The 12th Annual Pharmacogenetics in Psychiatry Meeting

A Category 1 CME Conference

Sponsored by the Zucker Hillside Hospital and the American Society of Clinical Psychopharmacology

May 31 – June 1, 2013

Westin Diplomat
3555 South Ocean Drive
Hollywood, Florida  33019
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May 31, 2013

Dear Colleagues,

It is our great pleasure to welcome you to “The 12th Annual Pharmacogenetics in Psychiatry Meeting” in Hollywood, FL. We hope that this meeting will continue to provide a forum for all investigators working in this field to present their latest data, exchange new ideas, and discuss ongoing developments in this area. Further, we hope to bring together investigators working in diverse areas of research, from molecular geneticists to clinical trials researchers, from academia and industry, to engender true interdisciplinary approaches to the problem of variation in clinical response to psychotropic drugs. It is our hope that each participant will come away from this meeting with an appreciation of the breadth of this evolving field; additionally, we hope to generate interest in pharmacogenetics in young investigators considering their future research endeavors.

This year’s meeting is organized into four sessions:

**Friday, May 31st**

I. *Pharmacogenetics of Antipsychotic Drug Induced Adverse Events*

II. *Pharmacogenetics of Antidepressant Drug Response*

**Saturday, June 1st**

III. *Pharmacogenetics of Anxiety and Attentional Disorders*

IV. *Pharmacogenetics of Antipsychotic Drug Response*
Our annual poster session will take place the evening of Friday, May 31, in the Regency 1 Ballroom in conjunction with a wine and hors d’oeuvres reception. We believe that this event should be both informative and entertaining, and we encourage all meeting participants to attend and interact with the poster presenters, as well as meet with other colleagues.

This conference would not be taking place without the efforts of many individuals. In particular, the Organizing Committee would like to thank Ms. Katherine Norris of the Zucker Hillside Hospital and Sarah Timm of Parthenon Management Group for their continual, invaluable work in all aspects of the planning and preparation of the meeting.

Finally, we are indebted to our financial supporters. These include the Feinstein Institute for Medical Research, the National Institute of Mental Health, and industry partners. Funding for this conference was made possible (in part) by (R13 MH090652) from the National Institute of Mental Health. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

This year’s meeting is our first in conjunction with the NCDEU annual meeting, and our first in Florida. We hope that you will have some time to enjoy our new surroundings. If there is anything we can do to make your visit a more enjoyable one, please let us know.

Sincerely,

Anil K. Malhotra, M.D.
Program Chair
On behalf of the Organizing Committee
CONTINUING MEDICAL EDUCATION INFORMATION

STATEMENT OF NEED: This annual meeting will provide a forum for the presentation and discussion of new developments in the emerging field of psychiatric pharmacogenetics. Updates will include a review of the clinical responses to new antipsychotic drugs, a discussion on genes associated with the development of adverse side effects, an identification of new polymorphisms influencing gene product function as well as novel statistical approaches to dissect the heterogeneity of drug response. An international review of the recent research in this area will be presented.

PROGRAM GOALS: An international faculty will educate and update the psychiatric researcher by presenting the most current research findings in this emerging and continuously evolving field of psychiatry.

PROGRAM OBJECTIVES:

At the conclusion of this course participants should be able to:

• Describe the latest information in the field of pharmacogenetics.

• Evaluate new approaches to the problem of variation in response to psychiatric drugs.

• Identify new genes associated with the development of adverse side effects.

• Recognize novel statistical approaches to dissect the heterogeneity of drug response.

AUDIENCE: Psychiatrists, Psychiatric Researchers, Psychiatry Fellows and Residents as well as mental health professionals interested in psychiatric research.

ACCREDITATION: The American Society of Clinical Psychopharmacology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The American Society of Clinical Psychopharmacology takes responsibility for the content, quality, and scientific integrity of this CME Activity.
The Society designates this live meeting for a maximum of 8.25 AMA PRA Category 1 Credit(s)™. Each physician should claim only those hours of credit that (s) he actually spent in the educational activity.

Verification of Attendance: Certificates will be provided to all professionals who attend this CME Conference.

Americans with Disabilities Act: It is the policy of ASCP not to discriminate against any person on the basis of disabilities. If you feel you need services or auxiliary aids mentioned in this act in order to fully participate in this continuing education activity, please call the Executive Office at 615-649-3085 or send an email to info@ascpp.org

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**CONFERENCE COORDINATED BY**

American Society of Clinical Psychopharmacology

**DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS**

It is the policy of the American Society of Clinical Psychopharmacology to require disclosure of financial relationships from individuals in a position to control the content of a CME activity; to identify and resolve conflicts of interest related to those relationships; and to make disclosure information available to the audience prior to the CME activity. Presenters are required to disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentations.

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This program is supported in part by a grant from:

The National Institute of Mental Health
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EVALUATION OF MEETING

CONFERENCE:  The 12th Annual Pharmacogenetics in Psychiatry Meeting

DATE:  May 31-June 1, 2013

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In order to complete the PIP 2013 Meeting evaluation and obtain CME credit, please visit www.PharmacogeneticsinPsychiatry.com & click on the meeting evaluation. Evaluations must be completed by July 2, 2013.

Questions: Please contact info@ascpp.org.
FRIDAY, MAY 31, 2013

8:00 AM   Continental Breakfast
8:45 AM   Welcome and Introduction

SESSION I: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG INDUCED ADVERSE EVENTS
Chair: David Goldman, M.D.

9:00 AM   Attenuation of Metabolic Consequences from Atypical Antipsychotic Use in Schizophrenia: Folate Supplementation and the Role of Pharmacogenomics
Vicki Ellingrod, Pharm.D.
University of Michigan, College of Pharmacy, Department of Clinical Social and Administrative Sciences, University of Michigan, School of Medicine, Department of Psychiatry

9:25 AM   Metabolic Syndrome in Schizophrenia: The Role of SREBF1 Polymorphism
Marta Bosia, M.D.
San Raffaele Scientific Institute, Department of Clinical Neurosciences, Milan, Italy

9:50 AM   Antipsychotic-induced Weight Gain: Novel Analyses in Hypothalamic Genes Implicates the NPY2R Gene
Daniel J. Müller, M.D.
Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
10:15 AM  Common Variants in Chromosome 6q23.3 are Associated with Antipsychotic Drug Induced Akathisia in Patients with First Episode Schizophrenia
Jianping Zhang, M.D., Ph.D.
Division of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY, USA

10:40 AM  Break

11:00 AM  Exome Sequence Analysis of Finnish Patients with Clozapine-induced Agranulocytosis
Arun Tiwari, Ph.D.
Neurogenetics Section, Neuroscience Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

11:25 AM  The Vesicular Monoamine Transporter SLC18A2 Gene in Tardive Dyskinesia, Replication and Interaction with Dopamine System Genes
Clement Zai, Ph.D.
Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

12:00 PM  Lunch (on your own)

SESSION II: PHARMACOGENETICS OF ANTIDEPRESSANT DRUG RESPONSE
Chair: John Kelsoe, M.D.

2:00 PM  Finding New Functional Loci for Pharmacogenetic Responses in Old Animal Models
David Goldman, M.D.
National Institute of Alcohol Abuse and Alcoholism, Bethesda, MD, USA

2:30 PM  CYP2C19 Genotype is Associated with Response to Tricyclic Antidepressants in Affective Disorders
Maju Mathew Koola, M.D.
Clinical Research Programs, Sheppard Pratt Health System, Baltimore, MD, USA
FRIDAY, MAY 31, 2013 (continued)

2:55 PM  
*Gene Expression as Predictors of Antidepressant Response using ROC Analysis in the GENDEP Study*
Annamaria Cattaneo, Ph.D.
Institute of Psychiatry, King’s College London, UK

3:20 PM  
Break

3:35 PM  
*CHL1 Gene and Antidepressant Response: Results from Three Independent Samples*
Alessandro Serretti, M.D., Ph.D.
Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

4:00 PM  
*Pharmacogenetics of Lithium Response*
John Kelsoe, M.D.
University of California, San Diego, La Jolla, CA, USA

4:25 PM  
*Catechol-O-Methyltransferase Genotype as Modifier of Superior Responses to Venlafaxine Treatment in Major Depressive Disorder*
Seth C. Hopkins, Ph.D.
Sunovion Pharmaceuticals, Inc., USA

4:50 PM  
*GWAS on Treatment-resistant Depression on 1561 Individuals: Single Locus Results and Polygenic Scoring with Results from SCZ, BIP, MDD and CDG from the PGC*
Stephan Ripke, M.D.
Harvard Medical School, USA

5:30 PM  
*Poster Session*
SATURDAY, JUNE 1, 2013

8:30 AM CONTINENTAL BREAKFAST

SESSION III: PHARMACOGENETICS OF ANXIETY AND ATTENTIONAL DISORDERS
Chair: James Kennedy, M.D.

9:00 AM  *Dopamine Transporter Genotypes Influence on ADHD Medication Effects on Cortical Inhibition*
Zhewu Wang, M.D.
Medical University of South Carolina, Charleston, SC, USA

9:25 AM  *Variation in the PACAP and PAC1 Receptor Genes and Treatment Response to Venlafaxine XR in Generalized Anxiety*
Falk W. Lohoff, M.D.
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

9:50 AM  *Pharmacogenetics of Twelve Candidate Genes and Antidepressant Response in Obsessive-compulsive Disorder*
Gwyneth Zai
Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, Canada

10:15 AM  Break
SCHEDULE OF EVENTS

SATURDAY, JUNE 1, 2013 (continued)

SESSION IV: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG RESPONSE
Chair: Alessandro Serretti, M.D., Ph.D.

10:30 AM Pharmacogenomics of Glutamate and Dopamine Genes and Antipsychotic Response in First Episode Psychosis
Jeffrey R. Bishop, Pharm.D.
Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy, USA

10:55 AM A Genome-wide Pharmacogenomic Study of Patients with Schizophrenia suggests that GRM7 Mediates the Effects of Risperidone on Positive Symptoms
Chiara Magri
Division of Biology and Genetics, Department of Molecular and Translational Medicine, University of Brescia, Italy

11:20 AM Genetic Predictors of Antipsychotic Pharmacokinetics and Pharmacodynamics
Kristin Bigos, Ph.D.
Lieber Institute for Brain Development, Baltimore, MD, USA

11:45 AM Pharmacogenomic Analysis of Homozygous Common Genetic Variants in the CATIE Trial
Tim Ramsey
SureGene, LLC

12:10 PM Meeting adjourns
**Friday, May 31, 2013**

**SESSION I: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG INDUCED ADVERSE EVENTS**  
Chair: David Goldman, M.D.

9:00 a.m. – 9:25 a.m.  
**Attenuation of Metabolic Consequences from Atypical Antipsychotic Use in Schizophrenia: Folate Supplementation and the Role of Pharmacogenomics**

Vicki L. Ellingrod, PharmD, FCCP1,2, Tyler B. Grove, B.S.1,2, Kyle J. Burghardt, PharmD1, and Stephan F. Taylor, M.D.2.  
1University of Michigan, College of Pharmacy, Department of Clinical Social and Administrative Sciences and 2University of Michigan, School of Medicine, Department of Psychiatry

**Introduction:** Metabolic syndrome may be related to dietary folate, its pharmacogenetically regulated metabolism, and atypical antipsychotic (AAP) exposure. We examined how folate supplementation would affect metabolic measures and endothelial functioning (RHI) in AAP treated schizophrenia subjects meeting NCEP-ATP-III metabolic syndrome criteria.

**Methods:** Subjects were given 5mg/day open label folate for 3 months. Baseline and 3 month measurements included RHI, BMI, fasting metabolic laboratory measures, C-reactive protein, homocysteine, IL-6, and leptin. DNA was genotyped for the methylenetetrahydrofolate reductase (MTHFR) 677C/T and catechol-O-methyltransferase (COMT) 158 Val/Met variants.

**Results:** Thirty-five subjects with a mean age of 50±9 years and 70% Caucasian. After 3 months supplementation, RHI improved by 20% (p=0.02), mean homocysteine decreased 14% (p=0.006), and IL-6 decreased 13% (p=0.09). Subjects exercised 15% less during the study (p=0.05). At baseline 61% met endothelial dysfunction criteria (RHI<1.67), which decreased to 27% (p=0.0006) at endpoint. The MTHFR 677C/C+COMT 158Met/Met subjects had a 44% RHI improvement versus 10% improvement for MTHFR 677T/COMT Val allele carriers (p=0.06). The MTHFR 677C/C+COMT 158Met/Met group also showed significant reduction in those meeting endothelial dysfunction (83% baseline and 16% endpoint), compared to the MTHFR T+COMT Val allele carriers (54% baseline and 31% endpoint[p=0.001]).
9:00 a.m. – 9:25 a.m.
**Attenuation of Metabolic Consequences from Atypical Antipsychotic Use in Schizophrenia: Folate Supplementation and the Role of Pharmacogenomics (continued)**

**Conclusion:** Folate may reduce AAP-associated metabolic risks and we report significant reductions in the number of subjects meeting endothelial dysfunction. This is remarkable given that ALL subjects met metabolic syndrome criteria. This may prove as a useful avenue to reducing CVD risk. Those with the MTHFR T or COMT Met alleles may not benefit from folate, but this needs further follow up.

9:25 a.m. – 9:50 a.m.
**Metabolic Syndrome in Schizophrenia: The Role of SREBF1 Polymorphism**

*Marta Bosia¹,², Marco Spangaro¹, Andrea Zanoletti¹, Carmelo Guglielmino¹, Federica Cocchi¹, Cristina Lorenzi¹, Adele Pirovano¹, Enrico Smeraldi¹, Roberto Cavallaro¹.*

¹San Raffaele Scientific Institute, Department of Clinical Neurosciences, Milan, Italy; ²Institute for Advanced Study, IUSS, Center for Neurolinguistics and Theoretical Syntax (NeTS), Pavia, Italy

Patients with schizophrenia are at risk for Metabolic Syndrome (MS) [1] due to different factors: lifestyle, diet and side effects of antipsychotic medications (APs). One of the ways by which APs contribute to MS development is increasing lipid biosynthesis through activation of Sterol Regulatory Element-Binding Protein (SREBP) transcription factors [2]. A recent study found that a SREBF1 SNP (A/G, rs11868035) is associated with schizophrenia, suggesting that variation in lipid biosynthesis affects disease susceptibility [3].

We investigated possible associations between rs11868035 and SM in a sample of 106 clinically stabilized patients with schizophrenia treated with APs, assessed with diagnostic criteria for MS according to the International Diabetes Federation (IDF).

Fisher’s Exact Test evidenced a trend for higher frequency of SM among subjects homozygous for the G, compared to A carriers (p=0.069). A separate slope regression was run to evaluate if the effect of duration of antipsychotic therapy on the presence/absence of MS could differ depending on genotype, showing a significant
interaction between genotype and duration of therapy (F=3.51; p=0.035). Among A carriers the duration of antipsychotic treatment resulted more influent on the presence/absence of MS (p=0.043; β=0.313), compared to subjects homozygotes for the G allele.

Results suggest that SREBF1 SNP could interact with APs modulating the development of MS in schizophrenia. Although these data are preliminary and need to be replicated, identification of specific mechanisms underlying interaction between SREBP1 genotype and APs in the development of MS could help define future strategies to improve APs pharmacological tolerability.

References
Antipsychotic-induced Weight Gain: Novel Analyses in Hypothalamic Genes Implicates the NPY2R Gene

Daniel J. Müller1*, Arun K. Tiwari1, Nabilah I. Chowdhury1, Jeffrey A. Lieberman2, Herbert Y. Meltzer3, James L. Kennedy1

1Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Toronto, ON, Canada; 2Department of Psychiatry, College of Physicians and Surgeons, Columbia University and the New York State Psychiatric Institute, New York City, NY, USA; 3Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Background: Over the past ten years, we have made large efforts to investigate the genetic causes in the serious side effect of antipsychotic induced weight gain. We have recently unravelled several important hypothalamic gene variants of the leptin-melanocortin energy homeostasis system associated with antipsychotic-induced weight gain. We investigated novel hypothalamic expressed genes and findings from the neuropeptide Y 2-receptor (NPY2R) gene will be presented.

Methods: A total of 237 patients who underwent treatment for chronic schizophrenia or schizoaffective disorder were evaluated for antipsychotic response and induced weight gain for up to six months. The sample consisted mainly of individuals of European descent exposed to clozapine for their first time. Fifteen SNPs in the NPY2R gene were genotyped. SNPs were selected for having a minor allele frequency of at least 5% and in order to allow for a dense coverage, regions 10kb upstream and 2kb downstream were included. In addition, SNPs were selected based on their functional relevance reported in the literature.

Results: Our analyses with the NPY2R gene showed that patients of European ancestry who were treated with clozapine or olanzapine and who were carriers of the T-allele of SNP rs12507396 gained on average significantly more weight than non-carriers (p=0.025). This result became even more significant when we corrected for duration of treatment (p = 0.01). Haplotype analyses and findings in the other remaining SNPs yielded some interesting trends which will be discussed.

Conclusion: Our results tentatively suggest novel associations between functionally relevant markers of the NPY2R genes in schizophrenic patients treated with antipsychotic medication associated with high risk for metabolic abnormalities and weight gain. We are currently performing replication studies.
Common variants in chromosome 6q23.3 are associated with antipsychotic drug induced akathisia in patients with first episode schizophrenia

Jianping Zhang, M.D., Ph.D., Delbert Robinson, M.D., John Kane, M.D., Todd Lencz, Ph.D., Anil K. Malhotra, M.D.
Division of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY

Background: Akathisia is a common side effect of antipsychotic drugs (APDs), and often causes patients to stop taking their medications. To date, there is no good clinical predictor for APD-induced akathisia. Genetic markers can be potentially useful in predicting akathisia and help in the tailoring of medication treatment for individual patients.

Methods: Eighty-one patients with first-episode psychosis participated in a randomized double-blind clinical trial in which they were treated with either risperidone or olanzapine. Akathisia was assessed weekly using the Barnes Akathisia Rating Scale. Patients were genotyped on the Illumina Omni-1 Quad platform. After quality control, 442,187 SNPs were entered into a genome-wide association study (GWAS). The assessed phenotype was the highest akathisia score during the first 12 weeks of treatment.

Results: The genome-wide association study yielded 4 single nucleotide polymorphisms (SNP) at a single locus in the Chr 6q23.3 region, exceeding a statistical threshold of p<10^-5. The top SNP was rs631204, p<10^-7, which is located about 180kb from TNFAIP3, and is also close to other immune function-related genes including OLG3, IFNGR1, and IL22RA2. Effects were recessive, with 63.2% (12/19) of minor allele homozygotes having akathisia, compared to only 13.3% (8/60) of non-homozygotes. There was no significant difference in type of APD, sex, and age between genotype groups.

Discussion: We found that the chr 6q23.3 region seems to be associated with APD-induced akathisia using GWAS. This region includes multiple genes that are implicated in autoimmune diseases, which suggests that APD-induced akathisia may be partially mediated by autoimmune pathways. This novel finding requires replication in other samples.
11:00 a.m. – 11:25 a.m.

*Exome Sequence Analysis of Finnish Patients with Clozapine-induced Agranulocytosis*

Arun K. Tiwari¹, Anna C. Need², Clement C. Zai¹, Nabilah I Chowdhury¹, Daniel J. Müller¹, Anu Putkonen³, Eila Repo-Tiihonen³, Tero Hallikainen³, A. Elif Anil Yağcioğlu⁴, Jari Tiihonen³,⁵, James L. Kennedy¹*, Herbert Y. Meltzer⁶

¹Neurogenetics Section, Neuroscience Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; ²Center for Human Genome Variation, Duke University, Durham, NC, USA; ³Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland; ⁴Hacettepe University Faculty of Medicine, Ankara, Turkey; ⁵Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden; ⁶Department of Psychiatry and Behavioral Sciences, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Clozapine is the prototypical atypical antipsychotic drug used primarily for treatment resistant schizophrenia. In spite of its efficacy, the use of clozapine is markedly curtailed by its side effects such as metabolic syndrome and agranulocytosis. While metabolic syndrome is more common than agranulocytosis, it is the latter which is the major reason that clinicians and patients are reluctant to consider the use of clozapine. Clozapine-induced agranulocytosis (CIA) occurs in about 0.8% of clozapine treated patients, generally within the first 18 weeks of treatment. The aetiologic mechanism is unknown although several hypotheses including nitrenium ion-mediated apoptosis, mitochondrial oxidative stress-induced apoptosis, or an immune-mediated toxicity mechanism have been proposed. In this study we have utilized exome sequencing to comprehensively identify the genetic variations in the transcribed region of the genome in Finnish patients with (n=24) and without CIA (n=26). A total of 143,258 SNVs and 14,778 INDELs were identified in the 50 individuals at ≥5x read depth. None of the SNVs or INDELs was significantly associated with CIA after Bonferroni correction (p>4.6x10⁻⁷ after correction for 109,131 non-private SNVs and p<4.7x10⁻⁶ after correction for 10,579 non-private INDELs). This is the first time that rare genetic variants have been investigated in relation to clozapine-induced agranulocytosis on a genome-wide scale and the results suggest some level of genetic complexity, even in this relatively homogenous population. We did observe multiple nominally significant associations with single nucleotide variants in the HLA-C/HLA-B gene region (p<0.001), supporting the immune-mediation hypothesis of CIA, and warranting further investigation.
The rate of tardive dyskinesia (TD) has been declining with use of newer atypical antipsychotics, but the risk of TD has not been eliminated. Typical neuroleptics appear to be as effective in treating schizophrenia symptoms as atypical antipsychotics. Thus, understanding the development of TD remains clinically important. Recently, Tsai et al (2010) analyzed 128 candidate genes for possible association with TD occurrence in the CATIE sample, and their top finding was the rs2015586 marker in the SLC18A2 gene. The SLC18A2 gene codes for the vesicular monoamine transporter 2, which is a target of tetrabenazine, an inhibitor that has been used to treat hyperkinetic movement disorders including TD. We aim to follow up on this association finding by investigating for a possible association between nine tag single-nucleotide polymorphisms across the SLC18A2 gene and TD occurrence based on the Schooler and Kane criteria as well as Abnormal Involuntary Movement Scale scores in our sample of schizophrenia patients of European ethnicity (N=187).

We found four SLC18A2 SNPs to be associated with TD occurrence and total AIMS scores (p<0.05), including the rs2015586 marker. The risk allele for the rs2015586 from our study agreed with the one from the Tsai et al (2010) study. We are expanding these findings by investigating the interaction of these SLC18A2 SNPs with other dopamine genes to estimate the portion of that risk for TD that can be explained by SNPs in this neurotransmission system. Pending
further independent replication, our study findings support an involvement of the SLC18A2 gene in TD development.

SESSION II: PHARMACOGENETICS OF ANTIDEPRESSANT DRUG RESPONSE
Chair: John Kelsoe, M.D.

2:00 p.m. – 2:30 p.m.
Discovery of Genes Influencing Addiction by Deep Sequencing Humans and Model Organisms

David Goldman, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism

Rare and uncommon alleles contribute to vulnerability to addictions and other behavioral disorders. They are a major part of the missing heritability or “dark matter” subsequent to genome wide association studies. To identify these variants and tie them to behavior we apply deep sequencing in contexts where effects of rare alleles can be measured. In Finns, a founder population, we discovered a stop codon in the HTR2B serotonin receptor. It leads to uncompensated loss of function, can lead to severe impulsivity and alcoholism, and is restricted to Finns in line with the founder characteristics of this population. The behavioral effects of loss of Htr2b function were validated in the Htr2b knockout mouse and extended to the level of neural function, including the role of this receptor in regulating phasic dopamine release in the mesolimbic system. Via exome sequencing of the alcohol preferring (P) rat, one of the most widely accepted model organisms for alcoholism, we found a stop codon in the Grm2 metabotropic glutamate receptor gene. This stop codon was genetically fixed by selection in the P rat, leads to uncompensated effects on glutamate function, and – as shown by genetic studies- is partially responsible for the increased alcohol preference in these rats.
Background: There is strong evidence for the role of cytochrome enzymes CYP2D6 and CYP2C19 in the metabolism of tricyclic antidepressants (TCAs), and some prior evidence of association with clinical response and adverse drug reactions (Bertilsson et al, 1993; Spina et al, 1997; Steimer et al, 2005).

Methods: Subjects (N=41) had major depressive disorder (N=37) or bipolar disorder (N=4) treated with TCAs (the most frequently prescribed being amitriptyline) in a tertiary referral center. Venous blood was taken for genetic analysis and for levels of the TCAs and their primary metabolites, and was phenotyped for CYP2D6 activity using debrisoquine. Patients were assessed at baseline and at six weeks for severity of depression using the Hamilton Depression Rating Scale (HDRS), and were also rated for side effects at six weeks.

Results: There was no association between clinical response or adverse drug reaction and CYP2D6 phenotype or genotype. However, an association between clinical response to these TCAs and CYP2C19 genotype was found (p=0.005). The direction of effect was such that it implies that the parent TCA may be more potent than its demethylated metabolite, consistent with the dual (serotonin-norepinephrine) reuptake inhibitory effect of TCAs such as amitriptyline, and the sample being of patients who had a severe illness (mean pre-treatment HDRS score 25.9). In addition, the level of demethylated TCA was associated with anticholinergic side effects.
Conclusion: This study indicates that in patients with affective disorders, clinical response to TCAs may be predicted by CYP2C19 genotype.

Funding and Acknowledgements: The authors would like to acknowledge Mahesh Patel, who conducted the debrisoquine metabolic ratio measurement, and Dr. Ingelman-Sundberg’s laboratory for assistance with set-up of the CYP2C19*17 assay. Dr. Aitchison collected the sample whilst a Research Registrar and Research Fellow (Wellcome Mental Health Research Fellowship, grant 045968), and would like to thank Professor Stuart Checkley, previous Consultant of the National Affective Disorders Unit at South London and Maudsley NHS Foundation Trust, the patients and other staff members for their assistance in this work, and Brian Smith, previously at the Maudsley Pathology Laboratory. We would also like to thank the Rosetrees Trust for contributing funding towards the genotyping costs.

Gene Expression as Predictors of Antidepressant Response using ROC Analysis in the GENDEP Study

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To improve the “personalized-medicine” approach to the treatment of depression, we need to identify biomarkers that, assessed before starting treatment, predict future response to antidepressants. We tested the leukocyte mRNA expression levels of genes belonging
to glucocorticoid receptor function, inflammation and neuroplasticity, in 34 healthy controls and 74 depressed patients, as part of the GENDEP study. In a previous report (Cattaneo et al., Neuropsychopharmacology, 2012), we found that the levels of IL-1β, MIF and TNF-α at the baseline were all strongly and negatively correlated with treatment response (IL-1β, r=-0.56; MIF, r=-0.62; and TNF-α, r=-0.44; all p<0.0001). However, the contribution of the 15 genes to prediction may have not been adequately captured by simple correlation analyses.

In order to better evaluate the accuracy of these predictors, we have run a receiver operating characteristic (ROC) analysis. N=23 patients (31%) did not respond to antidepressants (escitalopram or Nortryptiline), that is, did not show a reduction in MADRS score of 50% or more. Using “lack of response” as positive actual state in the ROC analysis, four genes plotted above the reference line (that is, higher gene expression predicting lack of response) with areas under the curve (AUCs) that were indicative of at least “fair” predictive value: MIF (0.9), IL-1β (0.8), TNF-α (0.8) and FKBP-5 (0.7). All the other genes had AUCs <0.7, indicating poor predictive values. Further analyses indicated that the expression values of these genes that had the best combination of sensitivity and specificity in predicting lack of response were: 1.35 for MIF, 1.56 for IL-1β, 1.55 for TNF-α, and 1.34 for FKBP-5. Our data suggest that monitoring the levels of these genes could identify depressed patients who are least likely to respond to first-line antidepressants, and this could allow doctors to consider early introduction of more assertive therapeutic approaches of combining antidepressants or adding adjuvant therapies.
CHL1 - a gene coding for a neuronal cell adhesion protein – was recently proposed as antidepressant response predictor. Thus, 6 SNPs (rs4003413, rs2133402, rs9841789, rs1516340, rs2272522 and rs1516338) in CHL1 were genotyped in two independent samples (n=368 and 96) with major depressive disorder and treated with antidepressants. Logistic regression was used to investigate associations with response/remission at week 4. Secondly, String Interaction Network (http://string-db.org) and Reactome (www.reactome.org/) were used to identify proteins that have interaction with CHL1, and a pathway analysis was performed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genome-wide study (n=1861). Genes belonging to the index pathway were imputed through IMPUTE2 taking CEU HapMap 1000 genomes as reference. The prevalence of variations showing 0.01<p<0.09 was compared between the index pathway and a random pathway by a Fisher exact test. 10e5 permutations were run.

In the largest sample rs2133402 T allele was associated with non response (p=0.019) and non remission (p=0.010), while in the other negative results were found. In the STAR*D the top CHL1 marker
CHL1 Gene and Antidepressant Response: Results from Three Independent Samples (continued)

was rs17330105 (p=0.0004, 4200 bp from rs2133402). The index pathway showed a trend of association with response (permuted p=0.095). Especially NRP1, ITGA1 and HSPA8 were responsible of the result. ITGA1 is involved in cell adhesion and migration and NRP1 is critical for the formation of neuronal circuits. HSPA8 mRNA level changes in rat frontal cortex after antidepressant treatment were previously reported. CHL1 and its pathway may be promising candidates for involvement in antidepressant response; further studies would deepen their role.

Pharmacogenetics of Lithium Response

John Kelsoe, M.D., University of California, San Diego, USA

No abstract submitted.

Catechol-O-Methyltransferase Genotype as Modifier of Superior Responses to Venlafaxine Treatment in Major Depressive Disorder

Seth C. Hopkins¹, David S. Reasner¹, Keith A. Wesnes²,³, Kenneth S. Koblan¹

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The range of response rates following antidepressant treatment is suggestive of genetic factors, and the utilization of robust genetic markers of treatment response would increase the efficiency, safety and economic benefit of existing therapies. Since COMT activity influences dopamine levels in brain areas where dopamine transporter expression is low, we hypothesized that COMT functional variant rs4680 (Val158Met) might influence noradrenergic effects when norepinephrine transporters are inhibited therapeutically. The clinical responses of subjects with major depressive disorder treated with venlafaxine were analyzed according to COMT genotype using data collected from a Phase 2 randomized, double-blind, placebo-controlled clinical study (NCT00584974). Venlafaxine subjects
catechol-O-methyltransferase genotype as modifier of superior responses to venlafaxine treatment in major depressive disorder (continued)

(N=126) improved relative to placebo subjects (-3.6 points, p = 0.0006 in change from baseline on the HAM-D-17 scale) over 8 weeks of treatment. The clinical improvement in Val/Val genotypes treated with venlafaxine appeared larger than in Met/Met genotypes, when analyzed by either HAM-D-17 (-5.9 points, p = 0.013 unadjusted) or CGI scales. Response rates in Val/Val genotypes were superior to those of venlafaxine versus placebo in the overall population. These results suggest that COMT activity may be a genetic modifier of venlafaxine response, and that inhibition of NET may alter noradrenergic flux differentially according to COMT activity. Superior efficacy of venlafaxine in Val/Val genotypes warrants testing directly in directed, large-scale genotype-controlled clinical studies with optimized sampling of homozygous COMT genotypes.

GWAS on Treatment-resistant Depression on 1561 Individuals. Single Locus Results and Polygenic Scoring with Results from SCZ, BIP, MDD and CDG from the PGC

Stephan Ripke, M.D., Jordan W. Smoller, M.D., Roy H. Perlis, M.D., MSc Harvard Medical School

Background: Up to one third of individuals with major depressive disorder do not reach remission despite two or more adequate antidepressant treatment trials. Such treatment-resistant depression has been suggested to be associated with unrecognized or subsyndromal bipolar disorder or psychotic disorder. The availability of genomewide association data from very large cohorts of individuals with bipolar disorder and schizophrenia provides an opportunity to directly test this hypothesis.

Method: We utilized GWAS data from the i2b2-TRD and STARD treatment resistant depression cohorts, which include 532 TRD cases and 1029 antidepressant-responsive controls of Northern European descent. Polygenic risk scores were created based upon meta-analytic results from the published PGC GWAS datasets from schizophrenia, bipolar, major depression and cross-disorder analysis. These scores were compared for TRD cases and controls using logistic regression models.
4:50 p.m. – 5:15 p.m.

**GWAS on Treatment-resistant Depression on 1561 Individuals. Single Locus Results and Polygenic Scoring with Results from SCZ, BIP, MDD and CDG from the PGC (continued)**

**Results:** Polygenic analyses and single-loci results will be presented. **Discussion:** The utility of polygenic analysis for examining overlap in psychiatric phenotypes will be discussed, with particular application to its potential role in pharmacogenomic studies.
Saturday, June 1, 2013

SESSION III: PHARMACOGENETICS OF ANXIETY AND ATTENTIONAL DISORDERS
Chair: James Kennedy, M.D.

9:00 a.m. – 9:25 a.m.
Dopamine Transporter Genotypes Influence on ADHD Medication Effects on Cortical Inhibition

Zhewu Wang1,2, Howard Mendal1, Mark Hamner1,2, Donald L. Gilbert3
1Charleston VA Medical Center, Charleston, SC; 2Institute of Psychiatry, Medical University of South Carolina, Charleston, SC; 3Department of Neurology, Cincinnati Children Hospital Medical Center, Cincinnati, OH

Background: Attention deficit hyperactivity disorder (ADHD) is a common and highly heritable neuropsychiatric disorder that affects children and adults. Methylphenidate (MPH), a psychostimulant, and atomoxetine (ATX), a selective norepinephrine reuptake inhibitor (NRI) are highly effective in attenuating the symptoms of ADHD patients, but individual response to treatments varies widely. Motor cortex inhibition, measured with transcranial magnetic stimulation (TMS), and dopamine transporter (DAT1) 3′ untranslated region-variable number tandem repeats (3′ UTR-VNTR) polymorphisms have previously been linked to ADHD diagnosis and stimulant treatment responses but results between studies vary. Our primary objective was to determine DAT1 genotypes influence the effects of MPH and ATX on TMS-evoked cortical inhibition in children with ADHD.

Methods: Sixteen children with ADHD were given oral doses of 0.5 mg/kg MPH and 1.0 mg/kg ATX at visits separated by one week in a randomized, double-blind crossover design. We used TMS to measure conditioned and unconditioned motor evoked potential amplitudes at inhibitory and facilitatory inter-stimulus intervals before and after drug administration. Subjects were genotyped for the DAT1 3′-UTR-VNTR polymorphism. Treatment and genotype effects were estimated with repeated measures, mixed model regression.

Results The effects of both MPH and ATX on cortical inhibition differed significantly in ADHD children with DAT 9/10 versus 10/10 genotypes (F2,13 = 13.04, p = 0.0008). This medication x genotype effect was specific for cortical inhibition and did not distinguish between ATX and MPH.
9:00 a.m. – 9:25 a.m.  
*Dopamine Transporter Genotypes Influence on ADHD Medication Effects on Cortical Inhibition* (continued)

**Conclusion:** TMS-evoked cortical inhibition is an endophenotype of ADHD which is sensitive to DAT1-mediated effects of both stimulant and NRI ADHD treatments.

9:25 a.m. – 9:50 a.m.  
*Variation in the PACAP and PAC1 Receptor Genes and Treatment Response to Venlafaxine XR in Generalized Anxiety Disorder*

**Alissa J. Cooper, BA\(^1\), Sneha Narasimhan, BA\(^1\), Karl Rickels, MD\(^2\), Falk W. Lohoff, MD \(^1,2^*\)**

\(^1\) Psychiatric Pharmacogenetics Laboratory, Center for Neurobiology and Behavior, Department of Psychiatry, University of Pennsylvania  
\(^2\) Mood & Anxiety Disorders Section, Department of Psychiatry, University of Pennsylvania

**Background:** Pituitary adenylate cyclase-activating peptide (PACAP) is known to be involved in stress response and anxiety. Recent studies have implicated a role of genetic variations in the PACAP (ADCYAP1) and PAC1 receptor (ADCYAP1R1) genes and post-traumatic stress disorder (PTSD). Given that antidepressant drugs are currently considered the first line treatment for PTSD but also are effective for various other anxiety disorders, we examined whether single nucleotide polymorphisms (SNPs) in the PACAP (ADCYAP1) and PAC1 (ADCYAP1R1) gene predict response to antidepressant treatment in patients with generalized anxiety disorder (GAD).

**Methods:** 156 patients diagnosed with GAD received venlafaxine XR treatment as part of an 18-month relapse prevention study. Genotypes were obtained for PACAP gene SNPs rs2856966, rs928978, rs1610037, rs1893154, rs2231187, rs2846811, and rs8192595 and PAC1 gene SNP rs2267735 in patients of European American ethnicity (EA n=112).

**Results:** Results show a significant association between the rs2856966 (Asp54Gly) SNP in the PACAP gene and antidepressant treatment response in GAD (HAM-A remission: genotypic \(p=0.0013\)). None of the other tested SNPs was associated with outcome. There were no significant associations when the analysis was conducted in females only.
Conclusion: Our results indicate that the potentially functional variant Asp54Gly in the PACAP gene may play a role in treatment response to venlafaxine XR in GAD.

9:50 a.m. – 10:15 a.m.
Pharmacogenetics of Twelve Candidate Genes and Antidepressant Response in Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a strong genetic component. Genetic associations between OCD and several candidate genes including the glutamate transporter (SLC1A1), monoamine oxidase (MAOA), glutamate NMDA receptor 2B (GRIN2B), serotonin 2A receptor (5HTR2A), serotonin transporter (SLC6A4), and catecholamine-O-methyltransferase (COMT) genes have been reported with inconsistent results. Pharmacogenetics represents an alternate to investigate inter-individual genetic variation in drug response. We investigated 12 different genes including those mentioned above in addition to the disks large (drosophila) homolog-associated protein 2 (DLGAP2), myelin oligodendrocyte glycoprotein (MOG), serotonin 1B receptor (5HT1B), chromosome 9 open reading frame 68 (C9orf68), adenosine deaminase, RNA-specific, B2 (ADARB2), and oligodendrocyte lineage transcription factor 2 (OLIG2) genes. Two to 16 SNPs in the DLGAP2, MOG, 5HT1B, SLC1A1, C9orf68, MAOA, ADARB2, GRIN2B, 5HTR2A, SLC6A4, OLIG2, and COMT genes respectively were genotyped in 117 OCD patients with retrospective response data on multiple serotonin reuptake inhibitor (SRI) trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported “minimal”, “no change”, or “worsening”. Genotypes and response data were examined on a
drug-by-drug and combined basis. Significant response associations were detected in DLGAP2 and paroxetine/clomipramine ($P=0.008$-$0.042$), 5HT1B and clomipramine/SRI(s) ($P=0.0003$-$0.045$), SLC1A1 and sertraline/fluvoxamine/citalopram/SSRI(s)/SRI(s) ($P=0.0008$-$0.035$), C9orf68 and clomipramine/fluvoxamine/SSRI(s) ($P=0.007$-$0.031$), MAOA and citalopram ($P=0.028$), GRIN2B and fluoxetine/paroxetine/fluvoxamine/citalopram/clomipramine ($P=0.004$-$0.024$), 5HTR2A and clomipramine ($P=0.024$), SLC6A4 and paroxetine ($P=0.0006$-$0.010$), OLIG2 and paroxetine ($P=0.008$), and COMT and paroxetine/sertraline/citalopram/SSRI(s)/SRI(s) ($P=0.007$-$0.044$). These results suggest that genetic variants may play a role in SRI response to OCD.

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3. Dr. James L. Kennedy; Tel: (416) 979-4987; Fax: (416) 979-4666; Email: james_kennedy@camh.net
We have previously shown that variation in the type-3 metabotropic glutamate receptor gene (GRM3) is associated with symptom response to antipsychotics as well as treatment-resistant symptoms in patients with schizophrenia. Additionally, GRM3 variants may modulate performance on cognition in chronically treated patients, particularly executive function tasks dependent upon prefrontal systems. We extended this work to examine relationships between glutamate and dopamine system genes with cognitive performance and symptoms in 140 first episode psychosis patients phenotyped with eye movement neurophysiology studies of spatial working memory, smooth pursuit, reflexive attention, and response inhibition evaluated before and after antipsychotic treatment. In untreated patients, variation in DRD2 was associated with two measures of smooth pursuit initiation, while GRM3 SNPs were related to pursuit maintenance. In a subset of patients followed over the course of 6 weeks of antipsychotic treatment, DRD2 SNPs were related to change in pursuit latency while GRM3 variants were associated with change in pursuit maintenance, spatial working memory, and negative symptoms. These findings highlight the importance of D2 signaling as it relates to initiation of motor responses dependent
on fronto-striatal circuitry. Furthermore, GRM3 findings indicate that glutamate signaling is important for performance on cognitive measures of pursuit and spatial working memory that are dependent upon prefrontal functions to maintain internal representations to guide behaviors, and the extent to which antipsychotics influence these functional systems.

10:55 a.m. – 11:20 a.m.
A Genome-wide Pharmacogenomic Study of Patients with Schizophrenia Suggests that GRM7 Mediates the Effects of Risperidone on Positive Symptoms

Magri Chiara¹, Minelli Alessandra¹, Traversa Michele¹, Valsecchi Paolo², Scassellati Catia⁴, Sacchetti Emilio², Gennarelli Massimo¹,²,³, Gennarelli Massimo¹,⁴
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Antipsychotic response is often variable, therefore, identification of genetic markers helping in predicting the treatment response is extremely interesting. The Positive and Negative Syndrome Scale (PANSS) is widely used in clinical and research settings and its factor structure analysis could better identify symptoms clusters for the treatment response assessment.

We performed a genome wide association study on a group of schizophrenia patients in monotherapy with risperidone, whose symptoms improvement was measured after two weeks using the five and seven factors models.

No SNPs achieved a genome wide significant association p-value (p<5x10^-8) with the PANSS total score, or with the five and seven factors models. However, an association p-value (p=6.88x10^-8) very close to the threshold for declaring significance was observed for a SNP inside the metabotropic glutamate receptor 7 (GRM7) gene and Emsley scale’s positive symptoms. Seven factors model showed that risperidone gave a worst amelioration of positive symptoms after two weeks treatment in recessive homozygous subjects compared to
A Genome-wide Pharmacogenomic Study of Patients with Schizophrenia Suggests that GRM7 Mediates the Effects of Risperidone on Positive Symptoms (continued)

others. The same trend was observed for the Marder scale’s positive symptoms. Glutamatergic system is a promising target for novel antipsychotic compounds and its dysfunction is one of the major hypotheses to explain the pathogenesis of schizophrenia. Based on these considerations our preliminary data appear very promising and require further investigation in other data sets. In conclusion, this study suggests that a better characterization of endophenotypes using factor model analysis of PANSS could be useful in pharmacogenomics of antipsychotic drugs response.

11:20 a.m. – 11:45 a.m.
Genetic Predictors of Antipsychotic Pharmacokinetics and Pharmacodynamics

Kristin Bigos, Ph.D., Lieber Institute for Brain Development

Antipsychotics have a high rate of discontinuation due to inefficacy and/or adverse effects. An ancillary study to the CATIE trials aimed to identify and quantify sources of variability in the clearance of antipsychotics. We have previously shown that sex and smoking are associated with differential clearance of several antipsychotics (Bigos et al. J Clin Pharmacol 2008; 48(2):157-165). We are currently using pharmacokinetic and genetic data from the CATIE schizophrenia trial to identify genetic predictors of antipsychotic pharmacokinetics using non-linear mixed effects modeling. A candidate gene approach has identified several genetic variants in cytochrome P450 genes that highly predict the clearance of antipsychotics. We have shown that CYP3A43 significantly predicts clearance of olanzapine (Bigos et al. Molecular Psychiatry 2011; 16:620-625). We have recently found that the same SNP in CYP3A43 also significantly predicts 30% of risperidone clearance. Of the 230 SNPs in CYP450s, the CYP3A43 SNP (rs472660) was the most significantly associated with both risperidone and olanzapine clearance, and predicted most and the entire previous race effects in drug clearance, respectively. African Americans have a greater proportion of carriers of the fast metabolizing allele. This CYP3A43
SNP did not predict either quetiapine or ziprasidone, which was predicted based on the lack of racial effects on their clearance. The most significant predictors of ziprasidone and quetiapine clearance were SNPs located in the CYP2A/2B families of genes on chromosome 12. SNPs in other CYP gene families were also associated with clearance of one or more of the antipsychotics. We are also conducting a GWA study using the original CATIE Affy 500K chip, and we have identified novel genetic predictors, which have not previously been associated with drug metabolism, including ST6GAL1 which best predicts olanzapine clearance. A long-term goal is to use these genetic variants to build models of predictors of antipsychotic drug metabolism in order to guide dosing. A separate goal is to use the variability in antipsychotic clearance as a covariate in studies designed to identify genetic predictors of antipsychotic drug response. We have shown that patients with schizophrenia who carry the risk allele for KCNH2, are 5-times less likely to discontinue olanzapine, only after controlling for differences in olanzapine clearance (Apud et al. *Am J Psychiatry*. 2012;169:725-734). The overall goal of this research is to use genetics to identify and characterize sources of variability in pharmacokinetics and response to psychotropics in order to optimize treatment strategies.

References:
Variation in response to antipsychotic treatment complicates the treatment of patients with schizophrenia. Several studies have been published on pharmacogenomic response to antipsychotics, most of which have focused on GWAS approaches using common variants evaluating only additive genetic models. Generally overlooked is the possibility that homozygosity for commonly occurring genetic variants could potentially impact drug response even in those cases where a single copy of the variant has little or no impact. In the current study, we explore this possibility by testing the recessive model of genetic variation on atypical antipsychotic response in the Caucasian subset of Phases 1, 1A, and 2 of CATIE study. More results with p-values < 5 x 10^{-5} than expected by chance were observed for olanzapine (three times as many) and quetiapine (twice as many), but not for risperidone or ziprasidone. The list of variants which met the 5 x 10^{-5} cutoff included those in several genes with potential biological relevance to psychopathology and/or drug response, including \textit{ABCB5}, \textit{CNTN4}, \textit{ERBB4}, \textit{SV2C}, \textit{SVIL}, \textit{KCND3}, \textit{KCTD16}, \textit{NLGN}, and \textit{NRG3}.

\textsuperscript{1}All authors are employees of SureGene, LLC. Ramsey and Brennan are equity holders in SureGene.
1. Genetics of Functional Disability in Schizophrenia and Bipolar Disorder: Preliminary Results from VA CSP 572
   Philip D. Harvey, Ph.D.
   University of Miami, Miller School of Medicine
   Miami, Florida, USA

2. Possible Influence of PDE7B, NMBR AND EPM2A Genes Variants on Antipsychotics Response in Schizophrenia Patients
   Alessandro Serretti, M.D., Ph.D.
   Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

3. Endothelial Nitric Oxide Synthetase Genetic Variants, Metabolic Syndrome and Endothelial Function in Schizophrenia
   Kyle J. Burghardt, Pharm.D.
   University of Michigan, Department of Clinical Social and Administrative Sciences, College of Pharmacy
   Ann Arbor, Michigan, USA

4. DAT and DRD4 Gene Differences Influence Drinking and Craving in Early but not Later Stage Alcoholics; Importance for Pharmacotherapy?
   Raymond Anton, M.D.
   Medical University of South Carolina
   Charleston, South Carolina, USA

5. Dysregulation of the Histone Demethylase KDM6B in Alcoholism
   Andrea L. Johnstone, Ph.D.
   University of Miami, Miller School of Medicine
   Miami, Florida, USA

6. The ERK Pathway Involved in Treatment Side Effects in BD-I
   Antonio Drago, M.D.
   Department of Biomedical and Neuromotor Sciences Institute of Psychiatry, University of Bologna, Italy
7. **Predicting Antidepressant Treatment Response through Genomewide Interaction and Enrichment Analysis**  
    Niki Antypa, Ph.D.  
    Department of Biomedical and NeuroMotor Sciences, Institute of Psychiatry, University of Bologna, Italy

8. **Influence of MAPK1 and CREB1 Polymorphisms on Treatment Remission in Mood Disorder Patients**  
    Concetta Crisafulli, Ph.D.  
    Department of Biomedical Science and morphological and functional images, University of Messina, Italy

9. **PPP3CC Gene: A Putative New Marker of Antidepressant Response**  
    Chiara Fabbri (Presented by: Concetta Crisafulli, Ph.D.)  
    Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

10. **Effect of Adjunctive L-Methylfolate 15 mg in Depressed Patients Stratified by Biomarker Levels and Genotype**  
    Maurizio Fava, M.D.  
    Massachusetts General Hospital  
    Boston, Massachusetts, USA

11. **Implementing Pharmacogenomic Clinic for Treatment Refractory Depression**  
    Susan G. Leckband, RPh, BCPP  
    Veterans Affairs San Diego Healthcare System  
    San Diego, California, USA

12. **Antipsychotic-induced Weight Gain and the Role of Histamine Receptor H1 and H3 Variants**  
    Trehani Fonseka, BHSc (Honours)  
    Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada
13. Association of the Glucagon-like Peptide 1 and the Glucagon-like Peptide 1 Receptor Genes with Antipsychotic-induced Weight Gain  
Eva J. Brandl, M.D.  
Pharmacogenetics Research Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada

14. Association between CYP2D6 and Tardive Dyskinesia in Antipsychotic-Treated Schizophrenia  
Maju Mathew Koola, M.D.  
Clinical Research Programs, Sheppard Pratt Health System Baltimore, MD, USA

15. Association Analysis of N-Methyl-D-Aspartic Acid Receptor Subunit Gene (GRIN2B) in Antipsychotic Response to Clozapine in Patients with Schizophrenia  
Danielle L. Taylor, BSc.  
Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada

16. Role of Translocator Protein (TSPO) Gene in Antipsychotic Response and Antipsychotic induced Weight Gain  
Jennie G. Pouget, BSc.  
Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada

17. Exploration of the Melanocortin-3 Receptor Gene in Antipsychotic Induced Weight Gain  
Nabilah Chowdhury, BSc.  
Campbell Family Institute, Neurogenetics Section, Neuroscience Department, Centre for Addiction and Mental Health Toronto, Ontario, Canada

18. Genes and Antidepressant Efficacy in Major Depressive Disorder: A Comprehensive Meta-analysis  
Tomihisa Niitsu, M.D., Ph.D.  
Institute of Psychiatry, University of Bologna, Italy
19. Genotyping of CyP2D6 and CyP2C19 Metabolizer Status to Guide Psychiatric Drug Treatment: Updates from the CAMH Pharmacogenetics Research Clinic
Janna Fe Notario, B.Sc(Hons.)
Centre for Addiction and Mental Health & Dept. of Psychiatry, University of Toronto, Ontario, Canada

20. 5HT1A Genotypes & Cognitive Function in Major Depressive Disorder
Keith A. Wesnes, Ph.D., Fss, Cpsycho, FBPsS
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Goring on Thames, UK

21. Developmental Changes in Functional Activation during Cognitive Control
Katherine Karlsgodt, Ph.D.
Division of Psychiatry Research, Zucker Hillside Hospital
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22. Multiple Obesity-related Genes are Associated with Antipsychotic-induced Weight Gain in Drug Naïve Pediatric Patients
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23. Adjusting Antipsychotic Dosage in Schizophrenia: Association Analysis of 384 SNPs and CPZ Equivalents
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Background: Given the prominence of cognitive impairment and disability in both schizophrenia and bipolar disorder, substantial interest has arisen in identification of their determinants. Recent findings regarding the heritability of cognitive impairment and everyday disability has led to the suggestion that the cognitively demanding component skills that underlie disability, referred to as functional capacity, may also be heritable and associated with specific genetic polymorphisms. The current study addresses these issues, and here we are presenting initial data on recruitment and characterization of the sample. These data are particularly relevant to bipolar disorder because of reduced attention paid to

Methods: This study, VA Cooperative Studies Program #572, is recruiting and assessing as many as 9,000 Veterans with either schizophrenia (SZ) or bipolar I (BP) disorder. A related VA initiative, the Million Veteran Program, has already recruited over 100,000 Veterans that will serve a source population for psychiatrically-healthy controls. Patients with SZ or BP at 26 VA medical centers are being enrolled and evaluated regarding cognition (NP tests), functional capacity (UPSA-B), suicidality (CSSRS), and comorbid conditions such as PTSD. The functional capacity measures are the primary focus of the assessment, as they have not yet been well-examined for genetic correlates. A pilot analysis will use genotyping and exome sequencing methods on a subsample of participants.

Results: A total of 6,280 veterans (46% SZ, 54% BP) have been recruited and assessed to date. Veterans with SZ were more likely to never have been married or employed (other than military service) compared to Veterans with BP; lifetime PTSD and suicidality were more common in the BP patients. Performance on the functional
capacity measures for both patient groups was, on average, within one point of all previously published studies with the UPSA-B, and the BP patients performed slightly better than SZ patients. Similarly consistent results were found for NP test performance, with mean t-scores for the Veterans with SZ of 35 (-1.5 SD) and 40 (-1.0 SD) for the Veterans with BP.

Discussion: This large and expanding sample of Veterans with schizophrenia and bipolar disorder is very representative of previous studies in terms of patients’ performance and co-morbidities. Future analyses will examine the genetic correlates of these performance-based measures of cognition and disability. This will be the largest studies of the genetics of BPI with patients assessed in person with performance-based tests.

Board #2
Possible Influence of PDE7B, NMBR and EPM2A Genes Variants on Antipsychotic Response in Schizophrenic Patients

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Background and aims: evidence from family, twin, and adoption studies suggests a strong genetic component in the etiology of schizophrenia (SKZ). Similarly, a genetic contribution for antipsychotic outcome has been suggested. However, any attempt to unequivocally uncover the genetic factors underpinning the response to antipsychotic treatment in SKZ remains inconclusive so far, pointing to the need for further investigations in the field [1]. In the present paper we focused on the study of eight single nucleotide polymorphisms (SNPs) within three genes that could be potentially involved into antipsychotic response. Particularly, we investigated phosphodiesterase 7B (PDE7B), neuromedin B receptor (NMBR) and epilepsy progressive myoclonus type 2A (EPM2A) genes. To the best of our knowledge, these genes have never been investigated in pharmacogenetic studies.
Board #2 (continued)

Methods: 573 in-patients of Korean ethnicity were genotyped for 2 PDE7B, 3 NMBR and 3 EPM2A SNPs. Patients were eligible for inclusion if they had a documented clinical diagnosis of SKZ according to the DSM-IV TR criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.). There was not any particular restriction with regard to the choice of the antipsychotic. Additionally, the following clinical and demographic variables were recorded: age, sex, age at onset, familiar history of psychiatric disorders, lifetime suicide attempts, duration of the illness, antipsychotic dosages (expressed in chlorpromazine equivalents). The main outcome measures of the present study was the possible influences of the 8 SNPs within the 3 genes under investigation on clinical improvement as measured with the Positive and Negative Symptoms Scale (PANSS) total score and PANSS subscales scores in SKZ patients. Repeated measures ANOVA was used to test possible influences of ! SNPs on treatment efficacy. In case of positive findings, clinical and demographic variables were added as covariates, in order to investigate possible stratification effects. Allelic analysis and haplotypes analysis were also performed.

Results: rs1415744 within the EPM2A gene was associated with PANSS negative clinical improvement (p=0.02). This result was confirmed in the allelic analysis and inclusion of the covariates did not influence the significance of these associations. Further, several alleles within all the three genes were associated with clinical improvement and several haplotypes blocks within the EPM2A and NMBR genes were associated with better outcome.

Discussion: the main strengths of the present study are represented by the large sample size and the high ethnical homogeneity of the Korean population. On the other hand, the incomplete coverage of genes under investigation and the use of different antipsychotics with different mechanisms of action could explain the discrepancies in the results of the present study. However, our decision to include patients treated with different drugs could have the advantage of being closer to “real world” clinical practice. Conclusion: our preliminary findings suggest a possible effect of PDE7B, NMBR and EPM2A genes on antipsychotic efficacy in schizophrenic patients. However, further research is needed to confirm our findings in patients treated with specific drugs or classes of drugs.

Board #3
Endothelial Nitric Oxide Synthetase Genetic Variants, Metabolic Syndrome and Endothelial Function in Schizophrenia

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Objective: Increasing rates of metabolic syndrome and cardiovascular disease in schizophrenia has led to investigation into their causes including atypical antipsychotics and pharmacogenetics variants. This study focuses on the peripheral vasculature as a cardiovascular phenotype and the influence of atypical antipsychotics, the aberrant metabolism of nitric oxide caused by endothelial nitric oxide synthetase (eNOS) genetic variants and metabolic syndrome in a cross-sectional sample of schizophrenia subjects.

Methods: Associations between eNOS variants (the eNOS T-786C and Glu298Asp variants) and endothelial function was assessed in a cohort of schizophrenia patients taking antipsychotics, undergoing a clinical assessment for endothelial functioning as well as metabolic syndrome screening. ANOVA and regression analysis were conducted on the entire cohort then again after stratifying by metabolic syndrome to investigate the effect of the eNOS variants on, metabolic syndrome risk and endothelial functioning.

Results: 203 subjects with a mean age of 46 years were included. The cohort was 36% female, 36% met metabolic syndrome criteria and 85% were currently using atypical antipsychotics. Associations between the eNOS T-786C and worse endothelial functioning were found only in schizophrenia patients without metabolic syndrome (p=0.02).

Conclusions: Our results suggest that when schizophrenia patients progress to meet metabolic syndrome criteria, the genetic protection of the eNOS T-786C variant on endothelial function is no longer seen and other factors of this pro-inflammatory state may be overriding this protection. The results of this study need replication and the factors driving endothelial dysfunction in patients with metabolic syndrome warrant further investigation.
Board #4

DAT and DRD4 Gene Differences Influence Drinking and Craving in Early but not Later Stage Alcoholics; Importance for Pharmacotherapy?

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Introduction: Carriers of the dopamine transporter (DAT) 9 VNTR (loss of function, increasing DA) and the DRD4 L (>7 repeats) have greater brain response to “reward”. This study evaluated DAT and DRD4 genetic differences in relationship to drinking and craving in early stage (E.STG) non-treatment seeking, and later stage (L.STG) treatment-seeking alcoholics.

Methods: 265 Caucasian E.STG (average age about 29, 80% male, 6 drinks/day) and 201 L.STG (average age 49, 65% male, 10 drinks/day) individuals meeting criteria for alcohol dependence (AD) had leucocyte DNA extraction, DAT and DRD4 VNTR’s measured by specific primer based PCR amplification, and subsequent agarose-gel separation. DAT 9,9 and 9,10 genotypes were compared to 10,10, while DRD4 (LL and LS) were compared with DRD4 SS on drinking and craving (OCDS).

Results: E.STG alcoholics with at least one copy of the DAT 9 VNTR: 1) had more drinks/drinking day 2) had more craving (p= 0.02) if they had DRD4 SS genotypes (p=0.025). In L.STG alcoholics there were no main effects or interactions of either gene on drinking or craving.

Conclusion: DAT and DRD4 genes differences influence alcohol consumption and craving in E.STG but not in L.STG alcoholics. This suggests that reward based neurochemical systems (dopamine) genetic differences might play a larger role in the development of AD but other systems like opioid, GABA and glutamate might play a larger role in maintaining it. This might suggest that medications that target dopamine systems might be more important for treatment of early stage vs. later stage alcoholics.

Supported by NIAAA grants P50 AA010761, R01 AA017633, K05 AA017435
Environmental factors can be translated into chronic alterations in gene expression by epigenetic signaling pathways, which act through post-translational modifications to DNA and histone tails. Recent findings have garnered an increasing appreciation for epigenetic mechanisms in the pathophysiology of psychiatric diseases such as alcoholism. Although alcoholism is known to be influenced by environmental variables and to involve changes in gene expression, the mechanism by which genes are chronically dysregulated is poorly elucidated. We hypothesized that alcohol exposure can alter the expression of epigenetic enzymes, thus influencing gene expression and ultimately contributing to alcohol addiction. Using RNA sequencing, Nanostring, and qRT-PCR, Histone 3 lysine 27 (H3K27) demethylase KDM6B mRNA was found to be downregulated in both the prefrontal cortex and nucleus accumbens of alcohol exposed rats. In contrast, KDM6B protein was upregulated in the nucleus accumbens, suggesting a negative feedback loop. In a cohort of postmortem human brain tissue, KDM6B was differentially expressed within a region of the prefrontal cortex of alcoholics compared to controls. Thus, alcoholism is associated with dysregulation of KDM6B at multiple levels in both human and rodent brains. Ongoing experiments aim to investigate levels of H3K27 methylation, to identify genomic regions regulated by KDM6B, and to study the behavioral effects of KDM6B knockdown. These studies may elucidate how an epigenetic mechanism translates alcohol exposure into the chronic physiological and behavioral manifestations of alcoholism. Because KDM6B is recognized as a druggable target, these experiments could also potentially aid in the development of novel therapies for alcoholism.
The ERK Pathway Involved in Treatment Side Effects in BD-I

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Background: There is now evidence that the antimanic agents robustly activate the ERK signaling cascade. In the present study we analyze the genes that belong to the ERK pathway as risk factors for tremors after treatment with antimanic drugs.

Methods: 681 BD-I patients (STEP-1, 307 males) were analyzed. Having had at least one episode of clinical relevant tremor was the investigated phenotype. The clinical variables associated with the phenotype were included in the genetic analysis. A diagnosis of a neurological disease other than BD-I was an exclusion criteria. 30 genes harboring 334 SNPs were selected from the ERK cascade. After imputation, pruning and quality control, a resulting lambda of 1.01 excluded major stratification factors. A molecular pathway analysis was then conducted to test whether the SNPs associated with the investigated phenotype at an exploratory p threshold <0.05 significantly clustered within the selected genes.

Results: 253 patients (37%) had at least one episode of clinical evident tremor. The ERK pathway had 30 out of the 304 investigated SNPs associated with the phenotype, twice the expected number (10⁵ permutations, p = 0.006). The phosphatase 2A catalytic subunit (PPP2CA) was particularly disrupted (56% of the SNPs associated). This gene is implicated in the negative control of cell growth and division.

Conclusions: We bring evidence that the ERK pathway may be involved in movement side effects after antimanic treatment in BD-I patients. PPP2CA could be of prime relevance. Further research in larger samples is required.
Board #7
Predicting Antidepressant Treatment Response through Genomewide Interaction and Enrichment Analysis

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Genomewide association studies (GWAS) on antidepressant efficacy have yielded modest results. A possible reason is that response is influenced by other factors, which possibly interact with genetic variation. In this study, we used a GWAS model to predict antidepressant response, by including predictors previously known to affect response, such as quality of life (QoL). We also evaluated the role of genes, previously implicated in gene-environment (GxE) interactions using an enrichment analysis.

We examined a sample of 1426 depressed patients from the STAR*D trial: 774 responders and 652 non-responders and a subset of 418,865 single nucleotide polymorphisms (SNPs) were analysed. In a GWAS model, we examined whether genetic variations interact with the patients’ levels of QoL to predict response to citalopram, after controlling for demographics, severity and population stratification. Secondly, we conducted an enrichment analysis exploring whether candidate genes that have emerged from prior GxE studies on depression are associated with treatment response.

The GWAS model, with QoL as a moderator, yielded one SNP associated with response, in the NEDD4L gene (p=3.64E-08). Other genes among the top findings include FKBP1A and TNFRSF10B. The enrichment analysis showed that SNPs associated with treatment response were more frequently found within the enriched pathway compared to elsewhere in the genome, with serotonergic genes containing the most significant markers that predicted response. Our findings point to possible target genes, which are proposed for further independent replication. Our enrichment analysis provides support of the role of serotonergic genes in influencing antidepressant response in a genomewide context.
Board #8

**Influence of MAPK1 and CREB1 polymorphisms on treatment remission in mood disorder patients**

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Treatment resistant depression (TRD) is a significant clinical and public health problem. Among others, neuroplasticity and inflammatory pathways seem to play a crucial role in the pathomechanisms of antidepressant efficacy. The aim of this study was to investigate whether a set of single nucleotide polymorphisms (SNPs) within two genes implicated in neuroplasticity and inflammatory processes (the mitogen activated protein kinase 1, MAPK1 (rs3810608, rs6928, rs13515 and rs8136867), and the cyclic AMP responsive element binding protein 1, CREB1 (rs889895, rs6740584, rs2551922 and rs2254137)) were associated with antidepressant treatment resistance (according to two different definitions), response or remission. Three hundred sixty-seven unipolar and bipolar patients were screened in the context of a European multicenter project. No association between both the investigated genes and treatment resistance and response survived to multivariate analysis. However, considering remission, higher remission rates have been reported in both carriers of the MAPK1 rs8136867 AG genotype and carriers of the CREB1 rs889895 GG genotype.
Board #8 (continued)

Present results suggest that some genetic polymorphisms in both MAPK1 and CREB1 could be associated with treatment remission. Although further research is needed to draw more definitive conclusions, such results are intriguing since suggest a potential role of two genes implicated in neuroplasticity and inflammatory processes in symptom remission after antidepressant treatment.

Board #9

**PPP3CC Gene: A Putative New Marker of Antidepressant Response**

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In antidepressant pharmacogenetics candidate studies often showed poor covering of gene variability and focus on a relative small number of candidates, thus the present study aimed to investigate SNPs selected by tagging procedure in both old and innovative candidate genes.

38 SNPs within monoamine (COMT and HTR2A), neuroplasticity (BDNF, GSK3B, PLA2G4A, PPP3CC, ST8SIA2), circadian rhythm (RORA and VIPR2), and transcription factor (ZNF804A and SP4) pathways were genotyped in two independent samples (n=369 and 93) of Caucasian patients with major depressive disorder who were treated with antidepressants. Phenotypes were response and remission at week 4 and 8. Logistic regression corrected for age and gender was performed. Secondly, genes associated with outcome at p<0.05 were
checked in the in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genome-wide study (n=1861).
In both original samples markers associated with response were concentrated in PPP3CC (rs2249098 and rs7430, rs11780915 and rs10108011, respectively). In only one sample VIPR2 (rs2657340; p=0.0096) and GSK3B (rs1381841; p=0.045) were associated with response while HTR2A (rs643627; p=0.02) and VIPR2 (rs2657340; p=0.01) with remission. In the STAR*D a cluster of SNPs associated with response was found around rs643627 (especially rs1923888, rs1745837, and rs2296972).
Our study confirmed the role of HTR2A in antidepressant response. Among innovative candidates, PPP3CC seems promising, despite only rs2461494 showed a trend of association with response in the STAR*D (p=0.06). PPP3CC may have a role in the calmodulin activation of calcineurin, a neuron-enriched phosphatase that regulates synaptic plasticity. Further studies are needed to confirm PPP3CC involvement in antidepressant effect.

Board #10
Effect of Adjunctive L-Methylfolate 15 mg in Depressed Patients Stratified by Biomarker Levels and Genotype

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Background and Objective: Genetic or biological markers may increase the risk of major depressive disorder (MDD) or inadequate response to therapy. The objective of this analysis was to evaluate the effect of specific markers alone and in combination on the antidepressant efficacy of adjunctive L-methylfolate 15 mg versus placebo added to SSRIs from a trial of inadequate responders to SSRIs.
Methods: This was a double-blind, randomized, placebo-controlled trial using the sequential parallel comparison design (SPCD).
Outpatients with MDD and SSRI-resistant depression received L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days or placebo for 60 days. The effects of biological and genetic markers individually and combined on treatment response were evaluated.

**Results:** Seventy-five patients were enrolled. Patients with a BMI ≥30 kg/m² had significantly greater symptom reduction with L-methylfolate versus placebo (p=0.001), as did patients with levels of 4-HNE (p=0.003) above the median, and SAM/SAH ratio below the median (p=0.005). Average mean changes from baseline for HDRS-28 with combinations of these biomarkers with MTHFR C677T, MTR 2756 AG/GG or MTRR 66 AG/GG polymorphisms were significantly greater with L-methylfolate vs. placebo (all p<0.002). Average mean changes from baseline for HDRS-28 with combinations of MTHFR C677T plus MTR 2756 AG/GG and MTR 2756 AG/GG plus MTRR 66 AG/GG were significant (p<0.001).

**Conclusion:** Surrogate biomarkers or genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant MDD who are responsive to adjunctive therapy with 15 mg L-methylfolate.

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**Board #11**

*Implementing Pharmacogenomic Clinic for Treatment Refractory Depression*

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*Industry Support or Sponsorship: Pathway Genomics, UCSD CTRI*

**Background:** Many patients with bipolar disorder (BD), depressed, or major depressive disorder (MDD) are unresponsive to medication or have dose-limiting side effects. These patients, referred to as treatment refractory depression (TRD), often either metabolize medications too rapidly (UM), resulting in a lack of effect, or too slowly (PM), leading to bothersome side effects, or are treated with inappropriate medication choices based on diagnosis. We plan to use genetic testing in TRD to identify differences in metabolism as well as different forms of illness.
Aims and Objectives: Our hypothesis is that patients who receive pharmacogenetic testing and guided treatment will have better clinical outcomes and suffer fewer side effects after 4 months of treatment. We expect to precisely identify which decisions are best informed by genetic testing, and that patient will be motivated and eager to participate in testing.

Study Population: We plan to enroll 200 veterans with TRD. Subjects will have been depressed for >3 months and will have failed at least one prior medication trial of adequate dose/duration.

Methods: After collecting past medication trials and confirming diagnosis, we will obtain DNA using established protocols. Subjects will be randomized to receive either treatment as usual (TAU) using the TMAP guidelines, or pharmacogenomic guided treatment (PGT), which will have objective, genetically guided decisions made by the prescriber. For example, TMAP may recommend a switch in antidepressants but not dictate which medication to use, whereas genetic testing may indicate which antidepressant is preferable based on drug metabolism or will recommend skipping certain steps if indicated (e.g., early use of lithium augmentation given a favorable genotype).

Analysis and Interpretation: Prospective assessment of outcome: compare the number of subjects who achieve recovery as assessed by BDI, CGI, YMRS, ISS, CGI, and Side Effect Questionnaire. Retrospective Analysis of Clinical Decision Making: at conclusion, all subjects will have their genetic test results examined to identify variants that predict atypical drug metabolism or poor clinical response. Patient concerns and expectations of genetic testing: subjects will be administered the MACGNET scale, used to assess concerns about genetic testing.

Outcome: We will report the number of subjects enrolled in each arm and present preliminary findings.
Board #12
Antipsychotic-induced Weight Gain and the Role of Histamine Receptor H1 and H3 Variants

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Background: Weight gain and development of metabolic syndrome are the most common deleterious side effects following treatment with antipsychotic drugs. However, the mechanisms underlying these negative effects are not fully understood. In this study we investigate whether variants in the genes coding for the Histamine receptors H1 (HRH1) and H3 (HRH3) are associated with antipsychotic-induced weight gain (AIWG). Clozapine and olanzapine, the antipsychotics associated with the highest risk of weight gain, have high affinity for HRH1.

Methods: We investigated 40 tag and/or putative functional SNPs (HRH1=34 and HRH3=6) in 219 schizophrenia or schizoaffective disorder patients treated mainly with clozapine and olanzapine for up to 14 weeks. Overall, these SNPs cover almost 100% of the common variation in the HRH1 and HRH3 receptors.

Results: We observed significant association of an intronic SNP, rs7639145, in HRH1 with AIWG (p=0.021). Carriers of the GG genotype gained more weight when treated with clozapine or olanzapine (GG vs. GA+AA, 5.2kg ±4.8 vs. 2.9kg ±3.9, p=0.026). In HRH3 trends of association were observed for rs1615746 (p=0.057) and rs6587299 (p=0.06). However, none of the other SNPs were significantly associated with AIWG. A limitation is that the above associations do not remain significant after correcting for multiple testing.

Discussion: We have carried out a comprehensive analysis of genetic variation in HRH1 and HRH3 genes with AIWG that yielded some interesting findings. However, our observations suggest that SNPs in the HRH1 and HRH3 may not play a major role in AIWG. Potential remote regulatory variants and downstream pathways require further investigation.
Association of the Glucagon-like Peptide 1 and the Glucagon-like Peptide 1 Receptor Genes with Antipsychotic-induced Weight Gain

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Background: Atypical antipsychotic medication can lead to rapid changes in glucose metabolism followed by development of weight gain and/or diabetes. Glucagon-like peptide 1 (GLP-1) plays an important role in glucose sensitivity and appetite regulation and is down regulated during antipsychotic treatment. A beneficial effect of using GLP-1 analogues to treat antipsychotic-induced weight gain (AIWG) has been reported. Our study is the first to investigate the impact of genetic variation in the encoding gene, GCG, and in the gene encoding GLP-1 receptors, GLP1R, on AIWG.

Methods: In 216 schizophrenic patients treated with various antipsychotics for up to 14 weeks, we investigated single-nucleotide polymorphisms in or near GCG (N=4) and GLP1R (N=32) using a customized Golden-Gate Assay. Statistical analysis was done using ANCOVA with baseline weight and treatment duration as covariates.

Results: In patients of European ancestry treated with olanzapine or clozapine (N=87), we observed association of rs13429709 near GCG (p corr=.008) with AIWG with higher weight gain in patients carrying the C-allele. Eight GLP1R polymorphisms (rs2300613, rs2268641, rs2268640, rs2268639, rs2894420, rs4714210, rs2206942, rs9296291) showed a trend for an association (p<.050) with AIWG; however, no significant finding was observed after correction for multiple testing.

Discussion: We could demonstrate a significant association of genetic variation of GCG with AIWG. Although there was no significant association of variants in GLP1R with AIWG after multiple test correction, the observed trends suggest this to be an interesting candidate gene for future examination. Since our study was the first to investigate GCG and GLP1R, more research is necessary to validate our findings.
Board #14

**Association between CYP2D6 and Tardive Dyskinesia in Antipsychotic-Treated Schizophrenia**

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Drs. Koola and Tsapakis contributed equally and are joint first authors. Drs. Nugent and Aitchison are joint senior authors.

**Background:** An association between cytochrome P450 2D6 metabolizer status and susceptibility to typical antipsychotic-induced tardive dyskinesia (TD) has previously been reported; however, overall the data are inconclusive. Our aim was to examine whether there was an association between TD and number of functional CYP2D6 genes.

**Methods:** A Caucasian sample of 70 patients was recruited in 1996-1997 from South London and Maudsley NHS Trust. Subjects had a DSM-III-R diagnosis of schizophrenia and were treated with typical antipsychotics at doses equivalent to at least 100 mg chlorpromazine daily for at least 12 months prior to assessment. Subjects were examined for TD using the Abnormal Involuntary Movements Scale (AIMS). All patients were genotyped for CYP2D6 alleles*3-5, *41, and for amplifications of the gene. The AmpliChip CYP450 Test® was performed in eight subjects for whom CYP2D6 genotype could not initially be definitively called. Group differences were explored using Chi square, t-tests, and logistic regression statistics.

**Results:** There were 13 patients with TD. The mean (SD) years of duration of antipsychotic treatment in TD positive was 15.8 (7.9) vs. TD negative 11.1 (7.4) p=0.04. Increased odds of experiencing tardive dyskinesia were associated with increased ability to metabolize CYP2D6, as measured by genotypic category (OR=4.2, 95% CI:1.1-15.7),
increasing duration in treatment (OR=1.0, 95% CI:1.0-1.0), and having drug induced Parkinsonism (OR=9.7, 95% CI: 1.4-68.4).

**Discussion:** There is a significant association between CYP2D6 genotypic category and TD with the direction of effect being an increase in the number of functional CYP2D6 genes being associated with an increased risk of TD.

**Funding and Acknowledgements:** Dr K. J. Aitchison was previously funded by the Wellcome Trust (UK) as a Wellcome Mental Health Research Training Fellow, grant 045968, during which period she undertook much of the sample genotyping and is now an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta (Canada). We thank Jing Hua Zhao for previous relevant statistical advice, Roche Molecular Systems for the provision of the AmpliChip CYP450 Test® and associated support, and Johnson and Johnson Pharmaceuticals Research and Development for support for salary support to Dr. Tsapakis whilst undertaking the remainder of the genotyping. The manuscript preparation of Maju Koola was supported by the NIMH funded T32 grant MH067533-07 (Carpenter, PI) and the American Psychiatric Association/Kempf Fund Award for Research Development in Psychobiological Psychiatry (Koola, PI).
Background: Schizophrenia (SCZ) is a debilitating mental health disorder that causes immeasurable pain and suffering to those afflicted. Response to antipsychotic treatment for SCZ is highly variable, and twin studies suggest a genetic component. Altered N-Methyl-D-Aspartic acid receptor (NMDAR) activity has been implicated in the etiology of SCZ, as well as in response to the atypical antipsychotic clozapine (CLZ) through its ability to enhance NMDAR mediated neurotransmission.

Objective: The study aimed to investigate genetic associations between the NMDA receptor subunit gene (GRIN2B) and antipsychotic response to clozapine (CLZ).

Methods: Eight GRIN2B polymorphisms were assessed in 252 patients diagnosed with SCZ using DSM-IV criteria. SNPs were selected based on potential functionality (promoter, 3’UTR, intron-exon splice sites locations) and recent citations from the literature. Standard Taqman genotyping procedures were used. Power calculations were performed using Quanto 1.2.4 and linkage disequilibrium was determined using Haploview 4.2. In terms of genetic analyses, dichotomous variables were analyzed using χ²-test and continuous variables were analyzed using analysis of covariance (ANCOVA), with baseline scores as a covariate.

Results and Conclusions: Our subgroup of 172 European SCZ patients with categorical response data and 90 patients with continuous response data had over 80% power to detect an odds ratio of 2.50 and...
detect $\geq 8\%$ of variance, respectively (non-responder frequency=48%; $\alpha=0.05$, two sided; minor allele frequency=0.143; additive model). Prior to correction for multiple testing, a trend was observed for SNP rs1072388 ($p=0.067$) in which A allele carriers (AA+AG) responded better to CLZ than GG homozygotes. In conclusion, GRIN2B may not play a major role in CLZ response in our sample of SCZ patients.

Board #16

Role of Translocator Protein (TSPO) Gene in Antipsychotic Response and Antipsychotic Induced Weight Gain

Jennie G. Pouget$^{1,2}$, Arun K. Tiwari$^1$, Jeffrey A. Lieberman$^3$, Herbert Y. Meltzer$^3$, Daniel J. Müller$^1$*, James L. Kennedy$^1$*
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Introduction: TSPO regulates mitochondrial function, suspected to play a key role in antipsychotic-induced weight gain (AIWG). Treatment with clozapine enhances TSPO function, suggesting TSPO may mediate clozapine response or side effects. Marker rs6971 (Ala147Thr) predicts a large portion of variance in TSPO binding; the Thr/Thr genotype confers lower TSPO binding affinity.

Objectives:
1) Investigate association between rs6971 genotype and clozapine response
2) Investigate association between rs6971 genotype and AIWG

Methods:
Objective 1
Genomic DNA was obtained from blood samples of SCZ patients with Brief Psychiatric Rating Scale (BPRS) scores measured before and after 6 months of clozapine treatment ($n=114$). rs6971 genotyping was done using a TaqMan assay (Applied Biosystems). Association between rs6971 genotype and % change in BPRS score was tested using ANCOVA.
Board #16 (continued)

Objective 2
Blood samples were collected from SCZ patients (n=214) with weight change observed after at least 6 weeks of antipsychotic treatment. rs6971 genotyping and analysis were done as above. Results: There was no significant association between rs6971 genotype and % BPRS score change in the total clozapine response sample (p=0.828), or in sub-analyses stratified by ethnicity. No significant association between rs6971 genotype and % weight change was observed in the total AIWG sample (p=0.271). In a sub-analysis of European ancestry patients prescribed clozapine or olanzapine (n=76) weight change was 8.19% greater for Thr/Thr homozygotes compared to Ala/Ala homozygotes (95% CI: 2.7 – 13.7%, p = 0.004).

Discussion: The rs6971 Thr allele may predispose patients of European ancestry to weight gain when treated with clozapine and olanzapine.

Board #17
Exploration of the Melanocortin-3 Receptor Gene in Antipsychotic Induced Weight Gain

Nabilah I. Chowdhury1, Arun K. Tiwari1, Herbert Y. Meltzer2, Jeffrey A. Lieberman3, James L. Kennedy1, Daniel J. Müller1

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Introduction: Second-generation antipsychotic treatment can result in substantial body weight gain. The melanocortin-3 receptor (MC3R) is highly expressed in the hypothalamus, a key brain region for weight regulation. MC3R knockout mice have been reported to exhibit increased fat mass and reduced lean body mass. We investigated the potential role of common MC3R polymorphisms to assess whether these were associated with antipsychotic induced weight gain (AIWG).

Methods: Nine MC3R SNPs (rs6127698, rs6024731, rs1543570, rs6024730, rs6014649, rs1926064, rs6014646, rs11697509, rs3827103) were selected by tagSNP. Illumina GoldenGate Genotyping Assays
Board #17 (continued)

were used to genotype 217 schizophrenia patients who underwent treatment with antipsychotics and evaluated for weight gain for up to 14 weeks. Weight change (%) across genotypic groups was compared using analysis of covariance (SPSS15.0).

**Results:** Significant genotypic associations were found between the MC3R polymorphisms and weight gain (p<0.05) in a refined sub-sample consisting of European ancestry patients treated with either olanzapine or clozapine (n=83). Carriers of the MC3R rs6016469 ‘A’-allele (AA+AG) gained more weight (7.54% ± 5.6) than GG homozygotes (3.73% ± 5.4), p = 0.011. Patients who were carriers of the MC3R rs3746619 ‘A’-allele (AA+AG) gained more weight (6.90% ± 5.7) than the GG homozygotes (3.81 ± 5.5), p =0.034.

**Conclusions:** We observed that two MC3R gene variants were nominally associated with AIWG. These findings suggest that this gene may have a role in the development of AIWG. In addition, this finding may lead to novel targets for psychiatric drug development. Our observations warrant further investigation and replication in larger sample sets.

Board #18

**Genes and Antidepressant Efficacy in Major Depressive Disorder: A Comprehensive Meta-analysis**

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A number of candidate gene studies focused on major depressive disorder (MDD) and antidepressant (AD) efficacy have been carried out, but results mainly remain inconclusive.

We performed a comprehensive meta-analysis of candidate gene studies focused on AD efficacy in MDD to evaluate the cumulative evidence. A random-effect model was applied to study the polymorphisms with genotypic counts available from at least three independent studies. On the base of previous evidence, the analysis was stratified by ethnicity (Caucasian, Asian, and other/mixed), and AD class (SSRIs and mixed/other ADs).
Board #18 (continued)

Genotypic data were available from a total of 14 polymorphisms in 11 genes. After the exclusion of 5 polymorphisms included in very recent meta-analysis, 9 polymorphisms in 8 genes were included in the present meta-analysis (BDNF rs6265, SLC6A4 STin2, GNB3 rs5443, FKBP5 rs1360780 and rs3800373, TPH1 rs1800532, COMT rs4680, SLC6A2 rs5569, and HTR6 rs1805054).

Our results suggested that BDNF rs6265 (Val66Met) heterozygous may be associated with better SSRIs response compared to the homozygous genotypes, particularly in Asians (OR = 1.56, 95%CI 1.14-2.13, p = 0.006). STin2 in SLC6A4, rs5443 in GNB3, rs1360780 and rs3800373 in FKBP5 showed associations with response, but these results were highly dependent from one or two single studies. In conclusion, our findings suggested the BDNF Val66Met as the best single candidate involved in AD response, with a selective effect in Asian populations and SSRI treatment. Our overall results supported no major effect of any single gene variant on AD response.

Board #19

Genotyping of CYP2D6 and CYP2C19 Metabolizer Status to Guide Psychiatric Drug Treatment: Updates from the CAMH Pharmacogenetics Research Clinic

Janna Fe Notario, Arun K. Tiwari, Eva J. Brandl, Natalie Freeman, Margaret A. Richter, James L. Kennedy, Daniel J. Mueller

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Background: Antipsychotic and antidepressant medication continues to be the main treatment for many psychiatric conditions including schizophrenia, mood and anxiety disorders including obsessive-compulsive disorder (OCD). Two polymorphic enzymes, CYP2D6 and CYP2C19, metabolize a large number of these medications. Functional polymorphisms in these enzymes can confer altered enzymatic activity, potentially leading to toxic or subtherapeutic drug levels.

Methods: As part of our ongoing study at our Pharmacogenetics Research Clinic, 69 patients with a diagnosis of schizophrenia and mood disorders with complicated medication histories have been enrolled prospectively and genotyped for CYP2D6 and CYP2C19. At study entry, clients are informed in detail about potential advantages and limitations related to the genetic testing of liver
enzyme activities. Patients participate in a structured diagnostic interview and are assessed of current and previous treatment response and occurrence of side effects. Physicians are then provided with an interpretation of the genotypic results and informed in detail about the potential clinical implications which they will discuss with their patients. Serum drug levels of the CYP2D6 and/or CYP2C19 metabolized drugs are also assessed and after 6 weeks the physician completes a questionnaire evaluating the usefulness of the genotypic information provided by the study. After 12 weeks, the clients are assessed again to monitor potential adjustments of medications and their overall treatment outcome. Selected case reports will be presented and discussed in detail at the conference.

**Results:** Overall, physicians have returned mostly very good feedback that the genotyping results have been helpful in allowing them to either select medications their patients are likely to better tolerate, or to adjust doses based on genotype results and serum levels.

**Discussion:** Our findings suggest that CYP2D6 and CYP2C19 genotyping provides useful information that help physicians improving pharmacotherapy in individual patients.

**Board #20**

*5HT1A Genotypes & Cognitive Function in Major Depressive Disorder*

Keith A. Wesnes 1,2, Seth C. Hopkins 3, Kenneth S. Koblan 3

1Bracket, Goring on Thames, UK; 2Swinburne University, Melbourne, Australia; 3Sunovion Pharmaceuticals Inc, Marlborough, MA, USA

**Background:** Bosia et al (2011) studied the effects of the 5-HT1A-R genotype on cognition in schizophrenic patients, and identified that the 5-HT1A-R C/C genotype was associated with significantly higher scores on a Picture Sequencing Task than the C/G and G/G genotypes. The purpose of this study was to determine whether 5-HT1A-R genotype had an influence on the profile of cognitive function in patients with major depressive disorder (MDD).

**Methods:** The study sample was 455 MDD patients between the ages of 18 and 55 years who met DSM-IV criteria for MDD, with current-episode duration of at least 1 month but not longer than 12 months. The patients underwent 5-HT1A-R genotyping and also performed a selection of automated tests of attention, information processing,
executive control, working and episodic memory from the CDR System. The volunteers had on a previous occasion performed the entire 20 minute sequence of tests on two occasions to overcome practice and familiarity effects. Performance on the various tests was contrasted between the three 5-HT1A-R genotypes using ANOVA.

**Results:** There were no differences between the three genotypes on HAM-D-17 (p=0.92), Sheehan Disability Scale total score (p=0.52) or age (p=0.96). Significant differences were seen on accuracy measures from 2 working memory (articulatory and spatial) and 4 episodic memory tasks (verbal: immediate recall, delayed recall and recognition; picture recognition). These were seen on validated factor scores for working memory (p=0.047), episodic memory (p=0.014) and a combined score (p=0.006). No effects were seen for measures of sustained or focussed attention, information processing speed or attentional fluctuations (p=0.34 to 0.98). Neither was an effect seen for the speed of retrieval of information in the working and episodic recognition tasks (p=0.55). For the combined working end episodic memory accuracy score, the C/C homozygotes scored significantly higher (66.8%; 95% CI 64.5,69.1) than both the C/G heterozygotes (62.4%; 95% CI 60.8,63.9) and the G/G homozygotes (63.3%; 95% CI 61.2, 65.4), the p values being 0.0016 and 0.0246 respectively.

**Discussion & Conclusions:** This is to our knowledge the first data in MDD showing a difference in cognitive function between different 5HT1A-R genotypes, and besides the data in schizophrenia, the first in any psychiatric or neurological condition. The finding that the C/C homozygotes were selectively superior on the ability to hold and retrieve information in working and episodic memory; while not showing differences in retrieval speed or on various measures of attention and information processing is clearly worthy of future attention; particularly as there were no differences between the genotypes in depression or disability scores.

Developmental Changes in Functional Activation during Cognitive Control

Katherine H. Karlsgodt, Bart D. Peters, Toshikazu Ikuta, Pamela DeRosse, Kimberly Cameron, Angelica A. Bato, Philip R. Szeszko, Anil K. Malhotra

Background: Schizophrenia has been associated with a range of cognitive deficits, including impairments in cognitive control, a construct associated with performance monitoring, rule maintenance, response inhibition, and coordination of cognitive subprocesses. Schizophrenia has a strong developmental component, making it important to understand how these cognitive processes change with age. By investigating age-related changes in cognitive control in healthy children and adolescents, we aim to provide the basis to understand alterations in the developmental trajectory of disordered individuals.

Methods: We assessed 54 healthy individuals aged 8-18 years using the Multi-Source Interference Test (MSIT) during functional magnetic resonance imaging (fMRI). The MSIT is known to activate an executive network including frontal cortex, parietal cortex, and anterior cingulate.

Results: A preliminary analysis indicates that performance on the interference condition, but not the control condition, is positively correlated with age. Across the whole group, controlled for age and sex, the MSIT robustly activated superior parietal cortex, lateral frontal cortex and the anterior cingulate. In a voxel-wise regression, we found an inverse correlation between age and parietal activation, potentially indicating less efficient networks in younger subjects.

Conclusions: The MSIT is a useful tool for probing executive network development. Age related changes observed in preliminary analyses indicate that younger subjects perform more poorly and show less efficient patterns of functional activation than older individuals. Understanding the way that the cognitive control circuitry develops in healthy individuals is an important step towards characterizing the developmental problems that occur in neuropsychiatric disorders.
Background: Weight gain is a serious side effect of antipsychotic drugs (APD). We hypothesized that the risk genes in the general population may also be risk genes for APD-induced weight gain. We used the genes that are associated with obesity in the general population as candidate genes, and examined whether they are significantly associated with APD-induced weight gain in a drug-naive pediatric sample.

Methods: Published genome-wide association studies of obesity in the general population revealed 69 single nucleotide polymorphisms (SNPs) from 44 genes/regions reached genome-wide significance. 139 drug-naive pediatric patients undergoing treatment with APD for 12 weeks were genotyped for 68 SNPs (from 43 genes/regions). Separate association tests were performed on each of these SNPs. For genes/regions that have multiple SNPs, one was selected based on LD to represent the gene/region. Change in BMI from baseline to 12 weeks was the phenotype.

Results: Of 43 association tests (43 SNPs in additive, dominant, recessive models, i.e., 43x3 = 129), 10 were significant at p<0.05 level (23.3%). This was significantly more than what is expected by chance, p<0.0001. Each SNP was examined to determine whether risk alleles were consistent with the original publications. Out of 68 SNPs, 44 were consistent. Of 43 genes/regions, 28 were consistent. These were more than what is expected by chance, p<0.05 (binomial test).

Discussion: Some risk genes of obesity in the general population appear also to be risk genes of antipsychotic-induced weight gain. Further studies are needed to elucidate the biological mechanisms of antipsychotic-induced weight gain.
Board #23

**Adjusting Antipsychotic Dosage in Schizophrenia: Association Analysis of 384 SNPs and CPZ equivalents**

Vincenzo De Luca, Ahmed Hassan, Clement Zai, Sogand Namdar, Monica Hazra, Nuwan Hettige, Ali Bani-Fatemi, James L. Kennedy

Schizophrenia Program, CAMH, Department of Psychiatry, University of Toronto, Canada

**Background:** In the recent years several studies have investigated genetic polymorphisms of antipsychotic drug metabolizing enzymes and receptors. However, most of the studies focused on drug response and very few have investigated the genetic influence on antipsychotic (AP) dosage. The aim of the present study is to test the association between AP dosage and candidate genes.

**Methods:** The current dosage of AP medications was collected from 232 schizophrenic patients. The AP dosage was standardized using three different methods: CPZe according to Gardner et al. 2010, defined daily dose according to the WHO (2010) and percentage of maximum dose according to the Compendium of Pharmaceuticals and Specialties 2012 (Canada). The patients were then genotyped using a Customized Illumina Chip comprising 384 SNPs. All markers were screened for nominal significance and for statistical significance after multiple-testing correction, using the FDR method.

**Results:** The preliminary analysis showed that the top SNP associated with CPZe was the rs1799978 (p=0.006) however when we consider the percentage of maximum dose, the top SNP was the rs1286769 on chromosome 3.

**Discussion:** In this sample of 232 adults, the common variants investigated had no major impact on the amount of antipsychotic medications that had been prescribed. However, studies combining large prescription databases and genome-wide data may identify genetic predictors to adjust the dose of antipsychotic medication.
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