Genome-wide association study identifies genetic loci associated with body mass index and high density lipoprotein-cholesterol levels during psychopharmacological treatment — a cross-sectional naturalistic study

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ABSTRACT

Metabolic and cardiovascular side effects are serious clinical problems related to psychopharmacological treatment, but the underlying mechanisms are mostly unknown. We performed a genome-wide association study of metabolic and cardiovascular risk factors during pharmacological therapy. Twelve indicators of metabolic side effects as well as cardiovascular risk factors were analyzed in a naturalistic sample of 594 patients of Norwegian ancestry. We analyzed interactions between gene variants and three categories of psychopharmacological agents based on their reported potential for side effects. For body mass index (BMI), two significantly associated loci were identified on 8q21.3. There were seven markers in one 30-kb region, and the strongest signal was rs7838490. In another locus 140 kb away, six markers were significant, and rs6989402 obtained the strongest signal. Both of these loci are located upstream of the gene *matrix metalloproteinase 16* (*MMP16*). For high density lipoprotein cholesterol (HDL-C), marker rs11615274 on 12q21 was significant. The results highlight three genomic regions potentially harboring susceptibility genes for drug-induced metabolic side effects, identifying *MMP16* as a candidate gene. This deserves to be replicated in additional populations to provide more evidence for molecular genetic mechanisms of side effects during psychopharmacological treatment.

1. Introduction

Effective psychopharmacological treatment for schizophrenia and affective disorders was introduced with the discovery of antipsychotics in the 1950s. Antipsychotics, antidepressants and mood-stabilizers are still cornerstones in their treatment. However, a large proportion of patients experience adverse effects, which are often a limiting factor in obtaining successful treatment effects.

First generation antipsychotics are typically associated with extrapyramidal syndromes (Correll and Schenk, 2008), while several of the second generation antipsychotics are associated with metabolic disturbances including dyslipidemia, elevated glucose levels and weight gain (Meyer and Koro, 2004; Meyer et al., 2008; Leucht et al., 2009), as well as cardiovascular disturbances (Ray et al., 2009). Similar adverse effects are also observed for several mood-stabilizing drugs (Andersohn et al., 2009).

Metabolic and cardiovascular adverse effects are of major clinical importance because of their relevance for the increased mortality seen in severe mental disorders, which is mainly due to increased somatic morbidity (Colton and Manderscheid, 2006; Tiihonen et al., 2009). A better understanding of the mechanisms underlying metabolic and cardiovascular adverse effects associated with current psychopharmacological drugs is therefore imperative, and can lead to the development of more tolerable drugs. Most studies of the mechanisms related to adverse effects of psychopharmacological agents are based on randomized controlled trials (RCT). These studies are necessary to establish effect. However, RCT studies have limitations in terms of representativity

due to strict inclusion and exclusion criteria. As an example, in the CATIE study approximately three fourths of the patients discontinued the treatment (Lieberman et al., 2005). Thus, it is important to also investigate the mechanisms of adverse drug effects in a naturalistic setting, since in clinical practice treatment is adjusted in order to limit side effects. It is of interest to identify the mechanisms related to adverse effects in the context of satisfaction with the treatment from both the patient and clinician, and with time spans that goes far beyond the duration of RCTs. It is this long-term aspect of treatment that contributes to the most important outcome, mortality (Tiihonen et al., 2009). Recent genome-wide association studies have successfully identified genetic variants related to body-mass index (BMI) (Thorleifsson et al., 2009; Willer et al., 2009), waist circumference (Fox et al., 2007), triglycerides (TG) (Kathiresan et al., 2008; Waterworth et al., 2010), high density lipoprotein cholesterol (HDL-C) (Willer et al., 2009; Ma et al., 2010), low density lipoprotein cholesterol (LDL-C) (Wallace et al., 2008; Willer et al., 2009) and total cholesterol (TC) (Aulchenko et al., 2009; Ma et al., 2010), as well as heart rate (Newton-Cheh et al., 2007; Eijgelsheim et al., 2010) and blood pressure (Levy et al., 2009; Newton-Cheh et al., 2009) in the general population. It would be expected that some of the same genetic factors influence the risk of metabolic disturbances in patients with severe mental disorders. In addition, genetic susceptibility factors that are specific for adverse effects of psychopharmacological drug treatment could also be involved.

Twin studies have also indicated that part of the risk of metabolic adverse effects of antipsychotics may be heritable (Theisen et al., 2005). Several candidate genes have been examined for the association to drug-induced weight gain, with most promising findings for the 5-HT$_{2C}$ receptor (Reynolds et al., 2002), leptin (Zimmermann et al., 2003) and insulin-induced gene 2 (LeHellard et al., 2009). Recently, a genome-wide approach in the CATIE study identified 21 markers related to antipsychotic-induced side effects involving MEIS2, PRKAR2B, GPR98, FHOD3, RNF144A, ASTN2, SOX5, and ATF71P2, as well as various intergenic regions (Adkins et al., 2010). This study was conducted in an ethnically heterogeneous sample from the USA. Scandinavians constitute more ethnically homogenous populations, since these countries have only recently experienced non-Caucasian immigration. In the current study, heterogeneity was further reduced by including only patients with Norwegian heritage.

The aim of the present study was thus to identify genetic variants associated with psychopharmacological-induced metabolic and cardiac side effects in a naturalistic setting, using a genome-wide cross-sectional approach in a genetically homogenous sample of Norwegian patients. Our sample consisted of 594 patients with a severe mental disorder (schizophrenia or bipolar disorder) from the Thematically Organized Psychosis (TOP) study. The TOP study is a naturalistic study, where patients, due to good clinical practice, tend to be preselected according to individual drug preferences. Thus, differences in metabolic or cardiovascular adverse effects expected to be found in study samples randomized to different treatments are minimized (Birkenaes et al., 2009). We have previously shown in a subsample of this population, that drug-induced increase in body mass was minimal, probably because of awareness of this treatment hazard among clinicians. However, independently of body mass, more "hidden" adverse effects were significantly associated with psychopharmacological treatment (Birkenaes et al., 2008). In the current study, the patients were examined for 12 indicators of metabolic side effects (BMI, waist circumference, TC, HDL-C, LDL-C, HDL-C/TC ratio, TG, glucose, and C-reactive protein), and cardiovascular variables (blood pressure and heart rate) were measured.

2. Method

2.1. Study sample

A total of 837 Caucasian individuals with severe mental disorders were recruited and successfully genotyped on Affymetrix Genome-Wide Human SNP array 6.0

(Affymetrix Inc., Santa Clara, CA, USA) and passed quality control measures. Of these, we had 594 patients with information on their psychopharmacological treatment that passed our inclusion criteria. The subjects participated in a large ongoing study on schizophrenia and bipolar disorder, the Thematically Organized Psychosis (TOP) study, from May 2003 through May 2009.

The patients were not only mainly included from the outpatients units of Oslo University Hospital, but also from intermediate- and long-term treatment units. The health care system is catchment area based and free of charge. The patients were invited to participate in the study by the clinician responsible for their treatment. The sample is previously described in detail (Athanasiu et al., 2010; Djurovic et al., 2010). In brief, the subjects in the TOP study had to be registered in one of the psychiatric services at Oslo University Hospital, aged 18 to 65 years, meet DSM-IV criteria for any major psychotic or bipolar disorder, understand and speak a Scandinavian language, have no history of severe head trauma or neurological disease; and have an Intelligence Coefficient (IQ) score over 70. In addition, we excluded patients who had received psychopharmacological treatment for less than 4 weeks. All patients were born in Norway and the vast majority had two Norwegian-born parents. To assure proper compliance, the serum concentrations of all psychopharmacological agents were determined by the Laboratory of Clinical Psychopharmacology, St. Olav Hospital, Trondheim, Norway. Further, patients' drug intake was also measured with a self-report. For more details, see Jonsdottir et al. (2010). Patients were excluded if no appropriate serum concentration was detected in blood samples, or they reported non-compliance.

In total, 594 patients were successfully screened for the metabolic and cardiovascular outcome measures and genotyped. These subjects were included in the analysis, consisting of schizophrenia spectrum disorders ($n=283$), bipolar disorder ($n=213$) and psychosis (not otherwise specified (NOS)) ($n=98$).

Participants received a detailed description of the study, and they signed a written informed consent. The study was approved by the Ethics Board.

2.2. Metabolic and cardiovascular outcome measures

All patients were subjected to a physical examination by a physician at inclusion into the TOP study. Height and weight for BMI (kg/m^2), waist circumference and heart rate (beats/minute) were obtained. Blood pressure (BP) was recorded manually in a sitting position after resting, and waist circumference was measured midway between the lower rib and the iliac crest in the upright position using non-elastic tape.

Before the physical examination, blood samples were drawn after an over-night fasting and analyzed for fasting plasma glucose, TG, HDL-C, LDL-C, TC and C-reactive Peptide. All serum analyses were performed at the Department of Clinical Chemistry, Oslo University Hospital, Oslo, Norway, on an Integra 800 (Roche Diagnostics, IN, USA), using standard methods. In addition, patients were asked about their smoking habits. To obtain normally distributed variables, all outcome measures besides LDL-C and TC were log transformed.

For more information, see Birkenaes et al. (2008, 2009).

2.3. Psychopharmacological agents

The patients recruited used antipsychotics, mood stabilizers and/or antidepressants. The individual medications were divided in three groups with respect to their potential to induce metabolic- and cardiovascular side effects, based on recent reviews (Andersohn et al., 2009). Group I included drugs with the lowest potential, group II medium, and group III the highest. Group I also included patients using no medication ($n=107$). The reason for combining patients receiving drugs with the lowest side effect potential with patients using no medication in group I is to avoid too low statistical power. This approach reduces the risk of type I errors, but could potentially lead to type II errors, since the group becomes more heterogeneous.

Table 1
Psychopharmacological agents. Overview of the medications used by the patients in the TOP study and their assigned medication groups.

Medication group	Count	Medication group	Count	Medication group	Count
Group I		Group II		Group III	
Escitalopram	14	Zuclopenthixol	7	Clozapine	15
Citalopram	7	Venlafaxine	9	Levomepromazine	8
Fluoxetine	3	Mirtazapine	10	Valproic acid	29
Lamotrigine	21	Risperidone	35	Carbamazepine	3
Methylphenidate	3	Amitriptyline	1	Chlorprothixene	6
Paroxetine	1	Quetiapine	69	Olanzapine	182
Amisulpride	3	Mianserin	3	Total	243
Topiramate	1	Perfenazin	12		
Ziprasidone	18	Sertindole	1		
Sertraline	3	Total	147		
Aripiprazole	21				
Bupropion	2				
No medication	107				
Total	204				