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. Genetic factors contribute to the differential response to opioids by regulating their pharmacokinetics (metabolizing enzymes and transporters) and pharmacodynamics (receptors and signal transduction). The μ-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. In vitro experiments show that variant receptors are associated with higher binding affinity to and potency of the endogenous ligand, β-endorphin, but lower 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 μ-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 for a viscus

**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 (I² = 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.
potency of the exogenous opioid ligands, such as morphine.\textsuperscript{4–6} Studies in mouse models with analogous substitution of human \textit{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.\textsuperscript{7,8} A previous research also showed that \textit{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.\textsuperscript{9} These findings suggest that the 118G allele may result in an altered function, although clinical studies have not consistently reported an altered pain phenotype.\textsuperscript{10}

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.\textsuperscript{11} 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.\textsuperscript{12,13} 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.\textsuperscript{14}

We investigated the impact of the \textit{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.

\section*{Materials and Methods}

\subsection*{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),\textsuperscript{15} 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.

\subsection*{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 \textit{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.\textsuperscript{*} 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.

\section*{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.\textsuperscript{16} If only the interquartile range was available, we estimated the SD as proposed by the Cochrane handbook with the formula: \textit{SD} = \textit{interquartile range}/1.35.\textsuperscript{17}

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),\textsuperscript{18} mean ± 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.\textsuperscript{19,20} 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).\textsuperscript{21} In addition, to unify the actual scales for opioid doses, we requested data from authors regarding the total amounts of opioids in their studies.\textsuperscript{22–23}

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.\textsuperscript{24} This required recalculation of the mean and SD,\textsuperscript{10} since some of the studies had reported for the three genotype groups. Among points to be considered in genetic association reports,\textsuperscript{25} we checked for departure from HWE with Michael H. Court’s online calculator to explore the quality of studies.\textsuperscript{†} The distributions of the
genotypes were not in HWE in some of the studies. 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.

**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). 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. 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.

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. We also performed a trim and fill procedure as sensitivity analysis. 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 = 1), 41 Estonia (n = 1), 42 Denmark (n = 1), 43 Italy (n = 1), 44 and Korea (n = 1). 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 nonvisceral surgery (i.e., arthroplasty, orofacial surgery, 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.

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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), 23,33–35 Singapore (n = 3), 36–38 United States (n = 2), 29,40 Taiwan (n = 2), 26,27 Japan (n = 2), 24,29 France (n = 1), 41 Estonia (n = 1), 42 Denmark (n = 1), 43 Italy (n = 1), 44 and Korea (n = 1). 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 nonvisceral surgery (i.e., arthroplasty, orofacial surgery, thyroidectomy, and orthopedic surgery).

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

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**Downloaded From:** http://anesthesiology.pubs.asahq.org/pdfsaccess.ashx?url=/data/journals/jasa/931037/ on 06/21/2017
Hwang et al. OPRM1 A118G and Opioid Response

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).

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. The study included a variety of clinical settings, such as

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Population</th>
<th>HWE</th>
<th>N</th>
<th>Genotype Frequencies (%)</th>
<th>Opioid</th>
<th>Surgery</th>
<th>Additional Data from Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al.</td>
<td>Taiwan</td>
<td>Asian</td>
<td>NE</td>
<td>120</td>
<td>AA: 61.7; 27.5; 10.8</td>
<td>MOR</td>
<td>Total knee arthroplasty</td>
<td></td>
</tr>
<tr>
<td>Janicki et al.</td>
<td>Pennsylvania</td>
<td>Caucasian</td>
<td>E</td>
<td>101</td>
<td>AA: 69.3; 29.7; 1.0</td>
<td>MOR</td>
<td>Laparoscopy</td>
<td></td>
</tr>
<tr>
<td>Coulbault et al.</td>
<td>France</td>
<td>Caucasian</td>
<td>E</td>
<td>74</td>
<td>AA: 77.0; 20.3; 2.7</td>
<td>MOR</td>
<td>Colorectal surgery</td>
<td></td>
</tr>
<tr>
<td>Chou et al.</td>
<td>Taiwan</td>
<td>Asian</td>
<td>NE</td>
<td>80</td>
<td>AA: 53.8; 23.8; 22.5</td>
<td>MOR</td>
<td>Hysterectomy</td>
<td></td>
</tr>
<tr>
<td>Sia et al.</td>
<td>Singapore</td>
<td>Asian</td>
<td>E</td>
<td>585</td>
<td>AA: 46.3; 40.0; 13.7</td>
<td>MOR</td>
<td>Cesarean section</td>
<td></td>
</tr>
<tr>
<td>Fukuda et al.</td>
<td>Japan</td>
<td>Asian</td>
<td>E</td>
<td>280</td>
<td>AA: 30.7; 51.1; 18.2</td>
<td>FEN</td>
<td>Orofacial surgery</td>
<td>Yes†</td>
</tr>
<tr>
<td>Tan et al.</td>
<td>Singapore</td>
<td>Asian</td>
<td>E</td>
<td>994</td>
<td>AA: 39.1; 43.8; 17.1</td>
<td>MOR</td>
<td>Colorectal section</td>
<td></td>
</tr>
<tr>
<td>Fukuda et al.</td>
<td>Japan</td>
<td>Asian</td>
<td>E</td>
<td>108</td>
<td>AA: 28.7; 50.0; 21.3</td>
<td>FEN</td>
<td>Mandibular osteotomy</td>
<td>Yes†</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>China</td>
<td>Asian</td>
<td>E</td>
<td>174</td>
<td>AA: 49.4; 38.5; 12.1</td>
<td>FEN</td>
<td>Gynecologic surgery</td>
<td></td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>China</td>
<td>Asian</td>
<td>E</td>
<td>164</td>
<td>AA: 48.8; 37.8; 13.4</td>
<td>FEN</td>
<td>Gynecologic surgery</td>
<td></td>
</tr>
<tr>
<td>Kolesnikov et al.</td>
<td>Estonia</td>
<td>Caucasian</td>
<td>E</td>
<td>102</td>
<td>AA: 80.4; 19.6; 0.0</td>
<td>MOR</td>
<td>Lower abdominal surgery</td>
<td></td>
</tr>
<tr>
<td>Zwisler et al.</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>E</td>
<td>266</td>
<td>AA: 82.3; 16.2; 1.5</td>
<td>OXC</td>
<td>Primarily thyroidectomy</td>
<td>Yes*</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Korea</td>
<td>Asian</td>
<td>E</td>
<td>196</td>
<td>AA: 36.7; 49.0; 14.3</td>
<td>FEN</td>
<td>Hysterectomy</td>
<td></td>
</tr>
<tr>
<td>De Gregori et al.</td>
<td>Italy</td>
<td>Caucasian</td>
<td>E</td>
<td>98</td>
<td>AA: 68.4; 26.5; 5.1</td>
<td>MOR</td>
<td>Abdominal/urological surgery</td>
<td>Yes†‡</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>China</td>
<td>Asian</td>
<td>E</td>
<td>128</td>
<td>AA: 42.2; 41.4; 16.4</td>
<td>FEN</td>
<td>Radicale gastrectomy</td>
<td>Yes†‡</td>
</tr>
<tr>
<td>Sia et al.</td>
<td>Singapore</td>
<td>Asian</td>
<td>E</td>
<td>973</td>
<td>AA: 36.4; 48.7; 14.9</td>
<td>MOR</td>
<td>Hysterectomy</td>
<td></td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>China</td>
<td>Asian</td>
<td>E</td>
<td>96</td>
<td>AA: 36.5; 46.9; 16.7</td>
<td>FEN</td>
<td>Cesarean section</td>
<td></td>
</tr>
<tr>
<td>Henker et al.</td>
<td>Pittsburg</td>
<td>Caucasian</td>
<td>E</td>
<td>68</td>
<td>AA: 75.0; 22.1; 2.9</td>
<td>Mixed</td>
<td>Orthopedic trauma surgery</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

* 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.

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).
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. Therefore, we limited our inclusion criteria to the postoperative setting. The effects of OPRM1 A118G on requirements for analgesics for postoperative pain remain controversial. 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 2. Effect of OPRM1 118A>G Polymorphism on Requirement for Postoperative Opioids in Subgroup Meta-analyses by Various Factors

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

* Fixed-effects model.
HWE = Hardy–Weinberg equilibrium; SMD = standardized mean difference.
We observed in this study that the 

**OPRM1 A118G polymorphism and requirement for postoperative opioids in the recessive and additive genetic model**

<table>
<thead>
<tr>
<th></th>
<th>No. of Studies</th>
<th>No. of A−</th>
<th>No. of GG</th>
<th>SMD (95% CI)</th>
<th>I²</th>
<th>No. of A−</th>
<th>No. of G−</th>
<th>SMD (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>16</td>
<td>3,783</td>
<td>621</td>
<td>−0.35 (−0.61 to −0.08)</td>
<td>86.0%</td>
<td>3,783</td>
<td>2,435</td>
<td>−0.12 (−0.20 to −0.03)</td>
<td>50.8%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4</td>
<td>493</td>
<td>13</td>
<td>−0.21 (−0.77 to 0.34)</td>
<td>16.7%</td>
<td>493</td>
<td>112</td>
<td>0.03 (−0.17 to 0.24)</td>
<td>0%</td>
</tr>
<tr>
<td>Asian</td>
<td>12</td>
<td>3,290</td>
<td>608</td>
<td>−0.37 (−0.67 to −0.08)</td>
<td>89.3%</td>
<td>3,290</td>
<td>2,323</td>
<td>−0.14 (−0.23 to −0.04)</td>
<td>59.7%</td>
</tr>
<tr>
<td>Morphine</td>
<td>7</td>
<td>2,491</td>
<td>433</td>
<td>−0.35 (−0.46 to −0.25)</td>
<td>15.7%</td>
<td>2,491</td>
<td>1,669</td>
<td>−0.17 (−0.24 to −0.11)</td>
<td>0%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>7</td>
<td>964</td>
<td>182</td>
<td>−0.34 (−1.00 to 0.31)</td>
<td>93.6%</td>
<td>964</td>
<td>702</td>
<td>−0.09 (−0.27 to 0.10)</td>
<td>69.7%</td>
</tr>
<tr>
<td>Viscus</td>
<td>11</td>
<td>3,034</td>
<td>528</td>
<td>−0.40 (−0.73 to −0.06)</td>
<td>89.6%</td>
<td>3,034</td>
<td>2,054</td>
<td>−0.13 (−0.24 to −0.02)</td>
<td>62.3%</td>
</tr>
<tr>
<td>Nonviscus</td>
<td>5</td>
<td>749</td>
<td>93</td>
<td>−0.24 (−0.67 to 0.19)</td>
<td>60.9%</td>
<td>749</td>
<td>381</td>
<td>−0.07 (−0.20 to 0.06)</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Fixed-effects model.

SMD = standardized mean difference.

**Table 3.** The 

**OPRM1 A118G polymorphism and requirement for postoperative opioids in each genotype**

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

Appropriate models (fixed-effect or random-effect) were applied in each analysis based on the value of Higgin’s I².

SMD = standardized mean difference.

We observed in this study that the 

**OPRM1 A118G polymorphism and requirement for postoperative opioids in Asians, but not in Caucasians. Ethnicity is the major factor explaining variations in pain response.**37,47,48 Despite solid evidence of enormous differences in pain sensitivity and/or analgesia across ethnic groups,49–51 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.**22,33,34,37,50,52 Second, relatively low frequencies of the 118G minor allele in Caucasians may limit the identification of the association that observed in Asian populations.22,33,34,37,50,52 Third, other putative variants that are in linkage disequilibrium with A118G polymorphism could affect μ-opioid receptor function. Assumed that the extent of the linkage disequilibriums could be varied by ethnic populations,51,53 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.54–56 Finally, different environments, which can be ethnically divergent (**e.g.,** rates of smoking or local dietary habits), may also contribute.57,58

On the basis of the diverse functional selectivity of 

**OPRM1,**59 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.60 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.61,62

Subanalysis for the type of surgery showed a significant effect of the 

**OPRM1 A118G polymorphism on vissus 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
pain, in contrast to somatic pain, is difficult to treat with
traditional μ-opioid agonists.63,64 Compared with somatic
origin, visceral nociceptive mechanisms are more complex65
and characterized by the lack of a separate sensory pathway
in the central nervous system with few afferent fibers.66
Clinical observations showed that visceral pain is differen-
tially induced according to the type of stimuli.67 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.21,22,37,38 Finally, many studies used total opio-
doid dose delivered by patient-controlled analgesia as the pri-
mary outcome and surrogate for pain and analgesic response.
However, a fundamental question is whether one can con-
clude that an increase in postoperative opioid consumption
administered by patient-controlled analgesia necessarily
indicates increased postoperative pain and/or reduced opi-
oid efficacy.68 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.69 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)22,44 that affect responses
to opioids. In addition, data were not adjusted for nongenetic
confounders,41,70–73 such as sex, age, underlying disease, and
concomitant multimodal analgesia including nonsteroidal
antiinflammatory drugs or paracetamol as an adjuvant reg-
imen. 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.74 Further large, high-quality randomized con-
trolled trials are required to investigate whether this polymor-
phism 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 post-
operative pain response in patients who were Asian, used
morphine, or received vicus surgery. In this special subpop-
ulation, 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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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

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.)

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