

M23. ENRICHMENT OF GENETIC VARIANTS ASSOCIATED WITH CLINICAL RESPONSE TO LITHIUM IN CIRCADIAN CLOCK SYSTEM GENE SETS

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Background A connection between the mechanism of action of lithium in bipolar disorder and circadian rhythms has been suggested. Nonetheless the relationship between the “clock genes” that regulate circadian rhythms and lithium treatment response is not completely understood. Some studies, based on candidate-gene approaches have attempted to find the association of specific genes in the clock system with treatment response. However, to our knowledge there has not been a systematic pathway / enrichment analysis of clock genes in the context of the clinical response to lithium in bipolar disorder. The objective of this study is to perform a gene-based analyses and formal gene set enrichment analyses based on circadian clock system genes, using the currently available summary statistics from The International Consortium on Lithium Genetics (ConLiGen) GWAS.

Methods Based on previous literature (Pizarro et al., 2013; Chen et al., 2016) and available resources (e.g. <http://circadb.hogeneschlab.org/>) we have generated curated gene sets related to circadian control that are grouped as ‘clock modulator (upstream) genes’, ‘core clock genes’ and ‘clock controlled (downstream) genes’. Summary statistics derived from the ConLiGen GWAS on continuous/dichotomous lithium response were used as reference. For gene-set enrichment, analyses involved the use of two softwares in order to cross-validate the results: INRICH and MAGMA, the later being also used for gene-based analyses.

Results None of the significant associations obtained in gene-based analyses survived multiple testing correction. However gene-set enrichment analyses using INRICH and MAGMA reported a significant enrichment of a set of core clock genes with respect to the dichotomous lithium response phenotype (INRICH: corrected $P=0.008$; MAGMA: competitive $P=0.005$). No enrichment was observed using the continuous lithium response as target phenotype.

Discussion Our results suggest the involvement of those genes that constitute the core clock machinery in the determination of the clinical response to lithium in bipolar disorder patients. Enrichment analyses based on other methods and other psychiatric phenotypes are ongoing in order to i) further validate these findings and ii) evaluate their specificity.

References

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