Prostate Cancer Related JAZF1 Gene is Associated with Schizophrenia

Ke-Sheng Wang*, Lingjun Zuo1, Daniel Owusu1, Yue Pan2 and Xingguang Luo3

1Department of Biostatistics and Epidemiology, East Tennessee State University, USA
2Department of Psychiatry, Yale University School of Medicine, USA
3Department of Public Health Sciences, University of Miami, USA

*Corresponding author: Kesheng Wang, Department of Biostatistics and Epidemiology, College of Public Health, East Tennessee State University, PO Box 70259, Lamb Hall, Johnson City, TN 37614-1700, USA

Received: July 29, 2014; Accepted: August 08, 2014; Published: August 11, 2014

Abstract

Background: Epidemiological studies have shown that there is a reduced risk of prostate cancer among persons diagnosed with Schizophrenia (SCZ). However, the mechanism of such relationship is not clear. The reduced incidence of cancer observed in SCZ patients may be related to differences in genetic background. Recently, the JAZF1 gene is found to be associated with prostate cancer and type 2 diabetes. However, no study has focused on the association of JAZF1 with the risk of SCZ.

Methods: We examined genetic associations of 118 Single-Nucleotide Polymorphisms (SNPs) within the JAZF1 gene with SCZ using one European American (EA) sample of 1,149 cases and 1,347 controls. Logistic regression analysis of SCZ as a binary trait was performed using PLINK software.

Results: The most significant association with SCZ was observed with rs10258132 (p = 0.0011); while the next best signal was rs17156259 (p = 0.0031). The third best associated SNP was rs7791865 (p = 0.0089). In addition, haplotype analyses revealed that the A-C haplotype from rs10244184 and rs986032 was associated with SCZ (p = 0.00093); and the G-G haplotype from rs17156238 and rs17156259 was associated with SCZ (p = 0.00455).

Conclusion: These findings provide evidence of several genetic variants in JAZF1 gene influencing the risk of SCZ and will serve as a resource for replication in other populations.

Keywords: Schizophrenia; Prostate cancer; JAZF1; Single nucleotide polymorphism; Pleiotropy

Introduction

Schizophrenia (SCZ) is the most tragic psychiatric disorder with high degree of genetic and clinical heterogeneity. The prevalence of SCZ is approximately 1% worldwide and currently affects 1.1% of the Unites States (US) population over the age of 18 [1-3]. SCZ is known to be a multifactorial disorder with a demonstrated heritability of 80% in family studies and meta-analysis of multiple twin studies [4,5]. Prostate Cancer (PrCa) is the most common non-skin malignancy in testis, followed by colon, ovary, prostate, and placenta, but lower risk of prostate cancer among persons diagnosed with SCZ [11-13]. For example, the incidence of PrCa in individuals with SCZ is significantly lower than expected [14,15]. Cancer risks in schizophrenic patients were negatively associated with age in the general populations (e.g. stomach cancer, pancreatic cancer and PrCa) [16]. Furthermore, patients with SCZ showed higher co-occurrence of SCZ with breast cancer, yet lower co-occurrence of melanoma and PrCa with SCZ [17]. Additionally, Ibáñez et al [18] found inverse expression deregulations between Central Nervous System (CNS) disorders (Alzheimer’s disease, Parkinson’s disease, and SCZ) and three cancer types (lung, prostate, and colorectal cancers). However, other studies found no evidence that SCZ confers protection against cancer in general [19].

The reduced incidence of cancer observed in SCZ patients could potentially attributed to differences in genetic background [20]. For example, Catts and Catts [21] suggested that the reduced incidence of cancer observed in SCZ patients might be linked to differences in apoptosis, and proposed p53, a tumor suppressor gene, which is considered as a candidate gene for the susceptibility. Park et al [20] found that the p53 polymorphism specifically identified in Korean SCZ patients may be associated with reduced vulnerability to lung cancer.

The juxtaposed with another zinc finger protein 1 (JAZF1) also known as TAK1-interacting protein 27 (TIP27) or zinc finger protein 802 (ZNF802) gene is located at 7p15 [22] and is highly expressed in testis, followed by colon, ovary, prostate, and placenta, but lower
expressed in pancreas, brain, and liver [23]. Li et al [24] stated that the first 3 exons of JAZF1 are joined to the last 15 exons of JJJAZ1 in the JAZF1/JJAZ1 fusion transcript, and suggested that there is a genetic pathway for progression of a benign precursor to a sarcoma involving increased cell survival, followed by accelerated cellular proliferation upon allelic exclusion of the unarranged copy of that gene. JAZF1 has been associated with somatic fusion proteins in endometrial cancers [22,25-27]. Using a large genome-wide association study (GWAS), Thomas et al [28] found that Single-Nucleotide Polymorphisms (SNP) rs10486567 within JAZF1 was associated PrCa. Later, this variant was found to be associated with PrCa in a multiethnic sample of 2,768 incident PrCa cases and 2,359 controls from a multiethnic cohort (African Americans, European Americans, Latinos, Japanese Americans, and Native Hawaiians) [29]. Eeles et al [30] confirmed the association of this SNP with PrCa from the second stage of genotyped 43,671 SNPs among 3,650 PrCa cases and 3,940 controls. Another study established rs10486567 as a bona-fide marker for association with susceptibility to PrCa in individuals of European ancestry [31]. Recently, the association of rs10486567 was validated in a African American population [32] and confirmed by a meta-analysis [33]. Other studies showed the JAZF1 locus was associated with height [34], and type 2 diabetes (T2D) [35,36].

Previous studies have shown that zinc finger protein genes such as Zinc Finger Protein 74 (ZNF74) and 804A (ZNF804A) are associated with SCZ [37-40]. However, no study has focused on the association of JAZF1 with the risk of SCZ. This study explored the association of 118 SNPs within JAZF1 gene with the risk of SCZ in a European American (EA) population [32] and confirmed by a meta-analysis [33]. The results of the top 15 SNPs with p<0.05 are summarized in Table 2. The mean values of age are 42.9 and 49.8 years for cases and controls, respectively.

Material and Methods

Samples

NonGAIN sample is part of the Molecular Genetics of Schizophrenia (MGS) genome wide association study of 3,972 cases and 3,629 controls after quality control (dbGaP Study Accession: phs000167.v1.p1). Unrelated adult cases with DSM-III-R (SGI study) or DSM-IV (MGS1, MGS2 studies) SCZ or schizoaffective disorder were collected under institutional review board-approved protocols in three studies, Schizophrenia Genetics Initiative (SGI), Molecular Genetics of Schizophrenia Part 1 (MGS1), and MGS23. Cases selected met criteria for SCZ or schizoaffective disorder per the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV). The details about these subjects were described elsewhere [41-43]. Genotyping data using the Affymetrix Genome-wide Human SNP Array 6.0 (total 729,454 SNPs) were available for the sample. 1,179 European American (EA) patients with SCZ and 1,364 EA controls were selected from the nonGAIN Sample. We investigated the genetic associations of 118 SNPs within the JAZF1 gene with the risk of SCZ.

Statistical methods

For the initial Analysis, HelixTree Software (http://www.goldenhelix.com/SNP_Variation/HelixTree/index.html, Golden Helix, Bozeman, MT) was used to assess control genotype data for conformity with Hardy-Weinberg equilibrium (HWE). To deal with population stratification, the principal-component analysis approach with ten principal components [44] in HelixTree was used to identify outlier individuals. Then, logistic regression analysis of SCZ as a binary trait, adjusted for age and sex, was performed for the nonGAIN sample using PLINK v1.07 [45]. The asymptotic p values for this test were observed while the Odds Ratios (ORs) and standard errors of ORs were estimated. For logistic regression, the additive model was applied. In addition to obtaining nominal p values, empirical p-values were generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK. Minor Allele Frequency (MAF) was determined for each SNP and the Linkage Disequilibrium (LD) structure was constructed using Haploview software [46]. Haplotype analysis based on a slide-window was performed using PLINK.

Results

Based on the analysis of the first ten principal components using HelixTree and other exclusion criteria, 1,149 cases and 1,347 controls were left for further analyses. Participant characteristics are presented in Table 1. The mean values of age are 42.9 and 49.8 years for cases and controls, respectively.

All 118 SNPs are in Hardy-Weinberg equilibrium in the controls. The results of the top 15 SNPs with p<0.05 are summarized in Table 2. From single marker analysis, the strongest association with SCZ was observed with rs10258132 (p = 0.0011); while the next best signal was rs17156259 (p = 0.0031). The third best associated SNP was rs7791865 (p = 0.00889). All 15 SNPs had empirical pointwise p-values <0.05 using a permutation procedure (Table 2).

Table 1: Descriptive Characteristics of Schizophrenia Cases and Controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1,149</td>
<td>1,347</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>803(69%)</td>
<td>669(50%)</td>
</tr>
<tr>
<td>Females</td>
<td>346(31%)</td>
<td>678(50%)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>42.9 ± 11.9</td>
<td>49.8 ± 15.8</td>
</tr>
<tr>
<td>Range</td>
<td>18-84</td>
<td>18-90</td>
</tr>
</tbody>
</table>
We conducted a candidate gene association study to identify possible SNPs within JAZF1 gene for the risk of SCZ. Totally, 15 SNPs showed significant associations with SCZ (p<0.05). Haplotype analysis further supported the single marker analysis results. Results provide support for the candidacy of JAZF1 as a potential target region that contributes to the risk of SCZ. To our knowledge, this is the first candidate gene study which investigates the associations between JAZF1 polymorphisms and SCZ.

JAZF1 is a large gene of approximately 350 kb. Previous studies have identified SNP rs10486567 located in intron 2 associated with risk of PrCa [28-31,47]. Recently, several SNPs located close to each other in another LD block within intron 2 were associated with decreased risk of PrCa but were not associated with diabetes. In addition, some studies did not find an effect of the T2D risk variant on susceptibility to PrCa [31].

Reduced risk of some cancers among persons diagnosed with SCZ was identified [11-13]. Others observed that patients with SCZ have a significantly higher risk of colon cancer [61], breast cancer [62,63] and lung cancer [62]. Moreover, decreased risks for several types of cancer such as PrCa and malignant melanoma were observed in both siblings and parents of schizophrenic patients when compared to the general population, providing further support for genetic protection against cancer in families with SCZ [62,64]. Gal et al [65] observed a statistically significant reduction of risks for overall cancer in SCZ among patients for both parents combined and for both fathers and mothers taken singly and a marginal reduction effect for PrCa; whereas the familial aggregation did not show an association with a significant increased risk for cancer. However, the mechanism of such association is not clear. The shared genetic variations may explain part of the associations among these diseases. Closer attentions to the shared network between core cell cycle regulators and non-cell cycle functions in neurons will be informative for neuroscience [66]. Furthermore, Wang et al [67] suggested that these mechanisms may be important clues for the schizophrenia
First, our current findings might be spurious or subject to type I error. Second, these findings need to be replicated in additional samples. Third, this study focused on association between the JAZF1 gene and SCZ rather than functional study.

Conclusion

Our results demonstrate that several genetic variants in PrCa related JAZF1 gene were associated with the risk of SCZ. These findings may serve as a resource for replication in other populations. Future functional study of this gene may help to better characterize the genetic architecture of the risk of SCZ.

Acknowledgement

Funding support for the companion studies, Genome-Wide Association Study of Schizophrenia (GAIN) and Molecular Genetics of Schizophrenia - nonGAIN Sample (MGS_nonGAIN), was provided by Genomics Research Branch at NIMH and the genotyping and analysis of samples was provided through the Genetic Association Information Network (GAIN) and under the MGS U01s: MH79469 and MH79470, and K01 DA029643, R21 AA021380, R21 AA023019, and the National Alliance for Research on Schizophrenia and Depression (NARSAD) Award 17616. Assistance with data cleaning was provided by the National Center for Biotechnology Information. The MGS dataset(s) used for the analyses described in this manuscript were obtained from the database of Genotype and Phenotype (dbGaP) found at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000167.v1.p1 (nonGAIN). Samples and associated phenotype data for the MGS GWAS study were collected under the following grants: NIMH Schizophrenia Genetics Initiative U01s: MH46276 (CR Cloninger), MH46289 (C Kaufmann), and MH46318 (MT Tsuang); and MGS Part 1 (MGS1) and Part 2 (MGS2) R01s: MH67257 (NG Buccola), MH59588 (BJ Mowry), MH59571 (PV Gejman), MH59565 (Robert Freedman), MH59587 (F Amin), MH60870 (WF Byerley), MH59566 (DW Black), MH59586 (JM Silverman), MH61675 (DF Levinson), and MH60879 (CR Cloninger). Further details of collection sites, individuals, and institutions may be found in data supplement Table 1 of Sanders et al. (2008). This study was approved by Internal Review Board (IRB), East Tennessee State University.

References


Table 3: Haplotype analysis of JAZF1 gene.

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequencya</th>
<th>ORb</th>
<th>p-Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10244184</td>
<td>G C</td>
<td>0.02</td>
<td>0.94</td>
</tr>
<tr>
<td>rs10258132</td>
<td>G A</td>
<td>0.03</td>
<td>0.85</td>
</tr>
<tr>
<td>rs10285832</td>
<td>A G</td>
<td>0.01</td>
<td>0.99</td>
</tr>
</tbody>
</table>

a Odds ratio for the single haplotype. b Haplotype frequency in the sample. c p-value for the single haplotype.
Ke-Sheng Wang


