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TCF4 gene polymorphism and cognitive performance in patients with first episode psychosis

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ABSTRACT

Background: Single nucleotide polymorphisms in *TCF4* gene have been consistently associated with schizophrenia in genome wide association studies, including the C allele of rs9960767. However, its exact role in modulating the schizophrenia phenotype is not known.
Aims: To comprehensively investigate the relationship between rs9960767 risk allele (C) of *TCF4* and cognitive performance in patients with first episode psychosis (FEP).
Methods: 173 patients with FEP received a comprehensive neurocognitive evaluation and were genotyped for rs9960767. Carriers of the risk allele (CA/CC) were compared to non-carriers (AA) using Multivariate Analysis of Covariance MANCOVA. Ethnicity, negative symptoms and substance abuse were included as covariates.
Results: Carriers of the risk allele had a statistically significant lower performance in the cognitive domain of Reasoning/Problem-Solving compared to non-carriers ($F_{1,172} = 4.4$, $p = .038$). There were no significant genotype effects on the other cognitive domains or general cognition. This effect on the Reasoning/Problem-Solving domain remained significant even when controlling for IQ ($F_{1,172} = 4.3$, $p = .039$).
Conclusions: rs9960767 (C) of *TCF4* appears to be associated with neurocognitive deficits in the Reasoning/Problem-Solving cognitive domain, in patients with FEP. A confirmation of this finding in a larger sample and including other *TCF4* polymorphisms will be needed to gain further validity of this result.

1. Introduction

Schizophrenia (SCZ) is a debilitating neurodevelopmental disorder with an estimated heritability of 80% (Sullivan et al., 2003; Lichtenstein et al., 2009). Recently, genome wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) on the transcription factor 4 gene (*TCF4*) that confer risk of SCZ (Stefansson et al., 2009; Li et al., 2010; Steinberg et al., 2011). In 2009, a large case/control GWAS associated SCZ with the C allele of rs9960767, a SNP located in intron 3 of *TCF4* (Stefansson et al., 2009). This association was further confirmed and strengthened in a large meta-analysis of SCZ GWAS ($p = 4.2 \times 10^{-9}$, OR = 1.20, 95% CI = 1.13–1.27) (Steinberg et al., 2011). Li et al. attempted to replicate this association in a large Han Chinese sample (Li et al., 2010). Interestingly, rs9960767 was not polymorphic in this sample, but rs2958182 (located in the same intron and in high Linkage Disequilibrium (LD) with rs9960767) was significantly associated with SCZ. Furthermore, rs17512836 of *TCF4* (in moderate LD with rs9960767) and rs12966547 (in weak LD with rs9960767) were among the top 10 identified SNPs in a SCZ GWAS (Schizophrenia Psychiatric Genome-Wide Association Study, 2011). The most recent SCZ GWAS identified 22 risk loci for SCZ including SNP's near *TCF4*; although, rs9960767 was not reported in this GWAS (Ripke et al., 2013). The association between *TCF4* polymorphisms and SCZ was further confirmed in a recent family-based replication study of a large meta-analysis of SCZ GWAS ($p = 2.53 \times 10^{-10}$, OR = 1.6) (Aberg et al., 2013). Moreover, a Convergent Functional Genomics (CFG) of SCZ study by Ayalew et al. identified *TCF4* as one of the top SCZ candidate genes using a comprehensive approach that integrates multiple lines of evidence including GWAS, other genetic studies and gene expression studies, in both animal model and human studies (Ayalew et al., 2012).

TCF4 encodes transcription factor 4 (TCF4), a basic helix–loop–helix, known to play a critical role in cortical development and to be highly expressed throughout the development of the central nervous system in humans (Flora et al., 2007; de Pontual et al., 2009). Recent studies suggest that *TCF4* regulates the expression of many other genes that are involved in cell differentiation, cell survival and neurodevelopment (Forrest et al., 2013). Moreover, the expression of *TCF4* passed the

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transcriptome-wide significance ($p = 1.4 \times 10^{-5}$) for positive correlation with gray matter thickness during normal cerebral aging (Kochunov et al., 2013). Additionally, *TCF4* is tightly co-expressed with many other genes and is a known target of micro RNAs (miRNAs) that are implicated in neurodevelopment and neurodevelopmental disorders (Navarrete et al., 2013). In addition to its implication in neurodevelopment, disruptions in *TCF4* have been associated with a range of neurodevelopmental disorders. More specifically, the haploinsufficiency of *TCF4* results in Pitt–Hopkins syndrome (PHS), a neurodevelopmental disorder characterized by mental and growth retardation, breathing abnormalities, seizures, microcephaly and characteristic facial features (Zweier et al., 2007). Furthermore, milder disruptions in *TCF4* were associated with milder neurocognitive dysfunctions without classical PHS (Kalscheuer et al., 2008). Also, balanced chromosomal abnormalities and copy number variants affecting *TCF4* were found to be more common in subjects with neurodevelopmental disorders including Autism Spectrum Disorder compared to controls (Talkowski et al., 2012). These aforementioned studies provide evidence suggesting the implication of *TCF4* abnormalities in cognitive dysfunction across different neurodevelopmental disorders.

Neurocognitive deficits are an important core feature of SCZ that exist prior to the onset of clinical symptoms (Lencz et al., 2006). Numerous studies have described "generalized" deficits across almost all cognitive domains; however, specific cognitive deficits such as in Verbal Memory, Episodic Memory, Processing Speed and Executive Functioning have also been reported (Heinrichs and Zakzanis, 1998; Johnson-Selfridge and Zalewski, 2001; Seidman et al., 2002; Pelletier et al., 2005; Dickinson et al., 2007; Mesholam-Gately et al., 2009; Schaefer et al., 2013). Similarly, global cognitive deficits have been reported in patients with FEP, with maximal deficits occurring in the cognitive domains of Processing Speed, Reasoning/Problem-Solving and Attention (Bozikas and Andreou, 2011; Andersen et al., 2013). Moreover, cognitive deficits are shared by non-affected relatives of patients with SCZ and may serve as endophenotypes with putative closer links to the genetic determinants of SCZ (Gottesman and Gould, 2003; Toulopoulou et al., 2010).

Consequently, recent studies explored the association between *TCF4* variants and neurocognitive functioning in patients with SCZ. More specifically, Lennertz et al. investigated the relationship between rs9960767 (C) and verbal declarative memory (VDM) in 401 patients with SCZ using the Rey Auditory Verbal Learning Test (RAVLT) (Lennertz et al., 2011). In contrast to their hypothesis, carriers of the *TCF4* risk allele performed better than non-carriers in recognition memory ($p = 0.049$) and the two genotype groups did not significantly differ in total VDM, immediate recall memory or delayed recall memory. Quednow et al. studied the role of *TCF4* variants in two SCZ endophenotypes, sensorimotor gating (SMG) as measured by prepulse inhibition (PPI) and auditory sensory gating (ASG) as measured by P50 suppression of the auditory evoked potentiation (Quednow et al., 2011; Quednow et al., 2012). In their first study, *TCF4*'s rs9960767 (C) was associated with reduced PPI in two independent samples, patients with SCZ spectrum and healthy subjects ($n = 113$ and $n = 107$ respectively). This finding is consistent with an earlier study in animals reporting decreased sensorimotor gating in transgenic mice that over express *TCF4* (Brzozka et al., 2010). Their subsequent study on 1821 healthy subjects revealed that *TCF4* SCZ risk alleles (including rs9960767) were significantly associated with decreased ASG and, interestingly, this association was more robust in heavy smokers. Zhu et al. examined the relationship between *TCF4* risk allele and performance on four attention-related cognitive tasks: Attention Network Task, Stroop Task, Dot Pattern Expectancy Task, and the Wechsler Forward Digit Span. The *TCF4* risk allele was associated with better cognitive performance in SCZ patients ($n = 526$), but with lower performance in controls ($n = 421$). Collectively, these studies suggest an important but complex relationship between *TCF4* polymorphisms and neurocognition in SCZ patients, warranting further exploration. Additionally, *TCF4* is a known target of miRNA-137 encoded by *MIR137*, which is known to be both associated with SCZ in GWAS and possibly with a SCZ sub-type with severe cognitive impairments (Green et al., 2013; Ripke et al., 2013; Wright et al., 2013).

The purpose of the current study was to conduct a systematic investigation of the relationship between *TCF4* rs9960767 variants and neurocognitive performance in patients with FEP. We believe that investigating this association in young patients with psychosis has the advantage of avoiding a number of confounding factors, particularly cognitive decline resulting from chronic illness, social isolation, long term vocational deprivation and long-term exposure to medication.

2. Materials and methods

2.1. Subjects

Subjects were recruited through the Prevention and Early Intervention Program for Psychoses (PEPP — Montréal), in the Douglas Mental Health University Institute between 2003 and 2012. This publicly funded program provides intensive medical and psychosocial management to patients with FEP, its details have been described previously (Malla et al., 2003). Patients aged 14–35 years old presenting with non-affective (DSM-IV diagnoses of Schizophrenia, Schizoaffective Disorder, Schizophreniform disorder, Delusional Disorder and Psychosis Not Otherwise Specified) and affective (DSM-IV diagnoses of Bipolar Disorder and Major Depressive Disorder with psychotic features) first episode psychosis and who have not been exposed to antipsychotics for longer than 30 days are accepted to the program. Patients in this program are started on a second-generation anti-psychotic medication (SGA) following a protocol and are closely monitored for improvement and side effects with comprehensive assessments. Psychosocial interventions are provided to patients who refuse pharmacotherapy. The sample included is likely to be representative of a treated incidence sample as there are no competing private or public treatment facilities in the catchment area. The current study was explained to the participants and informed written consent was obtained from them. This study was approved by the Ethics Review Board at the Douglas Hospital.

2.2. Clinical and neurocognitive assessment

The clinical diagnosis was made using the Structured Clinical Interview for DSM IV (Diagnostic and Statistical Manuel for Mental Disorders, fourth edition, text revised) (First et al., 2002) and all diagnoses were confirmed at a consensus meeting attended by a senior research psychiatrist (RJ or AM). Positive and negative symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) respectively. Dosages of antipsychotics were converted to chlorpromazine equivalent doses based on the International Consensus Study of Antipsychotic Dosing (Gardner et al., 2010). Nicotine use was assessed using the Chemical Use Abuse Dependence Scale (CUAD).

Test batteries were administered by trained professionals when patients had reached a stable but not necessarily asymptomatic condition. The six domains of cognitive performance were derived from the standardized neuropsychological testing battery that the patients underwent, representing six cognitive domains according to the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Green et al., 2004; Nuechterlein et al., 2004). The six MCCB domains were: Verbal Memory derived from the Logical Memory sub-tests of the Wechsler Memory Scale 3rd Edition (WMS-III) (Wechsler, 1997b) (immediate recall, delayed recall, recognition memory), Visual Memory derived from the Visual Reproduction WMS-III (immediate recall, delayed recall, and recognition memory), Working Memory from the Spatial Span sub-tests of the WMS-III and the Digit Span sub-tests of the Wechsler Adult Intelligence Scale — third edition (WAIS-III)