THE 12TH ANNUAL
PHARMACOGENETICS IN PSYCHIATRY MEETING
FRIDAY, MAY 31, 2013

POSTER PRESENTATIONS

1. **Genetics of Functional Disability in Schizophrenia and Bipolar Disorder: Preliminary Results from VA CSP 572**
   Philip D. Harvey, Ph.D.
   University of Miami, Miller School of Medicine
   Miami, Florida, USA

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

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

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

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

6. **The ERK Pathway Involved in Treatment Side Effects in BD-I**
   Antonio Drago, M.D.
   Department of Biomedical and Neuromotor Sciences Institute of Psychiatry, University of Bologna, Italy

7. **Predicting Antidepressant Treatment Response through Genomewide Interaction and Enrichment Analysis**
   Niki Antypa, Ph.D.
   Department of Biomedical and NeuroMotor Sciences, Institute of Psychiatry, University of Bologna, Italy

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

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

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

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

12. **Antipsychotic-induced Weight Gain and the Role of Histamine Receptor H1 and H3 Variants**
    Trehani Fonseka, BHSc (Honours)
    Pharmacogenetics Research Clinic, Neuroscience Department, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada

13. **Association of the Glucagon-like Peptide 1 and the Glucagon-like Peptide 1 Receptor Genes with Antipsychotic-induced Weight Gain**
    Eva J. Brandl, M.D.
    Pharmacogenetics Research Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto, Ontario, Canada

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

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

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

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

18. **Genes and Antidepressant Efficacy in Major Depressive Disorder: A Comprehensive Meta-analysis**
    Tomihisa Niitsu, M.D., Ph.D.
    Institute of Psychiatry, University of Bologna, Italy

19. **Genotyping of CYP2D6 and CYP2C19 Metabolizer Status to Guide Psychiatric Drug Treatment: Updates from the CAMH Pharmacogenetics Research Clinic**
    Janna Fe Notario, B.Sc(Hons.)
    Centre for Addiction and Mental Health & Dept. of Psychiatry, University of Toronto, Ontario, Canada

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

21. **Developmental Changes in Functional Activation during Cognitive Control**
    Katherine Karlsgodt, Ph.D.
    Division of Psychiatry Research, Zucker Hillside Hospital
    Glen Oaks, New York, USA

22. **Multiple Obesity-related Genes are Associated with Antipsychotic-induced Weight Gain in Drug Naïve Pediatric Patients**
    Jianping Zhang, M.D., Ph.D.
    Division of Psychiatry Research, Zucker Hillside Hospital
    Glen Oaks, New York, USA

23. **Adjusting Antipsychotic Dosage in Schizophrenia: Association Analysis of 384 SNPs and CPZ Equivalents**
    Vincenzo De Luca, Ph.D.
    Department of Psychiatry, University of Toronto
    Toronto, Ontario, Canada

POSTER SESSION ABSTRACTS
Friday, May 31, 2013

Board #1

Genetics of Functional Disability in Schizophrenia and Bipolar Disorder: Preliminary Results from VA CSP 572

Philip D. Harvey, Ph.D.[1], Larry J. Siever, M.D.[2], John Concato, M.D.[3], J. Michael Gaziano, M.D.[4], Alysia Maffucci, J.D.[5]

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Background: Given the prominence of cognitive impairment and disability in both schizophrenia and bipolar disorder, substantial interest has arisen in identification of their determinants. Recent findings regarding the heritability of cognitive impairment and everyday disability has led to the suggestion that the cognitively demanding component skills that underlie disability, referred to as functional capacity, may also be heritable and associated with specific genetic polymorphisms. The current study addresses these issues, and here we are presenting initial data on recruitment and characterization of the sample. These data are particularly relevant to bipolar disorder because of reduced attention paid to

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

Results: A total of 6,280 veterans (46% SZ, 54% BP) have been recruited and assessed to date. Veterans with SZ were more likely to never have been married or employed (other than military service) compared to Veterans with BP; lifetime PTSD and suicidality were more common in the BP patients. Performance on the functional

Board #1 (continued)

capacity measures for both patient groups was, on average, within one point of all previously published studies with the UPSA-B, and the BP patients performed slightly better than SZ patients. Similarly consistent results were found for NP test performance, with mean t-scores for the Veterans with SZ of 35 (-1.5 SD) and 40 (-1.0 SD) for the Veterans with BP.

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

Board #2

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

Stefano Porcelli[1], Beatrice Balzarro[1], Chi-Un Pae[2,3], Diana De Ronchi[1], Alessandro Serretti[1]

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

Board #2 (continued)

Methods: 573 in-patients of Korean ethnicity were genotyped for 2 PDE7B, 3 NMBR and 3 EPM2A SNPs. Patients were eligible for inclusion if they had a documented clinical diagnosis of SKZ according to the DSM-IV TR criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.). There was not any particular restriction with regard to the choice of the antipsychotic. Additionally, the following clinical and demographic variables were recorded: age, sex, age at onset, familiar history of psychiatric disorders, lifetime suicide attempts, duration of the illness, antipsychotic dosages (expressed in chlorpromazine equivalents). The main outcome measures of the present study was the possible influences of the 8 SNPs within the 3 genes under investigation on clinical improvement as measured with the Positive and Negative Symptoms Scale (PANSS) total score and PANSS subscales scores in SKZ patients. Repeated measures ANOVA was used to test possible influences of ! SNPs on treatment efficacy. In case of positive findings, clinical and demographic variables were added as covariates, in order to investigate possible stratification effects. Allelic analysis and haplotypes analysis were also performed.
Results: rs1415744 within the EPM2A gene was associated with PANSS negative clinical improvement (p=0.02). This result was confirmed in the allelic analysis and inclusion of the covariates did not influence the significance of these associations. Further, several alleles within all the three genes were associated with clinical improvement and several haplotypes blocks within the EPM2A and NMBR genes were associated with better outcome.
Discussion: the main strengths of the present study are represented by the large sample size and the high ethnical homogeneity of the Korean population. On the other hand, the incomplete coverage of genes under investigation and the use of different antipsychotics with different mechanisms of action could explain the discrepancies in the results of the present study. However, our decision to include patients treated with different drugs could have the advantage of being closer to "real world" clinical practice. Conclusion: our preliminary findings suggest a possible effect of PDE7B, NMBR and EPM2A genes on antipsychotic efficacy in schizophrenic patients. However, further research is needed to confirm our findings in patients treated with specific drugs or classes of drugs.

1. Ikeda, M., et al., Identification of novel candidate genes for treatment response to risperidone and susceptibility for schizophrenia: integrated analysis among pharmacogenomics, mouse expression, and genetic case-control association approaches. Biol Psychiatry, 2010. 67(3): p. 263-9.

Board #3

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

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

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

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

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

Board #4

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

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

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

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

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

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Board #5

Dysregulation of the Histone Demethylase KDM6B in Alcoholism

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

Board #6

The ERK Pathway Involved in Treatment Side Effects in BD-I

Antonio Drago[1,2], Concetta Crisafulli[3], Alessandro Serretti[1]

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

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

Results: 253 patients (37%) had at least one episode of clinical evident tremor. The ERK pathway had 30 out of the 304 investigated SNPs associated with the phenotype, twice the expected number (10^5 permutations, p = 0.006). The phosphatase 2A catalytic subunit (PPP2CA) was particularly disrupted (56% of the SNPs associated). This gene is implicated in the negative control of cell growth and division.

Conclusions: We bring evidence that the ERK pathway may be involved in movement side effects after antimanic treatment in BD-I patients. PPP2CA could be of prime relevance. Further research in larger samples is required.

Board #7
Predicting Antidepressant Treatment Response through Antidepressant Treatment Response through Genomewide Interaction and Enrichment Analysis

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Genomewide association studies (GWAS) on antidepressant efficacy have yielded modest results. A possible reason is that response is influenced by other factors, which possibly interact with genetic variation. In this study, we used a GWAS model to predict antidepressant response, by including predictors previously known to affect response, such as quality of life (QoL). We also evaluated the role of genes, previously implicated in gene-environment (GxE) interactions using an enrichment analysis.
We examined a sample of 1426 depressed patients from the STAR*D trial: 774 responders and 652 non-responders and a subset of 418,865 single nucleotide polymorphisms (SNPs) were analysed. In a GWAS model, we examined whether genetic variations interact with the patients' levels of QoL to predict response to citalopram, after controlling for demographics, severity and population stratification. Secondly, we conducted an enrichment analysis exploring whether candidate genes that have emerged from prior GxE studies on depression are associated with treatment response.
The GWAS model, with QoL as a moderator, yielded one SNP associated with response, in the NEDD4L gene (p=3.64E-08). Other genes among the top findings include FKBP1A and TNFRSF10B. The enrichment analysis showed that SNPs associated with treatment response were more frequently found within the enriched pathway compared to elsewhere in the genome, with serotonergic genes containing the most significant markers that predicted response.
Our findings point to possible target genes, which are proposed for further independent replication. Our enrichment analysis provides support of the role of serotonergic genes in influencing antidepressant response in a genomewide context.

Board #8

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

Concetta Crisafulli[1], Raffaella Calati[2], Edoardo Spina[3], Marco Calabrò[1,3,4], Diego Albani[5], Serena Rodilossi[5], Isabelle Massat[6], Siegfried Kasper[7], Joseph Zohar[8], Alzbeta Juven-Wetzler[8], Daniel Souery[9], Stuart Montgomery[10], Alessandro Serretti[11], and Julien Mendlewicz[12]

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

Board #8 (continued)

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

Board #9
PPP3CC Gene: A Putative New Marker of Antidepressant Response

Chiara Fabbri[1], Diego Albani[2], Gloria Biella[2], Agnese Marsano[1], Raffaella Calati[1], Concetta Crisafulli[3], Marco Calabrò[3,4], Siegfried Kasper[5], Joseph Zohar[6], Alzbeta Juven-Wetzler[6], Daniel Souery[7], Stuart Montgomery[8], Julien Mendlewicz[9], Alessandro Serretti[1]

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In antidepressant pharmacogenetics candidate studies often showed poor covering of gene variability and focus on a relative small number of candidates, thus the present study aimed to investigate SNPs selected by tagging procedure in both old and innovative candidate genes.
38 SNPs within monoamine (COMT and HTR2A), neuroplasticity (BDNF, GSK3B, PLA2G4A, PPP3CC, ST8SIA2), circadian rhythm (RORA and VIPR2), and transcription factor (ZNF804A and SP4) pathways were genotyped in two independent samples (n=369 and 93) of Caucasian patients with major depressive disorder who were treated with antidepressants. Phenotypes were response and remission at week 4 and 8. Logistic regression corrected for age and gender was performed. Secondly, genes associated with outcome at $p<0.05$ were

Board #9 (continued)

checked in the in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genome-wide study (n=1861).
In both original samples markers associated with response were concentrated in PPP3CC (rs2249098 and rs7430, rs11780915 and rs10108011, respectively). In only one sample VIPR2 (rs2657340; p=0.0096) and GSK3B (rs1381841; p=0.045) were associated with response while HTR2A (rs643627; p=0.02) and VIPR2 (rs2657340; p=0.01) with remission. In the STAR*D a cluster of SNPs associated with response was found around rs643627 (especially rs1923888, rs1745837, and rs2296972).
Our study confirmed the role of HTR2A in antidepressant response. Among innovative candidates, PPP3CC seems promising, despite only rs2461494 showed a trend of association with response in the STAR*D (p=0.06). PPP3CC may have a role in the calmodulin activation of calcineurin, a neuron-enriched phosphatase that regulates synaptic plasticity. Further studies are needed to confirm PPP3CC involvement in antidepressant effect.

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

Maurizio Fava, M.D.[1]; George I. Papakostas, M.D.[1]; Richard C. Shelton, M.D.[2]; John Zajecka, M.D.[3]; Teodoro Bottiglieri, Ph.D.[4]; Clair Cassiello, BA[1]; Stephen M. Stahl, M.D., Ph.D.[5]; Joshua Roffman, M.D., MSc[1]

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Background and Objective: Genetic or biological markers may increase the risk of major depressive disorder (MDD) or inadequate response to therapy. The objective of this analysis was to evaluate the effect of specific markers alone and in combination on the antidepressant efficacy of adjunctive L-methylfolate 15 mg versus placebo added to SSRIs from a trial of inadequate responders to SSRIs.
Methods: This was a double-blind, randomized, placebo-controlled trial using the sequential parallel comparison design (SPCD).

Board #10 (continued)

Outpatients with MDD and SSRI-resistant depression received L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days or placebo for 60 days. The effects of biological and genetic markers individually and combined on treatment response were evaluated.
Results: Seventy-five patients were enrolled. Patients with a BMI ≥30 kg/m2 had significantly greater symptom reduction with L-methylfolate versus placebo (p=0.001), as did patients with levels of 4-HNE (p=0.003) above the median, and SAM/SAH ratio below the median (p=0.005). Average mean changes from baseline for HDRS-28 with combinations of these biomarkers with MTHFR C677T, MTR 2756 AG/GG or MTRR 66 AG/GG polymorphisms were significantly greater with L-methylfolate vs. placebo (all p≤0.002). Average mean changes from baseline for HDRS-28 with combinations of MTHFR C677T plus MTR 2756 AG/GG and MTR 2756 AG/GG plus MTRR 66 AG/GG were significant (p<0.001).
Conclusion: Surrogate biomarkers or genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant MDD who are responsive to adjunctive therapy with 15 mg L-methylfolate.

Board #11
Implementing Pharmacogenomic Clinic for Treatment Refractory Depression

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Industry Support or Sponsorship: Pathway Genomics, UCSD CTRI

Background: Many patients with bipolar disorder (BD), depressed, or major depressive disorder (MDD) are unresponsive to medication or have dose-limiting side effects. These patients, referred to as treatment refractory depression (TRD), often either metabolize medications too rapidly (UM), resulting in a lack of effect, or too slowly (PM), leading to bothersome side effects, or are treated with inappropriate medication choices based on diagnosis. We plan to use genetic testing in TRD to identify differences in metabolism as well as different forms of illness.

Board #11 (continued)

Aims and Objectives: Our hypothesis is that patients who receive pharmacogenetic testing and guided treatment will have better clinical outcomes and suffer fewer side effects after 4 months of treatment. We expect to precisely identify which decisions are best informed by genetic testing, and that patient will be motivated and eager to participate in testing.
Study Population: We plan to enroll 200 veterans with TRD. Subjects will have been depressed for >3 months and will have failed at least one prior medication trial of adequate dose/duration.
Methods: After collecting past medication trials and confirming diagnosis, we will obtain DNA using established protocols. Subjects will be randomized to receive either treatment as usual (TAU) using the TMAP guidelines, or pharmacogenomic guided treatment (PGT), which will have objective, genetically guided decisions made by the prescriber. For example, TMAP may recommend a switch in antidepressants but not dictate which medication to use, whereas genetic testing may indicate which antidepressant is preferable based on drug metabolism or will recommend skipping certain steps if indicated (e.g., early use of lithium augmentation given a favorable genotype).
Analysis and Interpretation: Prospective assessment of outcome: compare the number of subjects who achieve recovery as assessed by BDI, CGI, YMRS, ISS, CGI, and Side Effect Questionnaire. Retrospective Analysis of Clinical Decision Making: at conclusion, all subjects will have their genetic test results examined to identify variants that predict atypical drug metabolism or poor clinical response. Patient concerns and expectations of genetic testing: subjects will be administered the MACGNET scale, used to assess concerns about genetic testing.
Outcome: We will report the number of subjects enrolled in each arm and present preliminary findings.

Board #12
Antipsychotic-induced Weight Gain and the Role of Histamine Receptor H1 and H3 Variants

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Background: Weight gain and development of metabolic syndrome are the most common deleterious side effects following treatment with antipsychotic drugs. However, the mechanisms underlying these negative effects are not fully understood. In this study we investigate whether variants in the genes coding for the Histamine receptors H1 (HRH1) and H3 (HRH3) are associated with antipsychotic-induced weight gain (AIWG). Clozapine and olanzapine, the antipsychotics associated with the highest risk of weight gain, have high affinity for HRH1.
Methods: We investigated 40 tag and /or putative functional SNPs (HRH1=34 and HRH3=6) in 219 schizophrenia or schizoaffective disorder patients treated mainly with clozapine and olanzapine for up to 14 weeks. Overall, these SNPs cover almost 100% of the common variation in the HRH1 and HRH3 receptors.
Results: We observed significant association of an intronic SNP, rs7639145, in HRH1 with AIWG (p=0.021). Carriers of the GG genotype gained more weight when treated with clozapine or olanzapine (GG vs. GA+AA, 5.2kg ±4.8 vs. 2.9kg ±3.9, p=0.026). In HRH3 trends of association were observed for rs1615746 (p=0.057) and rs6587299 (p=0.06). However, none of the other SNPs were significantly associated with AIWG. A limitation is that the above associations do not remain significant after correcting for multiple testing.
Discussion: We have carried out a comprehensive analysis of genetic variation in HRH1 and HRH3 genes with AIWG that yielded some interesting findings. However, our observations suggest that SNPs in the HRH1 and HRH3 may not play a major role in AIWG. Potential remote regulatory variants and downstream pathways require further investigation.

Board #13

Association of the Glucagon-like Peptide 1 and the Glucagon-like Peptide 1 Receptor Genes with Antipsychotic-induced Weight Gain

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

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

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

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

Board #14

Association between CYP2D6 and Tardive Dyskinesia in Antipsychotic-Treated Schizophrenia

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

Background: An association between cytochrome P450 2D6 metabolizer status and susceptibility to typical antipsychotic-induced tardive dyskinesia (TD) has previously been reported; however, overall the data are inconclusive. Our aim was to examine whether there was an association between TD and number of functional *CYP2D6* genes.
Methods: A Caucasian sample of 70 patients was recruited in 1996-1997 from South London and Maudsley NHS Trust. Subjects had a DSM-IIIR diagnosis of schizophrenia and were treated with typical antipsychotics at doses equivalent to at least 100 mg chlorpromazine daily for at least 12 months prior to assessment. Subjects were examined for TD using the Abnormal Involuntary Movements Scale (AIMS). All patients were genotyped for *CYP2D6* alleles**3-5*, **41*, and for amplifications of the gene. The AmpliChip CYP450 Test® was performed in eight subjects for whom *CYP2D6* genotype could not initially be definitively called. Group differences were explored using Chi square, t-tests, and logistic regression statistics.
Results: There were 13 patients with TD. The mean (SD) years of duration of antipsychotic treatment in TD positive was 15.8 (7.9) vs. TD negative 11.1 (7.4) p=0.04. Increased odds of experiencing tardive dyskinesia were associated with increased ability to metabolize *CYP2D6*, as measured by genotypic category (OR=4.2, 95% CI:1.1-15.7),

Board #14 (continued)

increasing duration in treatment (OR=1.0, 95% CI:1.0-1.0), and having drug induced Parkinsonism (OR=9.7, 95% CI: 1.4-68.4).
Discussion: There is a significant association between CYP2D6 genotypic category and TD with the direction of effect being an increase in the number of functional CYP2D6 genes being associated with an increased risk of TD.
Funding and Acknowledgements: *Dr K. J. Aitchison was previously funded by the Wellcome Trust (UK) as a Wellcome Mental Health Research Training Fellow, grant 045968, during which period she undertook much of the sample genotyping and is now an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta (Canada). We thank Jing Hua Zhao for previous relevant statistical advice, Roche Molecular Systems for the provision of the AmpliChip CYP450 Test® and associated support, and Johnson and Johnson Pharmaceuticals Research and Development for support for salary support to Dr. Tsapakis whilst undertaking the remainder of the genotyping. The manuscript preparation of Maju Koola was supported by the NIMH funded T32 grant MH067533-07 (Carpenter, PI) and the American Psychiatric Association/Kempf Fund Award for Research Development in Psychobiological Psychiatry (Koola, PI).*

Board #15

Association Analysis of N-Methyl-D-Aspartic Acid Receptor Subunit Gene (GRIN2B) in Antipsychotic Response to Clozapine in Patients with Schizophrenia

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Background: Schizophrenia (SCZ) is a debilitating mental health disorder that causes immeasurable pain and suffering to those afflicted. Response to antipsychotic treatment for SCZ is highly variable, and twin studies suggest a genetic component. Altered N-Methyl-D-Aspartic acid receptor (NMDAR) activity has been implicated in the etiology of SCZ, as well as in response to the atypical antipsychotic clozapine (CLZ) through its ability to enhance NMDAR mediated neurotransmission.
Objective: The study aimed to investigate genetic associations between the NMDA receptor subunit gene (GRIN2B) and antipsychotic response to clozapine (CLZ).
Methods: Eight GRIN2B polymorphisms were assessed in 252 patients diagnosed with SCZ using DSM-IV criteria. SNPs were selected based on potential functionality (promoter, 3'UTR, intron-exon splice sites locations) and recent citations from the literature. Standard Taqman genotyping procedures were used. Power calculations were performed using Quanto 1.2.4 and linkage disequilibrium was determined using Haploview 4.2. In terms of genetic analyses, dichotomous variables were analyzed using χ^2-test and continuous variables were analyzed using analysis of covariance (ANCOVA), with baseline scores as a covariate.
Results and Conclusions: Our subgroup of 172 European SCZ patients with categorical response data and 90 patients with continuous response data had over 80% power to detect an odds ratio of 2.50 and

Board #15 (continued)

detect ≥8% of variance, respectively (non-responder frequency=48%; α=0.05, two sided; minor allele frequency=0.143; additive model). Prior to correction for multiple testing, a trend was observed for SNP rs1072388 (p=0.067) in which A allele carriers (AA+AG) responded better to CLZ than GG homozygotes. In conclusion, GRIN2B may not play a major role in CLZ response in our sample of SCZ patients.

Board #16
Role of Translocator Protein (TSPO) Gene in Antipsychotic Response and Antipsychotic Induced Weight Gain

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Introduction: TSPO regulates mitochondrial function, suspected to play a key role in antipsychotic-induced weight gain (AIWG). Treatment with clozapine enhances TSPO function, suggesting TSPO may mediate clozapine response or side effects. Marker rs6971 (Ala147Thr) predicts a large portion of variance in TSPO binding; the Thr/Thr genotype confers lower TSPO binding affinity.
Objectives:
1) Investigate association between rs6971 genotype and clozapine response
2) Investigate association between rs6971 genotype and AIWG
Methods:
Objective 1
Genomic DNA was obtained from blood samples of SCZ patients with Brief Psychiatric Rating Scale (BPRS) scores measured before and after 6 months of clozapine treatment (n=114). rs6971 genotyping was done using a TaqMan assay (Applied Biosystems). Association between rs6971 genotype and % change in BPRS score was tested using ANCOVA.

Board #16 (continued)

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

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

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Introduction: Second-generation antipsychotic treatment can result in substantial body weight gain. The melanocortin-3 receptor (MC3R) is highly expressed in the hypothalamus, a key brain region for weight regulation. MC3R knockout mice have been reported to exhibit increased fat mass and reduced lean body mass. We investigated the potential role of common MC3R polymorphisms to assess whether these were associated with antipsychotic induced weight gain (AIWG).
Methods: Nine MC3R SNPs (rs6127698, rs6024731, rs1543570, rs6024730, rs6014649, rs1926064, rs6014646, rs11697509, rs3827103) were selected by tagSNP. Illumina GoldenGate Genotyping Assays

Board #17 (continued)

were used to genotype 217 schizophrenia patients who underwent treatment with antipsychotics and evaluated for weight gain for up to 14 weeks. Weight change (%) across genotypic groups was compared using analysis of covariance (SPSS15.0).
Results: Significant genotypic associations were found between the MC3R polymorphisms and weight gain ($p<0.05$) in a refined sub-sample consisting of European ancestry patients treated with either olanzapine or clozapine (n=83). Carriers of the MC3R rs6016469 'A'-allele (AA+AG) gained more weight (7.54% ± 5.6) than GG homozygotes (3.73% ± 5.4), $p = 0.011$. Patients who were carriers of the MC3R rs3746619 'A'-allele (AA+AG) gained more weight (6.90% ± 5.7) than the GG homozygotes (3.81 ± 5.5), $p = 0.034$.
Conclusions: We observed that two MC3R gene variants were nominally associated with AIWG. These findings suggest that this gene may have a role in the development of AIWG. In addition, this finding may lead to novel targets for psychiatric drug development. Our observations warrant further investigation and replication in larger sample sets.

Board #18
Genes and Antidepressant Efficacy in Major Depressive Disorder: A Comprehensive Meta-analysis

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A number of candidate gene studies focused on major depressive disorder (MDD) and antidepressant (AD) efficacy have been carried out, but results mainly remain inconclusive.
We performed a comprehensive meta-analysis of candidate gene studies focused on AD efficacy in MDD to evaluate the cumulative evidence. A random-effect model was applied to study the polymorphisms with genotypic counts available from at least three independent studies. On the base of previous evidence, the analysis was stratified by ethnicity (Caucasian, Asian, and other/mixed), and AD class (SSRIs and mixed/other ADs).

Board #18 (continued)

Genotypic data were available from a total of 14 polymorphisms in 11 genes. After the exclusion of 5 polymorphisms included in very recent meta-analysis, 9 polymorphisms in 8 genes were included in the present meta-analysis (BDNF rs6265, SLC6A4 STin2, GNB3 rs5443, FKBP5 rs1360780 and rs3800373, TPH1 rs1800532, COMT rs4680, SLC6A2 rs5569, and HTR6 rs1805054).
Our results suggested that BDNF rs6265 (Val66Met) heterozygous may be associated with better SSRIs response compared to the homozygous genotypes, particularly in Asians (OR = 1.56, 95%CI 1.14-2.13, p = 0.006). STin2 in SLC6A4, rs5443 in GNB3, rs1360780 and rs3800373 in FKBP5 showed associations with response, but these results were highly dependent from one or two single studies. In conclusion, our findings suggested the BDNF Val66Met as the best single candidate involved in AD response, with a selective effect in Asian populations and SSRI treatment. Our overall results supported no major effect of any single gene variant on AD response.

Board #19
Genotyping of CYP2D6 and CYP2C19 Metabolizer Status to Guide Psychiatric Drug Treatment: Updates from the CAMH Pharmacogenetics Research Clinic

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Background: Antipsychotic and antidepressant medication continues to be the main treatment for many psychiatric conditions including schizophrenia, mood and anxiety disorders including obsessive-compulsive disorder (OCD) Two polymorphic enzymes, CYP2D6 and CYP2C19, metabolize a large number of these medications. Functional polymorphisms in these enzymes can confer altered enzymatic activity, potentially leading to toxic or subtherapeutic drug levels.
Methods: As part of our ongoing study at our Pharmacogenetics Research Clinic, 69 patients with a diagnosis of schizophrenia and mood disorders with complicated medication histories have been enrolled prospectively and genotyped for CYP2D6 and CYP2C19. At study entry, clients are informed in detail about potential advantages and limitations related to the genetic testing of liver

Board #19 (continued)

enzyme activities. Patients participate in a structured diagnostic interview and are assessed of current and previous treatment response and occurrence of side effects. Physicians are then provided with an interpretation of the genotypic results and informed in detail about the potential clinical implications which they will discuss with their patients. Serum drug levels of the CYP2D6 and/or CYP2C19 metabolized drugs are also assessed and after 6 weeks the physician completes a questionnaire evaluating the usefulness of the genotypic information provided by the study. After 12 weeks, the clients are assessed again to monitor potential adjustments of medications and their overall treatment outcome. Selected case reports will be presented and discussed in detail at the conference.
Results: Overall, physicians have returned mostly very good feedback that the genotyping results have been helpful in allowing them to either select medications their patients are likely to better tolerate, or to adjust doses based on genotype results and serum levels.
Discussion: Our findings suggest that CYP2D6 and CYP2C19 genotyping provides useful information that help physicians improving pharmacotherapy in individual patients.

Board #20
5HT1A Genotypes & Cognitive Function in Major Depressive Disorder

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Background: Bosia et al (2011) studied the effects of the 5-HT1A-R genotype on cognition in schizophrenic patients , and identified that the 5-HT1A-R C/C genotype was associated with significantly higher scores on a Picture Sequencing Task than the C/G and G/G genotypes. The purpose of this study was to determine whether 5-HT1A-R genotype had an influence on the profile of cognitive function in patients with major depressive disorder (MDD).
Methods: The study sample was 455 MDD patients between the ages of 18 and 55 years who met DSM-IV criteria for MDD, with current-episode duration of at least 1 month but not longer than 12 months. The patients underwent 5-HT1A-R genotyping and also performed a selection of automated tests of attention, information processing,

Board #20 (continued)

executive control, working and episodic memory from the CDR System. The volunteers had on a previous occasion performed the entire 20 minute sequence of tests on two occasions to overcome practice and familiarity effects. Performance on the various tests was contrasted between the three 5-HT1A-R genotypes using ANOVA.
Results: There were no differences between the three genotypes on HAM-D-17 (p=0.92), Sheehan Disability Scale total score (p=0.52) or age (p=0.96). Significant differences were seen on accuracy measures from 2 working memory (articulatory and spatial) and 4 episodic memory tasks (verbal: immediate recall, delayed recall and recognition; picture recognition). These were seen on validated factor scores for working memory (p=0.047), episodic memory (p=0.014) and a combined score (p=0.006). No effects were seen for measures of sustained or focussed attention, information processing speed or attentional fluctuations (p=0.34 to 0.98). Neither was an effect seen for the speed of retrieval of information in the working and episodic recognition tasks (p=0.55). For the combined working end episodic memory accuracy score, the C/C homozygotes scored significantly higher (66.8%; 95% CI 64.5,69.1) than both the C/G heterozygotes (62.4%; 95% CI 60.8,63.9) and the G/G homozygotes (63.3%; 95% CI 61.2, 65.4), the p values being 0.0016 and 0.0246 respectively.
Discussion & Conclusions: This is to our knowledge the first data in MDD showing a difference in cognitive function between different 5HT1A-R genotypes, and besides the data in schizophrenia, the first in any psychiatric or neurological condition. The finding that the C/C homozygotes were selectively superior on the ability to hold and retrieve information in working and episodic memory; while not showing differences in retrieval speed or on various measures of attention and information processing is clearly worthy of future attention; particularly as there were no differences between the genotypes in depression or disability scores.

Bosia M et al (2011). Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. Psychiatry Research 188: 187–190.

Board #21

Developmental Changes in Functional Activation during Cognitive Control

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

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

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

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

Conclusions: The MSIT is a useful tool for probing executive network development. Age related changes observed in preliminary analyses indicate that younger subjects perform more poorly and show less efficient patterns of functional activation than older individuals. Understanding the way that the cognitive control circuitry develops in healthy individuals is an important step towards characterizing the developmental problems that occur in neuropsychiatric disorders.

Board #22

Multiple Obesity-related Genes are Associated with Antipsychotic-induced Weight Gain in Drug Naïve Pediatric Patients

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Background: Weight gain is a serious side effect of antipsychotic drugs (APD). We hypothesized that the risk genes in the general population may also be risk genes for APD-induced weight gain. We used the genes that are associated with obesity in the general population as candidate genes, and examined whether they are significantly associated with APD-induced weight gain in a drug-naïve pediatric sample.

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

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

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

Board #23

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

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Background: In the recent years several studies have investigated genetic polymorphisms of antipsychotic drug metabolizing enzymes and receptors. However, most of the studies focused on drug response and very few have investigated the genetic influence on antipsychotic (AP) dosage. The aim of the present study is to test the association between AP dosage and candidate genes.
Methods: The current dosage of AP medications was collected from 232 schizophrenic patients. The AP dosage was standardized using three different methods: CPZe according to Gardner et al. 2010, defined daily dose according to the WHO (2010) and percentage of maximum dose according to the Compendium of Pharmaceuticals and Specialties 2012 (Canada). The patients were then genotyped using a Customized Illumina Chip comprising 384 SNPs. All markers were screened for nominal significance and for statistical significance after multiple-testing correction, using the FDR method.
Results: The preliminary analysis showed that the top SNP associated with CPZe was the rs1799978 (p=0.006) however when we consider the percentage of maximum dose, the top SNP was the rs1286769 on chromosome 3.
Discussion: In this sample of 232 adults, the common variants investigated had no major impact on the amount of antipsychotic medications that had been prescribed. However, studies combining large prescription databases and genome-wide data may identify genetic predictors to adjust the dose of antipsychotic medication.