Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Polygenic Risk Score associated with specific symptom dimensions in first-episode psychosis

Sarojini M. Sengupta [a,b,*], Kathleen MacDonald [a,b], Ferid Fathalli [a,b], Anita Yim [c], Martin Lepage [a,b,d], Srividya Iyer [a,b], Ashok Malla [a,b], Ridha Joober [a,b,d,e]

[a] Douglas Mental Health University Institute, 6875 LaSalle Blvd, Verdun, Quebec H4H 1R3, Canada
[b] Department of Psychiatry, McGill University, Ludmer Research & Training Building, 1033 Pine Ave. West, Montreal, Quebec H3A 1A1, Canada
[c] Department of Medicine, Université de Sherbrooke, Local E5-1283, Sherbrooke, Québec J1K 2R1, Canada
[d] Integrated Program in Neuroscience, McGill University, Room 141, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec H3A 2B4, Canada
[e] Department of Human Genetics, McGill University, Room N5-13, Stewart Biology Building, 1205 Dr. Penfield Ave., Montreal, Quebec H3A 1B1, Canada

ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 21 November 2016
Accepted 24 November 2016
Available online xxxx

Keywords:
Schizophrenia
First-episode psychosis
Polygenic Risk Score
General psychopathology
PANSS
Anxiety

ABSTRACT

Recent Genome-Wide Association Studies (GWAS) have provided evidence for the involvement of a number of genetic variants in schizophrenia (SCZ). The objective of the current study was to examine the association between these variants and symptom dimensions, evaluated prospectively over a period of 24 months, in a clinically well-characterized sample of individuals (n = 241) with first-episode psychosis (FEP). The genetic variants were analyzed collectively as captured through a Polygenic Risk Score (PRS), calculated for each individual. At each evaluation time point (baseline, 1, 2, 6 and 24 months), correlation analysis was conducted with PRS and symptom dimension scores assessed by the Positive and Negative Syndrome Scale (PANSS). We also examined the association of PRS with global symptom rating, depression, anxiety, social and occupational functioning as measured by widely used and well validated scales. At baseline, significant positive correlation was observed between PRS and the general psychopathology dimension of the PANSS but no associations were observed with the positive or negative symptom dimensions. Anxiety, assessed using the Hamilton Anxiety Rating Scale, was also significantly correlated with the PRS. No significant correlation was observed with other symptom dimensions or with the PANSS score at the later evaluations. These results provide novel evidence of an association between general psychopathology and PRS in young people with first episode psychosis. They also demonstrate that it is important to note the dynamic changes of symptoms over time when trying to refine the relationship between genetic factors and phenotypes.

1. Introduction

Schizophrenia (SCZ) spectrum psychoses are often regarded as the most serious of all mental disorders. The primary symptoms are positive (delusions, hallucinations, disorganization of thought and behavior), with to a varying degree, negative (poverty of thought and affect, apathy and social withdrawal), depressive, manic and anxiety symptoms in the acute phase; and residual symptoms and social disability in the longer term. With onset typically occurring during adolescence or early adulthood, psychotic disorders have serious long-term implications including reduced life expectancy (Chang et al., 2011), disruption of social and emotional development, education underachievement, unemployment (Świtaj et al., 2012), and suicide (Hor and Taylor, 2010).

Schizophrenia spectrum disorders have a strong genetic component, and it is now well-elucidated that a large number of independent loci contribute to their etiology, each adding only a small risk. Both common and rare risk variants have been implicated. It has been estimated that a half to one-third of the genetic risk is indexed by common alleles that can be assayed in Genome-Wide Association Studies (GWAS) (International Schizophrenia Consortium et al., 2009; Ripke et al., 2013). Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium reported results of the most recent GWAS conducted with a sample size >150,000 (36,989 cases and 113,075 controls) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). 108 independent genetic loci were shown to be associated with SCZ, passing criteria for genome-wide significance ($P \leq 5 \times 10^{-8}$). A recent advancement in psychiatric genetics has been the use of a Polygenic Risk Score (PRS) in association analyses (International Schizophrenia Consortium et al., 2009). A PRS is essentially derived by aggregating genetic risk variants identified from GWAS into one score. The major advantage of this approach is that the

* Corresponding author at: Douglas Mental Health University Institute, 6875 LaSalle Blvd, Verdun, Quebec H4H 1R3, Canada.
E-mail address: sarojini.sengupta@douglas.mcgill.ca (S.M. Sengupta).

http://dx.doi.org/10.1016/j.schres.2016.11.039
0920-9964/

power of a large GWAS can be robustly utilized for a smaller sample, since the statistical power of a PRS is exponentially better compared to that of a single SNP (Dima and Breen, 2015).

Several recent studies have examined the association between SCZ PRS score with symptoms of the disorder. In one of the first studies of this kind, PRS score was shown to be significantly different when comparing cases versus controls (Derks et al., 2012). However, within the affected group, no association was observed between PRS and any of the 5 symptom dimensions of psychosis analyzed (depression, disorganization, mania, positive and negative symptoms). A second study reported a lack of association between SCZ PRS and "psychotic experiences" in a large non-clinical community sample of adolescents between 12 and 18 years of age (Sieradzka et al., 2014). Here the instrument used was the Specific Psychotic Experiences Questionnaire (SPEQ) which includes self-reported paranoia, hallucinations, cognitive disorganization, grandiosity, anhedonia, and parent-rated negative symptoms. This group also used the Psychotic-Like Symptoms Questionnaire (PLIKS-Q), but observed no association with SCZ PRS. In yet another study, conducted with the large non-clinical ALSPAC cohort, no association was observed between SCZ PRS and psychotic experiences (Zammit et al., 2014). Psychotic experiences were assessed, at 12 years of age, as a single categorical construct (i.e. any one of a number of different positive experiences).

In the studies described above, SCZ PRS was derived from earlier GWAS that identified 13 risk loci (Ripke et al., 2013). More recent studies have derived a SCZ Polygenic Risk Score from the 108 loci implicated in the most recent GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In a study conducted with adolescents from the ALSPAC cohort, measures of negative symptoms, depressive and anxiety disorders were added to the PLIKS-Q described above (Jones et al., 2016). As before, no association was observed with psychotic experiences. However, significant association was observed between SCZ PRS and negative symptoms as well as anxiety disorders. In another recent study, no association was observed with symptom severity and overall functioning as measured by the Global Assessment of Functioning (GAF) scale, nor with antipsychotic dosage (Hettige et al., 2016).

While the results of these studies are interesting, the major disadvantage is that they were most likely conducted in patients at different stages of the illness and treatment, which may obscure any relationship between symptoms and PRS. A recent study, conducted with a sample of first-episode psychosis (FEP) patients, concluded that PRS was a reliable predictor of case-control status (Vassos et al., 2016). However, no analysis was presented on the association of PRS with symptom dimensions of SCZ. The objective of the current study was to use a clinically well-characterized sample of individuals with FEP, who are engaged in a structured treatment program: (1) to refine the association between the SCZ PRS and symptom dimensions of psychotic disorder, and, (2) to examine the association of SCZ PRS with symptom dimensions over the course of the two-year treatment period. The advantages of such a sample are that the clinical manifestations of illness are not confounded by long-term exposure to medication, chronicity, and social deprivation.

2. Materials and methods

2.1. Subjects

Individuals were recruited from among FEP patients treated at the Prevention and Early Intervention Program for Psychoses in Montreal (PEPP- Montréal) between 2003 and 2013. This program is a specialized, publicly-funded, early-intervention service that provides intensive medical and psychosocial management over a 24 month period (Iyer et al., 2015). PEPP- Montréal is an integrated clinical and research program that constitutes the only service for FEP patients within a large catchment area (population of 400,000) in southwest Montréal, without alternative competing programs in its vicinity. Inclusion criteria are as follows: (1) age between 14 and 35 years; and (2) diagnoses of affective (Bipolar Disorder and Major Depressive Disorder with psychotic features) or non-affective (Schizophrenia, Schizoaffective Disorder, Schizophreniform disorder, Delusional Disorder and Psychosis Not Otherwise Specified) FEP. The clinical diagnosis is made using the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manuel for Mental Disorders, fourth edition, text revised). All diagnoses are confirmed at a consensus meeting attended by a senior research psychiatrist (RJ or AM). Only individuals with <30 cumulative days of treatment with antipsychotic medication are included in the program.

Of the 660 clients meeting criteria for admission to PEPP-Montreal, 573 consented to participate in the research arm of the program. These individuals were subsequently approached to participate in the genetic study, and written informed consent was obtained from those interested (n = 241). This study was approved by the Ethics Review Board at the DMHUI and McGill University.

As part of the program, patients are stabilized on second-generation anti-psychotic medication following a defined protocol. The program uses standardized structured evaluations to monitor symptoms, and implement treatment plans tailored to the needs of the patient. Evaluations are conducted at regular intervals (baseline and months 1, 2, 3, 6, 12, 18 and 24) by highly trained research staff. Inter-rater reliability sessions are regularly held and any observed drift in ratings is corrected.

2.2. Instruments and assessment

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988; Kay et al., 1989). This scale is a standardized, validated instrument devised for the assessment of symptoms. It consists of 30 items, each rated on a 7-point scale of severity. Of the 30 items, an equal number of items are summed in the overall positive symptom score (7 items) and negative symptom score (7 items). The remaining 16 items constitute a measure of "general psychopathology". The inclusion of a scale to measure general psychopathology has been noted to be one of the key advantages over the other instruments widely used to assess symptoms: Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) (Kay et al., 1988). The general psychopathology index was intended to serve as a measure of overall severity of illness, independent of positive and negative symptoms. Symptomatic state/outcome was assessed using the Global Assessment of Functioning (GAF) scale. Since comorbid anxiety disorders and depression are common with psychotic disorders, assessment using the Hamilton Anxiety Rating Scale (HARS) (Hamillton, 1959) and Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) were also conducted at each evaluation. Psychosocial functioning was assessed at baseline and 24-month follow-up using the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). These scales are extensively used in treatment outcome studies.

2.3. Genetics

DNA was extracted from blood or saliva samples collected from each participant. Of the 128 initial sites showing a significant association in the SCZ GWAS, several overlapping regions were implicated (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In order to define loci conservatively so as to include only physically independent regions of the genome, associated regions that were not separated by at least 250 kb were merged to obtain 108 loci in the GWAS. From each of these merged regions, only one single nucleotide polymorphism (SNP) was selected for genotyping. A total of 10 chromosomal regions lacking a unique SNP ID (chr1_8424984_D; chr2_146436222_I; chr2_149429178_D; chr2_200825237_I; chr5_140143664_I; chr6_84280274_D; chr7_2025096_I; chr7_24747494_D; chr11_46350213_D; chr11_46350213_D) were not included in the panel for genotyping.

Please cite this article as: Sengupta, S.M., et al., Polygenic Risk Score associated with specific symptom dimensions in first-episode psychosis, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.11.039