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Polygenic risk for type 2 diabetes mellitus among individuals with psychosis and their relatives

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ABSTRACT

Background: An elevated prevalence of Type 2 diabetes (T2D) has been observed in people with psychotic disorders and their relatives compared to the general population. It is not known whether this population also has increased genetic risk for T2D.
Methods: Subjects included probands with schizophrenia, schizoaffective disorder, or psychotic bipolar I disorder, their first-degree relatives without psychotic disorders, and healthy controls, who participated in the Bipolar Schizophrenia Network for Intermediate Phenotypes study. We constructed sets of polygenic risk scores for T2D ($PGRS_{T2D}$) and schizophrenia ($PGRS_{SCHIZ}$) using publicly available data from genome-wide association studies. We then explored the correlation of $PGRS_{T2D}$ with psychiatric proband or relative status, and with self-reported diabetes. Caucasians and African–Americans were analyzed separately. We also evaluated correlations between $PGRS_{SCHIZ}$ and diabetes mellitus among Caucasian probands and their relatives.
Results: In Caucasians, $PGRS_{T2D}$ was correlated with self-reported diabetes mellitus within probands, but was not correlated with proband or relative status in the whole sample. In African–Americans, a $PGRS_{T2D}$ based on selected risk alleles for T2D in this population did not correlate with proband or relative status. $PGRS_{SCHIZ}$ was not correlated with self-reported diabetes within Caucasian probands.
Conclusion: Differences in polygenic risk for T2D do not explain the increased prevalence of diabetes mellitus observed in psychosis probands and their relatives.

1. Introduction

An elevated prevalence of diabetes mellitus among individuals with psychosis has been noted long before the invention of atypical antipsychotic medication. In *The Pathology of Mind*, published in

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1897, Sir Henry Maudsley observed that "diabetes often shows itself in families in which insanity prevails". In 1991, before common use of atypical antipsychotics, the Schizophrenia Patient Outcomes Research Team (PORT) found that the rate of diabetes mellitus among people with schizophrenia was 15%, exceeding the general population (Dixon et al., 2000). In the post-antipsychotic era, the prevalence of Type 2 diabetes mellitus (T2D) is reportedly in the range of 11–15% in individuals with schizophrenia and is around 12% in those with bipolar disorder (Regenold et al., 2002; Ruzickova et al., 2003).

Many possible reasons have been proposed for this elevated prevalence, including lifestyle choices, poor compliance with or access to medical care, and most notably, the effects of antipsychotic medication. However, an increased genetic risk of T2D among those with schizophrenia or bipolar disorder is an underexplored possibility (Holt and Mitchell, 2015). Studies of antipsychotic naïve individuals with schizophrenia have observed elevated plasma insulin levels (Chen et al., 2013; Ryan et al., 2003; Venkatasubramanian et al., 2007), lower insulin growth factor (IGF-1) levels (Venkatasubramanian et al., 2007), impaired glucose tolerance (Fernandez-Egea et al., 2008; Spelman et al., 2007) and elevated fasting glucose, even when health habits are accounted for (Kirkpatrick et al., 2012; Ryan et al., 2003). However, other studies have not confirmed these findings (Sengupta et al., 2008). In addition, some studies have noted increased rates of T2D among relatives of people with schizophrenia (Fernandez-Egea et al., 2008; Mothi et al., 2015; Mukherjee et al., 1989), and a clustering of diabetes mellitus and psychosis in family histories of people with psychosis (Foley et al., 2015). These family data raise the possibility of shared genetic and environmental risk factors between T2D and psychosis.

Some studies have explicitly explored whether specific genes are shared between these two disorders. Several association studies have reported significant correlations between schizophrenia and well-replicated candidate genes for T2D, including *ARHGEF11* (Mizuki et al., 2014), *IGF2BP2* (Zhang et al., 2013), and *TCF7L2* (Hansen et al., 2011; Irvin et al., 2009), among others (Lin and Shuldiner, 2010). In a cross-disorder analysis, Stringer et al. (2014) found that a polygenic risk score for schizophrenia was correlated with T2D in a case-control sample of individuals with and without T2D (Stringer et al., 2014). However, no study has examined whether polygenic risk for T2D is associated with psychosis. Also, while several studies have reported increased prevalence of diabetes mellitus among relatives of people with psychosis, it is not known whether increased genetic risk for T2D accounts for this finding.

The primary aim of this study was to evaluate whether polygenic loading for T2D correlates with psychotic disorder proband status, or with first-degree relative status. Our additional goals were to determine (1) whether polygenic loading for T2D correlates with self-reported diabetes mellitus among probands and their relatives; and (2) whether polygenic loading for schizophrenia correlates with diabetes mellitus among probands or their relatives.

2. Materials and methods

2.1. Study design and measures

Analysis was conducted on data from the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study, a multi-site investigation of psychosis biomarkers. This investigation was approved by the Institutional Review Boards for each site and was conducted in accordance with the Declaration of Helsinki. Subjects included individuals with schizophrenia, schizoaffective disorder, or bipolar I with psychosis, their first-degree relatives, and healthy controls. Relatives with Axis I or II psychotic disorders (e.g. schizoid, schizotypal, or paranoid personality disorders), or who reported taking antipsychotics, were excluded so that the remaining sample consisted of subjects with familial risk of psychosis but without the experience of having a chronic psychotic disorder. Demographic data are presented in Table 1. The Structured Clinical Interview for DSM-IV (First et al., 2002) was performed on all subjects and diagnosis was determined using a consensus process, led by a senior clinician, which involved review of the structured diagnostic interview, medical and psychiatric records. Subjects were asked to self-report current co-morbid medical diagnoses, including any type of diabetes mellitus. The data collection process did not distinguish between Type 1 and Type 2 diabetes mellitus. Subjects also reported whether or not they were taking medication to treat diabetes. Those who either reported a diagnosis of diabetes or being on medication to treat diabetes were classified as having diabetes mellitus.

2.2. Collection and quality control of genetic data

Genomic data were collected using the Illumina Infinium PsychArray BeadChip™ platform. Genotype calling was performed at the Broad Institute using methods detailed online (Broad Institute, 2015), and genotypes underwent quality control using PLINK 1.9 (Chang et al., 2015; Purcell et al., 2007), based on a standardized protocol (Anderson et al., 2010). Details have been described in earlier work (Meda et al., 2014; Narayanan et al., 2015). To summarize, markers were removed if they had a missing rate greater than 5%, deviated from Hardy–Weinberg equilibrium ($p < 0.000001$), had a very low minor allele frequency (<0.01), or demonstrated a significantly different call rate between psychiatric probands and controls ($p < 0.00001$). Subjects were removed for discordant sex information, outlying heterozygosity (>3 standard deviations above the mean), or excessive proportion of missing genotype data (>0.05).

2.3. Imputation

Imputation of genetic data was performed using ShapeIt for prephasing (Delaneau et al., 2012, 2013; Howie et al., 2012) and Impute2 for imputation (Howie et al., 2009, 2012), using the multiethnic 1000 Genomes phase 3 data as a reference panel (Howie et al., 2011). Chromosomes were phased, then divided into 5 million base pair chunks for imputation. Imputed SNPs were removed for poor quality (information score less than 0.5) (Marchini and Howie, 2010) or a minor allele frequency < 0.01. For polygenic risk score analyses, linkage disequilibrium pruning was performed in PLINK 1.9 based on a pairwise R^2 of 0.5 and a window of 50 SNPs, shifting 5 SNPs at a time. 390 SNPs that approached genome-wide significance (p-value under 5×10^{-6}) in a multiethnic T2D study (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014) were also retained.

2.4. Population stratification and treatment of ethnicity effects

Principal component analysis was performed in the pre-imputed whole sample (Caucasians and African–Americans) using the "—pca" function in PLINK 1.9, and the first five components were retained as covariates to control for population stratification in subsequent analyses.

Due to potential confounding effects of race, Caucasians and African–American were subsequently analyzed separately. This decision was made because the odds ratios used to construct polygenic risk scores for schizophrenia ($PGRS_{SCHIZ}$) and diabetes