

# OPRM1 A118G Gene Variant and Postoperative Opioid Requirement

## A Systematic Review and Meta-analysis

In Cheol Hwang, M.D., Ph.D., Ji-Young Park, M.D., Ph.D., Seung-Kwon Myung, M.D., Ph.D., Hong Yup Ahn, Ph.D., Ken-ichi Fukuda, M.D., Ph.D., Qin Liao, M.D., Ph.D.

### ABSTRACT

**Background:** Although a number of studies have investigated the association of the *OPRM1* A118G polymorphism with pain response, a consensus has not yet been reached.

**Methods:** The authors searched PubMed, EMBASE, and the Cochrane Library to identify gene-association studies that explored the impact of the *OPRM1* A118G polymorphism on postoperative opioid requirements through July 2013. Two evaluators independently reviewed and selected articles on the basis of prespecified selection criteria. The authors primarily investigated the standardized mean difference (SMD) of required amounts of opioids between AA homozygotes and G-allele carriers. The authors also performed subgroup analyses for race, opioid use, and type of surgery. Potential bias was assessed using the Egger's test with a trim and fill procedure.

**Results:** Three hundred forty-six articles were retrieved from databases, and 18 studies involving 4,607 participants were included in the final analyses. In a random-effect meta-analysis, G-allele carriers required a higher mean opioid dose than AA homozygotes (SMD,  $-0.18$ ;  $P = 0.003$ ). Although there was no evidence of publication bias, heterogeneity was present among studies ( $I^2 = 66.8\%$ ). In the subgroup meta-analyses, significance remained robust in Asian patients (SMD,  $-0.21$ ;  $P = 0.001$ ), morphine users (SMD,  $-0.29$ ;  $P < 0.001$ ), and patients who received surgery for a viscus (SMD,  $-0.20$ ;  $P = 0.008$ ).

**Conclusions:** The *OPRM1* A118G polymorphism was associated with interindividual variability in postoperative response to opioids. In a subpopulation, identifying *OPRM1* A118G polymorphism may provide valuable information regarding the individual analgesic doses that are required to achieve satisfactory pain control. (**ANESTHESIOLOGY 2014; 121:825-34**)

OPIOIDS are currently the most versatile analgesics, making them the drugs of choice for moderate to severe pain associated with invasive procedures, cancer, and various other chronic disease states. However, there is a large interindividual response to the analgesic effect of opioids and a relatively narrow therapeutic index.<sup>1</sup> Genetic factors contribute to the differential response to opioids by regulating their pharmacokinetics (metabolizing enzymes and transporters) and pharmacodynamics (receptors and signal transduction).<sup>2</sup>

The  $\mu$ -opioid receptor (*OPRM1*) A118G single nucleotide polymorphism has been a major focus of research into the pharmacogenetics of opioid response. Emerging knowledge regarding the molecular mechanisms regulating pain in animal models has increased the hopes of identifying personalized pain therapies.<sup>3</sup> *In vitro* experiments show that variant

#### What We Already Know about This Topic

- Interpatient variability in responses to opioids is governed by genetic and environmental factors
- The A118G single nucleotide polymorphism of the  $\mu$ -opioid receptor has been implicated in these differences

#### What This Article Tells Us That Is New

- In a meta-analysis involving 18 studies and more than 4,600 patients, carriers of the G-allele were observed to exhibit higher opioid analgesic requirements
- These genetic effects were strongest in Asian patients, morphine users, and those receiving surgery to a viscus

receptors are associated with higher binding affinity to and potency of the endogenous ligand,  $\beta$ -endorphin, but lower

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Submitted for publication December 11, 2013. Accepted for publication April 23, 2014. From the Department of Family Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea (I.C.H.); Department of Clinical Pharmacology and Toxicology, Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea (J.-Y.P.); Molecular Epidemiology Branch, Research Institute, National Cancer Center, Goyang, Republic of Korea (S.-K.M.); Department of Statistics, Dongguk University, Seoul, Republic of Korea (H.Y.A.); Division of Dental Anesthesiology, Department of Oral Health and Clinical Science, Tokyo Dental College, Suidoubashi Hospital, Tokyo, Japan (K.-i.F.); and Department of Anesthesiology, The Third Xiangya Hospital of Central South University, Changsha, China (Q.L.).

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potency of the exogenous opioid ligands, such as morphine.<sup>4–6</sup> Studies in mouse models with analogous substitution of human *OPRM1* A118G showed reduced analgesic response to morphine in some regions of the mouse brain with the GG genotype when compared with the AA genotype.<sup>7,8</sup> A previous research also showed that *OPRM1* 118A messenger RNA was 1.5- to 2.5-fold more abundant than the 118G messenger RNA in heterozygous brain autopsy tissues. In addition, 118G caused a 10-fold reduction in the protein level of the  $\mu$ -opioid receptor.<sup>9</sup> These findings suggest that the 118G allele may result in an altered function, although clinical studies have not consistently reported an altered pain phenotype.<sup>10</sup>

In contrast to animal studies of standardized pain tests, analgesia in humans is usually evaluated in patients with actual pain, particularly in the settings of cancer and surgery. Patients with acute postoperative pain after standardized procedures may be more optimal candidates for investigating relationships between genes and drug effects.<sup>11</sup> In contrast, it is difficult to study gene–drug effect associations in cancer-related pain, because the mechanism, severity, and nature of pain are highly variable from patient to patient. Like other types of pain, postoperative pain is poorly controlled in the vast majority of patients, which affects outcomes and results in increased medical expenses.<sup>12,13</sup> Opioids are commonly administered for postoperative pain control. Genetic evaluation may be one of the promising tools for clinicians who wish to personalize postoperative management.<sup>14</sup>

We investigated the impact of the *OPRM1* A118G polymorphism on the requirement of opioids in postoperative settings by performing a comprehensive meta-analysis of various factors, such as ethnicity (Caucasians and Asians, the two major groups that have been studied), administered opioids, and type of surgery.

## Materials and Methods

### Information Sources and Search Strategy

Following guidance from the Human Genome Epidemiology Network (HGENet) on gene–disease association studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),<sup>15</sup> we searched PubMed, EMBASE, and the Cochrane Library from their inception to July 17, 2013 without language restrictions. The search terms were “OPRM1 or A118G” and “pain.” A manual review of references from primary and review articles was performed to locate any additional relevant studies.

### Study Selection and Eligibility Criteria

We included original observational studies published in full text and those for which we had full access to all original data and protocols. We primarily excluded reviews, case reports,

and author replies. The polymorphism of *OPRM1* needed to be designated by its single nucleotide polymorphism database identifier (rs1799971) of National Center for Biotechnology Information, messenger RNA nucleotide exchange (118A>G), or Human Genome Variation Society name (c.304A>G) to avoid ambiguity.\* Articles were excluded for the following reasons: (1) the report focused exclusively on other topics, such as addiction or sensitivity; (2) a nonoperative setting (*i.e.*, cancer or labor pain) or opioid-tolerant patients (any chronic pain) were included; (3) no human data were included; (4) no intravenous opioid administration (*i.e.*, intrathecal or epidural) or different outcome measures (*i.e.*, duration of opioid efficacy or numerical rating score) were included; and (5) the human 118A>G variant was not included, or no data were reported for this variant.

### Data Collection Process and Extracted Items

All of the potentially relevant articles were independently reviewed by two investigators (I.C.H. and J.-Y.P.). Disagreements between evaluators were resolved by consensus or consultation with a third author (S.-K.M.). The authors of articles in which data were reported in a format that did not allow inclusion in the meta-analysis were contacted and asked to release data. If only the median and range (min–max) were available, we estimated the mean and SD as proposed by Hozo *et al.*<sup>16</sup> If only the interquartile range was available, we estimated the SD as proposed by the Cochrane handbook with the formula:  $SD = \text{interquartile range}/1.35$ .<sup>17</sup>

The following data were extracted for each study: first author, year of publication, surgery name, race, used opioid, whether genotype frequencies agreed with the Hardy–Weinberg equilibrium (HWE),<sup>18</sup> mean  $\pm$  SD amounts of opioids, and sample size with three or two genotype groups. If a study presented various types of outcomes, we selected only the opioid amounts. Intravenous oxycodone has a similar potency as intravenous morphine (1:1) in patients receiving superficial surgeries, such as thyroid surgery.<sup>19</sup> Therefore, although the exact dose may not be reflected due to the varying properties of different analgesics, we converted the dose of each agent into the equivalent dose of opioids to standardize units. In the case of intravenous fentanyl, we followed the current guidelines based on the results of a comparative study of response to intravenous bolus doses (1:100).<sup>20</sup> In addition, to unify the actual scales for opioid doses, we requested data from authors regarding the total amounts of opioids in their studies.<sup>21–23</sup>

Because there is not sufficient information about the clinical effects associated with different genetic models, we analyzed the data using the dominant, recessive, and additive model, respectively.<sup>24</sup> This required recalculation of the mean and SD,<sup>10</sup> since some of the studies had reported for the three genotype groups. Among points to be considered in genetic association reports,<sup>25</sup> we checked for departure from HWE with Michael H. Court's online calculator to explore the quality of studies.<sup>†</sup> The distributions of the

\* National Center for Biotechnology Information. Available at: [http://www.ncbi.nlm.nih.gov/SNP/snp\\_ref.cgi?type=rs&rs=rs1799971](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?type=rs&rs=rs1799971). Accessed June 10, 2013.

† Available at: [http://www.tufts.edu/~mcourt01/Documents/Court lab - HW calculator.xls](http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20HW%20calculator.xls). Accessed June 10, 2013.

genotypes were not in HWE in some of the studies.<sup>26,27</sup> A deviation from HWE in an association study may be due to many factors, such as genotyping errors, population stratification, enrollment bias, and other artifacts.<sup>28</sup>

### Main and Subgroup Analyses

We primarily investigated the required amounts of opioids in AA homozygotes and G-allele carriers (per the dominant genetic model) during postoperative periods. We also performed subgroup analyses by race (Asian *vs.* Caucasian), administration of opioids (morphine *vs.* fentanyl), type of surgery (visceral *vs.* nonvisceral), and HWE.

### Statistical Analysis

We utilized Higgins  $I^2$  to test heterogeneity by measuring the percentage of total variation across trials.  $I^2$  ranged from 0 to 100% ( $I^2 > 50\%$  showed significant heterogeneity and  $I^2 < 25\%$  indicated insignificant heterogeneity).<sup>29</sup> If substantial heterogeneity was observed, we calculated the difference in means with the DerSimonian and Laird random-effects model, which is the generally preferred approach in these types of cases.

Individual study-effect sizes were calculated with Cohen's  $d$ , which quantified the standardized difference in parameters and was calculated as  $d = \text{Mean}_1 - \text{Mean}_2 / \text{SD}_{\text{combined}}$ . The accepted interpretation is that a value of  $d = 0.2$  indicates a small effect, 0.5 indicates a medium effect, and 0.8 indicates a large effect.<sup>30</sup> Effect sizes were pooled with inverse variance methods to generate a summary of effect size and a 95% CI. We calculated and compared the standardized mean differences (SMDs) between homozygotes for the wild-type A-allele and G-allele carriers.<sup>24</sup>

We performed the Egger's test to construct plots displaying the standardized effect and the corresponding standard errors (precision) to assess potential bias from the effects of a small study.<sup>31</sup> We also performed a trim and fill procedure as sensitivity analysis.<sup>32</sup> All statistical analyses were performed with the Stata SE version 10.0 software package (StataCorp., College Station, TX).

## Results

### Study Selection and Characteristics

Figure 1 shows a flow diagram indicating how relevant studies were identified. Three hundred forty-six articles were identified from three databases, that is, PubMed, EMBASE, and the Cochrane library. After excluding 129 duplicated articles, two authors independently reviewed and excluded an additional 73 nonoriginal articles. We reviewed the full texts of the remaining 144 articles and excluded 126 articles for the following reasons. They addressed an unrelated topic ( $n = 63$ ). The studies were performed in a nonpostoperative setting ( $n = 33$ ). They were not human studies ( $n = 15$ ). They were performed with a different measurement system ( $n = 9$ ), or they provided insufficient data ( $n = 3$ ). Eighteen studies were included in the final analysis.

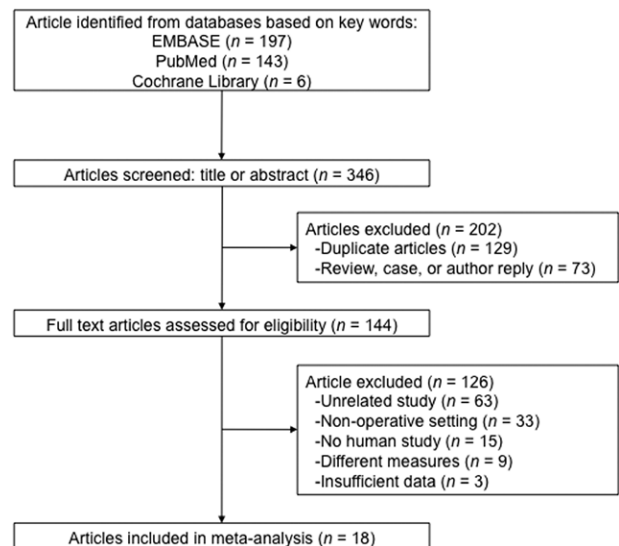


Fig. 1. Flow diagram for identification of relevant articles.

Table 1 shows the general characteristics of the 18 studies included in the final analysis. There were 4,607 participants represented in the 18 studies, including 2,121 with the AA genotype and 2,486 with the AG/GG genotype. The number of participants per study ranged from 68 to 994. The countries in which the studies were conducted were China ( $n = 4$ ),<sup>23,33–35</sup> Singapore ( $n = 3$ ),<sup>36–38</sup> United States ( $n = 2$ ),<sup>39,40</sup> Taiwan ( $n = 2$ ),<sup>26,27</sup> Japan ( $n = 2$ ),<sup>21,22</sup> France ( $n = 1$ ),<sup>41</sup> Estonia ( $n = 1$ ),<sup>42</sup> Denmark ( $n = 1$ ),<sup>43</sup> Italy ( $n = 1$ ),<sup>44</sup> and Korea ( $n = 1$ ).<sup>45</sup> Twelve studies were performed in Asian patients. Sixteen studies were consistent with HWE, and nine studies used morphine. The types of surgery varied. We classified surgeries into two types for our analysis: viscus surgery and nonviscus surgery (*i.e.*, arthroplasty, orofacial surgery, osteotomy, thyroidectomy, and orthopedic surgery).

### Primary Analyses

The relative SMD of the requirement for postoperative opioids in each study is presented in a forest plot, along with the overall results of the meta-analysis. Compared with homozygotes for the wild-type A-allele, G-allele carriers required a higher dose of opioid (SMD,  $-0.18$ ; 95% CI,  $-0.30$  to  $-0.06$ ;  $P = 0.003$ ) with significant heterogeneity ( $I^2 = 66.8\%$ ;  $P < 0.001$ ) (fig. 2). This relationship remained robust regardless of consistent HWE (table 2). The SMD in the dominant genetic model was lower than that in the recessive genetic model for most of the analyses. The results derived from the recessive and additive genetic model are presented in table 3. The current analysis showed a “dose-dependent” effect for the G-allele, with each additional copy increasing the need for opioids (table 4).

### Subgroup Analyses

In the subgroup meta-analysis for ethnicity, we found that the effect in the Asian population was the major contributor to the overall effect of the *OPRM1* A118G polymorphism

**Table 1.** Characteristics of the Included Studies for the Effects of the *OPRM1* 118A>G Polymorphism on the Opioids Requirement for Postoperative Pain

Source	Location	Population	HWE	N	Genotype Frequencies (%)			Opioid	Surgery	Additional Data from Authors
					AA	AG	GG			
Chou <i>et al.</i> , <sup>27</sup> 2006	Taiwan	Asian	NE	120	61.7	27.5	10.8	MOR	Total knee arthroplasty	
Janicki <i>et al.</i> , <sup>39</sup> 2006	Pennsylvania	Caucasian	E	101	69.3	29.7	1.0	MOR	Laparoscopy	
Coulbault <i>et al.</i> , <sup>41</sup> 2006	France	Caucasian	E	74	77.0	20.3	2.7	MOR	Colorectal surgery	
Chou <i>et al.</i> , <sup>26</sup> 2006	Taiwan	Asian	NE	80	53.8	23.8	22.5	MOR	Hysterectomy	
Sia <i>et al.</i> , <sup>36</sup> 2008	Singapore	Asian	E	585	46.3	40.0	13.7	MOR	Cesarean section	
Fukuda <i>et al.</i> , <sup>21</sup> 2009	Japan	Asian	E	280	30.7	51.1	18.2	FEN	Orofacial surgery	Yes†‡
Tan <i>et al.</i> , <sup>37</sup> 2009	Singapore	Asian	E	994	39.1	43.8	17.1	MOR	Cesarean section	
Fukuda <i>et al.</i> , <sup>22</sup> 2010	Japan	Asian	E	108	28.7	50.0	21.3	FEN	Mandibular osteotomy	Yes†‡
Zhang <i>et al.</i> , <sup>33</sup> 2010	China	Asian	E	174	49.4	38.5	12.1	FEN	Gynecologic surgery	
Zhang <i>et al.</i> , <sup>34</sup> 2011	China	Asian	E	164	48.8	37.8	13.4	FEN	Gynecologic surgery	
Kolesnikov <i>et al.</i> , <sup>42</sup> 2011	Estonia	Caucasian	E	102	80.4	19.6		MOR	Lower abdominal surgery	
Zwisler <i>et al.</i> , <sup>43</sup> 2012	Denmark	Caucasian	E	266	82.3	16.2	1.5	OXC	Primarily thyroidectomy	Yes*
Kim <i>et al.</i> , <sup>45</sup> 2013	Korea	Asian	E	196	36.7	49.0	14.3	FEN	Hysterectomy	
De Gregori <i>et al.</i> , <sup>44</sup> 2013	Italy	Caucasian	E	98	68.4	26.5	5.1	MOR	Abdominal/urological surgery	
Zhang <i>et al.</i> , <sup>33</sup> 2013	China	Asian	E	128	42.2	41.4	16.4	FEN	Radical gastrectomy	Yes†‡
Sia <i>et al.</i> , <sup>38</sup> 2013	Singapore	Asian	E	973	36.4	48.7	14.9	MOR	Hysterectomy	
Zhang <i>et al.</i> , <sup>35</sup> 2013	China	Asian	E	96	36.5	46.9	16.7	FEN	Cesarean section	
Henker <i>et al.</i> , <sup>40</sup> 2013	Pittsburg	Caucasian	E	68	75.0	22.1	2.9	Mixed	orthopedic trauma surgery	Yes*

\* Only one genetic model was applicable. † Data of total amounts independent of participants' weights. ‡ No access to full text.

E = equilibrium; FEN = fentanyl; HDC = hydrocodone; HWE = Hardy-Weinberg equilibrium; MOR = morphine; NE = nonequilibrium; OXC = oxycodone.

in the primary analyses. An association between the A118G allele and the requirement for postoperative opioids was observed in Asians, but not in Caucasians (table 2). The G-allele was responsible for the higher amounts of opioids in Asians during the postoperative period (SMD,  $-0.21$ ; 95% CI,  $-0.34$  to  $-0.08$ ;  $I^2 = 68.6\%$ ; random-effects model). In addition, the subanalysis for opioid administration and type of surgery revealed significant effects of this polymorphism in morphine users (SMD,  $-0.29$ ; 95% CI,  $-0.42$  to  $-0.15$ ;  $I^2 = 58.2\%$ ; random-effects model) and subjects receiving viscus surgery (SMD,  $-0.20$ ; 95% CI,  $-0.35$  to  $-0.05$ ;  $I^2 = 73.5\%$ ; random-effects model) (table 2).

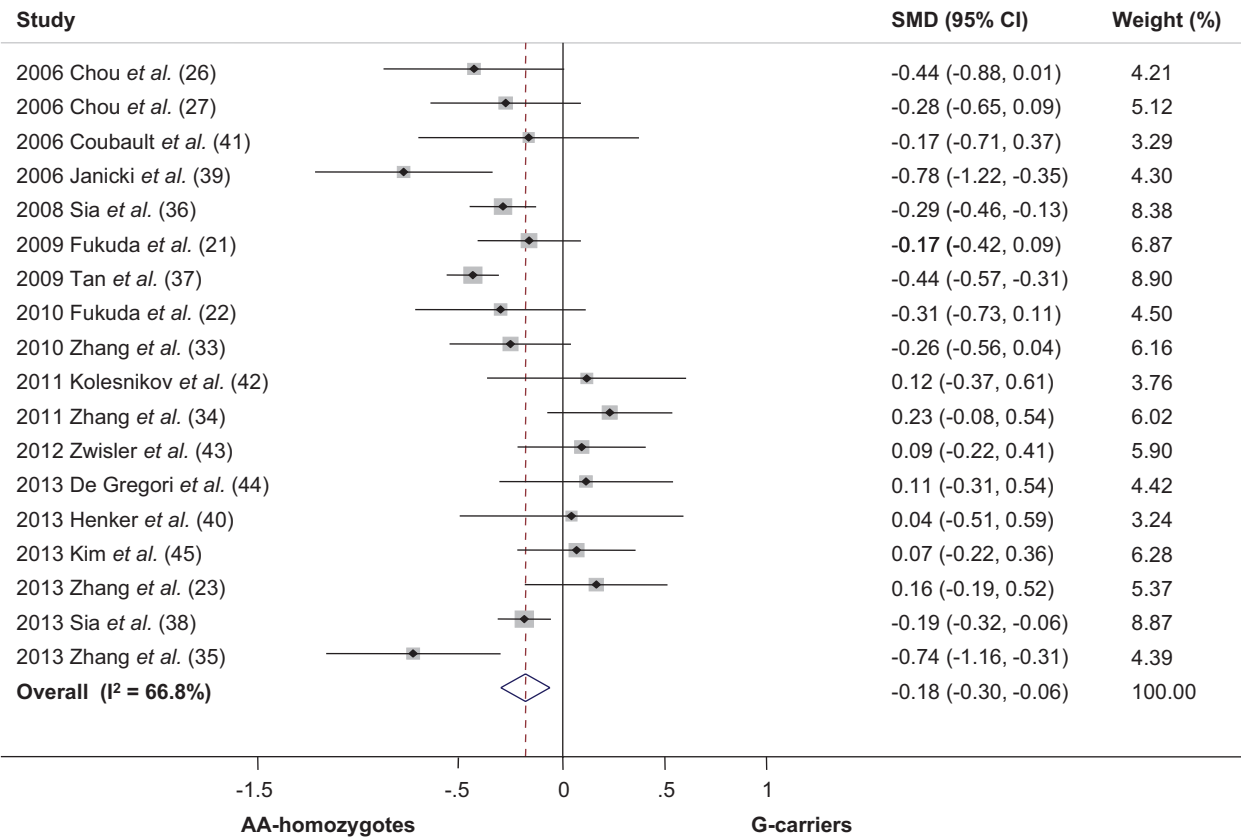
### Publication Bias

The bias plot of the 18 studies included in the main analysis is presented in figure 3. The Egger's test indicated an

absence of heterogeneity among studies and selection biases (bias = 1.04,  $P = 0.247$ ). The trim and filled analysis suggested that three studies were missing. The weighted SMD of 21 studies per the random-effects summary was  $-0.25$  (95% CI,  $-0.38$  to  $-0.13$ ), obtained after symmetrically filling the funnel plot. A significant difference between before and after filling potentially missing studies was not noted ( $P = 0.052$ ) (fig. 4).

### Discussion

There are few data regarding the pharmacogenetic contribution to pain response to opioids. A recent meta-analysis investigating the influence of *OPRM1* A118G on pain response suggested that it was premature to integrate pharmacogenetics into the clinic with respect to pain control.<sup>10</sup> That study included a variety of clinical settings, such as



**Fig. 2.** Effect of the *OPRM1* 118A>G polymorphism on the requirement for postoperative opioids in the dominant genetic model. SMD = standardized mean difference.

**Table 2.** Effect of *OPRM1* 118A>G Polymorphism on Requirement for Postoperative Opioids in Subgroup Meta-analyses by Various Factors

	AA Homozygotes vs. G-carriers				
	No. of Studies	No. of AA	No. of AG + GG	SMD (95% CI)	Heterogeneity, I <sup>2</sup>
All	18	2,121	2,486	-0.18 (-0.30 to -0.06)	66.8%
HWE					
Equilibrium	16	2,004	2,403	-0.16 (-0.30 to -0.03)	70.1%
No equilibrium	2	117	83	-0.35 (-0.63 to -0.06)	0%*
Ethnicity					
Caucasian	6	546	163	-0.09 (-0.39 to 0.59)	61.0%
Asian	12	1,575	2,323	-0.21 (-0.34 to -0.08)	68.6%
Opioids					
Morphine	9	1,407	1,720	-0.29 (-0.42 to -0.15)	58.2%
Fentanyl	7	444	702	-0.12 (-0.34 to 0.09)	67.7%
Type of surgery					
Viscus	13	1,660	2,105	-0.20 (-0.35 to -0.05)	73.5%
Nonviscus	5	461	381	-0.13 (-0.28 to 0.03)	0%*

\* Fixed-effects model.  
HWE = Hardy-Weinberg equilibrium; SMD = standardized mean difference.

cancer, postoperative, labor, and chronic pain. Recently, it, however, has been suggested that not all clinical pain syndromes will be equally affected by a specific pharmacogenetic marker, just as not all pain models are equally responsive to opioids.<sup>46</sup> Therefore, we limited our inclusion criteria to the postoperative setting. The effects of *OPRM1*

A118G on requirements for analgesics for postoperative pain remain controversial.<sup>34,42,43</sup> We performed a meta-analysis of 18 association studies on the response of clinical pain to opioids to gain a clearer picture of the genetic factors. We found that the *OPRM1* genetic variant had overall effects on the requirement for postoperative opioids.

**Table 3.** Association between *OPRM1* 118A>G Polymorphism and Requirement for Postoperative Opioids in the Recessive and Additive Genetic Model

	Recessive Model					Additive Model			
	No. of Studies	No. of A-	No. of GG	SMD (95% CI)	I <sup>2</sup>	No. of A-	No. of -G	SMD (95% CI)	I <sup>2</sup>
All	16	3,783	621	-0.35 (-0.61 to -0.08)	86.0%	3,783	2,435	-0.12 (-0.20 to -0.03)	50.8%
Caucasian	4	493	13	-0.21 (-0.77 to 0.34)	16.7%	493	112	0.03 (-0.17 to 0.24)	0%*
Asian	12	3,290	608	-0.37 (-0.67 to -0.08)	89.3%	3,290	2,323	-0.14 (-0.23 to -0.04)	59.7%
Morphine	7	2,491	433	-0.35 (-0.46 to -0.25)	15.7%	2,491	1,669	-0.17 (-0.24 to -0.11)	0%*
Fentanyl	7	964	182	-0.34 (-1.00 to 0.31)	93.6%	964	702	-0.09 (-0.27 to 0.10)	69.7%
Viscus	11	3,034	528	-0.40 (-0.73 to -0.06)	89.6%	3,034	2,054	-0.13 (-0.24 to -0.02)	62.3%
Nonviscus	5	749	93	-0.24 (-0.67 to 0.19)	60.9%	749	381	-0.07 (-0.20 to 0.06)	0%*

\* Fixed-effects model.

SMD = standardized mean difference.

**Table 4.** The *OPRM1* 118A>G Polymorphism and the Requirement for Postoperative Opioids in Each Genotype

	No. of Studies	AA vs. AG		AG vs. GG		AA vs. GG	
		SMD	P Value	SMD	P Value	SMD	P Value
Overall	16	-0.189	<0.001	-0.217	0.035	-0.396	0.004
Ethnicity							
Caucasian	4	+0.081	0.474	-0.298	0.325	-0.169	0.552
Asian	12	-0.216	<0.001	-0.273	0.047	-0.439	0.004
Opioids							
Morphine	7	-0.195	0.015	-0.216	<0.001	-0.507	<0.001
Fentanyl	7	-0.008	0.182	-0.279	0.359	-0.397	0.228
Type of surgery							
Viscus	11	-0.143	0.034	-0.314	0.050	-0.445	0.011
Nonviscus	5	-0.087	0.300	-0.183	0.395	-0.308	0.016

Appropriate models (fixed-effect or random-effect) were applied in each analysis based on the value of Higgin's I<sup>2</sup>.

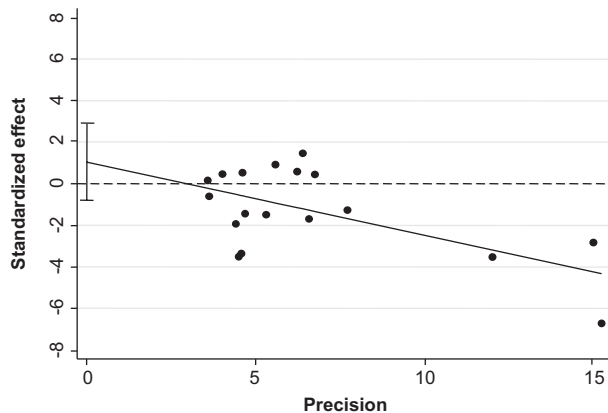
SMD = standardized mean difference.

We observed in this study that the *OPRM1* A118G polymorphism was associated with the requirement for postoperative opioids in Asians, but not in Caucasians. Ethnicity is the major factor explaining variations in pain response.<sup>37,47,48</sup> Despite solid evidence of enormous differences in pain sensitivity and/or analgesia across ethnic groups,<sup>49-51</sup> previous studies for *OPRM1* included little ethnic diversity. The exact mechanisms for this ethnic difference remain unclear but it is possible to postulate as follows: first, the G-allele carriers showed increased pain responses among Asians, leading to a higher dose requirement for analgesics, and similarly these findings were also documented in the postoperative setting.<sup>22,33,34,37,50,52</sup> Second, relatively low frequencies of the 118G minor allele in Caucasians may limit the identification of the association that observed in Asian populations. Third, other putative variants that are in linkage disequilibrium with A118G polymorphism could affect  $\mu$ -opioid receptor function. Assumed that the extent of the linkage disequilibria could be varied by ethnic populations,<sup>51,53</sup> the ethnic difference in responses could be speculated. In addition, polymorphisms in other genes concerning the pharmacokinetics (*i.e.*, *ABCB1*, *CYPs*, or *UGTs*) could influence the response of opioids in a population-specific manner

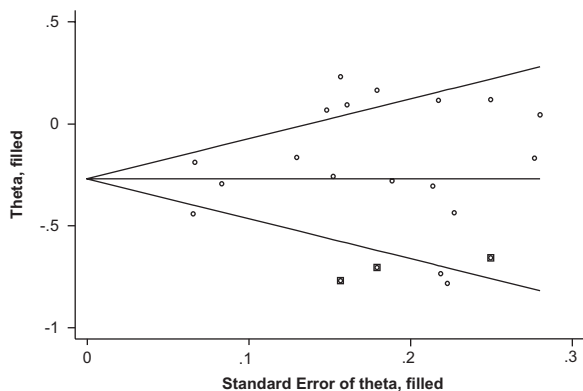
through the changes of blood levels.<sup>54-56</sup> Finally, different environments, which can be ethnically divergent (*e.g.*, rates of smoking or local dietary habits), may also contribute.<sup>57,58</sup>

On the basis of the diverse functional selectivity of *OPRM1*,<sup>59</sup> we further investigated the effects of different types of opioids. Opioids exhibit different affinities for binding sites, which may determine analgesic capacity. Subgroup analysis suggested that the A118G affected the requirement for postoperative morphine but not fentanyl. Our finding was supported by a recent experimental study. In a humanized mouse model, sensory neurons expressing the *118GG* gene displayed reduced morphine (but not fentanyl) potency and efficacy compared with 118AA.<sup>60</sup> This suggests that pharmacogenetic response to opioid agonists may be ligand dependent. However, it should be noted that various opioids including fentanyl exhibit broadly different clinical responses in association with different pharmacokinetic properties.<sup>61,62</sup>

Subanalysis for the type of surgery showed a significant effect of the *OPRM1* A118G polymorphism on viscus surgery. These findings have substantial implications for postoperative pain control, because insufficient analgesia and/or excessive adverse effects often limit the use of opioids, particularly in the viscera. There is solid evidence that visceral



**Fig. 3.** Egger's publication bias plot for association studies of the *OPRM1* A118G polymorphism on postoperative requirement for opioids. The *diagonal line* represents the regression line, and *space between the bar* indicates the 95% confidence limits for the expected distribution of studies in the absence of heterogeneity between studies and absence of selection biases (bias = 1.04,  $P = 0.247$ ).



**Fig. 4.** Trimmed and filled funnel plot ( $n = 21$ ). The plot shows the correlation between the standardized mean difference and its standard error with pseudo 95% confidence limits. *Squares* represent the studies that have been filled. No significant difference was noted between before and after filling studies ( $P = 0.052$ ).

pain, in contrast to somatic pain, is difficult to treat with traditional  $\mu$ -opioid agonists.<sup>63,64</sup> Compared with somatic origin, visceral nociceptive mechanisms are more complex<sup>65</sup> and characterized by the lack of a separate sensory pathway in the central nervous system with few afferent fibers.<sup>66</sup> Clinical observations showed that visceral pain is differentially induced according to the type of stimuli.<sup>67</sup> The effect of *OPRM1* A118G variants on postoperative pain response was prominent only in recipients of viscus surgery. We do not have a clear explanation for this finding, but it is possible that there were many confounding factors.

Several points need to be considered for postoperative opioid doses. The first is the time period during which the opioid was used. Total "perioperative" opioid consumption that is not limited to the postoperative period is likely to be appropriate, although the intraoperative dose was not

significantly influenced by genotype in some studies. The second point to be considered for estimating amounts of opioids is the subject's body weight. "Weight-adjusted dose" is a more appropriate index than total amount according to several studies.<sup>21,22,37,38</sup> Finally, many studies used total opioid dose delivered by patient-controlled analgesia as the primary outcome and surrogate for pain and analgesic response. However, a fundamental question is whether one can conclude that an increase in postoperative opioid consumption administered by patient-controlled analgesia necessarily indicates increased postoperative pain and/or reduced opioid efficacy.<sup>68</sup> This surrogate marker does not take into account other opioid-induced effects, such as euphoria or anxiolysis. Subjects might use more opioids because they feel better regardless of pain levels. This may be reflected in the observed increase in morphine use in one group compared with the other, rather than an increased requirement for analgesia. However, comparisons of opioid requirements for patients with similar pain scores may also be an ethical issue.

There were several limitations in this study. First, the sample size of subgroups not reaching significance was small, and type II error could not be dismissed. This limitation is a crucial determinant of the power to detect a causal variant in genetic association studies.<sup>69</sup> In addition, the lack of enough studies in Caucasian prevented further subanalysis in separate ethnic cohorts. Second, data related to mean dose were not adjusted for other genes (*i.e.*, *COMT*)<sup>42,44</sup> that affect responses to opioids. In addition, data were not adjusted for nongenetic confounders,<sup>41,70-73</sup> such as sex, age, underlying disease, and concomitant multimodal analgesia including nonsteroidal antiinflammatory drugs or paracetamol as an adjuvant regimen. The consequences of genetic polymorphisms may be partly explained by genetic-epigenetic interactions and not by genetics alone. The A118G polymorphism alters transcription of *OPRM1* via methylation of adjacent sites where a cytosine nucleotide occurs next to a guanine nucleotide, decreasing opioid potency.<sup>74</sup> Further large, high-quality randomized controlled trials are required to investigate whether this polymorphism has a true association with postoperative pain response. Third, although the analyses of publication bias did not show a statistical significance, a potential small study bias (including publication bias) could have occurred in our review.

Our meta-analysis provided an evidence that the *OPRM1* A118G polymorphism in *OPRM1* was associated with postoperative pain response in patients who were Asian, used morphine, or received viscus surgery. In this special subpopulation, identifying genotypes and haplotypes of *OPRM1* A118G polymorphism may provide valuable information regarding the individual analgesic doses that are required to achieve satisfactory pain control.

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## Competing Interests

The authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Myung: Molecular Epidemiology Branch, Research Institute, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi-do 410-769, Republic of Korea. msk@ncc.re.kr. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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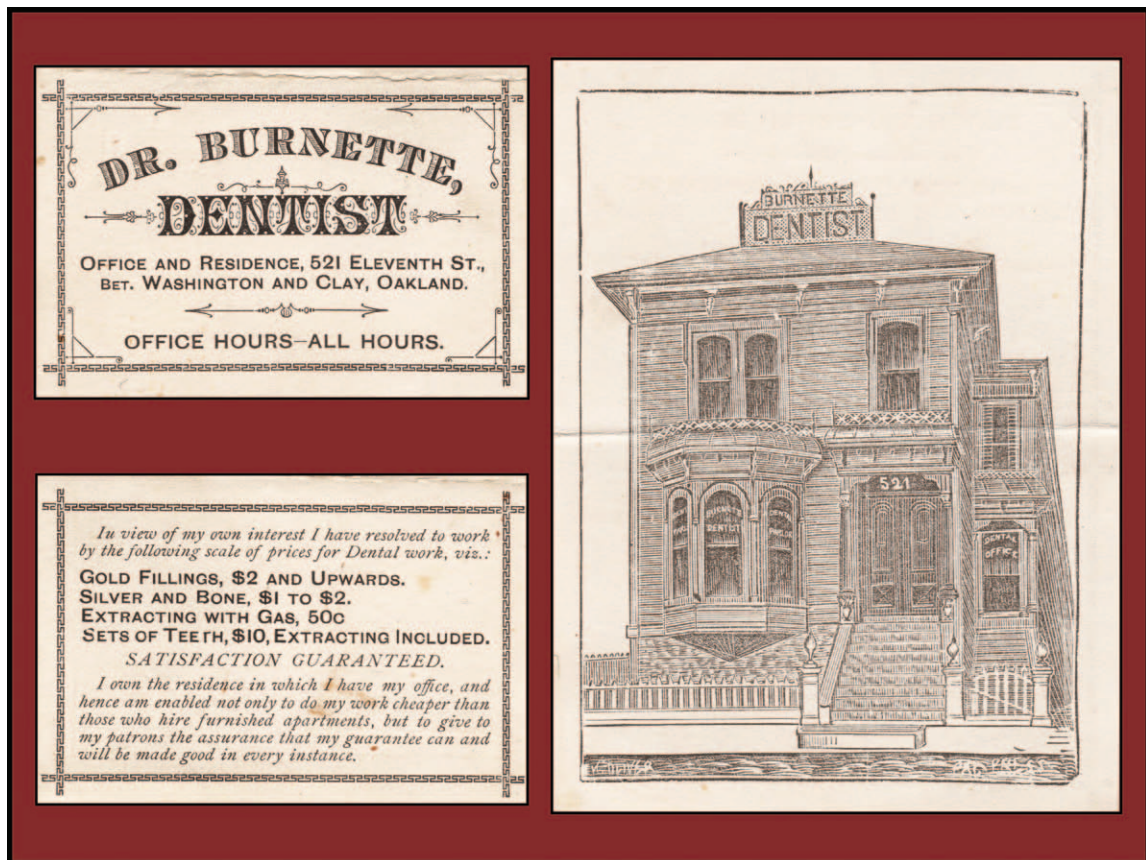


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### Burnette's Folding Trade Card with Laughing "Gas" Surcharge



According to this rare folding trade card issued by Dr. T. C. Burnette, he provided dental extractions with an option for nitrous oxide anesthesia "ALL HOURS" (*upper left*) in Oakland, California. For literacy-challenged patients, this trade card unfolds to reveal an etching (*right*) by "K. Oliver" of the exterior of Burnette's office building. The back of the folded trade card (*lower left*) notes that extracting teeth with "Gas" cost 50 cents or about 5% beyond the \$10 cost extracted from patients for dentures fitted after gas-free dental extractions. This trade card is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.