Schizophrenia Research 106 (2008) 258–264

Contents lists available at ScienceDirect

Schizophrenia Research

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

Association of *Sult4A1* SNPs with psychopathology and cognition in patients with schizophrenia or schizoaffective disorder

Herbert Y. Meltzer [a,*], Mark D. Brennan [b], Neil D. Woodward [a], Karu Jayathilake [a]

[a] *Psychiatric Hospital at Vanderbilt University, Nashville, TN, United States*
[b] *Department of Biochemistry and Molecular Biology, University of Louisville, KY and SureGene, LLC Louisville, KY, United States*

ARTICLE INFO

Article history:
Received 5 June 2008
Received in revised form 23 August 2008
Accepted 27 August 2008
Available online 27 September 2008

Keywords:
Sulfotransferase-4A1
SNP
Psychopathology
Neuropsychology
Schizophrenia

ABSTRACT

A number of genes located on chromosome 22q11–13, including catechol-*O*-methyltransferase (COMT), are potential schizophrenia susceptibility genes. Recently, the sulfotransferase-4A1 (*Sult4A1*) locus within chromosome 22q13 was reported to be linked to schizophrenia in a family TDT study. *Sult4A1* is related to metabolism of monoamines, particularly dopamine and norepinephrine, both of which have been implicated in the pathophysiology of the psychopathology and cognitive dysfunction components of schizophrenia. An available, prospectively collected data base was interrogated to determine how three *Sult4A1* SNPs: rs138060, rs138097, and rs138110, previously shown to be associated with schizophrenia might be associated with psychopathology, cognition, and quality of life in a sample of 86 Caucasian patients with schizophrenia or schizoaffective disorder. The majority of patients met criteria for treatment resistant schizophrenia and had been drug-free for one week or longer at the time of evaluation. The major findings were: 1) patients heterozygous (T/G) for rs138060 had significantly worse Brief Psychiatric Rating Scale (BPRS) Total and anxiety/depression sub-scale scores, and higher Scale for the Assessment of Positive Symptoms (SAPS) Total scores than G/G homozygous patients; and 2) patients heterozygous (A/G) for rs138097 demonstrated significantly worse performance on neuropsychological testing, specifically on tests of executive function and working memory, compared to patients homozygous for the G and A alleles. RS138110 was unrelated to psychopathology and cognition. These results provide the first evidence of how genetic variation in *Sult4A1* may be related to clinical symptoms and cognitive function in schizophrenia, and permit future studies to attempt to replicate these potentially important findings.

1. Introduction

A number of genes located on chromosome 22q11–13 have been identified as increasing the risk for schizophrenia through association studies. Microdeletions of the 22q11 locus are associated with a greatly increased risk of developing schizophrenia (Karayiorgou and Gogos, 2004). Among the genes in the 1.5 Mb critical region of 22q11 which are candidates for increasing the risk are PRODH, ZDHHC8, TBX1 and COMT. There is; however, considerable evidence for one or more susceptibility genes distal to 22q11, e.g. in 22q12 or 22q13 (DeLisi et al., 2002; Mowry et al., 2004; Takahashi et al., 2003, 2005). One such gene may be the sultotransferase-4A1 (*Sult4A1*) gene, located in 22q13, which was first reported to be a candidate gene for schizophrenia on the basis of a microsatellite marker study targeting a polymorphism in its 5′ nontranslated region in 27 families having at least two siblings with schizophrenia or schizophrenia spectrum disorder (Brennan and Condra, 2005). Three single nucleotide polymorphism (SNPs) spanning a 37 kb segment which contained the Sult4A gene were evaluated. D22s1749e was found to be associated with risk for schizophrenia or

* Corresponding author. Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN 37212, United States. Tel.: +1 615 327 7049.
E-mail address: herbert.meltzer@vanderbilt.edu (H.Y. Meltzer).

0920-9964/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.08.029

schizophrenia spectrum disorder. Global chi-square analysis of haplotypes involving the single nucleotide polymorphisms (SNPs) (rs138060, rs138097 and rs138110) as well as D22s1749E showed significant transmission disequilibrium test (TDT) values. Subsequently, a more distal locus, centered at 61 cM, was also found to be associated with a broader disease definition which included schizotypal personality disorder (Condra et al., 2007). It was concluded that at least two separable, but closely linked, loci within 22q13 may influence susceptibility to schizophrenia spectrum disorders.

Phenolsulfotransferases, which catalyze the formation of dopamine sulfate (Goldstein et al., 2003), have been implicated in schizophrenia, based upon two studies which found elevated levels of dopamine sulfate in the cerebrospinal fluid of patients with schizophrenia (van Kammen et al., 1986; Risby et al., 1993), and a correlation between dopamine sulfate levels and negative symptoms (Risby et al., 1993). There is, as yet, no clarification of the specific importance, if any, of *Sult4A1* for specific symptoms of schizophrenia. Demonstrating a relationship between *Sult4A1* SNPs and psychopathology or cognitive disturbance in patients with schizophrenia would add to the evidence of the importance of *Sult4A1* for schizophrenia and suggest possible avenues by which its effects, if any, on brain monoamines and neurosteroids could be further investigated.

The *Sult4A1* gene is highly conserved between species and shows no variation in the coding sequence in a sample of 118 ethnically diverse humans (Hildebrandt et al., 2007). *Sult4A1* encodes a cytoplasmic sulfotransferase which is specific to the brain. It, and other members of the sulfotransferase superfamily, are involved in the sulfation and inactivation of neurotransmitters, including dopamine (DA) and norepineprhine, steroids (including neurosteroids), drugs and xenobiotics (Yu et al., 1985; Falany et al., 2000; Sakakibara et al., 2002; Liyou et al., 2003). Sulfotransferases have been implicated in the etiology of Alzheimer's disease (Miyata et al., 2007; Kimoto et al., 2001).

This study retrospectively examined associations between three *Sult4A1* SNPs and clinical symptoms, cognitive function, and quality of life in a sample of 86 Caucasian patients with schizophrenia.

2. Methods

2.1. Subjects

The subjects in this study included all Caucasian subjects for whom DNA was available from a larger group of patients with schizophrenia or schizoaffective disorder who participated in a comprehensive study of the biology of schizophrenia between 1986 and 1995 that was directed by the senior author (H.Y.M). All subjects provided written informed consent. The assessment of patients who participated in these studies has been described in detail elsewhere (Lee et al., 1999; Hagger et al., 1993; Kenny and Meltzer, 1991; Woodward et al., 2007). Briefly, diagnoses were established on the basis of structured interviews of the patient, examination of all available medical records, and confirmatory information from family members whenever possible. Diagnoses were a mixture of DSM-III-R or ICD-9 criteria but all have been updated to DSM-IV criteria by a research psychiatrist (H.Y.M). Exclusion criteria included history of learning disabilities, head trauma, stroke, or neurological illness, and active alcohol or drug abuse at the time they were assessed. Patients were assessed during inpatient admission and the majority of patients (67.4%) were medication free at the time, with 64% of subjects having undergone a minimum one day medication washout. With the exception of five patients, for whom medication status was unknown, the remaining subjects were receiving a typical APD, usually haloperidol. Clinical symptoms were rated on the Brief Psychiatric Rating Scale (BPRS: Overall and Gorham, 1962), Scale for Assessing Positive Symptoms (SAPS: Andreasen, 1984), Global Assessment of Function (GAF) from the DSM-IIIR, and Global Assessment Scale (GAS: Endicott et al., 1976). Social, occupational, and overall quality of life was assessed with the Heinrichs Quality of Life Scale (HQLS: Heinrichs et al., 1984). GAS and GAF data were unavailable for 6 subjects, 11 subjects were not rated on the SAPS, and the HQLS was completed on a subset of 66 patients. In addition, 49 subjects completed all or part of a neuropsychological assessment that included tests of attention, learning and memory, including working memory, and executive functions. The number of patients completing neuropsychological testing was lower because such testing was not initially part of the investigational protocol. A complete description of the tests included in the neuropsychological battery is included in a prior report (Woodward et al., 2007). Factor analysis of the neuropsychological battery revealed three factors that collectively accounted for 69% of the total variance and the minimum loading of any test on its respective factor was .58. The three factors were denoted: 1) Memory Function; 2) Attention and Verbal Fluency; and 3) Executive Function (Woodward et al., 2007). For the neuropsychological test data, the factor scores are reported as *Z*-scores which were created by standardizing each test variable (mean=0, SD=1) to a control sample that consisted of 26 subjects and averaging the standardized scores included in each factor (Woodward et al., 2007). A global cognitive score was created by averaging the mean *Z*-scores of all neuropsychological variables and this served as the primary outcome measure for the neurocognitive analysis.

2.2. Genotyping

Forty-seven of the blood samples were collected and sent to the Clarke Institute of Psychiatry in Toronto, Ontario, Canada. Genomic DNA was extracted from white blood cells using the high-salt method (Lahiri and Nurnberger, 1991). The DNA from the rest of the blood samples was extracted directly from fresh blood samples. Each subject's *Sult4A1* genotype status was determined by the Vanderbilt University Human Genetics Core Laboratory using the TaqMan assay developed by Applied Biosystems. A large proportion of the samples were also genotyped at the University of Louisville as described in Brennan and Condra (2005) with complete agreement between the two methods. For the TaqMan assay, the genomic sequence flanking the SNP was submitted to Applied Biosystems for development of an assay-by-design. Each unique TaqMan minor-grove-binding (MGB) allele-specific probe was labeled with either a 5′-FAM or a 5′VIC reporter dye. PCR amplifications of genomic DNA was performed in a 384-well plate in an ABI PRISM 7900. Allele