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Rapporteur Summaries of Plenary, Symposia, and Oral sessions from the XXIII[rd] World Congress of Psychiatric Genetics Meeting in Toronto, Canada, October 16-20, 2015

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Abstract

The XXIIIrd World Congress of Psychiatric Genetics (WCPG) meeting, sponsored by the International Society of Psychiatric Genetics (ISPG), was held in Toronto, ON, Canada, on October 16-20, 2015. Approximately 700 participants attended to discuss the latest state-of-the-art findings in this rapidly advancing and evolving field. The following report was written by trainee travel awardees. Each was assigned one session as a rapporteur. This manuscript represents the highlights and topics that were covered in the plenary sessions, symposia, and oral sessions during the conference, and contains major notable and new findings.

Keywords

International Society of Psychiatric Genetics (ISPG); DNA; genome-wide association study (GWAS); mood disorders; psychiatric genetics; schizophrenia; World Congress of Psychiatric Genetics (WCPG)

Introduction

The International Society of Psychiatric Genetics (ISPG) was founded in 1992 with a mission to facilitate research in the genetics of psychiatric disorders and related traits and to promote education in psychiatric genetics. It sponsors an annual meeting, which is held in alternating cities between North American and European countries. The XXIIIrd World Congress of Psychiatric Genetics (WCPG) took place in Toronto, ON, Canada from October 16-20, 2015. Over 650 attendees in psychiatry, psychology, genetics, and other related fields had the opportunity to attend 65 scientific sessions. This meeting provided early investigator travel awards to 34 international and 11 local trainees to present their work at this meeting. One of the goals of this conference is to expand our reach to and involve other developing countries. Of the 32 international awardees who attended the meeting, nine (28%) presented work from their developing countries including Brazil, Cuba, India, Nigeria, Serbia, and South Africa. The 2015 congress was chaired by Dr. James L. Kennedy and the WCPG Rapporteur Program were chaired and organized by both Dr. Gwyneth Zai and Dr. Kennedy. Rapporteurs for the 65 conference sessions were early investigator awardees, each with a task to summarize individual session in addition to relevant discussions. This has been the tradition to summarize the conference sessions into a publication since 2007 in New York.

The following sections are organized based on the date of the sessions, followed by sub-section of plenary sessions, symposia, and oral sessions.

Friday October 16, 2015

Keynote Lecture

Data Integration for Disease Gene Identifications: Genome × Transcriptome × EMR (reported by Robert Maier): Professor Nancy Cox (Vanderbilt University, USA) presented trait mapping results using PrediXcan (Gamazon et al., 2015), a gene-based association method that utilizes genetic and transcriptome data to understand the molecular mechanisms of disease phenotypes. In the first step, the Genotype-Tissue Expression (GTeX) database was used to train tissue-specific genetic predictors of gene expression levels for those 20% - 40% of genes whose transcript levels are at least moderately heritable. The least absolute shrinkage and selection operator (LASSO) regression analysis resulted in predictors of transcript levels that are based on approximately 60 – 80 cis expression quantitative trait loci (eQTLs) per gene. Half of those predictors have a prediction R^2 greater than 0.2. Using predictors that are based only on the genetically determined part of expression has the advantage of bypassing reverse causation of phenotype on transcript levels. These predictors of transcript levels were then applied to the large BioVU dataset, the Vanderbilt's biorepository of DNA that has been extracted from discarded blood collected during routine clinical testing and are linked to de-identified medical records. The goal of the study was to perform a phenome wide association study (PheWAS) in which associations between disorders and predictors of gene expression are identified. The BioVU repository consists of electronic medical records (EMR) for more than two million individuals, 20,000 of which have been genotyped to date. Results from the gene-disease association tests based on approximately 5,000 BioVU subjects with heart tissue expression predictors of approximately 500 genes were then presented. One of the most interesting examples was a

significant association between reduced predicted expression of the glutamate receptor, ionotropic kainate 5 (*GRIK5*) gene and various eye related disorders. A clustered regularly-interspaced short palindromic repeats (CRISPR) zebrafish knockout model subsequently validated the role of *GRIK5* in eye development. Examples of genes associated with neurological and psychiatric phenotypes (which Professor Cox termed the "quintessential human phenotypes") include the beta-1,4-N-acetyl-galactosaminyl transferase 4 ((*B4GALNT4*) gene with mood disorders, the direct IAP (inhibitor-of-apoptosis)-binding protein with low pI (*DIABLO*) gene with psychosis, and the cytohesin 2 (*CYTH2*), synaptic vesicle glycoprotein 2A (*SV2A*), chymotrypsin-like elastase family, member 2A (*CELA2A*), and prostate and testis expressed 2 (*PATE2*) genes with addiction, alcohol disorders and "failure to thrive", respectively. Future plans include extension of the analysis to larger sample and additional genes, with particular focus on: a) genes related to Mendelian diseases and drug targets; b) experimental validation of current significant associations; c) prediction and association of up-regulated (as opposed to down-regulated) gene expression; and d) comparisons of PrediXcan predictions and polygenic risk score (PRS) predictions.

The first question in the Q&A session was regarding the lack of significant associations of genes which have previously been associated with psychiatric disorders. Dr. Cox explained that she presented preliminary results based on only 500 genes, which have been analyzed to date. Dr. Mark Daley (Broad Institute, USA) inquired about statistical significance after multiple testing with many gene-phenotype combinations. Dr. Cox pointed out that the complex correlation structure in the EMR complicates corrections for multiple testing and that the use of eigenphenotypes could be helpful.

Saturday October 17, 2015

Plenary Sessions

International Initiatives in Cancer Genomics and Big Data (reported by Chris Cole): As the efficiency and accuracy of human genome sequencing increases, a new field of care has emerged. Precision medicine (formerly known as personalized medicine), tailoring therapies to the individuals based on their genetics, has gone from science fiction to scientific reality. Cancer medicine especially has become the vanguard of this rapidly advancing field, says Dr. Thomas Hudson, the president and scientific director of the Ontario Institute for Cancer Research (OICR) in Canada. Genetic information, only readily attainable after the recent 100,000-fold decrease in sequencing costs, is used to predict individual risk, optimize screening programs, and identify disease at earlier stages. Diagnostic genetics can lead to more precise diagnosis and more accurate prognostic interventions. The potential benefits of individualized therapy are large, as can be attested by the successes of several early interventions such as *Gleevec* and human epidermal growth factor receptor 2 (*HER2*) therapies, and the rate of discovery and clinical approval has been accelerating. Such discoveries, however, require global collaboration of a large scale, which is not often achievable. Dr Hudson has been at the heart of several efforts to centralize and standardize the collection and utilization of genomic data for healthcare. With 85 standardized projects deployed across the world, some of the preexisting mysteries of cancer are becoming clearer. From discovering 24 unique carcinogenic patterns of mutations to identifying Aristolochic acid in traditional medicine as carcinogenic, the approximately $20

million investment per center is starting to pay dividends. With tremendous amount of data being gathered, OICR has become the hub to deal with data privacy and availability. On the clinical side, Dr. Hudson has started a feasibility study with five sites in Ontario. The study, testing protocols as well as outcomes, examines the effect of personalized therapy on actionable genes in a population of patients beyond the standard of care. Though certain genes may be involved in disease pathways, the individual variants are often novel. The fact that many patients may have a unique mutation encourages the sharing of crucial data between physicians and researchers. To this end, Dr. Hudson and other international colleagues have established the Global Alliance for Genomics and Health, an international collaboration to accelerate progress in human health research and standardize procedures. Similar to the World Wide Web consortium assigning a standardized IP address, the Global Alliance allows researchers from around the world to speak the same language and quickly integrate their data. With 350 members in 35 counties and four separate working groups, the Global Alliance has tackled some of the most pressing issues of the genomic era. From a novel application program interface (API) for interacting with genomic data to a framework for the responsible sharing of genomic and health related data, the consortium has utilized expertise from clinical medicine, genetics, and computer science. Their current projects include the Beacon project, which allows physicians to light a “beacon” when a particular mutation is observed, and the breast cancer (BRCA) Challenge, where physicians can obtain a standardized answer to whether their patient's mutation is clinically significant. With emerging and growing new and exciting data, Dr. Hudson reminds us that individuals are keys to creating tools, and organizations are the best ways to gather and incorporate experiences from around the globe. The recent advances in sequencing technologies, cancer genomics, and targeted therapies have created the perfect platform for personalized medicine. It's up to us to capture and transform this potential into clinical practice.

The Regulome in Psychiatric Therapy: Integrating Chromosomal Architecture, Genetic Variation, Epistasis, and Evolution (reported by Eric Monson): Dr. Wolfgang Sadee (The Ohio State University, USA) began his talk on the point that we are nearing the post-genome-wide association study (GWAS) era. GWAS findings have yielded a wealth of information but many results remain with unclear clinical significance, particularly because greater than 90% of these results reside within intergenic and intronic genomic regions (Welter et al., 2014). If further explored, these variants may offer critical insight to disease etiology, risk, and therapies. Dr. Sadee explained that the clinical significance of variants may depend on evolution, the three-dimensional architecture of human deoxyribonucleic acid (DNA), and/or epistatic interactions. Variants may be deleterious (typically rare variants) or provide fitness benefits except when combined with certain environmental stressors and/or epistatic effects (typically common variants). Such risk factors may remain hidden in GWAS analyses (Sadee et al., 2014). Variants may affect well-conserved but undescribed regulatory networks leading to broad effects not readily detectable in single nucleotide polymorphism (SNP) GWAS associations (Stergachis et al., 2014). Dr. Sadee cautioned that, due to these complexities, analysis focus must be balanced to capture only the information needed to describe causative variant effects and to avoid noise from surrogate markers and overlapping/competing regulatory systems in broad examinations (Sadee et al., 2014). Such noise may explain the recent lack of detected epistasis in GWAS

assessments (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Dr. Sadee then described methods, which are useful for the exploration of functional regulatory variant effects. Allelic expression imbalance (AEI) (Johnson et al., 2008) can identify variants that perturb the transcription, splicing, and translation of proteins. Broadening the scope of an initially narrow investigation can also help identify epistatic interactions. For example, Dr. Sadee's team examined the cytochrome P450 2D6 (*CYP2D6*) variant rs16947 (the *CYP2D6**2 allele), described to have no effect on expression levels, but shown to have inconsistent behavior. They identified that rs16947 reduces *CYP2D6* expression if present alone; however, if the high linkage disequilibrium (LD) variant, rs5758550, which is located 100kb away from *CYP2D6*, interacts with its promoter by DNA looping, increased expression is observed. The net result is normalized expression of *CYP2D6*, indicating the need to include both variants in clinical metabolism panels (Wang et al., 2014). Dr. Wang in Dr. Sadee's research group has also detected previously unknown regulatory networks between SNPs within/near the *CYP3A* family of genes via the circularized chromosome conformation capture (4C) analysis (unpublished results), which can identify potentially distant DNA regions that interact with a known site through chromosome conformation changes. Finally, Dr. Sadee's team found that the dopamine D2 receptor gene (*DRD2*) SNP rs2514218 is associated with schizophrenia and resides largely in the opposite haplotype to two SNPs (rs1076560 and rs2283265) that were found to disrupt splicing (Zhang et al., 2007). It was further found that the *DRD2* SNP rs1076560 interacts with several dopamine transporter gene (*SLC6A3*) variants and environmental stress, which drastically increases the risk of death associated with heavy cocaine abuse (Sullivan et al., 2013). These findings demonstrated that future efforts to identify the function of disease-associated variants should thoughtfully utilize tools and evolutionary understanding to unravel potentially complex regulatory systems. Successes can offer important insights into the underlying basis of disease and offer appropriate targets for clinical applications.

Worldwide Opportunities in Psychiatric Genetics Research (reported by Zoe Robaina): Dr. Lin He (Shanghai Jiao Tong University, China) reported the current developments in China, the value of special populations, and opportunities for international collaborations. He showed the significant progress in the identification of candidate genes for schizophrenia and other mental disorders by analyzing the genetic structure, GWAS and CNV in the Han Chinese population, as well as results of his team's investigations in a Chinese schizophrenia sample using various genetic approaches including GWAS, epigenetics, pharmacogenetics study, and knock-out mouse model study. Dr. Jingjing Zhao (Shaanxi Normal University, China and National University of Ireland, Ireland) commented that Dr. He's work represented a good example for worldwide opportunities in psychiatric genetic research and to foster international collaborations. Dr. Zhao also agreed with Dr. He's opinion that the ISPG board of directors should include representatives from China and other developing countries and that one of the future WCPG annual meetings should be held in China in order to promote worldwide opportunities in psychiatric genetics.

Dr. Thelma B.K. (University of Delhi South Campus, New Delhi, India) highlighted the utility of studying populations of different ethnicities to unravel the genetic basis of both complex as well as monogenic disorders in humans using the contemporary genome-wide

SNP arrays and whole exome sequencing tools. Drawing examples from complex traits in the genetically distinct Indian population that her group has been working on, she demonstrated: a) the differences in the genome architecture of the Indian populations in comparison to the Caucasian and other HapMap populations; b) consequent limited replication of Caucasian meta-analysis findings in Indian case-control cohort studies in rheumatoid arthritis (RA) and ulcerative colitis (UC); c) discovery of novel susceptibility loci from GWASs of Indian RA and UC cohorts; and d) the contribution of such a population to the international consortium on celiac disease for example. She further shared her team's exciting findings of novel disease causal variants in Mendelian forms of X-linked intellectual disability, Parkinson's disease, and schizophrenia. She elaborated her work on schizophrenia using exome sequencing technique. This study sample consisted of 17 families of Indian origin with at least two or more members having a diagnosis of schizophrenia. Novel variants including compound heterozygotes in a few biologically/pharmacologically relevant genes have been found to segregate with disease in some of the families. Her team's recent discovery of a mutation in the trace amine associated receptor 1 (*TAAR1*) gene in a family with autosomal dominant form of schizophrenia has provided a strong genetic evidence for the role of this gene, of potential pharmacological relevance in disease etiology.

Dr. Homero Vallada (University of Sao Paulo Medical School, Brazil) spoke about the Brazilian population admixture, which is generally more diverse than the Caucasian population. The observed diversity in the Brazilians is in part due to the large geographical landscape and the migration of several different ancestral origins in Brazil throughout history. The population distribution within the large country gives raise to isolated or semi-isolated groups, which offer good platforms for genetic investigation in general and psychiatric genetic research. Differences in genetic profile and exposure to specific environments may result in different phenotypes including potential psychopathologies. Dr. Vallada presented his work on the molecular genetics investigations of crack cocaine addiction and significant association was detected for genetic variations in the butyrylcholinesterase (*BChE*) gene and the risk of crack cocaine addiction. He also reported that crack cocaine appeared to be more addictive than the powder form of cocaine.

Dr. Chunyu Liu (University of Chicago, USA) discussed the ISPG Global Diversity Task Force with the goals to increase global efforts in psychiatric genetics research and to reduce barriers for global research and education. Therefore, a workshop in South Africa (2015) and two annual meetings in China, the first and second “Summit on Chinese Psychiatric Genetics” (2014 and 2015), were organized to address these aims. During the Chinese summits, investigators were given the opportunity to present their latest research and discuss the current state and future directions of psychiatric genetics. In line with the Task Force's mission, the participation of early career investigators was strongly encouraged. This informal research organization is steadily growing with more than 30 participants representing researchers from various countries. It will be spearheading initiatives to promote collaborations and data sharing in China. This project will serve as a blue print for similar activities to be held in Eastern Europe, Latin America, India, and Africa in the future.

Challenges in Genetic Testing and Counselling (reported by Erik Boot): In this plenary panel session, Dr. Francis McMahon (Johns Hopkins University and NIMH, USA) started by presenting a general overview on "genetic testing and precision medicine in psychiatry". He first discussed potential uses of genetic testing, including the formulation of differential diagnosis, the prediction of treatment outcomes in terms of response and adverse events, and the identification of high-risk individuals. He continued speaking on several key questions related to genetic testing in clinical psychiatric practice. The first question that he raised was whether a certain genetic marker can be genotyped *reliably*. Another question was how *valid* the association is between the genetic marker and psychiatric disease. Finally, he raised the question whether the test result has any *clinical utility*. Dr. McMahon noted that genetic testing has already been utilized in psychiatry in terms of commercial panels marketed to psychiatrists and psychologists and direct-to-customer tests for patients, their relatives, and other individuals. He provided several examples of promising genetic and pharmacogenetic testing in addition to tests currently in use. He noted that the best studied predictive factors to date are not from genetics, but are based on diagnosis, clinical features, family history, treatment adherence, comorbidity, and other biomarkers. Dr. McMahon raised the issue of incidental and secondary findings that can arise from any GWASs. He stated that there is currently no consensus protocol in place to deal with this concern of identifying, reporting and counselling based on unanticipated findings. He mentioned that the American College of Medical Genetics published recommendations for reporting incidental findings in clinical whole exome sequencing findings that should be reported back to the patients; however, guidelines are not yet in place to interpret them. Dr. McMahon discussed that individuals considering genetic testing should receive genetic counselling prior to testing in order to discuss the impact of anticipated and incidental results. Finally, he stressed the importance of providing further education to clinicians and patients, and the need for additional research.

Dr. Jehannine Austin (University of British Columbia, Canada) led a case discussion on practical and psychosocial issues that can emerge from genetic testing for psychiatric disorders. Subjects of discussion included appreciation of the importance of exploring and explaining in lay language the etiology of mental illness to patients and their family members, in addition to reviewing how to address psychosocial issues associated with genetic counseling and genetic testing for mental illness. Dr. Austin presented a simplified version of the additive model of risk of developing a psychiatric disorder using the "*mental illness jar*" analogy. Psychiatric disorders are likely caused by a combination of genetic and environmental factors (i.e., if the jar becomes full with factors depicted as shapes in the jar [crosses the threshold of normal behaviour], the individual experiences an episode of mental illness). Finally, she emphasized that genetic tests will not be able to 100% predict whether a person will or will not develop a mental illness; however these tests may provide important contributions to clinical practice in psychiatry.

Oral Sessions

ADHD/Child Behaviour (reported by Qi Chen): Dr. Andrea Johansson Capusan (Linkoping University, Sweden) described findings from a population based twin study of 18,000 adult twins. The study aimed to investigate the extent to which the association

between childhood maltreatment and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in adults can be explained by familial confounding (i.e. familial factors that are shared by siblings within the same family but different between families) and whether or not it is consistent with a causal interpretation. The results showed that childhood maltreatment was significantly associated with higher self-rated DSM-IV ADHD symptom scores in adults. Within twin pair analysis showed decreasing but significant estimates for dizygotic (DZ) twins and monozygotic (MZ) twins, indicating that the association is in part explained by familial confounding, but is likely to be causal.

Dr. Qi Chen (Karolinska Institutet, Sweden) shared findings from a population based family study on the familial aggregation of ADHD in over eight million relative pairs consisting of twins, full siblings, maternal and paternal half siblings, full cousins, half cousins. Significant associations measured by hazard ratios (HRs) were observed in all subgroups of relative pairs. The magnitude of HRs was reduced with decreasing genetic relatedness. The study found no obvious etiological difference in ADHD between males and females. If family members were affected by ADHD persistent into adulthood, the familial aggregation appeared to be even stronger, indicating such families could be considered a high-risk group and may require diagnostic screening.

Dr. Ditte Demontis (Aarhus University, Denmark) presented findings from a meta-analysis of GWASs of ADHD based on the largest ADHD data freeze to date, consisting of 18,000 ADHD cases and 34,000 controls. The study revealed 10 genome-wide significantly associated loci with ADHD and served as an important step leading towards future research in dissecting the genetic architecture of ADHD.

Dr. Beate St Pourcain (University of Bristol, UK) presented a study in which social-communication difficulties were found to be genetically correlated with ADHD traits and clinical ADHD. The genetic correlations varied with age, with stronger correlation being observed before age 10 and after age 12 for ADHD traits. The findings supported that there are shared genetic influences between social-communication difficulties and ADHD traits in the general population, as well as clinically-diagnosed ADHD, which may depend on developmental stage.

Dr. Evie Stergiakouli (University of Bristol, UK) presented a study investigating the association between ADHD and smoking status and alcohol consumption during pregnancy and breastfeeding. Polygenetic risk score analysis was used to disentangle the genetic effects from prenatal environmental risks. Higher polygenic score of ADHD was associated with higher odds of smoking but not for alcohol before pregnancy and in non-breastfeeding mothers. The findings confirmed that shared genetic effects may play a role in the association between ADHD and smoking during pregnancy and breastfeeding.

Dr. Christie Burton (University of Toronto, Canada) presented a hypothesis-driven genome-wide association study (GWAS-HD) of a quantitative obsessive-compulsive (OC) trait in youth from the community. Two SNPs in an intron of protein tyrosine phosphatase receptor type D *(PTPRD)* gene reached genome-wide significance for the OC traits. SNPs in neuronal PAS domain protein 2 (*NPAS2*) and the central nervous system (CNS)

developmental gene set and the CNS development gene-set as a whole were also associated with OC traits, supporting the hypothesis that genetic variants with functional implication in brain development may be involved in obsessive-compulsive disorder (OCD). This session emphasized the power of using GWAS-HD approach and the importance of using quantitative trait in the general population to boost statistical power for future psychiatric genetic research.

Bipolar and Mood Disorders (reported by Sascha Fischer): Dr. Melvin McInnis (University of Michigan, USA) presented results from a gene expression study in induced pluripotent stem cells reprogrammed to neurons and glial cells, from individuals affected with Bipolar Disorder (BD) and controls. They found a total of 82 differentially expressed microRNAs (miRNAs). Differences in neuronal lineage allocation were also observed: whereas BD neurons prefer ventral medial ganglionic eminence derivatives, control neurons prefer dorsal cortical precursors. In addition to these results, differences in calcium signaling were detected in BD neurons. BD neurons were more active than control neurons but displayed reduced calcium signaling with lithium pre-treatment.

Dr. Niamh O'Brien (University College London, UK) reported study results from a High Resolution Melting (HRM) analysis of four calcium channel genes in 1,098 patients affected with BD. Two non-synonymous *CACNG4* variants were associated with mental illness (rs371128228, $p=1.05\times10^{-4}$, OR=4.39 and 17:65026851 (C/T), p=0.0005, OR=9.52). The rs371128228 marker was associated with reduced glutamate receptor AMPA 1 level at the cell surface. Based on a replicated GWAS finding in the *CACNA1C* gene, data from 99 whole-genome sequenced BD individuals were analyzed. Two variants associated with BD (p=0.015, OR=1.15) were detected in the third intron of *CACNA1C*. These variants were associated with significantly decreased gene expression.

Ms. Niamh Mullins (King's College London, UK) reported on her GWAS and PRS results of suicide attempts in mood disorders, mainly BD and Major Depressive Disorder (MDD) from PGC data. They analyzed 1,075 suicide attempters and 7,081 non-attempters with MDD, 1,852 suicide attempters and 3,285 non-attempters with BD, as well as 18,771 controls in two ways: within-cases analysis (attempters versus non-attempters) and attempters versus controls; separately for each cohort and between cohorts. In suicide-attempters with MDD vs. controls, one genome-wide significant finding was identified on chromosome 14 (rs8013144, $P=8.60\times10^{-11}$, OR=2.2).

Dr. Andreas J. Forstner (University of Bonn, Germany) reported on his findings of shared risk loci and pathways between schizophrenia and BD. Association testing was conducted for the 128 schizophrenia-associated SNPs (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014) in a large GWAS dataset of BD comprising 9,747 patients and 14,278 controls (Mühleisen et al., 2014). After reimputation and correction for control overlap, 22 schizophrenia-SNPs showed nominally significant p values in the BD GWAS. The strongest associated SNP was located near the tetratricopeptide repeat and ankyrin repeat containing 1 (*TRANK1*) gene ($p=8.8\times10^{-8}$). Pathway analysis using INRICH and Ingenuity pathway analysis revealed 25 nominally significant canonical pathways including calcium and glutamate signaling.

Dr. Fernando Goes (Johns Hopkins University, USA) presented findings of a whole-exome sequencing study on a BD family sample. Four to five affected individuals from each of eight multiplex families were exome sequenced and analyzed for rare variants (minor allele frequency [MAF] <1%). Eighty-four rare damaging, segregating variants in 82 genes were detected and association testing was conducted in independent samples with a total of 3,541 BD cases and 4,774 controls. No significant association for genes or variants remained after correction for multiple testing. The detected risk genes in BD families displayed an overlap with recently identified genes for autism and schizophrenia.

Ms. Monika Budde (Medical Center of the University of Munich, Germany) presented a study on the genetic basis of functional outcome in BD. 2,957 LD-based regions were tested for their association with the Global Assessment of Functioning (GAF) score, a measure of social, occupational, and psychological functioning. In a joint analysis of linkage disequilibrium (LD) blocks with putative functional pertinence across 511 German and 1,081 US BD patients, one LD block on chromosome 15 was significantly associated with GAF (kernel score test: $p=1.29\times10^{-5}$ metric GAF; $p=5.64\times10^{-6}$ GAF-extremes).

Schizophrenia: Pathways, RNA and CNVs (reported by Marina Mihaljevic): Mr. Aswin Sekar (Harvard Medical School, Boston, USA) reported on complex structural variation in the Major Histocompatibility Complex (MHC) locus as underlying the association of schizophrenia to the MHC region (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Using novel methods, he characterized various structural forms of the complement component 4 (*C4*) gene and showed that these structural forms affect expression of C4 in human brain tissue and are associated with schizophrenia risk in proportion to their effect on C4 expression. He also presented data suggesting a role for *C4* in synaptic pruning in mice and concluded that these findings could potentially help explain the pathological finding of synapse loss in schizophrenia brains.

Mr. Mads Engel Hauberg (Aarhus University, Denmark) further explored the potential role of miRNAs in the etiology of schizophrenia. He presented a statistical ‘gene set association’ approach to find miRNAs that are regulators of schizophrenia genes and functional genetic variants relating to miRNA. He highlighted that *miR-9-5p* and *miR-137* are regulators of common variant schizophrenia risk genes and are themselves also risk genes.

Ms. Jeannie Pouget (Centre for Addiction and Mental Health, Canada) presented the first comprehensive evaluation of genetic overlap between schizophrenia and 18 autoimmune diseases, according to their epidemiological associations (Benros et al., 2014). She systematically analyzed genome-wide significant autoimmune SNPs with the Psychiatric Genomic Consortium (PGC) genotype data. Results showed no evidence of genetic overlap between schizophrenia and any of the 18 autoimmune diseases and no support for autoimmune-driven subsets of schizophrenia. Further research will include SNPs with more liberal thresholds for association with autoimmune diseases.

Dr. Peter Holmans (Cardiff University, UK) investigated extensive pathway analysis of the largest PGC schizophrenia dataset. He combined results from seven pathways analysis methods which had been applied to 9,016 pathways from large generic pathway sets and 183

candidate pathways regarding particular biological hypotheses. This multiple analysis confirmed significant enrichment of pathways related to dopaminergic synapse, postsynaptic density, seizures, calcium channels and FMRP targets, with considerable genes overlapping among the aforementioned pathways, and suggested further study of their biological mechanisms.

Dr. Daniel Howrigan (Massachusetts General Hospital, Boston, USA) presented novel methods for the analysis of rare copy number variants (CNVs) in schizophrenia, applied to cohort from PGC study of schizophrenia. CNV association testing was controlled for genotyping platforms, ancestry and CNV calling metrics. Results confirmed increased CNV burden in schizophrenia. Deletions were significantly enriched among gene sets related to synaptic function and activity-regulated cytoskeleton-associated (ARC) protein complex. Duplications showed enrichment in N-methyl-D-aspartate (NMDA) receptor complex. He presented evidence for Xq28 to emerge as a schizophrenia CNV 'hotspot'.

Dr. Jacob Vorstman (Rudolf Magnus Institute, Utrecht, Netherlands) discussed new data on the cumulative burden of genetic double hits in schizophrenia. He combined concurrent CNV and SNP data in large Dutch cohort recruited from the Genetic Risk and Outcome in Psychosis (GROUP) Consortium. Preliminary results showed increased burden of deleterious impact inferred by double hits in deleted sequence in schizophrenia and difference between cases and controls driven by higher number of and higher degree of deleteriousness of the disease-associated SNPs (dSNPs: functional SNPs in genes affected by CNVs). These dSNP effects were not detected in duplicated sequence. He concluded that deletions co-occurring with a functional SNP on the remaining allele could be an additional mechanism involved in etiology of schizophrenia.

Symposia Sessions

Genetic Aspects of Behavioural Addictions: New Insights from Human and Pre-Clinical Methods (reported by Cristina Bares and Fotis Tsetsos): Dr. Daniela Lobo (Centre for Addiction and Mental Health, Canada) spoke about pathological gambling and described a study in which addiction related genes were selected from previous studies and their own research in the KARG (Knowledgebase for Addiction Related Genes) database. In their study in humans, Dr. Lobo observed an association between pathological gambling and the rs167771 single-nucleotide polymorphism in the dopamine receptor (*DRD3*) gene, after correction for age. When they corrected for sex, they found an association with the calcium/calmodulin-dependent protein kinase 2 delta (*CAMK2D*) rs3815072 marker (Lobo et al., 2014). The *DRD3* functional marker Ser9Gly has been previously associated with addiction (Kreek et al., 2005), but Dr. Lobo did not find an association in her study (Mulert et al., 2006).

Dr. Fiona Zeeb (Center for Addiction and Mental Health, Canada) focused on the environmental factor of gambling disorder. As dopamine sensitization is present in pathological gamblers, Dr. Zeeb examined whether repeated exposure to gambling opportunities caused dopamine sensitization and possibly contribute to problem gambling. Using the rat gambling task (rGT), developed by Zeeb and colleagues, she found that rats exposed to repeated sessions of uncertainty (akin to chronic gambling scenarios in human

patients) resulted in dopamine sensitization. This uncertainty exposure also increased risky decision-making on the rGT. Furthermore, increased risky decision-making also enhanced sensitization.

Dr. Jose Nobrega (Centre for Addiction and Mental Health, Canada) used the rGT to examine possible brain changes by in situ hybridization (ISH) in the genes identified by Dr. Lobo. The ratio of high vs low risk choices was analyzed for correlations with the ISH. A significant correlation was observed between the levels of DRD3 in the islands of Calleja and high-risk options. He also investigated the link between impulsivity and deep brain stimulation (DBS) in rats, with inconclusive results. Lastly, by using the rGT in a depression model, he reported that escapable stress might have beneficial effects to impulsivity, but inescapable stress may worsen the condition.

Mr. Michael Barrus (University of British Columbia, Canada) talked about the gambling models that they have developed, the cued version of the rGT, the rodent slot machine task, the rodent betting task and the loss chasing, and their applicability in their research. He reports that the use of all models provides insight into different biological aspects of gambling, such as the dopamine D4 receptor in the anterior cingulate cortex.

The discussion, which was led by Dr. Vincenzo de Luca (University of Toronto, Canada), focused on the validity of what is measured in the animal models, how the measurements in rats map to human behavior. Other topics of discussion included: the variability of the animals in terms of age and strain and the validity of the time out negative reinforcer. It was mentioned that the negative reinforcer used in the rGT and negative reinforcers used by other groups cannot fully capitulate the losses experienced by problem gamblers. However, the use of timeout periods detracted from the main reward in the rGT. Therefore, the negative reinforcement is somewhat similar to what human gamblers experience. It was acknowledged that the way by which loss is modeled is a limitation of the paradigm.

Polygenic Score Methodology in Psychiatric Genetics (reported by Janine Arloth and Lauren Seaman): Dr. Frank Dudbridge (London School of Hygiene and Tropical Medicine, UK) presented an enlightening overview of the theory and applications of PRSs. He described the technique as a vital component to examine the missing heritability of a multitude of complex psychiatric disorders since risk prediction for these phenotypes is typically challenging. He provided information on previously reported study design parameters to help researchers who are interested in using this informative analysis. (Dudbridge, 2013) In brief, he ended with a discussion of novel software, AVENGEME, which can investigate “chip heritability” (i.e., the heritability explained by SNPs on a specific genotyping array), genetic correlations, and the effect size of SNPs to the risk of developing the examined trait or disorder. Overall, the field aims to move from gene discovery to optimizing phenotypic prediction, as well as to address the entire genetic risk of these enigmatic diseases.

Mr. Jack Euesden (King's College London, UK), introduced a single command line tool to measure PRSs called “PRSice” (Eusden et al., 2015). It provides the best-fit PRS for all calculated and tested PRSs of different SNP sets at different p-value thresholds. He

discussed the importance of controlling for variants in LD when performing PRSs. PRSice handles this problem by using the PLINK software command “clump” (Chang et al., 2015). Furthermore, he discussed the issue of causal variants, which are more likely to reside in functional regions. He compared the performance of PRSice to penalized regression models (LASSO and elastic-net models) and found that PRSice outperforms these latter models. Finally he showed a new PRS method, called “PRSlice”, to identify biomarkers/PRSs for a phenotype without having GWAS data for this phenotype available.

Mr. Robert Maier (University of Queensland, Australia) presented his work on multivariate PRSs, which is based on genotype summary statistics. Standard PRS methods do not account for LD structure and thereby losing information by simply excluding SNPs based on a certain LD measure and p-value threshold. He showed two methods to measure PRS without excluding any SNP and without having the full genotype data available. At first, he showed how to use approximate Best Linear Unbiased Prediction (BLUP) to estimate effects from GWAS. Such SNP-BLUP models intrinsically account for LD between SNPs. The second method he showed was the multi-trait BLUP that evaluates risk across multiple disorders by combining single trait BLUP into multi-trait BLUP of random effects. Finally, he showed an application of both methods using the PGC data for schizophrenia and BD. (Maier et al., 2015) He identified a small decrease in prediction accuracy when using summary statistics (single-trait BLUP) in comparison to using samples with full genotype data. Furthermore, by combining SNP effects from different traits (multi-trait BLUP for two traits: schizophrenia and BD), the prediction accuracy was further improved.

Ms. Hilary Finucane (Massachusetts Institute of Technology, USA) discussed how to employ GWAS summary statistics to partition heritability by functional categories. This approach can shed new light into statistical models for quantitative phenotypes or endophenotypes, especially in large psychiatry samples, since some of these categories can disproportionately contribute to the observed heritability. She spoke about the concern that, while there is much information to be extracted from large meta-analyses, variance components methods are intractable with the increased sizes as well as requiring complete genotypic data. Her group's proposed method is to utilize summary statistics (i.e., LD and stratified LD score regressions) to calculate partitioned heritability (Finucane et al., 2015).

Insights into the Genetic Architecture and Molecular Markers of Major Depression from the CONVERGE Project (reported by Diego Rovaris and Khethelo Xulu): Dr. Kenneth Kendler (Virginia Commonwealth University, USA) opened the symposium by introducing the CONVERGE (China Oxford and VCU Experimental Research on Genetic Epidemiology) project. Dr. Kendler explained the main purpose of the CONVERGE study, emphasizing a large sample size (N = 12,000). The CONVERGE project aims to identify molecular markers conferring susceptibility to the development of MDD. To reduce genetic heterogeneity, it was designed to include only Chinese Han women and exclude cases with depression related to substance abuse. To date, it is the largest single study consisting of one single consistent phenotype. The CONVERGE project consists of 59 participating hospitals from 45 cities of 21 provinces in China. To reduce the likelihood of misclassification of controls, all control participants were personally interviewed. In addition, the CONVERGE

project has information regarding environmental risk factors for both cases and control participants. This allowed for the modeling of genome wide gene-environment interactions.

Researchers from the CONVERGE study presented results across a variety of completed or in-progress analyses. Dr. Tim Bernard Bigdeli (Virginia Commonwealth University, USA) started by reporting on the progress made in understanding the genetic architecture of MDD of Chinese Han women. The project has identified two genome-wide significant variants contributing to the risk of MDD development (CONVERGE Consortium, 2015). These two loci are located on chromosome 10, one in the 5′ region of the sirtuin1 (*SIRT1*) gene ($P = 2.53 \times 10^{-10}$) and another in an intron of the phospholysinephosphohistidine inorganic pyrophosphate phosphatase (*LHPP*) gene ($P = 6.45 \times 10^{-12}$). When the analysis of 4,509 cases was restricted to a severe subtype of MDD, melancholia, there was an increase in the effect size and significance of the signal at the *SIRT1* locus. The CONVERGE project attributed their success to the recruitment of a homogeneous cohort with severe illness. Results were replicated in a sample of Chinese Han men and women but were not replicated in the PGC MDD samples of European descent, which is perhaps due to differences in allele and haplotype frequencies.

Dr. Roseann Peterson (Virginia Commonwealth University, USA) talked about gene-environmental (G×E) interactions in the CONVERGE project. Significant main effects of childhood sexual abuse (CSA) and stressful life events (SLE) on MDD were found and accounted for upwards of 11% of the variance in MDD, as well as interesting G×E interactions between variants in the *SIRT1* gene and CSA (P = 0.008), and variants in the *LHPP* gene and SLE (P = 0.0002). Dr. Peterson also showed that environmental risk factors can change GWAS results: When individuals of high environmental exposure were removed from genetic analyses additional genetic variants were implicated in MDD risk including variants in the mitochondrial iron transporter (*SLC25A37*), lysophosphatidylglycerol acyltransferase 1(*LPGAT1*), and the putative uncharacterized protein Clorfl95/inositol-trisphosphate 3-kinase B (*Clorfl95/ITPKB*) genes.

Ms. Na Cai (Oxford University, UK) presented results showing molecular changes and potential molecular markers of MDD from the CONVERGE study (Cai et al., 2015). Here, they followed up on the findings from the human studies by using animal models to investigate any changes of mitochondrial DNA (mtDNA) and telomere length, using stressed mice versus controls. Stressed mice have been found to have more mtDNA in comparison to controls. Furthermore, telomere length in stressed mice was shortened when compared to controls, corroborating the results found in humans. In addition, to test whether the hypothalamicpituitary-adrenal axis plays a role, mice were injected with corticosterone. Mice that were injected with corticosterone were found to have decreased telomere length in comparison to controls. The series of findings suggested that the molecular changes might be a consequence of MDD.

Dr. Bradley Todd Webb (Virginia Commonwealth University, USA) spoke about associations between oral microbiome and MDD in the CONVERGE study. He showed that the oral microbiome is robustly associated with MDD and these differences between cases and controls can be shown quantitatively and qualitatively. Moreover, this association may

be partly influenced by the use of medication. Dr. Bradley pointed out that these results come from an exploratory study, which does not allow a clear distinction between correlation and causation.

Finally, Dr. Douglas Levinson (Stanford University, USA) briefly discussed the findings obtained in the CONVERGE study. He recognized the effort to collect a large and homogeneous sample and also spoke on the SNP-heritability results found in the CONVERGE GWAS, which was one of the greatest successes in MDD genetic research to date.

Sunday October 18, 2015

Plenary Sessions

The Notorious Past and Bright Future of Psychiatry (reported by Katherine Tombeau Cost): Dr. Jeffrey Lieberman (New York State Psychiatric Institute and Columbia University, USA) presented a plenary session on the mystery of mental illness and psychiatry's notorious efforts to solve it. Dr. Lieberman's comments were largely based on his recently published book, SHRINKS: The Untold Story of Psychiatry (Lieberman, 2015) http://www.jeffreyliebermanmd.com/index.html.

He began by noting that psychiatry was the only specialty in all of medicine to have a specific movement opposed to it. The “anti-psychiatry” initiative was started about 50 years ago, by Thomas Szasz, a psychiatrist at State University of New York in collaboration with L. Ron Hubbard, a science fiction author and founder of the Church of Scientology. Dr. Szasz's motivation stemmed from a desire to be an academic provocateur, while Mr. Hubbard's desire to discredit psychiatry derived from an economic and competitive market share interests to convince potential converts of the value of his Dianetics philosophy and the Scientology approach over psychiatric medicine.

The anti-psychiatry movement gained steam in the cultural turmoil of the 1960's and evolved into an aggressive, pernicious, and persistent effort to deny the existence of mental illness and the ability of psychiatry to understand and treat it. According to Dr. Lieberman, this disaffection with psychiatry was not entirely unfounded, and contributed to by the historical missteps of the profession. Until the latter twentieth century, psychiatry was not scientifically driven and had largely been unable to accurately explain the bases of mental disorders, and had produced minimal effective treatments to alleviate the symptoms and ease the suffering of patients. Although psychiatric illnesses have been documented for centuries, it was not until relatively recently that more accurate diagnoses and effective treatments became available.

Dr. Lieberman described several notable milestones in the history of psychiatry. In 1844, psychiatrists formed the first medical specialty professional association called the Association of Medical Superintendents of American Institutions for the Insane, which was a precursor to the American Psychiatric Association (APA). At the time, the prevailing scientific approach to understanding human disease was to examine anatomical pathology, and this was more difficult and less fruitful in psychiatry. Therefore, mental illness was often

ascribed to meta-physical causes, which often resulted in ineffective, silly, inhumane, and often harmful “cures”.

Philippe Pinel (1745-1826) was heralded for releasing asylum patients from their chains and creating humane environments where “moral therapy” was practiced. But still, from the late 18th century to the mid-20th century, over millions of patients were held in institutions under deplorable conditions. During this time, the theories of Francis Galton on eugenics, Sigmund Freud on psychoanalysis, and Walter Freeman on lobotomies flourished. In the 1970's the APA commissioned Robert Spitzer to revamp the nosology of psychiatry, in attempt to make diagnoses more empirically based and less arbitrary. Spitzer worked with many groups and professionals to develop consensus on the conditions listed in the DSM-III, famously declassifying homosexuality as a mental illness and, in collaboration with Dr. Nancy Andreason, to formally classify Post Traumatic Stress Disorder (PTSD). At this same time, effective psychopharmacology (including antipsychotic, antidepressant, mood stabilizing and anxiolytic drugs) and psychosocial treatments (such as Dr. Aaron Beck's Cognitive Behaviour Therapy [CBT] and Gerald Klerman and Myrna Weissman's Interpersonal Therapy [IPT]) were developed and experimentally verified to reduce suffering.

Psychiatry has finally become a scientifically based and clinically competent medical specialty that is able to benefit from progress through research. Consequently, the previous “stepchild of medicine” is now able to meet the challenges of mental illness and mental health care including reducing stigma, dysfunctional and inequitable health care policy and financing, inadequate infrastructure, services, and workforce needs.

Epigenetics of Psychiatric Disease: Progress, Problems and Perspectives (reported by Bonnie Alberry): Dr. Art Petronis (Centre for Addiction and Mental Health, Canada) discussed epigenetics in psychiatric disease. He introduced epigenetics as instructions – how DNA should be read. He highlighted that a perfect genome could be ruined with erroneous epigenetics. Dr. Petronis outlined epigenetic relevance to disease using three postulates. First, epigenetic factors contribute to phenotype, evidenced by the agouti mouse phenotype (Morgan et al., 1999). Second, there is partial stability, whereby marks are modified by developmental programs via environmental or stochastic events. Partial stability is exemplified through the ten-eleven translocation (TET) enzymes, which actively demethylate cytosines. Third, epigenetics are a secondary mechanism of heritability. Epigenetics were initially considered only heritable in somatic cells. Due to two large epigenetic reprogramming events –in primordial germ cells and in zygotes – transgenerational inheritance was thought to be impossible. Many exceptions have since been found, including the agouti mouse model (Morgan et al., 1999). As the zygotic reprogramming event is less harsh, epigenetic recombination occurs at fertilization, underlying uniqueness of zygotes.

Dr. Petronis explained epigenetics as responsible for disease etiology (Petronis, 2010). MZ twins have DNA modification differences, due to environmental or stochastic factors. Meanwhile, DZ twins have greater differences (Kaminsky et al., 2009). Dr. Petronis suggested epigenetic differences in DZ twins are due to zygote epigenetic diversity. The question of how to identify DNA-independent zygotic epigenetic heritability was then

explored. Dr. Petronis and his team employed a model using inbred mice to generate artificial MZ twins, gestating genetically identical offspring and a MZ twin pair (Gartner and Baunack, 1981). In mice, Gartner and Baunack (1981) found MZ twins had greater similarity than polyzygotic littermates, and intangible variation was not explained by genetics or environment. Dr. Petronis suggested DNA modifications as a candidate to explain heritability through zygotic epigenomes.

Dr. Petronis introduced work investigating SNPs exhibiting allele-specific DNA modification (ASM-SNPs). Brain ASM-SNPs were significantly enriched in schizophrenia patients in GWAS. The distribution of ASP-SNPs was skewed towards the most significant GWAS SNP p-values. ASM-SNPs were most common in functional sites, stressing the importance of DNA modifications in regulatory regions.

Lastly, Dr. Petronis used epigenetic studies of lactose intolerance to model the development of schizophrenia, emphasizing temporal dimension. Dr. Petronis suggested psychiatric disease behaves like multiple, age-dependent, ‘lactose-intolerance’-like epigenetic situations. As time passes, DNA modifications accumulate at schizophrenia risk SNPs, leading to symptom peaks. In discussion, Dr. Petronis addressed histone modifications also playing an important, epigenetic role. However, he suggested that while relevant, less is known in disease context, DNA modifications are more stable to investigate than histone modifications. Dr. Petronis added that while DNA methylation changes with age, there are also fluctuations that may contribute to the episodic nature of psychiatric illnesses.

Identifying Illness and Treatment Biological Markers through Transcranial Magnetic Stimulation (reported by Viviane Labrie): Dr. Zafiris Jeffrey Daskalakis from the Centre for Addiction and Mental Health presented a plenary lecture on the benefits of transcranial magnetic stimulation (TMS) in treating major depression and as a method to probe neurophysiological function in psychiatric disorders. He first presented data showing that GABA neurotransmission deficits in psychiatric disorders can be detected using a TMS-based motor inhibition paradigm. Inhibitory neurotransmission mediated by the GABA system can be activated by TMS resulting in a cortical silent period – a suppression of motor response. Several psychiatric disorders have deficits in the cortical silent period, though patterns of deficits differ between disease types (Radhu et al., 2013). The atypical antipsychotic clozapine was found reverse the impaired cortical silent period in schizophrenia, suggesting that clozapine may mediate symptomatic relief through the GABA pathway. Dr. Daskalakis also demonstrated that TMS can be applied to assess GABA-mediated cortical inhibition in the prefrontal cortex, a brain area of considerable importance to psychiatric illness. Interestingly, prefrontal cortical inhibition was shown have some degree of heritability, where deficits in cortical inhibition were significantly higher among healthy relatives of patients with schizophrenia than in unrelated controls. This demonstrated evidence that cortical inhibition could be a useful biomarker to help identify psychiatric diseases like schizophrenia. Dr. Daskalakis completed his talk by demonstrating the applicability of TMS for medication-resistant depression. Induction of therapeutic seizures by magnetic stimulation was found to be a useful alternative to electroconvulsive therapy for depression, as the seizures could be better localized to the affected neural tissues,

which minimized side effects while significantly improving symptoms in treatment-resistant depression.

Symposia Sessions

Sequencing, Direct-To-Consumer-Testing, Biobanking: The Explosion of Ethical Challenges in Psychiatric Genetics (reported by Laura Flatau and Prachi Kukshal): Dr. Jehannine Austin (University of British Columbia, Canada) gave a talk on how to apply genetic counselling to problems arise in adolescent psychiatry. The major concerns in this area include counselling families with an affected child or parent and the impact of psychiatric disorders on the child or adolescent, family dynamics, and social stigma. Dr. Austin reported that the process of counselling with family members is more important than disclosing the exact risk of developing an illness. She recalled times during her genetic counselling practice when it was crucial for her to handle the problems mentioned above empathetically. She presented several case examples and illustrated the need for thoughtful and tailored counselling to help patients to deal with their family dynamics and to discuss a well-rounded approach in explaining the genetics and environmental risk of psychiatric illnesses.

Ms. Rosa Spencer Tansley (Bournemouth University, UK) presented a study on the quantitative and qualitative methods focusing on the responses of patients and their families to psychiatric genetic counselling. She reported that the perception and expectations towards genetic counselling influence the patient's engagement with the service and patient outcome. The data (57 patients and 29 family members) that she presented suggested that although many perceived psychiatric genetic counselling as beneficial, misconceptions about the service and ethical considerations in regard to its delivery were noted, indicating an urgent need to educate the public regarding genetics, gene-environment interaction, genetic counselling as a discipline, and its application in psychiatry. Her study showed that there is a strong demand for psychiatric genetic counselling but public awareness is relatively low and therefore, there is a need to resolve misconceptions by educating the public.

Ms. Laura Flatau (Ludwig-Maximilians-University Munich, Germany) talked about the ‘Right Not To Know’ especially in the context of incidental findings. She presented the results of a quantitative survey study with 536 participants including the general population, patients and medical healthcare professionals. Her findings suggested that although the majority of individuals (~80%) would like to receive information about an incidental finding, there are specific cases (i.e., hereditary cancer) in which 25% of the participants would choose their ‘Right Not To Know’. Comparing the attitudes between different groups, individuals with a higher education level tended to be more critical towards genetic testing, and they were more likely to choose their ‘Right Not To Know’. Attitude towards wanting information versus the ‘Right Not to Know’was found to be affected by the way the question was asked (i.e., concrete scenarios vs. simple questions) and the individual to whom was asked (i.e., general population or health care professionals).

Mr Fuji Nagami (Tohoku University, Japan) presented data from the Tohoku Medical Megabank project (ToMMo). It is an ongoing project to reconstruct and establish the public health systems in a community of 150,000 participants who have been affected by the 2011

Tohoku earthquake and tsunami in Japan. The aim of the project was to use research findings of common diseases (i.e., cancers, cardiovascular diseases, strokes, diabetes, and mental diseases) with gene-environment interaction for the constructive regeneration of such disastrous events. By addressing the various ethical issues related to psychiatric problems arising from such stressful situation, the project aimed to build an integrated biobank. This biobank contains bio-specimens, questionnaire data, and physiological survey data from cohort studies and analytical datasets, including genomic and other omics data from a subset of the total sample. The examination of various aspects of psychological well-being including the occurrence of mental health problems (i.e., posttraumatic stress reaction [PTSR], anxious state, and depressive state) showed a negative impact of natural disasters on mental health. Individuals who were affected by the earthquake had almost double the national average rate of mental health problems including PTSR, anxious and depressive state. Mr. Nagami identified several ethical issues (i.e., biobank by genome cohort studies, return of results, mental health research in area affected by disaster, and data sharing) related to the setup of the Tohoku Medical Megabank Project, including the collection of large amount of data while protecting the privacy of individuals.

Dr. Marcella Rietschel (Clinical Institute of Mental Health, Germany) was the moderator and Dr. Thomas G. Schulze (University of Munich, Germany) was the chair for the session. Dr. Austin and others stressed the need to improve the education of medical trainees and psychiatrists in patient counselling besides prescribing drugs. Counselling should be tailored to each individual on a case-by-case basis using clinical judgment and at the same time, respecting the individual's autonomy if one chooses the ‘Right Not To Know’. Furthermore, discussion was focused on the extent of psychiatric genetic counselling and the differences between general and psychiatric genetic counselling given that such distinction may lead to further stigmatization of psychiatric illnesses.

Dissecting the Genetic Contribution to Depression: Progress at Last (reported by Elisabetta Maffioletti and Roseann Peterson): Dr. Douglas F. Levinson (Stanford University, USA) opened the symposium with a discussion of the difficulty faced in the identification of specific genetic variants predisposing to MDD. Despite considerable heritability, as demonstrated by twin and family studies (Sullivan et al., 2000), earlier efforts by the PGC showed no genome-wide significant results, even with sample sizes of over 9,000 MDD cases and 9,000 controls (Ripke et al., 2013a). Dr. Levinson suggested that the lack of findings may be due to the need for even larger sample sizes to reach the ‘inflection point’ at which sample size and significance of variants increases proportionately (Ripke et al., 2013a). The heterogeneity of MDD may require the identification of homogeneous subgroups in which statistical power to detect the modest effect sizes expected is maximized. He concluded by emphasizing that screening of controls (to reduce the probability of MDD in the control sample), stricter definition of case status, as well as limiting analyses to more severe forms of MDD (i.e., recurrent depression subtype) will likely aid gene finding efforts.

Dr. Naomi R. Wray (University of Queensland, Australia) examined potential sources of heterogeneity across studies leading to differences in SNP-based heritability estimates for MDD between PGC-MDD1 (18%) and PGC-MDD2 (9%). First, she examined the genetic

correlation (rG) between males and females, finding estimates near unity, indicating that it was premature to conclude that there was lower rG between the sexes for MDD when compared to other psychiatric disorders. Dr. Wray then highlighted that there were significant differences in SNP-based heritability by cohort, indicating unknown sources of heterogeneity across samples, and also reported lower rG among individual MDD cohorts when compared to schizophrenia and BD samples. She suggested that this heterogeneity may be due to potential different environmental factors across studies, loose definitions between cases and controls, and broad ascertainment biases.

Dr. Cathryn M. Lewis (King's College London, UK) presented recent genome-wide association meta-analyses of MDD conducted by the PGC, using an expanded sample size of over 16,000 cases. In the current PGC-MDD ‘data freeze’ of 29 cohorts, no genome-wide significant findings were detected. However, when examining results by sex, significant associations were identified for females only in nitric oxide synthase 1 (*NOS1*) (rs76821249, $p=2.2\times10^{-8}$) and for males only in leucine rich repeat and fibronectin type III domain containing 5 (*LRFN5*) (rs8016327, $p = 5.5\times10^{-8}$). Adding to PGC-MDD29, the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort (7,162 cases, 38,307 controls), and 23andMe (14,906 cases, 41,465 controls) which comprised a total sample size of 38,991 cases and 105,404 controls yielded a significant hit on chromosome 5 (hg19 position: 103903810; $p=3.8\times10^{-8}$). When stratifying the sample by sex, significant associations of a marker in the Major Histocompatibility Complex, Class I, human leukocyte antigen B (HLA-B)region ($p=2.9\times10^{-8}$) in females and a locus in the Huntingtin gene (*HTT*) ($p=1.1\times10^{-8}$) in males were found. When further meta-analyzed with the CONVERGE sample, a variant in the *LRFN5* gene, which was previously significant in males of PGC-MDD29 sample, was also associated with MDD in the combined analysis ($p=4.5\times10^{-8}$).

Dr. Kenneth S. Kendler (Virginia Commonwealth University, USA) presented results from the CONVERGE study, a whole-genome sequencing study of 5,303 Han Chinese women with recurrent MDD and 5,337 screened controls. The data were collected from 59 hospitals across China and represented one of the largest and most homogeneous MDD cohorts with the following inclusion criteria: (a) recruiting females only, (b) cases with severe form of recurrent major depressive episodes through clinical interview, and (c) screened controls past the age of typical MDD onset. Dr. Kendler reported that they successfully detected and replicated two common variants contributing to MDD risk on chromosome 10q: upstream of *SIRT1* and in an intron of *LHPP* (Converge Consortium, 2015). He also commented on the genetic architecture of MDD, reporting that (1) genome-wide SNP-based heritability was estimated as 21-28%, (2) the heritability in MDD explained by each chromosome was proportional to its length (r=0.680) thus supporting a highly polygenic etiology, (3) the variance explained was distributed across the allelic frequency spectrum, (4) partitioning by genic annotation indicated a greater contribution of SNPs in coding regions and within the 3′-UTR regions, and (5) that DNase hypersensitive sites in many cell types including brain-related cells were enriched for associations with MDD (Peterson et al., submitted to *Mol Psychiatry*).

Dr. Patrick F. Sullivan (University of North Carolina at Chapel Hill, USA and Karolinska Institutet, Sweden) presented evidence for shared genetic contributions between MDD and both psychiatric traits and physical characteristics, using a GWAS summary statistics approach (Bulik-Sullivan et al., 2015a). Dr. Sullivan reported significant genetic correlations between MDD and schizophrenia (rG=0.396), BD (rG=0.407), ADHD (rG=0.505), depression symptoms (rG=1.0), neuroticism (rG=0.831), smoking status (rG=0.286), early onset stroke (rG=0.312), migraine without aura (rG=0.169), and cardiovascular disease (rG=0.188). He also noted several limitations of the study including (1) limited power of the studied samples included, (2) the use of summary statistics as opposed to using full raw information, (3) the rG approach (Bulik-Sullivan et al., 2015b) applied has not been designed for analysis across multiple ancestry groups, (4) inability to rule out confounding genetic effects, and (5) potential sampling bias. Dr. Sullivan concluded by stating that this approach may be useful for interconnections of psychiatric disorders and to highlight common genetic architecture across complex disorders.

Mitochondria Genetics and Function in Psychosis (reported by ZsófiaBánlaki): The chairs of the symposium, Dr. Vanessa Goncalves and Dr. James L. Kennedy (Centre for Addiction and Mental Health, Canada) introduced the session highlighting that the investigation of mtDNA variants is a promising but technically challenging, and yet under-explored field in psychiatric genetics. One reason can be explained by the variable mtDNA copy number, which can reach 1,000 per cell and the presence of heteroplasmy. Wildtype and mutant mtDNA proportions are highly variable. Thus, as Dr. Goncalves described, although deficit in the oxidative phosphorylation (OXPHOS) of mitochondria has been implicated in schizophrenia, the recent PGC GWAS did not support a role of mitochondrial function in schizophrenia (Ripke et al., 2013b; Schizophrenia Working Group of the Psychiatric Genomics, 2014); however, this GWAS did not investigate genes within the circular mtDNA genome. Very few studies focusing on mtDNA variants showed that somatic mutation rates vary with tissue types and are higher in certain brain regions of schizophrenia patients when compared to healthy individuals (Rollins et al., 2009; Sequeira et al., 2012; Sequeira et al., 2015). The present study analyzed 42 common and 167 rare single nucleotide polymorphisms (SNPs) in 4,778 cases and 5,819 controls. A rare and six common variants reached nominal significance, but they did not survive testing for multiple comparisons. Haplogroup analysis detected a higher rate of schizophrenia in the J-T group characteristic to the European Caucasian population. The mitochondrially encoded cytochrome b (*MT-CYB*) rs3088309 marker was the top hit for association with schizophrenia. The fact that rs3088309 is a missense variant with potential functional relevance (unpublished data) further supports its role in the pathogenesis of schizophrenia. As it was remarked during the discussion period, maternal inheritance in schizophrenia could provide additional evidence for the relevance of mtDNA variants, but this has not been analyzed in the present study and literature data are controversial.

Dr. Marquis Vawter (University of California, USA) reported on the findings of mitochondrial hypofunction in schizophrenia and the genetic background of schizophrenia. Previous literature data have consistently implicated mitochondrial dysfunction in the pathophysiology of schizophrenia; however, it is difficult to differentiate between the cause

and effect of this dysfunction. Dendritic spine loss, reduction in mitochondria copy number, and decreased expression of mitochondria encoded transcripts are all characteristics of schizophrenia. Evidence suggests that epistasis between genes from the nuclear and mtDNA may play an important role in the etiology of schizophrenia. eQTL analysis showed a strong enrichment of approximately 1,000 autosomal mitochondrial genes in the cortex (Kim et al., 2014), and common mtDNA variants were found to contribute to the risk of several common complex diseases including schizophrenia (Hudson et al., 2014, Sequeira et al., 2012). Dr. Vawter presented preliminary analysis of some large recent GWAS results showing a modest over-representation of nuclear encoded mitochondria genes in schizophrenia. Preliminary data showed an increase in the rate of non-synonymous mtDNA mutations. The exact localization and copy number of mitochondria within dendrites and axons using a case-control study design is currently in progress. A question was raised regarding the issue of clonal expansion and Dr. Vawter discussed that although heteroplasmic mutations are generally not tissue-specific, certain types of mutation can accumulate at specific sites, such as large deletions in dopamine innervated regions. This may be related to mtDNA dynamics, stability, and non-homologous recombination. Thus, it was recommended that large GWAS studies should incorporate mtDNA variants along with nuclear SNPs for epistatic interactions between both genomes.

Dr. Dost Ongur (McLean Hospital/Harvard Medical School, USA) presented the results on his magnetic resonance spectroscopy (MRS) studies of bioenergetic abnormalities in psychosis. Since gamma oscillation producing cells such as inhibitory GABAergic interneurons consume high level of energy as shown by their enrichment with mitochondria, these cells are believed to be critical in the development of cognitive disorders when energy supply is depleted (Kann et al., 2014). MRS has previously been shown to be a useful tool for assessing the levels of the rapidly mobilizable energy reserve phosphocreatine (PCr) and the immediate energy source adenosine triphosphate (ATP) *in vivo* (Du et al., 2012). In both chronic and first-episode schizophrenia patients, marked reduction was observed in the PCr peak, providing evidence for a reduced enzymatic reaction rate for creatine kinase (Du et al., 2014). The pH scale also became more acidic in chronic patients when compared to first-episode patients, suggesting enhanced anaerobic glycolysis. Correlation analysis between ATP/PCr levels and pH is currently underway. In contrast to patients with schizophrenia, bipolar I disorder patients detected normal PCr/ATP level and pH. However, upon photic stimulation, ATP but not PCr level was reduced in the visual cortex of patients with bipolar I disorder, whereas the pattern was reversed in healthy individuals, indicating an inability to decrease the PCr level in bipolar I disorder patients at high energy demand (Yuksel et al., 2015). Investigation of creatine kinase function is in progress. These findings implicated that schizophrenia may be characterized by a severe and pervasive bioenergetic failure and bipolar I disorder may require brain activation to unmask abnormality in a compensated bioenergetics system at rest. This further suggested bioenergetic dysfunction in response to environmental factors in bipolar I disorder. Compromised bioenergetics thus may lead to abnormal brain function in psychotic disorders. This may potentially reveal novel drug targets related to the mitochondria.

Dr. Dorit Ben-Shachar (Rambam Health Care Campus and Technion-Israel Institute of Technology) provided evidence for a multifaceted mitochondrial dysfunction in peripheral

cells and postmortem brains. Dr. Ben-Shachar reported that the enzymatic activity of complex I of the OXPHOS system, nicotinamide adenine dinucleotide (NADH) dehydrogenase, was found to be higher in both medicated and non-medicated schizophrenia patients at the acute state, while reduced at the residual state, as compared to major depression and bipolar I disorder patients and healthy controls. This activity was accompanied by altered expression of three nuclear encoded genes, NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa (*NDUFV1*), NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa (*NDUFV2*) and NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (*NDUFS1*), encoding different subunits of complex I. These abnormalities were accompanied with reduced synthesis rate of complex I, pathological interaction between dopamine and the complex and impaired cell respiration. Dr. Ben-Shachar also reported that neuronal differentiation of induced pluripotent stem cells (iPSCs) reprogrammed from schizophrenia hair follicle keratinocytes showed that differentiation into dopaminergic neurons was severely impaired, while glutamatergic neurons failed to mature. These impairments were associated with various deficits in mitochondria, similar to those previously observed in schizophrenia (Robicsek et al., 2013). Transfer of isolated active normal mitochondria into schizophrenia cells restored respiratory function, and reduced dopamine toxicity, while only partially restored mitochondrial network dynamics. These significant positive effects lasted for about three weeks, and then gradually faded. In addition, transfer of healthy mitochondria improved differentiation of schizophrenia derived iPSC into glutamatergic neurons. The presented data pinpoint mitochondria as an additional pathological factor in schizophrenia and suggest a role for mitochondria in neuronal differentiation. Mitochondria transfer may lead to new treatment approaches for brain diseases with developmental connectivity and bioenergetics abnormalities such as schizophrenia. During the discussion, a comment was provided regarding mitochondria haplogroup effects, which could also be considered at transfer and that the impact of complex I inhibitors in animal models would be intriguing to investigate.

Oral Sessions

Genome-wide Approaches in Other Disorders (reported by Andrea Vereczkei): Dr. Erin Dunn (Harvard Medical School, USA) reported on a GWAS conducted on a Hispanic sample with generalized anxiety disorder (GAD). Since the Hispanic population is highly underrepresented in psychiatric genetic research it was important to see which genetic variants are common among this population. GWAS was carried out on GAD symptoms and a SNP, rs78602344 in the thrombospondin 2 gene (*THBS2*) reached genome-wide significance. However, efforts to replicate this finding in three independent Hispanic samples did not confirm this result. Since the disease prevalence in Hispanic population is approximately half of the European population, larger replication sample sizes are needed for future studies in anxiety disorders of Hispanics.

Dr. Sandra Meier (Center for Register-based Research, Denmark) presented the associations of anxiety disorders and depression with increased mortality. Clinical anxiety represents a core symptom of several different anxiety disorders, which is highly heterogeneous because patients with an anxiety disorder often present with comorbid psychiatric conditions. The goal of the study was to compare the mortality rate between different anxiety disorders

including GAD, social anxiety disorder, agoraphobia, specific phobia, panic disorder, OCD, acute stress reaction and posttraumatic stress disorder (PTSD) in 50,000 patients with an anxiety disorder followed between 2002 and 2011. The results showed no familial confounding factors. Patients with anxiety disorders had higher rate of natural and unnatural causes of death. Individuals with comorbid depression were particularly more likely to die by unnatural causes.

Mr. Eric Monson (University of Iowa, USA) discussed the results of a whole-exome sequencing study of BD patients who attempted suicide. Suicidal behavior is the most severe outcome of psychiatric disorders, and has a heritability of 30-50%. Primarily candidate gene studies and GWASs have been used to examine common variation in suicidal behavior to date. This study examined rare functional variations within suicidal behavior. 387 BD patients with a history of suicide attempts and 631 BD patients with no past suicide attempts were enrolled in the study. Mr. Monson analyzed over 800k genetic variations and no genome-wide significance was identified. Top hit genes with $p<0.01$ were chosen for further analyses. Within these analyses, a significant enrichment score of synapse associated genes was detected.

Dr. Chia-Yen Chen (Massachusetts General Hospital, USA) presented findings from a GWAS on army soldiers with a history of trauma exposure in the United States. Trauma exposure is an essential diagnostic criterion for PTSD and also poses an increased risk for depression, substance use disorders, and anxiety. Twin studies also showed a 47-60% heritability for trauma exposure. In the Army Study To Assess Risk and Resilience in Service members (Army STARRS) sample, life-time cumulated trauma exposure was analyzed in GWAS. Two cohorts were included in the study: new soldiers and soldiers deployed to Afghanistan, with a total of approximately 18,000 samples with genotype data. Association study was carried out based on different ethnic groups. In the European American samples, a locus in the low-density lipoprotein receptor class A domain-containing protein 4 (*LDLRAD4*) gene on chromosome 18 was implicated in suggestive association with trauma. This gene was previously found to be associated with BD and schizophrenia. In the African American population, a locus in the leucine rich repeat containing 4C (*LRRC4C*) gene, which was previously found to be associated with BD, was significantly associated with trauma. Both findings were not replicated in other populations.

Dr. Laura Bierut (Washington University School of Medicine, USA) discussed the role of the cholinergic receptor, nicotinic, alpha 5 (*CHRNA5*) gene in nicotine dependence, smoking status, and lung cancer. Smoking behaviour and lung cancer have been linked to markers on chromosome 15. The present study shows evidence for a complex relation amongst rs16969968 SNP, also known as Mr. Big of *CHRNA5* and smoking quantity, smoking cessation, as well as lung cancer risk. However, the allele frequency of this marker varies across different populations (35% in Central European, 6% in African-American, 3% in Asian), although the odds ratios remain similar. This study also showed that exhaled carbon-monoxide is a stronger predictor of lung cancer than self-reported smoking status. Dr. Bierut concluded that the rs16969968's low- and high-risk genotypes may be associated with a 4-year delay in smoking cessation. This may in turn provide earlier detection of lung cancer in these patients.

Dr. Laramie Duncan (Harvard Medical School, USA) reported GWAS results on anorexia nervosa. Female adolescents are amongst the highest risk of developing anorexia nervosa. It is characterized by preoccupation with weight, body image, and food. It also has the highest mortality rate of all psychiatric disorders. Approximately 4,000 cases were analyzed in the present GWAS and one single SNP reached the genome-wide significance level: rs11174203 in the family with sequence similarity 19 (chemokine [C-C motif]-like), member A2 (*FAM19A2*) gene on chromosome 12. Heritability for anorexia was calculated using LD score regression (LDSC), and the point estimate of 0.23 is comparable to other psychiatric disorders. Genetic correlations were positive and significant with schizophrenia and BD, but negative (and yet significant) with body mass index (BMI).

Epigenetics and Other Approaches (reported by Ryan K. C. Yuen): Dr. Therese Murphy (University of Exeter, UK) presented a study of DNA methylation profiling in the brains of MDD suicide completers. The DNA methylation profiles between 20 depressed suicide completer cases and 20 non-psychiatric, sudden-death controls in two brain regions (Brodmann Area 11 [BA11] and Brodmann Area 25 [BA25]) were compared. They identified a region at an immune-related non-coding gene, psoriasis susceptibility 1 candidate 3 gene (*PSORSIC3*), which was significantly hypomethylated in cases compared to controls. Dr Murphy further identified a co-methylated module, which was significantly correlated with both MDD and a Suicide attempt polygenic risk score.

Dr. Eilis Hannon (University of Exeter, UK) investigated the correlation of DNA methylation between blood and brain to determine if blood sample can be used as a surrogate for DNA methylation studies of the brain. Comparing the inter-individual variation of DNA methylation in blood, prefrontal cortex, entorhinal cortex, superior temporal gyrus and cerebellum from 75 individuals, she found that the predictive power of blood for the brain was low, only less than 20% of the variance can be explained. Sites with positive correlation were found, but much of the correlation was due to genetic influence on DNA methylation.

Dr. Carolin Purmann (Stanford University, USA) presented a novel approach called Combined Long-Insert Paired-End and Capture (CLIP-Cap) sequencing to resolve complex genomic rearrangements. With the use of average ~9kb insert size paired-end sequencing targeting on chromosome 22q, she showed that CLIP-Cap was capable of determining the heterozygous terminal 22q13.3 deletion and the isodicentric breakpoints. She further showed that the assay was able to detect other balanced structural variations, such as the Philadelphia translocation. She suggested that this approach can potentially detect all the structural variants in the captured reads as long as the target region is known.

Dr. Gail Davies (University of Edinburgh, UK) reported a large-scale genome-wide association study on verbal-numerical reasoning (n=36,035), memory (n=112,067), and reaction time (n=111,483). Using a customized Affymetrix array targeting on common SNPs, she reported genome-wide significant regions on chromosomes 7, 14 and 22 for verbal-numerical reasoning, chromosomes 2 and 12 for reaction time, but no significant region was found for memory.

Mr. Tarjinder Singh (Wellcome Trust Sanger Institute, UK) presented a meta-analysis of whole exome sequencing studies in schizophrenia including data from the UK10K consortium. By analyzing the *de novo* and rare (MAF<0.1%) loss-of-function (LoF) variants in a total of 4,264 cases and 9,343 controls, they found that the LoF variants in the *KMT2F* gene coding for SET domain containing 1A were significantly associated with schizophrenia (P=3.3E-9). There were 3 *de novo* LoF variants from trio families and 7 LoF variants identified from case-control samples. *KMT2F* is a member of a family of genes where disruptive variants result in dominant Mendelian disorders of histone machinery.

Substance Abuse (reported by Ibene Ekpor): Dr. Andrew Bergen (SRI International, USA) introduced the 'SmokeScreen Genotyping Array' as a genome-wide array designed for addiction studies. He presented his work on Modeling Tobacco Exposures including the role of Nicotine Metabolic Enzymes. He explained that available data from the Total Exposure Study (TES) was analyzed including evaluation of nucleic acid quality, bio specimens and clinical chemistries. The results were correlated with existing data. The findings were that multivariate analysis participants with banked bio specimens were significantly more likely to self-identify as white, to be older, to have increased total nicotine equivalents per cigarette and decreased serum cotinine. In an analysis of three existing nicotine metabolism studies with participants of three continental ancestries using the smoke screen array, Dr. Bergen and collaborators identified genome-wide significant association of common variants at *CYP2A6*. They estimated that the top ranked SNP accounts for 12 – 27% of nicotine metabolite ratio (NMR) variation. Dr. Bergen disclosed that they were able to identify individual SNPs at nicotine metabolic enzymes in nicotine metabolism that can be used to model nicotine metabolism and increase the power of models.

Dr. Ian Gizer (University of Missouri, USA) presented the result of their research work on the whole genome sequence analysis of cannabis dependence across two independent cohorts. He explained that qualitative genetic studies have established a genetic etiology of cannabis use disorder. He reported that their study was focused on gene-and path-way-based analysis of both common and rare variants obtained via whole-genome sequencing from two cohorts of predominantly European ancestry and predominantly Native American ancestry. The participants (n = 2,529) were people who met DSM-IV cannabis dependence based on the Semi-Structured Assessment for the Genetic of Alcoholism (SSAGA). All the participants whole genome sequence data was analyzed, while gene-based analysis of rare variants were conducted using the optimized sequence Kernel association test (SKAT-O). The result showed that gene-based analysis of rare coding variants (MAF<0.02) yielded significant evidence of association for a single gene with cannabis dependence (*C1ORF110*), and a suggestive evidence of an association with a second gene (microfibrillar associated protein 3 [*MFAP3*]). In addition, pathway analyses revealed significant evidence for the enrichment of genes related to potassium ion transport. He suggested that the results require replication with large samples.

Mr. Eric Diehl (University of Western Ontario, Canada) described changes in the hippocampus in a mouse model of fetal alcohol spectrum disorder (FASD). Diehl explained that epigenetic dysregulation of genetic programs in the brain are involved in FASD. Diehl's laboratory's model of FASD shows learning and memory impairment and persistent changes

in the brain gene expression into adulthood in a mouse model of FASD. 70 days old Mouse pups injected with saline or ethanol at post-natal days 4 and 7 had their hippocampus isolated and used for gene and miRNA expression microarray, methylated DNA immunoprecipitation microarray and histone H33 lysine 41 trimethylation and H33 lysine 27 trimethylation ChIP-chip. The results were dozens of gene and miRNA expression changes in the hippocampus of adult mice exposed to ethanol during development and hundreds of epigenetic methylation changes. These genes were predominantly oxidative stress-related. One of the ways alcohol induces oxidative stress of the developing brain is to reduce antioxidant levels and increase reactive oxygen species. The observed oxidative stress footprint may persist into adulthood hence identification of this mechanism may provide potential diagnostic targets or therapeutic approaches to help those affected by FASD.

Dr. Jennifer Ware (University of Bristol, UK) explained the relevance of using biomarkers to carry out objective assessment of the various behavioural phenotypes of tobacco users. She discussed the results of a GWAS meta-analysis of levels of cotinine, the primary metabolite of nicotine based on 4,548 daily smokers of European ancestry, and identified variants in two genomic regions, 15q25.1 and 4q13.2, to be associated with cotinine levels. Furthermore, she discussed the limitation and benefits of GWAS employing alternative tobacco use biomarkers such as exhaled carbon monoxide levels. Dr. Jack Euesden (Kings College London, UK) commented on the importance of looking at smoking behaviour as a relevant phenotype in further studies.

Ms. Bonnie Alberry (University of Western Ontario, Canada) discussed the result of the effect of continuous prenatal alcohol exposure (PAE) and post-natal maternal separation in mouse behavior as well as gene expression in the hippocampus. Behavioral tests showed learning deficit due to PAE and postnatal maternal separation. The expression of a large number of genes was also altered as a result of PAE with or without postnatal maternal separation. Ms. Alberry drew the following conclusions: the experimental model they used represents a realistic model; independent and comprehensive assessment of array gene expression as well as RNA sequencing will yield a highly reliable list of altered genes than relying on qPCR for confirmation of a few select genes.

Monday October 19, 2015

Plenary Session

Mitochondria and their Potential Role in Neuropsychiatric Disorders (reported by Maren Lang): A pressing question in biomedical science today, according to Dr. Douglas Wallace of the Center for Mitochondrial and Epigenomic Medicine at the Children's Hospital of Philadelphia, USA is why can't we understand and cure the common “complex” disorders. He postulates that our lack of success in addressing these crucial clinical concerns is the inadequacy of the underlying assumptions upon which we have based our investigations.

The prevailing conceptual frameworks (paradigms) of western medicine are that diseases are anatomically based and that all genes are located on chromosomes and thus inherited according to the laws of Mendel. Indeed, all anatomical genes are chromosomal and

Mendelian. However, to be alive requires not only anatomy but also the energy which animates us and this energy is generated primarily by the mitochondrial oxidation of our food with the oxygen that we breathe via mitochondrial oxidative phosphorylation (OXPHOS). The most important OXPHOS energetic genes are coded by a DNA located within the mitochondrion, the mitochondrial DNA (mtDNA), while all of the anatomical genes for the mitochondrion are located in the nuclear DNA (nDNA).

The mtDNA is maternally inherited and present in hundreds to thousands of copies per cell. The high mtDNA copy number means that cells can contain mixtures of mutant and normal mtDNAs (heteroplasmy) which randomly segregate during mitosis and meiosis to give variable energetic defects. Different organs rely on mitochondrial energy to different extents. The brain has the highest mitochondrial energy demand, representing 2% of our body weight yet using 20% of our oxygen, so mild, systemic, mitochondrial, energy defects preferentially affect the brain. Hence, Wallace proposes that mild mitochondrial defects are the primary cause of neuropsychiatric disease.

Mitochondrial energy defects can result from alterations in mtDNA or nDNA coded mitochondrial genes or from aberrant interactions between the two sets of mitochondrial genes. Mitochondria also communicate the cellular energetic status to the nucleus through mitochondrially-generated high energy intermediates that modulate the cellular signal transduction pathways and the epigenome. For example, the mtDNA $tRNA^{Leu(UUR)}$ mutation at nucleotide (nt) 3243A>G is associated with autism and diabetes at 10-30% 3243G mutant, neuromuscular disease at 50-90% mutant, and lethal perinatal disease at 100% mutant. The phase-like changes in phenotype in response to continuous changes in 3243G heteroplasmy are the result of abrupt changes in the nDNA transcriptional profile, presumable reflecting epigenomic transitions.

The mtDNA also accumulated mutations along the maternal lineages as women populated Africa. After only two mtDNA successfully left Africa, the mtDNA accumulated additional mutations as women migrate to Eurasia and the Americas. A subset of these mutations caused functional changes in OXPHOS which permitted regional adaption to local environments giving rise to groups of descendent haplotypes known as haplogroups. The physiological differences between regional haplogroups have been found to predispose to a wide range of neurologic and psychologic disorders including Alzheimer and Parkinson Disease, stroke, macular degeneration, deafness, and depression.

Mutations in nDNA coded mitochondrial genes also cause disease. The severity of the nDNA mutation phenotypes can be further modulated by the mtDNA variation.

To establish the causal role of mitochondrial variation in neuropsychological disease, Wallace reported the generation of a series of mouse lines with genetic alterations in nDNA and/or mtDNA mitochondrial mutations. Creation of the analogous mouse nDNA and mtDNA mutation combinations found in humans resulted in the same phenotypic manifestations. Mixing two normal mouse mtDNAs within the female mouse germline resulted in mice with a bipolar-like phenotype associated with a severe memory defect. Mice harbouring various nDNA or mtDNA mutations were found to show strikingly different

responses to stress. Mild mitochondrial defects were also found to impaired embryonic migration of interneurons, which Wallace hypothesized cause of the excitation-inhibition imbalance associated with attention deficient-hyperactivity syndrome, compulsive behaviour, autism, and schizophrenia.

Wallace concluded that mitochondrial energetics and associated high energy mitochondrial intermediates are the mediators between environmental energy availability and demands and the genome. If energetics is in balance with the cellular and environmental demands then this is health. However, if there is a chronic energy deficit this leads to disease and ultimately death.

Symposia Sessions

Genetic Architecture Insights from Joint Investigators of Rare CNVs and Common SNPs (reported by Sarah Gagliano and Kirti Mittal): All of the speakers in this symposium were female, which is inspirational.

Dr. Lea Davis (University of Chicago, USA) presented her work testing the hypothesis that an individual may develop disease by surpassing either a polygenic or a variant liability threshold. Given this hypothesis, one would expect there to be a negative correlation between the polygenic burden (genomic risk scores) and rare variant burden (genic CNVs >500kb in less than 1% of samples) among cases. For proof of principle, Type 1 Diabetes, which has a known risk locus in the HLA region with large effects, was examined. She then presented results from three psychiatric disorders, Tourette syndrome, OCD, and autism spectrum disorders (ASD). Results showed a modest but significant negative association among cases between scores and rare CNVs in analyses for the childhood-onset disorders (Tourette syndrome and ASD), but not for OCD.

Ms. Lingxue Zhu (Carnegie Mellon University, USA) noted that although each common variation tends to have smaller effects than rare variation, the former accounts for a large portion of liability (50%). She presented two models for predicting ASD risk from common SNPs: Genomic-BLUP (G-BLUP) and linear mixed model (LMM). G-BLUP is a random effects model assuming all small effects. LMM measures fixed effects. To select SNPs that have large fixed effects, weighted lasso was applied, resulting in 50, 250, or 1,100 SNPs to include into the LMM. The G-BLUP model (LMM with no SNPs having fixed effects) performed best (area under the curve = 0.74). When additional fixed effects were included, accuracy decreased. Ms. Zhu presented her work on a related trait, head circumference deviation. Those predictions were more accurate when parental head size was included, but common variants did not add much.

Ms. Niamh Mullins (King's College London, UK) presented her work done at deCODE Genetics (Iceland), investigating selection pressures on genetic variants for psychiatric disorders in the general Icelandic population. PRS for five psychiatric disorders were used to predict fecundity (number of children), using linear mixed effects models. PRS for autism was associated with reduced fecundity in the population, excluding patients. This effect was specific to males. PRS for the other disorders were not significantly associated with fecundity. Neuropsychiatric CNVs implicated in autism and schizophrenia, were associated

with reduced fecundity, with larger effects in males. The results from this population suggest that, with the exception of autism, selection pressures may operate on some but not all components of the genetic architecture of psychiatric disorders.

Dr. Sarah Bergen (Karolinska Institute, Sweden) discussed the contribution of CNVs and SNPs to schizophrenia risk in the Psychiatric Genomics Consortium samples. Polygenic scores were compared for carriers and non-carriers of implicated CNV risk loci (individually and in aggregate), large CNV deletions, and in terms of total genomic CNV burden. Cases with implicated CNVs and large deletions had lower polygenic scores than other cases, and an inverse relationship with total CNV burden was also significant. These relationships were not observed in controls. These results converged to broadly support a liability threshold model of genetic risk for schizophrenia.

The session finished with a discussion led by Dr. Naomi Wray (University of Queensland, Australia) who concluded that despite limited power, the results from the speakers suggested that PRS do tend to be lower for individuals who carry rare CNVs of large effect. If one has rare CNVs, then there is a lower threshold of polygenic risk disease burden, and it also seems that such CNVs decrease fecundity.

The Genetic Dissection of Bipolar Disorder: From Common to Rare Risk Variation (reported by Niamh O'Brien): Dr. John Kelsoe (University College San Diego, USA) reported the findings from the Psychiatric Genomics Consortium Bipolar Disorder (PGC2-BIP32) genome wide association analysis. The case-control sample for this study consists of 20,352 BD cases and 31,358 controls. The analysis identified 19 BD associated loci, 12 of which are novel and provides refinement of known BD associated loci such as *TRANK1* (p=5.54×10^{-14}) (Chen et al., 2013). Subphenotype analysis identified six new genes associated with BD-I and three new genes for a combined analysis of BD-II and schizoaffective disorder. A z-score mixture model suggested that BD is more polygenic than schizophrenia. Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT) pathway analysis implicated brain-related pathways including the calcium and potassium ion transporters and glutamatergic signalling in the pathophysiology of BD (Pers et al., 2015).

Dr. Tadafumi Kato (Riken Brain Science Institute, Japan) reported on sequencing analysis looking at *de novo* point mutations in BD. The study focused on 79 probands with BD. Seventy *de novo* point mutations were found, 64 single nucleotide variants (SNVs) and 6 insertion/deletions (indels). Global enrichment analysis showed an enrichment of *de novo* loss of function and protein-altering mutations in individuals with BD-I and schizoaffective disorder. BD probands with protein-altering *de novo* changes showed significantly earlier age-of-onset. Genes hit by *de novo* or protein altering variants are significantly enriched for intolerant genes. Intolerant genes are depleted for protein-altering mutations as determined by a Residual Variation Intolerance Score (RVIS) (Petrovski et al., 2013). A gene encoding microtubule-actin crosslinking factor 1 (*MACF1*) is the most intolerant gene reported in this analysis and is hit by a frameshift variant.

Dr. Peter Zandi (Johns Hopkins, Bloomberg School of Public Health, USA) reported on data from the Bipolar Sequencing Consortium (BSC). The goal of this study is to identify rare

genetic variants that influence the risk of BD. The founding cohorts consist of 4,733 BD cases and 9,246 controls. The preliminary analysis consists of 3,633 BD cases and 4,992 controls. Dr. Zandi reports that the MAF did not differ across study groups despite the different platforms used for exome sequencing. A gene-wise burden test showed 10,043 genes with disruptive variants, 5,050 of these genes harbour less than one variant. Neither the gene-wise burden test nor single variant analysis showed significant results.

Dr. Seth Ament (Institute for Systems Biology, USA) reported on family data from the BSC. The study consisted of a uniform analysis pipeline with ANNOtate VARiation (ANNOVAR) (Wang et al., 2010); focused on protein altering variants that are present in two or more affected individuals and have a MAF of less than 0.01 in the 1,000 genome project. Dr. Ament reported 143 pedigrees from 652 pedigrees that contained 526 loss of function SNVs and 11,856 rare coding SNVs. The top ontology enriched pathways for rare coding variants in the BSC pedigrees highlighted pathways different to those previously reported such as DNA binding and DNA strand elongation. There was an excess of genes in which a rare SNV segregates with BD in multiple pedigrees, such as two loss of function variant in the gamma-aminobutyric acid A receptor, alpha 6 gene (*GABRA6*). Currently there are no genome wide significant hits but aggregation of individual level data and case control cohorts will help elucidate the effects of rare variants in family study of BD.

Current Approaches to Genetic/Genomic Studies on Alcoholism (reported by Caroline Camilo and Bhagya Shankarappa): Dr. Dayne Mayfield (University of Texas at Austin, USA) was the chair of this session and introduced the current approaches to genetic studies on alcoholism.

Dr. Howard Edenberg (Indiana University *School of Medicine, USA*) began the session describing the complex trait of alcoholism, which is likely caused by a combination of multiple genes and environmental factors. He stated that alcoholism runs in families and has a high rate of psychiatric comorbidity. He reported the importance of identifying genetic and epigenetic modifications that may contribute to the risk of alcoholism. Dr. Edenberg showed that common and rare variants require different strategies to investigate the risk of disease given that common variants tend to have small effects on risk whereas rare variants have larger effects. He cited several approaches such as family-based GWAS, exome sequencing of rare variants, genomic studies of lymphoblastoid cell lines (LCLs), iPSCs, and brain tissue in addition to epigenetics and prospective studies of adolescents to identify genes that may contribute to the risk of developing alcoholism and the important interactions between phenotype, environment, and genetics in alcoholism.

Dr. Sean Farris (University of Texas at Austin, USA) reported his study on the neurogenomic networks that are involved in alcohol use disorder (AUD). He showed a variant-driven gene network with strong interaction between the genes in the human prefrontal cortex. He presented his data on the gene network for lifetime alcohol consumption and dysregulation of gene expression including epigenomics networks. He discussed that datasets continue to grow in size and complexity. He also stated that gene networks support disease-gene associations and show system-wide perturbations related to

alcohol dependence. Dr. Farris concluded by stating that there is converging evidence for multiple candidate genes and epigenetics involvement implicated in alcohol dependence.

Dr. Subhash Pandey (University of Illinois at Chicago, USA) spoke about adolescent alcohol exposure and epigenetic mechanisms, explaining the interaction between neurobiological and behavioral changes in addition to epigenetic factors (i.e., histone and DNA modifications) in adolescence with alcohol consumption. Evidence suggests that these changes can alter gene expression. He presented his study on adolescent intermittent ethanol (AIE) exposure paradigm in an alcohol binge-drinking model in rats. Particularly, Dr. Pandey and his colleagues investigated brain-derived neurotrophic factor (*BDNF*) gene expression and also examined histone acetylation (H3K9&14) of *BDNF* exons I and IV promoter regions in the amygdala of adolescent intermittent saline (AIS) and AIE rats in adulthood. They found a decrease in *BDNF* gene expression in the amygdala after AIE in adulthood. This appears to be due to AIE-induced decrease in histone acetylation of *BDNF* in the amygdala in adulthood. He also discussed about the effect of AIE on changes in expression of the lysine specific demethylase 1 (*LSD1*) and neuron specific LSD1+8a enzymes. The expression of LSD1 and LSD1+8a were decreased in the amygdala of AIE compared to AIS in adulthood, which in turn increases the methylation of histone H3K9 dimethylation (me2) without producing any change in the levels of H3K4me2, leading to increased anxiety and alcohol consumption in adulthood.

Dr. Shizhong Han (University of Iowa, USA) discussed the importance of GWAS in AUD, describing the polygenic nature of AUD. He presented his data on the integrated GWAS and protein-protein interaction network analysis in AUD. He utilized the GWAS of AUD and tissue-specific gene expression data to examine the relationship of AUD risk genes in brain and non-brain tissues. The results showed that AUD risk genes are highly connected in brain regions, but not in other non-brain tissues. Furthermore, he spoke about his approaches of constructing a brain-specific network for gene prioritization. He summarized his presentation by discussing that the nominally significant findings of genes are functionally related in human brain tissues, and form networks that underline relevant biological mechanism. One example is the suppressor of cytokine signaling 6 (*SOCS6*) gene, which plays an important role in AUD. Altered gene expression and increased cytokines have been reported in human postmortem AUD brain tissues. He concluded that brain-specific gene networks may help to prioritize AUD risk genes for future studies.

Dr. Abbas Parsian (National Institute of Health/NIAA, USA) closed the session by summarizing the results and discussing the interactions between the genetics and environmental factors in alcoholism.

Tracking the Descent to Mental Illness – Insights into the Trajectory to Illness from Studies of Youth at High Risk of Bipolar Disorder (reported by Søren Dinesen Østergaard): Improving the possibilities for early identification of mental disorder has been a priority in psychiatry for many years (Akiskal et al., 1983; Goldberg et al., 2001; Ostergaard et al., 2014). However, early detection of mental disorders remains challenging due to the absence of strong biological and psychopathological predictors. This symposium

focused on initiatives aiming at identifying such predictors based on studies of high-risk individuals.

Dr. Uher (Dalhousie University, Canada) showed preliminary results from the Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) study (Uher et al., 2014) in which children of parents with severe mental illness are recruited and followed over time. In the FORBOW study, the cohort members and their parents undergo detailed structured interviews. The preliminary results indicated that there is a same sex-specific parent of origin effect in anxiety (i.e., mood disorders in mothers predict anxiety in daughters), while there is an opposite sex-specific parent of origin effect in psychosis (i.e., severe mental illness in mothers predict psychosis in sons). Furthermore, the results indicate that early psychopathological antecedents are associated with later development of severe mental illness.

Dr. John I. Nurnberger (Indiana University School of Medicine) showed results from the Bipolar High Risk Study Group and the Bipolar Disorder Genome Study (BiGS) (Nurnberger et al., 2011; Monahan, Stump et al., 2015). From the prediction perspective, the key findings were that anxiety and externalizing disorders predicted development of major affective disorder (BD or recurrent major depression) in individuals at high-risk.

Dr. Janice M. Fullerton (Neuroscience Research Australia, Australia) described results from analyses of neuroimaging and genetic data from the Bipolar Kids & Sibs Study. This initiative recruited young individuals with BD or with a first-degree relative with BD. Based on the magnetic resonance imaging (MRI) data, it was demonstrated that individuals with high familial risk for BD have reduced interhemispheric connectivity. Furthermore, these individuals also have a higher genetic load for BD (as quantified by PRS) when compared to controls (Fullerton et al., 2015).

Dr. Andrew M. McIntosh (University of Edinburgh, UK) presented outcomes from the Scottish Bipolar Family Study. Individuals with first-degree family history of BD and healthy controls were recruited for a structured psychiatric interview and MRI scanning at baseline and follow-up. The results indicated that increased activation of the insula cortex at study baseline was associated with an increased risk of developing major depression during follow-up (Whalley et al., 2015).

Dr. Philip Mitchell (University of New South Wales, Australia)raised the issue of potential lack of power in the individual studies described above, and suggested forming a consortium, which can utilize a meta-analytical approach with the gathered data to predict the risk of BD in high-risk individuals.

Genetics of Research Domain Criteria (RDoC) (reported by Tristram Lett): Dr. Paul Arnold (University of Calgary, Canada) and Stephen Glatt (SUNY Upstate Medical University, USA) introduced the session and key issues on the next steps in genetic research on RDoC domains and constructs.

Dr. Sarah Morris (NIMH, USA) gave a brief overview of RDoC including: (a) the RDoC initiative as a National Institute of Mental Health (NIMH)-led effort to change how patients

(and non-patients) are characterized for research purposes, and (b) the RDoC framework for classifying subjects to neurobehavioral constructs based on our understanding of brain and behaviour. She stated that these homogenous subgroups potentially capture more subthreshold (subclinical) individuals based on DSM-5 or ICD-10 diagnostic categories alone. Furthermore, that RDoC is a dynamic framework that will evolve with new research.

Dr. Joan Kaufman (Kennedy Krieger Institute/Johns Hopkins, USA) described the genetics of childhood trauma related to psychiatric disorders. In an ongoing study of 400 maltreated children of which 125 subjects had undergone functional magnetic resonance imaging (fMRI), dimensional measures of child maltreatment predicted hippocampal activation and functional connectivity to regions involved in fear response. Moreover, the effect of trauma on hippocampal sensitivity decreased with social support. These studies demonstrated the advantages of the RDoC framework by identifying an interacting stress by social support mechanism on clinical intermediate phenotypes in a high risk group with diverse psychiatric outcome.

Dr. Paul Arnold discussed dimensionality and heritability of OCD in a community-based study of 16,718 children (6-18 years) collected at the Ontario Science Centre in Canada. The children were administered the Toronto Obsessive Compulsive Scale. In a subset of 220 twin pairs, a consecutive heritability analysis was undertaken. He reported a high heritability of obsessive-compulsive dimensions varying between 30-77%. The results of this study applying a dimensional approach supported the use of RDoC in OCD patients.

Dr. Yanli Zhang-James (SUNY Upstate Medical University, USA) reviewed four types of genetics studies of aggression including human twin and GWAS studies, rodent knock-out models and candidate genes, rare genetic disorders with antisocial/aggressive behavior from the Online Mendelian Inheritance in Man database (OMIM), and transcriptomics of rodent models. Among OMIM genes with antisocial behavior, nominal GWAS findings, rodent knock-out models, and aggresso-type candidate genes, several common pathways regulating synaptic transmission emerged including serotonergic, dopaminergic, and GABAergic signaling. There was further evidence implicating mitochondrial dysfunction and MAPK (mitogen-activated protein kinases, originally called ERK, extracellular signal-regulated kinases) signaling.

Dr. Kristin Nicodemus (University of Edinburgh, UK) focused on the RDoC language construct. She used latent semantic analysis (LSA) to derive variables in free speech data in individuals at high-risk for psychosis. Semantic coherence, phrase length, and use of determiners was 100% accurate at predicting transition to psychosis. In a subsequent candidate language gene study of schizophrenia patients, healthy siblings and controls, the disrupted in schizophrenia (*DISC1*) rs12133766 variant was associated with vector length; however, this association was not observed using standard measures of verbal fluency. She concluded that using this RDoC framework for a broader definition of language can provide novel understanding of the genetic and neurobiological mechanisms of language dysfunction.

Genetics of Comorbidity between Substance Use Disorders and Other Severe Mental Illness (reported by Jennie Pouget): Many patients with mental illness suffer from more than one disease, and substance use disorders are particularly prevalent comorbidities. The underlying reasons for substance use comorbidities are not clear. In the genomic era, we are reaching a point where we can articulate hypotheses about comorbidity across psychiatric disorders and test them with reasonable statistical power.

Dr. Nelson Freimer (UCLA, USA) gave an overview of a large study comprising pedigrees ascertained for severe bipolar disorder from founder populations of Colombia and Costa Rica. These pedigrees have provided insights into the genetic relationships between bipolar disorder and cognitive and neuroimaging endophenotypes, identifying 53 heritable endophenotypes associated with bipolar disorder including cortical thickness in prefrontal and temporal regions (Fears et al., 2014). Currently, these families are being revisited for detailed phenotyping of substance use disorders, which will help uncover genetic factors underlying substance use comorbidities in bipolar disorder.

Dr. Sarah Hartz (Washington University in Saint Louis, USA) presented genetic data evaluating the comorbidity between nicotine dependence and schizophrenia. Dr. Hartz identified 16 genetic variants previously associated with schizophrenia that were also associated with nicotine dependence ($p < 0.05$) in a recent GWAS of 17,074 ever smokers (Hancock et al., 2015). Most notable was rs8042374, an intronic variant of the gene encoding the neuronal nicotinic acetylcholine receptor α3 subunit *(CHRNA3)*, which is the first variant to reach genome-wide significance in two psychiatric disorders.

Dr. Kerry Ressler (Emory University, USA) provided a thought-provoking overview of insights obtained from a sample of highly traumatized patients ascertained in the inner city of Atlanta (Khoury et al., 2010). In this cohort, the level of substance use strongly correlated with childhood abuse and current PTSD symptoms. Accumulating evidence suggests that the neuro-circuitry of addiction and PTSD may be shared, with communication between the amygdala and cortex playing an important role in both of these disorders. One salient example is variant rs1433375 in the gene encoding sodium channel and clathrin linker 1 (*SCLT1*), which was associated with comorbid alcohol use (measured by the by the Alcohol Use Disorders Identification Test) in this highly traumatized cohort. *SLCT1* is highly expressed in the cerebellum, and carriers of the A risk allele for rs1433375 showed less dorsolateral prefrontal cortex connectivity to the cerebellum than patients with the G allele in a follow-up imaging study.

As discussant, Dr. Patrick Sullivan (UNC Chapel Hill, USA) emphasized that the dissection of psychiatric comorbidity – including substance use disorders – may be the most important emerging problem in psychiatric research because it has been largely neglected up until this point. He challenged the field to focus on this issue, with a particular emphasis on the utility of prospective longitudinal studies.

Oral Sessions

Schizophrenia (reported by Chenyao Wang): Mr. Jonathan Hess (SUNY Upstate Medical University, USA) reported that they have succeeded in providing a framework by which to

integrate single-nucleotide polymorphisms emerging from GWAS with multi-omic datasets. There is a critical gap in our understanding of the functional consequences of psychiatric disorder-associated variants in context of gene-expression regulation. Particular splicing-factor motifs were altered by schizophrenia- or bipolar disorder-associated variants more often than expected by chance, in genes such as CUG triplet repeat, RNA binding protein (*CUGBP*), elav-like family members 1 and 4 (*CELF1* and *CELF4*) for schizophrenia, and epithelial splicing regulatory protein 1 (*ERSP1*), and serine/arginine-rich splicing factor 5 (*SRSF5*) for BD. Their research team implicated several risk variants in abnormal splice site binding with predictive methods, and linked these observations to gene expression levels in brain tissue.

Dr. Pippa Thomson (Institute of Genetics and Molecular Medicine, UK) presented results from their clinical and genetic re-evaluation of the Scottish t(1:11) family in which a translocation disrupts *DISC1* and the DISC1 fusion partner 1 (*DISC1FP1*) gene. The t(1;11) family presented with a broad spectrum of psychiatric diagnoses including schizophrenia, BD and recurrent MDD. Genome-wide significant linkage to major psychiatric illness was identified between broad peaks across both translocation breakpoints; with a LOD (logarithm [base 10] of odds) score of 6.1 for translocation status. Additional linkage peaks with LOD scores greater than 3 were identified on chromosomes 3q and 5q. PRS derived from the PGC schizophrenia and BD GWASs also predicted illness within the family. These results confirm the linkage of the translocation with major mental illness in this family and identify additional loci which may explain the variable presentation of illness.

Dr. George Kirov (Cardiff University, UK) clarified the role of maternal and paternal duplications at 15q11-q13 in neuropsychiatric disorders. Maternal duplications are highly pathogenic, resulting in neurodevelopmental disorders in around 75% of carriers. Individuals with paternal duplications have an increased risk of developing autistic spectrum disorder, developmental delay, or multiple congenital anomalies, but not schizophrenia. About 60% of duplications are de novo. Despite their lower pathogenicity, paternal duplications are less frequent in the general population, possibly due to reduced fecundity of carriers and survival of embryos.

Dr. Douglas Ruderfer (Icahn School of Medicine at Mount Sinai, USA) clarified CNVs in intolerant genes would be more likely to have deleterious effects using a large sample and an empirical approach they calculated frequency and tolerability of CNV at the gene level. While directly using the Exome Aggregation Consortium (ExAC) CNV data as a convenience control sample runs a high risk of bias, they demonstrated improved power to detect schizophrenia loci when considered along with an appropriate matched control sample.

Dr. Menachem Fromer (Icahn School of Medicine at Mount Sinai, USA) presented RNA-seq data of dorsolateral prefrontal cortex and anterior cingulate cortex from post-mortem brain of schizophrenia patients and controls. They overlaid the resulting expression quantitative trait loci with the 108 common variant loci associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and found significant overlaps in the genes between the two datasets.

Dr. Evangelos Vassos (King's College London, UK) estimated the predictive power of PRS in discriminating case-control status in first episode psychosis and to predict the development of schizophrenia as opposed to other psychoses. PRS was a powerful predictor of case-control status in Europeans, even though half of the cases did not have an established diagnosis of schizophrenia at the time of assessment. The PRS also showed some ability to distinguish between those first-episode psychosis cases who developed schizophrenia from those who did not.

Advances in Autism (reported by Megan Crow): Dr. Jakob Grove (Aarhus University, Denmark) presented results from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) Autistic Spectrum Disorder (ASD) GWAS, focusing only on the strict European cluster (11,661 ASD and 21,427 controls) combined with data from the PGC-ASD GWAS. Six loci with genome-wide significance were found and LD score regression against the PGC-ASD GWAS showed significant genetic correlation (~76%, $p=2.9\times10^{-13}$). An analysis of the ASD results at the PGC-schizophrenia loci showed that 96/128 indices had the same direction of effect in ASD as in schizophrenia ($p<5\times10^{-8}$). LD score regression provided evidence for widespread overlap between ASD and schizophrenia (~23%, $p=2.8\times10^{-6}$), and a positive genetic correlation with educational attainment (~20%) and childhood intelligence (~30%).

Mr. Jack Kosmicki (Harvard University, USA) presented his work studying ASD-related *de novo* variants using the ExAC database. Mr. Kosmicki found that approximately one third of previously identified ASD-related *de novo* single-nucleotide variants were present in other individuals in ExAC. *De novo* protein truncating variants (PTVs) absent from ExAC ('non-ExAC') and those in likely haplo-insufficient genes were enriched in cases (odds ratio [OR]=1.98 for all non-ExAC *de novo* PTVs, OR=3.4 for non-ExAC likely haplo-insufficient *de novo* PTVs), and the non-ExAC *de novo* PTV rate predicted intelligence quotient (IQ) ($p=5\times10^{-4}$). Similar trends were observed for inherited PTVs (OR=1.4 for likely haplo-insufficient non-ExAC variants). In ASD cases, a reduced 3:1 male:female bias in *de novo* rate was observed with non-ExAC likely haplo-insufficient *de novo* variants, whereas a 6:1 male:female bias was observed with all other *de novo* PTVs, indicating that females are more likely to have rare *de novo* PTVs in putative haplo-insufficient genes.

Dr. Elise Robinson (Massachusetts General Hospital, USA) presented an analysis of the heritability of continuous social and communication traits using data from iPSYCH-ASD, PGC-ASD, the Avon Longitudinal Study of Parents and Children (ALSPAC), the Simons Simplex Collection (SSC) and ExAC. Using LD score regression Robinson found that ~25% of ASD common variation (with PGC-ASD and iPSYCH-ASD being considered separately) is shared with common variation that influences the social and communication disorders checklist in the ALSPAC cohort. This was also the case for *de novo* variants in that the rate of non-ExAC *de novo* loss of function and predicted damaging missense variants in the SSC cohort linearly predicted impairment measured by the Vineland Scales of Adaptive Behavior ($p<0.01$ for both cases and controls).

Dr. Janita Bralten, PhD (Radboud University, Netherlands) presented the results of a GWAS of autistic traits in the general population. Dr. Bralten validated a self-report questionnaire,

then tested the association between genotypes in an ASD candidate gene set (146 genes) and trait scores across 5 sub-categories in a population sample (n=1981). An association was observed between “rigidity” and ASD candidates in a competitive gene set analysis test (p=0.005), which was primarily driven by genes associated with “neurite outgrowth” (p=0.003); a SNP in the MET proto-oncogene, receptor tyrosine kinase (*MET*) gene was statistically significant after controlling for the family-wise error rate ($p=1.4\times10^{-4}$).

Dr. Ryan Yuen (The Hospital for Sick Children, Canada) presented his work studying *de novo* variation in 200 ASD simplex families and 258 control families. Yuen found that ~70% of single-nucleotide variants and insertion-deletions were paternally derived, and that the number of *de novo* variants correlated with paternal age. The somatic mutation rate was 3.6 per genome in ASD, and the sequence context of these mutations differed from germline mutations. Damaging variants were enriched in cases, and ASD *de novo* variants were enriched for functions related to synaptic transmission, chromatin modification and translation.

Dr. Katri Kantojärvi (National Institute for Health and Welfare, Finland) presented an association study on nine previously identified psychiatric-related calcium channel, voltage-dependent, L type, alpha 1C subunit (*CACNA1C*) SNPs in infant sleep regulation using a cohort of 1,017 Finnish eight-month-old babies. Four SNPs were associated with parent-reported sleep latency overall ($p<0.05$), and some sex differences were observed. In a subset of 60 babies, an association was found between one SNP and three polysomnographically measured sleep traits ($p<0.05$).

Neuroimaging and Alternate Phenotypes (reported by Sejal Patel): Dr. Derrek Hibar (University of Southern California, USA) discussed the use of brain imaging data from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium and investigating potential intermediate phenotypes for psychiatric disorders such as OCD. Genetic variations from genome wide association studies under the international collaboration, ENIGMA-OCD working group was examined in eight substructure brain volumes. There was no evidence of pleiotropy; however, in the test for concordance, there was significant association between genetics variants and an increase in nucleus accumbens and putamen volumes in addition to an increase risk for OCD.

Dr. Ida Sønderby (Norwegian Centre for Mental Disorders Research, Oslo) presented the ENIGMA-CNV project that aims to associate CNVs with brain imaging phenotypes. Approximately 12,000 individuals from 16 cohorts worldwide with both genetics and neuroimaging data have been collected for analysis. Preliminary analysis on a specific CNV supports previous findings. More cohorts were encouraged to join.

Dr. Arash Nazeri (Centre for Addiction and Mental Health, Canada) presented a genome wide interaction study, investigating interaction effects between genetic variants and serum urate on striatal dopamine transporter density binding ratio (as indexed by DaTscan striatal binding ratio) in people with Parkinson's disease. The interaction of gene variant and serum urate on MRI-derived regional brain volumes (voxel-based morphometry) and clinical status were also investigated. The inositol polyphosphate 5-phosphatase K (*INPP5K*) rs1109303

(T>G) variant showed a significant interaction effect on striatal dopamine transporter density with the association between serum-urate level and striatal dopamine transporter being positive in G-allele carriers and negative in TT genotype carriers. Similar interaction effect was observed on prefrontal cortex volume and clinical severity of Parkinson's disease. In conclusion, *INPP5K* rs1109303 genotype could inform pharmaco-therapeutic approaches targeting urate pathway in Parkinson's disease.

Dr. Daniel Felsky (Centre for Addiction and Mental Health, Canada) presented the interaction between the sortilin-like receptor (*SORL1*) gene and *BDNF*. Post-mortem brains were used to quantify 13 *SORL1* transcripts isoforms. The T allele of the rs12364988 on the transcript isoform *SORL1*-005 reduced the expression of *SORL1* in the *BDNF* Val/Val homozygotes and increased the expression of *SORL1* in *BDNF* Met carriers. This result demonstrated a novel interaction between *SORL1* and *BDNF*, which may play a role in *SORL1* alternative splicing.

Dr. Danielle Posthuma (Vrije Universiteit University, Netherlands) discussed the importance of gene and environment interaction on psychiatric traits. A meta-analysis was done on 3,306,594 twin pairs investigating the genetic and environmental factors in 47 distinct psychiatric traits. The heritability of all psychiatric traits was 0.462, with a higher heritability (0.518) in young age group (0-11) when compared to other age groups. Results demonstrated that most psychiatric traits are influenced by additive genetic variance.

Dr. Margaret Maciukiewicz (Centre for Addiction and Mental Health, Canada) presented her study on MDD in relation to response to a serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine. Nine gene variants (imputed and genotyped) were selected for Lasso regression. In support vector machine (SVM) models, the accuracy was 61.75%. When non-genetic predictors were added to the model, the accuracy increased to 80.29% in SVM but further refinement is needed for clinical settings.

Tuesday October 20, 2015

Plenary Session

Dopamine, Schizophrenia, and the Process of Discovery in the Brain Sciences (reported by Jingjing Zhao): Professor Arvid Carlsson's discovery of dopamine as an important neurotransmitter has contributed considerably toward the genetics and neurobiology of various diseases as well as drug discovery and treatments to clinical patients. This plenary session started with watching a recorded video interview of Professor Carlsson, followed by a live skype call with Professor Carlsson.

In the video interview, Professor Carlsson first described his scientific career development in the 1950s and his early experiments that led to his discovery of dopamine as an important neurotransmitter. He commented on the challenges for himself to choose a direction that was different from his supervisor and appreciated that his supervisor did not oppose him to proceed on his own direction even though it challenged the scientific opinions of the time. He spoke about his experience when he was notified that he won the Nobel Prize in 2000. Surprisingly, the first question that he asked when he received the phone call from the Nobel notifier was: “How do you formulate the reason to give me the prize?” Professor Carlsson

especially pointed out the importance of considering the negative and side effects of long-term treatment in drug development and suggested that new medications should be careful in stabilization, balancing the “brake” and “accelerator”, and should keep the plasticity of brain at an optimum level. Regarding the recent financial cut-back in Europe for neuroimaging studies, Professor Carlsson was in favour of studying the brain as a promising direction and believed that a lack of harmony of the brain were coupled with many diseases. Finally, Professor Carlsson summarized the challenges for research without hypothesis such as the GWAS of schizophrenia and commented on the disadvantages of the current classification of disorders.

In the skype call, Professor Carlsson answered questions from the audience with various backgrounds. Professor Carlsson provided advice to both young researchers and old scientists as to how to proceed in the field respectively. He suggested young researchers to start with a simple project to gathers better motivation to do research. For senior scientists, he rather encouraged them to fulfil their early scientific dreams that they did not have the chance to reach in their early academic career. Professor Carlsson answered a question from Dr Chunyu Liu (University of Illinois, USA) about new types of neurotransmitters other than dopamine and agreed that compounds having signaling properties may all have important functions in diseases. Professor Carlsson also commented on the release of dopamine, a question laid out by Professor Robin Murray (King's College London, UK). He believes that both pre- and post-synaptic components of dopaminergic transmission play a role in schizophrenia. In the skype meeting, Professor Carlsson emphasized again the importance of balanced functions of a new drug and highlighted that it would be a mistake for not taking side effect into account when inventing new drugs given how vulnerable the brain is and how important plasticity of brain would play a role at early stage of life and for the entire life. Finally, Professor Carlsson completed his skype call by answering a question about the opportunity of female scientists raised by a female postdoctoral researcher from the University of Cambridge. Professor Carlsson acknowledged the tremendous role of women in his academic career. He admitted that although a lot of development and progress for providing equal opportunity to female scientists have achieved as decades passed, the final goal was still not reached and females still did not have the same opportunities to the top positions as males.

Oral Sessions

Dissecting the Schizophrenia Phenotype (reported by Umut Kirli): Dr. Daniel Howrigan (Massachusetts General Hospital, Boston, USA) discussed the contribution of *de novo* coding mutations to schizophrenia risk. He presented findings from analysis of exome sequencing data on 1,697 schizophrenia trios. While an emerging pattern of *de novo* risk is evident among well-characterized gene sets and an excess of genes with recurrent damaging mutations, the increased liability toward schizophrenia due to *de novo* mutations comprises only a modest fraction of the overall genetic liability and to date no single gene has been established as a putative *de novo* schizophrenia risk factor.

Dr. Tristram Lett (Charite University Hospital, Berlin, Germany) presented a study investigating the influence of the functional rs3749034 variant in the glutamic acid

decarboxylase 1 (*GAD1*) gene on brain structure and working memory performance in schizophrenia patients and healthy controls. The effect of this variant on long-interval cortical inhibition (LICI) in the dorsolateral prefrontal cortex (DLPFC) was subsequently examined using TMS with electroencephalogram (TMS-EEG). He discussed the findings indicating that genetic variation in *GAD1* may affect white matter fractional anisotropy, GABAergic inhibitory neurotransmission in the DLPFC and working memory performance.

Dr. Alexander Richards (Cardiff University, UK) presented preliminary data from EU-GEI (EUropean network of national schizophrenia networks studying Gene-Environment Interactions), a cohort of ultrahigh risk and frank psychosis cases in UK, Netherlands, Italy, France, Turkey, Spain, Serbia, Ireland and Brazil. The research is focusing on non- affective psychosis (not only schizophrenia); cognitive scales, social and environmental risk variables are available to examine interactions with genetic risk.

Mr. Ahmed Al Amri (University of Leeds, UK) presented an autozygosity mapping in combination with whole-exome sequencing study conducted in a first-cousin consanguineous family, in which two out of eight siblings were affected with psychosis. He reported a missense mutation, c.C1348T:p.R450C, in the deafness, autosomal recessive 31 (*DFNB31*) gene at 9q32, which was predicted by all mutation prediction packages to be pathogenic and co-segregated with psychosis in the family in a manner consistent with recessive inheritance. This variant was suggested to impair the interaction of *DFNB31* with *UBR4* (ubiquitin protein ligase E3 component N-recognin 4), which is known to have roles in neurogenesis, neuronal migration and neuronal signaling.

Dr. Giulio Genovese (Broad Institute, Cambridge, USA) presented a schizophrenia case-control cohort investigating rare disruptive mutations in constrained genes (that harbor the expected amount of synonymous variations but significantly under-represented missense variations). He reported that overall 24% of schizophrenia cases (and just 17% of controls) harbored private disruptive mutations in the most constrained genes.

Dr. Emma Dempster (University of Exeter, UK) presented a study examining the role of epigenetic variation in schizophrenia, focusing on DNA methylation differences in disease-discordant MZ twins. She reported that the most significant differentially methylated position was located in the histone deacetylase 4 (*HDAC4*) gene, encoding a histone deacetylase implicated in synaptic plasticity and memory formation and a differentially methylated region (DMR) was identified in the HLA region which had been implicated in previous GWASs of schizophrenia.

Biostatistics and Bioinformatics (reported by Kartikay Chadha): Dr. Megan Crow (Cold Spring Harbor Laboratory, USA) presented her research exploring cell-type specific co-expression of genes with recurrent loss-of-function *de novo* mutations in ASD. Dr. Crow built co-expression networks for six genetically targeted adult mouse inhibitory interneuron types and analyzed their functional connectivity using a neighbor voting algorithm in cross-validation. This enabled her to conclude that ASD candidate genes are strongly co-expressed in inhibitory interneuron networks, with further investigation indicating that this is primarily driven by high expression of these genes.

Dr. Raymond Walters (Massachusetts General Hospital/Broad Institute, USA) suggested a hypothesis that “GWAS of continuous traits in population samples can be used to improve power to detect the loci for psychiatric phenotypes”. Dr. Walters and his team demonstrated efficient power enrichment of transforming dichotomous phenotypes to continuous latent liability variables, and the effect of genetic covariance on the relationship between the latent liability variables and the continuous phenotypes by varying genetic architectures through simulation studies before applying the proposed approach to studies of ADHD with the EArly Genetics & Lifecourse Epidemiology (EAGLE) Consortium and the PGC.

Mr. Christaan de Leeuw (Vrije Universiteit Amsterdam, the Netherlands) presented his work to investigate the self-contained and competitive gene-set analysis methods of the GWAS data. The simulation studies showed a high false-reporting rate for the self-contained approach for the analysis of a polygenic phenotype, particularly in large gene sets and increasing sample sizes. Christaan concluded that self-contained analysis doesn't provide reliable results, and the alternative competitive methods may have biases as well. He added, “obtaining higher statistical power is difficult for strongly heritable traits, and that power doesn't improve significantly with increasing sample size”.

Dr. Verneri Anttila (Massachusetts General Hospital/Broad Institute, USA) spoke about his research on a joint analysis of 23 brain diseases to reveal novel patterns in the genetic background of psychiatric and neurological diseases via a cross-disorder heritability analysis, using the LD score regression approach for all GWAS data. His research showed a general trend in psychiatric diseases to have considerable risk-increasing co-morbidity with a variety of other psychiatric diseases, notably with schizophrenia and major depression, showing considerable co-morbidity with most of the studied psychiatric phenotypes.

Dr. Sarah Gagliano (Centre for Addiction and Mental Health, Canada) presented her research of prioritizing genetic risk variants for psychiatric disorders based on functional genomic information using a machine learning approach. She trained an elastic net model using 14 different functional annotations including splice sites, nonsynonymous SNPs, and DNase I hypersensitive sites. The data was divided into training and test sets, and the resulting model had reasonable accuracy (with area under the receiver operating characteristic curve of around 0.7). She then presented a comparison of statistical learning methods using different combinations of three previously published annotation sets with three algorithms (Gagliano et al., 2015).

Dr. Wim Verleyen (Cold Spring Harbor Laboratory, USA) introduced the audience to a tool for customized network analysis called SAPLING (sapling.cshl.edu). SAPLING is a web application which utilizes heterogeneous data resources for in-depth analysis; existing tools, for example, GENEMANIA (Warde-Farley et al., 2010) and DAPPLE (Rossin et al., 2011), lack these properties. He reported examples of using SAPLING in the context of psychiatric genetics (autism, synaptic interactions, and A) where the downstream analysis was customized with data and algorithms using the tool to produce results showing that aggregation across more network data and brain-related data improves performance while condition-specificity within the underlying data appeared to be difficult. He concluded that

customized network analysis might be needed to handle functional interpretation of gene lists related to psychiatric disorders.

Pharmacogenetics of Response and Side Effects (reported by Ellen Ovenden): Dr. Douglas Ruderfer (Mount Sinai School of Medicine, USA) opened the session by discussing his research on the genetic overlap between schizophrenia susceptibility and antipsychotic treatment response. Known and predicted drug target genes were investigated for enrichment for schizophrenia susceptibility loci. The majority of significantly enriched loci fell within novel predicted antipsychotic target genes (277 of 347 total genes; $P = 0.019$). Additionally, Dr. Ruderfer found that there is an enrichment for rare mutations within drug targets when assessing treatment resistant patients.

Dr. Raquel Iniesta (King's College London, UK) presented a machine learning approach to antidepressant treatment response. Her hypothesis was that utilizing a combination of clinical and genetic variables could more accurately predict treatment outcome. Dr. Iniesta collected various clinical and genetic information from patients (N = 430). The machine learning approach used a training (N = 280) and testing (N = 150) dataset to predict future outcomes using the collected information. Dr. Iniesta observed that accuracy was improved by combining genetic and clinical variables for both nortriptyline ($R^2 = 16\%$) and citalopram ($R^2 = 15\%$) subgroups.

Dr. Arun Tiwari (Centre for Addiction and Mental Health, Canada) discussed his study on the orexin receptors and antipsychotic-induced weight gain (AIWG). Several polymorphisms in the human copper transporter 2 (*HCTR2*) gene were nominally associated ($P \sim 5\times10^{-3}$) with AIWG. Dr. Tiwari pointed out that these variants fall in a region that has been predicted to have weak enhancer activity (The ENCODE Project Consortium, 2012). Dr. Tiwari and his colleagues also constructed a preliminary risk model for AIWG that predicted 67% of the variance.

Ms. Sophie Legge (Cardiff University, UK) reported on her exploration of genetic factors associated with clozapine-induced neutropenia. The patient sample included patients with clozapine-induced neutropenia from the CLOZUK and CardiffCOGS cohorts (defined by Rees et al., 2013), and clozapine-treated controls (without clozapine-induced neutropenia). For the GWAS findings, two intergenic variants reached genome-wide significance. After replication, one variant affecting both solute carrier organic anion transporter family members 1B3 (*SLCO1B3*) and 1B7 (*SLCO1B7*) transcripts was significant. This is a novel finding for clozapine research, although the *SLCO* genes have previously been associated with adverse drug reactions (SEARCH Collaborative Group, 2008).

Dr. Joanna Biernacka (Mayo Clinic, USA) reported on her results of a pharmacogenomic GWAS on antidepressant-induced weight gain. The aim was to identify genetic variants that predict weight gain or loss during the course of treatment with citalopram or escitalopram. Although baseline weight was available, weight was not measured at follow-up visits, and therefore retrospective recall data derived from the Quick Inventory of Depressive Symptomatology (QIDS) was used to define weight change after initiation of treatment. At week 4, one variant close to the complexin 1 gene reached genome-wide significance for

weight loss, and at week 8, a different variant within the aldo-keto reductase family 1 member C2 (*AKR1C2*) gene was significantly associated with weight loss. Dr. Biernacka pointed out that both genes are candidates for antidepressant-induced weight gain/loss based on prior evidence of their impact on insulin exocytosis and adipogenesis, respectively.

Dr. Todd Lencz (Zucker Hillside Hospital, USA) discussed the pharmacogenetics of antipsychotic-naïve patients. His study made use of a subset of the Malhotra *et al.* (2012) cohort to investigate risperidone-induced hyperprolactinemia and/or weight gain. Both of the top hits occurred within the CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*) gene with the first SNP associated with increased prolactin and the second with increased weight gain. The mechanism involved leads to abberant proinsulin accumulation (Wei *et al.*, 2011). Dr. Lencz announced that the Phase II data from 1,000 first episode psychosis patients will be presented during the next meeting in 2016.

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Abbreviations

4C	Circularized chromosome conformation capture
ADHD	Attention deficit hyperactivity disorder
AEI	Allelic expression imbalance
AIE	Adolescent intermittent ethanol
AIS	Adolescent intermittent saline
AIWG	Antipsychotic-induced weight gain
AKR1C2	Aldo-keto reductase family 1 member C2 gene
ALSPAC	Avon Longitudinal Study of Parents and Children

ANNOVAR	ANNOtate VARiation
APA	American Psychiatric Association
API	Application program interface
ARC	Activity-regulated cytoskeleton-associated
Army STARRS	Army Study To Assess Risk and Resilence in Service members
ASD	Autistic spectrum disorders
ASM	Allele-specific DNA modification
ASM-SNPs	SNPs exhibiting allele-specific DNA modification
ATP	Adenosine triphosphate
AUD	Alcohol use disorder
B4GALNT4	Beta-1,4-N-acetyl-galactosaminyl transferase 4 gene
BA	Brodmann Area
BChE	Butyrylcholinesterase gene
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor gene
BiGS	Bipolar Disorder Genome Study
BLUP	Best Linear Unbiased Prediction
BMI	Body mass index
BSC	Bipolar Sequencing Consortium
C4	Complement component 4 gene
CACNA1C	Calcium channel, voltage-dependent, L type, alpha 1C subunit gene
CAMK2D	Calcium/calmodulin-dependent protein kinase 2 delta gene
CBT	Cognitive behavioural therapy
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1 gene
CELA2A	Chymotrypsin-like elastase family, member 2A gene
CELF1	Elav-like family member 1 gene
CELF4	Elav-like family member 4 gene
CHRNA3	Cholinergic receptor, nicotinic, alpha 3 gene

CHRNA5	Cholinergic receptor, nicotinic, alpha 5 gene
CLIP-Cap	Combined Long-Insert Paired-End and Capture
Clorfl95/ITPKB	Clorfl95/inositol-trisphosphate 3-kinase B gene
CNS	Central nervous system
CNVs	Copy number variants
CONVERGE	China Oxford and VCU Experimental Research on Genetic Epidemiology
CRISPR	Clustered regularly-interspaced short palindromic repeats
CSA	Childhood sexual abuse
CUGBP	CUG triplet repeat, RNA binding protein gene
CYP2D6	Cytochrome P450 2D6 gene
CYTH2	Cytohesin 2 gene
DBS	Deep brain stimulation
DEPICT	Data-driven Expression-Prioritized Integration for Complex Traits
DFNB31	Deafness, autosomal recessive 31 gene
DISC1	Disrupted in schizophrenia gene
DISC1FP1	Disrupted in schizophrenia fusion partner 1 gene
DLPFC	Dorsolateral prefrontal cortex
DMR	Differentially methylated region
DNA	Deoxyribonucleic acid
DRD2	Dopamine D2 receptor gene
DRD3	Dopamine D3 receptor gene
dSNPs	Disease-associated single nucleotide polymorphisms
DZ	Dizygotic
EAGLE	EArly Genetics &Lifecourse Epidemiology
EMR	Electronic medical records
ENIGMA	Enhancing NeuroImaging Genetics through Meta-Analysis
eQTLs	Expression quantitative trait loci
ERSP1	Epithelial splicing regulatory protein 1 gene

ExAC	Exome Aggregation Consortium
EU-GEI	EUropean network of national schizophrenia networks studying Gene-Environment Interactions
FAM19A2	Family with sequence similarity 19 (chemokine [C-C motif]-like), member A2 gene
FASD	Fetal alcohol spectrum disorder
fMRI	Functional magnetic resonance imaging
FORBOW	Families Overcoming Risks and Building Opportunities for Well-being
GABRA6	Gamma-aminobutyric acid A receptor, alpha 6 gene
GAD	Generalized anxiety disorder
GAD1	Glutamic acid decarboxylase 1 gene
GAF	Global Assessment of Functioning
G-BLUP	Genomic-BLUP
GERA	Genetic Epidemiology Research on Adult Health and Aging
GRIK5	Glutamate receptor, ionotropic kainate 5 gene
GROUP	Genetic Risk and Outcome in Psychosis
GTeX	Genotype-Tissue Expression
GxE	Gene-environmental
GWAS	Genome-wide association study
GWAS-HD	Hypothesis-driven genome-wide association study
HCTR2	Human copper transporter 2 gene
HDAC4	Histone deacetylase 4 gene
HER2	Human epidermal growth factor receptor 2
HLA-B	Major histocompatibility complex, class I, human leukocyte antigen B
HRs	Hazard ratios
HRM	High Resolution Melting
HTT	Huntingtin gene
IAP	Inhibitor-of-apoptosis

indels	Insertion/deletions
INPP5K	Inositol polyphosphate 5-phosphatase K gene
iPSCs	Induced pluripotent stem cells
iPSYCH	The Lundbeck Foundation Initiative for Integrative Psychiatric Research
IPT	Interpersonal therapy
IQ	Intelligence quotient
ISPG	International Society of Psychiatric Genetics
KARG	Knowledgebase for Addiction Related Genes
KMT2F	SET domain containing 1A gene
LASSO	Least absolute shrinkage and selection operator
LCLs	Lymphoblastoid cell lines
LD	Linkage disequilibrium
LDSC	Linkage disequilibrium score regression
LHPP	Phospholysinephosphohistidine inorganic pyrophosphate phosphatase gene
LMM	Linear mixed model
LOD	Logarithm (base 10) of odds
LoF	Loss-of-function
LPGAT1	Lysophosphatidylglycerol acyltransferase 1 gene
LRFN5	Leucine rich repeat and fibronectin type III domain containing 5 gene
LRRC4C	Leucine rich repeat containing 4C gene
LSA	Latent semantic analysis
LSD1	Lysine specific demethylase 1 gene
MACF1	Microtubule-actin crosslinking factor 1 gene
MAF	Minor allele frequency
MAPK	Mitogen-activated protein kinases
MDD	Major depressive disorder
MET	MET proto-oncogene, receptor tyrosine kinase gene

MFAP3	Microfibrillar associated protein 3 gene
MHC	Major Histocompatibility Complex
miRNAs	MicroRNAs
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MT-CYB	Mitochondrially encoded cytochrome b gene
mtDNA	Mitochondrial DNA
MZ	Monozygotic
NADH	Nicotinamide adenine dinucleotide
nDNA	Nuclear DNA
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
NMR	Nicotine metabolite ratio
NOS1	Nitric oxide synthase 1 gene
NPAS2	Neuronal PAS domain protein 2 gene
OC	Obsessive-compulsive
OCD	Obsessive-compulsive disorder
OICR	Ontario Institute for Cancer Research
OMIM	Online Mendelian Inheritance in Man database
OR	Odds ratio
OXPHOS	Oxidative phosphorylation
PAE	Prenatal alcohol exposure
PATE2	Prostate and testis expressed 2 gene
PCr	Reserve phosphocreatine
PGC	Psychiatric Genomic Consortium
PGC2-BIP32	Psychiatric Genomic Consortium Bipolar Disorder

PheWAS	Phenome wide association study
PRS	Polygenic risk score
PSORSIC3	Psoriasis susceptibility 1 candidate 3 gene
PTPRD	Protein tyrosine phosphatase receptor type D gene
PTSD	Posttraumatic stress disorder
PTSR	Posttraumatic stress reaction
PTVs	Protein truncating variants
QIDS	Quick Inventory of Depressive Symptomatology
RA	Rheumatoid arthritis
RDoC	Research Domain Criteria
rG	Genetic correlation
rGT	Rat gambling task
RVIS	Residual Variation Intolerance Score
SCLT1	Sodium channel and clathrin linker 1 gene
SIRT1	Sirtuin 1 gene
SKAT-O	Optimized sequence Kernel association test
SLC25A37	Mitochondrial iron transporter gene
SLC6A3	Dopamine transporter gene
SLCO1B3	Solute carrier organic anion transporter family member 1B3 gene
SLCO1B7	Solute carrier organic anion transporter family member 1B7 gene
SLE	Stressful life events
SNP	Single nucleotide polymorphism
SNRI	Serotonin-norepinephrine reuptake inhibitor
SNVs	Single nucleotide variants
SOCS6	Suppressor of cytokine signaling 6 gene
SORL1	Sortilin-like receptor 1 gene
SRSF5	Serine/arginine-rich splicing factor 5 gene
SSAGA	Semi-Structured Assessment for the Genetic of Alcoholism

SCC	Simons Simplex Collection
SV2A	Synaptic vesicle glucoprotein 2A gene
SVM	Support vector machine
TAAR1	Trace amine associated receptor 1 gene
TES	Total exposure study
TET	Ten-eleven translocation
THBS2	Thrombospondin 2 gene
TMS	Transcranial magnetic stimulation
TMS-EEG	Transcranial magnetic stimulation with Electroencephalogram
ToMMo	Tohoku Medical Megabank project
TRANK1	Tetratricopeptide repeat and ankyrin repeat containing 1 gene
UBR4	Ubiquitin protein ligase E3 component N-recognin 4 gene
UC	Ulcerative colitis
WCPG	World Congress of Psychiatric Genetics