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Association of Genetic Variants with Postsurgical Pain: A Systematic Review and Meta-analyses

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Abstract

Background: Postsurgical pain is a key component of surgical recovery. However, the genetic drivers of postsurgical pain remain unclear. A broad review and meta-analyses of variants of interest will help investigators understand the potential effects of genetic variation.

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Competing Interests

Dr. Brummett is a consultant for Heron Therapeutics (San Diego, California) and Vertex Pharmaceuticals (Boston, Massachusetts) and has received one-time consultancy fees from the Benter Foundation (Pittsburgh, Pennsylvania) and Alosa Health (Boston, Massachusetts). He also provides expert witness consultation. None of these disclosures are relevant to the work presented. Dr. Bicket has received grants from the National Institutes of Health (Bethesda, Maryland), grants from the Centers for Disease Control and Prevention (Atlanta, Georgia), grants from the Michigan Department of Health and Human Services (Lansing, Michigan), grants from the Arnold Foundation (Washington, D.C.), and grants from the Patient-Centered Outcomes Research Institute (Washington, D.C.) outside the submitted work. The other authors declare no competing interests.

Methods: This article is a systematic review of genetic variants associated with postsurgical pain in humans, assessing association with postsurgical pain scores and opioid use in both acute (0 to 48 h postoperatively) and chronic (at least 3 months postoperatively) settings. PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from 2000 to 2022 for studies using search terms related to genetic variants and postsurgical pain in humans. English-language studies in adult patients examining associations of one or more genetic variants with postsurgical pain were included. The primary outcome was association of genetic variants with either acute or chronic postsurgical pain. Pain was measured by patient-reported pain score or analgesic or opioid consumption.

Results: A total of 163 studies were included, evaluating 129 unique genes and 594 unique genetic variants. Many of the reported significant associations fail to be replicated in other studies. Meta-analyses were performed for seven variants for which there was sufficient data (*OPRM1* rs1799971; *COMT* rs4680, rs4818, rs4633, and rs6269; and *ABCB1* rs1045642 and rs2032582). Only two variants were associated with small differences in postsurgical pain: *OPRM1* rs1799971 (for acute postsurgical opioid use standard mean difference = 0.25; 95% CI, 0.16 to 0.35; cohort size, 8,227; acute postsurgical pain score standard mean difference = 0.20; 95% CI, 0.09 to 0.31; cohort size, 4,619) and *COMT* rs4680 (chronic postsurgical pain score standard mean difference = 0.26; 95% CI, 0.08 to 0.44; cohort size, 1,726).

Conclusions: Despite much published data, only two alleles have a small association with postsurgical pain. Small sample sizes, potential confounding variables, and inconsistent findings underscore the need to examine larger cohorts with consistent outcome measures.

More than 100 million surgical procedures are performed in the United States each year, and up to 80% of patients experience postsurgical pain.[1] Patients with higher levels of pain after surgery are more likely to develop persistent pain and opioid use,[2] feeding into a chronic pain epidemic that has a greater annual societal cost than that for cancer, heart disease, and diabetes combined.[3] Unfortunately, for a condition that is widespread and with significant financial and societal costs, there is insufficient knowledge of the pathophysiology of postsurgical pain. Several risk factors have been identified, such as the presence of presurgical pain[4] and specific surgical factors like invasiveness, location, and likelihood of nerve injury.[5,6] However, although these risk factors are informative, they do not fully predict the interpatient variability of postsurgical pain and offer limited insight into the pathophysiology of pain.[7]

Over the last decade and a half there has been increased investigation into genetic factors that may influence the development and degree of postsurgical pain. However, identification has proven difficult due to inconsistent findings and poor replicability of results.[8] Pharmacogenomic analyses, which focus on interpatient variability of opioid pharmacokinetics, differ in key characteristics from investigations of genes that influence the development, sensitization, and chronification of postsurgical pain. While there has been a significant amount of research into the pharmacogenomics of opioid therapy, consensus guidelines have focused on a small number of genes and variants and note mixed and inconsistent evidence for the association with analgesia or opioid requirements.[9]

The inconsistent results for genes and variants associated with postsurgical pain can partially be explained by differing patient and surgical populations and/or various outcome measures, but there is still often little consensus on the degree (and even direction) of association for any particular allele. As an example, the *OPRM1* A118G (rs1799971) allele is the most researched variant in terms of postsurgical pain, with several studies reporting increased pain scores and opioid requirements with the G allele.[10–19] However, numerous other studies have shown no significant difference between genotypes,[20–29] with some even reporting an inverse relationship of genotype and postsurgical pain (*i.e.*, the A allele is associated with more postsurgical pain or opioid requirement).[30] Conflicting results such as these confound attempts to create a unified understanding of postsurgical pain genetics. The identification of verified and validated genetic targets would potentially allow for targeted prediction, prevention, and treatment of postsurgical pain.

The purpose of this systematic review was to summarize the entirety of the literature regarding genetic variation that has been associated with or implicated in the variable development of postsurgical pain. Here, we report on all genetic variants that have been investigated for association with postsurgical pain, regardless of whether a significant association was found or not. For those individual alleles for which there was sufficient data, we conducted meta-analyses to compile the data from several studies into a single estimate of effect. The data from the included studies was grouped as acute (0 to 48 h postoperatively) or chronic (more than 3 months postoperatively), as well as assessing postsurgical pain *via* patient-reported pain scores or opioid consumption.

Materials and Methods

Search Strategy and Information Sources

Literature searches and meta-analysis were conducted and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Supplemental Table 1, https://links.lww.com/ALN/D220).[31,32] Before initiating the review, we uploaded a protocol to the Prospero online database (Prospero ID CRD42022320424). Briefly, we searched the National Library of Medicine PubMed, Elsevier Embase, and Wiley Cochrane Central Register of Controlled Trials databases for studies on genes and variants associated with postsurgical pain. The time frame of the search was from January 2000 to June 2022. A detailed description of our search strategy is provided in the Supplemental Methods (https://links.lww.com/ALN/D213).

Study Selection Criteria

We searched for English-language studies in adult patients examining associations of one or more genetic variants with postsurgical pain. The following exclusion criteria were used: not in English; not in a surgical population; lacks data specific to adult population (18 yr of age or older); publication date before 2000; and did not refer to postsurgical pain. Full-text articles were then retrieved and reviewed to verify inclusion in the final review. Any disagreements were discussed between the authors. The review exclusion criteria were the following: does not meet initial eligibility criteria (confirmation of primary screening);

is not primary literature or data (*i.e.*, reviews or meta-analyses); does not compare genetic factors contributing to patient postsurgical pain; and does not specify specific genes, alleles, or variants contributing to postsurgical pain. Those articles that were not excluded in the abstract or title or full-text screening comprised our final list of included studies.

Outcomes

The primary outcome was postsurgical pain, determined as either total analgesic use or patient-reported pain scores. Analgesic use and pain scores were not converted to oral morphine equivalents or standardized pain scores, respectively. The exception was if multiple opioids were utilized; the dosages were then converted to oral morphine equivalents for comparison between groups within the same analysis.[33]

Data Extraction

For each included study, data on both the study characteristics and reported alleles or single nucleotide polymorphisms were recorded. Study characteristics included: first author, year published, title, PubMed ID (if applicable), type of study, and total number of participants. Data on outcomes were extracted and included surgical type(s), outcome type, outcome measurement, analgesic(s) used (if applicable), continuous *versus* categorical outcomes, and outcome time point(s). For each study, data regarding each reported variant was extracted and included gene or genetic locus, variant identifier (*i.e.*, rs#), DNA change or substitution, genetic region, amino acid change (if applicable), minor allele frequency (if reported or able to be calculated), whether the association of the individual variant was statistically significant, and direction of association (if applicable). Gene functions were assigned based on the categories detailed by Zorina-Lichtenwalter *et al.*[34]

Meta-analyses

Meta-analyses were performed on selected single nucleotide polymorphisms for which data were sufficient (defined as three or more studies with 300 or more total subjects), comparable, and extractable. We extracted data from those studies for which means and standard deviations were reported or could be derived. For those studies selected to be included in one or more meta-analyses, the Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E) tool was used to assess each study's risk of bias and strength of evidence.[35] The results of the ROBINS-E assessment for each study are shown in Supplemental Table 2 (https://links.lww.com/ALN/D221). Correction for multiple comparison was performed *via* Bonferroni test and significance set at $P = 0.01$ (the rationale for this value is detailed in the Supplemental Methods, https://links.lww.com/ALN/D213). Time periods were defined as acute (0 to 48 h post-operatively) or chronic (at least 3 months postoperatively); there were limited studies reporting on the 48-h to 3-month time period. Detailed methods for the meta-analyses are provided in the Supplemental Methods (https://links.lww.com/ALN/D213).

Results

Study Selection

We obtained 3,895 results from the combined PubMed, Embase, and Cochrane Library searches. We manually eliminated 840 duplicates using the EndNote20 citation manager. The remaining results were inputted into the Covidence web platform, and an additional 126 duplicates were identified. The titles and abstracts of 2,929 studies were then screened for relevance. Subsequently, 2,671 studies were excluded, leaving 258 studies for full text assessment. After further excluding 96 studies (list of studies and reasons for exclusion shown in Supplemental Table 3, https://links.lww.com/ALN/D222) and including 1 from manual curation, a total of 163 studies were included in the final review (Supplemental Table 4, https://links.lww.com/ALN/D223). A PRISMA flowchart is shown in Supplemental Figure 1 (https://links.lww.com/ALN/D214).

Characteristics of Included Studies and Identified Genetic Associations

The included studies were conducted between 2003 and 2022, with most conducted between 2010 and 2016. Six genome-wide association studies evaluated the association with variants across the genome, while 157 targeted gene or variant association analyses. Only one genome-wide association study had a cohort size greater than 500 (n = 613). The studies were fairly heterogeneous in regard to surgical procedures, outcome time frames, and pain assessment. The majority (more than 80%) of studies had cohort sizes of less than 400 participants. The summary characteristics of the included studies and their cohorts are detailed in table 1, with a detailed list of each included study presented in Supplemental Table 5 (https://links.lww.com/ALN/D224).

Table 2 shows the summary characteristics of all identified genes and variants; there were 129 unique genes investigated by the included studies, with a total of 594 separate genetic variants. A list of all variants reported to have a statistically significant association with postsurgical pain in at least 1 study is shown in Supplemental Table 6 (https://links.lww.com/ALN/D225); 35 alleles were investigated by at least 3 studies, with less than half (n = 14, 40%) found to be significant in at least 50% of their reporting studies. The complete details of each investigated gene and variant are presented in Supplemental Table 7 (https://links.lww.com/ALN/D226). The most common functions of the examined genes were neurotransmission and immune response, both among all genes (n = 51 [40%] and n = 28 [22%], respectively) and among the 80 genes identified as significantly associated with postsurgical pain in at least 1 study (n = 35 [44%] and n = 14 [18%], respectively).

Meta-analyses

Seven single nucleotide polymorphisms in three genes met the criteria to perform meta-analysis (*OPRM1* rs1799971, *COMT* rs4680, *COMT* rs4818, *COMT* rs4633, *COMT* rs6269, *ABCB1* rs1045642, and *ABCB1* rs2032582). Where possible, we evaluated the association of each single nucleotide polymorphism with both postsurgical pain scores and opioid use, in both acute and chronic settings and under both recessive and dominant inheritance models. Of the 25 meta-analyses performed, only 3 showed statistically significant associations, and almost half (12 of 25) had at least moderate heterogeneity

(I^2 greater than or equal to 50%; table 3; Supplemental Fig. 2, https://links.lww.com/ALN/D215; Supplemental Fig. 3, https://links.lww.com/ALN/D216; Supplemental Fig. 4, https://links.lww.com/ALN/D217; Supplemental Fig. 5, https://links.lww.com/ALN/D218; Supplemental Fig. 6, https://links.lww.com/ALN/D219).

OPRM1 rs1799971

A total of 57 studies evaluated the association of the rs1799971 allele with postsurgical pain. Only the dominant model was used for analysis as the minor (G) allele has a low frequency in several Caucasian populations.[36] We found the presence of the G allele to be significantly associated with increased opioid use in the acute post-surgical period (standard mean difference, 0.25; 95% CI, 0.16 to 0.35; $P < 0.00001$; Supplemental Fig. 2A, https://links.lww.com/ALN/D215). The presence of this allele was also associated with increased acute post-surgical pain scores (standard mean difference, 0.20; 95% CI, 0.09 to 0.31; $P = 0.0004$; Supplemental Fig. 2B, https://links.lww.com/ALN/D215). We found no association between the rs1799971 allele and chronic postsurgical pain scores (Supplemental Fig. 2C, https://links.lww.com/ALN/D215).

COMT rs4680, rs4818, rs4633, and rs6269

The four *COMT* alleles (rs4680, rs4818, rs4633, and rs6269) were analyzed individually. The rs4680 allele is the most commonly investigated *COMT* polymorphism; it is a G-to-A substitution that encodes a non-synonymous V158M change. We found that the presence of the rs4680 A allele is significantly associated with an increased incidence in chronic postsurgical pain scores (standard mean difference, 0.26; 95% CI, 0.08 to 0.44; $P = 0.004$; Fig. 3A, https://links.lww.com/ALN/D216). Conversely, we found that there was no significant difference in pain scores or opioid consumption among carriers of the rs4680 allele in the acute postsurgical setting, in either dominant or recessive inheritance models (Supplemental Fig. 3, B to E, https://links.lww.com/ALN/D216).

We found that in both dominant and recessive inheritance models, the rs4818 and rs4633 alleles were not associated with acute postsurgical pain scores or opioid use (Supplemental Fig. 4, A to D, https://links.lww.com/ALN/D217; Supplemental Fig. 5, A to D, https://links.lww.com/ALN/D218). A meta-analysis was not possible for the association of the rs6269 allele with acute postsurgical pain scores or opioid use due to limited data. Finally, we found no association between the rs4818, rs4633, or rs6269 alleles and chronic postsurgical pain scores (Supplemental Fig. 4E, https://links.lww.com/ALN/D217; Supplemental Fig. 5, E and F, https://links.lww.com/ALN/D218).

ABCB1 rs1045642 and rs2032582

Two *ABCB1* alleles, rs1045642 and rs2032582, were analyzed for association with postsurgical pain. There was no association of the rs1045642 allele with either postsurgical opioid use or pain scores in either a dominant or recessive inheritance model (Supplemental Fig. 6, A to D, https://links.lww.com/ALN/D219). We were unable to use one study[29] for the recessive model meta-analyses, as it reported data only in the dominant model (*i.e.*, homozygous wild type [CC] *vs.* heterozygous and homozygous mutant [CT + TT]).

For the rs2032582 allele, there was no association with acute postsurgical opioid use in either a dominant or a recessive inheritance model (Supplemental Fig. 6, E to F, https://links.lww.com/ALN/D219). We were only able to use four studies for the recessive-model meta-analysis, as one study[37] reported data only in the dominant model (*i.e.*, homozygous wild type [TT] *vs.* heterozygous and homozygous mutant [GT + GG]).

COMT Haplotype Analysis

Several studies investigated *COMT* alleles collectively as haplotypes. However, due to the inconsistent definitions for each haplotype and use of different methodologies, we were unable to perform a meta-analysis for the associations of each haplotype with postsurgical pain.

The association of 1 or more *COMT* haplotypes with postsurgical pain was investigated in 12 studies.[16,24,26,38–46] Three main haplotypes encompassing more than 95% of the human population and based on the characterization by Diatchenko *et al.*[47] are designated as low, average, and high pain sensitivity. Each haplotype is determined by the combination of genotypes at four *COMT* single nucleotide polymorphisms: rs6269, rs4633, rs4818, and rs4680. The specific patterns of alleles for each haplotype are shown in table 4. Of the 12 studies, only 7 used all 4 single nucleotide polymorphisms to determine haplotypes in their cohorts. The single nucleotide polymorphisms employed by each study to categorize *COMT* haplotype is shown in table 5. We found that the reported associations of each haplotype with postsurgical pain varied greatly between studies, even when comparing studies that utilized the same outcome measure and time frame. A summary of the findings from each study is shown in table 5.

Discussion

Here, we have conducted a comprehensive systematic review and meta-analyses on the genetic determinants of postsurgical pain, finding that despite 129 reported genes and 594 reported variants, only two variants showed significant association with postsurgical pain after meta-analysis. Previous systematic reviews in this area have looked at specific genes, patient populations, or clinical outcomes or were limited in scope.[30,36,48–56] We sought to broadly encompass all studies reporting on the genetics of postsurgical pain, so as to exhaustively present the current literature and understanding. We utilized a thoroughly designed search algorithm to ensure that as many relevant articles as possible would be included in our search results.

Among the 163 included studies, only 6 were genome-wide association studies, with the rest being candidate-gene association studies. In combination with the relatively small cohort sizes of the included studies (more than 80% had cohort sizes smaller than 400 patients), a large number of candidate-gene association studies may lead to increased type I error (false positive) rates. Additionally, the six genome-wide association studies also had small cohort sizes (613 patients or less), and each identified different associated loci (*ZNF429*, *LAMB3*, *CREB1*, *HCRTR2*, *NAV3*, and *PRKCA*, respectively).[57–62] This underscores the inconsistency of reported data on genetic associations with postsurgical pain. Many of the reported significant associations fail to be replicated in other studies; Supplemental Table

6 (https://links.lww.com/ALN/D225) shows that for nearly all alleles investigated by more than a handful of studies, only a small subset of studies found significant associations with postsurgical pain.

Among the genes investigated, more than half were involved in either neurotransmission or the immune response, a result that remained true when looking at only those genes for which there was significant association for at least one allele reported. At a minimum, this result indicates that genes involved in neurotransmission have proven the most successful avenues of investigation.

Additionally, multiple genes and alleles likely influence complex traits such as postsurgical pain. Candidate-gene association studies can fail to appreciate the small additive contributions from multiple genes. Further avenues to study the effects of multiple genes or alleles on postsurgical pain include genome-wide pathway analyses and the development of polygenic risk scores.

An important element to consider is how nongenetic and nonsurgical factors interact with genetic influences on the development of postsurgical pain. Patient age, body mass index, and psychologic factors such as preoperative anxiety and catastrophizing have all been found to be important determinants of postsurgical pain in a variety of cohorts.[63–66] Although an individual's genetics may represent one contribution among many other biopsychosocial factors, the multiple layers of pain modulation may explain the generally mild effects of single variants.

Meta-analyses Show Association with Postsurgical Pain for Only Two Single Nucleotide Polymorphisms

Part of the difficulty in the identification of genes and variants that affect postsurgical pain is inconsistent findings and poor replicability of results.[8] Due to the conflicting data from multiple studies, we performed several meta-analyses evaluating the association of specific single nucleotide polymorphisms with postsurgical pain. Postsurgical pain is assessed in some studies by opioid consumption, in some studies by patient-reported pain scores, and in some studies by both measures; therefore, we evaluated opioid consumption and pain scores as separate outcomes in our meta-analyses. The majority of studies assessed pain in either the acute (0 to 48 h postoperatively) or chronic (at least 3 months post-operatively) time period (table 1). Because of this, we analyzed acute and chronic postsurgical pain separately, although it is understood that both are related, with an ability to transition from acute to chronic pain and variable pain trajectories between individuals.[67]

It is important to note that the majority of the meta-analyses we performed showed no association (table 3; Supplemental Fig. 2, https://links.lww.com/ALN/D215; Supplemental Fig. 3, https://links.lww.com/ALN/D216; Supplemental Fig. 4, https://links.lww.com/ALN/D217; Supplemental Fig. 5, https://links.lww.com/ALN/D218; Supplemental Fig. 6, https://links.lww.com/ALN/D219). For each allele, we looked for association with acute postsurgical pain scores, acute opioid consumption, and chronic postsurgical pain scores. Additionally, we performed analyses using both dominant and recessive inheritance models where appropriate and possible. Despite these efforts, association with postsurgical pain was

found for only two alleles under three conditions (table 3; Supplemental Fig. 2, A and B, https://links.lww.com/ALN/D215; Supplemental Fig. 3A, https://links.lww.com/ALN/D216).

The *OPRM1* A118G (rs1799971) allele is the most investigated for association with postsurgical pain. We found it is associated with both increased postsurgical opioid use and pain scores in the acute setting. This concurs with several previous meta-analyses.[36,50,51,56] The rs1799971 allele causes a substitution from asparagine to aspartic acid (N40D), thereby causing a loss of a putative glycosylation site.[68] The full physiologic effects of this mutation have not been definitively clarified, although it may alter receptor binding affinity.[69]

Of the four *COMT* single nucleotide polymorphisms evaluated *via* meta-analysis, only the V158M (rs4680) variant was found to be associated with postsurgical pain, and only when assessing for the incidence of chronic postsurgical pain scores. Thus, despite the interest in COMT variants in the context of postsurgical pain, when aggregated together, the data resulted in mostly null findings. The V158 allele encodes for a COMT protein with reduced enzymatic activity to metabolize catecholamines.[70] It is possible that reduced COMT activity leads to chronically elevated catecholamine levels and subsequent altered and/or maladaptive peripheral and central sensitization.[71–73] However, this mechanism has not been definitively evidenced in human subjects.

COMT Haplotypes Analysis

The four *COMT* single nucleotide polymorphisms have also been investigated collectively as haplotypes, termed low, average, or high pain sensitivity depending on the combination of alleles. A haplotype is potentially more physiologically impactful than any single allele by exerting the combined effect of the constituent alleles (which we have shown to be nonsignificant in three of the four single nucleotide polymorphisms). Additionally, individual haplotypes have different mRNA structures and stabilities and subsequently variable protein levels and enzymatic activity.[74]

Due to the variable outcome measures, haplotype definitions, and accessible data, we were unable to perform a meta-analysis for any of the haplotypes. However, it is evident even without meta-analysis that the effects of each haplotype are inconsistent across studies (tables 4 and 5). This inconsistency may result from the mild to moderate effect of each haplotype being extrapolated across different surgical cohorts with different outcome measures. Additionally, the effect of each haplotype may vary in the acute *versus* chronic postsurgical time frame, as seen with the rs4680 single nucleotide polymorphism. This raises concerns that without a large cohort the effects of individual haplotypes may be too mild or varied to detect and interpret; we cannot currently draw any conclusion as to the effects, if any, of the *COMT* haplotypes on the development of postsurgical pain.

Clinical Context and Future Directions

Only two single nucleotide polymorphisms (*OPRM1* A118G and *COMT* V158M) showed significant associations with postsurgical pain. The degree of each association was surprisingly mild as well, indicating that the clinical effects of isolated variants may be too modest to see without large and/or homogenous populations. Therefore, studies

professing to show genetic associations with postsurgical pain should be critically assessed, as results based on limited populations or variable outcomes may not hold up to more rigorous approaches. The inconsistency of results from previous studies is underscored by the heterogeneity of our meta-analyses; almost half (12 of 25) of our analyses had heterogeneity estimates (I^2) greater than 50%. Additionally, the limited genetic association with postsurgical pain identified thus far may indicate poor heritability of this phenotype. Although the heritability of chronic nonsurgical pain is estimated to be ~45%,[75] reduced heritability would possibly explain the lack of genetic associations detected. Larger cohorts with clearly defined *a priori* outcomes are needed.

Although the few genetic variants thus far found to be associated with postsurgical pain have rather subtle effects, they can still provide insight into the biology and pathophysiology of pain. Understanding this pathophysiology is critical to considering novel treatments and precision medicine approaches to treating postsurgical pain.

Limitations

This review does have some limitations, most notably the exclusion of non-English language articles. We therefore can miss important findings published in other languages. Indeed, we were unable to utilize two articles (Wen *et al.* 2015 and Tang *et al.* 2009) that were included in a previous meta-analysis,[51] as they were available only in Chinese (referred in the previous meta-analysis as Wen *et al.* 2015 and Tang *et al.* 2009). Additionally, while we developed rigorous PubMed, Embase, and Cochrane Library searches to be both broad and selective for relevant articles (see Supplemental Methods, https://links.lww.com/ALN/D213), we may have missed those that did not fall into our search criteria but would have been otherwise relevant. By design, our review focused on variation in the genetic sequence, and as such, biologic regulations at the transcriptomic and translational levels, including post-translational modifications, are not captured in this review. Our review is also limited by the available data; therefore, the heterogeneity of surgical procedures, patient populations, and outcome measures, as well as limited cohort sizes, affect our findings.

Importantly, our findings are biased toward those genes or alleles that have been previously investigated, especially as the specific genes and alleles in candidate-gene association studies were likely chosen based on previous scientific findings and hypotheses. We therefore cannot address the potential association of variants for which little or no previous research exists, a bias that can overestimate the effect size of the association between alleles and postsurgical pain and raise the type I error rate. Additionally, publication bias may inflate the perceived effects of a genetic exposure over what exists in truth. We have sought to mitigate this bias by reported on all alleles, including those not associated with postsurgical pain. More than 70% of the variants reported here were not significantly associated with postsurgical pain.

This review does not address the pharmacogenetics of therapy with opioids or other analgesics. Our focus was and is on genetic modifiers of postsurgical pain, although this outcome has been often measured through opioid consumption. Finally, we performed meta-analyses on only seven single nucleotide polymorphisms due to the limited number

of studies with comparable data, heterogeneity of the available data, and sometimes limited availability of necessary data.

Conclusions

We have conducted a comprehensive systematic review on the genetic markers of postsurgical pain, and each subsequent meta-analyses incorporates the greatest amount of the available data. The large amount of interest and investigations into this area has unfortunately produced rather inconsistent and sometimes contradictory results thus far. Despite 129 reported genes and 594 reported variants, only two variants showed significant association with postsurgical pain after meta-analyses. Subsequent genetic studies in larger cohorts with consistent outcome measures and controlled confounding variables will further our understanding of the influence of genetics on postsurgical pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Multiple genes and alleles likely influence the complex phenome-non of postsurgical pain, potentially contributing to a wide variation in the degree of postsurgical pain and analgesic use
- Previous preclinical and clinical studies have proposed a variety of neurotransmitter- and immune-related candidate genes to explain this variability

What This Article Tells Us That Is New

- In this comprehensive systematic review, only a small subset of candidate genes had sufficient data to allow meta-analysis, and most were not significantly associated with postsurgical pain, with many of the previously reported significant associations failing to be replicated
- Meta-analysis revealed that μ-opioid receptor variant (*OPRM1* A118G [rs1799971]) was modestly associated with increased postsurgical opioid use and pain scores in the acute setting, and a catecholamine metabolism enzyme variant (*COMT* V158M [rs4680]) was modestly associated with incidence of chronic postsurgical pain

Table 1.

Characteristics of Included Studies

Characteristic	n (%)
Study type	
Genome-wide association study	6 (4)
Targeted association analysis	157 (96)
Surgery type *	
Genera l/gastrointestinal	47 (29)
Gynecology	29 (18)
Orthopedic	26 (16)
Oral/maxillofacial/dental	23 (14)
Cesarean section	20 (12)
Mastectomy	19 (12)
Urology	13 (8)
Thoracic	12 (7)
Cardiac	4 (2)
General/hepatobiliary	4 (2)
General/endocrine	3 (2)
Otolaryngology	3 (2)
Neurosurgery	2 (1)
Oncologic †	2 (1)
Vascular	2 (1)
Plastics	1 (1)
Multiple types	19 (12)
Time frame *	
0 to 24 h	123 (75)
24 to 48 h	44 (27)
48 h to 1 week	18 (11)
1 to 2 weeks	0 (0)
2 weeks to 1 month	0 (0)
1 to 3 months	10 (6)
3 to 6 months	20 (12)
6 months to 1 yr	14 (9)
> 1 yr	5 (3)
Multiple time points	54 (33)
< 48 h	126 (77)
> 3 months	32 (20)
Included patients	
≤ 200	97 (60)
201 to 400	35 (21)
401 to 600	11 (7)

Characteristic	n (%)
601 to 800	5 (3)
801 to 1,000	8 (5)
>1,000	7 (4)
Outcome type	
Analgesic only	42 (26)
Pain score only	65 (40)
Both	56 (34)
Pain score modality	
Numeric rating scale	49 (40)
Visual analog scale	63 (52)
Likert scale	2 (2)
Brief Pain Inventory	2 (2)
DN4 questionnaire	1 (< 1)
Verbal rating scale	1 (< 1)
Verbal pain scale	1 (< 1)
Activity Assessment Scale	1 (< 1)
Analgesic used	
Morphine	38 (35)
Fentanyl	36 (33)
Sufentanil	10 (9)
Oxycodone	7 (6)
Tramadol	6 (6)
Codeine	3 (3)
Piritramide	3 (3)
NSAID (any)	2 (2)
Alfentanil	1 (< 1)

*Percentages do not add up to 100 as some studies used multiple surgery types or time frames.

†NOT mastectomy.

NSAID, nonsteroidal anti-inflammatory drug.

Table 2.

Characteristics of Investigated Genes and Alleles

Characteristic	n (%)
Gene function	
All genes	
Neurotransmission	51 (40)
Immune response	28 (22)
Transcription regulation	9 (7)
Pharmacokinetics	7 (5)
Neuronal function	6 (5)
Cell signaling	5 (4)
Adrenergic receptor	5 (4)
Immune system	4 (3)
Hormone	3 (2)
DNA binding	2 (2)
Other	2 (2)
Cellular structure	2 (2)
Transporter	2 (2)
Vasopressin receptor	1 (1)
Hormone receptor	1 (1)
Membrane transport	1 (1)
Significant genes	
Neurotransmission	35 (44)
Immune response	14 (18)
Neuronal function	6 (8)
Pharmacokinetics	5 (6)
Transcription regulation	4 (5)
Immune system	4 (5)
Adrenergic receptor	3 (4)
Cell signaling	2 (3)
Other	2 (3)
Cellular structure	2 (3)
DNA binding	1 (1)
Hormone	1 (1)
Membrane transport	1 (1)
Variant type	
Single nucleotide polymorphism	580 (98)
Insertion/deletion	6 (1)
Tandem repeats	6 (1)
Human leukocyte antigen allele (haplotype)	2 (< 1)
Variant location	
All alleles	

Characteristic	n (%)
Intron	330 (56)
Coding	116 (20)
Upstream	61 (10)
Downstream	34 (6)
3’-Untranslated region	33 (6)
5’-Untranslated region	12 (2)
Splice variant	2 (< 1)
Significant alleles	
Intron	80 (50)
Coding	48 (30)
Upstream	15 (9)
Downstream	7 (4)
3’-Untranslated region	7 (4)
5’-Untranslated region	2 (1)
Splice variant	2 (1)
Minor allele frequency	
All alleles	
0 to 0.1	96 (14)
0.1 to 0.2	98 (15)
0.2 to 0.3	133 (20)
0.3 to 0.4	163 (24)
0.4 to 0.5	136 (20)
0.5 to 0.6	24 (4)
0.6 to 0.7	8 (1)
0.7 to 0.8	8 (1)
Significant alleles	
0 to 0.1	14 (7)
0.1 to 0.2	30 (16)
0.2 to 0.3	47 (25)
0.3 to 0.4	55 (29)
0.4 to 0.5	33 (17)
0.5 to 0.6	8 (4)
0.6 to 0.7	2 (1)
0.7 to 0.8	1 (1)

Table 3.

Meta-analyses Results

Gene	Allele	Outcome	Time Frame	inheritance Model	Studies, No.	Subjects, No.	Standard Mean Difference [95% CI]	I^2, %	*P* Value
OPRM1	rs1799971	Opioid use	< 48 h	Dominant	33	8,227	0.25 [0.16, 0.35]	73	< 0.00001
		Pain score	< 48 h	Dominant	18	4,619	0.20 [0.09, 0.31]	59	0.0004
		Pain score	> 3 months	Dominant	6	1,282	1.08 [0.78, 1.50] *	0	0.62
COMT	rs4680	Opioid use	< 48 h	Dominant	12	2,259	−0.08 [−0.21,0.04]	30	0.19
				Recessive	11	2,136	0.02 [−0.18, 0.22]	62	0.84
		Pain score	< 48 h	Dominant	8	1,752	0.06 [−0.11,0.24]	50	0.49
				Recessive	8	1,752	0.09 [−0.09, 0.28]	40	0.33
		Pain score	> 3 months	Dominant	9	1,726	0.26 [0.08, 0.44]	43	0.004
	rs4633	Opioid use	< 48 h	Dominant	5	1,381	0.02 [−0.21,0.24]	55	0.89
				Recessive	5	1,381	−0.05 [−0.28, 0.18]	34	0.66
		Pain score	< 48 h	Dominant	4	1,256	0.00 [−0.16, 0.17]	22	0.98
				Recessive	4	1,256	−0.08 [−0.26, 0.09]	0	0.36
		Pain score	> 3 months	Dominant	5	1,272	−0.11 [−0.42, 0.20]	76	0.48
	rs4818	Opioid use	< 48 h	Dominant	6	1,526	−0.06 [−0.23, 0.12]	48	0.55
				Recessive	6	1,526	0.04 [−0.22, 0.30]	53	0.76
		Pain score	< 48	Dominant	4	1,249	0.10 [−0.02, 0.21]	0	0.09
				Recessive	4	1,249	0.06 [−0.21,0.33]	36	0.67
		Pain score	> 3 months	Dominant	4	1,079	−0.02 [−0.37, 0.33]	80	0.90
	rs6269	Pain score	> 3 months	Dominant	6	1,531	−0.03 [−0.49, 0.43]	88	0.90
ABCB1	rs1045642	Opioid use	< 48 h	Dominant	12	2,066	−0.02 [−0.18, 0.13]	54	0.76
				Recessive	11	1,800	−0.09 [−0.38, 0.20]	82	0.56
		Pain score	< 48 h	Dominant	5	1,366	0.05 [−0.12, 0.22]	42	0.57
				Recessive	4	1,100	0.12 [−0.17, 0.42]	71	0.41
	rs2032582	Opioid use	< 48 h	Dominant	5	402	0.21 [−0.06, 0.49]	30	0.13
				Recessive	4	346	0.09 [−0.16, 0.34]	0	0.49

The table shows the results for each meta-analysis, including the specific alleles and the outcomes analyzed.

*Odds ratio [95% CI].

Table 4.

Specific Allele of Each Variant from Included Studies

Haplotype	rs6269	rs4633	rs4818	rs4680
Low pain sensing	G	c	G	G
Average pain sensing	A	T	c	A
High pain sensing	A	c	c	G

Table 5.

Summary of *COMT* Haplotype Results from Included Studies

	Alleles Used				Pain Sensing		
	rs6269	**rs4633**	**rs4818**	**rs4680**	**High**	**Average**	**Low**
Acute postsurgical pain							
DeGregori	X	X	X	X	NS	↓	NS
Henker	X	X	X	X	↑	NS	NS
Khalil	X	X	X	X	NS	NS	NS*
Zhang	X	X	X	X	NS	NS	↑
Baber		X	X	X	NS	NS	NS
Matic		X	X	X	NS	↑	↓
Tan		X	X	X	↓	NS	↑
Chronic postsurgical pain							
Rut	X	X	X	X	NS	NS	↓
Omair	X	X	X	X	NS	NS	NS
Knisely	X	X	X	X	↑†	NS	NS
Belfer	X	X	X		↑	NS	↓
George		X	X		NS	↑	↑

The table details the alleles that were utilized by each study to define the haplotypes of the patients in their respective cohorts. The right columns describe the effect of each haplotype reported by each study.

*The haplotype had no significant effect independently but was associated with lower pain scores in combination with the *OPRM1* rs1799971 AA genotype.

†The haplotype was only associated with inclusion in the severe pain class.

NS, no significant effect; ↑, increased postsurgical opioid use or pain score; ↓, decreased postsurgical opioid use or pain score.