Personalised medicine in psychiatry: Biomarker for the prediction of disease stages, course of illness and treatment response

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Psychiatry as a Clinical Discipline is largely driven by a symptom-based approach that underpins current diagnostic and therapeutic decision making processes. Reliable biological markers are largely absent from current diagnosis and treatment decision making processes. Does Psychiatry as a field has the opportunity to develop beyond a clinically driven “wait-and-see” approach? In this symposium, various studies will be presented on biomarker based evidence for treatment response and diagnostic aspects across psychiatric disorders. Specifically, latest research on biomarkers for treatment response in bipolar disorder (Baune), metabolic markers of antipsychotic treatment in schizophrenia (Li), biomarkers for the diagnosis and treatment response for PTSD (Liu) and mood disorders (Ng) and latest findings in the pharmacogenomics of antipsychotic treatment of schizophrenia (Yu) will be presented. The outlined talks will be presented in the context of Personalized Medicine in Psychiatry.

PRESENTER 1 – Biomarker for the prediction of lithium treatment response in Bipolar Disorder

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Introduction
Lithium is a first-line mood stabilizer for the treatment of bipolar affective disorder (BPAD). However, the efficacy of lithium varies widely, with a nonresponse rate of up to 30%. Biological response markers are lacking. Genetic factors are thought to mediate treatment response to lithium, and there is a previously reported genetic overlap between BPAD and schizophrenia (SCZ). To test whether a polygenic score for SCZ is associated with treatment response to lithium in BPAD and to explore the potential molecular underpinnings of this association.

Methods
A total of 2586 patients with BPAD who had undergone lithium treatment were genotyped and assessed for long-term response to treatment between 2008 and 2013. Weighted SCZ polygenic scores were computed at different P value thresholds using summary statistics from an international multicenter genome-wide association study (GWAS) of 36,989 individuals with SCZ and genotype data from patients with BPAD from the Consortium on Lithium Genetics. For functional exploration, a cross-trait meta-GWAS and pathway analysis was performed, combining GWAS summary statistics on SCZ and response to treatment with lithium. Data analysis was performed from September 2016 to February 2017. Treatment response to lithium was defined on both the categorical and continuous scales using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score. The effect measures include odds ratios and the proportion of variance explained.

Findings
Of the 2586 patients in the study (mean [SD] age, 47.2 [13.9] years), 1478 were women and 1108 were men. The polygenic score for SCZ was inversely associated with lithium treatment response in the categorical outcome, at a threshold $P \leq 5 \times 10^{-2}$. Patients with BPAD who had a low polygenic load for SCZ responded better to lithium, with odds ratios for lithium response ranging from 3.46 (95% CI, 1.42-8.41) at the first decile to 2.03 (95% CI, 0.86-4.81) at the ninth decile, compared with the patients in the 10th decile of SCZ risk. In the cross-trait meta-GWAS, 15 genetic loci that may have overlapping effects on lithium treatment response and susceptibility to SCZ were identified. Functional pathway and network analysis of these loci point to the HLA antigen complex and inflammatory cytokines.
Conclusion
This study provides evidence for a negative association between high genetic loading for SCZ and poor response to lithium in patients with BPAD. These results suggest the potential for translational research aimed at personalized prescribing of lithium.

PRESENTER 2 – Metabolic changes in initial antipsychotic drug treatment: rapid development and differential drug effects

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Objectives
To investigate how metabolic measures change during the early stages of monotherapy with different antipsychotics.

Methods
Randomized, open-label pharmacological trial was conducted among inpatients with schizophrenia in 32 hospitals across China. Patients were randomly assigned to 7 groups (ziprasidone, aripiprazole, olanzapine, quetiapine, risperidone, haloperidol, and perphenazine) and assessed at baseline, 2, 4 and 6 weeks. Primary outcome measures included body mass index (BMI), waist circumference (WC), blood pressure (BP), glucose (Glu), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and metabolic syndrome (MetS).

Findings
In total, 2,550 (718 drug-naive) of 2,778 patients finished the study. We found significant changes for BMI, WC, TG, and LDL-C, with TG and LDL-C reaching a plateau. Interactions between baseline metabolic condition and changes over time were observed for BMI, WC, systolic BP, Glu, and TG. Antipsychotics generally had greater negative effects on patients who were initially screened as metabolically normal. After controlling for other associated factors, antipsychotics resulted in differing risk for incident MetS, with a similar pattern to findings in other populations: olanzapine ≈quetiapine ≈perphenazine ≈risperidone >aripiprazole ≈haloperidol = ziprasidone.
Conclusions
Metabolic traits should be monitored frequently in early stages of antipsychotic treatment. BMI and WC should be examined weekly and TG should be assessed before 4 weeks. Clinicians should not assume low risk for patients with normal metabolism at baseline.

Trial registration: Chinese Clinical Trials Registry, ChiCTR-TRC-10000934.

PRESENTER 3 – Identification of a potential biomarker and therapeutic marker for the diagnosis and treatment of PTSD

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Introduction
Post-traumatic stress disorder (PTSD) can develop after exposure to severe psychological trauma, leaving patients with disabling anxiety, nightmares and flashbacks. Current treatments are only partially effective, and development of better treatments is hampered by limited knowledge of molecular mechanisms underlying PTSD.

Objectives
To identify potential biomarkers and therapeutic markers for the diagnosis and treatment of PTSD.

Methods
Co-immunoprecipitation and Western blot analysis, GST fusion protein pull-down assay, Real-time PCR, Cued Fear Conditioning, Surface plasmon resonance, Immunocytochemistry.

Findings
We have discovered that the glucocorticoid receptor (GR) and FKBP51 (FK506 Binding Protein 51) form a protein complex that is elevated in fear-conditioned mice, an aversive learning paradigm that models some aspects of PTSD, and in PTSD patients compared to unaffected control subjects as well as subjects exposed to trauma without PTSD. We created a peptide that disrupts GR-FKBP51 binding, and in fear-conditioned mice, reduces freezing time. Our peptide also normalizes decreased GR phosphorylation and increases both GR-FKBP52 binding and nuclear translocation of the GR in fear-conditioned mice.

Conclusions
Our results demonstrate a novel molecular mechanism contributing to PTSD and identify a new therapeutic target for preventing or treating PTSD.

PRESENTER 4 – Clinical application of pharmacogenetics in the treatment of mood disorders

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Given the growing disease burden of depression and other mood disorders at the population level, there is potential to improve patient treatment outcomes. Individual differences in therapeutic and adverse effects of psychotropics are largely determined by genetic factors. Current availability and affordability in genotyping technology have shown utility in predicting individual metabolic phenotypes, risks for side effects and likelihood of antidepressant drug response. Using pharmacogenetic tools may optimize clinical efficacy and prevent unwanted side effects for individual patients from diverse backgrounds. Through systematic characterization of the functional effects of polymorphisms, genotype-guided pharmacotherapy could significantly improve the cost-effectiveness of medications for mood disorders, and provide personalised treatment recommendations. However, despite a rapidly growing number of pharmacogenetics tests relevant to treatments in mood disorders being available commercially, most of these pharmacogenetic tests have yet to be adequately assessed in the real world clinically or have been evaluated in diverse populations. The availability of pharmacogenetic tests and genetic information to prescribers does not ensure clinical applicability or
delivery of personalised medicine. Larger studies of personalized psychopharmacology in mood disorders are needed, especially research related to the effectiveness and utility of pharmacogenetic tools in clinical practice across diverse settings.

References:

PRESENTER 5 – Pharmacogenomic study of antipsychotic medicines in Chinese Han population


In the present study, we did a two-stage pharmacogenomic genome-wide association study of treatment response or antipsychotic-induced weight gain (AIWG) in patients with schizophrenia. The patients randomly assigned to aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol, and perphenazine. The sample size of this study (n=2413 in the discovery cohort and 1379 in the replication samples) is one of the largest reported so far.

We have detected five novel significant loci (MEGF10, SLC1A1, PCDH7, CNTNAP5, and TNIK) associated with general treatment response (ie, combining all antipsychotics). We calculated the genetic risk score on the basis of five significant SNPs, the discriminative power to distinguish responders from non-responders remained moderate (best area under the curve 71.3%).

For the AIWG, the two-stage GWAS identified two genome-wide significant SNPs with AIWG at two genes: the PTPRD gene (protein tyrosine phosphatase, receptor type D; rs10978083, \( P=4.34\times10^{-12} \)) and PEPD gene (peptidase D; rs731839, \( P=5.50\times10^{-10} \)), respectively. Furthermore, the polygenic risk score calculated based on the two SNPs (rs10978083 and rs731839) could significantly predict AIWG in the discovery (\( P=1.47\times10^{-12} \)) and follow-up cohort (\( P=1.39\times10^{-2} \)).

We have identified genes related to synaptic function, neurotransmitter receptors, and schizophrenia risk that are associated with response to antipsychotics. We have also identified genes related to metabolic process that are associated with AIWG. These findings improve understanding of the mechanisms underlying treatment responses, and the identified biomarkers could eventually guide choice of antipsychotic in patients with schizophrenia.