Systematic Review

The Relevance of the OPRM1 118A>G Genetic Variant for Opioid Requirement in Pain Treatment: A Meta-Analysis

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Background: There is obvious difference in individual response to opioids. Many studies have examined the correlation between the μ-opioid receptor 1 (OPRM1) 118A>G genetic variation and opioid requirement in pain treatment, but the conclusion remains elusive.

Objectives: To investigate whether the OPRM1 118A>G genetic variation is associated with the opioid requirement.

Study Design: Systematic review and meta-analysis.

Methods: PubMed, Cochrane library, and EMBASE databases were systematically searched up to May 5, 2018, using the keywords “OPRM1,” “genetic variant,” “opioid,” and “pain” to identify reviews or meta-analyses on this topic. Two independent reviewers performed the data extraction and assessed study quality. The authors investigated the standardized mean difference (SMD) of opioid requirement between AA homozygotes and G allele carriers. The authors also examined the association between the OPRM1 118A>G genetic variation and adverse effects such as nausea and vomiting. Potential bias was assessed using the Egger’s test and the Begg’s test.

Results: A total of 530 articles were retrieved from the databases searched, and 36 studies involving 8,609 patients were included in the final analysis. G allele carriers required a higher mean opioid dose (SMD: 0.17; 95% confidence interval [CI]: [0.12, 0.22]; P < 0.001) and displayed less nausea risk difference (RD): –0.04; 95% CI: [–0.06, –0.01]), but the incident rate of vomiting has no relationship than AA homozygotes in a random-effects meta-analysis. Although there was no evidence of publication bias (Begg’s test: P = 0.333; Egger’s: P = 0.561), heterogeneity was present among studies (I² = 54.3%). In the subgroup meta-analyses, there was also significance observed in the postoperative pain setting.

Limitations: In all of the articles reviewed, postoperative pain and cancer pain were mostly discussed except for one in other pain setting.

Conclusions: In this meta-analysis, the results indicate the OPRM1 A118G polymorphism was associated with the opioid requirement and the adverse effects in pain treatment especially in postoperative pain. This may provide valuable information for clinicians to adopt personalized pain management by properly using the opioids in individual patients.

Key words: OPRM1, genetic variation, opioid, pain, side effect, review, meta-analysis

Pain management is mainly relying on drug treatment. Opioids are currently the most effective analgesics used for moderate to severe pain. Morphine, fentanyl, sufentanil, and oxycodone are commonly used opioids in the clinic. However, individual differences in pain sensitivity and response make it difficult for clinicians to use opioids properly. Inappropriate use of opioids may be one
of the main causes of side effects such as nausea, vomiting, respiratory depression, constipation, and others. Therefore, patients are either suffering from inadequate pain relief or suffering from side effects caused by drugs when the opioids are not properly used (1). Genetic factors may be an important cause of these individual differences (2-4). The μ-opioid receptor 1 (OPRM1), a primary binding site for morphine, is an important target for treating pain (5,6). The OPRM1 A118G genetic variation has been a major area of focus for research in the pharmacogenetics study of opioid response (7-9). Some animal or human studies show G carriers have reduced analgesic response to morphine compared with the AA homozygotes (10,11). However, the same correlation was not observed in other studies (12). A large number of research has been conducted to study the correlation between OPRM1 A118G genetic variation and opioid needs and the corresponding adverse effects. Therefore, it is very important to provide accurate evidence to prove the association between OPRM1 A118G genetic variation and opioid requirements in different pain settings that remains elusive. Therefore, a systematic review and meta-analysis was performed to evaluate this association.

METHODS

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions 6 and presented based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search Trials

We searched the PubMed, Cochrane library, and EMBASE databases from the inception dates to May 5, 2018, using the keywords “OPRM1,” “genetic variation,” “opioid,” and “pain” to identify published systematic reviews or meta-analyses evaluating the association between OPRM1 A118G genetic variation and opioid requirements in different pain settings. The references of the identified original articles or review articles were also retrieved and reviewed to provide a complete and precise literature search.

Study Selection and Inclusion Criteria

Two researchers (X.Y.Z. and Y.Y.) independently assessed the articles for their eligibility for inclusion. The following criteria was used to determine the articles eligibility for inclusion, articles must be: 1) randomized or cohort studies; 2) in clinical pain settings including postoperative pain, cancer pain, or other pain; 3) containing opioid dosage requirements; and 4) containing side effects such as nausea, vomiting, and respiration depression.

Data Extraction

Two researchers (X.Y.Z. and Y.Y.) independently extracted the following information from each study: first author, year of publication, race, numbers of patients, genetic variants, whether genotype frequencies agreed with the Hardy–Weinberg equilibrium (HWE), amounts of opioids (mean ± standard deviation [SD]), pain setting, and clinical outcome. Disagreements between the 2 researchers were resolved by consensus or consultation with a third author (F.X.H.). We determined whether the genotype frequencies agreed with HWE by calculating the $\chi^2$ goodness-of-fit. The endpoints of our meta-analysis included opioid consumption and side effects during the pain treatment. When the data format in the articles were not suitable for the analyses, we contacted the article corresponding author to get the data set. If the data included in the article were not complete and the authors could not be contacted for more information, the article was excluded for analysis. The details for identifying qualified studies and the exclusion of the studies are shown in Fig. 1. The main information extracted from the included studies are shown in Table 1.

Statistical Analysis

Data extracted from each article were processed and analyzed using RevMan 5.2 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) and Stata SE Version 12.0 (StataCorp LP, College Station, TX) software packages. We calculated the standardized mean difference (SMD) to standardize the data of opioid consumption because this was represented in different units. We used odds ratio as the parameters of drug side effects. A random-effects model was used to pool the data, and statistical heterogeneity between summary data were evaluated using the $I^2$ statistic. $I^2$ ranged from 0 to 100% ($I^2 > 50\%$ shows significant heterogeneity) (13). The results are illustrated as point estimates and 95% confidence intervals (CIs). We used the Egger’s test and the Begg’s test to construct plots illustrating the standardized effect and the corresponding standard errors to evaluate potential bias.
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Review: the Role of OPRM1 A118G in Pain

The μ-opioid receptor gene OPRM1, a member of the G-protein-coupled receptor superfamily, is one of the genes with a high probability of relevance for pain and pain treatment. It encodes the predominant receptor of opioids, which are still the major analgesics used in pain therapy, and it was among the first pain-related genes screened for functional variants. Genetic variants of OPRM1 were found to be associated with opioid individual responses in different pain conditions including acute postoperative pain (8,14-16), chronic pain (17,18), and cancer-related pain (19,20).

The OPRM1 118 A>G (rs1799971) genetic variation emerged as one of the most promising candidates for a genetic modulation of analgesia. The variant G allele carriers of cancer patients and postoperative patients requires an increase in the doses of morphine to achieve pain control (7,21). Although a meta-analysis showed G allele carriers indeed need an increase in mean opioid dose than in AA homozygotes carriers, the evaluation is only performed in the postoperative pain setting (22).

For the side effects of opioids and OPRM1 A118G, the correlation remains unclear. A study genotyped 165 Chinese women undergoing gynecologic surgery and showed no correlation between OPRM1 A118G with individual variation of postoperative nausea and vomiting, which are common side effects of fentanyl (23). However, some studies showed opposite results that the severity of postoperative nausea and vomiting in carriers of the variant haplotype was significantly lower than in the carriers of the other haplotypes (24).

Results

Study Selection and Characteristics

The details of identifying qualified studies and the exclusion criteria are shown in Fig. 1. A total of 530 articles were retrieved from PubMed, Cochrane library, and EMBASE databases, and 36 studies involving 8,609 patients were included in the final analyses. From the 530 articles, 188 articles were removed owing to duplication, with the remainder independently reviewed by 2 researchers. A total of 91 reviews were excluded. The full texts of the remaining 251 articles were reviewed and among them 215 articles were excluded for the following reasons: 154 articles were not consistent with our research topics; 34 articles were nonhuman experiments; and 27 articles did not have effective data that we needed. In the final analysis, 36 articles were included, of these, 28 articles were regarding the relationship between OPRM1 and opioid demand, and 15 articles and 12 articles included were regarding the study on nausea and vomiting, respectively.

Table 1 shows the general characteristics of the 36 studies included in the final analysis. There were 8,609 patients represented in these studies, and the sample size of each study ranged from 38 to 994. There were 4,586 AA homozygous genotypes and 4,023 G carriers including GG homozygote and AG heterozygote. Sixteen studies chose Caucasians as research subjects, 18 selected Asians, and 2 additional studies included mixed races. The countries in these studies include China (12), United States (5), Japan (3), Singapore (3), France (2), Korea (2), Germany (1), Sweden (1), Finland (1), Norway (1), Lebanon (1), Estonia (1), Czech (1), Denmark (1), and Australia (1). Thirty-one studies were in the postoperative pain setting, 4 studies were in the cancer pain setting, and one study was in another pain setting.

Meta-Analysis of A118G and Opioid Intake Requirement

Opioid consumption data including the numbers, mean dose, and SD of opioid consumption in each group, were available from 28 studies (7,9,11,14,15,19,23,25-46). These studies included 3,782 homozygous 118AA patients and 3,245 118G allele carriers. The relative SMD of the pain treatment requirement for opioids in each study is presented in a forest plot, along with the
Table 1. The general characteristics of the 36 studies included in the final analysis.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Study</th>
<th>Country</th>
<th>Population</th>
<th>N</th>
<th>AA</th>
<th>G carriers</th>
<th>HWE</th>
<th>Setting</th>
<th>Opioid</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>Lee et al (2016) (49)</td>
<td>Korea</td>
<td>Asian</td>
<td>88</td>
<td>36</td>
<td>52</td>
<td>Yes</td>
<td>Postoperative pain</td>
<td>MOR</td>
<td>Nausea</td>
</tr>
</tbody>
</table>

Abbreviations: PIR, Piritramide; MOR, Morphine; OXC, Oxycodone; FEN, Fentanyl; RFEN, remifentanil; SFEN, sufentanil

The overall results of the meta-analysis (Fig. 2). The results showed G allele carriers required a higher dose of opioids when compared with the wild-type AA homozygotes (SMD: 0.17; 95% CI: [0.12, 0.22]; P < 0.001). The heterogeneity was significant (I² = 54.3%; P < 0.001). We performed analysis in the subgroups based on the type of pain setting such as postoperative pain, cancer pain, and other pain. The results are shown in
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In the postoperative pain group, the results showed that G allele carriers required a higher dose of opioids when compared with the requirement for the wild-type AA homozygotes (SMD: 0.18; 95% CI: [0.13, 0.23]; \( P < 0.001 \)). The heterogeneity was not significant (I\(^2\) = 48.7%). In the cancer pain group, similar results were shown. The heterogeneity was also not significant (I\(^2\) = 44.7%).

We used the Egger’s test and the Begg’s test to plot the standardized effect and the corresponding standard errors to evaluate potential bias. The results showed no publication bias in these studies (Fig. 4. Begg’s test: \( P = 0.333 \); Egger’s: \( P = 0.561 \)).

We also conducted the influence analysis, and the results showed that the impacts of these articles on the results were relatively stable, and the quality of the literature was relatively high (Fig. 5).

**Meta-Analysis of A118G and Drug Side Effects**

Data for side effects, including nausea and vomiting, were available from 16 studies (14,23,24,29,30,38,39,42,47-54). They were divided into 2 groups: nausea and vomiting. The nausea group included 1,475 118AA homozygotes and 1,687 118G carriers, whereas the vomiting group included 1,361 118AA homozygotes and 1,521 118G carriers. We performed the analysis in these 2 groups separately (Figs. 6 and 7). For the nausea group, the results showed less nausea events in G carriers than in the AA homozygotes (RD: -0.04; 95% CI: [-0.06, -0.01]), but in the vomiting group, there was no significant correlation found between the A118G and vomiting (RD: 1.29; 95% CI: [0.99, 1.69]).

**Discussion**

OPRM1, ending gene for the predominant receptor of opioids, is one of the genes with a high probability of relevance for pain and pain treatment. Although there has been a meta-analysis about this scheme in 2009 (55), the meta-analysis only included 9 articles. Moreover, their results showed only weak evidence of increased opioid dosage requirements in homozygous carriers of the G allele. The authors did not perform a meta-analysis on the available evidence of the clinical relevance of the OPRM1 118A>G polymorphism. Our meta-analysis and review included 36 articles of OPRM1 A118G and opioid requirement and side effects in pain management. The main findings of our meta-analysis showed that the OPRM1 G allele carriers required a higher mean opioid dose, but the events of nausea were reduced than in AA homozygotes in a random-effects meta-analysis. In another meta-analysis of genetic variation on sensitivity to opioid analgesics in
patients with postoperative pain, the results show that the G carrier is not only related to reduced nausea events but also is related to vomiting (56). This may account for the increased number of studies from our research in recent years (51), which weights 9.8% in the results from 12 articles (Fig. 7), and its results showed there was no significant association between OPRM1 A118G and nausea or vomiting.

Our meta-analysis showed that the sensitivity to opioids of 118G allele carriers had reduced, reflected by increased opioid consumption and reduced nausea events. This can be partially explained by related basic research studies, but for the main findings of the opioid requirement, the heterogeneity of these 28 articles remained high. To investigate the source of this heterogeneity, we carried out the subgroup analysis based on the different pain settings including postoperative pain, cancer pain, and other pain. The results show that this heterogeneity is mainly derived from the different pain settings (Fig. 3).

With the development of gene
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sequencing and bioengineering, it has been possible to prevent and treat diseases through genetic testing. Individual differences make pain treatment very difficult to manage. The research progress on pain-related genes has led to new directions in pain management. Supported by a large amount of literature, and based on our results of meta-analysis, OPRM1 A118G genetic variation has a great influence on the sensitivity of individuals to pain. Based on the type of gene mutation, clinicians may be able to individualize pain treatment to achieve better effects.

CONCLUSIONS

Our meta-analysis also had some limitations. Some other factors including nongenetic ones such as ages, gender, race, and genetic factors like gene-to-gene interaction may also influence the requirement of opioids. Also, only one of the articles included in our
analysis had pain settings other than postoperative pain and cancer pain.

**Acknowledgments**

The authors would like to thank to Professor Chu and Professor Liang for the instructions on this meta-analysis.

**References**


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