E-Poster Presentation

EPP0304

Pharmacogenetic CYP2D6 variability, phenoconversion and treatment outcomes: A Danish population-based cohort study in 6,798 individuals initiating atomoxetine treatment

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Introduction: Atomoxetine, a first-line treatment option for ADHD, is affected by pharmacogenetic (PGx) variation of the drug-metabolizing enzyme CYP2D6. Despite the recommendation of CYP2D6 testing, the use of PGx-guided dosing remains low in Denmark.
Objectives: We investigated wide-ranging clinical outcomes in atomoxetine users in association with PGx variability.
Methods: We analyzed 6,798 individuals (55% children) with a first prescription for atomoxetine identified from the Danish population-based iPSYCH case-cohort study linking biobank information with Danish registers. Individuals were categorized based on their single-nucleotide-polymorphism-based CYP2D6 genotype into normal (NM), intermediate (IM), and poor metabolizer (PM). Clinical outcomes included treatment switching, discontinuation, psychiatric inpatient-, outpatient-, and emergency contact, suicide attempt/self-harm, sleep problem, and depression. Individuals' CYP2D6-status could change due to drug-drug-interactions of weak, intermediate, or strong-CYP2D6 inhibitors (phenoconversion), which we accounted for by time-varying phenotype assessment. Incidence rate ratios (IRR) were estimated using Poisson regression analyses and adjusted for a wide range of potential confounders and covariates.
Results: Over two-thirds of the individuals had a hospital diagnosis of ADHD at the first atomoxetine prescription. The distribution of CYP2D6 phenotypes was similar in children and adults. IM/PM children had a significantly higher risk of a sleeping problem compared with NM children (IRR 1.25, 95% CI 1.01-1.54). Compared with NM adults, those with IM/PM had a higher risk of switching (1.15, 95% CI 0.98-1.35).
Conclusions: This is the first study showing the potential impact of PGx variability on clinical outcomes of atomoxetine users in a population-based setting, highlighting the utility of PGx testing.

Disclosure: No significant relationships.
Keywords: treatment switching; CYP2D6 inhibitors; adhd; sleeping problem

EPP0303

Predicting involuntary admission among patients with psychotic disorder

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Introduction: Involuntary admissions are increasing in numbers across Europe.[1] They can be traumatic for the patients[2] and are associated with large societal costs.[3] Individuals with psychotic disorder are at particularly elevated risk of involuntary admission.
Objectives: This study aims to investigate whether machine learning methods including natural language processing can predict involuntary admission among patients with psychotic disorder.
Methods: We have obtained a dataset based on electronic health records for all patients having had at least one contact with the psychiatric services in the Central Denmark Region from 2011 to 2021. This dataset covers more than 120,000 patients, of which approximately 10,000 have been diagnosed with a psychotic disorder. The dataset contains both structured data, such as diagnoses, blood tests etc., as well as unstructured data (text). We will train machine learning models, basic logistic regression-models as well as state-of-the-art neural networks, to predict involuntary admission after contacts to the psychiatric services.
Results: As the machine learning models are under development, no results are available at this time. Preliminary results are expected in spring 2022.
Conclusions: If involuntary admission can be predicted among patients with psychotic disorder based on data from electronic health records, it will pave the way for potentially preventive interventions. References: 1. Sheridans-Rains, L et al., 2019 2. Frueh, B.C et al., 2005 3. Smith,S., 2020

Disclosure: No significant relationships.
Keywords: Precision Psychiatry; PSYCHOTIC DISORDERS; Involuntary admission

EPP0304

Upside down: dissecting impulsivity in attention-deficit hyperactivity disorder through genotype-phenotype association analyses

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Introduction: Better evaluation and understanding of the core symptoms have key importance both in clinical practice and the research of attention-deficit hyperactivity disorder (ADHD). One hallmark neurocognitive feature of ADHD is impaired inhibition, related to impulsivity. Given the high heritability of ADHD, the

assessment of genetic background of impaired inhibition may contribute to our knowledge about the genetic background of the disorder.

Objectives: In our study we investigated whether different forms of impulsivity (attentive, motor, and nonplanning) and polymorphisms in genes of the noradrenergic, serotonergic, and dopaminergic neurotransmission, i.e. dopamine transporter-1 (DAT1), cathecoloamin-O-metiltransferase (COMT), and serotonin receptor-1B (HTR1B genes show association.

Methods: 208 aADHD patients diagnosed according to DSM-5 criteria from a clinical sample and 142 individuals from a population sample who screened positive for aADHD were included in the study. DNA samples were genotyped for the HTR-1B gene rs1321041 and the COMT gene rs4680 SNPs, moreover the DAT-1 VNTR polymorphism. Dimensional variables for impulsivity were compared between genotypes with the Generalized Linear Model procedure corrected for sex and age, using the PLINK 1.9 statistical software.

Results: The 9 repeat polymorphism in DAT1 was associated with the severity of hyperactivity, moreover, all impulsivity factors. The A allele in COMT was associated with hyperactivity and better motor inhibition activity. In carriers of the G allele in HTR1B we detected significantly higher inattention scores and increased reaction time.

Conclusions: Our results support the putative role of the investigated genetic polymorphisms in the etiology of impulsivity. Nevertheless, these polymorphisms demonstrate a heterogeneous associations.

Disclosure: No significant relationships.
Keywords: adhd; Impulsivity; DAT1; hyperactivity

EPP0306

Clinical impact of functional CYP2C19 and CYP2D6 gene variants on treatment outcomes in patients with depression: a Danish cohort study

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Introduction: Pharmacogenetic (PGx) targets to optimize drug therapy, but its implementation is rare.

Objectives: We evaluate the clinical utility of PGx testing in psychiatry by investigating the one-year risks of clinical outcomes in patients with depression taking sertraline, (es)citalopram or fluoxetine by their Cytochrome P450 (CYP) 2C19/2D6 phenotypes.

Methods: We investigated 17,297 individuals born between 1981-2005 with a depression diagnosis between 1996-2012 from the iPsych2012 case-cohort. Based on array-based single-nucleotide-polymorphism genotype data, individuals were phenotyped as CYP2C19/CYP2D6 normal (NM, reference group), ultra-rapid-

(UM), rapid- (RM), intermediate- (IM), or poor-metabolizer (PM). Outcomes were treatment switching or discontinuation, psychiatric in-, out-, and emergency room contacts (ER), and suicide attempt/self-harm. Incidence rate ratios (IRR) by age groups were estimated using Poisson regression analysis with 95% confidence intervals, adjusted for potential confounders.

Results: Risks of switching (IRR=1.89[1.22-2.93]), ERs (1.69 [1.01-2.81]) and suicide attempt/self-harm (2.73 [1.49-5.01]) were higher in CYP2C19 PMs <19 years taking (es)citalopram. Fluoxetine users <19 years had a decreased risk of discontinuation in CYP2D6 PMs (0.5 [0.27-0.95]) and decreased risk of out-patient contacts in CYP2D6 PMs and IMs (IRR$_{IM}$=0.83 [0.68-1.00] and IRR$_{PM}$=0.59 [0.37-0.96]). We observed an increased risk for ERs in CYP2D6 PMs aged 19-25 years taking fluoxetine (4.53 [1.54-13.35]). In CYP2C19 UMs >25 years taking (es)citalopram the risk of suicide attempt/self-harm was more than three-fold increased (3.64 [1.01-13.19]). We found no significant results in users of sertraline.

Conclusions: PGx variability was associated with treatment outcomes in depression in patients with CYP2C19 PM or UM status taking (es)citalopram, or CYP2D6 PM or IM status taking fluoxetine.

Disclosure: No significant relationships.
Keywords: pharmacogenetics; sertraline; (es)citalopram and fluoxetine; Depression

EPP0308

Body mass index and depressive rumination are positively associated with each other only in case of GG genotype of catenin alpha 2 gene rs13412541 variant

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Introduction: Catenin alpha 2 gene (*CTNNA2*) is important in the stability of hippocampal synapses and also in brain development. Our recent paper (Eszlari et al, *Pharmaceuticals* 2021, 14, 850) has demonstrated that rumination on sad mood mediates the association of *CTNNA2* only towards psychiatric symptoms, but not towards cardiovascular risk phenotypes.

Objectives: Our present aim was to test the moderating role of rumination and its two subtypes, brooding and reflection, in genetic associations between *CTNNA2* and the same cardiovascular risk phenotypes.

Methods: 633 unrelated subjects from the Budakalasz Health Examination Survey with non-missing phenotypic data, and 160 single-nucleotide *CTNNA2* variants remaining after quality control, were included. Linear regression models were run in Plink 1.9 for separate outcomes of body mass index (BMI), and Framingham risk scores for cardiovascular disease, coronary heart disease, myocardial infarction, and stroke. With each variant, predictors were the variant, rumination or its subtype, the variant x rumination interaction, sex, age, and the top ten principal components of