The female-specific effect of 5-hydroxytryptamine receptor 3A gene on postoperative vomiting in Taiwan

Yi-Mei Joy Lin a,*, Cheng-Da Hsu b, Hsiao-Yen Hsieh b, Chia-Chih Alex Tseng c,**

a Institute of Biomedical Sciences, National Chung Hsing University, Taichung, Taiwan
b Department of Medical Research, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan
c Department of Anesthesiology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan

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Abstract Postoperative vomiting (POV) is a common complication after general anesthesia. Clarifying the genetic factors that affect POV are important for evaluating a patient’s susceptibility to the condition. Although evidence suggests that the 5-hydroxytryptamine (serotonin) receptor 3A (HTR3A) gene may be important in the occurrence of POV, associations for HTR3A polymorphisms with POV have not been investigated in a Taiwanese population. Three single nucleotide polymorphisms (SNPs) of the HTR3A gene were used to study the genetic association with POV in 369 postoperative Taiwanese adults who underwent general anesthesia. Although no significant differences were found at the single-locus level for HTR3A polymorphisms, a significant haplotype-based association was found between HTR3A and POV. In addition, because female sex is associated with a higher risk of PONV (postoperative nausea and vomiting), we separately analyzed the haplotypic associations for both sexes to test whether HTR3A genetic factors interact with female sex and specifically contribute to the etiology of POV. We found that a significant haplotype effect was identified only for females. The CTT haplotype, the most common, showed a significant protective effect (odds ratio: 0.68), and the CTG haplotype was associated with a significantly higher risk (odds ratio: 2.08) for POV in females.

** Corresponding author. Department of Anesthesiology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan.
E-mail addresses: ymjlin@nchu.edu.tw (Y.-M.J. Lin), cctmay888@yahoo.com.tw (C.-C.A. Tseng)

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Introduction

Postoperative vomiting (POV) is a common but important complication after anesthesia. POV is accompanied by postoperative nausea (PON) and summarized as PONV (postoperative nausea and vomiting). Without prophylactic medication, PONV in the postoperative period is approximately 20−30%, but may even rise to 80% in high-risk patients. A family history has been proposed as an important risk factor for PONV, and genetic factors have been suggested as important modulators of the occurrence and phenotypic variability of PONV. Thus, identifying specific genetic variations associated with increased susceptibility or just identifying specific subtypes of PONV should contribute a great deal to its prevention. Physiologically, PON and POV are two related but distinct phenomena. They have different incidences: PON usually has a higher incidence than POV. Because we hypothesized that the risk factors involved were different and that they should be separately analyzed, the present study specifically focused on identifying the genetic component of POV.

Serotonin type 3 (5-hydroxytryptamine type 3; 5-HT3) receptors are pentameric ligand-gated ion channels of the Cys-loop receptor superfamily. The activation of 5-HT3 receptors mediates fast excitatory responses of neurotransmission in the central nervous system (CNS) and peripheral nervous system (PNS). 5-HT3 receptors are expressed in different regions and modulate many diverse physiological functions, including the initiation of the vomiting reflex. The function of 5-HT3 receptors in diseases and drug development has been intensively studied. For example, 5-HT3 receptors are involved in the mediation of several different diseases such as schizophrenia, irritable bowel syndrome, nausea, and vomiting. This may help to give direction to personalized medicine that could tailor therapies to more individual healthcare.

Current research suggests that 5-HT3 receptors are important in the etiology of POV. A theory related to the vomiting mechanism has proposed that the activation of 5-HT3 receptors in the chemoreceptor trigger zone (CTZ) of the brain can provoke emesis, or on gastrointestinal vagal afferents, which send signals directly to the vomiting center in the medulla oblongata. Moreover, recent research says that antagonists which target 5-HT3 receptors can be used to prevent and suppress POV by inhibiting serotonin from binding to 5-HT3 receptors. Therefore, we hypothesized that genetic variations in HTR3 genes modulate susceptibility to POV. Among the five different subunit genes of HTR3 (HTR3A–E), HTR3A is essential in the functional HTR3 channel. HTR3A is also the only single component that can form functional homopentameric channels, and all other subunit subtypes must heteromerize with HTR3A subunits.

Although the HTR3A gene has attracted interest for its effects on POV because of its important role in the physiology of vomiting and clinical successes using HTR3 antagonists, there has been no thorough assessment of POV in Taiwanese patients who carry the HTR3A polymorphisms. In this study, we evaluate the risk of HTR3A polymorphisms of POV after general anesthesia in a Taiwanese population. In addition, a growing body of research has reported that female patients are particularly susceptible to PONV after general anesthesia. Our study also separately assesses for males and females the genetic risk of HTR3A gene polymorphisms on POV.

Materials and methods

Study participants and DNA preparation

Adult patients (>20 years old) scheduled to undergo general anesthesia were recruited to join the prospective perioperative outcome cohort. The Ethics Committee of the Ditmanson Medical Foundation Chia-Yi Christian Hospital granted approval for this study. Signed and written informed consent was obtained from all participants. Patients with nine different types of surgeries were recruited: lower abdominal (Operation 1), upper abdominal (Operation 2), thoracic (Operation 3), cardiac (Operation 4), spinal (Operation 5), laparoscopic intra-abdominal (Operation 6), thyroid (Operation 7), breast (Operation 8), and oral (Operation 9).

Patient demographic data—sex, age, body weight, height, calculated BMI, smoking status, alcohol drinking status, and other validated PONV risks—were collected during preoperative visits to the ward. Regular monitoring [noninvasive arterial pressure measurement, electrocardiography with heart rate, and arterial oxygen saturation (pulse oximetry)] began before the induction of anesthesia. After preoxygenation, anesthesia was administered using standard tracheal intubation. All patients underwent volume-controlled ventilation with a tidal volume of 7−10 mL/kg and a respiratory rate of 10−12 breaths/minute without nitrous oxide. The anesthetic used and details about the patient’s course were intraoperatively documented. Recording of specific anesthetic drugs focused on which volatile was used, and the types and doses of opioids that were used irrespective of the specific compound.

Three hundred sixty-nine patients who had undergone general anesthesia and who met inclusion criteria were considered for the current study. Patients undergoing emergency surgery, those who could not communicate well, and those who refused to participate in our study were excluded. To remove the possible influence on PONV outcomes, patients who took prophylactic drugs, such as...
steroids or droperidol, patients who did not take any postoperative opioids and patients who took antiemetics were excluded. Genomic DNA was prepared from peripheral blood using DNA extraction kits (QuickGene DNA Whole Blood Kit; Fujifilm Life Science, Stamford, CT, USA).

POV scoring method

The main outcome of interest was any incidence of POV during a 24-hour postoperative observation period. A research assistant interviewed the patients in the post-anesthesia recovery (PAR) room and 24 hours after they had returned to the ward about their instances of POV. All recorded answers were dichotomized into "yes" or "no", and were labeled as the POV incidence in 24 hours. The severity of the vomiting was not considered.

Marker selection and genotyping procedures

Selected SNPs of the HTR3A gene were genotyped and analyzed for a genetic association with the POV phenotype. To test whether the HTR3A genotype has different effects on the incidence of POV, the participants were assigned to the POV group (POV at least once within the first 24 postoperative hours) or controls (no POV within the first 24 postoperative hours). Three SNPs within the human HTR3A gene region—rs33940208, rs1985242, and rs10160548—were selected from the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), depending on their genomic distribution, allele frequencies in our population and their relative functional significance. SNPs with minor allele frequency (MAF) < 0.05 were excluded. A high-throughput assay (predesigned TaqMan SNP Assays; Applied Biosystems, Foster City, CA, USA) was used to genotype all participants with a sequence detecting system (ABI PRISM 7500; Applied Biosystems).

Statistical analysis

A χ² test (SNPAlyze 4.1; Dynacom, Kanagawa, Japan) was used to analyze both the Hardy-Weinberg equilibrium of each marker and the differences in genotypic and allelic distributions between patients with POV and controls. Standardized pairwise disequilibrium coefficients (D') for measuring linkage disequilibrium between the three SNPs, the construction of haplotypes, and haplotype-based association were also estimated using SNPAlyze. The Graphical Overview of Linkage Disequilibrium (GOLD) program (http://www.sph.umich.edu/csg/abecasis/GOLD/) was used to plot the linkage disequilibrium distribution.

Results

From 2009 to 2011, 1500 eligible patients were invited to participate in this study. They were all adults scheduled to undergo general anesthesia for different types of surgery. In all, 960 surgical patients with completed case report forms of PONV were recruited. In addition to 223 patients transferred directly to the Intensive Care Unit (ICU), there were 737 with PONV data from the PAR. Patients who did not meet our inclusion criteria were excluded. Patients undergoing bariatric surgery, 100% of whom had PONV, were also excluded from the final dataset. Finally, 369 patients participated in this study. The collected demographic data and some reported risk factors of PON were used to evaluate the risk effect on POV occurrence and are shown in Table 1. These reported PONV risk factors also showed a significant association with POV occurrence during 24 postoperative hours in our examined population.

Polymorphism genotyping and single-locus association analysis

Three selected SNPs from all our participants were genotyped. The genotyping coverage was about 94%; the missing rates ranged from 0% to 14%. The genotype distributions of all studied SNPs in both groups were in HWE (p = 0.12–0.99). General population-based allele frequencies were similar to the data from the dbSNP.

The associations of each polymorphism of the HTR3A gene and patients with POV were analyzed to compare allelic and genotypic frequencies between the two groups using the Pearson χ² test. There were no significant differences in single alleles or genotype distributions (Table 2).

Linkage disequilibrium mapping and risk haplotype analysis

Pairwise linkage disequilibrium (LD) analyses were done between the three SNPs across the HTR3A gene in all patients. Pairwise LD coefficients (D' values) were estimated to represent the LD (Fig. 1). The LD patterns are distinctly different between the two study populations. In patients without POV, strong LD was detected between adjacent SNP pairs (D' from 0.70 to 0.98), and the D' slightly dropped as the distance between the pairs increased (D' = 0.56 between rs33940208 and rs10160548). In contrast, strong LD
in patients with POV was present only in the shorter region between rs33940208 and rs1985242 (D\textsuperscript0 \textsuperscriptZ \textsuperscript1), and dropped faster for long-distance SNP-pairs (D\textsuperscript0 from 0.03 to 0.52). The distinct LD patterns suggested a possible disease-related effect; therefore, we investigated the genetic associations in haplotype-based analysis.

In our current analysis, there were five common haplotypes with a frequency >5% in all participants. Haplotype-based genetic association tests were done using the estimated haplotype frequencies. Although there was no single locus association between any HTR3A polymorphisms in patients with POV, there was a significantly different distribution of several haplotypes between groups (Table 3). In addition, significant differences were detected even after a rigid 1000 consecutive permutation tests. Haplotype TAG carries a significant protective effect (permutation p = 0.018; OR: 0.56; 95% CI: 0.34—0.93). Both haplotypes CTG and TAT were associated with significantly risk effects (permutation p = 0.043 and 0.032; OR: 1.72 and 1.78; 95% CI: 1.02—2.90 and 1.03—3.03, respectively). Significant differences were also assessed in overall haplotype frequency profiles (total p = 0.008; global permutation p = 0.005).

**Sex-specific risk haplotype analysis**

The female sex risk for POV was also evaluated. Significant associations between female sex and POV occurrence during 24 postoperative hours were found in our population (Table 1; p for Pearson χ\textsuperscript2: <0.001). To investigate sex-

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**Table 2** Genotypic and allelic distribution of human HTR3A gene polymorphisms.

<table>
<thead>
<tr>
<th>SNP (alternative alleles)</th>
<th>Group (N)</th>
<th>Genotype\textsuperscripta Number (frequency)</th>
<th>Pearson test p</th>
<th>Allele\textsuperscripta Number (frequency)</th>
<th>Pearson test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs33940208 (C/T)</td>
<td>Vomiting (98)</td>
<td>63 (0.64) 29 (0.30) 6 (0.06)</td>
<td>0.79</td>
<td>155 (0.79) 41 (0.21)</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>54/9 24/5 6/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonvomiting (271)</td>
<td>164 (0.61) 90 (0.33) 17 (0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>82/82 46/44 6/11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1985242 (T/A)</td>
<td>Vomiting (96)</td>
<td>36 (0.38) 45 (0.47) 15 (0.16)</td>
<td>0.80</td>
<td>117 (0.61) 75 (0.39)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>30/6 37/8 15/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonvomiting (261)</td>
<td>104 (0.40) 112 (0.43) 45 (0.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>53/51 62/50 17/28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10160548 (T/G)</td>
<td>Vomiting (84)</td>
<td>31 (0.37) 39 (0.46) 14 (0.17)</td>
<td>0.93</td>
<td>101 (0.60) 67 (0.40)</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>25/6 34/5 13/1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonvomiting (234)</td>
<td>88 (0.38) 111 (0.47) 35 (0.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female/male</td>
<td>49/39 51/60 16/19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SNP = single nucleotide polymorphism.
\textsuperscripta Major allele = 1, minor allele = 2.

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**Figure 1** Linkage disequilibrium (LD) plot in the HTR3A gene. Absolute standardized linkage disequilibrium coefficient (D\textsuperscript0) was calculated to represent pairwise linkage disequilibrium of the HTR3A single nucleotide polymorphisms in patients with and without POV. LD was plotted using the Graphical Overview of Linkage Disequilibrium (GOLD) program. Red indicates complete linkage (D\textsuperscript0 \textsuperscriptZ \textsuperscript1), and blue indicates no linkage (D\textsuperscript0 = 0). The three polymorphisms are listed in the 5′→3′- orientation (left to right).
specific differences between individuals carrying particular HTR3A haplotypes and the occurrence of POV occurrence, males and females were separately analyzed for haplotype-based genetic associations. Neither single nor overall haplotype carriers were significantly associated with POV for males, but they were for females (Table 4). The overall comparison of all haplotypes were significantly different between female patients with and without POV (total $p = 0.006$; global permutation $p = 0.009$). In single haplotype analysis, CTG and TAT haplotypes were also significantly different between patients with and without POV ($p = 0.025$ and 0.04, respectively), and showing risk effects (OR: 2.08 and 1.98, respectively), but the significance for the distribution of the TAT haplotype disappeared in a permutation test ($p = 0.055$). In addition, the most common haplotype, CTT, which has a female-specific protective effect, (permutation $p = 0.048$; OR: 0.68; 95% CI: 0.47–0.99) was not detected when both males and females were analyzed together. These data imply the involvement of the HTR3A gene in the development of POV in female surgical patients.

### Discussion

POV is one of the major postoperative concerns for patients. One recent study suggests that using association analysis will provide acceptable power to detect genetic effects on complex phenotypic traits like POV. The present study investigated the effect of the HTR3A gene effect on POV susceptibility in the Taiwanese population. Although female sex is one of the well-recognized risk factors for PONV, rational explanations for the biological mechanism have not been presented. The increased incidence in female patients persists throughout life, even following menopause, which excludes the modulating effect of reproductive hormones. Confounding factors will affect a diversified incidence. To minimize effects from this important confounder, we separately tested the genetic contribution of the HTR3A gene in both sexes.

In the present study, we found that, although the selected HTR3A gene polymorphisms were not significantly associated with POV on single-locus level, LD-mapping and the interaction-considered haplotype-based analysis showed that the HTR3A gene had a significant effect on POV. In agreement with the widely accepted theory that haplotype-based combinations of multiple loci has a dramatic impact on the etiology of diseases, when associations with disease at single locus level are not significant. Most importantly, when we separately analyzed the haplotype associations, the significant haplotype was detected only in groups of females but not in groups of males.

### Table 3

<table>
<thead>
<tr>
<th>Haplotype$^a$</th>
<th>Number (frequency)</th>
<th>$p$</th>
<th>OR (95% CI)</th>
<th>Permutation test$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTT</td>
<td>424 (0.53)</td>
<td>0.193</td>
<td>0.81 (0.59–1.11)</td>
<td>0.197</td>
</tr>
<tr>
<td>CAG</td>
<td>132 (0.17)</td>
<td>0.416</td>
<td>1.19 (0.79–1.79)</td>
<td>0.447</td>
</tr>
<tr>
<td>TAG</td>
<td>116 (0.14)</td>
<td>0.024</td>
<td>0.56 (0.34–0.93)</td>
<td>0.018</td>
</tr>
<tr>
<td>CTG</td>
<td>67 (0.08)</td>
<td>0.040</td>
<td>1.72 (1.02–2.90)</td>
<td>0.043</td>
</tr>
<tr>
<td>TAT</td>
<td>63 (0.08)</td>
<td>0.033</td>
<td>1.78 (1.04–3.03)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

POV = postoperative vomiting.

$^a$ Haplotypes were constructed with HTR3A SNPs: (from left to right) rs33940208, rs1985242, and rs10160548.

$^b$ One thousand permutations were replicated to evaluate the permutation $p$ value.

$^c$ The global $p$ value was calculated using a permutation test ($n = 1000$).

### Table 4

<table>
<thead>
<tr>
<th>Haplotype$^a$</th>
<th>Number (frequency)</th>
<th>$p$</th>
<th>Odds ratio (95% CI)</th>
<th>Permutation test$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTT</td>
<td>254 (0.53)</td>
<td>0.042</td>
<td>0.68 (0.47–0.99)</td>
<td>0.048</td>
</tr>
<tr>
<td>CAG</td>
<td>81 (0.17)</td>
<td>0.227</td>
<td>1.35 (0.83–2.18)</td>
<td>0.251</td>
</tr>
<tr>
<td>TAG</td>
<td>64 (0.13)</td>
<td>0.067</td>
<td>0.58 (0.33–1.04)</td>
<td>0.070</td>
</tr>
<tr>
<td>CTG</td>
<td>40 (0.08)</td>
<td>0.025</td>
<td>2.08 (1.08–3.99)</td>
<td>0.034</td>
</tr>
<tr>
<td>TAT</td>
<td>39 (0.08)</td>
<td>0.040</td>
<td>1.98 (1.02–3.82)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

POV = postoperative vomiting.

$^a$ Haplotypes were constructed with HTR3A SNPs: (from left to right) rs33940208, rs1985242, and rs10160548.

$^b$ One thousand permutations were replicated to evaluate the permutation $p$ value.

$^c$ The global $p$ value was calculated using a permutation test ($n = 1000$).
There are several risk factors for PONV: sex, nonsmoking, history of motion sickness or PONV, postoperative opioid use, and so on. Nonetheless, previous epidemiologic investigations indicate that there is no reliable independent predictor. For example, although a history of PONV suggests a high risk of susceptibility, the prediction rate was poor using the patient’s history alone, whereas the four-factor risk score was significantly better. The present study provides additional evidence that female sex and in particular HTR3A haplotypes interact and this information should allow a more stratified and precise prediction of the occurrence of POV. Many scoring systems have been developed to identify clinical risk parameters and to establish PONV prediction models. However, most of them have only moderate discriminating power and, therefore, are not clinically accurate or useful. Apparently, some important risk factors were missed, including possible genetic factors. Our current finding suggests the sex-specific genetic risk of the HTR3A haplotype can be included to improve the discriminating power of current PONV prediction system.

Haplotype-based analysis allows multiple potentially causal loci to be simultaneously tested for genetic associations, and might represent the interactive effect of assayed markers and the potential effect of untyped causal markers. Results from our haplotype analyses imply a possibility of interactions between different SNPs of the HTR3A gene. In haplotype analyses of female patients, the CTT haplotype showed a significant protective effect (OR = 0.68; 95% CI = 0.47–0.99). In contrast, the CTG haplotype (which replaces a “T” allele of rs10160548 with a “G” allele) showed a significant risk for POV (OR = 2.08; 95% CI = 1.08–3.99). The results for the TAG and TAT haplotypes were similar: the alternative third-position allele was also associated with inverse distributions in the two groups, although the significant differences observed only when both males and females were analyzed together. These data suggest a possible interaction between two 5’ polymorphisms with the third allele of rs10160548 determines the significant effect. Although there was no detectable effect based on rs10160548 alone, our results indicated that the rs10160548 polymorphism may have a potential to modify the gene effects in the form of haplotypes. The possible interaction was also supported by our LD-mapping data: there is distinct LD of rs10160548 with other polymorphisms between the two study groups. Although it has not yet been confirmed, the interaction between the sites of polymorphisms that modify the effects of genes on disease development has been previously reported: interaction between sites of the β2-adrenoceptor gene is associated with a protective effect against asthma.

Most current research on the effects of genetic polymorphisms on nausea and vomiting are focused on their pharmacogenetic roles: they investigate the efficacy of nausea- and vomiting-related drugs; specific-drug-induced nausea and vomiting (i.e., chemotherapy, antidepressant); and so on. For example, the polymorphism of the µ-opioid receptor gene OPRM1:c.118A > G was recently reported not to protect against intravenous patient controlled analgesia morphine-induced nausea or vomiting. Polymorphisms of the HTR3B, COMT, and CHRM3 genes may be correlated with the variability of nausea in cancer patients taking opioids. The roles of the HTR3A and HTR3B genes as pharmacogenetic predictors for antiemetic treatment in patients with cancer have also been tested. There are still few genetic risk factors used to predict PONV or PONV. One study on a Japanese population showed that dopamine type-2 receptor (DRD2) Taq1A polymorphism is associated with the occurrence of early PONV, and one SNP within the CHRM3 gene was significantly associated with PONV in a genome-wide association study.

The present study differed from above studies because it specifically focused on investigating the genetic determinants of PONV only. Clearly phenotypic dissection have been promised as a key point to successfully mapping the genetic components of diseases with complex etiology. Our results support the phenotypic dissection strategy which assumes that only one specific clinical symptom can successfully identify and provide new insight into the genetic components of PONV, which is a heterogeneous event. There is another study applied the phenotypic dissection strategy to study the genetic components of PONV only, and successfully identified the PONV associated genes. Although the observation periods (6 hours after surgery in Rueffer’s study) and studied polymorphisms are different, both data from our and Rueffer’s study suggest that the genetic variations of the HTR3A gene is associated with developing PONV.

Our findings suggest that the HTR3A haplotypes are significantly associated with the PONV of Taiwanese female patients during the first 24 postoperative hours. That two of the three polymorphisms that we assessed in this study are located on introns, and that fact the significant association can be detected only using haplotype-based analysis and does not appear in single-locus analysis implies that the biological functional variants related to PONV could be other variants within the HTR3A gene or neighboring genes, and that they are worth additional investigation. In particular, the gene that encodes HTR3B, is located just beside the HTR3A gene, and specifically modifies its function is a good candidate for further investigation. However, the functional effects of these three polymorphisms should not, therefore, be neglected. They may have minor regulatory effects that could not be determined in the present study. Although the finding from our genetic analysis seems significant, because of the limited sample size, the chances of false-positives cannot be totally excluded. Thus, further investigations with larger Taiwanese cohorts are required to confirm the significance of the HTR3A gene on the etiology of PONV in Taiwan. To our knowledge, the present study is the first to show that the HTR3A gene haplotype may affect the incidence of PONV in Taiwanese female under general anesthesia. Results from this study are worth validating in an independent cohort, and have the potential to become population-specific predictive biomarkers for sex-specific PONV in the Taiwanese population.

Conflicts of interest

All authors have no conflicts of interest to declare.
Acknowledgments

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