PREFRONTAL ACTIVITY AND COMT GENOTYPE EFFECTS IN SCHIZOPHRENIA

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Background: Dopamine levels in the prefrontal cortex (PFC) seem to play a crucial role in cognitive function in schizophrenia. The COMT enzyme has a functional polymorphism (val158met): val/val individuals have a higher functioning enzyme leading to lower dopamine levels in PFC and therefore to poorer cognitive performance. This genetic polymorphism could mediate the relationship between dopamine levels, cognitive functioning and neural activity of PFC. We used global neuropsychological and specific cognitive assessments and fMRI to study the influence of COMT genotype on cognition and brain function in schizophrenia spectrum disorder patients, relatives and healthy control subjects.

Methods: 73 schizophrenia spectrum disorder patients, 54 relatives and 42 healthy controls performed the MATRICS Consensus Cognitive Battery to evaluate several neuropsychological domains. A sample of 19 schizophrenia spectrum disorder patients, 17 relatives and 20 controls performed the Dot version of the expectancy AX continuous performance task (DPX task) to study context processing. We used functional Magnetic Resonance Imaging (fMRI) during the performance of the DPX task.

Results: For the MATRICS battery, no group x genotype interaction was observed for any cognitive measure. There was a significant main effect of group for all neuropsychological subtests. Verbal learning (HVLT retention) showed a main effect of genotype ($F=3,28$; $p=0,04$). For the context processing task (DPX test) a genotype effect was present behaviorally and in the brain activations. Relative to controls, patients need to activate more PFC regions (DLPFC, BA10) to perform the context processing task, reflecting inefficiency. In patients there are frontal activity differences according to the genotype, with met carriers activating more DLPFC (left BA47, right BA 45) and anterior cingulate (BA32) than val carriers.

Conclusions: COMT genotype exerts little impact on neuropsychological functions. Differences in cognitive performance across groups are reliably measured by the MATRICS Consensus Cognitive battery, however this instrument seems to be not sensitive enough to capture COMT genotype effects.

Specific cognitive domains (context processing) are more sensitive to COMT genotype effects. Although patients with schizophrenia spectrum disorder exhibit more prominent deficits in context processing, these deficits are also seen in their relatives. The DPX task, which assesses context processing, is sensitive to COMT genotype in patients. Val/val carriers exhibit more contex processing impairment than met/met carriers, probably due to less dopamine availability in the PFC.

Prefrontal brain activity of context processing deficits in schizophrenia may be mediated by COMT genotype effects.

THE NMDA RECEPTOR GENE GRIN2B IN TARDIVE DYSKINESIA

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Background: Increased glutamatergic activity has been a hypothesized pathophysiological mechanism of tardive dyskinesia (TD), and only one recent study analyzed the NMDA receptor 2B (Grin2B) subunit gene in TD, and found three tested markers not associated with TD in a sample of Chinese schizophrenia patients. It is noteworthy that the Grin2B protein interacts directly with the dopamine D1 receptor (Lee FJ et al, Cell, 2002), thus providing a link between the glutamate and dopamine hypotheses of TD. We aim to explore the Grin2B gene for possible association with TD in our sample.

Methods: Our sample consists of 196 schizophrenia patients of European ethnic origin with TD assessment using the Schooler and Kane criteria (79 with TD). We genotyped four single-nucleotide polymorphisms in the Grin2B gene (NR2B) using commercially available assays, and we analyzed the genotypes and alleles for association with TD and AIMS scores.

Results: We found the C-T haplotype encompassing the rs1806201 and rs890 polymorphisms in the NR2B gene to be associated with lower risk for TD (Haploview single-marker and haplotype permutation p=0.02; OR=0.44, 95% CI:0.24-0.79). Results for the other tested Grin2B gene polymorphisms were not significant.

Conclusions: Our results suggest that the Grin2B gene may be associated with TD. We will be assessing other polymorphisms in Grin2B in addition to other glutamate system genes to further investigate the glutamatergic hypothesis of TD. We will also be exploring the possible interaction between Grin2B and DRD1 polymorphisms.

SCHIZOPHRENIA SEVERITY AND CLOZAPINE TREATMENT ASSOCIATION WITH OXYTOCINERGIC GENES

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Antipsychotic drugs are the best means available for symptomatically treating individuals suffering from schizophrenia; however, there is a significant variability in clinical response to these psychotropic medications. Previous findings connect oxytocin with schizophrenia and antipsychotic action. Therefore, we have evaluated if oxytocin and oxytocin receptor genes might play a role in the symptom severity and clozapine treatment response in schizophrenia subjects. The rs2740204 variant in the oxytocin gene was significantly associated with treatment response (after 1000 permutations p = 0.042) and nominally associated with negative symptoms in our sample. Furthermore, variants in the oxytocin receptor were nominally associated with severity of overall symptoms accessed using the Brief Psychiatric Rating Scale (rs237885 and rs237887) as well as on the improvement of the positive symptoms (rs11706648, rs4686301 and rs237899). Additional association studies in independent samples can evaluate whether oxytocin and oxytocin receptor genes are truly playing a role in the clozapine treatment outcome.

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GENETIC VARIATIONS LOCATED IN THE GENES RELATED TO THE GLUTAMATERGIC SYSTEM IMPACT THE SIDE EFFECT PROFILE OF HALOPERIDOL PHARMACOTREATMENT

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Background: Schizophrenia is a serious, progressive and devastating illness. The definition of tailored treatment is an essential goal, for which pharmacogenetics may provide a keen biological perspective.

Methods: 101 acutely ill psychotic patients were recruited at the Department of Psychiatry, Ludwig-Maximilians-University of Munich, Germany, and treated with haloperidol. Blood samples were obtained and a set of 174 SNPs located in 42 candidate genes were genotyped. Candidate genes included among others: genes related to the glutamatergic system, gabaergic system, dopaminergic system and genes involved in stress response. PANSS and ESRS tests were administered at days 3, 7, 14, 21 and 28. Primary outcome was the variation over time of psychotic symptomatology and motor side effects (PANSS and ESRS respectively). Repeated measure ANCOVA was the test of choice, stratification factors were identified in a previous published study and entered the analysis as covariates. Bonferroni correction was applied.

Result; None of the investigated variations could singularly impact the PANSS total scores distribution over time after Bonferroni correction was applied to the whole analysis. The glutamatergic SLC6A5 variant rs2298826 was found to be associated with a rapid rise of motor side effects at the beginning of the treatment (P=0.0002), followed by a subsequent fast adaptation. Haplotype analysis strengthened the relevance of SLC6A5 by identifying the association between the C-A-C haplotype (rs1443548, rs883377, rs1945771) and higher ESRS scores (overall P=0.01, haplotype P= 0.000001).

Conclusion: This result further stresses the relevance of the glutamatergic system in modulating the effects of haloperidol treatment, especially with regards motor side effects.

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INFLUENCE OF TAAR6, DAOA, DTNBP1 AND FAT VARIANTS ON RESPONSE TO ARIPIPRAZOLE

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Aim of the study: The aim of the present study is to investigate whether a set of single nucleotide polymorphisms (SNPs) in TAAR6 (rs8192625, rs4305745, rs4305746, rs6903874, rs6937506), DAOA (rs2391191, rs947267 and rs3918342), DTNBP1 (rs3213207, rs1011313, rs2005976, rs760761 and rs2619522) and FAT (rs2306987, rs2306990, rs2637777 and rs2304865) genes could influence response to aripiprazole in a sample of 87 Korean schizophrenia patients.

Methods: Efficacy was assessed at baseline and weeks 1, 2, 4, 6, 8 using CGI-S, CGI-I, BPRS and SANS. Side effects were evaluated through SAS, BAS and AIMS. Multivariate analysis of covariance was used to test possible influences of single SNPs on clinical and safety scores. Tests for associations using multi-marker haplotypes were performed using the statistics environment “R”.

Results: A significant time per genotype interaction was found between rs4305746 in TAAR6 and repeated measures of ANOVA on BPRS scores. Also, Individuals carrying rs2391191 A allele in DAOA were more likely to improve over time in comparison to subjects carrying the G allele, as measured by BPRS. Additionally, rs2391191-rs947267 A-T haplotype (DAOA) was protective towards a worsening of symptoms at week 1. On the other hand, no significant association between DTNBP1 and FAT SNPs under investigation and clinical or safety score at any time was observed.

Discussion: Our results suggest that some variants in TAAR6 and DAOA could influence the response to aripiprazole. However, on account of a number of limitations including the small sample size and the use of a single drug, further investigations are required.

ADRENERGIC SYSTEM GENES AND ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: FINITE MIXTURE MODEL ANALYSIS

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Atypical antipsychotics have high affinity for many neurotransmitter receptors. Among these receptors, antipsychotics are antagonist at alpha and beta adrenergic receptors and this pharmacological property has been postulated to be involved in the mechanism of action of these drugs with respect to both clinical response and adverse effects. We tested the hypotheses that antipsychotic-induced weight gain is associated with genetic variation in adrenergic receptors and pathway enzymes. The hypothesis was tested for 9 genetic polymorphisms across 6 adrenergic genes (ADRA1A, ADRA2C, BETA3, DBH, MAOA and COMT). Hundred-thirty-nine patients with schizophrenia were prospectively assessed for antipsychotics induced weight gain measured as percentage change from baseline weight. The Finite Mixture Model analysis decompounded the observed distribution of weight gain into a mixture of two normal theoretical distributions. The best fitting model had two components with a mean (SD) of 2.61 (3.73) and 8.65 (8.75) comprising respectively 55% and 44% of the sample respectively. We obtained a cut-off point at +8% enabling the sample to be divided into two subgroups in order to identify the weight gainers and non-weight gainers. Weight gain was not associated with any adrenergic gene. Our results suggest that the adrenergic system may not play a main role in antipsychotics-induced weight gain, although replication in independent samples is required to confirm this finding.

ASSOCIATION STUDY OF MELANOCORTIN-4 RECEPTOR (MC4R) GENE POLYMORPHISMS WITH ANTIPSYCHOTIC INDUCED WEIGHT GAIN

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Background: Antipsychotic induced weight gain results in non-compliance and the metabolic syndrome in schizophrenia patients. Recently, single nucleotide polymorphisms (SNPs) located downstream of the Melanocortin-4 receptor (MC4R) gene have been associated with body mass index and waist circumference in healthy human populations. Mutations in the MC4R gene cause 3-6% of early onset childhood obesity and 0.5-2.5% of adult obesity. Activation of MC4R by alpha-MSH results in suppression of food intake and activation of energy expenditure. Thus, we hypothesized that SNPs near MC4R can influence antipsychotic-induced weight gain in schizophrenia patients.

Materials & Methods: Four tagged SNPs were analysed in 224 patients who underwent treatment (with either clozapine, olanzapine, haloperidol or risperidone) for chronic schizophrenia and were evaluated for antipsychotic induced weight gain for up to 14 weeks.

Results: We compared weight change (%) across genotypic groups for the three tagSNPs ($r^2 \geq 0.8$, minor allele frequency ≥0.05) in the MC4R gene. One SNP WAS monomorphic in our population. The polymorphism rs8087522 was associated weight gain in patients of European ancestry treated with clozapine or olanzapine. Carriers of the 'A' allele gained more weight (AA+AG vs GG; 5.53±5.7% vs 2.96±4.8%; p=0.039). No association was observed between rs17728313 and weight gain (p=0.802).

Conclusion: In this study we provide first evidence that the MC4R gene may be associated with antipsychotic-induced weight gain in chronic schizophrenia patients. However these observations were made in a relatively small patient population. Therefore, these results need to be replicated in larger sample sets.

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THE CAMH PHARMACOGENETICS RESEARCH CLINIC: TOWARDS CYP2D6 AND CYP2C19 GENOTYPING IN PSYCHIATRIC PRACTICE

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Antipsychotic and antidepressant medication continues to be the main treatment for many psychiatric conditions including schizophrenia and obsessive-compulsive disorder (OCD), respectively. Two polymorphic enzymes, CYP2D6 and CYP2C19, metabolize a large number of these medications.

As part of the Toronto Roche AmpliChip© Study, 39 individuals with OCD were genotyped for CYP2D6 and CYP2C19. Abnormal CYP2D6 activity was disproportionately associated with non-response to medication. 20% of non-response was observed in ultrarapid metabolibzers (UM) and only 2% of response, while 5% of non-response was observed in poor metabolizers (PM) and 0% of response ($p = 0.009$). This data, and a chart review, show that these patients are more likely to have complicated medication histories and suggest that CYP2D6 and CYP2C19 genotyping could have aided in selecting medications and dosages, potentially improving response and reducing side effects.

As part of a new study at the Pharmacogenetics Research Clinic, the first patients with complicated medication histories and a diagnosis of schizophrenia have been genotyped for CYP2D6 and CYP2C19. Patients' physicians also complete a questionnaire evaluating the usefulness of the information provided by the study. Case reports will be presented and discussed in detail at the conference.

Physicians have given feedback indicating that genotyping results have been helpful in 1) allowing them to select medications their patients may tolerate better, 2) allowing them to increase dosages when therapeutic responses were not adequate, or 3) to reduce dosages when responses were sufficient and serum levels were high. Though preliminary, our findings suggest that CYP2D6 and CYP2C19 genotyping provides useful information that may help physicians to improve pharmacotherapy for individual patients.

APPLICATION OF A GENOTYPING PLATFORM CENTERED ON PHARMACOGENETICS TESTING FOR PSYCHIATRY PATIENTS

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Psychiatric professional sources give particular importance to the genetic analysis of liver enzyme gene variants that can affect the pharmacokinetics of commonly prescribed antipsychotic and antidepressant drugs – cytochrome P450 CYP2D6 and CYP2C19. These results are useful to clinicians who can use the recommendations for drug dosing and therapeutics strategy, thus reducing the possibility of adverse reactions and potentially lengthy trial-and-error processes when selecting the appropriate drug and dose for the individual patient.

Several commercial tests are available for CYP gene testing, the most prominent being the Roche AmpliChip CYP450 Test and the Luminex Tag-It Mutation Detection Kit. These tests are currently employed by clinical labs in the United States. The limitations of these tests are that they are costly, require multiple sample preparation steps before analysis can occur and cannot be customized to the user's needs. As an alternative, Applied Biosystems (ABI) offers individual single-nucleotide polymorphism (SNP) and copy number variation (CNV) assays thus providing flexibility in test design and minimal hands-on manipulation. To validate the use of the ABI assays in-house, we have analyzed six samples across all three platforms: the Roche AmlipChip test was performed by trained staff at the Mayo Clinic; the Tag-It test was performed by the Luminex Research and Development team at Luminex Molecular Diagnostics, Inc., (Toronto) and we have conducted our own tests of the ABI assays in-house.

After comparing the results across the three platforms, we have found that the Luminex and ABI results were more in agreement than the genotypes inferred by the Roche AmpliChip test. A possible explanation for the differences in results is that the allele calls depended on what SNPs were genotyped and how the genotypes were interpreted by the user. Based on our findings, the reproducibility of CYP2D6 and CYP2C19 variant testing using ABI assays are comparable to those employed in licensed clinical labs.

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ASSOCIATION OF A SEROTONIN RECEPTOR 2A POLYMORPHISM WITH MEMORY AND ATTENTION IN EARLY-ONSET SCHIZOPHRENIA AND THEIR RELATIVES

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Background: We sought to investigate the association between T102C polymorphism on the 5-HT2A gene and cognition in individuals with early-onset schizophrenia (EOS; onset before adulthood) and their biological relatives.

Methods: We conducted a neuropsychological test battery on 53 EOS probands and 117 first-degree relatives. The Wechsler Memory Scale-Revised (WMS-R) and California Verbal Learning Test (CVLT) was used to measure memory and verbal learning and recognition, respectively. Visual information processing was measured using the Span of Apprehension test (SPAN), and sustained attention was assessed using the degraded-stimulus Continuous Performance Test (DS-CPT). The structured clinical interview for DSM-IV yielded four diagnostic groups: EOS probands, relatives with mood disorders; other Axis I diagnoses; and no Axis I diagnosis (healthy relatives). The polymorphism of the 5-HT2A gene was genotyped by specific polymerase chain reaction.

Results: Individuals with the rs6313 CC genotype showed poorer memory performance on all composite WMS-R indices than genotypes TC or TT. A differential effect of 5-HT2A variants was found on verbal learning and recognition, in which rs6313 TT homozygozity produced a greater number of perseverations than the CC genotype. In the SPAN alone, there was a significant effect of genotype whereby homozygotes with the rs6313 C allele produced fewer correct responses and more false alarms than heterozygotes with the rs6313 T allele. The influence of other clinical features on 5-HT2A will be presented.

Conclusions: The rs6313 C allele may impact specific cognitive impairments in individuals with a genetic predisposition to schizophrenia regardless of diagnosis.

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ATYPICAL ANXIOLYTIC GB-115 ATTENUATED THE DEVELOPMENT OF DIAZEPAM WITHDRAWAL-INDUCED ANXIETY IN RATS

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According to statistics the abrupt discontinuation of chronic benzodiazepine treatment is accompanied by withdrawal syndrome with heightened anxiety as one of the main symptoms in humans (0.5-7.0%). Similar behavioral changes were observed in rodents. Since fear is associated with the high level of neuropeptide cholecystokinin in CNS, it is suggested that blockade of CCK-receptors should prevent the development of stress response in BDZ-withdrawal animals. Previously it was reported that GB-115 ($Ph(CH_2)_5CO$-Gly-Trp-NH_2), a retropeptide analogue of endogenous cholecystokinin, produced selective anxiolytic action in animals with genetically controlled “freezing” reaction to emotional stress with no effect in animals with active response to stress. There were no signs of tolerance after GB-115 *per se* chronic treatment.

The aim of the present work was to examine the effects of GB-115 (0.0125-0.1 mg/kg) on the anxiety-related behavior in the “elevated plus maze” test induced by 48 h withdrawal from chronic diazepam (DZP) (4.0 mg/kg, 30 days) treatment with subsequent analyses of monoamine levels in the hypothalamus, striatum, frontal cortex and hippocampus measured after decapitation using HPLC-ED technique. The discontinuation of daily administration of DZP induced withdrawal anxiogenesis and proconvulsant effect. However, GB-115 (0.1 mg/kg) antagonized only the anxiety, but not the proconvulsant effect following diazepam-withdrawal. The most notable changes in neurotransmitter pattern were observed in striatum in DA and DOPAC levels in DZP-withdrawn group. GB-115 after acute single administration appeared to restore the disrupt balance in DA ($p<0.01$) and DOPAC ($p<0.05$) content in abstinent animals.

These results demonstrated the ability of GB-115 to reduce DZP withdrawal-induced anxiety in rat behavioral model. It is supposed that GB-115 psychotropic effect is partly due to upregulation of dopaminergic system in diazepam experienced rats.

PHARMACOGENOMIC STUDY OF LADASTEN, A NOVEL PSYCHOTROPIC DRUG.

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Ladasten (N-(2-adamantil)-N-p-brominephenylamine) was synthesized and pharmacologically studied at the Zakusov Institute of Pharmacology RAMS. Previous studies revealed psychostimulatory and anxiolytic effects of this drug. The aim of this work was to study the genes expression induced in rat brain cells by a single injection of ladasten at doses corresponding to IC50. The main technique used was hybridization on Atlas TM Rat cDNA Expression Array (BD Biosciences, United States), which allowed to simultaneously compare changes in expression of 588 known rat genes. Using bisulfate sequencing, we have analyzed the methylation character of 5'-flanking tyrosine hydroxylase (TH) gene region.

A combined utilization of expression cDNA macrochips and quantitative RT-PCR showed that ladasten affected cell functions by changing the expression status of 16 genes encoding different structural and functional proteins. We for the first time showed that ladasten influenced the functional state of the genes encoding the enzymes of the glycolytic pathway (NSE and GAPDH), the biological synthesis of endogenous neuropeptides (CARB H), and the synaptic transport protein GAT3. It was shown that ladasten in concentrations that have psychotropic action induces expression of the key genes of the synthesis of catecholamines—tyrosine hydroxylase and DOPA decarboxylase—in rat hypothalamus and striatum. The effect observed correlates with changes in the content of the products depended on these enzymes.

The data obtained allow us to conclude that the psychostimulatory and anxiolytic action of ladasten can be mediated by monoamine and $GABA_A$ systems.