EFFECTS OF *COMT* VAL158MET GENOTYPE IN AFRICAN- AND EUROPEAN AMERICAN SMOKERS AND INTRAVENOUS NICOTINE ADMINISTRATION

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Abstract: The *COMT* val158met (rs4680) polymorphism has been studied extensively with respect to several smoking-related phenotypes. We investigated the role of *COMT* val158met, comparing Val/Val vs. Met/Val and Met/Met genotypes, on subjective, physiological, and cognitive effects of intravenous (IV) nicotine ([two doses:0.5 mg/70kg and 1.0 mg/70kg] smokers inhale on average 1–2 mg of nicotine per cigarette, extended over 5 min, compared to the 0.5 and 1.0 mg nicotine infused over 60 s in our study) in African Americans (AAs) (n=57) and European Americans (EAs) (n=68) with nicotine dependence (ND). AA subjects with the Val/Val genotype had higher systolic and diastolic blood pressure during saline and both nicotine doses. Additionally, Val/Val AAs had higher negative affect related to their cigarette smoking, and worse cognitive performance both before and after nicotine infusions In EAs, Val/Val subjects had significantly higher Feel Bad drug effects during the 1.0 mg/70 kg dose of nicotine. Val/Val EA subjects had heightened placebo response to subjective effects of Stimulated, High and Sedated. Taken together, cigarette smokers in our study who had the Val/Val genotype tended to have greater blood pressure, negative subjective responses and worse cognitive function, which were largely independent from IV nicotine infusion. Results from this study may have implications in smoking cessation pharmacotherapy.

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VARIATION IN OPRM1 MODERATES THE EFFECT OF DESIRE TO DRINK ON SUBSEQUENT DRINKING AND ITS ATTENUATION BY NALTREXONE TREATMENT

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The role of the Asn40Asp SNP in the mu-opioid receptor gene (OPRM1) in regulating drinking behavior and moderating naltrexone's ability to attenuate drinking is controversial. We used a daily diary method in the context of a randomized clinical trial to evaluate its effects.

Methods: Problem drinkers (N=158; 92 males; 36 Asp40-allele carriers) participating in a 12-week study to reduce drinking were treated with 50 mg naltrexone (N = 81) or placebo (N = 77). Patients reported by telephone each evening on their current desire to drink and their drinking over the preceding day. We examined the main and interaction effects of genotype (Asp40 carriers vs. Asn40 homozygotes), medication (naltrexone vs. placebo), and desire to drink in predicting nighttime number of drinks consumed, controlling for daytime drinking levels.

Results: Asp40 carriers showed a stronger positive association between desire and subsequent drinking levels than Asn40 homozygotes (p = 0.019). The des! ire X genotype X medication condition interaction was also significant (p = 0.009) and reflected a significant desire X genotype interaction for the placebo group (p = 0.001), but not the naltrexone group (p = 0.74).

Conclusions: During periods of greater desire to drink, Asp40 carriers were at greater risk to drink heavily than Asn40 homozygotes, an effect that was attenuated by naltrexone. Daily reports may help to clarify the moderating effects of genetic variation on rapidly changing phenotypes, such as the relation between desire to drink and alcohol consumption, and the effects of medication on such phenotypes.

ASSOCIATION STUDY OF 50 CANDIDATE GENES AND LITHIUM RESPONSE IN BIPOLAR DISORDER

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Lithium is the original mood stabilizer for bipolar disorder and remains the drug with the strongest evidence for efficacy. Lithium responders have a distinct clinical profile and lithium response has been reported to be familial suggesting a genetic basis. 288 Caucasian subjects with bipolar disorder were retrospectively assessed for lithium response based on patient interview, lifechart and medical records. These include an original previously reported sample of 184 subjects and a new additional sample of 104. Patients were also interviewed using the DIGS in order to assess clinical characteristics of their illness. 50 candidate genes were selected based on lithium's purported mechanisms of action and reported association to risk for bipolar disorder. Analyses were conducted using logistic regression as implemented in plink. The strongest evidence for association in the overall sample was obtained for a SNP in the neuregulin 1 gene (NRG1, rs2975498, p=0.0008) which was supported by two other nearby SNPs with nominal significance. Support was also obtained for the gene for stargazin (CACNG2, rs140040, p=0.004) where a total of six SNPs had evidence for at least nominal significance. NTRK2 and PDE11A, which we have previously reported to be associated with response, continued to be supported in this expanded sample. The evidence for PDE11A in particular came primarily from subjects with a strong family history of bipolar disorder (rs7585543, p=0.0002). PIK3CG also showed evidence for association primarily in subjects with a family history (rs4727661, p=0.003). These results provide further support for a previous report of association to the CACNG2 gene. Pathway analyses are consistent with involvement of neurotrophin signaling.

IMPACT OF GENETIC VARIATION IN CYP ENZYMES ON TREATMENT RESPONSE IN OCD

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Background: Only 40-60% of patients with obsessive-compulsive disorder (OCD) are responders to antidepressant medication. Currently, no valid prediction regarding medication response is possible. Previous work by our group and others indicates a genetic influence on treatment response. There are various reports regarding the impact of genetic variation in drug metabolizing enzymes, mainly CYP2D6 and CYP2C19, on antidepressant response in depression treatment, but not for OCD. We therefore investigated if genetic variants of these genes are associated with treatment response in OCD.

Methods: 192 OCD patients were treated with different antidepressant drugs (fluoxetine, paroxetine, fluvoxamine, venlafaxine, sertraline, clomipramine, citalopram, escitalopram, mirtazapine and duloxetine) and assessed for treatment response using CGI-I, and occurrence of side effects. Metabolizer status (poor, intermediate, extensive, ultrarapid) was determined after genotyping for CYP2C19 (*2,*3,*17) and CYP2D6 (*3,*4,*5,*10, *17, *41) was performed using TaqMan Assays. Statistical analyses were done using Chi-square and ANOVA.

Results: We found significant impact of CYP2D6 metabolizer status on occurrence of side effects to venlafaxine (p=.022) and a non-significant trend for association of CYP2C19 genotype with response to sertraline (p=.075). There was no association of CYP2C19 or CYP2D6 metabolizer status with treatment response and/or occurrence of side effects for the other antidepressant drugs.

Conclusion: Although inconclusive, our data indicate some impact of genetic variation in drug metabolizing enzymes on treatment response and occurrence of side-effects in OCD. Limitations include heterogeneous medication and small sample size. Further investigation on the use of CYP2C19 and CYP2D6 genetic testing in clinical care of OCD patients remains necessary.

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IDENTIFYING TRANSCRIPTOMIC BIOMARKERS FOR RESPONSE TO ESCITALOPRAM IN THE INFLAMMATORY CYTOKINE PATHWAY

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Converging evidence suggests that the activation of the inflammatory cytokine pathway is important in the pathophysiology of unipolar depression [1]. Antidepressants have anti-inflammatory properties and evidence suggests that the clinical heterogeneity in response to antidepressants may reflect genetic differences in the inflammatory cytokine pathway. In particular, levels of Tumour Necrosis Factor (*TNF*) and the SNPs rs1126757 in interleukin-11 (*IL11*), and rs7801617 in interleukin 6 (*IL6*), have previously been implicated in the clinical response to the antidepressant escitalopram [2,3]. The aim of the current study was to investigate the transcription of *TNF*, *IL11* and *IL6* as well as genes in the wider inflammatory cytokine pathway in depressed patients who were either responders (n=25) or non-responders (n=21) to escitalopram using a subset of samples in GENDEP. Responders and non-responders were categorized based on percentage changes in MADRS scores. Blood was collected at baseline and after eight weeks of treatment with escitalopram. Expression of mRNA was assessed using the Human Inflammatory Cytokines & Receptors PCR Arrays (SABiosciences) containing probes for 86 genes in this pathway. Binary logistic regressions revealed significant expression differences at baseline between responders and non-responders in *TNF* (p=0.02), and after escitalopram treatment in *TNF* (p=0.009) and *IL11* (p=0.015). Differences in *IL11* after treatment were found to be driven by drug-induced genotype-specific expression differences relating to the rs1126757 SNP. There were no significant differences in genes in the *a priori* component of the study after correcting for multiple testing, however pathway analysis revealed the most significant hits were targets of TNF.

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VARIATION IN THE SEROTONIN TRANSPORTER GENE (SLC6A4) AND SEROTONIN RECEPTOR 2A GENE (HTR2A) PREDICT 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 transporter gene (SLC6A4) and serotonin receptor 2A gene (HTR2A) in treatment response to antidepressants. We tested the hypothesis that the genetic polymorphisms 5HTTLPR in the SLC6A4 gene and rs7997012 in the HTR2A gene predict 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. Genotypes were obtained using standard procedures (5-HTTLPR L/S and rs25531 a/g; HTR2A rs7997012). Genotype and allele frequencies were compared between groups using chi-square contingency analysis.

Results: For the 5HTTLPR polymorphism, we found a significant association between La/La individuals (versus La/S and S/S) and treatment response to VEN at 6 months outcome (HAM-A response: p=0.01). Exploratory analysis showed these significant effects with treatment response occurred as early as 16 weeks (p=0.03). Interestingly, we found subjects homozygous for La/La showed better treatment response than S carriers (p=0.003). For the HTR2A gene polymorphism 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 5HTTLPR polymorphism and the HTR2A rs7997012 variant in anxiety disorders suggesting that two genes involved in serotonergic neurotransmission predict treatment response to a serotonin-norepinephrine reuptake inhibitor. Epistatic effects might be important to consider when carrying out pharmacogenetic studies of drug response. Future studies with larger sample sizes are necessary to further characterize this effect in treatment response to antidepressants in GAD.

META-ANALYSIS OF ANTIDEPRESSANT-ASSOCIATED SUICIDALITY IN MAJOR DEPRESSIVE DISORDER

GENDEP investigators, MARS investigators and STAR*D investigators

Presenter: Stephan Ripke

A small subset of individuals experience onset or worsening of suicidal thoughts or behaviors after initiation of antidepressants, a phenomenon reflected in a black box warning in US labeling . While genome-wide association studies have been successful in identifying associations for rare serious adverse events outside of psychiatry, individual studies of suicidality have to date failed to identify common genetic variation.

We developed consistent phenotypic definitions of suicidality across three large antidepressant trials in the US and Europe for which genome-wide association data were available. The three cohorts that took part in the meta-analysis were STAR*D from the US, GENDEP from UK, and MARS from Germany.

The primary phenotype examined was at least a 1-point increase in the primary clinician-rated measure of suicidal ideation to at least passive suicidality at any post-baseline visit up to 12 weeks. These subjects were compared to those without these symptoms who received at least 4 or more weeks of antidepressant treatment. A handful of secondary phenotypes were defined and subsequently analyzed. The largest phenotype group consisted of 250 cases and 1834 controls.

Each of the three groups performed HapMap3 imputation and standard association analyses, incorporating genetic and clinical covariates. Standard-error weighted meta-analysis was performed with METAL.

Primary analysis failed to identify any genome-wide significant result. Though replication studies are ongoing, we will concentrate this presentation on secondary analyses (polygene-score, gene-based tests).

In conclusion, the currently available GWAS datasets for this subphenotype seem to be too limited in size to find clearly distinguishable results.

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ANTIPSYCHOTIC INDUCED WEIGHT GAIN AND THE IMPORTANT ROLE OF HYPOTHALAMUS GENES – UPDATE AND NOVEL FINDINGS IN THE NPY GENE

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One of the most debilitating side effects emerging with many newer antipsychotic drugs is substantial weight gain associated with cardiovascular complications and metabolic syndrome. Since previous findings strongly implicated genes acting on hypothalamic pathways in antipsychotic-induced weight gain (e.g., leptin, MC4R, BDNF etc.), we here present results obtained in variants of the neuropeptide Y (NPY) gene.

A total of 237 patients who underwent treatment for chronic schizophrenia or schizoaffective disorder were evaluated for antipsychotic response and induced weight gain for up to six months. The sample consisted mainly of individuals of European descent exposed to clozapine for their first time. SNPs rs16147, rs16475, rs5573 and rs5574 and rs10551063 were genotyped.

In patients of European ancestry who received either clozapine or olanzapine, significant genotypic and allelic association of rs16147 with weight change was observed ($P_{corrected}$=0.012, 0.018 respectively). Carriers of the C-allele gained significantly more weight compared to individuals with TT-genotype (CC+CT vs. TT; 5.82%±5.6 vs. 2.25%±4.8; p=0.001). Similarly, two other polymorphisms (rs5573 and rs5574) were also significantly associated with weight change ($P_{corrected}$=0.018 and 0.03) although these three associated polymorphisms were found to be in high linkage disequilibrium. In addition, we observed a significant gene-gene interaction between the rs16147 in NPY and rs806378 in the cannabinoid receptor 1 ($P_{corrected}$ =0.011).

Our results tentatively suggest novel associations between functionally relevant markers of NPY genes in patients treated with antipsychotic medication for schizophrenia. These findings will be reviewed in the context of previous studies helping to dissect hypothalamic pathways involved in antipsychotic-induced weight gain.

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THE INFLUENCE OF METABOLIC SYNDROME, PHYSICAL ACTIVITY, AND GENOTYPE ON CATECHOL-O-METHYL TRANSFERASE PROMOTER-REGION METHYLATION IN SCHIZOPHRENIA

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Abstract: The catechol-o-methyl transferase (*COMT)* 158Val/Met variant has been suggested to play a role in *COMT* function. Epigenetic regulation of *COMT* may further influence the prevalence of metabolic syndrome in these patient populations. This study examined the correlation between *COMT* promoter methylation and metabolic syndrome in schizophrenia patients receiving atypical antipsychotic (AAP) therapy. DNA was extracted from peripheral blood samples of schizophrenia subjects screened for metabolic syndrome. Pyrosequencing was used to analyze two methylation sites of the *COMT-s* promoter region. Associations between AAP use, lifestyle variables, metabolic syndrome, and *COMT* genotype with peak methylation values were analyzed. Data are reported in 85 subjects. Methylation on CpG site 1 had a mean of 79.08% (± 4.71) and 12.43% (±1.19) on site 2. *COMT* genotype proved to be an indicator of *COMT* methylation status on site 1 ($F_{(2,84)}$ = 5.78, p=0.0044) and site 2 ($F_{(2,84)}$, p=0.027). A significant negative correlation between physical activity and *COMT* promoter region methylation was found in Val/Val homozygous patients (Site 1: p=0.013 and Site 2: p=0.019). Those homozygous for Met/Met showed a positive correlation between promoter site methylation and physical activity (Site 1: p=0.027, Site 2: p=0.005), and between CpG site methylation and metabolic syndrome (Site 1: p=0.002; Site 2: p=0.001). The results of this study suggest *COMT* promoter region methylation is largely influenced by *COMT* genotype and that physical activity plays a significant role in epigenetic modulation of *COMT*.

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COMMON VARIANTS NEAR THE MELANOCORTIN 4 RECEPTOR GENE ARE ASSOCIATED WITH SEVERE ANTIPSYCHOTIC DRUG-INDUCED WEIGHT GAIN

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Second-generation antipsychotics (SGAs) are the cornerstone of treatment for many psychotic and non-psychotic disorders. Unfortunately, these medications are associated with substantial weight gain, including the development of obesity and other cardiovascular risk factors.

We conducted a genome-wide association study (GWAS) of SGA-induced weight gain in patients undergoing initial exposure to SGA treatment. We next tested selected SNPs in three independent cohorts of subjects undergoing antipsychotic drug treatment, including two additional cohorts of subjects undergoing initial treatment.

GWAS yielded twenty SNPs at a single locus exceeding a statistical threshold of $p < 10^{-5}$. This locus, approximately 190kb downstream from the *MC4R* gene, overlaps a region previously identified by large-scale GWAS of obesity and BMI in the general population. Effects were recessive, with rare allele homozygotes gaining extreme amounts of weight (~17% over baseline) over the 12-week trial. These results were replicated in the three additional cohorts with SNP rs489693 demonstrating consistent and statistically significant recessive effects in each cohort; meta analysis revealed a strong, genome-wide significant effect (Stouffer's z trend, p=5.59E-12). Moreover, we observed consistent effects on related metabolic indices, including triglycerides, leptin, insulin, and HOMA-IR in our discovery cohort.

These data implicate the *MC4R* locus in extreme SGA-induced weight gain and related metabolic disturbances. *A priori* identification of high-risk subjects could lead to alternative treatment strategies in this population, and may have implications for future antipsychotic drug development. Moreover, the large effect sizes obtained in this GWAS suggest that genetic discoveries in complex phenotypes may be accelerated by pharmacological challenge paradigms, in which major environmental factors are tightly controlled.

EFFECTS OF GENOME-WIDE SUPPORTED RISK VARIANTS ON BRAIN CONNECTIVITY ACROSS THE ADULT LIFESPAN

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Introduction: Impaired brain connectivity may render individuals susceptible to neurodevelopmental and neurodegenerative disorders. Neurodevelopmentally, Neurexin1gene may exert risk for schizophrenia and autism via effects on fronto-striato-thalamic circuitry. With respect to dementias, little is known regarding how genome-wide supported variants confer neural risk across the adult lifespan.

Method: All subjects were healthy individuals, who completed genetics, and MRI-based neuroimaging protocols. In a sample of 77 individuals from age 18-59, we examined effects of the putatively functional Neurexin1 rs1045881 variant on striato-thalamo-frontal circuitry. In a sample of 97 individuals ranging from 18-85, we examined the effects of Alzheimer's GWAS risk variants including the EXOLC32 on limbic circuitry.

Results: The Neurexin1 variant with both thalamic and striatal volumes, e.g. at the right putamen ($F_{1,73}=5.3$, $p=.02$, and with decreased brain surface folding in frontal and temporal gyri of the left hemisphere. Among the Alzheimer's GWAS variants, the EXOC3L2 variant exerted effects on left amygdala volume ($F_{1,92}=5.5$, $p=0.018$, and integrity of the left inferior longitudinal fasciculus ($F_{1,92}=4.1$, $p=0.04$, which connects visual cortex to fusiform gyrus to amygdala.

Discussion: Our data support a putatively functional Neurexin1 variant as a genetic risk mechanism for schizophrenia and autism in the brain via its effects on striato-thalamo-frontal circuitry. We also demonstrate novel effects for the Alzheimer's GWAS risk variant EXOC3L2 within limbic circuitry, primarily in a fear-based network. Our data support that psychiatric risk genes cut across diagnostic boundaries to confer disease risk patterns in the brain. Further, signatures of neural risk for AD are present in the brain before symptoms of disease appear.

RARE VARIANTS IN SCHIZOPHRENIA

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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. In this presentation, we will review recent evidence from large-scale international collaborations in schizophrenia, and will present new data on several types of rare variants, including: runs of homozygosity, copy number variations, and exonic mutations. Challenges in working with whole-genome sequencing data will also be discussed in the context of pharmacogenetics and the application of personalized medicine to psychiatry.

ESTABLISHING BIOLOGICAL SAMPLING METHODOLOGY FOR PHARMACOGENOMICS IN YOUNG PEOPLE

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Background: Establishing appropriate biological sampling methodology for pharmacogenetic analysis in young people is part of the research funded in Workpackage 3 of the STOP study (www.stop-study.com), Suicidality: Treatment Occurring in Paediatrics.

Methods: DNA was extracted from four different sample types (5ml venous blood, buccal swabs, 2.5ml saliva using the Oragene.Dx® kit, and in-house salivary collection methods), quantified, and subjected to quality control analyses including various genotyping methodologies.

Results: *QC analysis.* In samples collected by KCL, the mean concentration (by UV spectrophotometer) of DNA extracted from blood samples was comparable to that extracted from Oragene.Dx® kits (227±44ng/µl vs. 224±184ng/µl), and greater than that extracted from the latter two methods (72.5±45ng/µl and 74.8±60ng/µl respectively). CIMH collected the latter three types of samples, and similarly found that the Oragene.Dx® kit performed the best out of these three (total yield on NanoDrop quantification: 220.9±119µg vs. 1.4±1µg vs. 53.1±46µg). UB collected samples using the Oragene.Dx® kit from 3 different age groups: children (3-7 years), adolescents (13-15 years), and adults, and found that the resulting DNA concentration was adults>adolescents>children. *Genotyping.* KCL genotyped 8 samples from the 4 sample types using the Affymetrix DMETPlus® Array, and found comparable call rates to 3 Affymetrix controls (99.68±0.19, 99.51±0.33, 99.56±0.21, 99.13±1.45 vs. 99.67±0.03). CIMH conducted genotyping of the *DAT1* intron 8 variable number tandem repeat (VNTR) marker and single nucleotide polymorphism (SNP) genotyping of rs1006737 using a TaqMan assay for all their sample types successfully.

Conclusion: DNA derived from the Oragene.Dx® kit is suitable for such pharmacogenomic analysis.

Funding: STOP was funded by the European Commission Framework 7 under grant agreement number 261411.

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THE FACTOR STRUCTURE FOR THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) IN PHARMACOGENETICS: 102T/C 5-HT2A POLYMORPHISM AND RESPONSE TO RISPERIDONE

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The measurement of symptom severity is an essential aspect for the evaluation of the drugs response. The Positive and Negative Syndrome Scale (PANSS) was developed in an attempt to provide a more comprehensive assessment of the symptoms of schizophrenia evaluating three main domains: positive, negative and general psychopatology. The PANSS is widely used in clinical and research settings however a consistent literature have proposed factor structure of the PANSS in order to better identify symptoms clusters and use them to help define the clinical profile and treatment response.

In our previous study we found an association between the 5-HT2A 102T/C polymorphism and the early treatment outcome. In particular, analyzing 81 patients in monotherapy with risperidone where drug response was assessed at admission (T0), following 1-week (T1) and 2-weeks (T2) of treatment, the T allele carriers of 5-HT2A 102T/C polymorphism showed a greater improvement in general symptomatology ($p=0.04$).

In order to clarify this effect and better understand the cluster of symptoms affected we analyzed our data with the five and seven factor models (Marder et al., 1997 and Emsley et al., 2003 respectively). Five model showed that risperidone gave a better amelioration of excitement and cognitive dysfunction symptoms in T allele carriers ($p=0.05$ and $p=0.04$) whereas in seven models analysis was found a greater amelioration in excitement, cognitive dysfunction and anxiety symptoms ($p=0.02$, $p=0.05$, $p=0.04$ respectively).

The study suggests that factor model analysis of PANSS may be important in pharmacogenetics. A better characterization of endophenotypes could be usefulness in predicting response to antipsychotic medications.

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ANTIPSYCHOTIC TREATMENT AND COPY NUMBER VARIATIONS – A PILOT STUDY

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Introduction: The identification of multiple genetic high risk factors of schizophrenia seems to suggest the existence of a corresponding number of etiological subtypes of the disorder; subtypes that might well be characterized by correspondingly distinct profiles of response to medical therapy. To test this hypothesis, we conducted a blinded, matched case-control pilot study to examine the correlation between effect of antipsychotic treatment and CNV status.

Methodology: 12 schizophrenia patients carrying CNVs associated with schizophrenia were matched one-by-one on age and gender to 12 schizophrenia patients without CNVs. Clinical data from ten years of medical records (2000-2010) and data from the comprehensive, national health registers were collected for all 24 patients.

Results: Paired analysis showed that body mass index, smoking, CYP2D6 phenotype, substance abuse, suicidal behavior and habitation were similar between the two groups. The CNV carriers had experienced fewer positive antipsychotic drug trials than the non-carriers (1.42±1 vs. 2.08±1) and more antipsychotic drug trials altogether (3.42±2.31 vs. 2.72±1.60), corresponding to a significant lower success rate per drug trial (p=0.019). Also, we found an indication that CNV carriers might have an earlier age of onset (p = 0.086) and were more hospitalized during their illness, measured as percentage of time spent in hospital during their illness (p = 0.062). A sample size of 48 patients with the same outcome would have yielded significant results for these last two trends.

Conclusions: These observations seem to support general expectations that CNV-carrying patients may have an earlier onset of illness which also could explain their greater deal of hospitalization and poorer effect of antipsychotic treatment.

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AKAP13, CACNA1, GRIK4 AND GRIA1 GENETIC VARIATIONS MAY BE ASSOCIATED WITH HALOPERIDOL EFFICACY DURING ACUTE TREATMENT

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We previously investigated a sample of psychotic patients acutely ill and acutely treated with haloperidol in the search for genetic predictors of response at PANSS scores during the first month of treatment. In the present work we extend the analysis to a wider panel of genetic variations including SNPs harbored by genes whose products are involved in molecular pathways consistent with the latest results of genome-wide association studies (GWAS) of antipsychotic efficacy. 101 schizophrenic patients were investigated. The results were replicated in an independent sample of bipolar manic patients treated with antipsychotics (n tot = 470, the sample was retrieved from the STEP-BD). Outcomes were the PANSS variation through time in the first sample, and changes of mania symptomatology at any two consecutive observations in the STEP-BD replication sample. A list of variations harbored by AKAP13, CACNA1, GRIK4 and GRIA1 were associated with outcome in both samples (different set of variations for each sample). This finding stresses the relevance of the glutamatergic system and regulatory molecular cascades in antipsychotic response. Nonetheless, the level of significance and the indirect and incomplete replication mandate cautiousness and further replication.