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Genetic risk factors for type 2 diabetes with pharmacologic intervention in African-American patients with schizophrenia or schizoaffective disorder

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ABSTRACT

An increased prevalence of type 2 diabetes (T2D) in schizophrenia (SCZ) patients has been observed. Exposure to antipsychotics (APs) has been shown to induce metabolic dysregulation in some patients but not all treated patients. We hypothesized that important candidate genes for T2D may increase risk for T2D in African-American patients with SCZ or schizoaffective disorder. The PAARTNERS study comprises African-American families with at least one proband with SCZ or schizoaffective disorder. The current study of PAARTNERS SCZ and schizoaffective disorder cases ($N = 820$) examined single nucleotide polymorphisms (SNPs) within select T2D candidate genes including transcription factor 7-like 2 (TCF7L2), calpain 10 (CAPN10), and ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (ENNP1) for association with prevalent T2D. We report the association of TCF7L2 (rs7903146) with T2D under both additive and recessive models for the risk allele T. Specifically, the odds ratio (OR) for having T2D was 1.4 ($p = 0.03$) under an additive model and 2.4 ($p = 0.004$) under a recessive model. We also report a marginally significant TCF7L2 by AP treatment interaction that should be investigated in future studies. CAPN10 (rs3792267) was marginally associated with T2D with OR = 1.5 ($p = 0.08$) when considering the model GG vs. AG/AA with risk allele G. ENPP1 (rs1044498) was not associated with T2D. We conclude TCF7L2, a risk factor for T2D in the general population, is also a risk factor for T2D in African-American patients with SCZ or schizoaffective disorder. Research is needed to determine if T2D associated polymorphisms are of interest in the pharmacogenetics and future treatment choices of antipsychotics in African-American patients.

1. Introduction

The inheritance of T2D is the result of many gene variants each with a modest effect on disease risk, along with environmental factors, that combine to determine an individual's susceptibility to developing the disease (Muoio and Newgard, 2008). After many years of limited success the genetic architecture of T2D is finally being uncovered with recent genome-wide association studies (GWAS) (Sladek et al., 2007; Saxena et al., 2007; Scott et al., 2007; Zeggini et al., 2007; Steinthorsdottir et al., 2007; Rampersaud et al., 2007; Meigs et al., 2007; Wu et al., 2008). It is well studied and accepted that APs can trigger T2D in treated patients (Arranz et al., 2004; Howes et al., 2004; Gianfrancesco et al., 2002; Ananth et al., 2002). However, not all patients develop T2D after AP treatment initiation (de Leon and Diaz, 2007). This study investigates the association of important T2D candidate gene polymorphisms with T2D in African Americans diagnosed with SCZ or schizoaffective disorder.

Linkage and association studies have identified important candidate genes for T2D including transcription factor 7-like 2 (*TCF7L2*), calpain 10 (*CAPN10*), and ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (*ENNP1*) that we

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investigated for association with T2D in our study. *TCF7L2* on chromosome 10q25 is the most important T2D candidate gene identified to date (Weedon, 2007). Its association with T2D has been highlighted in several recent GWAS (Sladek et al., 2007; Saxena et al., 2007; Scott et al., 2007; Zeggini et al., 2007; Steinthorsdottir et al., 2007) and has been associated with disease in multiple ethnic groups (Yan et al., 2009; Helgason et al., 2007; Miyake et al., 2008). TCF7L2 is a member of the T-cell factor (TCF)/lymphoid enhancing factor family of transcription factors (Nelson and Nusse, 2004; Prunier et al., 2004) belonging to the Canonical Wnt signaling pathway (Galceran et al., 1999) involved in regulating growth and differentiation (Stadeli et al., 2006; Willert and Jones, 2006). How TCF7L2 affects T2D pathology is not completely understood, though it is known to be associated with insulin-secretory defects in the general population rather than insulin resistance (Weedon, 2007). The association of the *TCF7L2* SNP we studied (rs7903146) has been replicated in multiple studies including several genome-wide association studies (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007) and at least three studies of populations of African descent (Helgason et al., 2007; Yan et al., 2009; Sale et al., 2007). This SNP lies within intron 3, thus, its association with T2D is most likely explained by an effect on gene expression (Sale et al., 2007).

Calpain 10 (*CAPN10*) on chromosome 2q37.3 encodes for a cytoplasmic protease (Ridderstrale et al., 2005). The exact mechanism of CAPN10 in T2D remains unclear though several pathways have been described with more than one involving deficits in glucose stimulated insulin secretion (Harris et al., 2006). *CAPN10* rs3792267 has been localized to intron 3 and, thus, is also suspected to effect gene expression rather than protein function (Garant et al., 2002).

Ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (ENPP1, also known as plasma cell membrane glycoprotein 1, or PC-1) on chromosome 6q22 is a class II membrane glycoprotein (Maddux et al., 1995; Dong et al., 2005). The functional missense SNP in exon 4 (rs1044498) examined in this study causes an amino acid change from lysine to glutamine at codon 121 (K121Q) (Pizzuti et al., 1999). Studies *in vitro* have shown that the 121Q variant of *ENPP1* has a stronger interaction with the insulin receptor than the K variant and reduces insulin receptor autophosphorylation (Costanzo et al., 2001). It is therefore a stronger inhibitor of insulin signaling and has been associated with insulin resistance in Sicilians (Pizzuti et al., 1999), South Asians (Abate et al., 2003), and Finns and Swedes (Gu et al., 2000; Kubaszek et al., 2003). However, the role of the *ENPP1* 121Q allele on the pathogenesis of insulin resistance in other ethnic groups remains controversial (Rasmussen et al., 2000; Gonzalez-Sanchez et al., 2003; Morrison et al., 2004).

The current ancillary study of African-American SCZ and schizoaffective disorder cases ($N = 820$) from the PAARTNERS Study examined select genetic risk factors for T2D. No other studies of metabolic disease that we know of in patients with psychoses have considered genetic risk factors for T2D from the general population; rather the focus has been on treatment related risk for weight gain and/or glucose dysregulation (Newcomer, 2005), and even genetic variation in possible neurochemical modulators of weight gain on AP treatment (Bellivier, 2005). Many studies note significant weight gain with the use of APs prior to the development of T2D and imply T2D develops as a consequence (Wirshing et al., 2002; Newcomer, 2005; Allison and Casey, 2001). Still other studies note impaired glucose control with AP treatment initiation independent of changes in weight or BMI (Howes et al., 2004; Meyer, 2002; Stahl et al., 2009). Given that the mechanism by which AP drugs may cause diabetes is not fully understood (Tschoner et al., 2009; Ananth et al., 2004) we considered the novel hypothesis that T2D candidate gene by treatment interactions may be important risk factors for AP induced T2D. For instance extensive research, including data obtained through clinical trials, has clearly demonstrated that all effective antipsychotics are dopamine (DA) D_2 receptor antagonists and that DA D_2 receptor antagonism is essential for the alleviation of psychosis (Kapur and Remington, 2001). However, a number of important issues remain unresolved concerning antipsychotics mechanism of action downstream of DA D_2 antagonism (Sutton et al., 2007). Interestingly, recent studies show the mechanism by which APs reduce positive symptoms of psychosis may be through the canonical Wnt signaling pathway of which TCF7L2 is a component, (Alimohamad et al., 2005; Kang et al., 2004; Sutton et al., 2007) providing evidence for a possible relationship between AP treatment and increased risk for T2D.

The continued examination of risk for T2D in patients treated with antipsychotics is important. The increased prevalence of glucose dysregulation among patients treated with antipsychotics is a considerable public health problem given that these medications are prevalent and prescribed in a variety of conditions including bipolar disorder and dementia (Groleger, 2007). Ultimately, a continued examination of risk factors for metabolic disease during antipsychotic treatment may lead to treatments that benefit persons at risk of serious metabolic side effects.

2. Methods

2.1. Study population

The PAARTNERS Study ($N \sim 3000$), comprised of African-American families with at least one SCZ or schizoaffective proband, was designed to investigate genetic risk factors for SCZ. Probands were recruited at one of eight sites in the southeastern US and Pennsylvania from various sources including clinician referral, inpatient and outpatient clinic screening, and advertisements. With permission from the proband family was contacted concerning willingness to participate. The standard for diagnostic assessment was the Diagnostic Interview for Genetic Studies (DIGS) (Aliyu et al., 2006; Nurnberger et al., 1994). The current study is an ancillary study with independent approval from the University of Alabama at Birmingham Internal Review Board. As both SCZ and schizoaffective disorder have significant psychotic components, tend to coaggregate in families (DeLisi et al., 2002), and patients are exposed to similar treatment regimens, we grouped persons with these two mental illnesses together for our study. PAARTNERS study participants were included in the current study if the best estimate final diagnosis (BEFD) was SCZ or schizoaffective disorder as recorded in the PAARTNERS narrative summary. The narrative summary, created for each PAARTNERS participant, has been described (Aliyu et al., 2006). T2D cases were identified in the