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The Ninth Annual Pharmacogenetics in Psychiatry Meeting report

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Abstract

The Ninth Annual Pharmacogenetics in Psychiatry meeting was held in New York City on 23–24 April 2010 with a series of panel presentations, as well as a debate on the commercialization of genetic testing and a poster reception. The following is a brief report of the meeting presentations.

Keywords

antidepressant; antipsychotic; gene; meeting; pharmacogenetics; psychiatry

The first session of the The Ninth Annual Pharmacogenetics in Psychiatry focused on the pharmacogenetics of addiction (Chairman: David Goldman, National Institute of Alcohol Abuse and Alcoholism, Rockville, Maryland, USA). Rachel Tyndale [Centre for Addiction and Mental Health (CAMH), Toronto, California, USA] presented data on the effects of pharmacogenetic variation in the drug metabolizing enzymes on smoking cessation. The data suggest that metabolic rate of the CYP2A6 enzyme influences abstinence associated with nicotine patch treatment. Marcus Munafò (University of Bristol, Bristol, UK) discussed empirical evidence of the cost-effectiveness of personalized approaches to treatment from a randomized clinical trial of different dosages of nicotine replacement. Results indicated a modest, yet significant effect in favor of the group of patients that received tailoring by genotype, compared with tailoring by phenotype. Keith Heinzerling (University of California, Los Angeles, California, USA) assessed the relationship between the *COMT* Val158Met variant and methamphetamine dependence in a small cohort of Hispanic and European–Americans. Preliminary results suggest that there may be difference in allele frequencies between methamphetamine dependent patients and HapMap controls, but further study is ongoing to enlarge the sample size and fully assess genotypic differences across ethnic groups. Aryeh I. Herman (Yale University, New Haven, Connecticut, USA) reported on a pharmacological challenge study in which response to intravenous nicotine was assessed in relation to variation at the rs16969968 single nucleotide polymorphism (SNP) in the *CHRNA5* gene. Strengths of this approach included the standardization of nicotine intake and the rapid onset of effects, but cardiac monitoring is required. Data collected to date suggest that the SNP may modulate the subjective effect of nicotine. Orna Levran (The

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Rockefeller University, New York, USA) ended the session with data from a study that examined multiple intronic and coding region SNPs within the *ABCB1* gene and the effective methadone dose in heroin addicts, and found that specific genotypes required higher maintenance doses of methadone.

The second session on the pharmacogenetics of anti-psychotic drugs (Chairman: James Kennedy, CAMH) included a number of presentations on adverse events. Daniel J. Müller (CAMH) conducted a comprehensive analysis of the dopamine system (DRD1–DRD5) and weight gain associated with antipsychotic drug treatment. *DRD2* was the most promising gene in early results, and meta-analysis of all samples provided evidence for association of the C957T SNP in *DRD2* and weight gain. This relationship may be due to the effects of this SNP on reward sensitivity or an effect on *DRD2* expression. Vicki Ellingrod (University of Michigan, Ann Arbor, Michigan, USA) examined the relationship between the *MTHFR* and *COMT* genes and the metabolic syndrome, and found that there was a significant relationship after controlling for age, smoking status, and antipsychotic drug use. Moreover, these genes were associated with homocysteine concentrations, suggesting a potential role for folate in this population. Arun Tiwari (CAMH) presented data suggesting that the cannabinoid receptor 1 gene was marginally associated with antipsychotic-induced weight gain and tardive dyskinesia, although the group does not have data on cannabis use. Todd Lencz (The Zucker Hillside Hospital, Glen Oaks, New York, USA) presented on pharmacogenetic studies of weight gain in patients with minimal or no prior exposure to antipsychotic drug treatment. In a candidate gene study, they observed that a functional promoter region SNP in *DRD2* influenced weight gain associated with olanzapine and risperidone treatment. Recent genome-wide association study in a separate cohort of pediatric cases suggests a genome-wide significant peak that is currently being followed.

The third session featured presentations on the pharmacogenetics of antidepressants and mood stabilizers (Chairman: Anil Malhotra, Zucker Hillside Hospital). Gonzalo Laje (National Institute of Mental Health, Bethesda, Maryland, USA) assessed 23 SNPs within the genes for *IDO1* and *IDO2* and their relationship to antidepressant response in the Sequenced Treatment Alternatives to Relieve Depression trial. Although no SNP provides evidence for significant association, two haplotypes within *IDO2* were associated with phenotypes of antidepressant response, remission, and change scores. John Kelsoe (University of California, San Diego, La Jolla, California, USA) provided data on a newly initiated project on the pharmacogenetics of lithium response. An initial retrospective study of 92 lithium responders versus nonresponders identified several candidates, including *NTRK2*. A prospective replication study in 77 patients was consistent with these data, as *NTRK2* influenced time to relapse on lithium. His group will now conduct a Pharmacogenomics Research Network supported study to confirm and expand these results. Katherine J. Aitchison (Institute of Psychiatry, London, UK) updated the meeting on the latest data from the Genome-Based Therapeutic Drugs for Depression study, a large-scale prospective pharmacogenetic study of the antidepressants, nortriptyline and escitalopram. Findings include association between *BDNF/NTRK2* and increasing suicidal ideation, as well as gene expression data suggesting reduced BDNF mRNA levels in depressed patients at baseline that was normalized after treatment with escitalopram. Steven Hamilton (University of California, San Francisco, San Francisco, California, USA) concluded the

session by reporting on a genome-wide association study of side effect burden within the citalopram treatment arm of the Sequenced Treatment Alternatives to Relieve Depression study. Although no SNP achieved genome-wide significance, a number of interesting candidates emerged, including a relationship between *NPAS3*, a gene previously associated with iloperidone response and side effect burden.

The second day of the meeting included sessions on the pharmacogenetics of anxiety (Chairman: Katherine Aitchison, Institute of Psychiatry) and new approaches to genetic variation (Chairman: John Kelsoe, University of California, San Diego). Zhewu Wang (Medical University of South Carolina, Charleston, South Carolina, USA) detected an association between the LL and LS genotypes of the oft-studied *5-HTTLPR* variant and posttraumatic stress disorder in a small study focused on the monoamine system. Falk Lohoff (University of Pennsylvania, Philadelphia, Pennsylvania, USA) reported on an open label trials of venlafaxine for generalized anxiety disorder and found a trend indicating that the *5-HTTLPR 1* allele predicted response at 6 months of treatment, suggesting that the genetic effects on antidepressant efficacy may overlap across disorders. Gwyneth Zai (CAMH) reported on a retrospective study of drug response in 119 patients with obsessive–compulsive disorder. A SNP, C270T, within the *BDNF* gene was associated with response to serotonin reuptake inhibitors, consistent with a previously published study implicating this gene in treatment response in obsessive–compulsive disorder.

Aristotle Voineskos (CAMH) presented new data using brain imaging of the white matter (diffusion tensor imaging) to assess the functional effects of genetic variation. The data implicate genes associated with myelination (*MAG*) as well as neurotrophic growth factors (*BDNF*) on white matter phenotypes. Cathy Barr (University of Toronto, California, USA) reported on her group's genome-wide studies to map the position of gene regulatory elements for genes associated with psychiatric disorders using an approach that combines chromatin immunoprecipitation coupled with high-throughput sequencing. The final speaker, Pamela DeRosse (Zucker Hillside Hospital), discussed a next generation sequencing project focused on *DTNBP1*, a candidate gene for schizophrenia, cognitive function and negative symptoms. Multiple novel variants were detected, including a large number with minor allele frequencies greater than 5%. Validation with capillary sequencing and associated analyses are underway.

This year, the meeting also included a poster reception, which consisted of 20 posters on topics ranging from candidate gene pharmacogenetic studies, meta-analyses, and clinical applications of pharmacogenetic testing, and facilitated multiple informal networking opportunities for meeting participants. Finally, a lively debate was conducted on the pros and cons of the commercialization of genetic testing between David Goldman (National Institute of Alcohol Abuse and Alcoholism) and James Kennedy (CAMH). Dr Goldman argued that the pace of genetic testing and discovery is moving too slowly, and despite some societal and ethical issues to be worked out, needs to be encouraged. Dr Kennedy countered that several areas need to be addressed prior to large scale commercialization, including issues of better predictive validity, clinician education, and stigma associated with 'negative' results. Of note, both debaters used the movie 'GATTACA' to argue their points, as well as video clips and candid photo montages of the opposition debater.

Acknowledgments

Finally, meeting organizer Anil Malhotra announced that a NIMH Grant (R13MH090652) has been secured to help support the meeting. Young Investigator Travel Awards will be available to help support junior investigators' attendance for future meetings. Next year, the meeting will be on 15–16 April 2011 in New York City (http://pharmacogeneticsinpsychiatry.com for information).