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

Elena Milanesi1, Irena Voinsky2, Adva Hadar2, Carlo Maj1, John R. Kelsoe3, Tatiana
Shekhtman3, Peter Zandi4, Fernando Goes4, James B. Potash5, Michael Greshovits6,
Shlomit Gilad6, Massimo Gennarelli1, Thomas G. Schulze7, David Gurwitz8

1Genetics Unit, Centro San Giovanni di Dio Fatebenefratelli, Italy, 2Department of
Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv
University, Israel, 3Department of Psychiatry, University of California San Diego, La
Jolla, California, 92093, USA, 4Department of Psychiatry, Johns Hopkins University,
Baltimore, Maryland 21218, USA, 5Department of Psychiatry, University of Iowa
Carver College of Medicine, Iowa City, Iowa., 6The Nancy & Stephen Grand Israel
National Center for Personalized Medicine, Weizmann Institute of Science, Rehovot,
Israel, 7Institute of Psychiatric Phenomics and Genomics, Ludwig-Maximilians-
University Munich, Germany; Department of Genetic Epidemiology in Psychiatry,
Central Institute of Mental Health, Mannheim, Germany, 8Department of Human
Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv
University Israel

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.

**Disclosure:** Nothing to Disclose.