Susceptibility genes for schizophrenia and their functional relationships

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SOX11 is a novel schizophrenia candidate gene

Association of SOX11 Polymorphisms in 3’UTR with Susceptibility for Schizophrenia

Zhilin Luan, Xin Dai, Tianlan Lu, Yan Ruan, Weihua Yue, Eric Boddeke, Sjef Copray, Dai Zhang.
Abstract

Diverse and circumstantial evidence suggests that schizophrenia is a neurodevelopmental disorder. Genes contributing to neurodevelopment may thus be potential candidate genes for schizophrenia. The human *SOX11* gene is a member of the *SOX* (Sry-related HMG box) transcription factor gene family that is essential for development and is mapped to chromosome 2p, a potential candidate region for schizophrenia. Our previous genome-wide association study (GWAS) implicated association of *SOX11* with schizophrenia in a Chinese Han population. To further investigate the association between polymorphisms at *SOX11* and schizophrenia, we performed an independent replication case-control association study in a sample including 786 schizophrenia cases and 1348 healthy controls. After rigorous Bonferroni correction, four SNPs in *SOX11* 3’UTR, significantly associated with schizophrenia in the allele frequencies: rs16864067 (allelic p=0.0022), rs12478711 (allelic p=0.0009), rs2564045 (allelic p=0.0027) and rs2252087 (allelic p=0.0025) were found. The haplotype analysis of the selected SNPs showed different haplotype frequencies for two blocks (rs4371338- rs7596062- rs16864067- rs12478711 and rs2564045- rs2252087- rs2564055- rs1366733) between case and control groups. Our results confirm that the *SOX11* gene is to be considered as a susceptibility gene for schizophrenia.

Key Words

Schizophrenia; Genetic association; Single nucleotide polymorphism (SNP); Haplotype; *SOX11*; Neurodevelopment.
Introduction

Schizophrenia is a chronic and devastating neuropsychiatric disorder afflicting approximately 1% of the general population worldwide [1]. It inflicts physical and mental suffering on affected individuals and their families. Family, twin and adoption studies indicate an explicit hereditary contribution to the etiology of schizophrenia with heritability estimates of approximately 80% [2]. Genome-wide association studies (GWAS), have provided insights into potential candidate genes involved. Since the first GWAS for schizophrenia was published in 2008, a large number of small risk genetic risk factors of schizophrenia has contributed to the conclusion that schizophrenia is a polygenic and complex disorder [3]. Clearly the most important and challenging task is to interpret and dissect and weigh the large number of potential schizophrenia susceptibility loci.

Despite more than a century of research, the pathophysiological basis of schizophrenia remains largely undefined. As mentioned above, substantial evidence suggests that schizophrenia is a neurodevelopmental disorder [4, 5]. Neurodevelopment comprises multiple, delicately tuned processes, including proliferation, differentiation, migration and integration of a variety of neural cell types [4]. Although neurodevelopment takes place mostly during embryonic, fetal and puberty periods, neurogenetic activity persists in adulthood. The risks and insults to neurodevelopment occurring during the prenatal and postnatal stages have been related to the formation and activation of aberrant neural circuits and emergence of schizophrenia symptoms [6].

In our previous GWAS, performed in a Chinese Han population [7], besides the most prominent genes, we also identified several other schizophrenia candidate genes with statistical significance, among which was the human SOX11 gene. SOX11 is a member of the developmentally essential SOX (Sry-related HMG box) transcription factor gene family. Sox proteins have been described as major regulators of cell fate, survival and differentiation across nearly all developing organ systems and thus dysfunction of Sox proteins can lead to all kinds of developmental diseases [8, 9]. SOX11 plays a crucial role in neurodevelopment and organogenesis. Sox11 expression decreases along neurodevelopmental progression and is absent in most normal adult tissues except some stem cell niches. The current study aimed to further establish the association of the human SOX11 gene with susceptibility for schizophrenia in an independent Chinese Han case-control sample.

Materials and Methods

Subjects

All subjects were unrelated persons of Chinese Han nationality and have been recruited in the North of China. The sample-set consisted of 768 patients affected by schizophrenia (360 males and 408 females; mean age: 33.5±8.7 years) and 1348 healthy controls (658 males and 690 females; mean age: 31.1±13.2 years). Consensus diagnoses were confirmed by at least two experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria (DSM-IV, American Psychiatric Association, 2000). None of the patients had severe medical complications. The healthy controls included in the current study had no history of mental illness or any other neurological or medical condition that are suspected to be associated with schizophrenia; they were well matched to the patient group for gender, age, education and ethnicity. All the healthy controls were recruited from communities via a simple none-structured interview performed by psychiatrists. All subjects provided written informed consent for the genetic study, which was approved by the Ethical Committee of the Institute of Mental Health, Peking University.
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**SNP Selection**

The human **SOX11** gene is a single-exon gene with no introns, which means that most of the nucleotides in the gene region are nominated as the flanking sequences. The SNPs were selected by downloading the information of all the SNPs within and neighboring the human **SOX11** gene from the International HapMap project database on dbSNP (http://www.ncbi.nlm.nih.gov/SNP/). The total coverage of the 15 selected SNPs was approximately 180kb. Detailed information and location of the selected SNPs are shown in Table 1 and Figure 1.

**Figure 1.** Genomic structure and linkage disequilibrium (LD) of the **SOX11** gene.

Genotyping

Genomic DNA was extracted from venous blood using a commercially available QIAamp®DNA Blood Mini Kit (QIAGEN, German). The SNPs were genotyped by either polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) analysis or direct DNA sequencing. All primers were designed by software Oligo 6.0 (MBI Inc., Colorado, USA). PCR products were either completely digested with 4U restriction enzyme overnight and then separated by agarose gel electrophoresis (2-3%) stained with ethidium bromide or sequenced on an ABI PRISM 377-96 DNA Sequencer (Applied Biosystems, Foster City, California, USA) after purifying them using a BigDye Terminator Cycle Sequencing Ready Reaction Kit. All the results were checked and confirmed independently by two experienced technicians.

Luciferase assay

Mouse Neuro2A neuroblastoma cells with endogenous Sox11 expression were seeded in 24-well plates and transiently transfected with equimolar amounts of various pGL3-promoter vectors (Promega, USA.) containing different inserted SNP-site(s) by using LipofectamineTM 2000 (Invitrogen, USA). The sequences with **SOX11** SNP-site(s) were cloned from the human genome. Single site mutations were performed with the QuikChange II Site-Directed Mutagenesis Kit (Agilent Technologies, USA.)
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to attain the alleles of opposite risk. Four assembled sequences containing three protective alleles of SNP6, SNP7 and SNP8, three risk alleles of SNP6, SNP7 and SNP8, three protective alleles of SNP9, SNP10 and SNP11, or three risk alleles of SNP9, SNP10 and SNP11 were synthesized respectively. In these synthesized sequences, each SNP-site was at the center of its own harboring sequence, 10 bp on both 5’ and 3’ ends. pRLCMV (Promega, USA.) was co-transfected as an internal control of transfection efficiency. The transfected cells were harvested after 48h. Luminescence was measured by the dual-luciferase reporter assay system (Promega, USA.) using a Centro LB960 96-well luminometer (Berthold Technologies, Germany).

**Cell line culture and transfection**

Mouse neuroblastoma cell line Neuro2A were maintained in DMEM (Invitrogen, USA.) supplemented with 10% FBS. Transient transfection of the cell lines was performed with LipofectamineTM 2000 (Invitrogen, USA.) according to the manufacturer’s instructions.

**Statistics**

Deviation of the genotypes from the Hardy-Weinberg equilibrium was examined by a chi-square goodness-of-fit test (Table 1). Distribution of gender and the difference of age between cases and controls were evaluated by Pearson χ²-test and Student’s t-test with the Statistical Package for Social Science (SPSS Inc., Illinois, USA) 17.0. Statistical differences in genotypic and allelic distribution between patients and controls were evaluated by the Pearson χ²-test at a significance level of 0.05. The haplotype frequencies were estimated by the expectation maximization algorithm. Under the null hypothesis, the affected and control individuals are assumed to have identical frequencies of all haplotypes. Under the alternative hypothesis, the candidate at-risk haplotype is allowed to have a higher frequency in affected than in control individuals, whereas the ratios of the frequencies of all other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses, and corresponding 1-degree of freedom likelihood-ratio statistics is used to evaluate statistical significance. Pairwise linkage disequilibrium (LD) between any two alleles was evaluated by D’ and r² values. Odds ratio (OR) and their 95% confidence intervals (95%CI) were calculated to evaluate the effect of different alleles and haplotypes. The analyses were performed by the Haploviev version 4.1 (http://www.broad.mit.edu/mpg/haploviev) [10] and SHEsis (http://analysis2.bio-x.cn/myAnalysis.php) [11, 12]. The statistical power of the sample size was calculated by the genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/gpc2.html)[13]. The sample had approximately 80% power to detect allele frequency differences assuming an OR of 1.5 with a minor allele frequency of 0.1. Bonferroni correction for multiple testing was carried out to control inflation of the type I error rate. Results were considered significant at two tailed p<0.05.

<table>
<thead>
<tr>
<th>rs code</th>
<th>Marker</th>
<th>Position a</th>
<th>Distance from SNP1 (kb)</th>
<th>Allele Change</th>
<th>HCB b</th>
<th>Sample-set</th>
<th>Case HWE p</th>
<th>Control HWE p</th>
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<td>0.160</td>
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<td>T&gt;G</td>
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<td>SNP3</td>
<td>5727884</td>
<td>56.2</td>
<td>G&gt;A</td>
<td>0.389</td>
<td>0.268</td>
<td>0.259</td>
<td>0.665</td>
</tr>
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<td>SNP4</td>
<td>5739199</td>
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<td>0.390</td>
<td>0.757</td>
<td>0.403</td>
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<td>rs4721338</td>
<td>SNP5</td>
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<td>82.8</td>
<td>A&gt;G</td>
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<td>0.159</td>
<td>0.383</td>
<td>0.255</td>
</tr>
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<td>SNP6</td>
<td>5772751</td>
<td>101.1</td>
<td>T&gt;G</td>
<td>0.500</td>
<td>0.517</td>
<td>0.426</td>
<td>0.793</td>
</tr>
</tbody>
</table>

Table 1. List of SNPs included in the present study
SOX11 is a novel schizophrenia candidate gene

Results
SOX11 is associated with schizophrenia in a Chinese Han population

Single-marker analysis
None of the genotype distributions of the 15 selected SNPs in case- and control groups deviated from Hardy-Weinberg equilibrium. The complete association results including their statistical analysis, are listed in the Table 2. Of the 15 SNPs, nine SNPs (rs4485539-SNP2, rs7596062-SNP6, rs16864067-SNP7, rs12478711-SNP8, rs2564045-SNP9, rs2252087-SNP10, rs2564055-SNP11, rs1366733-SNP12 and rs11892518-SNP13) showed statistical differences in allele or/and genotype frequencies between cases and controls. After rigorous Bonferroni correction, four SNPs remained significantly associated with schizophrenia in the allele frequencies; SNP7 (allelic p=0.0022), SNP8 (allelic p=0.0009), SNP9 (allelic p=0.0027) and SNP10 (allelic p=0.0025).

Haplotype analysis
To further analyze the haplotype structure, pairwise LD (linkage disequilibrium) of the 15 SNPs in our sample set was computed according to the standardized measure D’ value method. A D’ value of two SNPs ranging between 0.8 and 1.0 indicated strong LD. Four strong LD haplotypes were constructed. The LD haplotype structure is shown in Figure 1. To investigate if any haplotype would result in a higher risk for schizophrenia, all specific and global haplotypes of the 15 SNPs were tested. Specific p-values for individual haplotype combinations, global p-values for each haplotype and estimated haplotype frequencies in cases and controls have been summarized in Table 3. The global association analyses revealed positive results for the second haplotype (χ²=11.941, p=0.0076) and third haplotype (χ²=9.729, p=0.0078). All the four haplotypes had specific haplotype combinations associated with schizophrenia. For the first haplotype, the C-A haplotype combination was different in frequency between cases and controls (χ²=4.683, p=0.0305). For the second haplotype, the A-G-A-A haplotype combination showed a distribution difference between cases and controls (χ²=10.136, p=0.0015). For the third haplotype, two haplotype combinations were associated with schizophrenia; A-G-A-C (χ²=8.502, p=0.0036) and G-T-C-T (χ²=7.921, p=0.0049). For the last haplotype, the T-A-C haplotype combination showed association with schizophrenia (χ²=4.418, p=0.0356).

The schizophrenia-associated SNPs are functional
To assess whether these six SNPs are functional, we synthesized several DNA fragments into the pGL3-promoter vector and performed reporter gene expression assays using the Mouse Neuro2A
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Figure 2. The relative luciferase activity values from transfected Neuro2A cells

Luciferase activities in Neuro2A cells transfected with the pGL3-promoter vector containing high or low risk alleles of SOX11 schizophrenia-associated SNPs were assessed to identify the potential effect of these SNPs and corresponding haplotypes. Data were representative of at least three independent experiments. *p <0.05; **p <0.01.

Discussion

In the present study, we applied an association study for the human SOX11 gene to investigate its possible association with schizophrenia in an independent case-control sample-set including Chinese 786 schizophrenia patients and 1348 healthy controls. Allelic frequencies of 9 out of 15 selected SNPs covering the whole SOX11 gene region showed differences between cases and controls. After strict Bonferroni correction, 4 SNPs (rs16864067-SNP7, rs12478711-SNP8, rs2564055-SNP11) were still significantly associated with schizophrenia. Two LD blocks containing the four significant SNPs also showed global differences in frequency between cases and control. These four SNPs are in 3’UTR or 3’ near gene region of SOX11 with potential transcriptional function.
Therefore, beside the genetic association, we examined whether the allelic variants of associated SNPs have biological effect on gene transcription by an in vitro luciferase reporter assay. We observed that significant loss in promoter activity was related to risk alleles of the associated SNPs and risk haplotypes of the linkage disequilibrium blocks including the associated SNPs, indicating that these SNPs may influence SOX11 gene expression. These data suggest that SOX11 is a susceptibility gene for schizophrenia.

SOX11 is mapped to chromosome 2p [14, 15], which contains a potential candidate region for schizophrenia [16, 17]. Genes mapped to this region may be candidates for schizophrenia susceptibility genes. Schizophrenia has been reported as a neurodevelopmental disorder with circumstantial and compelling evidence of schizophrenia onset at late adolescence or early adulthood, risk factors operating mostly prenatally or during early childhood, general differences in intellect and behavior many years before onset, structural brain changes at or before onset, cognitive impairment, and functional alternatives of several neurodevelopmental genes (DISC1, NRG1, RELN, BDNF and etc.)[4, 18-21]. Therefore, genes involved in neurodevelopment may contribute to etiology of schizophrenia. The expression profile of SOX11 in nervous system is wide-spread during the embryonic stage and at later stages restricted to the subventricular zone (SVZ) and hippocampus dentate gyrus (DG) where adult neural stem cells remain resident[22], suggesting a role of SOX11 in early neurodevelopment and adult neurogenesis. It has also been reported that Sox11 is co-expressed with Doublecortin (DCX), a specific marker for neuronal precursor cells and immature neurons in neurogenic niches [23]. In Xenopus, it has been confirmed that Sox11 directly interacts with a MAP kinase NLK, thus linking Sox11 with Wnt signaling, in which may cause aberrant expression and function of many genes relevant to patients with schizophrenia [24]. Sox11 expression increases instantly and significantly after electroconvulsive shock (ECS), an effective treatment for patients suffering from schizophrenia and major depression disorders [25]. Sox11 and its putative binding partner Brn1 was induced in CA1 and/or DG of hippocampus following transient forebrain ischemia in rat [26]. It has been reported that Sox11 is required for NSC differentiation, neuronal survival, neurite growth, neuronal maturation, and transcriptionally regulates many genes related to cell survival and death. As a pleiotropic growth factor influencing neuronal survival, differentiation, synaptic plasticity and regeneration, brain-derived neurotrophic factor putative involvement of BDNF, and modulation by Sox11 has been deeply investigated in schizophrenia[27]. It is notable that expression level of Sox11 is spontaneously up-regulated in neurogenic niche regions, suggesting an indispensable role of Sox11 in neuroplasticity. Therefore, in addition to the role in early-stage neurodevelopment, abnormal expression of Sox11 may lead to clinical symptoms due to loss of adaptation capacity of schizophrenia patients for adverse stimuli from the environment. The significant SNPs located in SOX11 3’UTR may contribute to normal neurodevelopment and fine response to environmental alterations by conditionally regulating SOX11 expression level.

Our case-control association study confirmed a previously noted, significant association between 4 potential functional polymorphisms located 3’UTR of the human SOX11 gene and schizophrenia, indicating that SOX11 may contribute to the risk for schizophrenia. However, more than one thousand schizophrenia candidate genes have been reported with poor repeatability and verification by thousands of candidate gene and genome-wide association studies since 1965[28]. Thus, elaborate and convinced interpretation of SOX11 in schizophrenia emergence is critical for approval of its involvement in schizophrenia etiology.
SOX11 is a novel schizophrenia candidate gene

Table 2. Genotype and allele frequencies of 15 SNPs in the human SOX11 gene between schizophrenia patients and controls.
SOX11 is a novel schizophrenia candidate gene.

| SNP   | Control (
|       | 688 (0.584) | 577 (0.428) | 911 (0.698) | 699 (0.504) | 448 (0.518) | 430 (0.589) | 585 (0.375) | 678 (0.357) | 682 (0.357) | 698 (0.357) | 709 (0.357) | 870 (0.357) | 682 (0.357) | 510 (0.446) | 620 (0.446) | 620 (0.446) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |
|       | 578 (0.357) | 505 (0.375) | 430 (0.589) | 430 (0.589) | 565 (0.428) | 678 (0.357) | 709 (0.357) | 682 (0.357) | 870 (0.357) | 682 (0.357) | 698 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) | 682 (0.357) |

Significant p values (<0.05) are in boldface. Frequencies are shown in parenthesis. Significant p value after the strict Bonferroni correction.
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### Table 3. Estimated haplotype frequencies and case-control haplotype results of the human SOX11 gene.

<table>
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<th>Combinations</th>
<th>Haplotype</th>
<th>Haplotype frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$\chi^2$</th>
<th>p</th>
<th>OR (95%CI)</th>
<th>global $\chi^2$</th>
<th>p</th>
</tr>
</thead>
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<td></td>
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<td>case</td>
<td>control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP2-SNP3</td>
<td>C-A</td>
<td>518.94(0.338)</td>
<td>999.81(0.371)</td>
<td>4.683</td>
<td>0.0305</td>
<td>0.87(0.76-0.99)</td>
<td>4.711</td>
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<tr>
<td></td>
<td>T-A</td>
<td>95.06(0.062)</td>
<td>155.19(0.058)</td>
<td>0.325</td>
<td>0.5687</td>
<td>1.08(0.83-1.41)</td>
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<tr>
<td></td>
<td>T-G</td>
<td>920.94(0.600)</td>
<td>1537.81(0.570)</td>
<td>3.356</td>
<td>0.0670</td>
<td>1.13(0.99-1.28)</td>
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</tr>
<tr>
<td>SNP5-SNP6</td>
<td>A-G-A-A</td>
<td>576.50(0.376)</td>
<td>889.03(0.331)</td>
<td>10.136</td>
<td><strong>0.0015</strong></td>
<td>1.24(1.09-1.42)</td>
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<tr>
<td>SNP7-SNP8</td>
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<td>126.03(0.082)</td>
<td>249.09(0.093)</td>
<td>1.171</td>
<td>0.2793</td>
<td>0.88(0.71-1.10)</td>
<td>11.941</td>
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<td></td>
<td>A-T-G-G</td>
<td>47.62(0.031)</td>
<td>112.79(0.042)</td>
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<td>0.0819</td>
<td>0.74(0.52-1.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G-T-G-G</td>
<td>703.19(0.458)</td>
<td>1315.78(0.490)</td>
<td>3.077</td>
<td>0.0795</td>
<td>0.89(0.78-1.01)</td>
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<tr>
<td>SNP9-SNP10</td>
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<td>846.14(0.551)</td>
<td>1363.17(0.506)</td>
<td>8.502</td>
<td><strong>0.0036</strong></td>
<td>1.21(1.06-1.37)</td>
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<td>SNP11-SNP12</td>
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<td>402.90(0.262)</td>
<td>817.71(0.304)</td>
<td>7.921</td>
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<td>0.82(0.71-0.94)</td>
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<tr>
<td></td>
<td>G-G-A-C</td>
<td>253.77(0.165)</td>
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<td>T-A-C</td>
<td>608.66(0.397)</td>
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<td>4.418</td>
<td><strong>0.0356</strong></td>
<td>1.15(1.01-1.31)</td>
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<sup>a</sup> Frequencies are shown in parenthesis.

Significant p values (<0.05) are in boldface.
SOX11 is a novel schizophrenia candidate gene

References


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