Sunday, June 15, 2014

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

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

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

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

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GWAS in Antipsychotic-induced Weight Gain Dissecting the CATIE Sample (continued)

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

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9:30 a.m. – 10:00 a.m.

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

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

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

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

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

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

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

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

Funding and Acknowledgements
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1. Cole T.J. and Green P.J. (1992) *Stat Med* 11:1305-19.
2. Becer E., Mehmetçik G., Bareke H., Serakınc N. *Gene* 529: 16-20.
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10:00 a.m. – 10:30 a.m.
Recent Progress in the Search for Genetic Markers for Clozapine-induced Agranulocytosis

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

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

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Recent Progress in the Search for Genetic Markers for Clozapine-induced Agranulocytosis (continued)

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

10:30 a.m. – 10:45 a.m. **Break**

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

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

Dan Rujescu
University of Munich

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

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

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Pharmacogenomics of Typical Antipsychotics (continued)

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

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

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

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

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Potential Lethal Side-effects of Clozapine: Clozapine-induced Agranulocytosis in Perspective of Contemporary Evidence (continued)

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

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

James Walters
Cardiff University School of Medicine

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

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

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

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

Joey Trampush
The Zucker Hillside Hospital, Glen Oaks, NY

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

2:15 p.m. – 2:45 p.m.

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

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

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

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

Anil Malhotra
The Zucker Hillside Hospital, Glen Oaks, NY

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

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

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

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

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

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

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

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

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

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

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

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

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

John R. Kelsoe[1,2,3], Jun Yao[4], Kangguang Lin[5], Kristen Brennand[6], Fred Gage[4], Christopher Woelk[7], Cory White[8], The Pharmacogenomics of Bipolar Disorder Study
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One of the challenges facing pharmacogenetics is the cost and labor involved in assessing the phenotype of drug response. The gold standard prospective clinical trial generally assesses several hundred subjects, where tens of thousands have been required for success in recent genome wide association studies of disease susceptibility.

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

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

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Cellular Models of Lithium Response in Bipolar Disorder (continued)

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

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