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RESEARCH

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Genome-wide landscape of RNA-binding protein (RBP) networks as potential molecular regulators of psychiatric co-morbidities: a computational analysis

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Abstract

Background Psychiatric disorders are a major burden on global health. These illnesses manifest as co-morbid conditions, further complicating the treatment. There is a limited understanding of the molecular and regulatory basis of psychiatric co-morbidities. The existing research in this regard has largely focused on epigenetic modulators, non-coding RNAs, and transcription factors. RNA-binding proteins (RBPs) functioning as multi-protein complexes are now known to be predominant controllers of multiple gene regulatory processes. However, their involvement in gene expression dysregulation in psychiatric co-morbidities is yet to be understood.

Results Ten RBPs (QKI, ELAVL2, EIF2S1, SRSF3, IGF2BP2, EIF4B, SNRNP70, FMR1, DAZAP1, and MBNL1) were identified to be associated with psychiatric disorders such as schizophrenia, major depression, and bipolar disorders. Analysis of transcriptomic changes in response to individual depletion of these RBPs showed the potential influence of a large number of RBPs driving differential gene expression, suggesting functional cross-talk giving rise to multi-protein networks. Subsequent transcriptome analysis of post-mortem human brain samples from diseased and control individuals also suggested the involvement of ~ 100 RBPs influencing gene expression changes. These RBPs were found to regulate various processes including transcript splicing, mRNA transport, localization, stability, and translation. They were also found to form an extensive interactive network. Further, hnRNP, SRSF, and PCBP family RBPs, Matrin3, U2AF2, KHDRBS1, PTBP1, and also PABPN1 were found to be the hub proteins of the RBP network.

Conclusions Extensive RBP networks involving a few hub proteins could result in transcriptome-wide dysregulation of post-transcriptional modifications, potentially driving multiple psychiatric disorders. Understanding the functional involvement of RBP networks in psychiatric disorders would provide insights into the molecular basis of psychiatric co-morbidities.

Keywords RNA-binding proteins, Protein-protein interactions, Psychiatric disorders, Co-morbidities, Molecular psychiatry, Post-transcriptional regulation

Background

Mental illnesses are a major cause of morbidity and mortality across age groups globally [1]. Depression, schizophrenia, and bipolar disorders account for an estimated 264 million, 20 million, and 45 million cases of psychiatric disorders respectively [2]. Existing treatments for these disorders help only a small subset of patients. Thus,

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there is a need for a better understanding of the biological basis of these disorders and identify novel therapeutic targets. Notably, psychiatric disorders are known to manifest as co-morbid conditions, indicating a potentially shared underlying biology. Patients with schizophrenia are known to have higher risk of anxiety and depression, substance use disorders, post-traumatic stress disorder, as well as obsessive–compulsive disorder [3, 4]. Similarly, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD) [5], and substance use disorders [6] are known to be co-morbid. The molecular basis of these psychiatric disorders and co-morbidities are yet to be understood [7]. Recent research has highlighted the importance of understanding the biological basis of disease co-morbidities [8]. Thus, delineating the molecular regulation of psychiatric co-morbidities would be imperative for more efficient treatment strategies.

Several studies have revealed extensive gene expression dysregulation associated with psychiatric conditions. A number of genes are also known to be commonly dysregulated across psychiatric disorders [9, 10]. A better understanding of the regulatory mechanisms resulting in gene expression dysregulation could provide further insights into multiple genes and their networks affected by common regulatory factors. In this regard, most studies on molecular regulation in mental illnesses have focused on transcription factors, microRNAs, long non-coding RNAs, alternative splicing, and epigenetic modifications [11–14]. However, recent research has highlighted the dominant role of RNA-binding proteins (RBPs) on gene regulatory processes [15, 16]. Though the involvement of RBPs in disorders such as cancers [17], genetic diseases [18], cardiovascular diseases [19], diabetes [20], and neurodegenerative diseases [21] has been established, their potential involvement in mental illnesses is only beginning to be understood. A recent report has suggested the involvement of dysregulated RBP-binding sites in psychiatric conditions [22]. Hence, further understanding of the involvement of RBPs in gene expression dysregulation in mental illnesses could provide new insights into the molecular basis of these disorders.

RBPs are known to function as multi-protein complexes. RBP networks composed of multi-protein clusters are known to regulate common targets. Such RBP clusters could form master-regulatory modules of cellular processes [23]. The complexity and functional implications of these RBP networks are now beginning to be understood [24]. Owing to the progress in our understanding of the importance of RBPs in disease conditions, therapeutic approaches such as RBP-PROTACs are being developed to manipulate RBP functioning [25]. However, since manipulating the functions of individual RBPs could potentially affect multiple other RBPs and RBP networks, a holistic understanding of the RBP networks would be of high scientific and clinical importance.

In light of these research reports, the present study focused on identification of RBPs involved in psychiatric disorders, and the analysis of their potential interactions could give rise to RBP networks and combinatorial gene regulatory modules. To this end, the RBPs associated with psychiatric disorders and their potential interactions were identified. Subsequently, publicly available transcriptome data were analysed to identify other RBPs which could be functionally related. Further, transcriptome data from human post-mortem brain samples were retrieved from public repositories and analysed to identify RBPs implicated in gene expression dysregulation in psychiatric conditions (major depression, schizophrenia, and bipolar disorder). These analyses suggested a significant number of RBPs potentially involved in psychiatric disorders. Next, the interactive networks of the identified RBPs were analysed, which revealed extensive connections among them. Subsequently, hub proteins having more pronounced inter-connections were identified, which showed hnRNP, PCBP, SRSF family RBPs, Matrin3, and PTBP to be among the hub RBPs. Thus, the present study identified RBPs and their networks, which could be driving transcriptomic dysregulation in multiple psychiatric disorders. In future, large-scale human studies to understand their functional implications in mental health could be of importance, towards a holistic understanding of molecular regulation of psychiatric co-morbidities.

Materials and methods

Identification of RBPs associated with psychiatric disorders and their potential interactions

In order to identify RBPs associated with psychiatric disorders, the genes curated onto PsyGeNET database (v2.0) (http://www.psygenet.org/web/PsyGeNET/menu) [26] were compared with the known RBPs from Transite database (v1.2.1) (transite.mit.edu/) [27]. PsyGeNET is an expert-curated database of disease-gene associations in psychiatric disorders, comprising 1549 genes and 117 diseases. Transite provides a computational platform for the analysis of RBP-mediated gene expression changes in transcriptomic studies, encompassing a database of ~ 150 RBPs from human and mouse, with known target motifs. Thus, comparing the psychiatric disease-associated genes from PsyGeNET with RBPs from Transite yielded the RBPs associated with psychiatric disorders. Subsequently, potential interactions between these RBPs were analysed via STRING (https://string-db.org/) (v11.5).

Analysis of transcriptome-wide differential gene expression and identification of potential RBPs driving gene expression changes

Due to combinatorial functioning, modulating individual RBPs could affect a multitude of other RBPs. In order to understand such potential interaction networks, the transcriptomes of human cell lines subjected to genetic manipulation (knock-down/knockout/overexpression) of the psychiatric disease-associated RBPs were analysed. The transcriptome studies related to the gene expression patterns associated with genetic manipulation of the considered RBPs were identified on GEO database (https://www.ncbi.nlm.nih.gov/geo/). The studies on human cell lines with at least two replicates per condition (control and knock-down/knockout/overexpression) were considered. Differential gene expression patterns of RNA-seq and microarray studies were analysed using OneStopRNAseq (v1.0.0; https://mccb.umassmed.edu/OneStopRNAseq/index.php) [28] and GEO2R tools (https://www.ncbi.nlm.nih.gov/geo/geo2r/), respectively. OneStopRNAseq is a comprehensive platform for the analysis of RNA-seq data, including quality check (via FastQC v0.11.5 and MultiQC v1.6), alignment (via STARv. 2.7.5a), read summarization (via featureCountsv.2.0.0), and differential gene expression (via DESeq2v 1.28.1). Human genome hg38 (gencode. v34.primary_assembly) was used as reference. The differentially expressed genes (DEGs) were identified with a false discovery rate (FDR) threshold of 0.05 and minimum log2 fold change threshold of 0.585. The microarray datasets were analysed through GEO2R (using default settings). GEO2R identifies statistically significant DEGs via GEOquery and limma packages within R framework. The gene expression levels in knockout/knock-down/overexpression (experimental) groups were compared to those of control datasets. Similarly, transcriptome studies of human post-mortem brain samples involving at least two psychiatric disorders were identified on GEO database (shown in Table 2), followed by differential gene expression analysis as described above.

Further, the RBPs having enriched binding sites within 5' and 3' untranslated regions (UTRs) of the DEGs were identified using Transite (https://transite.mit.edu/) (v1.2.1) [27]. Transite performs global computational identification of RBPs involved in post-transcriptional regulation (PTGR) of gene expression using RNA-seq or microarray data. Transcript Set Motif Analysis (TSMA) was employed to identify statistically significant overrepresentation of RBP target motifs in the UTRs of DEGs. TSMA was performed via k-mer and matrix-based approaches. k-mer-based approach identifies RBPs by comparing the hexamer/heptamer (k-mer) sequences between the foreground (DEGs) and background (all genes identified in the transcriptomic study) datasets. Matrix-based approach identifies the potential RBP-binding sites by scoring the sequence positions within the foreground and background datasets. Thus, the platform identifies statistically significant RBP target motifs potentially contributing to RBP-mediated PTGR.

Analysis of protein–protein interaction network, identification of significant modules, and hub proteins

Protein interaction network was obtained using STRING database (https://string-db.org/) (v11.5). Experimentally deciphered as well as the predicted interactions were visualized using default settings, against *Homo sapiens* database. The network from STRING was exported to Cytoscape (v3.8) [29]. The significant modules within the network were identified using MCODE (v2.0.0) plug-in of Cytoscape, using default settings (degree cut-off = 2, node score cut-off = 0.2, k-core = 2, maximum depth = 100). The hub proteins of the network were identified using Cytoscape through the cytoHubba (v0.1) plug-in [30]. Top 20 hub proteins were identified and ranked using maximal clique centrality (MCC) method.

Analysis of gene ontology and expression levels

The functional aspects affected by the selected RBPs were identified by analysing the enriched gene ontology terms of biological processes, associated with them. ShinyGO (v0.75) web server (http://bioinformatics.sdstate.edu/go/; [31]) was used to perform gene ontology analysis, using default settings. The gene expression levels in different brain regions were obtained using the human protein atlas (v.21.0) (https://www.proteinatlas.org/).

Results

Identification of RBPs associated with psychiatric disorders and analysis of their potential interactions

Comparison of the genes associated with psychiatric diseases (from PsyGeNET database) with human/mouse RBPs (from Transite database) yielded ten common RBPs: QKI, ELAVL2, EIF2S1, SRSF3, IGF2BP2, EIF4B, SNRNP70, FMR1, DAZAP1, and MBNL1 (Fig. 1a). The gene names and associated disorders for each gene are provided in Additional file 3: Table S1. Overall, these RBPs were associated with schizophrenia, major depressive disorder, bipolar disorder, and mixed anxiety. The analysis of interactions between these RBPs showed that they could potentially form an interactive network (Fig. 1b). Thus, it could be inferred that combinatorial functioning of RBPs could influence psychiatric disorders.

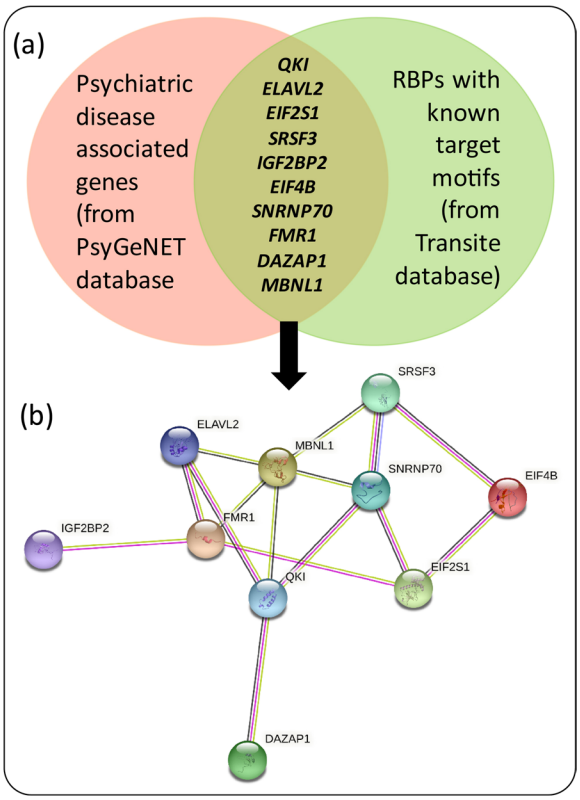

Fig. 1 Psychiatric disorders-associated RBPs. **a** Psychiatric disease-associated genes from PsyGeNET database (http://www.psygenet.org [26]) were compared with RBPs curated onto Transite (https://transite.mit.edu/ [27]), to identify RBPs associated with psychiatric disorders. This comparison identified ten RBPs to be associated with psychiatric disorders. **b** The identified RBPs were also found to form a potential interactive network

Identification of RBPs driving differential gene expression in response to in vitro genetic manipulation of psychiatric disorder-associated RBPs

Owing to the combinatorial functioning, modulating the activity of individual RBPs could influence other RBPs and larger networks. In the present study, transcriptome-wide gene expression changes in response to manipulation of individual RBPs were analysed for the potential involvement of other RBPs in modulating gene expression through 5′ and 3′UTRs of DEGs. For this purpose, the transcriptomic datasets associated with gene expression changes in response to knock-down (KD)/knockout (KO)/overexpression of RBPs were selected. The details of transcriptome datasets considered for this study are given in Table 1. These transcriptome datasets were analysed to identify DEGs. (The number of DEGs found in each dataset is given in Table 1.) Subsequently, the RBPs having overrepresented target motifs within the 5′ and 3′ UTRs of DEGs were identified. A compiled list of RBPs with significant overrepresentation ($p < 0.05$) of target motifs, potentially influencing the transcriptome, are given in Additional file 1. The number of RBPs having enriched binding sites in the UTRs of DEGs in response to depletion of the individual RBPs is shown in Fig. 2. 3′UTRs of the DEGs were found to have a higher number of RBP target motifs across the datasets (Fig. 2). Also, depletion of *SRSF3* and *DAZAP1* was found to potentially cause widespread gene expression changes via 3′UTRs as well as 5′UTRs, mediated by multiple other RBPs (Fig. 2).

RBPs influencing gene expression changes in diseased post-mortem human brain samples

Transcriptomic data from diseased post-mortem human brain samples (schizophrenia, bipolar, and major depressive disorders; Table 2) were analysed to identify DEGs with respect to control individuals. The DEGs were further studied to detect overrepresented RBP-binding sites within their 5' and 3' UTRs, which could influence differential gene expression. Thirteen RBPs were found to be common in all the three disorders—CPEB3/CPEB4, DAZAP1, ELAVL1/ELAVL3, hnRNPC, hnRNPCL1, PCBP4/PCBP1/PCBP3, PCBP4/PCBP3, PTBP1/PTBP2/ROD1, RBMS2/RBMS1, SF3B4, TARDBP, U2AF2, and YBX2/CSDA (Fig. 3), indicating their potential involvement in molecular dysregulation of multiple disorders. The dataset-wise number of RBPs found to be influencing differential gene expression in diseased samples is given in Table 2.

RBPs common between in vitro and human brain datasets

In order to get insights into the overall interactive networks of the identified RBPs, common RBPs between those found to be involved in psychiatric disorders, as well as those driving gene expression changes in in vitro datasets were identified. This comparison yielded 132 RBPs (Additional file 2). The functions of these RBPs were analysed through gene ontology terms (biological processes) significantly associated with them. As shown in Fig. 4, the identified RBPs were found to be involved in multiple aspects of transcript regulation including RNA splicing, stabilization, degradation, transport, as well as localization. Thus, it could be inferred that the RBP networks potentially involved in dysregulated gene expression in diseased conditions could affect multiple processes at the post-transcriptional level.

Analysis of interaction network of the identified RBPs, significant modules, and identification of hub proteins

The RBPs found to be common between in vitro and human brain datasets were analysed for their potential interactions, via STRING. This analysis revealed a protein interaction network containing 120 nodes and 1447 edges (Fig. 5a). Further identification of significant

Table 1 Human cell line-based transcriptome datasets considered in the present work

S. No	RBP	Dataset (GEO ID)	Cell line	DEGs (up/down regulated)	Experiment (Knock-down/KD or knockout/KO)	Reference
1	*QKI*	GSE153803	C25Cl48 (muscular cell line)	None	siRNA KD, RNA-seq	[32]
2	*ELAVL2*	GSE69092	Primary neural progenitor cells	0/3	shRNA KD, RNA-seq	[33]
3	*EIF2S1*	GSE80933	HepG2 (human liver cancer cell line)	2656/2748	shRNA KD, RNA-seq	[34]
		GSE80900	K562 (lymphoblasts)	37/25	shRNA KD, RNA-seq	
4	*SRSF3*	GSE98016	MDA-MB231 (epithelial cell line from breast cancer tissue)	2909/3394	shRNA KD, RNA-seq	[35]
		GSE130501	Primary glioma stem-like cells (GSCs)	257/180	CRISPR KO, RNA-seq	[36]
		GSE177820	K562 (lymphoblasts)	2277/1455	CRISPR KO, RNA-seq	[34]
		GSE71095	HeLa cells	36/2	siRNA KD, RNA-seq	[37]
		GSE71745	A2780 (ovarian cancer cell line)	None	siRNA KD, microarray	[37]
5	*IGF2BP2*	GSE80946	K562 (lymphoblasts)	1144/289	shRNA KD, RNA-seq	[34]
		GSE80890	HepG2 (human liver cancer cell line)	1709/1926	shRNA KD, RNA-seq	
		GSE146726	UMUC3 (Bladder carcinoma)	472/631	siRNA KD, RNA-seq	[38]
			J8	566/511		
6	*EIF4B*	GSE177138	HepG2 (human liver cancer cell line)	9/7	CRISPR KO, RNA-seq	[34]
		GSE80923	K562 (lymphoblasts)	20/43	shRNA KD, RNA-seq	
		GSE80875	HepG2 (human liver cancer cell line)	2490/2474		
7	*SNRNP70*	GSE88425	HepG2 (human liver cancer cell line)	1960/1877	shRNA KD, RNA-seq	
8	*FMR1*	GSE177341	K562 (lymphoblasts)	1346/1058	shRNA KD, RNA-seq	
		GSE117248	hiPSC-derived neurons	2788/2864	KO, RNA-seq	[39]
9	*DAZAP1*	GSE88637	K562 (lymphoblasts)	261/51	shRNA KD, RNA-seq	[34]
		GSE88114	HepG2 (human liver cancer cell line)	531/651		
		GSE80929	HepG2 (human liver cancer cell line)	1450/1060		
		GSE153803	C25Cl48 (Muscular cell line)	None	siRNA KD, RNA-seq	[32]
		GSE97262	SH-SY5Y (neuroblastoma cell line)	1684/3346		[40]
10	*MBNL1*	GSE149435	MDA-MB-231 (epithelial breast cancer cell line)	673/693	siRNA KD, RNA-seq	[41]
		GSE114383	PC3 (Prostate cancer cell line)	903/15	Antisense oligonucleotide-mediated KD, RNA-seq	[42]
		GSE41987	HeLa	None	MBNL1-overexpression, microarray	-
		GSE88116	K562 (lymphoblasts)	1467/527	shRNA KD, RNA-seq	[34]
		GSE76487	MDA-MB-231(breast cancer cell line)	0/6	shRNA KD, RNA-seq	[43]
		GSE153803	C25Cl48 muscular cell line	None	siRNA KD, RNA-seq	[32]

modules in this network showed the presence of four prominent modules of interacting proteins. Module-1 consisted of 37 nodes and 615 edges, comprising hnRNP family proteins, SRSF, and PABP family RBPs among others (Fig. 5b). Module-2 consisted of 5 nodes and 8 edges, consisting of the RBPs QKI, RBM4, KHDRBS3, PTBP2, and RBFOX2 (Fig. 5c). The two other modules consisted of 3 nodes and 3 edges each. ESRP2, KHDRBS2, and RBM24 constituted module-3, while module-4 consisted of CPEB family proteins (Fig. 5d, e). Thus, the identified RBPs were found to have potentially extensive inter-connections, with significant modules containing hnRNP, CPEB, and RBM family proteins.

Further, the network was analysed to identify top twenty hub proteins, which revealed hnRNP and SRSF family proteins, PTBP1, PABPN1, PCBP2, MATR3, and PCBP1 to be among the hub proteins of the network (Fig. 6a and Table 3). Additionally, the expression levels of the hub proteins were analysed in different regions of human brain. Interestingly, the expression levels of hnRNPA1 were found to be relatively high in most regions considered, except olfactory bulb and hippocampal formation (Fig. 6b). The expression levels of most genes were higher in cerebral cortex, while they were substantially low in olfactory bulb. Hypothalamus

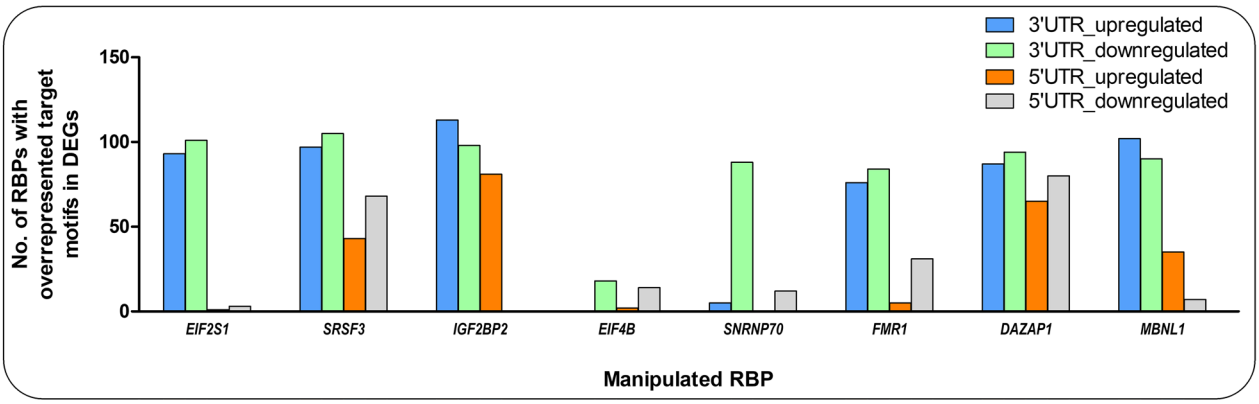

Fig. 2 Effect of the depletion of psychiatric disorder-associated RBPs on global gene expression regulation by RBPs. Transcriptomic changes in human cell lines subjected to genetic manipulation (knock-down/knockout) of the selected RBPs were analysed to identify up/downregulated genes (differentially expressed genes/DEGs). The untranslated regions (UTRs) of DEGs were screened to identify overrepresented target motifs of known RBPs, using Transite (https://transite.mit.edu/) [27]. A number of RBPs with overrepresented binding sites in the UTRs of DEGs (y-axis) associated with the selected RBPs (x-axis) are shown. Overall, 3'UTRs were found to be highly enriched for RBP target motifs

Table 2 Differential gene expression and RBP analysis of transcriptome datasets from post-mortem human brain samples

S. No	Dataset [Reference]	Disorders	Sample size	Brain regions	No. of DEGs (control vs. diseased brain samples)	RBPs influencing differential expression
1	GSE53987 [44]	MDD, BD, and SCZ	BD:18–19 Control:17–19; SCZ:15–18	Hippocampus, PFC[a], and striatum	MDD and BD: none; SCZ: 4835 (hippocampus), 19 (PFC)	NA
2	GSE92538 [45]	MDD, BD, and SCZ	BD: 12 Control: 56 MDD: 29 SCZ:31	DLPFC[b]	BD: none; SCZ: 681; MDD: 1760	MDD: 97 SCZ: 94
3	GSE120340 [46]	BD and SCZ	BD with psychosis: 6 BD without psychosis: 4 SCZ: 10 Control: 10	DLPFC[b]	None	NA
4	GSE35977 [47]	BD, depression, and SCZ	BD: 45 Control: 50 Depression: 14 SCZ: 51	Parietal cortex	BD and depression: none; SCZ: 38	NA
5	GSE35974 [48]	BD, depression, and SCZ	BD: 37 Control: 50 Depression: 13 SCZ: 44	Cerebellum	BD: 953; depression: 6; SCZ: 373	BD: 15 SCZ: 1
6	GSE12679 [49]	BD and SCZ	BD: 5 Control: 5–6 SCZ: 11	Endothelial cells/neurons isolated from post-mortem DLPFC[b]	None	NA

[a] Prefrontal cortex

[b] Dorsolateral prefrontal cortex

was found to have a higher expression of the hnRNP family RBPs, except hnRNPH1 and hnRNPDL.

Discussion

Psychiatric conditions such as schizophrenia, major depression, and bipolar disorders often manifest as co-morbidities [3, 4]. Understanding the genetic and regulatory basis of psychiatric co-morbidities could provide insights into their molecular underpinnings and open-up potential therapeutic strategies. The available research reports on gene expression dysregulation in psychiatric conditions have focused on microRNA-mediated processes, alternative splicing, epigenetics, and non-coding RNAs [11–14]. Recent studies have established RBPs

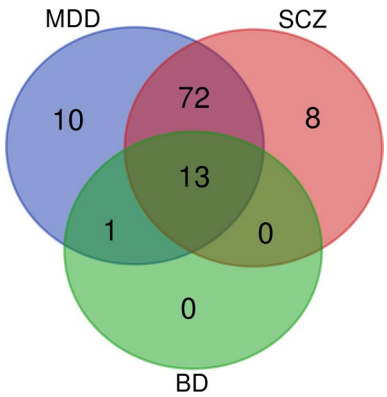

Fig. 3 Number of RBPs potentially driving differential gene expression in diseased post-mortem human brain samples. Differentially expressed genes within the transcriptome datasets of post-mortem human brain samples (schizophrenia/SCZ, major depressive disorder/MDD, and bipolar disorder/BD) were analysed to identify the potential RBPs driving gene expression changes in disease conditions. Thirteen RBPs (CPEB3/CPEB4, DAZAP1, ELAVL1/ELAVL3, hnRNPC, hnRNPCL1, PCBP4/PCBP1/PCBP3, PCBP4/PCBP3, PTBP1/PTBP2/ROD1, RBMS2/RBMS1, SF3B4, TARDBP, U2AF2, and YBX2/CSDA) were found to be involved in the three disorders considered, indicating their potential central roles in multiple disorders

as a dominant class of regulatory proteins influencing multiple aspects of transcript regulation [15]. However, their potential involvement in psychiatric disorders is only beginning to be understood. RBPs form protein–protein interaction networks which could act as master regulators of gene expression [23, 50]. The present study employed computational approaches to identify RBPs potentially driving gene expression dysregulation in psychiatric conditions and co-morbidities. As a result, RBP network consisting of hub proteins including hnRNP, SRSF, PCBP family members, as well as Matrin3, PTBP, and PABPN1, was identified to be potentially involved in psychiatric co-morbidities.

To begin with, PsyGeNET, a database of genes associated with psychiatric disorders [26], was screened to find the RBPs implicated in various psychiatric disorders, identifying ten RBPs, viz. *QKI*, *ELAVL2*, *EIF2S1*, *SRSF3*, *IGF2BP2*, *EIF4B*, *SNRNP70*, *FMR1*, *DAZAP1*, and *MBNL1*. These RBPs are known to regulate multiple aspects of neural biology, thereby influencing disease conditions. The mRNA levels of *QKI* isoforms *QKI5*, *6*, and *7* have been reported to be strongly perturbed in several cortical regions and hippocampus, in schizophrenic patients [51]. QKI has been implicated in astrocyte maturation in mouse brain, wherein it was found to

Fig. 4 Gene ontology analysis of the identified RBPs. Biological processes associated with the common RBPs were identified via gene ontology (GO) enrichment analysis (ShinyGO v0.75; http://bioinformatics.sdstate.edu/go/) [31]. Significantly enriched GO terms were identified with FDR cut-off of 0.05, using human database

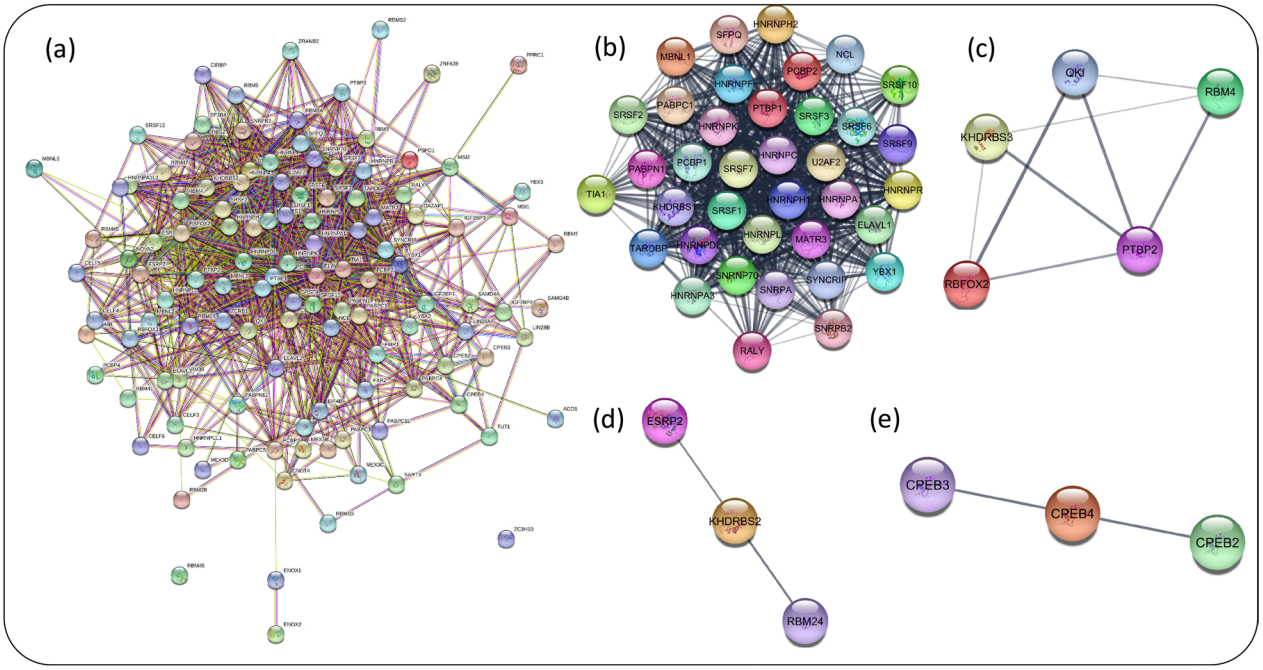

Fig. 5 Protein–protein interaction networks of the identified RBPs, and significant modules within the network. **a** The interaction network was obtained through STRING database (v11.5) (https://string-db.org/), using default settings. **b-e** Subsequently, significant modules within the network were identified using Cytoscape (v3.8.0) [29], through the MCODE plug-in. Four modules were identified, having a high degree of connectivity with other proteins in the network

be important in stabilizing its target transcripts [52]. QKI proteins are now known to regulate multiple aspects of

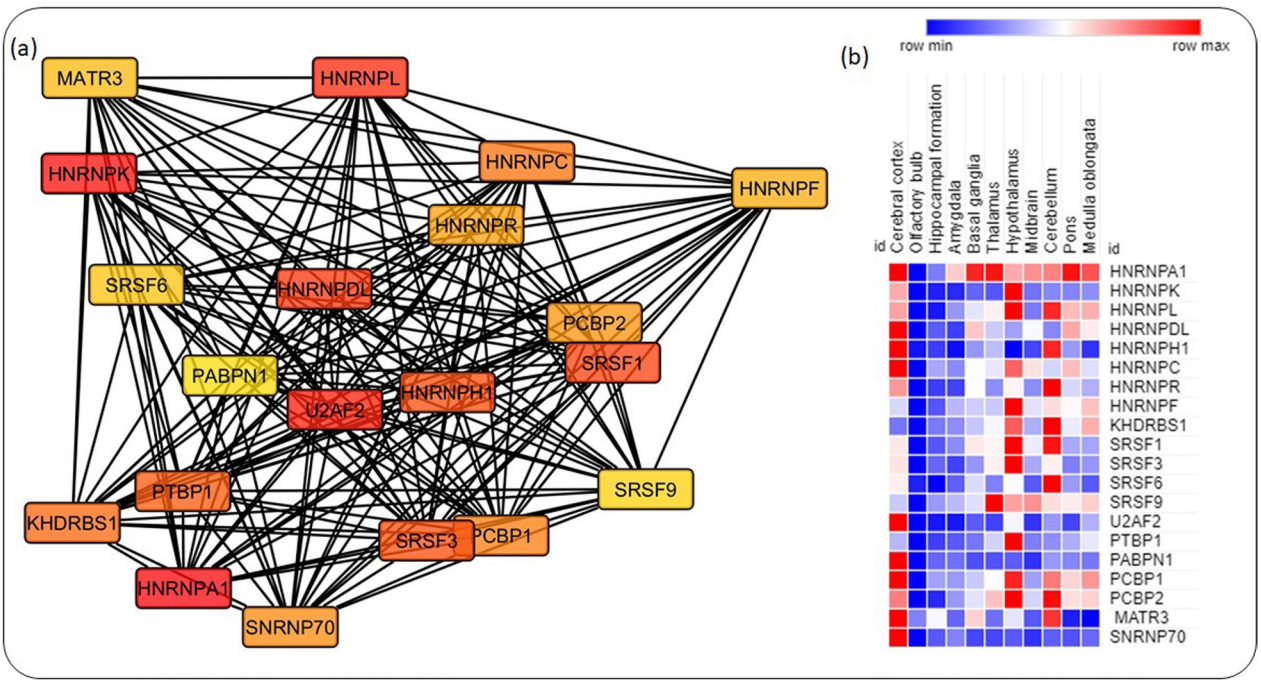

Fig. 6 Top 20 hub RBPs in the protein interaction network and their expression levels. **a** The hub RBPs were identified using cytoHubba plug-in [30] of Cytoscape (v3.8.0), ranked by maximal clique centrality (MCC) method. **b** Gene expression levels in different regions of the brain were obtained from the human protein atlas (https://www.proteinatlas.org/)

Table 3 Top 20 hub proteins identified in the RBP network

Rank	Hub RBP	Protein name
1	HNRNPA1	Heterogeneous nuclear Ribonucleoprotein A1
2	HNRNPK	Heterogeneous nuclear Ribonucleoprotein K
3	U2AF2	U2 small nuclear RNA auxiliary factor 2
4	HNRNPL	Heterogeneous nuclear Ribonucleoprotein L
5	HNRNPDL	Heterogeneous nuclear Ribonucleoprotein D like
6	SRSF1	Serine- and arginine-rich splicing factor 1
7	SRSF3	Serine- and arginine-rich splicing factor 3
8	HNRNPH1	Heterogeneous nuclear ribonucleoprotein H1
9	PTBP1	Polypyrimidine tract-binding protein 1
10	KHDRBS1	KH RNA-binding domain containing, signal transduction-associated 1
11	HNRNPC	Heterogeneous nuclear ribonucleoprotein C
12	PCBP1	Poly(rC)-binding protein 1
13	SNRNP70	Small nuclear ribonucleoprotein U1 subunit 70
14	PCBP2	Poly(rC)-binding protein 2
15	HNRNPR	Heterogeneous nuclear ribonucleoprotein R
16	HNRNPF	Heterogeneous nuclear ribonucleoprotein F
17	MATR3	Matrin3
18	SRSF6	Serine- and arginine-rich splicing factor 6
19	SRSF9	Serine- and arginine-rich splicing factor 9
20	PABPN1	Poly(A)-binding protein nuclear 1

gene expression regulation, including alternative splicing, mRNA stability, transcription, and translation [53]. ELAVL2 is known to be associated with schizophrenia and has been reported to be involved in regulation of *MMP-9* (*Matrix metalloproteinase-9*, implicated in several disorders including those of nervous system) mRNA stability in hippocampal neurons [54]. FMRP, encoded by *FXR1*, is widely studied for its involvement in brain function and plasticity. Mutations in *FXR1* are known to be associated with several psychiatric disorders including autism spectrum disorders, attention deficit and hyperactivity disorder, obsessive–compulsive disorder, and substance abuse [55, 56]. SRSF3 (serine-/arginine-rich splicing factor 3) is a member of SR family RBPs, involved in multiple regulatory processes including alternative splicing and polyadenylation, mRNA export, translation, and also microRNA processing [57]. SRSF3 is also implicated in bipolar disorder, wherein its mRNA levels were found to be elevated in peripheral white blood cells [58]. Aberrant mRNA translation is associated with a number of psychiatric conditions including schizophrenia, major depression, and bipolar disorder [59]. The translation initiation factor EIF4B was reported to be associated with major depressive disorder, wherein its levels were found to be reduced in prefrontal cortices of MDD patients [60]. It was also reported to be potentially involved in neuronal plasticity and synaptic changes [61]. The expression of EIF2, another initiation factor, was found to be dysregulated in schizophrenia [62]. EIF2S1 is a main initiation factor controlling protein synthesis, with important roles in cellular stress response associated with mitochondrial dysfunction in psychiatric disorders [63]. IGF2BP2 was reported to be involved in susceptibility to schizophrenia, indicating potential similarities in genetic bases of schizophrenia and diabetes [64]. DAZAP1 is a conserved hnRNP protein potentially involved in mRNA localization, alternative splicing, and translation [65] and is also a potential marker of bipolar disorder and schizophrenia [66]. On PsyGeNET database, SNRNP70, a major component of spliceosome, was associated with alcohol dependence. This protein was reported to regulate local protein synthesis in the synapses and also influence axonal growth and synapse formation [67]. MBNL1 is another protein involved in splicing, and a marker of schizophrenia [68]. Thus, multiple RBPs regulating transcript splicing, localization, and stability were found to be associated with psychiatric disorders.

RBPs are known to form interactive clusters and chains, and co-bind to their targets. Such clusters could contain cooperating/competing RBPs, giving rise to complex regulatory modules [23]. In order to get insights into multi-RBP networks modulating gene expression, it would be important to identify the RBPs potentially interacting with psychiatric disorder-associated RBPs. To this end, transcriptome studies related to gene expression changes in response to genetic manipulation (knockout/knock-down/overexpression) of the selected RBPs were identified, followed by their analysis to index all the RBPs which could be influencing differential gene expression. As a result, downregulation of individual RBPs associated with psychiatric disorders was found to result in global gene expression changes potentially driven by multiple other RBPs. 75–100 RBPs were found to influence transcriptomic changes in response to the depletion of *EIF2S1*, *SRSF3*, *IGF2BP2*, *FMR1*, *DAZAP1*, and *MBNL1*, mainly through the 3'UTRs of DEGs.

Subsequently, publicly available transcriptome data from diseased and control human brain samples were analysed to identify RBPs potentially driving differential gene expression in multiple psychiatric disorders, which could be an underlying molecular feature of psychiatric co-morbidities. Next, the RBPs obtained via the two approaches (analyses of in vitro and human brain transcriptomes) were compared to identify those RBPs commonly present in both the sets, which yielded 132 RBPs. These RBPs were found to be involved in multiple processes of post-transcriptional regulation, including splicing, mRNA transport, localization, and stabilization. Since mRNA transport and localization could have a profound impact on neuronal processes and plasticity

[69], RBPs controlling these processes could potentially contribute to local differential gene expression within the neurons and synapses. For example, RBPs such as TDP-43 (Transactive Response DNA-Binding Protein 43) and SMN (survival motor neuron) are known to influence local mRNA translation within axons and dendrites [70].

An analysis of potential interactions between the identified RBPs showed an extensive network. Four discrete modules were identified within this network. The larger module (with 37 nodes and 615 edges) was composed of hnRNP, SRSF, PCBP, and ELAVL family RBPs, implicating their widespread interactions. In agreement with this observation, further analysis of the network also identified hnRNP, SRSF, and PCBP family RBPs to be among the hub proteins. hnRNP family RBPs associate with the pre-mRNA and control their splicing, stability, and translation. Multiple hnRNPs have been implicated in neurological disorders and cancers. For example, hnRNPA1, A2, F, H, and K are known to regulate splicing, translation, and stability of the target transcripts, and are associated with amyotrophic lateral sclerosis [71]. hnRNPA2 and hnRNPC1 were found to be associated with Alzheimer's disease (AD), while hnRNPC1 is involved in fragile X syndrome [71]. These proteins interact with other RBPs, and disrupting such interactions could contribute to diseases like spinal muscular dystrophy and ALS [71]. hnRNPA1, which was the top ranked hub protein, is known to be associated with several neurological diseases including ALS, SMN, multiple sclerosis (MS), AD, and Huntington's disease [72]. Mutations and altered expression of hnRNPA1 could lead to dysregulated splicing, translation, and transport of the target transcripts [72]. PABPN1 is associated with oculopharyngeal muscular dystrophy (OPMD), characterized by $(GCN)_n$ mutation [73]. The SRSF proteins are involved in regulating alternative splicing [74]. *SRSF1*, *3*, *6*, and *9* were found to be among the hub proteins of the RBP network. SRSF1 is known to be important in functioning of T cells and is implicated in autoimmune diseases [75]. SRSF3 is involved in alternative splicing and polyadenylation, mRNA export, and also miRNA processing. Further, it is also associated with bipolar disorder, tauopathies, and AD [57], while SRSF6 was reported to be potentially associated with Huntington's disease [76]. PCBP1 and 2 are also potentially associated with neurological conditions. The target transcripts of PCBP1 were reported to be associated with neuropathies [77], while PCBP2 was found to be downregulated in ALS [78]. Matrin3 is an established RBP associated with ALS [79], which was also detected to be a hub RBP in the network. Thus, the hub proteins identified in the RBP network in this study are known to be involved in a number of neurological conditions, which suggests a shared molecular basis underlying these disorders.

The potential dysregulation of RBP activity in psychiatric disorders is recently being examined. SF3B4 (splicing factor 3B subunit 4) was associated with ADHD, bipolar disorder, and major depression [22]. Also, EFTUD2 (Elongation Factor Tu GTP-Binding Domain-Containing 2) was associated with ADHD, bipolar disorder, and schizophrenia, providing insights into shared molecular dysregulation in multiple psychiatric disorders [22]. Thus, the present study catalogued RBPs which could be potentially driving psychiatric co-morbidities. Future studies in this regard could elucidate the functional importance of these RBPs in disease conditions.

Conclusions

The present study involved the identification of RBPs associated with psychiatric disorders and also their interaction networks. The RBPs potentially driving gene expression changes in diseased human brain samples were also identified. Subsequently, hnRNP, PCBP, and SRSF family RBPs and a few other RBPs were found to form highly inter-connected hubs, representing their interactions with multiple other RBPs. These RBPs functioning as multi-protein networks could regulate multiple post-transcriptional regulatory processes. Disruption of one or a few RBPs could lead to dysfunction of the larger modules and networks, leading to multiple psychiatric conditions. The number of human studies conducted in this regard so far is limited, which could be a potential limitation of the present study. In future, large-scale functional studies to delineate the involvement of these RBPs in psychiatric co-morbidities could provide insights into gene regulatory processes underlying such conditions, which can help identify drug targets and design effective treatment strategies.

Abbreviations

AD	Alzheimer's disease
ADHD	Attention-deficit/hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
BD	Bipolar disorder
CPEB	Cytoplasmic polyadenylation element-binding protein
DAZAP1	DAZ-associated protein 1
DEG	Differentially expressed gene
DLPFC	Dorsolateral prefrontal cortex
EFTU	Elongation Factor Tu GTP-Binding Domain-Containing 2
EIF2S1	Eukaryotic translation initiation factor 2
EIF4B	Eukaryotic translation initiation factor 4B
ELAVL2	ELAV like neuron-specific RNA-binding protein 2
ESRP2	Epithelial splicing regulatory protein 2
FDR	False discovery rate
FMR1	Fragile X mental retardation 1
FMRP	Fragile X mental retardation protein
GO	Gene ontology
HNRNP	Heterogeneous nuclear ribonucleoprotein
IGF2BP2	Insulin-like growth factor 2 mRNA-binding protein 2

KD	Knock-down
KHDRBS1	KH RNA-binding domain containing, signal transduction-associated 1
KHDRBS3	KH RNA-binding domain containing, signal transduction-associated 3
KO	Knockout
MATR3	Matrin3
MBNL1	Muscleblind-like splicing regulator 1
MCC	Maximum clique centrality
MDD	Major depressive disorder
OPMD	Oculopharyngeal muscular dystrophy
PABP	Poly(A)-binding protein
PABPN1	Poly(A)-binding protein nuclear 1
PCBP	Poly(rC)-binding protein
PFC	Prefrontal cortex
PTBP	Polypyrimidine tract-binding protein
PTGR	Post-transcriptional regulation
RBM	RNA-binding motif protein
RBP	RNA-binding protein
SCZ	Schizophrenia
SF3B4	Splicing factor 3B subunit 4
SNRNP70	Small nuclear ribonucleoprotein U1 subunit 70
SRSF	Serine- and arginine-rich splicing factor
TDP-43	Transactive response DNA-binding protein 43
TSMA	Transcript Set Motif Analysis
U2AF2	U2 small nuclear RNA auxiliary factor 2
UTRs	Untranslated regions

Supplementary Information

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Additional file 1. RBPs influencing DEGs.

Additional file 2. Common RBPs.

Additional file 3. RBPs and psychiatric disorders disorders.

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Author contributions
NMJ and SJ were involved in conceptualization, analysis, interpretation, and manuscript writing and revision. Both authors read and approved the final manuscript.

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Declarations

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