

## 5-HT2C GENE VARIANTS AND ANTIPSYCHOTIC INDUCED WEIGHT GAIN: NEW FINDINGS IN AN EVER PRESENT CANDIDATE

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**INTRODUCTION:** Associations between gene variants of the 5-HT2C gene and antipsychotic induced weight gain are the most established findings in this area of research pertaining to antipsychotic induced weight gain. However, polymorphisms of the 5-HT2C gene have yet to be studied extensively.

**METHODS:** Our study aims to investigate four 5-HT2C polymorphisms (including rs498207, -759C/T, -697G/C, Cys23Ser) using four different samples (total n=222). Samples were collected in North America (A, B and C; total n=139) and Germany (D; n=83). Sample A and B (n=80) were 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 after approximately 11 weeks. Sample D was assessed for up to six weeks using a variety of antipsychotics. Since the 5-HT2C gene is X-linked, we also performed analyses in the total sample by taking into consideration the X chromosome and analysing males and females separately.

**RESULTS:** Genotypic, allelic, and haplotypic analysis of percent weight change, and at least 7% weight gain change, revealed a significant association with the 5-HT2C gene. Specifically, we found a significant over representation of -759C, -697G, Cys23 haplotype in patients with weight gain (OR= 1.93; 95% C.I.: 1.04-3.56 p=0.0015). Similarly, haplotype analyses of percentage weight change were also significant (p=0.029) with the -759C, -697G, Cys23 haplotype associated with the highest average percent weight gain. Observations in the polymorphisms are consistent with previous studies.

**CONCLUSION:** According to our results, the four polymorphisms analyzed may play a role in predicting weight gain associated with antipsychotics. However, more polymorphisms need to be considered in all the serotonin receptor genes along with larger sample sizes. We are currently expanding our analyses in a sample collected in the UK.

## EVIDENCE FOR A ROLE OF THE SYNAPTIC VESICLE GLYCOPROTEIN 2C GENE IN ANTIPSYCHOTIC RESPONSE

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The Synaptic vesicle glycoprotein 2C gene (SV2C) is expressed in dopaminergic neurons of the substantia nigra and the ventral tegmental area. The SV2C protein plays a role in synaptic vesicle exocytosis. Using samples from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, we evaluated the impact of 64 SV2C SNPs on response to olanzapine, quetiapine, risperidone, and ziprasidone using both last observation carried forward (LOCF) and mixed model repeat measures (MMRM) as the dependent variables. In the Caucasian sample, homozygosity for the T allele of rs11960832 correlated with worsening of PANSS for subjects treated with olanzapine in Phase I of the trial (N=93; LOCF,  $P = 9 \times 10^{-5}$ ; MMRM,  $P = 1.4 \times 10^{-5}$ ). Patients having this genotype also displayed somewhat diminished response for the other atypical antipsychotics, but the results were not significant for the other drugs as a group (N=240) or for the individual arms. Thus, further investigation of the role of this gene in differential response to atypical antipsychotic medications seems warranted.

## ASSOCIATION STUDY OF MELANOCORTIN-4 RECEPTOR GENE POLYMORPHISMS WITH ANTIPSYCHOTIC WEIGHT GAIN

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**INTRODUCTION:** Antipsychotic induced weight gain (AIWG) may result in the metabolic syndrome in schizophrenia patients. A recent genome wide association study of (AIWG) found the highest main peak in the region of the MC4R gene, at the downstream marker rs489693. Thus, we examined additional variants to investigate a larger MC4R gene region.

**METHODS:** Four SNPs (rs2229616, rs17782313, rs11872992, rs8087522) were genotyped in 237 patients who underwent treatment for chronic schizophrenia and were evaluated for AIWG for up to 14 weeks. We compared weight change (%) across genotypic groups using analysis of variance and covariance for three SNPs ( $r^2 \geq 0.8$ ). Variants were genotyped using ABI TaqMan assays. In the case of a positive association, we investigated in silico and in vitro for functional relevance of the SNP.

**RESULTS:** The rs2229616 SNP was monomorphic in our population and thus excluded from analyses. No significant genotypic or allelic associations were found between rs11872992, rs17782313 or rs8087522 polymorphisms and weight gain ( $p > 0.05$ ). However, a subsequent analysis showed that patients of European ancestry who were carriers of the rs8087522 A-allele (AG+AA) on clozapine gained significantly more weight than non-carriers ( $p=0.027$ ). Electrophoretic mobility shift assay suggested that the presence of the A-allele appears to create a transcription factor-binding site.

**CONCLUSIONS:** In this study, we observed that the rs8087522 SNP of the MC4R gene may be associated with AIWG in schizophrenia patients of European origin. There may be functional effects of this SNP on transcription factor binding. Further investigation is warranted for these findings.

## MEASUREMENT OF ANTIPSYCHOTIC DRUGS IN ORAL FLUID, CAPILLARY BLOOD, AND DRIED BLOOD SPOTS

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**BACKGROUND:** Antipsychotics are used in children and adolescents to treat schizophrenia, attention deficit hyperactivity disorder, and autism. Few such drugs have a defined posology in these populations, in part because pharmacokinetic and pharmacodynamic studies are often lacking. Because of the inherent difficulties of performing such studies, not least that surrounding conventional blood sampling, use of alternative matrices [oral fluid, capillary blood, and dried blood spots (DBS)] has been investigated.

**METHODS:** Oral fluid collected from volunteers by drooling and heparinised human whole blood were used to prepare solutions containing amisulpride, aripiprazole/dehydroaripiprazole, clozapine/norclozapine, olanzapine, risperidone/9-hydroxyrisperidone, and sulpiride, respectively. Whole blood solutions (30 µL) were applied to a range of filter papers, including coated forms developed for DBS analysis, and dried (24 h, ambient temperature). A 3 mm diameter spot punched from the centre of each DBS was vortex-mixed (5 min) with aqueous Tris (2 mol/L, pH 10.6). Oral fluid or extracted DBS (200 µL), Tris (2 mol/L, pH 10.6) (100 µL), internal standard solution (25 µL) and butyl acetate:butanol (9+1) or methyl tert-butyl ether (75 µL) were vortex-mixed, centrifuged, and a portion (20 µL) of the extract analysed HPLC-APCI-MS/MS.

**RESULTS:** Olanzapine was unstable in oral fluid and whole blood. Olanzapine excepted, recoveries of 80–100 % were achieved routinely from DBS. There was no marked difference in recovery between the different papers studied.

**CONCLUSIONS:** Some antipsychotics and metabolites may be measured in oral fluid and in DBS. However, the relationship between oral fluid, DBS, and plasma analyte concentrations remains to be established.

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## TREATMENT RESISTANT SCHIZOPHRENIA: ANALYSIS OF POLYMORPHIC CPG SITES IN 5HT RECEPTORS

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Serotonin receptor blockade is the major basis for the antipsychotic action of atypical antipsychotic drugs (AP) and a necessary but not sufficient basis for the action of atypical APs such as clozapine and other multireceptor antagonists. Genetic factors affecting the density and/or function of serotonin receptors and enzymes may therefore affect AP response.

This exploratory study investigates the effect of 20 single nucleotide polymorphisms (SNPs) from HTR3A, HTR3B and HTR4 genes on antipsychotics response in two distinct schizophrenic populations refractory or not-refractory according to the APA criteria.

This study included 242 DSM-IV schizophrenics. Genotyping was determined by 5'-exonuclease fluorescence assays. Within each population, distributions of response measures were compared between genotype, allele and haplotype groups using analysis of chi-square. The analysis of CpG sites was also performed considering the number of methylation site available.

In this sample, no significant associations were found for any individual SNP or haplotype analyses. In the CpG analysis we found that the percentage of available CpG sites was almost the same in resistant and non-resistant patients.

This exploratory analysis suggests that HTR3 and HTR4 genes may not affect antipsychotic response. Furthermore our novel polymorphic CpG sites analysis suggests that methylation difference in these genes are unlikely influenced by the CpG allele nevertheless we suggest the polymorphic CpG mapping as preliminary step of candidate gene methylation analysis.

## GLUTAMATERGIC PATHWAY DISSECTION AND INDICATIONS FOR GENETIC ASSOCIATION STUDIES IN MAJOR DEPRESSIVE DISORDER

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**INTRODUCTION:** The glutamatergic pathway has been consistently involved in the physiopathology of depressive disorder, however a complete dissection and integration of its role in the context of other known mechanisms is lacking. We summarized and integrated the evidence of various levels of interaction between glutamatergic and monoaminergic pathways to provide a detailed list of possible candidates with practical suggestions for association studies planning.

**METHODS:** We identified six molecular pathways, some of which with specific regional distribution within the brain. From the six pathways we identified the key proteins and their coding genes. Hapmap database ([hapmap.ncbi.nlm.nih.gov](http://hapmap.ncbi.nlm.nih.gov)) served for the identification of the tagging variations. Pubmed database (<http://www.ncbi.nlm.nih.gov>) served for the identification of all the validated variations and functional variations for each candidate. All the identified validated variations for each candidate were forced as input in the Hapmap dataset in order to retrieve the maximum coverage of each candidate under a tagging approach.

**RESULTS:** Reviewing the lines of evidence of two fundamental theories of major depressive disorder (MDD) we disentangled six main metabolic pathways that could be pivotal in the pathophysiology of the disease: the CAM kinase II, the MAP kinase and ERK, PKA and PKC, the inositols pathway, the NO cascade, the axon guidance and actin cytoskeleton and the cellular death pathway.

**CONCLUSIONS:** We obtained a list of pivotal enzymes out of which we numbered the covering genetic variations. Such coverage may provide a genetic framework to serve future genetic association studies.

## TRAJECTORIES OF RESPONSE TO ANTIDEPRESSANT TREATMENT ARE IMPACTED BY SOCIODEMOGRAPHIC VARIABLES IN THE STAR\*D SAMPLE: A NEEDED BACKGROUND FOR GENETIC ASSOCIATION STUDIES?

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Pharmacogenetics holds the promises to delineate the biological variables that predict response to antidepressant treatment. Nonetheless, decades of research in the field did not cast conclusive results<sup>1 2</sup>. Stratification factors may have played a role in slowing the genetic association researches insofar. Sociodemographic variables are associated with response to antidepressant treatment<sup>3</sup> and their effect should be separated from the genetic load in identifying the biological cornerstones of antidepressant efficacy. We identified the same three main trajectories of response in the STAR\*D (level 1, n=1680) and in the Italian sample (n=236) of depressed subjects treated with antidepressant pharmacotreatment. We found that patients who simultaneously had higher education, higher money income, were not living alone and with a good employment status (n=185 and n=70 in the STAR\*D and Italian samples respectively) had the same higher chance to be classified as responders to the antidepressant treatments in both samples. In particular, the odds ratios were 2.6 and 2.2 in the American and in the Italian groups respectively (p= 0.0005 and p=0.002). Finding that the magnitude of impact of the sociodemographic predictors towards antidepressant response is grossly similar in both groups was surprising in that American patients were treated in a variety of specialized or not specialized units widespread in their country, whilst the Italian patients were inpatients treated in a highly specialized structure specialized in mood disorders. These variables should be taken in consideration when re-analyzing the STAR\*D sample for genetic associations, alone or in combination with other databases.

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## ASSOCIATION ANALYSIS OF *SIGMAR1* WITH MAJOR DEPRESSIVE DISORDER AND SSRI RESPONSE

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**BACKGROUND:** Several investigations have suggested the possible involvement of sigma 1 non-opioid intracellular receptor 1 (sigma 1 receptor) in the pathophysiology of major depressive disorder (MDD). Sigma 1 receptors are also one of the major pharmacological therapeutic targets of selective serotonin reuptake inhibitors (SSRIs). To evaluate the association of sigma 1 receptor gene (*SIGMAR1*) and MDD and SSRIs therapeutic response in MDD, we conducted a case-control study of Japanese samples (466 MDD patients, 516 controls and 208 MDD patients treated by fluvoxamine or sertraline).

**METHOD:** We defined a clinical response as a decrease of more than 50% in baseline the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D) within 8 weeks, and clinical remission as an SIGH-D score of less than 7 at 8 weeks. Therefore, we selected rs1800866 in *SIGMAR1* for the following association analysis.

**RESULTS:** In the logistic regression analysis, we detected an association of the phenotypes (MDD or controls) with rs1800866 genotype. However, we did not detect an association between rs1800866 and SSRI therapeutic response in Japanese MDD. In addition, remission with SSRI was not associated with rs1800866. Also, we did not detect a novel polymorphism in *SIGMAR1* when we performed a mutation search using MDD treated by SSRIs samples.

**CONCLUSION:** Our results suggest that rs1800866 in *SIGMAR1* may play a role in the pathophysiology of MDD in the Japanese population. Also, *SIGMAR1* does not play a role in the therapeutic response to SSRI in Japanese MDD patients. However, because our sample was small, a replication study using another population and larger sample will be required for conclusive results.

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## 5-HTTLPR/RS25531 AND FKBP5 POLYMORPHISMS EPISTASIS IN TREATMENT-RESISTANT DEPRESSED PATIENTS

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Major Depression Disorder (MDD) is a serious mental illness that is one of the most disabling diseases worldwide. In addition, approximately 15% of depressed patients are defined treatment-resistant (TRD).

Clinical and preclinical studies support a dysfunction of serotonin metabolism and HPA axis functionality in depression and in treatment response. In particular, the functional polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR/rs25531) are involved in the SSRI treatment response and recently, have been associated with the TRD. Moreover, genetic variations of FKBP5 (co-chaperonin of glucocorticoid receptor) were linked with antidepressant treatment response in depression.

In order to evaluate the role of these variants in TRD a total of 294 DSM-IV MDD patients judged treatment-resistant and 301 healthy volunteers were enrolled and genotyped for the 5-HTTLPR/rs25531 and FKBP5 rs1360780 polymorphisms.

Regarding the 5-HTTLPR/rs25531 the results showed that the L<sub>A</sub>L<sub>A</sub> homozygotes were more represented in the controls group (p=0.003, OR=0.75, 95%CI: 0.62-0.92) whereas for the FKBP5 the T allele in homozygosis was more represented in healthy subjects (p=0.034, OR=0.71, 95%CI: 0.50-1.01). The interaction between the two polymorphism demonstrated that L<sub>A</sub>L<sub>A</sub> & TT genotypes greatly enhances the protective effect ( $\chi^2 = 10.51$ , p = 0.001 OR = 4.82 95%CI: 1.30 - 17.91).

In conclusion, this preliminary study represents the first evidence of the role of FKBP5 in TRD and an epistatic effect with 5-HTTLPR/rs25531 polymorphism.

## HTR1A, HTR2A, HTR6 AND ANTIDEPRESSANT RESPONSE IN MAJOR DEPRESSIVE DISORDER: CASE-CONTROL STUDY AND META-ANALYSIS

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**OBJECTIVE:** The 5-HT receptor gene might be one of the therapeutic targets for SSRIs in MDD. To evaluate the association between *HTR1A*, *HTR2A* and *HTR6* and the efficacy of SSRI treatment in Japanese MDD patients, we conducted a case-control study in a Japanese population. We further aimed to conduct a meta-analysis of rs6295 in *HTR1A*, rs6311, rs6313 and rs7997012 in *HTR2A* and rs1805054 in *HTR6*.

**METHODS:** 268 patients were treated with SSRIs. The MDD patients in this study had scores of 12 or higher on the 17-item SIGH-D. We defined a therapeutic response as a  $\geq 50\%$  decrease in SIGH-D from baseline within 8 weeks, and clinical remission as a SIGH-D score of  $< 7$  at 8 weeks. To identify studies eligible for the meta-analysis, we searched PubMed citations through December 2010.

**RESULTS:** *HTR1A* was associated with therapeutic response to SSRIs in the Japanese MDD population both in the allele and genotype analysis. In addition, rs6295 in *HTR1A* was associated with the therapeutic antidepressant response in MDD in the meta-analysis. *HTR2A* was associated with the therapeutic response to SSRIs in Japanese MDD patients in a haplotype-wise analysis, but not in the meta-analysis. Conversely, *HTR6* was associated neither with therapeutic antidepressant response in the allele/genotype, haplotype nor meta-analysis.

**CONCLUSIONS:** *HTR1A* may play an important role in the pathophysiology of SSRI response in MDD. Furthermore, it will be necessary to conduct a meta-analysis for haplotypes of *HTR2A*.

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## THE PUTATIVE FUNCTIONAL RS1045881 MARKER OF NRXN1 IN CLOZAPINE RESPONSE

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**BACKGROUND:** *In silico* analysis revealed that the rs1045881 polymorphism in the *neurexin-1* gene (*NRXN1*) is a putative microRNA binding site that may be of functional significance in regulating *NRXN1* expression. *NRXN1* modulates recruitment of NMDA receptors. Furthermore, clozapine reduces hyperactivity of NMDA receptors. Thus, regulation of *NRXN1* may mediate clozapine's efficacy at reducing cortical hyperactivity. In this study, we aim to examine the association between rs1045881 and schizophrenia, and the potential role in clozapine response.

**METHODS:** We analyzed the allele and genotype frequency of rs1045881 for association with schizophrenia in 302 paired case-controls; next, we genotyped rs1045881 in 169 European-American schizophrenia patients assessed prospectively for clozapine response. Treatment response was defined as a 20% reduction in Brief Psychiatric Rating Scale (BPRS) at the time of enrolment into the study (baseline) to after six months of clozapine treatment.

**RESULTS:** The rs1045881 variant was not significantly associated with schizophrenia. However, we did observe an association with clozapine response (20% reduction in BPRS scores; Allelic:  $p = 0.0121$ , OR = 2.199 [1.185-4.080]; Genotypic:  $p = 0.0296$ , OR= 2.153 [1.077-4.304]). Repeated measures ANOVA of baseline and after six months BPRS scores revealed rs1045881 genotype by treatment period trend ( $F_{1,87}=3.151$ ,  $p=0.079$ ,  $N=91$ ).

**DISCUSSION:** This result suggests that the rs1045881 *NRXN1* polymorphism may influence clozapine response. Independent replication is necessary to confirm our results.

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## COMT GENOTYPE AND RESPONSE TO COGNITIVE REMEDIATION IN SCHIZOPHRENIA

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**BACKGROUND:** A functional polymorphism of the catechol-O-methyltransferase (COMT) gene (Val158Met) partially influences cognitive performance both in schizophrenia and in healthy controls by modulating prefrontal dopaminergic activity. Our aim is to evaluate the effect of COMT Val108/158 Met genotype with the response to computerized neurocognitive remediation (CRT) in patients with chronic schizophrenia. We present initial pilot data.

**METHOD:** COMT Val108/158 Met polymorphism was analyzed for 102 inpatients with schizophrenia out of a planned 144. Patients were evaluated on a battery of neuropsychological assessments, functional skills, and PANSS at baseline and at endpoint (Week 12). Met heterozygote were combined as Met carriers (Met/Val = 48) with Met homozygote (Met/Met = 9) and compared to Val homozygote (Val/Val n = 45). Response to CRT was defined as  $\geq 20\%$  performance improvement on the Trail Making tests (TMT) and Continuous Performance Test (CPT-IP) as a cut-off criterion for two groups: (1) Responders and (2) Non-responders. Mixed model analysis was conducted for each cognitive domain (Executive Functioning, Processing Speed, Working Memory, Attention/Vigilance, Global Cognitive Index) and was based on Met/Val + Met/Met (n = 48+9) vs. Val/Val (n = 45).

**RESULTS:** No significant demographic, neuropsychological or functional differences were seen between groups at baseline, or between responder vs. non-responder classification and the COMT classification (Met/Val + Met/Met vs. Val/Val). Mean overall PANSS was  $78.12 \pm 12.84$ . A significantly greater improvement was found for the global cognitive index score ( $p = 0.050$ ;  $\eta^2 = .231$ ), TMT processing speed ( $p = 0.049$ ;  $\eta^2 = .291$ ) and working memory (WMS®-III, Spatial Span, LNS;  $p = 0.048$ ;  $\eta^2 = .231$ ) for the Met group compared to the Val/Val group. Mean d' of the CPT-IP was  $1.17 \pm 1.1$  for the Val/Met+Met/Met genotypes, and  $0.91 \pm 1.0$  for Val/Val. There was a significant effect of COMT genotype ( $p = 0.05$ ;  $\eta^2 = 0.251$ ), and years of education ( $p = 0.05$ ;  $\eta^2 = 0.201$ ).

**CONCLUSIONS:** COMT polymorphism influences improvement of cognitive functioning after CRT. The presence of low activity Met allele was associated with significantly greater improvements in overall neurocognitive functioning, processing speed, working memory and attention/vigilance after 12-weeks of CRT. Due to the small sample size, positive findings could be due to Type I Error.

## **BIPOLAR DISORDER AND SUBSTANCE ABUSE: GENETIC AND CLINICAL PREDICTORS OF DEPRESSIVE OUTCOME**

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Little is known about factors associated with treatment outcome of depression in Bipolar Disorder (BD). In our study we extensively evaluated a sample of BD patients for clinical features, including substance use disorder (SUD) comorbidity, personality disorders and traits, and social functioning, together with polymorphisms in 8 candidate genes for BD and response to antidepressant treatment.

One-hundred and thirty-one BD patients and 65 healthy controls were recruited at the Department of Psychiatry and the Centre of Addiction at the Gemelli hospital of Rome, Italy. Patients were characterized for demographic and clinical variables and evaluated by the Hamilton scales for depression and anxiety (HAMD, HAMA), the Global assessment of functioning scale (GAF), the Temperament and character inventory (TCI), the Social adjustment scales, self report (SASS) and the Quality of life scale (QoL). Polymorphisms in the following genes were genotyped in both BD patients and controls: Serotonin transporter (SLC6A4), Serotonin receptor 2C (5HTR2C), Tryptophan hydroxylase (TPH), Dopamine receptor D2 (DRD2), Dopamine receptor D4 (DRD4), Brain derived neurotrophic factors, Interleukin 1 beta (IL1b), Nitric oxide synthase 1 adaptor protein (NOS1AP), Transient receptor potential channel 2 (TRPM2). Moreover, 92 patients satisfying criteria for a depressive episode were entered in a 12-months follow-up under naturalistic treatment with antidepressants, mood stabilizers and/or antipsychotics.

Comorbidity for SUD was more frequent in BD type II and in patients with a Personality disorder, was associated with poorer social functioning but did not impact treatment outcome. Clinical factors associated with response to treatments were baseline severity and the temperamental trait of Harm avoidance. A polymorphism within 5HTR2C was found associated with BD in case-control analysis. Trends of association were observed between haplotypes in TPH1 and BD, and IL1b and SUD. The BDNF gene was found to independently influence the outcome of treatment, while variants in SLC6A4 did influence the outcome in interaction with levels of Harm avoidance.

Data derived from this study confirmed an involvement of 5HTR2C in BD as well as a potential role of TPH1. Other genes were not associated with the risk for BD, while IL1b may play a role in SUD. SUD and personality disorders did not impact significantly the outcome of bipolar depression, while the temperamental trait of Harm avoidance seem to play a critical role. Nevertheless, the effect of Harm avoidance may be mediated by variants in the SLC6A4 gene, while it is independent from the effect of other genes. Finally, BDNF may play a critical role in treatment outcome as well, independently from other individual features.

## 102T/C 5-HT2A POLYMORPHISM AND EARLY RESPONSE TO ANTIPSYCHOTICS

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Second-generation antipsychotics display high affinities for serotonin (5-HT) receptors. In support of this hypothesis, pharmacogenetic studies using 5-HT2A polymorphisms were carried out in last decade. Nonetheless the results of these researches are heterogeneous, there is a general agreement that 5-HT2A functional polymorphisms, such as 102T/C, play a role in antipsychotic response mechanism.

However, all these studies focused on long treatment period, making these results of limited use in clinical practice. Recently it was shown that the response to treatment at two weeks is a strong and valid predictor of longer-term outcome.

Thus the aim of this study was to investigate putative associations between early antipsychotic treatment outcome (2 weeks) and 5-HT2A 102T/C polymorphism.

We analysed 95 patients in monotherapy with risperidone and 76 with olanzapine; drug response was assessed by Positive and Negative Syndrome Scale (PANSS) at admission (T0), following 1-week (T1) and 2-weeks (T2) of antipsychotic treatment.

No significant association was found in the patients group treated with olanzapine while an influence of 5-HT2A 102T/C polymorphism on risperidone outcome was obtained. In particular, the T allele carriers showed a greater improvement in positive and general symptomatology ( $p=0.01$ ;  $p<0.01$  respectively).

The study results suggest an involvement of 5-HT2A receptor in the mechanism of drug action of risperidone and not olanzapine. In particular the carriers T allele 5-HT2a 102T/C polymorphism are associated with a better improvement to symptomatology such as persecution, hostility, anxiety, hallucinations, in schizophrenia patients after two week of risperidone treatment.



## **AMP-ACTIVATED PROTEIN KINASE 1 (AMPK-1) GENES ARE ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC-INDUCED WEIGHT GAIN**

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**INTRODUCTION:** Antipsychotic induced weight gain has emerged as a serious complication in the treatment of patients with atypical antipsychotics, especially with clozapine and olanzapine. These particular drugs may induce weight gain by histamine H1 receptor-linked activation of hypothalamic AMP-kinase (AMPK) genes, as suggested by a mice-study (Kim et al., 2007). The AMPK protein is composed of catalytic  $\alpha$  subunits and regulatory  $\beta$  and  $\gamma$  subunits, encoded by genes called PRKA-A, -B and -G, respectively.

**METHODS:** We investigated whether PRKAA1, A2, B1 and B2 gene polymorphisms were associated with antipsychotic-induced weight gain. Overall, we analyzed ten polymorphisms in 209 schizophrenia subjects derived from two US-samples and one sample from Germany, treated mostly with clozapine and olanzapine for up to 14 weeks.

**Results:** In the sample treated with clozapine and olanzapine, we found significant associations with induced weight gain and genotypes and for SNP rs3805494 in the PRKAA1 ( $p = .02$ ) and for SNP rs10789038 in the PRKAA2 gene ( $p < .02$ ). Allelotypic analyses became even more significant for rs3805494 and rs10789038 ( $p = .007$ ). In the smaller subgroup of patients with European ancestry, a trend for an associations for both SNPs was observed ( $p = .09$  and  $p = .05$ , respectively).

**CONCLUSIONS:** We observed significant associations between polymorphisms in AMPK subunit genes and weight gain induced by clozapine and olanzapine. Results of the haplotypic and gene-gene interaction analyses, as well as findings from an ongoing replication study in a UK sample will be presented.

## **FINDING GENE EXPRESSION REGULATORS IMPLICATED IN MAJOR DEPRESSIVE DISORDER (MDD) USING FORMALDEHYDE ASSISTED ISOLATION OF REGULATORY ELEMENTS (FAIRE)**

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The exact cellular mechanisms that underline (MDD) remain unclear but dysregulation of neuronal gene expression is thought to play an important role in MDD and other mood disorders. We aimed to identify novel genomic regions that act as regulators of gene transcription in neurons involved in aetiology of MDD via a two-stage strategy. First, we isolated genomic regions that become transcriptionally active when stimulated by a battery of MDD relevant mood stabilizers and hormones in a neuroblastoma cell model (SHSY5Y) using the FAIRE technique. Second, based on the principle that sequence conservation in non-coding portions of the genome across evolutionary time are indicative of transcriptional regulatory regions, we selected 45K evolutionary conserved regions (ECRs, LOD>600, UCSC genome browser Hg18) and included them in a custom-made ECR microarray (Nimblegen platform 2.1 features, 12sub-array, 135K per sub-array, n=3 probes per ECR). Finally, we hybridised the material obtained in the first part against our ECR array.

We found 10 transcriptionally active ECRs results when SHSY5Y cells were stimulated with Lithium, Valproate and b-17 estradiol (threshold of significance with 95% confidence, set at  $p < 1.1E-06$ , based on Bonferroni correction, similar results with Benjamini and Hochberg false discovery rate [FDR] method to correct for multiple testing). Our preliminary results indicate that this bioinformatic and biochemical approach is useful for identifying non-coding regions of the human genome with a significant regulatory function after exposure to stimuli known to be associated to onset and treatment of MDD.

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## A CANDIDATE GENE EXPRESSION STUDY INVESTIGATING THE EFFECTS OF VALPROIC ACID IN RELATION TO SEROTONIN TRANSPORTER HAPLOTYPES REVEALS INCREASED TRANSCRIPTION OF CREB

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Recent studies involving the mood-stabilizers lithium and lamotrigine have revealed changes in the transcription of the serotonin transporter gene (5-HTT) and in its regulatory transcription factors, YB-1 and CTCF on exposure to these drugs. Furthermore, such drug-induced expression changes were affected by genomic variants in the serotonin transporter (5-HTTLPR and Stin2). The aim of the current study was to investigate the changes in expression of six candidate genes: *5-HTT*, *YB-1*, *CTCF*, *BDNF*, *CREB* and *REST*, on exposure to the mood-stabilizer valproic acid, in relation to serotonin transporter haplotypes. Peripheral blood samples were collected from participants as part of the Depression Case Control Consortium. Lymphoblastoid cell lines were then generated and selected based on polymorphisms in the serotonin transporter. These include the s/s 10/10 and the l/l 12/12 haplotypes. The cells were treated with 0, 0.06, 0.3 or 0.6mM valproic acid for 24 hours. Subsequently, real-time qPCR studies determined the expression of candidate genes. Real-time quantification analyses revealed there was an increase in the expression of *CREB* on exposure to the highest concentrations (0.6 mM) valproic acid treatment. There were no significant expression changes in the other target genes and no haplotypic differences were observed. The finding that valproic acid increases the expression of *CREB* is novel and warrants further investigation. If gene expression changes in the peripheral blood were found to translate to brain, it may help to elucidate a potential mechanism of action of valproic acid and identify a potential peripheral biomarker indicative of therapeutic efficacy.

## INFLUENCE OF *TPH2*, *DAOA* AND *BDNF* VARIANTS ON DIAGNOSIS AND RESPONSE TO TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE, BIPOLAR DISORDER AND SCHIZOPHRENIA

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**BACKGROUND:** Current evidence suggests that several genes including the tryptophan hydroxylase 2 (*TPH2*), the D-amino acid oxidase activator (*DAOA*) and the brain derived neurotrophic factor (*BDNF*) could be involved in the etiology and response to treatment of several psychiatric disorders. Accordingly, we aimed to investigate whether some SNPs within these genes, including rs4570625, rs10748185, rs11179027, rs1386498, rs4469933, rs17110747 (*TPH2*), rs3916966, rs3916967, rs2391191, rs3916968, rs7139958, rs9558571, rs778293 (*DAOA*), rs2030324, rs7103873, rs10835210, rs11030101 and rs6265 (*BDNF*) could be associated with major depression (MD), bipolar disorder (BD) and schizophrenia and whether they could predict clinical outcomes in Korean in-patients treated with antidepressants, mood stabilizers and antipsychotics respectively.

**METHODS:** One hundred forty five patients with MD, 132 patients with BD, 221 patients with schizophrenia and 170 psychiatrically healthy controls were genotyped for the SNPs mentioned above. Baseline and final clinical measures, including MADRS, YMRS and PANSS scores for patients with MD, BD and schizophrenia respectively were recorded.

**Results:** Rs10835210 CA and rs11030101 AT genotype frequencies were higher in BD and schizophrenia patients than in healthy and MD subjects. In patients with MD, rs4570625-rs10748185 G-A haplotype was associated with higher endpoint MADRS severity. Additionally, Rs7139958 AA and rs9558571 TT genotypes as well as rs7139958 A and rs9558571 T alleles were associated with higher baseline PANSS positive subscale scores in patients with schizophrenia.

**CONCLUSION:** Some associations have been observed between genetic variants under investigation and specific psychiatric disorders and clinical outcomes. However, current evidence is far from being conclusive and further replications are required.

## **META-ANALYSIS OF THE ASSOCIATION BETWEEN THE SEROTONIN TRANSPORTER GENE PROMOTER POLYMORPHISM AND THE ANTIDEPRESSANT EFFICACY**

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**BACKGROUND:** within the past ten years the serotonin transporter gene promoter polymorphism (HTTLPR) was one of the most studied genetic variant as predictor of antidepressant response. Nevertheless, results are not consistent across studies and previous meta-analysis, since it is not clear if this polymorphism has a significant effect on antidepressant response and what allele or genotype predicts better response.

**METHODS:** we systematically reviewed literature and selected 19 studies on Caucasian samples and 13 on Asian ones in order to perform meta-analyses. Using the Cochrane review manager we tested two phenotypes - remission and response rates - and two genotype comparisons - ll versus ls/ss and ss versus ll/s -. Evaluations were performed for SSRIs and mixed/other drugs separately and for Caucasians and Asians separately.

**RESULTS:** in Caucasians we found a significant association between SSRI response and l/l genotype ( $p=0.007$ ), and l allele as well ( $p=0.007$ ). This last association remained significant also considering all antidepressant classes ( $p=0.003$ ). Moreover, l/l genotype showed greater remission rate during SSRI treatment ( $p=0.04$ ) and l carriers showed greater remission rate both with SSRIs ( $p=0.01$ ) and mixed antidepressants ( $p=0.009$ ). In Asians, a significant association was found between l/l genotype and remission ( $p=0.02$ ) only considering all antidepressant classes together.

**CONCLUSION:** in Caucasians HTTLPR is likely a predictor of antidepressant response and remission, particularly for SSRIs, whilst in Asians it does not appear to play a major role.

## IS PHARMACOGENETIC TESTING READY FOR ANTIDEPRESSANT TREATMENT? EVIDENCE FROM A SIMULATED COST-EFFECTIVENESS MODEL

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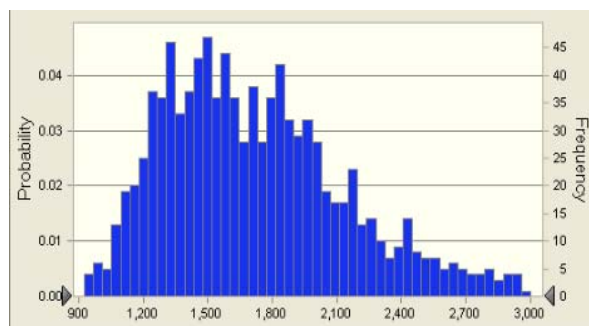
**BACKGROUND & AIMS:** Pharmacogenetics may represent a valuable tool to improve drug choice by identifying likely responders a priori, however the exact benefit in routine activity has been scarcely investigated. Therefore we implemented a theoretical analytic model to compare the cost-effectiveness of two treatment strategies for Major depressive disorder (MDD) within a 12-weeks trial: A. SSRI monotherapy B. alternative administration of serotonergic or noradrenergic antidepressants under guidance from genetic testing (5-HTTLPR polymorphism).

**METHODS:** The model was based on Italian Mental Health setting and managed care was conducted according to APA guidelines. Cost data were drawn from WHO\_CHOICE project (World Health Organization) and Italian official sources. All costs were deflated to 2005 and expressed in international dollars. The effect size of 5-HTTLPR was estimated from a meta-analysis of pharmacogenetic trials.

**RESULTS:** The use of genetic test increased remitters by 5%, with an estimated gain of 0.07 Quality-Adjusted Life Weeks. This projected ICER to \$ 3,269 (largely above cost-effectiveness threshold), but only for the worse case scenario, while the distribution was largely below threshold. Sensitivity analysis demonstrated the strongest impact of genetic test cost on ICER. Quality of life (HRQL) assigned to untreated depression and 5-HTTLPR effect size were less important contributors. Modeling variations in these parameters, pharmacogenetic approach became cost-effective. Under base-case conditions genetic test should cost \$75 or less to drop below cost-effectiveness threshold. In severe depression with low HRQL the cost of genetic testing could raise to \$270.

**CONCLUSIONS:** To date performing a pharmacogenetic test before starting antidepressant treatment may be moderately cost-effective in selected groups of patients with severe and disabling MDD. A widespread use of pharmacogenetics may become convenient for clinical practice if prediction power of tests is improved and costs drop to \$50 - \$100.

Figure 1. Probability distribution of outcome forecasts after Monte Carlo simulation



## A PRELIMINARY INVESTIGATION OF *CREB1*, *PTGS2*, *GRIK4* AND *GNB3* POLYMORPHISMS ON TREATMENT RESISTANCE IN MAJOR DEPRESSION

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**INTRODUCTION:** Several genes including those coding for the transcription factor cyclic adenosine monophosphate response element binding (*CREB1*) protein, the prostaglandin-endoperoxide synthase enzyme 2 (*PTGS2*), the glutamate ionotropic kainate 4 receptor (*GRIK4*) and the guanine nucleotide binding protein beta polypeptide 3 (*GNB3*) have been repeatedly involved in the aetiology and response to treatments of major depression (MD). Accordingly, The aim of the present paper is to investigate whether a set of single nucleotide polymorphisms (SNPs) within *CREB1* (rs2709376, rs2253206, rs7569963, rs7594560, rs4675690), *PTGS2* (rs4648276, rs2066826 and rs689466), *GRIK4* (rs1954787) and *GNB3* (rs5443) genes was associated with MD as well with antidepressant response, remission and treatment resistance.

**METHODS:** 194 MD patients and 76 healthy controls treated with antidepressants at adequate doses for at least 4 weeks were genotyped for *CREB1*, *PTGS2*, *GRIK4* and *GNB3* SNPs. Response, remission and treatment resistance were recorded.

**RESULTS:** A allele of rs7569963 as well as rs2253206-rs7569963 A-A and rs7569963-rs4675690 A-C haplotypes in *CREB1* were significantly associated with treatment resistance. No significant association was observed between any of the remaining genotypic, allelic and haplotypic variants under investigation and outcomes of interest.

**CONCLUSION:** Some genetic polymorphisms in *CREB1* could influence treatment resistance to antidepressants. On the other hand, there is no evidence suggesting any association between *CREB1*, *PTGS2*, *GRIK4* and *GNB3* and treatment response or remission and with MD. However, on account of the several limitations of the present study including a relatively small sample size and the incomplete coverage of genes under investigation, further research is needed.

## 5-HTT POLYMORPHISMS—SIGNIFICANT IMPACT ON RESPONSE AND SIDE EFFECTS UNDER SSRI THERAPY

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**BACKGROUND:** The 5-HTT transporter is the therapeutic target of selective serotonin reuptake inhibitors (SSRIs). A length polymorphism in the promoter region (5-HTTLPR) combined with a SNP (rs25531) nearby was reported to influence transcription activity.

**METHODS:** 349 psychiatric inpatients treated with various antidepressants were evaluated psychopathologically by the PD self rating scale and the clinical global impressions scale (CGI) at admission to hospital and 4 weeks thereafter. Side effects were assessed with a modified version of the Dosage-Record-and-Treatment-Emergent-Symptoms scale (DOTES). Genotyping was performed using validated thermocycler and RT-PCR assays. The high expression variant L<sub>A</sub> (5-HTTLPR-L-allele plus rs25531-A-allele) was compared to the 5-HTTLPR-S-allele and the L<sub>G</sub>-variant (5-HTTLPR-L-allele plus rs25531-G-allele). Numbers of response and side effects data for the analyzed subgroups were available as described below.

**RESULTS:** Carriers of 5-HTT-promoter-polymorphisms (SS, SL<sub>G</sub>, L<sub>G</sub>L<sub>G</sub>) receiving solely SSRIs as antidepressants had higher CGI-Severity and PD-S-depression-score-ratings after a 4-week-treatment than all other genotypes (Mann-Whitney-U-test, p=0.014, n=19 vs. 79; p=0.053, n=19 vs. 68). They stayed longer in hospital and suffered from more gastrointestinal side effects than patients without these genotypes (Mann-Whitney-U-test, p=0.008, n=24 vs. 91; p=0.0004, n=21 vs. 81).

Compared to patients carrying the same 5-HTT-promoter-polymorphisms but receiving other antidepressants their hospital stay was longer and the scores of 4-weeks-CGI-severity-ratings and gastrointestinal side effects were higher (Mann-Whitney-U-test, p=0.002, n=24 vs. 102; p=0.074, n=19 vs. 90; p=0.011, n=21 vs. 87).

**CONCLUSION:** The observed impact of 5-HTT-polymorphisms on therapeutic outcome might be relevant in clinical practice because severe side effects were accompanied by longer hospitalization. If confirmed, pre-treatment identification of these genotypes might help to reduce therapy costs.

## SEXUAL DYSFUNCTION, ANTIDEPRESSANT TREATMENT, AND THE 5-HTTLPR

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**OBJECTIVES:** Sexual dysfunction (SD) is a frequently reported side-effect of antidepressant treatment, particularly of selective serotonin reuptake inhibitors (SSRIs). In the multicentre clinical and pharmacogenetic study GENDEP (Genome-based Therapeutic Drugs for Depression), the effect of the serotonin transporter gene promoter polymorphism *5-HTTLPR* on sexual function was investigated during treatment with escitalopram (SSRI) and nortriptyline (tricyclic antidepressant).

**METHODS:** Four hundred ninety-four subjects with an episode of DSM-IV major depression were randomly assigned to treatment with escitalopram or nortriptyline. Over twelve weeks, depressive symptoms and SD were measured weekly with the Montgomery-Asberg Depression Rating Scale, the Antidepressant Side-Effect Checklist, the UKU Side Effect Rating Scale, and the Sexual Functioning Questionnaire.

**RESULTS:** The incidence of reported SD after twelve weeks of treatment was relatively low, and did not differ significantly between the two antidepressants (14.9% escitalopram, 19.7% nortriptyline). There was no significant interaction between the *5-HTTLPR* and antidepressant on SD. Improvement in depressive symptoms and younger age were both associated with lower SD. There was a suggestion that the effect of age on SD was moderated by the *5-HTTLPR*.

**CONCLUSIONS:** In GENDEP, the rates of reported SD during treatment were lower than those described in previous reports. There was no apparent effect of the *5-HTTLPR* on the observed decline in SD.



## ASSOCIATION STUDY OF NEURONAL PAS DOMAIN PROTEIN 3 (NPAS3) GENE WITH RESPONSE TO CLOZAPINE IN CHRONIC SCHIZOPHRENIA PATIENTS

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**BACKGROUND:** Antipsychotic drugs have been the cornerstone of treatment for schizophrenia. Inter-individual variability in response to antipsychotics is being observed and part of this variability may be attributed to genetic factors. A translocation in the NPAS3 intron 3 has also been associated with schizophrenia in one family pedigree. Furthermore, mice deficient in *Npas3* exhibit behavioral and neuroanatomical abnormalities related to human schizophrenia. Recently, polymorphisms in the neuronal PAS domain protein 3 (*NPAS3*) have been associated with response to iloperidone (Lavedan *et al.*, 2009).

**METHODS:** We analysed four single nucleotide polymorphisms (SNPs) previously associated with response in the iloperidone study (rs17100345, rs11851892, rs17583667, rs12588898) as well as three additional polymorphisms (rs7154972, rs6571574, rs12434716) for association with response to clozapine in our schizophrenia patients of European ancestry (n=176). We compared both categorical definition of response (20% decrease in the Brief Psychiatric Rating Scale score, BPRS) as well as change in BPRS score from baseline using  $\chi^2$ -test and analysis of covariance, respectively.

**RESULTS:** All the SNPs tested were in Hardy-Weinberg equilibrium ( $p>0.05$ ). No allelic or genotypic association was observed between the seven SNPs and response ( $p>0.05$ ). Similarly, no association was observed when we compared the mean change in BPRS from baseline across genotypic categories ( $p>0.05$ ).

**CONCLUSION:** Our results suggest that SNPs that we investigated in the NPAS3 gene are unlikely to be associated with response to clozapine based on findings in our patient sample. However, given the relative large size of the gene, further genetic analyses are warranted.

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## **BIPOLAR DISORDER: EVIDENCE OF AN INTERACTION WITH CALCIUM SIGNALLING GENES, TRPM2 AND iPLA2 ON THE DISEASE RISK**

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**INTRODUCTION:** Altered intracellular calcium ( $\text{Ca}^{2+}$ ) homeostasis has been implicated in the pathophysiology of bipolar disorders (BD). Interestingly, TRPM2 and iPLA2 $\beta$  play important roles in modulating and multiplexing intracellular  $\text{Ca}^{2+}$  signalling dynamics, and have been implicated in pathophysiology of BD. We have demonstrated that TRPM2-exon 11 single nucleotide polymorphism (SNP, rs1556314) associated with BD-I followed by confirmation using family study design. Moreover, two SNPs (rs4375 and rs3788533) in iPLA2 $\beta$  (also called PLA2G6) gene showed borderline association with BD (Xu et al., 2006, 2008, and 2009). We hypothesized that polymorphisms in the two genes may interact to influence the BD susceptibility.

**RESEARCH DESIGN & METHODS:** The objective of this study is to examine whether an epistatic influence (gene-gene interaction) of TRPM2 and iPLA2 $\beta$  enhance vulnerability to BD, we re-analyzed of a total of three SNPs in the two TRPM2 and iPLA2 $\beta$  genes in 190 BD cases and 278 control subjects using a logistic regression in PLINK.

**RESULTS:** Interaction analyses among three SNPs (or two pair SNPs) identified TRPM2-rs1556314 and iPLA2b-rs4375 SNP-pairs with case-control ( $P = 3.1 \times 10^{-3}$ ) epistatic signals. No significant finding was observed in case-only study design ( $P > 0.05$ ).

**CONCLUSIONS:** The results in the current study suggest interaction between two calcium signalling genes (TRPM2 and iPLA2b) plays an important role in the disease risk due to the complex networking of genetic regulations. However, the findings need to be confirmed in larger independent samples.

## POSSIBLE ASSOCIATION OF ERBB4 GENE WITH TARDIVE DYSKINESIA

Clement C. Zai, Nabilah I. Chowdhury, Arun K. Tiwari, Vincenzo de Luca, Daniel J. Mueller, Aristotle N. Voineskos, Herbert Y. Meltzer, Jeffrey A. Lieberman, Steven G. Potkin, Gary Remington, James L. Kennedy.

Tardive dyskinesia (TD) is a side effect of chronic antipsychotic medication characterized by involuntary movements mostly in the orofacial regions. Its etiology remains unclear. A recent study on genetically modified mice pointed to a possible role of neuregulin in orofacial dyskinesia (Tomiya et al, 2009). Although the NRG1 gene has been associated with schizophrenia, its role in TD has not been investigated. We explored the possible association of polymorphisms in the genes for neuregulin (NRG1) and its receptor (ERBB4) with TD. We genotyped three single-nucleotide polymorphisms in the NRG1 and ERBB4 genes in our European sample of schizophrenia patients who had been assessed for the presence of TD using the Schooler and Kane criteria (n=196). We compared the genotype frequency distributions between schizophrenia patients with and without TD. Our preliminary findings revealed that the NRG1 markers rs35753505 and rs6994992 were not associated with TD status, while the ERBB4 marker rs839523 C allele was over-represented in schizophrenia patients with TD (OR=2.71; 95% confidence interval: 1.48-4.95). Total AIMS scores were higher in patients carrying the rs839523 CC genotype compared to carriers of the other two genotypes, after including age as a covariate (p=0.016). Our results suggest that ERBB4 plays a role in TD. Further analysis with additional polymorphisms and functional study of the associated polymorphisms are required to better interpret these