Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Polygenic risk score prediction of antipsychotic dosage in schizophrenia

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ARTICLE INFO

Article history:
Received 19 August 2015
Received in revised form 17 December 2015
Accepted 22 December 2015
Available online xxxx

Keywords:
Polygenic risk score
Antipsychotic dosage
Schizophrenia
Chlorpromazine equivalents
Defined daily dose

ABSTRACT

Objective: Genetic variants have yet to be identified as reliable predictors of antipsychotic dosage. The purpose of this study is to quantify significant genetic risk variants prioritized from the Psychiatric GWAS Consortium (PGC2) study for schizophrenia as a polygenic score to test our hypothesis that it may represent symptom severity in patients and therefore predict antipsychotic dosage.
Methods: Antipsychotic medication and dosage were collected in our sample of 83 patients with schizophrenia spectrum disorders of a homogeneous European background. Antipsychotic dosage was standardized according to the Product Monograph (PM%), chlorpromazine equivalents (CPZe), and Defined Daily Dose (DDD). We calculated polygenic risk scores (PRS) for the significant risk loci identified from the PGC2 GWAS to predict dosage using a linear regression model.
Results: In our analysis, the PRS showed no significant association with PM%, CPZe, and DDD dosage. Considering symptom severity and overall functioning, our PRS was similarly not significantly associated with Global Assessment of Functioning (GAF) scores.
Discussion: Our results do not provide evidence for a polygenic inheritance of schizophrenia that influences levels of antipsychotic dosage. To the best of our knowledge, this is one of the first studies of its kind to use the PRS from the PGC2 significant risk variants to predict a clinically relevant phenotype. The PRS offers a novel approach to analyzing the genetic liability for many clinically relevant phenotypes in schizophrenia.

1. Introduction

Schizophrenia is a mental health disorder associated with a significant hereditary influence (Ahn et al., 2014). The underlying genetic predisposition of this disorder, similar to many other psychiatric disorders, is widely multifaceted in nature. Schizophrenia has a large polygenic component, which is dependent on the impact of specific genetic variants and their accumulated effects. The risk alleles believed to lead to the symptoms of the disorder can be detected by conducting genome-wide association studies (GWAS). A GWAS is a collective examination of many common genetic variants or SNPs (single nucleotide polymorphisms) in individuals to see if a variant is associated with a certain trait (Musliner et al., 2015). In 2014, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC2) published a genome-wide association study which identified 108 distinct genetic loci implicated in schizophrenia etiology (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Following the publications of GWA studies on schizophrenia, it became apparent that rather than finding common variants with a large effect there were thousands of variants of very small effect that together acted to increase or reduce risk. By analyzing many of these variants at once as a polygenic risk score (PRS), these scores may offer a more representative genetic effect for the susceptibility of schizophrenia. A polygenic risk score is a quantified sum of trait-associated alleles across many genetic loci (Tesli et al., 2014). These risk scores offer a unique approach on utilizing the predictive power of GWAS findings and applying them to a clinically relevant phenotype (Dudbridge, 2013). Based on the holistic understanding that many genetic variants with small individual effects might not meet sufficient thresholds for expression, conjointly they may have an additive, stronger, and expressed effect (Dima and Breen, 2015). In the present study, we hypothesize that individuals with higher risk scores would demonstrate an increased risk for psychosis and symptom severity, requiring a higher dosage administration of antipsychotics.

Antipsychotic medications are commonly used to treat individuals with psychosis and schizophrenia in attempts to reduce psychotic symptoms (Harrow et al., 2014). A medical practitioner's thorough evaluation of positive and negative symptoms in a person with schizophrenia aids to establishing not only the type of antipsychotic medication to be prescribed, but the dosage of such medication. Administered dosage depends on a multitude of factors (early/late-onset of illness, comorbidity, side effects, tolerance, etc.) and must be adjusted and monitored for

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http://dx.doi.org/10.1016/j.schres.2015.12.015
0920-9964/

efficacy throughout a patient's course of treatment (Lally and MacCabe, 2015). For example, those with late-onset schizophrenia often have a higher prevalence of the paranoid subtype, and require lower doses of antipsychotic medications than those with earlier-onset schizophrenia (Desai and Grossberg, 2010). Furthermore, the severity of a patient's symptoms is generally seen as the main guiding determinant of medication dosage. On average, prescribed antipsychotic dosing is mildly to moderately correlated with illness severity (Ho et al., 2012). If a patient is more symptomatic, the dosage of antipsychotic medication is generally expected to be higher than for a patient who is less symptomatic. For the most severe cases there is a tendency for higher doses to be related to better improvement in positive symptoms and in negative symptoms (Aronson, 2008), though this relationship is not found in least severe cases. Therefore, the supported notion implies that in more severe cases higher doses should be prescribed, while in milder cases lower doses may be sufficient (Aronson, 2008). As a high risk score may potentially represent more severe symptomology, we predict that the PRS could potentially serve as a basis for identifying an appropriate antipsychotic dosage.

This study aimed to use PRS calculated for the genome-wide significant risk variants that were found to be more prevalent in schizophrenia compared to healthy controls from the PGC2 GWAS. A high PRS translates to having an increased number of risk alleles, which potentially indicates more severe symptoms in individuals with schizophrenia. Highly symptomatic cases are generally treated with higher antipsychotic doses. Therefore we aimed to assess the relationship between PRS and antipsychotic dosage. The PRS for schizophrenia may act as a prognostic tool which anticipates the requirement for higher doses of antipsychotic medication.

2. Methods

2.1. Study subjects and assessments

Our analysis incorporated 83 participants recruited from the Centre for Addiction and Mental Health (CAMH) in Toronto. All participants met the criteria for schizophrenia or schizoaffective disorder based on the structured clinical interview for DSM-IV (SCID-I/P). Exclusion criteria included observed intellectual disability and the presence of neurodegenerative disorders. Furthermore, participants with a history of head trauma leading to a loss of consciousness and a history of major substance abuse prior to the onset of psychosis were excluded. Written informed consent was obtained for participation in the study as well as for the release of participants' medical history according to CAMH Ethics Board approval.

Clinical information was collected for each participant through a cross-sectional assessment using the structure clinical interview procedure and self-report questionnaires. We incorporated the structured clinical interviews according to DSM-IV (SCID-IV) criteria in order to confirm a diagnosis of either schizophrenia or schizoaffective disorder for each participant. In situations where a diagnosis could not be reliably defined, the individual was excluded from the analysis.

Our sample consists of chronic schizophrenia patients who have been on a consistent dose and heterogeneous medications. Current antipsychotic medication and dose at the time of the interview were collected through verbal reports and were confirmed by reviewing their clinical charts. Our final analysis included participants with consistent use of antipsychotic medication and treatment adherence. All individuals with inconsistent, incomplete or inaccurate reports of antipsychotic medication and/or dosage were excluded from our analysis.

Antipsychotic dosage was standardized according to three standardization procedures: Chlorpromazine Equivalents (CPZe) (Gardner et al., 2010), Defined Daily Dose (DDD) (WHO, 2010) and the percentage of maximum dosage (PM%) according to the product monograph from the Compendium of Pharmaceutical and Specialties (Repchinsky et al., 2012). Global Assessment of Functioning (GAF) scores were given during study assessments. Cases in which GAF scores were not available, participants' medical records were reviewed to obtain a GAF score along with the prescribed medication and dosage at the time of the GAF assignment.

2.2. Genotyping and imputation

Participants were genotyped using the Illumina-2.5 Omni SNP array. For each locus, standard quality control filtering was applied. Individuals with missing genotype rates of ≥5% were excluded from the analysis. Markers were excluded if they had missing data rates ≥5% or had a Hardy–Weinberg equilibrium threshold below 0.01.

We imputed risk alleles using IMPUTE2 (Howie et al., 2012) and the October 2014 1000 Genomes reference panel. The imputation output was then converted to PLINK (Purcell et al., 2007) format using GTOOL (Genetics Software Suite, © 2007, The University of Oxford) with an imputation score threshold of 0.9.

The Multidimensional Scaling (MDS) approach was used to correct for ethnic stratification and confirm the selection of individuals in our sample on the basis of white European ancestry according to 1,568,215 ancestry-informative markers using PLINK v1.07. Three reference populations were used from the HapMap Phase II project (The International HapMap Consortium, 2007): European Caucasians (North/Western Europeans from Utah [CEU]), East Asians (Han Chinese and Japanese individuals [CHB + JPT]), and Africans from Nigeria (Yoruba from Nigeria [YRI]). Individuals within six standard deviations from the mean of the European reference population for the stratifying principal component were included in our analysis. All statistical analyses were conducted in R version 3.2.0 (http://www.r-project.org/).

2.3. Polygenic risk score calculation

For a given locus with two alleles, cases in which one risk allele was present would be given a value of 1, the presence of two risk alleles would be given a value of 2, and a value of 0 would be given in cases where no risk allele is present (Plomin and Deary, 2015). The sum of these values can then be used to generate a risk allele count or unweighted polygenic risk score. Furthermore, for each locus, the allele count can also be given a weight by multiplying by the given effect size for each SNP; described here as a weighted polygenic risk score.

The unweighted score may be more useful in case of errors in estimating true effect sizes, population heterogeneity, and confounding by population structure (Dudbridge, 2013). However, unweighted scores assume that all markers have the same effect on the trait, whereas it may be the case that some markers contribute significantly more to the risk trait than others. In our analysis, we considered both weighted and unweighted risk scores to maximize the potential of detecting a relationship between the selected variants and our trait of interest.

The risk variants selected for the polygenic score calculation were derived from the PGC genome-wide association study (PGC2, 2014) that passed genome-wide significance ($p < 5 \times 10^{-8}$). From the list of significant SNPs, the allele present at a higher frequency in cases compared to controls was considered the risk allele. On the other hand, an allele with a lower frequency in cases is referred to as the protective allele. For the protective alleles that had an odds ratio of less than 1, we inverted the odds ratio using the alternate allele as the risk allele. A polygenic score was calculated by adding a given value for each locus with an associated risk allele. Weighted risk scores were calculated using the scoring option for PLINK v1.07. Each score was given a weight according to the natural log transformed odds ratio provided for every significant risk variant. The unweighted risk score was calculated as the number of risk alleles counted for each individual. We chose to calculate our PRS by selecting one marker per locus to avoid inflation in the score calculation due to tight linkage disequilibrium. Our pruning method involved taking the marker, from each locus, with the highest effect size from the initial PGC2 discovery sample.

Please cite this article as: Hettige, N.C., et al., Polygenic risk score prediction of antipsychotic dosage in schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2015.12.015