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Analysis of Dopamine Receptor D2 Gene Polymorphism and Correlation with Dyslipidemia in the Chinese Population

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Keywords
DRD2 · C957T polymorphism · Dyslipidemia · Susceptibility · CT genotype

Abstract
Objective: The study aimed to explore the genotype and allele distributions of dopamine D2-like receptor (*DRD2*) gene -141C and C957T polymorphisms in the Chinese Han population with dyslipidemia, as well as their association with serum lipid levels. ***Methods:*** One hundred fifty patients with dyslipidemia and 150 healthy people were recruited as the case and the control groups, respectively. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol levels were detected. The target sequence of *DRD2* polymorphisms was amplified by polymerase chain reaction and genotyped via Sanger sequencing. ***Results:*** In *DRD2* gene C957T (rs6277), three genotypes of CC, CT, and TT were detected with the frequencies of 92.67%, 6.67%, 0.67% in dyslipidemia cases, and 83.33%, 14.67%, 2.00% in the controls, respectively. The CT genotype and T allele frequencies were significantly low in the case group relative to the control group. After adjusting to other clinical indicators, the CT genotype of C957T polymorphism (hazard ratio = 0.401, 95% confidence interval = 0.181–0.890, $p < 0.05$) was still related to a significantly reduced risk of dyslipidemia. The C957T CT genotype carriers had the lowest values of serum TC, TG, LDL, and the highest values of serum HDL-C. ***Conclusion:*** *DRD2* gene C957T polymorphism was an independent influencing factor associated with the susceptibility to dyslipidemia, and the CT genotype was associated with decreased odds of susceptibility to dyslipidemia.

Introduction

Dyslipidemia refers to abnormal blood lipid levels in the blood caused by dysfunction of fat metabolism or transport [Li et al., 2022]. It is characterized by elevated levels of total cholesterol (TC) and triglyceride (TG) [Luo et al., 2018]. Due to social and economic development, changes in diet structure, and living habits, the prevalence of dyslipidemia in the population increased significantly, with a trend toward younger subjects [He et al., 2014]. Dyslipidemia is one of the independent risk factors for coronary heart disease and ischemic death [Ming et al., 2021]. Its characteristic of elevated low-density lipoprotein cholesterol (LDL-C) or TC is the known risk factor for atherosclerotic cardiovascular disease [Yu et al., 2022]. Hypertension, diabetes, coronary heart disease, and other cardiovascular diseases caused by dyslipidemia seriously threaten people's life and health, and increase people's economic and medical burden. Therefore, it is

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very important to formulate effective management for dyslipidemia in the early stage to lessen the morbidity and mortality of cardiovascular and cerebrovascular diseases.

Single nucleotide polymorphism (SNP) refers to DNA sequence polymorphism due to single nucleotide variation at the genome level [Cao et al., 2022]. SNP involves only variations of a single base and is widespread in the human genome, which is the most common heritable variation in humans [Guo et al., 2022]. SNPs may be located in coding regions of genes or noncoding sequences [Ma et al., 2020]. It has been widely used and studied in the genetic analysis due to its advantages of high genetic stability, high distribution density, and easy automatic detection [Hu et al., 2019]. Dopamine is the main catecholamine neurotransmitter in the mammalian brain. It is involved in a variety of biological functions, including motor activity, cognition, food intake, and hormone secretion [Klein et al., 2019]. The dopamine D2-like receptor is one of the receptors for dopamine, which is encoded by dopamine D2-like receptor (*DRD2*) gene [Szlaga et al., 2022]. *DRD2* gene consists of eight exons and seven introns [Neuman et al., 2022]. It encodes G-protein-coupled receptors that are highly expressed in dopaminergic neurons in the striatum and prefrontal cortex to regulate synaptic dopamine signaling [Martel and Gatti McArthur 2020]. SNPs of *DRD2* gene have been reported to be associated with memory, cognitive activity, attention, and brain diseases [Xu et al., 2007; Zhang et al., 2014; Niewczas et al., 2021]. Notably, a close association has been identified between low DRD2 density and obesity in both animal and human research [Volkow et al., 2011; Pak et al., 2023]. *DRD2* -141C insertion/deletion (rs1799732) and C957T (rs6277) are two commonly studied SNPs in the *DRD2* gene. Importantly, C957T is suggested to be related to increased serum TG levels in the Western Mexico population [Ramos-Lopez et al., 2018]. However, the association of *DRD2* gene polymorphisms with the susceptibility of dyslipidemia has not been examined.

The present study attempted to explore the genotype and allele distributions of *DRD2* gene -141C and C957T polymorphisms in the Chinese Han population with dyslipidemia. Moreover, the genetic correlation of different C957T genotypes with serum lipid levels was examined.

Materials and Methods

Study Population

One hundred fifty patients with dyslipidemia from the Bishan Hospital of Chongqing Medical University were selected as the study objects. Dyslipidemia was diagnosed based on the China Adult Dyslipidemia Prevention Guide in 2007 (Joint Committee of Chinese Adult Dyslipidemia Prevention Guideline, 2007). If cases met one or more of the following criteria, dyslipidemia was diagnosed: serum TC concentration ≥6.22 mmol/L, serum LDL-C ≥4.14 mmol/L, serum TG ≥2.26 mmol/L, serum high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L. Exclusion criteria included were as follows: (1) cases who had cardiovascular disease and received medication or other interventional therapy; (2) those who took hormones, steroids, and other drugs within 1 month before the study began; (3) patients with severe diseases of the liver and kidney system, neuropsychiatric system, or reproductive system. All participants in this study were Chinese Han population and signed informed consent prior to the study. Another 150 healthy subjects with normal blood lipid were included as the control group.

Detection of Basic Indexes and Serum Biochemical Indexes

The physical examination includes measurements of height, weight, blood pressure, etc., which were performed by a trained physician using the same apparatus. Subjects were asked to rest for at least 15 min before their blood pressure was measured. The body mass index (BMI) = weight (kg)/height^2 (m^2).

All patients were fasting for 12 h, and 5 mL of venous blood was extracted in the morning. Then, centrifugation was performed at 1,500 r/min, and the blood supernatant was taken. Automatic biochemical analyzer (Abbott Laboratories, Abbott Park, IL, USA) was applied for the measurement of serum TG, TC, HDL-C, LDL-C levels.

Genotyping

Genomic DNA was extracted from serum samples using a DNA purification kit (Spin Columns). The purity of DNA was determined by spectrophotometer, then the integrity of DNA was determined by 0.7% agarose gel electrophoresis, and the target sequence of SNPs was amplified by polymerase chain reaction. The polymerase chain reaction condition consisted of initial denaturation at 94°C for 3 min and 35 cycles, each consisting of 94°C 30 s, 55°C 30 s, and 72°C 90 s. The final denaturation occurred at 72°C for 3 min. After the reaction, the DNA was sequenced by Sanger sequencing on an ABI 3730 sequencer (Applied Biosystems).

Statistical Analysis

SPSS 21.0 software was applied for data analysis. The genetic counting method was used to calculate the genotype and allele frequency, while the continuous variable data were expressed as mean and standard deviation. The mean between the two groups was compared using the *t* test of two independent samples. The relationship between genotype and abnormal rate of lipid components was analyzed by χ^2 test and logistic regression.

Results

Basic Clinical Characteristics of the Study Population

Table 1 displays the basic clinical characteristics of the study population. In the study, 65 males and 85 females consisted of the control group with the mean age of 53.85 ± 12.57 years old. The case group included 69 males

Table 1. Comparison of basic characteristics between the case and control groups

Items	Control group (n = 150)	Case group (n = 150)	p value
Age, years	53.85±12.57	52.72±11.40	0.417
Sex, male/female	65/85	69/81	0.642
BMI, kg/m^2	24.81±3.86	25.80±4.27	0.037
WHR	0.87±0.10	0.90±0.18	0.139
SBP, mm Hg	127.69±20.92	130.86±22.98	0.213
DBP, mm Hg	77.65±15.53	76.59±15.30	0.549
FBG, mmol/L	5.24±0.44	5.25±0.48	0.839
TC, mmol/L	5.11±0.63	6.31±0.58	<0.001
TG, mmol/L	1.60±0.37	2.14±0.32	<0.001
HDL-C, mmol/L	1.39±0.21	0.88±0.10	<0.001
LDL-C, mmol/L	3.31±0.46	3.62±0.87	<0.001

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

and 81 females, the mean age was 52.72 ± 11.40 years old. Individuals in the case group possessed high values of BMI than those in the control group ($p < 0.05$). In addition, serum lipid parameters showed a significant difference between the case and control groups, including TC, TG, HDL-C, and LDL-C ($p < 0.01$). But waist-to-hip ratio (WHR), systolic pressure, diastolic blood pressure, and fasting blood glucose had no significant difference between groups ($p > 0.05$).

Genotype and Allele Distributions of DRD2 Gene Polymorphisms in Case and Control Groups

Two common loci of *DRD2* gene (-141C and C957T) were analyzed in the study population, and their genotype and allele distributions between the healthy control group and dyslipidemia cases are exhibited in Table 2. The frequency of both *DRD2* -141C and C957T polymorphisms conforms to the Hardy-Weinberg equilibrium in the control group ($p^{HWE} > 0.05$). The results demonstrated no significant differences in both genotype and allele distribution of *DRD2* -141C between dyslipidemia cases and negative controls ($p > 0.05$). Statistical analysis results revealed a remarkable difference in genotype and allele distribution of *DRD2* gene C957T polymorphism ($p < 0.05$). In *DRD2* gene, C957T polymorphism (rs6277), three genotypes of CC, CT, and TT (online suppl. Fig.; for all online suppl. material, see https://doi.org/10.1159/000533637) were detected with the frequencies of 92.67%, 6.67%, 0.67% in dyslipidemia cases, and 83.33%, 14.67%, 2.00% in the controls, respectively. The CT genotype frequency was significantly low in the case group relative to the control group ($p < 0.05$). The allele frequency of *DRD2* gene C957T polymorphism was also significantly different between the case and control groups ($p < 0.05$). It was concluded that *DRD2* gene C957T CT genotype (OR = 0.409, 95% confidence interval [CI] = 0.186–0.897) and T allele (OR = 0.405, 95% CI = 0.202–0.812) were associated with a decreased odds of susceptibility of dyslipidemia compared to CC genotype carriers.

Furthermore, all clinical indicators and C957T genotypes were introduced into the multivariable logistic regression model to evaluate the independent influence factors related to the onset of dyslipidemia. As shown in Table 3, after adjusting to other clinical indicators, the CT genotype of C957T polymorphism (hazard ratio = 0.401, 95% CI = 0.181–0.890, $p < 0.05$) was still significantly related to a decreased risk of the occurrence of dyslipidemia.

Serum Lipid Levels of Cases with Different C957T Genotypes

Serum lipid levels of cases carrying different C957T genotypes were compared. As shown in Figure 1, the C957T CT genotype carriers had the lowest values of serum TC, TG, LDL, and highest values of serum HDL-C, and the differences were significant from those with CC genotype ($p < 0.01$). Similarly, cases carrying TT genotype also exhibited a similar trend, but the difference did not reach a significant level ($p > 0.05$).

Discussion

The occurrence of cardiovascular events is caused by multiple risk factors, among which dyslipidemia is an important risk factor [Lucchi 2021]. In recent years, the

Table 2. Genotype and allele distributions of *DRD2* gene polymorphisms in case and control groups

Genotype/allele	Control, n = 150 (%)	Case, n = 150 (%)	χ^2	p value	OR (95% CI)
-141C (rs1799732)					
CC	96 (64.00)	103 (68.67)	–	–	1
CT	43 (28.67)	33 (22.00)	1.529	0.216	0.715 (0.420–1.218)
TT	11 (7.33)	14 (9.33)	0.160	0.689	1.186 (0.514–2.740)
C	235 (78.33)	239 (79.67)	–	–	1
T	65 (21.67)	61 (20.33)	0.161	0.688	0.923 (0.623–1.367)
p^{HWE}	0.102				
C957T (rs6277)					
CC	125 (83.33)	139 (92.67)	–	–	1
CT	22 (14.67)	10 (6.67)	5.229	0.022	0.409 (0.186–0.897)
TT	3 (2.00)	1 (0.67)	1.208	0.272	0.300 (0.031–2.919)
C	272 (90.67)	288	–	–	1
T	28 (9.33)	12	6.857	0.009	0.405 (0.202–0.812)
p^{HWE}	0.057				

HWE, Hardy-Weinberg equilibrium.

Table 3. Multivariable logistic regression analysis of factors related to dyslipidemia

Items	HR	95% CI	p value
Age, years	1.373	0.858–2.195	0.186
Sex	1.151	0. 712-1.861	0.565
BMI	1.359	0.850–2.171	0.200
WHR	1.361	0.846–2.190	0.203
SBP	1.376	0.862–2.198	0.181
DBP	1.130	0.705–1.811	0.613
FBG	1.070	0.669–1.711	0.778
C957T phenotype			0.026
CT	0.401	0.181–0.890	0.025
TT	0.261	0.049–1.381	0.114

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HR, hazard ratio; CI, confidence interval.

incidence of atherosclerosis and cardiovascular diseases caused by hyperlipidemia continues to increase, which has seriously threatened the life health of patients [Sandesara et al., 2019]. In the current study, 150 cases with dyslipidemia were enrolled, with the main manifestations of high TC, TG, LDL-C, and low HDL-C. Although the rate of dyslipidemia is increasing year by year, the awareness rate, treatment rate, and control rate of dyslipidemia are still very low in China [writing committee of the report on cardiovascular and diseases in 2022]. According to the basic clinical characteristics data, cases with dyslipidemia exhibited high values of BMI relative to the control group. It was speculated that high BMI might be a risk factor for the occurrence of dyslipidemia. Consistently, elevated BMI has been considered to be related to the diagnosis of dyslipidemia [Crum-Cianflone et al., 2008]. Besides, a high value of WHR is known to be a risk factor for the occurrence of dyslipidemia [Nagar et al., 2022]. However, the present data indicated no significant difference in WHR between the case and control groups, which might be because of the small sample size.

The occurrence of disease is the result of the combined effects of genes and environment. With the development of research, people have become more aware of the correlation between gene polymorphisms and dyslipidemia [Matey-Hernandez et al., 2018]. The close relationship of gene polymorphisms with the development of dyslipidemia has been widely identified [Srinivasan et al., 2021]. Previous study has reported the regulatory role of *DRD2* gene in metabolism through mediating food intake behavior. In a study on childhood obesity, the rs2075654 polymorphism of *DRD2* gene was determined to be associated with long-term obesity alleviation in obese Chinese children and adolescents [Zhu et al., 2018]. Besides, Cardel et al. have also reported the close relationship between the Taq1a polymorphism (rs1800497) of *DRD2* gene with diet and adiposity in a multi-ethnic cohort of children [Cardel et al., 2019]. The present statistical analysis results revealed a remarkable difference in genotype and allele distribution of *DRD2* gene C957T polymorphism between dyslipidemia cases and the control group. It was concluded that *DRD2* gene C957T CT genotype and T allele were associated with decreased

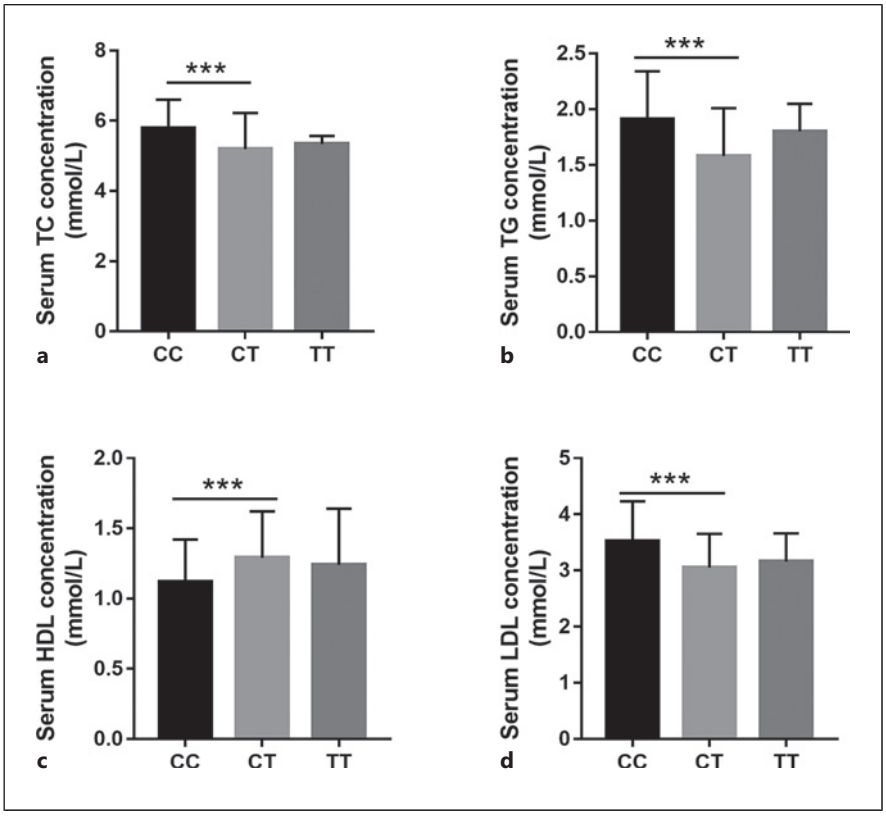

Fig. 1. Serum lipid levels of cases carrying different C957T genotypes. The C957T CT genotype carriers had the lowest values of serum TC (**a**), TG (**b**), and LDL (**d**), and the highest values of serum HDL-C (**c**).

odds of susceptibility to dyslipidemia compared to CC genotype carriers. In a case-control study from Western Mexico, high values of TG were detected in cases carrying C957T CC genotype compared with those with CT genotype, indicating the contribution of C957T polymorphism in serum TG levels [Ramos-Lopez et al., 2018]. Our present findings were consistent with the previous evidence. Moreover, the multivariable logistic regression analysis further evaluated the independent influence factors related to the onset of dyslipidemia. As expected, the CT genotype of C957T polymorphism was still significantly related to a decreased risk of the occurrence of dyslipidemia after adjusting to other clinical indicators.

Furthermore, serum lipid levels of cases carrying different C957T genotypes were compared. It was found that the C957T CT genotype carriers had the lowest values of serum TC, TG, LDL, and the highest values of serum HDL-C. The findings prompted that there may be a definite correlation between different C957T genotypes and serum lipid concentration in the dyslipidemia population. Therefore, the clinical treatment plan can be evaluated according to the genotype difference. However, due to the small number of people enrolled in this study and the fact that all the patients were dyslipidemia, the mutations of related genes and the characteristics of lipid indexes in dyslipidemia patients had certain limitations. And the sample size needed to be expanded in the later study to verify the present findings.

In conclusion, the present findings indicated that *DRD2* gene C957T polymorphism was an independent influence factor for the susceptibility to dyslipidemia, the CT genotype was associated with decreased odds of susceptibility to dyslipidemia compared to CC genotype carriers. Our findings provided exciting prospects for the mechanism exploration of dyslipidemia and its early intervention.

Statement of Ethics

This study protocol was reviewed and approved by Bishan Hospital of Chongqing Medical University (Approval Number: 2020-216). All patients provided written informed consent.

Conflict of Interest Statement

The authors have declared no conflict of interest.

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Author Contributions

Liangjun Tang and Haibo Tan designed the research study. Zhixue Wang and Jiaxuan Zhang performed the research. Maohua Huang provided help and advice. Jide Chen and Fengqi Li analyzed the data. Haibo Tan wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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