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Exploring the multifactorial nature of postoperative nausea and vomiting in women following surgery for breast cancer

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Abstract

Background—Postoperative nausea and vomiting (PONV) are two of the most frequent and distressing complications following surgical procedures, with as many as 80% of patients considered to be at risk. Despite recognition of well-established risk factors and the subsequent use of clinical guidelines, 20–30% of women do not respond to antiemetic protocols, indicating that there may be a genetic risk.

Objective—The purpose of this pilot study was to describe the incidence and explore the risk factors associated with PONV after surgery in women diagnosed with early stage breast cancer.

Methods—A prospective cohort design was employed to measure PONV in women recruited prior to surgery. DNA was extracted from saliva samples collected prior to discharge. Polymorphisms for seven candidate genes with a known role in one of the neural pathways associated with PONV were included in this study; serotonin receptor (HTR3A), serotonin transport (SLC6A4), tryptophan (TPH), dopamine receptors (DRD2/ANKK and DRD3), catechol-*O*-methyltransferase (COMT) and histamine (H1).

Results—Twenty-nine (29.8%) women experienced nausea and 10 (11%) experienced nausea and vomiting while in the PACU despite administration of multiple antiemetic medications. Women who experienced PONV had higher levels of pain and received more opioids than those women who did not experienced PONV. Odds ratios demonstrated that alleles for the COMT, DRD3, and TPH genes were associated with decreased PONV.

Conclusion—The understanding of the multifactorial nature of PONV and the recognition of genetic risk will ultimately lead to the development of personalized interventions to manage these frequent and often debilitating symptoms.

Keywords

Nausea; Vomiting; PONV; Genetics; Neurotransmitters; Breast cancer surgery

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1. Introduction

In 2016 it is estimated that over 240,000 women in the United States will be diagnosed with breast cancer (www.cancer.org). Surgery is the primary treatment for women with early stage breast cancer, and as many as 80% of these women will experience postoperative nausea and vomiting (PONV) (Gan et al., 2014). PONV can lead to aspiration, wound dehiscence, bleeding, hematoma, dehydration, electrolyte imbalance, exhaustion, delayed mobilization, recovery and ability to begin oral medications. (Miaskowski, 2009; Jolley, 2001). PONV is one of the strongest predictors of prolonged hospital stay and unanticipated admission for outpatient surgery patients accounting for millions of dollars of health care costs annually (Gan et al., 2014; Janicki and Sugino, 2014; Marla and Stallard, 2009). The use of opioids for postoperative pain has long been recognized as a primary predictor of PONV, and other known predictors include female gender, a negative smoking history and previous experience of PONV or motion sickness (Apfel et al., 2008; Meng and Quinlan, 2006; Murphy et al., 2006; Wesmler et al., 2013; White et al., 2008). Type and duration of anesthesia, and medications used during the surgical procedures are also known to be associated with PONV (Gan et al., 2014; Janicki et al., 2011). Additionally, in patients with breast cancer, preoperative psychological factors including distress increase the severity of PONV (Montgomery et al., 2010; Wesmler et al., 2016). Certainly the use of 5-HT₃ antagonists, and more recently the neurokinin 1 receptor antagonists have improved the management of PONV, but despite progress based upon evidence from voluminous clinical trials examining the efficacy of antiemetic regimens, 25–30% of postoperative patients continue to suffer from vomiting, and to a greater extent, nausea. Nausea is less well understood, and yet is considered by patients to be far more of a problem because of its debilitating nature.

Growing evidence, including our own, suggests that the gap in the ability to control nausea and vomiting may be explained by genomic variability (Fasching et al., 2008; Laugsand et al., 2011; Wesmler et al., 2014). Because the first choice of antiemetic medications are serotonin receptor antagonists (Gan et al., 2014), we first focused on the genes of the serotonin pathway and the CYP450 family (hepatic enzymes responsible for the metabolism of these medications). We found that individuals characterized as *CYP2D6* poor metabolizers experience increased PONV (Wesmler et al., 2013). We also found that variability in the promoter region of the serotonin transport gene was associated with increased nausea and vomiting in women with breast cancer after surgery yet prior to initiation of adjuvant chemotherapy (Wesmler et al., 2014). Other single nucleotide polymorphisms (SNPs) in the serotonin receptor genes *HTR3A* and *HTR3B* gene have been identified which independently influenced the incidence of PONV (Laugsand et al., 2011; Ma et al., 2013; Reuffert et al., 2009). Because droperidol and metoclopramide are dopamine antagonists that have a history of successfully preventing PONV, variability in dopamine receptors is also a logical target to study.

Several human nausea and vomiting studies have focused on the popular dopamine receptor gene *DRD2* Taq1 polymorphism finding that the *A2A2* genotype of the *DRD2* rs1800497 may be associated with an increased risk for vomiting but not nausea (Frey et al., 2016; Nakagawa et al., 2008). The COMT enzyme metabolizes catecholamines including

dopamine, noradrenaline and adrenaline. The most studied polymorphism in the *COMT* gene is rs4680, also known as the Val158Met functional polymorphism, which has been associated with variability in the perception of pain and analgesic requirements (Rakvag et al., 2008). Several studies have reported a higher incidence of PONV in subjects that carried the AA genotype for A118G of the mu-opioid receptor gene (Chou et al., 2006a; Chou et al., 2006b; Lee et al., 2015; Sia et al., 2008; Zhou et al., 2012).

Given the association of anxiety and PONV (Montgomery et al., 2010), it is realistic to consider acetylcholine receptors as potential targets. In the only GWAS study reported on genetic association of PONV, acetylcholine receptor 3 subtype (*CHRM3*) was associated with PONV (Janicki et al., 2011). Though no research has been reported on histamine and PONV, pregnancy-induced nausea and vomiting has been successfully treated with antihistamines (Goecke et al., 2010). It is clear that PONV is related to multiple neuro-pathways in addition to physiologic and environmental factors, and it is also clear that some patients respond well to multiple drug antiemetic protocols and others do not. It is imperative to understand the potential of genomic variability in the mechanisms underlying PONV. Therefore, the purpose of this preliminary prospective study was to describe the variability of PONV in women undergoing surgery for early stage breast cancer, and explore risk factors that are associated with that variability, focusing on genes of the serotonin and dopamine pathways.

2. Methods

2.1. Subjects

This study, which was approved by the University of Pittsburgh Institutional Review Board, included 93 women, aged 18–80 years with a diagnosis of early stage breast cancer (stages 1, 2, or 3a) based on the tumor, nodes, metastasis classification of malignant tumors (Edge et al., 2010) with no clinical evidence of distant metastases and scheduled for surgery. Exclusion criteria included a previous history of neurologic conditions such as stroke, head injury, spinal cord injury, and intra-cerebral hemorrhage that could also contribute to nausea. Women scheduled for a surgical procedure that was expected to last longer than 4 h were also excluded, due to increased nausea from extended exposure to anesthesia (Gan, 2006).

2.2. Phenotype data

This study employed a prospective cohort design to investigate the association of genetic variation with the variability in the occurrence of PONV following breast cancer surgery. Study participants were recruited in the preoperative holding area of a large women's hospital that houses a nationally known comprehensive breast cancer program. After informed consent was obtained, preoperative phenotype data were collected including history of PONV, history of motion sickness, smoking history, age, race and preoperative antiemetic medications. Immediately following surgery, and while participants were in the Post-Anesthesia Care Unit (PACU), post-operative phenotype data including pain scores, nausea scores, frequency of vomiting, anxiety and all medications including anesthesia agents given during the surgical procedure were collected for all study participants. Pain and Nausea were measured on an 11 point verbal scale, with 0 representing no pain or no nausea,

and a score of 10 representing the most pain or nausea ever experienced. Anxiety was measured by the Profile of Mood States Anxiety Tension Short Form (POMS-SF) (Wyrwich and Yu, 2011).

2.3. Genotype data

Polymorphisms for seven candidate genes with a known role in one of the neural pathways associated with PONV were included in this pilot study; serotonin receptor (*HTR3A*), serotonin transport (*SLC6A4*), tryptophan (*TPH*); a precursor to serotonin, dopamine receptors (*DRD2/ANKK* and *DRD3*), catechol-*O*-methyltransferase (*COMT*) and histamine (*H1*) (Horn et al., 2014). The polymorphisms included in the analysis are described in Table 1. For this study, primarily, the focus was on genes of the dopaminergic and serotonergic pathway.

Two milliliters of saliva were obtained from all participants using the Oragene DNA self-collection kit (DNA Genotek Inc.) before discharge from the hospital for genotype data collection. DNA was extracted utilizing the protocol and reagents from the manufacturer. TaqMan allele discrimination technology and commercially available assays (Thermo Fisher Scientific, Waltham, MA) or polymerase chain reaction with restriction fragment length polymorphism (PCR/RFLP) were used for determination of genotypes. Genotypes were double called by technicians blinded to phenotypes. *SLC6A4* genotyping was performed using PCR [flanking primers 5'-TCCTCCGCTTTGGCGCCTCTCC-3' (forward) and 5'-TGGGGGTTGCAGGGGAGATCCTG-3' (reverse)] to capture the promoter variation as well as the rs25531 A > G SNP. The amplified product was digested with *MspI* (New England Biolabs, Beverly, MA) and electrophoresed on 3.5% agarose gels to genotype both variants simultaneously (Edenberg and Reynolds, 1998). For all the polymorphisms with the exception of the Val/Met polymorphism of *COMT*, subject genotypes were classified for data analysis based on the presence (heterozygous or homozygous variant) or absence (homozygous wild type) of the minor allele. For the functional HTTLPR polymorphism analysis we compared those subjects with both L (long) alleles with subjects with at least one S (short allele). For the *COMT* analysis, we compared the three genotype groups; Val-Val, Val-Met and Met-Met.

2.4. Data analysis

Data were analyzed using IBM® SPSS® Statistics 23.0 (IBM Corporation, Armonk, NY). Given the level of measurement of the descriptor and its observed data distribution, appropriate descriptive statistics were computed to describe the total sample and groups based on PONV status. Each SNP included in the analysis was tested for Hardy–Weinberg equilibrium using a Chi square goodness-of-fit test. In addition, univariate binary logistic regression was used to estimate crude (unadjusted) odds ratios (ORs) with 95% confidence intervals for both genetic and individual risk factors for PONV. The level of statistical significance for two-sided hypothesis testing was set at 0.05.

2.5. Justification of sample size

Our planned sample size of 100 was based partly on feasibility of time and resources for this pilot study. We also used known proportions of allele frequency of a common 5-HT3A

(rs71176713) variant and PONV from a previous study (Reuffert et al., 2009) which reported an odds ratio of 2.97. Based on that odds ratio, a sample size of 100, would produce a 2-sided 95% confidence interval for the odds ratio with a width equal to 6.140 when the estimated sample proportion 1 is 0.61, the estimated sample proportion 2 is 0.35, and the sample OR is 2.86.

3. Results

3.1. Phenotype, clinical and demographic results

The study sample characteristics based on PONV status are presented in Table 2. Study participants were an average 58.31 years in age, only 12 (13%) were smokers and 44 (47%) had a positive history of PONV. The majority of women were Caucasian, with only 7(8%) African-American women. Twenty-nine participants (34%) experienced PONV (either nausea and or vomiting) despite administration of ondansetron and dexamethasone as standard protocol during surgery, and the addition of other antiemetics in those women who were known to be high risk. There was not a significant difference in the average age of the two groups. 13 patients (14%) had a scopolamine patch placed, and seven patients were administered an oral substance P antagonist prior to the operating room while still in the preoperative holding area. Twenty-nine women experienced postoperative nausea, 10 of these women also vomiting while in the PACU. No study participants experienced vomiting without nausea. Using two-sample t-tests, we compared women who experienced PONV with those who did not, and found that women with PONV had significantly higher verbal pain scores ($p = 0.003$) and received a greater amount of total amount opioids ($p = 0.001$). Using the chi-square test of independence, a history of previous PONV was found to be significantly more common ($p = 0.001$) in the group with PONV. Smoking status was not a significant predictor of PONV in this study, but only 12 women were current smokers. Of those 12 women, only 3 experienced PONV. Additionally, a trend was found for women with PONV reporting higher anxiety scores as measured by the POMS-SF; however, not significantly different ($p = 0.3$). Only one subject of African American descent reported the presence of nausea and none experienced vomiting. Forty-one women (40%) in this study received IV acetaminophen (Table 2). There was no significant difference in the incidence of PONV between women who received IV acetaminophen and those who did not receive IV acetaminophen. The average pain score for the women who received IV acetaminophen was significantly higher ($p = 0.01$), as was the amount of opioids received in the PACU ($p = 0.022$).

3.2. Genotype data results

Unadjusted odds ratios for all polymorphisms analyzed as part of this study are included in Table 3. The *COMT* genotypes fell into three very distinct genotypes; Val/Val, Val/Met and Met/Met, thus clinical data are also presented in Fig. 1 across the three genotypes. All the polymorphisms were in Hardy-Weinberg equilibrium with the exception of *DRD3* and 5-HTTLPR that fell slightly short ($p = 0.04$). The polymorphisms of *5-HTT3A* (OR = 0.48, 95% CI = 0.73–5.86) and *DRD3* (*Ser9Gly*) (OR = 0.432, CI = 0.173–1.079) were associated with decreased risk for PONV. The serotonin transport polymorphism HTTLPR was not associated with variability of PONV in this sample, nor were the *TPH*, *H1* or *DRD2* (TaqIA)

polymorphisms. When the three *COMT* polymorphism genotypes were compared using analysis of variance (ANOVA), there were significant differences (Fig. 1) among the three groups for the verbal pain score ($p < 0.003$) and the total number of opioids administered in the post-anesthesia care unit (PACU) ($p < 0.001$). Women with the Val/Val genotype experienced the highest level of pain, received the highest amount of opioids in morphine equivalents and also reported the highest severity of nausea in the PACU. Women in the heterozygous Val/Met polymorphism group reported less pain, less nausea and had the least amount of opioids when compared to the Val/Val and Met/Met groups. The results of binary regression analysis, controlling for PONV, opioids and pain are found on Table 4. None of the polymorphisms were found to be statistically significant.

4. Discussion

The primary goal for this prospective study was to describe the variability of in women undergoing surgery for early stage breast cancer, and explore risk factors that are associated with that variability, including genes of the serotonin and dopamine pathways. Despite attention to high-risk patients, 34% of the women in this study experienced PONV which is consistent with most PONV studies. The addition of pre-operative antiemetics as recommended for high risk patients (Gan et al., 2014), either an oral neurokinin-1 antagonist or a scopolamine patch were effective half of the time that they were used. Certainly the clinical guidelines (Gan et al., 2014), suggest we would find that the addition of another antiemetic to the standing order of ondansetron/dexamethasone in high risk patients should decrease the risk for PONV (Apfel et al., 2012a). Our findings regarding the 40 women who received IV acetaminophen group after their surgery are not consistent with other studies, (Apfel et al., 2013) as IV acetaminophen has been reported to decrease postoperative pain and postoperative opioid usage, and then consequently PONV. Our findings that increased postoperative verbal pain scores, use of postoperative opioids and a previous history of PONV increased the risk for PONV are consistent with previous studies (Apfel et al., 2012a; Apfel et al., 2012b; Le and Gan, 2010). The amount of opioids given in the OR, nor the type of anesthesia agents used influenced PONV. Consistent with previous research is the finding that nausea was more prevalent than vomiting (Odom-Forren et al., 2013). Age was not a significant risk factor in this sample, however when we examined the same group by decades, we found that those women over 70 reported higher levels of pain and less PONV than women under 70 years of age (Kudach et al., 2016). Race has not been found in most studies to be a significant predictor of nausea and vomiting (Apfel et al., 2012a). However, our finding that only one of the women of African-American descent experienced PONV is consistent with two published papers. One report found that Caucasian children had more side effects from smaller amount of opioids than their African-American counterparts, while another report from South Africa suggested the need for a modified risk score due to decreased frequency of PONV in Black African patients (Sadhasivam et al., 2012; Rodseth et al., 2010).

In our study, three of the polymorphisms showed trends toward association, though were not significantly associated with PONV following surgery. They were *DRD3*, (rs6280) and *5-HTR3A* (rs1176173) and *COMT*. The Val/Val genotype for *COMT* was significant for increased pain and use of opioids and strongly associated with severity of nausea. This

polymorphism causes a substitution from a valine (Val) to a methionine (Met), leading to a three- to four-fold reduced activity of the COMT enzyme (Rakvag et al., 2008). In addition, the Met/Met genotype has been associated with increased density of mu-opioid receptors (Zubieta, 2015) which could help explain the decreased pain and need for opioids in the PACU in our results. Our results are also consistent with Candiotti and colleagues, who reported that individuals with the Val/Val genotype needed 36% more opioids than patients homozygous for the Met/Met group ($p = 0.009$). However, they did not find significant differences among the three genotype groups for pain scores or emesis medication use in the first 24 h after surgery (Candiotti et al., 2014).

The DRD3 Ser9Gly polymorphism was protective for PONV in this study. Though the Ser9Gly polymorphism has been associated with sickle cell pain (Jhun et al., 2014) and chronic pain (Potvin et al., 2009), only one nausea and vomiting study was identified that included the DRD3 polymorphism in the analysis. In that study, Laugsand did not find the DRD3 to be associated with nausea and vomiting in patients taking opioids for cancer pain (Laugsand et al., 2011). Our results found the SNP rs1176713 for the serotonin receptor gene type A was also protective for PONV. This finding is consistent with work reported by Reuffert and colleagues (Reuffert et al., 2009).

The other polymorphisms examined in this study, though selected for known association with PONV from our research or others, were not significantly associated with PONV. We found in a previous study that the serotonin transport polymorphism HTTLPR was associated with nausea experienced by women up to a month following breast cancer surgery (Wesmler et al., 2014). Those results were not replicated in this study; consistent with other researchers that have reported conflicting results with HTTLPR (Aapro et al., 2012; Grassi et al., 2010; Schillani et al., 2012). The *DRD2* Taq1A polymorphism was not significant for association in this study. Frey et al. (2016) showed that postoperative nausea was not associated with Taq1A polymorphisms, but the incidence of retching/vomiting was > 34% higher than subjects who were genotyped *A1A1* (Frey et al., 2016). When we compared the incidence of vomiting in the PACU and the Taq1A polymorphism, there was not a difference between the two genotype groups.

4.1. Limitations/next steps

We believe, that a strength of this study was that all data were collected in a single center with the same surgical team. However, that also may limit the generalizability as practices in regard to administration of pre and postoperative medications may have influenced the outcome. In addition, because of the small number of subjects who were not Caucasian our findings cannot be generalized to other racial/ethnic groups. A larger fully powered study is planned to increase the ethnic and racial diversity of subjects included to better describe the experience of PONV in all women following breast cancer surgery. This pilot study has provided the foundation for our next study, which will include a significantly larger group of candidate genes and polymorphisms associated with the neural pathways and enzymes involved with treatment-induced nausea and vomiting.

5. Conclusion

The biology and control of nausea and vomiting has gained much attention in recent years. Future research now must be directed toward increasing our knowledge of the multiple factors including the genetic underpinnings of PONV that will help us identify individuals who are at greater risk for the problems and lead to new prevention and treatment strategies.

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Fig. 1.

A comparison of subjects in the three genotype groups of COMT rs4680 (Val/Met158) and opioid use as measured in morphine equivalents, pain as measured by a 0–10 verbal pain scale, and severity of nausea as measured by a 0–10 verbal nausea scale. When the three groups were compared using ANOVA, verbal pain scores and total opioids were significantly different across groups (*) (pain $p < 0.002$, opioids required for pain relief $p < 0.003$). Verbal nausea rating scores were not significantly different.

Table 1

Genotype data for candidate genes and associated polymorphisms.

Genotype data presented as PONY/NO PONY										
Polymorphism	Gene symbol	Gene name	Variant	Major/minor allele frequency	Hardy Weinberg <i>p</i> value	Homozygous wild type	Heterozygous genotype	Homozygous genotype	Major alleles	Minor alleles
rs1176713	<i>HTR3A</i>	Serotonin receptor	C > T	0.75/0.25	0.604	23/39	4/20	2/1	50/98	8/22
5-HTTLPR	<i>SLC6A4</i>	Serotonin transport	Long/*short	0.65/0.34	0.04	15/29 (ll)	10/22 (ls)	4/11 (ss)	40/80 (l)	18/44 (s)
rs25531	<i>SLC6A4</i>	Serotonin transport	A > G	0.86–0.138	0.334	23/50	5/11	1/1	51/111	7/13
rs180049	<i>DRD2/ANKK</i>	Dopamine receptor 2	A > G	0.52/0.48	0.535	16/35	9/17	0/2	41/87	9/21
rs6280	<i>DRD3Ser/Gly</i>	Dopamine receptor 3	A > G	0.66/0.34	0.04	14/19	14/44	0/0	42/84	14/44
rs4680	<i>COMT</i>	Catechol- <i>O</i> -methyltransferase	A > G	0.53/0.47	0.40	11/15	9/30	8/13	31/60	27/56
rs901865	<i>HI</i>	Histamine	A > G	0.84/0.157	0.926	18/33	6/15	1/1	42/81	8/17
rs1800532	TPH1	Tryptophan	A > C	0.68/0.32	0.985	11/17	13/25	3/10	35/59	19/45

* The short (s) and long (l) alleles are defined by a 43 bp insertion/deletion length polymorphism.

Table 2

Comparison of participant characteristics based on presence of PONV following surgery.

Characteristic	Total (n = 93) n (%)	PONV (n = 29) mean $\pm$ SD or n (%)	No PONV (n = 64) mean $\pm$ SD or n (%)	OR (95% CI)	Test statistic <i>p</i> -value
Age (years)	58.3 $\pm$ 9.1	58.48 $\pm$ 9.5	57.76 $\pm$ 8.4	0.99 (0.95, 1.04)	$t = 0.353$ $p = 0.73$
Race					
Caucasian	86 (92%)	28 (96%)	58 (90%)	2.89	$X^2 = 0.254$
African American	7 (8%)	1 (4%)	6 (10%)	(0.33, 25.2)	$p = 0.50$
Smoking status					
Non-Smoker ^a	81 (87%)	26 (89%)	55 (85%)	1.42	$X^2 = 0.254$
Current smoker	12 (13%)	3 (11%)	9 (15%)	(0.35, 5.68)	$p = 0.61$
History of PONV					
Yes	44 (47%)	23 (52.3%)	21 (47.7%)	7.85	$X^2 = 18.08$
No	49 (53%)	6 (21%)	43 (52.3%)	(2.7, 22.18)	$p < 0.001$
Verbal pain score (0 – 10)	3.91 $\pm$ 3.07	5.31 $\pm$ 2.6	3.28 $\pm$ 3.04	1.27 (1.08, 1.49)	$t = -3.082$ $p = 0.003$
Anxiety score (POMS tension-anxiety SF)	10.30 $\pm$ 5.6	11.17 $\pm$ 4.8	9.90 $\pm$ 5.8	1.04 (0.96, 1.13)	$t = 1.005$ $p = 0.317$
Opioids in the PACU (morphine equivalents)	5.93 $\pm$ 6.0	8.87 $\pm$ 6.2	4.60 $\pm$ 5.5	1.13 (1.02, 1.22)	$t = -3.338$ $p = 0.001$
IV Tylenol given in the OR prior to discharge to PACU	40 (43%)	12 (29%)	28 (71%)	1.10 (0.45–2.68)	$X^2 = 0.46$ $p = 0.831$

OR = odds ratio; CI = confidence interval.

^aReference group.

Table 3

Unadjusted odds ratios for genetic data from selected candidate genes and PONV included in this study.

Gene ^a	Polymorphism	df	p	Odds ratio	95% confidence interval
<i>5-HTT3A</i>	rs1176713	1	0.17	0.48	0.17, 1.37
<i>DRD2/ANKK</i>	rs180049 (Taq1A)	1	0.90	1.04	0.39, 2.78
<i>DRD3</i>	rs6280 Ser/Gly	1	0.07	0.43	0.17, 1.07
<i>TPH</i>	rs1800532	1	0.47	0.71	0.27, 1.84
<i>SLC6A4</i>	HTTLPR	1	0.660	0.80	0.34, 1.98
<i>SLC6A4</i>	HTTLPR with rs25331 (La/La vs all others)	1	0.954	9.73	0.38–2.64
<i>H1</i>	rs901865	1	0.630	0.80	0.28, 2.31
COMT	rs4680	2	0.229		
COMT (1)		1	0.104	0.409	0.139–1.201
COMT (2)		1	0.770	0.839	0.259–2.718

^aHeterozygous and homozygous variant genotype groups were combined and compared to the homozygous wild type group, the reference group.

Table 4

Binary logistic regression results for genes controlling for history of PONV, opioids and pain when predicting PONV.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)		
							Lower	Upper	
PACU opioids	0.229	0.119	3.691	1	0.055	1.258	0.995	1.589	
HxPONV(1)	2.105	0.825	6.511	1	0.011	8.204	1.629	41.312	
PACU VPS	-0.050	0.228	0.049	1	0.825	0.951	0.608	1.486	
Total opioids in 48 h	-0.011	0.038	0.084	1	0.772	0.989	0.919	1.065	
SNP1combined (1)	-1.942	1.060	3.358	1	0.067	0.143	0.018	1.145	
ANKK1combined (1)	0.239	0.898	0.071	1	0.790	1.270	0.218	7.388	
TPH1combined (1)	-0.183	0.881	0.043	1	0.836	0.833	0.148	4.683	
DRD3combined (1)	-0.614	0.820	0.561	1	0.454	0.541	0.109	2.699	
Histaminecombined (1)	-1.147	0.804	2.037	1	0.153	0.318	0.066	1.534	
COMTcombined (1)	0.307	0.904	0.116	1	0.734	1.360	0.231	7.993	
Constant	-1.944	1.243	2.446	1	0.118	0.143			