M37. RNA-SEQUENCING OF BIPOLAR DISORDER PATIENTS LYMPHOBLASTOID CELL LINES IMPLICATES A NOVEL NEUROTROPHIC FACTOR IN THE EFFICACY OF LITHIUM AS MOOD STABILIZING DRUG

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Background Lithium remains one of the oldest and most effective treatments for mood stabilization in bipolar disorder (BD), and is still the first-line BD treatment even that individual response is variable. Indeed, at least 30% of patients are only partially responsive, and more than 30% do not respond to lithium therapy. Biomarker predictors for lithium response have been studied by using electroencephalography, neuroimaging and molecular genetics reporting findings that mostly remain modest and unconfirmed. Human lymphoblastoid cell lines (LCLs) and, recently, also iPS cell-derived neurons from BD patients have been employed for searching genes and non-coding RNAs whose expression is modulated by lithium using gene candidate approaches and microarray gene expression technologies. RNA-sequencing (RNA-seq) provides advantages over microarray technologies; it allows detecting transcript differences with low background noise avoiding cross-hybridization issues and allows a large dynamic range of expression level evaluation.

Methods This study aimed to identify biomarkers predictive for lithium response, based on comparing RNA-seq information derived from LCLs of lithium responsive (LR) vs. lithium non-responsive (LNR) BD patients, for assessing the patients' genomic variability related to their therapeutic response to lithium. RNA-seq was carried out on 24 LCLs from female BD patients collected at UCSD classified as 12 LR and 12 LNR (according to combined Alda scale) and followed by a RT-PCR validation in an independent cohort of 41 BD patients (25 LR and 16 LNR) collected at JHMI.

Results Our RNA-seq study found few genes with borderline significance differential expression ($p=0.06$) comparing LR and LNR BD LCLs after correcting for multiple-testing. After filtering for $p<0.01$ (before multiple-testing correction), 264 genes were found nominally significant, whereas filtering for $1.3>FC<-1.3$ and nominal $p<0.01$ identified 56 differentially expressed transcripts. RT-PCR analyses on the first cohort validated the top two RNA-seq identified genes, Hepatoma-Derived Growth Factor, Related Protein 3 (HDGFRP3 or HRP-3) and SOX18 as differentially expressed between LR and LNR BD LCLs with $FC=+1.8$ ($p=0.001$) and $FC=-2.28$ ($p=0.03$), respectively. Analysis of the same transcripts in the 2nd cohort did not show

significant differences, yet, when pooling both cohorts, the expression of HDGFRP3 was found significantly elevated in LR BD LCLs (FC=+1.4; p=0.03).

Discussion HDGFRP3 is a protein coding gene found to have growth promoting activity for neurons as well as inducing differentiation of endothelial cells. HDGFRP3 is the only HDGF family member whose expression is almost restricted to the CNS. It is strongly expressed in the adult mice bulbus olfactorius, piriform cortex and amygdala and in cultured cells is predominantly expressed in neurons and slightly in glial cells. In mouse cortical neurons it promotes neuritogenesis via its interaction with microtubules and soluble HRP-3 acts a neurotrophic factor. Thus, we found an upregulation of HRP-3 in LCLs from lithium responder BD patients, suggesting its involvement in lithium response likely via its neurotrophic activity.

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