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Dopamine D2 receptor Taq IA polymorphism is associated with postoperative nausea and vomiting

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Abstract
Purpose. The dopamine D2 receptor (*DRD2*) is considered to be involved in the development of postoperative nausea and vomiting (PONV). Our aim was to examine the relationship between *DRD2* Taq IA polymorphism and the occurrence of PONV.
Methods. We enrolled 1070 patients who were scheduled to undergo elective surgery under general anesthesia. Patients who vomited or required rescue antiemetics for severe nausea at two time points (within 6 and within 24 h after surgery) were defined as having early and total PONV, respectively. A polymerase chain reaction with confronting two-pair primers (PCR-CTPP) technique was adopted for *DRD2* genotyping allele (A1A1, A1A2, or A2A2). The relationship between *DRD2* Taq IA polymorphism and the occurrence of PONV was examined by multivariate logistic regression analysis.
Results. The incidences of early PONV were 9.0%, 9.3%, and 14.4% in patients with the A1A1, A1A2, and A2A2 alleles, respectively. Sex, nature of the disease, smoking status, type of surgical department, duration of anesthesia, and the *DRD2* Taq IA polymorphism were related to the emergence of early PONV. On multivariate analysis, the relative risk associated with the A2A2 allele in comparison with the A1A1 or A1A2 allele was 1.58 (95% confidence interval [CI], 1.05–2.37) for early PONV. The incidences of total PONV were 12.5%, 13.6%, and 17.2% in patients with the A1A1, A1A2, and A2A2 alleles, respectively. Sex, smoking status, type of surgical department, and duration of anesthesia were related to the emergence of total PONV. On multivariate analysis, the relative risk associated with the A2A2 allele in comparison with the A1A1 or A1A2 allele was 1.27 (95% CI, 0.88–1.84) for total PONV.
Conclusion. The *DRD2* Taq IA polymorphism affected the occurrence of early PONV. Analysis of patients' genetic backgrounds may improve risk-stratification for PONV.

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Key words PONV · Dopamine D2 receptor (*DRD2*) · Taq IA polymorphism

Introduction

Postoperative nausea and vomiting (PONV) is an unpleasant complication after general anesthesia, and the etiology of PONV is complicated and multifactorial. Many kinds of strategies, such as modification of anesthetics, the use of preventive and rescue drugs, and risk stratification of patients, are used for PONV control. However, the problem of PONV has not yet been solved.

The Human Genome Project heralds new opportunities for using genetic information to individualize drug therapy, called pharmacogenomics [1]. Some reactions to physiological stress and drugs are related to genomic differences [2,3]. PONV is an adverse reaction to surgical stimulation and anesthesia-related drugs, therefore, the genetic background of individuals may be associated with the emergence of PONV.

Many neurotransmitters, such as the dopamine type 2 receptor (*DRD2*), muscarinic cholinergic type 1 receptor, serotonin type 3 receptor, and opioid receptor, are involved in the emergence of PONV. The dopamine antagonists droperidol and metoclopramide are often used for the treatment and prevention of PONV [4,5]. This suggests that the *DRD2* may play some role in the development of PONV. In addition, *DRD2* Taq IA polymorphism could affect human habits that are related to dopaminergic neurotransmission, such as nicotine dependence and drug abuse [6,7]. The aim of this study was to examine the relationship between the *DRD2* Taq IA polymorphism and the occurrence of PONV, and to clarify the effect of the *DRD2* Taq IA polymorphism on PONV.

Patients and methods

The study subjects were consecutive patients at one cancer center who underwent elective surgery under general anesthesia, with or without epidural anesthesia, between January and October 2002. During this period, 1966 patients were scheduled for surgery, and 1271 patients (64.6%) entered this study after providing written consent. After excluding 201 patients in whom we were not able to evaluate the occurrence of PONV or who received regional anesthesia, the number of eligible patients was 1070. This study was approved by the Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

Anesthesia was induced with propofol and fentanyl, and endotracheal intubation was facilitated by the administration of vecuronium. In patients for whom epidural anesthesia was suitable, an epidural catheter was inserted at a suitable site for surgery before anesthesia induction. Anesthesia was maintained by the continuous infusion of propofol with or without a low dose of sevoflurane, and intermittent fentanyl, given by IV administration, or the epidural administration of local anesthetics (1% mepivacaine or 0.375%–0.75% ropivacaine).

In patients who received epidural anesthesia, continuous epidural infusion of 0.5% lidocaine and morphine (daily morphine dose, 3–5 mg) was given for postoperative pain management. In patients who did not receive epidural anesthesia, rectal administration of diclofenac was used for postoperative pain relief.

At two time points of postoperative visits, within 6 h and within 24 h after the end of surgery, the attending anesthesiologists asked the patients whether or not they suffered from a feeling of nausea or vomiting, and also reviewed the medical records written by the attending surgeons or nurses. Patients who vomited or required rescue antiemetics for severe nausea before each of the two visiting points of within 6 and within 24 h after the end of surgery were defined as having early and total PONV, respectively.

A 7-ml blood sample was obtained during anesthesia for genotyping. The buffy coat was separated by centrifugation at 3000 rpm at room temperature for 10 min and stored at –80°C until DNA extraction. DNA was extracted from 200 µl of buffy coat by a QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA, USA). A polymerase chain reaction with confronting two-pair primers (PCR-CTPP) technique [8,9] was adopted for DNA genotyping. The following primers were used for the determination of the *DRD2* Taq IA polymorphism (RS#1800497): F1, 5′ TGA GCC ACC ACG GCT GG; R1, 5′ CAT CCT CAA AGT GCT GGT CG; F2, 5′ AGC TGG GCG CCT GCC TT; and R2, 5′ CTC TTG GAG CTG TGA ACT GG. The nucleotides underlined here are the sites of single-nucleotide polymorphism.

The PCR reaction mixture in a volume of 25 µl contained genomic DNA (30 ng to 100 ng), 0.1 mM dNTPs, 12.5 pmol of each primer, 0.5 units of AmpliTaq Gold (Perkin-Elmer, Foster City, CA, USA), and 2.5 µl aliquot of 10*PCR Buffer including 15 mM $MgCl_2$. A 2.5 µl aliquot of glycerol was added for the genotyping of the Taq IA polymorphism. The PCR conditions were as follows: initial denaturation at 95°C for 10 min, followed by 30 cycles of 95°C for 1 min, 56°C for 1 min, and 72°C for 1 min, and a final extension at 72°C for 5 min.

All PCR products were visualized on a 2% agarose gel with ethidium bromide staining. Genotyping of Taq IA results in a 292-bp band for the A1 (T) allele and a 207-bp band for the A2 (C) allele with a common 493-bp band. The distribution of genetic polymorphisms was examined for fitness for Hardy-Weinberg equilibrium.

The occurrence of PONV in relation to background characteristics was examined using the χ^2 test. For applying the χ^2 test, age and duration of anesthesia were divided into quartile groups.

It has been reported that sex, age, smoking status, technique and duration of anesthesia, and type of surgery were related to the development of PONV [10]. In addition, the nature of the disease was adjusted as a possible confounding factor in the analysis for controlling the effect of preoperative anticancer therapy. Therefore, in the present study, information on these factors was obtained from the patients' medical charts, and the data were adjusted in the logistic regression analysis to calculate the odds ratio of PONV occurrence according to the *DRD2* Taq IA polymorphism.

At a genotypic locus, the number of subjects homozygous for the variant alleles was small. Therefore, we examined only a dominant model for the *DRD2* polymorphism in logistic regression analysis, as has been performed in a previous study [11].

In these analyses, $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 13.0J; SPSS, Tokyo, Japan).

Results

Our study subjects were all Japanese, and their background characteristics are summarized in Table 1. The genotype distribution of the *DRD2* Taq IA polymorphism was in Hardy-Weinberg equilibrium for both sexes ($P = 0.41$ for males; $P = 0.44$ for females).

Early PONV was observed in 121 persons (11.3%), and total PONV was observed in 159 persons (14.9%).

Table 1. Background characteristics of the study subjects ($n = 1070$)

Sex	
Male	511 (47.8%)
Female	559 (52.2%)
Age (years)	
Mean ± SD	57.5 ± 12.7
Nature of disease	
Nonmalignant diseases	184 (17.2%)
Malignant disease	884 (82.8%)
Smoking status	
Never smoker	492 (46.8%)
Ex-smoker	464 (43.4%)
Smoker	95 (8.9%)
Type of surgical department	
Gastrointestinal surgery	303 (28.3%)
Breast surgery	162 (15.1%)
Gynecologic surgery	136 (12.7%)
Otorhinolaryngologic surgery	126 (11.8%)
Thoracic surgery	123 (11.5%)
Urologic surgery	79 (7.4%)
Orthopedic surgery	68 (6.4%)
Neurosurgery	40 (3.7%)
Cardiovascular surgery	19 (1.8%)
Hematology	14 (1.3%)
Technique of anesthesia	
General without epidural anesthesia	523 (48.9%)
General with epidural anesthesia	547 (51.1%)
Duration of anesthesia (min; mean ± SD)	274.8 ± 166.7
Duration of surgery (min; mean ± SD)	204.9 ± 155.9
DRD2 TaqI A polymorphism	
Males	
A1A1	64 (12.5%)
A1A2	246 (48.2%)
A2A2	200 (39.2%)
Females	
A1A1	80 (14.3%)
A1A2	248 (44.4%)
A2A2	231 (41.3%)

The genotype could not be determined in one patient

The effects of subjects' background characteristics on the emergence of PONV are summarized in Table 2.

The emergence of early PONV was influenced by sex, nature of the disease, smoking status, type of surgical department, duration of anesthesia, and the *DRD2* Taq IA polymorphism. The emergence of total PONV was influenced by sex, smoking status, type of surgical department, and duration of anesthesia.

Univariate logistic regression analysis revealed that the factors: female, never-smoker, ex-smoker, neurosurgery and the A2A2 allele of the *DRD2* Taq IA polymorphism had positive relationships with the development of early PONV, while the duration of anesthesia and malignant nature of disease had a negative relationship with the development of early PONV. On multivariate analysis, the factors: female, never-smoker, ex-smoker, epidural anesthesia, department of neurosurgery, and the A2A2 allele of the *DRD2* Taq IA polymorphism were significant risk factors for the development of early PONV (Table 3). The development of total PONV had positive relationships with the factors: female, never-smoker, ex-smoker, and neurosurgery, while the duration of anesthesia had a negative relationship with the development of total PONV. On multivariate analysis, female, never-smoker, ex-smoker, and department of neurosurgery remained as significant risk factors for the development of total PONV (Table 3).

Discussion

This study aimed to examine the genetic background of the occurrence of PONV, and clarified that individuals who have the A2A2 allele of the *DRD2* Taq IA polymorphism, have a higher incidence of early PONV than those who have the A1A1 or A1A2 allele.

Taq IA is located 10 kb into the 3′ untranslated region of the *DRD2* gene; thus, it is unclear how this polymorphism affects the expression of the gene. This polymorphism may reflect linkage disequilibrium with some unidentified mutations that alter *DRD2* density [12]. It has been reported previously reported that the *DRD2* Taq IA polymorphism was related to *DRD2* density in the striatum [13] and caudate nuclei [14], and that individuals with the A2A2 alleles showed high *DRD2* density.

DRD2 receptors are located in the stomach, nuclei tractus solitarii, and the chemotrigger zone, and are involved in one of the mechanisms of the development of PONV. Although there has been no report on the relationship between the *DRD2* Taq IA polymorphism and *DRD2* density in the stomach, nuclei tractus solitarii, and chemotrigger zone, it is possible that individuals with the A2A2 alleles also have a high *DRD2* density in those areas. Thus, we believed that patients with A2A2 alleles would be sensitive to dopaminergic stimulation, and they showed a high rate of occurrence of early PONV in the present study.

Early PONV was divided from total PONV in our study, because we considered that early PONV would be strongly affected by intraoperative anesthesia-related drugs. Logistic regression analysis revealed that the impact of the *DRD2* Taq IA polymorphism was stronger on the development of early PONV than total PONV. That is, early PONV may develop by the dopaminergic stimulation that is evoked by intraoperative surgical stimulation and anesthesia-related drugs.

Univariate analyses revealed that the duration of anesthesia had a weak negative relationship with both early and total PONV. It is well known that an increase in the duration of anesthesia increases the risk of PONV

Table 2. PONV occurrence according to background characteristics of study subjects (n = 1070)

	Early PONV	*P* value	Total PONV	*P* value
Total number of patients	121 (11.3%)		159 (14.9%)	
Sex				
Male	22 (4.3%)	0.000	23 (4.5%)	0.000
Female	99 (17.7%)		136 (24.3%)	
Age (years; mean ± SD)				
1st quartile age subjects (40.1 ± 7.8)	34 (12.8%)	0.499	46 (17.4%)	0.606
2nd quartile age subjects (54.7 ± 2.2)	24 (9.3%)		37 (14.3%)	
3rd quartile age subjects (62.6 ± 5.5)	28 (10.4%)		36 (13.4%)	
4th quartile age subjects (72.0 ± 4.2)	35 (12.6%)		40 (14.4%)	
Nature of disease				
Nonmalignant disease	29 (15.8%)	0.033	33 (17.9%)	0.187
Malignant disease	91 (10.3%)		125 (14.1%)	
Smoking status				
Never smoker	57 (11.6%)	0.027	81 (16.5%)	0.008
Ex-smoker	59 (12.7%)		72 (15.5%)	
Smoker	3 (3.2%)		4 (4.2%)	
Type of surgical department				
Gastrointestinal surgery	18 (6.0%)	0.000	22 (7.3%)	0.000
Breast surgery	22 (13.6%)		37 (22.8%)	
Gynecologic surgery	29 (21.3%)		35 (25.7%)	
Otorhinolaryngologic surgery	6 (4.8%)		12 (9.5%)	
Thoracic surgery	16 (13.0%)		18 (14.6%)	
Urologic surgery	9 (11.4%)		10 (12.7%)	
Orthopedic surgery	2 (2.9%)		4 (5.9%)	
Neurosurgery	16 (40.0%)		17 (42.5%)	
Cardiovascular surgery	2 (1.7%)		2 (10.5%)	
Hematology	1 (7.1%)		2 (14.3%)	
Technique of anesthesia				
General without epidural anesthesia	61 (11.6%)	0.795	86 (16.3%)	0.190
General with epidural anesthesia	60 (11.1%)		73 (13.5%)	
Duration of anesthesia (min; mean ± SD)				
1st quartile (120.4 ± 37.3)	22 (8.5%)	0.015	37 (14.3%)	0.036
2nd quartile (196.9 ± 17.4)	44 (15.7%)		55 (19.6%)	
3rd quartile (269.3 ± 26.9)	33 (12.7%)		38 (14.6%)	
4th quartile (510.0 ± 153.1)	22 (8.2%)		29 (10.8%)	
DRD2 Taq IA polymorphism				
A1A1	13 (9.0%)	0.034	18 (12.5%)	0.212
A1A2	46 (9.3%)		67 (13.6%)	
A2A2	62 (14.4%)		74 (17.2%)	

The genotype could not be determined in one patient

in procedures that last for less than 180 min [15,16]. However, compared to the duration of anesthesia in previous reports, the mean duration of anesthesia in the present study was longer than 180 min. Also, it has been shown that the frequency of PONV might decrease in procedures that last for more than 180 min [15]. Thus, it was felt that we needed to examine the relationship between the duration of the procedure and the frequency of PONV in procedures that lasted for more than 180 min.

There were a some limitations in the present study, given that the incidence of PONV according to the *DRD2* Taq IA polymorphism could be influenced by confounding factors, such as patient-specific, anesthetic, and surgical risk factors [10]. In this study, we collected information on patient age, sex, and smoking status; the technique and duration of anesthesia; the type of surgical department, and nature of the disease. Our findings were in agreement with previous reports that these factors influence the emergence of PONV [10], and they were adjusted in the multivariate analysis.

Other factors, i.e., preoperative anticancer therapy, may also be confounding factors. However, in our hospital, if nausea and vomiting occur due to anticancer therapy, the patient's surgical operation is postponed until they are free of these symptoms. Taking this into account, we thought that the effect of anticancer therapy would have been small. Also, as the preoperative therapy was determined by the nature of the disease, we included the nature of the disease in the multivariate analysis for controlling the effect of preoperative therapy on the emergence of PONV.

Table 3. Factors associated with the occurrence of early and total PONV

Variable	Reference	Value	Odds ratio					
			Univariate	95% CI	*P* value	Multivariate	95% CI	*P* value
Early PONV								
Sex	Male	Female	4.77	2.96–7.71	0.000	5.28	3.15–8.85	0.000
Age	For every additional 5 years		1.00	0.93–1.08	0.983	1.07	0.98–1.16	0.135
Nature of disease	Nonmalignant	Malignant	0.61	0.39–0.97	0.034	0.81	0.46–1.43	0.469
Smoking status	Smoker	Never-smoker	4.02	1.23–13.11	0.021	4.29	1.25–14.75	0.021
		Ex-smoker	4.47	1.37–14.57	0.013	5.24	1.53–17.99	0.008
Type of surgical department	Non-neurosurgery	Neurosurgery	5.87	3.02–11.40	0.000	7.73	3.21–18.60	0.000
Technique of anesthesia	Without epidural anesthesia	With epidural anesthesia	0.95	0.65–1.39	0.795	1.95	1.22–3.11	0.005
Duration of Anesthesia	For every additional 10 min		0.99	0.97–1.00	0.041	0.99	0.97–1.01	0.207
DRD2 Taq IA	A1A1 or A1A2	A2A2	1.65	1.13–2.41	0.010	1.58	1.05–2.37	0.028
Total PONV								
Sex	Male	Female	6.81	4.30–10.79	0.000	7.26	4.44–11.88	0.000
Age	For every additional 5 years		0.97	0.91–1.04	0.357	1.04	0.97–1.12	0.290
Nature of disease	Nonmalignant	Malignant	0.75	0.49–1.15	0.188	1.06	0.63–1.79	0.829
Smoking status	Smoker	Neve-smoker	4.48	1.60–12.55	0.004	4.57	1.55–13.48	0.006
		Ex-smoker	4.18	1.49–11.73	0.007	4.61	1.56–13.62	0.006
Type of surgical department	Non-neurosurgery	Neurosurgery	4.62	2.41–8.86	0.000	6.41	2.73–15.08	0.000
Technique of anesthesia	Without epidural anesthesia	With epidural anesthesia	0.80	0.57–1.19	0.191	1.50	0.99–2.27	0.053
Duration of anesthesia	For every additional 10 min		0.99	0.97–1.00	0.010	0.99	0.98–1.01	0.339
DRD2 Taq IA	A1A1 or A1A2	A2A2	1.35	0.96–1.90	0.084	1.27	0.88–1.84	0.196

We selected continuous infusion of propofol for general anesthetsia, because this technique was standard for us in the period of the present study. It was reported that propofol infusion could reduce the relative risk of the incidence of PONV by 20% [17]; thus, the use of propofol may have obscured the findings in our present study. However, we assumed that, in the patients with PONV, even if propofol had been used, their reactions were strongly affected by other systems, such as the dopaminergic system.

As stated above, the genetic background of the patient may influence the development of PONV, and we were able to show the possibility that patients at high risk of PONV could be classified according to genetic analysis. Recently, relationships between polymorphisms of other genes, such as the opioid receptor [18,19] and cytochrome P450 [20], and the emergence or treatment of PONV have been reported. This genetic information could improve the management of PONV.

Genetic backgrounds vary according to ethnicity. For example, the prevalence of the A2A2 allele was reported to be about 40% in Chinese, in contrast to about 60% in Germans [21], and it was reported to be about 40% in Japanese [22]. In the present study, we examined only Japanese; thus, further studies are needed to examine whether or not the results of this study could apply to other ethnic groups.

Recently, a number of pharmacogenetic studies not only about PONV but also about other adverse effects of drugs have been carried out. For example, such studies of analgesics [19,23] and cardiovascular drugs [24] were reported. Such pharmacogenetic studies are of increasing importance as they may help practicing anesthesiologists to anticipate individual patient responses to drugs and the potential for the development of side effects.

The A2A2 allele of the *DRD2* Taq IA polymorphism increased the occurrence of early PONV. Analysis of patients' genetic backgrounds may improve risk-stratification for PONV.

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