M36. CO-EXPRESSED TRANSCRIPTOME ANALYSES REVEAL CONSISTENT BIOLOGICAL PATHWAYS FOR MANIC EPISODE

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Background Bipolar disorder (BD) is a highly heritable psychiatric disorder with recurrent episodes of depression and mania. Despite progress made for identifying genetic variants for BD, limited studies focus on its episodic feature in nature. In the current study, we aimed to investigate the mechanisms underlying manic episodes at a genome-wide level to identify potential molecular targets, in particular the gene/transcript expression patterns.

Methods Two sets of transcriptome data were analyzed for manic episode. First, we enrolled 6 BD patients and followed them from manic episode to remission. The Young Mania Rating Scale (YMRS) score was assessed to evaluate the severity of manic-state (YMRS score >20 as acute phase and <7 as remission). The Affymetrix HTA-array was used for transcriptome analysis. Differentially expressed (DE) transcripts between two time points were analyzed by pair-t test. Top DE transcripts were validated by qRT-PCR. We also performed weighted gene co expression network analysis (WGCNA) to identify co expression modules that are correlated with manic episode. For replication, we downloaded GSE46416 data from Gene Expression Omnibus, which consisted of 11 BD patients with similar study design. The transcriptome data were generated using Affymetrix HuEx 1.0 array. We compared results in the two data to identify consistent genes/modules that are correlated with manic episodes. We further performed intra-module pathway analysis using DAVID Bioinformatics Tools v6.8 to identify pathways that are regulated by suggestive genes in the modules.

Results In the discovery samples, most of the transcripts were down-regulated in manic state comparing with remission. The top significant DE transcripts were DLC1, NFASC, and CLMN. Their expression patterns were validated by qRT-PCR with the same direction in HTA-array. Using WGCNA, six and three modules were found to be significantly related to manic episode in GSE46416 and ours data, respectively. Among these modules, results from intra-module pathway analysis revealed consistent pathways in the two datasets. The common pathways that were positively correlated with manic state included actin cytoskeleton, nervous system development, and response to redox state. On the other hand, calcium ion binding, synaptic transmission, and adaptive immune system were negatively correlated with manic-state.

Discussion Genome-wide high-throughput transcriptome analyses are useful in identifying biomarkers for manic state in BD patients. In addition to DE transcripts analysis, network analysis based on transcripts co-expression might provide more biological insights for etiology study. In conclusion, our network and functional pathway-level analyses identify consistent modules and pathways for manic episode. These findings have potential to assist conducting therapeutic studies and to explore pathologic mechanisms underlying bipolar disorder in the future.

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