ASSOCIATION STUDY OF 17 CANDIDATE GENES WITH OBESITY PHENOTYPES IN SCHIZOPHRENIA PATIENTS TAKING ANTIPSYCHOTICS AND CONTROLS

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We have updated our previous review (Chagnon Curr Drugs Target 2006) of genes showing association with weight gain in schizophrenic (SZ) patients receiving antipsychotics (APS). The number of genes showing some association raised from 6 to 19 where 7 genes showed more then one positive result. Fifteen other genes including several APS receptors and obesity-related genes were negative. We evaluated the association with the body mass index (BMI; kg/m^2) and the waist circumference (cm) of the 17 positive genes having single nucleotide polymorphisms (SNP) genotyped (Illumina HumanBeadchip 300K) in our sample of 247 unrelated SZ taking APS (mainly olanzapine, clozapine, risperidone, quetiapine) and 137 unrelated controls. Covariance analysis of BMI and waist among genotypes was made with age and sex as covariates, and after stratifying for the 4 main APS used. Eight of the 17 positive genes showed significant evidences of association in our sample after adjusting the p values for multiple testing within genes, whereas 6 genes showed suggestive results (nominal p value < 0.05). Associations were observed or not with the same APS previously reported, while either BMI or waist circumference or both detected specific gene x APS effects. Four of our positive association results represent a first confirmation of the association of these genes with an APS effect on weight. Finally, some genes showed also an association or a trend for an association with BMI and/or waist circumference in controls, which indicated that these genes share a common pathway in both kind of obesity, common and APS-induced.

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ANTIPSYCHOTIC INDUCED WEIGHT GAIN: UPDATE AND INVESTIGATION OF THE CB-1 AND DRD3 GENES

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Weight gain has emerged as serious problem with the use of many antipsychotics in particular with clozapine and olanzapine. We will present an update of the genetics of antipsychotics induced weight gain presenting new findings in the DRD3 gene and the Cannabinoid-1 (CB-1) receptor gene. Both genes are thought to be directly targeted by antipsychotics and to be involved in appetite and satiety regulation.

We analyzed three different samples from the US (A, B and C; total n = 139) and one sample from Germany (D; n = 70). Sample A and B (n = 80) was treated exclusively with clozapine and weight gain was assessed after 6 weeks. Sample C (n = 59) was treated with four antipsychotics (clozapine, olanzapine, haloperidol and risperidone) and weight gain was assessed on average for 11 weeks. Sample D was assessed for 6 weeks using a variety of antipsychotics including clozapine and olanzapine.

Regarding the CB-1 gene, SNP rs806378 was significantly associated with weight gain in the sample of Europeans (n = 123), where carriers of the C/T and T/T genotypes gained more weight ($p = .049$, corrected for baseline weight). Patients on clozapine or olanzapine revealed a more significant association ($F[2,72] = 4.48$, $p = .01$. The most significant finding was obtained when examining only patients treated with clozapine $F[2,61] = 7.49$, $p = .001$.

Regarding the DRD gene, carriers of the ser allele (either gly/ser or ser/ser) proved to have a higher risk for clozapine induced weight gain ($F[1, 59] = 6.74$, $p = .01$).
Altogether, our findings support the notion that CB-1 and DRD3 gene variants are associated with weight gain induced by antipsychotic treatment.

A GENOME-WIDE ASSOCIATION STUDY OF INTOLERANCE TO CITALOPRAM IN THE STAR*D SAMPLE

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Background: Intolerance to an antidepressant medication is a common reason patients will stop their prescribed pharmaceutical treatment. In particular, there are several side-effects commonly reported from patients on the SSRI, citalopram, namely gastrointestinal and sexual side-effects. We report on several phenotypes addressing intolerance to citalopram, and their strongest genetic variant associations from a whole genome association study.

Methods: 1,953 individuals from the Sequenced Treatment Alternatives for Depression (STAR*D) study were treated with citalopram and genotyped using Affymetrix 5.0 and 500K human mapping arrays. Multi-dimensional scaling was used to correct for population stratification in our sample of Non-Hispanic Caucasians, Hispanic Caucasians, and African Americans. Analyses were also controlled for gender and other clinical/demographic variables. We tested correlation using logistic regression between all genetic variants passing quality control measures and the phenotypes of: STAR*D definition of tolerance; the frequency, intensity and burden of side-effects; and SSRI specific side-effects involved in sexual, gastrointestinal, nervous system, and sleep systems.

Results: We found six SNPs with $p < 2.0 \times 10^{-6}$ for sexual side-effects, when males and females are analyzed separately. For other SSRI specific side-effects and general intolerance phenotypes, we found SNP associations on the order of $p < 1 \times 10^{-6}$.

Conclusions: Technical validation of these findings are underway, however, replication in an independent sample is still desired. These results make progress towards the ultimate goal of predicting, based on one's genetic constitution, if a patient will be able to tolerate citalopram without specific adverse side-effects. The pathways implicated in these results are novel for citalopram intolerance and for the specific phenotypes tested.

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ASSOCIATION OF CCL2 POLYMORPHISM WITH RISK OF DEPRESSION DURING INTERFERON-ALPHA TREATMENT

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Treatment of hepatitis-C patients with pegylated interferon (IFN)-alpha commonly induces depressive symptoms. In some patients these symptoms become severe enough to necessitate IFN-alpha dosage reduction or discontinuation. Identification of predictors of IFN-alpha-induced depression therefore merits investigation. We hypothesized that genetic factors might modulate IFN-alpha-induced depressive symptoms. Accordingly, associations between the development of moderate to severe depressive symptoms and clinical and genetic factors were examined in 808 Caucasian subjects participating in a clinical trial investigating IFN-alpha treatment parameters (the Schering Plough IDEAL trial). Depression severity was measured by the Center for Epidemiologic Studies Depression Scale (CES-D) before, during and after IFN-alpha therapy. The strongest predictor of moderate to severe depressive symptoms during the first 24 weeks of IFN-alpha treatment was a history of mood disorder ($p<0.0001$). After accounting for a history of mood disorder and baseline CES-D score, a significant interaction was found between a history of mood disorder and SNPs in *Chemokine, CC Motif Ligand 2* (*CCL2*) predicting the development of moderate to severe depressive symptoms [rs1024611 (-2510A/G), $p=0.0335$; rs4586 (Cys35Cys), $p=0.0034$; and rs2530797, $p=0.0005$]. Additionally, subjects with a history of mood disorder carrying relevant *CCL2* risk alleles had a dose-dependent increase in the maximum change in CES-D scores from baseline to 24 weeks ($p=0.044$-0.001). These data are consistent with recent findings that CCL2 concentrations are increased in cerebrospinal fluid of subjects undergoing treatment with pegylated IFN-alpha. Thus, polymorphisms in the *CCL2* may contribute to an IFN-alpha-induced inflammatory response in the brain, which in turn is associated with depression.

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A ROLE FOR THE SEROTONIN RECEPTOR GENE 5HTR2A IN PREDICTING SRI RESPONSE IN OBSESSIVE-COMPULSIVE DISORDER (OCD)

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Background: Recently the serotonin 2A (5HTR2A) receptor gene has been shown to predict citalopram response in depression (McMahon et al, 2006), but the utility of this gene as a predictor of OCD response is relatively unknown. We have previously reported association between 5HTR2A and response to specific selective serotonin reuptake inhibitors (SSRI); we therefore decided to investigate this gene in greater depth.

Method: Retrospective response data on multiple SRI trials was collected in 107 individuals meeting DSM-IV criteria for OCD. Individuals were genotyped for 16 polymorphisms in 5HTR2A. Individuals were grouped into those who improved following an adequate trial of one or more medications as compared with those who reported "minimal", "no change" or "worsening" in response to medications tried. This was followed by exploratory analyses on a drug-by-drug basis. In total, N=88 individuals had complete data for adequate trials of one or more medication.

Results: The 5HTR2A marker reported by McMahon et al., rs7997012, was associated with response to any SSRI (allelic p=0.02) and response to any SRI (all SSRIs and the tricyclic antidepressant clomipramine)(allelic p=0.03). The same marker was specifically associated with response to fluoxetine (allelic p=0.003, genotype p=0.007) and sertraline (allelic p=0.04). The SNP rs1328684 showed a trend toward association with response to any SRI (genotype p=0.07) and clomipramine specifically (genotype p=0.04).

Conclusion: Although results are not consistent across SRI drugs, these data support the utility of the pharmacogenetics approach, and previous work suggesting a role for 5HTR2A and antiobsessional response.

THE ROLE OF THE SEROTONIN-SYSTEM REGULATORY TRANSCRIPTION FACTOR FEV IN CITALOPRAM RESPONSE

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Background: The murine gene Pet-1 is expressed exclusively in serotoninergic neurons and ablating Pet-1 expression results in a ~70% decrease in the number of central serotoninergic neurons. We examined the role of the human homologue of this gene, FEV, in citalopram response by examining FEV genotypes in the STAR*D sample. We also investigated the role of Pet-1 in behavioral responses to antidepressants and in activating the expression of genes required for serotonin synthesis and reuptake.

Methods: Genotypes for SNPs at the FEV locus were obtained for 1,914 subjects in the STAR*D study and then tested for association to treatment response of citalopram, after controlling for population stratification. Adult Pet-1 knockout and wild type control littermates were injected intra-peritoneally with 10 mg/kg citalopram and then assessed for drug response in the tail suspension test. Quantitative PCR studies were conducted to measure expression of serotonin-pathway genes.

Results: SNP analyses showed association between five of the FEV variants and antidepressant response phenotypes (all $p \leq 0.005$). Mice deficient for Pet-1 showed impaired behavioral responses to citalopram, as well as an >85% reduction in expression of *tph2* and *slc6a4*.

Conclusions: Our association analysis between response to citalopram and FEV SNPs suggests that SSRI response in major depression is affected by DNA variation at this locus. Our murine studies suggest that Pet-1 is necessary for the antidepressant effects of citalopram, at least in part because Pet-1 regulates genes necessary for the synthesis and reuptake of serotonin.

PHARMACOGENETICS OF ANTIDEPRESSANT RESPONSE: CLOSE TO CLINICAL USE?

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Up to 60% of depressed patients do not respond completely to antidepressants and up to 30% do not respond at all. Among the many reasons leading to non response, such as inadequate treatments and comorbid conditions, genetic liability plays an important role. Genetic factors contribute in fact for about 50% of the antidepressant response. This means that the knowledge of the patient genetic profile may predict antidepressant response thus leading to alternative treatments since the beginning. Can we use this information in our everyday practice? This presentation will try to answer to this question.

In fact, a genetic profile will be a routine test in everyday clinical practice only when all genes influencing response will be discovered and validated. Studies are still underway and we have preliminary but sound results. During the recent years the possible influence of a set of candidate genes as genetic predictors of antidepressant response efficacy were investigated and will be reviewed here. A growing number of gene variants were independently associated with short term SSRIs antidepressant efficacy. They include the functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), the A218C gene variant on the tryptophan hydroxylase gene (TPH), the C(-1019)G variant in the 5HT1A receptor, some variants in the 5HT2A receptor, the G-protein beta3-subunit (Gbeta3) C825T gene variant, Catechol-O-methyltransferase (COMT) gene variant, Angiotensin I and II converting enzyme I/D (ACE I/D), the Norepinephrine Transporter (NET), Dystrobrevin-binding-protein 1 (DTNBP1), the glucocorticoid receptor-regulating cochaperone (FKBP5) and the Circadian Locomotor Output Cycles Kaput (CLOCK). The effects of 5-HTTLPR were further investigated with a new variant. The "long" alleles (16-A, 16-D and 16-F) and the "short" alleles (14-A, 14-B) have different consensus sequences for some transcriptional factors binding and resulted in different SSRI response. Further, a symptomatology dissection evidenced a specific effect on anxiety and core depressive symptoms of 5-HTTLPR. Similarly, CLOCK and PER3 variants evidenced specific effects on symptomatology (CLOCK on insomnia, PER3 on various personality aspects). Marginal associations were reported for ADRB1, BDNF, APOE, MAOA, 5HT3A, 5HT6, DAT, CRHR1, TPH2, PDE and IL-1beta. DRD2, DRD4, SERT-STin2, 5HT1B, MDR1P, NOS gene variants were not associated with outcome. For 5 SNPs we could retrieve sufficient studies and performed meta-analysis about association of ADs treatment response or side effects 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, gene variants influence human behavior, liability to disorders and treatment response, many of them are supposed to do so in a subtle, interconnected and environment modulated way. The final stage of an individualized profile of susceptibilities to be used in clinical practice is getting closer.

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GENDEP CLINICAL TRIAL ANALYSIS UPDATE

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Background: GENDEP is a European multicentre integrated pharmacogenomic study aiming to identify genomic correlates of antidepressant response including adverse drug reactions (ADRs) (http://gendep.iop.kcl.ac.uk/results.php - references cited are listed on this url).

Methods: White European subjects with major depression were treated with escitalopram or nortriptyline, in a part-randomised potential crossover design, and prospectively rated for clinical response and ADRs using measures including the MADRS, HDRS, BDI, UKU, and ASEC (the latter is a self-report measure developed for GENDEP). Haplotype-tagging SNPs, microsatellites and functional repeat polymorphisms were genotyped in 13 candidate genes.

Results: Factor analysis and Item Response Theory applied to the three measures of depression employed in the study generated three symptom dimensions (Uher et al, 2008). Mixed effect linear regression showed no difference between escitalopram and nortriptyline on the three original scales, but symptom dimensions revealed drug-specific advantages (Uher et al, in press, a): observed mood and cognitive symptoms improved more with escitalopram than with nortriptyline; neurovegetative symptoms improved more with nortriptyline than with escitalopram. The *5-HTTLPR* moderated the response to escitalopram with long allele carriers improving more than short allele homozygotes. A significant three-way interaction between the *5-HTTLPR*, drug and gender isolated the effect to the male subgroup (Huezo-Diaz and Uher et al, in press). On analysis of the serum level data, *CYP2C19* genotypic category significantly predicted steady-state (week 8) escitalopram concentration (P=0.0006; Perroud et al, under review). Analysis of weight as a predictor revealed that higher BMI and obesity predicted poor response to nortriptyline but did not significantly influence response to escitalopram. The moderation of response by body weight was due to differential improvement in neurovegetative symptoms, including sleep and appetite (Uher et al, in press b). On analysis

of the ADR measures, there was good agreement between the UKU and the ASEC. Diarrhoea and decreased appetite predicted discontinuation of escitalopram (Uher et al, under review).

Conclusion: Comprehensive prospective data collection and novel analytical approaches is yielding findings of research interest and clinical relevance.

Funding: GENDEP was funded by a European Commission Framework 6 grant, EC Contract LSHB-CT-2003-503428. Lundbeck provided both nortriptyline and escitalopram free of charge for the GENDEP study. Roche Molecular Systems provided the AmpliChip CYP450 Test® and associated support. GlaxoSmithKline contributed by funding an add-on project in the London centre, and latterly the London centre also received additional funding from the Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and South London and Maudsley NHS Foundation Trust (funded by the National Institute for Health Research, Department of Health, UK).

TRANSLATIONAL GENETICS APPROACH TO AMPHETAMINE SENSITIVITY

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This talk will describe studies that have used both mice and humans to elucidate genes that influence sensitivity to the subjectively euphoric effects of amphetamine. We used mice as an initial screening tool to identify specific candidate genes. These candidate genes were then examined in human subjects to determine whether they influenced the subjectively euphoric effects of amphetamine. Finally, mice were used to investigate the mechanism by which these genes influence drug sensitivity. This approach takes advantage of the strengths of model organism genetics as well as human genetics and has yielded specific and testable hypotheses. In both cases the genes identified through this process have subsequently been implicated in drug abuse by independent groups, demonstrating the utility of this approach for understanding disease processes.

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THE ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) GENE VARIANTS IN ANTIPSYCHOTIC RESPONSE

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Background: Brain-derived neurotrophic factor (BDNF) has extensive effects on the nervous system including cell survival, differentiation, neuronal growth and maintenance, as well as cell death. Moreover, it promotes synaptic plasticity and interacts with dopaminergic and serotonergic neurons, suggesting an important role on the alteration of brain function with antipsychotic medications in schizophrenia patients. The differential effects of BDNF gene variants could lead to changes in brain circuitry that would in turn cause variable response to antipsychotic. Therefore, we hypothesized that genetic variation in this candidate gene may predict antipsychotic response.

Method: We examined the functional Val-66-Met polymorphism and (GT)n microsatellite in addition to 13 other single nucleotide polymorphisms across the BDNF gene. Prospective BPRS change scores after 6 weeks, 3 months and 6 months were obtained from 115 patients with schizophrenia who completed a structured antipsychotic trial.

Results: Genotypes Met-Met and Val-Met in addition to the Met allele from Val-66-Met were associated with non-response to antipsychotic treatment (genotype: χ^2=6.187, P=0.045; allele: χ^2=5.378, P=0.028). Moreover, genotype distributions and allelic frequencies of rs11030104 (genotype: χ^2=8.246, P=0.016; allele: χ^2=5.534, P=0.024), rs2049045 (genotype: χ^2=4.845, P=0.089; allele: χ^2=3.683, P=0.071), rs7103411 (genotype: χ^2=5.514, P=0.063; allele: χ^2=4.463, P=0.039), and rs7934165 (genotype: χ^2=6.437, P=0.040; allele: χ^2=5.618, P=0.025) were nominally significant in antipsychotic response.

Conclusion: BDNF genetic variant might play an important role in predicting antipsychotic response. However, replication in larger and independent samples is required. We are currently examining additional relevant phenotypes such as BPRS subscales.

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GRIA1, GRIA4, GRIA3 AND GRIK4 GENETIC VARIATIONS INFLUENCE HALOPERIDOL EFFICACY AND SIDE EFFECTS IN A SAMPLE OF SCHIZOPHRENIC PATIENTS

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Glutamate system abnormalities provide an intriguing explanation for the pathophysiology of schizophrenia. Consistently, they may play a role as modulators of antipsychotic response. We investigated a set of 50 SNPs in 11 genes coding for subunits of glutamatergic receptors as possible modulators of antipsychotic efficacy and motor side effect profile in a sample of 101 schizophrenic patients treated with haloperidol. Patients were assessed with PANSS and ESRS at baseline and at day 3, 7, 14, 21 and 28. MANCOVA analysis for repeated measures FPR corrected and Post Hoc analyses were applied. Two variations (rs472792 and rs1461231 (GRIA1)) were found to be associated with response. Those findings provide further support to the glutamatergic theory of schizophrenia identifying putative modulators of the antipsychotic effect.

DOPAMINE D2 RECEPTOR GENETIC VARIATION AND CLINICAL RESPONSE TO ANTIPSYCHOTIC DRUG TREATMENT: A META-ANALYSIS

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Background: Although multiple lines of evidence suggest that antipsychotic drug efficacy is mediated by dopamine D2 receptor (*DRD2*) blockade there remains limited data on the relationship between *DRD2* genetic variation and antipsychotic drug response. We have previously reported relationships between the -141C Ins/Del polymorphism and clinical response in both chronic (Malhotra et al. 1999) and first episode (Lencz et al. 2006) patient groups, but these studies are limited by small sample sizes and the use of different response parameters. To more comprehensively address the role of the strongest candidate gene for antipsychotic drug response, we have conducted the first meta-analysis of the relationship between *DRD2* variation ands antipsychotic drug response, incorporating data from multiple studies comprising over 700 patients.

Method: Medline search (12/31/2008) yielded 18 prospective studies examining *DRD2* variation and antipsychotic response in schizophrenia patients, and 10 independent studies met criteria for inclusion. Clinical response to antipsychotic treatment was defined as a 50% reduction of either BPRS or PANSS total score at approximately 8 weeks follow-up. Odds ratio (OR) was the primary effect size measure and was computed for each polymorphism in each study. Sufficient data were available for two *DRD2* polymorphisms, *-141C Ins/Del* and *Taq1A*.

Results: Six studies reported results on the *-141C Ins/Del* polymorphism (n=698). The *Del* allele was significantly associated with poorer antipsychotic drug response, compared to the *Ins/Ins* genotype, OR=.65, p=.03. Post hoc analysis of first-episode patients showed a stronger relationship (OR=.53, p=.05) in studies comprised of first-episode patients. Eight studies assessed the *Taq1A* polymorphism and antipsychotic response (n=748). There was no significant difference in response rate in *A1* carrier vs. *A2/A2* genotype or *A2* carrier vs. *A1/A1* genotype. No significant publication bias was detected.

Conclusions: *DRD2* genetic variation at the -141C Ins/Del polymorphism is modestly associated with clinical response to antipsychotic treatment. Studies of first episode schizophrenia may be particularly sensitive to genetic effects by avoiding confounds related to variation in prior medication exposure.

SEARCH FOR FUNCTIONAL POLYMORPHISMS IN PHARMACOGENETIC CANDIDATE GENES: APPLICATION IN PSYCHIATRY.

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Numerous candidate genes have been implicated in modulating the response to drug therapy of CNS disorders, such as schizophrenia and depression. However, despite intense investigations, the genetic factors underlying these complex disorders and drug response or toxicity remain only partially understood. As a result, no single pharmacogenomic biomarker test has been classified as required for clinical practice in conjunction with a specific drug therapy – see FDA list of validated tests, each labeled "for information only", "recommended", or "required" (http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm) (testing of *HLA-B*1502* to assess risk of carbamazepine toxicity is the only CNS drug test laveled "recommended"). Either, genetic factors play only a minor role, or multiple factors cooperate making it difficult to develop clinically useful marker panels, or genetic variants of sufficient penetrance have yet to be discovered. We and others have proposed that regulatory polymorphisms that affect transcription, mRNA processing, and translation may be more abundant than those directly altering protein sequence and function, but most have yet to be discovered. We have developed a panel of methods to discover regulatory polymorphisms that are based on the notion that in heterozygous carriers for any regulatory polymorphism, expression from each allele differs from the other in the relevant target tissue. Thereby, allelic expression imbalance (AEI) provides a quantitative measure of regulatory polymorphisms, enabling characterization of regulatory variants that can occur anywhere in the gene locus. With this approach, we have successfully discovered a number of regulatory polymorphisms in key candidate genes, such as *DRD2*, *TPH2*, and *CYP3A4*. Importantly, the newly discovered variants have detectable impact on clinical phenotypes relevant to CNS disorders. An ongoing large-scale discovery project will reveal how prevalent regulatory polymorphisms are and how we will be able to integrate these with therapy of CNS disorders.

RARE STRUCTURAL VARIANTS IN SCHIZOPHRENIA

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In contrast to the few genes identified by genetic association, evidence is mounting rapidly that multiple rare structural variants of the human genome, confer a high risk for psychiatric disease.

We and others have shown that the genomewide burden of rare copy number variants (CNVs): duplicated or deleted regions of the human genome, is significantly increased (1.15-3 fold) in schizophrenia. Many CNVs identified in schizophrenia cases are singleton events and disrupt genes in neurobiological pathways suggesting that they are highly penetrant risk factors for the disease. In particular, rare recurrent CNVs at 1q21, 15q13 and 15q11 significantly increase the risk of schizophrenia (OR 2-11). Adding to these specific loci, we associated rare 16p11.2 microduplications in schizophrenia 1921 cases and 4062 controls ($P = 5.3x10^{-5}$, OR = 12.8). Microduplications also associated significantly in a replication sample of 2645 cases and 2420 controls (P = 0.022, OR = 8.3). We also examined the spectrum of psychiatric diseases in a meta-analysis of 16p11.2 data and found that 16p11.2 microduplications significantly increased the risk of autism and weakly associated with bipolar disorder. In contrast, microdeletions of 16p11.2 specifically associated with autism. Furthermore, analysis of quantitative clinical data showed that head circumference was significantly larger in microdeletion carriers and moderately smaller in microduplication carriers (P=0.0001).

Our findings add 16p11.2 to the growing list of hotspots that significantly increase the risk of schizophrenia and other psychiatric disorders. The spectrum of diseases associated with 16p11.2 is consistent with the association of multiple phenotypes at other schizophrenia risk loci and suggest that common neurobiological pathways may underlie shared phenotypes between the disorders. Finally the association of 16p11.2 rearrangements with head circumference mirrors association of head size with 1q21 deletions and duplications. These results point to a potential genetic basis for early brain overgrowth in autism and observations of smaller brain volume in schizophrenia.

RUNS OF HOMOZYGOSITY AND RARE VARIANTS

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Although schizophrenia (SCZ) is strongly heritable, clear identification of genetic risk factors has remained an elusive goal. Candidate gene studies have been marked by extremely modest effect sizes and failures to replicate, while genomewide association studies have not been as successful in psychiatric disorders as in other complex disease. Increasingly, the common disease/common variant model of complex genetics leaves considerable unexplained variance. At the same time, recent studies suggest that rare, highly penetrant variants may play an important role in SCZ etiology. In other complex disorders, it is widely observed that small Mendelian subtypes of illness exist even while a majority of observed cases derive from polygenic etiology.

We have recently provided evidence suggesting that highly penetrant recessive loci may underly a subset of SCZ cases. We developed a novel analytic approach to SNP microarray data, termed whole genome homozygosity association (WGHA), which first identifies patterned clusters of SNPs demonstrating extended homozygosity and then employs both genomewide and regionally-specific statistical tests for association to disease. In genomewide analysis, SCZ patients had significantly more runs of homozygosity (ROHs) than controls (mean 32 ± 4 vs 28 ± 4). Moreover, frequency of nine specific ROHs significantly differed between patients and controls at a nominal $p<.01$; importantly, each of these demonstrated greater frequency in cases. Four of the 9 risk ROHs contain or immediately neighbor genes that have been previously linked to schizophrenia, and three risk ROHs fall within regions that are amongst the top hits in linkage meta-analysis. These converging studies suggest that particular family ascertainment strategies may be optimal for identification of homogeneous, recessively transmitted molecular subtypes of SCZ. Implications for pharmacogenetics will be discussed.

TRANSCRIPTIONAL PROFILING IN DEPRESSION AND ANXIETY

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It is recognized that the diagnostic criteria for major depressive disorders encompass pathophysiologically heterogeneous groups of patients. Attempts to include biologically-based diagnostic criteria are discussed for the new diagnostic manual (DSM-V). However, clinically valid phenotypes which allow clinicians to distinguish biological subgroups and subsequently to tailor treatment strategies are not available yet. In recent years, data are emerging suggesting that molecular markers, including genomic (transcription) and genetic (polymorphisms) markers, when combined with good phenotyping, can help identify biologically distinct subtypes of major depression. However, a systematic approach and a replication of findings are often not pursued, thereby limiting the use of most molecular markers published so far.

On one hand, the identification of molecular markers of depression can advance our understanding of distinct biological pathways leading to depressive disorders. On the other hand, such clinical markers can be utilized to develop animal models that reproduce certain biologically robust findings in depression and thereby help to profile novel treatment targets for specific subtypes of depression.

Our Translational Research efforts in depression and anxiety research concentrate on the understanding of the human disease, the translation into preclinical models and the discovery of markers predictive for the treatment response to existing and new antidepressants. With regard to molecular markers, we focus on transcription profiles in blood samples, as these are easy to obtain, particularly in humans.

Using sophisticated methods such as dynamic modeling, we have identified groups of patients who share a similar transcription profile. Based on these findings, we can select preclinical models and examine drug effects.

Furthermore, transcription profiles in patients can guide identification of new candidate genes, by identifying first biologically more homogenous patient groups and then investigating genetic polymorphisms associated with a particular patient segment. Advantages and disadvantages of this approach will be presented.

LITHIUM MEDIATED EXPRESSION CHANGES IN LYMPHOBLASTOID CELL LINES

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Lithium (Li) is an effective maintenance therapy of bipolar disorder (BPD). There are several hypotheses on the mechanism of lithium's action, many derived from studies that have utilized post-mortem brain tissue from bipolar individuals. The changes of gene expression in postmortem tissue exposed to Li are confounded by agonal and other factors such as postmortem interval, tissue pH, medication status, age, and sex. Lymphoblastoid cell lines (LCL) derived from subjects with the illness of interest represent an accessible proxy cellular system to study gene expression patterns. We studied gene expression in 12 LCLs cultured with and without presence of 1 mM LiCl in the culture for 4, 8, and 16 day using he Illumina RefSeq8_v2 BeadChip microarrays. We identified 218 transcripts that showed significant changes over the time course of Li treatment at false discovery rate (FDR) < 5%. Of the 218 significant transcripts, only C8orf33 showed a consistently positive slope change in expression pattern, and the rest showed negative slope changes in expression. C8orf33 is a novel gene mapped to the region of 8q24 linked to BPD. Molecular interaction analysis using the Michigan Molecular Interaction data base (MiMI) search algorithms identified that C8orf33 directly interacted with three other genes (GIT1, GPRASP1, and HAP1), and through indirect interactions forms a network of total 144 nodes (genes) and 345 edges. Among the 144 nodes, 21% of them were reported to be regulated by Li in mouse brain (McQuillin et al., 2007). Functional annotation analysis using the EASE algorithms suggests that the 144 genes in the network are enriched in biological pathways, including a G-protein coupled receptor protein signaling pathway (P=2.27E-8), neuroactive ligand-receptor interaction(P = 7.38E-16), calcium signaling pathway (P = 7.90E-10), and regulation of actin cytoskeleton (P = 3.16E-05). Our data suggest that individual gene expression changes induced by Li treatment are modest. The results reported here suggest a model that includes the effect from networked genes contributes to the molecular basis of Li's therapeutic action.

NTRK2, GRK3 AND PDE11A ARE ASSOCIATED WITH LITHIUM RESPONSE IN BIPOLAR DISORDER

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Lithium is the oldest mood stabilizer and the one with the strongest data for efficacy and reduction of suicide. A subset of bipolar patients has a robust response to lithium. The degree of response to lithium suggests that these individuals may have a distinct illness with a different biological basis. There is a great clinical need for better predictors of drug response in bipolar disorder. We identified 92 good lithium responders and 92 non-responders based on SCID or DIGS interview and examined them at a series of candidate genes. 732 SNPs were examined in 50 candidate genes. The strongest positive associations were with SNPs in the PDE11A gene ($p=0.0001$) and the NTRK2 gene ($p=0.0015$). Bcl-2, IMPA1 and IMPA2 also had nominally significant associations. When considered in the context of phenotype, the SNP in NTRK2 was associated with response in euphoric rather than dysphoric mania. GRK3 ($p=0.006$) was associated with response in those with dysphoric and not euphoric mania. In contrast, the SNP in the PDE11A gene was associated with response in both euphoric and dysphoric mania. NTRK2 codes for TrkB, the receptor for brain derived neurotrophic factor (BDNF). The BDNP/TrkB signaling pathway regulates neuronal development and plasticity and activates multiple downstream intracellular cascades. PDE11A is a phosphodiesterase that regulates second messengers cAMP and cGMP. Increased intracellular concentrations of cAMP/cGMP activate enzymes PKA and PKG which phosphorylates substrates such as ion channels and transcription factors. Together these data suggest that lithium responsive bipolar disorder is a genetically distinct form of illness that involves the BDNF/NTRK2 pathway. Lithium may work through this pathway. They also suggest that PDE11A may operate on a final common pathway shared by both euphoric and dysphoric mania.