Published in final edited form as:

Pharmacogenomics J. 2009 December ; 9(6): 358–361. doi:10.1038/tj.2009.47.

The 8th Annual Pharmacogenetics in Psychiatry Meeting Report

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The 8th Annual Pharmacogenetics in Psychiatry Meeting was held in New York City on 17 and 18 April 2009 with a series of panel presentations, as well as plenary lectures and a debate on the strengths and weakness of the meta-analytic approach. The following is a report of the meeting presentations.

Pharmacogenetics of adverse events (Chair: James Kennedy; University of Toronto)

Yvon Chagnon (Laval University, Canada) presented an association study of 17 candidate genes with obesity phenotypes in patients with schizophrenia taking antipsychotics (APs) and in controls, and association analysis of 10 genes with AP-induced weight gain. The sample comprised 247 unrelated patients with schizophrenia, who had had several years of AP treatment, and 137 controls. His literature review noted 20 genes with prior reported association in the following groups: serotonergic (*HTR6*, *HTR2A*, *SLC6A4*, *HTR2C*), adrenergic (*ADRB3*, *ADRA2A*), dopaminergic (*DRD4*), drug transporter and metabolizing enzyme (*ABCB1*, *CYP2D6*), neurotransmitter signaling (*NPYF5*, *BDNF*, *GNB3*, *PMCH*, *SNAP25*), and lipid pathways (*LEP*, *LEPR*, *INSIG2*, *SCARB1*, *APOA4*, *APOE*). Of these, 17 genes were selected for association analysis using single-nucleotide polymorphisms (SNPs) ($N = 1-30$ per gene, covering up to 5-kb 5' and 3'), genotyped using the Illumina Bead Chip 355K (Genizon, St Laurent, Quebec). Analysis was by analysis of covariance of body mass index (BMI; kgm^{-2}) or waist circumference (cm) by genotype, with age and sex as covariates and stratifying for the four APs used (olanzapine, clozapine, quetiapine and risperidone). BMI was categorized as follows: underweight ($18.5 \leq \text{BMI} < 25$), overweight (≥ 25 and < 30) and obese (≥ 30). Two of the seventeen genes (*SLC6A4* and *SCARB1*) showed significant association after adjusting for multiple testing using the unstratified phenotypes; five (*HTR2A*, *HTR2C*, *ADRA2A*, *CYP2D6* and *SNAP25*) showed suggestive association on stratification by AP ($P < 0.05$). It can be noted that some markers also showed an association with the phenotypes of interest in the controls, suggesting a common pathway.

Daniel Mueller (University of Toronto) presented data on the cannabinoid-1 receptor (*CNR-1*) and dopamine D_3 receptor gene (*DRD3*) on weight gain. Three samples were combined, two from the United States ($N = 139$ treated with clozapine) and one ($N = 70$) from

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Conflict of interest

Dr Aitchison receives commercial support from Roche Molecular Systems for research support. She is also an advisory board member for Roche Diagnostics. Dr Serretti is a consultant to Aventis and Clinical Data, Inc. He also serves on the speaker's bureau for Boehringer. Dr Malhotra is a consultant to Vanda, Janssen-Ortho Inc., Roche and Clinical Data, Inc. He is also on the Speaker's Bureau for Bristol-Myers Squibb. The remaining authors declare no conflict of interest. The 8th Annual Pharmacogenetics in Psychiatry meeting received financial support from the following companies: PGx Health, Janssen, Merck & Co. and AstraZeneca.

Germany (treated with a variety of APs), with weight gain being measured prospectively after 6 weeks. In *CNR-1*, rs806378 gave a significant result in those of European origin ($N = 123$) on clozapine or olanzapine ($P = 0.01$), whereas those on clozapine alone had the most significant association ($P = 0.001$). Preliminary analyses revealed that rs806378 was in the consensus sequence for a transcription factor (ARNT)-binding site. The results for *DRD3* were less conclusive: there was a tendency for increased weight gain in the European Ser9 allele carriers.

Holly Garriock (University of California, San Francisco) presented a genome-wide association study of intolerance to citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) sample of 1953 individuals. Two intolerance phenotypes were examined using data from the patient rated inventory of side effects (PRISE) measure: headache (present and distressing) and sexual dysfunction. Half of the sample was genotyped using Affymetrix (Santa Clara, CA, USA) 500K arrays, half on 5.0 SNP arrays. There were no associations attaining a genome-wide level of significance. However, for headache, the following suggestive associations were found: rs11602918, rs11218108, rs35852547 and rs2523443, including markers in *NKX2.1*, which is expressed in the cerebral cortical GABAergic neurons and is involved in neuronal migration, and in *GABBR1*. In regard to sexual dysfunction, a common adverse drug reaction on citalopram, Dr Garriock reported that they found associations between *GRIN3A* and *SLC1A1* (encoding the glutamate transporter) for difficulties with orgasm; *SLC1A1* for erectile function; and *SLC1A1* for diminished libido; with the *SLC1A1* association withstanding Bonferroni correction for erectile function and libido.

Dr Alicia Smith (Emory University, GA) reported an association study of a polymorphism in *CCL2* (CC motif ligand 2, also known as monocyte chemotactic protein-1, or MCP-1) with the risk of depression during interferon (IFN)- α treatment. The cerebral spinal fluid (CSF) concentration of MCP-1 has been shown to increase in subjects undergoing IFN- α treatment. Samples were taken from European subjects undergoing pegylated IFN- α treatment as part of the individualized dosing efficacy vs. flat dosing to assess optimal pegylated interferon therapy (IDEAL) and pneumococcal risk factor of IFN- α -induced neuropsychiatric side effects (PROFILE) studies ($N = 808$ total), with those with depression or on psychotropic medication at baseline being excluded. The center for epidemiologic studies depression (CES-D) scale was used to measure depression, with analysis including a dichotomous (CES-D < 21 versus the rest) and a linear approach (maximum change, or 'delta max' in CES-D score at any time point in the study). Regression analyses were used to assess the interaction between self-reported history of mood disorder and *CCL2* SNPs to predict depression severity, adjusting for baseline. Baseline depression score explained 13% of the variance ($P < 0.0001$), and a self-reported history of mood disorders was also significantly associated. A history of mood disorder interacted with the above *CCL2* SNPs to predict depression during treatment (rs1024611, $P = 0.0335$; rs4586, $P = 0.0034$; rs2530797, $P = 0.0005$), and subjects with a previous history of mood disorders and carrying *CCL2* risk alleles had a dose-dependent increase in the maximum change in CES-D scores from baseline to 24 weeks ($P = 0.044-0.001$). It was concluded that polymorphisms in *CCL2* might contribute to the central inflammatory response and, therefore, to treatment-emergent depression on IFN- α treatment for hepatitis C.

Pharmacogenetics of antidepressants (Chair: Anil Malhotra; The Zucker Hillside Hospital, NY)

Peggy Richter (University of Toronto) noted that there have been relatively few pharmacogenetic studies of obsessive-compulsive disorder (OCD), despite the fact that drug response in this illness may be a relatively robust phenotype for investigation. She and her group have assessed response to serotonin reuptake inhibitors (SSRIs) in a cohort of 107

patients with OCD and observed that the serotonin 5-HT_{2A} receptor SNP previously associated with citalopram response in depression in the STAR*D sample is also associated with antidepressant response to multiple SSRIs in OCD.

Steven Hamilton (University of California, San Francisco) presented a novel translational research approach to the pharmacogenetics of antidepressant response. They assessed knockout mice for the gene *Pet-1* (associated with density of serotonergic neurons) for citalopram response and found that these mice showed impaired behavioral responses, and had large reductions in the gene expression of key serotonergic genes, *TPH2* and *SLC6A4*. Moreover, the human homolog of *Pet-1*, *FEV*, was found to influence clinical response to citalopram in the STAR*D sample (all *P* values ≤ 0.005). These data from animal and human studies provide convergent lines of evidence that the *FEV* gene may be associated with antidepressant drug response.

Alessandro Serretti (University of Bologna, Italy) provided an update on the current status of antidepressant pharmacogenetics. During recent years, the influence of a set of candidate genes as genetic predictors of antidepressant response efficacy have been investigated with a growing number of gene variants independently associated with short-term SSRI efficacy. The strongest findings have focused on the upstream regulatory region of the serotonin transporter gene (*5-HTTLPR*), the *A218C* gene variant on the tryptophan hydroxylase gene (*TPH*), variants in the 5-HT_{2A} receptor, particularly for side effects, dystrobrevin-binding protein 1 (*DTNBP1*) and the glucocorticoid receptor-regulating cochaperone (*FKBP5*). He also noted that although influence of genetic variant on human behavior ranges from increased disease susceptibility to influences on treatment response in a subtle, interconnected and environmentally modulated way, the development of an individualized profile for use in clinical practice may soon be approaching.

Kathy Aitchison (Institute of Psychiatry, London) presented an update on the analysis from the genome based therapeutic drugs for depression (GENDEP) (<http://gendep.iop.kcl.ac.uk/results.php>). The *5-HTTLPR* moderated the response to escitalopram with long allele carriers improving more than short allele homozygotes in the male subgroup. *CYP2C19* genotypic category significantly predicted steady state (week 8) escitalopram concentration (*P* = 0.0003). Analysis of weight as a predictor revealed that female subjects with low baseline BMI responded best to nortriptyline, especially on the somatic symptom dimension. On analysis of the adverse drug reaction measures, there was a good agreement between the UKU and novel self-report checklist for adverse effects of antidepressants developed for GENDEP (the ASEC) and made publicly available. Urinary problems, dry mouth, blurred vision and orthostatic hypotension predicted discontinuation of either drug.

Pharmacogenetics of AP drugs (Chair: Katherine Aitchison; Institute of Psychiatry, UK)

Gwyneth Zai (University of Toronto) reported on a pharmacogenetic study that assessed the relationship between the brain-derived neurotrophic factor (*BDNF*) gene and AP drug response in 115 patients treated with clozapine. *BDNF* was genotyped at the functional Val66Met polymorphism that has previously been linked with hippocampal volume, as well as 14 other variants across the gene. Several SNPs were nominally associated with response as assessed with the Brief Psychiatric Rating Scale, including the Val66Met allele. Dr Zai concluded that the results were intriguing and would benefit from replication in additional samples.

Alessandro Serretti (University of Bologna) presented new data about possible *GRIA1*, *GRIA4*, *GRIA3* and *GRIK4* influence on haloperidol efficacy and side effects in a sample of

schizophrenic patients. Glutamate system abnormalities provide, in fact, an intriguing explanation for the pathophysiology of schizophrenia. Two variations (rs472792 and rs1461231 (*GRIA1*)) were found to be associated with response. Those findings provide further support to the glutamatergic theory of schizophrenia identifying putative modulators of the AP effect.

Anil Malhotra (The Zucker Hillside Hospital, NY) presented an update on the ongoing investigations of his group of the relationship between the dopamine 2 receptor (*DRD2*) gene and AP drug response. Previously, they have reported that a functional polymorphism, -141 C Ins/Del in the promoter region of the gene is associated with acute response to the APs, olanzapine and risperidone, in a cohort of first-episode schizophrenia patients.¹ Moreover, recent study has indicated that the same polymorphism may mediate the weight gain associated with treatment with these two agents, such that at 6 weeks of treatment, *Del* allele carriers had gained 6 lb more than noncarriers. Finally, a recently completed meta-analysis of the relationship of this polymorphism with AP drug response indicated significant relationship across studies incorporating a total of 700 subjects, with the effect size being larger in the studies that used first-episode patient cohorts. He concluded that the *DRD2* gene may influence variation in AP drug response, and that the use of first-episode, AP drug-naïve samples may enhance the power of the pharmacogenetic approach.

New approaches to genetic variation and pharmacogenetics (Chair: David Goldman; NIAAA, MD)

Shane McCarthy (Cold Spring Harbor Laboratory, NY) presented study on the identification of copy number variants (CNVs) in neuropsychiatric disorders. They have identified multiple rare CNVs in a number of neuropsychiatric disorders, including a chromosome 16p microduplication that is associated with schizophrenia in two independent cohorts each containing ~5000 subjects, as well as association of this CNV with autism and bipolar disorder. Moreover, this CNV may have a role in mediating head circumference, suggesting that the effects of this CNV on multiple neuropsychiatric disorders could be mediated through its effects on brain structure.

Todd Lencz (The Zucker Hillside Hospital, NY) presented the study of his group on the development of a novel data-analytic strategy to detect rare variants that influence risk for schizophrenia, using the detection of runs of homozygosity (ROH) from a genome-wide association study platform.² He reported that ROHs were more common overall in schizophrenia, and that specific ROHs were markedly overrepresented in schizophrenia patients. He also used this data set to replicate associations between the *DRD1* gene and schizophrenia, as well as extended previous genome-wide association study implicating a SNP within *ZNF804A* in schizophrenia to include an effect of this variant on neurocognitive function and brain structural variation.

Irina Antonijevic (Lundbeck Research USA, NJ) presented on the identification of biomarkers in depression and anxiety. They have focused on transcriptional profiles derived from peripheral blood samples and used dynamic modeling to identify groups of patients with shared profiles. From this, they have identified several promising candidate genes, which are being investigated for relationships to drug response, and may lead to the detection of novel targets for new drug development.

Pharmacogenetics and bipolar disorder (Chair: Alessandro Serretti; University of Bologna)

Melvin McInnis (University of Michigan) reported on a study, which aimed to identify genes whose expression is modified by lithium. Lymphoblastoid cell lines derived from subjects with bipolar disorder were experimentally incubated with 1 mM LiCl for 4, 8 and 16 days. Expression profiling revealed that C8orf33 was significantly over-expressed after lithium exposure, with 217 genes found to have significantly reduced expression profiles. C8orf33 activity was found to be associated with relevant molecular events, including G protein-coupled receptor protein signaling pathway, neuroactive ligand–receptor interaction, Ca²⁺ signaling pathway and the regulation of the actin cytoskeleton.

John Kelsoe (University of California, San Diego) assessed 732 SNPs located in 50 candidate genes for lithium response in a sample of 92 good lithium responders and 92 poor lithium responders. The result of this study implicated the *BDNF/TrkB* pathway as a regulator for the response in euphoric bipolar patients, whereas a *GRK3*-related pathway was found to be more associated with response in dysphoric patients. Finally, the *cAMP*- and *cGMP*-related pathways regulated by the *PDE11A* were found to affect response in both dysphoric and euphoric bipolar patients. Professor Kelsoe suggested that two different molecular pathways—*BDNF/TrkB* and *GRK3* related—influence the response of different subsamples of bipolar patients, but they may have a common final pathway characterized by the *cAMP/cGMP/PDE11A* activation.

Plenary lectures

Abraham Palmer (University of Chicago) presented on a comprehensive translational approach to understanding differences in amphetamine response. Mice were first characterized for their drug response, examined for gene expression differences, and assessed for associated quantitative trait loci to identify candidate genes for the variation in response. These results suggested that the gene casein kinase 1 epsilon gene (*Csnk1e*) contributed to the phenotypic variability among these mice. A parallel preclinical study showed that polymorphisms in human *CSNK1E* were associated with the differences in the sensitivity to the euphoric effects of D-amphetamine in a large cohort of healthy (nondrug abusing) volunteers.³ More recently, a convergent finding from a case–control study of heroine addiction also implicated *CSNK1E*.⁴ These data suggest that studies using this translational approach may offer considerable opportunities for pharmacogenetics research.

Wolfgang Sadee (Ohio State University) reported on the strategy of his group to identify functional polymorphisms in candidate genes of interest to psychiatric pharmacogenetics. His group focuses on the assessment of regulatory polymorphisms as they are more abundant than those altering gene structures and may offer more explanatory power for complex phenotypes. Using allelic expression imbalance, they have identified functional variants in a number of candidate genes for drug response, including *DRD2*, as well as implicated these variants in behavioral and brain imaging phenotypes.⁵ Dr Sadee noted that they are markedly expanding their search space to incorporate hundreds of genes, and results from this project will provide informative data for pharmacogenetic studies across psychiatric disorders.

Debate

Finally, the meeting also included a debate intended to facilitate dialog in controversial and complex issues in pharmacogenetics. This year's debate was conducted on the topic of meta-analysis, a tool that has been increasingly used both for discovery and for the purpose of 'weeding the garden', by David Goldman (NIAAA) and Marcus Munafò (University of Bristol, UK).

As elegantly reviewed by Dr Munafò, meta-analysis is a powerful and increasingly widely used set of statistical methodologies. Although only relatively recently invented, it is having a powerful and positive impact in biomedicine. Balancing his presentation, Dr Munafò identified some pitfalls that can be avoided in the meta-analysis, or even detected through appropriate application of meta-analytic tools. These include the problem of publication bias, which can reveal itself in several ways, including the tendency of smaller studies to produce stronger significant effects. In addition, meta-analysis reveals that studies reported in higher profile journals are paradoxically difficult to replicate.

Dr Goldman countered that meta-analysis is best applied not in the discovery context but for better estimating effect sizes of treatments, genes and environments, and even then with limitations. He criticized the tendency of meta-analyses to synthesize disparate studies, focusing on cruder aspects of investigations, and the tendency to overinterpret both positive and negative results achieved through meta-analysis. False positives remain a problem in meta-analysis because of systematic biases that can occur across studies and that including ethnic stratification, ascertainment and variations in lifestyle. False negatives are a particular problem because of conflation of heterogeneous studies, the focus on cruder variables, inability to integrate multilevel information and a tendency towards a lack of criticality. He advocated the position that advances and validation of these advances is chiefly accomplished through the use of multiple models and different types of measures, and contrasted the relatively limited contributions of this statistical tool with the advances made by procedural scientific approaches relying on hypothesis generation/validation and mechanistic understanding.

Conclusion

Finally, the meeting also included a poster session in which a variety of posters spanning study across the field of pharmacogenetics in psychiatry were presented, and which facilitated multiple informal networking opportunities for meeting participants. Next year's meeting is scheduled for 23 and 24 April 2010 in New York City (<http://pharmacogeneticsinpsychiatry.com> for information).

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