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The 12th annual pharmacogenetics in psychiatry meeting report

J. Zhang
Hofstra Northwell School of Medicine

K. J. Aitchison

A. K. Malhotra
Hofstra Northwell School of Medicine

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The 12th Annual Pharmacogenetics in Psychiatry Meeting Report

Jian-Ping Zhang, MD, PhD[1,2,3], **Katherine J. Aitchison, MD**[4,5], and **Anil K. Malhotra, MD**[1,2,3]

[1]The Zucker Hillside Hospital, Glen Oaks, NY, USA

[2]The Feinstein Institute for Medical Research, Manhasset, NY, USA

[3]Hofstra North Shore-LIJ School of Medicine, Hemptead, NY, USA

[4]Departments of Psychiatry and Medical Genetics, University of Alberta, Edmonton, AB T6G 2E1, Canada

[5]King's College London, Institute of Psychiatry, London, SE5 8AF, UK

The twelfth Annual Pharmacogenetics in Psychiatry meeting was held in Hollywood, FL, on May 31st to June 1st, 2013, in conjunction with the American Society of Clinical Psychopharmacoloy annual meeting (also known as the NCDEU meeting: New Clinical Drug Evaluation Unit) . It included 20 oral presentations divided in four sessions and 23 poster presentations in one session.

The first session of the meeting focused on the pharmacogenetics of antipsychotic drug induced adverse events, chaired by David Goldman (National Institute of Alcohol Abuse and Alcoholism). The session included six oral presentations. Vickie Ellingrod (University of Michigan, Ann Arbor, MI, United States) presented data from a 3-month open label trial of dietary folic acid supplementation in 35 schizophrenia patients treated with second generation antipsychotics (SGAs). Folate significantly reduced endothelial dysfunction, a cardiovascular risk marker. Patients with the C/C genotype of *MTHFR* single nucleotide polymorphism (SNP) rs1801133 (NM_005957.4:c.665C>T; p.Ala222Val) and the Met/Met genotype of *COMT* SNP rs4680 (NM_000754.3:c.472G>A; p.Val158Met) showed a greater improvement in endothelial function on treatment than those with other genotypes. These findings suggested that folic acid may reduce SGA-associated metabolic and cardiovascular risks and that the effects may be moderated by *MTHFR* and *COMT* genotypes. Marta Bosia (San Raffaele Scientific Institute, Milan, Italy; Institute for Advanced Study, Pavia, Milan) outlined a cross-sectional study of 106 schizophrenia patients investigating the relationship between metabolic syndrome and a SNP, rs11868035, in *SREBF1* (Sterol Regulatory Element-Binding Protein Transcription Factor), a gene important in lipid metabolism. Patients who were homozygous for the G allele were more likely to have metabolic syndrome. There was also a significant interaction between genotype and duration of antipsychotic drug therapy. She concluded that *SREBF1* may be involved in the development of metabolic syndrome in patients treated with antipsychotic drugs. Daniel Mueller (University of Toronto, Canada) reviewed previous genetic studies on

Correspondence: Anil K. Malhotra, MD, Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004, amalhotr@nshs.edu.

antipsychotic-induced weight gain (AIWG) highlighting the prominent role of hypothalamic genes. He reported a genetic association study of variants in *NPY2R* (Neuropeptide Y 2-receptor) with AIWG. Neuropeptide Y is an important orexigenic peptide, expressed in the hypothalamus. It interacts with multiple other neurotransmitters and peptides in the regulation of food intake, and is therefore a plausible candidate for antipsychotic-induced weight gain. They assessed 15 SNPs in 237 patients with chronic schizophrenia treated mainly with clozapine. In preliminary analysis, patients with European ancestry who were T allele carriers for rs12507396 (in the promoter region of NPY2R) gained more weight than other patients. Jianping Zhang (Zucker Hillside Hospital, Glen Oaks, NY, United States) conducted a genome-wide association study (GWAS) of antipsychotic drug-induced akathisia (a common adverse drug reaction that may be associated with medication non-adherence and suicidal ideation), in patients with a first psychotic episode of schizophrenia. A GWAS meta-analysis of two samples (total n=175) revealed several novel loci approaching whole-genome significance. SNPs in genomic regions 13q33.1, 6q26, and 5q35.1 indicated possible roles for *DAOA* (D-amino acid oxidase activator), *PARK2* (Parkinson protein 2, E3 ubiquitin protein ligase), and *NEURL1B* (Neuralized homolog 1B) in drug-induced akathisia. Arun Tiwari (Center for Addiction and Mental Health, Toronto, Canada) conducted exome sequencing in order to identify rare genetic variants associated with clozapine-induced agranulocytosis in 50 Finnish schizophrenia patients (24 cases and 26 controls). Although none of the variants reached statistical significance after correction for multiple testing, they did observe multiple nominal hits in the HLA-C/HLA-B region, supporting the immune-mediated hypothesis of clozapine-induced agranulocytosis. Clement Zai (Center for Addiction and Mental Health, Toronto, Canada) ended the session by presenting a study that replicated the association between *SLC18A2* and tardive dyskinesia (TD), a finding from the CATIE study, in 187 patients with chronic schizophrenia of European decent. They also examined gene-gene interaction between *SLC18A2* and *DRD2*. Further replication was called for.

The second session, chaired by John Kelsoe (University of California, San Diego, CA, United States), was on the pharmacogenetics of antidepressant drug response. David Goldman (National Institute of Alcohol Abuse and Alcoholism, Bethesda, MD, United States), discussed a novel application of deep sequencing in discovering rare genetic variants using traditional animal models. He presented data from a series of studies on a stop codon in *HTR2B*, which leads to uncompensated loss of function resulting in severe impulsivity and alcoholism. Maju Mathew Koola (Sheppard Pratt Health System, Baltimore, MD, Unites States) presented data on a genetic association study between *CYP2D6* and *CYP2C19* and response to treatment with tricyclic antidepressants in 41 patients with mood disorders. At 6 weeks of treatment, neither *CYP2D6* genotype nor phenotype was associated with drug efficacy or adverse events, while *CYP2C19* genotype was associated with clinical response and anticholinergic side effects. Annamaria Cattaneo (King's College London, UK) presented gene expression data from the GENDEP study. This is a follow-up analysis from her previous study (Cattaneo et al., 2012) examining genes involved in glucocorticoid receptor function, inflammation, and neuroplasticity. A Receiver Operating Characteristic (ROC) analysis was then used to assess the accuracy of the identified biomarkers to predict antidepressant non-response. Four genes showed good predictive value: *MIF*, *IL-1β*, *TNF-α*,

and *FKBP-5*. Alessandro Serretti (University of Bologna, Bologna, Italy) investigated the role of *CHL1*, a gene coding for a neuronal cell adhesion protein, in predicting antidepressant treatment response in three independent samples. Pathway analysis and reactome analysis were conducted to examine potential interactions of *CHL1* with other genes. A *CHL1* SNP (rs2133402) was associated with non-response and non-remission, which may be mediated by several genes including *NRP1*, *ITGA1*, and *HSPA8*. Further studies are needed to replicate these findings. John Kelsoe (University of California, San Diego, CA, United States) discussed recent progress in pharmacogenetic research of response to treatment with lithium, including the ongoing pharmacogenetic clinical trial of 700 patients treated with lithium. State of the art technology including genome-wide association study (GWAS), exome sequencing, as well as induced pluripotent stem cells from skin biopsies will be utilized to study lithium treatment response. Seth Hopkins (Sunovion Pharmaceuticals, Marlborough, MA, United States) presented a study of *COMT* rs4680 genotype as a predictor of venlafaxine treatment response in a phase 2, randomized, double-blind, placebo-controlled clinical trial. Depressed patients with the Val158Val genotype of this functional *COMT* variant did better in response to venlafaxine treatment than those with the Met158Met genotype. The findings suggested that *COMT* may be a genetic moderator of venlanfaxine response, and that inhibition of the norepinephrine transporter by venlafaxine may alter noradrenergic flux differentially according to *COMT* activity. Laramie Duncan (on behalf of Roy Perlis and Stephan Ripke, Massachusetts General Hospital, Boston, MA, United States) ended the session by presenting data from a patient DNA repository in which GWAS on treatment resistant depression had been conducted. Samples also included patients from the STAR*D trial. Although no hit reached genome-wide significance, further analyses were being carried out to explore the findings.

Session three of the meeting covered the pharmacogenetics of anxiety and attentional disorders, chaired by James Kennedy (Center for Addiction and Mental Health, Toronto, Canada) and included three paper presentations. Zhewu Wang (Medical University of South Carolina, Charleston, SC, United States) reported the effects of ADHD medication (methylphenidate or atomoxetine) on cortical inhibition, an ADHD endophenotype, in 16 pediatric patients. A variable number tandem repeat polymorphism (VNTR) in the 3'-UTR of *DAT1* (encoding the dopamine transporter) was found to significantly predict cortical inhibition induced by both drugs (equally). Falk Lohoff (University of Pennsylvania, Philadelphia, PA, United States) presented data on the association of variations in PACAP (pituitary adenylate cyclase-activating peptide) genes with antidepressant treatment response in 156 patients with generalized anxiety disorder. Several SNPs in *ADCYAP1* and *ADCYAP1R1* were genotyped in patients undergoing an 18-month relapse prevention study with venlafaxine; the rs2856966 (Asp54Gly) SNP was significantly associated with treatment response. Gwyneth Zai (Center for Addiction and Mental Health, Toronto, Canada) investigated 12 candidate genes for association with antidepressant response in obsessive-compulsive disorder (OCD). Significant associations were found for rs7022369 and rs3780413 in *SLC1A1* (the glutamate transporter), and rs1544325 in *COMT*, as well as a few SNPs in other genes. These results suggested that genetic variations may play a role in OCD response to antidepressants, but replication is required.

The final session of the meeting was on the pharmacogenetics of antipsychotic drug response with emphasis on efficacy, chaired by Alessandro Serretti (University of Bologna, Bologna, Italy). Jeffrey Bishop (University of Illinois, Chicago, IL, United States) investigated variation in *GRM3* (type-3 metabotropic glutamate receptor), *DRD2* (dopamine D_2 receptor), and *COMT* (Catechol-O-methyltransferase) in neurocognitive response to six weeks of antipsychotic drug treatment in 140 first episode psychosis patients. *COMT* was associated with baseline working memory, but change in spatial working memory after treatment did not differ by *COMT* genotypes. Change in spatial working memory was associated with *GRM3* variants, but not with *DRD2*. Chiara Magri (University of Brescia, Brescia, Italy) presented a GWAS of change in factor models of the Positive and Negative Symptoms Scale (PANSS) in 106 patients with schizophrenia undergoing treatment with risperidone. No SNPs reached genome-wide significance for any phenotype, but a few SNPs in *GRM7* (metabotropic glutamate receptor 7) approached genome-wide significance for association with the positive factor of the Emsley seven-dimension model of PANSS. The results suggested that factor model analysis of PANSS may be a good phenotype for pharmacogenetic research. Kristin Bigos (Lieber Institute for Brain Development, Baltimore, MD, United States) presented a GWAS of antipsychotic pharmacokinetic data from the CATIE study. After modeling drug clearance, there were multiple hits for association with the clearance of olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine. SNPs in *ST6GAL1* (ST6 beta-galactosamide alpha-2,6-sialyltranferase 1) predicted olanzapine clearance, which in turn predicted reason of discontinuation from olanzapine. SNPs in *CYP3A43* also predicted olanzapine and risperidone clearance. This shows the promise of studying pharmacokinetic parameters in pharmacogenetic research. Tim Ramsey (SureGene LLC, Louisville, KY, United States) gave the final presentation of the meeting: analysis of homozygous common variants in relation to antipsychotic drug response also from CATIE. Using a recessive model, he showed that there were more results with p-values $< 5\times10^{-5}$ than expected by chance for olanzapine and quetiapine. Several genes had variants that reached the 5×10^{-5} threshold, including *ABCB5*, *CNTN4*, *ERBB4*, and *NRG3*.

This year's meeting also included a poster session with reception. Twenty-three posters were presented with topics ranging from candidate gene pharmacogenetic studies, to GWAS, gene-gene interactions of drug response, and clinical applications of pharmacogenetic testing. The session provided ample opportunities for discussion and networking among colleagues from different institutions. Five young investigators, Eva Brandl (Centre for Addiction and Mental Health, Toronto, Canada), Niki Antypa (University of Bologna, Bologna, Italy), Marta Bosia (San Raffaele Scientific Institute, Milan, Italy), Annamaria Cattaneo (King's College London, London, United Kingdom), and Jianping Zhang (Zucker Hillside Hospital, Glen Oaks, NY, United State) were selected for PIP travel awards sponsored by a conference grant from the National Institute of Mental Health (R13MH090652). For information on next meeting in 2014, please visit www.pharmacogeneticsinpsychiatry.com.