DRD4 uVNTR and TP53 Codon72 Polymorphisms in Schizophrenia (R1)

Running Title: TP53 Pro72Arg in schizophrenia

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Abstract

Background: TP53 is a recently suspected to be involved in neural apoptotic events. Also, TP53 codon72 and long-form variants of DRD4 uVNTR polymorphism are reported to be conferred susceptibility to schizophrenia, respectively.

Methods: Nine hundred and thirty-four schizophrenia patients and 433 healthy individuals were recruited, genotyped for TP53 codon72 and DRD4 uVNTR polymorphism by using PCR, PCR-RFLP and direct sequencing.

Results: No significant difference was found in both genotype and allele frequency of TP53 codon72 polymorphism between schizophrenia patients and controls. However, long-form alleles (≥5-repeat) of DRD4 uVNTR polymorphism were more frequent in schizophrenia patients (P = 0.001), which may a risk factor to be associated with enhanced vulnerability to schizophrenia (OR = 3.189, 95% C.I. = 1.535-6.622). In logistic regression, long-from variants did predict schizophrenia after controlling age and gender (P = 0.036, OR = 2.319), but not the genotype CC or GG of TP53 codon72 polymorphism.

Conclusions: The long-form variants of DRD4 uVNTR polymorphism associate with schizophrenia, which independent to TP53 codon72 polymorphism. Also, the TP53 codon72 polymorphism is more likely uncorrelated to schizophrenia, if any; the genetic effect is very small. The other SNPs of p53 gene or others apoptosis-related genes need to be explored to clarify their role in synaptic dysfunction involves in pathogenesis of schizophrenia.

Key Words: schizophrenia, TP53 codon72 polymorphism, DRD4 uVNTR
Background

The results of neuropsychological and neuroimaging studies suggest that abnormal connections between various cortical and subcortical brain regions plays an important role in the pathogenesis of schizophrenia [1,2]. During the last two decades, remarkable progress has been made in identifying changes in the brain that are related to the pathophysiology of schizophrenia. Although the etiology remains unknown, the experimental evidence comes from neuropathological and neuroimaging studies, have been identified several converging findings, including progressive loss of cortical gray matter in first-episode psychosis, reduced synaptic markers, reduced neuropil and layer-specific reductions of neurons suggest that disrupted cortical synaptic circuitry is a central deficit in schizophrenia [3]. In fact, the underlying mechanisms lead to synaptic dysfunction of those schizophrenia patients still unknown; however, dysregulation of neuronal apoptosis is suggested to be one of the reasons and contributes to disease pathophysiology [4,5]. The pro-apoptotic events that have been demonstrated within the brain regions of schizophrenia patients did not reflect in the reduced cortical neurons in the prefrontal cortex [6,7], but shows a reduction of neuropil accompanied with high neuronal density [8].

Among the apoptosis-related proteins, the Bcl-2 was found to reduce by 25% in middle temporal gyrus in schizophrenia compared to control. A high Bax/Bcl-2 ratio also detected in neurons and glia of temporal cortex in schizophrenia [9], which suggested that these cells might more susceptible to pro-apoptotic stimuli in term of uncontrolled cytochrome c releasing. The excess cytochrome c releases into cytosol which in turn initiate caspase cascade [10,11]. The TP53 gene, a well-known tumor suppressor that regulates apoptosis, has been proposed as upstream regulator of Bax-mediated intrinsic apoptotic pathway [12]. In general, TP53 triggers either grow arrest through p21 and/or apoptosis via PUMA-Bax signaling in response to DNA damage [13]. Moreover, it has been shown that increasing
TP53 expression corresponds to γ-irradiation in mouse embryonic brain results in neuronal damage [14]. It has also been observed that TP53 gene acts to control the elimination of cells with genetic abnormalities, by inducing p53-mediated neuronal apoptosis in schizophrenia [15,16]. Thus, it was of concern that whether TP53 gene confers disease vulnerability to schizophrenia. The TP53 codon72 polymorphism, an Arg (CGC)/Pro (CCC) substitution polymorphism at codon 72 of p53 gene, is speculated to be involves in its apoptosis induction. Two genetic variants have been reported with distinct function, which Arg72 variant is considered to be more efficiently trigger apoptosis than Pro72 variant. Moreover, Arg72 variant is also identified to be localized to mitochondria and induce excess cytochrome c release into cytosol [17]. By contrast, this polymorphism is also reported to be associated with cancer vulnerability, which Pro/Pro genotype is risk factor to be associated with enhanced vulnerability to epithelial cancers, such as lung cancer (OR=2.98) [18], colorectal cancer (OR=1.699) [19], and transitional cell carcinoma [20], but the SNP-disease association to schizophrenia remains unclear.

DRD4 uVNTR polymorphism is a simple tandem repeat variation comprises 2-10 repeats at exon3, which is a cytoplasmic region of this membrane span and critical for its biological function [21,22]. According to the experimental evidence from function study, the 4-repeat and 2-repeat variants were associates higher cAMP reduction activity compared to 7-repeat variant [9,23]. This polymorphism has been linked to variation of dopaminergic signaling and confers disease susceptibility to schizophrenia, especially the long-form variants [21,24]. The abnormalities in dopaminergic signaling usually seem in schizophrenia patients [25]. Porat et al have suggested that higher dopamine concentrations can induce apoptosis and increase TP53 gene level [26]. These findings might link TP53 gene in relation to the dopaminergic signaling, even though it is yet known whether TP53 interacts with DRD4. Hence, in this study, we aimed at exploring the role of TP53 codon72 polymorphism
in schizophrenia. In addition, the possible interaction term between DRD4 uVNTR and the TP53 codon72 polymorphism is also investigated.

Methods

Participants

Nine hundred and thirty-four schizophrenia patients (643 were male with an average age of 36.69 years, S. D. = 12.20) were recruited from Southern Taiwan in this study. These patients are sourced from outpatient services, department of intensive care unit, community psychiatric clinic, psychiatry referrals and acute hospice wards of our hospital. All patients were diagnosed by senior psychiatrists in a teaching hospital, based on the criteria of the Diagnostic Statistical Manual, Fourth edition [27], and were yet receiving antipsychotic medication while blood sampling. At least two psychiatrists gave their assessments independently according to case records and interviews with patients. The interview was administered by trained and reliable raters and diagnosis was made by consensus of two raters. Written informed consents were obtained from all participants and study protocol was also approved by the Institutional Review Board of our hospital.

DNA extraction

DNA extraction was performed using the DNeasy Kit (Qiagen, Hilden, Germany), all experimental procedures were according to the manufacturer’s instructions. The extracted DNA was diluted into a final concentration of 100 ng/µl and stored at –80°C freezer for further use.

Genotyping of TP53 codon72 polymorphism

The Pro72Arg polymorphism of TP53 was determined by the PCR-RFLP. The PCR was performed using the hot-start technique in a final reaction volume of 25 µl with 1.5 mM MgCl2. The primers for PCR amplification were: forward 5’-CAA CGT TCT GGT AAG
GAC AA-3’; reverse 5’-GCC TAA GGG TGA AGA GGA A-3’. The PCR condition was 35 cycles of 30 s at 94°C (denaturation), 30 s at 55°C (annealing), and 30 s at 72°C (extension). PCR products were subjected to restriction enzyme digestion with BstUI at 60°C for 2 h, and then visualized on 2% agarose gel containing 0.5 µg/ml ethidium bromide. The original PCR product was 488 bp in length. The Arg72 (CGC) variant specific PCR product was digested into 222 and 266 bp by BstUI and the Pro72 (CCC) specific product was undigested. The genotypes were recorded by at least two well-trained raters who were blinded to the clinical characteristics of the study sample.

**DNA sequencing**

Direct sequencing was applied to confirm the results of PCR-RFLP. Briefly, the PCR product was firstly purified by using QIA quick purification columns (Qiagen, Valencia, USA), followed by performing the cycle sequencing reactions with BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, USA), according to the manufacturer’s instructions. The extended products were separated on an ABI PRISM™ 3130 Genetic analyzer (Applied Biosystems, Foster City, USA) after performing an alcohol precipitation.

**Statistical analysis**

The variables were analyzed using the SPSS for Windows version 15.0 software package (SPSS, Chicago, IL, USA). Continuous variables were shown as means ± SD and categorical variables were presented in proportions. An unpaired t test was used to make comparisons between groups for continuous variables, and Pearson’s χ² test was applied for categorical variables. Chi-square tests were used to test the consistency of genotype frequencies at each SNP locus with Hardy–Weinberg equilibrium. Also, Chi-square test was applied to discriminate whether inter-group difference in genotype distribution and allelic frequency of TP53 codon72 polymorphism and DRD4 uVNTR polymorphism is significant.
between cases and controls. Moreover, hierarchical logistic regression analysis was used to evaluate the whether TP53 codon72 polymorphism and DRD4 uVNTR polymorphism are the independent factor to be associated with vulnerability to schizophrenia by using dummy variables. The possible interaction term also determine in the logistic regression. A total of three dummy variables were created and to be brought into logistic regression analysis including p53CC, p53GG and DRD4c. For the variable p53CC, 1 refers to the CC genotype of TP53 codon72 polymorphism and 0 refer to others genotypes; for p53GG, 1 refers to the GG genotype of TP53 codon72 polymorphism and 0 refer to others genotypes and for DRD4c, 1 refers to the long-form allelic variants of DRD4 uVNTR polymorphism (≥ 5-repeat) and 0 refers to the short-form allelic variants (≤ 4-repeat). By following, structure equation modeling was utilized to exhibit the interrelationships among the age, gender, genotype CC of TP53 codon72 polymorphism, long-form variants (≥ 5-repeat) of DRD4 uVNTR polymorphism and schizophrenia via AMOS verison7 (SPSS, Chicago, IL, USA). Structural equation modeling techniques made use of all the information that was provided by the regression techniques and path analysis. If structural equation modeling showed that p values was more than 0.05 and adjusted goodness-of-fit index was more than 0.9, which means the null model corresponded to the real structure.

Results

In this study, the subjects comprises 934 schizophrenia patients (643 were male with an average age of 36.69 years, S. D. = 12.20) and 433 community controls (190 were male with an average age of 45.33 years, S. D. = 13.91). The distributions of genotypes and alleles for the TP53 codon72 polymorphism and DRD4 uVNTR poymophism was shown in Table 1. The genotypic distribution of the TP53 codon72 polymorphism in both cases and controls were in Hardy-Weinberg equilibrium (case: HWE-p = 0.884, control: HWE-p = 0.084)
(Table 1). No significant inter-group difference was found in genotypic distribution and allelic frequency of TP53 codon72 polymorphism between cases and controls (genotype: P = 0.229, allele: P = 0.404). By contrast, the 4/4, 2/4 and 2/2 are the three most common genotypes of DRD4 uVNTR polymorphism in our study cohorts (case: 4/4 = 57.00%, 4/2 = 28.77%, 2/2 = 6.56%; control: 4/4 = 66.19%, 4/2 = 18.44%, 2/2 = 11.58%). In general, the long-form allele (≥6-repeat) containing genotypes of DRD4 uVNTR polymorphism were rarely found in our population. The genotypic distribution of DRD4 uVNTR polymorphism between cases and controls was significant different (P < 0.001). All detected DRD4 uVNTR alleles were further categorized into dichotomous group as short-form alleles (≤4-repeat) and long-form alleles (≥5-repeat). By following, carrying the long-form alleles (≥5-repeat) of DRD4 uVNTR polymorphism was more frequent in schizophrenia to a statistical significant level (P = 0.001), which the allele carriers were estimates for 3.189 times risk to be associated with schizophrenia compared to control (OR = 3.189, 95% C.I. = 1.535 – 6.622). In logistic regression analysis, age and gender were found to be associated with schizophrenia to a significant level (P < 0.001, data not shown); therefore, the followed analyses for genetic effect that contribute from two polymorphisms was stratified with age and gender. Both dummy variables of p53CC and p53GG were insignificant to be in relation to schizophrenia after controlling the age and gender effects (Table 2a, p53CC: P = 0.203, p53GG: P = 0.571). However, dummy variable DRD4c was significant associated with schizophrenia (Table 2b, P = 0.036, OR = 2.319), which indicated that long-form variants (≥5-repeat) plausibly confer vulnerability to schizophrenia in our population. In addition, no interaction term between dummy variable DRD4c and p53CC was found, subsequently, exerts a significant effect in relation to schizophrenia (Table 2c, P = 0.166). This result may
suggested that long-form variants (≥5-repeat) of DRD4 uVNTR polymorphism are independent to TP53 codon72 polymorphism and contribute to disease risk modulation of schizophrenia. For the specific aim to distinguish possible interaction term between two polymorphisms, structure equation modeling was introduced to clarify the interrelationships among age, gender, p53CC, DRD4c and schizophrenia. A conceptual structure was achieved that it fulfilled the criteria of P-value of Chi-square test needs to be greater than 0.05 and adjusted goodness-of-fit index should more than 0.9 at the same time. As the null-hypothesized structure shown in Figure 1, the non-genetic effect attributed from age and gender was more correlated to schizophrenia compared to genetic effect from two polymorphisms. The age was negatively associated with schizophrenia with a highest correlation coefficient (-0.26), followed by gender (-0.184), DRD4c (0.061) and p53CC (0.020). This result indicated that increasing age and female gender are negatively correlated to schizophrenia, which consistent with the epiphenomenon of higher incidence in younger age and male. The long-form variants (≥5-repeat) of DRD4 uVNTR polymorphism did more positively correlated to schizophrenia compared to genotype CC of TP53 codon72 polymorphism. However, both of them did not parallel to age and gender, which still not reach the evident degree. According to the path analysis, consistent with the result from logistic regression, it did show no interaction between p53CC and DRD4c. This finding may strengthen that these two polymorphisms associate with schizophrenia independently. Also, the TP53 codon72 polymorphism is more likely uncorrelated to schizophrenia, if any; the genetic effect is very small.

**Discussion**

Schizophrenia is a complex trait with strong genetic background [28,29], whose detailed
pathogenesis is still unclear. More recently, several studies have been described an epiphenomenon that the cancerous incidence is decreased in schizophrenia patients compared to general population [30]. Also, several interesting findings have been rationalized to be linked to tumor resistance in schizophrenia patients, including excess dopamine secretion, enhanced natural killer cell activity, accelerated apoptosis, and the unexpected anti-mutagenic effects of antipsychotics [18,30,31]. The p53 gene, another candidate, is speculated to be involved in such tumor resistance in schizophrenia. The apoptosis induction and tumor suppressive abilities of p53 gene may account for neurodevelopmental abnormalities as well as tumor resistance associated with schizophrenia is of concern. Among the SNPs in p53 gene, CAA Ins/Del and 16 bp Ins/Del polymorphisms are found to be associated with schizophrenia in a case-control study using Toronto residents. Also, CAA Ins/Del polymorphism was reported to be transmitted unequally in Portuguese schizophrenia family using TDT analysis [32]. The SNP rs2078486-A allele and a 3-marker haplotype CAC were detected more frequent in Chinese schizophrenia patients, which suggested that p53 gene plays a role in susceptibility to schizophrenia [33]. Regarding to p53 polymorphisms, we have previously found a higher frequency of genotype CC (Pro/Pro) of codon72 polymorphism in Taiwanese cancer patients [19,20], especially genotype CC was in relation to progression of colorectal cancer. However, it remains unclear about the role of this SNP in schizophrenia patients in Taiwan even though it had been reported that has no association with schizophrenia, age of onset [31] and deficits in the neurocognitive profile [34]. Also, little is known about gene-gene interactions between TP53 codon72 polymorphism and others schizophrenia-related SNPs. Hence, this case-control study was aimed to explore the genetic association between the TP53 codon72, DRD4 uVNTR polymorphisms and schizophrenia in a Taiwanese population.

In this study, the frequency of the Pro72 allele (C allele) was found to be higher in schizophrenia patients than in community controls (45.75% versus 44.03%), which was
consistent with the results of a study by Chiu et al. (46.8% vs. 40.5%) [31]. However, these differences yet reach significant level. There was no statistical difference in both genotype and allele frequency between patients and community controls after stratifying for gender and age. Interestingly, we have previously shown that the Pro72 allele was more prevalent in colorectal cancer (56.1%) and transitional cell carcinoma patients (62.7%) [19,20]. Taken together, this may suggested that Pro72 allele associates with cancer vulnerability, but not in relation schizophrenia. Also, this finding consistent with previous result from two independent case-control studies, which the major findings reject a link between TP53 codon72 polymorphism and the increased susceptibility to schizophrenia [18,31]. Does the TP53 gene act bi-functionally to control neuronal apoptosis and serve as a protective factor against cancer in schizophrenia patients? The answer is more likely inconclusive, even though TP53 gene was ever suspected that it involves in synaptic dysfunction in schizophrenia [35]. Several lines of evidence indicate that p53-mediated apoptotic activity might be modulated by its mutation status. Among these mutations, the codon72 polymorphism of particularly has been reported for different apoptosis induction ability. However, the Pro72 homozygote was found more frequent in cancer patients when compared to controls; but it was not significantly less prevalent in schizophrenia patients. Thereby, our results add evidence about p53 is more likely not correspond to tumor resistance of schizophrenia patients.

Schizophrenia is a multi-factorial genetic disease [28,29], and it is suggested that caused by a synergistic effect contribute from different genetic variants [36]. We have previously reported for carrying the long-form alleles of DRD4 uVNTR polymorphism may a risk factor that confers vulnerability to schizophrenia [24]. Therefore, in this study, we analyzed the possible interaction between TP53 codon72 and DRD4 uVNTR polymorphism. In a cell base assay, the high dopamine level can induce apoptosis, as well as increases TP53 gene
expression level [26]. In addition, the excess dopamine secretion and synaptic dysfunction (probably the consequence of pro-apoptotic activity in neuron) can be observed in schizophrenia patients. These finding raise a possibility of domapinergic signaling involves both neural differentiation and apoptosis in dose dependent manner, and such activity is in relation to p53 function. The TP53 also suggested that serves as negative regulator to governing the dopamine-triggered apoptosis which response to DNA breakage under oxidative stresses. However, in this study, no interaction term between these two polymorphisms was observed to be associated with schizophrenia in different statistical models. According to our results, it was suggested that long-form variants of DRD4 uVNTR polymorphism and genotype CC of TP53 codon72 polymorphism (Pro72 homozygote) may not have a synergistic effect on risk of schizophrenia. Also, the CC genotype of TP53 codon72 polymorphism is unlikely to be associates with schizophrenia, if any, the genetic effect is small. Nevertheless, our results need to view in the light of some limitations. First, regarding to the p53 SNPs, we only explored the association between TP53 codon72 polymorphism and schizophrenia, as well as its possible interaction with long-form variants of DRD4 uVNTR polymorphism without analyzing others schizophrenia-associated SNP sites that has been described elsewhere [32,33]. A relative few markers across the p53 gene plausibly do not fully determine its role in schizophrenia, of particular, its function involves in apoptosis induction. Second, this study was designed as case-control paradigm, thereby, lack of family-based strategies, it may insufficient to clarify the gene-disease association. Also, the transmission rate and information of linkage of disequilibrium are unable to be accessed. Third, no non-Asian subjects were recruited for this study, the ethnic heterogeneity can only identify through meta-analysis. However, the meta-analysis was not performed to discern whether our result may a false negative finding due to population stratification. Finally, the schizophrenia is a complex disorder and cannot be independently distinguished
by SNP analysis, multi-approaches include genetic and environmental perspective should be considered.

Conclusions

Involvement of the DRD4 VNTR polymorphism in the pathogenesis of schizophrenia has previously been documented [19,21]. The TP53 Pro72Arg polymorphism has been associated with tumor metastasis in colorectal cancer and transitional cell carcinoma [19,20], but not with schizophrenia. In addition, the polymorphism is associated with the grade of malignancy rather than disease onset. In the present study, DRD4 uVNTR polymorphism rather than TP53 Pro72Arg polymorphism confers vulnerability to schizophrenia. No interaction term was found in the statistical model. Thus, the other SNPs of p53 gene or others apoptosis-related genes need to be explored to clarify their role in synaptic dysfunction involves in pathogenesis of schizophrenia.

Abbreviations

None

Competing interests

All authors have no conflict of interest to declare.

Author’s Contributions

All authors contributed to the design of the study. FW conceived of the study, participated in the design of the study, performed the statistical analysis and helped to draft the manuscript. BC participated in its design and helped to draft the manuscript. WT carried out the molecular genetic studies and drafted the manuscript. CN, YC and DS participated in its design, collected the data and coordination and helped to draft the manuscript. All authors have revised the manuscript and have approved the final manuscript.

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Table 1. The distributions of genotypes and alleles for the TP53 codon72 polymorphism and DRD4 uVNTR polymorphism

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotypes counts frequency (%)</th>
<th>HWE-p</th>
<th>P-value</th>
<th>Allele counts frequency (%)</th>
<th>P-value</th>
<th>Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>rs8064946</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia (n = 917)</td>
<td>193 (21.05)</td>
<td>453 (49.40)</td>
<td>271 (29.55)</td>
<td>0.884</td>
<td>0.229</td>
<td>839 (45.75)</td>
</tr>
<tr>
<td>Community control (n = 427)</td>
<td>74 (17.33)</td>
<td>228 (53.40)</td>
<td>125 (29.27)</td>
<td>0.084</td>
<td></td>
<td>376 (44.03)</td>
</tr>
<tr>
<td>DRD4 uVNTR</td>
<td>2/2 2/3 2/4 2/5 3/3 3/4 4/4 4/5 4/6 5/6</td>
<td></td>
<td></td>
<td>Short (≤ 4-repeat)</td>
<td></td>
<td>Long (≥ 5-repeat)</td>
</tr>
<tr>
<td>Schizophrenia (n = 914)</td>
<td>60</td>
<td>0</td>
<td>263</td>
<td>8</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Community control (n = 423)</td>
<td>49</td>
<td>1</td>
<td>78</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

17 schizophrenia patients and 6 controls lack of genotyping results of TP53 codon72 polymorphism; 20 schizophrenia patients and 10 controls without genotyping information of DRD4 uVNTR polymorphism; HWE-p: p value of chi-square test for Hardy-Weinberg Equilibrium; a: the odds ratio of C allele to G allele of TP53 codon72 polymorphism in relation to schizophrenia; b: the odds ratio of long-form variants (≥ 5-repeat) to short-form variants (≤ 4-repeat) confers enhanced risk of vulnerability to schizophrenia.
Table 2. The result of hierarchical logistic regression analysis aimed at determining whether TP53 codon72 polymorphism and DRD4 uVNTR polymorphism associate with schizophrenia after controlling the effect attributed from age and gender.

<table>
<thead>
<tr>
<th>A.</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
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<tr>
<td>Gender</td>
<td>-0.891</td>
<td>0.128</td>
<td>48.735</td>
<td>1</td>
<td>&lt; 0.001**</td>
<td>0.410</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.045</td>
<td>0.005</td>
<td>83.772</td>
<td>1</td>
<td>&lt; 0.001**</td>
<td>0.956</td>
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<tr>
<td>P53CC</td>
<td>0.218</td>
<td>0.171</td>
<td>1.618</td>
<td>1</td>
<td>0.203</td>
<td>1.244</td>
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<tr>
<td>P53GG</td>
<td>0.083</td>
<td>0.146</td>
<td>0.320</td>
<td>1</td>
<td>0.571</td>
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<td>185.052</td>
<td>1</td>
<td>&lt; 0.001</td>
<td>42.954</td>
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<table>
<thead>
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<th>B.</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
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<td>-0.045</td>
<td>0.005</td>
<td>83.772</td>
<td>1</td>
<td>&lt; 0.001**</td>
<td>0.956</td>
<td></td>
</tr>
<tr>
<td>DRD4c</td>
<td>0.841</td>
<td>0.401</td>
<td>4.393</td>
<td>1</td>
<td>0.036*</td>
<td>2.319</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>3.777</td>
<td>0.270</td>
<td>195.381</td>
<td>1</td>
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<td>43.668</td>
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<th>C.</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
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<tbody>
<tr>
<td>Gender</td>
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<td>0.128</td>
<td>48.735</td>
<td>1</td>
<td>&lt; 0.001**</td>
<td>0.410</td>
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</tr>
<tr>
<td>Age</td>
<td>-0.045</td>
<td>0.005</td>
<td>83.772</td>
<td>1</td>
<td>&lt; 0.001**</td>
<td>0.956</td>
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<tr>
<td>DRD4c by p53CC</td>
<td>1.459</td>
<td>1.054</td>
<td>1.916</td>
<td>1</td>
<td>0.166</td>
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<td>Constant</td>
<td>3.819</td>
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<td>200.781</td>
<td>1</td>
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<td>45.573</td>
<td></td>
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</table>

B: coefficient of regression; S.E.: Standard Error; Wald: the index of regression effect; df: degrees of freedom; Sig: p-value; Exp(B): odds ratio; p53CC: dummy variable which 1 refers to the CC genotype of TP53 codon72 polymorphism and 0 refer to others genotypes; p53GG: dummy variable which 1 refers to the GG genotype of TP53 codon72 polymorphism and 0 refer to others genotypes; DRD4c: dummy variable which 1 refers to the long-form allelic variants of DRD4 uVNTR polymorphism (5-repeat) and 0 refers to the short-form allelic variants (4-repeat); DRD4c by p53CC: the genetic effect that was attributed from possible interaction term between long-form variants of DRD4 uVNTR polymorphism and CC genotype of TP53 codon72 polymorphism; The asterisk indicates statistical significant.
Chi-square = 3.553
df = 1
P = 0.059
AGFI = 0.998

Figure 1. Structural equation modeling of interrelationships among variables in schizophrenia.

p53CC: dummy variable which 1 refers to the CC genotype of TP53 codon72 polymorphism and 0 refer to others genotypes; DRD4c: dummy variable which 1 refers to the long-form allelic variants of DRD4 uVNTR polymorphism (≥5-repeat) and 0 refers to the short-form allelic variants (≤4-repeat); AGFI: adjusted goodness-of-fit index. The numbers are the coefficient of correlation between two variables.