Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment

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ABSTRACT

Regard of functional pharmacogenetic polymorphisms may further the success of pain therapy by adopting individualized approaches. The μ-opioid receptor gene (OPRM1) 118A>G polymorphism is a promising candidate for both opioid effects and pain because of both biological reasonability and apparent experimental and clinical evidence. We analyzed its importance for pain therapy using a meta-analytic approach to studies relating it to opioid pain therapy. Data from suitable studies selected from hits of a PubMed search for “OPRM1” were independently extracted by two authors. The meta-analysis included phenotypes by OPRM1 genotype (opioid dosing, pain, and side effects), publication year, diagnostic status, proportion of male study participants, and whether genotype frequencies agreed with Hardy-Weinberg equilibrium. We found no consistent association between OPRM1 118A>G genotypes and most of the phenotypes in a heterogeneous set of eight clinical studies. Only weak evidence of an association with less nausea (effect size, Cohen’s $d = -0.21$, $p = 0.037$) and of increased opioid dosage requirements ($d = 0.56$, $p = 0.018$) in homozygous carriers of the G allele was obtained. This indicates that despite initially promising results, available evidence of the clinical relevance of the OPRM1 118A>G polymorphism does not withhold a meta-analysis. This discourages basing personalized therapeutic concepts of pain therapy on OPRM1 118A>G genotyping at the present state of evidence.

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1. Introduction

The human μ-opioid receptor gene (OPRM1 [44]) variant 118A>G (dbSNP Accession No. rs1799971) has been under investigation since its description [4,46] and the appearance of first reports about a functional consequence for opioid effects [29]. With an allelic frequency ranging from 0.8% in persons with Sub-Saharan ethnicity through 8.2–17% in Caucasians [40] to 48.9% in Asians (for details, see http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1799971), it is carried sufficiently often to be of clinical interest for opioid therapy. Its functional association with pain therapy is biologically reasonable because it affects the main target of clinically relevant opioid analogesics, the μ-opioid receptor. It leads to an exchange of the amino acid asparagine (N) to aspartic acid (D) at position 40 of the extracellular receptor region (N40D) that affects a putative glycosylation site of the receptor [4]. Evidence of a biological function of this variant has been recently provided. It is associated with reduced μ-opioid receptor expression across the brain [47] or with decreased opioid receptor signaling efficiency at the secondary somatosensory area as a pain-relevant brain region [31].

The 118A>G single nucleotide polymorphism (SNP) has therefore been the center of interest of pharmacogenetic research addressing opioids. With emerging evidence of its clinical relevance [19] and therapeutic predictive value [5], inclusion of the 118A>G variant into personalized pain therapeutic concepts is increasingly contemplated. We therefore assessed whether current evidence about the clinical relevance of the OPRM1 118A>G polymorphism for pain therapy withholds a meta-analytic evaluation.

2. Methods

2.1. Search strategy and paper inclusion criteria

A PubMed database search (http://www.ncbi.nlm.nih.gov/sites/entrez) for “OPRM1” on February 15, 2009 resulted in 174 hits. Papers were excluded for the following reasons: (i) no human data or only in vitro assessment, (ii) the human 118A>G variant was not included or no separate data were reported for this variant, which excluded haplotypes without reports of SNP effects, (iii) no clinical data from patients were reported, which excluded preclinical studies employing experimental models in healthy volunteers, (iv) no reference was made to pain or analgesia, which excluded the reports focusing exclusively on addiction, (v) opioid effects were not addressed, which excluded observations of genetic effects but not pharmacogenetic effects, (vi) overlap of reported data between...
papers, in which case the report with the larger sample size was preferred [19,36], (vii) interpretative reports of single cases or small case series without statistical comparisons, and (viii) reviews or letters to the editor without original controlled study data.

### 2.2. Selection of phenotypes

Phenotypes of clinical pain therapy were defined as (i) opioid dosage requirements and the typical clinical effects of opioids subdivided into (ii) analgesia and the so-called side effects. The latter were (iii) respiratory depression, (iv) psychotropic effects such as sedation, (v) tolerance or addiction to opioid analgesics, (vi) nausea and vomiting, (vii) constipation and (viii) “other side effects” such as blurred vision, decreases in heart rate or blood pressure, and itching. Meta-analyses were done when results from more than two authors with subsequent cross-checking and solving of discrepancies. Where data were reported in a format that did not allow inclusion in the meta-analysis, the authors of those papers were contacted directly and asked to release data. As done in a similar analysis [2], for each study the following data were extracted: first author, year of publication, location, diagnostic status, whether genotype frequencies agreed with the Hardy–Weinberg equilibrium [12], which we checked by calculating $\chi^2$ goodness of fit, number of male and female participants, age of sample, and mean, standard deviation, and sample size by three genotype groups according to the number of variant OPRM1 118G alleles. Where more than one study sample was reported, data were treated as subgroups in the same study. Where data were recorded at several occasions, the reports of the paper’s abstract were preferred or the assessment that was most consistent with other assessments of that study was taken.

### 2.3. Data extraction

Data were extracted from eligible papers independently by two authors with subsequent cross-checking and solving of discrepancies. Where data were reported in a format that did not allow inclusion in the meta-analysis, the authors of those papers were contacted directly and asked to release data. As done in a similar analysis [2], for each study the following data were extracted: first author, year of publication, location, diagnostic status, whether genotype frequencies agreed with the Hardy–Weinberg equilibrium [12], which we checked by calculating $\chi^2$ goodness of fit, number of male and female participants, age of sample, and mean, standard deviation, and sample size by three genotype groups according to the number of variant OPRM1 118G alleles. Where more than one study sample was reported, data were treated as subgroups in the same study. Where data were recorded at several occasions, the reports of the paper’s abstract were preferred or the assessment that was most consistent with other assessments of that study was taken.

### 2.4. Statistical analysis

Without concise a priori information about a clinical effect, that is whether it may be conferred already by the mere presence of the variant OPRM1 118G allele or whether it needs to be present homozygously, meta-analyses were repeated for AA versus AG/GG and for AA/AG versus GG genotypes. For most
Mean means and standard deviations were mostly reported for three genotype groups. Meta-analyses were done with the Comprehensive Meta-Analysis software version 2.0 for Windows (Biostat, Inc., Englewood, NJ, USA). Heterogeneity of the sets of studies submitted to meta-analysis was assessed by means of Q statistics [17] and by calculating the value of \( I^2 \) [14] (\( I^2 > 50 \) showing significant heterogeneity and \( I^2 < 25 \% \) indicating insignificant heterogeneity).

Data were analyzed within a random effects framework, and individual study effect sizes were calculated using Cohen’s \( d \), which quantifies the standardized difference in parameter means between the group of interest, \( OPRM1 \) 118G or GG, and the rest of the subjects, AA or AA/AG, respectively, and is calculated as

\[
d = \frac{\text{Mean}_1 - \text{Mean}_2}{\text{SD}_{\text{Combined}}}
\]

The accepted interpretation is a value of \( d = 0.2 \) as indicative of a small effect, 0.5 of a medium and 0.8 of a large effect size [8]. Effect sizes were pooled using inverse variance methods to generate a summary effect size and its 95% confidence interval (95% CI). A random effects framework assumes that between-study variation is due to both chance or random variation and study effect. Random effects models are more conservative than fixed effects models and generate a wider confidence interval. The significance of the pooled effects size was determined using Z statistics. In contrast, a fixed effects framework assumes that the effect of the genotype is constant across studies and between-study variation is due to chance or sampling error. In case of significant effects, moderating effects of sex, age and year of publication and provenance (ethnic origin) of the study population (European versus non-European) were tested using meta-regression of the individual study effect sizes against the respective study characteristics, for example, against the proportion of male study participants in the case of the assessment of the influence of sex. Forest plots were generated to visualize the standardized difference in means between genotype groups and 95% CI per study. Additional Forest plots were generated showing which result of the meta-analysis would have been obtained if the respective study was not included. Publication bias was assessed by testing for classic fail-safe N [35].

3. Results

3.1. Studies included

The final data set consisted of eight clinical studies of 23 studies published between 2002 and 2009 where data on opioid analgesics were reported by \( OPRM1 \) 118A\( \rightarrow \)G genotype (Table 1). Between-study differences included the kind of opioid, parameters recorded (Table 1), study provenance related to the patients’ ethnicity, age and gender distribution, and the adherence of the genotype distri-

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1 Means and standard deviations were mostly reported for three genotype groups. Regrouping the heterozygous subjects to either wild-type or homozygous carriers was done by combining means and standard deviations from two groups. Specifically, combined means were calculated from group means and case numbers as

\[
\text{Mean}_{\text{Combined}} = \frac{n_1 \times \text{Mean}_1 + n_2 \times \text{Mean}_2}{n_1 + n_2}
\]

where \( n \) denotes the case count per group 1 or 2. Standard deviations, SDs, were combined between two groups from the reported values by

\[
\text{SD}_{\text{Combined}} = \sqrt{\frac{(n_1 - 1) \times \text{SD}_1^2 + (n_2 - 1) \times \text{SD}_2^2 + n_1 \times \text{Mean}_1^2 + n_2 \times \text{Mean}_2^2 - (n_1 + n_2) \times \text{Mean}_{\text{Combined}}^2}{n_1 + n_2 - 1}}
\]

In the case of reported 95% confidence intervals, CIs, the respective group’s standard deviation was obtained from means and lower limit of the CI as

\[
SD = \sqrt{n \times (\text{Mean} - \text{CI}_{\text{lower}})^2}
\]

and subsequently combined between groups as shown above.

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In brief, key features of the studies included are as follows (Table 1): Cancer patients (\( n = 99 \)) were screened for effects of four frequent \( OPRM1 \) variants on chronic opioid therapy [19]. Those homozygous for the variant 118G allele (\( n = 4 \)) needed more morphine to achieve pain control than heterozygous (\( n = 17 \)) and homozygous wild-type (\( n = 78 \)) individuals. This investigation was continued and the effects of the 118A\( \rightarrow \)G variant were again addressed in an enlarged cohort [36] that included the first cohort [19]. Again, carriers of an \( OPRM1 \) 118G genotype required higher morphine doses than carriers of the A alleles. Since the two studies overlap, we preferred the second one [36] except for side effects only reported in the earlier study [19]. In another study [6], women (\( n = 80 \)) undergoing elective total hysterectomy surgery carrying the 118G variant consumed more morphine to achieve adequate pain relief via patient-controlled analgesia (33 ± 10 mg) in the first 24 h after surgery than non-carriers (27 ± 10 mg). However, morphine consumption at 48 h was similar between groups. Similarly, morphine consumption in patients undergoing total knee arthroplasty was reported to depend on the 118A\( \rightarrow \)G genotype [7]. Patients with an \( OPRM1 \) 118GG genotype consumed significantly more morphine (40.4 ± 22.1 mg) than those with an AA (25.3 ± 15.5 mg) or AG (25.6 ± 11.7 mg) genotype during the first 48 h postoperatively. A similar pattern of higher morphine requirements in carriers of the variant was seen in 588 women needing postcesarean analgesia [39]. The 24-h self-administered intravenous morphine consumption was lowest in carriers of the 118A allele (mean 5.9 mg) in contrast to 8 mg in carriers of the 118G genotype, and 9.4 mg in homozygous carriers of the G allele. Moreover, pain scores increased with increasing number of G alleles. In a further study [13] investigating the effects of five \( OPRM1 \) SNPs on clinical opioid analgesia in 138 adult Japanese patients who underwent major open abdominal surgery, the 118G homozygous patients required more 24-h postoperative analgesics than heterozygous or wild-type patients. Finally, among 145 patients undergoing morphine-based cancer pain relief therapy [5] AA homozygotes were associated with a significantly higher decrease in pain (decrease in numerical rating scale, \( \Delta \text{NRS} = 3.73 \pm 1.72 \)) than GG homozygotes, whose response was virtually undetectable (\( \Delta \text{NRS} = 0.30 \pm 1.8 \)), whereas heterozygotes (\( \Delta \text{NRS} = 1.95 \pm 1.73 \)) showed no significant difference compared to homozygous carriers of the G allele. These so far apparently consistent findings of higher opioid requirements or less pain relief in carriers of the \( OPRM1 \) 118G allele were only marginally or not at all reproduced, or even contradicted, in three more recent studies. That is, in 352 patients under chronic therapy with various opioids [28], the daily opioid doses ranging from 4 to 1750 mg oral morphine equivalents [43] showed a statistically non-significant (\( \rho = 0.094 \)) tendency toward reduced rather than increased opioid requirements in carriers of the variant G allele (AA: 142.8 ± 221.9 mg, AG: 112.7 ± 126 mg, GG: 34 ± 18 mg). Such an effect directly opposed to the expectations from earlier studies was significant in women receiving fentanyl for labor analgesia [21]. There, the intrathecal fentanyl \( ED_{50} \) for analgesia was 26.8 \( \mu g \) in wild-type patients but was only 17.7 mg in carriers of the variant G allele. The same was seen in a second, parallel, cohort of that study receiving a modified dose allocation strategy. Finally, the \( OPRM1 \) 118G allele could not explain why some pain patients suffering from Crohn’s disease were high-morphine consumers [18], i.e., the genetic association was absent.

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8 Effect sizes were pooled using inverse variance methods to generate a summary effect size and its 95% confidence interval (95% CI). A random effects framework assumes that between-study variation is due to both chance or random variation and study effect. Random effects models are more conservative than fixed effects models and generate a wider confidence interval. The significance of the pooled effects size was determined using Z statistics. In contrast, a fixed effects framework assumes that the effect of the genotype is constant across studies and between-study variation is due to chance or sampling error. In case of significant effects, moderating effects of sex, age and year of publication and provenance (ethnic origin) of the study population (European versus non-European) were tested using meta-regression of the individual study effect sizes against the respective study characteristics, for example, against the proportion of male study participants in the case of the assessment of the influence of sex. Forest plots were generated to visualize the standardized difference in means between genotype groups and 95% CI per study. Additional Forest plots were generated showing which result of the meta-analysis would have been obtained if the respective study was not included. Publication bias was assessed by testing for classic fail-safe N [35].
3.2. Opioid doses

Eight studies, comprising nine independent samples [6,7,13,18,19,21,28,39], contributed to the meta-analysis, which included 677 carriers of the 118G allele and 1005 wild-type subjects with several different clinical settings and diagnoses, opioids and dosing parameters (Table 1). Opioid doses were reported as total 24-h [7,13,19,28,39] or 48-h [6] doses except one paper reporting the fentanyl dose needed to obtain half maximum analgesia quantified as ED50 [21], and one paper reporting the number of patients needing high doses defined as more than two standard deviations above the average dose [18].

Across all studies, the presence of the variant 118G allele (i.e., grouping AA versus AG/GG) was not sufficient to identify an association with opioid dosing by means of the random effects meta-analytic model (d = −0.015, p = 0.93; Fig. 1, top). This negative result did not owe to a single study and therefore no change could be observed when studies were removed one-by-one from the analysis (Fig. 1, top, right Forest plot).

The effects of the homozygous presence of the 118G allele on opioid dosages had to be assessed from a reduced set of studies because data for homozygous women were not reported or provided for a study [21] suggesting lower G allele-associated opioid doses contrasting to several other studies. Reduced data set meta-analysis suggested a medium-sized pharmacogenetic effect, with homozygous subjects requiring higher opioid doses (d = 0.56, p = 0.018; Fig. 1). When any of the studies [6,7,13] was removed from this analysis, the confidence interval of the standardized 118GG effect included zero (Fig. 1, bottom, right Forest plot). The lack of a probably important study was reflected in the significance of classic fail-safe N (p < 0.001) showing publication bias of that reduced study set. This weakened the conclusion of a significant effect in homozygous variant G allele carriers. Meta-regression for the GG study set. This weakened the conclusion of a significant effect in included zero (Fig. 1, bottom, right Forest plot). The lack of a probably important study was reflected in the significance of classic fail-safe N (p < 0.001) showing publication bias of that reduced study set. This weakened the conclusion of a significant effect in homozygous variant G allele carriers. Meta-regression for the GG study set. This weakened the conclusion of a significant effect in included zero (Fig. 1, bottom, right Forest plot). The lack of a probably important study was reflected in the significance of classic fail-safe N (p < 0.001) showing publication bias of that reduced study set. This weakened the conclusion of a significant effect in included zero (Fig. 1, bottom, right Forest plot).

3.3. Pain

Pain data were available from independent samples reported in six studies [5,6,19,28,39]. They included 561 carriers of the 118G allele and 919 wild-type subjects, with several different clinical settings, opioids and dosing parameters (Table 1). Actual 24-h pain was reported from ordinal scales (11 points, ranging from zero for no pain to 10 for maximum pain) in most studies, whereas one reported the differences to baseline pain after two months of morphine treatment [5]. The presence of the G allele was not significantly associated with increased pain (random effects model: d = 0.27, p = 0.074; Fig. 2, top). Homozygous presence of the 118G allele also did not confer increased pain (d = 0.28, p = 0.24; Fig. 2, bottom). This was consistently observed regardless of the removal of single studies from the analysis (Fig. 2, bottom, right Forest plot).

3.4. Side effects

Side effects were not systematically listed and the total number of patients from whom information was available is therefore smaller than those for opioid doses or pain scores. Some studies listed the side effects as number of events or averages of numerical ratings scales, others merely reported the total number of side effects with a mention that the OPRM1 118A>G genotype had no statistically significant association. Only nausea and vomiting were reported more often [6,7,19,28,39]. Meta-analysis of this small data set showed no significant protection conferred by the 118G allele alone (random effects model: d = −0.165, p = 0.139). When one data set [28] was excluded, a slight protective effect of the 118G allele against nausea/vomiting became statistically significant (d = −0.214, p = 0.139). However, a significant protective effect against nausea/vomiting was found with homozygous
of exogenous opioids with N40D

4. Discussion

Decreased pharmacodynamic consequences of the interaction of exogenous opioids with N40D μ-opioid receptors as suggested by molecular analyses [31,47] may be expected to trigger increased opioid requirements and/or decreased wanted and unwanted opioid effects. In preclinical experimental studies this has been found quite consistently (Table 1). However, the present meta-analysis of clinical studies showed that the pharmacogenetic effect translates only to a minor degree to the clinical setting of pain treatment. Although on average the effects pointed toward the expected directions, effect sizes showed wide confidence ranges including zero and the few positive findings were obtained from data sets with significant publication bias. Closest to a relevant pharmacogenetic effect came protection from nausea/vomiting agreeing with an experimental observation [40], however, depending in its significance on the completeness of a small study set.

This analysis thus shows that the accumulated heterogeneous evidence of a functionality of the OPRM1 118A>G polymorphism in pain in pain patients in various clinical settings. Meta-analysis indicates no significant association of the N40D μ-opioid receptor variant. Statistics and Forest plots of the standardized differences in means between groups (top: 118AG/GG versus 118AA, bottom: 118GG versus 118AA/AG) with 95% confidence intervals are shown for each study. The relative weight that each study was given in the meta-analysis is indicated by a bar chart at the right side of the first Forest plot. The second Forest plot at the right side of the figure indicates, for each study, the meta-analysis result that would have been obtained when that particular study had not been included.

The presence of the variant G allele (\(d = -0.21\), \(p = 0.037\)). This protective effect depended on each study in the data set. When any of the studies was removed, it became insignificant.

4. Discussion

Decreased pharmacodynamic consequences of the interaction of exogenous opioids with N40D μ-opioid receptors as suggested by molecular analyses [31,47] may be expected to trigger increased opioid requirements and/or decreased wanted and unwanted opioid effects. In preclinical experimental studies this has been found quite consistently (Table 1). However, the present meta-analysis of clinical studies showed that the pharmacogenetic effect translates only to a minor degree to the clinical setting of pain treatment. Although on average the effects pointed toward the expected directions, effect sizes showed wide confidence ranges including zero and the few positive findings were obtained from data sets with significant publication bias. Closest to a relevant pharmacogenetic effect came protection from nausea/vomiting agreeing with an experimental observation [40], however, depending in its significance on the completeness of a small study set.

This analysis thus shows that the accumulated heterogeneous evidence of a functionality of the OPRM1 118A>G SNP is insufficient to claim its general clinical importance for pain therapy. An important in special clinical settings is also justified by not more than single reports. For example, lower fentanyl requirements in laboring women are based on one study [21], whereas higher postoperative morphine requirements are based on two parallel reports [6,7]. The latter included cohorts compliant with the Hardy–Weinberg law, which may indicate genotyping error [22]. Despite such single positive reports, pooled evidence suggests poor clinical relevance. Therefore, OPRM1 genotyping continues to be of scientific rather than practical clinical interest. This corresponds to the clinical reality of pain therapy that has so far been reluctant to include genotyping, probably because of the perceived unconvincing evidence that is substantiated in the present results.

While additional evidence will increase the basis of a meta-analytic judgment of the relevance of the 118A>G SNP in particular clinical settings and reduce publication bias, the fraction of clinical variance in pain therapy explained by this single variant will probably remain small. The finding of comparatively increased opioid requirements by homozygous 118G carriers explained only 7% of the total between genotype group variance across studies.\(^2\) In the clinical setting, other concomitantly present functional genetic polymorphisms concur with the effects of a single variant [23]. Many non-genetic factors such as gender, compliance, underlying disease, age, and concomitant medications may have greater impact on opioid therapy in the average patient than N40D variant μ-opioid receptors. It has recently even been questioned whether genetics may explain a relevant part of the interindividual variance at all [11]. However, several clinically relevant pharmacogenetic associations in other fields than pain (e.g., treatment with tamoxifen [10], fluorouracil [30], and irinotecan [1]) encourage a cautiously optimistic view of genetics-based approaches to personalized pain therapy. This might include further genes or addressing special sub-populations that may benefit from genotyping.

Besides study heterogeneity and concursing sources of variance, the dual phenotypic effect of the N40D variant as suggested from molecular assessments may have contributed to the poor overall effect. That is, the variant decreases the effects of exogenous opioids [31,47] but appears to increase the effects of endogenous opioids. This may lead to decreased nociception [9,16,27] by increased endogenous opioid tone [4]. Depending on the activation of the endogenous opioid system, opposite effects may be seen, with either increased opioid requirements due to decreased effects of exogenous opioids or decreased opioid requirements due to lower pain following the increased activation of the endogenous opioid system [19,21]. However, the underlying molecular assumptions of increased endorphin binding [4] or decreased efficiency of exogenous opioids [31] at the variant N40D μ-opioid receptors have to acknowledge their non-reproduction at the molecular level [3,20].

In summary, despite several clinical investigations of the OPRM1 118A>G SNP, the available evidence of its clinical relevance does not withhold a meta-analysis. At best, a slight protection from nausea and possibly, but with even weaker evidence basis, a slight increase in opioid requirements can be expected for homozygous carriers. This discourages broadly basing personalized concepts of

\(^2\) Cohen’s d can be transformed into a value of \(r^2\) [26] indicating the fraction of explained variance from the total variance by \(r^2 = \left(\frac{d}{\sqrt{d^2 + 4}}\right)^2\). It follows that correlations of 0.1, 0.3, and 0.5 correspond to standardized differences in means of 0.20, 0.63, and 1.15 [27].
pain therapy on OPRM1 118A>G genotyping at the present state of evidence.

Conflict of interest

The authors declare no conflict of interest.

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