Letting the Gene out of the Bottle

OPRM1 Interactions

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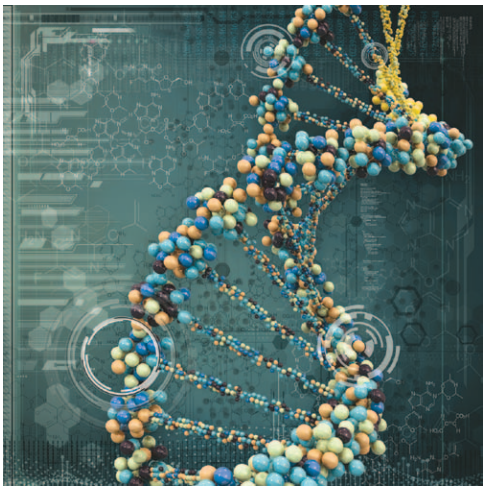
OPIOID analgesics are the most widely used drugs to treat moderate to severe pain. High individual variability has been reported in both pain intensity and in response to pharmacological analgesia. Furthermore, patients' responses vary for both analgesic efficacy and side effects to different opioids, despite the fact that most clinically used opioids are selective for μ-opioid receptors (OPRM1). Thus, there is a considerable need to identify predictive biological markers of opioid therapy outcomes, and genetic markers are among those that have generated both interest and hope. In this issue, Hwang *et al.*[1] present a meta-analysis in which the influence of the *OPRM1* A118G polymorphism on postoperative opioid requirement and analgesic response is evaluated, thereby contributing to a body of literature suggesting that understanding the heritable factors related to analgesic control may provide objective guidance to clinicians.



"… understanding the heritable factors related to analgesic control may provide objective guidance to clinicians."

The single nucleotide polymorphism *A118G* codes for an amino acid substitution Asp to Asn at the codon 40 and it is the most widely studied genetic variant of *OPRM1*. Minor allele *G*, with 24% frequency in Hispanics, 25 to 47.4% in Asians, and 14% in Caucasians was proposed to mediate a significant proportion of the observed variability in clinical effects. However, the molecular and cellular mechanisms by which the *A118G* polymorphism contributes to OPRM1 receptor activation and function are not fully understood. For example, the minor *G* allele has been shown to increase the affinity of the receptor for β-endorphin by three-fold.[2] But others have reported no difference in binding affinity, functional coupling, or internalization of receptor.[3,4] Alternatively, a substantial reduction in the expression of the *G* variant allele at both the RNA and protein levels has been reported.[4,5] In line with the latter findings, it has been reported that the *G* variant introduces a new CpG-methylation site into the *OPRM1* gene locus, resulting in greater epigenetic control over receptor expression down-regulation.[6] It is plausible that opposite molecular regulatory events are affected by the minor *G* allele and the net result of the substitution depends on cell type, state of the cell activation, and nature of ligand.

In parallel with molecular genetic studies, a multitude of association analyses have been conducted for A118G variation and its relationship to various phenotypes including risk of opioid or alcohol dependence, prediction for naltrexone treatment response, and opioid analgesic efficacy. Although meta-analysis of the association between *OPRM1* A118G and naltrexone efficacy for treatment of alcoholism has shown convincing consistency, clinical studies of A118G contribution to opioid analgesic sensitivity have displayed widely varying levels of association. Moreover, the directionality of the minor allele effect(s) is not uniform, with some evidence for G allele carries being less sensitive to opioids.[7]

The current study makes a step toward clarifying the seemingly inconsistent prior findings with a very well-controlled meta-analysis that reveals the essential elements of the relationship between *OPRM1* genotype and opioid analgesia. Using PubMed, EMBASE, and the Cochran Library, the essential studies were identified in which *OPRM1* polymorphism and pain phenotypes were measured in the same-ethnicity population after only surgical procedures in patients who were not suffering from chronic pain before surgery. By analyzing the findings from 18 published studies including 4,607 participants, the authors found that the effect of *OPRM1* A118G on postoperative pain is greatly driven by ethnicity and is most obvious in Asian but not Caucasian patient populations. In agreement with prior studies showing significant differences in pain between ethnic groups,[8] Hwang *et al.*[1] report that ethnicity strongly predicts postoperative need for opioid analgesia and shapes the effect of the *OPRM1* genotype on analgesic response in the way

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Corresponding article on page 825.

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that minor G allele carriers require more opioid analgesics. Although the underlying mechanism(s) for the effects of ethnicity and its interplay with genetic factors are unknown, the authors offer a number of plausible hypotheses that include the relatively low frequency of G allele in Caucasians, the potential for differences in genotypic structure between Asian and Caucasian populations, variations in single nucleotide polymorphism × single nucleotide polymorphism interaction within and outside of *OPRM1* locus, and divergence of environmental pressures.

Furthermore, the authors report that the predictive power of *OPRM1* genotype for postoperative analgesic need is prominent only when patients have undergone visceral as opposed to somatic surgeries. Prior research has shown that μ-opioid agonists can effectively manage postoperative somatic pain but are not particularly well suited to treatment of visceral pain due in part to constipating and dysmotility effects which add significantly to symptom burden.[9] As a result, visceral pain is more medically difficult to treat; and higher doses of OPRM1 agonists that could potentially offer pain relief are contraindicated due to their effects on gastrointestinal function. Perhaps, the strong effect of *OPRM1* genotype on visceral pain is driven by an interaction of these two latter factors: visceral surgery patients require more opioids but they also have stronger side effects which contributes to exacerbation of symptom burden.

Finally, only the OPRM1 effect on morphine but not fentanyl analgesia has been found to be significant. Although this result may be a consequence of difference in the size of the analyzed opioid treatment subgroups, with morphine being the biggest treatment group, this finding may also reflect differential receptor dynamics upon binding different opioid ligands. Along these same lines, both the report of *in vitro* endorphin-specific effects of minor G variants binding[2] and the recent report in a humanized mouse model,[10] where sensory neurons expressing the *118GG* gene displayed reduced morphine (but not fentanyl) potency and efficacy compared with 118AA, would suggest that pharmacogenetic response to opioid agonists may be ligand dependent.

This study has a number of strengths including the careful definition and adherence to selection criteria for the published reports that produced the most homogeneous patient groups for combining the meta-analysis and sufficient power to detect the genetic effect produced by this method compared with original reports that had limited representation of homozygote groups within studied populations. In fact, the study exemplifies how a meta-analysis should be conducted and how important it is to control for critical confounders in association studies testing common genetic variants.

The study, however, may be still underpowered for subanalysis of the Caucasian groups given the lower sample sizes in original reports and lower frequency of minor *G* allele in Caucasians. It should also be noted that the other variations within the *OPRM1* gene locus[11] and in other genes with a known role in opioid pharmacogenetics (*e.g.*, catechol-*O*-methyltransferase functional alleles)[12,13] may further interact with both *A188G* single nucleotide polymorphism and environmental factors affecting pain and analgesia in different ethnic groups. Finally, *OPRM1* genetic variation may influence analgesic requirements and response in sex-specific way, similarly it does in case of pain sensitivity[14] and susceptibility[15] adding more complexity to its ethnic and ligand specificity. Neglecting those complex interactions may result in obscuring the primary effect of the *OPRM1* genotype on the behavioral outcome of postoperative analgesia, misleading the field due to the lack of uniformity and reliability of the reported findings and, consequently, delaying full consideration of *OPRM1* in analgesia in clinical practice.

The foundation of individualized health care rests on the identification of innate and environmental factors that contribute to individual differences in health status and drug response. The current study suggests that a relatively simple model combining genotype, ethnicity, type of *OPRM1* agonist, and type of surgery may eventually allow clinicians to determine a patient's analgesic needs postsurgery and, thereby, guide the medical team for optimum choice of analgesic type and dose well before the day of surgery.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Hwang IC, Park J-Y, Myung S-K, Ahn HY, Fukuda, K, Liao Q: OPRM1 A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis. Anesthesiology 2014; 121:825–34
2. Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L: Single-nucleotide polymorphism in the human μ-opioid receptor gene alters β-endorphin binding and activity: Possible implications for opiate addiction. Proc Natl Acad Sci U S A 1998; 95:9608–13
3. Befort K, Filliol D, Decaillot FM, Gaveriaux-Ruff C, Hoehe MR, Kieffer BL: A single nucleotide polymorphic mutation in the human μ-opioid receptor severely impairs receptor signaling. J Biol Chem 2001; 276:3130–7
4. Beyer A, Koch T, Schröder H, Schulz S, Höllt V: Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human μ-opioid receptor. J Neurochem 2004; 89:553–60
5. Zhang Y, Wang D, Johnson AD, Papp AC, Sadée W: Allelic expression imbalance of human μ-opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 2005; 280:32618–24
6. Oertel BG, Doehring A, Roskam B, Kettner M, Hackmann N, Ferreirós N, Schmidt PH, Lötsch J: Genetic-epigenetic interaction modulates μ-opioid receptor regulation. Hum Mol Genet 2012; 21:4751–60

7. Diatchenko L, Robinson JE, Maixner W: Elucidation of μ-opioid gene structure: How genetics can help predict responses to opioids. Eur J Pain Suppl 2011; 5:433–8
8. Portenoy RK, Ugarte C, Fuller I, Haas G: Population-based survey of pain in the United States: Differences among white, African American, and Hispanic subjects. J Pain 2004; 5:317–28
9. Ahlbeck K: Opioids: A two-faced Janus. Curr Med Res Opin 2011; 27:439–48
10. Mahmoud S, Thorsell A, Sommer WH, Heilig M, Holgate JK, Bartlett SE, Ruiz-Velasco V: Pharmacological consequence of the A118G μ opioid receptor polymorphism on morphine- and fentanyl-mediated modulation of Ca^{2+} channels in humanized mouse sensory neurons. Anesthesiology 2011; 115:1054–62
11. Shabalina SA, Zaykin DV, Gris P, Ogurtsov AY, Gauthier J, Shibata K, Tchivileva IE, Belfer I, Mishra B, Kiselycznyk C, Wallace MR, Staud R, Spiridonov NA, Max MB, Goldman D, Fillingim RB, Maixner W, Diatchenko L: Expansion of the human μ-opioid receptor gene architecture: Novel functional variants. Hum Mol Genet 2009; 18:1037–51
12. Landau R, Liu SK, Blouin JL, Carvalho B: The effect of OPRM1 and COMT genotypes on the analgesic response to intravenous fentanyl labor analgesia. Anesth Analg 2013; 116:386–91
13. Kolesnikov Y, Gabovits B, Levin A, Veske A, Qin L, Dai F, Belfer I: Chronic pain after lower abdominal surgery: Do catechol-*O*-methyl transferase/opioid receptor μ-1 polymorphisms contribute? Mol Pain 2013; 9:19
14. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III: Sex, gender, and pain: A review of recent clinical and experimental findings. J Pain 2009; 10:447–85
15. Olsen MB, Jacobsen LM, Schistad EI, Pedersen LM, Rygh LJ, Røe C, Gjerstad J: Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor μ 1 gene: Evidence of a sex and genotype interaction. J Neurosci 2012; 32:9831–4

OPRM1 A118G Gene Variant and Postoperative Opioid Requirement

A Systematic Review and Meta-analysis

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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.[1] Genetic factors contribute to the differential response to opioids by regulating their pharmacokinetics (metabolizing enzymes and transporters) and pharmacodynamics (receptors and signal transduction).[2]

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.[3] *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 to a viscus

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potency of the exogenous opioid ligands, such as morphine.[4–6] 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.[7,8] 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 μ-opioid receptor.[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.[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.[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.[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.[14]

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),[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.

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.*[16] If only the interquartile range was available, we estimated the SD as proposed by the Cochrane handbook with the formula: SD = interquartile range/1.35.[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),[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.[19] 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).[20] In addition, to unify the actual scales for opioid doses, we requested data from authors regarding the total amounts of opioids in their studies.[21–23]

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.[24] This required recalculation of the mean and SD,[10] since some of the studies had reported for the three genotype groups. Among points to be considered in genetic association reports,[25] we checked for departure from HWE with Michael H. Court's online calculator to explore the quality of studies.† 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. Accessed June 10, 2013.

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

genotypes were not in HWE in some of the studies.[26,27] 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.[28]

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).[29] 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.[30] 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.[24]

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.[31] We also performed a trim and fill procedure as sensitivity analysis.[32] 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.

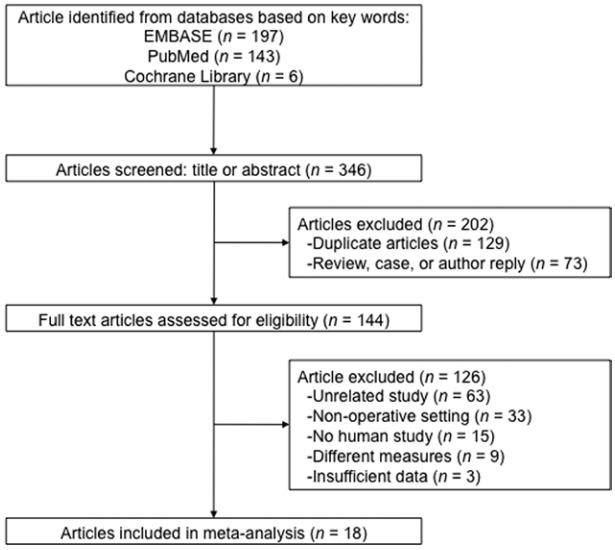

Fig. 1. Flow diagram for identification of relevant articles.

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),[23,33–35] Singapore (n = 3),[36–38] United States (n = 2),[39,40] Taiwan (n = 2),[26,27] Japan (n = 2),[21,22] France (n = 1),[41] Estonia (n = 1),[42] Denmark (n = 1),[43] Italy (n = 1),[44] and Korea (n = 1).[45] 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 *et al.*,[27] 2006	Taiwan	Asian	NE	120	61.7	27.5	10.8	MOR	Total knee arthroplasty	
Janicki *et al.*,[39] 2006	Pennsylvania	Caucasian	E	101	69.3	29.7	1.0	MOR	Laparoscopy	
Coulbault *et al.*,[41] 2006	France	Caucasian	E	74	77.0	20.3	2.7	MOR	Colorectal surgery	
Chou *et al.*,[26] 2006	Taiwan	Asian	NE	80	53.8	23.8	22.5	MOR	Hysterectomy	
Sia *et al.*,[36] 2008	Singapore	Asian	E	585	46.3	40.0	13.7	MOR	Cesarean section	
Fukuda *et al.*,[21] 2009	Japan	Asian	E	280	30.7	51.1	18.2	FEN	Orofacial surgery	Yes*†
Tan *et al.*,[37] 2009	Singapore	Asian	E	994	39.1	43.8	17.1	MOR	Cesarean section	
Fukuda *et al.*,[22] 2010	Japan	Asian	E	108	28.7	50.0	21.3	FEN	Mandibular osteotomy	Yes*†
Zhang *et al.*,[33] 2010	China	Asian	E	174	49.4	38.5	12.1	FEN	Gynecologic surgery	
Zhang *et al.*,[34] 2011	China	Asian	E	164	48.8	37.8	13.4	FEN	Gynecologic surgery	
Kolesnikov *et al.*,[42] 2011	Estonia	Caucasian	E	102	80.4	19.6		MOR	Lower abdominal surgery	
Zwisler *et al.*,[43] 2012	Denmark	Caucasian	E	266	82.3	16.2	1.5	OXC	Primarily thyroidectomy	Yes*
Kim *et al.*,[45] 2013	Korea	Asian	E	196	36.7	49.0	14.3	FEN	Hysterectomy	
De Gregori *et al.*,[44] 2013	Italy	Caucasian	E	98	68.4	26.5	5.1	MOR	Abdominal/ urological surgery	
Zhang *et al.*,[33] 2013	China	Asian	E	128	42.2	41.4	16.4	FEN	Radical gastrectomy	Yes†‡
Sia *et al.*,[38] 2013	Singapore	Asian	E	973	36.4	48.7	14.9	MOR	Hysterectomy	
Zhang *et al.*,[35] 2013	China	Asian	E	96	36.5	46.9	16.7	FEN	Cesarean section	
Henker *et al.*,[40] 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.[10] That study included a variety of clinical settings, such as

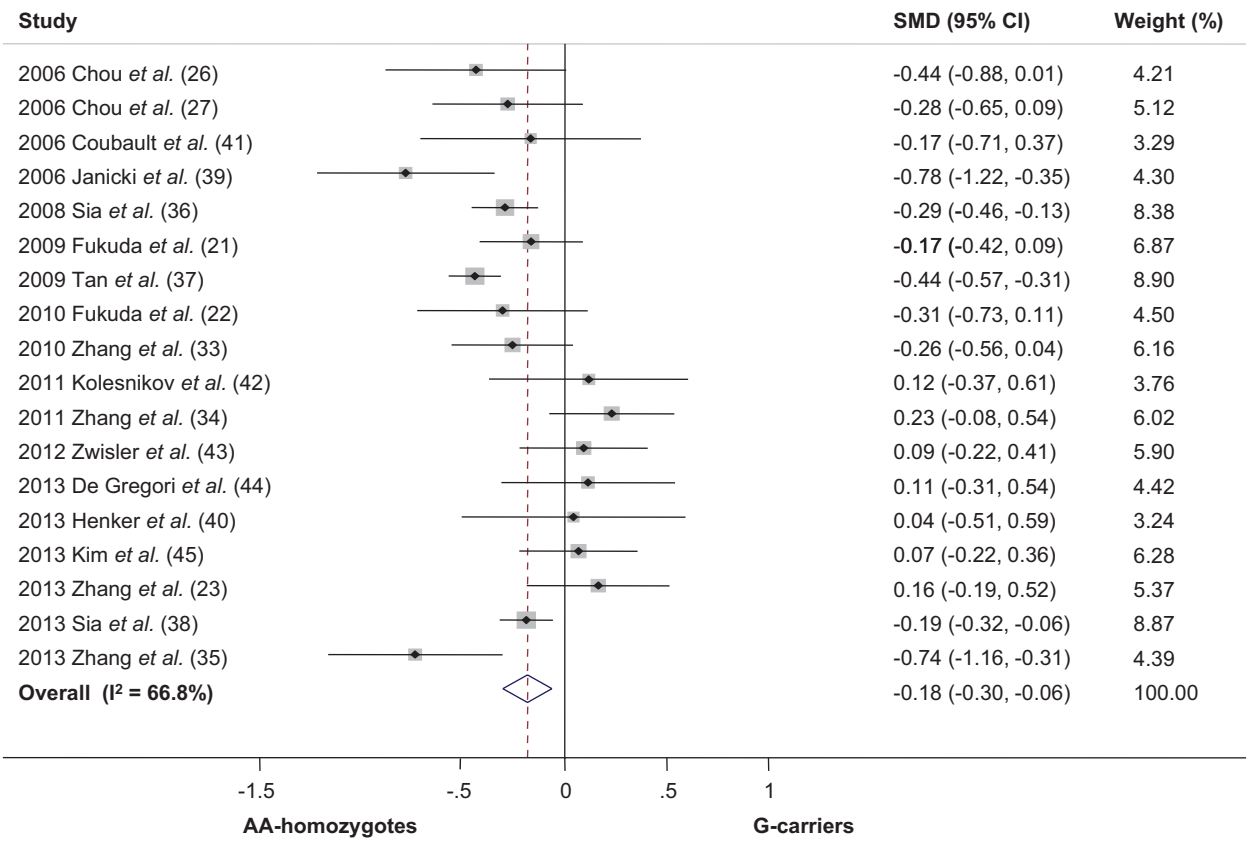

Fig. 2. Effect of the *OPRM1* 118A>G polymorphism on the requirement for postoperative opioids in the dominant genetic model. SMD = standardized mean difference.

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^2
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.[46] Therefore, we limited our inclusion criteria to the postoperative setting. The effects of *OPRM1* A118G on requirements for analgesics for postoperative pain remain controversial.[34,42,43] 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^2	No. of A–	No. of –G	SMD (95% CI)	I^2
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

		AA *vs.* AG		AG *vs.* GG		AA *vs.* GG	
	No. of Studies	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^2.

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.[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. 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 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

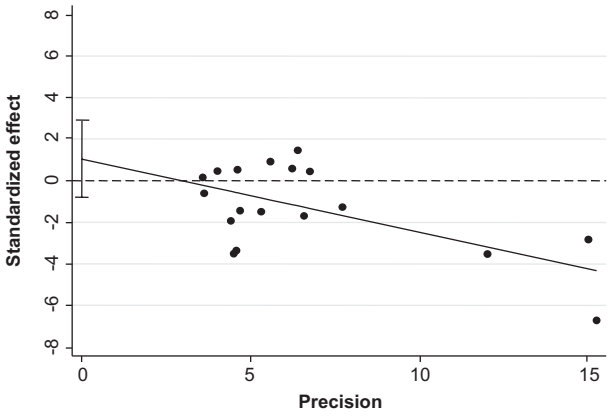

Fig. 3. Egger's publication bias plot for association studies of the *OPRM1* A118G polymorphism on postoperative requirement for opioids. The *diagonal line* represents the regression line, and *space between the bar* indicates the 95% confidence limits for the expected distribution of studies in the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

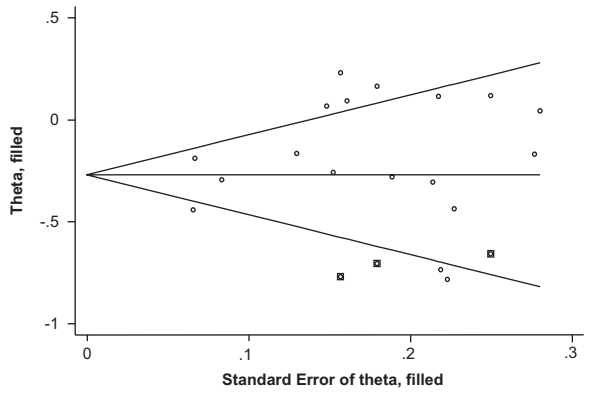

Fig. 4. Trimmed and filled funnel plot (n = 21). The plot shows the correlation between the standardized mean difference and its standard error with pseudo 95% confidence limits. *Squares* represent the studies that have been filled. No significant difference was noted between before and after filling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

pain, in contrast to somatic pain, is difficult to treat with traditional μ-opioid agonists.[63,64] Compared with somatic origin, visceral nociceptive mechanisms are more complex[65] 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 differentially 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 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.[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*)[42,44] 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 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.[74] 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.

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References

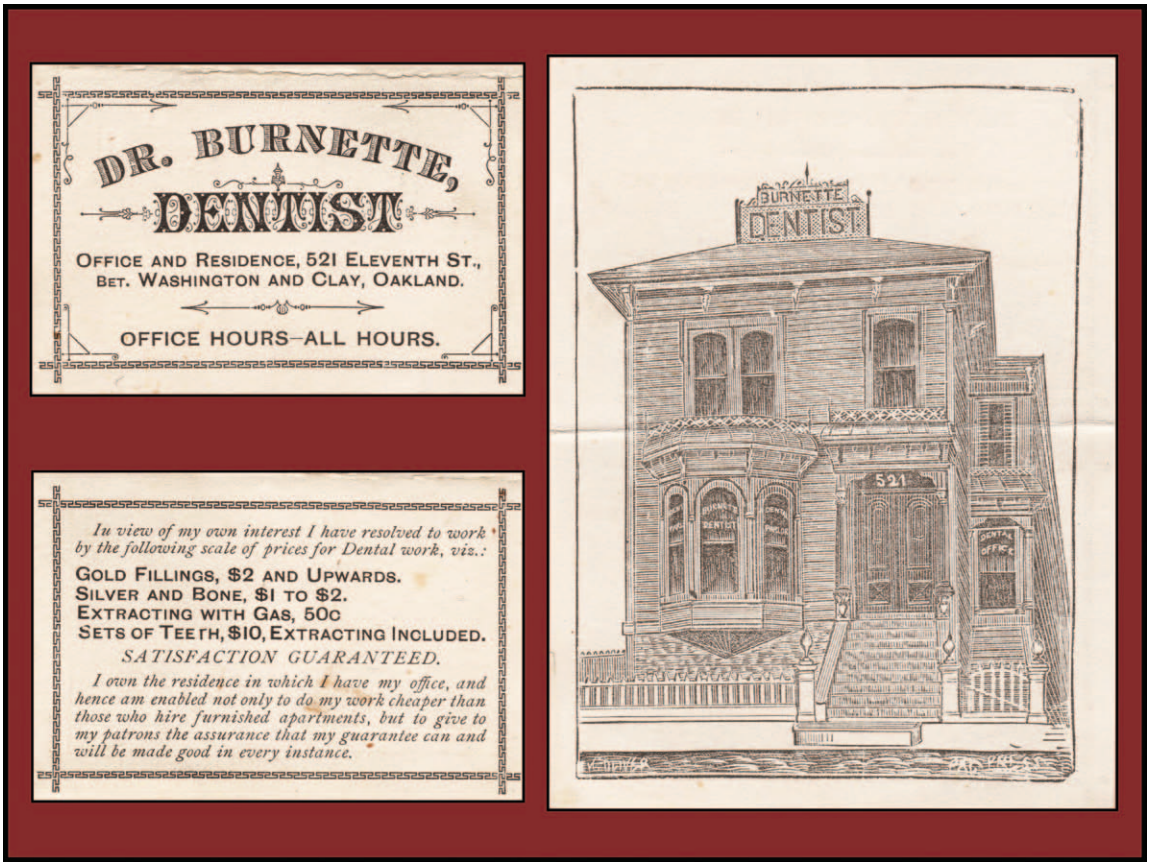
1. Droney J, Riley J, Ross JR: Evolving knowledge of opioid genetics in cancer pain. Clin Oncol (R Coll Radiol) 2011; 23:418–28
2. Somogyi AA, Barratt DT, Coller JK: Pharmacogenetics of opioids. Clin Pharmacol Ther 2007; 81:429–44
3. Mura E, Govoni S, Racchi M, Carossa V, Ranzani GN, Allegri M, van Schaik RH: Consequences of the 118A>G polymorphism in the OPRM1 gene: Translation from bench to bedside? J Pain Res 2013; 6:331–53
4. Beyer A, Koch T, Schröder H, Schulz S, Höllt V: Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. J Neurochem 2004; 89:553–60
5. Kroslak T, Laforge KS, Gianotti RJ, Ho A, Nielsen DA, Kreek MJ: The single nucleotide polymorphism A118G alters functional properties of the human μ opioid receptor. J Neurochem 2007; 103:77–87
6. Oertel BG, Kettner M, Scholich K, Renné C, Roskam B, Geisslinger G, Schmidt PH, Lötsch J: A common human micro-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. J Biol Chem 2009; 284:6530–5
7. Mague SD, Isiegas C, Huang P, Liu-Chen LY, Lerman C, Blendy JA: Mouse model of OPRM1 (A118G) polymorphism has sex-specific effects on drug-mediated behavior. Proc Natl Acad Sci U S A 2009; 106:10847–52
8. Wang YJ, Huang P, Ung A, Blendy JA, Liu-Chen LY: Reduced expression of the μ opioid receptor in some, but not all, brain regions in mice with OPRM1 A112G. Neuroscience 2012; 205:178–84
9. Zhang Y, Wang D, Johnson AD, Papp AC, Sadée W: Allelic expression imbalance of human μ opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 2005; 280:32618–24
10. Walter C, Lötsch J: Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. Pain 2009; 146:270–5
11. Ikeda K, Ide S, Han W, Hayashida M, Uhl GR, Sora I: How individual sensitivity to opiates can be predicted by gene analyses. Trends Pharmacol Sci 2005; 26:311–7
12. Wu CL, Raja SN: Treatment of acute postoperative pain. Lancet 2011; 377:2215–25
13. Costantini R, Affaitati G, Fabrizio A, Giamberardino MA: Controlling pain in the post-operative setting. Int J Clin Pharmacol Ther 2011; 49:116–27
14. Allegri M, De Gregori M, Niebel T, Minella C, Tinelli C, Govoni S, Regazzi M, Braschi A: Pharmacogenetics and postoperative pain: A new approach to improve acute pain management. Minerva Anestesiol 2010; 76:937–44
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6:e1000097
16. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13
17. Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. Oxford, The Cochrane Collaboration, 2011
18. Hardy GH: Mendelian proportions in a mixed population. Science 1908; 28:49–50
19. Kokki H, Kokki M, Sjövall S: Oxycodone for the treatment of postoperative pain. Expert Opin Pharmacother 2012; 13:1045–58
20. Swarm R, Abernethy AP, Anghelescu DL, Benedetti C, Blinderman CD, Boston B, Cleeland C, Coyle N, Deleon-Casasola OA, Eilers JG, Ferrell B, Janjan NA, Karver SB, Levy MH, Lynch M, Moryl N, Murphy BA, Nesbit SA, Oakes L, Obbens EA, Paice JA, Rabow MW, Syrjala KL, Urba S, Weinstein SM; NCCN Adult Cancer Pain: Adult cancer pain. J Natl Compr Canc Netw 2010; 8:1046–86
21. Fukuda K, Hayashida M, Ide S, Saita N, Kokita Y, Kasai S, Nishizawa D, Ogai Y, Hasegawa J, Nagashima M, Tagami M, Komatsu H, Sora I, Koga H, Kaneko Y, Ikeda K: Association between OPRM1 gene polymorphisms and fentanyl sensitivity in patients undergoing painful cosmetic surgery. Pain 2009; 147:194–201
22. Fukuda K, Hayashida M, Ikeda K, Koukita Y, Ichinohe T, Kaneko Y: Diversity of opioid requirements for postoperative pain control following oral surgery—Is it affected by polymorphism of the μ-opioid receptor? Anesth Prog 2010; 57:145–9
23. Zhang F, Liao Q, Li L, Wang SY, Hu R, Tang YZ, Ouyang W: The correlation between post-operative fentanyl requirements and μ-opioid receptor gene A118G polymorphism in patients undergoing radical gastrectomy. Exp Ther Med 2013; 5:1147–52
24. Lettre G, Lange C, Hirschhorn JN: Genetic model testing and statistical power in population-based association studies of quantitative traits. Genet Epidemiol 2007; 31:358–62
25. Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr, Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS: Replicating genotype-phenotype associations. Nature 2007; 447:655–60
26. Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC, Jawan B: Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. ANESTHESIOLOGY 2006; 105:334–7
27. Chou WY, Yang LC, Lu HF, Ko JY, Wang CH, Lin SH, Lee TH, Concejero A, Hsu CJ: Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 2006; 50:787–92
28. Zintzaras E: Impact of Hardy-Weinberg equilibrium deviation on allele-based risk effect of genetic association studies and meta-analysis. Eur J Epidemiol 2010; 25:553–60
29. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539–58
30. Cohen J: A power primer. Psychol Bull 1992; 112:155–9
31. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34

32. Duval S, Tweedie R: Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56:455–63
33. Zhang W, Chang YZ, Kan QC, Zhang LR, Lu H, Chu QJ, Wang ZY, Li ZS, Zhang J: Association of human micro-opioid receptor gene polymorphism A118G with fentanyl analgesia consumption in Chinese gynaecological patients. Anaesthesia 2010; 65:130–5
34. Zhang W, Yuan JJ, Kan QC, Zhang LR, Chang YZ, Wang ZY: Study of the OPRM1 A118G genetic polymorphism associated with postoperative nausea and vomiting induced by fentanyl intravenous analgesia. Minerva Anestesiol 2011; 77:33–9
35. Zhang S, Li S, Tan X: [Human μ-opioid receptor A118G polymorphism affects epidural patient-controlled analgesia with fentanyl]. Nan Fang Yi Ke Da Xue Xue Bao 2013; 33:309–11
36. Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC: A118G single nucleotide polymorphism of human μ-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 2008; 109:520–6
37. Tan EC, Lim EC, Teo YY, Lim Y, Law HY, Sia AT: Ethnicity and OPRM variant independently predict pain perception and patient-controlled analgesia usage for post-operative pain. Mol Pain 2009; 5:32
38. Sia AT, Lim Y, Lim EC, Ocampo CE, Lim WY, Cheong P, Tan EC: Influence of mu-opioid receptor variant on morphine use and self-rated pain following abdominal hysterectomy. J Pain 2013; 14:1045–52
39. Janicki PK, Schuler G, Francis D, Bohr A, Gordin V, Jarzembowski T, Ruiz-Velasco V, Mets B: A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006; 103:1011–7
40. Henker RA, Lewis A, Dai F, Lariviere WR, Meng L, Gruen GS, Sereika SM, Pape H, Tarkin IS, Gowda I, Conley YP: The associations between OPRM 1 and COMT genotypes and postoperative pain, opioid use, and opioid-induced sedation. Biol Res Nurs 2013; 15:309–17
41. Coulbault L, Beaussier M, Verstuyft C, Weickmans H, Dubert L, Trégouet D, Descot C, Parc Y, Lienhart A, Jaillon P, Becquemont L: Environmental and genetic factors associated with morphine response in the postoperative period. Clin Pharmacol Ther 2006; 79:316–24
42. Kolesnikov Y, Gabovits B, Levin A, Voiko E, Veske A: Combined catechol-*O*-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. Anesth Analg 2011; 112:448–53
43. Zwisler ST, Enggaard TP, Mikkelsen S, Verstuyft C, Becquemont L, Sindrup SH, Brosen K: Lack of association of OPRM1 and ABCB1 single-nucleotide polymorphisms to oxycodone response in postoperative pain. J Clin Pharmacol 2012; 52:234–42
44. De Gregori M, Garbin G, De Gregori S, Minella CE, Bugada D, Lisa A, Govoni S, Regazzi M, Allegri M, Ranzani GN: Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. Eur J Clin Pharmacol 2013; 69:1651–8
45. Kim KM, Kim HS, Lim SH, Cheong SH, Choi EJ, Kang H, Choi HR, Jeon JW, Yon JH, Oh M, Shin JG: Effects of genetic polymorphisms of OPRM1, ABCB1, CYP3A4/5 on postoperative fentanyl consumption in Korean gynecologic patients. Int J Clin Pharmacol Ther 2013; 51:383–92
46. Kindler LL, Sibille KT, Glover TL, Staud R, Riley JL III, Fillingim RB: Drug response profiles to experimental pain are opioid and pain modality specific. J Pain 2011; 12:340–51
47. Anderson KO, Green CR, Payne R: Racial and ethnic disparities in pain: Causes and consequences of unequal care. J Pain 2009; 10:1187–204
48. Green CR, Anderson KO, Baker TA, Campbell LC, Decker S, Fillingim RB, Kalauokalani DA, Kaloukalani DA, Lasch KE, Myers C, Tait RC, Todd KH, Vallerand AH: The unequal burden of pain: Confronting racial and ethnic disparities in pain. Pain Med 2003; 4:277–94
49. Hastie BA, Riley JL III, Kaplan L, Herrera DG, Campbell CM, Virtusio K, Mogil JS, Wallace MR, Fillingim RB: Ethnicity interacts with the OPRM1 gene in experimental pain sensitivity. Pain 2012; 153:1610–9
50. Tan EC, Lim Y, Teo YY, Goh R, Law HY, Sia AT: Ethnic differences in pain perception and patient-controlled analgesia usage for postoperative pain. J Pain 2008; 9:849–55
51. Hernandez-Avila CA, Covault J, Wand G, Zhang H, Gelernter J, Kranzler HR: Population-specific effects of the Asn40Asp polymorphism at the mu-opioid receptor gene (OPRM1) on HPA-axis activation. Pharmacogenet Genomics 2007; 17:1031–8
52. Hayashida M, Nagashima M, Satoh Y, Katoh R, Tagami M, Ide S, Kasai S, Nishizawa D, Ogai Y, Hasegawa J, Komatsu H, Sora I, Fukuda K, Koga H, Hanaoka K, Ikeda K: Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. Pharmacogenomics 2008; 9:1605–16
53. Levran O, Awolesi O, Linzy S, Adelson M, Kreek MJ: Haplotype block structure of the genomic region of the μ opioid receptor gene. J Hum Genet 2011; 56:147–55
54. Ameyaw MM, Regateiro F, Li T, Liu X, Tariq M, Mobarek A, Thornton N, Folayan GO, Githang'a J, Indalo A, Ofori-Adjei D, Price-Evans DA, McLeod HL: MDR1 pharmacogenetics: Frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. Pharmacogenetics 2001; 11:217–21
55. Saito K, Moriya H, Sawaguchi T, Hayakawa T, Nakahara S, Goto A, Arimura Y, Imai K, Kurosawa N, Owada E, Miyamoto A: Haplotype analysis of UDP-glucuronocyltransferase 2B7 gene (UGT2B7) polymorphisms in healthy Japanese subjects. Clin Biochem 2006; 39:303–8
56. Bernard S, Neville KA, Nguyen AT, Flockhart DA: Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: Clinical implications. Oncologist 2006; 11:126–35
57. Chen YT, Tsou HH, Kuo HW, Fang CP, Wang SC, Ho IK, Chang YS, Chen CH, Hsiao CF, Wu HY, Lin KM, Chen ACh, Tsai-Wu JJ, Liu YL: OPRM1 genetic polymorphisms are associated with the plasma nicotine metabolite cotinine concentration in methadone maintenance patients: A cross sectional study. J Hum Genet 2013; 58:84–90
58. Zheng H, Zou H, Liu X, Chu J, Zhou Y, Loh HH, Law PY: Cholesterol level influences opioid signaling in cell models and analgesia in mice and humans. J Lipid Res 2012; 53:1153–62
59. Raehal KM, Schmid CL, Groer CE, Bohn LM: Functional selectivity at the μ-opioid receptor: Implications for understanding opioid analgesia and tolerance. Pharmacol Rev 2011; 63:1001–19
60. Mahmoud S, Thorsell A, Sommer WH, Heilig M, Holgate JK, Bartlett SE, Ruiz-Velasco V: Pharmacological consequence of the A118G μ opioid receptor polymorphism on morphine- and fentanyl-mediated modulation of Ca^{2+} channels in humanized mouse sensory neurons. Anesthesiology 2011; 115:1054–62
61. Pasternak GW: Preclinical pharmacology and opioid combinations. Pain Med 2012; 13(suppl 1):S4–11
62. Smith HS: Variations in opioid responsiveness. Pain Physician 2008; 11:237–48
63. Staahl C, Christrup LL, Andersen SD, Arendt-Nielsen L, Drewes AM: A comparative study of oxycodone and morphine in a multi-modal, tissue-differentiated experimental pain model. Pain 2006; 123:28–36
64. De Schepper HU, Cremonini F, Park MI, Camilleri M: Opioids and the gut: Pharmacology and current clinical experience. Neurogastroenterol Motil 2004; 16:383–94
65. Aziz Q, Botha C, Willert R: Pharmacology of visceral pain: Central factors. Dig Dis 2009; 27(suppl 1):31–41
66. Cervero F: Visceral *versus* somatic pain: Similarities and differences. Dig Dis 2009; 27(suppl 1):3–10

67. Ness TJ, Gebhart GF: Visceral pain: A review of experimental studies. Pain 1990; 41:167–234
68. Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B: Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. Anesthesiology 2003; 98:1415–21
69. Spencer CC, Su Z, Donnelly P, Marchini J: Designing genome-wide association studies: Sample size, power, imputation, and the choice of genotyping chip. PLoS Genet 2009; 5:e1000477
70. Edwards RR, Fillingim RB, Ness TJ: Age-related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 2003; 101:155–65
71. Fillingim RB, Gear RW: Sex differences in opioid analgesia: Clinical and experimental findings. Eur J Pain 2004; 8:413–25
72. Gear RW, Miaskowski C, Heller PH, Paul SM, Gordon NC, Levine JD: Benzodiazepine mediated antagonism of opioid analgesia. Pain 1997; 71:25–9
73. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N: Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: A systematic review. Br J Anaesth 2011; 106:292–7
74. Oertel BG, Doehring A, Roskam B, Kettner M, Hackmann N, Ferreirós N, Schmidt PH, Lötsch J: Genetic-epigenetic interaction modulates μ-opioid receptor regulation. Hum Mol Genet 2012; 21:4751–60

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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