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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 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 like 7 (TCF7L2), calpain 10 (CAPN10), and ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1) for association with prevalent T2D. We report association of TCF7L2 (rs7903146) with T2D under both an additive and recessive model 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.

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Conflict of Interest

All authors declare there is no conflict of interest.

Keywords

TCF7L2; CAPN10; ENPP1; Antipsychotics

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 (Muio 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; Rumpersaud 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 like 7 (*TCF7L2*), calpain 10 (*CAPN10*), and ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (*ENPP1*) that we 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 pyrophosphate 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 with 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) D₂ receptor antagonists and that D₂ DA 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) D₂ 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~3000), comprised of African-American families with at least one SCZ or schizoaffective proband, was designed to investigate genetic risk factors for SCZ. Proband 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, Jr. 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 narrative summary by 1) self-report of diabetes 2) self report of a glucose control medication, or 3) a report of diabetes or glucose control medication in the medical record. Age at diagnosis of diabetes was not available from PAARTNERS study records and diabetic persons reporting insulin treatment were excluded. We realize this may exclude some type 2 diabetics as many progress to require insulin treatment, however this decision was made to exclude those with type 1 diabetes (and a different diabetes related genetic background) and there were few insulin treated diabetics (N<15).

2.2 Antipsychotic classification and covariates

Current treatment with AP medications by self-report and/or the medical record was available in the narrative summary data. PAARTNERS records did not include duration of treatment or dose for these medications. For purposes of the current study AP treatment was examined as current treatment vs. no current treatment. Since weight gain, which is highly correlated with T2D (Jarrett 1989), is a common side effect described for patients treated with mood stabilizers, especially valproic acid and lithium, (Bowden and Singh 2005; Dinesen et al. 1984; Ketter et al. 2006; Torrent et al. 2008) we additionally modeled the effects of current mood stabilizer treatment in our study. Age is one of the strongest predictors of T2D and risk starts to significantly increase in the fourth decade with close to linear trend (Jarrett 1989), thus age was categorized ≤ 39 , $40 \leq 49$, $50 \leq 59$, and ≥ 60 and modeled additively in this manner (Wild et al. 2004). Medical comorbidity data was collected on all PAARTNERS participants and we adjusted for self-reported hypertension and cardiovascular disease since these comorbidities are highly correlated with metabolic disease (Jarrett 1989). Covariate data was available from the narrative summary.

2.3 Selection of Candidate Genes, Genotyping and Genetic Models

Both functional SNPs and, when not available, non-functional SNPs for a candidate gene, were examined for 1) replication of association including at least one sample of African descent, 2) frequency (minor allele frequency >0.1), and 3) if possible, biological plausibility for interaction with antipsychotic mechanism of action. One SNP in each candidate gene was selected for the study. We chose not to focus on polymorphisms identified in recent GWAS studies of T2D in Caucasian populations as the literature suggests that replicated variants in Caucasian populations do not significantly contribute to inter-individual susceptibility to T2D in African Americans (Lewis et al. 2008). Genotyping assays for each SNP were purchased from Applied Biosystems (AB) (<http://www.appliedbiosystems.com>) including *TCF7L2* (rs7903146, C/T, assay ID C_29347861_10), *CAPN10* (rs3792267, A/G, assay ID C_27483762_10) and *ENPP1* (rs1044498, A/C, assay ID C_1207994_20). We utilized the AB 7500 Fast Real-Time PCR System using the TaqMan nuclease assay following manufacturer's conditions (Applied Biosystems, Foster City, CA). Genotypes were independently confirmed visually by two readers. Ambiguous genotypes that were not separated by discrete clusters were repeated, and those that could not be assigned definite genotypes were set to missing.

We employed a recessive genetic model for *ENPP1* (KK, KQ v. QQ) where Q corresponds to the C allele which is the same model used in another study of this SNP in an African-American population (Chandalia et al. 2007). For the SNP genotyped in *CAPN10* the major allele G is the risk allele. Due to low frequency of minor allele homozygote, the model GG vs. AG/AA was employed identical to the model shown in a previous study of this SNP in African Americans (Garant et al. 2002). Most studies of Caucasians point to an additive effect of the T allele at *TCF7L2* rs7903146 (Saxena et al. 2006; Weedon 2007; Groves et al. 2006) though, like many other studies (Florez et al. 2006; Groves et al. 2006; Sale et al. 2007), we considered other genetic models for this SNP.

2.4 Statistical Methods for Models with Type 2 Diabetes as the Outcome

Descriptive statistics were obtained and differences were tested using chi square tests. Models of association of SNP alleles, AP treatment, and covariates were considered. Persons in our study could be related in the first degree though many probands did not have an affected first degree relative. Statistical methods for correlated data, such as generalized estimating equations (GEE) can provide valid variance estimates in random samples of families (Zeger and Liang 1986). In SAS Proc Genmod we specified a compound symmetry (i.e. constant correlation) covariance model among related participants. Specifically, the model relates gene and treatment effects adjusted for covariate effects linearly to the logit of the probability of having T2D:

$$\text{Log} \frac{P(y)}{1 - P(y)} = \beta X + \gamma G + \delta T$$

Equation 1

For this analysis covariates (X), gene (G), and treatment (T) are modeled as described in equation 1. The resulting estimates (β , γ , δ) can be exponentiated to obtain the OR estimates. This model can be easily extended to include a G*T interaction term.

3. Results

Demographics describing the SCZ and schizoaffective disorder participants in the current study are presented in Table 1. T2D was identified in 18% of our study population. As expected the majority of the population is currently treated with antipsychotics (90%) and only 3.7% report never antipsychotic therapy. Table 1 shows age category, gender, current mood stabilizer treatment, a diagnosis of schizoaffective disorder versus SCZ, and hypertension are significantly associated with T2D ($p < 0.01$), and CVD is marginally associated with T2D with $p < 0.10$ in univariate comparisons.

SNPs were in Hardy Weinberg equilibrium (HWE) within our study population with the exception of *CAPN10* rs3792267 ($p = 0.04$). This slight departure from HWE could be due to the fact some genotypes were not independent since some cases in our group are related in the first degree. There was no significant departure from HWE for this SNP among non-related probands in our study ($N = 630$, $p = 0.08$). Allele frequencies reported in our study are in close agreement with allele frequencies reported in the literature for the same SNPs in other populations of African descent (Chandalia et al. 2007; Garant et al. 2002; Yan et al. 2009). Only *TCF7L2* was associated with T2D at the univariate level (Table 2).

Main effect associations of each SNP with T2D adjusted for AP treatment and other covariates are presented in Table 3. *TCF7L2* (rs7903146) was significantly associated with prevalent T2D under an additive model for the T allele, while *CAPN10* (rs3792267) was marginally associated with T2D. *ENPP1* was not associated with T2D after adjustment. In a model similar to that presented in Table 3 we also considered a dominant (TT, CT vs. CC) and recessive (TT vs. CT, CC) model for the *TCF7L2* rs7903146 T allele with OR=1.30 ($p = 0.20$) and OR=2.39 ($p = 0.0041$), respectively. HTN was highly correlated with T2D in this patient group with the largest OR (6.57, $p < .0001$) of any covariate included in the model. Interestingly, mood stabilizer treatment had a magnitude of effect similar to AP treatment, but a greater level of significance ($p = 0.003$ vs. $p = 0.04$). We also considered gene by AP treatment interactions. While our study showed no evidence of an AP treatment by SNP interaction for *ENPP1* or *CAPN10*, results were suggestive of an interaction between *TCF7L2* (for the model TT vs. CT, CC) and AP treatment with $OR_{Tt} = 3.02$ ($p = 0.008$), $OR_{SNP} = 16.7$ ($p = 0.008$) and $OR_{Tt*SNP} = 0.11$ ($p = 0.05$). We recognize this marginal result for a potential SNP by AP treatment interaction could be a false positive result as power to test this model was low (<25%).

4. Discussion

This study replicates a main effect association of *TCF7L2* (rs7903146) with T2D in an African-American population and is suggestive of a main effect association of *CAPN10* (rs3792267) with T2D. Our study is unique in that the population under study is an African-American population of SCZ and schizoaffective disorder patients. Our results show genetic risk factors for T2D in the general population are also risk factors for T2D in African-American patients with SCZ or schizoaffective disorder. Since, diabetes among persons treated with APs is a serious public health problem we feel our study suggests further research of genetic risk factors for T2D in the general population as risk factors for T2D in patients under AP treatment is needed. Specifically, genetic risk factors for T2D could compound the problem of AP induced diabetes. This could conceivably be through an additive effect of genetic risk factors and treatment risk factors or even through a multiplicative effect where AP treatment interacts with genes important in T2D disease pathways.

Consistent with our study, a study of the *TCF7L2* rs7903146 SNP in West Africans (N=1069) reported OR=1.45 (95% CI 1.19–1.77), $p=0.0002$ under an additive model (Helgason et al. 2007). Other studies have reported a positive association of *TCF7L2* rs7903146 with T2D in African Americans with end stage renal disease (ESRD) (Sale et al. 2007) and recently in the Atherosclerosis Risk in Communities study (Yan et al. 2009). In our study, current AP treatment versus no treatment increased the odds of T2D 2 times ($p=0.04$) after adjustment. This is a general treatment category that suited our study, but in future, larger studies it will be necessary consider more detailed categorizations of AP treatment such as class or specific medications. Our results are suggestive of an interaction between AP treatment and *TCF7L2* rs7903146 on the multiplicative scale. This interaction is biologically plausible given that recent studies have shown the mechanism through which APs may reduce symptoms of psychosis is through the canonical Wnt signaling pathway of which *TCF7L2* is a component (Sutton et al. 2007). There are other instances in the literature of pharmacologic alterations of metabolism that may be altered by genes. For example thiazide diuretics have been shown to interact with genes in the renin-angiotensin system and salt sensitivity genes to affect risk of incident diabetes with treatment (Bozkurt et al. 2009). However, despite our exciting result, we stress it is not conclusive and should be examined in other larger studies as our sample was underpowered for this analysis.

The magnitude of effect we report for *CAPN10* (Table 3) is consistent with the main effect reported (OR=1.38, 95% CI 1.04–1.83, $p=0.03$) under the same genetic model in another study of African Americans from the Atherosclerosis Risk in Communities Study (N=1594) (Garant et al. 2002). However, the same study mentioned above of African Americans with ESRD did not report a significant association of this SNP in *CAPN10* with T2D (Sale et al. 2007). Our study did not replicate an association of the *ENPP1* K121Q SNP (rs1044498) with T2D reported by another study (Chandalia et al. 2007). In fact, our study showed the direction of the association for carriers of the minor allele versus the risk allele homozygotes (Table 3) to be in the opposite direction compared to that study which reported OR=0.17 (95% CI 0.05–0.63) $p=0.005$. The frequency of the risk allele Q reported by that group was identical to ours (Table 2) and we had >80% power to see an effect as strong as that group reported. At least one other study did not report association of the 121Q variant with T2D a population of African descent (Keene et al. 2008).

The current study had several limitations due to its ancillary nature, but, overall, is strengthened by its novelty. The PAARTNERS study was designed to investigate genetic risk factors for SCZ not genetic and treatment related risk factors for T2D in SCZ. We were unable to determine the time of onset of diabetes and what specific AP medications and dosages were used at T2D onset. Power was low for some models especially those examining gene by treatment

interactions. Weight is highly correlated with diabetes (Jarrett 1989), and is a significant side effect of certain antipsychotics (Ketter et al. 2006), but weight was not recorded in PAARTNERS. Future studies should incorporate information concerning weight gain and perhaps genes associated with antipsychotic induced weight gain. Additionally, in this exploratory study we only examined one SNP per gene and future studies should better cover genetic variation in candidate genes of interest and adjust for multiple testing. Population stratification due to genetic admixture can confound population association studies (Ewens and Spielman 1995) and unfortunately funds were not available to control for ancestry using ancestry informative markers. However, despite these limitations we are the first that we know of to examine both genetic and psychiatric treatment related risk factors for T2D in African Americans affected with SCZ or schizoaffective disorder.

The PAARTNERS study offered a unique population to study genetic and treatment related risk factors for T2D in African-American SCZ and schizoaffective disorder patients. This study is novel for its investigation of the potential for increased risk for T2D associated with select T2D candidate genes in the presence of antipsychotic treatment. We conclude *TCF7L2* is a risk factor for T2D in African-American patients with SCZ or schizoaffective disorder and suggest that a potential gene by AP treatment interaction should be further investigated. Research in larger populations of patients including other racial groups is needed confirm any gene by treatment interaction and to determine if such polymorphisms are of interest in the pharmacogenetics of antipsychotic treatment.

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Table 1

Comparison of the type 2 diabetes affected group (T2D+) versus the unaffected group (T2D-) in the current study of African Americans with schizophrenia or schizoaffective disorder

Variable	T2D ⁻ N=663	T2D ⁺ N=158	P-Value
Age ≤39	310 (47%)	28 (18%)	
40≤49	202 (30%)	66 (42%)	
50≤59	127 (19%)	47 (30%)	
≥60	24 (4%)	16 (10%)	<.0001
Gender (F)	254 (38%)	80 (50%)	0.006
Current Antipsychotic (Y)	586 (89%)	142 (90%)	0.12
Never Antipsychotic (Y)	26 (4%)	4 (3%)	0.41
Current Mood Stabilizer (Y)	136 (20%)	51 (32%)	<0.0001
Diagnosis (Schizoaffective Disorder)	119 (18%)	50 (32%)	0.0001
Hypertension (Y)	173 (26%)	114 (72%)	<0.0001
Cardiovascular Disease (Y)	68 (10%)	24 (15%)	0.07

Table 2

Univariate association of genotypes with type 2 diabetes in the current study of African Americans with SCZ or schizoaffective disorder

Single Nucleotide Polymorphism	T2D+	T2D–	P-Value
<i>TCF7L2</i> rs7903146 CC	77	338	0.03
<i>TCF7L2</i> rs7903146 CT	60	281	
<i>TCF7L2</i> rs7903146 TT	21	44	
<i>ENPP1</i> rs1044498 CC	90	418	0.35
<i>ENPP1</i> rs1044498 AC	59	220	
<i>ENPP1</i> rs1044498 AA	9	25	
<i>CAPN10</i> rs3792267 GG	121	464	0.21
<i>CAPN10</i> rs3792267 AG	34	189	
<i>CAPN10</i> rs3792267 AA	3	10	

Table 3

Association of candidate gene polymorphisms, psychiatric treatment and covariates with type 2 diabetes

Variable	OR	95% CI	P-Value
Age Category (≤ 39 , $40 \leq 49$, $50 \leq 59$, ≥ 60)	1.29	1.0–1.6	0.025
Gender (F)	1.02	0.7–1.5	0.92
Current Antipsychotic (Y)	2.06	1.0–4.1	0.037
Current Mood Stabilizer (Y)	2.10	1.3–3.4	0.003
Hypertension (Y)	6.57	4.3–10.1	<.0001
Cardiovascular disease (Y)	0.97	0.5–1.7	0.92
Schizoaffective Disorder vs. SCZ	1.52	0.9–2.5	0.10
<i>TCF7L2</i> (rs7903146) additive model for T	1.40	1.0–1.9	0.03
<i>CAPN10</i> (rs3792267) GG vs. AG,AA	1.49	0.9–2.4	0.09
<i>ENPP1</i> (rs1044498) KQ, KK vs. QQ	1.27	0.8–1.9	0.26