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Genetics of long-term treatment outcome in bipolar disorder

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ABSTRACT

Bipolar disorder (BD) shows one of the strongest genetic predispositions among psychiatric disorders and the identification of reliable genetic predictors of treatment response could significantly improve the prognosis of the disease.

The present study investigated genetic predictors of long-term treatment–outcome in 723 patients with BD type I from the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) genome-wide dataset. BD I patients with >6 months of follow-up and without any treatment restriction (reflecting a natural setting scenario) were included. Phenotypes were the total and depressive episode rates and the occurrence of one or more (hypo)manic/mixed episodes during follow-up. Quality control of genome-wide data was performed according to standard criteria and linear/logistic regression models were used as appropriate under an additive hypothesis. Top genes were further analyzed through a pathway analysis.

Genes previously involved in the susceptibility to BD (*DFNB31*, *SORCS2*, *NRXN1*, *CNTNAP2*, *GRIN2A*, *GRM4*, *GRIN2B*), antidepressant action (*DEPTOR*, *CHRNA7*, *NRXN1*), and mood stabilizer or antipsychotic action (*NTRK2*, *CHRNA7*, *NRXN1*) may affect long-term treatment outcome of BD. Promising findings without previous strong evidence were *TRAF3IP2-AS1*, *NFYC*, *RNLS*, *KCNJ2*, *RASGRF1*, *NTF3* genes. Pathway analysis supported particularly the involvement of molecules mediating the positive regulation of MAPK cascade and learning/memory processes.

Further studies focused on the outlined genes may be helpful to provide validated markers of BD treatment outcome.

1. Introduction

Bipolar disorder (BD) is a chronic disease characterized by the alternation of periods of (hypo)mania and depression, resulting in high personal and socio-economic burden in terms of poor quality of life, increased rates of suicide, and direct and indirect costs (Whiteford et al., 2013). An adequate treatment may allow for long-term remission and good functioning in the majority of patients, but the lack of biological

Abbreviations: BD, Bipolar Disorder; STEP-BD, Systematic Treatment Enhancement Program for Bipolar disorder; DFNB31, Deafness, Autosomal Recessive 31; SORCS2, Sortilin-Related VPS10 Domain Containing Receptor 2; NRXN1, Neurexin 1; CNTNAP2, Contactin Associated Protein-Like 2; GRIN2A, Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 2A; GRM4, Glutamate Receptor, Metabotropic 4; GRIN2B, Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 2B; DEPTOR, DEP Domain Containing MTOR-Interacting Protein; CHRNA7, Cholinergic Receptor, Nicotinic, Alpha 7; NTRK2, Neurotrophic Tyrosine Kinase, Receptor, Type 2; TRAF3IP2-AS1, TRAF3IP2 Antisense RNA 1; NFYC, Nuclear Transcription Factor Y, Gamma; RNLS, Renalase, FAD-Dependent Amine Oxidase; KCNJ2, Potassium Channel, Inwardly Rectifying Subfamily J, Member 2; RASGRF1, Ras Protein-Specific Guanine Nucleotide-Releasing Factor 1; NTF3, Neurotrophin 3; MAPK, mitogen-activated protein kinases; SLC6A4, Solute Carrier Family 6, Member 4; INPP1, Inositol Polyphosphate-1-Phosphatase; GSK3β, Glycogen Synthase Kinase 3 Beta; CREB1, CAMP Responsive Element Binding Protein 1; BDNF, Brain Derived Neurotrophic Factor; CNS, Central Nervous System; GWAS, Genome-Wide Association Study; GRIA2, Glutamate Receptor, Ionotropic, AMPA 2; ACCN1, Acid Sensing Ion Channel 2; SLC4A10, Solute Carrier Family 4, Sodium Bicarbonate Transporter, Member 10; GADL1, Glutamate Decarboxylase-Like 1; DRD2, Dopamine Receptor D2; ANKK1, Ankyrin Repeat And Kinase Domain Containing 1; XBP1, X-Box Binding Protein 1; SNP, Single Nucleotide Polymorphism; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; CMF, Clinical Monitoring Form; SD, Standard Deviation; MAF, Minor Allele Frequency; QQ, Quantile-Quantile; IBS, Identity-By-State; PCC, Pairwise Population Concordance; IBD, Identity-By-Descent; FDR, False Discovery Rate; GO term, Gene Ontology term; ETS1, V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 1; C6orf163, Chromosome 6 Open Reading Frame 163; TSPAN5, Tetraspanin 5; mTORC1, Mammalian Target of Rapamycin Complex 1; MTOR, Mechanistic Target Of Rapamycin; MLST8, MTOR Associated Protein, LST8 Homolog; RPTOR, Regulatory Associated Protein Of MTOR, Complex 1; AKT1S1/PRAS40, AKT1 Substrate 1; PFC, Prefrontal Cortex; VPS10, Vacuolar Protein Sorting 10; KCNQ2 and KCNQ3, Potassium Channel, Voltage Gated KQT-Like Subfamily Q, Member 2 and 3; KCNN3, Potassium Channel, Calcium Activated Intermediate/Small Conductance Subfamily N Alpha, Member 3; KCNA4 and KCNA1, Potassium Channel, Voltage Gated Shaker Related Subfamily A, Member 4 and 1; KCNAB1, Potassium Channel, Voltage Gated Subfamily A Regulatory Beta Subunit 1; KCNS3, Potassium Voltage-Gated Channel, Modifier Subfamily S, Member 3; JAM3, Junctional Adhesion Molecule 3; PTPRD, Protein Tyrosine Phosphatase, Receptor Type, D; NMDA, N-methyl-d-aspartate; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LRRK2, Leucine-Rich Repeat Kinase 2; MARS, Munich Antidepressant Response Signature.

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markers for guiding drug choice makes often difficult the identification of the most effective treatment. Limited treatment efficacy and side effects often due to polypharmacy contribute to treatment non-adherence that occurs at a rate between 12% and 64% among individuals with BD (Leclerc et al., 2013).

BD shows one of the highest genetic predispositions among psychiatric disorders and the heritability index is estimated to be 0.85 (McGuffin et al., 2003). Genetics accounts for 20% to 95% of variability in CNS drug disposition and pharmacodynamics (Cacabelos et al., 2012), supporting the hypothesis that treatment efficacy in BD may significantly be affected by genetic variants.

Previous pharmacogenetic studies were mainly focused on the investigation of predictors of lithium response and they applied both candidate gene and genome-wide association approaches.

Candidate gene studies mainly investigated genes pertaining to the monoaminergic system (especially *SLC6A4* and genes coding for dopaminergic receptors), intracellular second messengers (especially *INPP1*, *GSK3β*, and *CREB1*), and neurotrophin system (especially *BDNF*) (Rybakowski, 2013).

Genome-wide association studies (GWAS) represent a fundamental turning point since they allow the genotyping of several hundreds of thousands polymorphisms throughout the whole genome, providing the opportunity to uncover the multiple variants with small effect size that are supposed to be involved. Two independent groups of researchers identified the chromosomal region 18q23 as connected with lithium response (Ewald et al., 1999; Turecki et al., 2001), but no specific genes were identified within this region. In the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) study, the risk for recurrence among patients treated with lithium was associated with a region on chromosome 4q32 spanning the *GRIA2* gene, coding for the glutamate AMPA receptor (Perlis et al., 2009). Results from a GWAS on a small Italian sample indicated the *ACCN1* gene as a potential candidate for response to lithium (Squassina et al., 2011). The gene codes for a cation channel with high affinity for sodium that may play a role in neurotransmission. Thanks to the ConLiGen initiative (Schulze et al., 2010) a sample including more than 1200 patients characterized for response to lithium was collected and first results suggested *SLC4A10* gene as the top finding (despite it did not reach the genome-wide significance threshold) (Schulze, 2012). The gene codes for solute carrier family 4, sodium bicarbonate transporter, member 10, which belongs to a family of sodium-coupled bicarbonate transporters. *SLC4A10* is highly expressed in the hippocampus and cerebral cortex. Interestingly, it has been proposed as a susceptibility gene for recurrent major depression (Schosser et al., 2011). A recent study on Chinese Han bipolar patients reported two SNPs in high linkage disequilibrium in the *GADL1* gene as correlated with lithium efficacy with impressive p values (10e−37) (Chen et al., 2014). Nevertheless, the risk alleles found by this study are rare in persons of European ancestry and following evidence did not confirm this finding (Consortium on Lithium Genetics et al., 2014).

The pharmacogenetics of mood stabilizers different from lithium was much less studied. Some candidate gene studies exist and provided negative findings (Yun et al., 2008; Wang et al., 2013), while some preliminary results indicated that *DRD2/ANKK1* polymorphisms may be associated with dextromethorphan augmentation to valproate (Lee et al., 2012) and the -116C/G SNP in the *XBP1* gene may correlate with valproate response (Masui et al., 2006; Kim et al., 2009).

Previous studies mainly investigated short-term treatment response and lithium. Despite lithium is considered as a first choice mood stabilizer for the treatment of BD according to current guidelines, polypharmacy is actually the most frequent scenario in the clinical practice (Sachs et al., 2014). Thus, the identification of genetic markers of treatment outcome in a real clinical setting may provide helpful information to identify patients at higher risk of poor outcome who should receive additional clinical attention.

In addition to the investigation of individual genes and polymorphisms, the analysis of molecular pathways that harbor genes of interest represents a recent and exciting challenge for pharmacogenetics. Pathway analysis allows to integrate various "omics" data such as gene expression and GWAS, and several considerations support its application. Indeed, genes are not expected to work alone, but in a complex network of interactions; further, complex phenotypes are supposed to be caused by the dysregulation of multiple targets in connected pathways and/or different genes in the same pathways. Under a statistical point of view, pathway analysis can balance the heterogeneity of genome-wide data (e.g. due to population stratification or differential rates of genotyping error between the groups under analysis) and provide a focused set of genes for validation (e.g. by sequencing) (Fabbri et al., 2013). The identification of pathways associated with treatment response in BD can help to understand the biological mechanisms involved and potentially to develop new treatment strategies.

Given the aforementioned issues, the present study aimed to investigate the genetic predictors of long-term treatment efficacy (more than 6 months) in the STEP-BD genome-wide study, including all treatment regimens in order to reflect a real clinical practice scenario. Depressive and (hypo)manic recurrences were both separately and jointly considered. Both individual polymorphisms/genes and molecular pathways were analyzed.

2. Methods

2.1. Sample

Systematic treatment enhancement program for bipolar disorder (STEP-BD) is the largest clinical prospective trial including BD patients to date (Sachs et al., 2003). STEP-BD was a prospective study, designed to develop and expand knowledge on the management and treatment of BD and evaluate the longitudinal outcome of the disease. Included patients were required to meet DSM-IV criteria for bipolar I disorder, bipolar II disorder, cyclothymia, bipolar disorder not otherwise specified (NOS), or schizoaffective manic or bipolar subtypes. Patients received pharmacological interventions as clinically indicated by the principles of evidenced-based medicine in a naturalistic setting and visits occurred according to clinical demand. Further details on study design and sample are provided elsewhere (Sachs et al., 2003).

Genotyping was performed at the Center for Genotyping and Analysis of the Broad Institute and was performed using the Affymetrix GeneChip Human 500 K Mapping Array Set (Sklar et al., 2008).

2.2. Phenotypes

Prospective clinical information at each visit was registered using the clinical monitoring form (CMF), that included the assessment of manic and depressive symptoms with clinical diagnosis of acute episodes of each polarity according to DSM-IV criteria. More in detail, recovery was defined as two or fewer syndromal features of a mood episode for at least 8 weeks, and recurrence was defined as meeting full DSM criteria for a mood episode on any single subsequent visit. The presence of subsyndromal mood symptoms during follow-up was not considered recurrence (Perlis et al., 2009). In order to provide information about the long-term outcome of treatment, mood episodes occurring within follow-up were considered after excluding patients with follow-up duration <6 months, accordingly to previous studies (Post et al., 2012). Patients were included independently from any ongoing pharmacological treatment. Considering the naturalistic design of the study, a treatment was considered as ongoing when it was prescribed to the patient for more than 50% of the available visits.

Three phenotypes were considered: 1) the total number of episodes/total number of visits ratio; 2) the number of depressive episodes/total number of visits ratio; and 3) the occurrence of at least one hypomanic, manic or mixed episode during follow-up. Thus 1) and 2) are