A GENOMEWIDE ASSOCIATION STUDY OF A PATTERN OF SUSTAINED ANTIDEPRESSANT RESPONSE

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Background: The discovery of genetic predictors of antidepressant response may depend critically on the classification of clinical outcomes. Commonly used 'response vs. non-response' outcomes that are based on symptom severity at a single endpoint do not account for the stability or persistence of symptomatic improvement. We applied a new statistical approach, Growth Mixture Modeling (GMM), to the Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D) dataset and identified subjects having sustained versus unsustained patterns of response. We contrasted subjects in these two different groups to examine whether common genetic variation influences durability of response during antidepressant treatment.

Method: Subjects included STAR*D Level 1 participants who were identified as sustained (n= 869) or unsustained (n = 247) responders based on GMM of change in symptom severity over twelve weeks of citalopram treatment. Single nucleotide polymorphisms (SNPs; n = 430,198) from Affymetrix arrays were examined in association analyses after correction for population stratification.

Results: No SNPs met the threshold for genomewide significance. The strongest finding involved a SNP within theacyl-CoA synthetase short-chain family member 3 gene ACSS3, a mitochondrial enzyme predicted to generate acetyl-CoA for energy generation (p-value = 4.5 x 10-6, OR = 0.61). Notable genes among the most associated regions include SEMA5A (p = 2.23 x 10-5, OR = 2.82), CSGALNACT1 (p = 7.72 x 10-6, OR = 2.14).

Conclusions: Results of this approach may identify new genes or pathways related to clinically useful patterns of response, although the lack of genome-wide significance in our GWAS renders any speculation premature.

ANTIDEPRESSANT RESPONSE IN BIPOLAR PATIENTS: GENOME-WIDE AND MOLECULAR PATHWAY ANALYSIS

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Objective: The genetics of antidepressant response in bipolar patients has been poorly investigated. The authors studied the genetics of antidepressant response in bipolar depression. Method.524 bipolar depressed patients from the Systematic Treatment Enhancement Program for Bipolar Disorder study, standard care pathway, were available for the analysis according to the outcome definition. Outcome was the number of following visits during which patients were still depressed after an episode of bipolar depression. 1256145 SNPs were available after imputation and quality control. A genome-wide analysis and a genome-wide molecular pathway analysis were undertaken. A logistic regression served for the genome-wide analysis, covariates were age, gender and the genetic admixture of the dataset. A deviance from the expected distribution of the significant associations (Chi2 test) at a p level of 0.05 within and out of specific pathways was the test of choice for the molecular pathway analysis. We had sufficient power (0.80) to detect a genotype relative risk of 2 to 2.2 when considering the frequency of the risk allele from 0.20 to 0.10 under an additive model in the pathway analysis.

Results: No significant association was found between the single variations and the outcome. A significantly higher distribution of SNPs with a low level of significant association with the outcome was found for the D-Arginine and D-ornithine metabolism pathway. The main gene within this pathway is the D-amino acid oxidase (DAO) which was found to be associated with Schizophrenia and Bipolar Disorder in previous publications. In particular, the DAO oxidizes D-amino acids to the corresponding imino acids, producing ammonia and hydrogen peroxide, and it is a candidate susceptibility gene in the glutamatergic mechanisms of schizophrenia for its role in the metabolism of D-serine.

Conclusions: The authors found evidence that a gene involved in the glutamatergic regulation ¨C the DAO - may modulate the response to common pharmacological treatments during bipolar depression. Our sample was underpowered to detect a genome-wide significance for single SNPs.

Key words: bipolar, antidepressant, genome-wide

INFLUENCE OF ANKK1 AND DRD2 POLYMORPHISMS IN RESPONSE TO HALOPERIDOL

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Background and aims: current evidence suggest that ANKK1 and DRD2 genes could affect vulnerability and treatment response in some psychiatric disorders. The present study explores whether ANKK1 and DRD2 variants could predict efficacy and tolerability of haloperidol in the treatment of psychotic patients.

Methods: 88 acutely psychotic patients were genotyped for 9 ANKK1 (rs877138, rs17600713, rs4938015, rs11604671, rs2734849, rs1800497, rs2587550, rs1003641, rs2242592 and , rs6279) and 27 DRD2 (rs1124492, rs1124493, rs1079595, rs1079594, rs6277, rs6275, rs1800499, rs2075654, rs2002453, rs2245805, rs2734836, rs1116313, rs1125393, rs7131440, rs12800853, rs12364051, rs4436578, rs17115583, rs4648318, rs4274224, rs7131056, rs4648317, rs7117915, rs4938019, rs1799978, rs10891556 and rs658937) Single Nucleotide Polymorphisms (SNPs). Treatment efficacy and tolerability were assessed at baseline and weeks 1, 2, 3 and 4 using the Positive and Negative Symptoms Scale (PANSS) and the Udvalg for Kliniske Undersogelser side effects (UKU) rating scales, respectively. Multivariate analyses were employed to test possible influences of single nucleotide polymorphisms on clinical and safety variables. Analysis of haplotypes was also performed.

Results: rs1003641 (p=0.015) and rs2242592 (p=0.008) within ANKK1 gene, rs1124493 (p=0.001) and rs2245805 (p=0.026) within DRD2 gene were associated with clinical improvement. None of the SNPs under investigation was associated with side effects. Results were confirmed in the allelic analysis.

Conclusion: our findings support a possible role of ANKK1 and DRD2 variability on haloperidol efficacy. However, due to the small sample size, our results need further validation.

GLUTAMATERGIC GENES AND EARLY ANTIDEPRESSANT EFFICACY IN THE STAR*D

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Background: A recent scientific debate about the role of the glutamatergic system as a modulator of antidepressant response was animated. A candidate gene analysis was then conducted on 632 subjects of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

Methods: 1808 SNPs harbored by 71 glutamatergic genes were available from the STAR*D genome-wide dataset after quality control. The primary outcome was early response (2nd week) and later response (from the 4th to the 14th week) compared to non response in the STAR*D level 1. The secondary outcome was the occurrence of symptom relapse after achieving response through the first 14 weeks of treatment. Only white subjects were included in order to avoid ethnic stratification. A linear regression model with age and gender as covariates was employed as implemented in PLINK. A Bonferroni correction for multiple testing was applied.

Results: Two markers in linkage disequilibrium (rs2268133 and rs2268132) within the GRIN2B gene predicted response after correction for multiple testing, with the G/G and A/A genotypes associated to early response (β=0.2934, p=2.83e-05; β=0.3103, p=5.40e-05, respectively). Patients with early response showed the same rate of response maintaining as later responders through 14 weeks of treatment (Chi2=0.233, df=1, p=0.629) and no marker was found associated to the risk of symptom relapse. No evidence of population stratification was found (genomic inflation factor λ=1).

Conclusion: Glutamatergic genes may be useful markers of early antidepressant efficacy. This result may be relevant in further understanding the pathophysiology of the drug induced antidepressant effect.

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INFLUENCE OF COX-2 AND OXTR POLYMORPHISMS ON TREATMENT OUTCOME IN DEPRESSION DISORDERS

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Introduction: Recent studies support the concept that inflammatory mechanisms play a crucial role in the pathomechanisms of antidepressant efficacy. Among proteins that are involved in inflammatory cascade ciclooxygenase-2 (Cox-2) plays an important role. Moreover, several evidences suggest that oxytocin regulates inflammatory processes in several tissues. The aim of this study is to investigate whether a set of single nucleotide polymorphisms (SNPs) within COX-2 (rs5275 and rs20417) and OXTR (rs53576 and rs2254298) genes was associated with pharmacological treatment resistance, response or remission.

Methods: Three hundred seventy-two patients were recruited in the context of a multicenter resistant depression study. They were genotyped for COX-2 and OXTR SNPs. Treatment resistance, response and remission were recorded.

Results: We did not observe any significant association between the genotypes or alleles under investigation and resistance, response and remission in the whole sample.

Conclusion: There is no evidence suggesting any association between our set of single nucleotide polymorphisms (SNPs) within COX2 and OXTR and treatment resistance, response or remission. Our results are consistent with those of some studies but not with those of other ones. Indeed, several factors could be involved in the discrepancy observed across studies. They include sample size, environmental factors, differences in ethnicity, different study designs, different definitions of responders, or different treatment.

Independent replications with larger sample sizes are needed in order to better understand the potential role of COX2 and OXTR on the short term and long term antidepressant treatment outcome.

GENETIC PREDICTORS OF ANTIDEPRESSANT SIDE EFFECTS

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The unwanted effects associated with antidepressant medications are key determinants of treatment adherence in depression and genetic variation may play a role in influencing individual propensity for such side effects. However, previous work attempting to ascertain those genetic variants involved has had limited success. In this study, adverse drug reactions detected using the Antidepressant Side-Effect Checklist (ASEC) were categorized based upon their likely pharmacological basis; adrenergic, cholinergic, serotonergic and histaminergic. A candidate gene analysis was performed, to identify genetic predictors of susceptibility to each group of side effects, in a large cohort (N=810) of moderately to severely depressed patients. Putative serotonergic side effects (i.e. nausea, diarrhea, insomnia and decreased appetite) were significantly associated with variation in the HTR2C gene, which supports the hypothesis of serotonin receptor-mediated mechanisms underlying such effects and the use of a pharmacological approach to grouping side effects. However, specific predictors of presumed adrenergic, cholinergic and histaminergic adverse drug reactions were not found. Despite our relatively large sample this could still reflect inadequate power. Further work is needed, not only to verify these findings and consider their translational value, but also to explore how genetic variability in the HTR2C gene leads to the observed differences in liability to serotonergic side effects.

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BDNF MET POLYMORPHISM, STATIN USE AND INSULIN RESISTANCE MEASURES IN BIPOLAR AND SCHIZOPHRENIA POPULATION

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Purpose: The Brain-derived Neurotrophic Factor (BNDF) Val66Met variant has been implicated in insulin resistance with a possible increased risk of diabetes. HMG-COA reductace inhibitors (statins) may also increase insulin resistance risk. Given the elevated risk for metabolic syndrome within schizophrenia and bipolar disorder, we sought to determine the effect of the BDNF Met variant and statin medication use on insulin resistance using the Quantitative Insulin Sensitivity Check Index (QUICKI, ≤0.33 cutoff for insulin resistance).

Methods: Using a cross-sectional design, we examined bipolar and schizophrenia patients screened for metabolic syndrome. Patients with diabetes or on any medications affecting glucose regulation were excluded. Associations between insulin resistance and genotype were then analyzed by one-way ANOVA. Subjects were grouped by BDNF genotype as well as presence of absence of statin use resulting in 3 groups ((1)BDNF Met allele and statin use, (2)BDNF Met or statin use, (3) BDNF Val allele and no statin use).

Results: A total of 193 subjects were included, with a mean age of 43±11 years. The group was 50% female, 17% African American and 51% had a diagnosis of bipolar disorder; 61% and 16% were receiving atypical antipsychotics(AAPs) and statin medications, respectively. No differences were seen in age, race, gender, and AAP or statin use based on the BDNF genotype. Our regression analysis showed subjects with the BDNF met allele who were receiving a statin had significantly lower QUICKI scores (indicating worse insulin resistance) compared to the other groups ($F = 4.62$, $df = 2,246$, $p = 0.011$). Insulin resistance criteria were met in 100%, 82% and 71% of groups 1, 2 and 3 respectively.

Conclusions: Our data suggests that in the metabolically high-risk populations of schizophrenia and bipolar the BDNF met allele in combination with statin medications is associated with higher insulin resistance. Further validation of the associations between BDNF genotype, statin medication use and insulin resistance outcomes remain necessary.

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A PHARMACOGENETIC DISSECTION OF SSRI SIDE-EFFECTS IN OLDER ADULTS

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A novel approach in the personalization of medicine is the use of genetics to choose treatment based on prevention of side-effects. It is likely that genetic variability in the serotonin transporter and other receptors is associated with differential experience of SSRI side-effects. Therefore, we investigated the association between genetic polymorphisms in the serotonin transporter and serotonin 1a and 2c receptors with side-effects reported during a 12-week randomized controlled trial of escitalopram vs placebo for anxious older adults. Side-effects were measured using the UKU side-effect rating scale. The triallelic haplotype of the serotonin transporter (L/S+rs2553) and the 1a (rs6295) and 2c (rs518147) receptors were genotyped. We examined 4 side-effects that showed a clear drug-placebo separation (increased duration of sleep, headache, diarrhea, and micturition disturbance). We computed 2-way ANOVAs for each side-effect by treatment group and by high- vs low-expressing genotype for the 3 receptors. Diarrhea was significantly more frequent in those with low-expressing genotype at 5HTR1A ($F=25.64$, $p<.0001$) and micturition disturbance was significantly more frequent in those with low-expressing genotype at the triallelic haplotype of the serotonin transporter ($F=18.27$, $p<.0001$). In conclusion, there is genetic variability in serotonin receptors 1a and in the triallelic haplotype of the serotonin transporter that is significantly associated with increased frequency of reported side-effects in patients receiving escitalopram. With replication, findings such as these can contribute to personalized SSRI pharmacotheray with the goal of side-effect prevention.

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VALIDITY OF THE ALDA SCALE IN THE RETROSPECTIVE ASSESSMENT OF LITHIUM RESPONSE

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Small sample sizes have been a significant limiting factor in pharmacogenetic studies in psychiatry. While most genome-wide association studies (GWAS) in psychiatry now include thousands of subjects, the substantially greater effort and expense of prospective assessment of drug response has generally limited pharmacogenetic studies to much smaller sample sizes. Though prospective assessment with quantitative methods is undoubtedly superior, retrospective assessment based on patient report and chart review can yield much larger sample sizes. The Alda Scale, developed in order to standardize the retrospective assessment of lithium response, uses information gathered from medical records, patient interview and family informants by raters blind to genotypic status. A score for quality of response ("A" score) is determined, and then corrected by subtracting points for quality of information ("B" score) yielding a combined score. Studies such as the Consortium on Lithium Genetics (ConLiGen), are employing the Alda Scale to assess lithium response in a collaborative sample of over a thousand subjects assembled for GWAS analysis. In order to assess the validity of the Alda scale, we have retrospectively assessed a group of 38 bipolar subjects who have also participated in a prospective trial of lithium response. In our prospective pharmacogenetic lithium trial, subjects are first stabilized on lithium while other drugs are discontinued over a 12 week period (stabilization phase). After a one month observation on lithium monotherapy, they are entered into the maintenance phase where they are followed for 2 years on monotherapy. Subjects are terminated from the study if they fail stabilization, relapse during maintenance, complete the maintenance phase or fail to tolerate lithium. Subjects who had been terminated from the prospective study were retrospectively assessed using the Alda scale. Raters had access to the clinical chart and physician's notes, but were blind to all prospective study research data including rating scales and reasons for termination. The prospective measure of number of weeks in the study at termination was highly correlated with either the Alda "A" score ($r=0.70$, $p<0.0001$) or the Alda combined score ($r=0.68$, $p<0.0001$). The mean Alda combined score was also significantly different between those who were successfully stabilized on lithium monotherapy and those who were not ($p<0.0001$). These results indicate strong validity of the Alda score in the retrospective assessment of lithium response.

SEROTONIN AND DOPAMINE TRANSPORTER GENOTYPES: IMPACT ON TREATMENT OUTCOME IN PTSD

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Background: PTSD is a disorder often associated with treatment resistance; however, genetic factors may influence individual outcomes. The present investigation examines the effects of combined functional serotonin and dopamine transporter gene polymorphisms (5-HTTLPR/rs25531 and DAT1) among patient samples receiving 12 weeks of paroxetine (N=71) or prolonged exposure (PE; N=36).

Methods: 5-HTTLPR/rs25531 and DAT1 polymorphisms were genotyped within two veteran samples. 21% of paroxetine patients received concurrent psychotherapy while 38% of PE patients received concurrent pharmacotherapy. Outcome measures for these samples were change in pre- to post-treatment CAPS and PCL scores, respectively.

Results: Among paroxetine patients, an effect of serotonin transporter gene polymorphism emerged controlling for concurrent psychotherapy ($p=.029$, $\eta 2P=.11$). L'/L' genotype carriers evidenced the greatest response (n=19; M=-41.6) followed by S'/L' (n=30; M=-27.5) and S'/S' (n=22; M=-15.6) carriers. L'/L' ($p=.013$; $d=1.24$) and S'/L' ($p=.031$; $d=.58$) polymorphisms demonstrated significantly larger CAPS reductions relative to S'/S' carriers. Dopamine transporter polymorphism was unrelated to outcome.

Similar effects were noted among PE patients controlling for concurrent pharmacotherapy ($p=.047$, $\eta 2P=.20$). L'/L' carriers demonstrated greatest reduction (n=7; M=-25.9) followed by S'/L' (n=16; M=-17.1) and S'/S' (n=13; M=-6.9) groups. L'/L' polymorphism demonstrated significantly larger PCL reductions relative to S'/L' ($p=.037$; $d=.85$) and S'/S' ($p=.014$; $d=1.92$) groups. Dopamine transporter polymorphism was unrelated to outcome.

Conclusion: Our data indicate a medium to large effect of serotonin transporter polymorphism on response to pharmacotherapy and psychotherapy. The presence of low transcriptionally efficient genotype (S'/S') of 5-HTTLPR/ rs25531 may constitute a risk factor for PTSD treatment resistance.

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THE ROLE OF PROOPIOMELANOCORTIN (POMC) AND COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT (CART) VARIANTS IN INCREASED RISK OF WEIGHT GAIN DURING ANTIPSYCHOTIC TREATMENT

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Introduction: Antipsychotic induced weight gain (AIWG) may induce the metabolic syndrome in schizophrenia (SCZ) patients. Two populations of neurons are co-localized in the arcuate nucleus of the hypothalamus, the cocaine amphetamine and regulated-transcript (CART) and polypeptide proopiomelanocortin (POMC), both of which have a regulatory role in weight regulation in animal models and in human populations. Thus, we investigated the potential role of CART and POMC single nucleotide polymorphisms (SNPs) with antipsychotic induced weight gain.

Methods: Five CART (rs10515115, rs3763153, rs3857384, rs11575893, rs16871471) and two POMC SNPs (rs6713532 and rs1047521) were genotyped in 200 schizophrenia patients who underwent treatment and were evaluated for AIWG for up to 14 weeks. We compared weight change (%) across genotypic groups using analysis of covariance for three SNPs ($r2 \geq 0.8$).Variants were genotyped using ABI TaqMan assays. In the case of a positive association, we ran in silico analyses for functional relevance of the SNP.

Results: No significant genotypic associations were found between the POMC rs1042571 and rs6713532 polymorphisms and weight gain ($p > 0.05$). The CART variants were significantly associated with antipsychotic induced weight gain (rs10515115, $p=0.005$, rs3763153, $p = 0.007$, rs3857384 = 0.003, rs11575893, $p= 0.003$, rs16871471, $p = 0.013$).

Conclusions: In this study, we observed that POMC gene variants were not significantly associated with antipsychotic induced weight gain. Five CART SNPs gene are associated with AIWG in chronic schizophrenia patients. In silico analyses showed that the CART rs11575893 & rs3763153 may regulate transcription factor binding sites. Our observations warrant further investigation and replication.

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IS THE GENETIC VARIANT OF MAOA OR COMT ASSOCIATED WITH ANTIDEPRESSANT RESPONSE IN OBSESSIVE-COMPULSIVE DISORDER?

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Background: Obsessive-compulsive disorder (OCD) is a chronic and debilitating disorder with a strong genetic component. The dopaminergic system has been implicated in the pathoetiology of OCD. Significant genetic associations between OCD and monoamine oxidase A (MAOA) and catecholamine-O-methyl-transferase (COMT) genes have been reported albeit with inconsistent results. Pharmacogenetics represents a valuable alternative approach, investigating inter-individual genetic variation and drug response, which may help clarify the role of these putative candidate genes in OCD.

Method: Ten and six polymorphisms in the COMT and MAOA genes respectively were genotyped in 106 individuals with OCD and retrospective response data collected on multiple SRI trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported “minimal”, “no change”, or “worsening” in response to SRI(s) tried. Genotypes and response data were examined by exploratory analyses on a drug-by-drug basis.

Results: For COMT, significant associations were observed between response to citalopram and rs1544325 ($\chi2=5.966$, $P=0.051$) in addition to response to paroxetine and rs740603 ($\chi2=6.287$, $P=0.043$) and rs4680 ($\chi2=6.311$, $P=0.043$). Furthermore, significant associations were detected between response to fluoxetine and MAOA rs1465107 ($\chi2=6.032$, $P=0.049$) as well as response to citalopram and MAOA rs1465108, MAOA rs979606, MAOA rs1465107, MAOA rs6323, and MAOA rs979605 ($\chi2=8.597$, $P=0.014$). Analyses for association with response to any drug trial were negative.

Conclusion: These results suggest COMT and/or MAOA genetic variants may play an important role in SRI response in OCD. However, replication in larger and independent samples is required.

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THE SCHIZOPHRENIA RISK GENE GAD1 (GAD67) PROMOTER VARIANTS AND FRONTO-LIMBIC SYSTEM DISCONNECTIVITY

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Aim of Investigation: Postmortem schizophrenia studies implicate hypofunction of GABAergic interneurons in prefrontal cortex and hippocampus. Single nucleotide polymorphisms in the 5' flanking region of the glutamic acid decarboxylase (GAD1) gene have been associated with schizophrenia, mRNA levels in prefrontal cortex (PFC), and dorsal PFC activation during working memory tasks. The purpose of this study was to examine GAD1 schizophrenia risk SNPs and their effects on fronto-limbic circuitry.

Methods: We genotyped two functional SNPs in the 5' flanking region of GAD1 in 69 Caucasian healthy individuals (aged 18-60) that had MRI and DTI scans. Effects of GAD1 genotype on hippocampal volume, temporal and frontal cortical thickness, and fronto-temporal white matter tract integrity were assessed. For DTI, 23 directions and 2 b=0 images were obtained with 3 averages. Segmentation and measurement of the left and right uncinate, arcuate, and cingulate fasciculi was performed. For MRI, automated measures of bilateral frontal and temporal cortical thickness and hippocampus volumes were made.

Results: Both GAD1 SNPs were associated with hippocampal volume (rs1978340: $F_{65,1}=7.658$, $p(\text{uncorrected})=0.007$; rs3749034: $F_{1,65}=5.513$, $p(\text{uncorrected})=0.022$). The rs1978340 SNP was associated with cortical thickness in the PFC ($F_{2,66}=4.26$, $p(\text{uncorrected})<0.001$). The rs3749034 SNP was also associated with fractional anisotropy in the left uncinate fasciculus ($F_{1,65}=5.249$, $p(\text{uncorrected})=0.025$).

Conclusions: Our results highlight the potential impact of GAD1 promoter variants on fronto-limbic circuitry. They suggest that schizophrenia risk variants in the GAD1 region may confer risk for disease via their effects on this core vulnerability brain network, and may be an important therapeutic target for working memory deficits in schizophrenia.

ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN DIFFERENT POPULATIONS: ASSOCIATION WITH SELF-REPORT AND PCA-DETERMINED ETHNICITY

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The aim of this study was to explore the role of ethnic origin in the treatment of schizophrenia. Treatment outcomes were studied in a post-hoc analysis of Caucasian and African-American adults treated with four different antipsychotics in two trials conducted in the US from three different clinical sites. There were significant differences in antipsychotics induced weight change in Caucasians and African-Americans. The African-American ethnicity was a risk factor for antipsychotics induced weight-gain ($p=0.004$). Drug exposure for the Caucasian and the African-American cohorts was not significantly different. Both cohorts showed similar symptom improvements. When we apply the PCA using 199 SNPs to determine the ethnicity we did find the same association with African Ancestry (identified by the first principal component) associated with weight gain ($p<0.05$) confirming the results of the self reported analysis. Although study findings were limited by the small cohort they suggest that while many outcomes were similar in both cohorts, clinicians could benefit from the awareness of factors (social or genetic) that possibly influence antipsychotic induced weight-gain in the African-American population.

RE-ANALYSIS OF CATIE GWAS DATA USING A RUN OF SIGNIFICIANT FINDINGS APPROACH, FOCUS ON TARDIVE DYSKINESIA

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Tardive dyskinesia (TD) is a serious, potentially irreversible motor side effect that arises in patients treated long-term with typical antipsychotic medication. A number of genome-wide association studies have been conducted in the recent past, but none gave genome-wide significant findings. Even the most significant markers did not replicate between the two GWAS on the same data from the CATIE trial.

We propose to search for runs of significant findings ($p<0.05$) in the CATIE sample using plink and R. We performed the analysis on baseline total Abnormal Involuntary Movement Scale (AIMS) and overall TD severity scores on 385 European and 210 African schizophrenia patients identified by MDS analysis separately.

Using a sliding window size of 10, and the criterion of a minimum of six SNPs with $p<0.05$ within each window, we identified 37 runs of significant markers that correspond to 18 chromosomal regions for AIMS in the African sample. We also identified 53 runs of significant markers that correspond to 15 chromosomal regions for AIMS in the European sample. Our preliminary findings suggest a role for the GABA transporter gene SLC6A11 (Inada et al, 2008) in AIMS in the African sample. Other runs of significant markers were found in genes that have been implicated in inherited ataxias (SCA27), genes that have suggested roles in the motoneuron development, and the regulation of neuronal excitation in the brain.

As might be anticipated, none of the runs of significant findings were replicated between the African and European sample. Lack of replication between these two samples could also suggest that the genetic susceptibility for TD may be different between these two populations.

CYP2D6 AND CYP2C19 GENOTYPING HELPS IMPROVE PSYCHIATRIC CARE: NOVEL UPDATES FROM THE PHARMACOGENETICS RESEARCH CLINIC AT CAMH

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Background: Antipsychotic and antidepressant medication continues to be the main treatment for many psychiatric conditions and most of them are metabolized by two polymorphic enzymes, CYP2D6 and CYP2C19. Functional polymorphisms in these enzymes can confer altered enzymatic activity, potentially leading to toxic or sub-therapeutic drug levels.

Methods: The first 50 patients (35 males, 15 females; age range 21-70 years old) with a diagnosis of schizophrenia and mood disorders were enrolled in our Pharmacogenetics Clinic. Most patients presented with complicated medication histories and were genotyped for CYP2D6 and CYP2C19. At study entry, patients participate in a structured diagnostic interview and are assessed of current and previous treatment response and occurrence of side effects. Physicians are then provided with an interpretation of the genotypic results and informed in detail about the potential clinical implications, which they will discuss with their patients. After 6 weeks the physician completes a questionnaire evaluating the usefulness of the genotypic information provided by the study. After 12 weeks, the clients are assessed to monitor potential adjustments of medications and their overall treatment outcome.

Results: Overall, questionnaires have been returned with mostly very good feedback that the genotyping results have been helpful in allowing them to either select medications their patients are likely better to tolerate, or to adjust doses based of genotype results and serum levels. Selected case reports will be presented and discussed in detail.

Discussion: Our findings suggest that CYP2D6 and CYP2C19 genotyping provides useful information that helps physicians to improve pharmacotherapy for individual patients.

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LEPTIN AND LEPTIN RECEPTOR GENES VARIANTS IN ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

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Background: Antipsychotic-induced weight gain (AIWG) is a serious side-effect of antipsychotic medication leading to metabolic syndrome and increased cardiovascular morbidity. The leptin system plays a major role in regulation of food intake and energy homeostasis, making the genes encoding leptin (LEP), and the leptin receptor (LEPR) interesting candidates for AIWG. Results from previous studies indicating an impact of genetic variation within these genes have been inconclusive. Therefore, this study sought to investigate polymorphisms in both genes for an association with AIWG.

Methods: A total of 181 schizophrenic and schizoaffective patients treated with various antipsychotics were genotyped for five polymorphisms in LEP and LEPR (LEP: rs7799039 (-2548G/A polymorphism), rs10954173, rs3828942; LEPR: rs1137101 (Q223R polymorphism), rs1327120) using TaqMan assays. In addition, leptin plasma levels were obtained for a small subset of patients. Statistical association with percent weight change from baseline weight was performed using ANCOVA with baseline weight as covariate.

Results: ANCOVA showed a non-significant trend for genotype association of the rs7799039 marker (p=.068). No significant association of the other LEP and LEPR SNPs with AIWG was detected. However, a significant association between a haplotype of LEP rs7799039G-rs10954173G-rs3828942G (p=.035) and AIWG was found. The G-allele of rs7799039 (p=.042) and rs3828942 (p=.032) were associated with increased weight gain.

Conclusion: Our study supports the hypothesis of an impact of LEP gene variation on AIWG. Limitations of our study include heterogeneous samples, short treatment duration and multiple comparisons. Further studies including more gene variants and gene interaction analyses of the leptin-melanocortin pathway are warranted.

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HIGH DOSAGE OF ANTIPSYCHOTICS IN SCHIZOPHRENIA TREATMENT: ANALYSIS OF CLINICAL AND GENETIC FACTORS

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This study investigated whether genes confer risk for suicidal behavior in schizophrenia, and whether patients who have attempted suicide are treated with higher doses of antipsychotic medication (AP). We recruited 246 patients from CAMH diagnosed with schizophrenia. This preliminary analysis included 37 patients. For the gene association analysis, we genotyped 384 markers across 45 candidate genes, and assessed risk for suicide. For the investigation of suicide attempt and AP dose, we calculated the percentage of the maximum AP dose that each subject was taking, and compared this between suicide attempters and non-attempters using an analysis of covariance (ANCOVA) with duration of illness as a significant covariate. The maximum dose was determined by the Compendium of Pharmaceuticals and Specialties (CPS).

Suicide attempters had a mean percent maximum dose (max = 1) of 0.76, SD=+/- 0.44, and non attempters had a mean of 0.40, SD= +/-0.177.

The results of the genotype association analysis were not significant after Bonferroni correction for all candidate genes (all p-values=N.S). However, the ANCOVA AP dose analysis including duration of illness was significant and patients who had a history of a suicide attempt (s) were receiving higher AP doses, $F(1,34)=7.043$, $p=.016$.

This preliminary analysis shows that subjects who have attempted suicide are receiving higher doses of AP medication, but that there is no evidence that these candidate genes influence risk for suicide attempts. Future investigations will include a larger sample size and will asses whether certain genes are associated with high AP dose in suicide attempters and non-attempters.

PATHWAYS INTO DEAD END MENTAL HEALTH CARE: CAN PHARMACOGENETIC KNOWLEDGE RESOLVE THIS PROBLEM?

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Many, if not most psychotherapeutic drugs marketed today interact with the CYP450 system of Phase I metabolism as substrates, inducers or inhibitors. Approaches using testing for variant alleles in relevant CYP450 genes, in addition to using decision support software to help predict CYP450 drug-drug interactions, are becoming increasingly well recognized as rational preventive measures that may help to prevent adverse drug reactions in the clinic.

Introduction: In an ongoing naturalistic study of subjects referred to a medico-legal psychiatric practice in Sydney, Australia, a series of >140 persons who had experienced either adverse events, or lack of efficacy, with antidepressant and/or antipsychotic agents were tested for variant alleles in the CYP450s: 2D6, 2C9 and 2C19. We previously published a detailed description of those individuals in this population who had experienced serious adverse drug reactions (akathisia, suicidality, violence and hallucinosis) to antidepressants and had committed or attempted homicide.

Results: Here we present a detailed study of 12 individual cases where their recreational substance use resulted in conditions that attracted initial treatment with antipsychotic medication. Recreational substances in these cases with known or possible involvement of CYP450 in metabolism included cannabis, amphetamines, and MDMA ("ecstasy"), heroin and cocaine. These subjects became re-diagnosed with "major depression," "bipolar disorder" or "intractable schizophrenia" with attendant difficulties resulting from the ensuing labeling or stigma in addition to difficulties associated with adverse drug reactions to antipsychotics.

All had diminished mutations in CYP450 enzymes – with 2D6 and 2C9 most frequently represented. There was one Asian/African subject and had CYP2D6 *1/*2 and CYP2C19 *1/*17 genotypes. We also provide individual allele and genotype frequencies for the three genes (2D6, 2C9 and 2C19) tested for the entire group of referred subjects.

Conclusion: The trebling (since 1990) of the number of persons under mental health care in NSW, would appear to perhaps be largely due in part to adverse reactions to antidepressants prescribed for trivial purposes like work stress, the next most common form of entry comes from the use of new drugs for the psychosis caused by recreational substances, which when combined with genetic polymorphisms can predicate further adverse drug reactions to psychiatric drugs.

An adverse or psychotic response to street drugs should alert treaters to possible CYP450 polymorphisms, which, if present, can also complicate treatment with psychiatric medications. Retrospective studies of adverse drug reactions can help develop tools to alert treaters prospectively. To differentiate 'functional' mental illness from neurotoxic delirium, the latter of which is more akin to a bad dream, one needs to attend carefully to the exclusion criterion set out in DSM-IV "not caused by substance or medication" that follows the rest of the criteria for mental illness.

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ANTIDEPRESSANT-INDUCED AKATHISIA-RELATED HOMICIDES ASSOCIATED WITH DIMINISHING MUTATIONS IN METABOLIZING GENES OF THE CYP450 FAMILY

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Background Project: When testing for three cytochrome enzymes became available in Australia it was offered to persons who had serious adverse drug reactions (ADRs) to antidepressants and other drugs metabolised by the Cytochrome P450 system. Among 120 tested were 10 who had committed homicide and more who had made serious attempts. This paper describes the unmotivated homicides and serious attempts to kill.

Null Hypothesis: People who become violently akathisic, suicidal or homicidal on single doses of antidepressants do not metabolize drugs normally and do not have 'wild type' Extensive Metabolizer (EM) genes.

Alternate hypothesis: Similar outcomes may be achieved by overmedication and co prescribing of drugs that compete for or inhibit CYP450 metabolism or by [prescribing drugs synergistic for neurotoxicity,

Method: 120 persons were tested for CYP450 activity because they had developed akathisia, suicidal and/or homicidal thoughts, impulses and actions and sleepwalking behaviours in a study whose initial goal was to correlate these serious adverse reactions, with metabolizing genes of the CYP450 family. (14 more first degree relatives were tested, 3 for having no analgesic response from prodrugs, 1 for aggression on hypericum and one who sleepwalked to her death on zolpidem/zopiclone.) All were coded into a Filemaker database constructed for this purpose. The reported persons gave written permission to publish. Patients signed informed consent to testing and inclusion in the series. No ethics approval was required to document observations and test results, so none was sought.

Results: The null hypothesis, one capable of falsification, was not falsified in our study. Decreased CYP450 metabolism appeared to be causally linked to the most severe and violent side effects of antidepressants. However we know of one young person who committed homicide with normal genetics: Clancy who had overdosed on citalopram and committed an akathisia homicide and suicide 9 days later and was found to have toxic level in his blood. The perpetrator in the famous Tobin vs. GSK committed multiple homicide and suicide after taking 40 mg paroxetine and 20 mg zolpidem, which are two drugs which can cause neurotoxicity. Therapeutic levels of both drugs were found in post mortem blood, so synergy was operation. The problem appears to be drug toxicity and/or synergy.

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ASSOCIATION STUDY OF GENETIC VARIATION IN TBC1D1 WITH ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

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Background: Antipsychotic-induced weight gain (AIWG) is a serious side-effect of antipsychotics. Previous studies have been shown that antipsychotics with a high propensity to induce AIWG influence glucose transporter type 4 (GLUT4) mediated glucose intake. Variation in the gene encoding TBC1 domain family member 1 (TBC1D1), a Rab-GTPase activating protein regulating GLUT4 trafficking, has been associated with obesity in the general population. Therefore, we investigated the impact of TBC1D1 polymorphisms on AIWG.

Methods: We analyzed two polymorphisms in the TBC1D1 gene (rs9852, rs35859249) in schizophrenia subjects (N=195), treated mostly with clozapine or olanzapine (N=118) for up to 14 weeks. Association was tested using analysis of covariance with change (%) from baseline weight as the dependent variable and baseline weight as covariate.

Results: Carriers of the minor allele of rs9852 gained significantly less weight than carriers of only the wild-type allele (CT/TT vs. CC carriers: 2.57% vs. 5.32%, p=.029). This effect was more pronounced in the subgroup of patients treated with clozapine or olanzapine (p=.018) and in women (N=67; p=.030), while in men only no significant effect was observed (p=.228). For rs35859249, no significant association with AIWG could be found.

Conclusions: The association of rs9852, located in the 3'UTR of the gene near a miRNA binding site, indicates an influence of TBC1D1 variation on AIWG. Rs35859249, associated with obesity in previous studies, showed no significant results; however, the minor allele frequency was low. Since this is the first report on TBC1D1 and AIWG, further investigation of the gene remain necessary.

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