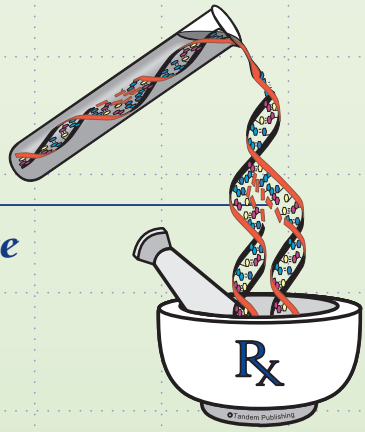
The 13th Annual Pharmacogenetics in Psychiatry Meeting



A Category 1 ***CME Conference***

June 15, 2014

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

Westin Diplomat
Hollywood, Florida

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June 15, 2014

Dear Colleagues,

It is our great pleasure to welcome you to *"The 13th Annual Pharmacogenetics in Psychiatry Meeting"* in Hollywood, FL. We hope that this meeting will continue to provide a forum for all investigators working in this field to present their latest data, exchange new ideas, and discuss ongoing developments in this area. Further, we hope to bring together investigators working in diverse areas of research, from molecular geneticists to clinical trials researchers, from academia and industry, to engender true interdisciplinary approaches to the problem of variation in clinical response to psychotropic drugs. It is our hope that each participant will come away from this meeting with an appreciation of the breadth of this evolving field; additionally, we hope to generate interest in pharmacogenetics in young investigators considering their future research endeavors.

This year's meeting is organized into four sessions:

Sunday, June 15th

I. *Pharmacogenetics of Antipsychotic Drug Induced Side Effects*

II. *Update on CRESTAR Project*

III. *Genetics and Pharmacogenetics of Neurocognitive Function*

IV. *Pharmacogenetics of Bipolar Disorder*

Our annual poster session will take place this evening in the Regency 2 Ballroom in conjunction with a wine and hors d'oeuvres reception. We believe that this event should be both informative and entertaining, and we encourage all meeting participants to attend and interact with the poster presenters, as well as meet with other colleagues.

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

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

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

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

PROGRAM OBJECTIVES:

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

- Describe the latest information in the field of pharmacogenetics.
- Evaluate new approaches to the problem of variation in response to psychiatric drugs.
- Identify new genes associated with the development of adverse side effects.
- Recognize novel statistical approaches to dissect the heterogeneity of drug response.

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

ACCREDITATION: The American Society of Clinical Psychopharmacology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The American Society of Clinical Psychopharmacology takes responsibility for the content, quality, and scientific integrity of this CME Activity.

CONTINUING MEDICAL EDUCATION INFORMATION

The Society designates this live meeting for a maximum of *6 AMA PRA Category 1 Credit(s)*™. Each physician should claim only those hours of credit that (s) he actually spent in the educational activity.

Verification of Attendance: Certificates will be provided upon request for professionals who attend this CME Conference.

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

CONFERENCE COORDINATED BY:

American Society of Clinical Psychopharmacology

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS

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

Course Directors/ Planners	Commercial Interest:	For:
Anil Malhotra	Genomind, Inc.	Advisory Board Member
Kathy J. Aitchison	Nothing to disclose	
David Goldman	Nothing to disclose	
John Kelsoe	Nothing to disclose	
James Kennedy	Eli Lilly Roche Novartis	Honorarium Consultant Honorarium
Thomas Lehner	Nothing to disclose	
Alessandro Serretti	Abbott Lundbeck Italfarmaco Polifarma	Consultant Consultant Consultant Consultant

Faculty Presenters:	Commercial Interest:	For:
Agnieszka Basta-Kaim	Nothing to disclose	
Isabelle Bauer	Nothing to disclose	
Katherine Burdick	Dainippon Sumitomo Pharma	
Tania Carrillo-Roa	Nothing to disclose	
Anna Cattaneo	Nothing to disclose	
Enrico Cocchi	Nothing to disclose	
Dan Cohen	Nothing to disclose	
Vincezo DeLuca	Nothing to disclose	
Chiara Fabbri	Nothing to disclose	
Brodie Heywood	Nothing to disclose	
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Maju Koola	Nothing to disclose	
Jean-Pierre Lindenmayer	Envivo Genentech Janssen Neurocrine Pfizer Roche	
Anil Malhotra	Geomind, Inc.	Consultant
Laura Mandelli	Nothing to disclose	
Daniel Müeller	Nothing to disclose	
Chi-Un Pae	Nothing to disclose	
Stefano Porcelli	Nothing to disclose	
David Rossolatos	Nothing to disclose	
Dan Rujescu	Nothing to disclose	
Alessandro Serretti	Abbott Lundbeck Italfarmaco Polifarma	Consultant Consultant Consultant Consultant
James Stevenson	Nothing to disclose	
Joey Trampush	Nothing to disclose	
Sandeep Vaishnavi	SureGene, Inc.	Travel/Conference Expenses
Aristotle Voineskos	Nothing to disclose	
James Walters	Nothing to disclose	
Zhewu Wang	Nothing to disclose	
Clement Zai	Eli Lilly Canada Gershon Lehrman Group, Inc.	Fellowship Consultant Fee – Council Member
Gwyneth Zai	Nothing to disclose	

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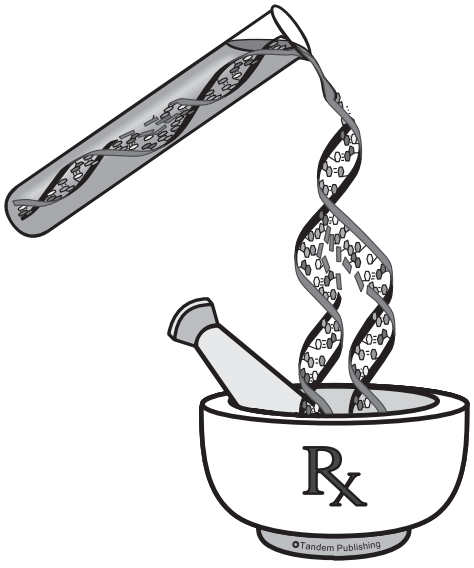
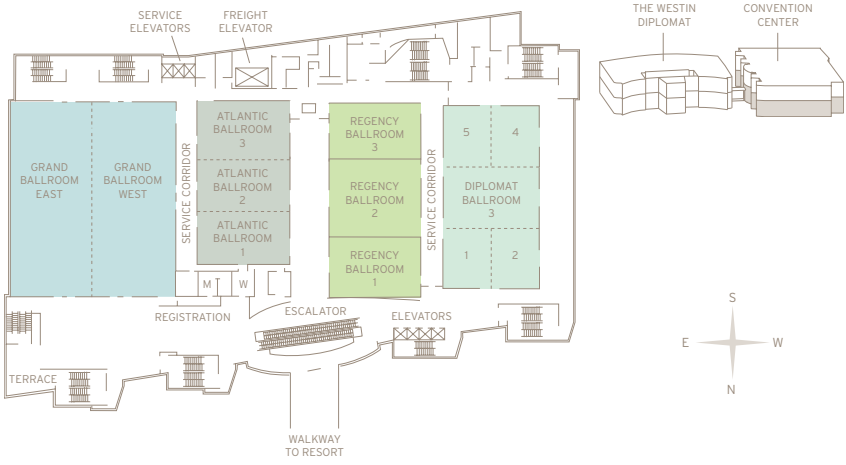


EVALUATION OF MEETING

In order to complete the PIP 2014 Meeting evaluation and obtain CME credit, please visit www.PharmacogeneticsinPsychiatry.com & click on the meeting evaluation. Evaluations must be completed by July 15, 2014.

Questions: Please contact info@ascpp.org.

2ND FLOOR CONVENTION CENTER



The 13th Annual Pharmacogenetics in Psychiatry Meeting
June 15, 2014
Westin Diplomat, Hollywood, FL
Regency Ballroom 3

SUNDAY, JUNE 15, 2014

8:00 AM Continental Breakfast

8:45 AM Welcome and Introduction

SESSION I: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG INDUCED SIDE EFFECTS
Chair: David Goldman

9:00 AM *GWAS in Antipsychotic-induced Weight Gain Dissecting the CATIE Sample*
Daniel J. Müller
Centre for Addiction and Mental Health, Ontario, Canada

9:30 AM *The LEPR Arg223Arg Variant is Associated with Weight Gain in Children and Adolescents Treated with Risperidone*
David Rossolatos
University of Alberta, Canada

10:00 AM *Recent Progress in the Search for Genetic Markers for Clozapine-induced Agranulocytosis*
James Kennedy
Centre for Addiction and Mental Health, Ontario, Canada

10:30 AM Break

SESSION II: UPDATE ON CRESTAR PROJECT
Chair: James Kennedy

10:45 AM *Pharmacogenomics of Typical Antipsychotics*
Dan Rujescu
Martin-Luther-University Halle-Wittenberg, Munich, Germany

SUNDAY, JUNE 15, 2014 *(continued)*

11:15 AM *Potential Lethal Side-effects of Clozapine: Clozapine-induced Agranulocytosis in Perspective of Contemporary Evidence*
Daniel Cohen
Mental Health Care Organization North-Holland North, The Netherlands

11:45 AM *Genomics of Treatment-resistant Schizophrenia*
James Walters
Cardiff University School of Medicine, Cardiff, UK

12:15 PM Lunch (on your own)

SESSION III: GENETICS AND PHARMACOGENETICS OF NEUROCOGNITIVE FUNCTION
Chair: John Kelsoe

1:45 PM *GWAS of Cognitive Abilities: Overlap with Schizophrenia*
Joey Trampush
The Zucker Hillside Hospital, Glen Oaks, NY

2:15 PM *Gene-gene Interaction within an Early Risk Pathway for Alzheimer's Disease Predicts Cortical Thickness and Cerebral Infarcts*
Aristotle Voineskos
University of Toronto, Ontario, Canada

2:45 PM *Pharmacogenetic Strategies to Cognitive Enhancement*
Anil Malhotra
The Zucker Hillside Hospital, Glen Oaks, NY

3:15 PM Break

SUNDAY, JUNE 15, 2014 *(continued)*

SESSION IV: PHARMACOGENETICS OF BIPOLAR DISORDER
Chair: Katherine Aitchison

3:30 PM *Lithium/Valproate Response in the STEP-BD Study*
Alessandro Serretti
University of Bologna, Italy

4:00 PM *Dopaminergic Genetic Variation and Treatment Response in Bipolar Disorder*
Katherine Burdick
Icahn Mount Sinai School of Medicine, New York, NY

4:30 PM *Pharmacogenetics of Lithium Response*
John Kelsoe
University of California, San Diego, La Jolla, CA

5:00 PM Meeting adjourns

5:30 PM Poster Session and Reception in Regency 2

Sunday, June 15, 2014

9:00 a.m. – 10:30 a.m.
SESSION I: PHARMACOGENETICS OF ANTIPSYCHOTIC DRUG INDUCED SIDE EFFECTS
Chair: David Goldman

9:00 a.m. – 9:30 a.m.
GWAS in Antipsychotic-induced Weight Gain Dissecting the CATIE Sample

Daniel J. Müller, Eva J. Brandl, Arun K. Tiwari, Clement C. Zai, Nabilah I. Chowdhury, Tamara Arenovich, Jiangshan J. Shen, James L. Kennedy
Centre for Addiction and Mental Health, Ontario, Canada

Background: Antipsychotic drugs frequently cause marked weight gain in genetically susceptible individuals. A previous GWAS revealed a highly significant and consistently replicated finding at the MC4R locus using 139 children/adolescents with first exposure to antipsychotics (Malhotra et al., 2012). Previous GWAS in the CATIE trial was limited by several important factors such as use of patients with different ethnicities and medications with different propensities to cause weight gain. In addition, mechanisms for AIWG may differ in younger vs. older populations and in earlier vs. later periods of antipsychotics exposure (e.g., Wallace et al., 2011). This prompted us to conduct a new set of analyses using rigorous inclusion criteria in order to obtain a more homogeneous study sample.
Methods: Our refined sample of patients consisted exclusively of individuals who were not exposed to high risk medication for weight gain prior to study inclusion, who did not show marked obesity (BMI >40) at baseline (T0) or were exposed to low risk medication for weight gain during the CATIE trial (e.g. ziprasidone). This refined sample (n=358) was used for mixed models analyses on 328,733 SNPs analyzed in each individual. In order to rule out the effect of population stratification, we plotted the MDS components and selected patients within the cluster corresponding to European ancestry as the largest cohort. The GWAS analysis presented here was conducted on 189 individuals treated with risperidone, quetiepine, or olanzapine.
Results: The top hit of the GWAS was rs12924003 (p=1.06x10-5) located downstream of the SAL-1 gene on chromosome 16. The

9:00 a.m. – 9:30 a.m.
GWAS in Antipsychotic-induced Weight Gain Dissecting the CATIE Sample (continued)

sal-like-1 gene functions as a zinc finger domain containing transcriptional repressor and is associated with developmental syndromes. The second hit, SNP rs4771655 (p=1.91 x10-5) is ~194kb upstream of IRS2 gene (insulin receptor substrate 2). IRS2 mediates effects of insulin and several cytokines and has been associated with insulin resistance, coronary artery disease and cancer in the general population. The third hit, rs4751427 (p=2.4 x10-5) is located ~59kb upstream of the Neuropeptide S gene. The 20 amino acid peptide coded by this gene has been shown to influence food intake, anxiety, locomotion, memory, and drug addiction. **Conclusion:** Our analysis presented here using stringent inclusion and exclusion criteria on the CATIE GWAS data has revealed interesting new genes that may be associated with antipsychotic induced weight gain. Two of our top hits, IRS2 and NPS, were previously shown to be involved in regulation of insulin sensitivity and food intake in other populations. Direct functional effects of the identified SNPs are yet unknown and functional studies as well as replication in independent samples are required. Beside the main limitations that none of the SNPs was significant at the usual genome-wide threshold (p = 5x10-8) and the relatively small sample size, our findings are an important contribution to understanding genetic mechanisms of AIWG by using a genome-wide approach.

Corresponding Author:
Daniel J. Müller
Centre for Addiction and Mental Health
Ontario, Canada
Daniel.Mueller@camh.ca

9:30 a.m. – 10:00 a.m.

The LEPR Arg223Arg Variant is Associated with Weight Gain in Children and Adolescents Treated with Risperidone

Noor B. Almandil,[1] David Rossolatos,[2] Caitlin Slomp,[2] Ruth I. Ohlsen,[3] Macey L. Murray,[1] Abdulsalam A. Al-Sulaiman,[4] Paul Gringras,[5] Frank M.C. Besag,[6] Katherine J. Aitchison,[2,7‡] Ian C.K. Wong[8‡]

[1]The Department of Practice and Policy, UCL School of Pharmacy, UK; [2]Department of Psychiatry, University of Alberta, Canada; [3]Department of Post Graduate Research (affiliated with Mental Health), Florence Nightingale School of Nursing And Midwifery, King's College London, UK; [4]Vice President, University of Damman, Kingdom of Saudi Arabia; [5]Evelina Children's Hospital, Guy's and St Thomas' NHS Trust, UK ; [6]Child and Adolescent Mental Health Service, Learning Disability Team (CAMHS LD), SEPT: South Essex Partnership University NHS Foundation Trust, UK; [7]Department of Medical Genetics, University of Alberta, Canada; [8]Department of Pharmacology and Pharmacy, The University of Hong Kong.

Introduction: Children and adolescents with various psychiatric diagnoses are commonly treated with antipsychotics such as risperidone.

Methods: Data on weight gain and other relevant variables was collected from 200 children and adolescents treated with risperidone in the Kingdom of Saudia Arabia (KSA) and the United Kingdom (UK). Body Mass Index (BMI) was measured at baseline when medication-free (T0), and at an average of 3 months follow-up (T1). BMIZ was calculated using the LMS growth method.[1] The following SNPs were genotyped by TaqMan: rs8179183 (in the leptin receptor gene, *LEPR*), rs1414334 (in *HTR2C*), rs1137100 (in *LEPR*), rs1137101 (in *LEPR,* Gln223Arg, A>G), and rs7799039 (in *LEP*); the call rate was 99% As the primary outcome variable, change in BMIZ (between T0 and T1), was significantly skewed, this was log transformed.

Results: Increased weight gain was seen in *LEPR* Arg223Arg individuals, in male patients from KSA (p=0.021 by linear regression analysis). Other variables (including baseline age and weight) correlated with the outcome variable and were therefore excluded.

Discussion: Interestingly, in recent a study of adult attendees of an outpatient Endocrinology Department, Becer et al (2013)[2] reported that obese patients with the *LEPR* Arg223Arg had significantly higher triglyceride levels and waist and hip circumferences. Should our finding in children and adolescents be replicated, it could

9:30 a.m. – 10:00 a.m.
The LEPR Arg223Arg Variant is Associated with Weight Gain in Children and Adolescents Treated with Risperidone (continued)

become the basis of a biomarker test for prediction of weight gain for young people of relevant ethnicity on risperidone treatment, and the development of targeted clinical interventions.

Funding and Acknowledgements
KJA holds a Government of Alberta funded Alberta Centennial Addiction and Mental Health Research Chair. NBA was funded by a scholarship from the Ministry of Higher Education, Kingdom of Saudi Arabia.

1. Cole T.J. and Green P.J. (1992) *Stat Med* 11:1305-19.
2. Becer E., Mehmetçik G., Bareke H., Serakınc N. *Gene* 529: 16-20.
Corresponding Author: Dr. Katherine J Aitchison, Psychiatry Research Offices KATZ 5-020, Katz Group Center for Pharmacy and Health Research, University of Alberta, Edmonton, AB Canada T6G 2E1, kaitchis@ualberta.ca. tel: 780-492-4018, fax: 780-492-7789

10:00 a.m. – 10:30 a.m.
Recent Progress in the Search for Genetic Markers for Clozapine-induced Agranulocytosis

James L. Kennedy, Arun Tiwari, Nabilah Chowdhury, Daniel J. Müller
Neurogenetics Section, Centre for Addiction and Mental Health, University of Toronto

Clozapine was the original atypical antipsychotic drug. In spite of its efficacy, the use of clozapine is severely limited by its side effects such as metabolic syndrome and agranulocytosis. However, agranulocytosis is the major reason that inhibits the use of clozapine. Clozapine-induced agranulocytosis (CIA) occurs in 0.8% of clozapine-treated patients, generally within the first 18 weeks of treatment and is characterized by a decrease in absolute neutrophil count (ANC) below 500 cells per cubic mm. Among several hypothesized causes of agranulocytosis, an immune-mediated mechanism is most often proposed, and a few HLA region sites have been implicated over the past 20 years (reviewed by Chowdhury et al, 2011). Tiwari et al (2013) have utilized exome sequencing to comprehensively identify genetic variation in the transcribed region of the genome in clozapine treated Finnish patients, 24 with CIA and 27 without CIA.

10:00 a.m. – 10:30 a.m.
Recent Progress in the Search for Genetic Markers for Clozapine-induced Agranulocytosis (continued)

Although no sites reached study-wide significance, the genes PPPF1A4, USP43, ACTN1, PODNL1, and SPATS1 were the highest ranking 'hits' exhibiting odds ratios for agranulocytosis or neutropenia of 9 or higher. Unfortunately the HLA region loci results were unreliable in this study due to low resequencing coverage of the region. Another large international study of CIA is being conducted by the CIA Consortium (CIAC) with over 200 cases of agranulocytosis or neutropenia. GWAS and exome sequencing have been completed and the data are currently undergoing analysis in this CIAC project.

10:30 a.m. – 10:45 a.m. **Break**

10:45 a.m. – 12:15 p.m.
SESSION II: UPDATE ON CRESTAR PROJECT
Chair: James Kennedy

10:45 a.m. – 11:15 a.m.
Pharmacogenomics of Typical Antipsychotics

Dan Rujescu
University of Munich

One major drawback of the therapy with psychopharmacologic agents is the lack of efficacy in many of the patients and the occurrence of side effects that can both limit therapy and compliance. Thus, the availability of a predictive tool for the response to psychopharmacologic agents in the therapy of psychiatric disorders is desirable opening a unique avenue for a real personalized psychiatry.

Typical antipsychotics, like Haloperidol are benchmark drugs for the pharmacological treatment of Schizophrenia but the genetics of its efficacy is still to be elucidated. As Haloperidol can lead to serious side effects, a predictive genetic risk profile before treatment would be of greatest benefit.

10:45 a.m. – 11:15 a.m.
Pharmacogenomics of Typical Antipsychotics (continued)

Therefore we performed a genome-wide association analysis in a sample of patients treated with haloperidol and the results were replicated in a larger sample of patients treated with second generation antipsychotics or perphenazine. PANSS % score decrease was the outcome in both samples. The period of observation was restricted to one month in the replication sample and the most severe cases were included, to best balance the replication. Dan Rujescu will present newest results on this GWA and discuss them in the context of literature.

11:15 a.m. – 11:45 a.m.
Potential Lethal Side-effects of Clozapine: Clozapine-induced Agranulocytosis in Perspective of Contemporary Evidence

Dan Cohen
Department of Community Mental Health, Mental Health Care Organization North-Holland North, The Netherlands

The history of clozapine-induced lethal agranulocytosis still reverberates today. Not only in the strict monitoring guidelines of monthly white blood cell monitoring obligatory until 4 weeks after clozapine discontinuation, but also in the minds of the psychiatric community. This attention for agranulocytosis comes it seems at the cost of the attention for other potentially lethal side-effects of clozapine treatment, such as diabetic keto-acidosis (DKA), gastro-intestinal hypomotility (GIH) and myocarditis. When the data of the incidence and mortality of all clozapine-associated potentially lethal side-effects are looked at critically, a different picture emerges. Probably due to the strict monitoring guidelines, the mortality of the affected cases is low, between 2%-4%. In contrast, the mortality rate of the affected cases of GIH, with the same incidence of agranulocytosis, is 4-10 times as high: 15%-27%. The mortality of DKA, with a fifty percent lower incidence rate, is even higher: 20%-30% of the affected cases die. Myocarditis is a case in itself: for unknown reasons, all publication, case-reports, review, guidelines, are of Australian and/or New-Zealand origin. Outside these South Pacific countries, the very low incidence rates of myocarditis, 10-100 times lower than in the South Pacific, do not warrant routinely monitoring.

11:15 a.m. – 11:45 a.m.
Potential Lethal Side-effects of Clozapine: Clozapine-induced Agranulocytosis in Perspective of Contemporary Evidence (continued)

Close monitoring of treatment emergent diabetes in the first 3 months of treatment and steady monitoring of defecation and if necessary, prescription of laxatives, are effective measures in normalizing mortality of DKA and GIH.

11:45 a.m. – 12:15 p.m.
Genomics of Treatment-resistant Schizophrenia

James Walters
Cardiff University School of Medicine

Dr. Walters will present results examining the genetic nature of treatment resistant schizophrenia using CNV and GWAS studies of the CLOZUK sample. This is a large sample (n=12 000 cases and controls) of those with treatment-resistant schizophrenia (TRS) taking the antipsychotic clozapine. With collaborators the Cardiff group has performed a GWAS of this sample identifying several genome-wide significant variants. Replication results will be presented from international clozapine samples particularly focusing on results that are specific to treatment-resistant schizophrenia. He will also present work on CNV analyses of the CLOZUK sample comparing this to generic schizophrenia samples. In this way he will provide evidence that the genetic architecture of treatment resistance is largely consistent with that of generic schizophrenia but that genetic signals from these analyses suggest genes and pathways specifically involved in TRS.

12:15 p.m. – 1:45 p.m. **Lunch (on own)**

1:45 p.m. – 3:15 p.m.
SESSION III: GENETICS AND PHARMACOGENETICS OF NEUROCOGNITIVE FUNCTION
Chair: John Kelsoe

1:45 p.m. – 2:15 p.m.
GWAS of Cognitive Abilities: Overlap with Schizophrenia

Joey Trampush
The Zucker Hillside Hospital, Glen Oaks, NY

This presentation will focus on recent findings from the Cognitive Genomics Consortium (COGENT). COGENT is a large genome-wide association study (GWAS) collaboration initially organized to evaluate the classic endophenotype hypothesis of schizophrenia, which states that allelic variation associated with reduced cognitive ability in healthy individuals should also serve to increase risk for schizophrenia (Lencz et al., 2014). Phase 1 of COGENT conducted a GWAS of general cognitive ability ("*g*") in ~5,000 individuals from nine international, nonclinical cohorts, as well as a polygene analysis of polymorphisms associated with reduced cognitive functioning in four independent schizophrenia case-control GWAS cohorts. The Phase 1 analysis provided the first molecular confirmation of the genetic overlap between schizophrenia and general cognitive ability. Phase 2 of COGENT is currently underway. We have acquired several new samples and collaborative partnerships. The latter half of the presentation will highlight the primary aims and analyses to be carried out as COGENT moves forward.

2:15 p.m. – 2:45 p.m.

Gene-gene Interaction within an Early Risk Pathway for Alzheimer's Disease Predicts Cortical Thickness and Cerebral Infarcts

Aristotle Voineskos, Daniel Felsky, David Bennet, Philip De Jager, Julie Schneider, Benoit Mulsant, Mallar Chakravarty
University of Toronto, Ontario, Canada

Purpose of Study: We have shown that variants within two replicated Alzheimer's (AD) risk genes (apolipoprotein E (APOE) and sortilin related receptor (SORL1)) are individually associated with structural brain changes across the lifespan. These genes are biologically related. Therefore, we evaluated the statistical interaction of two known SORL1 and APOE risk variants on in vivo cortical thickness and postmortem cerebral infarcts in older healthy people and in people with Mild Cognitive Impairment (MCI) and AD.
Methods: From CAMH, 135 healthy subjects underwent imaging-genetics procedures. Cortical thickness was calculated using the CIVET pipeline. From the Rush University Religious Orders Study and Memory and Aging Project (ROS/MAP), 884 postmortem brains (310 healthy, 226 MCI, 348 AD) underwent neuropathological examination; cerebral infarcts were quantified as present or absent. Subjects were genotyped for SORL1 rs689021 and APOE ε4, and interactions were modeled using regression with appropriate covariates.
Results: In the CAMH sample, SORL1 by APOE interaction predicted average cortical thickness ($p = 0.04$). Post - hoc tests showed a diffuse pattern of effect across neocortical lobes. In ROS/MAP, SORL1 by APOE interaction predicted risk for cerebral infarcts ($p = 0.0009$). Importantly, individuals with combined ε4/SORL1 AA risk genotypes had both the lowest average thicknesses and highest proportion of cerebral infarcts.
Conclusions: Our results suggest that common genetic variation in SORL1 and APOE may interact to predict AD - related brain changes in a cerebrovascular context. Understanding how effects of one genotype are modified by another is critical for dissecting the complexity of the AD risk profile, and may be relevant for other cognitive disorders.

2:45 p.m. – 3:15 p.m.
Pharmacogenetic Strategies to Cognitive Enhancement

Anil Malhotra
The Zucker Hillside Hospital, Glen Oaks, NY

Background: To date, cognitive enhancement strategies in schizophrenia and related disorders have been unsuccessful. In part, this may be due to a lack of data on the molecular underpinnings of cognitive function, as well as the limited data on key brain structure –function relationships.
Methods: We have conducted a series of studies that aim to 1) identify the critical brain regions mediating cognitive function in a cohort of over 120 healthy pediatric subjects aged 8-21 years assessed with MRI (diffusion tensor imaging, resting state and structural MR), cognitive and genetic measures, 2) identify relationships between polyunsaturated fatty acids (PUFAs) and neurodevelopmental processes in a cohort of early – onset schizophrenia patients and, 3) detect a genetic marker that predicts brain development across the age range.
Results: We observed significant increases of fractional anisotropy (FA) in the left superior longitudinal fasciculus (SLF) that correlated with improved performance on a measure of verbal fluency. Second, we have found a significant ($p < .05$, corrected) relationship between FA throughout multiple brain regions and erythrocyte membrane PUFA concentrations in early phase schizophrenia patients. Finally, a genetic association study between functional SNPs/haplotypes within the genes *FADS1* and *FADS2*, which encode the rate-limiting enzymes for fatty-acid conversion, and assessments of white matter development indicate that these functional variants may influence brain development in young adults.
Conclusions: Our data point to an important role of connectivity in the superior longitudinal fasciculus and cognitive function. Variation in the development of this, and other tracts, may be related to polyunsaturated fatty acid metabolism, which is in turn influenced by functional genetic elements. We have now initiated a biomarker-based treatment study with PUFA augmentation in early phase schizophrenia with an aim of enhancing cognitive function.

3:15 p.m. **Break**

3:30 p.m. – 5:00 p.m.
SESSION IV: PHARMACOGENETICS OF BIPOLAR DISORDER
Chair: Katherine Aitchison

3:30 p.m. – 4:00 p.m.
Lithium/Valproate Response in the STEP-BD Study

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

Bipolar disorder (BD) is a disabling mental disorder that is associated with increased risk of suicide and poor quality of life. Lithium and valproate are considered first line mood stabilizers for the treatment of both (hypo)manic episodes and maintenance therapy. Nevertheless, the risk of relapse during maintenance therapy is around 65% in 24 months. Previous evidence suggested a relevant genetic component of lithium and valproate efficacy, and mechanisms of action of these drugs are partially overlapping.
The present study aimed to identify polymorphisms involved in lithium/valproate medium-term efficacy. The frequency of acute phases within a 6-12 months follow-up period was analyzed, since it is expected to highly impact on quality of life. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) genome-wide dataset was used after standard quality control. Linear regression was performed including appropriate covariates. Finally, pathway enrichment was assessed through cytoscape program and geneMANIA plugin in order to identify possible molecular mechanisms involved.
478 patients with BD type I were included. Interesting results were found when considering the frequency of (hypo)manic episodes, that was influenced by genes coding for metalloproteinases (ADAMTS2, MMP16), zinc finger proteins (ZNF516), and neuron navigator gene family (NAV2). Pathways involved in regulation of cellular movement, cell junction organization, axon guidance, and cellular response to growth stimuli may mediate the therapeutic effect of treatment.
The present study supported the hypothesis of neuron growth and plasticity as common mechanism of lithium and valproate action in the prevention/treatment of the (hypo)manic pole of BD.

3:30 p.m. – 4:00 p.m.
Lithium/Valproate Response in the STEP-BD Study (continued)

Corresponding author:
Alessandro Serretti
Department of Biomedical and NeuroMotor Sciences, University of Bologna,
Viale Carlo Pepoli 5, 40123 Bologna, Italy
Tel +39 051 6584233
Fax +39 051 521030
Email: alessandro.serretti@unibo.it

4:00 p.m. – 4:30 p.m.
Dopaminergic Genetic Variation and Treatment Response in Bipolar Disorder

Katherine Burdick, Raphael J. Braga, and Anil K. Malhotra
Icahn Mount Sinai School of Medicine, New York, NY

Pramipexole has been implicated in the emergence of risk-seeking behaviors such as pathological gambling in multiple case reports and cross-sectional studies in patients with Parkinson's disease (PD). A purported mechanism for this effect is related to pramipexole's high selective affinity for D3 receptors, which are primarily expressed in the mesocorticolimbic dopamine (DA) pathway – a circuitry that is active during impulsive decision-making. Indeed, several studies that have used pramipexole in *single-dose* challenge paradigms have confirmed its actions on reward-related neural networks, primarily at low doses and in healthy individuals (Riba et al, 2008; Ye et al, 2011); however, low doses of pramipexole (e.g. 0.25 – 0.5 mg) are thought to influence reward via a "paradoxical" effect related to activation of the presynaptic D2 autoreceptor, resulting in a *blockade* of phasic DA release and a *blunted* response to rewarding stimuli (Riba et al. 2008). *In contrast*, higher doses of pramipexole, including those in the range used to treat Parkinson's disease and in the range used in our cognitive enhancement trial in bipolar patients, act as specific agonists both presynaptically and postsynaptically to *enhance* DA activity (Mierau et al. 1995). These higher doses of pramipexole are the ones that have been linked to pathological gambling and anti-anhedonic (antidepressant) effects across several major psychiatric disorders.

4:00 p.m. – 4:30 p.m.
Dopaminergic Genetic Variation and Treatment Response in Bipolar Disorder (continued)

To date, the effects of pramipexole on reward processing have been limited to single-dose (low-dose) challenge paradigms and have not yet been extended to include higher, clinically-relevant doses. Preliminary evidence will be discussed which suggests that pramipexole (1.5 mg/day) has a direct effect on performance on the Iowa Gambling Task such that after 8 weeks of treatment, euthymic bipolar patients made more high-risk/high-reward choices as a result of an increased attention to feedback associated with monetary wins vs. losses (Burdick et al. 2013 *Neuropsychopharmacology*). These results stand somewhat in contrast to the beneficial effects of the agent on measures of attention and working memory in the same cohort (Burdick et al. 2012 J Clin Psychiatry). Preliminary data will be presented with regard to the effects of variation within the dopamine transporter gene (DAT) on outcome after pramipexole treatment in our cohort. The results of this clinical trial will be discussed in the context of how modulation of dopamine through D2/D3 receptors influences brain function in healthy individuals and in patients with schizophrenia and bipolar illness with an eye toward future study design.

4:30 p.m. – 5:00 p.m.
Cellular Models of Lithium Response in Bipolar Disorder

John R. Kelsoe[1,2,3], Jun Yao[4], Kangguang Lin[5], Kristen Brennand[6], Fred Gage[4], Christopher Woelk[7], Cory White[8], The Pharmacogenomics of Bipolar Disorder Study
[1]Department of Psychiatry, University of California San Diego; [2]Department of Psychiatry VA San Diego Healthcare System; [3]Institute for Genomic Medicine, University of California San Diego; [4]Salk Institute; [5]University of Hong Kong; [6]Mt Sinai School of Medicine; [7]University of Southamptom; [8]Department of Medicine, University of California San Diego

One of the challenges facing pharmacogenetics is the cost and labor involved in assessing the phenotype of drug response. The gold standard prospective clinical trial generally assesses several hundred subjects, where tens of thousands have been required for success in recent genome wide association studies of disease susceptibility.

4:30 p.m. – 5:00 p.m.
Cellular Models of Lithium Response in Bipolar Disorder (continued)

One approach to this challenge is to use cellular models to identify a subset of genes more likely to be involved in response. By focusing on this smaller set of genes, fewer statistical tests are employed and the power of the smaller sample is preserved. The Pharmacogenomics of Bipolar Disorder is a 13 site NIH sponsored consortium whose goal is to identify genes associated with lithium response. Bipolar I subjects undergo a 2.5 year long prospective clinical trial of lithium monotherapy. After screening, subjects are stabilized on lithium monotherapy over a 16 week period. Those who respond and achieve remission on monotherapy are then followed for 2 years in order to detect relapse. Lithium response can then be quantified as time to relapse, as well as, degree of symptom control. Lymphoblasts from 8 lithium responders, 8 non-responders and 8 controls were treated in vitro with 1 mM lithium for one week. RNA was then harvested and poly-T selection conducted to obtain mRNA. This RNA was then sequenced using an Ion Torrent PGM and analyzed using Ion Torrent analytic tools and edgeR. Expression levels were then compared within each subject with and without lithium. The striking result was that 10-20 times more genes underwent significant changes in expression in the responders as compared to either non-responders or controls. The gene CRIP2 showed the largest fold change (18x) in response to lithium in both responders and non-responders. Though little is known of CRIP2, it has been associated with cortical thickness. Pathway analysis revealed activation of translational machinery and immunoglobulin production. A similar experiment was conducted using neurons derived from induced pluripotent stem cells (iPS). Skin biopsies were obtained from 3 prospectively documented responders, 3 non-responders and 4 controls. Fibroblasts were reprogrammed to iPS cells using Sendai virus, and then differentiated to *prox1*+ glutamatergic dentate gyrus granule cells. Pluripotency and differentiated cell phenotype were documented using the appropriate markers. Patch clamp experiments were conducted on all cells and demonstrated a "hyperexcitable" phenotype. Neurons from both responders and nonresponders showed a greater frequency and amplitude of spontaneous action potentials, and a more prolonged train of action potentials following K+ depolarization. This phenotype was rescued by lithium treatment in the responders but not in the nonresponders. Imaging studies of

4:30 p.m. – 5:00 p.m.
Cellular Models of Lithium Response in Bipolar Disorder (continued)

calcium flux which closely correlates with action potentials showed a similar phenomenon. RNAseq was also conducted in these cells and replicated the 10-20 fold difference in gene expression between responders and non-responders seen in the lymphoblasts. The neurons also showed a dramatic upregulation of CRIP2, changes in mitochondrial genes and measures of mitochondrial size. Genes that are changed by lithium in the responders and not in the non-responders will be selected for a focused examination by genotyping or sequencing in search of variants associated with lithium response.

5:00 p.m. **Meeting adjourns**

THE 13TH ANNUAL PHARMACOGENETICS IN PSYCHIATRY MEETING JUNE 15, 2014

POSTER PRESENTATIONS

1. **The Modulatory Effect of Antidepressant Drugs Administration on the Brain Insulin Receptor Substrates IRS1/IRS2: A Link to Depression**
   Agnieszka Basta-Kaim
   Department of Experimental Neuroendocrinology, Institute of Pharmacology

2. **Molecular Predictors of Antidepressant Treatment Outcome**
   Tania Carrillo-Roa
   Max Planck Institute of Psychiatry

3. **Sulfur Aminoacid Metabolic Process Pathway may Modulate Bipolar Disorder with Alcohol Dependence Comorbidity**
   Enrico Cocchi
   Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

4. **The Genetics of Vascular Incidents Associated with Second-generation Antipsychotic Administration**
   Enrico Cocchi
   Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

5. **The Extracellular Domains may Hold the Pruning Related Events that are Risk Factors for Schizophrenia and Bipolar Disorder**
   Enrico Cocchi
   Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

6. **Genetics of Treatment-induced Side Effects in the STEP-BD Study**
   Chiara Fabbri
   Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

7. **The Complexity of Genetic Effects in Pharmacogenetics: Focus on Neuroplasticity, Environmental Stress and Response to Antidepressants**
   Laura Mandelli
   University of Bologna, Bologna, Italy

8. **Analysis of Drug Target Gene Sequences with Suicide Severity in Bipolar Disorder**
   Clement C. Zai
   Centre for Addiction and Mental Health, Toronto

9. **Pharmacogenetics of Remote Regulatory Variants of 14 Obsessive-Compulsive Disorder Candidate Genes in Antidepressant Response**
   Gwyneth Zai
   Centre for Addiction and Mental Health, Toronto

10. **Abelson Helper Integration Site-1 Gene Variants on the Diagnosis and Treatment Outcomes in Mood Disorder**
    Chi-Un Pae
    The Catholic University of Korea

11. **Effect of Glutamate Transporter Gene Methylation on PTSD Symptomatology and Treatment Outcome**
    Zhewu Wang
    Charleston VA Medical Center and Institute of Psychiatry, Medical University of South Carolina

12. **The Role of Opioid Receptor Genes in the Pharmacotherapy of Drug Addiction**
    Isabelle E. Bauer
    University of Texas

13. **Increased MIF and IL-1β mRNA Blood Levels and Childhood Trauma Events as Accurate Predictors of Treatment Response in Depressed Patients**
    Anna Cattaneo
    King's College London, Institute of Psychiatry

14. **Treatment Resistant Schizophrenia: Run of Homozygosity Analysis**
    Vincenzo De Luca
    CAMH, Department of Psychiatry, University of Toronto

15. **Exploring Interactions between *COMT*, *BDNF* and *AKT1* and Cannabis Consumption in the Genesis of Psychosis**
    Brodie Heywood
    Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

16. **Brain-derived Neurotrophic Factor Val66Met Polymorphism and Antipsychotic-induced Tardive Dyskinesia**
    Maju Mathew Koola
    Sheppard Pratt Health System and Department of Psychiatry, University of Maryland School of Medicine

17. **Genetic Correlates of Cognitive Remediation Response in Schizophrenia**
    J.P. Lindenmayer
    New York University, Nathan S. Kline Institute for Psychiatric Research, Manhattan Psychiatric Center

18. **Pharmacogenetics of Clozapine Response and Metabolic Side Effects: A Comprehensive Review and Meta-analysis**
    Stefano Porcelli
    Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

19. **First Episode Psychosis Pharmacogenetics: Does Glutamate Affect Antipsychotic Response?**
    James M. Stevenson
    Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy

20. **Use of Pharmacogenetic Testing in Routine Clinical Practice Improves Outcomes for Psychiatric Patients**
    Sandeep Vaishnavi
    The Neuropsychiatric Clinic (NPC) at Carolina Partners, Duke University Medical Center

POSTER SESSION ABSTRACTS
Sunday, June 15, 2014

Board #1

The Modulatory Effect of Antidepressant Drugs Administration on the Brain Insulin Receptor Substrates IRS1/IRS2: A Link to Depression

A. Basta-Kaim, K. Glombik, B. Budziszewska, M. Leskiewicz, E. Trojan, J. Slusarczyk, E. Szczesny*

Department of Experimental Neuroendocrinology, Institute of Pharmacology, PAS, Krakow, Poland

Among the proteins binding to the intracellular subunit of the IGF-1 receptor in brain, insulin receptor substrates (IRS) are the most important. Researchers postulate that phosphorylation of IRS-1 may occur at many sites, and that the serine phosphorylation of IRS-1 leads to inactivation of the IGF-1 receptor and intracellular pathways. The aim of this study was to verify whether prenatal stress and antidepressant treatment alter the expression of IRS-1/IRS-2 genes and protein expression in the frontal cortex of adult rats.

Pregnant Sprague-Dawley rats were subjected to stress session from 14th day of pregnancy until delivery. At 3 months of age, control and prenatally stressed rats were tested in Porsolt test. After behavioral verification, control and prenatally stressed male rats were injected with imipramine, fluoxetine or tianeptine (10 mg/kg i.p. 21 days). 24 hours after the last injection rats were decapitated and brains were dissected. Biochemical study was conducted with use of ELISA and RT-PCR.

We found that the expression of phospho-IRS-1 (Ser-312) in the frontal cortex of prenatally stressed rats rats was increased. Furthermore, chronic treatment with antidepressants normalized its level. Administration of imipramine and fluoxetine decreased IRS-2 protein level in the frontal cortex of prenatally stressed rats.

It was suggested that antidepressants ameliorate the dysfunction of IGF-1 receptor evoked by prenatal stress. Better understanding of IRS1/IRS2- antidepressant drugs interactions can contribute to improved efficiency of antidepressant treatment.

This work was supported by the Operating Program of Innovative Economy 2007-2013, grant No. POIG.01.01.02-12-004/09.

Board #2
Molecular Predictors of Antidepressant Treatment Outcome

Tania Carrillo-Roa[1], Caleb A. Lareau[2], Callie L. McGrath[3], Boadie W. Dunlop[3], Elisabeth B. Binder[1,3], Helen S. Mayberg[3,4]

[1]Max Planck Institute of Psychiatry, [2]Department of Mathematics, University of Tulsa, [3]Department of Psychiatry and Behavioral Sciences, Emory University, [4]Department of Neurology, Emory University

Major depression is a prevalent disease with high rates of treatment resistance and non-remission. Recently, our group described that resting state brain activity patters of six specific brain regions (ROIs) can predict differential response to either escitalopram (sCIT) or cognitive behavioural therapy (CBT) (McGrath et al. 2013). The aim of this study is to identify molecular markers that associate with these brain activity patterns, in the hope to identify predictive measures that are more easily obtained in clinical practice than neuroimaging measures. Patients were recruited at Emory University and randomized at baseline to 12 weeks sCIT, or 16 sessions of CBT. Genome-wide genotypes (Illumina OmniExpress) and DNA methylation (Illumina HM-450K) were measured in peripheral blood DNA drawn at baseline. Genome-wide SNPs and CpGs univariate and multivariate association analyses including ROIs combinations were conducted in 76 MDD patients. We observed genome-wide significant association of rs34383296 ($p = 9.4x10\text{-}9$) in a multivariate analysis that included three brain regions. Univariate analyses did not reveal genome-wide significant associations. The associated variant lies in a gene dense region on chromosome 9 within the NDOR1 gene and it is an eQTL for ARRDC1, a gene ~400kb downstream related to arrestin-mediated internalization of cell surface receptors. This SNP was genotyped in an independent larger MDD sample and predicted differential response to CBT vs. drug (sCIT and Duloxetine). No epigenome-wide significant association was observed. Our data suggest that using quantitative neuroimaging endophenotypes and genomic approaches may be able to identify markers to guide individualized depression therapy choices.

Board #3
Sulfur Aminoacid Metabolic Process Pathway may Modulate Bipolar Disorder with Alcohol Dependence Comorbidity

Enrico Cocchi[1], Antonio Drago[2], Alessandro Serretti[1]

[1]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy; [2]IRCCS Centro S. Giovanni di Dio, Fatebenefratelli, Brescia, Italy

Background: A relationship between alcohol and Bipolar Disorder (BD) has far been detected. A record of alcohol dependence may worsen the course of BD. Nevertheless, the genetic underpinnings of this comorbidity have not been completely elucidated. Authors investigated the impact of a set of genetic variations as possible risk factors for the pathological mood swings in bipolar patients with a record of alcohol dependence.
Methods: A list of candidate genes identified as risk loci by GWAS studies in last 10 years were tested in a sample of 802 bipolar patients from the STEP-BD study. Variations harbored by these genes were checked for quality, imputed and pruned. A set of 260 genes embedded in 160 different pathways were analyzed as predictors of the frequency of severe (YMRS>11) manic events and depressive phases (MADRS>19) during the period of observation (1139 days for manic relapses and 1856 for depressive phases). Their effect was tested in combination with alcohol comorbidity. Clinical and sociodemographic variables entered the study as covariates.
Results: We found a strong impact of alcohol dependence positive record with an higher frequency of severe manic (p=0.02) and depressive (p=0.0006) phases. A positive association between a pathway related to the Sulfur aminoacid metabolic process (GO:0000096) and an increased frequency of severe depressive phases was detected for BD subjects with a record of alcohol dependence.
Discussion: We found an association between GO:0000096 (Sulfur aminoacid metabolic process pathway) and severe depressive episodes in BD patients with a record of alcohol dependence in their clinical story.

Board #4
The Genetics of Vascular Incidents Associated with Second-generation Antipsychotic Administration

Enrico Cocchi[1], Antonio Drago[2], Diana de Ronchi[1], Alessandro Serretti[1]

[1]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy; [2]IRCCS Centro S. Giovanni di Dio, Fatebenefratelli, Brescia, Italy

Second-generation antipsychotics (SGA) have been associated with risk of stroke in elderly patients, but the molecular and genetic background under this association has been poorly investigated. The aim of the present study was to prioritize a list of genes with an SGA altered expression in order to characterize the genetic background of the SGA-associated stroke risk. Genes with evidence of an altered expression after SGA treatments in genome-wide investigations, both in animals and men, were identified. The Genetic Association Database (GAD) served to verify which of these genes had a proven positive association with an increased stroke risk, and along with it each evidence was tested and recorded. Seven hundred and forty five genes had evidence of a change of their expression profile after SGA administration in various studies. Nine out of them have also been significantly related to an increased strokes risk. We identified and described nine genes as potential candidates for future genetic studies aimed at identifying the genetic background of the SGA-related stroke risk. Further, we identify the molecular pathways in which these genes operate in order to provide a molecular framework to understand on which basis SGA may enhance the risk for stroke.

Board #5
The Extracellular Domains may hold the Pruning Related Events that are Risk Factors for Schizophrenia and Bipolar Disorder

Enrico Cocchi[1], Antonio Drago[2], Diana de Ronchi[1], Alessandro Serretti[1]

[1]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy; [2]IRCCS Centro S. Giovanni di Dio, Fatebenefratelli, Brescia, Italy

Objectives: Pruning may be a key event for Schizophrenia (SKZ) and Bipolar Disorder (BD). Authors identified the proteins involved in pruning and tested the rate of their aminoacidic conservation (global and local rates) in three different species (Humans, Chimpanzees and Rats), tested the hypothesis that the less conserved proteins cluster in some specific molecular aspects (intracellular vs extracellular events), and tested the hypothesis that the less conserved proteins are more at risk for SKZ and BD.
Methods: Methods included systematic literature research (Pubmed, Embase), the use of CLUSTAL W for calculating the animoacid conservation rate and the use of ANOVA for testing the hypotheses under analysis.
Results: 117 key proteins were identified. Less conserved proteins were significantly involved in extracellular events. Proteins for which an association with SKZ or BD was retrievable from literature were significantly more frequent in the extracellular group (SKZ p=0.! 0307 F=4.9; BD p=0.035, F=4.8;)
Conclusions. Authors provide a list of proteins related to pruning that may be candidate of investigation for SKZ and BD and suggest that the higher complexity of pruning in the human brain mostly takes place in the extracellular matrix and is led by the less conserved proteins.

Board #6
Genetics of Treatment-induced Side Effects in the STEP-BD Study

Chiara Fabbri, Alessandro Serretti

Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

Bipolar disorder (BD) is a disabling disorder that is associated with increased risk of suicide and poor quality of life. The treatment of BD usually requires the use of polypharmacotherapy, that raises the critical issue of the emergence of unwanted side effects, and the consequent possibility of low treatment adherence. Most notably, metabolic, extrapiramidal (EPS) and sexual side effects have been associated with genetic risk variants.
The present study aimed to identify polymorphisms that influence the risk of psychic (sedation and memory), EPS, autonomic (dry mounth, constipation, diarrhea), and sexual side effects. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) genome-wide dataset was used after standard quality control. Linear regression was performed including appropriate covariates. Pathway enrichment was assessed through the cytoscape program and geneMANIA plugin in order to identify possible molecular mechanisms involved.
854 patients (743 treated with polypharmacotherapy) were included. Most interesting findings were in LINGO2 (involved in neuronal differentiation and synaptic plasticity), cell-cell adhesion and regulation of locomotion pathways for autonomic side effects; regulators of gene expression (RASSF5 and NR2C) and neurocognition (WDR72), Wnt receptor signaling and cytokine production pathways for EPS; PPARGC1B (involved in circadian regulation), transmembrane receptor protein phosphatase activity and protein deacetylation pathways for psychic side effects; PARK2 for sexual dysfunction. PARK2 mutations were demonstrated to alter activity in basal ganglia that are involved in sexual arousal.
The present study suggested some candidate genes and molecular pathways that may be involved in psychotropic-induced side effects in BD; further studies should confirm their role.

Corresponding author:
Alessandro Serretti
Department of Biomedical and NeuroMotor Sciences, University of Bologna,
Viale Carlo Pepoli 5, 40123 Bologna, Italy
Tel +39 051 6584233
Fax +39 051 521030
Email: alessandro.serretti@unibo.it

Board #7
The Complexity of Genetic Effects in Pharmacogenetics: Focus on Neuroplasticity, Environmental Stress and Response to Antidepressants

Laura Mandelli, Roberta Emiliani, Agnese Marsano, Martina Balestri, Siegfried Alberti, Diego Albani, Alessandro Serretti

University of Bologna, Italy

In the last years, interest has been increased in the potential involvement of neurotrophic and growth factors (neuroplasticity) in psychiatric disorders' risk and psychotropic drugs' effects. However, studies have provided mixed and conflicting results so far, suggesting that these effects may be moderated by other influences than genetics. We preliminarily evaluate the role of genetic variation within two genes involved in neuroplastic processes in early response to antidepressants (ADs): the Brain derived neurotrophic factor (BDNF) and Sialyltransefarase X (ST8SIA2). We also tested potential differential effect of genetic variants depending on exposure to stressful life events (SLEs).

One-hundred and fourteen patients affected by Mood or Anxiety disorders, enrolled for treatment with ADs, were evaluated at baseline and weekly thereafter until the fourth week by the Hamilton Rating Scale for Depression (HRSD). Alleles in two SNPs in BDNF (rs11030101, rs11030104) and in two SNPs in ST8SIA2 (rs11853992, rs17522085) were associated to a slower response to ADs only if non-exposed to SLEs at onset, whilst they had a similar response compared to the carriers of the opposite variant if exposed to SLEs. Haplotype analyses confirmed these trends.

Variants in BDNF and ST8SIA may influence differentially the early response to ADs depending on exposure to SLEs at illness onset. The complex interplay between genetic effects, environmental factors, as well as other biological systems deserves further investigation by means of sophisticated methods of investigation.

Board #8
Analysis of Drug Target Gene Sequences with Suicide Severity in Bipolar Disorder

Clement C. Zai, Vanessa Goncalves, Vincenzo de Luca, Arun K. Tiwari, Sarah Gagliano, Jo Knight, John B. Vincent, James L. Kennedy

Centre for Addiction and Mental Health, Toronto

Suicide claims one million lives a year worldwide, and for each suicide there are 20 attempts, making suicidal behaviour a serious public health problem. The mechanism of susceptibility for suicidal behaviour in unclear, however genetic factors appear to play a prominent role.
We analyzed 3199 DNA variants across 202 drug target genes in our sample of bipolar disorder patients of European ancestry (N=227). We analyzed the phenotype of suicide severity score from the Schedule for Clinical Assessment in Neuropsychiatry). We conducted preliminary analysis, including individual variant tests using PLINK, and gene-based test using GRANVIL, including history of alcohol use disorder, sex, and age as covariates.
Among the findings, we found a number of common DNA variants in TGFBR1 to be nominally associated with suicide severity scores (uncorrected $p<0.05$). The gene-based tests also pointed to TGFBR1 to be associated with suicide severity (corrected $p<0.02$).
Conclusions: We analyzed high-throughput targeted sequence data with suicide severity in bipolar disorder and found a number of gene regions to be possibly associated with suicidality, including TGFBR1. We will be incorporating functional annotation in further analysis of this data. We will attempt to replicate the validated results in other bipolar disorder and psychiatric samples.

Corresponding author:
James L. Kennedy
Jim.kennedy@camh.ca
Ph: 1-416-9794987
Fax: 1-416-9794666

Board #9
Pharmacogenetics of Remote Regulatory Variants of 14 Obsessive-Compulsive Disorder Candidate Genes in Antidepressant Response

Gwyneth Zai[1,2], Clement Zai [1], Vanessa Goncalves [1], Karen Wigg [4], James L. Kennedy [1,2], Margaret A. Richter [2,3]

[1]Neurogenetics Section, Centre for Addiction and Mental Health, Toronto; [2]Department of Psychiatry, University of Toronto; [3]Department of Psychiatry, Sunnybrook Health Science Centre, Toronto; [4]Genes and Development Division, Toronto Western Hospital, University Health Network, Toronto

Obsessive-Compulsive Disorder (OCD) is a chronic and debilitating disorder with a strong genetic etiology. Genetic associations between OCD and several candidate genes including the glutamate transporter (SLC1A1), monoamine oxidase (MAOA), glutamate NMDA receptor 2B (GRIN2B), serotonin 2A receptor (5HTR2A), serotonin transporter (SLC6A4), brain-derived neurotrophic factor (BDNF), and catecholamine-O-methyl transferase (COMT) genes have previously been reported. Pharmacogenetics represents a valuable alternative strategy to define subtypes of OCD and to define clinically useful inter-individual genetic variation in drug response. We investigated 14 genes including those mentioned above as well as top hit genes from a recent OCD genome-wide association study: Disks Large (drosophila) homolog-associated protein 1 (DLGAP1), BTB (POZ) domain containing 3 (BTBD3), serotonin 1B receptor (5HT1B), SLIT and NTRK-like family (SLITRK5), Fas apoptotic inhibitory molecule 2 (FAIM2), glutamate receptor, ionotropic, kainite 2 (GRIK2), and fucosyl-transferase 2 (FUT2). We examined a total of 32 single nucleotide polymorphisms across these candidate genes and their regulatory regions using a custom-made 32-SNP OpenArray® chip and genotyping was performed using the QuantStudio™ 12K Flex Real-Time PCR System in 222 OCD patients with retrospective response data on multiple serotonin reuptake inhibitor (SRI) trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported "minimal", "no change", or "worsening". Genotypes and response data were examined on a combined SSRI/SRI basis. Interesting associations ($P<0.05$) were detected for DLGAP1, SLITRK5, BTBD3, 5HT1B, and SLC1A1 in SSRI/SRI response. These results suggest that genetic variants may play a

Board #9 (continued)

role in SRI response to OCD. Combination of these variants may be clinically useful in predicting treatment resistance versus response in OCD.

Corresponding Authors:
1. Gwyneth Zai; Tel: (416) 535-8501 ext. 30145; Fax: (416) 979-4666; Email: gwyneth.zai@camh.ca, gwyneth.zai@mail.utoronto.ca
2. Peggy Richter; Tel: (416) 480-6832; Fax: (416) 480-5119; Email: peggy.richter@sunnybrook.ca
3. James L. Kennedy; Tel: (416) 979-4987; Fax: (416) 979-4666; Email: jim.kennedy@camh.ca

Board #10
Abelson Helper Integration Site-1 Gene Variants on the Diagnosis and Treatment Outcomes in Mood Disorder

Stefano Porcelli, Chi-Un Pae[1], Beatrice Balzarro, Siegfried Alberti, Diana De Ronchi, Alessandro Serretti

[1]The Catholic University of Korea

Objective: The present study aimed to explore whether 4 single nucleotide polymorphisms (SNPs) within the AHI1 gene could be associated with major depressive disorder (MD) and bipolar disorder (BD), and whether they could predict clinical outcomes in mood disorders.
Methods: One hundred and eighty-four (184) patients with MD, 170 patients with BD and 170 healthy controls were genotyped for 4 AHI1 SNPs (rs11154801, rs7750586, rs9647635 and rs9321501). Baseline and final clinical measures for MD patients were assessed through the Hamilton Rating Scale for Depression (HAM-D). Allelic and genotypic frequencies in MD and BD subjects were compared with those of each disorder and healthy group using the $\chi 2$ statistics. Repeated measures ANOVA was used to test possible influences of SNPs on treatment efficacy.
Results: The rs9647635 A/A was more represented in subjects with BD as compared with MD and healthy subjects together. With regard to the allelic analysis, rs9647635 A allele was more represented in subjects with BD and rs7750586 C frequency was higher in subjects suffering from BD and MD as compared with healthy subjects together.

Board #10 (continued)

Conclusion: Our findings provide potential evidence of an association between some variants of AHI1 and mood disorders susceptibility but not with clinical outcomes. However, we will need to do more adequately-powered and advanced association studies to draw any conclusion due to clear limitations.

Board #11
Effect of Glutamate Transporter Gene Methylation on PTSD Symptomatology and Treatment Outcome

Zhewu Wang[1,2], Antonina Farmer[2], Jingmei Zhang[2], Howard Mendal[1], Kathleen Robinson[2], Floyd Sallee[2], Mark Hamner[1,2]

[1]Charleston VA Medical Center; [2] Institute of Psychiatry, Medical University of South Carolina

Background: Posttraumatic Stress Disorder (PTSD) is a debilitating disorder related to disturbance of fear acquisition and extinction. A growing body of evidence suggests that glutamatergic neurotransmission may be involved in the biological mechanisms underlying stress response and anxiety-related disorders. The glutamatergic system mediates the acquisition and extinction of fear-conditioning. Our primary objective was to determine glutamate transporter gene (GAT) methylation in the development of PTSD and comorbid depression.
Methods: One hundred combat veterans with and without PTSD were recruited. DNA methylation analysis of GAT performed on the 100 combat veterans 50 with PTSD and 50 controls)
Results: Patients with PTSD are much more likely to be methylated compared with controls (X^2 = 9.37, p = .002). Of the PTSD group, those who were methylated were more likely to also have major depression disorder (MDD, X^2 = 5.13, p = .02), and had higher HAM-D scores (B = .10, p = .005).
Conclusion: Our preliminary data indicate that the presence of high methylation of GAT may constitute a risk factor for PTSD development following exposure to trauma, and the same methylation may specifically associated with comorbid PTSD and MDD, further to treatment resistance. Further research is needed to confirm our results, as our sample size, especially in the clinical treatment arm.

Corresponding: Zhewu Wang: Ph#: 843-792-7135; Fax: 843-792-6851; email: wanzh@musc.edu.

Board #12
The Role of Opioid Receptor Genes in the Pharmacotherapy of Drug Addiction

Isabelle E. Bauer, Jair C. Soares, and David A. Nielsen

University of Texas

Background: Drug addiction is a serious illness with deleterious functional and social consequences for both the affected individuals and their families. In spite of the abundant research on substance dependence, there is no fully effective treatment for this disease. Growing evidence suggests that gene expression profiling can help predict treatment response and assist in developing effective treatments for drug addiction.
Objective: Given the crucial role of the endogenous opioid system in the development and maintenance of substance abuse disorder we reviewed the literature on the opioidergic system and examined the role of opioidergic genes in pharmacotherapies of alcohol, opioid and cocaine addiction.
Results: The μ, δ and κ opioid receptors OPRM1, OPRD1 and OPRK1 genes have been found to be promising markers of treatment efficacy for these substance use disorders. An individual's opioid receptor genotype modulates treatment response to opioid antagonists such as naltrexone, and methadone, as well as the cocaine vaccine.
Conclusions: Pharmacogenetics is a promising field that has the potential to improve patient care and reduce health care costs related to drug addiction. However, more research is needed to validate current findings and lead to relevant clinical recommendations that may be used to treat and alleviate specific drug addictions.

Board #13

Increased MIF and IL-1β mRNA Blood Levels and Childhood Trauma Events as Accurate Predictors of Treatment Response in Depressed Patients

A. Cattaneo[1], R. Uher[2], L. Bocchio-Chiavetto[3], M.A. Riva[4], C.M. Pariante[1]

[1]King's College London, Institute of Psychiatry, Department of Psychological Medicine, Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology (SPI-Lab); [2]King's College London, Institute of Psychiatry, Social Genetic Developmental Psychiatry; [3]Neuropsychopharmacology Unit, Istituto di Ricovero e Cura a Carattere Scientifico San Giovanni di Dio, Fatebenefratelli Centre; [4]Department of Pharmacological and Biomolecular Sciences, University of Milan

A third of patients do not respond to any currently available antidepressants and there is a need to establish predictive biomarkers of treatment response useful for therapy personalization. To identify predictive biomarkers of treatment response to be easily replicated in different laboratories we measured the absolute blood mRNA expression of MIF and IL-1β, two proinflammatory genes that we previously found associated with treatment response (Cattaneo et al., 2013). The absolute number of molecules for MIF and IL-1β were higher in non-responders (83.1±4.8 x106 for IL-1β and 102.5±4.2x106 for MIF) as compared with responders (50.4±2.1x106 for IL-1β, and 55.4±1.9x106 for MIF). By using a Linear Discriminant Analysis we combined MIF and IL-1β values with treatment response and we defined a rule able to discriminate responders vs. non-responders. We also calculated MIF and IL-1β cut-off values and the relative probability of being a responder or a non-responder.

We then validated these findings in an independent sample of depressed patients and we found that our predictive model had 14% of false positives and 16% of false negatives. Interestingly the patients which erroneously have been identified as non-responders, because of high baseline levels of cytokines, showed a reduction in the cytokines levels -to levels similar to responders- already at week 4; moreover, the patients which were erroneously classified as responders, because of normal baseline cytokine levels, reported severe childhood trauma events. Our data suggest that both high cytokines levels and a history of childhood trauma may provide a clinically-suitable approach to identify patients who are non-responders to classic antidepressants and maybe benefit from immune-targeted therapy.

Board #14
Treatment Resistant Schizophrenia: Run of Homozygosity Analysis

Vincenzo De Luca, Jiali Song, Ali Bani-Fatemi, Tiffany Leung, Ariel Graff

CAMH, Department of Psychiatry, University of Toronto

The treatment of patients with schizophrenia who fail to respond to antipsychotics is a major challenge and the proportion of treatment-resistant patients is estimated to be 20–40%. There are few genetic association studies that have compared resistant versus non-resistant schizophrenic patients; however, many genetic association studies focusing on antipsychotic response have been published. This contribution investigates the genetics of treatment-resistant schizophrenia, testing genome-wide more 2 million variants. First, we identified a subgroup of treatment-resistant patients in a sample of 122 schizophrenia patients using the American Psychiatric Association criteria and then we genotyped all patients using the Illumina Omni 2.5 Chip comprising of 2.4M SNPs. We screened all subjects for run of homozygosity using the function implemented in SVS. No significant difference in the length of run of homozygosisty were found between resistant and non-resistant patients. Our run of homozygosity analysis did not indicate any robust association with treatment-resistant schizophrenia. However, this phenotype can be assessed retrospectively in cross-sectional studies and these preliminary results point out the importance of choosing alternative phenotypes in psychiatric pharmacogenetics.

Board #15
Exploring Interactions between *COMT*, *BDNF* and *AKT1* and Cannabis Consumption in the Genesis of Psychosis

Brodie Heywood,[1] Beatriz Carvalho Henriques,[1] David Rossolatos,[1] Darren Bugbee,[2] Aleksandra Dimitrijevic,[2] Alexandra Loverock,[3] Carol Bolt,[4] Georgina Macintyre,[1,2,6] Phil Tibbo,[5] Katherine J. Aitchison,[1,6,7] Scot E. Purdon[1,3,4]

[1]Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [3]Edmonton Early Psychosis Intervention Clinic, Edmonton, Alberta, Canada; [4]Neuropsychology, Alberta Hospital Edmonton, Edmonton, Alberta, Canada; [5]Nova Scotia Psychosis Research Unit, Dalhousie University, Halifax, Nova Scotia, Canada; [6]Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada; [7]King's College London, Institute of Psychiatry, MRC Social Genetic and Developmental Psychiatry Centre, London, UK

*Brodie Heywood and Beatriz C. Henriques contributed equally and are joint first authors.

Background: Although psychosis is a relatively treatable condition, the mechanisms that trigger psychotic symptoms are still being elucidated. For example, it is known that the consumption of substances such as cannabis can induce psychosis, but how this interacts with other factors such as genetic vulnerability still requires further exploration and replication in a variety of samples. If genetic vulnerabilities to cannabis exposure were better understood, appropriate measures in public health education could be taken. *COMT*, *BDNF*, and *AKT1* are amongst candidates for genes leading to susceptibility to psychosis following cannabis use (Decoster *et al*, 2012; van Winkel *et al,* 2011; Di Forti *et al,* 2012).
Methods: In this study, we are seeking to explore the role of markers in the above candidate genes and cannabis use in a sample of patients with psychosis recruited in Edmonton and Halifax. The markers are rs4680 (Val158Met) in *COMT*, rs2494732 in *AKT1*, and rs6265 (Val66Met) in *BDNF*. Data on substance use and other relevant variables including cognition have been collected.
Results: The proportion of our sample that has used cannabis in their lifetime is approximately 70%, with a smaller proportion having problematic substance use. The *COMT* genotypes were in Hardy-Weinberg equilibrium. Analysis stratifying for cannabis use is underway.

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Conclusions: It will be interesting to see whether or not findings identified in European Caucasians hold up in our Albertan and Nova Scotia samples, and specifically whether or not there are gene-by-cannabis effects on cognitive performance.

Funding and Acknowledgements: This study was funded by the Canadian Institutes of Health Research (CIHR): NPAS3 variants in schizophrenia and other psychoses. KJA holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta (Canada). Thanks to The Applied Genomics Core (TAGC; University of Alberta) for assistance with genotyping.

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Corresponding Author
Katherine Aitchison
Psychiatry Research Offices KATZ 5-020
Katz Group Center for Pharmacy and Health Research
University of Alberta
Edmonton, AB Canada T6G 2E1
aitchadm@ualberta.ca
tel: 780-492-4018
fax: 780-492-7789

Board #16
Brain-derived Neurotrophic Factor Val66Met Polymorphism and Antipsychotic-induced Tardive Dyskinesia

Maju Mathew Koola,[1] Evangelia Tsapakis,[2] Benjamin Williams,[2] Paul Scully,[3] John Quinn,[3] Padraig Wright,[4] Shubulade Smith,[5] Ann Daly,[6] Michael Gill,[7] John Waddington,[3] Robert Kerwin (RIP),[8] Katherine Aitchison[2,9]

[1]Sheppard Pratt Health System and Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA; [2]King's College London, Institute of Psychiatry, MRC Social Genetic and Developmental Psychiatry Centre, UK ; [3]Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin, Ireland; [4]Takeda Development Centre, London, UK; [5]Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, King's College London, UK ; [6]Institute of Cellular Medicine, Medical School, Newcastle University, Newcastle upon Tyne, UK; [7]Department of Psychiatry & Neuropsychiatric Genetics Research Group, Trinity College, Dublin, Ireland; [8]Section of Clinical Neuropharmacology, King's College London, Institute of Psychiatry, London, UK; [9]Departments of Psychiatry and Medical Genetics, University of Alberta, Edmonton, Alberta, Canada.

Objective: The aim of this study was to examine the association between the brain-derived neurotrophic factor (*BDNF*) gene rs6265 (Val66Met) polymorphism and tardive dyskinesia (TD) whilst on antipsychotic treatment.
Methods: Subjects (N=233) were English or Irish Caucasians with schizophrenia or schizoaffective disorder. They were rated for TD (TD/non-TD=72/161) using the abnormal involuntary movement scale (AIMS). Genotyping was performed by TaqMan. Data were analysed by the $\chi 2$-test comparing genotypes in those with or without TD. In addition, multiple linear regression (dependent variable: total AIMS score; rs6265 genotype the independent predictor, controlling for potential confounding variables), was performed.
Results: The mean age distribution of the TD group was significantly higher than that of the non-TD group ($p<0.001$). However, patients in the TD group were on antipsychotics for longer duration ($p<0.001$). Duration of antipsychotic treatment was significantly correlated with age (Pearson correlation=0.682, $p<0.001$) and the presence or absence of Parkinsonism was significantly correlated with the presence or absence of TD ($p< 0.001$). In the whole sample of N=233, *BDNF* genotype distributions did not significantly differ from

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the Hardy-Weinberg equilibrium, and allelic frequencies did not differ significantly from these previously reported for Caucasians. There were no significant differences in the frequencies of *BDNF* genotypes ($\chi 2=0.307$, $df=3$, $p=0.959$) and *BDNF* alleles between the TD ($\chi 2=0.768$, $df=1$, $p=0.190$) and non-TD groups ($\chi 2=0.737$, $df=1$, $p=0.195$).
Conclusion: This study replicates previous negative findings on the association of *BDNF* Val66Met and susceptibility to TD.

Corresponding Author:
Maju Mathew Koola
Clinical Research Program
Sheppard Pratt Health System
6501 N Charles St. Baltimore, MD USA 21204
Tel: 410-938-5429
Fax: 410-938-5023
majujuju@yahoo.com

Board #17
Genetic Correlates of Cognitive Remediation Response in Schizophrenia

J.P. Lindenmayer[1,2,6], H. Lachman[3], S. Kaushik[4], A. Khan[2,6,7], S. McGurk[5], A. Thanju[6], L. Gao[7], T. Michaels[6], R. Jit[6], I. Ljuri [6]

[1]New York University, [2]Nathan S. Kline Institute for Psychiatric Research, [3]Albert Einstein College of Medicine, [4]St. Josephs Hospital, [5]Boston University, [6]Manhattan Psychiatric Center [7]ProPhase, LLC

Background: Single nucleotide polymorphisms (SNPs) of the catechol-O-methyltransferase (COMT) (Val108/158Met, rs4680), BDNF (Val66Met rs6265) and the ZNF804A genes make them strong candidates for investigating cognitive functions as well as with the response to interventions for improving cognition. The present study examined the effects of COMT, BDNF or ZNF804A on response in schizophrenia to cognitive remediation (CRT).
Methods: 304 subjects were recruited from a CRT trial of 36 sessions, over 12 weeks. 47.04% (n = 143) participated in the genetic study. Categorical and multivariate ANOVA were used to test the association of genotypes and measures of response to CRT (MCCB-MATRICS). Reliable Change Index (RCI) identified improvers and non-improvers.

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Results: 90 subjects were improvers (62.9%). A larger percentage of Val/Met (69.45%) and the Met/Met (65.00%) were identified as improvers (p = .043). There was a significant finding for ZNF804A and visual learning with the C/A + A/A allele showing greater change than the C/C group. There was significant mean change in COMT working memory for Val/Met (14.10 (8.96)) and Met/Met (13.15(10.72)) alleles compared to Val/Val allele ((9.00(8.05)), p = .006). ZNF408A (p = .010) C/C allele showed a larger increase in verbal learning (1.81 (3.48)) compared to the C/A + A/A (.08 (4.40)) allele.
Conclusions: The study confirms findings of the COMT genotype on response to CRT, but did not find effects of BDNF and a limited effect of ZNF804A. Data suggest that COMT genotype may influence the response to CRT and suggest a translational approach for subjects.

Board #18
Pharmacogenetics of Clozapine Response and Metabolic Side Effects: A Comprehensive Review and Meta-analysis

Stefano Porcelli[1], Florence Gressier[2], Raffaella Calati[1], Alessandro Serretti[1]

[1]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy; [2]InsermU669, Department of Psychiatry, Univ Paris Sud, Assistance Publique-Hôpitaux de Paris, Bicêtre University Hospital, Le Kremlin Bicêtre, France

Background: Clozapine (CLZ) is the prototype atypical antipsychotic and it has many advantages over other antipsychotic drugs [1]. Several data suggest that both CLZ response and tolerability are strong determined by genetic variability [2]. Aims: we aim to review the literature data about pharmacogenetics studies on CLZ efficacy, focusing on pharmacodynamic genes. Further, we performed meta-analyses when at least three studies for each polymorphism were available for inclusion.
Methods: An electronic search of the literature was performed to identify pertinent studies using PubMed, ISI Web of Knowledge and PsycINFO databases. We included in the paper only polymorphisms investigated at least in three independent samples. For meta-analyses, data were entered and analyzed through RevMan version 5.2.

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Results: Our literature search yielded 9266 articles on CLZ; among these, we identify 59 pertinent pharmacogenetic studies, which were included in the study. Genotype data were retrieved for 14 polymorphisms in 9 genes upon the total 168 polymorphisms in 44 genes that were investigated in literature. Among these, we had available data from at least three independent samples for 8 SNPs to perform meta-analyses. Although literature review provided conflicting results, four genetic variants within serotonin genes resulted associated to CLZ response in our meta-analyses: rs6311 and rs6314 within HTR2A gene, rs6318 within HTR2C gene and rs1062613 within HT3A gene.
Discussion: Our results suggest a strong importance of serotonergic genes on clinical response to CLZ. These findings could be others pieces of knowledge to move forward the simplistic dopaminergic hypothesis for schizophrenia.

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Board #19
First Episode Psychosis Pharmacogenetics: Does Glutamate Affect Antipsychotic Response?

James M. Stevenson[1], James L. Reilly[2], Margret S.H. Harris[3], Konasale M. Prasad[4], Judith A. Badner[5], Vishwajit Nimgaonkar[4,6], Matcheri S. Keshavan[7], John A. Sweeney[8], Jeffrey R. Bishop[1]

[1] Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy; [2] Department of Psychiatry and Behavioral Sciences Northwestern University Feinberg School of Medicine; [3] Jesse Brown Veteran's Administration Medical Center; [4] Department of Psychiatry, Western Psychiatric Institute and Clinic; [5] Department of Psychiatry, University of Chicago; [6] Department of Human Genetics, University of Pittsburgh; [7] Department of Psychiatry, Harvard Medical School; [8] Department of Psychiatry, University of Texas Southwestern Medical Center

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Background: Glutamate-related genes have been associated with antipsychotic response. Whether these findings are disease-specific or broadly related to a psychosis phenotype is unknown.
Methods: Eighty-eight untreated patients experiencing first episode psychosis (schizophrenia n=69, BPD with psychotic features n=11, MDD with psychotic features n=8) with no/minimal prior antipsychotic exposure were evaluated before and after six weeks of antipsychotic treatment (primarily risperidone, n=70) using the BPRS. Our hypothesis-driven approach examined 3,072 common SNPs in 58 glutamate-related genes using the Affymetrix SNP 6.0 array. Permutation analysis (n=10,000) was used to adjust for multiple comparisons. Models adjusted for baseline symptoms, ancestry, and chlorpromazine equivalent antipsychotic dose.
Results: Eight of 20 SNPs most strongly associated with symptom response, including the top two variants, were in *GRM7* (all $p<0.003$). Findings were primarily driven by changes in positive symptoms. Associated variants were predominantly localized to an 18kb region of *GRM7.* Findings related to rs2069062 represented BPRS change scores of 12.0 (C/C n=59), 5.6 (C/G n=25), and 1.8 (G/G n=4) ($p<0.001$ adjusted for clinical covariates). Findings were similar in the schizophrenia subgroup. Despite clinically-meaningful effect sizes, findings did not retain statistical significance after multiple comparisons adjustment.
Conclusions: *GRM7* encodes the presynaptic mGluR7 group-III metabotropic glutamate receptor-7. We identified a variant of the intronic rs2069062 associated with worse clinical response. Literature suggests that agonizing mGluR7 results in decreased NMDA activity. Results are consistent with the hypothesis that altered mGluR7 function represents a mechanism for treatment resistance during early treatment. These potentially clinically-meaningful effects warrant validation in additional study samples.

Corresponding author: James M. Stevenson; jmstev@uic.edu; 312-355-4104

Board #20
Use of Pharmacogenetic Testing in Routine Clinical Practice Improves Outcomes for Psychiatric Patients

Sandeep Vaishnavi[1, 3], Timothy Ramsey[2], Elizabeth Griffin[1], Qian Liu[2], and Mark Brennan[2]

[1]The Neuropsychiatric Clinic [NPC] at Carolina Partners, Raleigh, North Carolina; [2]SureGene, LLC Louisville, KY; [3]Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina

Introduction: In structured environments, pharmacogenetic (PGx) testing has been shown to improve outcomes in psychiatry, especially depression. However, few studies have examined whether or not this PGx effect would translate into routine clinical care across diagnoses. This study examined PGx testing in routine clinical practice at a single clinic.
Patients and Methods: This study retrospectively looked at data from patients from The Neuropsychiatric Clinic at Carolina Partners in Raleigh, NC who were either tested (n=74) or not tested (n=57) with a commercially available genetic test at physician's discretion. All subjects had at least four evaluations with the NeuroPsych Questionaire – Short Form (NPQ), a computer-based assessment that provided quantitative measures for 12 symptom dimensions: aggression, anxiety, attention, depression, fatigue, impulsivity, memory, mood, pain, panic, sleep, and suicide. The study looked at 300 days' data. Treatment effects were estimated using a general linear model incorporating all time points and baseline values for the 12 NPQ individual items.
Results: After correcting for multiple comparisons, anxiety, panic, and mood instability symptoms displayed significant daily improvement in the tested group, while no domains did so for the untested group. By day 300, tested patients experienced significantly greater improvement for aggression, anxiety, depression, fatigue, impulsivity, mood stability, panic, and suicide symptoms compared to untested patients ($p=10^{-8}$ to 10^{-20}).
Conclusions: In routine clinical practice, PGx testing can enable significant improvement in clinically important outcomes for psychiatric patients across a broad spectrum of diagnoses.

Communicating author: Timothy Ramsey
Email: tim.ramsey@suregene.net
Phone: 502.287.0903
Fax: 859.663.2984

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