How much oxycodone is needed for adequate analgesia after breast cancer surgery: The effect of *OPRM1* 118A>G polymorphism.

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<p>Tiivistelmä □□ Referat – Abstract</p> <p>Most clinically used opioids are mu-opioid receptor agonists. Therefore, genetic variation of the <i>OPRM1</i> gene that encodes the mu-opioid receptor is of interest. An amino acid changing polymorphism 118A>G (rs1799971) within the <i>OPRM1</i> gene affects the function of the receptor.</p> <p>We studied the association between the 118A>G polymorphism and oxycodone analgesia and pain sensitivity in 1,000 women undergoing breast cancer surgery. Preoperatively, experimental cold and heat pain sensitivity was tested. Postoperative pain was assessed at rest and during motion. I.v. oxycodone analgesia was titrated first by a research nurse and on the ward using a patient controlled analgesia device. The primary endpoint was the amount of oxycodone needed for the first state of adequate analgesia. The 118A>G polymorphism was genotyped using Sequenom MassArray. The association between this variant and the pain phenotypes was tested using linear regression.</p> <p>The 118A>G variant was significantly associated with the amount of oxycodone requested for adequate analgesia ($P=0.001$, $\beta=0.016$). Oxycodone consumption was highest in the individuals having the GG genotype (0.16 mg kg^{-1}), lowest in the AA-group (0.12 mg kg^{-1}) while the AG-group was in between (0.13 mg kg^{-1}). The G allele was also associated with higher postoperative baseline pain ratings ($P=0.001$, $\beta=0.44$). No evidence of association with the other examined pain phenotypes was seen.</p> <p>Words: 210</p>			
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1 Introduction

Increasing interest is being focused on genetic factors that are known to modify pain sensitivity and analgesic responses.³⁷ An example is the 118A>G polymorphism (rs1799971) in the *OPRM1* gene on chromosome 6 coding for the mu-opioid receptor. This polymorphism leads to asparagine being replaced by aspartate, which changes the N-glycosylation of the protein.^{2, 13} The polymorphism is relatively common, having a frequency around 10-15% in the European populations, but there is also large interethnic variability in the allele frequency.³⁴ This amino acid change alters the binding potential and half-life of the receptor and thereby modulates the downstream functions of the receptor.^{2, 6, 13} Also contradictory findings exist and it seems possible that the molecular consequences of this polymorphism are cell or tissue type specific.³⁴ As 118A>G has the highest allelic frequency of all amino acid altering *OPRM1* SNPs and the mu-opioid receptor conveys most of the opioid effects this polymorphism could significantly influence the response to opioid therapy.

Opioids are the most commonly used analgesics for moderate to severe pain.³² So far the impact of genetic variation of the mu-opioid receptor in analgesia has remained controversial. Several studies have associated the 118A>G polymorphism to increased opioid consumption and pain sensitivity^{29, 31} while others have failed to find any evidence of association between this polymorphism and opioid effectiveness or adverse effects.²² Many studies have had small sample sizes⁴⁰ or a low frequency of the G-allele.⁴

A meta-analysis from 2009 concluded that the 118A>G polymorphism showed no overall association with opioid analgesia.³⁵ However, that meta-analysis did not include any studies on oxycodone. In another recent meta-analysis the polymorphism was shown to be reproducibly associated with decreased opioid effects but due to the small effect size the clinical relevance of this association was questioned.³⁴

Non-cancer related use of oxycodone, including intravenous administration, is increasing worldwide.^{14, 25} The association between postoperative oxycodone consumption and the mu-opioid receptor polymorphism has been addressed before in only one small study which found no association between the *OPRM1* 1118A>G polymorphism and postoperative oxycodone analgesia.⁴⁰

The aim of our study was to assess the role of the *OPRM1* 118A>G polymorphism in postoperative oxycodone analgesia. Our study cohort consists of 1,000 well-characterized women undergoing surgery for breast cancer. A study sample of this size should enable estimation of the true effect size of this variant. We also used the amount of oxycodone needed for the first state of adequate analgesia as the primary outcome for oxycodone analgesia as other measures of opioid consumption are likely to be influenced more by pharmacokinetic factors. In addition, we studied the role of the *OPRM1* 118A>G polymorphism in experimental pain sensitivity using both heat and cold stimulation.

2 Methods

2.1 Ethics

The coordinating ethics committee (136/E0/2006) and the ethics committee of the Department of Surgery (Dnro 148/E6/05) of the Hospital District of Helsinki and Uusimaa had approved the study protocol. All patients provided a written informed consent.

2.2 Patients

The patients were recruited from the Breast Surgery Unit, Helsinki University Central Hospital between August 2006 and December 2010. The cohort consists of 1,000 women (aged 18-75 years) diagnosed with unilateral non-metastasized breast cancer who were to undergo elective mastectomy or breast conserving surgery with sentinel node biopsy, axillary clearance or both. The type of surgery was decided based on tumor characteristics and the patient's wishes. Patients scheduled for immediate breast reconstruction were excluded from the study.

Originally, 1149 of the 1536 eligible patients were invited to participate in the study (Figure 1). The remaining 387 patients could not be recruited for logistic reasons. A total of 126 patients declined and 23 were withdrawn due to a contraindication in the anaesthetic protocol, change in the type of surgery, violation of the study protocol or logistic reasons. The study cohort has been described in more detail by Kaunisto and others.¹⁸

Figure 1. Flowchart of patient selection and grouping by the type of surgery. AC= axillary clearance

2.3 Study procedure

The research nurse collected patient characteristics the day before the surgery. The background data included e.g. age, weight and height, number of previous operations (other than breast surgery) and previous chronic pain of any kind.¹⁸ Patients also answered psychological questionnaires, Beck Depression Inventory¹ and Spielberger State and Trait Anxiety Inventory.³⁰ Pain in the chest/axillary area was assessed using a numerical rating scale (NRS 0-10).

Before surgery the research nurse tested the patients for heat and cold pain sensitivity. In the heat pain test a 16 mm x 16 mm thermode (TSA-II NeuroSensory Analyzer, Medoc Ltd, Ramat Yishai, Israel) was set at 43°C and 48°C in this order and then held for 5 seconds on the volar side of the patient's forearm contralateral to surgery. Patients were asked to rate the intensity of pain using a numerical rating scale (NRS 0-10) where the anchors were 0 for "no pain" and 10 for "worst pain imaginable". In the cold pain test (JULABO USA Inc., Allentown, PA) the patients immersed their hand in cold water (2-4°) for the maximum time tolerated with a cut-off time of 90 s. Pain intensity was assessed every 15 seconds using NRS. If the patient withdrew the hand before 90 s, the pain intensity was recorded as 10 at all the following time points. The cold pain test was not performed to the first 100 patients because of unavailability of the device.

The anesthetic procedures were standardized. All patients were premedicated with diazepam 2.5-12 mg and acetaminophen 1 g orally, and anesthetized with intravenous propofol and remifentanyl. At the end of surgery all patients received 1 µg kg⁻¹ fentanyl iv. At the same time point they were given ondansetron 4 mg i.v. and droperidol 0.01 mg kg⁻¹ i.v. to prevent postoperative nausea and vomiting. A blood sample was collected from the patients for DNA isolation before transfer to the post anesthesia care unit (PACU).

In the PACU the patients were asked to rate the pain intensity at rest and during movement using NRS 0-10. Motion pain was assessed by asking the patient to raise the arm ipsilateral to surgery up to 90°. Analgesia was titrated by the research nurse who asked about the pain intensity every 5 minutes and administered 1-3 mg oxycodone until the patient rated the pain intensity <4 (NRS 0-10) or indicated otherwise that pain relief was adequate. Afterwards pain intensity was assessed every 15 min until the patient needed a new dose of oxycodone.

After two hours the patients were transferred to the ward and analgesia was provided with a patient-controlled analgesia device (PCA, Abbott Pain Management ProviderT, Abbott Laboratories, North Chicago, IL, USA, or CADD-LegacyT, Deltec, Inc., St. Paul, MN, USA) for up to 20 hours except for the outpatients (N=70). The total consumption of oxycodone was recorded (post anesthesia care unit and PCA). All patients were given acetaminophen 1g orally every eight hours as a basic analgesic.

2.4 Genotyping

DNA was extracted from peripheral blood using the Autopure LS automated DNA purification instrument (Gentra Systems, Inc., Minneapolis, MN, USA). *OPRM1* 118A>G (rs1799971) was genotyped using the Sequenom MassARRAY system and the iPLEX Gold Single Base Extension chemistry (Sequenom, San Diego, CA, USA).¹⁶ Both duplicate, positive and negative control samples were included in each DNA plate to confirm the accuracy of the genotyping results. Genotyping was performed blind to phenotypic information.

2.5 Statistical analysis

2.5.1 Power calculations

Post-hoc power calculations were conducted to estimate the size of the effect the 118A>G polymorphism should have on the studied phenotypes for our study

sample to have power to detect the effect. Calculations were performed using the freely available Quanto software, version 1.2.4.³³ Calculations were done using values retrieved from our study (minor allele frequency 0.17, means and standard deviations of the quantitative traits seen in our data). The level of significance was set to $P=0.05$. The options in effect were an additive genetic model and independent individuals.

2.5.2 Genetic association analyses

Statistical significance for assessing Hardy-Weinberg equilibrium for the *OPRM1* polymorphism was obtained using Plink software.²⁷ Association between the *OPRM1* A118>G polymorphism and studied phenotypes was evaluated using linear regression. An additive model was used. In the additive model, heterozygous individuals are assumed to have a phenotypic value between the two homozygous groups. Since all outcomes did not follow normal distribution, the results were confirmed with a permutation testing strategy. For this we used the max(T) permutation option of the Plink software. Each model was fitted 10.000 times and the original statistics were compared with the test statistics received from permutation.

The primary phenotype was the amount of oxycodone (mg kg^{-1}) the patients requested in order to achieve the first state of adequate analgesia. This phenotype was chosen to minimize possible pharmacokinetic effects at later time points.¹⁷ Secondary phenotypes included total oxycodone consumption during 20 h (mg kg^{-1}), baseline postoperative pain (first measurement after waking up), postoperative pain during movement when the patient needed the first dose of oxycodone and time from emergence from anesthesia to the first state of adequate analgesia. Furthermore, three experimental pain phenotypes were studied; cold pain intensity at 15s (NRS), heat pain intensity (NRS) and the total time the patients held their hand in cold water. Age, body mass index (BMI), state anxiety score, chronic pain and the type of surgery were used as covariates when analysing the association

between the phenotypes and genotypes. These covariates were selected based on our previous findings so that the factors showing corrected p-values ≤ 0.001 in the linear regression analysis for at least one of the phenotypes studied here were included.¹⁸ The 70 day surgery patients were removed from the analysis when assessing total oxycodone consumption as they did not use the PCA system.

The P-value for the primary phenotype was not corrected because only one test was performed. The P-values for the secondary phenotypes were Bonferroni corrected with the number of all tests performed (nine phenotypes). The level of statistical significance was set at a corrected empirical $P < 0.05$.

2.5.3 Multiple linear regression

Data were analyzed using the R program package version 2.14.2. Multiple Linear Regression models were created to evaluate the effect of the 118A>G polymorphism together with other variables on the amount of oxycodone (mg kg^{-1}) the patients requested in order to achieve the first state of adequate analgesia and on total oxycodone consumption during 20 h. The variables studied include type of surgery, age, BMI, state anxiety and the presence of any pre-operative chronic pain condition. Linear modeling was done both including and without the 118A>G polymorphism to be able to estimate the effect of the polymorphism alone. The effect of the whole model on the studied variables i.e. the proportion of the total variance explained is presented using a multiple r-squared value.

3 Results

3.1 Patient characteristics

Patient characteristics grouped by the *OPRM1* 118A>G genotype are shown in Table 1. The groups did not differ significantly for any of the studied variables. A total of 993 subjects were included in the analysis since genotyping was

unsuccessful in seven subjects. The majority of the patients underwent breast-conserving surgery (n=626) with or without axillary clearance (206 and 420, respectively). The remaining 374 patients underwent mastectomy and of these 234 had also axillary clearance. The effect of type of surgery on the amount of oxycodone needed for the first state of satisfactory analgesia is shown in Figure 2.

The mean time from emergence from anesthesia to the first state of adequate analgesia was 36 min (range 0-132 min) and the mean dose required to achieve adequate analgesia was 0.13 mg kg⁻¹ (range 0-0.59 mg kg⁻¹).

Table 1. Demographic means and SDs from study patients by <i>OPRM1</i> 118A>G genotype				
	AA (n=631)	AG (n=327)	GG (n=35)	p-value
Age (year)	56.7 (9.2)	57.4 (9.2)	57.7 (10.7)	0.262
Height (cm)	165 (6.1)	164.7 (5.8)	164.8 (5.1)	0.503
Weight (kg)	68.9 (12.1)	69.3 (12.3)	70.7 (8.9)	0.402
BMI	25.3 (4.3)	25.5 (4.3)	26.1 (3.3)	0.302
Anxiety score	40.6 (11.4)	40.2 (10.9)	36.2 (10.2)	0.118
Type of surgery (breast conserving surgery/mastectomy)	63.4% / 36.6%	62.1% / 37.9%	51.4% / 48.6%	
Sentinel biopsy/axillary clearance	45.0% / 55.0%	40.7% / 59.3%	57.1% / 42.9%	
Preoperative chronic pain condition (yes/no)	20.9% / 79.1%	30.3% / 69.7%	22.9% / 77.1%	

3.2 Genetic association studies

Genotype counts and frequencies in our cohort were 631 for AA (63.5%), 327 for AG (32.9%) and 35 for GG (3.5%). Genotypes were in Hardy-Weinberg Equilibrium (P=0.43). The allele frequencies were A=0.80 and G=0.20. The estimated effect sizes needed for our study to have sufficient power (80%) were reasonable. For the primary phenotype, the amount of

Figure 2. Cumulative percentage of patients achieving adequate analgesia for the first time with the respective dose range of oxycodone. Adequate analgesia was defined as the dose of oxycodone the patient needed for the pain intensity to be <4 (NRS 0-10) or indicated otherwise that pain relief was adequate. AC = axillary clearance.

oxycodone needed for the first state of satisfactory analgesia, sufficient effect size was estimated to be 0.015 mg kg⁻¹ per minor allele. For total oxycodone consumption the estimated effect size was 0.069 mg kg⁻¹, for cold pain at 15 s 0.53 NRS units and for cold pain tolerance 5.7 s per minor allele.

3.3 Postoperative pain

The association results for the postoperative phenotypes are shown in Table 2. The primary phenotype, the amount of oxycodone required by the patients for the first state of adequate analgesia showed a significant association with the 118A>G polymorphism (uncorrected P=0.001, β =0.016), with the GG-group requiring the largest (0.16 mg kg⁻¹) and the AA-group the lowest (0.12 mg kg⁻¹) amount of oxycodone. For the heterozygous individuals the required dose was closer to the AA-group, 0.13 mg kg⁻¹. The permuted P-value was also significant (P=0.001). The distribution of the required doses by genotype is shown in Figure 3.

Table 2. Mean values of the studied variables for each genotypic group and the association of *OPRM1* 118A>G with the primary and the secondary phenotypes.

	AA	AG	GG	Beta	P-value	Empirical P-	Corrected P-value*
Primary phenotype							
Oxycodone needed for first state of adequate analgesia (mg kg ⁻¹)	0.12 (0.09)	0.13 (0.09)	0.16 (0.12)	0.016	0.001	0.001	
Secondary postoperative phenotypes							
Motion pain (NRS)	5.0 (1.4)	5.1 (1.5)	5.1 (1.6)	0.11	0.193	0.196	1
Oxycodone in PACU (mg kg ⁻¹)	0.14 (0.09)	0.15 (0.09)	0.17 (0.11)	0.012	0.011	0.013	0.12
Total oxycodone (mg kg ⁻¹)	0.25 (0.18)	0.25 (0.17)	0.27 (0.20)	0.005	0.581	0.597	1
Time to first satisfaction (mg kg ⁻¹)	35.9 (16.4)	36.9 (15.1)	41.9 (17.0)	2.033	0.019	0.025	0.2
Secondary experimental pain phenotypes							
Cold pain intensity, 15 s (NRS)	5.7 (2.8)	5.7 (2.9)	5.3 (3.3)	-0.068	0.692	0.69	1
Cold total time(s)	46.6 (29.2)	45.6 (29.7)	56.0 (31.2)	1.16	0.507	0.498	1
Heat 48 °c (NRS)	3.5 (2.5)	3.5 (2.3)	3.8 (2.8)	0.011	0.934	0.935	1

Data are represented as means (SD).

Association results are based on linear regression analysis using age, BMI, anxiety score, chronic pain and type of surgery as covariates. Additive model was used. Empirical P-values are produced by performing 10.000 permutations.

* P-values for the secondary phenotypes are corrected for multiple testing using Bonferroni correction (eight phenotypes).

There was no statistically significant difference in the total oxycodone consumption during the 20 h (uncorrected $P=0.58$, $\beta =0.005$), even though the GG-group needed slightly more oxycodone than the AA- or AG-groups (0.265 mg kg^{-1} for AA and 0.249 mg kg^{-1} for AG, respectively). The first (baseline) postoperative pain intensity value during movement showed associated with the G allele (uncorrected $P=0.001$, $\beta =0.44$). However, neither the postoperative pain intensity during motion when needing the first dose of oxycodone nor time from waking to satisfaction showed any evidence of association with the 118A>G polymorphism.

Figure3. The percentage of patients receiving adequate analgesia for the 1st time with the respective oxycodone dosage by OPRM1 genotype. Adequate analgesia was defined as the dose of oxycodone the patient needed for the pain intensity to be <4 (NRS 0-10) or indicated otherwise that pain relief was adequate. The number of individuals is given in brackets.

3.4 Experimental pain

Data on experimental cold pain were available from 893 patients due to the unavailability of the device at the beginning of the study. No association was found

between 118A>G and either cold or heat pain. Association results for experimental pain are shown in Table 2.

3.5 Multiple linear regression models

The created multiple linear models are presented in Table 3. The age of the patient ($P=6.6 \times 10^{-08}$) and the type of surgery performed ($P=4.7 \times 10^{-09}$) were very significant factors in explaining the overall variance in the amount of oxycodone the patients requested in order to achieve the first state of adequate analgesia. The 118A>G polymorphism ($P=0.0009$) and anxiety ($P=0.006$) were also significantly associated. All these factors together explained approximately 12.6% of the variance. Based on the modelling results done excluding the polymorphism we concluded that although being a significant explaining factor, the 118A>G polymorphism alone explained less than 1% of the variance (data not shown). When a similar modeling approach was used for total oxycodone consumption, there was no evidence for the 118A>G polymorphism to be an explaining factor ($P=0.706$).

Table 3. Effects of each covariate on oxycodone consumption and the proportion of the total variance explained by the whole model. Beta shows the change in oxycodone consumption corresponding to each one unit increase in the covariate.

	Oxycodone needed for satisfactory pain relief (mg kg ⁻¹)		Oxycodone, total (mg kg ⁻¹)	
N (valid)	973		898	
Covariate	P-value	Beta (SD)	P-value	Beta (SD)
Type of surgery	4.68×10^{-09}	0.232 (0.027)	1.55×10^{-5}	0.019 (0.004)
Age	6.60×10^{-08}	0.013 (0.002)	$< 2 \times 10^{-16}$	-0.005 (0.001)
BMI	1.30×10^{-06}	-0.002 (0.0003)	5.40×10^{-5}	-0.005 (0.001)
Chronic pain	0.398	-0.003 (0.001)	2.95×10^{-5}	0.053 (0.013)
Anxiety score	0.006	0.005 (0.006)	2.70×10^{-5}	0.002 (0.001)
OPRM1 118A>G	0.001	0.001 (0.0002)	0.706	0.004 (0.010)
Proportion of variance (r^2) explained by the model	0.126		0.177	

4 Discussion

4.1 Postoperative opioid consumption

Our study shows wide variation in the individual oxycodone requirements in agreement with previous studies.^{21, 31, 36} Some patients needed no oxycodone in addition to acetaminophen given to all patients while some required 80 mg during the first 20 postoperative hours.

In our sample the 118A>G polymorphism showed a significant association with the amount of oxycodone required for the first state of adequate analgesia which was achieved during an average of 36 min. In order to have adequate analgesia the GG-individuals needed the largest amount of oxycodone but they did not report higher pain scores when needing the first dose. A number of studies have reported that the 118A>G polymorphism would affect postoperative pain scores.^{28, 29, 36} Also in our study the G allele was associated with higher postoperative baseline pain ratings when pain intensity was measured after surgery before titration of pain relief with oxycodone was started. However, pain intensity scores cannot be used as outcome measures if the patients are titrated to adequate analgesia according to their needs as in our study. When using opioid consumption as a proxy for postoperative pain it is important to bear in mind that other factors such as opioid-induced nausea may have an impact on the opioid dose. Our patients were premedicated with ondansetron and droperidol to prevent nausea.

Interestingly, we found no association between 118A>G polymorphism and the total oxycodone consumption during the first 20 h. This is in accordance with Zwisler and others⁴⁰ who performed the only previous study concerning *OPRM1* and postoperative oxycodone use in 268 patients of whom only four had the GG genotype. Our study showed a trend for the GG-group requiring the largest dose of oxycodone but this difference did not reach statistical significance. This might be because of the relatively low number of GG-individuals but also the effect size of

the polymorphism, based on this data, was small – only 0.005 mg kg⁻¹ per minor allele.

The difference between the two phenotypes (first state of adequate analgesia and total consumption of oxycodone over 20 h) in relation to their association with the genotype is quite interesting. It could be explained by the fact that the first state of adequate analgesia most closely reflects the amount of oxycodone needed to reach the mu-opioid receptors in the central nervous system to provide analgesia. The total consumption of oxycodone over 20 h may be affected by other important pharmacogenetic factors related to the pharmacokinetics of oxycodone. Previous studies have shown that adequate analgesia is achieved faster with intravenous oxycodone than morphine.¹⁷ This has been explained by pharmacokinetic factors as the steady state between plasma and brain concentrations is achieved faster with oxycodone than with morphine.²³ Furthermore, pain intensity decreases with time rendering the study less sensitive. Thus, considering the low number of GG-individuals the power of the study may not have been sufficient to show a difference at 20 h.

So far the impact of genetic variation of the mu-opioid receptor in analgesia has remained controversial. A meta-analysis published 2009 concluded the 118A>G polymorphism to be of minor importance.³⁵ Yet several studies have associated the 118A>G polymorphism to increased opioid consumption and pain sensitivity.^{7, 8, 28, 29, 31} In four studies large differences in total postoperative opioid consumption were seen.^{8, 28, 29, 31} All these studies had large sample sizes consisting of Asian patients and used morphine. In Caucasian populations the effect has been smaller or non-existent.^{4, 11, 21, 40} The GG genotype is much rarer in the Caucasian population^{21, 26, 40} compared with the Asian population^{10, 19, 31} which may explain some of the difference. In addition, many of the negative studies have had small sample sizes^{4, 9, 11} or a low frequency of the G-allele.^{3, 15, 21}

Two previous studies have used a different approach to measure the effect of mu-opioid receptor genotype on postoperative pain.^{5, 36} In these studies the amount of

opioids given to subjects has been standardized and the focus has been on the pain score. The study published by Wu and others ³⁶ reported significantly higher pain scores in the AG- and GG-group during the first postoperative hour compared to the AA-group. This is in agreement with our results.

When considering the association of the 118A>G polymorphism with the amount of oxycodone needed for the patient to achieve satisfactory analgesia, the estimated effect size was 0.016 mg kg⁻¹ per minor allele. The GG-group required on the average 30% more oxycodone compared with the AA-group even though the GG-group had a lower frequency of axillary clearances compared with the AA-group (Table 1). Axillary clearance was related to significantly more oxycodone consumption compared with sentinel biopsies (Figure 2).

There are many other factors affecting the need for analgesia as indicated in Table 3 which also shows that type of surgery, age, BMI, previous chronic pain, anxiety and the 118A>G polymorphism explain only 12.6 to 17.7% of the variation in oxycodone requirements at the first state of satisfaction and over 20 h, respectively. The effect of these other significant explaining factors has been discussed in our previous study. ¹⁸ Also, acute postoperative pain is modulated by many biological processes and hence by many different genes.

4.2 Experimental pain

The association of 118A>G polymorphism with experimental pain has not been much studied. Three studies with low numbers of subjects ^{7, 38, 39} have associated it with higher pain thresholds for experimental pain caused by pressure, cold or electrical stimulation. Fillingim and others ⁷ reported that carriers of the G-allele had lower pain thresholds for mechanical stimuli than non-carriers. Their results also suggested a gender difference as females carrying the G-allele reported higher heat pain scores whereas men reported lower pain scores compared with AA-

individuals. A similar trend was reported by Lötsch and others.²⁴ In our study there was no association between either experimental heat or cold pain sensitivity and the 118A>G polymorphism in agreement with Huang and co-workers.¹² It is not surprising that the fairly low intensity stimulation with 48°C for 5 s did not show any association with the polymorphism. However, one would have expected an association in the cold pain test, which is very unpleasant and could activate stress-induced analgesia which is at least partly mediated by the endogenous opioid system.²⁰

5 Study limitations

This study was performed in female patients only. Therefore, no conclusions can be made regarding males. Even though our cohort was large, the number of individuals homozygous for the minor allele (GG) was still relatively low. This affects the power of our study to detect effects specific to the homozygous carriers.

6 Conclusion

The mu-opioid receptor polymorphism 118A>G was associated with a significantly increased need for oxycodone in the early postoperative period but it was not associated with experimental pain sensitivity. Due to differences in allelic frequency of 118A>G the impact of this mutation is lower in the Caucasian population than in the Asian population. The higher allelic frequency of this polymorphism may render this mutation more eminent in the Asian population.

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