Genes Associated with Increased Fasting Glucose in Patients with Schizophrenia Spectrum Disorders

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Abstract
Background: Metabolic risk factors represent a major cause of increased coronary heart disease morbidity and mortality among psychosis patients. Although antipsychotic medication may lead to hyperglycemia, an association to severe mental illness was established before the introduction of antipsychotics.

Methods: We investigated the association between metabolic risk genes and elevated fasting glucose level in patients with schizophrenia spectrum disorder. We applied two association models; (i) case-case where psychosis patients with elevated fasting glucose level (≥5.6 mmol/l) or diagnosed diabetes (n=263) were compared to patients with normal glucose level (n=389), and (ii) case-control model where psychosis patients with elevated fasting glucose level were compared to population-derived controls (n=494). Association analyses were adjusted for age, sex, smoking, family history of diabetes, and waist circumference. (iii) We also investigated whether metabolic genes were associated with schizophrenia spectrum disorder independent of fasting glucose.

Results: No differences between schizophrenia spectrum diagnoses regarding genetic associations with increased fasting glucose were detected. In a case-case model, a genetic variant in IGF2BP2 was associated with elevated fasting glucose level among persons with schizophrenia spectrum disorder. In a case-control model associations were found with genetic variants in the NOTCH2, THADA, WFS1, P2RX7, and MNTR1B. A genetic variant in PPARD was nominally associated with schizophrenia spectrum disorder independent of glucose level.

Conclusion: Our findings indicate that common metabolic polymorphisms associated with elevated fasting glucose among schizophrenia spectrum disorder patients may at least partially be explained by increased vulnerability in schizophrenia spectrum disorders for genes associated with elevated fasting glucose in the population.

Keywords: Psychosis; Fasting glucose; Metabolic risk genes; Case-case; Case-control; Genetic association studies

Introduction
Schizophrenia is a severe psychiatric disorder characterized by ubiquitous psychotic features and symptoms such as disorganized thinking and behavior, representing social dysfunction. Symptoms overlap with other psychiatric disorders and schizophrenia is often considered as a broad spectrum disorder. Familial studies support strong heritability, estimated to 68 to 89 percent [1], and a number of genes have been shown to be associated with schizophrenia, although the effect sizes are limited.

Schizophrenia is the psychiatric disorder associated with the largest health care use [2]. In Sweden, a recent study showed that in schizophrenia life expectancy is reduced by 19 years for men and 17 years for women compared to the population [3]. Severe mental illness including schizophrenia has been shown to be associated with a significant excess of somatic illnesses including increased risk for hyperglycemia and diabetes type 2, evident long before the introduction of antipsychotic drugs, which however have further increased the diabetes risk, resulting in a more than doubled risk of dying from cardiovascular causes of death compared with the general population [4]. Although suicide rates are highly elevated in this group of patients, increased cardiovascular causes of death, not suicide, is the major contributor to excess mortality [4,5].

In a previous clinical study of metabolic risk in persons with schizophrenia or other psychosis compared with the population, we reported that psychosis per se was an important and independent risk factor for increased fasting glucose, controlling for differences in waist circumference, gender, age, blood pressure, tobacco use and family history of diabetes (OR 2.41, 95% CI 1.84-3.14) [6]. This increased diabetes risk could be mediated by hereditary factors, indicated by shared genetic vulnerability for diabetes type 2 and schizophrenia, thus motivating further genetic studies of diabetes risk in psychosis.

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The aims of the present study were to test in the same clinical patient material as the previous clinical study if reported genetic metabolic risk variants in the population were associated with elevated fasting glucose in schizophrenia spectrum patients in (i) case-case and (ii) case-control models, and (iii) to test if genetic metabolic risk variants were associated with schizophrenia spectrum disorder irrespective of glucose levels.

Materials and Methods

Ethics approval

Ethical approval was obtained from the Stockholm Regional Ethics Committee (Regionala etikprövningsnämnden i Stockholm) for both cases and controls. All patients and controls gave informed consent to participate.

Patients from the swedish study of metabolic risks in psychosis (SMRP)

Psychosis patients were participants from the Swedish study of Metabolic Risks in Psychosis (SMRP), recruited from specialized psychosis outpatient clinics mainly in Stockholm County, Sweden. These clinics are responsible for treatment of all outpatients with long-term psychotic disorders and especially schizophrenia in each catchment area. As part of a general health screening, all patients in clinical treatment from each clinic were asked to participate in the study. Clinical diagnoses were confirmed by an experienced clinician according to the Diagnostic and Statistical Manual of Mental disorders, 4th Ed. (DSM-IV). In the present study, 652 patients were included (Table 1). Of the 652 patients, 52% were men. Mean (±SD) age was 47 (±12) years. Mean waist circumference was 97 (±15) cm for women and 104 (±15) cm for men. Current smokers were 235 patients (36%). Positive family history of diabetes was present for 150 patients (23%). Of those 652 patients, 389 (60%) had normal fasting glucose (f-pg<5.6 mmol/L), and 235 (36%) had elevated fasting glucose (f-pg ≥ 5.6 mmol/L) while 28 (4%) were on drug treatment for diabetes. Patients were assessed with self-reported questionnaires on number and length of hospital admissions, age at disease onset, and duration of antipsychotic treatment and also asked about tobacco and alcohol use, and concomitant somatic disease. Data on diagnosis, level of functioning (Global Assessment on Functioning (GAF) and Clinical Global Impression (CGI)) and dosage and type of all medication was obtained. Blood pressure, weight, height and waist circumference were measured. Patients were given written instructions to fast overnight before the venous blood sampling. Serum glucose was assayed using the glucose oxidase method.

Stockholm diabetes prevention program controls (SDPP)

Control subjects were selected from the population based prospective Stockholm Diabetes Prevention Program (SDPP) [7], which comprised of 7949 participants selected in a population based way. Participants were included during 1992-1998. A follow up was performed eight to ten years later (2002–2006), and 5712 individuals (3329 women and 2383 men), 72% of baseline participants, took part. At inclusion, only subjects without known diabetes were enrolled. Half of the subjects had a positive family history for type two diabetes (FHD), defined as at least one first-degree relative with known diabetes. SDPP subjects were assessed both at inclusion and follow up with questionnaires on lifestyle factors, physical activity, tobacco and alcohol use, socioeconomic status, and psychosocial conditions. Data on weight, height, waist circumference, blood pressure, and fasting serum glucose was obtained. At follow up, 997 individuals (17%) had increased fasting glucose levels (f-pg ≥ 5.6 mmol/L) and 289 individuals (5%) were diagnosed with type 2 diabetes. From the SDPP follow up sample, 494 SDPP control subjects were selected for genetic association study. 404 individuals (82%) had normal fasting glucose levels, 66 (13%) had increased fasting glucose levels, and 24 (5%) were diagnosed with type 2 diabetes.

DNA preparation and genotyping

For the patients and controls, venous blood was drawn from each individual. DNA was extracted according to standard procedures. The genotyping process was performed on Open Array Real-Time PCR System Instrument (Applied Biosystems, Foster City, CA, USA). Allelic discrimination was performed with the TaqMan Genotype Software (Applied Biosystems).

Genetic markers assessed

Several SNPs were analyzed (Supplemental Table 1). Hardy Weinberg Equilibrium p-value cut-off was p ≤ 0.05 for both cases and controls. Candidate genes and genetic variants that had previously reported genome-wide significance levels and were reproducibly associated with type 2 diabetes and cardiovascular disorders were selected: NOTCH2 (rs10923931), THADA (rs7578597), ADMTS9 (rs4607103), IGF2BP2 (rs4402960), PPARG (rs1801282), CDKAL1 (rs7754840), JAZF1 (rs864745), SLC30A8 (rs13266634), CDKN2B (rs1081161), Nearest gene association- CDIIC123 (rs12779970) Nearest gene association- HHEX (rs1111875), IDE (rs2251101), TCF7L2 (rs7903146), KCNJ11 (rs5219), KCNQ1 (rs2237892), MTRN1B (rs10830963), Nearest gene association- TSPAN8/LGR5 (rs79611581),
HNF1A (rs2259816), FTO (rs8050136) [8,16], and associated with cardiovascular disorders CELSR2 (rs646776), MIA3 (rs17465637), No gene association (rs2943634), MRA5 (rs9818870), MTHFD1L (rs9022269), CDKN2B (rs4977574), CXXC1L2 (rs1746048), SMAD3 (rs17228212) [17-21].

In addition, a number of common genetic variants were selected based on previous reports to be associated with type 2 diabetes and cardiovascular disorders with inconsistent and varied results, thus there is interest in further studies of the effects of the variants. Genetic variants of WFS1 (rs10010131) and EXT2 (rs11037909, rs1113132, rs37408788) were significantly associated with type 2 diabetes in several studies [15,22,23]. Genetic variants of MTPP (rs1800804) and PPARD (rs1053049, rs2016520, rs2076167, rs34474204, rs6902123) were selected since they have been shown to be involved in ischemic heart disease, glucose and lipid metabolism [24-29]. Likewise, genetic variants near HHEX (rs7923837, and rs1544210) were associated with type 2 diabetes in several linkage studies [15,19,30]. Genetic variants of CAMKK2 (rs3817190) and P2RX7 (rs1718119, rs2230912, rs3751143) were associated with reduced risk of ischemic heart disease [31].

Statistical analyses

Differences in fasting glucose level between psychosis diagnoses were analyzed using ANOVA and significant effects were further investigated with Fisher’s least significant difference (LSD) post hoc analysis for multiple comparisons. ANOVA tests were performed in IBM SPSS Statistics 22. The cut off level for fasting plasma glucose level (f-PG<5.6 mmol/L) was defined according to the recently proposed criteria from the International Diabetes Federation (IDF); [www.idf.org/webdata/docs/Metabolic_syndrome_definition.pdf]. Patients were analyzed for allelic association in a case-case model where psychosis patients with elevated fasting glucose level were compared to psychosis patients with normal glucose level, and also in a case-control model where psychosis patients with elevated fasting glucose level were compared to control subjects from the follow up of the SDPP study. In both models, logistic regression was used to test for allelic association, where gender, age, smoking, waist circumference, and family history of diabetes were used as covariates. Associations were corrected for multiple testing by calculating the False discovery rate (FDR) according to the method by Benjamin Hochberg. To test the relationship between antipsychotic drug and the genetic associations, analyses restricted to patients on clozapine (n=62) were performed. The allelic distribution for all psychosis patients was compared to SDPP controls, where gender, age, smoking, waist circumference, family history of diabetes, and fasting glucose level were used as covariates.

All calculations were performed using PLINK in BC|SNPmax data management and analysis (http://pngu.mgh.harvard.edu/purcell/plink/) [32]. The level of nominal significance was 5 percent (two-tailed).

Results

All SNPs were in Hardy Weinberg equilibrium. No differences between schizophrenia spectrum disorder diagnoses regarding fasting glucose level were detected. The genetic polymorphisms nominally associated with elevated fasting glucose levels among schizophrenia spectrum disorder patients were located in IGF2BP2 in the case-case model, and in NOTCH2, THADA, WFS1, P2RX7, and MNTR1B in the case-control model (Table 2). Genetic effect sizes were lower, although not statistically significantly, for patients on clozapine compared to all patients with increased fasting glucose levels (Table 3). The genetic polymorphism in PPRAD was nominally associated to schizophrenia spectrum disorder independent of glucose level. None of the relationships survived correction for multiple testing of 43 SNPs.

Genetic findings in case-case analyses: IGF2BP2

In the case-case analysis of IGF2BP2, the minor allele T of rs4402960 (odds ratio (OR) =0.72, p=0.019) was less common among the psychosis patients with elevated fasting glucose levels. Thus, the major allele G of rs4402960 (OR=1.39, p=0.019) was nominally associated with elevated fasting glucose levels (Table 2).

Genetic findings in case-control analyses

NOTCH2, THADA, WFS1, P2RX7, and MNTR1B

In the case-control analysis, where controls were SDPP subjects, the minor allele T of rs10923931 (OR=1.84, p=0.011) in the NOTCH2 gene was nominally associated with elevated fasting plasma glucose levels. Likewise, the minor allele G of rs10830963 (OR=1.51, p=0.0039) in the MNTR1B gene was associated with elevated fasting glucose levels. The minor allele C of rs7578597 (OR=0.55, p=0.014) and the minor allele A of rs10010131 (OR=0.71, p=0.010) in THADA and WFS1, respectively, and the minor allele A of rs1718119 (OR=0.72, p=0.014) in the P2RX7 gene were less common among psychosis patients with elevated fasting plasma glucose. Thus, the major allele T of rs7578597 (OR=1.85, p=0.014) in THADA, the major allele G of rs10010131 (OR=1.43 p=0.010) in the WFS1 gene, and the major allele G of rs1718119

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Minor/major allele</th>
<th>Psychosis f-PG ≥ 5.6 (aa/ab/bb)%</th>
<th>Psychosis f-PG&lt;5.6 (aa/ab/bb)%</th>
<th>SDPP controls (aa/ab/bb)%</th>
<th>Allele OR [95% CI]*</th>
<th>P*</th>
<th>BH FDR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF2BP2</td>
<td>rs4402960</td>
<td>T/G</td>
<td>8/45/47</td>
<td>13/48/39</td>
<td>12/40/48</td>
<td>G</td>
<td>1.39 [1.05-1.74]</td>
<td>0.019</td>
</tr>
<tr>
<td>NOTCH2</td>
<td>rs10923931</td>
<td>T/G</td>
<td>2/19/79</td>
<td>1/15/84</td>
<td>0/15/85</td>
<td>T</td>
<td>1.84 [1.13-2.46]</td>
<td>0.011</td>
</tr>
<tr>
<td>WFS1</td>
<td>rs10010131</td>
<td>A/G</td>
<td>19/42/39</td>
<td>17/50/33</td>
<td>20/48/32</td>
<td>G</td>
<td>1.40 [1.03-1.9]</td>
<td>0.010</td>
</tr>
<tr>
<td>P2RX7</td>
<td>rs1718119</td>
<td>A/G</td>
<td>11/43/46</td>
<td>19/45/36</td>
<td>19/46/35</td>
<td>G</td>
<td>1.38 [1.21-1.89]</td>
<td>0.014</td>
</tr>
<tr>
<td>MNTR1B</td>
<td>rs10830963</td>
<td>G/C</td>
<td>10/42/48</td>
<td>8/37/55</td>
<td>6/34/60</td>
<td>G</td>
<td>1.51 [1.16-1.89]</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

Table 2: Allelic association with metabolic risk genes in psychosis patients with elevated fasting glucose, f-PG≥5.6 compared to psychosis patients with normal fasting plasma glucose (f-PG<5.6) and to SDPP controls.
The effect of clozapine treatment

For the SNPs with nominal association to elevated fasting glucose level in our material (cf. above), ORs were calculated for the SNP-glucose level relationships restricting the patients to those treated with clozapine, (Table 3). In the case-case analysis, OR for rs4402960 in IGF2BP2 was 1.15. In the case-control analysis the following SNP ORs were found: for rs10923931 in NOTCH2 (OR=1.33), for rs7578597 in THADA (OR=1.78), for rs7578597 in THADA (OR=0.90), for rs1718119 in P2RX7 (OR=1.29), and for rs10830963 in MTNR1B (OR=1.47) (Table 3).

Genetic associations regardless of fasting glucose levels: PPARD

The minor allele T of rs34474204 (OR=0.54, p=0.015) was less common among the psychosis patients. Thus, the major allele C in rs34474204 (OR=1.86, p=0.015) was nominally associated with psychosis irrespective of glucose level.

Discussion

Main findings

The main findings of this study were that elevated fasting glucose levels in patients with schizophrenia spectrum disorders were nominally associated with a SNP in the IGF2BP2 gene when compared with patients with normal fasting glucose levels, and with SNPs in the NOTCH2, THADA, WFS1, P2RX7, and MTNR1B genes in comparison with the population. Both analyses were adjusted for metabolic risk factors. Further, the PPARD gene was nominally associated with schizophrenia spectrum disorder irrespective of fasting glucose level.

Strengths and limitations

Psychosis illnesses such as schizophrenia spectrum disorders are clinically defined, thus there is limited knowledge of disease biology. Heterogenous clinical symptoms, which may be related to separate biological processes, are likely to contribute to differences in genetic diversity and hampers the identification of major genetic loci associated with psychiatric disorders. In addition, there is a genetic overlap with other psychiatric disorders, especially bipolar disorder. However, use of the case-case model in genetic analyses helps to reduce clinical heterogeneity and environmental differences between mental disorder groups [33]. The case-case model may represent a narrow subgroup of psychosis patients, more biologically correlated and hence more related to susceptibility genes than psychosis patients in general [34]. In the present study, we applied both a case-case and a case-control design.

The patient sample was recruited from psychosis outpatient clinics mainly in Stockholm County, Sweden. All patients in each participating clinic were invited to participate. In an analysis from one clinic the attrition rate was 23%. There were no differences in weight or BMI between those who participated and those who declined, but those who declined were older (52 vs. 48 years) [6]. No differences between diagnoses regarding fasting glucose were detected, thus different diagnoses were analyzed as one group. Family history of diabetes (FHID) was present in 23% of the patients, which is similar to the prevalence in general population for moderate familial risk [35]. The controls were selected to represent the whole SDPP cohort including 5% with diagnosed diabetes and 17% with increased fasting glucose levels. In our analyses, we adjusted for differences in FHD between patients and SDPP controls.

There are no strong internal genetic limits in the current Swedish population [36], and especially the middle/southern parts of Sweden, from where the participants of this study are derived, are genetically homogeneous [37]. None of the relationships found here survived correction for multiple testing. However, the study was not an exploratory investigation but an investigation based on a number of hypotheses. Thus, the correction for multiple testing might be regarded as stringent.

Findings from other studies

To date, the identification of major genetic polymorphisms for diabetes type 2 and psychosis have had limited success. The prevalence of diabetes among psychosis patients is about two times as high compared to the prevalence reported in the population [38,39]. Hyperglycemia, obesity, hypertension, and dyslipidemia have been associated with schizophrenia [40], and represent major causes of increased coronary heart disease morbidity and mortality among psychosis patients [41]. An increased prevalence of diabetes type 2 has been reported in first episode drug-naive psychosis patients [42], and also in unaffected first-degree relatives of people with schizophrenia [43,44]. In addition, a recently published study shows that family history of diabetes increases the prevalence of diabetes twofold when compared with persons without family history of diabetes [45]. On the other hand, the atypical antipsychotics are associated with weight gain, diabetes, insulin resistance and the metabolic syndrome [46], thus implicating that antipsychotic medication increases the risk of comorbidity in such patients. The underlying mechanisms of antipsychotics are still unclear. However, non-obese psychosis patients treated with clozapine and olanzapine show insulin resistance [47], suggesting antipsychotic induced insulin resistance occurs independently of weight gain. Interestingly, an animal model study reports harmful metabolic effects of clozapine and association with insulin resistance and hyperglycemia, without changes in body weight, suggesting antipsychotic induced insulin resistance occur independently of weight gain. Furthermore, increase in hepatic phosphorylase activity, and increase expression level of glucose-6-phosphatase are seen, suggesting it as a possible underlying mechanism of a clozapine-induced insulin resistance and hyperglycemia [48].

Insulin-like growth factor II mRNA binding protein 2 gene, IGF2BP2, is highly expressed in the pancreatic islets region, and plays a role in RNA localization, stability and translation of IGF-2 [49]. Particularly the genetic variation studied here, rs4402960 with a G → T substitution, is associated with diabetes type 2 in several studies [50] and with reduced beta cell function and insulin resistance [51]. In addition, a recent replicated study reports an association of the diabetic nephropathy and genetic polymorphism rs4402960 only in males with diabetes type 1 [52-54].
The melanin receptor 1B gene, MNTRIB, mainly expressed in the beta cells, is associated with increased fasting glucose level, with the strongest effect on reduced insulin secretion and sensitivity [55]. In addition, insulin secretion is inhibited by melanin [12]. In support of our finding, allele G of MNTRIB rs10830963 was associated with diabetes type 2 risk, as well as with increased MNTRIB expression [12]. Moreover, among overweight children reports the G allele of rs10830963 associated with elevated glucose level, independent of age and body mass index (BMI) [56].

Genetic variation in the purinergic receptor gene, P2RX7, has been associated with mood disorders [57,58], ischemic stroke and with myocardial infarction in smokers [31]. In support of our finding, the allele G of the non-synonymous variation rs1718119 showed a gain-of-function phenotype, and fibroblasts from type 2 diabetes patients are characterized by increased purinergic activity [59,60].

Wolf ram syndrome 1 gene, WFS1, is highly expressed in beta cells and encodes for a transmembrane protein localized in endoplasmic reticulum (ER) that is expressed in various tissue, including the brain. Genetic variants, e.g. allele G of rs10010131, have been associated with diabetes type 2 [23]. Recently, a novel non synonymous genetic variant of WFS1 gene is found to segregate completely with the diabetic phenotype [61,62].

The thyroid adenoma associated gene, THADA, and the allele T of rs7578397 are associated with increased risk of diabetes type 2 related progressions [63].

The neurogenic locus notch homolog 2 gene, NOTCH2, encodes for the transmembrane protein. Notch signaling pathway is important for the neuronal function and development [64]. The T allale of rs10923931 in the NOTCH2 is the strongest SNP-risk allele associated with type 2 diabetes [16].

The peroxisome proliferator-activated receptors (PPARs), including PPAR-delta (D), are nuclear hormone receptors acting as transcription factors. Genetic variation of PPARD has been associated with both fasting glucose level, obesity [65,66], and schizophrenia [66,67]. Moreover, fatty acids are ligands for PPARD [68], and lower level of essential polyunsaturated fatty acids are associated with severe symptoms in drug naive schizophrenia patients [69].

Among the different antipsychotic drugs, it is known that clozapine is associated with hyperglycemia and the weight gain, also in our patient sample [38]. To test the effects of antipsychotic medication on our here reported genetic associations, analyses were performed restricted to patients medicating with clozapine (n=62). The results suggested that the impact of antipsychotic drugs on SNP-glucose level associations was limited.

Glucose disturbances and diabetes type 2 are prevalent in patients with schizophrenia spectrum disorders. These findings long predate the introduction of antipsychotic drugs. The roles of here investigated genes in the pathophysiology of diabetes type 2 or psychosis are still unclear. The reported findings from this study may at least partially be explained by an increased vulnerability in schizophrenia spectrum disorders for genes associated with elevated fasting glucose level in the population.

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