Research Article

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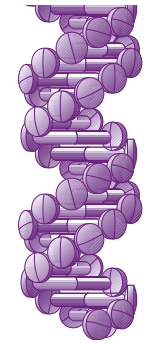
Pharmacogenomics



Advanced cancer pain: the search for genetic factors correlated with interindividual variability in opioid requirement

Aim: To assess association between genetic variants and opioid requirement in cancer patients. **Materials & methods:** A prospective observational trial of 243 advanced cancer patients with inadequate analgesia treated by the palliative care team was analyzed for *ABCB1*, *ARRB2*, *COMT*, *GCH1*, *IL1RN*, *KCNJ6*, *OPRM1*, *RHBDF2*, *SCN9A* and *Stat6* polymorphisms. **Results:** For patients carrying *OPRM1* 118AG/GG and *COMT* 472GG (Val158Val) or these genotypes alone, a significant higher median percentage dose increase was observed (95.2% [32.8–345]) compared with *OPRM1* 118AA and *COMT* 472GA/AA (158M*et* allele carriers; 48.5% [0–98.8]; p = 0.0016). No associations were found with morphine equivalent dose after consultation palliative care team or ketamine use. **Conclusion:** Patients with the combined *OPRM1* 118AG/GG and *COMT 472GG* genotype required 50% higher dose increase for sufficient analgesia.

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Maja Matic*[,‡,1,2], Joost LM Jongen[‡,3], Laure Elens[4,5], Saskia N de Wildt[2,6], Dick Tibboel[2], Peter AE Sillevis Smitt[3] & Ron HN van Schaik*[,1]

[1]Department of Clinical Chemistry, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Department of Pediatric Surgery, Erasmus MC – University Medical Center Rotterdam, Sophia Children's Hospital, Rotterdam, The Netherlands

[3]Department of Neurology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

[4]Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

[5]Louvain Centre for Toxicology & Applied Pharmacology (LTAP), Institut de Recherche Expérimentale et clinique (IREC), Université catholique de Louvain, Brussels, Belgium

[6]Department of Pharmacology & Toxicology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

*Author for correspondence:
Tel.: +31 107 043 396
r.vanschaik@erasmusmc.nl

‡Authors contributed equally

Pain is one of the most frequent and uncomfortable symptoms in cancer patients. It has an incidence ranging from 33% after curative treatment to up to 64% in the advanced stage of cancer [1]. Pain is also one of the most common indications in cancer patients arriving at the emergency department [2]. A European cancer survey illustrated that pain treatment is insufficient in this population, where moderate to severe pain was reported by 56% and breakthrough pain by 63%. The 'quality of life' aspect was insufficiently covered according to 50% of patients [3]. Daily opioid requirement among cancer patients ranges from 25 to 2000 mg, which makes pain treatment even more complicated [4]. Due to the complex etiology, a personalized treatment algorithm would have a great advantage in clinical practice.

Cancer pain is primarily caused by the tumor itself, and less frequent by cancer treatments such as surgery, chemotherapy and radiation [5]. The type and size of the tumor and the extent of pressure on or invasion into bones, nerves and other organs constitute principal determinants of the pain severity and phenotype. Apart from tumor characteristics, patient characteristics are also likely to explain the observed differences in pain experience [6,7]. The female sex is overrepresented in chronic pain conditions, where women tend to have a lower pain threshold, but, paradoxically, are more sensitive to morphine efficacy [8]. This gender effect is probably due to differences in anatomical and physiological compositions in the CNS circuits between males and females [9]. Ethnicity also seems the influence the pain expression, with the differences in pain most likely caused by language obstacles and low socioeconomic status in minority groups, although cultural background can also influence self-reports of pain [7,10].

Finally, the individual genetic make-up is contributing to observed differences in pain experience and analgesic responsiveness [11], and may in fact partly explain

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previously mentioned associations with sex and ethnicity. Most of the studies that addressed this topic were performed in the postoperative setting using a candidate gene approach or a genome wide analysis. Recently, a meta-analysis with 4607 postoperative patients showed that the genetic variation 118A>G in the μ-opioid receptor (MOR), encoded by the *OPRM1* gene, was associated with higher postoperative opioid dose requirement [12]. Studying a genetic contribution in cancer pain patients is more complicated. Indeed, in this particular condition, pain is confounded by even more factors, with more difficulties in proving the genetic contribution of selected candidate SNPs to its severity.

Investigating a large cohort (n = 1000) of female breast cancer patients, Cajanus *et al.* illustrated 33% higher postoperative oxycodone requirement in 118GG genotyped individuals [13]. In the large EPOS trial consisting of 2294 European cancer pain patients the researchers demonstrated an effect of *CYP3A4/5* SNPs on fentanyl concentrations in 620 patients [14], of *COMT* rs2020917 on constipation in 1568 patients [15], of an *HTR3B* genetic variant on opioid-induced nausea/vomiting in 1579 patients [16] and dyspnea in the total cohort (n = 2294) [17]. Yet, none of the SNPs correlated with opioid requirement in this cohort [18].

The aim of this study was to determine if polymorphisms in the candidate genes *ABCB1, ARRB2, COMT, GCH1, IL1RN, KCNJ6, OPRM1, RHBDF2, SCN9A*, and *Stat6* are associated with opioid requirement in patients with advanced clinical cancer who were referred to a pain consultation service due to inadequate analgesia. Our prospectively recruited cohort is unique as it represents moderate-to-severe cancer pain patients, who were treated according to a uniform algorithm in a single center.

Materials & methods

Patients with advanced clinical cancer, for whom the multidisciplinary Palliative Care Team (PCT) of Erasmus University Medical Center was consulted to treat pain, between October 2008 and December 2012, were eligible for inclusion. Clinical data were prospectively collected from a structured data collection sheet (demographical data, type of cancer, metastases, pain intensities and medication) and from the electronic health record (type of pain). The type of pain (nociceptive versus mixed nociceptive-neuropathic pain) was established by a clinical neurologist, using the definition of neuropathic pain (component) of the 'International Association for the Study of Pain' and the algorithm described by Treede *et al.* [19], which is in accordance with previous literature on the clinical distinction between nociceptive and mixed pain [20]. Pain intensity (numerical rating score, NRS) and opioid requirement were assessed at the time of first consultancy (T = 0 days) and after the patient was switched to another analgesic or alternatively, after the dose was changed (T = 3 days). Dose modifications and opioid rotations were done in accordance with the institutional pain protocol of Erasmus MC, which was based on the Dutch National Guideline 'Cancer Pain' [21].

The morphine equivalent dose (MED) was expressed as 10-mg parenteral morphine/24 h. Conversion factors were according to the Dutch Consensus Guideline 'Cancer Pain' [21]. The conversion factors used for calculating MED were 6.67, 0.07 and 0.05 for parenteral hydromorphone, oral tramadol and oral codeine, respectively [22]. For parenteral buprenorphine the same conversion factor as for fentanyl was used [23]. MED was calculated by combining the sustained release and continuous intravenous opioid medication. Although information on all rescue medication for individual patients was not collected, the maximum daily dosage of oral and intravenous rescue medication (opioids) as a rule consisted of 100% of the sustained release or continuous intravenous opioid dosage. When patients were using more than 50% of the rescue doses, sustained release or continuous intravenous opioid dosage was increased. Thus, the calculated MED represents 67–100% of the actual MED. The study was approved by the institutional review board of Erasmus MC (MEC2008–166) and registered at www.clinicaltrials.gov (NCT00956878). All patients gave written informed consent for DNA analysis.

Study outcomes

MED at T = 3d and the relative increase in MED between T = 3d and T = 0d (ΔMED/MED T = 0d) were the primary outcome measures for this study. By adjusting the change in dose for the dose received at baseline, the large variability between patients was reduced and we thus corrected for baseline analgesia. Three days was chosen as it corresponds to the median time point at which we have previously demonstrated adequate analgesia with 48 h after consultation of the PCT [24]. As secondary outcome measure, the use of ketamine as an adjuvant analgesic (indicating extreme pain phenotypes) was assessed.

Genotyping

Whole blood was obtained by venous puncture and DNA was isolated and frozen at -80°C until further analysis. The genomic DNA was isolated with the MagNA Pure LC 2.0 instrument (Roche Diagnostics®,

Almere, The Netherlands) according to the 'MagNA Pure LC DNA Isolation Kit Large Volume' protocol. DNA concentrations were measured on the NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific®, Bleiswijk, The Netherlands) and diluted to 10 ng/µl if concentrations exceeded this threshold. The selected candidate polymorphisms for this study were: *ABCB1* rs1128503, rs2032582, rs1045642, *ARRB2* rs1045280, *COMT* rs4680, 4818, 4633, *GCH1* rs8007267, rs10483639, rs3783641, *IL1RN**2 (86 VNTR), *KCNJ6* rs6517442, rs2070995, *METTL21A* rs2952768, *OPRM1* rs1799971, *RHBDF2* rs12948783, *SCN9A* rs6746030 and *Stat6* rs841718.

All SNPs, except *IL1RN**2, have been genotyped with the TaqMan allelic discrimination method. The predesigned or custom made SNP assays have been designed by the manufacturer (Life Technologies, Bleiswijk, The Netherlands). The patients were analyzed on a 96-well plate with the 7500 Real-Time PCR System (software version v2.0.5; Life Technologies). The *IL1RN**2 (86-bp tandem repeats) variation has been performed with PTC-200 Thermal Cycler, DNA Engine (Bio-Rad®, Veenendaal, The Netherlands) and examined with gel-electrophoresis [25].

The *COMT* and *GCH1* haplotype were estimated with R version 3.1.1 haplo.stats package. The haplotypes included in this analysis were estimated with a posterior probability >0.98. The original study describing the *COMT* haplotypes by Diatchenko *et al.* (2005) used SAS Proc haplotype for haplotype construction [26]. Both software packages make use of the expectation-maximization logarithm. By analyzing rs4680, rs4818 and rs4633 the *COMT* haplotype was determined with an accuracy of approximately 98% [26]. Patients genotyped GGC at these positions respectivley were categorized in the low pain sensitivity (LPS) group, ACT in average pain sensitivity (APS) group and GCC in high pain sensitivity (HPS). The following groups have been compared (LPS/LPS + LPS/APS vs APS/APS + LPS/HPS vs HPS/HPS + APS/HPS) in the analysis.

Analysis of the three *GCH1* SNPs leads to sensitivity and specificity of 100% of the 'pain-protective' haplotype, where noncarriers, carriers and homozygous carriers have been compared [27]. In addition to this haplotype, we are also interested in the combined allelic genotypic effect of *OPRM1* rs1799971 and *COMT* rs4680, as reported earlier by others [28] and our own research group [29,30]. Patients carrying the *OPRM1* 118G allele and the *COMT* Val158Val genotype or these genotypes alone were considered a predisposing factor to higher opioid consumption, while patients with the *OPRM1* 118AA genotype and *COMT* 158Met allele carriage were the low-risk genotype.

Statistical analysis

Current data were analyzed with the statistical software package SPSS version 21.0 for Windows. The categorical demographic and clinical data were analyzed with Pearson's χ^2 test or Fisher's exact test when appropriate. Continuous data were assessed with a nonparametric tests (Mann–Whitney or Kruskall–Wallis) or with a parametric test (students t-test or ANOVA) when normal distribution was not violated. Normality was tested numerically with the Shapiro–Wilk test. The genotype frequencies were assessed for violation of the Hardy–Weinberg equilibrium with the χ^2 test. In the SNP analysis the additive model was used when the genotype count into groups were separately ≥10. When this criterion was not met, a dominant model was used.

Multiple linear regression was used for assessment of the correlation between the SNPs with MED (T = 3d) and relative ΔMED. The independent factors type of pain (nociceptive vs mixed), pain intensity (T = 0d) (only used for MED [T = 3d] outcome), gender, age, type of cancer and treatment have been included as confounding factors. The association with ketamine use (extreme pain phenotypes) was assessed with logistic regression, in which the same independent variables have been used.

Multicollinearity between the independent factors was excluded since none of the factors had a variation inflation factor >3. Metastasis was not included in the model because no evidence exists on higher pain intensities for this group compared with primary cancer patients. Besides, since almost 80% of the population had a metastasis at time of inclusion, the cohort could be considered homogenous for this factor. The two-sided p-values in the multiple linear and logistic regression were adjusted for multiple testing with the Bonferroni correction ($p < 0.0028$).

Results

Patient characteristics

Two-hundred and forty three cancer patients were included in this prospective observational study. Three patients were not using opioids at baseline and after consultation PCT. These patients were consequently excluded from further analysis. From the remaining 240 patients, demographic and clinical characteristics are reported in Table 1. As illustrated in this Table, 72% of the patients were diagnosed with nociceptive pain, 79% had metastasized cancer, 9% required ketamine as an adjuvant analgesic and fentanyl was most frequently used at T = 0d (52.1%) and T = 3d (73.3%). Gastrointestinal, urological, lung and gynecological were the most prevalent tumor types. Twenty-six percent of the patients were treated with radiotherapy, 14.2% with chemotherapy

Table 1. Demographic and clinical characteristics.

Characteristic	n = 240
Age (years)	62 (54–68)
Gender (%)	
Male/female	138 (57.5)/102 (42.5)
Type of pain (%)	
Nociceptive/mixed	173 (72)/67 (28)
Type of cancer (%)	
Gastrointestinal	90 (37.5)
Urological	36 (15)
Lung	34 (14.2)
Gynecological	22 (9.2)
Other	14 (5.8)
Primary unknown	14 (5.8)
ENT	13 (5.4)
Breast	9 (3.8)
Hematological	8 (3.3)
Metastasis (%)	
Yes/no	189 (79)/51 (21)
Treatment (%)	
None or supportive	108 (45)
Radiotherapy	63 (26.3)
Chemotherapy	34 (14.2)
Surgery	18 (7.5)
Radiotherapy and chemotherapy	11 (4.6)
Surgery and radiotherapy	5 (2.1)
Surgery and chemotherapy	1 (0.4)
Ketamine use (%)	
Yes/No	21 (9)/219 (91)
Pain intensity T = 0d	6 (4–8)
Pain intensity T = 3d	4 (2–5)
Opioid T = 3d (%)	
Fentanyl	176 (73.3)
Oxycodone	43 (17.9)
Hydromorphone	11 (4.6)
Morphine	5 (2.1)
Buprenorphine	5 (2.1)
Morphine equianalgesic dose (T = 0d)	20 (10–53)
Morphine equianalgesic dose (T = 3d)	40 (20–80)

All values are expressed in median with corresponding interquartile range, unless stated otherwise.

and 7.5% underwent elective surgery. Forty-five percent of the patients had supportive (e.g., stents) or no cancer treatment at all at the time of inclusion.

Outcome measures

From the 240 patients the MED was decreased by the PCT in 18 (7.5%) individuals and in 48 (20%) cases the MED remained the same. From the latter group, 3 patients were rotated to an alternative opioid. In the total cohort, 84 patients were rotated to an alternative opioid. The median MED was 20 mg/24 h (IQR: 10–53) at T = 0d and 40 mg/24 h (IQR: 20–80) at T = 3d. In parallel, the pain intensity numerical rating score (NRS) decreased from 6 (IQR: 4–8) to 4 (IQR: 2–5), reflecting a statistically ($p < 0.0001$) and clinically significant improvement in pain. From the clinical factors age, gender, type of pain, type of cancer, type of treatment and pain intensity at baseline (T = 0d) only age ($p = 0.028$) and pain intensity at T = 0d ($p = 0.011$) were related with MED at T = 3d. Older patients required lower MED at T3d ($r_s = -0.14$; $p = 0.028$). MED postconsult (T3d) showed a weak correlation with NRS preconsult ($r_s = 0.18$; $p = 0.011$), while relative ΔMED and NRS preconsult were not correlated ($r_s = 0.12$; $p = 0.073$).

Whereas none of these clinical factors were related with relative ΔMED, the presence of mixed pain ($p = 0.009$) was associated with significant use of ketamine. Sixteen percent of the patients with mixed pain (n = 67) used ketamine against 5.7% with isolated nociceptive pain (n = 173). Additionally, a borderline association was observed with ketamine treatment being more frequently given to cancer patients with lung and hematological tumor origin compared with other cancer types (25 vs <10%, $p = 0.051$).

Several outliers have been identified within the outcomes MED (T = 3d) and relative ΔMED with the formulas Q3 + (3.3*[Q3-Q1]) and Q1 - (3.3*[Q3-Q1]). After LOG transformation no outliers were found within the MED (T = 3d) outcome and four outliers in the relative ΔMED outcome. None of these outliers had extreme genotypes that could explain the high increase/decrease in dose between T = 0d and T = 3d. Because absence of outliers is one of the assumptions in regression analysis these four outliers were removed.

Genetic associations

The genotype and haplotype frequencies of all assessed polymorphisms met the Hardy–Weinberg (HW) equilibrium ($p = 0.0028$). All allelic frequencies were in line with the frequencies reported in the SNP database (HAPMAP) on the NCBI website. The observed genotype frequencies of the determined genetic variants and haplotype overview are displayed in Table 2.

Table 2. Genotype frequencies (n = 240).

Gene	rs number	Wild-type allele	Heterozygous allele	Variant allele	Undetermined
ABCB1	rs1128503	84	115	40	1
	rs2032582	84	113	41	2
	rs1045642	60	105	73	2
ARRB2	rs1045280	30	94	112	4
COMT	rs4680	51	130	59	0
	rs4818	82	124	34	0
	rs4633	52	132	56	0
*GCH1**	rs8007267	144	88	7	1
	rs10483639	153	77	9	1
	rs3783641	143	87	8	2
KCNJ6	rs6517442	28	115	96	1
	rs2070995	10	81	147	2
IL1RN	*2	131	83	11	15
METTL21A	rs2952768	43	89	103	5
OPRM1	rs1799971	192	45	1	2
RHBDF2	rs12948783	159	74	7	0
SCN9A	rs6746030	169	63	6	2
STAT6	rs841718	42	124	69	5
COMT haplotype		LPS+LPS or LPS+APS	APS+APS or LPS+HPS	HPS+HPS or APS+HPS	
		144	69	25	2
GCH1 haplotype		Non-carrier	Heterozygous carrier	Mutant carrier	
		160	78	0	2

In the univariate analysis relative ΔMED was significantly associated with *COMT* rs4633 (p = 0.007), *COMT* rs4680 (p = 0.012) and combined *OPRM1*/*COMT* genotype (p = 0.001). None of the other SNPs were associated relative ΔMED in the univariate analysis (Table 3). After correction for clinical factors and Bonferroni correction only the effect between the relative ΔMED with combined *OPRM1*/*COMT* genotype remained significant (p < 0.0028). As displayed in Figure 1, cancer patients having the *OPRM1* 118G allele with the *COMT* Val158Val genotype or these genotypes alone require a higher median percentage increase in dose (after normalization to baseline dose; 95.2% [32.8–345]) compared with *OPRM1* 118AA in combination with the 158Met allele (48.5% [0–98.8]). Individuals with the 118G allele in combination with the Val-158Val genotype did not have significantly higher pain intensity before intervention by the PCT (p = 0.69). None of the selected SNPs and haplotypes (*ABCB1* rs1128503, *ABCB1* rs2032582, *ABCB1* rs1045642, *ARRB2* rs1045280, *COMT* rs4680, *COMT* rs4818, *COMT* rs4633, *COMT* haplotype, *GCH1* haplotype, *IL1RN**2, *KCNJ6* rs6517442, *KCNJ6* rs2070995, *OPRM1* rs1799971, *RHBDF2* rs12948783, *SCN9A* rs6746030, *Stat6* rs841718, *OPRM1*/*COMT* combined) were associated with MED at T = 3d after correction for confounding factors and multiple testing. Also no correlation with ketamine use was found. See Table 3 for the univariate and multivariate results concerning the genetic variants with MED at T3d, relative ΔMED and ketamine use.

Discussion

Our study illustrates that the combined *OPRM1*(rs1799971)/*COMT*(rs4680) genotype is related with a 50% higher relative increase in opioid dose required for sufficient analgesia after PCT consultation. Patients carrying the *OPRM1* 118G allele with the *COMT* Val158Val genotype or these genotypes

Table 3. Results univariate and multivariate genetic analysis.

Gene	SNP	Groups	MED T3d (univariate: p-value; multivariate: β†, p-value)	Relative ΔMED (univariate: p-value; multivariate: β†, p-value)	Ketamine use (yes/no) (univariate: p-value; multivariate: β†, p-value)
ABCB1	rs1128503	CC/CT/TT	0.063	0.86	0.62
			0.13	-0.088	1.21
			0.18	0.36	0.58
	rs2032582	GG/GT or GA/TT or AA	0.12	0.88	0.39
			0.040	-0.053	1.12
			0.39	0.26	0.49
	rs1045642	CC/CT/TT	0.73	0.47	0.52
			0.10	-0.006	1.17
			0.22	0.94	0.63
ARRB2	rs1045280	CC/CT/TT	0.57	0.44	0.63
			0.068	0.11	1.51
			0.45	0.24	0.29
COMT	rs4680	GG/GA/AA	0.54	0.012†	0.59
			-0.055	-0.24	1.31
			0.56	0.015†	0.49
	rs4818	CC/CG/GG	0.15	0.19	0.18
			0.073	0.15	1.00
			0.44	0.14	0.99
	rs4633	CC/CT/TT	0.59	0.007†	0.59
			-0.056	-0.25	1.36
			0.55	0.011†	0.43
	rs4680, rs4818, rs4633	LPS vs APS vs HPS	0.49	0.06	0.66
			-0.075	-0.065	0.56
			0.42	0.50	0.14
GCH1	rs8007267	Absence/ presence 1 protective allele	0.84	0.15	0.99
	rs10483639		-0.158	0.21	1.19
	rs3783641		0.24	0.13	0.74
IL1RN	*2		0.78	0.75	0.32
			0.046	0.009	1.66
			0.67	0.94	0.20
KCNJ6	rs6517442	AA/AG/GG	0.75	0.55	0.92
			-0.059	0.068	1.54
			0.59	0.56	0.35
	rs2070995	GG/GA/AA	0.37	0.29	0.62
			0.15	-0.11	1.26

†Unstandardized coefficient.
‡Significant at $p < 0.05$.
§Significant at Bonferonni threshold ($p < 0.0027$).

Table 3. Results univariate and multivariate genetic analysis (cont.).

Gene	SNP	Groups	MED T3d (univariate: p-value; multivariate: β†, p-value)	Relative ΔMED (univariate: p-value; multivariate: β†, p-value)	Ketamine use (yes/no) (univariate: p-value; multivariate: β†, p-value)
KCNJ6 (cont.)			0.11	0.26	0.54
METTL21A	rs2952768	CC/CT/TT	0.68	0.52	0.57
			-0.016	-0.141	1.58
			0.85	0.12	0.19
OPRM1	rs1799971	AA/G allele	0.50	0.059	0.97
			-0.072	0.29	0.97
			0.65	0.085	0.96
RHBDF2	rs12948783	GG/GA/AA	0.72	0.98	0.30
			0.22	0.046	0.86
			0.07	0.71	0.76
SCN9A	rs6746030	GG/GA/AA	0.95	0.34	0.73
			0.006	0.10	0.76
			0.96	0.44	0.58
Stat6	rs841718	CC/CT/TT	0.62	0.14	0.86
			0.019	-0.11	1.11
			0.84	0.27	0.78
OPRM1/ *COMT*	rs1799971/ rs4680	118AA+158Met/ 118G+Val158Val	0.67	0.001§	0.66
			-0.012	0.43	0.76
			0.93	0.0016§	0.60

†Unstandardized coefficient.
‡Significant at $p < 0.05$.
§Significant at Bonferonni threshold ($p < 0.0027$).

alone need a higher increase in dose, after correction for baseline dose (preconsult). While we have found only a trending effect of these SNPs separately on relative ΔMED, the association passed the multiple testing correction when combined in one genotype. These results are in line with a previous report in 207 cancer patients showing the highest morphine dose in *OPRM1* 118G allele carriers and *COMT* 158Val allele carriers [28]. This combined genotype was not related with pain intensity preconsult (T0d). This could be due to inadequate analgesia before PCT intervention, as that was the reason the PCT was consulted in the first place.

The COMT enzyme, mainly expressed in the prefrontal cortex and striatum [31], is responsible for the degradation of catecholamine's (e.g., dopamine, noradrenaline). Induced changes in dopamine signaling system affect the opioid system [32,33]. An *in vivo* study illustrated that COMT knock-out mice experienced an increased anxiety and stress response [34] but paradoxically an increased morphine response [35]. The *COMT* polymorphism rs4680 (Val158Met) leads to a decreased thermostability and reduced COMT activity [36]. In healthy volunteers it was demonstrated using positron emission tomography scans that AA genotyped individuals have lower MOR signaling upon pain challenge and a higher MOR binding potential [37]. The opposite effects of this variant on pain (increased) and analgesia (lower demand) can be explained by the presence of more 'available' receptors but not enough endogenous agonists to bind, as illustrated in animal models [38]. This is in line with our finding where we report that the *COMT* GG (Val158Val) genotyped patients with the *OPRM1* variant are predisposed to higher dosage step increase for sufficient analgesia.

The *OPRM1* 118A>G SNP has been related with reduced opioid effect as illustrated by means of an increased opioid requirement and reduced risk for adverse events [12,39]. Whether this effect is caused by a decrease in protein expression or decreased binding affinity/potency for exogenous opioids

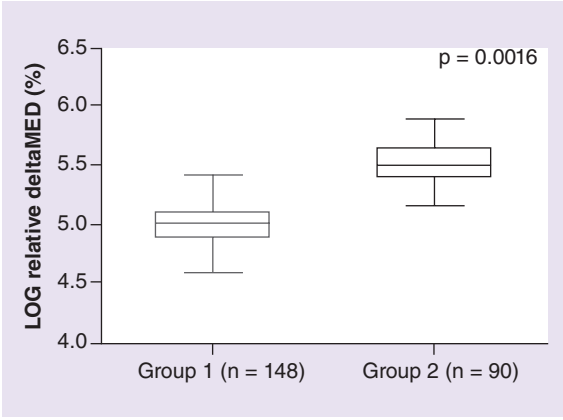

Figure 1. Logarithmic function of relative ΔMED (%) and *OPRM1*/*COMT* genotype. The combined *OPRM1*/*COMT* genotype is significantly associated with relative ΔMED (%) in the univariate analysis (p = 0.001) and after correction for gender, age, type of cancer, treatment and pain (p = 0.0016). The corrected relative ΔMED values for the previously mentioned clinical factors are displayed in this figure. This association also remained after Bonferroni correction (p < 0.0028). Patients genotyped *OPRM1* 118AG/GG with *COMT* Val158Val (Group 2) or these genotypes alone require higher dose increase (95.2% [32.8–345]) compared with patients genotyped *OPRM1* 118AA and *COMT* Val158Met/Met158Met (Group 1; 48.5% [0–98.8]).

remains inconclusive [40]. Independent of the functional consequence, the 118G allele will counteract the 'beneficial' effect of a person that carries the *COMT* 158Met allele. This could explain why different studies addressing the genetic variants in these genes were unable to illustrate an effect on pain sensitivity [41–43] or opioid demand [44,45].

A challenge of the current study is that information on opioid use before admission was missing in our cohort. Because of a chance of development of opioid tolerance, the length of prior opioid use is a potential confounder in the analysis of opioid requirement. Another limitation of this cohort is the heterogeneous nature of the population. However, none of our tumor type groups had a sufficient sample size in order to assess individually with adequate statistical power. Alternatively, we chose to adjust for known factors when possible and to correct our tests for multiple testing. On the other hand, one could argue that an effect seen in such a heterogeneous population is more likely to have real clinical meaning and has application potential as it overcomes the background noise of confounding factors.

In conclusion, we found that the combined *OPRM1* 118A>G and *COMT* Val158Met variants or these genotypes alone were related with 50% higher dosage increase of opioids in patients with advanced cancer. These genetic biomarkers may be helpful in identifying cancer pain patients with decreased opioid sensitivity and to relieve their pain more quickly and more adequately. Indeed, based on genetic information, the opioid dose could be adjusted proactively, with the ultimate goal to avoid excessive pain in these vulnerable and seriously ill patients.

Financial & competing interests disclosure

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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Summary points

- Inadequate analgesia in cancer pain is a serious concern with frequent hospitalizations as a consequence.
- Cancer related pain treatment is complex and illustrates major variability between patients due to the influence of several patient characteristics as well as tumor-related factors.
- The individual genetic make-up is one of those patient characteristics contributing to the observed differences in pain experience and analgesic responsiveness.
- Objective markers are needed to guide cancer-related pain adequately.
- Two hundred and forty-three patients with advanced clinical cancer and inadequate analgesia were seen by the palliative care team.
- The relative change in morphine equivalent dose between study entry and after consultation palliative care team was associated with combined *OPRM1* (rs1799971)/*COMT* (rs4680) genotype (p = 0.0016).
- Patients with the *OPRM1* 118G and *COMT* Val158Val genotype or these genotypes alone required higher increase in opioid dose for sufficient analgesia (95.2 [32.8–345]) compared with *OPRM1* 118AA/*COMT* 158Met allele individuals (48.5 [0–98.8]).
- The *OPRM1* and *COMT* genotype could be considered in the future in a multimodal treatment algorithm for cancer pain.

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