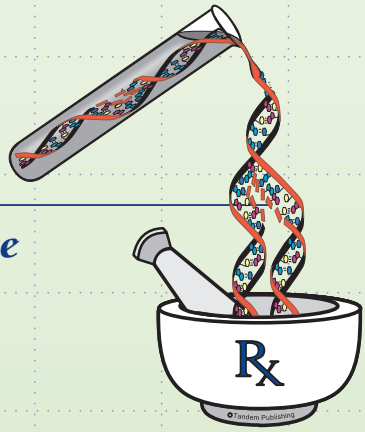
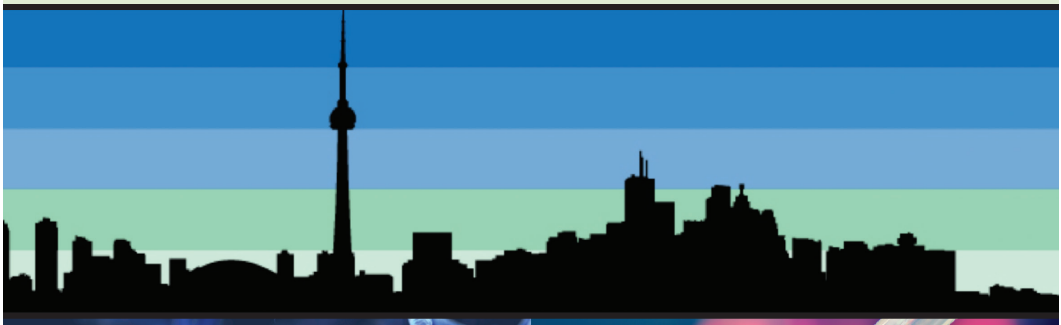
The 14th Annual Pharmacogenetics in Psychiatry Meeting



A Category 1 ***CME Conference***

October 15, 2015



Sponsored by the Zucker Hillside Hospital and the University of Toronto

Omni King Edward Hotel
37 King Street E
Toronto, ON M5C 1E9

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October 15, 2015

Dear Colleagues,

It is our great pleasure to welcome you to *"The 14th Annual Pharmacogenetics in Psychiatry Meeting"* in Toronto Canada. 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:

I. *Pharmacogenetics of Clozapine Response*

II. *Pharmacogenetics of Antipsychotic Drugs*

III. *Pharmacogenetics of Mood and Anxiety Disorders*

IV. *The Crestar Consortium: Development of Biomarkers for Schizophrenia*

Our annual poster session will take place this evening in the Palm Court, Pall Mall, and Vanity Foyer 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 Kelly Phy and Sarah Timm of Parthenon Management Group, as well as PIP coordinator Katherine Norris, 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 held in conjunction with the WCPG annual meeting. 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: Currently, there is a gap in the amount of knowledge psychiatrists and researchers have with regard to the benefits and uses of pharmacogenetics in the field. Psychiatrists have limited knowledge of the genetic methods available to treat patients. There is also a limited amount of knowledge about the use of genetics to predict psychotropic efficacy, and psychotropic drug-related side effects in patients. CME evaluations from previous pharmacogenetics in psychiatry meetings indicated that there's a lack of information available to researchers in the field. Additionally, a review article in a leading psychiatric journal: Malhotra AK, Murphy GM, Kennedy JL. Pharmacogenetics of psychotropic drug response. Am J Psychiatry 2004; 161: 780-796, states that clinicians are unaware of developments in the field. Lastly, two articles included in the supporting documentation, discuss the need for and importance of pharmacogenetics research.

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:

- Better understand the prediction of clinical response to antipsychotic drugs based on genes associated with the development of adverse side effects.
- Identify new polymorphisms influencing gene product function, and 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.

CONTINUING MEDICAL EDUCATION INFORMATION

ACCREDITATION:

Royal College of Physicians and Surgeons of Canada – Section 1

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, approved by Continuing Professional Development, Faculty of Medicine, University of Toronto up to a maximum of 6.75 hours.

Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to *AMA PRA Category 1 Credits™.* Information on the process to convert Royal College MOC credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

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

Americans with Disabilities Act: It is the policy of PIP 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 615-324-2365 or send an email to info@ispg.net.

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS

We are required to provide 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.

Course Directors/Planner Disclosures		
Anil Malhotra	Genomind, Inc. Forum Pharmaceuticals Vanda Pharmaceuticals	
Kathy J. Aichison	Nothing to Disclose	
David Goldman	Nothing to Disclose	
John Kelsoe	US NIH U01 MH92758, Department of Veteran Affairs	Research Support
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Faculty Disclosures		
David Collier	Nothing to Disclose	
Katharina Domschke	DFG, BMBF, EU	Research Support
David Goldman	Nothing to Disclose	
Eilis Hannon	UK Medical Research Council Eli Lily	Research Grant Research Grant

DISCLOSURES

Faculty Disclosures (Continued)		
Rebecca Harrison	National Institute for Health Research (NIHR) [Mental Health Biomedical Research Centre and/or Dementia Biomedical Research Unit] at South London and Maudsley NHS Foundation Trust and King's College London. This research also summarises independent research funded by the National Institute for Health Research (NIHR) under its IMPACT Programme (Grant Reference Number RP-PG-0606-1049). This research was part funded by the FP7 project CRESTAR	Research Support
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Dan Rujescu	Nothing to Disclose	
Alessandro Serretti	Abbott Abbvie Angelini Astra Zeneca Clinical Data Boheringer Bristol Myers Squibb Eli Lilly GlaxoSmithKline Innovapharma Italfarmaco Janssen Lundbeck Naurex Pfizer Polifarma Sanofi Servier	Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker Consultant/Speaker
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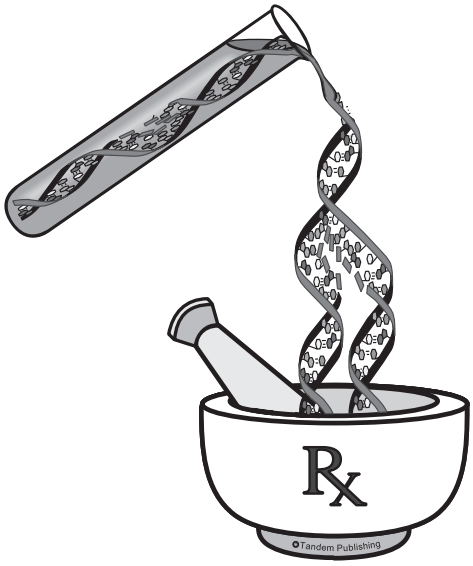

EVALUATION OF MEETING

In order to complete the PIP 2015 Meeting evaluation and obtain CME credit, please visit www.PharmacogeneticsinPsychiatry.com & click on the meeting evaluation. Evaluations must be completed by November 17, 2015.

Questions: Please contact info@ispg.net.

The 14th Annual Pharmacogenetics in Psychiatry Meeting

October 15, 2015
Omni King Edward Hotel, Toronto, Canada

Thursday, October 15, 2015

7:30 AM Continental Breakfast

8:00 AM Welcome and Introduction

SESSION I: PHARMACOGENETICS OF CLOZAPINE RESPONSE
Chair: Anil K. Malhotra

8:30 AM *Establishing the Characteristics of an Effective Pharmacogenetics Test for Clozapine Induced Agranulocytosis*
Moira Verbelen
King's College, London, UK

8:55 AM *An Epigenome-wide Association Study of Clozapine Use in Treatment-resistant Schizophrenia*
Eilis Hannon
University of Exeter, England, UK

9:20 AM *Neurobiological Correlates of Clozapine Response in Patient-derived Neurons*
Rakesh Karmacharya
Harvard University, Massachusetts, USA

9:45 AM Break

SESSION II: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUGS
Chair: James Kennedy

10:00 AM *Complex Genetic Overlap Between Schizophrenia Risk and Antipsychotic Response*
Douglas Ruderfer
Icahn School of Medicine at Mount Sinai, New York, USA

10:25 AM *Investigating the Functional Significance of Genome-wide Variants Associated with Antipsychotic Treatment Response*
Ellen Ovenden
Stellenbosch University, South Africa, Africa

10:50 AM *Schizophrenia Risk Variant at DRD2 Locus Predicts Antipsychotic Treatment Response in First Episode Psychosis*
Jianping Zhang
The Zucker Hillside Hospital, New York, USA

11:15 AM *Preliminary Evidence for Association of Genome-wide Significant DRD2 Schizophrenia Risk Variant with Clozapine Response*
Eric Huang
Centre for Addiction and Mental Health, Toronto, Ontario, Canada

11:40 AM *Pharmacogenetics of Antipsychotic-induced Weight Gain in Multiple Drug-naïve Cohorts*
Todd Lencz
The Zucker Hillside Hospital, New York, USA

12:05 PM Lunch on own

SESSION III: PHARMACOGENETICS OF MOOD & ANXIETY DISORDERS
Chair: David Goldman

1:30 PM *Epigenetics in Anxiety Disorders*
Katharina Domschke
University of Würzburg, Germany

1:55 PM *Common Genetic Markers for Lithium Response in Bipolar Disorder*
Francis J. McMahon
National Institute of Mental Health Intramural Research Program, Maryland, USA

2:20 PM *Genetics of Long-term Treatment Outcome in Bipolar Disorder*
Alessandro Serretti
University of Bologna, Italy

2:45 PM *Genome-wide Association Analyses in Clinical Response to Duloxetine and Placebo in Major Depression*
Daniel Müller
Centre for Addiction and Mental Health, Toronto, Ontario, Canada

3:10 PM *Genome-wide Association Study of Lithium Response in a Prospective Trial Sample- The Pharmacogenomics of Bipolar Disorder Study*
John Kelsoe
University of California, San Diego, California, USA

3:35 PM Break

SESSION IV: THE CRESTAR CONSORTIUM: DEVELOPMENT OF BIOMARKERS FOR SCHIZOPHRENIA
Chair: David A. Collier
Co-Chair: Dan Rujescu

3:45 PM *The CRESTAR Consortium: Overview*
David A. Collier
Eli Lilly and Company, Ltd.

4:00 PM *Pharmacogenomics of Agranulocytosis*
Dan Rujescu
Martin-Luther-University Halle-Wittenberg

4:20 PM *Genomics of Treatment-resistant Schizophrenia*
Antonio Pardinas
MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University

4:45 PM *Gene Expression Studies in Personalized Medicine*
Rebecca Harrison
King's College London

5:10 PM Meeting Adjourns

5:30 PM Poster Session and Reception

October 15, 2015

8:30 AM – 9:45 AM
SESSION I: PHARMACOGENETICS OF CLOZAPINE RESPONSE
Chair: Anil K. Malhotra

8:30 AM – 8:55 AM
Establishing the Characteristics of an Effective Pharmacogenetics Test for Clozapine Induced Agranulocytosis

Moira Verbelen[1], David A Collier[1,2], Dan Cohen[3], James H MacCabe[4], Cathryn M Lewis[1,5]
[1] SGDP Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]Discovery Neuroscience Research, Eli Lilly and Company Ltd., Lilly Research Laboratories, Surrey, UK; [3]Department of Severe Mental Illness, Mental Health Care Organization North-Holland North, The Netherlands; [4]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [5]Department of Medical and Molecular Genetics, King's College London, London, UK

Background: Clozapine is the only evidence-based therapy for treatment resistant schizophrenia, but it induces agranulocytosis, a rare but potentially fatal haematological adverse reaction, in less than 1% of users. To improve safety, the drug is subject to mandatory haematological monitoring throughout the course of treatment, which is burdensome for the patient and one of the main reasons clozapine is underused. Therefore, a pharmacogenetic test is clinically useful if it identifies a group of patients for whom the agranulocytosis risk is low enough to alleviate monitoring requirements.
Methods: Assuming a genotypic marker stratifies patients into a high risk and a low risk group, we construct the contingency table of true agranulocytosis status versus pharmacogenetic test prediction. We derive the algebraic relationship between test sensitivity, size of the two risk groups and agranulocytosis risk and explore this relationship graphically.
Results: We show that high test sensitivity in particular minimizes the agranulocytosis risk in the low risk group. Furthermore, a small high risk group further decreases the agranulocytosis risk in the low risk group.
Discussion: In order to achieve clinical utility, a pharmacogenetic test for clozapine induced agranulocytosis needs sufficiently high

8:30 AM – 8:55 AM
Establishing the Characteristics of an Effective Pharmacogenetics Test for Clozapine Induced Agranulocytosis (continued)

sensitivity to be able to reliably identify the small proportion of high risk patients and to allow less strict monitoring of the large group of patients at low risk.

8:55 AM – 9:20 AM
An Epigenome-wide Association Study of Clozapine Use in Treatment-resistant Schizophrenia

Eilis Hannon, Emma Dempster, Joe Burrage, Charles Curtis, Amy Gillespie, David Dempster, Cerisse Gunasinghe, Leonard Schalkwyk, Fiona Gaughran, Robin Murray, Marta Di Forti, the CRESTAR Consortium, David Collier, James MacCabe, Gerome Breen and Jonathan Mill

Schizophrenia is a severe psychiatric disorder characterized by episodic psychosis and altered cognitive function. Although effective in many patients, approximately one-third of schizophrenia cases are resistant to commonly prescribed antipsychotic medications. To date, the atypical antipsychotic drug clozapine is the only evidence-based treatment for these individuals, although its use is often associated with severe side-effects. Clozapine is known to influence chromatin remodelling and has previously been associated with global hypomethylation in the leukocytes of schizophrenic patients. We conducted a genome-wide analysis of DNA methylation changes associated with clozapine use in a sample of treatment-resistant schizophrenia patients to explore functionally-relevant epigenetic changes associated with exposure, and identify epigenetic predictors of response or adverse events. We quantified DNA methylation at ~480,000 sites across the genome using the Illumina 450K Human! Methylation array in whole blood samples derived from a cohort of chronic and first-episode schizophrenia patients, and unaffected control samples. Following stringent quality control, an epigenome-wide association study was performed comparing schizophrenia patients prescribed clozapine (n = 149) to i) chronic schizophrenia patients on alternative medications (n = 133), ii) first-episode schizophrenia patients (n = 301) and iiI) healthy controls not exposed to antipsychotic medications (n = 206). We identify multiple differentially methylated positions and differentially

8:55 AM – 9:20 AM
An Epigenome-wide Association Study of Clozapine Use in Treatment-resistant Schizophrenia (continued)

methylated regions in the clozapine-exposed samples, including sites located in the vicinity of genes involved in disease-relevant functional pathways and previously implicated in schizophrenia. In addition to reflecting clozapine-induced changes, we are exploring the hypothesis that these differences may represent useful markers of treatment resistant schizophrenia

9:20 AM – 9:45 AM
Neurobiological Correlates of Clozapine Response in Patient-derived Neurons

Rakesh Karmacharya
Harvard University

Clozapine is an antipsychotic medication with superior efficacy for schizophrenia compared to other antipsychotic medications but there is considerable variability in response among patients. We want to identify biological correlates of therapeutic response in vitro by comparing differences in cellular features in response to clozapine in neurons derived from clozapine responders and from clozapine non-responders. We are reprogramming fibroblasts from clozapine responders and non-responders to generate induced pluripotent stem cells (iPSCs) and differentiating them into cortical neurons. We plan to delineate cellular features that distinguish schizophrenia patients who respond well to clozapine compared to those who do not show clinical improvement. Postmortem studies of patients with schizophrenia show significant neuronal abnormalities in spine density and dendrite length specifically in layer III cortical pyramidal neurons. We hypothesize that these cellular features will also be different in layer III cortical neurons generated in vitro from schizophrenia patient iPSCs when compared to healthy controls. We further hypothesize that clozapine exposure in vitro will have differential effects on these morphometric parameters in neurons derived from clozapine responders compared to clozapine non-responders. We will study dendritic and spine morphologies in the presence/absence of clozapine in specific neuronal subtypes that have been implicated in disease biology and delineate cellular features that distinguish clozapine responders from non-responders. The ability to predict a priori who will respond well to clozapine could help guide treatment decisions for severe psychiatric disorders.

9:45 AM – 10:00 AM **Break**

10:00 AM – 12:05 PM
SESSION II: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUGS
Chair: James Kennedy

10:00 AM – 10:25 AM
Complex Genetic Overlap Between Schizophrenia Risk and Antipsychotic Response

Douglas M. Ruderfer[1,2,3], Alexander W. Charney[1,2], Ben Readhead[2], Brian A. Kidd[2], Anna K. Kähler[4], Paul J. Kenny[5], Michael J. Keiser[6], Jennifer L. Moran[3], Christina M. Hultman[4], Stuart A. Scott[2], Patrick F. Sullivan[7], Shaun M. Purcell[1,2,3,8], Joel T. Dudley[2], Pamela Sklar[1,2,9]
[1] Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA; [2]Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, USA; [3]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA; [4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [5]Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, USA; [6]Department of Pharmaceutical Chemistry, University of California, San Francisco, California, USA. Department of Bioengineering & Therapeutic Sciences, University of California, San Francisco, Institute for Neurodegenerative Diseases, University of California, San Francisco; [7]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA; [8]Analytic and Translational Genetics Unit, Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA; [9]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, USA

Background: Treatments for schizophrenia (SCZ) exist but do not alleviate symptoms for all patients and efficacy is limited by common, often severe side effects. Large-scale genetic studies have increased the number of genes and gene sets associated with SCZ risk. However, among the many important remaining questions is how these findings can inform and improve treatment.
Methods: Using two comprehensive and orthogonally created databases, we collated drug targets into 167 gene sets of pharmacologically similar drugs and examined enrichment of SCZ risk loci in these groups of drug targets. In addition, we assessed the contribution of rare variants to treatment response.

10:00 AM – 10:25 AM
Complex Genetic Overlap Between Schizophrenia Risk and Antipsychotic Response (continued)

Results: We identified significant enrichment of SCZ risk loci from both common and rare variation in known targets of antipsychotics (70 genes, p=0.0078), and novel predicted targets (277 genes, p=0.019). Furthermore, treatment resistant patients had a significant excess of rare disruptive variants in gene targets of antipsychotics (347 genes, p=0.0067) and in genes with evidence for a role in antipsychotic efficacy defined by PharmGKB (57 genes, p=0.0002).
Discussion: Our results support genetic overlap between SCZ pathogenesis and antipsychotic mechanism of action. This finding is consistent with treatment efficacy being polygenic in nature and not solely moderated by the dopamine and serotonin receptors thus implying that single target therapeutics may be insufficient. We further provide evidence of a role for rare functional variants in antipsychotic treatment response. We present this approach as a framework for enhancing both the understanding of treatment mechanism of action and disease pathology of complex disorders.

10:25 AM – 10:50 AM
Investigating the Functional Significance of Genome-wide Variants Associated with Antipsychotic Treatment Response

Ellen Ovenden, Britt Drögemöller, Lize van der Merwe, Robin Emsley, Louise Warnich

Response to antipsychotic treatment in schizophrenia is highly heritable, yet poorly understood. Recently, GWAS have become popular for researching such complex traits. Despite the majority of GWAS "hits" being in noncoding regions, interpretation is usually restricted to the closest gene. The Encyclopedia of DNA Elements (ENCODE) project has recently shown that noncoding variation can have complex regulatory effects on disease.
This study investigated the functionality of noncoding variants in schizophrenia treatment response. Firstly, variants previously associated with treatment response via GWAS were identified, and markers in linkage disequilibrium (LD) were obtained from publically available databases. The variants were analysed using several bioinformatic tools to determine regulatory potential. Subsequently, the top variants were genotyped in a South African

10:25 AM – 10:50 AM
Investigating the Functional Significance of Genome-wide Variants Associated with Antipsychotic Treatment Response (continued)

first episode schizophrenia cohort and analysed for association(s) with treatment outcomes.
This study implicated a region on chromosome 4q24 associated with treatment-refractoriness through involvement of the nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 gene (*NFKB1*). *NFKB1* is a master regulator of immunity with over 200 identified gene targets. Interestingly, *NFKB1* and immune dysregulation have both been implicated in schizophrenia susceptibility. The two most significantly associated variants at the specified 4q24 locus were both associated with inadequate improvement of negative symptoms ($P < 0.0001$).
These results illustrate the importance of the 4q24 region in treatment response and emphasise the genetic overlap between schizophrenia risk and drug response, and the potential role of regulation in treatment outcomes. Implicated genes and regions should be investigated as potential biomarkers of schizophrenia treatment response.

10:50 AM – 11:15 AM
Schizophrenia Risk Variant at DRD2 Locus Predicts Antipsychotic Treatment Response in First Episode Psychosis

Jian-Ping Zhang, Delbert Robinson, Juan Gallego, Jin Yu, John Kane, Anil Malhotra, Todd Lencz
The Zucker Hillside Hospital, Division of Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA; Hofstra North Shore LIJ School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, NY, USA; The Feinstein Institute for Medical Research, Manhasset, NY, USA

Recent findings from the Psychiatric Genomics Consortium (PGC) genome-wide association study (GWAS) showed that the DRD2 locus is associated with increased schizophrenia risks. Dopamine D2 receptor antagonism is a common mechanism of action for all effective antipsychotic drugs, and DRD2 variants were related to antipsychotic drug response in previous studies. However, the functional significance of the top DRD2 single nucleotide polymorphism (SNP) in the PGC GWAS (rs2514218) is unknown. The present study examined whether rs2514218 predicted antipsychotic

10:50 AM – 11:15 AM
Schizophrenia Risk Variant at DRD2 Locus Predicts Antipsychotic Treatment Response in First Episode Psychosis (continued)

drug response, including efficacy and adverse events, in a cohort of patients with first episode of psychosis treated with either risperidone or aripiprazole for 12 weeks. Subjects were genotyped using the Illumina Infinium HumanOmniExpressExom array platform. After standard quality control, data from 100 subjects were used in subsequent analysis. 49 was on aripiprazole and 51 was on risperidone treatment, who were assessed with psychotic symptoms and drug adverse events weekly for 4 weeks then biweekly for 8 week. Linear mixed model analysis revealed that the C/C homozygotes for rs2514218 had significantly more reduction in positive symptoms after 12 weeks of treatment, compared to the T allele carriers. In the aripiprazole group, C/C homozygotes also had more akathisia than the T allele carriers, but there was no difference between the two genotype groups in patients treated with risperidone. These findings suggest that the schizophrenia risk variant at DRD2 locus is associated with better antipsychotic drug response, and increased risk of akathisia on aripiprazole treatment.

11:15 AM – 11:40 AM
Preliminary Evidence for Association of Genome-wide Significant DRD2 Schizophrenia Risk Variant with Clozapine Response

Eric Huang[1,2], Malgorzata Maciukiewicz[2], Clement C. Zai[2], Arun K. Tiwari[2], Jiang Li[5], Steven G. Potkin[3], Jeffrey A. Lieberman[4], Herbert Y. Meltzer[5], Daniel J. Müller[2,6], James L. Kennedy[2,6]
[1]Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Canada; [2]Pharmacogenetic Research Clinic, Centre for Addiction and Mental Health, Toronto, Canada; [3]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA; [4]Department of Psychiatry, Columbia University Medical Center, New York, NY; [5]Feinberg School of Medicine, Northwestern University, Chicago, IL; [6]Department of Psychiatry, University of Toronto, Toronto, Canada

The 2014 Psychiatric Genomics Consortium genome-wide association study identified a SNP, rs2514218, located 47kb upstream of the DRD2 gene to be associated with risk for schizophrenia (SCZ) (OR=0.927, p=2.75e-11). Moreover, a recent study by Ikeda et al. provides evidence for significant enrichment of SCZ risk variants in non-responders to risperidone treatment, suggesting possible genetic

11:15 AM – 11:40 AM
Preliminary Evidence for Association of Genome-wide Significant DRD2 Schizophrenia Risk Variant with Clozapine Response (continued)

overlap between SCZ susceptibility and antipsychotic response. Given these findings as well as the fact that antipsychotics bind to dopamine D2 receptors, we examined whether rs2514218 may be associated with response to antipsychotic treatment.
We investigated the SNP in relation to treatment response in a prospective study consisting of 208 patients (151 Caucasians, 42 African-Americans, 15 others) treated with clozapine for six months. Treatment response was evaluated using the 18-item Brief Psychiatric Rating Scale (BPRS). Baseline score was included as a covariate.
rs2514218 was associated with total score change under an additive model (pcorr=0.033). Secondary analyses revealed that rs2514218 was not associated with either positive or negative symptom improvement, but was associated with change in the remaining eleven item scores (p=0.038).
Our finding provides preliminary evidence for rs2514218 association with clozapine response, but further replication is required before firm conclusions can be drawn. Our finding also suggests it may be worthwhile to closely re-examine DRD2 genetic variation in relation to antipsychotic response and whether specifically rs2514218 is associated with response to antipsychotics other than clozapine.

11:40 AM – 12:05 PM
Pharmacogenetics of Antipsychotic-induced Weight Gain in Multiple Drug-naïve Cohorts

Todd Lencz
The Zucker Hillside Hospital

Although second-generation antipsychotic drugs (SGAs) are the cornerstone of treatment for many psychotic and non-psychotic disorders, these medications are associated with substantial weight gain, including the development of obesity and other cardiovascular risk factors. Antipsychotic-induced weight gain (AIWG) is a critical factor underlying the reduction in life expectancy, estimated to reach 20–30 years, in those with chronic and severe mental illnesses. However, the extent of AIWG is highly variable across patients, and prognostic biomarkers are generally lacking. Further, the biological

11:40 AM – 12:05 PM
Pharmacogenetics of Antipsychotic-induced Weight Gain in Multiple Drug-naïve Cohorts (continued)

mechanisms underlying AIWG are poorly understood, hampering efforts to develop novel medications without these adverse effects. While prior pharmacogenetic studies have identified some promising candidate genes, most studies have been underpowered for genomewide association study (GWAS) approaches. Moreover, few studies have examined patients during their first episode of treatment with SGAs, when AIWG is more pronounced and is not confounded by effects of prior treatment. Consequently, we developed an international collaboration in order to assemble a relatively large cohort of patients (n>1000) undergoing first-ever SGA treatment in 7 different controlled or naturalistic trials across 3 continents. We are currently performing GWAS using dense arrays, and imputation to 1000 Genomes standards in order to comprehensively survey common variation across the genome. Results of meta-analysis across cohorts will be presented in detail at the meeting.

12:05 PM – 1:30 PM **Lunch on own**

1:30 PM – 3:35 PM
SESSION III: PHARMACOGENETICS OF MOOD & ANXIETY DISORDERS
Chair: David Goldman

1:30 PM – 1:55 PM
Epigenetics in Anxiety Disorders

Katharina Domschke
University of Würzburg

Katharina Domschke will present results from one of the first genome-wide DNA methylation analyses in panic disorder as well as from epigenetic and epigenetic x environment interaction studies of candidate genes (e.g. MAO-A, OXTR) in anxiety disorders and anxiety-related intermediate phenotypes. Additionally, epigenetic patterns predicting treatment response and/or constituting temporally

1:30 PM – 1:55 PM
Epigenetics in Anxiety Disorders (continued)

dynamic biological correlates of treatment success will be discussed from a therapy-epigenetic angle. The identification of epigenetic markers - intertwined with psychophysiological and neural network markers - in the etiology and course of mental disorders may aid in developing resilience-increasing indicated preventive measures in high-risk groups and more targeted, personalized treatment options for anxiety and mood disorders.

1:55 PM – 2:20 PM
Common Genetic Markers for Lithium Response in Bipolar Disorder

Consortium on Lithium Genetics (ConLiGen)[#]
Liping Hou[1], Urs Heilbronner[2,3], Franziska Degenhardt[4], Mazda Adli[5], Kazufumi Akiyama[6], Nirmala Akula[1], Raffaella Ardau[7], Bárbara Arias[8], Lena Backlund[9], Claudio E.M. Banzato[10], Antonio Benabarre[11], Susanne Bengesser[12], Abesh Kumar Bhattacharjee[13], Joanna M. Biernacka[14,15], Armin Birner[12], Clara Brichant-Petitjean[16], Elise T. Bui[1], Pablo Cervantes[17], Guo-Bo Chen[18], Hsi-Chung Chen[19], Caterina Chillotti[7], Sven Cichon[20,4], Scott R. Clark[21], Francesc Colom[11], David Cousins[22], Cristiana Cruceanu[23], Piotr M. Czerski[24], Clarissa R. Dantas[10], Alexandre Dayer[25], Bruno Étain[26], Peter Falkai[27], Andreas J. Forstner[4], Louise Frisén[9], Janice M. Fullerton[28,29], Sébastien Gard[30], Julie S. Garnham[31], Fernando S. Goes[32], Paul Grof[33], Oliver Gruber[3], Ryota Hashimoto[34], Joanna Hauser[24], Stefan Herms[20,4], Per Hoffmann[20,4], Andrea Hofmann[4], Stephane Jamain[26], Esther Jiménez[11], Jean-Pierre Kahn[35], Layla Kassem[1], Sarah Kittel-Schneider[36], Sebastian Kliwicki[37], Barbara König[38], Ichiro Kusumi[39], Nina Lackner[12], Gonzalo Laje[1], Mikael Landén[40,41], Catharina Lavebratt[9], Marion Leboyer[42], Susan G. Leckband[43], Carlos A. López Jaramillo[44], Glenda MacQueen[45], Mirko Manchia[46,47], Lina Martinsson[48], Manuel Mattheisen[49], Michael J. McCarthy[50], Susan McElroy[51], Marina Mitjans[8], Francis M. Mondimore[32], Palmiero Monteleone[52,53], Caroline M. Nievergelt[13], Markus M. Nöthen[4], Urban Ösby[54], Norio Ozaki[55], Roy H. Perlis[56], Andrea Pfennig[57], Daniela Reich-Erkelenz[2], Guy A. Rouleau[58], Peter R. Schofield[59,29], K. Oliver Schubert[21], Barbara W. Schweizer[32], Florian Seemüller[27], Giovanni Severino[60], Tatyana Shekhtman[13], Paul D. Shilling[13], Kazutaka Shimoda[61], Christian Simhandl[62], Claire M. Slaney[31], Jordan W. Smoller[56], Alessio Squassina[60], Thomas Stamm[5],

1:55 PM – 2:20 PM

Common Genetic Markers for Lithium Response in Bipolar Disorder (continued)

Pavla Stopkova[63], Sarah K. Tighe[64], Alfonso Tortorella[65], Gustavo Turecki[23], Julia Volkert[36], Stephanie Witt[66], Adam Wright[67], L. Trevor Young[68], Peter P. Zandi[69], James B. Potash[64], Jay Raymond DePaulo[32], Michael Bauer[57], Eva Reininghaus[12], Tomas Novák[63], Jean-Michel Aubry[25], Mario Maj[65], Bernhard T. Baune[21], Philip B. Mitchell[67], Eduard Vieta[11], Mark A. Frye[15], Janusz K. Rybakowski[37], Po-Hsiu Kuo[70], Tadafumi Kato[71], Maria Grigoroiu-Serbanescu[72], Andreas Reif[36], Maria Del Zompo[60], Frank Bellivier[16], Martin Schalling[9], Naomi R. Wray[18], John Kelsoe[13], Martin Alda[31], Marcella Rietschel[66], Francis J. McMahon[1], Thomas G. Schulze[1,2,3,32,66]

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Common Genetic Markers for Lithium Response in Bipolar Disorder (continued)

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1:55 PM – 2:20 PM

Common Genetic Markers for Lithium Response in Bipolar Disorder (continued)

OH, United States; [52]Neurosciences Section, Department of Medicine and Surgery, University of Salerno, Salerno, Italy; [53]Department of Psychiatry, University of Naples SUN, Naples, Italy; [54]Department of Neurobiology, Care sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden; [55]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan; [56]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States; [57]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden; [58]Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada; [59]Mental Illness, Neuroscience Research Australia, Sydney, Australia; [60]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy; [61]Department of Psychiatry, Dokkyo Medical University School of Medicine, Mibu, Japan; [62]Bipolar Center Wiener Neustadt, Wiener Neustadt, Austria; [63]National Institute of Mental Health, Klecany, Czech Republic; [64]Department of Psychiatry, University of Iowa, Iowa, IA, United States; [65]Department of Psychiatry, University of Naples, SUN, Naples, Italy; [66]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [67]School of Psychiatry, University of New South Wales, and Black Dog Institute, Sydney, Australia; [68]Department of Psychiatry, University of British Columbia, Vancouver, Canada; [69]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [70]Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan; [71]Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Brain Science Institute, Saitama, Japan; [72]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Psychiatric Hospital, Bucharest, Romania

Background: Lithium remains a first-line treatment in the therapy of bipolar disorder, but individual response is variable. Previous studies have suggested that lithium response is a heritable trait. However, no genetic markers have been reproducibly identified.

Methods: Here we report the results of a genome-wide association study of lithium response in 2,563 patients collected by 22 participating sites from the International Consortium on Lithium Genetics (ConLiGen); the largest attempted so far. Data from over 6 million common SNPs were tested for association with both a categorical and a continuous rating of lithium response.

1:55 PM – 2:20 PM
Common Genetic Markers for Lithium Response in Bipolar Disorder (continued)

Findings: A single locus of four linked SNPs met genome-wide significance criteria for association with lithium response. In an independent, prospective study of patients treated with lithium monotherapy for a period of up to two years, carriers of the response-associated alleles had a significantly lower rate of relapse than carriers of the alternate alleles.
Interpretation: The response-associated region contains two long non-coding RNAs (lncRNAs). LncRNAs are increasingly appreciated as important regulators of gene expression, particularly in the CNS. Further studies are needed to establish the biological context of these findings and their potential clinical utility. Confirmed biomarkers of lithium response would constitute an important step forward in the clinical management of bipolar disorder.

2:20 PM – 2:45 PM
Genetics of Long-term Treatment Outcome in Bipolar Disorder

Alessandro Serretti, Chiara Fabbri*
Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

Bipolar Disorder (BD) shows one of strongest genetic predisposition among psychiatric disorders and the identification of reliable genetic predictors of treatment response could significantly improve the prognosis of the disease.
The present study investigated genetic predictors of long-term treatment-outcome in 723 patients with BD type I from the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) genome-wide dataset. BD I patients with > 6 months of follow-up and without any treatment restriction (reflecting a natural setting scenario) were included. Phenotypes were the total and depressive episode rates and the occurrence of one or more (hypo)manic/mixed episode during follow-up. Quality control of genome-wide data was performed according to standard criteria and linear/logistic regression models were used as appropriate. Top genes were further analyzed through a pathway analysis (functional enrichment analysis using Cytoscape GeneMania plugin followed by a gene set enrichment analysis using a Fisher exact test to detect different

2:20 PM – 2:45PM
Genetics of Long-term Treatment Outcome in Bipolar Disorder (continued)

distributions of SNPs with p<0.05 and p<0.01 between the index pathway and a random matched pathway).
Genes previously involved in the susceptibility to BD (DFNB31, SORCS2, NRXN1, CNTNAP2, GRIN2A, GRM4, GRIN2B), antidepressant action (DEPTOR, CHRNA7, NRXN1), and mood stabilizer or antipsychotic action (NTRK2, CHRNA7, NRXN1) may affect long-term treatment outcome of BD. Promising findings without previous strong evidence were TRAF3IP2-AS1, NFYC, RNLS, KCNJ2, RASGRF1, NTF3 genes. Pathway analysis supported particularly the involvement of molecules mediating the positive regulation of MAPK cascade and learning/memory processes.
Further studies focused on the outlined genes may be helpful to provide validated markers of BD treatment outcome.

2:45 PM – 3:10 PM
Genome-wide Association Analyses in Clinical Response to Duloxetine and Placebo in Major Depression

Daniel J. Müller[1,2,6], Malgorzata Maciukiewicz[1], Victoria S. Marshe[1,2], Arun K. Tiwari[1], Trehani M. Fonseka[1,3,4], Natalie Freeman[1], Susan Rotzinger[3], Jane A. Foster[5], James L. Kennedy[1,2,6], Sidney H. Kennedy[2,3,4,6]
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Background: Major depressive disorder is a prevalent psychiatric disorder treated with antidepressant medications such as duloxetine. However, a substantial alleviation of depressed symptoms is also commonly observed with placebo medication which tend to obfuscate clinical trials. This study investigated genetic factors associated with duloxetine and placebo response and to explore whether both interventions may share mutual genetic components.
Methods: We performed a GWAS in patients treated with either

2:45 PM – 3:10 PM
Genome-wide Association Analyses in Clinical Response to Duloxetine and Placebo in Major Depression (continued)

duloxetine (n=215) or placebo (n=235) for up to 8 weeks. Treatment response was operationalized as MADRS score changes (%) from baseline and was used as the main outcome variable in an ANCOVA model, including baseline depression severity, length of treatment and cohort as covariates. High standard quality controls were applied followed by imputation analyses. The samples and clinical data were provided by H. Lundbeck A/S under Lu activity number 15761.
Results: Top hits for response to duloxetine were observed in regions on chromosome 1, 2, 7 and 19 implicating genes involved in cell cycle progression, endocytosis and cell adhesion molecules. However, none of these results reached significance at genome-wide level. In contrast, a region on chromosome 3 showed a genome-wide association with response to placebo) implicating a signal transduction gene expressed in nociceptive neurons (p=1.87E-09). We are currently evaluating our findings in independent samples.
Discussion: Our data provide new insights into genetic pathways implicated in response to antidepressant and placebo medication. To the best of our knowledge, this is the first study detecting a genome-wide significant association with response to placebo in depressed patients.

3:10 PM – 3:35 PM
Genome-wide Association Study of Lithium Response in a Prospective Trial Sample – The Pharmacogenomics of Bipolar Disorder Study

John Kelsoe
University of California, San Diego

Lithium is the gold standard for treatment in bipolar disorder with proven efficacy in both mania, depression and most importantly prophylaxis. In particular, a subset of patients experience a very robust response to lithium with almost complete elimination of episodes. Yet bipolar patients frequently must go through numerous medication trials before finding the optimal medication. The goal of this study is to identify genes associated with bipolar disorder towards developing a clinical predictor of response. We have conducted two prospective trials of lithium, one in US veterans at the VA Medical

3:10 PM – 3:35 PM
Genome-wide Association Study of Lithium Response in a Prospective Trial Sample – The Pharmacogenomics of Bipolar Disorder Study (continued)

Center in San Diego, the other as part of a NIH sponsored 10 site collaborative trial, the Pharmacogenomics of Bipolar Disorder study. In each study, bipolar I subjects were started on lithium and over 4 months stabilized on lithium monotherapy. Subjects were then observed for one month to document remission, and then entered a maintenance phase where they are followed for up to 2 years in order to detect relapse. 135 subjects have entered the VA study to date and 574 the PGBD study. Both the VA and PGBD prospective samples have completed GWAS genotyping and are being analyzed. The results of these genomewide analyses of lithium response will be presented. ConLiGen is another international consortium to identify genes associated with lithium response. ConLiGen recently reported genomewide association to a region including a lncRNA on chromosome 21. We have examined the four significant SNPs in our VA prospective sample and found evidence replicating this result (rs78015114, Cox proportional hazard test p=0.03, hazard ratio = 3.8). This independent replication provides support for the ConLiGen result, and focuses attention on this intriguing lncRNA.

3:35 PM – 3:45 PM **Break**

3:45 PM – 5:10 PM
SESSION IV: THE CRESTAR CONSORTIUM: DEVELOPMENT OF BIOMARKERS FOR SCHIZOPHRENIA
Chair: David. A. Collier
Co-Chair: Dan Rujescu

*Abstracts not available at time of print.

3:45 PM – 4:00 PM
The CRESTAR Consortium: Overview

David A. Collier
Eli Lilly and Company, LTD.

4:00 PM – 4:20 PM
Pharmacogenomics of Agranulocytosis

Dan Rujescu
Martin- Luther- University Halle-Wittenberg

4:20 PM – 4:40 PM
Genomics of Treatment-resistant Schizophrenia

Antonio Pardinas
MCR Centre for Neuropsychiatric Genetics and Genomics, Cardiff University

4:40 PM – 5:10 PM
Gene Expression Studies in Personalized Medicine

Rebecca Harrison
King's College London

THE 14TH ANNUAL PHARMACOGENETICS IN PSYCHIATRY MEETING THURSDAY, OCTOBER 15, 2015

POSTER PRESENTATIONS

1. **Differential Antipsychotic Treatment among Ethnic Groups: An Analysis of Social and Geographical Origin Determinants**
   Ali Bani Fatemi
   Centre for Addiction and Mental Health, Toronto

2. **The Role of the ITIH3 rs2535629 Variant in Antipsychotic Response**
   Tristram Lett
   Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany

3. **Behavioural and Transcriptomic Correlates with Clozapine Response in Zebrafish**
   Joana Viana
   Exeter University Medical School

4. **Open Board**

5. **In-depth Analyses of an Evolutionarily Conserved Region Downstream of the Melanocortin 4 Receptor (MC4R) Gene, Implicated in Antipsychotic-induced Weight Gain**
   Li Qin
   Centre for Addiction and Mental Health, Toronto

6. **The Identification of Novel Genetic Variants Associated with Antipsychotic Treatment Response Outcomes in First Episode Schizophrenia Patients**
   Louise Warnich
   Stellenbosch University

7. **The CREB-regulated Transcription Coactivator 1 (CRTC1) Gene and Antipsychotic-induced Weight Gain**
   Maxine Kish
   Centre for Addiction and Mental Health, Toronto

8. **Open Translational Science in Schizophrenia**
   Marsha A. Wilcox
   Janssen Research and Development, LLC

9. **Efficacy and Side Effect of Therapeutic Olanzapine Involves Altered Methylation in Genes and Pathways Implicated in Psychosis**
   Melkaye G. Melka
   Western University

10. **A Polygenic Risk Analysis for Antipsychotic Dosage Using Genome-wide Significant Markers for Schizophrenia**
    Nuwan Hettige
    Centre for Addiction and Mental Health, Toronto

11. **Gene Expression Analysis of Clozapine Treatment in Whole Blood of Patients with Psychosis**
    Rebecca Harrison
    King's College, London

12. **Comprehensive Genetic Analysis Implicates Novel Mechanisms for Clozapine-associated Neutropenia**
    Sophie Legge
    Cardiff University

13. **CACNA1C Gene and Schizophrenia: A Case-control and Pharmacogenetic Study**
    Alessandro Serretti
    University of Bologna

14. **Hot Genes in Schizophrenia: Case-control, Pharmacogenetics and Exploratory Analyses in Two Independent Samples**
    Alessandro Serretti
    University of Bologna

15. **Immunogenetic Biomarkers of Clozapine Treatment Response**
    Trehani Fonseka
    Centre for Addiction and Mental Health

16. **Structural Connectivity and Cortical Inhibition at the DLPFC Mediate the Association Between GAD1 and Working Memory Dysfunction Relevant to Schizophrenia**
    Tristram Lett
    Charité Universitätsmedizin Berlin

17. **Examining the Role of Mitochondrial Variants in Antipsychotic-induced Weight Gain**
    Vanessa Goncalves
    Centre for Addiction and Mental Health

18. **Unique Phenotypic Characterizations in Relation to Copy Number Variants in a Toronto Schizophrenia Population**
    Venuja Sriretnakumar
    Centre for Addiction and Mental Health

19. **Genome-wide Association Analysis to Predict Optimal Antipsychotic Dosage in Schizophrenia: A Pilot Study**
    Vincenzo De Luca
    Centre for Addiction and Mental Health

20. **Investigating SKA2 Genetic Variants and Response to Citalopram**
    Amanda J. Lisoway
    Centre for Addiction and Mental Health

21. **Cytokine Measurement In Patients With Obsessive-compulsive Disorder**
    Carolina Cappi
    University of São Paulo

22. **Genome-wide Association Study of Antidepressant Response: Involvement of the Inorganic Cation Transmembrane Transporter Activity Pathway**
    Alessandro Serretti
    University of Bologna

23. **Neuroplasticity and Second Messenger Pathways in Antidepressant Efficacy: Pharmacogenetic Results from a Prospective Trial Investigating Treatment Resistance**
    Alessandro Serretti
    University of Bologna

24. **Genetic Study of Neuregulin 1 and Receptor Tyrosine-protein Kinase erbB-4 in Tardive Dyskinesia**
    Clement C. Zai
    Centre for Addiction and Mental Health

25. **Genetic Markers of Antidepressant Response in a Cross-cultural Sample of Patients with Obsessive-compulsive and Related Disorders**
    Gwyneth Zai
    Centre for Addiction and Mental Health

26. **Meta-analysis of the Serotonin Transporter Promoter Variant (5-HTTLPR) in Relation to Adverse Environment and Antisocial Behavior: Evidence for a Gene-environment Interaction Effect**
    Jorim Tielbeek
    VU Medical Center, Amsterdam

27. **Epigenetic Changes in a Rodent Tic Model After Striatal 6-OH-Dopamine Lesion and L-DOPA Treatment**
    Luca Pagliaroli
    Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Buda

28. **Systems Genetics Analysis of Antidepressant Treatment**
    Majbritt Busk Madsen
    Mental Health Services of the Capital Region of Denmark

29. **GWAS-based Machine Learning Approach to Predict Duloxetine Response in Major Depressive Disorder**
    Malgorzata Maciukiewicz
    Centre for Addiction and Mental Health

30. **Neural-derived Plasma Exosomal MiRNAs as Promising Novel Biomarkers for Suicidality**
    Pamela E. Parker
    Birmingham VAMC

31. **Combining Clinical and Genetic Variables to Predict Antidepressant Treatment Response: A Machine Learning Approach**
    Raquel Iniesta
    Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry

32. Investigating Associations Between IL-1beta, IL-2, IL6, TSPO and BDNF Variants and Response to Duloxetine or Placebo Treatment in Patients with Major Depression
Victoria S. Marshe
Centre for Addiction and Mental Health

33. Open Board

34. Open Board

35. Calcium Signaling Genes Associated with Bipolar Disorder in the Latino Population
Chun Xu
Texas Tech University Health Sciences Center-El Paso

36. Duration of Therapy and Years of Illness Before Lithium Treatment Have Opposite Effects on Leukocyte Telomere Length in Bipolar Disorder Patients
Claudia Pisanu
University of Cagliari, Italy

37. Multinomial Regressions to Identify More Homogeneous Phenotypes in Obsessive-compulsive Disorder
Roseli Gedanke Shavitt
University of Sao Paulo, Brazil

38. Dopaminergic Polymorphisms in Methadone and Suboxone Replacement Therapy of Heroin Dependent Patients
Andrea Vereczkei
Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University

39. Identification of Rare Disruptive Variants in Voltage-gated Channel Genes (CACNA1C, CACNA1D, CACNA1S, CACNA1I) in Japanese Samples of Schizophrenia and Autism Spectrum Disorder Using Ion Torrent PGM Platform
Chenyao Wang
Nagoya University

40. **A Protocadherin Gene Cluster Regulatory Variant is Associated With Nicotine Withdrawal and the Urge to Smoke**
    Kevin P. Jensen
    Yale University School of Medicine and VA Connecticut Healthcare System

41. **CYP2D6 Impaired Metabolizer Status May Protect Against Neurotoxic Effects of Methamphetamine Use**
    Lauren Seaman
    University of California, Los Angeles

42. **Candidate Gene Study of Methamphetamine Use Frequency Among Methamphetamine Dependent Hispanic and Non-Hispanic Whites**
    Levon Demirdjian
    University of California, Los Angeles

43. **CNR1 and FAAH Variation and Affective States Induced by Marijuana Smoking**
    Rohan H.C. Palmer
    Alpert Medical School at Brown University

44. **Pharmacogenomic Influences on Cardiovascular Tolerability of ADHD Treatments**
    Erika L. Nurmi
    Semel Institute for Neuroscience, University of California, Los Angeles

45. **Functional Analysis of the Autism and Intellectual Disability Gene PTCHD1 Reveals Hedgehog Receptor-like Functions and PDZ-binding Domain-specific Regulation of CNTNAP1 and NLGN1**
    Kirti Mittal
    Centre for Addiction and Mental Health

46. **BioVUpsych: Electronic Medical Record-based Identification of DNA Samples for Disorders Underrepresented in the PGC**
    Takahiro Soda
    University of North Carolina Hospitals

47. Systematic Review of Effectiveness and Cost-effectiveness of Pharmacogenetic Testing for Deciding Drug Treatment in Psychiatry
G. Mustafa Soomro
Solent NHS Trust Hampshire UK

48. Analysis of Pharmacogenetic Studies: Comparing Traditional Statistical Inference with Machine Learning
Moira Verbelen
King's College London

Poster Session Abstracts
Thursday, October 15, 2015

Board #1
Differential Antipsychotic Treatment among Ethnic Groups: An Analysis of Social and Geographical Origin Determinants

Ali Bani Fatemi, Jiali Song, Nuwan Hettige, James L. Kennedy, Vincenzo De Luca
CAMH, Toronto, Canada

Background: The practice of antipsychotic prescription inconsistency among ethnicities has been known to occur in the mental health field. Differences in dose, type and amount of antipsychotics prescribed have been presented predominantly in American studies. For example, Studies have shown that African-American patients were more likely than white patients to receive higher doses of antipsychotic medication, a difference that has been unexplained by differences in clinical severity. Studies have also shown that the therapeutic dosage is lower in the Asian population as compared to the White patients. In this study by gathering genetic data we were able to see the geographical origin of participants and contrast this with their perceived ethnicity to see anti-psychotic treatment differences. Our goal was to determine whether these recognized differences in treatment are actually influenced by social factors, or whether these differences have a genetic origin.
Methods: From our sample of 276 participants with schizophrenia spectrum disorders, we conducted cross-sectional assessments to collect information regarding self-identified ethnicity, immigration history, and suicide history. Self-identified ethnicity was collected through self-report. Geographical ancestry was identified using 292 SNP markers from the HapMap project. Using a regression analysis, we tested whether a history of migration, ethnicity or geographical ancestry were predictive of differences in treatment.
Results: Our analysis failed to demonstrate a significant relationship between differences in antipsychotic treatment and migration, ethnicity or ancestry.
Conclusion: Although ethnicity and migration history are not predictive of differences in dose, they may hold predictive value for other aspects of treatment in psychiatric disorders.

Board #2
The Role of the ITIH3 rs2535629 Variant in Antipsychotic Response

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Introduction: Genetic risk factors determining the response to antipsychotic treatment in schizophrenia are poorly understood. Recent genome-wide analyses have demonstrated that common single nucleotide polymorphisms (SNPs) in and near the inter-alpha-trypsin inhibitor heavy chain H3 (*ITIH3*) gene are strongly associated with schizophrenia and related psychiatric disorders. To assess the pharmacogenetic relevance of *ITIH3*, we examined the impact of the top associated SNP (rs2535629) from a large genome-wide study on antipsychotic treatment response.
Methods: We genotyped rs2535629 in N=185 schizophrenia patients of European ancestry receiving various antipsychotics for up to 26 weeks. Among these individuals was a subgroup of patients receiving clozapine (N=88). Treatment response was assessed using the Brief Psychiatric Rating Scale (BPRS), and its positive and negative subscales.
Results: There was no association between rs2535629 and changes in total BPRS score in the entire sample (p=0.53) or the clozapine-treated subgroup (p=0.73). In the clozapine subgroup, schizophrenia risk allele carriers (rs2535629-A) had a significantly greater reduction of negative symptom subscale scores compared to major allele homozygotes (p=0.004).
Discussion: While there was no association of genotype with overall changes in BPRS scores, the better improvement of negative symptoms in minor allele carriers indicates that rs2535629 may

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identify a subset of schizophrenia patients with better treatment response to clozapine. Although replication is required, our findings provide further evidence that *ITIH3* is relevant in schizophrenia and may play a role in regulation of treatment response.

Board #3
Behavioural and Transcriptomic Correlates with Clozapine Response in Zebrafish

Joana Viana, Nick Wildman, Gregory Paull, Eduarda Santos and Jonathan Mill

Background: Schizophrenia is a severe neuropsychiatric disorder characterized by episodic psychosis and altered cognitive function. About 20% of the patients are resistant to the commonly-prescribed antipsychotic medications used to treat schizophrenia. Clozapine is an atypical antipsychotic drug often prescribed to treatment-resistant schizophrenia patients, although the functional pathways mediating its action are not well understood. Furthermore, 40-70% of patients treated with clozapine show an inadequate response. The majority of clozapine' side-effects are not serious, but a small percentage of the patients develop agranulocytosis, which causes low blood white cell count and can be fatal. Understanding the molecular pathways involved in antipsychotic response will help in the development of new improved therapeutics that act on pathogenicity rather than just treating the acute manifestations of schizophrenia.
Methods: We investigate gene expression changes in the brain in response to clozapine, using zebrafish as an *in vivo* model. We exposed zebrafish to a low (20ug/L) and a high dose (70ug/L) of clozapine during a period of three days. RNA was extracted from brain and profiled using RNA-seq. We recorded and analysed behavioural alterations in response to the medication in order to anchor the transcriptomic responses to behaviour endpoints. High-quality RNA was isolated from brain tissue and is currently being profiled using highly-parallel RNA-seq in an Illumina HiSeq 2500 platform, to identify transcriptomic changes induced by clozapine.
Results: Clozapine induced dramatic changes in behaviour in zebrafish. Exposure to clozapine resulted in zebrafish spending

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significantly more time at the top of the tank, however this did not affect dominance structure nor feeding and spawning behavior.
Discussion: Our data highlight the utility of zebrafish as a model for assessing the molecular and behavioural consequences of antipsychotic medications. Our data show notable behavioural effects induced by clozapine, presumably mediated by alterations in functional pathways in the brain. We are currently assessing transcriptomic changes that can be linked to these behavioural alterations.

Board #4
Open Board

Board #5
In-depth Analyses of an Evolutionarily Conserved Region Downstream of the Melanocortin 4 Receptor (MC4R) Gene, Implicated in Antipsychotic-induced Weight Gain

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Background: MC4R is primarily expressed in the hypothalamus and plays important roles in the regulation of appetite, energy expenditure and homeostasis. Mutations in *MC4R* gene are the most common monogenic cause of human obesity. Genome-wide association studies (GWAS) have identified genetic variants downstream of *MC4R* such as marker rs489693 to be associated with risks of obesity, type 2 diabetes and substantial antipsychotic-induced weight gain (Malhotra et al., 2012). These genetic variants are assumed to remotely affect *MC4R* gene expression.
Methods: Bioinformatics analysis was performed to explore the *MC4R* gene locus. An evolutionarily conserved region was identified, which likely regulates *MC4R* gene brain specific expression. A luciferase reporter assay was used to measure the enhancer activity of this regulatory element. Transcription factors (TFs) were then

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investigated which might bind to this enhancer. Such potential TFs are currently being constructed into a lentiviral plasmid. Gain- and loss-of-function strategy will be used to explore the relationship among brain specific TFs, two alternative RNAs transcribed from this element and *MC4R* brain specific gene expression.
Results: The evolutionarily conserved region was located 248kbp downstream of *MC4R* gene. The region contains two functional elements. One element transcribes two alternative RNAs (non coding RNAs), a short RNA and a long RNA. The second element is a RNA enhancer, which drives the two RNA expressions differentially and regulates the MC4R brain specific expression.
Discussion: In conclusion, our data provides first insights into a remote *MC4R* brain specific regulatory region that may represent an important aspect of its function at the hypothalamus.

Board #6
The Identification of Novel Genetic Variants Associated with Antipsychotic Treatment Response Outcomes in First Episode Schizophrenia Patients

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Background: Although antipsychotics are integral to the treatment of schizophrenia, they are not equally effective in all patients. Therefore, pharmacogenomics may play a valuable role in the optimisation of antipsychotic treatment. However, in order for pharmacogenomic studies to be successful, careful study designs utilising extensive clinical and genomic data need to be implemented.
Methods: This study utilised exome sequencing in combination with results from previous antipsychotic studies to design a panel of

Board #6 (continued)

variants that were genotyped in two well-characterised first episode schizophrenia cohorts. All patients were treated with antipsychotics over three months during which the response to treatment was regularly assessed. Association analyses were performed to determine if any of the variants were significantly associated with antipsychotic treatment response outcomes.
Results: Association analyses in the discovery cohort identified two non-synonymous variants that were significantly associated with antipsychotic treatment response outcomes (P<2.7x10-5), which were also significantly associated with the corresponding treatment response outcome in an independent replication cohort. Computational approaches revealed that both of these non-synonymous variants - rs13025959 in MYO7B (E1647D) and rs10380 in MTRR (H622Y) - were predicted to impair the functioning of their corresponding protein products.
Discussion: This study has demonstrated the value of well characterised cohorts and genomic data for antipsychotic pharmacogenomic applications and the use of these strategies made it possible to identify novel genetic variants that may be involved in antipsychotic treatment response. These findings should play a role in improving our understanding of antipsychotic treatment response and in so doing ultimately aid in the development of more effective treatment strategies.

Board #7
The CREB-regulated Transcription Coactivator 1 (CRTC1) Gene and Antipsychotic-induced Weight Gain

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Objectives: Our previous studies have revealed that gene variants involved in the hypothalamic control of food intake are particularly involved in antipsychotic-induced weight gain (AIWG). Interestingly, a marker of the hypothalamic CREB-regulated transcription coactivator 1 (CRTC1) gene (rs3746266; causing a missense polymorphism from threonine to alanine) was recently reported to be associated with obesity in psychiatric patients and in the general population (Choong et al., 2013).
Methods: We tested whether rs3746266 was associated with AIWG in our patient samples using Taqman(®) assay. We included 211 schizophrenia patients on antipsychotic treatment prospectively assessed for AIWG for up to 14 weeks. Mean weight change (%) from baseline was compared across genotypic groups using analysis of covariance (ANCOVA).
Results: The CRTC1 rs3746266 variant did not show significant association with antipsychotic-induced weight gain in our combined sample or in refined subsamples of patients of European or African ancestry or patients treated exclusively with clozapine or olanzapine (p=0.891 and 0.874 respectively).
Conclusions: Our analyses did not indicate a major role of this CRTC1 gene variant in AWIG. We are currently evaluating this marker in other samples as more research is warranted to elucidate its role on antipsychotic induced weight gain.

Board #8
Open Translational Science in Schizophrenia

Marsha Wilcox & Adam Savitz
Janssen

Background: Data from pharmaceutical clinical trials and NIH funded studies about schizophrenia have never been analyzed together before. The Open Translational Science in Schizophrenia (OPTICS) project is a new development in psychiatric pharmacogentics that is designed to be a true interdisciplinary approach to addressing fundamental questions about the treatment of patients with schizophrenia.
Objectives: Conduct a pilot project to demonstrate the value of an open-science approach using pharmaceutical clinical trial and federally-funded observational data to:
1. Advance efficacy and safety of medicines for schizophrenia;
2. Increase understanding of schizophrenia, including disease natural history, subtypes, and causes; and
3. Contribute to the development of analytic and design methods for disparate data types, including novel statistical methods and research designs.

Methods: Establish collections of Janssen's clinical trial (http://yoda.yale.edu/optics-trial-bundle) and genetic/genomic data about schizophrenia (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/collection.cgi?study_id=phs000887.v1.p1); invite qualified researchers to collaborate in the analyses of the data; collaborate with NCATS and the Harvard Catalyst to provide funding for researchers; meet to discuss results; publish results; evaluate the pilot.
Discussion: This is the first time data about the causes of the disorder and data from clinical trials of therapies will be available to researchers in one place. The ability to analyze these datasets together will enable researchers to address questions about the disease, therapies, and analytic methods in ways not possible before now.
The project was announced in June of this year (https://sites.google.com/site/opticsschizophrenia/). Members of the project's advisory board include Yale University School of Medicine, Rutgers University, Harvard T.H. Chan School of Public Health, the National Institute of Mental Health (Genomics Branch), and Janssen Pharmaceutical Research & Development.

Board #8 (continued)

Participant researchers will agree to meet the data access and use requirements of all data owners. They also must agree that any knowledge generated from this project (e.g., publications, models predicting outcome) will be dedicated to the public and will be free for everyone to use. One of the goals of the project is to encourage collaborations among industry and academia, including those that will exist outside traditional disciplines, such as econometrics and computer science.

Board #9
Efficacy and Side Effect of Therapeutic Olanzapine Involves Altered Methylation in Genes and Pathways Implicated in Psychosis

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Background: The complex aetiology of most mental disorders including psychosis involves gene-environment interactions via epigenetic mechanisms particularly DNA methylation. It explains most common features of such disorders including variable responses to antipsychotics. As it stands the mechanism of action of most antipsychotics is not fully understood, but needed for an effective and efficient treatment of such patients. This research deals with the effect of therapeutic equivalent treatment of olanzapine on genome-wide DNA methylation in a rat model *in vivo*.
Methods: Adult male Sprague-Dawley rats of 12 weeks of age (250 - 300g) were divided into two treatment groups with comparable means of weight. Treated rats received injections of olanzapine (Zyprexa, Lilly, IN, USA; 2.5 mg/kg, i.m.; n=8) and matched controls received vehicle (phosphate buffered saline (PBS); n=8). Rats were injected daily at the same time (1:30 pm and 3:00 pm) for 19 days. During this period, they were followed for anxiety and weight. They were sacrificed on day 20 and different tissues (cerebellum, hippocampus and liver) were dissected out. Genomic DNA isolated from such tissues was used to assess genome-wide DNA methylation using *MeDIP-Chip* analysis. All methylated DNA

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immunoprecipitation (*MeDIP*), sample labeling, hybridization, and processing were performed at Arraystar Inc. (Rockville, Maryland, USA). The identified gene promoters showing significant alterations to DNA methylation were further analyzed with ingenuity pathway analysis (Ingenuity System Inc, CA, USA).

Results: The results show that olanzapine causes changes in DNA methylation, most specific to the promoter region of specific genes. This response is tissue specific and involves a number of genes that are novel as well as those previously implicated in psychosis. Also, the genes affected by olanzapine-induced methylation changes have led to the identification of several pathways and networks significantly affected by DNA methylation in the cerebellum and hippocampus. These included the *Dopamine-DARPP32 feedback in cAMP signalling*, (*p*=1.65E-03), *Ephrin* receptor *signalling* (*p*=5.23E-04), *Gα12/13 Signalling* (*p*=9.2E-08) and *Wnt signalling* (*p*=0.01) pathways as contributors to psychosis that is based on its responsiveness to antipsychotics used in its treatment.

Discussion: The results show that olanzapine-induced DNA methylation changes are apparent on the promoter regions of a large number of genes. These include the dopamine receptor genes and cadherin/protocadherin genes. These changes directly affect a number of pathways. Interestingly, most pathways affected in the cerebellum and hippocampus are involved in psychosis and mental disorders. Further, changes in the liver affect metabolic defects that may contribute to the observed weight gain. Also, the known functions of affected genes suggest that the observed DNA methylation changes may underlie amelioration of symptoms as well as account for certain adverse effects including the metabolic syndrome. The results offer novel insight into the mechanisms of actions of olanzapine, in the understanding of therapeutic as well as side effects of antipsychotics.

Board #10
A Polygenic Risk Analysis for Antipsychotic Dosage Using Genome-wide Significant Markers for Schizophrenia

Nuwan Hettige, Christopher B. Cole, Vincenzo De Luca

Antipsychotic medications are commonly used to treat elderly patients with delirium, agitation and psychosis due to Alzheimer's disease, and schizophrenia. Schizophrenia is a debilitating mental health disorder that once diagnosed, remains throughout the lifetime. The first line of treatment for individuals with schizophrenia is to administer antipsychotic medication which aims to reduce the severity of psychotic symptoms, such as hallucinations and paranoia. As individuals with schizophrenia may be required to take antipsychotic medication for the duration of their life, antipsychotic dosage must be adjusted accordingly due to age-related neurobiological changes or symptom severity. The purpose of our study was to calculate polygenic risk scores for the risk alleles that reached genome-wide significance from the recent genome-wide association study by the Psychiatric GWAS Consortium for Schizophrenia. We hypothesized that a high risk score would potentially indicate incre! ased symptom severity and therefore require higher antipsychotic dosage. Polygenic risk scores were used to predict whether individuals with a higher score also require higher antipsychotic dosage. In our preliminary sample of 83 European Caucasian individuals, we found that the risk score was not significantly predictive of antipsychotic dosage. Incorporating the polygenic score in our model, however, better explained the variance in dosage compared to age and sex alone. The polygenic risk score may be a useful way of translating the knowledge acquired from GWAS to predict clinical outcomes and related endophenotypes.

Board #11
Gene Expression Analysis of Clozapine Treatment in Whole Blood of Patients with Psychosis

Rebecca N.S. Harrison, Robin M Murray, Lee Sang Hyuk, Jose Paya Cano, David Dempster, Charles Curtis, Danai Dima, Fiona Gaughran, Gerome Breen and Simone de Jong

Background: Clozapine is an atypical antipsychotic with a unique effect in treatment-resistant schizophrenia (TRS). We tested the effect of clozapine versus other drug treatments on peripheral blood gene expression in a sample of people with psychosis from the United Kingdom.
Methods: 186 baseline blood samples from individuals receiving treatment for established psychosis were analysed for gene expression on Illumina HumanHT-12.v4 BeadChips. After standard quality control procedures, 152 samples remained, including 55 from individuals receiving clozapine. Weighted Gene Correlation Network Analysis (WGCNA) was used to identify modules of co-expressed genes. The influence of mood-stabilisers, lithium carbonate/ lithium citrate and sodium valproate was studied to identify their possible roles as confounders. Confounders, identified through Principal Component Analysis, were corrected for in a linear model.
Results: Individuals receiving clozapine as their only antipsychotic (Clozapine monotherapy) demonstrated a nominal association with one module while no significant change in gene expression was found for lithium or valproate or other antipsychotics.
Conclusions: Overall, this study does not provide evidence that clozapine treatment evokes medium to large different gene expression patterns in human whole blood versus other antipsychotic treatments. This does not rule out the possibility of smaller effects as seen for other common antipsychotic treatments.

Board #12
Comprehensive Genetic Analysis Implicates Novel Mechanisms for Clozapine-associated Neutropenia

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Clozapine is uniquely effective in the management of treatment-resistant schizophrenia. Nonetheless its use in clinical practice is limited by the potential for a clinically important reduction of white blood cells during clozapine treatment. The causes of these clozapine induced blood disorders, in its severe form agranulocytosis, in its more benign precursor form neutropenia, are unknown, but a genetic contribution is widely expected. Seeking risk alleles for clozapine-associated neutropenia, we performed a genome-wide association study (GWAS), exome array single variant and gene-based analysis, and imputed classical-HLA alleles, in a sample of 66 clozapine-associated neutropenia cases and 5583 clozapine exposed, but neutropenia free controls. We then tested candidate-associated variants in a combined analysis with the recently published dataset of the Clozapine-Induced Agranulocytosis Consortium (CIAC). In the combined GWAS analyses, we identified a novel genome-wide

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significant association with clozapine-associated neutropenia at rs149104283 (OR=4.32, p=1.79x10-8) which is located between *SLCO1B3* and *SLCO1B7*, both of which members of a family of hepatic transporter genes. Other members of this family have been implicated in drug side effects, most prominently simvastatin-induced myopathy. In a gene-based test, we found evidence of cumulative effects of rare functional variants within *UBAP2* and *STARD9*. We also sought replication of a previously associated variant in *HLA-DQB1* by genotyping this polymorphism in 61 clozapine-associated neutropenia cases and 305 clozapine treated controls. We provide independent replication of this previously identified variant in *HLA-DQB1* (OR=31.5, P = 1.17 x 10^{-4}).

Board #13
CACNA1C Gene and Schizophrenia: A Case-control and Pharmacogenetic Study

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Founding: This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0003).
Aim: The present study aimed to explore whether 24 single nucleotide polymorphisms (SNPs) within the CACNA1C gene were associated with schizophrenia (SCZ) and antipsychotic response. **Methods**: A sample of 176 SCZ inpatients and 326 healthy controls of Korean ethnicity was collected for this purpose. Psychopathological status was evaluated at baseline and at discharge using the Positive and Negative Syndrome Scale (PANSS).
Results: In the case–control study, rs1006737 (P=0.05) and rs2239104 (P=0.03) were associated with SCZ. Further, the rs10848635–rs1016388–rs1006737 haplotype was also associated with SCZ

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(P=0.03, simulate P=0.02). In the pharmacogenetic analyses, we did not find any association among the investigated SNPs and improvement in the PANSS total score. However, rs723672 and rs1034936 were associated with improvement in the PANSS positive subscale (respectively, P=0.02 and 0.05), rs2283271 in the negative subscale (P=0.01), rs10848635 and rs1016388 in the general subscale (respectively, P=0.03 and 0.04), as well as the rs3819536–rs2238062 haplotype (global statistics, P=0.1; simulate P=0.04).
Conclusions: Our findings further support a role for the CACNA1C gene, particularly for the rs1006737, in SCZ [1]. Further, five SNPs were associated with improvement in PANSS subscales, suggesting a role for this gene in antipsychotic response as well. However, taking into account the limitations of the present study, further research is needed to confirm our findings.

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Board #14
Hot Genes in Schizophrenia: Case-control, Pharmacogenetics and Exploratory Analyses in Two Independent Samples

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Funding: This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0003).

We investigated the effects of genetic variants within PPP3CC, RORA, SP4, ST8SIA2 and ZNF804A genes in a Korean sample of 176 SCZ patients and 326 healthy controls and an Italian sample of 83 SCZ patients and 194 healthy controls. The PANSS was used to assess

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psychopathological severity and antipsychotic response (AR). Several clinical features were recorded in both samples. In the Korean sample RORA rs10438338 was associated with SCZ (p=0.03) as well as haplotype rs2282888-rs2237304-rs10272006-rs12673091 within SP4 gene (p=0.02). In the Italian sample 3 PPP3CC variants (rs11780915 p=0.006; rs10108011 p=0.01; rs2249098 p=0.0004), ZNF804A rs1344706 (p=0.02) and SP4 rs12673091 (p=0.02) were associated with SCZ. The haplotype rs11780915-rs10108011-rs2249098 within PPP3CC gene and the haplotype rs7603001-rs1344706 within ZNF804A gene were associated with SCZ as well (respectively p=0.03 and p=0.02). Further, several RORA variants were associated with AR (Korean sample: rs1871858 p=0.02; rs12900122 p=0.06, rs17204440 p=0.02, haplotype rs1020729-rs1871858 p=0.01; Italian sample: rs12900122 p=0.003). In the Italian sample also 2 SP4 variants (rs2282888 p=0.02; rs10272006 p=0.02) and ST8SIA2 rs4777989 (p=0.04) were associated with AR. Exploratory analyses suggested that: 1) PPP3CC, ST8SIA2 and SP4 genes may be implicated in the develop and severity of psychotic symptoms, 2) RORA gene may play a role in AR, particularly of negative symptomatology, as well as ZNF804A gene. Considering limitations linked to the sample size and candidate genes approach, our results further support a role for these gene in SCZ, as well as in AR. Analyses in well phenotyped samples could help researchers to refine the role of these genes for further, focused investigations.

Board #15
Immunogenetic Biomarkers of Clozapine Treatment Response

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Background: Clozapine (CLZ), the prototypical second-generation antipsychotic, is the most efficacious drug used in the treatment of schizophrenia, with superior clinical benefits among treatment-resistant subgroups. Nevertheless, CLZ response rates are considerably variable (30-60%), with inter-individual variation partly depending on genetic factors. CLZ has immunomodulatory properties which influence the expression of pro-inflammatory cytokines and may contribute to its treatment effects. Thus, we investigated whether polymorphisms across interleukin (IL)-1B, IL-2, and IL-6 genes are associated with CLZ treatment response.
Methods: Eighteen functional and tag single nucleotide polymorphisms (SNPs) across IL-1B, IL-2, and IL-6 were genotyped in 47 schizophrenia patients on CLZ treatment for ≤26 weeks. Tag SNPs ($r^2 \geq 0.8$, MAF>0.01) covered ~100% of the common genetic variation. SNPs were genotyped using Taqman® assays plated on OpenArray®. Mean Brief Psychotic Rating Scale (BPRS) score change (%) from baseline was compared across genotypic groups using ANCOVA. Dichotomized response status (responder/non-responder, ≥20% reduction in BPRS score) was tested using Pearson χ^2.
Results: No significant associations were found between IL-1B, IL-2, and IL-6 variants and CLZ treatment response ($p>0.05$) during ANCOVA and χ^2 analyses. However, IL-2 rs2069779 approached significance where patients homozygous for the G-allele experienced a greater reduction in BPRS score compared to heterozygotes (GG=-32.23±30.1% vs. GA=-13.12±22.5%, **p=0.091**). Similarly, carriers of the A-allele (AA+GA) for IL-1B rs16944 showed higher rates of non-response to CLZ compared to patients homozygous for the G-allele (68.8% vs.31.2%, **p=0.081**).
Conclusions: SNPs across IL-1B and IL-2 may have limited influence on CLZ response, however, further investigations in larger, independent samples are warranted.

Board #16
Structural Connectivity and Cortical Inhibition at the DLPFC Mediate the Association Between GAD1 and Working Memory Dysfunction Relevant to Schizophrenia

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γ-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the central nervous system modulating local neuronal circuitry, including noradrenergic, dopaminergic, and serotonergic neurons. GABAergic dysfunction has been implicated in the pathophysiology of schizophrenia, and in working memory impairment. We examined the influence of the functional rs3749034 variant in the glutamic acid decarboxylase 1 (GAD1) gene on brain structure, and working memory performance in schizophrenia patients and healthy controls (N=195). Using TMS-EEG, we subsequently examined the effect of rs3749034 on long-interval cortical inhibition (LICI), a neurophysiological marker of GABAergic inhibitory neurotransmission, in the DLPFC in an independent sample of schizophrenia patients and healthy controls (N=56). We found that the rs3749034 T-allele carrier risk group had lower voxel-wise white matter fractional anisotropy (FA) predominantly in the region (PFWE-corrected<0.05). Mixed-model regression revealed a significant effect on working memory performance across four performance measures (F1,182=11.5, p=8x10-4). FA in the frontal cortex was associated with digit-span performance. Voxel-wise mediation analysis revealed that the effect of the GAD1 risk variant on poorer digit-span performance statistically predicted the lower white matter FA (PFWE-corrected<0.05). Moreover, we found a prominent GAD1 genotype-by-diagnosis interaction on DLPFC LICI (F1,56=14.3, p=4.1x10-4). Our findings converge on genetic variation

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in the GAD1 gene predicting a susceptibility mechanism that affects white matter FA, GABAergic inhibitory neurotransmission in the DLPFC and working memory performance. Furthermore, via voxel-wise mediation analysis of FA and TMS-EEG intervention we provide convergent evidence for a potentially causal mechanism through which aberrant DLPFC GABA signaling may contribute to working memory dysfunction

Board #17
Examining the Role of Mitochondrial Variants in Antipsychotic-induced Weight Gain

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SCZ is a complex disorder characterized by psychosis and disturbed behaviour. There is increasing evidence from molecular pharmacology studies that antipsychotics such as clozapine and olanzapine modulate mitochondrial function, for example, inhibiting activity of the oxidative phosphorylation pathway. We have previously reported that the nuclear mitochondrial gene NDUFS1 is associated with antipsychotic-induced weight gain (AIWG) (Goncalves et al, 2014). Our objective here was to evaluate whether variants in the mitochondrial DNA play a role in AIWG. We have conducted sequencing analysis of mtDNA in 24 schizophrenia subjects thus far: those with the highest weight gain in our samples (N=12) versus those subjects with no weight gain (N=12). We have validated the sequencing protocol to work reliably on mtDNA, capturing all types of variation present in this genome, including common SNPs, small insertions/deletions, and heteroplasmy. We obtained more than 500x average sequence coverage per case and identified variants with high confidence (>98%). Association between each common mitochondrial SNP and AIWG was tested using logistic regression assuming an additive model in PLINK. We found 214 homoplasmic variants, in which 55% were transitions and 44% transversions.

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From the association analysis, 16 SNPs were found to be nominally significant with AIWG ($p<0.05$). There were no differences between the two groups in terms of number of heteroplasmic sites ($p=0.34$). Thus, despite modest sample size, mitochondrial DNA SNPs were suggestive to play a role in AIWG. We are currently increasing our sample size to 288 samples and replication in a larger sample is required.

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Board #18
Unique Phenotypic Characterizations in Relation to Copy Number Variants in a Toronto Schizophrenia Population

Venuja Sriretnakumar, Clement Zai, Malgorzata Maciukiewicz, Joyce So, James L. Kennedy

Increasing evidence supports the significance of copy number variants (CNVs) in the genetic contribution to psychiatric illnesses, particularly schizophrenia (SCZ). This study utilizes a robust approach to uncovering genetic variants within the heterogeneity of SCZ by delineating correlations between CNV data and extensive phenotypic data in SCZ patients.

Phenotypic and CNV data of 348 SCZ patients were collected from medical history records and Affymetrix SNP Array 6.0 assay, respectively. The number of autosomal, X-linked and total CNV counts were plotted against phenotypic characteristics in probands and proband's family history. Independent t-tests, Fischer's exact test, Pearson/Spearman correlations, and Bonferroni multiple testing corrections were performed among the various categories to identify significant associations.

The presence of head injury in probands is associated with the number of autosomal CNV duplications ($p=0.0449$) and deletions ($p=0.0490$). Suicide attempt in probands was also associated with the number of autosomal CNV duplications ($p=0.0088$), deletions ($p=0.0450$),

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the total number of CNVs (p=0.0274). Genetic associations of head injury and suicide attempt in probands did not reach statistical significance after correction for multiple testing. However, there are significant associations between suicide attempt in proband's family history and the number of autosomal CNV duplications (p=0.0017), deletions (p= 0.0016), and the total number of CNVs (p=0.0130). Trends were also seen between X-linked CNVs and age of onset of SCZ in probands; history of substance abuse in proband's family history; and digestive system disorders in probands. All X-linked associations did not survive sex correction.

These results suggest a strong association between CNV burden and specific phenotypic presentations in the SCZ patient population. This is compatible with the ever-increasing number of microdeletions and microduplications found to be associated with neurodevelopmental disorders, and our findings may contribute to expanding the neuropsychiatric phenotypes associated with these genetic variants. Sample size and power will be increased by genotyping the remaining individuals in this cohort to detect smaller effect sizes. Further analyses will be undertaken to define specific CNVs and genes contained within the implicated CNV regions to better characterize potential genetic effects on the phenotypic presentation of SCZ patients.

Board #19
Genome-wide Association Analysis to Predict Optimal Antipsychotic Dosage in Schizophrenia: A Pilot Study

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Background: In the last decade, several studies have investigated genetic polymorphisms of antipsychotic drug metabolizing enzymes and receptors. However, most studies focused on drug response and very few have investigated the genetic influence on antipsychotic dosage. The aim of the present study is to test the association between antipsychotic dosages at genome-wide level.
Methods: The current dosage of antipsychotic medications was collected from 79 schizophrenia patients. The dosage was standardized using three different methods: **chlorpromazine equivalent** (CPZe) according to Gardner et al. 2010, defined daily dose (DDD) according to the WHO (2010) and percentage of maximum dose according to the Canadian Compendium of Pharmaceuticals and Specialties (CPS) 2014. The patients were then genotyped using the Illumina HumanOmni2.5-8 BeadChip Kit. All markers were screened for significance using linear regression and the p-values were visualized using a Manhattan plot.
Results: The genome-wide analysis showed that the top SNPs associated with dosage variation were rs12546614 on chromosome 8 for CPZe, rs60994771 on chromosome 19 for DDD and rs4470690 on chromosome 4 for CPS. **However, there were no GWAS significant SNPs.**
Discussion: In this pilot sample, we found promising trends for pharmacodynamic targets associated with antipsychotic dosage. Therefore, studies combining large prescription databases may identify genetic predictors to adjust the dose of antipsychotic medication.

Board #20
Investigating SKA2 Genetic Variants and Response to Citalopram

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Background: Major Depressive Disorder (MDD) has a strong genetic component and is characterized by a number of physiological impairments, including diminished ability of the HPA axis to mediate stress response. The current process used to determine pharmacological treatments is markedly inefficient, with more than 50% of antidepressant treated patients failing to reach remission. Genetic and epigenetic variation in SKA2 (Spindle And Kinetochore Associated Complex Subunit 2) is implicated in mediating HPA axis function, and has recently been associated with suicidal behaviour. We hypothesized that genetic variation in SKA2 may play a role in predicting response to antidepressant medication.
Methods: 1471 Caucasian MDD patients (588 male, 883 female) were selected from the STAR*D sample. Change in HAMD-17 score was used to measure response to citalopram. ANCOVA was used to investigate the relationship between five single-nucleotide polymorphisms (SNPs) in SKA2 and percentage change in HAMD-17. Logistic regression was used to model the relationship between the SNPs according to response and remission status.
Results: None of the SNPs examined were significantly associated with percentage change in HAMD-17 scores, responder vs. non-responder status, or remission. Furthermore, no significant results were found when examining baseline score on the HAMD-17 suicidality item and the markers in SKA2.
Conclusions: These preliminary results suggest that SKA2 genetic variation may not be a significant predictor of therapeutic response to antidepressant medication in patients with MDD. Further work providing more extensive coverage of the SKA2 gene and incorporation of epigenetic information is currently underway.

Board #21
Cytokine Measurement in Patients With Obsessive-compulsive Disorder

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Previous studies examining cytokines levels in patients with obsessive-compulsive disorder (OCD) have shown inconsistent results, mainly due to confounding factors. Although the immune system has been clearly implicated in pathogenesis of at least some forms of OCD, the role of cytokine in OCD still has to be clarified. Cytokines abnormal profiles could be reflect early alterations related to the pathophysiology of OCD or to the disease state (i.g, severity of the symptoms, comorbidity and treatment response). The aims of this study were to evaluate the cytokine profiles (plasma levels of pro- and anti-inflammatory cytokines) in OCD patients in comparison to healthy controls and to investigate its association with clinical features of OCD, including OCD severity, presence of depressive or anxiety symptoms or tics, and treatment response (before and after treatment. Clinical and immunological evaluations were performed in 70 OCD patients and 101 healthy controls at baseline and 12 weeks later (after treatment in the OCD group). Plasma levels of the pro- and anti- inflammatory cytokines were assayed by glass chip-based-antibody microarrays. No significant differences were observed in cytokine levels between OCD patients and healthy controls, even

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when sample were split by gender. In addition, no association were found between cytokines levels and OCD severity, early-onset OCD, depressive or anxiety symptoms, or presence of tics. However, lower levels of IL1-β were associated with better treatment response, suggesting that IL1-β could represent a predictor of treatment response (state). Further studies are necessary to explore the association between cytokine profile and gene expression in OCD in addition to its role as preditor of treatment response.

Board #22
Genome-wide Association Study of Antidepressant Response: Involvement of the Inorganic Cation Transmembrane Transporter Activity Pathway

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Trial registration: Catholic Medical Center, Clinical Research Coordinator Center; approval number: HC10TISI0031.

Genome-wide association studies (GWAS) represent the current frontier in pharmacogenomics. Thousands of subjects of Caucasian ancestry have been included in previous GWAS investigating antidepressant response. GWAS focused on this phenotype are lacking in Asian populations.

A sample of 109 major depressive disorder (MDD) patients of Korean origin in antidepressant treatment was collected. Phenotypes were response and remission according to the Hamilton Rating Scale for Depression (HRSD). Genome-wide genotyping was performed using the Illumina Human Omni2.5-8 platform. The same phenotypes were used in the STAR*D level 1 (n=1677) for independent replication. In order to corroborate findings and increase the comparability

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between the two datasets, three levels of analysis (SNPs, genes and pathways) were carried out. Pathway analysis was performed using a functional enrichment analysis (Cytoscape GeneMania plugin: http://pages.genemania.org/plugin/) and enriched pathways were analyzed by a gene set enrichment analysis (a Fisher exact test was used to detect a different distribution of SNPs with $p<0.05$ and $p<0.01$ compared to a random matched pathway). 10e4 permutations were run.

Among the genes replicated across the two samples, *CACNA1A*, *CACNB2*, *CACNA1C*, *CACNB2*, *NBEA*, *NRG3*, *CTNNA3* appear promising. *HTR2A* and *SLC6A3* involvement in antidepressant response was confirmed. The inorganic cation transmembrane transporter activity pathway (GO:0022890) was associated with antidepressant efficacy in both samples after permutation ($p=2.9e-5$ in the Korean sample and $p=0.001$ in the STAR*D).

The present study pointed out the involvement of genes coding for subunits of L-type voltage-gated calcium channel and other innovative candidate genes in antidepressant efficacy across different ethnic groups.

Board #23
Neuroplasticity and Second Messenger Pathways in Antidepressant Efficacy: Pharmacogenetic Results from a Prospective Trial Investigating Treatment Resistance

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Genes belonging to neuroplasticity, monoamine, circadian rhythm, and transcription factor pathways have been previously investigated as modulators of antidepressant efficacy. The present study aimed to confirm and improve the knowledge about the pharmacogenetics of treatment-resistant depression (TRD).
220 patients with major depressive disorder who did not respond to a previous antidepressant during the current episode were included. Patients were treated with venlfaxine for 4-6 weeks and in case of non-response they were treated with escitalopram for 4-6 weeks. The phenotypes were response and remission to venlafaxine, non-response (TRD1) and non-remission (TRD2) to neither venlafaxine nor escitalopram. 53 tag SNPs in 16 genes belonging to the pathways of interest were tested using logistic regression models. KEGG pathways that included two or more of the genes associated with the phenotypes were investigated in the STAR*D genome-wide dataset (using a Fisher exact test to identify different distributions

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of SNPs with p<0.05 or p<0.01 between the index pathway and a random matched pathway).
Venlafaxine efficacy was affected by SNPs within the BDNF (rs6265 and rs11030104), HTR2A (rs17288723), PLA2G4A (rs6695515, rs10737276, rs10489407), ZNF804A (rs7603001), MAPK1 (rs6928), CREB1 (rs2254137) and CHL1 (rs1516340) genes. TRD1 and TRD2 were associated with the PLA2G4A, MAPK1 and CHL1 SNPs. No KEGG pathway was associated with the phenotypes, but the Ras signaling pathway showed a trend of significance (p=0.076).
Previously reported associations were confirmed, particularly in the BDNF, CHL1, CREB1, and ZNF804A genes. These genes play pivotal roles in synaptic plasticity, neural activity and connectivity, learning and memory.

Board #24
Genetic Study of Neuregulin 1 and Receptor Tyrosine-protein Kinase erbB-4 in Tardive Dyskinesia

Clement C. Zai, Arun K. Tiwari, Nabilah Chowdhury, Zeynep Yilmaz, Daniel J. Müller, Aristotle N. Voineskos, Steven G. Potkin, Jeffrey A. Lieberman, Herbert Y. Meltzer, Gary Remington, James L. Kennedy

Tardive dyskinesia (TD) is a motor disorder resulting from long-term treatment with antipsychotics, particularly typical neuroleptics. Its etiolopathophysiology is unclear, but the glutamate system has been suggested to play a role. More specifically, neuregulin 1 (NRG1) and its receptor Erbb4 are both schizophrenia candidate genes of which the gene expression could be altered by antipsychotics. Moreover, mice lacking NRG1 displayed incisor chattering. Thus, NRG1 and ERBB4 are interesting candidates for genetic studies of TD.
We analyzed single-nucleotide polymorphisms in NRG1 and ERBB4 genes in our schizophrenia sample of European ancestry (N=187). Analysis of TD occurrence showed that the C allele of the ERBB4 marker rs839523 was over-represented in schizophrenia patients with TD (OR=2.71; 95% confidence interval: 1.48-4.95). Patients carrying the rs839523 CC genotype had higher total AIMS scores than carriers of the other genotypes, after including age as a covariate (p=0.016). Our results suggest that ERBB4 plays a role in TD. Future work include testing additional NRG1 and ERBB4 markers, as well as gene-gene interaction analysis.

Board #25
Genetic Markers of Antidepressant Response in a Cross-cultural Sample of Patients with Obsessive-compulsive and Related Disorders

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Antidepressant medications are first-line pharmacological treatment for obsessive-compulsive and related disorders. However, approximately 50% of patients show poor/minimal response to these medications. We aimed to investigate the genetics of antidepressant response in obsessive-compulsive disorder (OCD) and body dysmorphic disorder (BDD) patients. We examined two OCD samples and one BDD sample. In the 222-Canadian OCD sample, we investigated 32 SNPs across 14 genes and their regulatory regions with antidepressant response using a custom-made 32-SNP QuantStudio Flex Real-Time PCR System Chip. Individuals were grouped into responders and non-responders using the Clinical Global Impression – Improvement (CGI-I) scale. Pearson χ^2 test was performed to detect differences in the number of responders versus non-responders across genotype groups. For the 74-Brazilian OCD sample, 45 SNPs across 18 genes were genotyped. Change in pre- and post-treatment Yale-Brown Obsessive-Compulsive Scale scores after completing an antidepressant trial were compared between genotype distributions. For the 35-USA BDD patients, we genotyped 10 SNPs across nine genes and response was determined using CGI-I. For the Canadian sample, interesting associations ($P<0.05$) were detected for the serotonin genes, *HTR2A* and *HTR1B* in antidepressant response. For the Brazilian sample, significant associations were detected for a gabaergic system gene, *GABRA3* and antidepressant response. For BDD, we did not detect any

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significant associations in any of the tested SNPs. The serotonergic and gabaergic system genes may be clinically useful in predicting treatment resistance versus response in patients with OCD across different ethnic groups. Future study with larger sample size is required to replicate these findings.

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Board #26
Meta-analysis of the Serotonin Transporter Promoter Variant (5-HTTLPR) in Relation to Adverse Environment and Antisocial Behavior: Evidence for a Gene-environment Interaction Effect

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Several studies have suggested an association between antisocial, aggressive and delinquent behavior and the short variant of the serotonin transporter gene polymorphism (5-HTTLPR). However, genome wide and candidate gene studies in humans have not convincingly shown a significant association between these behaviors and 5-HTTLPR. Nevertheless, several individual human

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studies have reported a significant environmental interaction with 5-HTTLPR, followed by replications and non-replications. We therefore performed a meta-analysis to test for the robustness of the potential interaction effect of the 'long-short' variant of the 5-HTTLPR genotype and environmental adversities, on antisocial behavior. Eight studies, comprising 11 independent samples, totaling 7565 subjects were included in the meta-analysis. Our results show a significant negative effect of the 'short' variant of the 5-HTTLPR genotype on antisocial behavior, in the presence of environmental adversities. These findings suggest a potential biosocial mechanism influencing the etiology of antisocial behavior. Future studies should extend to genome-wide genetic risk scores and the inclusion of covariate interaction terms is warranted.

Board #27
Epigenetic Changes in a Rodent Tic Model After Striatal 6-OH-Dopamine Lesion and L-DOPA Treatment

Luca Pagliaroli, Ester Nespoli, Borbala Veto, Piroska Devay, Pal Szabo, Bastian Hengerer, Csaba Barta and Tamas Aranyi

Introduction: Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by multiple motor tics and at least one vocal tic. The cause of TS remains elusive but dopamine (DA) appears to have a central role through the nigrostriatal pathway.
The aim of this project is to investigate epigenetic changes in an animal tic model due to L-DOPA treatment.
Methods: Animal Model: Juvenile male Wistar rats received unilateral injections of 6-hydroxydopamine in the medial forebrain bundle. This results in a degeneration of nigrostriatal neurons. Chronic application of L-dopa after the lesion leads to development of motor tics as a consequence of the striatal hypersensitivity to DA. This is a putative pathological mechanism of TS and the model is obtained by prior deprivation of the neurotransmitter. Lesioned and un-lesioned sides of striatum, cerebellum, prefrontal cortex and hippocampus have been collected for epigenetic analysis. DNA methylation:
5methyl-Cytosine (mC) and 5-hydroxy-methyl-cytosine (5hmC) analysis was performed by LC-MS/MS.

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Regional methylation patterns of the most CpG rich regions of the genome were screened by reduced representation bisulphite sequencing (RRBS). Histone Modifications: Chromatin immunoprecipitation (ChIP) has been performed to unravel chromatin activity by 4 different antibodies.
Results: We didn't detect global DNA methylation changes by LC-MS/MS. RRBS identified differentially methylated regions across the genome between lesioned and control sides. After setting up ChIP protocol sequencing of the samples has been performed and the bioinformatic analysis identified active and inactive genomic regions in lesioned and contralateral sides.
This work is supported by EU funding under FP7-PEOPLE-2012-ITN, TS-EUROTRAIN, GA 316978

Board #28
Systems Genetics Analysis of Antidepressant Treatment

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Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants used for treatment of major depressive disorder (MDD). The response to SSRI treatment varies among individuals, which primarily is thought to stem from genetic factors. Genome-wide association studies (GWAS) have attempted to identify predictive genetic markers for SSRI efficacy and tolerability with limited success, probably reflecting the need for larger sample sizes, which is difficult to achieve in pharmacogenetic studies. Thus, other methods are needed to identify genetic components, which can lead to stratification of patients and personalised treatment of MDD. Systems genetics is a novel approach for analysis of GWAS that incorporates biological information.
Previously, a GWAS has been performed on 499 SSRI treated MDD patients (1). MDD symptom severity was scored at baseline, after 4 and 8 weeks. Here we present systems genetics analysis of these

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GWAS data. Based on their pairwise correlations we selected the most connected SNPs and clustered them in modules. The genes tagged by the selected SNPs were analysed to uncover their involvement in pathways and tissue expression. The following tissues were enriched: nervous-, digestive-, cardiovascular systems, genitalia, bones and joints. Enriched pathways included those of motor skills and limb coordination, carbohydrate transportation and metabolism, behaviour, axon morphology, catecholamine transport and metabolism, acetylcholine receptor function, and vascular endothelial regulation. We suggest that the interpersonal variability of the SSRI treatment response is influenced by genes in the above mentioned pathways, and that the key to personalising SSRI treatment should be found within these genes.

1. Ji Y, Biernacka JM, Hebbring S, Chai Y, Jenkins GD, Batzler A, et al. Pharmacogenomics of selective serotonin reuptake inhibitor treatment for major depressive disorder: genome-wide associations and functional genomics. Pharmacogenomics J. Oktober 2013;13(5):456–63.

Board #29
GWAS-based Machine Learning Approach to Predict Duloxetine Response in Major Depressive Disorder

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Background: Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders, which affects up to 350 million people worldwide. Moderate to severe forms of MDD are typically treated through pharmacotherapy with antidepressant drugs, including serotonin-norepinephrine reuptake inhibitors (SNRI) such as duloxetine. However, there is a large inter-individual variability

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with respect to response and side effects with duloxetine and thus predictive models may help clinicians avoid current 'trial-and-error' approaches. Machine learning (ML) models may be used to predict outcome to duloxetine by incorporating gene-variants derived from a GWAS data set implicated in response.

Methods: In the first step, we conducted a GWAS to identify potentially significant variants related to duloxetine response from clinical trials made available through H. Lundbeck A/S. Standard quality control steps were applied to control for optimal sample integrity in a SNP data set. In order to enrich genome-wide coverage, we imputed additional variants using 1000 Genomes as reference. We defined response as 50% decrease in MADRS score and conducted association studies using logistic regression models corrected for the study duration and cohort using PLINK. Only the top variants ($p<10^{-5}$) were entered in our ML analyses. To extract the most promising predictors we applied a Lasso regression (glmnet package in R) and included variables with non-zero coefficients. In the next step, we utilized classification-regression trees (CRT) and support vector machines (SVM) to construct candidate models. Ten-fold, repeated cross-validation was used to obtain the best possible model. In the last step, we compared the classifier's performance by investigating the accuracy, specificity, sensitivity, and error rate. The initial dataset was randomly divided into train and test set (70% and 30% respectively) and the whole procedure was repeated 200 times. Training, testing and performance analyses were performed with the R package caret.

Results: The Lasso regression selected 9 gene variants (imputed and genotyped). CRT models were characterized by 63.3 % accuracy, whereas the SVM models had an accuracy of 61.75%. CRT resulted in higher sensitivity (81.15%, SVM=76.18%, proportion of correctly predicted responders), lower error rate (36.68%, SVM=38.25%) and specificity (20%, SVM=26.9%). In addition, we also investigated our original, pre-imputation dataset. The total number of6 potential predictors were included, but this resulted in using higher Lasso coefficients. These overall models performed better. Average accuracy equaled 71.73% for CRT and 78.57% for SVM. Specificity remained low for both classifiers 40.9% (CRT) and 51.92% (SVM); while the error rate dropped below 30%: CRT=28.26% and SVM=21.43%. When we added study duration and age as non-genetic predictors, the error rate dropped down to 20% for SVM and increased for

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CRT (29.69%). Although the accuracy reached 80.29% for SVM, the specificity remained relatively low (64.28%).
Discussion: We explored if GWAS top-hits may predict duloxetine response status using ML models. Our models managed to capture a fraction of responders (sensitivity), but failed to filter out non-responders (specificity). Although ~80% of accuracy and sensitivity seemed promising, further refinement of our model will be required to achieve clinically useful predictive models. Inclusion of additional non-genetic parameters (e.g. side-effects, plasma levels) may help improve our results.

Board #30
Neural-derived Plasma Exosomal MiRNAs as Promising Novel Biomarkers for Suicidality

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Background: The lack of biological markers for psychiatric illnesses has problematic for many years, hindering diagnosis and treatment. Recently, Dwivedi,et al have produced compelling evidence from animal and cadaver studies that an array of miRNAs may point to a state-specific finding of significance in suicidal persons. The recent success of measuring neutrally-derived exosomal miRNA from peripheral blood suggests potential for a novel clinically-available biomarker.
Methods: Our study will compare neural-derived exosomal miRNA from peripheral blood in 4 groups of participants (N=60 per group): Major Depressive Disorder with suicidality, PTSD with suicidality, MDD without suicidality, and PTSD without suicidality. The participants will be enrolled at the Birmingham VAMC and will complete assessments including MINI (diagnostic assessment), BSSI (suicidality), CAPS (PTSD subscales), BDHI (hostility), BGHI (aggression) in addition to blood draw. Participant use of fluoroquinolones will be collected as these medications may affect the levels of miRNA. Peripheral blood and miRNA will be studied in the laboratory of Yogesh Dwivedi, PhD at the University of Alabama at Birmingham.
Results: The Birmingham VAMC Institutional Review Board has approved the study and enrollment is anticipated to begin in August 2015.

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Discussion: This is the first large study of peripheral miRNAs in PTSD suicidal participants and it is expected to reveal new pathwa! ys in the search for biomarkers in psychiatric patients.

Board #31
Combining Clinical and Genetic Variables to Predict Antidepressant Treatment Response: A Machine Learning Approach

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The identification of predictors of response to antidepressant drugs has proved difficult. Several studies suggested that biomarkers should be added to clinical predictors to reach a clinically significant outcome prediction.
In this study, we used machine learning-based models to test the predictive ability of a combination of Genome Wide Single Nucleotide Polymorphisms (SNPs), transcriptomic and clinical variables (a total of 525015 predictors) to predict antidepressant treatment response in a total of 430 patients with unipolar depression from the Genome-based Therapeutic Drugs for Depression pharmacogenetic study (GENDEP). Participants were randomly allocated to a serotonin-reuptake-inhibiting or a norepinephrine-reuptake-inhibiting antidepressant drug-arm and followed for 12 weeks. The primary

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outcomes were the percentage change in depression severity and remission status at the final visit.
A model including 14 variables (4 clinical, 10 SNPs) explained a 3.76% of the variance of the percentage of symptoms improvement in the whole sample. By drug, a model including 20 SNPs showed a percentage of explained outcome variance of 16.03% in the nortriptyline-treated group and of 15.36% among patients in the escitalopram arm using 17 variables (5 clinical, 12 SNPs). Accuracy for remission prediction was 0.68 (pval=0.026), 0.79 (pval<0.001) and 0.70 (pval=0.004) for whole, nortriptyline and escitalopram samples respectively.
Our results suggest that clinical and genetic variables in combination can predict response to antidepressants with clinically meaningful accuracy. Prediction was mostly drug-specific suggesting a potential for individualized indications for antidepressant drugs. This work provides a basis that can be used to test the added benefits of more intensive measurements.

Board #32
Investigating Associations Between IL-1beta, IL-2, IL6, TSPO and BDNF Variants and Response to Duloxetine or Placebo Treatment in Patients with Major Depression

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Background: Major depressive disorder (MDD) is a prevalent psychiatric disorder treated with antidepressant medication such as duloxetine. In addition, placebo treatments have been shown to improve depressive symptoms in a subgroup of patients. This study examined the role of genetic variation of inflammatory markers (IL-1beta, IL-2, IL6, TSPO) including brain-derived-neurotrophic factor (BDNF) in response to duloxetine and placebo.
Methods: Twenty functional and tag single nucleotide polymorphisms (SNPs) across IL-1beta, IL-2, IL-6, TSPO and BDNF were genotyped in 215 patients receiving duloxetine and 235 patients receiving placebo for 6 weeks. Samples were obtained through a partnership between the Canadian Biomarker Integration Network for Depression (CAN-BIND) and Lundbeck. Interleukin tag SNPs ($r2 \geq 0.8$, MAF > 0.05) covered ~100% of the common genetic variation. MADRS score changes (%) from baseline to endpoint were used as dependent variables in ANCOVAs.
Results: Two SNPs in the IL-6 gene were associated with response to duloxetine after 6 weeks of treatment ($p < 0.05$). One of the IL-6 SNPs was also significantly associated with response to placebo after 6 weeks. When dichotomizing response into response vs. non-response defined by at least 50% of reduction of MADRS scores, markers of IL-6 were also found to be associated with response to duloxetine, but not placebo.
Conclusions: Therefore, SNPs across IL-6 may play a role in response to duloxetine and placebo, which warrants further investigation.

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Board #35
Calcium Signaling Genes Associated with Bipolar Disorder in the Latino Population

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Bipolar disorder (BD) comprises a group of episodic mood disorders characterized by recurrent, sustained periods of depressed or expansive/irritable mood. The cause of BD is unknown; however, epidemiologic evidence from family and twin studies demonstrates a high heritability (60-85%). The progress in gene discovery using SNP genotyping technology and GWAS has been slow with few satisfactory replications. Interactions between genes on specific biological pathway could partially explain the difficulties of one-dimensional approaches to identify genetic basis for BD and other complex diseases. Increasing attention is being focused on the complex genetics and the signaling pathways implicated in the pathophysiology of the disease. Compelling evidence implicates altered signal transduction in the pathophysiology of BD. Among the biological signals, alterations of intracellular calcium (Ca^{2+}) homeostasis (ICH) is considered the most reproducible cellular abnormality in BD. Therefore, 140 single nucleotide polymorphisms (SNPs) in the 19 calcium-related genes were chosen to be genotyped in 363 cases and 551 controls in an initial sample followed by a replication study in additional 616 cases and 681 controls from the Latino population. To increase density of markers, imputing genotypes with a suitable reference population and known LD pattern with typed markers selected from the HapMap were used. Untyped markers were imputed using the MACH1.0. After the quality control, logistic regression analysis of disease and sub-phenotypes (e.g., age of onset) as a binary trait (adjusted for age and sex) was then performed using the PLINK (Purcell et al 2007) and SNP and Variation Suite 7 (SVS7, Golden Helix, Inc.).

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We identified a number of SNPs in three genes (CREB1, CACNA1B and CALM1) in the small sample and two genes (MST1R and locus close to CREB1) strongly associated with BD after the Bonferroni correction. Only one gene/locus was detected by two sample sets, which again demonstrates the phenotypic and genotypic heterogeneity in BD. This is the first report of the common variants influencing BD using a comprehensive pathway analysis in two independent samples in the Latino population. These results also provide further evidence of calcium signaling involved in BD development. However, additional studies with a large sample are needed to confirm the current findings and future functional study is required to examine underlying mechanisms of these disease-associated genes.

Board #36
Duration of Therapy and Years of Illness Before Lithium Treatment Have Opposite Effects on Leukocyte Telomere Length in Bipolar Disorder Patients

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Several studies reported premature cell senescence in bipolar disorder (BD), while lithium treatment has been suggested to have a protective effect against telomere shortening. We sought to investigate the correlation between leukocyte telomere length (LTL) and long-term lithium treatment in a sample of 200 BD patients. LTL was measured using SYBR Green quantitative real-time PCR (qRT-PCR). In order to address some of the limitations of the qRT-PCR technique, new blood samples were obtained from a subset of 8 patients and telomere length was measured using both qRT-PCR and quantitative fluorescence in situ hybridization (Q-FISH).
LTL correlated negatively with age (P=0.0002). Partial correlation test corrected for age showed that LTL correlated positively with lithium treatment duration in patients with more than 24 months of treatment (n=150, p=0.037) and negatively with the number of years of illness before the start of lithium treatment (p=0.046). When the two variables were considered together in the model, correlation between LTL and lithium treatment was not significant (p=0.1). In the subset of 8 patients there was a significant correlation between measurement of telomere length with real-time PCR and Q-FISH (p = 0.01).
Our data support previous findings showing that long-term lithium treatment has a protective effect against telomere shortening in BD patients. Our results also suggest for the first time that a high number of years of illness before the start of lithium treatment could have a negative impact on LTL and could antagonize the protective effect of lithium treatment.

Board #37
Multinomial Regressions to Identify More Homogeneous Phenotypes in Obsessive-compulsive Disorder

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Further improvement in refining the OCD phenotype is required in order to advance genetics research in this field. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) has been used with the objective to describe five individual symptom dimensions and their respective severity in patients with OCD, plus one miscellaneous dimension comprising symptoms of the OCD-related conditions. Our main objectives are 1. To build an algorithm to compare the DY-BOCS with the Y-BOCS, in order to rewrite the DY-BOCS data in the same format of an existing Y-BOCS data set; 2. To propose a multinomial logistic regression to model and predict the phenotype (i.e., the most severe symptom dimension among the five homogeneous dimensions of the DY-BOCS) in a subject who has only Y-BOCS data; 3. To validate this model in different samples with data collected with both the Y-BOCS and DY-BOCS interviews. First, we tested the model using the "leave-one-out" cross validation in a sample of! 917 subjects, and used the fitted models to predict the response to the left-out subject. Data obtained from the YBOCS data of 642 subjects were validated in 275 subjects with data from both the Y-BOCS and the DY-BOCS. The model's goodness of fit, accepting a deviation of up to three points in the predicted DY-BOCS score, varied between 80% (symmetry/order) and 88% (hoarding dimension). This statistical procedure may allow for the extraction of dimensional severity ratings from existing Y-BOCS severity scores for use as a more refined phenotype in genetic studies.

Board #38
Dopaminergic Polymorphisms in Methadone and Suboxone Replacement Therapy of Heroin Dependent Patients

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Heroin dependence is a debilitating psychiatric disorder with a complex genetic background. Given dopamine's role in reward mechanisms, this pharmacogenetic study aims to better understand the genetic contribution to the outcome of methadone maintenance therapy (MMT) and suboxone maintenance therapy (SMT) of heroin dependent patients by the analysis of dopaminergic polymorphisms. We studied 7 SNPs and 4 VNTRs in the following dopaminergic genes. Dopamine D4 receptor gene: exon3 VNTR, rs1800955 (-521C/T), rs747302 (-616C/G) and rs936462 (-615A/G) SNPs and the 120bp duplication. Dopamin transporter: 3'UTR and intron8 VNTRs. Dopamine D2 receptor and ANKK1 genes: rs1800497 (TaqI A), rs1079597 (TaqI B) and rs1800498 (TaqI D). A total of 241 Hungarian heroin dependent patients (171 on MMT and 70 on SMT) were enrolled in the study and phenotypically characterized by psychological questionnaires and clinical data. Patients were grouped according to their treatment response. Our pharmacogenetic findings were further validated by a multivariate analysis of associations using Bayesian networks in Bayesian multilevel analysis.
Significant genetic effects regarding subtitution treatment response were observed in case of certain genotypes of the dopamine transporter gene intron8 VNTR (p=0.048) and the dopamine D4 receptor gene 120bp duplication (p=0.038). These results were also confirmed by the multivariate analysis. These findings might prove useful in the individualized choice of different addiction treatment modalities including substitution therapy for heroin dependent patients. This may enable clinicians to optimize therapeutic decision making and reduce economic burden on the healthcare system due to unsuccessful treatment cycles.
Study was funded by National Grant: OTKA F-46788

Board #39
Identification of Rare Disruptive Variants in Voltage-gated Channel Genes (CACNA1C, CACNA1D, CACNA1S, CACNA1I) in Japanese Samples of Schizophrenia and Autism Spectrum Disorder Using Ion Torrent PGM Platform

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Several large-scale whole exome sequencing studies in schizophrenia (SCZ) and autism spectrum disorder (ASD) identified rare variants with modest or strong effect size as genetic risk factors. Dysregulation of cellular calcium homeostasis might be involved in SCZ and ASD pathogenesis, and genes coding for L-type voltage-gated calcium channel (VDCC) subunits Cav1.1 (CACNA1S), Cav1.2 (CACNA1C), Cav1.3 (CACNA1D) and T-type VDCC subunit Cav3.3 (CACNA1I) were recently identified as risk loci for psychiatric disorders. We investigated rare mutations with possibly damaging effects in those genes in Japanese sample of SCZ and ASD.
We prioritized four candidate genes (CACNA1C, CACNA1D, CACNA1S, CACNA1I) for psychiatric disorders in subset of VDCC genes based on genome-wide association studies, exome sequencing and functional genomic studies. Then, mutation screening of exon regions of those 4 genes using Ion Torrent Personal Genome Machine (PGM) was performed in a Japanese sample of 370 SCZ patients and 192 ASD patients. Our AmpliSeq custom panel allowed us to cover 96.84% of the targeted sequences. Average coverage of depth in the target region was ~200, and ~80% of sequenced region was covered over 100x coverage. Variant call and annotation were performed with Torrent Suite 4.4 and Ingenuity Variant Analysis. Variant filtering were applied to identify those that were not registered in dbSNP database or have a minor allele frequency of less than 1% in East-Asian samples from the Exome Sequencing Project and 1000 Genomes, and are damaging non-synonymous, splicing site single nucleotide variants (SNVs) ! or small insertion and deletion predicted by in-silico analyses. All of those filtered mutations were

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confirmed by Sanger method. If parental samples were available, segregation analysis were employed for measuring the inheritance pattern. Under our filter, we discovered 1 nonsense SNV (p.C1471* in CACNA1D), 1 in-frame deletion (p.E1675del in CACNA1D), 2 de novo SNVs (p.A36V in CACNA1C, p.V947I in CACNA1S), 22 missense SNVs (list in poster) that are categorized as damaging by at least two different in-silico tools.
Our analysis investigated several rare and possibly damaging variants on the risk for SCZ and ASD in VDCC genes, especially within L-type VDCC genes. Ongoing work includes (1) genotyping of selected rare variants in additional cohorts and rare-variant association analysis (2) further functional assessment of possible disease-causing variants.

Board #40
A Protocadherin Gene Cluster Regulatory Variant is Associated with Nicotine Withdrawal and the Urge to Smoke

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Tobacco smoking is a persistent global public health problem responsible for over five million deaths annually. Nicotine withdrawal can make smoking abstinence difficult and prolong the harm caused by smoking. To investigate the molecular basis for this phenomenon we conducted a genomewide association study of DSM-IV nicotine withdrawal criteria in a sample of African American (AA) and European American (EA) smokers. Based on an AA+EA sample meta-analysis (n=8021) three highly correlated SNPs in the protocadherin (PCDH) -α, -β and -γ gene cluster on chromosome 5 were associated with nicotine withdrawal ($p<5x10^{-8}$). We studied one SNP, rs31746, in an independent sample of smokers who participated in an

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intravenous nicotine infusion study that followed overnight smoking abstinence. Subjects with the withdrawal risk allele experienced greater alleviation of their smoking urges following nicotine infusion. Prior work has shown that the expression of PCDH-α, -β and -γ! genes in neurons is tightly controlled. We found that rs31746 mapped to a long-range neuron-specific enhancer element shown previously to regulate PCDH-α, -β and -γ gene expression. Using BrainCloud (a previously developed mRNA expression resource) we identified a robust and specific association between rs31746 and PCDH-β8 mRNA expression in frontal cortex tissue ($p<1x10^{-5}$). We conclude that PCDH-α, -β and -γ gene cluster regulatory variation influences nicotine withdrawal and the urge to smoke. Further studies on the PCDH-α, -β and -γ genes are warranted given that understanding and potentially alleviating nicotine withdrawal could improve smoking cessation treatment and reduce the harm caused by tobacco smoking

Board #41
CYP2D6 Impaired Metabolizer Status May Protect Against Neurotoxic Effects of Methamphetamine Use

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Cognitive dysfunction is a common sequela of methamphetamine (MA) use disorder use; however, individual susceptibility is highly variable and the mechanism of degeneration is largely unknown. Common inactivating polymorphisms in the CYP2D6 enzyme appear to protect against cognitive impairment, perhaps due to the reduced exposure to toxic metabolic byproducts. To evaluate this hypothesis, we examined whether extensive metabolizers (EMs) relative to intermediate/poor metabolizers (IM/PMs) display other markers of neurotoxicity, differences in cerebral gray matter volume and white matter integrity. After 5 days of abstinence, a total of 86 MA-dependent subjects (60 EMs and 26 IM/PMs) were administered a comprehensive neurocognitive battery, provided a blood sample for genotyping, and received a 1.5 T structural MRI scan to capture structural differences between EMs and IM/PMs. EMs

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had a significantly slower go reaction time on the stop signal task than IM/PMs (p=0.048); however! , the two groups did not differ in stop signal reaction time. On the Wisconsin Card Sort Test, EMs had a higher percentage of perseverative errors (p=0.017). In whole brain analyses, relative to IM/PMs, EMs showed less gray matter volume in regions of the right cingulate and paracingulate gyri at uncorrected thresholds ($p < .001$). These data support the hypothesis that EMs are more vulnerable to methamphetamine-induced neurotoxic effects than IM/PMs, possibly because byproducts of MA metabolism are more toxic than the parent compound. CYP2D6 IM/PM status may therefore be a protective factor against cognitive dysfunction in the context of MA use. Knowledge of CYP2D6 genotype could be used to advise patient prognosis and inform treatment approaches, and even suggests possible protective treatments (CYP2D6 inhibitors) for future study.

This study was supported by NIDA 1R21DA034928-01 (Dean) and NIMH K23 MH094613-01 (Nurmi).

Board #42

Candidate Gene Study of Methamphetamine Use Frequency among Methamphetamine Dependent Hispanic and Non-Hispanic Whites

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Although stimulant dependence is highly heritable, few studies have examined genetic influences on methamphetamine dependence. We performed a candidate gene study of 52 SNPs and methamphetamine use frequency among 265 methamphetamine dependent Hispanic and Non-Hispanic White participants of several methamphetamine clinical trials in Los Angeles. Male sex ($p = 1.09 \times 10^{-5}$) and increasing Native America ancestry ($p = 0.0097$) assessed via ancestry informative markers were significantly associated with lower methamphetamine use frequency. One SNP, rs7591784 was significantly associated with

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methamphetamine use frequency following Bonferroni correction ($p < 0.001$) in males but not females. SNP rs7591784 is in a linkage disequilibrium block with rs2952768 which was previously found to be associated with greater postoperative opioid use in a GWAS and to influence expression of the transcription factor *CREB1,* suggesting that rs7591784 may effect methamphetamine use via epigenetic effects of altered*CREB1* expression. Future studies should attempt to replicate this finding and further explore potential biologic and psychosocial reasons for differential methamphetamine use frequency by sex and ethnicity.

Board #43
CNR1 and FAAH Variation and Affective States Induced by Marijuana Smoking

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Background: Studies suggest that the endocannabinoid system impacts cannabis use and dependence, as well as positive and negative affect. Further, variation in the cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH) genes is associated with cannabis use and problems and mood-related disorders. The current study examined moderation of the acute effects of marijuana on five mood states by variation within CNR1 and FAAH genes.
Methods: In a 2 X 2, expectancy (told delta-9-tetrahydrocannabinol (THC) vs. told no THC) by drug administration (smoked marijuana with 2.8% THC vs. placebo) between-subjects design, we examined the pharmacologic effect of marijuana on changes in negative and positive affect (measured by the POMS) with 135 weekly marijuana smokers. Diplotype scores for CNR1 and FAAH were determined using phased haplotypes. Linear models predicting follow-up POMS-subscales (Vigor-Activity, Tension-Anxiety, and Confusion-Bewilderment) with the drug, expectancy, and haplotype effects were fitted in SAS.
Results: Acute marijuana administration increased levels of tension-anxiety and confusion-bewilderment. Significant drug x genotype/haplotype and expectancy x genotype/haplotype interaction effects were observed for some but not all mood states.

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Discussion: These findings support the role of variation in CNR1 and FAAH genes in some but not all affective responses caused by acute marijuana administration and the expectancy of the effects of marijuana.
Disclosures: Funding for this study was provided by AA021113 (Palmer) and DA021403 (Metrik). NIAAA and NIDA had no role in the study design, collection, analysis, or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication

Board #44
Pharmacogenomic Influences on Cardiovascular Tolerability of ADHD Treatments

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Common side effects of standard attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy include changes in cardiovascular (CV) profiles, complicating treatment and representing a source of serious adverse events. Individual genetic background may help explain the variability in these side effects, facilitating the identification of those at risk and safe clinical treatment matching. We captured complete common variation across drug target and signaling pathways to examine genetic association with CV measures during common ADHD treatments in the NIMH TRECC sample of 202 children. Stimulant (dexmethylphenidate), α2 agonist (guanfacine), and combination treatments were associated with short-term CV changes that normalize over time. Combination treatment was well-tolerated and may alleviate many of the CV side effects of either monotherapy. A rare genetic variant in *CNR1* was associated with extreme diastolic blood pressure (BP) decrease on guanfacine ($p=4.0 \times 10^{-6}$), while variants in *CHRNA7* and *SLC6A4* predicted large systolic BP increases with dexmethylphenidate ($p=1.9 \times 10^{-5}$). Two independent variants in *CHRNA7* and a rare allele

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of *SLC6A2* predicted heart rate elevation on combination treatment ($p<0.0005$). Replication and cross-disorder validation of these findings was performed in two independent samples of children with autism spectrum disorder treated with methylphenidate and guanfacine respectively. Genetic background appears to influence differential CV response to treatment and suggests that genetically informed treatment may help prevent adverse effects by identification of individual risk. Our finding at the norepinephrine transporter replicates a prior published result; other findings are novel. Additionally, a genomewide screen is in progress and may reveal additional underlying targets not anticipated in candidate analyses.

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Board #45
Functional Analysis of the Autism and Intellectual Disability Gene PTCHD1 Reveals Hedgehog Receptor-like Functions and PDZ-binding Domain-specific Regulation of CNTNAP1 and NLGN1

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This study is focused on investigating the complex functional aspects of a recently identified gene -- PTCHD1, and how its disruption leads to Autism Spectrum Disorder and/or Intellectual Disability. Sonic hedgehog (Shh) signaling plays a pivotal role in the pattern formation of many embryonic tissues and also in homeostasis and regeneration of adult tissues. PTCHD1 shows sequence homology to the Shh receptors PTCH1 and PTCH2, and has previously shown similar Gli repression activity to PTCH1 and 2.
To establish the involvement of PTCHD1 in Hedgehog (Hh) pathway, transcription analysis was performed with Hh pathway genes and putative PTCHD1 partners. We also tested for a truncated construct lacking the C-terminal four amino acids, Ile-Thr-Thr-Val (ITTV) of PTCHD1, which is predicted to interact with the PDZ domains of proteins. PTCHD1 over-expression revealed increased levels of NLGN1 and CNTNAP1 mRNA, which suggests that interaction with proteins at the synapse (NLGN1) or at nodes of Ranvier or axo-glial junctions (CNTNAP1) may have a regulatory effect on these genes.

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The transcript levels were reduced with the PTCHD1 truncated construct, reversing the effect of PTCHD1 over-expression. These results suggest either a regulatory or a downstream effect on NLGN1 and CNTNAP1 genes via a PDZ-domain containing protein. As DLG4 (PSD-95) interacts with K+-voltage-gated channels KCNA1 and KCNA2 (both known interactors with CNTNAP1), and interacts with NLGN1, we hypothesize that ! PTCHD1 may have a synaptic role mediated by PSD-95. Alternatively, DLG3 (MPP3), SHANK1 or SHANK3 may mediate regulation of NLGN1.
We showed high levels of Shh, and its putative receptor, Ptchd1, a well as Smoothened (Smo) transcripts in mouse brains between E12 and P2. To assess the expression pattern of PTCHD1 and Smo in post mitotic neurons, we immunolabeled PTCHD1 and Smo in cultured hippocampal neurons- a model system that has been widely used to study signaling pathways in neuronal growth. Positive PTCHD1 immunolabeling was visible in the hippocampal neurons, and Smo immunolabeling was bright and intense in the distal sections of dendrites. We hypothesize that PTCHD1 localization to hippocampal neurons could inhibit the Hh pathway by excluding Smoothened and also allows cilia to function as chemo sensors for the detection of extracellular Shh, similar to PTCH1, during neuronal development and synapse formation. Preliminary results also suggest localization of PTCHD1 in cilia.

Board #46
BioVUpsych: Electronic Medical Record-based Identification of DNA Samples for Disorders Underrepresented in the PGC

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Background: The genetic architectures of psychiatric disorders are complex, therefore a large number of samples are required to unequivocally associate genetic variants with disease. Some have estimated that marked progress will require upto 100,000 DNA samples per disorder.
The Psychiatric Genomics Consortium (PGC) currently contains genetic data for ~150,000 cases across 10 disorders. However, the sample is highly skewed toward certain disorders with well over 15,000 cases (schizophrenia, major depression, bipolar disorder), while other disorders have yet to attain 5,000 cases (anorexia nervosa, OCD and Tourette's Syndrome). If these under-represented disorders can achieve larger sample sizes, they may experience the gene discovery inflection point that schizophrenia achieved at ~10,000 cases. BioVU is Vanderbilt University Hospital's biorepository of DNA extracted from discarded blood collected during routine clinical testing and all DNA is linked to de-identified medical records. BioVU contains a substantial number of samples for disorders that are under-represented in the PGC, namely anorexia nervosa (AN), obsessive-compulsive disorder (OCD), and Tourette's Syndrome (TS).

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Methods: The main intent of this study was to design and validate an algorithm to identify samples within BioVU from patients with AN, OCD and TS. The information we are using includes: current and past ICD-9 codes, prescription drug records, and natural language text mining of complete electronic medical records. A subset of the samples identified in this manner is currently being validated by manual chart review.
Results: Our preliminary analysis using the algorithm described above identified 985 AN, 627 OCD, and 74 TS cases with DNA currently existing in the BioVU Biobank. These samples will be sent, along with their appropriate controls, for DNA genotyping using the PsychChip. This represents a ~20% increase in the number of AN cases, 15% increase in OCD, and 9% increase in the total samples available for meta-analysis with the PGC's psychiatric GWAS studies for these disorders, respectively. The validation process is ongoing and these results will be presented.
Discussion: Sample size has been the limiting factor in gene discovery for psychiatric disorders. Therefore biobank resources, such as that presented here, represent an efficient way to maximize power for gene discovery for complex psychiatric disorders.

Board #47
Systematic Review of Effectiveness and Cost-effectiveness of Pharmacogenetic Testing for Deciding Drug Treatment in Psychiatry

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Introduction: Pharmacogenetic testing has been available in clinical psychiatric practice with the FDA approval of the AmpliChip CYP450 Test that genotypes for two cytochrome P450 2D6 (CYP2D6) and 2C19 (CYP2C19) genes. Additionally other pharamcogentic tests have been developed. The subject has been reviewed using traditional review methods – but no review has been done using high quality systematic review methodology.
Objectives: We planned to do a systematic review of pharmacogenetic testing compared to no pharmacogentic testing in deciding psychotropic drug treatment in psychiatry.

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Aims: The aim is to provide evidence based and generalisable knowledge.
Methods: The 'PICO' is as follows: **P**opulation: patients with mental disorder of any age and sex; **I**ntervention: pharmacogenetic testing in deciding choice of drug treatment by any route; **C**omparisons: drug treatment choice without pharmacogenetic testing; and **O**utcomes are effectiveness, cost-effectiveness and safety. Only RCTs or controlled clinical trials are eligible for this review. A comprehensive search is carried out of Medline, Embase, Psychinfo and other databases. Articles selection and data extraction is carried out by two reviewers independently for reliability. Articles are assessed for quality. Meta-analysis is preferred if warranted by heterogeneity assessment; otherwise narrative synthesis will be done after GRADE evaluation for quality and generalisability.
Results: The systematic review is underway. The effect sizes for effectiveness and safety would be as follows: for dichotomous outcomes relative risk, absolute risk change and numbers needed to treat; and for continuous outcomes mean difference or standardized mean difference. These would be sensitivity analyzed. If meta-analyses were not warranted, then narrative synthesis will be presented. Also cost effectiveness data if available will be analysed for incremental cost and cost-effectiveness acceptability curve.
Conclusions: Conclusions will be drawn for effectiveness, cost effectiveness and safety of using pharmacogenetic testing.

Board #48
Analysis of Pharmacogenetic Studies: Comparing Traditional Statistical Inference with Machine Learning

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Background: Typically, genetic studies explore pharmacogenetic associations at a single nucleotide polymorphism (SNP) on a SNP-by-SNP basis. Since the genetic architecture of many complex traits is polygenic, a multi-SNP association analysis may be more appropriate. Unlike traditional statistical inference, the elastic net machine learning method allows the simultaneous analysis of many covariates and performs variable selection, and so can identify several genetic associations.
Methods: We applied traditional inference and elastic net analysis to a pharmacogenetic candidate gene study in anti-depressant response (Eli Lilly trial n° NCT00795821 on edivoxetine, with 319 patients; 1138 SNPs in 33 candidate genes). Linear regression and elastic net were used to identify genetic association with drug response at the study endpoint, whereas linear mixed models and longitudinal elastic net were applied to explore longitudinal associations. A simulation study was performed to assess the power of the different methods in this sample.
Results: The 23 SNPs that were selected in an elastic net model for anti-depressant response at the end of the trial showed consistency with linear regression results, although no SNPs reached statistical significance. Moreover, elastic net has more power than linear regression to detect genetic associations in this sample. The longitudinal analyses did not identify any SNPs associated with treatment response.
Discussion: Elastic net proved to be a useful tool for the analysis of multiple SNPs in a single model, and can be used to identify genetic associations as well as to predict anti-depressant response. Replication of the results presented here in an independent sample is necessary to confirm the findings.

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