Research Article

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Pharmacogenomics

OPRM1 and *COMT* polymorphisms: implications on postoperative acute, chronic and experimental pain after cardiac surgery

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Aim: Investigate the potential role of *OPRM1* (mu-opioid receptor) and *COMT* (catechol-O-methyltransferase enzyme) polymorphisms in postoperative acute, chronic and experimental thermal pain. **Methods:** A secondary analysis of 125 adult cardiac surgery patients that were randomized between fentanyl and remifentanil during surgery and genotyped. **Results:** Patients in the fentanyl group with the *COMT* high-pain sensitivity haplotype required less postoperative morphine compared with the average-pain sensitivity haplotype (19.4 [16.5; 23.0] vs 34.6 [26.2; 41.4]; p = 0.00768), but not to the low-pain sensitivity group (30.1 [19.1; 37.7]; p = 0.13). No association was found between *COMT* haplotype and other pain outcomes or *OPRM1* polymorphisms and the different pain modalities. **Conclusion:** *COMT* haplotype appears to explain part of the variability in acute postoperative pain in adult cardiac surgery patients.

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Adequate pharmacological management of pain is hampered by large variability between individuals in pain sensitivity and in analgesic response. Factors contributing to the extensive variability observed in pain and analgesia are considered multifactorial, including among other sex [1,2], age [3], race [4,5], co-medication (chronic opioid history/opioid addiction), co-morbidities [6,7], psychological elements such as anxiety [8] and genetic predisposition [9]. The need for a personalized approach, by means of genetics, environmental, psychological and injury-specific factors, has been acknowledged previously [10]. Moreover, chronic postsurgical pain also necessitates the need for an individualized pain management approach. By identifying patients at risk for this chronic postoperative pain state prior to surgery, healthcare providers could prevent its occurrence by adaptions in the pre-operative and postoperative treatment.

The genetic contribution in pain and pain treatment has been extensively studied the last two decades in the adult population by use of knock-down animal studies, twin studies, candidate gene approaches and genome-wide analyses [11,12]. The most widely studied and confirmed variant is the mu-opioid receptor (*OPRM1)* polymorphism 118A>G, which has been associated with higher postsurgical opioid requirement in a recently performed meta-analysis [13]. The increased opioid requirement in 118G allele carriers was later confirmed in 1500 additional patients [14]. The 118G variant allele also relates with lower frequency of nausea and vomiting [14]. Both findings on opioid demand and adverse events are indicative for lower potency of exogenous opioids in carriers of the 118G allele.

Another important gene, repeatedly associated in studies with pain and pain treatment, is *COMT*, encoding the catechol-O-methyltransferase. The *COMT* rs4680 variant has been related with several phenotypes of pain [15] and opioid requirements [16–19]. Three different pain sensitivity haplotypes composed from this SNP and three other

variants (rs4818, rs4633 and rs6269), being low-pain sensitivity (LPS), average-pain sensitivity (APS) and high-pain sensitivity (HPS) have been identified [20]. The pain sensitivity haplotypes have been attributed to the differences in COMT activity, with the LPS haplotype having 4.8-times higher activity compared with the APS and 11.4 to HPS haplotype [20]. COMT is responsible for the breakdown of catecholamines such as (nor)epinephrine and dopamine. Decreased COMT activity in rats has been associated with increased pain sensitivity via amplified firing at the β_2 and β_3-adrenergic receptors [21]. Altered dopamine levels in rats have been related with the expression of the endogenous opioid agonist, enkephalin [22]. Confirming this hypothesis, the *COMT* variant Val158Met (rs4680) in healthy adults, leading to a fourfold decrease in activity [23], reduced mu-opioid receptor density [24].

Up to date these genes have not been addressed across three different pain etiologies (acute and chronic postoperative pain and experimental pain) within the same individuals. The main aim of this genetic study was to assess if the highly investigated genetic variants in *OPRM1* and *COMT* are related with acute postoperative pain reflected by postoperative opioid consumption and could predict the development of chronic postsurgical pain in cohort of patients undergoing cardiac surgery [25–27]. Additionally, the relation between these genetic variants and preoperative and postoperative thermal pain sensitivity has been assessed.

Methods

This is a candidate gene association study performed as a secondary analysis of a randomized clinical trial evaluating the effect of remifentanil versus fentanyl during cardiac surgery on the incidence of acute and chronic thoracic pain in the St Antonius Hospital in Nieuwegein, The Netherlands. The study received approval from the Regional Medical Ethical Review Board (Verenigde Commissies Mensgebonden Onderzoek R13.013) and was registered on the Clinical Trials register (ClinicalTrials.gov number NCT02031016). The study protocol has been published previously [26]. Participants who signed written informed consent and from which a blood sample for DNA analysis was available were included in the current study. Since this is a secondary study, details about the primary clinical outcome and experimental pain thresholds can be found elsewhere [25,27].

Participants

Inclusion criteria for the original study were age between 18 and 85 years, weight between 45 and 140 kg and planned cardiac surgery via sternotomy (i.e., elective coronary artery bypass grafting [CABG] and/or valve replacement). Exclusion criteria were pregnancy/breastfeeding, language barrier, history of drug abuse, chronic pain conditions (e.g., peripheral neuropathy, fibromyalgia), remifentanil/fentanyl/morphine/paracetamol allergy, BMI over 35 kg/m^2 and prior cardiac surgery.

Study protocol

In the original study, patients were randomized intraoperatively to either receive remifentanil continuous infusion (start 0.15 mcg/kg ideal bodyweight/min; adjusted when necessary) or extra fentanyl bolus (200–500 mcg), both on top of standard care with fentanyl bolus (200–500 mcg) on predetermined times (prior, during sternotomy, during aorta cannulation and during opening pericardium). The attending anesthesiologist determined, based on patient's clinical monitoring (e.g., hemodynamics and sweating) and characteristics such as bodyweight or ejection fraction), the exact dose of fentanyl and whether additional fentanyl was required. Anesthesia induction was standardized in all patients with intravenous midazolam (2.5–5.0 mg), followed by propofol bolus (1–2 mg/kg), pancuronium (0.05–2 mg/kg) and fentanyl (on time points as previously mentioned). 30 minutes before end of surgery all patients received 5–10 mg morphine intravenously.

Postoperative pain management after transfer to the ICU and the postanesthesia care unit included continuous morphine infusion (starting 2 mg/h) and paracetamol 4-times daily (oral/intravenous). Adaption of the morphine infusion and/or additional morphine bolus doses was standardized and based on the numerical rating scale (NRS). The NRS was assessed three-times daily by the nurse or was selfreported if possible, based on a previously reported pain titration protocol [28]. An NRS > 4 was indicative for insufficient pain control. In the case the patient was not or insufficiently awake the nurse judged pain with NRS. From 24-h postoperatively onward, patients experiencing insufficient pain control despite dose escalation or side effects, continued receiving morphine boluses or were switched, at discretion of the attending physician, to oral oxycodone or tramadol. The development of chronic thoracic pain was identified with a questionnaire partly based on the validated Brief Pain Inventory [29], which was sent by an e-mail or post mail at 3, 6 and 12 months after surgery by the same researcher. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS > 0) which the patient identified as related to surgery.

Quantitative sensory testing

Cold and heat detection and pain thresholds were determined in the cardiac patients one day before, 3 days after and 12 months after surgery with the Method of Limits (MLI) by use of the Thermal Sensory Analyzer II 2001 (Medoc Advanced Medical Systems, Israel). The thermode (30 × 30 mm^2) was attached to the nondominant hand. Patients responded on the thermal stimuli by clicking a computer mouse with the dominant hand, when the detection or pain threshold was reached. Before formal determination of the thresholds started, a minimum of two training sessions with a test–retest difference below 20% was required. The thresholds were constructed by taking the average of four formal thresholds. Since the MLI method is depending on the reaction time of the individual the analysis with the thermal thresholds was corrected for median reaction time. Reaction time was determined with the open-source software (http://delphiforfun.org/Programs/Reaction_times.htm) by clicking the computer mouse in reaction to the appearance of a blue ball on a white screen. This response was rehearsed three-times and followed by five formal measurements, of which the mean reaction time was calculated per individual. All quantitative sensory testing tests in this study were performed by the same researcher (SdH).

Outcomes

The outcomes studied in this candidate gene study were cumulative postoperative morphine requirements during the first 24 h (mg/24 h) and 48 h (mg/48 h); the development of chronic thoracic pain at 3, 6 and 12 months after surgery (yes/no); and thermal pain thresholds before surgery, 3 days and 12 months after surgery. Opioid requirements during first 48 h were calculated as morphine equivalents [30,31]. All outcomes were assessed for a relation with the genetic variant *OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, the *COMT* haplotype and the combined *OPRM1* rs1799971/*COMT* rs4680 effect.

Genotyping

The genetic analysis was performed at the department of Clinical Chemistry at the Erasmus University Medical Centre in Rotterdam (The Netherlands). DNA was extracted from 1 ml peripheral blood. DNA was isolated on the MagNA Pure LC 2.0 instrument (Roche®, Almere, The Netherlands) with the 'DNA Isolation Kit – Large volume' (Roche®, Almere, The Netherlands). The 7500 Fast Real-Time PCR System (software version 3.0.0; Applied Biosystems, Bleiswijk, The Netherlands) was used for determination of the *OPRM1* 118A>G (rs1799971), *COMT* 472G>A (rs4680, rs4818 and rs4633) genetic variants with ready-made TaqMan® SNP Genotyping Assays. All single nucleotide polymorphisms were checked for agreement with minor allele frequency reported in literature and violation of Hardy–Weinberg equilibrium (p-value > 0.013). R (version 3.1.1) haplo.stats package was used to estimate the *COMT* haplotype (posterior probability limit >90%). LPS group was encoded by the GGC (rs4680, rs4818, rs4633 resp.) haplotype, APS by ACT and HPS by GCC [32]. Participants with LPS/LPS and LPS/APS alleles were combined in the 'LPS' group, APS/APS and LPS/HPS in the 'APS' group and HPS/HPS and APS/HPS alleles in the 'HPS' group. Additionally, as previous findings indicate the combined effect of *OPRM1* rs1799971 and *COMT* rs4680, we assessed this combined genotype [33,34], with group 1 represented by *OPRM1* 118AA genotype with *COMT* 472A allele carriage and group 2 by *OPRM1* 118G allele carriage with/or *COMT* 472GG genotype.

Statistical analysis

IBM SPSS Statistics 21.0 was used for the statistical analysis. As previously reported [25], subjects that received continuous remifentanil infusion during surgery were predisposed to higher morphine consumption (median: 34.3 mg/24 h [interquartile range (IQR): 25.3; 48.2]) postoperatively compared with the fentanyl randomization group (30.2 [19.2; 38.1]). Due to this difference the cohort was stratified according to randomization group in the analysis between genetics and opioid consumption. After stratification the analysis with *OPRM1* rs1799971 and combined *OPRM1* rs1799971/*COMT* rs4680 genotype in relation to postoperative morphine requirement was performed with an Student's t-test. The analysis between *COMT* haplotype, *COMT* rs4680, rs4818 and rs4633 SNP with postoperative morphine requirement was calculated with the analysis of variance (ANOVA) test. A binominal logistic regression analysis was used in order to assess if the genetic variants, by adjusting for randomization arm (correction only made in analysis at 3 months) and age, could predict the likelihood of patients developing chronic thoracic pain at 3, 6 and 12 months after surgery. The association with the MLI thermal thresholds has been corrected for the composite variable age and reaction time (FAC1_1) in a multiple linear

Table 1. Demographics and clinical data cohort.

Demographic or clinical characteristics	Fentanyl (n = 63)	Remifentanil (n = 63)	p-value
Gender (male/female)	57/6	58/5	0.75
Age (years)	66.1 (7.6)	62.1 (9.0)	0.007
BMI (kg/m^2)	28.0 (3.1)	27.5 (3.6)	0.47
Ethnicity: – Caucasian – Asian	 62 1	 61 2	0.99
Diabetes (yes/no)	14/49	10/53	0.36
COPD (yes/no)	4/59	4/59	0.99
Depression (yes/no)	1/62	4/59	0.37
Type of surgery: – CABG – Valve replacement – Both	 51 9 3	 49 7 7	0.40
Length hospital admission (days)	5.0 [3.0–7.0]	5.0 [3.0–7.0]	0.67
Length ICU/PACU admission (hours)	19.5 [16.7–22.4]	19.6 [16.2–21.4]	0.77
NRS (before surgery)	0 [0–0]	0 [0–0]	0.77
Duration surgery (min)	187 (46.7)	198 (70.8)	0.32
Length of anesthesia (min)	219 (49.0)	233 (72.1)	0.18
Time to extubation (min)	548 [479–724]	532 [465–605]	0.31
Intra-operative fentanyl (mg)	2350 [1750–3000]	1750 [1500–2500]	0.001
Intraoperative remifentanil (mcg)	NA	2165 (696)	<0.001
Post-OK morphine consumption (mg/24 h)	30.2 [19.2–38.1]	34.3 [25.3–48.2]	0.028
Post-OK opioid consumption (mg/48 h)	39.0 [26.2–51.4]	46.8 [33.8–59.2]	0.047
Chronic thoracic pain 3 months after surgery (yes/no)	21/42	32/31	0.047
Chronic thoracic pain 6 months after surgery (yes/no)	20/42	17/45	0.56
Chronic thoracic pain 12 months after surgery (yes/no)	12/49	11/50	0.82

Continuous variables are displayed as mean (standard deviation) or median [IQR], depending on the distribution.
CABG: Coronary artery bypass grafting; IQR: Interquartile range; NRS: Numerical rating scale; PACU: Postanesthesia care unit.

regression. The corrected mean and standard deviations of the thermal thresholds are displayed per genotype group, which have been retrieved with two-way analysis of covariance (ANCOVA).

Per outcome (e.g., thermal pain, morphine requirement, chronic pain) six analysis (*OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, *COMT* haplotype and combined *OPRM1* rs1799971/*COMT* rs4680 genotype) were performed. Therefore, a two-sided p-value of 0.05/6 = 0.0083 (Bonferroni correction) was considered statistically significant.

For the original study, a sample size calculation was performed on the primary end point chronic thoracic pain, and was based on the findings of a previous study [35]. This resulted in a total number of 117 patients, with a power of 0.80 and a two-sided significance level of 0.05. Taking into account a mortality rate of 8% 1-year after surgery [35], the total number of patients is 126, which results in 63 subjects per arm.

Results

The original randomized controlled trial included 126 subjects (63 remifentanil/63 fentanyl) undergoing cardiac surgery at the St Antonius Hospital Nieuwegein. The cohort existed of mainly male individuals (91%) and was almost completely of Caucasian origin (98%), the remaining 2% (n = 3) had Asian descent. The most frequent cardiac procedure was CABG (79%), followed by valve replacement (13%) or patients having both procedures (8%). In almost all CABG patients (98%), the internal mammary artery (left, right or both) was used for coronary bypass. Totally, 56% of the patients was overweight (BMI: 25–29.9), 24% moderately obese (BMI: 30–35) and 20% had a normal BMI (18.5–24.9). For an overview of all demographic and clinical data according to randomization group see Table 1. One individual was excluded from further analysis due to a missing blood sample for DNA analysis. The selected genetic variants were in line with the frequencies reported in literature and did not deviate from the Hardy–Weinberg equilibrium (Table 2).

Table 2. Genotyping results according to randomization group.

Genotype	Fentanyl	Remifentanil	MAF observed (%)	MAF literature† (%)	HW equilibrium p-value‡
***OPRM1* (rs1799971)**			14	15	0.19
118AA	46	49			
118AG	16	10			
118GG	1	3			
***COMT* (rs4680)**			51	48	0.99
472GG	17	13			
472GA	30	33			
472AA	16	16			
***COMT* (rs4818)**			38	42	0.68
408CC	25	24			
408CG	24	33			
408GG	14	5			
***COMT* (rs4633)**			51	48	0.99
186CC	17	13			
186CT	30	33			
186TT	16	16			

†NCBI SNP database (European population).
‡HW equilibrium for the total cohort (n = 125).
HW: Hardy–Weinberg; MAF: Minor allele frequency.

Genetics versus acute postoperative pain

After stratification according to the intraoperative randomization group, the *COMT* haplotype was related with postoperative morphine consumption (mg/24 h) within the intraoperative fentanyl group (p = 0.009) but this was not the case for remifentanil (p = 0.29). Post-hoc test (Bonferroni) correction confirmed that only the HPS haplotype group required significantly less morphine compared with the APS haplotype group (median = 19.4 mg/24 h [16.5–23.0] vs 34.6 mg/24 h [IQR = 26.2-41.1]; p = 0.007). No significant difference could be observed between the LPS haplotype (30.1 mg/24 h [19.1–37.7]) with APS (p = 0.13) or HPS (p = 0.15) haplotype groups. Total postoperative opioid consumption within 48 h postoperatively was also decreased in the *COMT* HPS haplotype (p = 0.025), but no longer significant after Bonferroni correction. No associations were found between postoperative opioid consumption with *OPRM1* rs1799971, the individual *COMT* SNPs (rs4680, rs4818 and rs4633) composing the COMT haplotype or the combined *OPRM1*/*COMT* genotype. These results are shown in Tables 3 & 4. One male Asian patient with an opioid requirement of 122.6 mg/48 h was identified as an outlier (Grubb's test, $p < 0.05$). This patient with extremely high postoperative opioid consumption was found to be homozygote variant carrier of the *OPRM1* rs1799971 SNP.

Genetics versus Postoperative chronic pain

Chronic thoracic pain occurred 3, 6 and 12 months after cardiac surgery, respectively, in 53 patients (42.1%), 37 patients (29.8%) and 23 patients (18.8%). After stratification according to randomization group (only performed in the analysis at 3 months) and correction for age, the genetic variants (*OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, *COMT* haplotype and combined *OPRM1* rs1799971/*COMT* rs4680 genotype) were not associated with the development of chronic thoracic pain at 3, 6 and 12 months after cardiac surgery.

Genetics versus Preoperative & postoperative thermal pain thresholds

We have observed a trend between *COMT* haplotype with the pre-operative heat pain threshold (p = 0.014) and cold pain threshold (p = 0.045). Subjects with the LPS haplotype had the highest (mean: 44.9°C [standard error (SE): 0.32] heat pain thresholds followed by APS (44.2°C [0.39]) and HPS (43.2°C [0.62]). Individuals with the LPS haplotype were experiencing cold pain at a lower temperature compared with APS and HPS haplotype (7.52°C [0.98] vs 9.36°C [1.23] vs 11.7°C [1.94]). *COMT* rs4818 was associated with cold detection threshold (p = 0.041). The trend between *COMT* haplotype and cold pain threshold remained 3 days after surgery (p = 0.043), but not after 12 months. Also a trend was observed with the heat detection threshold and the *OPRM1* SNP at 12 months after surgery (p = 0.010). However, none of these findings passed significance after Bonferroni correction (p = 0.0083). The results are displayed in Table 5A–C. The mean and SE are corrected for the composite outcome age and reaction time.

Table 3. Morphine requirements until 24 hour after cardiac surgery.

Fentanyl group	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.75
AA	46	30.3	[19.2; 37.3]	5.10	52.5	
G carrier	17	25.1	[20.2; 38.3]	7.20	42.9	
OPRM1*/*COMT						0.67
118AA and 472A	32	30.2	[17.7; 38.4]	5.10	51.2	
118G and/or 472GG	31	30.2	[21.4; 38.1]	7.20	52.5	
***COMT* haplotype**						0.009†
LPS	35	30.1	[19.1; 37.7]	5.10	47.2	
APS	19	34.6	[26.2; 41.4]	10.1	52.5	
HPS	9	19.4	[16.5; 23.0]	13.2	33.4	
***COMT* rs4680**						0.14
472GG	17	28.5	[20.3; 36.3]	8.70	52.5	
472GA	30	26.1	[16.9; 37.8]	5.10	43.0	
472AA	16	34.5	[27.2; 41.1]	10.1	51.2	
***COMT* rs4818**						0.82
408CC	25	30.3	[18.7; 37.9]	10.1	51.2	
408CG	24	32.6	[18.9; 40.3]	5.10	52.5	
408GG	14	26.9	[19.2; 35.6]	8.70	47.2	
***COMT* rs4633**						0.14
186CC	17	28.5	[20.3; 36.3]	8.70	52.5	
186CT	30	26.1	[16.9; 37.8]	5.10	43.0	
186TT	16	34.5	[27.2; 41.1]	10.1	51.2	
Remifentanil group	**n**	**Median**	**IQR**	**Lowest**	**Highest**	**p-value**
OPRM1						0.25
AA	49	33.8	[25.2; 42.0]	5.40	55.0	
G carrier	13	39.2	[22.6; 49.5]	11.6	63.8	
OPRM1*/*COMT						0.48
118AA and 472A	36	33.8	[25.5; 42.1]	5.40	53.3	
118G and/or 472GG	26	37.1	[20.9; 43.9]	8.60	63.8	
***COMT* haplotype**						0.39
LPS	31	36.4	[26.3; 44.0]	11.6	55.0	
APS	23	28.7	[19.2; 39.9]	5.40	63.8	
HPS	8	38.3	[29.3; 41.6]	26.0	49.3	
***COMT* rs4680**						0.66
472GG	13	36.4	[20.3; 41.2]	8.60	55.0	
472GA	33	36.8	[26.2; 43.5]	11.6	55.0	
472AA	16	31.3	[24.9; 39.5]	5.40	63.8	
***COMT* rs4818**						0.92
408CC	24	34.8	[25.5; 40.7]	5.40	63.8	
408CG	33	34.3	[23.1; 43.5]	8.60	55.0	
408GG	5	36.4	[30.4; 41.5]	29.4	44.0	
***COMT* rs4633**						0.66
186CC	13	36.4	[20.3; 41.2]	8.60	55.0	
186CT	33	36.8	[26.2; 43.5]	11.6	55.0	
186TT	16	31.3	[24.9; 39.5]	5.40	63.8	

†Post Hoc test Kruskal–Wallis illustrated a significant difference between APS and HPS ($p = 0.00768$).
APS: Average-pain sensitivity; HPS: High-pain sensitivity; IQR: Interquartile range; LPS: Low-pain sensitivity.

Table 4. Morphine-equivalent requirements until 48 h after cardiac surgery.

Fentanyl group	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.99
AA	46	39.1	[25.5; 52.6]	5.10	77.5	
G carrier	17	35.1	[25.9; 54.6]	8.10	82.9	
OPRM1*/*COMT						0.17
118AA and 472A	32	34.8	[19.8; 50.3]	5.10	76.2	
118G and/or 472GG	31	41.0	[27.9; 58.1]	8.10	82.9	
***COMT* haplotype**						0.025†
LPS	35	41.0	[27.9; 58.1]	5.10	69.8	
APS	19	43.1	[31.8; 56.7]	16.0	82.9	
HPS	9	23.2	[18.7; 34.2]	16.3	35.1	
***COMT* rs4680**						0.27
472GG	17	41.0	[30.9; 60.7]	8.70	77.5	
472GA	30	34.8	[19.0; 52.8]	5.10	69.8	
472AA	16	41.1	[32.0; 51.1]	16.0	82.9	
***COMT* rs4818**						0.52
408CC	25	34.3	[22.1; 48.8]	16.0	82.9	
408CG	24	46.8	[25.8; 59.7]	5.10	77.5	
408GG	14	40.6	[33.1; 51.9]	8.70	67.2	
***COMT* rs4633**						0.27
186CC	17	41.0	[30.9; 60.7]	8.70	77.5	
186CT	30	34.8	[19.0; 52.8]	5.10	69.8	
186TT	16	41.1	[32.0; 51.1]	16.0	82.9	
Remifentanil group	**n**	**Median**	**IQR**	**Lowest**	**Highest**	**p-value**
OPRM1						0.25
AA	49	46.5	[33.8; 54.9]	18.0	98.3	
G carrier	13	59.2	[34.7; 71.8]	11.6	122.6	
OPRM1*/*COMT						0.27
118AA and 472A	36	45.4	[32.8; 57.5]	18.0	98.3	
118G and/or 472GG	26	49.3	[37.1; 66.1]	11.6	122.6	
***COMT* haplotype**						0.83
LPS	31	46.4	[32.6; 59.2]	11.6	98.3	
APS	23	37.7	[33.8; 58.2]	18.0	122.6	
HPS	8	54.1	[46.9; 60.4]	26.0	69.3	
***COMT* rs4680**						0.82
472GG	13	46.4	[37.5; 51.4]	18.6	75.0	
472GA	33	47.1	[33.7; 60.8]	11.6	98.3	
472AA	16	35.2	[30.0; 63.2]	18.0	122.6	
***COMT* rs4818**						0.81
408CC	24	47.7	[33.8; 60.4]	18.0	122.6	
408CG	33	44.3	[33.7; 60.0]	11.6	98.3	
408GG	5	46.4	[36.7; 50.1]	29.4	51.3	
***COMT* rs4633**						0.82
186CC	13	46.4	[37.5; 51.3]	18.6	75.0	
186CT	33	47.1	[33.7; 60.8]	11.6	98.3	
186TT	16	35.2	[30.0; 63.2]	18.0	122.6	

† Post Hoc test analysis of variance illustrated a significant difference between APS and HPS ($p = 0.021$) and between LPS and HPS ($p = 0.049$).
APS: Average-pain sensitivity; HPS: High-pain sensitivity; IQR: Interquartile range; LPS: Low-pain sensitivity.

Table 5a. Thermal detection and pain thresholds measured 1 day before cardiac surgery.

Genotype	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	92	36.3 (0.22)	94	29.7 (0.13)	95	44.4 (0.27)	95	8.40 (0.83)
118G allele	29	36.2 (0.40)	29	29.6 (0.24)	30	44.3 (0.48)	30	9.68 (1.48)
p-value†		0.82		0.89		0.81		0.45
***COMT* rs4680**								
472GG	28	36.4 (0.41)	30	29.3 (0.23)	30	44.7 (0.48)	30	8.80 (1.49)
472GA	61	36.2 (0.28)	61	29.7 (0.16)	63	44.4 (0.33)	63	8.44 (1.02)
472AA	32	36.3 (0.38)	32	29.9 (0.22)	32	44.2 (0.46)	32	9.14 (1.44)
p-value†		0.87		0.10		0.51		0.87
***COMT* rs4818**								
408CC	49	36.0 (0.31)	48	29.9 (0.18)	49	43.9 (0.37)	49	10.0 (1.15)
408CG	55	36.4 (0.29)	56	29.7 (0.17)	57	44.6 (0.34)	57	7.80 (1.07)
408GG	17	36.8 (0.52)	19	29.0 (0.28)	19	45.1 (0.59)	19	8.04 (1.85)
p-value†		0.16		0.014		0.051		0.22
***COMT* rs4633**								
186CC	28	36.4 (0.41)	30	29.3 (0.23)	30	44.7 (0.48)	30	8.80 (1.49)
186CT	61	36.2 (0.28)	61	29.7 (0.16)	63	44.4 (0.33)	63	8.44 (1.02)
186TT	32	36.3 (0.38)	32	29.9 (0.22)	32	44.2 (0.46)	32	9.14 (1.44)
p-value†		0.87		0.10		0.51		0.87
***COMT* haplotype**								
LPS	62	36.5 (0.27)	65	29.4 (0.15)	66	44.9 (0.32)	66	7.52 (0.98)
APS	42	36.2 (0.33)	42	29.9 (0.19)	42	44.2 (0.39)	42	9.36 (1.23)
HPS	17	35.4 (0.52)	16	29.9 (0.31)	17	43.2 (0.62)	17	11.7 (1.94)
p-value†		0.058		0.041		0.014		0.045
OPRM1*/*COMT								
118AA and 158Met	67	36.2 (0.26)	67	29.7 (0.15)	68	44.3 (0.32)	68	8.20 (0.97)
118G and/or 158Val/Val	54	36.3 (0.29)	56	29.5 (0.17)	57	44.5 (0.35)	57	9.31 (1.07)
p-value†		0.75		0.37		0.63		0.45

Data are displayed as age and reaction time corrected mean with corresponding standard error.
†p-value corrected for composite outcome age and reaction time.
APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

Discussion

In an effort to assess the potential influence of *OPRM1* and *COMT* genetic variants on postoperative acute, chronic and experimental (thermal) pain, 125 cardiac surgery patients were genotyped and analyzed. We found that the *COMT* HPS haplotype was related with decreased postsurgical morphine requirement during the first 24 h. This effect was only found in individuals that were randomized to intraoperative fentanyl, but not in the remifentanil group. Additionally, a trend was found between the *COMT* haplotype with thermal pain, which was not significant after Bonferroni correction.

The observed trend between *COMT* haplotype and thermal pain points toward increased pain sensitivity reflected by increased heat pain at lower temperatures and increased cold pain at higher temperatures. Increased pain responsiveness in HPS haplotype carriers is in line with initial literature in 202 healthy female volunteers with mixed racial background (85% European–Americans) on multiple pain evoking stimuli, with only thermal pain significantly associated [36]. In contrast, in another mixed population (European–Americans, African–Americans, Asian–Americans and Hispanics) of healthy subjects, no effect of the *COMT* haplotype was observed on thermal pain. In the latter study thermal pain was assessed via another method (briefly induced cold and heat pain) compared with the previous study [37], which could have confounded the results. Additionally, no effect of the COMT predicted phenotype group could be observed on thermal pain sensitivity in 1000 female patients undergoing breast surgery for cancer [38]. Focusing on other methods of experimentally induced pain, a study in healthy Chinese males could not confirm the effect of the *COMT* haplotype on pain evoked by transcutaneous electrical accupoint stimulation [39]. These studies suggest that the effect of *COMT* haplotype on pain seems to differ between pain modalities and patients, in the last case either due to ethnic background or diseased versus healthy subjects.

In our study, patients in the fentanyl group (n = 62) with the HPS haplotype had lower postoperative morphine need compared with the APS haplotype, while individuals with the HPS haplotype showed a trend towards higher pain responsiveness to experimental heat pain. These intuitively opposite effects can be attributed to the correlation between the dopaminergic and endogenous opioid system, as shown in animal models [40,41]. Stimulation of the dopamine system, which is comparable with the decreased COMT activity seen with the HPS haplotype, causes a

Table 5b. Thermal detection and pain thresholds measured 3 days after cardiac surgery.

Genotype	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	93	36.0 (2.22)	91	29.5 (0.17)	93	43.5 (0.29)	93	10.1 (0.92)
118G allele	30	36.2 (2.40)	30	29.5 (0.30)	30	43.0 (0.52)	30	12.5 (1.63)
p-value†		0.87		0.90		0.42		0.21
***COMT* rs4680**								
472GG	29	36.7 (0.42)	29	29.3 (0.31)	29	43.7 (0.53)	29	10.3 (1.67)
472GA	62	35.7 (0.28)	60	29.7 (0.21)	63	43.2 (0.36)	63	10.8 (1.13)
472AA	31	36.1 (0.40)	31	29.3 (0.30)	31	43.3 (0.51)	31	10.8 (1.61)
p-value†		0.31		0.96		0.56		0.85
***COMT* rs4818**								
408CC	47	35.9 (0.33)	47	29.5 (0.24)	48	42.9 (0.41)	48	11.8 (1.28)
408CG	56	35.9 (0.30)	56	29.5 (0.22)	56	43.4 (0.38)	56	10.5 (1.19)
408GG	19	36.9 (0.51)	19	29.4 (0.38)	19	44.1 (0.65)	19	8.33 (2.04)
p-value†		0.17		0.96		0.13		0.16
***COMT* rs4633**								
186CC	29	36.7 (0.42)	29	29.3 (0.31)	29	43.7 (0.53)	29	10.3 (1.67)
186CT	62	35.7 (0.28)	61	29.7 (0.21)	63	43.2 (0.36)	63	10.8 (1.13)
186TT	31	36.1 (0.40)	31	29.3 (0.30)	31	43.3 (0.51)	31	10.8 (1.61)
p-value†		0.31		0.97		0.56		0.85
***COMT* haplotype**								
LPS	66	36.1 (0.28)	66	29.6 (0.20)	66	43.7 (0.35)	66	9.29 (1.09)
APS	37	36.3 (0.37)	40	29.3 (0.26)	40	43.2 (0.44)	40	11.7 (1.40)
HPS	16	35.5 (0.57)	16	29.8 (0.41)	17	42.4 (0.68)	17	13.7 (2.14)
p-value†		0.54		0.96		0.086		0.043
OPRM1*/*COMT								
118AA and 158Met	65	35.8 (0.28)	66	29.6 (0.20)	67	43.2 (0.35)	67	10.1 (1.09)
118G and/or 158Val/Val	54	36.4 (0.31)	56	29.4 (0.22)	56	43.4 (0.38)	56	11.4 (1.19)
p-value†		0.17		0.48		0.70		0.44

Data are displayed as age and reaction time corrected mean with corresponding standard error.
†p-value corrected for composite outcome age and reaction time.
APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

decrease in the levels of endogenous peptides [40]. This decline leads to a compensatory rise in mu-opioid receptor expression, meaning that with the HPS haplotype there is less endogenous substrate to alleviate pain, but more receptors available for increased binding when exposed to exogenous opioids. Although our findings on morphine consumption are in line with the biological plausibility for the HPS and APS haplotype, we did not observe a higher postoperative consumption in the LPS group compared with the APS group. Also studies from literature on the direction of the effect of these haplotypes are inconclusive. For example, other studies found that individuals with the APS haplotype required the lowest morphine need [42,43]. Also opposite to our findings, a study in Han Chinese patients found higher postoperative fentanyl requirement after radical gastrectomy with the HPS haplotype [44].

Although in our cohort patients with the LPS haplotype indeed had higher morphine consumption compared with the HPS haplotype, the difference was not significant. As described in our method section the possible *COMT* haplotype outcomes (LPS/LPS, LPS/APS, APS/APS, APS/HPS and LPS/HPS) have been converted into three possible haplotype outcomes. This could have confounded the association. Unfortunately, our study cohort size was insufficient to perform the six haplotype outcomes separately in the analysis. Besides, we have decreased this size even further by the performed stratification (fentanyl vs remifentanil) of our cohort.

Interestingly, the *COMT* genetic effect on postoperative opioid demand was only observed in the fentanyl randomized patients and not in the remifentanil group. It could be that due to the considerable shorter half-life of remifentanil (3–10 min) compared with fentanyl (1–4 h) the mu-opioid receptor gets desensitized. This desensitization can omit the *COMT* haplotype effect of differences in mu-opioid receptor expression as a consequence of the genetic altered COMT activity. Remifentanil is also associated with opioid-induced hyperalgesia [45], probably due to its effect on the N-methyl-D-aspartate receptor [46]. It has been hypothesized that signaling of this N-methyl-D-aspartate receptor may lead to opioid induced hyperalgesia [47]. This could also be the explanation of the increased morphine consumption directly after surgery and increased postoperative pain 3 months after surgery that were reported in the primary analysis of this study [25].

In this cohort, we were unable to confirm the *OPRM1* 118A>G effect on thermal, postoperative acute and chronic pain. Although we have observed a trend with the heat detection threshold 12 months after surgery,

Table 5c. Thermal detection and pain thresholds measured 12 months after cardiac surgery.

Genotype	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	80	36.2 (2.41)	81	29.9 (0.13)	83	47.2 (0.33)	83	8.80 (0.99)
118G allele	28	35.1 (1.20)	27	30.0 (0.23)	28	46.2 (0.58)	28	10.2 (1.72)
p-value†		0.010		0.60		0.13		0.48
***COMT* rs4680**								
472GG	24	36.1 (0.45)	26	29.7 (0.23)	26	46.8 (0.60)	26	7.45 (1.77)
472GA	57	35.7 (0.29)	56	30.0 (0.16)	58	47.3 (0.40)	58	9.06 (1.18)
472AA	26	36.1 (0.44)	27	29.9 (0.23)	27	46.5 (0.59)	27	11.0 (1.73)
p-value†		0.92		0.61		0.68		0.16
***COMT* rs4818**								
408CC	42	35.8 (0.34)	41	29.9 (0.18)	43	46.5 (0.47)	43	10.8 (1.36)
408CG	49	35.9 (0.32)	51	30.0 (0.17)	52	47.3 (0.42)	52	8.78 (1.24)
408GG	16	36.4 (0.56)	16	29.6 (0.30)	16	47.1 (0.77)	16	5.94 (2.24)
p-value†		0.41		0.49		0.32		0.062
***COMT* rs4633**								
186CC	24	36.1 (0.45)	26	29.7 (0.23)	26	46.8 (0.60)	26	7.45 (1.77)
186CT	57	35.7 (0.29)	56	30.0 (0.16)	58	47.3 (0.40)	58	9.06 (1.18)
186TT	26	36.2 (0.44)	27	29.9 (0.23)	27	46.5 (0.59)	27	11.0 (1.73)
p-value†		0.92		0.61		0.68		0.16
***COMT* haplotype**								
LPS	59	36.0 (0.29)	57	29.9 (0.15)	59	47.4 (0.39)	59	7.71 (1.17)
APS	32	36.1 (0.39)	36	29.9 (0.19)	36	46.4 (0.50)	36	10.9 (1.50)
HPS	16	35.1 (0.55)	15	30.0 (0.29)	15	47.0 (0.77)	16	10.5 (2.24)
p-value†		0.25		0.87		0.27		0.13
OPRM1*/*COMT								
118AA and 158Met	59	36.2 (0.29)	59	29.9 (0.15)	61	47.2 (0.39)	61	9.30 (1.16)
118G and/or 158Val/Val	48	35.6 (0.32)	50	29.9 (0.17)	50	46.6 (0.43)	50	8.98 (1.28)
p-value†		0.18		0.74		0.30		0.85

Data are displayed as age and reaction time corrected mean with corresponding standard error.
†p-value corrected for composite outcome age and reaction time.
APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

this was not significant after correction. Other studies investigating the effect of *OPRM1* 118A>G genotype on experimental and postoperative pain showed inconclusive results, as recently was reviewed elsewhere [48]. A gene–gene interaction between *OPRM1* and *COMT* could have biased the association with pain thresholds and opioid consumption [49]. However, this was not the case in our cohort, as no gene–gene *OPRM1 COMT* interaction has been observed.

A *OPRM1* 118 A>G gene–gender interaction has been described in the literature, with opposite effect found on pain between males and females [50–53]. These studies in general reported lower pain ratings among men that carry the 118G allele and higher pain ratings among woman with the 118G allele [50,51,53], with the exception of one study that found the effect to be in the opposite direction [52]. Since our cohort existed of primarily males and we were consequently unable to illustrate an effect on thermal pain the effect might be less evident in males. Not acknowledging the interaction between this polymorphism with gender (and other clinical factors) might conceal the genotype effect on clinical outcomes and thus render its application for personalized pain treatment [54].

The gender–gene interaction is also described for *COMT*, namely in 143 healthy volunteers capsaicin-induced pain was solely higher among woman with the *COMT* HPS haplotype (low COMT activity) [55]. Decreased hepatic COMT activity has been reported in female individuals compared with males [56]. This gender difference may be related to estrogen levels, which has been supported by a study in rats illustrating downregulation of COMT activity by estrogen in the prefrontal cortex and the kidneys of the animals [57]. Due to the lower baseline levels in females they might be more prone to the decreased thermostability of the enzyme as a consequence of genetic variations in the *COMT* gene. In our primarily male cohort, we found an association between *COMT* haplotype and thermal pain thresholds. However, we were unable to assess if the effect of the *COMT* haplotype was larger in females due to the low inclusion rate of female subjects.

In this study, no genetic association between COMT and OPRM1 and the development of chronic pain was found. The role of the dopaminergic transmission in the development of chronic pain after surgery has been reviewed recently [58]. The COMT enzyme is one of the regulators of the dopaminergic transmission, by degradation of dopamine. As discussed in the previously mentioned review, studies have shown inconclusive results for this

particular gene. One of the arguments that have been mentioned is that the development of chronic pain is complex and most likely caused by a combination of biological (e.g., genetic) factors, physical and social interaction [58]. The same argument is applicable for the *OPRM1* genetic variant. We believe that the *COMT* haplotype analysis will not have a purpose as a standalone test in guiding pain therapy with opioids. However, this biomarker could be valuable in a multifactorial prediction model of opioid response and should be validated in an algorithm including other genetic and nongenetic factors.

A limitation of the study is that the remifentanil group also received fentanyl during surgery. In our design, we decided not to compare fentanyl with a study arm with remifentanil as single analgesic since it was expected that high doses of remifentanil would be needed in this painful and extended procedure. However, it is possible that the association between the genetic variants tested and postoperative morphine requirements in the remifentanil group is not found since this group received more intraoperative opioids.

Conclusion

In conclusion, we found the *COMT* haplotype to be associated with acute postoperative pain reflected by postoperative opioid consumption. Patients in the fentanyl group with the *COMT* HPS haplotype group required less postoperative morphine compared with the APS group. The *COMT* haplotype explained part of the variability in experienced postoperative pain directly after surgery, but not on the longer term after surgery.

Summary points

- *COMT* and *OPRM1* are highly investigated genes in postoperative pain.
- Our study, in a cardiac surgery cohort, shows that the *COMT* haplotype (rs4680, rs4633, rs4818) was associated with acute postoperative pain in a subset of patients.
- *COMT* haplotype was not associated with chronic postoperative and experimental pain.
- No effect of *OPRM1* rs1799971 variant was identified on postoperative acute, chronic and experimental pain.
- COMT haplotype will likely be valuable for the prediction of pain and response to opioids in a multifactorial model existing of biological, physical and social factors.

Author contributions

M Matic and S de Hoogd contributed equally to this research in collecting data, analyzing and preparing this manuscript. SN de Wildt, D Tibboel, CAJ Knibbe and RHN van Schaik studied the design and prepared the manuscript.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and /or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, informed consent has been obtained from the participants involved in this study.

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