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Polymorphisms in human endogenous retrovirus K-18 and risk of type 2 diabetes in individuals with schizophrenia

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Abstract

Type 2 diabetes is a major health problem in individuals with schizophrenia. The genetic basis of diabetes risk in individuals with schizophrenia has not been previously defined. We measured polymorphisms in a human endogenous retrovirus, Herv K-18, which is located in the CD48 signaling lymphocyte activating (SLAM) gene on chromosome 1. The study population consisted of 229 individuals with schizophrenia, 29 of whom had a history of type 2 diabetes, as well as 136 control individuals without a history of a psychiatric disorder or type 2 diabetes. We found that a haplotype defined by 2 polymorphisms in the envelope region of Herv K-18 is highly associated with type 2 diabetes in a population of 229 individuals with schizophrenia, with an odds ratio of 9.0 (95% confidence limits 2.3–34.7, $p<.001$) adjusted for race, gender and type of antipsychotic medication. Lower levels of association were found in other polymorphisms located in the 3′untranslated region of Herv K-18 and in adjacent loci in CD48. Polymorphisms in endogenous retroviruses which are located near immunomodulatory genes may constitute risk factors for diabetes in individuals with schizophrenia.

Keywords: Diabetes; Endogenous retrovirus; CD48

1. Introduction

Type 2 diabetes is a highly prevalent chronic medical condition affecting approximately 5.5% of the U.S. general population. Persons with schizophrenia have a particularly high risk for type 2 diabetes with a lifetime prevalence estimated to be two to four times that found in the general population (Rouillon and Sorara, 2005). The reasons that persons with schizophrenia are more prone to develop diabetes are not known with certainty but may include the high prevalence of obesity and the use of second-generation antipsychotic medications (Citrome et al., 2004; Leslie and Rosenheck, 2004). The relatively high rate of diabetes may contribute to the excess mortality among persons with serious mental illness (Harris and Barraclough, 1998).

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Recently, a number of genes associated with type 1 and type 2 diabetes have been discovered. These include genes in pathways including those which involve glucose homeostasis, metabolic activity, oxidative stress, or immune functioning (Bastard et al., 2006; Greenfield and Campbell, 2006; Rolo and Palmeira, 2006; Duffy 2007; Damiani et al., 2007). Of interest in terms of schizophrenia has been the finding of an association between risk of diabetes and polymorphisms in the Herv K-18 endogenous retrovirus located in the first intron of the signaling lymphocyte activation molecule (SLAM) CD48 gene on chromosome 1. Polymorphisms in the envelope region of the Herv K-18 endogenous retrovirus have been associated with increased risk of type 1 diabetes in some populations but not in others (Marguerat et al., 2004; Ramos-Lopez et al., 2006). The envelope region of this Herv K-18 encodes a superantigen (SAG) capable of modulating thymocyte selection and an altered repertoire of peripheral T-cells (Meylan et al., 2005). Altered T cell activity has also been noted in individuals with schizophrenia (Riedel et al., 2007; Müller et al., 2000) and an increased rate of autoimmune disorders has been detected in the first degree relatives of individuals with schizophrenia (Wright et al., 1996; Eaton et al., 2006). Furthermore, an insertional polymorphism in another Herv K retrovirus has been associated with the early onset of schizophrenia (Otowa et al., 2006) and individuals with schizophrenia have been shown to have altered expression of endogenous retrovirus transcripts in their blood (Yao et al., 2007), brains (Weis et al., 2007), and cerebrospinal fluids (Karlsson et al., 2001). Finally, the genomic localization of this Herv K-18 in the q21–q22 region of chromosome 1 is within a linkage area which has been associated with increased risk of schizophrenia in previous studies (Brzustowicz et al., 2002). We thus examined the association between risk of type 2 diabetes and polymorphisms in Herv K-18 and the adjacent CD48 gene in individuals with schizophrenia.

2. Materials and methods

Individuals with schizophrenia were recruited from outpatient treatment sites in central Maryland as previously described (Dickerson et al., 2003). Individuals in the schizophrenia sample all had a diagnosis of schizophrenia or schizoaffective disorder meeting criteria in the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) and were receiving antipsychotic medication at the time of study entry. Individuals in the non-psychiatric control sample were recruited as previously described from posted announcements at local health care facilities and universities in the same geographic region as the schizophrenia group (Dickerson et al., 2004). All control individuals were interviewed to rule out the presence of a current or past psychiatric disorder with the Structured Clinical Interview for DSM-IV Axis I Disorders — Non-patient Edition (SCID-I/NP; First et al., 1998). Control individuals were also excluded if they had a history of type 1 or type 2 diabetes. All participants from the schizophrenia group and the control group met the following additional criteria: 1) age between 18 and 65, inclusive; 2) absence of current substance abuse over the past one month and of any history of intravenous substance abuse; 3) absence of mental retardation; 4) absence of clinically significant medical disorders that would affect cognitive performance such as epilepsy, history of encephalitis or head trauma, or any other reported neurological disorder of the central nervous system that had resulted in past or current treatment.

In the schizophrenia sample, individuals were assessed as having diabetes if they were confirmed to be receiving at least one of the following medications for diabetes from a review of the medical record: acarbose, avandia, insulin, glimepiride, glipizide, glucophage, glyburide, metformin, orlistat, pioglitazone, repaglinide, rezulin, rosiglitazone, chlorpropamide, miglitol or tolazamide. Individuals with schizophrenia were excluded from the analysis if they had a history of type 1 diabetes or if they reported a history of diabetes but were not currently taking one of the above medications. There were a total of 229 individuals with schizophrenia from whom DNA was available for analysis; 29 of these had type 2 diabetes as defined by the above criteria. We also analyzed DNA from 136 control individuals without a history of a psychiatric disorder or of diabetes. The psychiatric symptoms of individuals in the schizophrenia sample were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991).

The genomic locations of the polymorphisms measured in this study are depicted in Fig. 1. The HervK-18 7086 C/T polymorphism and the HervK-18 8146 C/T polymorphisms within the coding region of the HervK-18 envelope gene were measured by specific polymerase chain reaction amplifications of the non-repetitive flanking region on chromosome 1q22 and subsequent real time polymerase chain analysis of the amplified products using fluorescent labeled hybridization probes as previously described (Yolken et al., 2007). The HervK-18 8146 C/T polymorphism results in a predicted amino change from isoleucine to valine while the HervK-18 7086 C/T polymorphism is synonymous with both forms encoding valine. We also measured the HervK-18 8914 C/T and the HervK-18 8594 C/T polymorphisms in the HervK-18 envelope