

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 sug-

gesting that 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



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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 direction-

ality of the minor allele effect(s) is not uniform, with some evidence for *G* allele carriers 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 Cochrane 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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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 \times 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 binding² 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 sub-analysis 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 locus¹¹ 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 sensitivity¹⁴ and susceptibility¹⁵ 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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