Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Cannabis abuse and age at onset in schizophrenia patients with large, rare copy number variants

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ARTICLE INFO

Article history:
Received 29 October 2013
Received in revised form 4 February 2014
Accepted 5 March 2014
Available online xxxx

Keywords:
Schizophrenia
Copy number variants
Genetics
Cannabis
Substance abuse
Age at onset

ABSTRACT

Background: Large deletions are found to a greater extent in patients with schizophrenia compared with healthy controls. This study aims to investigate clinical symptomatology and substance abuse rates in patients with large (>500 kb), rare (<1% of cohort) deletions and duplications compared with schizophrenia patients in general.
Methods: 633 schizophrenia patients, including 60 with large (>500 kb), rare (<1% of cohort) deletions and 74 with large, rare duplications, who formed part of a large genome-wide association study, were assessed for alcohol and cannabis abuse rates as well as a range of symptom measures using the Diagnostic Interview for Genetic Studies (DIGS), Family Interview for Genetic Studies (FIGS), and medical records.
Results: Patients with large, rare deletions had significantly less cannabis abuse rates but comparable alcohol abuse rates, with an age at onset later than those without large, rare deletions. There was no significant difference in any substance abuse or clinical symptom rates between patients with and without large, rare duplications, but an interaction did exist between cannabis abuse, duplication status, and age at onset, with cannabis abuse resulting in an earlier age at onset only in those without a large, rare duplication. Similarly, patients with a large, rare duplication had a later onset age for cannabis abuse/dependence.
Conclusions: Schizophrenia patients with large, rare deletions were less likely to have comorbid cannabis abuse over their lifetime. This provides support for a threshold model of risk with those carrying a schizophrenia-associated copy number variation less reliant on environmental insults. Patients with large, rare duplications were protected against earlier onset of schizophrenia in the presence of comorbid cannabis abuse in addition to later onset of cannabis abuse itself.

1. Introduction

The aetiology of schizophrenia is likely multifactorial with both genetic and environmental contributions. Heritability is approximately 0.8 (Cardno and Gottesman, 2000; Sullivan et al., 2003) with genome wide association studies (GWAS) providing evidence for polygenic risk contributions from common single nucleotide polymorphisms (SNPs), as well as rare (<1%) copy number variants (CNVs) (Mowry and Gratten, 2012), especially large (>500 kb) deletions (Owen et al., 2010). Substance abuse is higher in patients with schizophrenia, particularly cannabis abuse (Barnett et al., 2007), with longitudinal studies suggesting that cannabis use increases the risk for the disorder (Arseneault et al., 2004; Moore et al., 2007). In order to make sense of the number of genetic and environmental risk factors for schizophrenia, a threshold model has been proposed (McGue et al., 1983; Tsuang et al., 2001; McGuffin, 2004). Those with the strongest genetic predisposition for schizophrenia may need little or no environmental insult, whereas those with relatively low genetic vulnerability may require a greater environmental insult. Evidence from large GWA studies suggests that large, rare deletions but not duplications are seen at an excess in cases compared with controls (Owen et al., 2010; Levinson et al., 2011) and may result in increased neurodevelopmental instability (Yeo et al., 1999) lowering the threshold for polygenic or environmental risk factors to direct development towards psychosis.

Environmental factors in risk of schizophrenia have been comprehensively reviewed (van Os et al., 2010) with a consistent association found between cannabis abuse and schizophrenia (Minozzi et al., 2010). Studies have also shown that exposure to cannabis is not confounded by indices of genetic risk, with little of the association between cannabis abuse and psychosis explained by genetic confounds (Veling

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http://dx.doi.org/10.1016/j.schres.2014.03.004
0920-9964/

et al., 2008; GROUP Investigators, 2011; van Winkel, 2011). In healthy controls, cannabis abuse is associated with schizophrenia-like cognitive and behavioural changes (Morrison et al., 2009), and exacerbates the existing symptoms in patients with schizophrenia (D'Souza et al., 2005). Recent evidence, however, suggests that first-episode psychosis patients with comorbid cannabis abuse may actually perform better on a wide range of cognitive tests than those without comorbid cannabis abuse (Yucel et al., 2012). This could reflect a subgroup who only become psychotic due to cannabis abuse, with cognition remaining largely intact, because prior to the environmental insult, development was unperturbed by deleterious genetic factors.

Given the evidence for large deletions as genetic risk factors and cannabis abuse as an environmental risk factor, the following study will investigate rates of cannabis abuse in schizophrenia patients with and without large (>500 kb), rare (frequency <1% of the sample) copy number variants (both deletions and duplications). It is hypothesized that patients with large deletions will show lower rates of cannabis abuse than those without but similar levels of alcohol abuse, offering support for a threshold model of genetic and environmental influence on risk for schizophrenia. As large, rare duplications are not associated with schizophrenia, cannabis abuse should not differ according to duplication status. As previous studies have found that age at onset is earlier in patients with comorbid cannabis abuse (Weller et al., 1988; DeQuardo et al., 1994; Hambrecht and Hafner, 1996; Addington and Addington, 1998; Rabinowitz et al., 1998), an exploratory study into clinical factors, including age at onset, and patients with large, rare CNVs will be conducted.

2. Methods

This Australian sample was recruited as part of two consecutive collaborative US/Australian Molecular Genetics of Schizophrenia studies: (i) MGS1, a genomewide linkage study which included families with a proband with schizophrenia, and one or more siblings with schizophrenia or schizoaffective disorder (Suarez et al., 2006). Only the proband from each family was included in the current study; (ii) MGS2, a genome-wide association study that included unrelated individuals with schizophrenia or schizoaffective disorder plus a sample of healthy controls (Shi et al., 2009). Eligible individuals were recruited from a range of sources, including local treatment facilities, physician referrals, community organizations, supported accommodation facilities and advertisements. Probands and relatives with a diagnosis of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) schizophrenia or schizoaffective disorder were included. In order to standardize schizoaffective diagnoses, we operationalized the mood syndrome duration criterion at ≥30% of total illness duration (Suarez et al., 2006). Individuals were included if they met self-reported European Caucasian ancestry, later confirmed by genetic analysis. Exclusion criteria were: (i) inability to give informed consent to all aspects of the study; (ii) psychosis judged to be secondary to substance use or a known neurological disorder such as epilepsy; and (iii) severe intellectual disability (any impairment that precluded informed consent, and any individual with an IQ assessed below 55 according to formal testing/medical record evidence).

2.1. Clinical ascertainment

Individuals were comprehensively ascertained by trained clinicians using: (i) the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) (ii) Family Interview for Genetic Studies (FIGS) (Gershon et al., 1988; Maxwell, 1992); (iii) information extracted from all available medical records; (iv) Narrative summary prepared by the interviewer and based on all information obtained from the DIGS, FIGS and medical records. The narrative summary was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity; (v) Best Estimate Final Diagnosis (BEFD) (Leckman et al., 1982) was assigned by two experienced research psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis; one of us (BM) reviewed every Australian case. Diagnostic inter-rater reliability was assessed using standard procedures (Suarez et al., 2006).

2.2. Coding of clinical variables

Sources of data were audited (both electronic and hard copy), and all potential cases were identified for whom diagnostic information was available. Data were extracted from diagnostic interview databases, where possible, then responses were checked, corrected, and missing values retrieved from all available sources. Positive, negative/disorganized, and mood symptoms were scored using the Lifetime Dimensions of Psychosis Scale (LDPS) (Levinson et al., 2002) with severity and duration ratings totaled in line with the factor analysis carried out by Fanous et al. (2012). Age at onset of psychosis was defined as age when patients had their first documented psychotic symptoms.

Alcohol and cannabis abuse/dependence were coded according to DSM-IV criteria with information ascertained through interview with the patient using DIGS, with a family member using FIGS, and through a detailed search of available medical records. The criteria for lifetime cannabis or alcohol abuse was a maladaptive pattern of use, leading to significant impairment or distress, as manifested by at least one of the following occurring within a 12-month period:

- Recurrent use resulting in failure to fulfill major role obligations at work, school, or home
- Recurrent use in situations in which it is physically hazardous
- Recurrent substance-related legal problems
- Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

The criteria for lifetime cannabis or alcohol dependence was a maladaptive pattern of use, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period:

- Need for markedly more amounts to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount
- The characteristic withdrawal syndrome
- Using larger amounts or over a longer period than intended
- Persistent desire or one or more unsuccessful attempts to cut down or control use
- Important social, occupational, or recreational activities given up or reduced because of use
- A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking
- Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use

Cannabis abuse/dependence will be referred to as cannabis abuse from this point onwards for ease of reading. Age at onset for cannabis and alcohol abuse/dependence was the first documented or self-reported use that reached the DSM-IV-TR criteria for abuse or dependence.

2.3. Copy number variant identification

2.3.1. Original MGS study

Quality control, identification and analytic methods have been described previously (Levinson et al., 2011). Briefly, DNAs were assayed using Affymetrix 6.0 genotyping arrays, which included approximately 900,000 single-nucleotide polymorphisms (SNPs) and approximately

Please cite this article as: Martin, A.K., et al., Cannabis abuse and age at onset in schizophrenia patients with large, rare copy number variants, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.03.004