ELUCIDATING THE RELATIONSHIP BETWEEN DISC1, NDEL1, AND NDE1 AND THE RISK FOR SCHIZOPHRENIA: EVIDENCE OF EPISTASIS AND COMPETITIVE BINDING

Katherine E. Burdick[1, 2, 3*], Atsushi Kamiya[4], Colin A. Hodgkinson[5], Todd Lencz[1, 2, 3], Pamela DeRosse[1], Koko Ishizuka[4], Sarah Elashvili[4], Hiroyuki Arai[6], David Goldman[5], Akira Sawa[4, 7], Anil K. Malhotra[1, 2, 3].

[1] The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Department of Psychiatry Research, Glen Oaks, NY.
[2] Albert Einstein College of Medicine, Department of Psychiatry, New York, NY.
[3]The Feinstein Institute for Medical Research, Manhasset, NY.
[4] Johns Hopkins University, Department of Psychiatry, Baltimore, MD.
[5]Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.
[6]Department of Health Chemistry, Faculty of Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan.
[7]Johns Hopkins University, Department of Neuroscience, Graduate Program in Cellular and Molecular Medicine, Baltimore, MD.

DISC1 influences susceptibility to psychiatric disease and related phenotypes. Intact functions of DISC1 and its binding partners, NDEL1 and NDE1, are critical to neurodevelopmental processes aberrant in schizophrenia. Despite evidence of a NDEL1-DISC1 protein interaction, there have been no investigations of the *NDEL1* gene or the relationship between *NDEL1* and *DISC1* in schizophrenia. We genotyped 6 *NDEL1* SNPs in 275 Caucasian schizophrenia patients and 200 controls and tested for association and interaction between the functional SNP Ser704Cys in *DISC1* and *NDEL1*. We also evaluated the relationship between *NDE1* and *DISC1* genotype and schizophrenia. Finally, in a series of in-vitro assays, we determined the binding profiles of NDEL1 and NDE1, in relation to *DISC1* Ser704Cys.

We observed a single haplotype block within *NDEL1*; the majority of variation was captured by *NDEL1* rs1391768. We observed a significant interaction between rs1391768 and *DISC1* Ser704Cys, with the effect of *NDEL1* on schizophrenia evident only against the background of *DISC1* Ser704 homozygosity. Secondary analyses revealed no direct relationship between *NDE1* genotype and SZ; however, there was an opposite pattern of risk for *NDE1* genotype when conditioned on *DISC1* Ser704Cys, with *NDE1* rs3784859 imparting a significant effect but only in the context of a Cys carrying background. In addition, we report opposing binding patterns of NDEL1 and NDE1 to Ser704 versus Cys704, at the same DISC1 binding domain. These data suggest that *NDEL1* significantly influences risk for SZ via an interaction with *DISC1*. We propose a model where NDEL1 and NDE1 compete for binding with DISC1.

ALTERNATIVE STRATEGIES FOR COVARIATE INCORPORATION IN HAPLOTYPE ANALYSIS: APPLICATION TO MDR1 GENE IN TARDIVE DYSKINESIA

Vincenzo De Luca, Clement Zai, Renan de Souza, Emanuela Viggiano, Steven G. Potkin, Jeffrey Lieberman, Herbert Y. Meltzer, James L. Kennedy

CAMH, Department of Psychiatry, University of Toronto, Canada

ABSTRACT

Tardive dyskinesia (TD) is a neurological disorder caused by chronic antipsychotic medication. The mechanism of TD is not clear and many hypothesis have been made involving the dopaminergic, the glutamaergic system or structural abdormalities. Previous studies have demonstrated a genetic component in TD, and many polymorphisms of methabolism enzymes have been studied.

Pharmacogenetics, using a candidate gene association approach, investigates pharmacodynamic and pharmacokinetic gene factors that may influence drug response and side effects. For example, about 20% of patients with schizophrenia receiving antipsychotic treatment develop tardive dyskinesia (TD). To date though, there are no published reports correlating certain candidate genes (e.g. drug transporters) with the pathogenesis of TD.

This study, carried out at 4 sites and focusing on the Multi Drug Resistance 1 gene, recruited 158 patients with schizophrenia who were assessed for TD using the Abnormal Involuntary Movement Scale (AIMS). DNA samples were subsequently genotyped for the MDR1 C3435T polymorphism. The overall model was not significant. The functional polymorphism C3435T in the MDR1 gene has not been linked with TD in the present work. The analysis of data with different software for statistical analysis demonstrated that there is difference in the statistical significance, when clinical covariates are incorporate in the analysis using different statistical package.

THE GENETICS OF SYMPTOM-BASED PHENOTYPES: TOWARDS A MOLECULAR CLASSIFICATION OF SCHIZOPHRENIA

Pamela DeRosse[1] Ph.D, Todd Lencz[1,2,3] Ph.D, Katherine E. Burdick[1,2,3] Ph.D, John M. Kane[1,2,3] MD and Anil K. Malhotra[1,2,3] MD

[1]Department of Psychiatry Research, The Zucker Hillside Hospital, Division of the North Shore–Long Island Jewish Health System, Glen Oaks, NY, USA; [2]The Feinstein Institute for Medical Research, Manhasset, NY, USA; [3]Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA;

ABSTRACT

Objective: Genetic studies in schizophrenia have primarily focused on disease susceptibility. Recently, however, support for a quantitative, symptom-based approach has been provided by studies of candidate genes including *DTNBP1*, *DISC1* and *COMT*. Moreover, a limited number of studies have reported suggestive linkage to specific schizophrenia symptom domains. We examined these chromosomal regions for association to positive, negative and disorganized symptom clusters, using a dense set of single nucleotide polymorphisms (SNPs).

Methods: We ascertained 178 Caucasian patients with schizophrenia for lifetime severity of clinical symptomatology using a structured diagnostic interview. The cohort was genotyped with the Affymetrix 500K microarray, from which we selected, a priori, 4,128 SNPs located within chromosomal regions previously linked to specific symptom clusters. Parametric tests, corrected for multiple testing, were used to compare the effects of allelic variation within these SNPs to the lifetime severity of specific symptom domains implicated by prior linkage studies.

Results: We were able to extend previous reports of linkage between chromosome 6q and both positive and disorganized symptoms. Severity of positive symptoms was significantly ($p=2.50E^{-05}$) associated with a SNP in *ORC3L*, a gene implicated in synaptic plasticity. Level of disorganized symptoms was significantly ($p<6.00E^{-05}$) associated with two SNPs in *BAI3*, which is highly expressed in brain during development.

Conclusions: These data point towards specific candidate genes located within previously implicated linkage peaks for clinical symptomatology. Identification of functional variants within these regions and a characterization of the effect of these risk genotypes on the treatment of specific clinical symptoms are needed.

PHARMACOGENETIC STUDY OF THE NOVEL DIPEPTIDE ANXIOLYTIC GB-115 TARGETED ON "FREEZING" PHENOTYPE OF EMOTIONAL STRESS REACTION

L.G.Kolik, T.A.Gudasheva, S.B.Seredenin.
State Zakusov Institute of Pharmacology Russian Academy of Medical Sciences, Department of Pharmacogenetics, 8 Baltiyskaya str., 125315, Moscow, Russia.
Tel/fax: +74956012186, e-mail: lgkolik@mail.ru

On the basis of structure of endogenous tetrapeptide cholecystokinin (CCK_4) with panic-like action in humans a series of dipeptides was designed. It has been reported that GB-115 ($Ph(CH_2)_5CO$-Gly-Trp-NH_2), the compound with CCK-negative activity, at the dose range of 0.0025-2.0 mg/kg, i.p., produced selective anxiolytic action in animals with genetically determined "freezing" reaction to emotional stress (Balb/c mice, MR rats) with no effect in animals with active type of behavior (C57Bl/6 mice, MNRA rats) (L. Kolik, 2003).

The present studies were carried out to examine whether or not GB-115 (0.05-5.0 mg/kg) would be orally active. In standard psychopharmacological tests for anxiety it was shown that response to novel anxiolytic was found to be different in animals with active and passive emotional stress reaction. In Balb/c mice the drug dose-dependently increased the general locomotor activity in the "open field"; it also increased the number of open entries and open time in the "elevated plus-maze" test. At the same time in C57Bl/6 mice GB-115 at the high doses 0.5-5.0 mg/kg decreased the behavioral indices in the "open field" test. However, GB-115 didn't change the spontaneous locomotion in both mice strains. In contrast to DZP there were no tolerance and withdrawal-syndrome observed after 4-weeks of GB-115 administration in rats.

The pre-clinical study of pharmacokinetics showed GB-115 to be more resistant to the action of metabolizing enzyme system as compared to naturally occurring neuropeptides. The novel drug was subjected to weak biotransformation thus demonstrating rather good bioavailability.

It should be concluded that GB-115, the orally active dipeptide, might be considered as perspective novel selective anxiolytic which effects depend on genetically controlled type of emotional stress behavior.

PILOT GENOMEWIDE ASSOCIATION STUDY OF TREATMENT RESPONSIVENESS IN SCHIZOPHRENIA

Todd Lencz, Ph.D., Pamela DeRosse, Ph.D., John M. Kane, M.D., Anil K. Malhotra, M.D.

Background – While prospective randomized trials are the gold standard for pharmacogenetics, they are also expensive and time-consuming, resulting in a paucity of available data. To date, there have been no published genomewide association studies of response to antipsychotics in patients with schizophrenia. Consequently, we conducted a cross-sectional genomewide analysis of patients with schizophrenia or schizoaffective disorder, to identify genetic associations to the phenotype of poor treatment response. Assignment to clozapine was used as a proxy for poor response to prior trials of commonly used antipsychotics.

Methods – The total sample included 209 Caucasian patients (72F/137M) diagnosed with schizophrenia or schizoaffective disorder. Of these, 79 (38%) had been prescribed clozapine; cause of assignment (treatment nonresponsiveness) was confirmed by chart review and structured interview data. Genotyping was performed with the Affymetrix 500K chip set. After standard QC steps, 372,630 SNPs were available for analysis.

Results – One SNP (rs10879987) was significantly ($p<10^{-7}$) associated with clozapine assignment under additive and allelic models. This SNP lies within an intergenic region on chromosome 12q21.2. Heterozygotes (n=99) at this SNP had a similar rate of clozapine assignment (40%) to the total sample. Compared to heterozygotes, homozygotes of the minor (A) allele (n=41) demonstrated a 68% rate of clozapine assignment (OR=3.2; 95%CI=1.5-6.9). By contrast, major allele (G) homozygotes exhibited only a 17% rate of clozapine assignment (OR=0.295; 95%CI=0.23-0.74).

Conclusions – Clozapine assignment may be a useful proxy for poor response to standard D2 antagonist treatment. While rs10879987 is intergenic and uncharacterized, the nearest gene (*PHLDA1*) is highly expressed in brain, where it is involved in neuronal apoptosis.

CYP2D6 AND HEPATOTOXICITY DURING TREATMENT WITH RISPERIDONE

[1] E. López-Torres, [2*] **Peñas-LLedó** E,[4] Doña A, [2] Dorado P, [2,3] Adrián LLerena

[1]Department of Clinical Pharmacology, University Hospital Virgen de la Victoria, Málaga, Spain. [2]CICAB Clinical Research Centre, Extremadura University Hospital and Medical School, Servicio Extremeño de Salud, Badajoz, Spain. [3]CICS-Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal. [4]Department of Psychiatry, University Hospital Virgen de la Victoria, Málaga, Spain. ***Presenting author**

Risperidone is an atypical neuroleptic drug widely used due to the lower incidence and severity of hepatic adverse effects in comparison to phenothiazines and it has been related with some cases of cholestatic and immunoallergic hepatitis.
Risperidone is metabolized to 9-hydroxy (OH) risperidone by cytochrome P450 2D6 (CYP2D6). Two phenotypes have been described for CYP2D6 enzyme: Poor and Extensive metabolizers (PMs and EMs). The genetic polymorphism of *CYP2D6* might explain the interindividual variability in drug plasma concentration and the risk of development liver toxicity for R and 9-OH-risperidone.
We report a case of risperidone-induced hepatocellular damage.
A 19-year-old Caucasian man was admitted to our department of psychiatry due to hallucinations, irrational fears and thought disorder; paranoid schizophrenia was diagnosed and he was treated with risperidone (8mg/day). He has no medical history of interest and there was no family history of psychosis.
At admission, liver function tests were normal. After 3 weeks of treatment, he started with asthenia and weight loss. He reported no use of alcohol, any other drugs, or herbal remedies and had received no blood transfusions.
The results of a physical examination were normal. His level of aspartate aminotransferase was 283 IU/l (normal <30), and his alanine aminotransferase level was 778 IU/l (normal <36). His bilirubin and alkaline phosphatase levels were normal, as was his eosinophil count. Serology tests ruled out viral causes. Screening for autoantibodies produced negative results, and the results of an abdominal ultrasonographic examination were normal. Treatment with risperidone was discontinued and the patient was then given olanzapine (10 mg/day). Six days after drug withdrawal, alanine aminotransferase level fell more than 50%, and a complete return to normal was seen within 2 months.
A causal association between risperidone and hepatocellular damage can confidently be established because there was a temporal relationship between the administration of the drug and the onset of hepatic abnormalities, there was a rapid recovery after stopping the drug, and alternative explanations were ruled out. To the best of our knowledge this is the first report showing possible risperidone induced hepatocellular injury without immunoallergic reaction.
In poor metabolizers of CYP2D6, marked differences in the pharmacokinetic profile of R and 9-OH- risperidone might increase the risk of liver toxicity (6).To evaluate the influence of CYP2D6 genotype, and the risk of hepatotoxicity during treatment with R, the patient was genotyped for a total of six polymorphic CYP2D6 variant alleles and multiplications of alleles *(*3, *4, *5, *6, *10, *17)*. He was classified as

homozygous wild type for the *CYP2D6.* Therefore, the increased risk for developing hepatotoxicity can not be supported by this enzyme metabolic capacity. Although a limitation of the present study was that R plasma concentration was not measured. To the light of this case we recommend obtaining baseline liver function tests before starting risperidone and regular monitoring to screen patients for liver damage during therapy. Risperidone therapy should be discontinued as soon as the monitoring of liver function tests, including parameters indicating cytolysis, reveals marked alterations.

Financial Support*: The study was supported by Ministerio de Educación y Ciencia (SAF2006-13589), Plan Nacional (I+D+I) and Fondo Social Europeo (European Union-FEDER). Spanish Ministry of Health Instituto Carlos III-FIS to P. Dorado (CP06/00030) and to E. Lopez-Torres (CM04/00123), and CIBERSAM.*

PERSONALITY AND CYP2D6 IN HISPANICS HEALTHY VOLUNTEERS

Eva M. Peñas-LLedó, Bárbaro Pérez, Rodrigo Pacheco, Mayra Álvarez, Pedro Dorado, Idilio González, **Adrián LLerena***

Clinical Research Centre (CICAB) Extremadura University Hospital and Medical School, Servicio Extremeño de Salud, Badajoz, Spain, Instituto Superior de Ciencias Médicas de La Habana, Cuba. ***Presenting author**

Objectives: Previously we showed that interindividual variability on CYP2D6 hydroxylation capacity was related to personality differences on cognitive social anxiety in Spanish healthy volunteers. Thus, we aimed to analyze whether this relationship between personality and CYP2D6 phenotype and also genotype was found in a similar population of healthy volunteers from a different latitude and culture by using the same methodology.

Methods: A populations of 409 university students and staff from Badajoz, Spain (n=156) and Havana, Cuba (n=253) completed the Karolinska Scales of Personality (KSP), and were evaluated on CYP2D6 genotypes. Debrisoquine hydroxylation capacity was evaluated in the previous study in Spain and is now evaluated in the Cuban population. KSP scores were compared between four groups divided according to their CYP2D6 metabolic capacity: one of Poor and three of Extensive Metabolizers. Furthermore, KSP scores were compared between other four different groups divided according to their number of *CYP2D6* active genes: zero, one, two, and more than two.

Results: Cubans' differences on personality traits, cognitive social anxiety, with regard to CYP2D6 hydroxylation capacity were remarkably similar to those found in Spaniards. These differences also came out to be significant for psychic anxiety (p=0.02) and socialization (p=0.02). The same pattern of results obtained for the subscales of psychic anxiety, socialization, psychasthenia and inhibition of aggression with regard to phenotype in both the Cuban and Spanish studies, were seen with regard to *CYP2D6* genotypes (data to be shown).

Conclusions: These corroborating results further strengthen the relationship between CYP2D6 metabolic capacity and personality. Thus, research is warranted to determine CYP2D6 functional implications for interindividual differences in vulnerability to neuropsychiatric diseases and drug response.

Financial Support in Spain by Eurpean Union FEDED and *Ministerio de Sanidad Instituto Carlos III-FIS grant (PI06/1681) and fellowship to P.D. (CP06/0030) and CIBERSAM. The study was coordinated through the network Red Iberoamericana de Farmacogenética y Farmacogenómica (CYTED206RT0290).*

ACACA, ACACB AND NPY AND DYSLIPIDEMIA IN PATIENTS TREATED WITH ANTIPSYCHOTIC. A CROSS-SECTIONAL STUDY.

Alexandre Meary [1,2] , Jose de Leon[3] , Maria J. Arranz[1]

[1] Psychological Medicine, Institute of Psychiatry – King's College, London, United Kingdom
[2] INSERM, Unité 841; IMRB, Department of Genetics, Psychiatry Genetic, Créteil, F-94000, France
[3] University of Kentucky Mental Health Research Center at Eastern State Hospital, and University of Kentucky Colleges of Medicine and Pharmacy, Lexington, Kentucky.

Introduction:

The high prevalence of metabolic syndrome observed in clinical trials and observational studies indicate the need to fin predictors for antipsychotics induced dyslipidemia. This prediction may improve the treatment choice in the future. Previous results suggested the possible implication of acetyl-coenzyme A carboxylase α (ACACA) in hypertriglyceridemia and acetyl-coenzyme A carboxylase ß (ACACB) and neuropeptide Y (NPY) in hypercholesterolemia in patients treated by antipsychotics (de Leon et al, 2008). We have investigated the implication of polymorphisms of these three genes in dyslipidemia in a cohort of Caucasian patients treated with antipsychotics.

Methods:

321 Caucasian patients treated with antipsychotics were included in this cross-sectional study. Total and HDL cholesterol levels and triglycerides levels were obtained. 8 SNPs in ACACA, 6 in ACACB and 3 in NPY were selected in HapMap to obtain the best map of these genes with an R^2 of 0.8 and a minimum allelic frequency of 20%.
Genotyping was carried out using the Amplifluor® FAM-JOE Genotyping System. The association of these SNPs with dyslipidemia was studied individually with a Kruskal-Wallis test and linear regression including age and sex. A haplotype analysis was then performed.
These analyses were performed in the whole cohort and in two subgroups: patients treated by high risk treatments (olanzapine, quetiapine and chlorpromazine) and others.

Results:

The rs4795194 SNP in the ACACA gene was associated with total cholesterol level in the low risk treatment group (p=0.001). The rs2268384 SNP in the ACACB gene was associated with HDL cholesterol level in the same group (p=0.003). All the other associations had a p value higher than 0.005. The haplotype analysis didn't provide any improvement in the found associations.

Conclusion:
As these associations are found in the low risk treatment group, they do not provide arguments for an important implication of these three genes in antipsychotic induced dyslipidemia.

NOVEL SELECTIVE ANXIOLYTIC DRUG AFOBAZOL. PHARMACOGENETIC STUDY OF THE EFFECT ON MONOAMINE SYSTEMS IN THE RAT BRAIN

M.V. Voronin, I.A. Kadnikov

Afobazol is a derivate of 2-mercaptobenzimidazole, a novel drug combining selective anxiolitic effect and slight stimulating one. Also it is worth to mention the lack of any hypnosedative effect in contrast to ataraxic drugs of previous generations.

The main idea of the present study was to analyze the influence of Afobazol on monoamine systems of the rat brain. Within these frameworks effects of Afobazol were studied on the inbred strains of Maudsley Reactive (MR) and Maudsley non-Reactive (MNRA) rats with the opposite phenotype reactions on the emotional stress. The level of the monoamines in hypothalamus, nucleus accumbens and striatum were studied by the HPLC method. Afobazol was administrated by abdominal injection in dose providing anxiolytic effect (5 mg/kg), 30 min prior to locating to the open field test.

The influence of Afobazol on the level of monoamines, its metabolites, and its turnover in nucleus accumbens of MR and MNRA rats' brain in the condition of emotional stress appeared in decreasing of serotonin (5-HT) level in MR rats. In our opinion such change may reflect the serotoninergic component of selective anxiolytic effect of drug. We also marked the decrease of dopamine (DA) metabolism which appeared in decreasing of dopamine turnover, i.e. DOPAC/DA, HVA/DA and (DOPAC+HVA)/DA.

The influence of Afobazol on striatum of MR and MNRA rats appeared in the following way. It caused the decrease of 5-HT and it metabolite 5-hydroxyindoleacetic acid (5-HIAA) in MR striatum in comparison with MNRA rats. These changes in serotonin profile are the reason of locomotor activity increase. Also MR rats in comparison with control group were characterized by decrease of dopamine turnover (DOPAC/DA and (DOPAC+HVA)/DA) as the result of DOPAC level decrease.

The more precise trend in the decrease of the dopamine metabolism was observed in the group fallen under emotional stress in the open field. In comparison with control injection group MR rats in conditions of emotional stress responded by decrease of dopamine metabolites level, i.e. HVA and DOPAC. And as the result the same dopamine metabolism parameters decrease. Apparently the given changes underlie the increase of locomotor activity under the conditions of emotional stress.

We also observed changes in serotoninergic system which appeared in 5-HT level decrease. So MNRA rats under the condition of emotional stress in case of Afobazol injection exposed higher level than MR rats. Meanwhile in the same conditions MR rats were characterized by decreased level of 5-HIAA.

The character of the changes in the level of the neuromediators at MR rats occurred the identical one revealed in the same conditions for the MNRA rats. It is characterized by the active phenotype reaction to the emotional stress. Determined changes in the dopaminergic system functioning may underlie the behavior of the animals with the passive phenotype reaction to the emotional stress in case of Afobazol injection. These results directly point at hypothalamus as the structural target for Afobazol drug in the condition of emotional stress.

PHARMACOGENETICS OF ANTIPSYCHOTIC TREATMENT IN AFRICAN AMERICAN BIPOLAR PATIENTS

Authors: Charles U Nnadi, Todd Lencz, Pamela DeRosse, Katherine Burdick, and Anil K Malhotra.

Affiliation: The Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd Street, Glen Oaks, NY 11004

Introduction: Single nucleotide variations in the dopamine receptor type D2 (DRD2) gene could be associated with acute response to second-generation antipsychotic (SGA) drugs in African American patients diagnosed with bipolar disorder. Risperidone, one of the five SGAs with acute mania indication, has antagonist property at DRD2, serotonin-$5HT_{2A}$, and alpha-$adrenergic_{2c}$ receptors. This unique receptor profile has been theorized to be extremely important for the treatment of affective disorders. Clinicians are beginning to use risperidone monotherapy to treat acutely manic patients. Our center recently found *DRD2* promoter region alleles to be associated with treatment response in first-episode schizophrenia patients who were randomly assigned to risperidone or olanzapine treatment for 16 weeks (Lencz et al, 2007). Because risperidone will soon go off patent the associated savings in cost will encourage its use in acute mania. Therefore, the aims of this study are to examine the relationship of *DRD2* gene and risperidone response and risperidone-induced adverse events in a cohort of unrelated African American bipolar patients.

Methods: About 175 adult African American patients aged 18-65 years with Structured Clinical Interview for DSM-IV (SCID)-derived diagnosis of bipolar disorder, manic type will be recruited from our Inpatient Affective Disorders Unit. After a thorough description of the protocol, all patients will be required to sign an informed consent to participate in the study. All enrolled patients will be treated with risperidone monotherapy (up to 6mg/day) for 10 days. Trained raters will use the Clinician Administered Rating Scale for Mania (CARS-M), the Brief Psychiatric Rating Scale (BPRS), the 21-item Hamilton Depression Rating Scale (HAMD-21), the Simpson-Angus Rating scale for Extrapyramidal symptoms and the Barnes Rating Scale for Drug-Induced Akathisia to evaluate the severity of psychopathology and or side-effects at baseline and every third day until study end. Prolactin level will be assessed at baseline and at study end. About 30cc of venous blood will be collected for DNA extraction and to establish immortalized cell lines. We will genotype about 44 single nucleotide polymorphisms (SNPs) in the *DRD2* gene including some functional variations recently described by Zhang et al (PNAS 2007, vol 104, No 51). All SNPs will be drawn from the Phase II HapMap (International HapMap Consortium, 2007); SNPs with minor allele frequency (MAF) ≥ 5% in the Yoruba (YRI) sample will be prioritized. The Taq 1A variation (rs 1800497), which is not in the gene itself, will be genotyped. Analyses will examine the relationship of *DRD2* polymorphisms and treatment response defined as 50% or more reduction in the mania rating scale from baseline to study end. The association of *DRD2* gene and time to response will be examined using survival analysis.

Conclusions: The proposal will examine the pharmacogenetics of risperidone in African American patients diagnosed with bipolar disorder. The study could improve the prospect of individualized treatment using prospective genotyping for *DRD2*.

THE GENETIC OF BIPOLAR DISORDER AS A TOOL FOR PHARMACOGENETIC STUDIES

Alessandro Serretti, Laura Mandelli
Institute of Psychiatry, University of Bologna, Italy

Bipolar disorder (BPD) genetic investigations may drive to the choice of candidate genes for pharmacogenetic studies. In the recent years, a huge number of linkage and association studies have been conducted; nevertheless, data remain sparse and case-control studies often do not consider information derived from linkage analyses to choose candidate genes (positional candidate approach). In the present work we aimed to summarize results obtained from both linkage and association studies in BPD, in order to point out genomic regions of interest and promising genes that have to be further investigated, other than summarizing the current state of the art.
We reviewed published studies on the matter till March 2007. Regions where positive linkage was found were precisely localized and we further proceeded to identify nearby located genes. Combining linkage and association studies, we found many "hot regions" (consistently reported in positive linkage with BPD) that have been however investigated for new candidate genes, to be tested in case-control studies. By the "Entrez gene" database we identified more than three hundred genes located in these regions, which are expressed in the brain and whom their molecular function is known. Furthermore, the review of association studies gave interesting results, as a number of genes seem to be definitively involved in BPD, such as SLC6A4, TPH2, DRD4, SLC6A3, DAOA, DTNBP1, NRG1, DISC1 and BDNF. A number of other promising genes, which have received independent confirmations, and genes that need to be further investigated in BPD, have been also systematically listed.
In conclusion, a number of liability factors that underlie the genetic of BPD have been identified, the scattered knowledge that makes it difficult to candidate genes for pharmacogenetic studies has been here summarized.

DBNDD1, HSPS AND TAAR6 VARIATIONS INFLUENCE SCHIZOPHRENIC PHENOTYPE AND TREATMENT RESPONSE

Antonio Drago[3], Chi-Un Pae[1,2], Ashwin A. Patkar[2], Laura Mandelli[3], Diana De Ronchi[3], Alessandro Serretti[3]

[1]Department of Psychiatry, Kangnam St. Mary's Hospital, The Catholic University of Korea College of Medicine;
[2]Department of Psychiatry and Behavioural Sciences, Duke University;
[3]Institute of Psychiatry, University of Bologna, Italy

Schizophrenia is a disorder driven by unraveled mechanisms. Pharmacogenetics is aimed to disentangle the path. On this call, we studied a sample of 140 schizophrenic in patients (F=55%; age=34.8±12.2 years), and a set of variations running within three candidate genes. Genes were chosen on the basis of previous associations, reflecting three hypothesis: Schizophrenia is based on glutamatergic disrupted transmission (DBNDD1), on a neurodegenerative path (HSPs), or on a disrupted net of neurotransmission (TAAR6). PANSS test was administered by independent psychiatrists blind to the genotypes at intake and discharge. Retests were administered after a period of 45 days on average. Patients were treated with typical and atypical antipsychotics with low benzodiazepine doses as the only other treatment allowed. All the sample was from a Korean homogeneous population. Sociodemographic, clinical and treatment related variables entered the analysis as covariates. On average, we had a power of 0.8 to detect a minimum difference of about 2% in the PANSS scores. DBNDD1 haplotype A-T-A (rs3213207, rs1011313, rs2619522 respectively) was found to be associated with milder baseline symptomatology, HSPs A-C-G-G and A-C-G-G haplotypes (rs2075799, rs1043618, rs562047, rs539689 respectively) were found to be associated with clinical improvement, while TAAR6 rs8192625 G/G genotype was found to be associated with worse clinical presentation. Overall significance was $p<0.02$.
In conclusion, HSPs variations were found to influence the effect of antipsychotic treatment, while the effects of DBNDD1 and TAAR6 variations may independently influence baseline symptomatology.

REVIEW AND META-ANALYSES OF PHARMACOGENETICS OF ANTIDEPRESSANTS

Alessandro Serretti (a), Masaki Kato (a,b)
a) Institute of Psychiatry, University of Bologna, Bologna, Italy.
b) Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan.

This systematic review summarizes the emerging literature of pharmacogenetic studies on depression and aggregates such information into concise recommendation with meta-analysis.
Data were entered into the Cochrane Collaboration review manager software (RevMan version 4.2) and analyzed by RevMan analysis 1.01. Heterogeneity between the studies was assessed with chi-square test. Individual and pooled odds ratio (OR) and associated 95% CIs were calculated.
For 5 SNPs we could retrieve sufficient studies and performed meta-analysis about association of ADs treatment response or side effect except for 5-HTTLPR that was previously published separately.
As for treatment response, the pooled odds ratio (OR) of STin2 retrieving 6 studies including data from 816 subjects was highly significant with better response of 12/12 genotype (2.49, $p<0.00001$). The pooled OR of HTR1A C-1019G retrieving 5 studies including data from 756 subjects was not significant. The OR of HTR2A A-1439G/ T102C including 849 subjects from 6 studies demonstrated a non significant result, although, marginal significance could be found in studies evaluating SSRIs response. The OR of TPH1 A218C with 674 subjects from 6 studies was significant with C/C genotype associated with better response (1.7 $p=0.004$). On the other hand the OR of GNB3 C825T with 1117 subjects from 6 studies was not significant.
As for side effect, interestingly, pooled Relative Risk (RR) of 5 studies of side effects rate induced by SSRIs including 453 subjects was significant with higher risk of side effect for the HTR2A A-1439G/G genotype (1.37, $p=0.002$).
In conclusion, despite the large number of published studies, pooled analyses failed to evidence association for many promising candidates. This was due to different directions of association in Caucasians versus Asians and probably in different protocols used. However HTT Stin2, TPH1 and HTR2A showed some evidence of association in the ovarall sample.

GENETIC SUSCEPTIBILITY TO ANTIDEPRESSANT-INDUCED MANIA: ROLE OF DOPAMINERGIC PATHWAY GENES POLYMORPHISMS

Renan P Souza[1,2,3], Emanuela Mundo[1], Xingqun Ni[1], Pierandrea Muglia[1], Subi Tharmalingam[1], Nicole King[1], Marco A Romano-Silva[2,3], James L Kennedy[1].
[1]Neurogenetics Section, CAMH, Toronto, ON, Canada; [2]Grupo de Pesquisa em Neuropsiquiatria Clínica e Molecular, UFMG, Belo Horizonte, BRAZIL; [3]Saude Mental, UFMG, Belo Horizonte, BRAZIL.

Abstract
Several pharmacogenetic studies suggest that response to pharmacotherapy in bipolar disorder may be mediated by genetic factors. Dopaminergic system plays an important role in the regulation of synaptic plasticity and there are results suggesting a role in the pathogenesis of bipolar disorder. The present study investigated possible genetic association between some polymorphisms possibly involved in occurrence of manic or hypomanic switches during antidepressant treatment. We performed a case–control study to test for allelic/genotypic frequency differences and gene-gene interaction analyzes polymorphisms across six genes that encode proteins related with dopaminergic system (DRD1, DRD2, DRD3, DRD4, DRD5 and TH) between 27 patients with antidepressant-induced mania and 29 patients without antidepressant-induced mania. In our sample we found that DRD3 rs324035 polymorphism showed significant allelic association with antidepressant-induced mania occurrence.The significant association is not observed after correction for multiple testing (Bonferroni or permutation tests). Our results indicate nominally association between DRD3 rs324035 polymorphism and antidepressant-induced mania. Further studies are required to investigate other possible related genetic variants influencing the timing of manic-depressive cycle.

LACK OF ASSOCIATION OF THE CANNABINOID RECEPTOR (CNR1) GENE TO TARDIVE DYSKINESIA IN CHRONIC SCHIZOPHRENIA PATIENTS

Arun K. Tiwari[1], Clement C. Zai[1], Gary Remington[1], Herbert Y. Meltzer[2], Jeffrey A. Lieberman[3], Steven G. Potkin[4], James L. Kennedy[1*]

[1]Center for Addiction and Mental Health, Toronto, Ontario, Canada

[2]Psychiatric Hospital at Vanderbilt University, Nashville, TN, USA

[3]New York State Psychiatric Institute, Columbia University Medical Center, New York City, NY, USA

[4]Brain Imaging Center, Irvine Hall, University of California at Irvine, CA, USA

Tardive Dyskinesia (TD) is a severe potentially irreversible debilitating movement disorder developing in ~20-25% schizophrenia patients under long-term treatment with conventional antipsychotic drugs. The basal ganglia has been hypothesized to control movements through a balance between the D1 receptor expressing direct stimulatory pathway, and the D2 receptor expressing indirect inhibitory pathway. The neuronal canabinoid receptor (CNR1 or CB1) modulates dopaminergic signalling and is primarily expressed in the GABAergic medium spiny neurons and has been co-localized with both D1 and D2 receptors. Administration of canabinoid agonists has been reported to decrease hyperkinetic movements in Tourette's syndrome and DOPA induced dyskinesias. Therefore, CNR1 markers (rs806377 & rs806378-(5'Upstream region); rs6911472 3'UTR and rs1049353 Thr454Thr) were investigated.

Results: rs6911472 was monomorphic. No significant allelic, genotypic or haplotypic distribution differences in tested polymorphisms between TD-present and absent categories were observed. However, a significant difference in the genotypic distribution of rs806377 was observed in females (p=0.038). Severity of TD did not differ across genotypes. No significant interaction of CNR1 was observed with the DRD1 receptor. However, complex synergistic interactions were observed between rs1049353 in CNR1 and rs4274224 (intron4) in DRD2 gene (p=0.05).

Conclusion: No evidence for a main effect of the CNR1 gene in susceptibility to TD was observed; however, CNR1 may interact with DRD2 and other genes to contribute to this complex phenotype.

***Corresponding author:**
James L Kennedy,
R-31, Neurogenetics section,
Center for Addiction and Mental Health,
250 College Street, Toronto, Ontario, Canada M5T 1R8.

ASSOCIATION Study of Tardive Dyskinesia and Five DRD4 Polymorphisms in Schizophrenia Patients

Clement C. Zai(1,2), Vincenzo De Luca(1,2), Daniel J. Müller(1,3), Aristotle N. Voineskos (1,2), Gary Remington(1), Herbert Y. Meltzer(4), Jeffrey A. Lieberman(5), Steven G. Potkin(6), James L. Kennedy(1,2)

(1) Centre for Addiction and Mental Health, Toronto, Ontario, CANADA
(2) Institute of Medical Science, University of Toronto, Toronto, Ontario, CANADA
(3) Department of Psychiatry, Charité University Medicine Berlin, Campus Charité Mitte, Berlin, Germany
(4) Psychiatric Hospital at Vanderbilt University, Nashville, Tennessee, USA
(5) New York State Psychiatric Institute, Columbia University Medical Centre, New York City, New York, USA
(6) Brain Imaging Center, Irvine Hall, University of California at Irvine, California, USA

Tardive dyskinesia (TD) is observed, to varying degrees, with all antipsychotics. Nigro-striatal dopaminergic abnormalities have been linked to TD in part because antipsychotic agents which cause TD are potent D_2 antagonists. Thus, a number of studies have focused on the association of dopamine system gene polymorphisms and TD. The most consistent findings have been an association between TD and the Ser9Gly polymorphism of the *DRD3* gene and TaqIA 3' of the *DRD2* gene. The *DRD4* gene is a member of the D_2-like dopamine receptor family. The variable-number tandem repeat polymorphism in exon 3 of *DRD4* has been associated with TD; however, other polymorphisms have not been well studied. We investigated five polymorphisms spanning the *DRD4* gene and their association with TD in our European Caucasian sample (N=171). The exon 3 variable-number tandem repeat was not associated with TD, haplotypes consisting of four haplotype-tag polymorphisms were associated with TD in males. The present study suggests that *DRD4* may be involved in TD in the Caucasian population, though further replication studies are needed.

Corresponding author:
Dr. James L. Kennedy
James_Kennedy@camh.net