Zeenat Mirza and Mohammed H. Al-Qahtani); Manuscript writing (Sajjad Karim, Zeenat Mirza, Shakeel A. Ansari and Mahmood Rasool); Critical review of manuscript (Gazi Damanhouriand Mohammad A. Kamal).

LIST OF ABBREVIATIONS

CaN	=	Calcineurin
CNS	=	Central Nervous System
CREB	=	cAMP Response Element-Binding Protein
FDR	=	False Discovery Rate
GABA	=	γ-Aminobutyric Acid
GABAAR	=	GABAA Receptor
HLA	=	Human Leukocyte Antigen
IL	=	Interleukin
IPA	=	Ingenuity Pathways Analysis
NFAT	=	Nuclear Factor of Activated T-Cells

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGMENTS

This research was supported by Center of Excellence in Genomic Medicine Research and King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia. This project was funded by the National Plan for Science, Technology and Innovation (MAARIFAH) - King Abdulaziz City for Science and Technology - the Kingdom

of Saudi Arabia - award number (10-BIO1073-03, 10-BIO1258-03 and 08-MED120-03) and Deanship of Scientific Research, King Abdulaziz University, Jeddah, Saudi Arabia - award number (434/019-T and HiCi-1434-117-2). The authors also acknowledge with thanks lab staff for technical support.

REFERENCES

[1] Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gener Psychiatry 2003; 60(12): 1187-92.

[2] Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. Eur Arch Psychiatry Clin Neurosci 2000; 250(6): 274-85.

[3] Giegling I, Hartmann AM, Genius J, Benninghoff J, Moller HJ, Rujescu D. Systems biology and complex neurobehavioral traits. Pharmacopsychiatry 2008; 41 Suppl 1: S32-6.

[4] Konradi C. Gene expression microarray studies in polygenic psychiatric disorders: applications and data analysis. Brain Res Rev 2005; 50(1): 142-55.

[5] Mirnics K, Levitt P, Lewis DA. Critical appraisal of DNA microarrays in psychiatric genomics. Biol Psychiatry 2006; 60(2): 163-76.

[6] Iwamoto K, Kato T. Gene expression profiling in schizophrenia and related mental disorders. Neuroscientist 2006; 12(4): 349-61.

[7] Arion D, Unger T, Lewis DA, Levitt P, Mirnics K. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. Biol Psychiatry 2007; 62(7): 711-21.

[8] Middleton FA, Mirnics K, Pierri JN, Lewis DA, Levitt P. Gene expression profiling reveals alterations of specific metabolic pathways in schizophrenia. J Neurosci 2002; 22(7): 2718-29.

[9] Mowry BJ, Nancarrow DJ. Molecular genetics of schizophrenia. Clin Exp Pharmacol Physiol 2001; 28(1-2): 66-9.

[10] Hornig M, Mervis R, Hoffman K, Lipkin WI. Infectious and immune factors in neurodevelopmental damage. Mol Psychiatry 2002; 7 Suppl 2: S34-5.

[11] Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol Psychiatry 1999; 46(6): 729-39.

[12] Seeman P. Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987; 1(2): 133-52.

[13] Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Rev 2000; 31(2-3): 302-12.

[14] Yolken RH, Torrey EF. Viruses, schizophrenia, and bipolar disorder. Clin Microbiol Rev 1995; 8(1): 131-45.

[15] Logan DG, Deodnar SD. Schizophrenia, an immunologic disorder? JAMA 1970; 212(10): 1703-4.

[16] Noy S, Achiron A, Laor N. Schizophrenia and autoimmunity--a possible etiological mechanism? Neuropsychobiology. 1994; 30(4): 157-9.

[17] Knight J, Knight A, Ungvari G. Can autoimmune mechanisms account for the genetic predisposition to schizophrenia? Br J Psychiatry 1992; 160: 533-40.

[18] Ganguli R, Brar JS, Rabin BS. Immune abnormalities in schizophrenia: evidence for the autoimmune hypothesis. Harvard Rev Psychiatry 1994; 2(2): 70-83.

[19] Choi KH, Elashoff M, Higgs BW, *et al*. Putative psychosis genes in the prefrontal cortex: combined analysis of gene expression microarrays. BMC Psychiatry 2008; 8: 87.

[20] Liu Y, Blackwood DH, Caesar S, *et al*. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry 2011; 16(1): 2-4.

[21] Mathieson I, Munafo MR, Flint J. Meta-analysis indicates that common variants at the DISC1 locus are not associated with schizophrenia. Mol Psychiatry 2012; 17(6): 634-41.

[22] Baum AE, Hamshere M, Green E, *et al*. Meta-analysis of two genome-wide association studies of bipolar disorder reveals important points of agreement. Mol Psychiatry 2008; 13(5): 466-7.

[23] Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 2004; 10(1): 40-68.

[24] Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular Characterization of Schizophrenia Viewed by Microarray Analysis of Gene Expression in Prefrontal Cortex. Neuron 2000; 28(1): 53-67.

[25] Mistry M, Pavlidis P. A cross-laboratory comparison of expression profiling data from normal human postmortem brain. Neuroscience 2010; 167(2): 384-95.

[26] Torkamani A, Dean B, Schork NJ, Thomas EA. Coexpression network analysis of neural tissue reveals perturbations in developmental processes in schizophrenia. Genome Res 2010; 20(4): 403-12.

[27] Barnes M, Freudenberg J, Thompson S, Aronow B, Pavlidis P. Experimental comparison and cross-validation of the Affymetrix and Illumina gene expression analysis platforms. Nucleic Acids Res 2005; 33(18): 5914-23.

[28] Liu C, Cheng L, Badner JA, *et al*. Whole-genome association mapping of gene expression in the human prefrontal cortex. Mol Psychiatry 2010; 15(8): 779-84.

[29] Choi KH, Higgs BW, Wendland JR, Song J, McMahon FJ, Webster MJ. Gene expression and genetic variation data implicate PCLO in bipolar disorder. Biol Psychiatry 2011; 69(4): 353-9.

[30] Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008; 63(8): 801-8.

[31] Muller N, Schwarz MJ. Immune System and Schizophrenia. Curr Immunol Rev 2010; 6(3): 213-20.

[32] Muller N. Immunology of schizophrenia. Neuroimmunomodulation 2014; 21(2-3): 109-16.

[33] Brown AS, Begg MD, Gravenstein S, *et al*. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gener Psychiatry 2004; 61(8): 774-80.

[34] Brown AS. Prenatal infection as a risk factor for schizophrenia. Schizophr Bull 2006; 32(2): 200-2.

[35] Barnes MR, Huxley-Jones J, Maycox PR, *et al*. Transcription and pathway analysis of the superior temporal cortex and anterior prefrontal cortex in schizophrenia. J Neurosci Res 2011; 89(8): 1218-27.

[36] Maycox PR, Kelly F, Taylor A, *et al*. Analysis of gene expression in two large schizophrenia cohorts identifies multiple changes associated with nerve terminal function. Mol Psychiatry 2009; 14(12): 1083-94.

[37] Narayan S, Tang B, Head SR, *et al*. Molecular profiles of schizophrenia in the CNS at different stages of illness. Brain Res 2008; 1239: 235-48.

[38] Cattane N, Minelli A, Milanesi E, *et al*. Altered gene expression in schizophrenia: findings from transcriptional signatures in fibroblasts and blood. PloS One 2015; 10(2): e0116686.

[39] Bousman CA, Chana G, Glatt SJ, *et al*. Preliminary evidence of ubiquitin proteasome system dysregulation in schizophrenia and bipolar disorder: convergent pathway analysis findings from two independent samples. Am J Med Genet Part B Neuropsychiatr Genet 2010; 153B(2): 494-502.

[40] Lewis PA, Cookson MR. Gene expression in the Parkinson's disease brain. Brain Res Bull 2012; 88(4): 302-12.

[41] Chong MS, Goh LK, Lim WS, *et al*. Gene expression profiling of peripheral blood leukocytes shows consistent longitudinal downregulation of TOMM40 and upregulation of KIR2DL5A, PLOD1, and SLC2A8 among fast progressors in early Alzheimer's disease. J Alzheimer's Dis 2013; 34(2): 399-405.

[42] Mirza Z, Kamal MA, Buzenadah AM, Al-Qahtani MH, Karim S. Establishing genomic/transcriptomic links between Alzheimer's disease and type 2 diabetes mellitus by meta-analysis approach. CNS Neurol Disord Drug Targets 2014; 13(3): 501-16.

[43] Mirza Z, Schulten HJ, Farsi HM, *et al*. Molecular interaction of a kinase inhibitor midostaurin with anticancer drug targets, S100A8 and EGFR: transcriptional profiling and molecular docking study for kidney cancer therapeutics. PloS One 2015; 10(3): e0119765.

[44] Shi J, Levinson DF, Duan J, *et al*. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 2009; 460(7256): 753-7.

[45] Fellerhoff B, Laumbacher B, Mueller N, Gu S, Wank R. Associations between Chlamydophila infections, schizophrenia and risk of HLA-A10. Mol Psychiatry 2007; 12(3): 264-72.

[46] Baxter HC, Liu WG, Forster JL, Aitken A, Fraser JR. Immunolocalisation of 14-3-3 isoforms in normal and scrapie-infected murine brain. Neuroscience 2002; 109(1): 5-14.

[47] Berg D, Holzmann C, Riess O. 14-3-3 proteins in the nervous system. Nat Rev Neurosci 2003; 4(9): 752-62.

[48] Rittinger K, Budman J, Xu J, *et al*. Structural analysis of 14-3-3 phosphopeptide complexes identifies a dual role for the nuclear export signal of 14-3-3 in ligand binding. Mol Cell 1999; 4(2): 153-66.

[49] Fu H, Subramanian RR, Masters SC. 14-3-3 proteins: structure, function, and regulation. Annu Rev Pharmacol Toxicol 2000; 40: 617-47.

[50] Skoulakis EM, Davis RL. 14-3-3 proteins in neuronal development and function. Mol Neurobiol 1998; 16(3): 269-84.

[51] Li Y, Wu Y, Zhou Y. Modulation of inactivation properties of CaV2.2 channels by 14-3-3 proteins. Neuron 2006; 51(6): 755-71.

[52] Middleton FA, Peng L, Lewis DA, Levitt P, Mirnics K. Altered expression of 14-3-3 genes in the prefrontal cortex of subjects with schizophrenia. Neuropsychopharmacology 2005; 30(5): 974-83.

[53] Schubert KO, Focking M, Cotter DR. Proteomic pathway analysis of the hippocampus in schizophrenia and bipolar affective disorder implicates 14-3-3 signaling, aryl hydrocarbon receptor signaling, and glucose metabolism: Potential roles in GABAergic interneuron pathology. Schizophrenia Res 2015; 167(1-3): 64-72.

[54] Foote M, Qiao H, Graham K, Wu Y, Zhou Y. Inhibition of 14-3-3 Proteins Leads to Schizophrenia-Related Behavioral Phenotypes and Synaptic Defects in Mice. Biol Psychiatry 2015; 78(6): 386-95.

[55] Wong AH, Likhodi O, Trakalo J, *et al*. Genetic and post-mortem mRNA analysis of the 14-3-3 genes that encode phosphoserine/threonine-binding regulatory proteins in schizophrenia and bipolar disorder. Schizophr Res 2005; 78(2-3): 137-46.

[56] Bell R, Munro J, Russ C, *et al*. Systematic screening of the 14-3-3 eta (eta) chain gene for polymorphic variants and case-control analysis in schizophrenia. Am J Med Genet 2000; 96(6): 736-43.

[57] Muratake T, Hayashi S, Ichikawa T, *et al*. Structural organization and chromosomal assignment of the human 14-3-3 eta chain gene (YWHAH). Genomics 1996; 36(1): 63-9.

[58] Vawter MP, Barrett T, Cheadle C, *et al*. Application of cDNA microarrays to examine gene expression differences in schizophrenia. Brain Res Bull 2001; 55(5): 641-50.

[59] Kirov G, Pocklington AJ, Holmans P, *et al*. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. Mol Psychiatry 2012; 17(2): 142-53.

[60] Fromer M, Pocklington AJ, Kavanagh DH, *et al*. De novo mutations in schizophrenia implicate synaptic networks. Nature 2014; 506(7487): 179-84.

[61] Macian F. NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol 2005; 5(6): 472-84.

[62] Tian Y, Voineagu I, Pasca SP, *et al*. Alteration in basal and depolarization induced transcriptional network in iPSC derived neurons from Timothy syndrome. Genome Med 2014; 6(10): 75.

[63] Graef IA, Crabtree GR, Wang F. Calcineurin/NFAT Signaling in Development and Function of the Nervous System. Transcription Factors in the Nervous System: Wiley-VCH Verlag GmbH & Co. KGaA; 2006; pp. 353-78.

[64] Bannai H, Levi S, Schweizer C, *et al*. Activity-dependent tuning of inhibitory neurotransmission based on GABAAR diffusion dynamics. Neuron 2009; 62(5): 670-82.

[65] Wolfe SA, Zhou P, Dotsch V, *et al*. Unusual Rel-like architecture in the DNA-binding domain of the transcription factor NFATc. Nature 1997; 385(6612): 172-6.

[66] Chen L, Glover JN, Hogan PG, Rao A, Harrison SC. Structure of the DNA-binding domains from NFAT, Fos and Jun bound specifically to DNA. Nature 1998; 392(6671): 42-8.

[67] Miyakawa T, Leiter LM, Gerber DJ, *et al*. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. Proc Natl Acad Sci USA 2003; 100(15): 8987-92.

[68] Marks F, KlingmÙller U, Müller-Decker K. Cellular signal processing: an introduction to the molecular mechanisms of signal transduction. Garland Science; 2008.

[69] Fatemi SH, Folsom TD, Rooney RJ, Thuras PD. Expression of GABAA alpha2-, beta1- and epsilon-receptors are altered significantly in the lateral cerebellum of subjects with schizophrenia, major depression and bipolar disorder. Transl Psychiatry 2013; 3: e303.

[70] Ge S, Pradhan DA, Ming GL, Song H. GABA sets the tempo for activity-dependent adult neurogenesis. Trends Neurosci 2007; 30(1): 1-8.

[71] Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005; 6(4): 312-24.

[72] Koran LM. gamma-Aminobutyric-acid deficiency in schizophrenia. Lancet (London, England) 1976; 2(7993): 1025.

[73] Mohler H. GABAA receptors in central nervous system disease: anxiety, epilepsy, and insomnia. J Recep Signal Transduct Res 2006; 26(5-6): 731-40.

[74] Rothermundt M, Arolt V, Bayer TA. Review of immunological and immunopathological findings in schizophrenia. Brain Behav Immunity 2001; 15(4): 319-39.

[75] Smyth AM, Lawrie SM. The neuroimmunology of schizophrenia. Clin Psychopharmacol Neurosci 2013; 11(3): 107-17.

[76] Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 2007; 8(1): 45-56.

[77] Fries P. Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 2009; 32: 209-24.

[78] Lo WS, Harano M, Gawlik M, *et al*. GABRB2 association with schizophrenia: commonalities and differences between ethnic groups and clinical subtypes. Biol Psychiatry 2007; 61(5): 653-60.

[79] Papadimitriou G, Dikeos D, Daskalopoulou E, *et al*. Association between GABA-A receptor alpha 5 subunit gene locus and schizophrenia of a later age of onset. Neuropsychobiology 2001; 43(3): 141-4.

[80] Petryshen TL, Middleton FA, Tahl AR, *et al*. Genetic investigation of chromosome 5q GABAA receptor subunit genes in schizophrenia. Mol Psychiatry 2005; 10(12): 1074-88.

[81] Fatemi SH, Folsom TD, Thuras PD. Deficits in GABA(B) receptor system in schizophrenia and mood disorders: a postmortem study. Schizophr Res 2011; 128(1-3): 37-43.

[82] Quadrato G, Elnaggar MY, Duman C, Sabino A, Forsberg K, Di Giovanni S. Modulation of GABAA receptor signaling increases neurogenesis and suppresses anxiety through NFATc4. J Neurosci 2014; 34(25): 8630-45.

Received: September 15, 2015 **Revised: December 28, 2015** **Accepted: December 29, 2015**