Original Article

DRD2 Polymorphism and Smoking Habits in Japanese Males with Schizophrenia

Atsuko Kawai[1], Satoshi Nishino[2], Masatake Kurita[2], Masaaki Mitomo[2], Yukio Numata[2], Tadahiro Sato[2], Yoshiko Nishimatsu[3], Masakazu Nakamura[4], Nobuyuki Hamajima[5], Yoshikazu Nakamura[6]

[1]Social Medical Corporation, Koutokukai Total Health Clinic, Yamagata, Japan
[2]Social Medical Corporation, Koutokukai Sato Hospital
[3]Rissho University Faculty of Psychology
[4]Osaka Center for Cancer and Cardiovascular Disease Prevention
[5]Department of Preventive Medicine, Nagoya University Graduate School of Medicine
[6]Department of Public Health, Jichi Medical University

Abstract

Background：Dopamine D2 receptor（DRD2）TaqIA polymorphism was reported to be associated with the smoking habits. This study aimed to investigate the associations between DRD2 TaqIA polymorphism and smoking habits among Japanese males with schizophrenia. It is well-known that the smoking rate among them is higher and they are nicotine dependent.

Methods：Subjects were 105 male inpatients or outpatients with schizophrenia（mean age ± standard deviation, 44.8 ± 12.3 years）treated at Koutokukai Sato Hospital between 2001 and 2002, who gave informed consent for this study. DRD2 TaqIA（A1/A2）was genotyped with a PCT-CTPP（polymerase chain reaction with confronting two-pair primers）method. The associations was examined with smoking habits, the age at smoking initiation, number of cigarettes per day, nicotine dependence assessed with the Tobacco Dependence Screener（TDS）and the Fagerström Tolerance Questionnaire（FTQ）, and the longest duration of smoking cessation.

Results：Among 81 current smokers, number of cigarettes per day was significantly associated with the genotype（$p = 0.022$）；mean ± standard deviation was 16.1 ± 5.6 for A1A1, 22.7 ± 9.3 for A1A2, and 26.8 ± 12.4 for A2A2. The age-adjusted odds ratio was 0.09（95% confidence interval, 0.01-0.86）for A1A1 relative to A2A2. No significant associations were observed between DRD2 TaqIA polymorphism and the other smoking habits.

Conclusion：This preliminary study suggested that cigarette consumption was significantly reduced in schizophrenic male patients with DRD2 TaqIA A1A1 genotype in Japan. However, our finding needs further research because of its small sample size.

（**Key words**：schizophrenia, smoking, nicotine dependence, DRD2, polymorphism）

Introduction

The author of this study works as a physician at a psychiatry hospital and noted that many psychiatric patients smoke and have particular difficulty in discontinuing smoking. In fact, it has been reported that individuals with psychiatric disorders have a high smoking rate, find it difficult to give up smoking,[1-4] and exhibit high nicotine dependence.[5,6] Among psychiatric patients, the prevalence of medical co-morbidities is also high,[7] and it is thought that smoking is one of the reasons accounting for this fact.[8] According to the National Institutes of Health, people with psychiatric disorders tend to easily become smokers, and the importance of focusing smoking cessation efforts on individuals who are nicotine-dependent, have psychiatric disorders, and have co-morbid nicotine dependence and other psychiatric disorders is emphasized.[9] Thus, smoking is a significant problem that is recognized in

Correspondence to：Atsuko Kawai, MD　Social Medical Corporation, Koutokukai Total Health Clinic　1180-5 Kunugizuka, Nanyo City, Yamagata 999-2221, Japan　E-mail：kawaia@ms3.omn.ne.jp
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psychiatric patients including those with schizophrenia, and it is therefore important to determine the factors related to the development of smoking habits in these individuals.

It has also been reported that environment and genetic polymorphisms are related to smoking habits.[10-12] The secretion of neurotransmitters, such as noradrenaline, serotonin, dopamine, acetylcholine, gamma-amino-butyric acid, and glutamate, is increased by the binding of nicotine to central nicotine receptors.[2] DRD2 TaqIA,[13] 5-HTTLPR,[14] DRD4, MAO-A, MAO-B, SLC6A3, and COMTL[15] have been reported as smoking-related gene polymorphisms related to these neurotransmitters. DRD2 has also been identified as a candidate gene for the pathogenesis of schizophrenia.

DRD2 gene TaqIA polymorphism has been studied most intensively among the many polymorphism loci of DRD2. In Japan, Hamajima et al. revealed that the A2 allele of DRD2 TaqIA polymorphism is associated with smoking habits, contradicting the results of similar studies for Caucasians.[16] However, there are as yet no reports that have investigated the association between DRD2 TaqIA polymorphism and the smoking habits of Japanese schizophrenic patients. Therefore, we aimed to investigate whether DRD2 TaqIA polymorphisms, which are related to both nicotine dependence and schizophrenia, influence the smoking habits of Japanese males with schizophrenia.

In this study, we examined the association between DRD2 TaqIA polymorphism and smoking habits.

Methods

Study subjects

We obtained informed consent from 105 male inpatients or outpatients with schizophrenia who were treated at Koutokukai Sato Hospital between November 2001 and April 2002. Schizophrenia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The age of the participants ranged from 20 to 70 years (mean ± SD = 44.8 ± 12.3).

A peripheral blood sample and the recorded questionnaire related to smoking habits were obtained from each patient. On the questionnaire, participants were asked about their age at initiation of smoking, the number of cigarettes consumed per day, Tobacco Dependence Screener (TDS) and the Fagerström Tolerance Questionnaire (FTQ).[17, 18] In addition, participants who have quit smoking were also asked about the longest duration of smoking cessation.

This study was approved by the Ethics Committee of Koutokukai Sato Hospital.

Genotyping

DNA was extracted using a QIAamp® DNA Blood Mini Kit (QIAGEN, Valencia, CA). DRD2 TaqIA polymorphisms were determined using the PCR-CTPP method. PCR-CTPP reactions were performed using constructed primers (Forward 1：5'-TGA GCC ACC ACG GCT GG, Reverse 1：5'-CAT CCT CAA AGT GCT GGT CG, Forward 2：5'-AGC TGG GCG CCT GCC TT, Reverse 2：5'-CTC TTG GAG CTG TGA ACT GG) for TaqI A. The underlines indicate the exchanged bases of each single nucleotide polymorphism. For each reaction, genomic DNA (30 to 100 ng) was mixed with 0.18 mM dNTPs, 25 pmol of each primer, 2.5 μl of 10* PCR buffer including 15 mM $MgCl_2$, 0.5 units of AmpliTaq Gold® (Perkin-Elmer Corp., Foster City, CA), and H_2O up to a total volume 25 μl. The PCR conditions were 95 ºC for 10 min, followed by 30 cycles of 95 ºC for 1 min, 56 ºC for 1 min, 72 ºC for 1 min, and a final extension of 5 min at 72 ºC. The resulting PCR products were separated by electrophoresis on a 2% ethidium bromide-stained agarose gel and were visualized under UV light. Genotyping of TaqIA was 292 bp for the A1 (T) allele and 207 bp for the A2 (C) allele, with a 493 bp common band.

DRD2 TaqIA genotyping was carried out at Aichi Cancer Center Research Institute.

Statistical analysis

All statistical analyses were performed using STATA version 8 (STATA Corp. Inc., College Station, TX) statistical software. Accordance with the Hardy-Weinberg equilibrium, indicating an absence of discrepancy between genotype and allele frequencies, was checked for all participants using the chi-square test, which was also employed to examine the association between individual polymorphisms and smoking status. Patients who had never smoked were defined as individuals who had smoked 0 to 100 cigarettes in the past, former smokers were defined as individuals who had quit smoking more than one year prior to completing the questionnaire, and current smokers were defined as all others. We defined cases and controls as current smokers and those who had never smoked, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by an unconditional logistic model and were adjusted for age (aORs). Age-adjustment was conducted with age as a continuous variable. Smoking habits, age at initiation of smoking, number of cigarettes consumed per day, TDS and FTQ scores, and the longest duration of smoking cessation were compared between individuals with the A1A1 (TT), A1A2 (TC), and A2A2 (CC) genotypes of DRD2 using the Kruskal-Wallis equality of populations rank test. Five sets of cases and controls were defined as follows：(a) < 20 vs. ≥ 20 years of age at smoking initiation, (b) > 20 vs. ≤ 20 cigarettes per day, (c) ≥ 5 vs < 5 TDS score, (d) ≥ 7 vs < 7 FTQ score, and (e) < 14 vs ≥ 14 days for the longest duration of smoking cessation. ORs for these characteristics of current smokers were estimated using an unconditional logistic model and adjusted for age.

Results

Among the 105 male patients with schizophrenia examined in this study, 81 subjects were identified as current smokers, representing a smoking rate of 77.1%. With respect to the allele frequency of DRD2 TaqIA polymorphism, the distributions of the A2A2, A1A2, and A1A1 genotypes were 34.3, 51.4, and 14.3%, respectively, and was in Hardy-Weinberg equilibrium ($\chi^2 = 0.536$, $p = 0.464$) (Table 1). The frequency of gene polymorphism by smoking status did not show any significant difference (Table 2). Relative to patients with A2A2, patients with A1A2 had an age-adjusted odds ratio (aOR) for being a current smoker of 0.88 (95%CI, 0.28-2.74), and those with A1A1 had an aOR of 0.95 (95%CI, 0.19-4.72), and the differences between groups were insignificant (Table 3). Among the 81 current smokers, cigarette consumption was significantly and negatively associated with the A1A1 genotype ($p = 0.022$), with 16.1 ± 5.6, 22.7 ± 9.3 and 26.8 ± 12.4 cigarettes per day (mean ± SD) consumed by individuals with the A1A1, A1A2 and A2A2 genotypes, respectively (Table 4). The aOR was significantly lower in subjects with the A1A1 genotype (aOR =0.09 ; 95% CI, 0.01-0.86) (Table 5). No significant difference was observed in the other four examined smoking habits between the DRD2 Taq1A polymorphisms. Among the 81 smokers, 58 have quit smoking.

Table 1. Characteristics of study subjects n=105

Variables	n (%)
Age Group	
20-29 years	15 (14.3%)
30-39 years	22 (21.0%)
40-49 years	28 (26.7%)
50-59 years	27 (25.7%)
60-69 years	12 (11.4%)
70-79 years	1 (0.9%)
Age (years)[a]	44.8 ± 12.3
Smoking status [b]	
Never smoker	20 (19.1%)
Former smoker	4 (3.8%)
Current smoker	81 (77.1%)
DRD2 Taq IA	
A2A2	36 (34.3%)
A1A2	54 (51.4%)
A1A1	15 (14.3%)

The numbers represent the number of patients (percentage).

a: Mean ± SD (Standard deviation)

b: Never smokers were defined as those who had smoked 0 to 100 cigarettes in the past, Former smokers as those who quit smoking more than one year before the questionnaire study, and Current smokers as all others

Table 2. DRD2 TaqIA polymorphism by smoking status

DRD2 TaqIA	n	Never	Former	Current
A2A2	36	6 (30.0%)	1 (25.0%)	29 (35.8%)
A1A2	54	11 (55.0%)	3 (75.0%)	40 (49.4%)
A1A1	15	3 (15.0%)	0 (0.0%)	12 (14.8%)
Total	105	20 (100.0%)	4 (100.0%)	81(100.0%)

Never: Never smokers who had smoked 0 to 100 cigarettes in the past

Former: Former smokers who quit smoking more than one year before the questionnaire study

Current: Current smokers who ware all others

Table 3. Age-adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for being a current smoker (versus never smoked)

DRD2 Taq IA	n	aOR	95% CI
A2A2	36	1	Reference
A1A2	54	0.88	0.28-2.74
A1A1	15	0.95	0.19-4.72

Odds ratios and 95% confidence intervals were estimated by an unconditional logistic model and adjusted for age. Age-adjustment was conducted with age as a continuous variable.

Table 4. Characteristics of current smokers according to DRD2 genotype

DRD2 TaqIA	A2A2	A1A2	A1A1	p[a]
n (%)	29 (35.8%)	40 (49.4%)	12(14.8%)	
Age at smoking initiation ± SD (years)	19.7 ± 6.9	19.5 ± 2.8	22.0 ± 6.9	0.458
Cigarettes per day ± SD	26.8 ± 12.4	22.7 ± 9.3	16.1 ±5.6	0.022
TDS score[b] ± SD	6.5 ± 2.9	7.0 ± 2.3	7.2 ± 3.1	0.703
FTQ score[c] ± SD	5.1 ±1.6	6.0 ± 2.4	5.3 ± 2.3	0.355
Duration of smoking cessation ± SD (days)	95.3± 211.6	111.9 ± 222.0	141.6 ± 338.2	0.864

a p for Kruskal-Wallis test

b TDS (Tobacco Dependence Screener)

c FTQ (Fagerström Tolerance Questionnaire)

Table 5. Age-adjusted odds ratios (aOR) and 95% confidence interval (95% CI) among smokers

DRD2 TaqIA	N	Age at initiation of smoking (<20 vs. ≥20 years) aOR (95% CI)	Cigarettes/day (>20 vs. ≤20) aOR (95% CI)	TDS score (≥5 vs <5) aOR (95% CI)	FTQ score (≥7 vs <7) aOR (95% CI)	n	Duration of smoking cessation (<14 vs ≥14 days) aOR (95% CI)
A2A2	29	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	20	1 (Reference)
A1A2	40	0.58 (0.22-1.55)	0.46 (0.17-1.24)	2.48 (0.77-8.03)	2.09 (0.72-6.10)	31	1.28 (0.49-3.35)
A1A1	12	0.54 (0.13-2.2)	0.09 (0.01-0.86)	2.05 (0.36-11.7)	1.61 (0.35-7.34)	7	0.99 (0.23-4.24)

Odds ratios and 95% confidence intervals were estimated by an unconditional logistic model and adjusted for age. Age-adjustment was conducted with age as a continuous variable.

N: total number of smokers

n: number of subjects who have quit smoking.

Discussion

In this study, the distribution frequencies of DRD2 TaqIA gene polymorphisms in 105 Japanese males with schizophrenia were found to be 14.8, 49.4, and 35.8% for the A1A1, A1A2, and A2A2 genotypes, respectively. Our data did not significantly differ from those of Suzuki et al. who reported genotype frequencies of 8.8% for A1A1, 47.1% for A1A2, and 44.1% for A2A2 among Japanese males with schizophrenia.[19] The present results were also consistent with a study by Hamajima et al. who reported frequencies of 14.7% for A1A1, 44.2% for A1A2, and 41.0% for A2A2 among Japanese males.[16]

Our analyses revealed that the frequency of DRD2 TaqIA gene polymorphism by smoking status did not differ significantly. In addition, the aOR for being a current smoker was not significant among the three genotype groups, a finding that is identical to the study by Hamajima et al. in Japanese males without schizophrenia.[16]

Reward pathways of the brain are involved in nicotine dependence[20], and they comprise the nervous system from the ventral tegmental area in the midbrain to the nucleus accumbens in the frontal cortex, with dopamine serving as the neurotransmitter[21]. The presence of one or two A1 alleles is associated with reduced D2 receptor binding in all areas of the striatum.[22-24] Nicotine passes through the acetylcholine receptor at the end of these nerves and promotes the release of dopamine, which enhances pleasantness and a feeling of reward.

In Caucasians, it is considered easier for those with the A1 allele of the DRD2 TaqIA gene to become a smoker, as cigarette smokers,[25] both past and current, demonstrate a significantly higher prevalence of the A1 allele than nonsmokers.[26-28] Hamajima et al. showed that the A2 allele of DRD2 TaqIA is associated with smoking habits in Japanese males.[16,29] We studied DRD2, a candidate gene for susceptibility to schizophrenia and nicotine dependence, with the hope of elucidating the genetic basis of the high prevalence of smokers among schizophrenic patients. However, the allele frequencies of the DRD2 TaqIA polymorphism were not significantly associated with schizophrenia or without schizophrenia in Japanese males.[16,19] Similarly in the present study, the allele frequencies of the DRD2 TaqIA polymorphism were not significantly associated with Japanese male schizophrenics who smoke. The reason for the high prevalence of smokers among the schizophrenic patients is not clear. Despite extensive study on the association between the DRD2 TaqIA polymorphism and smoking or smoking-related behavior, no consensus has been reported,[30] suggesting potential involvement of other factors, such as race, sex, and subpopulation. Further study is needed to elucidate the genetic basis of the high prevalence of smokers among individuals with schizophrenia.

Similarly, several studies have reported an association between the DRD2 TaqIA allele and the propensity to consume alcohol, which is a psychoactive substance like nicotine, particularly among Caucasian participants；however, this association remains the subject of controversy.[31] However, as alcohol consumption is considered to be covariate, we could not obtain sufficient data related to alcohol.

Some studies have suggested that an association exists between DRD2 TaqIA gene polymorphism and cigarette consumption,[30,32,33] although one study did not.[34] In these studies, cigarette consumption was calculated based on the number of cigarettes consumed per day.[35] In the present study, we found that the number of cigarettes consumed per day significantly decreased in individuals with the A1A1 genotype. This is the first study to investigate the association between DRD2 TaqIA polymorphism and smoking habits among Japanese male schizophrenic patients. Although Caucasians with the A1 allele are reportedly prone to smoking,[25-28] no study has demonstrated the association between the DRD2 TaqIA polymorphism and cigarette consumption among schizophrenic Caucasians who smoke. With regard to Japanese males with smoking habits, a previous study has reported an association between the A2 allele and susceptibility to smoking.[16,29] In addition, the present study revealed that the number of cigarettes per day consumed by Japanese male schizophrenics with the A1A1 genotype was significantly fewer than that consumed by Japanese male schizophrenics with the A2A2 genotype. The significance of whether this finding is specific to schizophrenic patients requires a study on the association between the DRD2 Taq1A polymorphism and cigarette consumption among schizophrenic Caucasians who smoke.

Several limitations of our study warrant mention. First, the sample size was small, as it consisted of only 105 patients. Second, all data related to smoking habits were self-reported, and third, we could not evaluate how each person smoked, such as the smoking inhalation depth and nicotine levels in the cigarettes brands. Therefore, our finding that the A1A1 genotype is significantly associated with decreased cigarette consumption should be evaluated within these limitations.

Smoking was often considered to be "neglected problem" in the psychiatric field. However, many beneficial effects are expected to arise from the cessation of smoking, such as the prevention of diseases and smoking-related complications, reduction of the administration of medicine and decreased side effects, and improvements of mental status and quality of life. Therefore, the health benefits of smoking cessation are substantial, particularly in psychiatric patients, such as those suffering from schizophrenia. Although it is difficult for schizophrenic patients to quit smoking, pharmacogenetics research may improve treatment outcomes by identifying genetic polymorphisms predictive of therapeutic responses. Further studies considering the above limitations are needed to confirm these preliminary results.

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日本人男性統合失調症患者におけるDRD2遺伝子多型と喫煙習慣

川合　厚子[1]，西野　　敏[2]，栗田　征武[2]，御供　正明[2]，沼田由紀夫[2]，佐藤　忠宏[2]，西松　能子[3]，中村　正和[4]，浜島　信之[5]，中村　好一[6]

[1]社会医療法人公徳会トータルヘルスクリニック，〒999-2221 山形県南陽市椚塚1180-5
[2]社会医療法人公徳会佐藤病院
[3]立正大学心理学部
[4]大阪がん循環器病予防センター
[5]名古屋大学医学部
[6]自治医科大学公衆衛生学

要　約

2001年から2002年に公徳会佐藤病院で入院あるいは外来治療中の男性統合失調症患者で本研究の同意を得た105人（平均年齢±標準偏差，44.8±12.3歳）を対象に，ドーパミン D2受容体（DRD2）TaqIA 遺伝子多型と喫煙習慣との関連を検討した。81人の現喫煙者において，DRD2 TaqIA の遺伝子多型 A1A1 型は A2A2型に比べ 1 日喫煙本数が有意に少なかった（p＝0.022；平均±標準偏差は A1A1型で16.1±5.6，A1A2型で22.7±9.3，A2A2型で26.8±12.4）。A2A2型に対する A1A1型の年齢調整オッズ比は0.09（95% 信頼区間，0.01-0.86）であった。DRD2 TaqIA 遺伝子多型と喫煙開始年齢，ニコチン依存度テスト（TDS・FTQ），最長禁煙期間の間では有意な関係は認められなかった。ただし，本研究は対象数が少なく，さらなる調査が必要である。

（キーワード：統合失調症，喫煙，ニコチン依存症，DRD2遺伝子多型）

連絡先：川合厚子，社会医療法人公徳会トータルヘルスクリニック，〒999-2221 山形県南陽市椚塚1180-5，E-mail：kawaia@ms3.omn.ne.jp
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