Friday, May 31, 2013

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

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

Vicki L. Ellingrod, PharmD, FCCP[1,2], Tyler B. Grove, B.S.[1,2], Kyle J. Burghardt, PharmD[1], and Stephan F. Taylor, M.D.[2].
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Introduction: Metabolic syndrome may be related to dietary folate, its pharmacogenetically regulated metabolism, and atypical antipsychotic (AAP) exposure. We examined how folate supplementation would affect metabolic measures and endothelial functioning (RHI) in AAP treated schizophrenia subjects meeting NCEP-ATP-III metabolic syndrome criteria.
Methods: Subjects were given 5mg/day open label folate for 3 months. Baseline and 3 month measurements included RHI, BMI, fasting metabolic laboratory measures, C-reactive protein, homocysteine, IL-6, and leptin. DNA was gentoyped for the methylenetetrahydrofolate reductase (*MTHFR*) 677C/T and catechol-O-methyltransferase (*COMT*) 158 Val/Met variants.
Results: Thirty-five subjects with a mean age of 50±9 years and 70% Caucasian. After 3 months supplementation, RHI improved by 20% (p=0.02), mean homocysteine decreased 14% (p=0.006), and IL-6 decreased 13% (p=0.09). Subjects exercised 15% less during the study (p=0.05). At baseline 61% met endothelial dysfunction criteria (RHI<1.67), which decreased to 27% (p=0.0006) at endpoint. The *MTHFR* 677C/C+*COMT* 158Met/Met subjects had a 44% RHI improvement versus 10% improvement for *MTHFR* 677T/*COMT* Val allele carriers (p=0.06). The *MTHFR* 677C/C+*COMT* 158Met/Met group also showed significant reduction in those meeting endothelial dysfunction (83% baseline and 16% endpoint), compared to the *MTHFR* T+COMT Val allele carriers (54% baseline and 31% endpoint[p=0.001]).

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Attenuation of Metabolic Consequences from Atypical Antipsychotic Use in Schizophrenia: Folate Supplementation and the Role of Pharmacogenomics (continued)

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

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

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

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

Fisher's Exact Test evidenced a trend for higher frequency of SM among subjects homozygous for the G, compared to A carriers ($p=0.069$). A separate slope regression was run to evaluate if the effect of duration of antipsychotic therapy on the presence/absence of MS could differ depending on genotype, showing a significant

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Metabolic Syndrome in Schizophrenia: The Role of SREBF1 Polymorphism (continued)

interaction between genotype and duration of therapy (F=3.51; p=0.035). Among A carriers the duration of antipsychotic treatment resulted more influent on the presence/absence of MS (p=0.043; β=0.313), compared to subjects homozygotes for the G allele.

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

References

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9:50 a.m. – 10:15 a.m.

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

Daniel J. Müller[1], Arun K. Tiwari[1], Nabilah I. Chowdhury[1], Jeffrey A. Lieberman[2], Herbert Y. Meltzer[3], James L. Kennedy[1]*

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Background: Over the past ten years, we have made large efforts to investigate the genetic causes in the serious side effect of antipsychotic induced weight gain. We have recently unravelled several important hypothalamic gene variants of the leptin-melanocortin energy homeostasis system associated with antipsychotic-induced weight gain. We investigated novel hypothalamic expressed genes and findings from the neuropeptide Y 2-receptor (NPY2R) gene will be presented.
Methods: A total of 237 patients who underwent treatment for chronic schizophrenia or schizoaffective disorder were evaluated for antipsychotic response and induced weight gain for up to six months. The sample consisted mainly of individuals of European descent exposed to clozapine for their first time. Fifteen SNPs in the NPY2R gene were genotyped. SNPs were selected for having a minor allele frequency of at least 5% and in order to allow for a dense coverage, regions 10kb upstream and 2kb downstream were included. In addition, SNPs were selected based on their functional relevance reported in the literature.
Results: Our analyses with the NPY2R gene showed that patients of European ancestry who were treated with clozapine or olanzapine and who were carriers of the T-allele of SNP rs12507396 gained on average significantly more weight than non-carriers (p=0.025). This result became even more significant when we corrected for duration of treatment (p = 0.01). Haplotype analyses and findings in the other remaining SNPs yielded some interesting trends which will be discussed.
Conclusion: Our results tentatively suggest novel associations between functionally relevant markers of the NPY2R genes in schizophrenic patients treated with antipsychotic medication associated with high risk for metabolic abnormalities and weight gain. We are currently performing replication studies.

10:15 a.m. – 10:40 a.m.

Common Variants in Chromosome 6q23.3 are Associated with Antipsychotic Drug Induced Akathisia in Patients with First Episode Schizophrenia

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Background: Akathisia is a common side effect of antipsychotic drugs (APDs), and often causes patients to stop taking their medications. To date, there is no good clinical predictor for APD-induced akathisia. Genetic markers can be potentially useful in predicting akathisia and help in the tailoring of medication treatment for individual patients.
Methods: Eighty-one patients with first-episode psychosis participated in a randomized double-blind clinical trial in which they were treated with either risperidone or olanzapine. Akathisia was assessed weekly using the Barnes Akathisia Rating Scale. Patients were genotyped on the Illumina Omni-1 Quad platform. After quality control, 442,187 SNPs were entered into a genome-wide association study (GWAS). The assessed phenotype was the highest akathisia score during the first 12 weeks of treatment.
Results: The genome-wide association study yielded 4 single nucleotide polymorphisms (SNP) at a single locus in the Chr 6q23.3 region, exceeding a statistical threshold of $p<10^{-5}$. The top SNP was rs631204, $p<10^{-7}$, which is located about 180kb from *TNFAIP3*, and is also close to other immune function-related genes including *OLIG3*, *IFNGR1*, and *IL22RA2*. Effects were recessive, with 63.2% (12/19) of minor allele homozygotes having akathisia, compared to only 13.3% (8/60) of non-homozygotes. There was no significant difference in type of APD, sex, and age between genotype groups.
Discussion: We found that the chr 6q23.3 region seems to be associated with APD-induced akathisia using GWAS. This region includes multiple genes that are implicated in autoimmune diseases, which suggests that APD-induced akathisia may be partially mediated by autoimmune pathways. This novel finding requires replication in other samples.

11:00 a.m. – 11:25 a.m.

Exome Sequence Analysis of Finnish Patients with Clozapine-induced Agranulocytosis

Arun K. Tiwari[1], Anna C. Need[2], Clement C. Zai[1], Nabilah I Chowdhury[1], Daniel J. Müller[1], Anu Putkonen[3], Eila Repo-Tiihonen[3], Tero Hallikainen[3], A. Elif Anil Yağcıoğlu[4], Jari Tiihonen[3,5], James L. Kennedy[1], Herbert Y. Meltzer[6]*

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Clozapine is the prototypical atypical antipsychotic drug used primarily for treatment resistant schizophrenia. In spite of its efficacy, the use of clozapine is markedly curtailed by its side effects such as metabolic syndrome and agranulocytosis. While metabolic syndrome is more common than agranulocytosis, it is the latter which is the major reason that clinicians and patients are reluctant to consider the use of clozapine. Clozapine-induced agranulocytosis (CIA) occurs in about 0.8% of clozapine treated patients, generally within the first 18 weeks of treatment. The aetiologic mechanism is unknown although several hypotheses including nitrenium ion-mediated apoptosis, mitochondrial oxidative stress-induced apoptosis, or an immune-mediated toxicity mechanism have been proposed. In this study we have utilized exome sequencing to comprehensively identify the genetic variations in the transcribed region of the genome in Finnish patients with (n=24) and without CIA (n=26). A total of 143,258 SNVs and 14,778 INDELs were identified in the 50 individuals at ≥5x read depth. None of the SNVs or INDELs was significantly associated with CIA after Bonferroni correction ($p>4.6x10^{-7}$ after correction for 109,131 non-private SNVs and $p< 4.7x10^{-6}$ after correction for 10,579 non-private INDELs). This is the first time that rare genetic variants have been investigated in relation to clozapine-induced agranulocytosis on a genome-wide scale and the results suggest some level of genetic complexity, even in this relatively homogenous population. We did observe multiple nominally significant associations with single nucleotide variants in the HLA-C/HLA-B gene region ($p<0.001$), supporting the immune-mediation hypothesis of CIA, and warranting further investigation.

11:25 a.m. – 12:00 p.m.

The Vesicular Monoamine Transporter SLC18A2 Gene in Tardive Dyskinesia, Replication and Interaction with Dopamine System Genes

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The rate of tardive dyskinesia (TD) has been declining with use of newer atypical antipsychotics, but the risk of TD has not been eliminated. Typical neuroleptics appear to be as effective in treating schizophrenia symptoms as atypical antipsychotics. Thus, understanding the development of TD remains clinically important. Recently, Tsai et al (2010) analyzed 128 candidate genes for possible association with TD occurrence in the CATIE sample, and their top finding was the rs2015586 marker in the SLC18A2 gene. The SLC18A2 gene codes for the vesicular monoamine transporter 2, which is a target of tetrabenazine, an inhibitor that has been used to treat hyperkinetic movement disorders including TD. We aim to follow up on this association finding by investigating for a possible association between nine tag single-nucleotide polymorphisms across the SLC18A2 gene and TD occurrence based on the Schooler and Kane criteria as well as Abnormal Involuntary Movement Scale scores in our sample of schizophrenia patients of European ethnicity (N=187).

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

11:25 a.m. – 12:00 p.m.
The Vesicular Monoamine Transporter SLC18A2 Gene in Tardive Dyskinesia, Replication and Interaction with Dopamine System Genes (continued)

further independent replication, our study findings support an involvement of the SLC18A2 gene in TD development.

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

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

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

Rare and uncommon alleles contribute to vulnerability to addictions and other behavioral disorders. They are a major part of the missing heritability or "dark matter" subsequent to genome wide association studies. To identify these variants and tie them to behavior we apply deep sequencing in contexts where effects of rare alleles can be measured. In Finns, a founder population, we discovered a stop codon in the *HTR2B* serotonin receptor. It leads to uncompensated loss of function, can lead to severe impulsivity and alcoholism, and is restricted to Finns in line with the founder characteristics of this population. The behavioral effects of loss of Htr2b function were validated in the *Htr2b* knockout mouse and extended to the level of neural function, including the role of this receptor in regulating phasic dopamine release in the mesolimbic system. Via exome sequencing of the alcohol preferring (P) rat, one of the most widely accepted model organisms for alcoholism, we found a stop codon in the *Grm2* metabotropic glutamate receptor gene. This stop codon was genetically fixed by selection in the P rat, leads to uncompensated effects on glutamate function, and – as shown by genetic studies- is partially responsible for the increased alcohol preference in these rats.

2:30 p.m. – 2:55 p.m.

CYP2C19 genotype is Associated with Response to Tricyclic Antidepressants in Severe Affective Disorders

Maju Mathew Koola[1], Kopal Tandon[2], Patricia Huezo-Diaz[2,3] Mark Kinirons[4,5], Magnus Ingelman-Sundberg[6], Michael Gill[7], Peter McGuffin[8], Robert W. Kerwin (RIP), Katherine J. Aitchison[2,9]
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Drs. Koola and Tandon contributed equally and are joint first authors.

Background: There is strong evidence for the role of cytochrome enzymes CYP2D6 and CYP2C19 in the metabolism of tricyclic antidepressants (TCAs), and some prior evidence of association with clinical response and adverse drug reactions (Bertilsson et al, 1993; Spina et al, 1997; Steimer et al, 2005).
Methods: Subjects (N=41) had major depressive disorder (N=37) or bipolar disorder (N=4) treated with TCAs (the most frequently prescribed being amitriptyline) in a tertiary referral center. Venous blood was taken for genetic analysis and for levels of the TCAs and their primary metabolites, and was phenotyped for CYP2D6 activity using debrisoquine. Patients were assessed at baseline and at six weeks for severity of depression using the Hamilton Depression Rating Scale (HDRS), and were also rated for side effects at six weeks.
Results: There was no association between clinical response or adverse drug reaction and CYP2D6 phenotype or genotype. However, an association between clinical response to these TCAs and *CYP2C19* genotype was found (p=0.005). The direction of effect was such that it implies that the parent TCA may be more potent than its demethylated metabolite, consistent with the dual (serotonin-norepinephrine) reuptake inhibitory effect of TCAs such as amitriptyline, and the sample being of patients who had a severe illness (mean pre-treatment HDRS score 25.9). In addition, the level of demethylated TCA was associated with anticholinergic side effects.

2:30 p.m. – 2:55 p.m.
CYP2C19 genotype is Associated with Response to Tricyclic Antidepressants in Severe Affective Disorders (continued)

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

2:55 p.m. – 3:20 p.m.
Gene Expression as Predictors of Antidepressant Response using ROC Analysis in the GENDEP Study

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To improve the "personalized-medicine" approach to the treatment of depression, we need to identify biomarkers that, assessed before starting treatment, predict future response to antidepressants. We tested the leukocyte mRNA expression levels of genes belonging

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

to glucocorticoid receptor function, inflammation and neuroplasticity, in 34 healthy controls and 74 depressed patients, as part of the GENDEP study. In a previous report (Cattaneo et al., Neuropsychopharmacology, 2012), we found that the levels of IL-1β, MIF and TNF-α at the baseline were all strongly and negatively correlated with treatment response (*IL-1*β, r=-0.56; *MIF*, r=-0.62; and *TNF*-α, r=-0.44; all p<0.0001). However, the contribution of the 15 genes to prediction may have not been adequately captured by simple correlation analyses.

In order to better evaluate the accuracy of these predictors, we have run a receiver operating characteristic (ROC) analysis. N=23 patients (31%) did not respond to antidepressants (escitalopram or Nortryptiline), that is, did not show a reduction in MADRS score of 50% or more. Using "lack of response" as positive actual state in the ROC analysis, four genes plotted above the reference line (that is, higher gene expression predicting lack of response) with areas under the curve (AUCs) that were indicative of at least "fair" predictive value: MIF (0.9), IL-1β (0.8), TNF-α (0.8) and FKBP-5 (0.7). All the other genes had AUCs <0.7, indicating poor predictive values. Further analyses indicated that the expression values of these genes that had the best combination of sensitivity and specificity in predicting lack of response were: 1.35 for MIF, 1.56 for IL-1β, 1.55 for TNF-α, and 1.34 for FKBP-5. Our data suggest that monitoring the levels of these genes could identify depressed patients who are least likely to respond to first-line antidepressants, and this could allow doctors to consider early introduction of more assertive therapeutic approaches of combining antidepressants or adding adjuvant therapies.

3:35 p.m. – 4:00 p.m.

CHL1 Gene and Antidepressant Response: Results from Three Independent Samples

Alessandro Serretti[1], David Gurwitz[2], Julia Stingl[3], Chiara Fabbri[1], Concetta Crisafulli[4], Antonio Drago[1], Raffaella Calati[1], Diego Albani[5], Armando Chierchia[5], Edoardo Spina[6], Marco Calabrò[4,6], Siegfried Kasper[7], Joseph Zohar[8], Alzbeta Juven-Wetzler[8], Daniel Souery[9], Stuart Montgomery[10], and Julien Mendlewicz[11]
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CHL1 - a gene coding for a neuronal cell adhesion protein – was recently proposed as antidepressant response predictor.
Thus, 6 SNPs (rs4003413, rs2133402, rs9841789, rs1516340, rs2272522 and rs1516338) in CHL1 were genotyped in two independent samples (n=368 and 96) with major depressive disorder and treated with antidepressants. Logistic regression was used to investigate associations with response/remission at week 4. Secondly, String Interaction Network (http://string-db.org) and Reactome (www.reactome.org/) were used to identify proteins that have interaction with CHL1, and a pathway analysis was performed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genome-wide study (n=1861). Genes belonging to the index pathway were imputed through IMPUTE2 taking CEU HapMap 1000 genomes as reference. The prevalence of variations showing $0.01<p<0.09$ was compared between the index pathway and a random pathway by a Fisher exact test. 10e5 permutations were run.
In the largest sample rs2133402 T allele was associated with non response (p=0.019) and non remission (p=0.010), while in the other negative results were found. In the STAR*D the top CHL1 marker

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CHL1 Gene and Antidepressant Response: Results from Three Independent Samples (continued)

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

4:00 p.m. – 4:25 p.m.
Pharmacogenetics of Lithium Response

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

No abstract submitted.

4:25 p.m. – 5:30 p.m.
Catechol-O-Methyltransferase Genotype as Modifier of Superior Responses to Venlafaxine Treatment in Major Depressive Disorder

Seth C. Hopkins[1], David S. Reasner[1], Keith A. Wesnes[2,3], Kenneth S. Koblan[1]
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The range of response rates following antidepressant treatment is suggestive of genetic factors, and the utilization of robust genetic markers of treatment response would increase the efficiency, safety and economic benefit of existing therapies. Since COMT activity influences dopamine levels in brain areas where dopamine transporter expression is low, we hypothesized that COMT functional variant rs4680 (Val158Met) might influence noradrenergic effects when norepinephrine transporters are inhibited therapeutically. The clinical responses of subjects with major depressive disorder treated with venlafaxine were analyzed according to COMT genotype using data collected from a Phase 2 randomized, double-blind, placebo-controlled clinical study (NCT00584974). Venlafaxine subjects

4:25 p.m. – 4:50 p.m.
Catechol-O-Methyltransferase Genotype as Modifier of Superior Responses to Venlafaxine Treatment in Major Depressive Disorder (continued)

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

4:50 p.m. – 5:15 p.m.
GWAS on Treatment-resistant Depression on 1561 Individuals. Single Locus Results and Polygenic Scoring with Results from SCZ, BIP, MDD and CDG from the PGC

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

Background: Up to one third of individuals with major depressive disorder do not reach remission despite two or more adequate antidepressant treatment trials. Such treatment-resistant depression has been suggested to be associated with unrecognized or subsyndromal bipolar disorder or psychotic disorder. The availability of genomewide association data from very large cohorts of individuals with bipolar disorder and schizophrenia provides an opportunity to directly test this hypothesis.
Method: We utilized GWAS data from the i2b2-TRD and STARD treatment resistant depression cohorts, which include 532 TRD cases and 1029 antidepressant-responsive controls of Northern European descent. Polygenic risk scores were created based upon meta-analytic results from the published PGC GWAS datasets from schizophrenia, bipolar, major depression and cross-disorder analysis. These scores were compared for TRD cases and controls using logistic regression models.

4:50 p.m. – 5:15 p.m.
GWAS on Treatment-resistant Depression on 1561 Individuals. Single Locus Results and Polygenic Scoring with Results from SCZ, BIP, MDD and CDG from the PGC (continued)

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

Saturday, June 1, 2013

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

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

Zhewu Wang[1,2], Howard Mendal[1], Mark Hamner[1,2], Donald L. Gilbert[3]
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Background: Attention deficit hyperactivity disorder (ADHD) is a common and highly heritable neuropsychiatric disorder that affects children and adults. Methylphenidate (MPH), a psychostimulant, and atomoxetine (ATX), a selective norepinephrine reuptake inhibitor (NRI) are highly effective in attenuating the symptoms of ADHD patients, but individual response to treatments varies widely. Motor cortex inhibition, measured with transcranial magnetic stimulation (TMS), and dopamine transporter (DAT1) 3' untranslated region-variable number tandem repeats (3' UTR-VNTR) polymorphisms have previously been linked to ADHD diagnosis and stimulant treatment responses but results between studies vary. Our primary objective was to determine DAT1 genotypes influence the effects of MPH and ATX on TMS-evoked cortical inhibition in children with ADHD.
Methods: Sixteen children with ADHD were given oral doses of 0.5 mg/kg MPH and 1.0 mg/kg ATX at visits separated by one week in a randomized, double-blind crossover design. We used TMS to measure conditioned and unconditioned motor evoked potential amplitudes at inhibitory and facilitatory inter-stimulus intervals before and after drug administration. Subjects were genotyped for the DAT1 3'-UTR-VNTR polymorphism. Treatment and genotype effects were estimated with repeated measures, mixed model regression.
Results The effects of both MPH and ATX on cortical inhibition differed significantly in ADHD children with DAT 9/10 versus 10/10 genotypes ($F_{2,13} = 13.04$, $p = 0.0008$). This medication x genotype effect was specific for cortical inhibition and did not distinguish between ATX and MPH.

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

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

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

Alissa J. Cooper, BA[1], Sneha Narasimhan, BA[1], Karl Rickels, MD[2], Falk W. Lohoff, MD [1,2]*
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Background: Pituitary adenylate cyclase-activating peptide (PACAP) is known to be involved in stress response and anxiety. Recent studies have implicated a role of genetic variations in the PACAP (*ADCYAP1*) and PAC1 receptor (*ADCYAP1R1*) genes and post-traumatic stress disorder (PTSD). Given that antidepressant drugs are currently considered the first line treatment for PTSD but also are effective for various other anxiety disorders, we examined whether single nucleotide polymorphisms (SNPs) in the *PACAP* (*ADCYAP1*) and *PAC1* (*ADCYAP1R1*) gene predict response to antidepressant treatment in patients with generalized anxiety disorder (GAD).
Methods: 156 patients diagnosed with GAD received venlafaxine XR treatment as part of an 18-month relapse prevention study. Genotypes were obtained for PACAP gene SNPs rs2856966, rs928978, rs1610037, rs1893154, rs2231187, rs2846811, and rs8192595 and PAC1 gene SNP rs2267735 in patients of European American ethnicity (EA n=112).
Results: Results show a significant association between the rs2856966 (Asp54Gly) SNP in the PACAP gene and antidepressant treatment response in GAD (HAM-A remission: genotypic p=0.0013). None of the other tested SNPs was associated with outcome. There were no significant associations when the analysis was conducted in females only.

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

Conclusion: Our results indicate that the potentially functional variant Asp54Gly in the PACAP gene may play a role in treatment response to venlafaxine XR in GAD.

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

*Gwyneth Zai [*1,2], Eva Brandl [1], Jasna Deluce [3], James L. Kennedy [1,2], Margaret A. Richter [2,3]*
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Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a strong genetic component. Genetic associations between OCD and several candidate genes including the glutamate transporter (SLC1A1), monoamine oxidase (MAOA), glutamate NMDA receptor 2B (GRIN2B), serotonin 2A receptor (5HTR2A), serotonin transporter (SLC6A4), and catecholamine-O-methyl-transferase (COMT) genes have been reported with inconsistent results. Pharmacogenetics represents an alternate to investigate inter-individual genetic variation in drug response. We investigated 12 different genes including those mentioned above in addition to the disks large (drosophila) homolog-associated protein 2 (DLGAP2), myelin oligodendrocyte glycoprotein (MOG), serotonin 1B receptor (5HT1B), chromosome 9 open reading frame 68 (C9orf68), adenosine deaminase, RNA-specific, B2 (ADARB2), and oligodendrocyte lineage transcription factor 2 (OLIG2) genes. Two to 16 SNPs in the DLGAP2, MOG, 5HT1B, SLC1A1, C9orf68, MAOA, ADARB2, GRIN2B, 5HTR2A, SLC6A4, OLIG2, and COMT genes respectively were genotyped in 117 OCD patients with retrospective response data on multiple serotonin reuptake inhibitor (SRI) trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported "minimal", "no change", or "worsening". Genotypes and response data were examined on a

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Pharmacogenetics of Twelve Candidate Genes and Antidepressant Response in Obsessive-Compulsive Disorder (continued)

drug-by-drug and combined basis. Significant response associations were detected in DLGAP2 and paroxetine/clomipramine (P=0.008-0.042), 5HT1B and clomipramine/SRI(s) (P=0.0003-0.045), SLC1A1 and sertraline/fluvoxamine/citalopram/SSRI(s)/SRI(s) (P=0.0008-0.035), C9orf68 and clomipramine/fluvoxamine/SSRI(s) (P=0.007-0.031), MAOA and citalopram (P=0.028), GRIN2B and fluoxetine/paroxetine/fluvoxamine/citalopram/clomipramine (P=0.004-0.024), 5HTR2A and clomipramine (P=0.024), SLC6A4 and paroxetine (P=0.0006-0.010), OLIG2 and paroxetine (P=0.008), and COMT and paroxetine/sertraline/citalopram/SSRI(s)/SRI(s) (P=0.007-0.044). These results suggest that genetic variants may play a role in SRI response to OCD.

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

10:30 a.m. – 10:55 a.m.
Pharmacogenomics of Glutamate and Dopamine Genes and Antipsychotic Response in First Episode Psychosis

Jeffrey R. Bishop[1], Rebekka Lencer[2], James L. Reilly[3], Margret S.H. Harris[1], Shitalben Patel[1], Rick Kittles[4], Judith A. Badner[5], Konasale M. Prasad[6], Vishwajit L. Nimgaonkar[6,7], Matcheri S. Keshavan[8], John A. Sweeney[9]
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We have previously shown that variation in the type-3 metabotropic glutamate receptor gene (*GRM3*) is associated with symptom response to antipsychotics as well as treatment-resistant symptoms in patients with schizophrenia. Additionally, *GRM3* variants may modulate performance on cognition in chronically treated patients, particularly executive function tasks dependent upon prefrontal systems. We extended this work to examine relationships between glutamate and dopamine system genes with cognitive performance and symptoms in 140 first episode psychosis patients phenotyped with eye movement neurophysiology studies of spatial working memory, smooth pursuit, reflexive attention, and response inhibition evaluated before and after antipsychotic treatment. In untreated patients, variation in *DRD2* was associated with two measures of smooth pursuit initiation, while *GRM3* SNPs were related to pursuit maintenance. In a subset of patients followed over the course of 6 weeks of antipsychotic treatment, *DRD2* SNPs were related to change in pursuit latency while *GRM3* variants were associated with change in pursuit maintenance, spatial working memory, and negative symptoms. These findings highlight the importance of D2 signaling as it relates to initiation of motor responses dependent

10:30 a.m. – 10:55 a.m.
Pharmacogenomics of Glutamate and Dopamine Genes and Antipsychotic Response in First Episode Psychosis (continued)

on fronto-striatal circuitry. Furthermore, *GRM3* findings indicate that glutamate signaling is important for performance on cognitive measures of pursuit and spatial working memory that are dependent upon prefrontal functions to maintain internal representations to guide behaviors, and the extent to which antipsychotics influence these functional systems.

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

Magri Chiara[1], Minelli Alessandra[1], Traversa Michele[1], Valsecchi Paolo[2,3], Scassellati Catia[4], Sacchetti Emilio[2,3], Gennarelli Massimo[1,4].
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Antipsychotic response is often variable, therefore, identification of genetic markers helping in predicting the treatment response is extremely interesting. The Positive and Negative Syndrome Scale (PANSS) is widely used in clinical and research settings and its factor structure analysis could better identify symptoms clusters for the treatment response assessment.
We performed a genome wide association study on a group of schizophrenia patients in monotherapy with risperidone, whose symptoms improvement was measured after two weeks using the five and seven factors models.
No SNPs achieved a genome wide significant association p-value ($p<5x10-8$) with the PANSS total score, or with the five and seven factors models. However, an association p-value ($p=6.88x10-8$) very close to the threshold for declaring significance was observed for a SNP inside the metabotropic glutamate receptor 7 (GRM7) gene and Emsley scale's positive symptoms. Seven factors model showed that risperidone gave a worst amelioration of positive symptoms after two weeks treatment in recessive homozygous subjects compared to

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

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

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

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

Antipsychotics have a high rate of discontinuation due to inefficacy and/or adverse effects. An ancillary study to the CATIE trials aimed to identify and quantify sources of variability in the clearance of antipsychotics. We have previously shown that sex and smoking are associated with differential clearance of several antipsychotics (Bigos et al. *J Clin Pharmacol* 2008; 48(2):157-165). We are currently using pharmacokinetic and genetic data from the CATIE schizophrenia trial to identify genetic predictors of antipsychotic pharmacokinetics using non-linear mixed effects modeling
A candidate gene approach has identified several genetic variants in cytochrome P450 genes that highly predict the clearance of antipsychotics. We have shown that CYP3A43 significantly predicts clearance of olanzapine (Bigos et al. *Molecular Psychiatry* 2011; 16:620-625). We have recently found that the same SNP in CYP3A43 also significantly predicts 30% of risperidone clearance. Of the 230 SNPs in CYP450s, the CYP3A43 SNP (rs472660) was the most significantly associated with both risperidone and olanzapine clearance, and predicted most and the entire previous race effects in drug clearance, respectively. African Americans have a greater proportion of carriers of the fast metabolizing allele. This CYP3A43

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

SNP did not predict either quetiapine or ziprasidone, which was predicted based on the lack of racial effects on their clearance. The most significant predictors of ziprasidone and quetiapine clearance were SNPs located in the CYP2A/2B families of genes on chromosome 12. SNPs in other CYP gene families were also associated with clearance of one or more of the antipsychotics.

We are also conducting a GWA study using the original CATIE Affy 500K chip, and we have identified novel genetic predictors, which have not previously been associated with drug metabolism, including ST6GAL1 which best predicts olanzapine clearance. A long-term goal is to use these genetic variants to build models of predictors of antipsychotic drug metabolism in order to guide dosing. A separate goal is to use the variability in antipsychotic clearance as a covariate in studies designed to identify genetic predictors of antipsychotic drug response. We have shown that patients with schizophrenia who carry the risk allele for KCNH2, are 5-times less likely to discontinue olanzapine, only after controlling for differences in olanzapine clearance (Apud et al. *Am J Psychiatry.* 2012;169:725-734). The overall goal of this research is to use genetics to identify and characterize sources of variability in pharmacokinetics and response to psychotropics in order to optimize treatment strategies.

References:

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Apud, JA, Zhang, F, Decot, H, Bigos KL, Weinberger DR. Genetic variation in *KCNH2* associated with expression in brain of a unique Herg isoform modulates treatment response in patients with schizophrenia. *Am J Psychiatry.* 2012;169:725-734

11:45 a.m. – 12:10 p.m.

Pharmacogenomic Analysis of Homozygous Common Genetic Variants in the CATIE Trial

Tim Ramsey[1], Qian Liu[1], Mark Brennan[1]
[1]SureGene, LLC

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

[1]All authors are employees of SureGene, LLC. Ramsey and Brennan are equity holders in SureGene.