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Bioinformatic Analysis of Epigenomic Studies for Major Depressive Disorder

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Abstract

Background: Major depressive disorder (MDD) is a common psychiatric entity, being characterized by alterations in mood and in other clinical dimensions. Several epigenome-wide association studies (EWAS) for MDD have been published. Here, we aimed to identify common genes in EWAS and their convergence with multiple lines of genomic evidence. **Methods**: We carried out a computational analysis using data of EWAS, which included a meta-analysis for brain samples of MDD, a convergence analysis for brain and blood samples, and top results from available genome-wide expression and association data. Functional enrichment and protein-protein interaction network analyses were also performed. **Results**: The meta-analysis for brain samples detected a significant gene, FAM53B. A list of forty-four top differentially methylated (DM) candidate genes was found, including GRM8, *NOTCH4* and *SEMA6A*, in addition to known druggable genes. The binding-sites for brain-expressed transcription factors, CREB and FOXO1, were enriched in the top DM genes. The protein-protein interaction networks showed that DM genes for MDD, such as *RPRM* and *TMEM14B*, play a central role. **Conclusion**: In this study, we found integrative evidence for the possible role of novel candidate genes and pathways. These genes are involved in mechanisms of synaptic plasticity, which have been associated with several psychiatric disorders. Analysis of epigenetic factors have a great potential for the identification of the mechanisms involved in the pathogenesis of MDD, taking into account their possible role in the interaction between genetic factors and the environment.

Keywords: *Epigenomics, DNA Methylation, Psychiatric Genomics, Bioinformatics, Major depressive disorder.*

Introduction

Major depressive disorder (MDD) is a common psychiatric entity, being characterized by alterations in mood and in other clinical dimensions, which lead to functional impairment in patients.[1] MDD has an average 12-month prevalence of around 6%[1] and an estimated heritability of 35–45%.[2] A secondary analysis of available global data has shown that the number of incident MDD cases increased from 172 to 258 million in the 1990-2017 period, being one of the psychiatric disorders with the largest impact on burden of disease.[3]

In recent years, several genome-wide analyses have been carried out to identify the molecular risk factors associated with MDD,[2] as well as multiple genome-wide association studies (GWAS)[4] and genome-wide expression studies (GWES).[5] In this context, epigenetic mechanisms have been of interest in the study of the pathogenesis of MDD, as a possible way of finding the interaction between genetic factors and environmental variables (such as psychological stress).[6] Among several epigenetic factors, the analysis of DNA methylation levels has been studied for multiple psychiatric disorders, primarily because of the negative correlation that is found between DNA methylation in promoter regions (in CpG islands) and gene expression.[7]

Epigenome-wide association studies (EWAS) have appeared as important strategies for the analysis of DNA methylation

levels across the genome, based on available microarray platforms that include hundreds of thousands of probes.[6] Several EWAS for MDD and related phenotypes have been published,[8,9] but there is the need for a bioinformatic analysis of the convergence of results from several available EWAS with other genomic evidence.[5,10] In this study, we carried out a computational analysis of available genome-wide DNA methylation studies for MDD and their convergence with multiple lines of genomic evidence. In addition, we performed a meta-analysis for detecting differentially methylated genes in brain samples from subjects with MDD, considering the advantage of this approach to increase statistical power and to obtain more precise results through the combination of individual studies.[11]

Methods

Data processing and convergence analysis of EWAS in brain and blood samples

The NCBI GEO database, an online repository for microarray data,[12] was used to obtain raw data from available epigenome-wide association studies for MDD. Data from five EWAS were extracted from the following published articles: Guintivano, 2013;[9] Chen, 2014;[13] Murphy, 2017BA11 and Murphy, 2017BA25 (both from the same article)[14] and Crawford, 2018[15] (Table 1). The genome-wide DNA methylation data obtained were used to generate two groups for comparison (MDD patients and control subjects), which were then analyzed using the GEO2R tool[12] to identify the differentially methylated (DM) probes for each study. The annotation files from the NCBI GEO database were used for the mapping from microarray probes to human gene identifiers. Convergent differentially methylated genes in these studies were revealed using the Venn diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn).

Meta-analysis of EWAS in brain samples

Additionally, a meta-analysis was performed using the robust rank aggregation (RRA) method in the R program.[16] In this analysis, four studies that analyzed DNA methylation in brain tissue samples were included (Table 1). The R package "RobustRankAggreg" was employed following the previously described protocol.[17] For the current study, the list of significant DM genes identified by GEO2R was used, which were ranked according to their P values. The RRA method allows to integrate data from different studies and methodologies, and uses a prioritized list of genes.[16] An adjusted P value of <0.05 was considered significant in this analysis.

Table 1. Details of EWAS included

Author, Year	NCBI GEO	Tissue	Sample size	Platform	PMID
Guintivano, 2013	GSE41826	Frontal cortex	49 MDD and 49 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	23426267
Chen, 2014	GSE38873	Cerebellum	17 MDD and 17 controls	Illumina Human Methylation 27K Beadchip (GPL8490)	25243493
Murphy, 2017BA11	GSE88890	Frontal cortex, Brodmann area 11	20 MDD and 20 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	28045465
Murphy, 2017BA25	GSE88890	Frontal cortex, Brodmann area 25	17 MDD and 18 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	28045465
Crawford, 2018	GSE113725	Whole Blood	49 MDD and 48 controls	Illumina Human Methylation 450K Beadchip (GPL13534)	29790996

Abbreviations: PMID: PubMed identifier; NCBI GEO: NCBI GEO database identifier.

Convergence analysis for common genes in EWAS and other genome-wide studies

Records of significant genes from genome-wide expression studies were extracted from a published meta-analysis of GWES for MDD patients and controls (amygdala, anterior cingulate cortex, cerebellum and prefrontal cortex).[18] Lists of significant genes were also extracted from genome-wide association studies for depressive symptoms,[19] personality traits[20] and for the case-control design for MDD.[21] The significant genes obtained from EWAS for MDD, GWAS for depressive symptoms, GWAS for case-control studies of MDD, GWAS for personality traits and meta-analysis of GWES for MDD were analyzed for their convergence, using an online tool (http://bioinformatics.psb.ugent.be/webtools/Venn). The genes found on convergence were compared with the following available lists: genes known to harbor mutations for neuropsychiatric disorders[22] and genes that are highly expressed in human astrocytes and oligodendrocytes.[23]

Enrichment analysis for convergent genes in EWAS

A functional enrichment analysis was carried out using the DAVID online tool, version 6.8,[24] for the following categories: Transcription Factor Binding Sites (TFBS) and Tissue Expression (GNF U133A). The significant genes (that were convergent in five EWAS) were compared with the rest of the genome by using a Fisher exact p value, including a correction for multiple testing using a False Discovery Rate (FDR) method. In the case of TFBS, the significant genes were analyzed for their convergence with transcription factors expressed in the brain.[25]

Protein-protein interaction network for convergent genes in EWAS

An examination of the experimentally validated protein-protein interactions (PPI) was conducted using the online database of the Human Interactome Project [26] for the significant genes that were convergent in EWAS included in this work. The program, Cytoscape 3.8.0,[27] was used to visualize these interactions, in which a connected subnetwork system, using >2 edges, was employed,[28] along with a degree filter (In + Out) of 30-292.

Results

Genome-wide DNA methylation data were extracted from 5 EWAS for MDD, which had samples from different brain regions and whole blood (Table 1). Significant genes from the five EWAS were analyzed; results showed one hundred and seventy-one genes that were differentially methylated in common between the 5 EWAS. Combinations of 4 EWAS identified sixty-five to six hundred and thirty-eight common DM genes (Figure 1, Table S1A). Also, we carried out a meta-analysis for studies performed in brain samples using the robust rank aggregation method. Only one gene, *FAM53B* (family with sequence similarity 53 member B), was identified as significant (Score: 3.3085, P= 0.0160).

A merging of convergent genes from EWAS for MDD with genes available from 1) GWAS for depressive symptoms, 2) GWAS for case-control studies of MDD, 3) GWAS for personality traits and 4) meta-analysis of GWES for MDD, resulted in a list of 44 top candidate genes (Table 2), including *NOTCH4* (Neurogenic locus notch homolog protein 4) and *SEMA6A* (Semaphorin-6A). A number of these 44 genes have been found to harbor mutations for neuropsychiatric disorders (Table S2), such as *COL4A2* (Collagen alpha-2(IV) chain) and *RELN* (Reelin); and to be enriched in astrocytes and oligodendrocytes (Table S2), such as *FAM107B* (Protein Family With Sequence Similarity 107 Member B) and *TNS3* (Tensin-3).

Figure 1. Overview of differentially methylated (DM) genes from five EWAS for MDD.

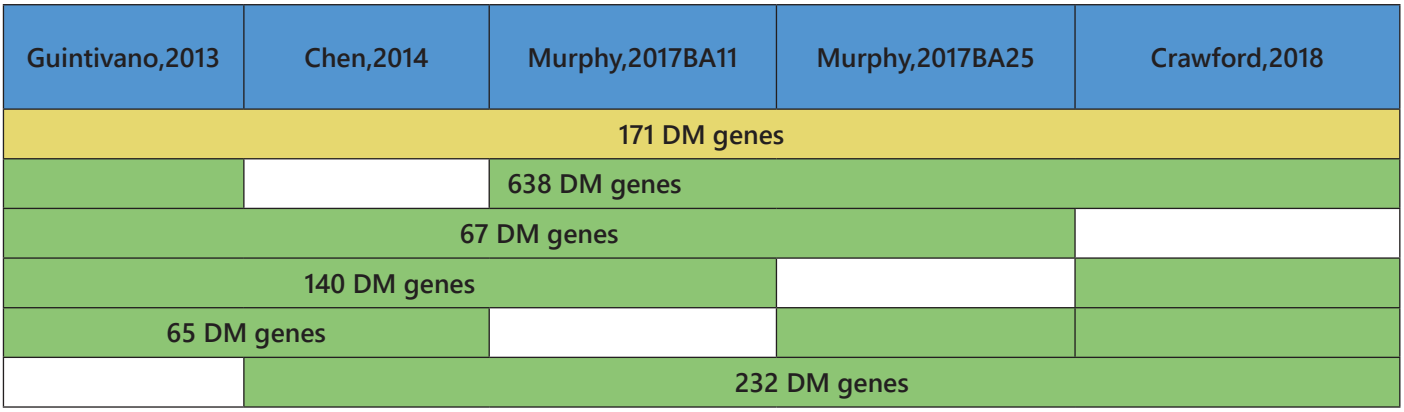


Table 2. Main top candidate genes. EWAS: EWAS for MDD; GWASD: GWAS for depressive symptoms; GWASM: GWAS for case-control studies of MDD; GWASN: GWAS for neuroticism; GWESM: GWES for MDD.

Gene	Protein Name	Evidence	Gene	Protein Name	Evidence
ASIC2	Acid-sensing ion channel 2	GWASD, GWESM	PIEZO2	Piezo-type mechanosensitive ion channel	GWASM, GWESM
C3orf70	UPF0524 protein C3orf70	GWASM, GWESM	PTDSS2	Phosphatidylserine synthase 2	EWAS, GWESM
CDO1	Cysteine dioxygenase type 1	GWASM, GWESM	RCAN2	Calcipressin-2	GWASN, GWESM
CPLX1	Complexin-1	GWASM, GWESM	RELN	Reelin	GWASM, GWESM
COL4A2	Collagen alpha-2(IV) chain	EWAS, GWASM	RPRM	Protein reprimo	GWASM, GWESM
DAD1	Dolichyl-diphosphooligosaccharide--protein	GWASN, GWESM	RYR2	Ryanodine receptor 2	EWAS, GWASM, GWESM
FAM107B	Protein FAM107B	EWAS, GWESM	SEMA6A	Semaphorin-6A	EWAS, GWASM
FHIT	Bis(5'-adenosyl)-triphosphatase	GWASD, GWASM	SMARCA2	Probable global transcription activator SNF2L2	GWASM, GWESM
GRM8	Metabotropic glutamate receptor 8	GWASM, GWESM	SSB	SPRY domain-containing SOCS box protein 2	EWAS, GWESM
IGSF21	Immunoglobulin superfamily member 21	EWAS, GWESM	STK39	STE20/SPS1-related proline-alanine-rich protein kinase	EWAS, GWESM
IL17RD	Interleukin-17 receptor D	GWASM, GWESM	TM7SF2	Delta(14)-sterol reductase TM7SF2	EWAS, GWESM
LOC102546299	[Uncharacterized]	GWASD, GWASM, GWASN	TMEM14B	Transmembrane protein 14B	GWASM, GWESM
LPCAT1	Lysophosphatidylcholine acyltransferase 1	GWASM, GWESM	TMEM241	Transmembrane protein 241	GWASM, GWESM
MRAP2	Melanocortin-2 receptor accessory protein 2	GWASM, GWESM	TNS3	Tensin-3	EWAS, GWESM
NCKAP1	Nck-associated protein 1	GWASM, GWESM	TRPM3	Transient receptor potential cation channel subfamily M member 3	GWASD, GWASM
NELL1	Protein kinase C-binding protein NELL1	GWASM, GWESM	TUSC3	Tumor suppressor candidate 3	GWASM, GWESM
NELL2	Protein kinase C-binding protein NELL2	GWASM, GWESM	UBA3	NEDD8-activating enzyme E1 catalytic subunit	GWASM, GWESM
NOTCH4	Neurogenic locus notch homolog protein 4	EWAS, GWASM	UNC13C	Protein unc-13 homolog C	GWASD, GWASM, GWASN
OFCC1	Orofacial cleft 1 candidate gene 1 protein	GWASD, GWASM	WIF1	Wnt inhibitory factor 1	GWASM, GWESM
PCP4	Calmodulin regulator protein PCP4	GWASM, GWESM	ZCCHC14	Zinc finger CCHC domain-containing protein 14	EWAS, GWASM
PEX5L	PEX5-related protein	GWASD, GWASM	ZCCHC24	Zinc finger CCHC domain-containing protein 24	GWASM, GWESM
PFKP	ATP-dependent 6-phosphofructokinase, platelet	EWAS, GWESM	ZIC2	Zinc finger protein ZIC 2	EWAS, GWESM

A functional enrichment analysis found an enrichment of binding-sites for brain-expressed transcription factors (Table 3), such as CREB (cAMP responsive element binding protein), FOXO1 (forkhead box O1), and *ZIC1* (Zinc family member 1). In addition, an analysis of the 44 candidate genes showed an enrichment of tissue expression as well, such as Pituitary and Olfactory Bulb (Table 3). A PPI network visualization showed that candidate genes for MDD, such as *TMEM14B* (transmembrane protein 14B) and RPRM (reprimo, TP53 dependent G2 arrest mediator homolog), play a central role in this network (Figure 2).

Table 3. Functional enrichment analysis of top DM candidate genes from EWAS for MDD. TFBS: Transcription Factor Binding Sites; GNF_U133A_QUARTILE: Expression in Multiple tissues.

Category	Term	P value	FDR
UCSC_TFBS	LHX3	9.39E-05	0.009014
UCSC_TFBS	FOXO3	2.92E-04	0.014018
UCSC_TFBS	RP58	6.78E-04	0.015651
UCSC_TFBS	ISRE	6.83E-04	0.015651
UCSC_TFBS	AP2REP	8.15E-04	0.015651
UCSC_TFBS	CDPCR3	0.001284	0.01727
UCSC_TFBS	FAC1	0.001571	0.01727
UCSC_TFBS	CART1	0.001609	0.01727
UCSC_TFBS	HNF1	0.001684	0.01727
UCSC_TFBS	P53	0.00194	0.01727
UCSC_TFBS	IRF2	0.002141	0.01727
UCSC_TFBS	SRY	0.002348	0.01727
UCSC_TFBS	TGIF	0.002659	0.01727
UCSC_TFBS	NFE2	0.002698	0.01727
UCSC_TFBS	CREB	0.00319	0.019138
UCSC_TFBS	AP1	0.003655	0.019969
UCSC_TFBS	IK3	0.004006	0.019969
UCSC_TFBS	ZIC1	0.004134	0.019969
UCSC_TFBS	SREBP1	0.004247	0.019969
UCSC_TFBS	HFH1	0.004501	0.019969
UCSC_TFBS	GATA	0.004576	0.019969
UCSC_TFBS	CDC5	0.004903	0.020465
UCSC_TFBS	TAL1BETAITF2	0.005666	0.022002
UCSC_TFBS	CDPCR1	0.00573	0.022002
UCSC_TFBS	FOXO4	0.006855	0.025311
UCSC_TFBS	STAT3	0.007589	0.026549
UCSC_TFBS	BRACH	0.007743	0.026549
UCSC_TFBS	AREB6	0.009089	0.028731
UCSC_TFBS	FOXO1	0.009868	0.028731
GNF_U133A_QUARTILE	Olfactory Bulb	1.24E-04	0.002084
GNF_U133A_QUARTILE	Dorsal root ganglia	6.72E-04	0.007502
GNF_U133A_QUARTILE	Pituitary	0.005969	0.047689

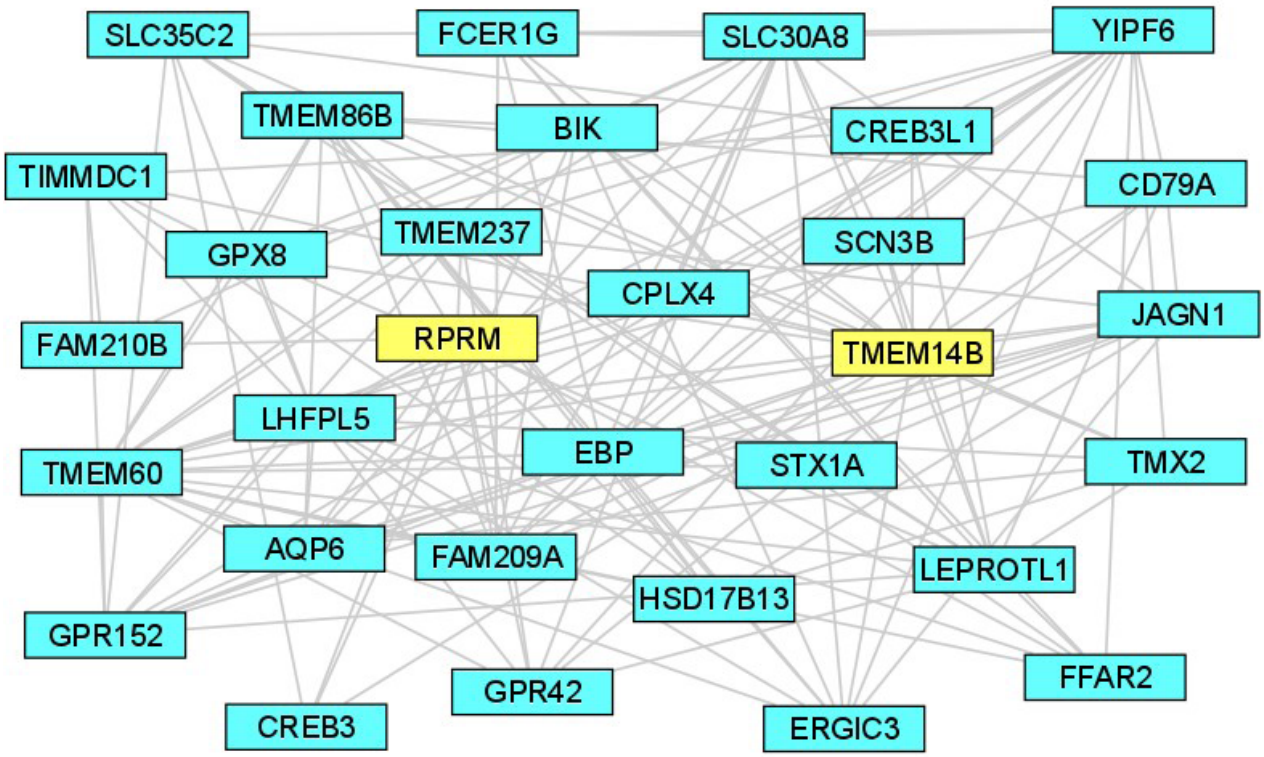
Discussion

Epigenetic factors have been of particular interest in the analysis of the mechanisms involved in the pathogenesis of MDD, considering the possible interaction between genetic factors and the environment.[6] Multiple epigenome-wide association studies for major depression and related phenotypes have been carried out and published in recent years.[6] A bioinformatic analysis of the convergence of results from several available EWAS with other genomic evidence[10,29,30] (D. A. Forero et al., 2017; Niculescu & Le-Niculescu, 2010) can be helpful for the identification of novel genes and pathways for MDD.

In this study, we found integrative evidence for the possible role of novel candidate genes and pathways. Key candidate genes such as *NOTCH4* and *SEMA6A* were found in convergence with those identified in GWAS and GWES. These genes are involved in mechanisms of synaptic plasticity, which have been associated with several psychiatric disorders.[18,31,32] Among the candidate genes found in this investigation, genes which harbor mutations for neuropsychiatric disorders, such as *COL4A2* and *RELN*, have been identified; as well as genes that are highly expressed in astrocytes and oligodendrocytes, such as *TNS3* and *FAM107B*. Furthermore, binding-sites for brain-expressed transcription factors, such as FOXO1 and CREB, are of particular importance, given the previous evidence of involvement in pathophysiology of depression[33,34] — with genes such as *TMEM14B* and *RPRM* observed to play a key role in the protein-protein interaction network.

Previously, Uddin et al found a difference in genome-wide DNA methylation patterns between unaffected and depressed individuals. Functional enrichment showed that methylated and unmethylated genes affect brain development, depending on specific pathways.[35] A study involving post-mortem frontal cortex samples found similar results for genes such as *CPSF3*, *LASS2* and *PRIMA1* having different methylation profiles.[36] Studies with candidate genes have complemented results from EWAS for MDD. A study with MDD patients showed higher levels of methylation at the *BDNF* gene.[37] Another case-control study also showed *BDNF*, *FKBP5*, *CRHBP* and *NR3C1* gene promoters to be significantly hypermethylated in MDD.[38]

Figure 2. Protein-protein interaction network for top candidate genes. Top DM candidate genes from EWAS for MDD were used. A highly connected subnetwork is shown and candidate genes are highlighted in yellow.



It is important for future MDD EWAS to be carried out in other regions of the world (such as Latin America or Africa),[18] that have millions of depression patients.[3]

Concerning the meta-analysis performed in this study, a DM gene, the *FAM53B*, was identified; which encodes a protein that is necessary to regulate the β-catenin-dependent Wnt signal transduction.[39] A GWAS has detected a variant in this gene as a risk for cocaine dependence in African-and European-American subjects.[40] Additionally, other polymorphisms in *FAM53B* are also associated with MDD and Alzheimer´s diseases.[41] Moreover, in a study that analyzed the effects of smoking on DNA methylation, a significant result for 525 genes including *FAM53B* was found.[42] These findings suggest that this gene could play an important role in the molecular mechanisms of different brain disorders. Interestingly, *FAM53B* was convergent with the study performed by Crawford, 2018, that analyzed DNA methylation in whole blood samples (Table S1). Despite the existence of additional EWAS performed in whole blood samples for depressive symptoms in middle-aged and elderly persons,[8] its raw data is unavailable and it was not possible to include their results in our study.

The number of EWASs included is one of the limitations of this study, as several primary EWAS do not have their data publicly available. Comprehensive meta-analyses of available EWAS could be performed if academic journals request for the public availability of such raw data.[28,43] Development of user-friendly computational tools would also facilitate such meta-analyses of large volumes of epigenomic data.[44]

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