GENDEP: RECENT PHARMACOGENETIC AND PHARMACOGENOMIC OUTPUT

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BACKGROUND: GENDEP, a European multicentre integrated pharmacogenomic study, aimed to identify genomic correlates of antidepressant response including adverse drug reactions (ADRs) (http://gendep.iop.kcl.ac.uk/results.php).

METHODS: For design of the clinical trial and genotyping methodolgy, see references the above URL.

RESULTS: Analysis of the data on sexual dysfunction and the 5-HTTLPR revealed no clear interaction with this polymorphism (Strohmaier et al, under review). GWAS analysis revealed an association between rs2500535 in the uronyl 2-sulphotransferase gene and response to nortriptyline, while response to escitalopram was predicted by a marker in the interleukin-11 (*IL11*) gene (Uher et al, 2010). Converging results from our genetic association and genome-wide association analyses (GWAS) indicate that *NTRK2* is associated with suicidality in GENDEP (Perroud & Aitchison et al, 2009; Perroud et al, 2010). The *CYP2D6* ultrarapid metaboliser (UM) genotype was associated with a significantly lower dose of both antidepressants over the 12-week trial (β=-0.56, 95% CI -0.88 to -0.25 $P < 0.001$; Keers et al, 2010). Rodent gene expression analysis and transcriptomic data from the clinical trial point to a role for *PPM1A* in response to antidepressants (Malki et al, 2010).

CONCLUSION: Converging pharmacogenetic and pharmacogenomic output is yielding encouraging findings.

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. Roche Molecular Systems provided the AmpliChip CYP450 Test® and associated support. GlaxoSmithKline and the Medical Research Council contributed by funding add-on projects in the London centre, and latterly the London centre also received additional funding from the Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, Institute of Psychiatry (funded by the National Institute for Health Research, Department of Health, UK).

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DAT AND DRD4 GENES ARE RELATED TO DRINKING AND CRAVING IN EARLY STAGE ALCOHOL DEPENDENT INDIVIDUALS: EFFECTS OF NALTREXONE AND OPRM1 GENOTYPE?

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BACKGROUND: Carriers of the dopamine transporter (DAT) 9 VNTR (loss of function, increasing DA) and the DRD4 L (≥7 repeats) have greater brain response to "reward". This study evaluated DAT and DRD4 genetic differences in relationship to drinking, craving and alcohol effects in early stage alcoholics before and after the opiate antagonist drug naltrexone or placebo (based on mu opioid receptor (OPRM1) genotype).

METHODS: 266 Caucasian non-treatment seeking alcoholics (average age about 29, 80% male) had leucocyte DNA extraction, DAT and DRD4 VNTR's measured by specific primer based PCR amplification, and subsequent agarose gel separation, and OPRM1 asp40 SNP measured by taqman analysis. DAT 9,9 and 9,10 genotypes (43%) were compared to 10,10 (57%), while DRD4 LL or LS (40%) were compared with DRD4 SS (60%) on drinking, craving, and post alcohol effects after a standard oral drink (BAC 20-30 mg%) prior to, and during, 5 days of 50mg naltrexone or placebo (in those with (n=43) or without (n=40) OPRM1 asp40 alleles).

RESULTS: Individuals with at least one copy of the DAT 9 VNTR had more drinks per day (p=0.06) while DRD4 SS had more craving (p= 0.028) prior to medication. After a standard drink DRD4 SS has less sedation (p=0.02). DAT interacted with OPRM1 status and medication (p=0.009) such that naltrexone response was greatest in DAT 9 VNTR with OPRM1 asn40.

CONCLUSION: Differences in DAT and DRD4 genes, affecting brain dopamine, also influence aspects of alcohol consumption. Opioid receptor based naltrexone response may be influenced by DAT genotype.

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GENETIC VARIATION IN CYTOCHROME P450 DRUG METABOLIZING ENZYMES IMPACTS CLEARANCE OF ANTIPSYCHOTICS

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BACKGROUND: Antipsychotics have a high rate of discontinuation due to inefficacy and/or adverse effects. A pilot study found that cytochrome P450 3A43 (CYP3A43) genotype predicted exposure to olanzapine, which resulted in variable response to olanzapine. This larger study aimed to identify genetic variants in CYP450 drug metabolizing enzymes that impact antipsychotic clearance using pharmacokinetic and genetic data from the CATIE trials.

METHODS: Clearance of atypical antipsychotics (olanzapine, risperidone, quetiapine, and ziprasidone) was estimated using nonlinear mixed-effects modeling. Single nucleotide polymorphisms (230 SNPs) in CYP450 metabolizing enzymes (CYP1A, CYP2A, CYP2B, CYP2C, CYP2E, and CYP3A families) were tested as possible predictors of antipsychotic clearance.

RESULTS: CYP3A43 genotype (rs472660), which previously predicted olanzapine clearance, also significantly predicted 30% of risperidone clearance (ANOVA overall p=2e-17, GG<AA p=4e-18). Of the 230 SNPs in CYP450s, the CYP3A43 SNP (rs472660) was the most significantly associated with both risperidone and olanzapine clearance, and predicted most and the entire previous race effects in drug clearance, respectively. This CYP3A43 SNP did not predict either quetiapine or ziprasidone, which was predicted based on the lack of racial effects on their clearance. The most significant predictors of ziprasidone and quetiapine clearance were SNPs located in the CYP2A/2B families of genes on chromosome 12. SNPs in other CYP gene families were also associated with clearance of one or more of the antipsychotics.

CONCLUSIONS: Genetic variation in CYP450 drug metabolizing enzymes are significantly associated with clearance of antipsychotics, which likely contributes to the wide variability in response and side effects to these medications.

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GENETIC AND FUNCTIONAL INFLUENCE OF FKBP-5 IN THE ANTIDEPRESSANT TREATMENT RESPONSE

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Major depression is one of the most common psychiatric disorders characterized by the interaction between genetic and environmental risk factors. Several studies supported an impairment in GR functionality in depression and a normalization during antidepressant treatment.

In order to better investigate the role of GR functionality in depression and in the treatment response we have analysed the levels of the GR and of FKBP-5 in leukocytes of 20 controls and 25 drug free depressed patients (DFD), before and during antidepressant treatment (18 responders and 8 non responders), and in 7 resistant depressed patients (TRD). Moreover we analysed the polymorphism rs1360780 within the FKBP-5 gene in 495 controls and 685 depressed patients (360 TRD and 325 responders).

We found a deficit in the levels of GR in DFD as compared to controls with no effect of treatment, and interestingly a GR reduction was observed even in TRD. Moreover we found increased levels of FKBP-5 in DFD and a decrease during the treatment, but only in patients who responded to the therapy; conversely FKBP-5 levels were maintained elevated in non responders and in TRD. Finally we observed that the T allele in homozygosis for the rs1360780 were less represented in TRD ($p=0.042$) but not in responders ($p=0.204$) as compared to controls.

Our data indicate a genetic and functional influence of GR functionality in the mechanisms associated with the lack of response of antidepressant treatment.

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IN VIVO microRNA CSF PROFILING IN PATIENTS WITH SCHIZOPHRENIA

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BACKGROUND: MicroRNAs are small non-coding RNA molecules that are involved in post-transcriptional regulation of messenger RNAs. Recent studies have started to link alterations in miRNA expression to schizophrenia and other psychiatric disorders. However, most of these studies have examined a small number of microRNAs and/or have used post-mortem brain tissue or whole blood as the source of transcript. By contrast, examination of a broad array of microRNAs in cerebrospinal fluid might provide an *in vivo* biomarker more directly reflecting functional changes in the brain. However, to our knowledge, no study has been conducted investigating the presence of microRNAs in CSF in schizophrenia or any other psychiatric disorder.

METHODS: Four healthy volunteers and four patients with chronic schizophrenia underwent lumbar puncture and a standard blood draw. For each subject, total RNA was separately extracted from 3-5ml of CSF and one PaxGene tube of blood. Expression of 381 validated microRNAs was assessed from each biofluid type for each of the subjects with the Taqman Human MicroRNA A array (Applied Biosystems), which uses real-time RT-PCR to quantify the number of amplification cycles (Ct) required to reach a given threshold.

RESULTS: In healthy volunteers (male: 100%, mean age: 38.8, black: 75%), a higher number of microRNAs achieved detectable levels of expression in CSF (mean: 135, range=127-147) compared to whole blood (mean= 87.3, range=60-114). Approximately one-third of all CSF-expressed microRNAs demonstrated robust levels of expression (Ct<30). Out of 381 microRNAs, 85 (22.3%) were expressed in one or more of the four CSF samples but not in any of the whole blood samples. Moreover, of those 85 microRNAs, 21 were expressed in all four CSF samples but none of the blood samples. By contrast, only 25 microRNAs (6.6%) were expressed in one or more of the whole blood samples but not in any CSF samples. CSF and whole blood samples from matched patients with schizophrenia (male: 100%, mean age: 41, black: 75%) are currently under analysis and will be available within the next month.

CONCLUSION: microRNAs can be readily recovered from whole blood and cerebrospinal fluid in healthy volunteers, and likely in patients with schizophrenia. A substantial number of microRNAs are detectably expressed in CSF but not in whole blood. Therefore, the investigation of these CSF-specific microRNAs may open a window to a better understanding of psychiatric diseases and particularly schizophrenia.

ASSOCIATION BETWEEN NON-SYNONYMOUS SNPs AND RESPONSE TO CITALOPRAM IN THE STAR*D SAMPLE

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BACKGROUND: Inter-individual variability in response to antidepressants may in part be influenced by DNA variation. To date, candidate gene and common variant GWAS approaches to antidepressant response have led to results that are equivocal or small in effect. Few previous studies focus on variants that alter protein structure. Here we report results from a scan of 20K non-synonymous SNP to look for novel functional genetic determinants of antidepressant response in a large clinical sample.

METHODS: 1,953 individuals from the Sequenced Treatment Alternatives for Depression (STAR*D) study were treated with citalopram and genotyped using ParAllele custom cSNP arrays. Multi-dimensional scaling was used to correct for population stratification in our multiethnic sample. Our outcomes were remission.. We tested for association in one half of the STAR*D sample using logistic regression and controlled for gender and other clinical and demographic variables in the analyses. We then genotyped the strongest associated SNPs using an iPlex assay in the second half of the sample.

RESULTS: We genotyped approximately 950 individuals and found no associations at experiment-wide significance levels. The strongest finding for remission occurred with a non-synonymous SNP (nsSNP) in the purinergic receptor P2RX4 ($p = 0.0002$, OR = 0.57), which is inhibited by SSRI's. The next best findings occurred with nsSNPs within two different intraflagellar transport proteins known to form a common protein complex (IFT74, $p = 0.0006$, OR=1.82; IFT88, $p = 0.0008$, OR = 0.60). Other promising associations occurred in a neurofilament gene (NEFH) and other genes of interest (CNAP1, CYP2C18). We have selected the most associated ($p<0.005$) findings for replication in an additional 950 STAR*D individuals.

CONCLUSION: These data may implicate previously unconsidered loci in antidepressant response by detecting direct association to potentially functional variants. The pathways suggested by these results are novel for citalopram response, and may warrant further investigation. Replication in multiple independent samples will be a critical next step for validation of our findings.

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GENOME-WIDE ASSOCIATION ANALYSES OF ADVERSE DRUG REACTIONS TO ANTIDEPRESSANTS IN GENDEP

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Adverse drug reactions (ADRs) to antidepressants are common, often severe and frequently interfere with treatment, resulting in non-compliance and discontinuation. Identification of genetic factors predictive of ADRs promises to allow for the selection of a treatment which is well tolerated in the long- term and provide insights into the genes and pathways involved.

Here we report results of a genome-wide association study (GWAS) of ADRs to two antidepressants in GENDEP (http://gendep.iop.kcl.ac.uk/results.php), a large multicentre pharmacogenomics project. GWAS data were available on 730 patients with moderate to severe major depression, treated with one of two antidepressants with divergent mechanisms of action and ADR profile: the pro-noradrenergic tricyclic antidepressant nortriptyline and the pro-serotonergic selective serotonin uptake inhibitor escitalopram. ADRs were evaluated weekly for 12 weeks using the ASEC, a self-report checklist (Uher et al, 2009)

While no SNPs were associated with ADRs at a genome-wide significance level, a number of plausible candidates emerged with suggestive levels of significance ($P < 5 \times 10^{-6}$). Several SNPs in the tetraspanin-8 gene (*TSPAN8)*, previously implicated in obesity were associated with changes in appetite ($P = 5.7 \times 10^{-7}$) and SNPs in the gene encoding the proinflammatory enzyme cyclooxygenase-1 (*PTGS1*) were associated with disorientation ($P = 3.9 \times 10^{-6}$). Perhaps the most interesting finding was in ankyrin 3 (*ANK3*), a gene which has been associated with bipolar disorder in a several studies, which mediated the occurrence of treatment-emergent insomnia ($P = 4.6 \times 10^{-6}$). If replicated, these findings suggest the involvement of several novel and plausible pathways in the adverse effects of antidepressants.

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PHARMACOGENETICS OF LITHIUM RESPONSE

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Lithium is the first and most widely used mood stabilizing medication for bipolar disorder. It has the highest demonstrated efficacy and well document reduction in suicide risk. A subset of patients with bipolar disorder have an excellent response to this medication with virtual elimination of episodes. Other data suggest a specific clinical profile for lithium responders, and it has been argued that lithium responsive bipolar disorder is a distinct form of illness. For these reasons, there is a great clinical need to predict lithium response and target those patients most likely to respond for lithium treatment. We are presently conducting several different studies of lithium pharmacogenetics. One is a retrospective study relying on history and patient report, while two are prospective studies one in the VA population and one a new multisite prospective study. In the retrospective sample, we have examined over 600 SNPs in 50 candidate genes. Significant evidence for association with lithium response was obtained for NTRK2, PDE11A and IMPA1. NTRK2 is particularly intriguing as it is the receptor for the neurotrophin BDNF, thought to be involved in lithium's mechanism of action. Of note, the association to NTRK2 was seen only in subjects with euphoric rather than dysphoric mania, consistent with the notion that lithium responsive illness is a distinct form of illness. The two top SNPs one in NTRK2 and one in PDE11A were then tested for replication in the VA prospective study. The same SNP and same allele of NTRK2 (rs1387923, p=0.028) was shown to be associated with lithium response in the prospective study. The evidence for association centers on the 3' UTR of the gene suggesting an error in RNA degradation. Recently, as part of the Pharmacogenomics Research Network, we have begun a large multisite prospective trial to extend this work. 10 international sites are collaborating as part of the Pharmacogenomics of Bipolar Disorder (PGBD) study. In this study, 700 subjects will be prospectively stabilized on lithium and then followed for two years. Time to relapse will provide a quantitative measure of response. Subjects that fail lithium will be crossed over to valproate to be followed in an identical arm. A subset of subjects will undergo skin biopsies in order to develop induced pluripotent stem cell lines from which neurons can be derived. These neurons will then be studied for their response to lithium in vitro. All subjects in the study will ultimately undergo GWAS or sequencing, together these samples and data will provide a useful resource for the field.

WHOLE EXOME SEQUENCING AND ANTIDEPRESSANT TREATMENT OUTCOME

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BACKGROUND: Genome-wide association studies of antidepressant treatment response have not identified reproducible common genetic variants informative of treatment outcome. It is possible that rare variants that may offer additional insight into the pathophysiology of this complex phenotype. For this purpose we undertook a whole exome sequencing experiment in individuals selected from the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D).

METHODS: In this exploratory pilot study we selected a limited number of Caucasian European-ancestry individuals from the STAR*D sample (n=8) who represented treatment-resistant cases and sustained treatment responders. Extreme non-responders were derived from Level 4. They had experienced failure with 4 treatment strategies. Additionally, we required that these cases were adherent to medication, had a HAM-D score of >=22 at study entry, a score of at least 17 at the end of Level 4, and no current drug or alcohol abuse. Sustained responders were matched on gender, anxious depression status, treatment adherence, drug and alcohol abuse, and ancestry. Additionally, controls, had a baseline Level 1 HAM-D >= 22, were remitters at Level 1 endpoint (QIDS-C<=5) and did not relapse in the 6 months post Level 1 completion (QIDS-SR<11). All samples were sequenced at EdgeBio using a SOLiD platform with ≥ 10X coverage.

RESULTS: At this time, we only report results pertaining to single nucleotide variants (SNVs). Variants were called using CLC Bio software and SNVs with < 4X coverage were excluded from our analysis. Each participant had about 90,000 SNVs on initial annotation. We screened uncommon SNVs (MAF <0.1) using the 1000 Genomes data and identified a total of 320,845 unique SNPs. There were 18 SNPs that were only present in non-responders; 22% were novel variants, and some were predicted to be damaging by Sift.

CONCLUSIONS: The detection of rare variants through high throughput sequencing may shed new insight into the pathophysiology of treatment-resistant depression.

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NOVEL PHENOTYPES IN PHARMACOGENETIC STUDIES: WEIGHT GAIN NI PREVIOUSLY UNTREATED PATIENTS

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To date, pharmacogenetic studies of antipsychotic-induced weight gain have been limited by the lack of optimally designed data sets. Most studies have utilized samples of convenience and included patients with extensive prior treatment histories, thereby blunting acute effects. Moreover, treatment adherence has not been comprehensively assessed, and therefore putative non-weight gainers may simply have failed to gain weight through non-adherence, and thus may be misclassified in the genetic analyses. Additionally, only a modest number of genetic loci have typically been examined, such that the vast majority of the genome has not yet been interrogated for its contribution to weight gain.

We conducted a genome-wide association study (GWAS) of weight gain in a unique sample of children and adolescents undergoing initial exposure to second-generation antipsychotic (SGA) treatment. PCA-corrected GWAS of the BMI-change phenotype revealed a significant effect under the recessive model; twenty SNPs at a single locus exceeded a statistical threshold of $p<10^{-5}$, with rare allele homozygotes gaining extreme amounts of weight (~17% over baseline) over the12-week trial. This locus, approximately 150kb downstream from the melanocortin 4 receptor gene (*MC4R*), overlaps a region previously associated with BMI in large cross-sectional studies of the general population. Results were replicated in two independent cohorts of patients treated with SGAs.

Although GWAS is optimized for the study of common (frequency > 5%) alleles, we also performed a separate exploratory analysis of rare missense variants available on the Illumina platform, which has been enhanced for coverage of coding SNPs and rare alleles of interest derived from the 1000 Genomes Project. Carriers of rare missense alleles were compared to non-carriers using PCA-corrected regressions under the dominant model. One missense SNP yielded a striking effect size (Cohen's d>1); nine carriers of the rare (G) allele demonstrated a mean 12-week change in BMI that was nearly twice as large as that observed in non-carriers. Notably, the gene altered by this SNP also plays a key role in the hypothalamic melanocortin pathway.

Finally, we sought to determine the extent to which these two genetic markers could improve prediction of 12-week weight gain relative to short-term (4-week) clinical prediction. As expected, initial (4-week) SGA-induced weight gain predicted about half the variance in total weight gain over the 12 weeks of exposure. However, stepwise regression analysis revealed that each of the two genetic markers described above contributed an additional 10% of explained variance to the model (p= .000014 and p=.009, respectively), after initial weight-gain had already been entered. Moreover, initial weight gain only marginally predicted weight gain in the subsequent 8 weeks of the trial (R^2=.024, p=.083), whereas the two SNPs contributed a combined 20% of variance explained ($p=10^{-7}$ for the model including only the two SNPs).

SEROTONIN RECEPTOR 2A (HTR2A) GENE POLYMORPHISM PREDICTS TREATMENT RESPONSE TO VENLAFAXINE XR IN GENERALIZED ANXIETY DISORDER

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Background: Generalized Anxiety Disorder (GAD) is a chronic psychiatric disorder with significant morbidity and mortality. Antidepressants are the preferred choice for treatment; however, treatment response is often variable. Several studies in major depression have implicated a role of the serotonin receptor gene (HTR2A) in treatment response to antidepressants. We tested the hypothesis that the genetic polymorphism rs7997012 in the HTR2A gene predicts treatment outcome in GAD patients treated with venlafaxine XR.

METHODS: Treatment response was assessed in 156 patients that participated in a 6-month open label clinical trial of venlafaxine XR for GAD. Primary analysis included HAM-A reduction at 6 months. Secondary outcome measure was the CGI-I score at 6 months. Genotype and allele frequencies were compared between groups using chi-square contingency analysis.

RESULTS: The frequency of the G-allele differed significantly between responders (70%) and non-responders (56%) at 6 months (p=0.05) using the HAM-A scale as outcome measure. Similarly, using the CGI-I as outcome, the G-allele was significantly associated with improvement (p=0.01). Assuming a dominant effect of the G-allele, improvement differed significantly between groups (p=0.001, OR=4.72). Similar trends were observed for remission although not statistically significant.

CONCLUSIONS: We show for the first time a pharmacogenetic effect of the HTR2A rs7997012 variant in anxiety disorders, suggesting that pharmacogenetic effects cross diagnostic categories. Our data document that individuals with the HTR2A rs7997012 SNP G-allele have better treatment outcome over time. Future studies with larger sample sizes are necessary to further characterize this effect in treatment response to antidepressants in GAD.

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HALOPERIDOL IN ACUTE PSYCHOSIS: CLINICAL FEATURES AND 133 GENETIC VARIATIONS IMPACT ON TREATMENT EFFICACY AND SIDE EFFECTS

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Response to antipsychotic treatment is uneasily predicted by clinical, sociodemographic or genetic variables alone. A detailed integration of these issues may grant better results. We analyzed a sample of 101 psychotic subjects, acutely ill, all treated with haloperidol. The study was conducted on a naturalistic basis, subjects were observed for a period of four weeks. We identified the clinical and sociodemographic variables that were significantly associated with response: improvement during the first two weeks of treatment was a significant predictor of response, further increasing the haloperidol doses (beyond 6.64+/-2.08 mg/day on average) in case of no response was useless to obtain a better outcome[1]. Age and gender were associated with dystonia during the early phases of treatment, but they were overall poor predictors of haloperidol efficacy or side effects[2]. 62 glutamatergic genetic variations located in GAD1, GRIA1, GRIA3, GRIA4, GRID2, GRIK1, GRIK2, GRIK3, GRIK4, GRIN2B, GRM1 and GRM4), and the transporter of glycine (SLC6A5) were not associated with response to the treatment with the exception of SLC6A5 variant rs2298826 which was found to be associated with a rapid rise of motor side effects at the beginning of the treatment followed by a subsequent adaptation, probably dependent on haloperidol doses down titration. This result was validated in two independent sample from Slovenia (n=71 and n=118) of schizophrenic patients treated with antipsychotics. Haplotype analysis strengthened the relevance of SLC6A5: the C-A-C haplotype (rs1443548, rs883377, rs1945771) was found to be associated with higher Extrapyramidal symptom rating scale scores[3]. Other 71 variations located in 21 candidate genes were found to be not significantly associated with side effects induced by haloperidol or haloperidol treatment efficacy[4].

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1 Ina Giegling et al., "Interaction of haloperidol plasma level and antipsychotic effect in early phases of acute psychosis treatment," *Journal of Psychiatric Research* 44, no. 8 (June 2010): 487-492.

2 Ina Giegling et al., "Sociodemographic and treatment related variables are poor predictors of haloperidol induced motor side effects," *Progress in Neuro-Psychopharmacology & Biological Psychiatry* (September 22, 2010), http://www.ncbi.nlm.nih.gov/pubmed/20868720.

3 Ina Giegling et al., "Glutamatergic gene variants impact the clinical profile of efficacy and side effects of haloperidol," *Pharmacogenetics and Genomics* (September 18, 2010), http://www.ncbi.nlm.nih.gov/pubmed/20859245.

4 Ina Giegling et al., "Lack of association between 71 variations located in candidate genes and response to acute haloperidol treatment," *Psychopharmacology* (November 16, 2010), http://www.ncbi.nlm.nih.gov/pubmed/21079921.

GENOME-WIDE PHARMACOGENETICS OF RESPONSE TO ANTIDEPRESSANTS: THE NEWMEDS PROJECT

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BACKGROUND: Major depressive disorder is a severe debilitating disorder with administration of antidepressants established as the initial step in treatment. Currently, the effectiveness of any particular antidepressant in an individual is not predictable. The current study is the largest antidepressant pharmacogenetic study to date investigating genetic determinants of why some individuals with depression respond to medication better than others. This work is being undertaken as part of the Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) project, a large multi-centre European Union funded collaboration between academia and industry.

METHOD: 1893 unrelated individuals of white European ancestry were administered either a serotonergic antidepressant (n=1271) or a noradrenergic antidepressant (n=622) as part of previous pharmacogenetic studies (GENDEP n=820; GenPod n=512; Pfizer=345; Glaxo-Smith Kline=134; GODS=82). Individuals were genotyped using Illumina Human 610-quad chip or 660W-quad chip and underwent routine quality control. Genotype information from quality controlled samples was tested for association with the adjusted percentage measurement change in the individual's primary measure of depression severity after 12 weeks using a linear regression under the additive genetic model.

RESULTS: Preliminary results highlight regions of interest on chromosomes 2, 5, and 6 that are associated with response to treatment with antidepressants. Results will be presented with genome-wide significance threshold of $p<5x10^{-8}$ and a suggestive significance threshold of $p<5x10^{-6}$.

CONCLUSIONS: Identification of genetic determinants of antidepressant response has a potential to transform the treatment of major depression disorder. Prediction of the probability of response of an individual to a specific antidepressant will be a major step toward personalised medicine.

USING IMAGING-GENETICS TO RETHINK OUR CLASSIFICATION OF SEVERE MENTAL ILLNESS

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BACKGROUND: Schizophrenia and bipolar disorder share considerable genetic risk, brain vulnerability, and clinical symptoms. The ZNF804A risk variant, rs1344706 confers susceptibility for both disorders. Therefore, the ZNF804A variant may exert its effects in cortical gray matter, white matter tracts or both, to confer risk for schizophrenia and bipolar disorder.

METHODS: In 62 healthy adults, the general linear model was used to examine the influence of the ZNF804A risk variant on cortical thickness, white matter tract integrity, and cognitive measures. High resolution multimodal MRI/DTI imaging was used to examine cortical thickness and major fronto-temporal and interhemispheric white matter tracts. Cognitive domains measured included attention control and working memory.

RESULTS: We found that T allele homozygotes (i.e. those homozygous for the risk variant) demonstrated reduced cortical gray matter thickness in both superior temporal gyrus and cingulate cortex compared to C allele carriers. No tract by genotype interaction was found, nor was any main effect of the risk variant found at microstructural integrity of white matter tracts. Reduced attention control was also found in T allele homozygotes, aligning with findings in cingulate cortex.

CONCLUSION: We localized effects of the ZNF804A risk variant to thickness of cingulate cortex and superior temporal gyrus, structures disrupted in both schizophrenia and bipolar disorder, but not at white matter tracts. Furthermore, a relationship of the ZNF804A variant with attentional control, a cognitive domain mediated largely by cingulate cortex was found. Our findings link shared genetic, imaging, and cognitive susceptibility in the major psychoses, and support the recent call to re-think our classification of severe mental illness.

INVOLVEMENT OF THE ATRIAL NATRIUETIC PEPTIDE TRANSCRIPTION FACTOR GATA4 IN ALCOHOL DEPENDANCE, RELPASE RISK AND TREATMENT RESPONSE TO ACAMPROSATE

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In alcoholism, both relapse to alcohol drinking and treatment response are suggested to be genetically modulated. This study set out to determine whether the top 15 single nucleotide polymorphisms (SNPs) of a recent genome-wide association (GWA) and follow-up study of alcohol dependence are associated with relapse behavior and pharmacological treatment response in 374 alcohol-dependent subjects who underwent a randomized, double-blind, placebo-controlled trial with acamprosate, naltrexone or placebo. The single nucleotide polymorphism, rs13273672, an intronic SNP in the gene for GATA-binding protein 4 (GATA4), was associated with relapse within the 90-day medical treatment period ($P<0.01$). Subsequent pharmacogenetic analyses showed that this association was mainly based on patients treated with acamprosate ($P<0.01$). In line with the observation that natriuretic peptide promoters are modulated by GATA4, a significant gene dose effect on the variance of atrial natriuretic peptide (ANP) plasma concentration in the different GATA4 genotypes ($P<0.01$) was found. Hence, genetic variations in GATA4 might influence relapse and treatment response to acamprosate in alcohol-dependent patients via modulation of ANP plasma levels. These results could help to identify those alcohol-dependent patients who may be at an increased risk of relapse and who may better respond to treatment with acamprosate.