Research Article

Prostate Cancer Related JAZF1 Gene is Associated with Schizophrenia

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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 = 0.00889). In addition, haplotype analyses revealed that the A-C haplotype from rs10244184 and rs10258132 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

Abbreviations

BMI: Body Mass Index; CNS: Central Nervous System; GWAS: Genome-wide Association Study; JAZF1: Juxtaposed with another Zinc Finger Protein 1; JJAZ1: Joined to JAZF1 protein 1; MAF: Minor Allele Frequency; LD: Linkage Disequilibrium; PrCa: Prostate Cancer; SCZ: Schizophrenia; TIP27: TAK1-interacting protein 27; T2D: Type 2 Diabetes; ZNF802: Zinc Finger Protein 802

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 cancer in the developed world and the second leading cause of cancer death in men [6,7]. In the US, approximately 240, 890 new cases and 33, 720 deaths were expected in 2011 [8]. The established risk factors for PrCa are age, ethnicity and family history [9]. Twin studies suggest that about 42% of the disease risk may be attributed to heritable factors [10].

It has been reported that there is a reduced risk of some cancers 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 Joined to JAZF1 protein 1 gene (JJAZ1) 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 unrearranged copy of that gene. JAZF1 has been associated with somatic fusion proteins in endometrial tumors [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 associaiton 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 valided in a African American populaiton [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) sample (1,149 cases and 1,437 controls) from the Molecular Genetics of Schizophrenia – non GAIN Sample.

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-IIIR (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

Table 1: Descriptive Characteristics of Schizophrenia Cases and Controls.

Variable	Cases	Controls
Number	1,149	1,347
Sex, N (%)		
Males	803(69%)	669(50%)
Females	346(31%)	678(50%)
Age, years		
Mean ± SD	42.9 ± 11.9	49.8 ± 15.8
Range	18-84	18-90

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).
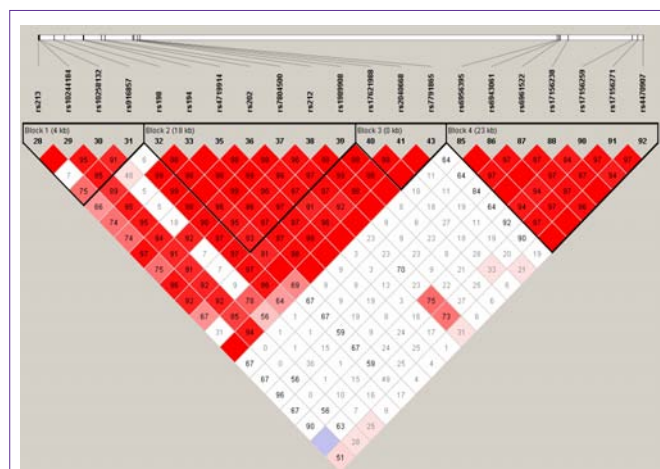

Figure 1: Linkage disequilibrium structure of 20 SNPs within JAZF1 including rs10258132, rs7791865 and rs17156259. The numbers indicate the D′ values between the corresponding two SNPs.

Table 2: 15 SNPs within JAZF1 gene associated with schizophrenia.

SNP	Position	Allele[a]	MAF[b]	HWE[c]	OR[d]	P[e]	EMP1[f]
rs10258132	27892688	C	0.10	0.50	1.39(1.14-1.70)	0.00127	0.0011
rs916857	27896645	G	0.41	0.78	1.16(1.03-1.31)	0.0139	0.0147
rs7791865	27919811	A	0.08	0.63	1.33(0.07-1.64)	0.00825	0.00889
rs17156100	27968765	G	0.09	0.93	1.24(1.02-1.52)	0.0343	0.0299
rs17156102	27969077	C	0.09	0.93	1.24(1.02-1.52)	0.0343	0.0299
rs17156173	28012128	C	0.02	0.71	0.62(0.41-0.93)	0.0213	0.0194
rs17156205	28020586	T	0.02	0.70	0.62(0.41-0.93)	0.0213	0.0194
rs6946007	28021711	G	0.02	0.21	0.65(0.44-0.96)	0.0305	0.0287
rs6956395	28032626	G	0.03	0.27	0.68(0.49-0.96)	0.028	0.0241
rs6943061	28033081	T	0.03	0.28	0.68(0.49-0.96)	0.028	0.0241
rs6961522	28033437	T	0.02	0.76	0.61(0.41-0.92)	0.0179	0.017
rs17156238	28035553	G	0.03	0.28	0.67(0.48-0.95)	0.0238	0.02
rs17156259	28052747	G	0.03	0.49	0.54(0.36-0.81)	0.003	0.0031
rs17156271	28054284	G	0.03	0.61	0.61(0.41-0.91)	0.0153	0.0145
rs10951191	28083358	C	0.25	0.12	0.86(0.75-0.99)	0.0374	0.0399

[a] Minor allele; [b] Minor allele frequency; [c] Hardy-Weinberg equilibrium p-value; [d] Odds ratio; [e] p-value based on logistic regression; [f] empirical p-value generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK.

Using Haploview software, we identified 4 haplotype blocks for 20 flanking SNPs including rs10258132, rs7791865 and rs17156259. Figure 1 shows the LD structure. The numbers indicate the D' values between the corresponding two SNPs. Haplotype analyses showed that the A-C haplotype from rs10244184 and rs10258132 (D'=0.91) was associated with SCZ (p = 0.00093); while the C-G haplotype from rs10258132 and rs916857 (D'=0.91) was associated with SCZ (p = 0.00326). Furthermore, the G-G haplotype from rs17156238 and rs17156259 (D'=0.97) was associated with SCZ (p = 0.00455); while the G-G haplotype from rs17156259 and rs17156271 (D'=0.97) was associated with SCZ (p = 0.00535) (Table 2).

Discussion

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 was associated with risk of PrCa [28-31,47]. Recently, several SNPs located close to each other in another LD block within intron 1 and ~210 Kb centromeric from rs10486567, have been associated with body stature [34], T2D [35,36], height [48], and arteriolosclerosis [49]. Epidemiological studies have shown an inverse correlation between T2D and PrCa [50-53], although some studies showed inconsistent results [54]. However, the basis for this association is unclear. It has been proposed that JAZF1 may be a possible direct causal link between T2D and PrCa [55,56]. Recently, it was found that the risk associated with the G allele of rs10486567 in the JAZF1 intron created an NKX3-1 binding site while destroying a FOXA1 binding site in line

with the DHT-dependent decrease in enhancer activity; it has been hypothesized that JAZF1 is likely to be a tumor suppressor influenced by this enhancer [57]. Recent evidence indicates that JAZF1 transcription factors bind to the nuclear orphan receptor TR4 which regulates PEPCK, the key enzyme involved in gluconeogenesis [58] (Table 3) . Jang et al [59] found that expression of JAZF1 in the liver also suppressed lipid accumulation and decreased droplet size. They suggested that JAZF1 may play a critical role in the regulation of lipid homeostasis and provide a new therapeutic target in the management of obesity and diabetes. Currently, there is no biological explanation for the functional implications for JAZF1 in prostate carcinogenesis [31]. However, Stevens et al [60] found that 2 JAZF1 SNPs rs6968704 and rs10486567 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

Table 3: Haplotype analysis of JAZF1 gene.

Haplotype		Frequency[a]	OR[b]	p-Value[c]
rs10244184	rs10258132			
A	C	0.1	1.42	0.00093
G	A	0.26	0.93	0.315
A	A	0.64	0.93	0.254
rs10258132	rs916857			
C	G	0.09	1.37	0.00326
A	G	0.33	1.04	0.518
A	A	0.58	0.86	0.0128
rs17156283	rs17156259			
G	G	0.02	0.54	0.00455
A	A	0.93	1.58	0.0102
rs17156259	rs17156271			
G	G	0.02	0.54	0.00535
A	A	0.98	1.76	0.00535

[a] Haplotype frequency in the sample.
[b] Odds ratio for each haplotype.
[c] p-value for the single haplotype.

research community in understanding the links between SCZ and cancer. It has been shown that p53 is a well characterized tumor suppressor protein with prominent roles in apoptosis. Several studies have shown an association between TP53 (the gene encoding p53) function and SCZ [21, 68-70]. Especially, 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 JAZF1 gene also known as zinc finger protein 802 (ZNF802) encodes a nuclear protein with three C2H2-type zinc fingers, and functions as a transcriptional repressor. Previous studies have shown that other zinc finger protein genes such as zinc finger protein 74 (ZNF74) and 804A (ZNF804A) are associated with SCZ [37-40]. To our knowledge, this is the first candidate gene study which investigates the associations between JAZF1 polymorphisms and SCZ. Although the JAZF1 gene is expressed in brain, the exact role of this gene product is not known. Laity and Andrews [71] reviewed that zinc is an essential nutrient, but toxic when accumulated to excess and provides a structural scaffold for many proteins such as zinc fingers, zinc clusters, and nuclear hormone receptors. Zinc deficiency has been linked to abnormal embryonic and fetal development [72], immune dysfunction, and neurological problems including T2D and SCZ [71,73-77]. Furthermore, the co-occurrence of SCZ and T2D has been well documented and may be, at least in part, driven by shared genetic factors [78-81]. Recently, several shared genes and common genetic pathways for T2D and SCZ have been proposed [78-81]. Considering the association of JAZF1 with T2D [35,36], it may be hypothesized that the JAZF1 may be part of mechcanism of the cormorbidity of PrCa, SCZ and T2D.

There are a number of strengths in this study. First, our sample size was relatively large for candidate gene association studies. Second, the haplotype analyses results further supported the single marker analysis findings. We also realized some limitations in this study. 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

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