EVIDENCE THAT GENES INVOLVED IN SERINE/THREONINE KINASE ACTIVITY ARE ASSOCIATED WITH BOTH BIPOLAR DISORDER AND HIGH BMI

Claudia Pisanu[1], Michael J Williams[2], Diana Maria Ciuculete[2], Gaia Olivo[2], Maria Del Zompo[1], Alessio Squassina[1], Helgi B Schiöth[2]

[1]Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari - Italy, [2]Department of Neuroscience, Unit of Functional Pharmacology, Uppsala University, Uppsala - Sweden

Introduction: Patients with bipolar disorder (BD) show an increased frequency of obesity and type 2diabetes (T2D). These metabolic comorbidities are associated with a detrimental course of illness and greatly contribute to increased mortality. The genetic determinants and molecular pathways underlying this comorbidity are largely unknown. We conducted a gene-based analysis and a meta-analysis of large genome-wide association datasets to investigate overlapping genes between BD and body mass index (BMI) or T2D and elucidate their functional role.

Material and methods: The study was conducted on three large genome-wide association study (GWAS) datasets: BD, Psychiatric Genomics Consortium (PGC), including 20,129BD cases and 21,524controls of European descent; BMI, GWA plus Metabochip meta-analysis dataset from the Giant Consortium, including 322,154subjects of European ancestry; T2D, DIAGRAM 1000G GWAS meta-analysis Stage 1dataset, including 26,676T2D cases and 132,532Caucasian controls. We integrated results from two complementary approaches: 1) we conducted a gene-based analysis using MAGMA, selected genes associated with BD and BMI or T2D and investigated their functional enrichment for gene ontology (GO) terms and Reactome pathways; and 2) we conducted two meta-analyses between BD and BMI, as well as BD and T2D using Metasoft. This software provides a posterior probability that an effect exists in each study (m-value statistics > 0.9). We selected single nucleotide polymorphisms (SNP) with a p-value < 5E-08and an m-value > 0.9and investigated their functional role as well as their role as druggable genes using different tools (FUMA, RegulomeDB and DGIdb).

Results: Our gene-based analysis identified 493and 397genes nominally associated with BD and BMI or BD and T2D, respectively. Genes associated with BD and BMI were enriched for different GO terms and pathways, including the protein serine/threonine kinase activity GO term [p=0.00007; false discovery rate (FDR) = 0.02] and the Signaling by Hedgehog pathway (p = 0.0004, FDR = 0.03), while genes associated with BD and T2D showed no significant enrichment. The meta-analysis conducted between BD and BMI using Metasoft identified 54significant SNPs relevant for both traits. The majority of SNPs was located in PPARG (best SNP: rs1899951, p = 1.96E-08), in ETV5(best SNP: rs1516725, p = 6E-24) or in a locus in chromosome 16spanning the NPIPL1, SH2B1, ATP2A1and RABEP2genes (best SNP: rs3888190, p = 4.85E-25). Interestingly, rs2650492(p-value = 1.63E-10) was located in the SBK1gene, a member of the serine/threonine kinase GO term which was not identified through the gene-based analysis approach. A total of 19SNPs located in 11genes were predicted to affect the binding of transcription factors by RegulomeDB. Finally, 13SNPs were located in druggable genes (PPARG, ATP2A1, PTGDR and SBK1) according to DGIdb. The meta-analysis between BD and T2D identified 40 significant SNPs. The majority of these SNPs was located in intergenic regions, while 11SNPs were located in FAF1(best SNP: rs17106184, p = 2.1E-08). Three SNPs were predicted to affect the binding of transcription factors by RegulomeDB, while two SNPs were located in druggable genes (IDE and PVRL2) according to DGIdb

Discussion and conclusions: Our results support the hypothesis of shared genetic determinants between BD and metabolic phenotypes. Genes commonly associated with BD and BMI were enriched for the protein serine/threonine kinase activity molecular go-term. Members of this biological network have been implicated in the pathophysiological bases of BD as well as in the mechanism of action of the mood stabilizer lithium. Future studies on independent samples for which information on comorbidities and potential confounding factors are available are needed to confirm our results and explore the potential role of these genes as druggable targets.