POSTER SESSION ABSTRACTS
Sunday, June 15, 2014

Board #1

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

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

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

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

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

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Board #2
Molecular Predictors of Antidepressant Treatment Outcome

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Board #9 (continued)

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

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

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

Board #10 (continued)

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

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

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

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

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

Board #13

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

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

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

Board #14
Treatment Resistant Schizophrenia: Run of Homozygosity Analysis

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

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

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

Board #15 (continued)

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

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

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

Board #16 (continued)

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

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Board #17
Genetic Correlates of Cognitive Remediation Response in Schizophrenia

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

Board #17 (continued)

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

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

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

Board #18 (continued)

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

References:
1. Leucht, S., et al., Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet, 2013. 382(9896): p. 951-62.
2. Theisen, F.M., et al., Clozapine-induced weight gain: a study in monozygotic twins and same-sex sib pairs. Psychiatr Genet, 2005. 15(4): p. 285-9.

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

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Board #19 (continued)

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

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

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

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