UPDATE ON GENETIC ASSOCIATION ANALYSIS FROM GENDEP

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GENDEP (Genome-based therapeutic drugs for depression) is a European multicentre integrated pharmacogenomic study. Haplotype-tagging SNPs, VNTRs and STRs have been genotyped in 13 candidate genes (SLC6A2, SLC6A4, TPH1, TPH2, HTR1A, HTR2A, BDNF, TRKB, GNB3, ADRA2A, CYP2D6, CYP2C19, and ABCB1). Factor analysis and Item Response Theory have been applied to integrate three outcome scales (Hamilton, Montgomery-Asberg and Beck) to provide 3 factor scores of 'observed mood and anxiety' (F1), 'reported cognitive symptoms' (F2) and 'neurovegetative symptoms' (F3) (Uher et al, 2007). Longitudinal change in factor scores are the outcome measures being used in the genetic association analysis using a mixed models approach. In addition, serum level data of antidepressants have been analysed versus CYP2D6 and CYP2C19. The change in F1 and F2, and in F3 scores were more marked in escitalopram- and nortriptyline-treated subjects respectively ($p \leq 0.001$). There was a significant association between the promoter polymorphism (5-HTTLPR) in SLC6A4 and with a SNP previously reported as functional in SLC6A4 and response to escitalopram as measured by change in F1 score. A significant association was found between the ratio of desmethylescitalopram to escitalopram levels at 8 weeks and also between escitalopram level at 8 weeks and CYP2C19 genotypic category ($p=0.006$ and $p=0.03$ respectively), adjusted for relevant covariates. The novel method of phenotypic data analysis is promising for pharmacogenomics, and the association identified with CYP2C19 suggests that genotyping could assist clinicians with starting dose of escitalopram, and hence reduce the incidence of ADRs.

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UPDATE ON GENETICS OF ADHD: SNAP25, DAT, AND CHIP-CHIP METHODS

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Strong evidence for a genetic component for attention-deficit hyperactivity disorder (ADHD) has been provided from twin, family and adoption studies and molecular genetic studies to identify susceptibility genes are now in progress by a number of groups worldwide. Progress in the field has been swift, with an unprecedented degree of agreement between studies for the field of psychiatric genetics. We have identified 11 genes associated to ADHD (*DAT1*, *DRD4*, *DRD5*, *SNAP25*, *5HT2A*, *5HT1B*, *Calcyon*, *DRD1*, *GRIN2B*, *G(olf) (GNAL)*, *EKN1/PTRG*, *DCDC2/VMP)* in a large sample of families with an ADHD proband. Screening of many of the genes associated to ADHD have failed to find coding regions changes that can explain the association, thus changes in gene expression are predicted. This is likely the case for genes contributing to complex traits with changes in gene regulation contributing to susceptibility. Outside of the promoter, regulatory elements can be located at any position in a gene and even megabases away from the gene. To identify gene regulatory elements for the associated genes, we used chromatin immunoprecipitation to acetylated histone 3 (H3ac) coupled with genomic tiling arrays (ChIP-chip) to identify regions marked by acetylated histones. Specific histone modifications (e.g. H3 and H4 acetylation, methylation) mark transcription regulatory elements (e.g. promoters, enhancers) and this property of histones has recently been used as a means for identifying regulatory regions across large genomic regions. Using this approach, we found regions marked by H3ac including the promoter region, intronic and 3' regions and regions remote from the gene. In some cases, remote marks point to cryptic promoters or the promoters of unannotated genes. The results from the genes studied thus far point to the location of putative regulatory elements, pinpointing the regions necessary to screen for susceptibility alleles.

GENETIC VARIATION IN THE PROTO-ONCOGENE MET IS ASSOCIATED WITH SCHIZOPHRENIA AND COGNITIVE FUNCTION IN HEALTHY VOLUNTEERS

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Background: Recent data suggest that the gene encoding for the MET receptor tyrosine kinase (MET) is significantly associated with autism. While MET signaling is primarily linked to metastasis in cancer, recent evidence suggests that MET influences cortical and cerebellar development. Several phenotypic traits are common to both autism and schizophrenia (SZ), including social deficits and cognitive impairment, indicating a potential overlap in the pathophysiology of these illnesses.

Methods: We examined the relationship between 25 SNPs in *MET* and SZ in 178 Caucasian SZ patients and 144 healthy controls (HCs) and tested for effects on neurocognitive functioning in both cohorts.

Results: We identified four haplotype blocks spanning the *MET* gene and found one block to be globally associated with SZ, surviving correction for multiple testing. Block 3 encompassed most of the *MET* coding region; the most common haplotype was over-represented in healthy subjects (~47%) versus SZ patients (~33%)($p= 5 \times 10^{-4}$; OR=0.57). This haplotype was also associated with better neurocognition in healthy subjects.

Discussion: These data suggest that variation in *MET* influences SZ risk and neurocognition, supporting a neurodevelopmental role across CNS-relevant phenotypes. These results also add to the growing body of evidence suggesting an intriguing relationship between genes related to cancer and risk for SZ.

DIFFERENTIAL RNA EXPRESSION IN IMMORTALIZED LYMPHOCYTES BETWEEN SCHIZOPHRENIC PATIENTS AND CONTROLS FOR 26 NEUROTRANSMITTER RECEPTORS SHOWING AFFINITY FOR THE ANTIPSYCHOTIC OLANZAPINE

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Abstract:
We have observed in immortalized lymphocytes (IML) of schizophrenic patients (SZ) a lower expression of the DTNBP1 and NRG1 genes associated to SZ (Chagnon et al Schiz Res In press). Moreover, this lower expression was specific to one of the two NRG1 isoforms studied. The RNA expression of DTNBP1 and NRG1 was not changed following stimulation of IML with the antipsychotic olanzapine. Near 30 receptors including serotonergic (HTR), dopaminergic (DRD), alpha-adrenergic (ADRA), muscarinic (CHRM) and histaminergic (HRH) receptors showed affinity for olanzapine (Roth et al Nat Rev 2004). We have contrasted between SZ and controls the RNA expression in IML of 26 of these receptors, three of them being evaluated for two different isoforms, and after stimulation with olanzapine. We observed some specificity in RNA expression with HTR and CHRM showing generally a lower expression in SZ than in controls, and DRD and HRH a higher expression. After olanzapine stimulation, near twice the number of genes than in unstimulated IML showed differential expression between SZ and controls. RNA expression was generally stimulated by olanzapine for HTR and HRH and lowered for DRD. Both higher and lower expressions were observed for CHRM genes, with no apparent effect for ADRA. Interestingly, the two isoforms of the three genes tested showed opposite RNA expression, one isoform showing a greater RNA expression in SZ, while the alternative isoform of the same gene showed a lower expression. It is hypothesized that differential isoforms expression could be involved in SZ and other mental diseases appearance.

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IMAGING GENETICS WITH ENDOPHENOTYPIC MEASURES OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER

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Objectives: Deficits in response inhibition are, amongst others, considered as candidate endophenotypes of altered prefrontal brain function in ADHD. Based on their superior time resolution, electrophysiological methods like Event-Related Potentials (ERPs) are adequate for the measurement of such endophenotypes, i.e. abnormalities in brain functions underlying psychiatric diseases like ADHD. Moreover, ERPs seem to be particular suited to measure effects of functionally relevant genetic variants directly affecting neurotransmission systems and brain function. This principle of imaging genetics with ERPs has been demonstrated as early as 1999 for the serotonin transporter promoter polymorphism affecting prefrontal brain function (Fallgatter et al., International Journal of Neuropsychopharmacology, 1999).

Design and Methods: We employed a multi-channel EEG during performance of a Go-NoGo task to assess the electrophysiological basis of the endophenotype response inhibition in healthy subjects as well as in patients with ADHD. The ERP-measure derived from this protocol was termed NoGo-Anteriorisation (NGA) and is characterized by a high interindividual stability, high short- and long-term test-retest reliability and, moreover, is independent from age- and gender.

Results: In patients with ADHD the NGA was diminished as compared to age- and sexmatched healthy controls. Furthermore, a three-dimensional source location analysis with Low Resolution Electromagnetic Tomography (LORETA) indicated an electrical dysfunction of the medial prefrontal cortex comprising the anterior cingulate cortex (ACC) in ADHD patients in childhood as well as in adulthood. Recent studies showed a significant influence of variants of dopaminergic as well as serotonergic genes on this measure of prefrontal brain function.

Conclusions: These results exemplify the imaging genetics approach by measurement of disease related disturbances in brain function with ERPs. Future studies will show whether such electrophysiological endophenotypes may contribute to the diagnosis of subgroups of ADHD and whether they may serve as endophenotypes to further clarify genetic contributions to the disease.

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5-HTTLPR AND BDNF VAL66MET POLYMORPHISMS AND RESPONSE TO RTMS TREATMENT IN DRUG RESISTANT DEPRESSION

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Repetitive Transcranial Magnetic Stimulation (rTMS) is a painless and safe brain stimulation technique that has been found to be effective in treating depression symptoms. The potential usefulness of rTMS, in particular to treat drug resistant patients, might be increased by identifying genetic predictors of efficacy. According to this rationale, we investigated the role of two functional polymorphisms in the genes coding for the serotonin transporter (5-HTTLPR) and the Brain Derived Neurotrophic Factor (BDNF Val66Met), and rTMS response in a group of thirty-six drug resistant patients affected by mood disorders. rTMS treatment significantly improved depression symptomatology ($t=6.51$, $p<0.0001$) and the response was significantly greater in 5-HTTLPR LL homozygotes compared to S carriers ($p=0.007$) and in BDNF Val/Val homozygotes compared to Met allele carriers ($p=0.024$).

These findings provide evidences about the involvement of both polymorphisms in rTMS antidepressant response. Further investigations in larger samples are needed to clarify the usefulness of 5-HTTLPR and BDNF Val66Met genotyping in the optimization of non-pharmacological treatments in mood disorders.

WHOLE GENOME ASSOCIATION STUDY OF RESPONSE TO CITALOPRAM IN THE STAR*D SAMPLE

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Background: Inter-individual variability in response to antidepressants is thought to be influenced at least in part by DNA variation. To date, candidate gene approaches to antidepressant response have led to results of marginal impact. We now report the second stage of a genome-wide association study to look for novel genetic determinants of antidepressant response in a large clinical sample.

Methods: We used a subset of subjects enrolled in the antidepressant trial Sequenced Treatment Alternatives to Relieve Depression (STAR*D). The number of subjects giving DNA was 1,953 and thus represents our sample in its entirety. Our citalopram response phenotypes included response (50% reduction in QIDS-SR), remission, and drug tolerance.. Population stratification was examined using principal components analysis.

Results: Markers were tested for association using Armitage trend test and results were ordered on the basis of the p-value. We observed about 44, 40, and 57 markers with p-values less than 0.0001, for remission, response, and tolerance, respectively. Validation of the results is underway.

Conclusions: Results from the first stage of the study must still be confirmed in our sample, then replicated in an independent sample. These data implicate previously unconsidered loci in antidepressant response.

GENETIC TESTING QUALITY: A ROLE FOR PSYCHIATRY PROFESSIONALS

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As the number of available genetic tests continues to grow, policy has increasingly focused on ensuring they are analytically and clinically valid and that information about them is truthful. In particular, concerns have been raised about certain tests offered directly to consumers (DTC), without the involvement of the patient's own health care provider. Several genetic tests currently on the market or in development target those with or at increased risk of mental illness. These include tests claiming to inform SSRI treatment and dosing decisions based on CYP450 genotype, to predict risk of bipolar disorder, and to detect "addictive tendencies," with customized nutritional supplements sold to combat such tendencies. Tests are in development for prediction of suicidality as a consequence of taking drugs in the citalopram family and for prediction of schizophrenia. There are few regulatory barriers to marketing genetic tests generally, and there has been virtually no government action to prohibit false and misleading claims by those selling the tests. Both the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) have issued statements addressing DTC genetic testing and making policy recommendations. Such statements are useful in educating policymakers as these issues are debated at the state and federal government level. What should the response of psychiatry professionals be towards DTC testing? What are the potential benefits and risks of such tests to both patients and to the future of psychiatric pharmacogenetics? This session reviews the regulatory status of genetic testing, with particular focus on DTC, and the statements of ACMG and ASHG. It then proposes options for interested in the success of pharmacogenetics in psychiatry meaningfully to contribute to policy development in this arena.

POSITRON EMISSION TOMOGRAPHY, A METHOD FOR STUDYING IN-VIVO GENE EXPRESSION IN PHARMACOGENETICS

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Background: Markers in HTR2A and GRIK4 have been associated with antidepressant response in pharmacogenetic studies; however there is limited information on how the described variations exert their effect. Positron Emission Tomography (PET) is a sensitive method for measuring brain chemistry, thus [11C]DASB, a radioligand with high sensitivity and specificity for the serotonin transporter (5-HTT) offers a direct way to study potential genetic regulators of 5-HTT (SLC6A4) expression.

Methods: To measure the index of serotonin transporter (5-HTT) density we used PET and [11C]DASB in depressed patients with either bipolar disorder or major depressive disorder and healthy controls. In order to explore the genetic architecture of this potential mood disorder phenotype, we undertook a candidate gene association study. Forty-five unmedicated subjects underwent PET scanning with [11C]DASB. DNA samples were genotyped with selected SNPs to cover HTR2A and GRIK4. Genetic association testing was carried out with covariates to control for race and ethnicity.

Results: An allelic association was found between rs7333412 (HTR2A) and 5-HTT binding potential in the thalamus (TH) ($p=0.000218$, permutation 0.048). This marker is in the same haplotype block with rs7997012, that was previously reported as associated with citalopram treatment (McMahon et al 2006). No association was found with the markers studied on GRIK4.

Conclusions: This is the first study to report significant association between 5-HTT binding potential and HTR2A in thalamus. This suggests that variation in HTR2A may play a regulatory role in the expression of 5-HTT and thus by this mechanism affect antidepressant treatment response.

RECRUITMENT OF AFRICAN AMERICANS FOR PHARMACOGENETIC STUDIES

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African Americans make up les then 5% of key pharmacological studies and less then 1% of all biological psychiatric published studies. The recent STAR* D and BIDII studies suggest the importance of pharmacogenetics. Presumably racial discrimination to self and others, knowledge about disparities in care, and human subject's abuse such as the Tuskegee syphilis study contribute to mistrust of research. Knowledge of the abuses of eugenics would further reduce willingness to volunteer for pharmacogenetics studies. We monitored the willingness to participate in two studies of the genetics of mood disorder. AA subjects volunteered in large numbers and the main exclusion was for failure to meet criteria, which involved 90% of volunteers. We have no data on those that did not volunteer. We evaluated knowledge of genetic transmission of psychiatric disorders and found that AA grossly misjudged the risk to first degree relatives. On the other hand a sizable majority supported genetic research. Research participation by AA may be complicated by access issues as well as unwillingness to participate.

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CATECHOL-O-METHYLTRANSFERASE (COMT) GENE AND RESPONSE TO COGNITIVE REMEDIATION IN SCHIZOPHRENIA: PRELIMINARY FINDINGS

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Objective: Genetic variation in the Catechol-O-Methyltransferase (COMT) gene may influence the susceptibility to schizophrenia and impairment on certain types of neurocognitive tasks. The aim is to evaluate the effect of the association of COMT $Val^{108/158}$ Met genotype with the response to a computerized neurocognitive rehabilitation treatment (CRT) in patients with chronic schizophrenia. In addition, we plan to expand the analysis to other identified genes and haplotypes.

Method: We expect a total enrollment of 142 subjects, however, for these preliminary results we analyzed the COMT $Val^{108/158}$ Met polymorphism in 38 inpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, who were assigned to CRT for 3 hours per week for a total duration of 12 weeks. Patients were evaluated on a standardized battery of neuropsychological assessments, a brief assessment of functional skills, and clinical symptoms (PANSS) at baseline and at endpoint (Week 12). Patients provided saliva samples for genetic analysis. The criterion of >= 20% performance improvement on the Trail Making tests and WCST test at baseline and at endpoint (12 week) was used as a cut-off criterion to categorize patients into two groups : (1) Responders (those who had normal or below normal performance at intake and increased performance at follow-up), and (2) Non-responders (those who had below-normal performance both at baseline and follow-up, and those with normal performance at baseline but below-normal performance at follow- up). Because of the small sample size of Met homozygous patients, for analysis we combined Met carriers (Met/Val = 17) and Met homozygotes (Met/Met = 2) in one group and compared them to Val homozygotes (Val/Val n = 19). We then divided our sample into four subgroups on the basis of genotype ((Val/Val) versus (Met/Val + Met/Met)) and (Responders versus Non-Responders). We analyzed Responder versus Non-Responder outcomes by using an interaction between conditions and having a normal performance (i.e. no change in score) at follow-up. Statistical tests for association and for case-control differences in allele frequencies were performed using log-linear modeling embedded within the expectation-maximization algorithm.

Results: No significant demographic, neuropsychological or functional differences were seen at baseline between groups. Among neuropsychological tests the RM ANOVA Mixed Models showed significantly greater improvement of the global cognitive index score ($p = 0.050$), Trail Making Test scores measuring processing speed ($p = 0.011$) and working memory tasks ($p = 0.049$) for (Met/Val + Met/Met) group who were Responders to CRT in comparison to Val/Val who were Non-Responders to CRT. A significant association was

observed between higher scores on the PANSS scale and genotypes Val/Val ($p = 0.044$) for rs4680. Therefore we correlated the changes in overall global cognitive score and PANSS total score, using a Pearson Correlation Analysis. The correlation between effect sizes of improvement (higher global cognitive index score and lower PANSS scores) was significant ($p = .038$).

Conclusions: The findings support the hypothesis that COMT polymorphism influences cognitive functioning through CRT, with the caveat that because of the small sample size, the positive findings could be due to type I error. Primarily, the presence of Met allele was associated with significantly greater improvements in overall neurocognitive functioning after 12-weeks of CRT. As we accrue a larger sample size we may be able to determine if the two effects (i.e. improvement from CRT and COMT polymorphism) act at different levels.

RELAXIN-3 PEPTIDE'S AND ITS RECEPTORS IMPLICATION IN ANTIPSYCHOTIC DRUGS SIDE EFFECTS: A CROSS-SECTIONAL NATURALISTIC STUDY

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Introduction:
Relaxin-3 (RLX3) is a newly identified member of the relaxin/insulin peptide family that is highly conserved. RLX3 is the endogenous ligand of two identified receptors: RLN3R1 and RLN3R2 which are expressed in human brain. Studies are still ongoing to understand the exact physiological functions of RLX3 in the brain. There is now evidence from anatomical studies indicating a broad modulatory activity of RLX3 in behavioural activation relating to autonomic and neuroendocrine control of metabolism and higher-order processes such as stress and cognition. In this study, we have investigated the role of eight previously-described non-exonic polymorphisms of RLX3 (3 SNPs), RLN3R1 (3 SNPs) and RLN3R2 (2 SNPs) in the occurrence of adverse-effects in a cross-sectional cohort of US Caucasian patients treated with antipsychotic drugs.

Material and method:
418 US Caucasian patients recruited in Kentucky Hospitals were evaluated with the UKU scale to assess the presence of side effects after antipsychotic treatment, and the AIMS to assess specifically the neurological side effects and the BMI. Probands were genotyped for three single nucleotide polymorphisms in the RLX3 gene (rs1982632, rs7249702 and rs12327666), 3 in the RLN3R1 gene (rs42868, rs6861957, rs7702361) and 2 in the RLN3R2 gene (rs1018730, rs1126422) using ABI automated genotyping techniques.

Results:
The RLX3 rs7249702 polymorphism was found associated to the presence of side effects (SE) (Genotype: p=0.03; Allele: p=0.008 ;) and to the presence of EPS (Allele: p=0.04). The RLN3R1 rs7702361 polymorphism was found associated to the presence of TD (Allele: p=0.05). The RLN3R2 rs1126422 polymorphism was found associated to the BMI (Logistic regression: p=0.02). The SE and the EPS variables were associated with a specific Relaxin 3 haplotype (A / C / G) (p=0.002 and p= 0.03, respectively). The TD variable was associated with a specific Relaxin receptor 1 haplotype (C / G / A) (p=0.02).

Conclusion:
These preliminary results suggest the implication of the RLX3 peptide in the occurrence of side effects in psychiatric patients treated by antipsychotics.

GENETIC VARIATION IN THE DAOA GENE COMPLEX: IMPACT ON SUSCEPTIBILITY FOR SCHIZOPHRENIA AND ON COGNITIVE PERFORMANCE

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Introduction: The genetic region coding for D-amino acid oxidase activator (*DAOA*) is considered an intriguing susceptibility locus for schizophrenia. However, association studies have often resulted in conflicting findings, and the risk conferring variants and their biological impact remain elusive. Our aim in this study was to investigate the relationship between *DAOA* variation and schizophrenia, and the influence of *DAOA* on cognitive performance.

Methods: We analyzed block structure and association patterns of a ~173 kb region on chromosome 13q33, applying genotype data of 55 SNPs derived from Caucasian North American sample (178 cases, 144 healthy controls). Haplotypes were assigned using the program PHASE and frequencies compared between cases and controls. We applied MANOVA to investigate the relationship between the identified risk haplotype on cognitive performance.

Results: We identified multiple haplotypes within the region containing the *DAOA* gene. Of these, one was significantly associated with schizophrenia, being over-represented in schizophrenia versus healthy controls. This haplotype was also associated with one aspect of cognitive performance, semantic fluency. Carriers of the risk haplotype showed better semantic fluency than non-carriers.

Conclusions: We report a significant effect of *DAOA* variation on risk for schizophrenia. Moreover, we identified a relationship between *DAOA* genetic variation and specific aspects of neurocognitive function. As the identified *DAOA* risk haplotype was associated with better performance on a semantic fluency measure, further work is required to identify the mechanism of *DAOA* action on CNS function, including the possibility of a role for balanced selection at this locus.

Keywords: *DAOA*, *DAO*, glutamate, genetics, neurocognition, schizophrenia

CLOCK GENE VARIANTS AND DRUG RESPONSE

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The Circadian Locomotor Output Cycles Kaput (CLOCK) gene is thought to be involved in the regulation of circadian rhythms, with its protein products driving transcription of other genetic components of the molecular oscillator. The possible role of 3111T/C CLOCK gene polymorphism in psychiatry is currently under investigation, given the high frequency of circadian rhythm disturbances in psychiatric illnesses, and the proposed role of chronobiological abnormalities in the pathogenesis of mood disorders.
A polymorphism in the 3' flanking region of the CLOCK gene have been shown to affect mRNA stability and half-life, with possible significant effects on the level of protein finally being translated. In mice, a mutation of CLOCK gene, called "C" variant, has been shown to lead to a lengthened circadian period and in healthy humans the CLOCK*C allele has been investigated as a predictor of "eveningness." Finally, a significantly higher recurrence rate of illness episodes has been found in bipolar patients homozygous for the C variant.
In a series of studies, we investigated the possible effect of CLOCK variants in mood disorders and drug response. In a sample of 620 subjects affected by Major Depressive Disorder (MDD) and Bipolar disorder (BD) we found a strong association between CLOCK genotype variants and occurrences of initial ($p=0.0001$), middle ($p=0.0009$) and late ($p=0.0008$) insomnia. This initial observation prompted us to investigate the possibility of a higher recurrence in patients with the CLOCK C variant given its association with sleep disruption and, in fact, we observed a significant association with recurrence. Further, we observed a significant association of CLOCK C carriers with blunted antidepressant response in terms of insomnia symptomatology, further suggesting a modulation effect of this variant on mood disorders. We also performed a sequencing analysis and identified 2 new DNA alterations in 2 patients: the first patient showed a G/T point mutation at the 3117 nucleotide of Clock gene, while in the second patient a A/G substitution was localized at nucleotide 3125 (Gene Bank Accession Number AF011568). In both patients we observed interesting sleep abnormalities.
Very recently, through actimetric monitoring, we observed that carriers of the C allele had a delayed sleep onset (mean 79 min later) and a reduced amount of sleep during the night (mean 75 min less).
Taken together, this evidence suggests that CLOCK gene variants modulate mood disorders in a subtle but consistent way, causing liability to a shorter and disrupted sleep, which is reflected in poorer sleep improvement during antidepressant therapy and eventually in a higher frequency of episodes. This also suggests the clinical usefulness of social rhythm therapy particularly in this subgroup of patients.

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LINKING AUTOANTIBODY FORMATION TO GENETIC VULNERABILITY TO PSYCHIATRIC DISORDERS AND PSYCHOTROPIC DRUG RESPONSE

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Evidence from various recent studies has suggested that active immune processes may be involved in the pathogenesis of major depressive disorders, schizophrenia, and bipolar illness. Specifically, a population-based epidemiological study has revealed that a parental history of schizophrenia is associated with a 5-fold risk for autoimmune diseases, whereas a parental history of autoimmune diseases increases this risk only slightly, by a factor of 1.45. To investigate the extent to which the genetic predisposition to inflammatory responses can be quantified and assessed in psychiatric patients, we have carried out a normative study of 1,042 subjects ascertained through index cases with a diagnosis of rheumatoid arthritis (RA) and genotyped for 5,728 Single Nucleotide Polymorphisms (SNPs) of a 0.4 Mb genome scan.

By means of a two-stage Neural Network (NN) approach, we were able to construct classifiers that predicted IgM levels in each individual case through the multivariate genotype at high sensitivity and specificity of > 90%, while *k*-fold cross-validation predicted a rate of 77.3% [±0.636] correctly classified subjects for new, unknown samples. The genotype explained roughly 50% of the observed IgM variation, with all subjects contributing to the explained variance. Even though our current activation model does not yet meet the clinical requirements of diagnostic tools, its performance was high enough to justify an analysis of the DNA of our existing samples of psychiatric patients. We are currently genotyping the DNA of 692 patients, treated with either antidepressants or antipsychotics, for 483 SNPs in genomic regions harboring genes that appear (1) to contribute to vulnerability to psychiatric disorders, (2) to be related to inflammatory processes, and (3) to influence response to psychotropic drugs.

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MANGANESE SUPEROXIDE DISMUTASE (MNSOD) ALA16VAL POLYMORPHISM AND CORTICAL THICKNESS IN SCHIZOPHRENIA: PRELIMINARY FINDINGS

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The gene for manganese superoxide dismutase (MnSOD), *SOD2*, is an anti-oxidant enzyme located at position 6q25 that protects components of the mitochondria from superoxide radicals released as a normal byproduct of respiration. *SOD2* is thus believed to play a crucial role as the cell's primary defense against free radical damage. Within *SOD2* there is a well-known functional polymorphism at amino acid 16 resulting in an alanine to valine substitution, which has been linked to alterations in the mitochondrial targeting sequence. There is now increasing evidence that oxidative stress and concomitant mitochondrial dysfunction may play a role in the pathogenesis of schizophrenia, but the mechanisms underlying these deficits are not well understood. In this study we investigated cortical grey matter thickness in 23 patients with schizophrenia and 21 healthy volunteers in relationship to the *SOD2* ala16val polymorphism. One hundred twenty four contiguous T1-weighted coronal MR images (slice thickness = 1.5mm) were acquired through the whole head using a 3D Fast SPGR IR Prep sequence on a 1.5T GE imaging system. Cortical pattern matching methods were used to compare gray matter thickness measured at thousands of spatially equivalent locations on the cortical surface. There were significant ($p < .05$) group-by-genotype interactions in frontal and posterior temporal regions. Post-hoc analyses revealed negative correlations between *SOD2* group (1=ala/ala, 2=ala/val and 3=val/val) and cortical grey matter thickness among healthy volunteers. In contrast, positive correlations were evident among patients in these same regions. These findings implicate genetic involvement of *SOD2* in variation of human gray matter thickness and are consistent with the hypothesis that this gene is associated with compensatory mechanisms to protect the cortex from oxidative damage, at least among healthy individuals. Our data further suggest that there is an abnormal association between SOD2 genotype and cortical gray matter thickness in schizophrenia.

OPPORTUNITIES AND CHALLENGES OF TECHNOLOGY TRANSFER FROM ACADEMIA TO MARKET IN PSYCHIATRIC PHARMACOGENETICS

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Psychiatric pharmacogenetics represents a rapidly growing market that provides many product development opportunities. A brief overview of the market, its key players (e.g. Roche, PGxHealth, NeuroMark, Theragenetics, Psynomics, SureGene, others) and products will be presented. Intellectual property (mostly developed in academia) related to novel pharmacogenetic markers needs to be protected at an early stage. Ownership of experimental data and rights to use samples (e.g. DNA) include some of the legal challenges of this protection. Research collaboration agreements and material transfer agreements become increasingly important in collaborative research that may result in novel discoveries of pharmacogenetic markers. These issues will be discussed in the context of CAMH efforts to commercialize markers such as DRD3 marker for tardive dyskinesia and 5HTT gene marker for prediction of antidepressant induced mania.

Product development is a multi-step, interdisciplinary process that includes discovery, assay development, validation, approval, and marketing. To provide real value to the health care system, pharmacogenetic markers discovered by researchers in academia need to be further validated. The issue of a sample size and odds ratios (is 2.0 useful?) for marker validation becomes a topic of heated discussions among scientists (see Science, January 2008). Criteria for a meaningful pharmacogenetic test, such as sensitivity/specificity, are a key issue. Academic tech transfer offices most often see early-stage discoveries, and thus are faced with the above challenges on the way from lab bench to market. How can academia add value to ensure that early stage pharmacogenetic discoveries turn into products and reach the market? Some of the solutions include nurturing early-stage programs; organizing networks of collaborators; possible IP pooling; and identification of various sources of funding to support programs beyond discovery and into development. Specific examples of challenges and solutions will be presented.

EFFECT OF A CILIARY NEUROTROPHIC FACTOR POLYMORPHISM ON SCHIZOPHRENIA SYMPTOM IMPROVEMENT IN AN ILOPERIDONE CLINICAL TRIAL

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Aims: Presence of the null *FS63TER* allele of the rs1800169 polymorphism in the gene encoding the ciliary neurotrophic factor (*CNTF*) may increase schizophrenia risk. This study prospectively evaluated *CNTF* rs1800169 genotype (G/G vs non-G/G) effects on response to iloperidone.

Patients and Methods: Iloperidone 24 mg/day was evaluated in a study of patients with schizophrenia. Efficacy measurements included PANSS-T, BPRS, and CGI scores. Patients were genotyped, and a step-down primary end point was the difference in PANSS-T scores based on *CNTF* rs1800169 G/G genotype.

Results: This study genotyped 417 patients (279 iloperidone, 138 placebo) for the rs1800169 polymorphism. Iloperidone significantly improved PANSS-T, PANSS-P, PANSS-N, BPRS, CGI-C, and CGI-S scores versus placebo. G/G versus non-G/G patients had greater improvement with iloperidone versus placebo in PANSS, BPRS, and CGI scores.

Conclusions: The relative treatment benefit of iloperidone compared to placebo in patients with schizophrenia is enhanced in patients homozygous (G/G) for the rs1800169 polymorphism.

Key words: CNTF, iloperidone, pharmacogenetics, polymorphism, schizophrenia