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Research paper

A comprehensive regional analysis of genome-wide expression profiles for major depressive disorder

Diego A. Forero[a,*], Gina P. Guio-Vega[a], Yeimy González-Giraldo[b]

[a] Laboratory of NeuroPsychiatric Genetics, Biomedical Sciences Research Group, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia
[b] Departamento de Nutrición y Bioquímica, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá, Colombia

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ABSTRACT

Background: Major depressive disorder (MDD) is a global health challenge. In recent years, a large number of genome-wide expression studies (GWES) have been carried out to identify the transcriptomic profiles for MDD. The objective of this work was to carry out a comprehensive meta-analysis of available GWES for MDD.
Methods: GWES for MDD with available raw data were searched in NCBI GEO, Array Express and Stanley databases. Raw GWES data were preprocessed and normalized and meta-analytical procedures were carried out with the Network Analyst program. 743 samples from 24 primary studies were included in our meta-analyses for blood (Blo), amygdala (Amy), cerebellum (Cer), anterior cingulate cortex (ACC) and prefrontal cortex (PFC) regions. A functional enrichment analysis was carried out.
Results: We identified 35, 793, 231, 668 and 252 differentially expressed (DE) genes for Blo, Amy, Cer, ACC and PFC regions. A region-dependent significant enrichment for several functional categories, such as gene ontologies, signaling pathways and topographic parameters, was identified. There was convergence with other available genome-wide studies, such as GWAS, DNA methylation analyses and miRNA expression studies.
Limitations: Raw data were not available for several primary studies that have been published previously.
Conclusions: This is the largest meta-analysis for GWES in MDD. The examination of convergence of genome-wide evidence and of the functional enrichment analysis provides a global overview of potential neural signaling mechanisms dysregulated in MDD. Our comprehensive analysis of several brain regions identified lists of DE genes for MDD that are interesting candidates for further studies.

1. Introduction

Major depressive disorder (MDD) is a main challenge for psychiatric research around the world, with an estimated global lifetime prevalence of around 11.2% (Whiteford et al., 2015). Data from the Global Burden of Disease Study have shown that MDD might account for 8.2% of global years lived with disability (YLDs) (Whiteford et al., 2015). In addition, it has been estimated that MDD is the second global cause of YLDs and that it is the brain disorder with the highest burden in terms of global disability adjusted life years (DALYs) (Whiteford et al., 2015). Large international efforts have been carried out with the objective of discovering the biological basis of MDD (Duman et al., 2016), including association studies for candidate genes and genome-wide association studies (GWAS) (which explore hundreds of thousands of polymorphisms) (Flint and Kendler, 2014), taking into account that the heritability for MDD has been estimated around 0.37 (Flint and Kendler, 2014).

In recent years, a large number of genome-wide expression studies (GWES) has been carried out to identify the transcriptomic profiles for MDD (Lin and Tsai, 2016). These studies have typically involved the analysis of expression of dozens of human samples, from different tissues, for a large number of protein-coding genes, using commercially available microarray platforms (Lin and Tsai, 2016). An enrichment analysis of functional categories, such as miRNA targets and gene ontologies, for the lists of differentially expressed (DE) genes is useful to identify biological pathways (Forero et al., 2010; Huang da et al., 2009a) and mechanisms that might be related to the pathogenesis of MDD. Considering the importance of meta-analyses for the identification of consistent molecular evidence from combined datasets with larger sample sizes (Ramasamy et al., 2008), in the current work we carried out a comprehensive meta-analysis of available GWES for MDD.

2. Matherials and methods

2.1. Search and inclusion of primary datasets

Our meta-analysis of microarray data followed published recom-

* Correspondence to: Laboratory of NeuroPsychiatric Genetics, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia.
E-mail address: diego.forero@uan.edu.co (D.A. Forero).

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mendations for this type of study (Ramasamy et al., 2008). GWES for MDD, using the case-control design with available raw data, were searched in NCBI GEO, Array Express and Stanley Medical Research Institute Online Genomics (Higgs et al., 2006) databases. It was complemented by a search of articles describing GWES for MDD in PubMed and Google Scholar (using "major depression" and "major depressive disorder" as keywords) and in reference lists of key review articles (Lin and Tsai, 2016). In case of published articles without associated records in microarray repositories, the corresponding authors were contacted by email to ask for availability of raw data. Studies that focused on analysis of miRNA expression or DNA methylation or that only provided raw data for control subjects were excluded.

2.2. Data processing and meta-analysis of genome-wide expression studies

Preprocessing and normalization of microarray datasets with raw data (.CEL files), based on the Affymetrix platforms, were carried out with the *affy* package (under the R environment, version 3.2.3), with the following parameters: RMA (for background correction), quantiles (for normalization), pmonly (perfect match correction) and median polish (as summary method). For the microarray datasets based on other platforms, such as Illumina (4 datasets) or Agilent (3 datasets), the processed data were downloaded and used for the subsequent analyses. Annotation files for the different microarray platforms were downloaded from the NCBI GEO database. The NetworkAnalyst online program (Xia et al., 2014) was used for the meta-analysis of genome-wide expression data, using a random effects model and a rank aggregation method, following published recommendations for this type of study (Tseng et al., 2012). A False Discovery Rate (FDR) of 0.05 was used to correct for multiple testing.

Six datasets were used (GSE19738, GSE52790, GSE38206, GSE76826, GSE32280, GSE39653) for blood (Blo), 2 datasets (GSE54566, GSE54564) for amygdala (Amy), 2 datasets (Feinberg and SklarB) for cerebellum (Cer), 5 datasets (GSE54565, GSE54571, GSE54572, GSE54562, GSE54563) for anterior cingulate cortex (ACC) and 9 datasets (Altar2005, AltarB, GSE54568, GSE54567, GSE54570, GSE54575, GSE12654, GSE53987, SklarA) for prefrontal cortex (PFC). We focused in these regions due to the availability of raw data from primary studies. To identify DE genes shared between the five regions, a Venn diagram was generated using an online tool (http://bioinformatics.psb.ugent.be/webtools/Venn).

2.3. Enrichment analysis of functional categories

To carry out a functional enrichment analysis of the DE genes found in the meta-analyses, DAVID and Babelomics 4.3 and 5.0 online tools (Alonso et al., 2015; Huang da et al., 2009b) were used. The following functional categories were analyzed: Gene Ontology (GO) terms, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Interpro domains, chromosomal location, miRNA targets, Transcription Factor Binding Sites (TFBS) and gene expression. A comparison with the rest of the genome was carried out (using the Fisher exact p value) and the FDR approach was used to correct for multiple testing.

2.4. Analysis of protein–protein interaction (PPI) networks

For the DE genes found in the Amy and PFC datasets, known protein–protein interactions (PPI) were identified using the Human Interactome Project (HIP) data. HI-II-14, Lit-BM-13, HI-I-05, Venkatesan-09 and Yu-11 were taken as sources (Rolland et al., 2014). Cytoscape 3.3.0 program (Shannon et al., 2003) was used to visualize the PPI networks and a subnetwork for PFC was generated for highly connected nodes (>20 edges) and another for Amy (>25 edges) (Guio-Vega and Forero, 2017). The SNOW tool from Babelomics 5 (Alonso et al., 2015) was used to carry out a PPI network enrichment analysis, studying the following topographical parameters: relative betweenness, connections and clustering coefficient.

2.5. Analysis of convergence between DE genes and other genomic and transcriptomic datasets

List of top SNPs were extracted from a mega-analysis of GWAS for MDD (using the case-control design) (Major Depressive Disorder Working Group of the Psychiatric et al., 2013), a large GWAS for depressive symptoms in population-based samples (Hek et al., 2013), a GWAS for response to treatment with selective serotonin reuptake inhibitors (Ji et al., 2013), a meta-analysis of GWAS for neuroticism (Genetics of Personality et al., 2015) and a GWES for response to two antidepressants in a murine model (Malki et al., 2012). The Ensembl IDs for the genes associated with the SNPs were retrieved using the Ensembl BioMart tool and these were converted to HGNC symbols with the bioDBnet online server. Human orthologues for murine genes were identified using the Ensembl BioMart tool. Top protein-coding genes were also extracted from genome-wide epigenetic (DNA methylation) analyses of MDD in brain (Sabunciyan et al., 2012) and peripheral blood (Cordova-Palomera et al., 2015) and top miRNAs were retrieved from a systematic study of miRNA expression in MDD (Garbett et al., 2015). Known experimentally-validated targets of candidate miRNAs were downloaded from the DIANA-TarBase v7.0 database (Vlachos et al., 2015). Additionally, DE genes from Amy and PFC regions were compared to a list of known druggable genes (Russ and Lampel, 2005), which encode proteins that are able to bind drug-like molecules.

3. Results

Twenty-four primary datasets (Belzeaux et al., 2012; Chang et al., 2014; Iwamoto et al., 2004; Liu et al., 2014; Miyata et al., 2016; Savitz et al., 2013; Spijker et al., 2010) with available genome-wide expression data for MDD patients and controls were identified and included in our meta-analyses, for a total of 743 independent samples (358 MDD patients and 385 control subjects) (Table 1). We identified 793, 667, 252 231 and 35 differentially expressed genes derived from meta-analyses of available GWES for Amy, ACC, PFC, Cer and Blo regions; complete lists of DE genes for these 5 regions are shown in Table S1. No single gene was identified as significant for all 5 regions (Fig. S1). An analysis of genomic convergence, using data from other genomic datasets (such as GWAS for MDD, response to antidepressant treatment, depressive symptoms and neuroticism, GWES for response to antidepressants in a murine model and genome-wide epigenetic analyses) identified a group of genes with a possible higher relevance to the etiology and pathogenesis of MDD (Table 2). A topographical analysis of PPI networks found significant parameters for proteins encoded by DE genes from PFC and their interactors: Relative betweenness, Connections and Clustering coefficient (p values of 0.0001, 0.0003 and 0.0095, respectively). An overview of the entire PPI network for PFC is shown in Fig. S2 and a highly connected subnetwork for PFC is shown in Fig. 1 (a highly connected subnetwork for Amy is shown in Fig. S3).

An enrichment analysis of functional categories identified several region-specific significant sets, such as gene ontologies and signaling pathways (Table 3 and Tables S2a and S2b for a complete list of categories and their respective genes). Of special interest, some DE genes for Amy and ACC are predicted to be significantly enriched as targets of several brain-expressed miRNAs (Table 3). Some of these miRNAs, previously known to be altered in samples from MDD patients (Garbett et al., 2015), are known to regulate proteins that are important for brain function (Fig. 2). A comparison with known druggable genes identified 81, 79 and 38 genes for DE genes from meta-analyses for Amy, ACC, and PFC, respectively (Table S3).

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