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Systematic review and meta-analysis of genetic risk of developing chronic postsurgical pain

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Abstract

Chronic postsurgical pain (CPSP) is a significant detriment to post-surgical recovery and a risk factor for prolonged opioid use. Emerging evidence suggests the estimated heritability for chronic pain is 45% and that genetic factors partially explain individual susceptibility to CPSP. The aim of this study was to systematically review, assess quality and summarize the studies in humans that have investigated genetic factors associated with CPSP. We also conducted a meta-analysis to derive a single effect size for evaluable genetic associations with CPSP. Our comprehensive literature search included review of 21 full-text articles evaluating variants of 69 genes for association with CPSP. We found significant gene variant associations reported for variants/haplotypes of 26 genes involved in neurotransmission, pain signaling, immune responses and neuroactive ligand–receptor interaction, with CPSP. Six variants of five genes (*COMT*: rs4680 and rs6269, *OPRM1*: rs1799971, *GCH1*: rs3783641, *KCNS1*: rs734784 and *TNFA:* rs1800629), were evaluated by more than one study and were included in the meta-analysis. At rs734784 (A>G) of *KCNS1*, presence of G allele marginally increased risk of CPSP (Additive genetic model; Odds ratio: 1.511; 95% CI 1 to 2.284; p-value 0.050), while the other variants did not withstand meta-analyses criteria. Our findings demonstrate the role of genetic factors with different functions in CPSP, and also emphasize that single genetic factors have small effect sizes in explaining complex conditions like CPSP. Heterogeneity in surgical cohorts, population structure and outcome definitions, as well as small number of available studies evaluating same variants, limit the meta-analysis. There is a need for large-scale, homogenous, replication studies to validate candidate genes, and understand the underlying biological networks underpinning CPSP.

Perspective

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Our systematic review comprehensively describes 21 studies evaluating genetic association with CPSP, and limitations thereof. A meta-analysis of 6 variants (5 genes) found marginally increased risk for CPSP associated with rs734784 A>G of the potassium voltage-gated channel gene (*KCNS1*). Understanding genetic predisposition for CPSP will enable prediction and personalized management.

Introduction

Chronic post-surgical pain (CPSP) is an important clinical problem of considerable magnitude, that negatively affects recovery after surgery. The initial criteria proposed by Macrae and Davies[55] in 1999, and modified by Werner and Kongsgaard[89] define CPSP as 1) pain that develops after a surgical procedure or increases in intensity after the surgical procedure, 2) pain of at least 3–6 months' duration and significantly affects quality of life, 3) pain that is a continuation of acute post-surgery pain or develops after an asymptomatic period, 4) pain localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome, and 5) other causes of the pain should be excluded. The incidence of CPSP varies between 5 and 85%, depending on the surgical location and type linked to duration, likelihood of nerve damage and perioperative factors.[55] This implies that at a minimum, about 23 million people are affected by CPSP every year.[16] Recent estimates suggest that CPSP incur mean annualized adjusted direct and indirect costs of *US$11,846 and US$29,617, respectively* per patient[63] and chronic pain conditions incur overall costs of $670 billion[25] related to healthcare costs and indirect costs through loss of productivity. Importantly, CPSP takes a toll on patient's psychological state, quality of life and results in disability and decreased contribution to society.[23; 37; 42]

Our and other studies have shown that CPSP involves multiple peripheral and central signaling and modulatory pathways regulated by genes, epigenetics, psychosocial, perioperative and gene-environmental interactions.[10; 12; 13; 28; 40; 64; 88] Chronic pain has a heritable risk of 45%,[91] and genetic factors explain some of the individual differences in pain perception.[3; 33; 61] However, a genetic basis for CPSP has been elusive[43; 44] leaving ***critical gaps*** in our knowledge of CPSP pathophysiology. This is attributed partly to lack of replicability[47] and inconsistent findings[56; 68] in genetic association studies.[5; 6; 51; 86] In addition, there is a lack of replication studies, as there has been little effort made to replicate findings in multiple independent cohorts.

Several genetic association studies have found variants associated with the risk of developing CPSP after different surgeries in different populations. We performed a comprehensive systematic literature review where we collected, analyzed and summarized available evidence from genetic association studies for CPSP. The advent of the Human Genome project in 2001 transformed medicine for some conditions; in this context, it transformed medicine with an astronomical increase in genomic data.[76]. We conducted a meta-analysis to synthesize the data from several studies into a single quantitative estimate or summary effect size for available genetic associations with CPSP. [82] This systematic review and meta-analysis aims to provide a basis and focus on potential genetic risk

polymorphisms (SNPs) which may be useful biomarkers for clinical prognosis and pharmacological targets in the management of CPSP. This study also aims to identify evidence-based gaps in literature that will provide impetus for future research in this field.

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) guidelines.[57] We conducted a comprehensive literature search limited to human studies using electronic databases including PubMed and MEDLINE, from January 2001 to December 2017, using the following search terms on PubMed: (“postoperative pain” OR “postsurgical pain” OR “post-operative pain” OR “post-surgical pain” OR “postoperative analgesia” OR “postoperative opioid” OR “CPSP” OR “chronic post surgical pain”) AND (genetic association OR polymorphism OR variant OR “genotype” OR “Genome wide association” OR “SNP”).

Study selection criteria

The searches were limited to English language articles, human studies, clinical studies, clinical trials, multicenter studies, observational studies and twin studies using PubMed filters. Inclusion criteria for articles required that each article evaluate the association of genetic variation (e.g., single nucleotide polymorphisms or other measure of genetic variation) with pain outcomes after surgery.

Data extraction

Articles were examined and screened independently by MA and VC, in addition to verification by SG (see acknowledgements). Full-text articles were retrieved and reviewed to verify inclusion in the analysis. Any disagreements were discussed between the authors. The following information was extracted from all included studies: first author, year, study type, population characteristics, genotype method, genes, genetic markers, surgery type, timing of outcome assessment, outcomes and results. STrengthening the REporting of Genetic Association studies (STREGA) scores were assessed.[36; 53] according to the Strengthening the Reporting of Genetic Association (STREGA) study guidelines.[36; 52] The score was calculated for each study based on the 22 key items grouped into 7 categories: title and abstract, background, study selection, statistical methods, reporting outcome, previous supporting evidence or validation, and funding source information. The checklist used is provided in Supplementary Table 1. These scores describe the transparency in report of the studies (maximum score 28). Quality of the studies were assessed using the Q-Genie tool by four of the authors (VC, LD, YG, VP) [39; 72] This tool helps rate the rationale for the study, definition of outcome, case/control groups, technical and non-technical classification of exposure (genetic testing), disclosure of bias, power analysis, statistical plan including controlling for confounders, and inferential testing on scale of 1–7 (poor-excellent). Possible range of scores is 11–77 for studies with control groups and 11–70 for studies with no control group. Scores above 45 and 40 indicate good quality studies respectively.

Meta-analysis

Studies with binary CPSP outcomes (yes/no based on presence of postoperative pain at least 3 months after surgery, or as defined by the study) and studies where relative risk/minor allele frequencies for cases/controls were provided, were included in the meta-analysis. Meta-analysis was conducted if SNPs and haplotypes reported in more than one study. Log-transformed odds ratio and its standard error were derived and used in meta-analysis for each study to get the effect size with fixed-effect meta-analysis. Statistical heterogeneity between studies was assessed using the I^2 statistic and significance of heterogeneity using the Cochran's Q test with statistical significance evaluated by the p-value of Q statistic. Forest plots were used in presenting the individual study results and meta-analysis pooled results. Funnel plots and Egger's test were used to visualize and investigate publication bias. All statistical analyses were performed using R version 3.5.1[77] and R package metfor.[84]

Results

Study selection

The literature search resulted in 212 studies. Abstracts and titles were initially screened to retain post-surgical pain studies. At this stage, 92 studies were excluded for the following reasons:2 animal studies; 3 design and methods only; 4 did not describe genetic analysis; 8 were editorials; 6 were review articles describing opioid metabolism pharmacogenetics; 63 did not study post-operative pain, and 6 were in a foreign language. The remaining 119 studies evaluating post-surgical pain were further screened using abstracts and if necessary, reading full-texts, to determine if chronic pain after surgery outcomes were studied. We excluded 104 articles as they detailed only immediate pain outcomes (less than 2 months after surgery). Of remaining articles, there were 3 review articles describing genetic polymorphisms and post-thoracotomy pain syndromes,[70] abdominal hernia[29] and post-mastectomy pain[18] and two reviews of genetics in chronic post-surgical pain.[14; 34] After including articles from these reviews of relevance to CPSP, we were left with 21 studies for inclusion in this meta-analysis of genetic associations with CPSP. The study screening strategy is illustrated in Figure 1.

Characteristics of included studies

Studies identified were conducted between 2010 and 2017 in adults. Characteristics of the study cohorts are detailed in Table 1. They were conducted in several surgical cohorts of which the most common were abdominal surgeries (n=4527, 38%) (excluding caesarian sections), followed by breast surgeries (n=2044; 17%). Break-up of surgical cohorts by proportion is presented in Fig 2. The included studies examined 11,192 subjects cumulatively; eight study cohorts included only female subjects, and three included only males, while sex composition of 4 study cohorts were not reported. Of the 11,192 subjects included, majority (37%) were Caucasian and the second largest group was Hispanic (25%). (Figure 2) The reported incidence of CPSP in the studies ranged from 7.6% to 50%. Most studies reported pain follow ups of 3–12 months in duration after surgery and were candidate gene association approaches. Although all the studies evaluated persistent after surgery at or beyond 3 months after surgery which is consistent with the prima facie definition of CPSP, different definitions for pain outcomes were used. The definitions used,

STREGA and Q-Genie scores are presented in Table 1. STREGA scores for the studies included were assessed to be between 19–27 out of a possible 28. [39; 72] Average Q-Genie scores for quality of association studies scores ranged from 46 to 70 for all studies with/without control groups, which indicate good quality of all included studies. The scores by different reviewers were well correlated (R: 0.613, $p<0.003$), which indicates consistency in generating these scores.

While 15 of the studies were candidate gene association studies evaluating one to several candidate genes, four studies employed integrated approaches using initial gene mapping in experimental animal pain models followed by targeted gene association in human chronic postsurgical pain cohorts [17; 60; 73; 90]. One study used a genome wide association study (GWAS) approach followed by meta-analysis using data from different pain cohorts.[87] Blinded assessors of genotyping were explicitly reported in only 2 studies [71; 74] and power analysis for sample size justification was only provided in a handful of studies.[26; 54; 58] In addition, haplotype and ancestry (race) were tested in some of the studies [17; 49; 60; 67; 73; 74] but not all.

Genetic associations with CPSP

In all, 229 genes were evaluated by these studies. After filtering out duplicates, there were 69 unique genes with potential to be considered for meta-analyses. Variants with significant p-values ($p<0.05$) are indicated in Table 2. Some were reported to have a minor allele associated with CPSP while others with significant p-values had no directionality reported. Genes whose variants were reported to be associated with CPSP are listed below along with reference to the study: COMT (rs6269, rs4633), GCH1 (rs3783641, rs8007267);[4] COMT rs4680;[32] ABCB1 C3435T;[71] 5HTR2A rs6311;[50]IFNG1 (rs2069727, rs2069718), IL1R1 rs3917332, IL1R2 rs11674595, IL4 rs2243248, IL10 (rs3024498, rs1878672, rs3024491), IL13 (rs1881457, rs1800925, rs1295686, rs20541), NFKB1 rs4648141;[74] HLA-DRB1*4 and DQB1/03:02;[21]PRKCA rs887797, CDH18 rs4866176, TG rs1133076; [87]ATXN1 rs179997, DRD2 (rs4648317, rs12364283), NFKB1A rs8904, GCH1 rs4411417;[58] CHRNA6 rs7828365;[90]KCND2 (rs17376373, rs702414, rs802340, rs12706292), KCNJ3 (rs6435329, rs11895478, rs3106653, rs3111006, rs12471193, rs7574878, rs12995382) KCNJ6 rs2835925; KCNK3 (rs1662988, rs7584568), KCNK9 rs2014712;[49] CACNG2 (rs4820242, rs2284015, rs2284017, rs2284018, rs1883988);[60] COMT (rs4680, rs6269)[67]P2X7R (rs208294, rs208296, rs7958311);[73] KCNS1 (rs734784, rs13043825);[17] TNF alpha rs1800629;[41] and GCH1 rs8007627. [31]

Meta-analysis

We retained studies where Odds ratios (OR) for binary outcomes were reported, and derived ORs, standers errors (SEs) and p-values whenever possible. There were 9 studies that satisfied these criteria with overall sample size of 5,219 subjects of whom 38.5% were females. [4; 17; 31; 32; 41; 48; 49; 58; 80] These studies were conducted in a variety of surgical cohorts undergoing herniotomy (N=1945, 37.3%), other abdominal surgeries (N=1297, 24.9%), limb amputation (N=299, 5.7%), breast surgery (N=969, 18.5%), thoracic surgery (N=402, 7.7%), joint surgery (N=104, 2%) and lumbar discectomy (N=203, 3.9%). These studies are highlighted in Table 1 which describes population characteristics, surgery

types, CPSP outcomes definition of these studies. Table 2 describes genetic models, covariates and allele frequencies for cases/controls when reported in the studies for all included variants in meta-analysis. At least 2 studies evaluated at least one of 6 variants of 5 genes (*COMT*: rs4680 G>A and rs6269 A>G; *OPRM1*: rs1799971 A>G; *GCH1*: rs3783641 T>A; *KCNS1*: rs734784 A>G or T>C and TNF alpha: rs1800629 G>A). These 6 variants were included in the meta-analysis. The studies, genes, variants and genetic association models tested in the meta-analysis are presented in Table 3, alongwith results of effect sizes for the particular SNP studied from our meta-analyses. Forest plots for each variant are provided in Figure 3. Of the variants investigated, the minor G allele at rs734784 of *KCNS1* gene had marginally significant associations with CPSP (Odds ratio: 1.511; 95% CI 1 to 2.284; p-value 0.050) using an additive genetic model (Figure 3). For *OPRM1* rs1799971, the meta-analysis of 5 studies from Caucasian/Hispanic populations did not show a significant association between the A118G variant of *OPRM1* and CPSP, using a dominant model (Odds ratio: 0.993; 95% CI 0.845 to 1.169; p-value 0.935). Dominant model was used as the G allele is the minor allele and has a low frequency in several Caucasian populations at this location. We evaluated 3 genetic models (additive, dominant and recessive) for COMT rs4680 based on data from 5 studies and an additive model for rs6269 from 2 studies (Caucasian and Hispanic populations). We did not find significance for associations with CPSP (in any model) evaluated for rs4680 A allele (Odds ratio 1.012–1.058 (p-value 0.888 – 0.541)) or the rs6269 G allele (Odds ratio: 0.993; 95% CI 0.845 to 1.169; p-value 0.935). There was high heterogeneity which could be due to differences among studies or wide confidence intervals (CIs) in the constituent studies leading to high variability in point estimates. The meta-analysis for *GCH1* (rs3783641 A allele) included data from 3 studies – it did not show any significance for association with CPSP (Odds ratio 1.123 (0.908–1.390; P= 0.285) using an additive model. Also, for *TNF alpha*: rs1800629 G allele, no significant association with CPSP was found (Odds ratio: 1.240; 95% CI 0.963 to 1.597; p-value 0.096) from a meta-analysis of findings from 2 studies, using an allelic model.

Discussion

This systematic review has summarized 21 genetic studies in humans that interrogated genetic associations with chronic post-surgical pain. We found significant genetic associations reported for variants/haplotypes of 26 genes involved in neurotransmission, pain signaling, immune response, neuroactive ligand–receptor interaction, apoptosis signaling, metabolism and transport. Six variants of 5 genes were evaluated for association with CPSP outcomes by more than one study and were hence included in the meta-analysis. Among these variants, we found marginal significance for association of *KCNS1* gene variant rs734784 with CPSP, using an additive genetic model, with higher odds of CPSP in carriers of the G allele t this location.

Acute to chronic pain transitions after surgery likely involve several biologic mechanisms encompassing prolonged stimulation of nociceptors as well as maladaptive peripheral/ central sensitization and facilitation of nociceptive pathways, leading to sustenance of pain. [9] Inadequate availability of replication studies restricting the meta-analysis is likely due to few studies to date in this field, and inconsistencies in methodology (differences in pain phenotype definitions, outcomes evaluated and patient treatment protocols (Belfer and Dai,

2010). The assessment of quality of the included studies using the Q-Genie tool gives us confidence that all the studies were of acceptable quality to be included in the meta-analysis. All CGAS studies provided good rationale for selection of genes and variants to be studied based on prior literature and known function of genes/variants. CGAS could be a cost-effective approach when allele frequencies are low, effect sizes are small, or the study population is limited or unique.[1] However, they are limited by availability of *a priori* knowledge and incapable of discovering possibly novel genetic variants.[2] Integrated animal-human approaches used by few of the evaluated studies are encouraging, but they identified different candidate genes/variants which may be reflective of the differences in animal and pain models used. Importantly, most of the studies did not include power analysis, account for missing values, conduct population stratification, mention blinded genotyping and recruited cohorts skewed for race/sex (for example, there were many studies that solely recruited female or male participants). Some studies did not have control groups or provide allele frequencies in non-CPSP and CPSP groups/odds ratios, which prevented their inclusion in the meta-analyses.

Most studies detailed statistical approaches adjusted for covariates such as psychological factors (such as anxiety, pain catastrophizing), surgery-specific factors and preoperative pain, which are important factors to control for in these studies.[9] In addition, some of the studies evaluated associations with psychophysical predictors (responses to quantitative sensory testing).[4] Function and pain scores are expected to correlate but it is not clear whether differences in CPSP outcome definitions based on different questionnaires evaluating pain (such as brief pain inventory, Numerical rating scale pain scores), functional disability or impairment related outcomes (such as Disabilities of the Arm, Shoulder, and Hand or Activity assessment scale) would render different genetic association findings. The nature of pain was not specified in some studies, while few studies used questionnaires (such as PainDetect, DN4) to specifically target neuropathic pain. Thus, the differences in the evaluated studies described above may have limited the meta-analysis findings. However, they all evaluate CPSP outcomes as defined by the IASP and the review/meta-analysis yields insight into important genetic factors as well as design of future studies, so comparisons can be made more meaningfully.[46] Some of the studies included evaluated gene-gene[48], gene-sex [50] and gene-psychological factor interactions.[27] Gene-epigenetic interactions, [62] epigenetics [7] and gene-gene interactions are important factors influencing the transition from acute to chronic post-surgical pain. Research in these fields are still in their infancy.

The genes whose variants were found to be associated with CPSP in the 21 studies reviewed were mainly involved in neurotransmission - Catechol-O-methyl transferase (*COMT*), voltage-gated ion channel activity (Calcium and potassium channel genes); immune responses (Major histocompatibility complex, class 1, B-7 alpha chain and class II, DQ beta 1 (*HLA-B and HLA-DQB1*), NF-kappa-B proteins (*NFkB1*) and interleukin signaling (interleukin genes, gamma interferon, tumor necrosis factor-alpha (*ILR1A, IL1R2, IL4, IL10, IL13, IFNG1, TNF – alpha*)); Tetrahydrofolate biosynthesis (GTP cyclohydrolase 1/ *GCH1*); and neuroendocrine receptor interactions (Protein kinase C, alpha (*PRKCA*), purine receptor signaling (*P2X7R)*, dopamine receptor (DRD2), opioid receptor (OPRM1)), Cholinergic Receptor Nicotinic Alpha 6 Subunit (*CHRNA6*) and opioid transport (ATP

binding cassette *ABCB1*). These findings are consistent with those described by a systematic review on CPSP previously [34] Among the genetic variants investigated in the meta-analysis, potassium ion channel variant was the only one that reached nominal significance thresholds. This is consistent with prior mechanistic knowledge of lowered activation thresholds and spontaneous/exaggerated neuronal firing in response to noxious stimuli predisposing to neuropathic pain.[15] The potassium voltage-gated channel, delayed-rectifier, subfamily S, member 1; Kv9.1 gene (*KCNS1*) codes for the potassium channel alpha subunit, and has been implicated in various chronic pain states. [17] The *KCNS1* variant rs734784 A>G (Ile48Val) is a missense SNP which was found to be associated with higher pain scores in patients with lumbar back pain with disc herniation, higher phantom limb pain and stump pain in amputees, more severe sciatica pain before operation and higher sensitivity to experimental pain. [17] However, in the same study, no evidence of association with post-mastectomy pain for this gene variant was found. Similarly, long-term pain after breast cancer surgery was also not significantly associated with *KCNS1* rs734784 variant in another study[49], which suggests that this variant might increase risk for neuropathic components of CPSP and may not play a role in surgeries where neuropathic pain is not expected. Our metanalysis shows that the G allele of this variant has a marginally increased risk of CPSP. This finding is supported by the finding that *KCNS1* was downregulated in the dorsal root ganglia after injury in three distinct neuropathic pain models.[17; 81] Although the alpha sub-unit coded by this gene is in itself non-functional, *KCNS1* works with other subfamilies of the K channel receptor to inhibit firing of action potentials important for sensory neuron signaling and pain.[66] In addition, the Val allele of this variant was also associated with more pain catastrophizing, suggesting additional psychological influences on pain.[26] Other SNPs and 1 haplotype across 4 genes (ie, *KCND2, KCNJ3, KCNJ6, KCNK9*) were associated with severe pain 6 months after breast surgery.[49] However, these were not evaluated here due to inadequate number of studies investigating these genes for dichotomous CPSP outcomes.

Among the other variants included in our meta-analysis, *OPRM1* rs1799971 was investigated in 5 studies for association with CPSP. This substitution of an adenine (A) with a guanine (G) at base 118 at this variant causes amino acid exchange at position 40 of the μ opioid receptor (asparagine to aspartic acid) and loss of N-glycosylation in the extracellular region of the receptor.[35] This leads to decreased opioid receptor binding potential in the brain[65] and decreased sensitivity to opioid effects – also corroborated by various studies reporting increased opioid requirements and poor pain control after surgery in those with the G allele at this location.[11; 30; 38] However, our meta-analysis did not find significant association for this variant with CPSP. This is aligned with findings where the *OPRM1* 118A>G polymorphism did not withhold a meta-analysis for association with acute post-surgical pain[86] or neuropathic pain[83] in previous reports.

The *COMT* gene codes for the catechol-O-methyl transferase enzyme which is involved in degradation of catecholamines. Decreased COMT enzyme activity increases catecholamines and leads to increased pain. Four common SNPs (rs6269, rs4633, rs4818 and rs4680) have been implicated in pain sensitivity. [19; 20] We investigated rs4680 and rs6269 in our meta-analyses. SNP rs4680 is coded by 472G>A, which causes the substitution of valine by methionine at amino acid position 158 (Val158Met). Val/Val genotypes have been shown to

be predictive of chronic pain in fibromyalgia, temporomandibular joint disorder[20] and acute postsurgical pain.[8] However, Met/Met seem to have larger pain ratings in experimental pain studies.[92] The effects of inconsistent results among different studies evaluating the same variant in our meta-analysis is worth a discussion. For example, the COMT rs6269 G allele was found to be protective by Belfer et. al.[4] (G allele frequency was 30% in cases versus. 40.3% in controls) but trended to be a risk allele (not statistically significant) in the study by Montes et. al.[59] A closer look at the studies show that both were prospective studies in patients mainly undergoing abdominal surgeries - 1761 patients undergoing hernia repair and 1200 more patients undergoing hysterectomies and thoracotomies, in Montes et. al.[59] and 429 patients undergoing herniotomy in Belfer et. al. [4]. The primary outcome was defined as “pain-related activity impairment at 6 months after surgery” in Belfer et. al and as “presence of pain at 4 months after surgery” in Montes et. al. That said, the incidence of CPSP was very comparable between the studies (12.8% in Belfer et al and 13.6% in Montes et al.). The age group of the cohorts (average 55, 60 years) and likely sex distribution (only males in Belfer et. al. and male/female in Montes, but subtracting the number of female patients undergoing abdominal and vaginal hysterectomy, it can be deduced that the hernia population was male dominant) were similar. Both studies statistically adjusted for similar factors including preoperative pain and psychological factors. The main differences seem to be in the ethnicity of the populations recruited - Belfer et.al recruited only Caucasian patients, while all the subjects in Montes et. al were Hispanic. Neither study controlled for genetic ancestry due to their homogenous populations. Unfortunately, surgery stratified genetic association results are not provided by Montes et. al. which could eliminate another source of difference between the studies. Thus, despite a lot of similarities in methodology of these two studies, the results vary either because of ethnicity/sex/surgical differences which could potentially influence development of chronic pain and risk for CPSP. In addition, gene-gene and other factor interactions might contribute to these contradictory observations, which could not be evaluated in this meta-analysis. COMT rs6269 is an intron variant which has been implicated in post-surgical pain.[45; 69] Another meta-analysis of surgical/non-surgical neuropathic pain reported similar findings in that neither rs1799971 in OPRM1 (OR, 0.55; CI, 0.27–1.11) nor rs4680 in COMT (OR, 0.95; CI, 0.81–1.13) were significantly associated with the pain outcomes.[83]

GTP cyclohydroxylase 1 (*GCH1*) codes for the rate-limiting enzyme GCH1 which is responsible for the synthesis of tetrahydrobiopterin (BH4), an essential cofactor of enzymes involved in the synthesis of hydroxylases involved in catecholamine metabolism. rs3783641A<T a variant of *GCH1* has been associated with decreased *GCH1* activity in vitro, and is pain-protective in experimental pain models in volunteers[78] and in patients undergoing diskectomy for persistent radicular low back pain.[79] However, our meta-analysis may indicate that the association is spurious or effect size dependent on multiple confounding variables, given the high heterogeneity. Other variants of this gene were reported to be significantly associated with CPSP (C allele of rs8007267 [31] and minor allele of rs4411417[58]); however, these variants could not be included in the meta-analysis due to lack of studies evaluating the variants.

Cytokine genes such as the Interleukin (*IL*) 1 receptor 2 rs11674595 and *IL10* haplotype A8 have also been described to be associated with prevalence of CPSP in women after surgery

for breast cancer.[74; 75] In this meta-analysis, only *TNF alpha* (rs1800629 G allele) was investigated due to lack of information from more than one study for other cytokine genes/variants. Tumor necrosis factor-alpha (TNF-α) is a potent pro-inflammatory and immunoregulatory cytokine which stimulates many other cytokines and mediates the cytokine cascade that causes inflammation. At this variant, the A allele is known to influence TNF-α levels and has higher transcriptional activity and often connected to autoimmune diseases and other chronic pain conditions.[22; 24] The two studies included here report non-significant effects for the G allele at this location, with CPSP.

This review excluded non-English language articles and may therefore have missed any important findings reported in other languages. Our meta-analyses results were limited by the small number of studies (2–5 studies per variant), relatively few eligible studies based on criteria used which may affect the robustness of the results. The heterogeneity (I^2) in data is >50% for some of the variants which either may reflect true differences between studies or it may be because the I^2 is difficult to estimate when studies are few in number.[85] Hence, sub-group analyses were not attempted to decrease heterogeneity. Although positive haplotype associations with CPSP were reported in some studies, they could not be included in meta-analyses due to inadequate number of studies evaluating same haplotypes.

In conclusion, we have presented a detailed literature review and the first meta-analysis of genetic associations with the prevalence of chronic postsurgical pain. Heterogeneity in the data and methodology makes it difficult to draw accurate conclusions. While there are large sample size studies, they are in different population cohorts and across different surgeries and different pain types which might be contributing to the lack of significant findings observed. Genome-wide association studies are inadequate in this field. Larger sample sizes, replication studies, and alignment of primary outcome measures and confounding variables will be necessary to enable sophisticated analyses in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Chronic post-surgical pain (CPSP) is an important problem with genetic underpinnings
- A systematic review and meta-analysis of genetic association studies for CPSP is presented
- 26 genes involved in different nociceptive pathways had significant associations with CPSP
- 6 variants of 5 genes (*COMT*, *OPRM1, GCH1*, *KCNS1, TNFA*) were included in meta-analysis
- At rs734784 (A>G) of *KCNS1*, presence of G allele was found to marginally increase risk of CPSP
- Limitations included study heterogeneity in surgical populations, methodology and outcomes

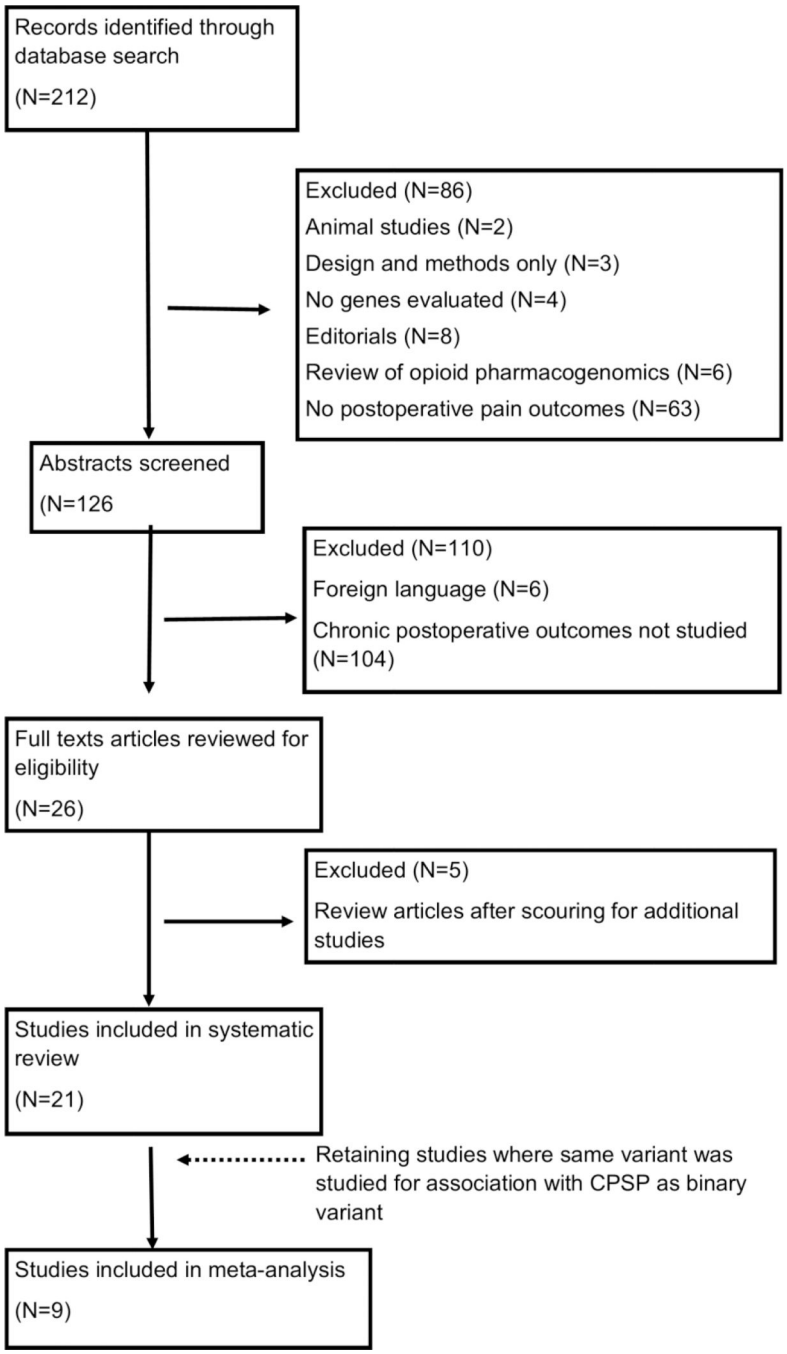

Figure 1:
PRISMA flow diagram represents the systematic literature search and assessment process used in this study.

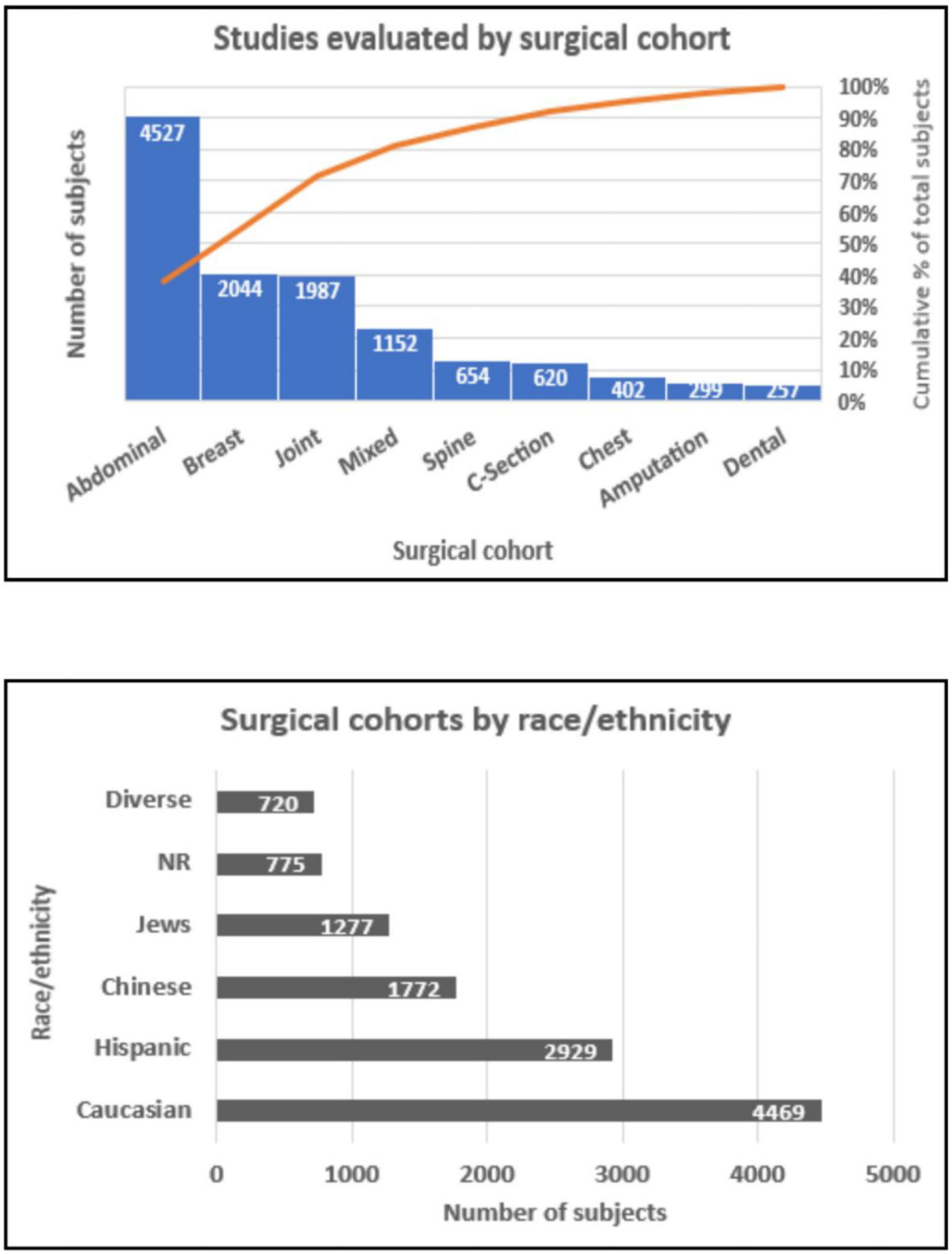

Figure 2:

Pareto chart and clustered bar chart depicting the different cohorts evaluated by studies in the systematic review by surgery (top panel) and race/ethnicity (lower panel) respectively are presented. Surgical cohorts have been classified according to the surgical incision location or type. For example, abdominal surgeries include hernia, gynecologic, urogenital surgeries etc. excluding caesarian sections which are presented as a different surgical class; joint surgeries include surgeries on any joint including knee, shoulder and hip surgeries. The pareto chart plots the distribution of the data in descending order of frequency (the number of patients

per category marked on the bar). The red line is the cumulative line on the secondary y-axis showing % of subjects per surgical type/total number of patients. The clustered bar chart shows the number of subjects per ethnicity/race overall in the cohort (number per category marked on the bar). The Caucasian cohort includes several European populations (including Danish, German, Irish, Swedish) and North American populations. Jewish population includes both Ashkenazi and non-Ashkenazi Jew cohorts studied. Although the Hispanic cohort presents the second largest racial group, they are represented in only one large study. NR: Not reported.

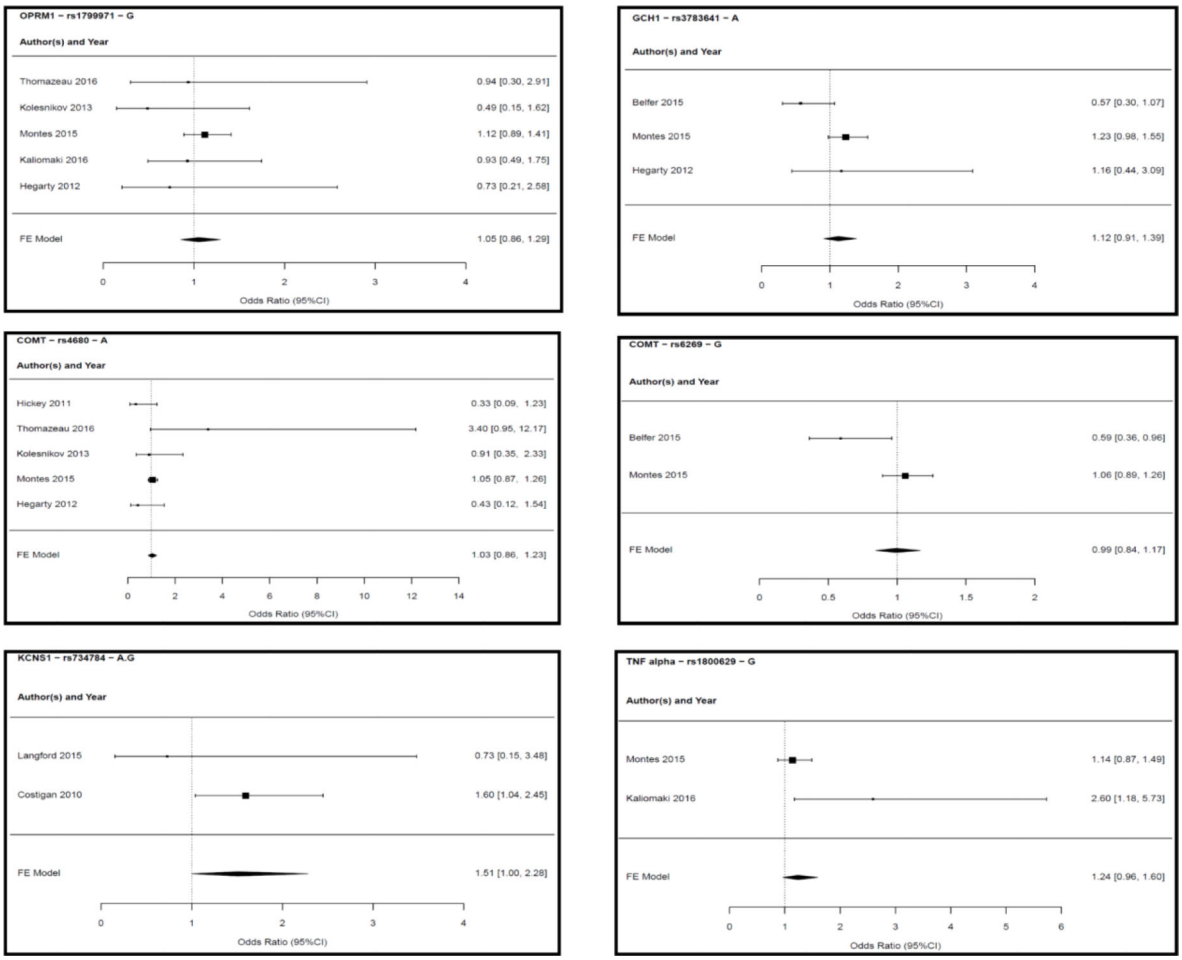

Figure 3:

Forest plots of studies reporting associations between polymorphisms and chronic post-surgical pain that were included in the meta-analysis are presented. Individual effect sizes of the studies included for the particular variant allele and fixed effect (FE) model odds ratios are presented with 95% confidence intervals (CI). For COMT rs4680 variant, 3 models were investigated (presented in table 3). Forest plot of dominant model (with least heterogeneity among them) is presented in this figure.

Table 1:

Descriptions of surgical cohorts, chronic post-surgical pain outcome definitions and STREGA/Q-Genie quality assessment scores for the studies evaluated in the systematic review

Author	Year	Study design	Incidence of CPSP	N	Surgery	Female (/%)	Age	Race	Measures assessed and CPSP Outcome definition and time frame	Genes studied	Strega score	Q-Genie score**
							Mean (SD)					
Sia	2010	Prospective	7.60%	620	Caesarian section	100%	18–45	Han Chinese	Scar pain 3 and 6 months after surgery **CPSP Outcome:** Persistent scar pain at 6 months after surgery	*ABCB1*	23	52 (NC)
Costigan	2010	Prospective	NR	151	lumbar discectomy	NR	NR	Caucasian (Maine)	Baseline, 2, 6 and 12 months after surgery; area-under-the-curve score for every pain variable was converted these to a z-score by comparing the patient with the rest of the cohort. **CPSP outcome**: mean of the four z-scores. RR defined.	*KCNS1*	24	58 (NC)
				199	Limb amputation	NR	NR	Israeli Jews				
				100	amputees	34%	59	Danish				
				529	post-mastectomy	100%	52.9	Israeli Jews				
Nissenbaum	2010	Retrospective	72.60%	549	Breast cancer surgery	100%	52.9	Ashkenazi and non-ashkenazi jews	**CPSP outcome**: Presence of pain at last 6 months (average 6.6 years) after surgery	*CACGN2*	21	64 (C)
Hickey	2011	Retrospective	43%	42	Breast reconstruction	100%	36.6 (9.7)	NR	**CPSP outcome**: Pain attributed to breast surgery over a 6 year period	*COMT, GCH1*	20	59 (C)
Lee	2011	Prospective	NR	98	Molar tooth extraction	NR	NR	Caucasian/Irish	Highest VAS pain at rest in the postoperative week, the highest VAS pain on movement in the postoperative week, days until no analgesia was required and total PoSSe score. **CPSP Outcome**: Pain score 3 months after surgery	*COMT/GCH1*	22	48 (NC)
Sorge	2012	Retrospective	50%	354	Mastectomy	100%	NR	NR	**CPSP Outcome** Intensity of a typical pain episode at least 6 months after surgery	*P2RX7*	19	46 (C)
Hegarty	2012	Prospective	37.70%		Lumbar discectomy			European	Pain at 3 month follow up: **CPSP Outcome**: not at least a 70% reduction in the VAS pain intensity at 3 months compared to preoperative VAS on movement	GCH1, OPRM1, CYP2D6	20	53 (NC)
				20	Pain cases	55%	40					
				32	Controls	44%	39					
Lebe	2013	Retrospective	30.40%	275	Lumbar disc surgery	42%	49.7(13.0)	NR	**CPSP Outcome**: pain, depression, physical functioning, disability 6 months after surgery	*5HTR1A, 5HTR2A*	19	57 (C)
Kolesnikov	2013	Prospective	34.30%	102	Abdominal/radical prostatectomy/ hysterectomy	44%	53.9 (9.8)	Caucasian	**CPSP Outcome**: Pain 3 months after surgery	*OPRM1, GCH1*	21	45 (NC)
Dominguez	2013	Case-control retrospective	24%	189	Inguinal hernia	56%	NR	Swedish	**CPSP Outcome**: Pain 6 months after surgery	*HLA-DRB1*	25	65 (C)
				231	replication	NR						
				436	control	NR						
Stephens	2014	Prospective	11.60%	172 (46/126)	Breast cancer surgery	100%	Control: 58.6 (11.4); Cases: 52.4 (9.4)	Diverse	**CPSP Outcome**: persistent pain to no pain trajectory 6 months after surgery	*IFNG, IL1R2, NFKB1, TNFA*	25	63 (NC)
Rut	2014	Prospective	39.50%	176	Lumbar discectomy	41%	46.7 (13.2)	Caucasian	**CPSP Outcome**: Back pain and disability index 12 months after surgery	*COMT*	20	55 (NC)
Liu	2015	.Prospective	21.40%	1152	Vascular, thoracic, orthopedic, general, urologic,	52%	NR	Chinese	**CPSP Outcome**: Surgical site pain at 12 months after surgery	*CTSG*	19	62 (NC)

Author	Year	Study design	Incidence of CPSP	N	Surgery	Female (/%)	Age	Race	Measures assessed and CPSP Outcome definition and time frame	Genes studied	Strega score	Q-Genie score**
							Mean (SD)					
					gynecologic, neuro/ spine surgery							
Belfer	2015	Prospective	12.80%	429	Herniotomy	0%	55.1 (13.3)	Caucasian (Danish/ German)	**CPSP Outcome**: moderate-to-severe pain-related activity impairment 6 months postoperatively (Activity Assessment Scale≥8.3)	*COMT, GCH1*	25	60 (NC)
Montes	2015	Prospective	18%	2929	Multiple cohorts (in all)	26%		Hispanic	Primary **CPSP Outcome**: Pain 4 months after surgery. Secondary: CPSP at 12 and 24 months after surgery	*90 genes: DRD2, ATXN1, NFKBIA OPRD1, GRIK3, FAAH/NSUN4, Unknown, PTGS2, IL19/IL10, POMC,SCN9A, GABRA4, GABRB1, SLC6A3/CLPTM1L, GABRB2/ GABRA6, GABRA1/LOC100287123, ATXN1, TNF/LTA, OPRM1, OPRK1, PENK, TRPA1, BDNFOS, BDNF, KIF18A/BDNF, DRD2,TMPRS S5/ DRD2, "Unknown gene*, SLCO1B3, SLCO1A2, NFKBIA, SAMD4A/GCH1, GCH1, WDHD1, SLC6A2, TRPV1, CCDC55, SLC6A4, MC4R/LOC728115, B9D2/TGFB1, COMT, MAOA*	27	73 (C)
			13.60%	1761	inguinal hernia		60 (39–76)					
			11.80%	416	vaginal hysterectomy		63 (45.7–76)					
			25.10%	350	abdominal hysterectomy		48 (41–63.8)					
			37.60%	402	thoracotomy		64 (49–76)					
Wieskopf	2015	prospective	46.60%	429	herniotomy	0%	55.1 (13.3)	Caucasian	**CPSP Outcome**: Moderate/severe pain 6 months after surgery; To derive a single composite value representing pain of the head and neck, seven individual responses (duration of facial pain, intensity of current facial pain, intensity of greatest pain in the last 6 months, intensity of average pain over the last 6 months, primary headache characteristics, percentage of lifetime suffering from primary headache, and count of comorbid pain conditions) were normalized by conversion to z scores and then summed	*CHRNA6*	23	58 (NC)
				159	replication (TMJ)	100%	36.8					
Langford	2015	Prospective longitudinal	27%	398	Breast cancer surgery	100%	Controls 58.6 (11.4), Cases 53.4 (11.5)	Diverse	**CPSP Outcome**: Latent classes of pain 6 months after surgery (No Pain, Mild Pain, Moderate Pain, Severe Pain)	*KCND2, KCNJ3, KCNJ6, KCNK9, KCNA1, KCND2, KCNS1, KCNJ3, KCNJ6, KCNK3, KCNK9*	23	60 (NC)
Thomazeau	2016	Prospective	28.80%	104	Knee replacement	0%	69 (9.0)	NR	**CPSP Outcome**: NRS score ≥ 1/10 over 8 days, 6 months after surgery.	*OPRM1, GCH1*	24	53 (NC)
George	2016	Prospective	NR	150	Arthroscopic shoulder surgery	34%	42.7 (16.4)	85% Caucasian; diverse	Brief Pain Inventory (BPI) Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire 3, 6 and 12 months postoperative: **CPSP Outcome**: 12 month pain intensity outcome	*ADRB2, OPRM1, AVPR1A, GCH1, KCNS1, IL1B, IL6, TNF/LTA*	27	61 (NC)
Kalliomaki	2016	Retrospective	NA	91	Hernia cases			Swedish	Inguinal pain questionnaire was used to assess pain. Neuropathic pain was defined as persisting pain in combination with sensory disturbance **CPSP Outcome:** pain of grade 3 (i.e.pain that could not be ignored but did not interfere with everyday activities) over the past week. Mean time since surgery was 49.1 months (SD 23.1 months)	*OPRM1 TNF-, GRIK3, GCH1, BDNF CACNA2D2*	*22*	60 (C)
					Pain cases	91%	58 (14.6)					
				93	Controls	94%	57.7 (14.8)					
Warner	2017	Retrospective	NR	613 (discovery) 212 and 908 (replication)	Total joint replacement	NR	NR	United Kingdom/ Netherlands	**CPSP Outcome**: Neuropathic pain (painDETECT score >12) – no time specified	*PRKCA*	25	60 (C)

NR: Not reported; NA: Not applicable; PoSse: VAS: Visual analog scale

Studies included in the meta-analysis are highlighted in gray color.

Gene names: COMT (catechol-O-methyltransferase); GCH1 (GTP cyclohydrolase 1); OPRM1 (opioid receptor mu 1); ABCB1 (ATP binding cassette subfamily B member 1); ADRB2 (adrenoceptor beta 2); AVPR1A (arginine vasopressin receptor 1A); TNF (tumor necrosis factor); LTA (lymphotoxin alpha); IL6 (interleukin 6); IL1R1 (interleukin 1 receptor type 1); IL1R2 (interleukin 1 receptor type 2); IL4 (interleukin 4); IL10 (interleukin 10); IL13 (interleukin 13); NFKB1 (nuclear factor kappa B subunit 1); HLA-DRB1 (major histocompatibility complex, class II, DR beta 1); PRKCA (protein kinase C alpha); CDH18 (cadherin 18); TG (thyroglobulin); OPRD1 (opioid receptor delta 1); GRIK3 (glutamate ionotropic receptor kainate type subunit 3); FAAH (fatty acid amide hydrolase); NSUN4 (NOP2/Sun RNA methyltransferase family member 4); PTGS2 (prostaglandin-endoperoxide synthase 2); IL19 (interleukin 19); POMC (proopiomelanocortin); SCN9A (sodium voltage-gated channel alpha subunit 9); GABRA4 (gamma-aminobutyric acid type A receptor alpha4 subunit); GABRB1 (gamma-aminobutyric acid type A receptor beta1 subunit); SLC6A3 (solute carrier family 6 member 3); CLPTM1L (CLPTM1 like); GABRB2 (gamma-aminobutyric acid type A receptor beta2 subunit); GABRA6 (gamma-aminobutyric acid type A receptor alpha6

subunit); GABRA1 (gamma-aminobutyric acid type A receptor alpha1 subunit); ATXN1 (ataxin 1); OPRK1 (opioid receptor kappa 1); PENK (proenkephalin); TRPA1 (transient receptor potential cation channel subfamily A member 1); BDNF (brain derived neurotrophic factor); KIF18A (kinesin family member 18A); DRD2 (dopamine receptor D2); TMPRSS5 (transmembrane serine protease 5); SLCO1B3 (solute carrier organic anion transporter family member 1B3); SLCO1A2 (solute carrier organic anion transporter family member 1A2); NFKBIA (NFKB inhibitor alpha); SAMD4A (sterile alpha motif domain containing 4A); WDHD1 (WD repeat and HMG-box DNA binding protein 1); SLC6A2 (solute carrier family 6 member 2); TRPV1 (transient receptor potential cation channel subfamily V member 1); SLC6A4 (solute carrier family 6 member 4); MC4R (melanocortin 4 receptor); B9D2 (B9 domain containing 2); TGFB1 (transforming growth factor beta 1); MAOA (monoamine oxidase A); CHRNA6 (cholinergic receptor nicotinic alpha 6 subunit); KCND2 (potassium voltage-gated channel subfamily D member 2); KCNJ3 (potassium voltage-gated channel subfamily J member 3); KCNJ6 (potassium voltage-gated channel subfamily J member 6); KCNK9 (potassium two pore domain channel subfamily K member 9); KCNA1 (potassium voltage-gated channel subfamily A member 1); KCNS1 (potassium voltage-gated channel modifier subfamily S member 1); KCNK3 (potassium two pore domain channel subfamily K member 3); CACNG2 (calcium voltage-gated channel auxiliary subunit gamma 2); PoSse: Postoperative symptom severity score; HADS = Hospital Anxiety and Depression Score

Strega score:

** Q-Genie scores: For studies with control groups (C) Scores ≤35 indicate poor quality studies, >35 and ≤45 indicate studies of moderate quality, and >45 indicate good quality studies.

For studies without control groups (NC): Scores ≤32 indicate poor quality studies, >32 and ≤40 indicate studies of moderate quality, and >40 indicate good quality studies.

Table 2:

Description of genes, variants, genetic association and covariates in the studies evaluated for the systematic review

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
Sia 2010	ABCB1	C3435T		T	1.66	1.03	2.67	**0.03**	**A**	No covariates described, no ancestry
		C1236T						NS		
		G2677T/A						NS		
Costigan 2010	KCNS1 (different cohorts)	rs734784 (LD)		G (Val). 45% vs: 22%	2.4 (RR)	1.2	4.5	**0.003**	**R**	Age, gender, population stratification; LD: Lumbar discectomy cohort ILAP: Israel limb amputation pain DLA: Denmark limb amputation PMP: Israel post-mastectomy pain
		rs13043825 (LD)						**0.03**		
		rs734784 (ILAP)		G				**0.0033**		
		rs13043825 (ILAP)						**0.056**		
		rs734784 (DLA)		G				**0.01**		
		rs734784 (PMP)		G				0.74		
		rs734784 (entire cohort)		G (Val)				**1.14 e −08**		
Nissenbaum 2010	CACNG2	rs4820242						**0.02**	**Multiplicative**	ethnicity, number of years since operation, chemotherapeutic treatment, and surgery type (mastectomy or lumpectomy
		rs2284015						**0.02**		
		rs2284017						**0.04**		
		rs2284018						**0.05**		
		rs1883988						**0.03**		
			rs4820242, rs2284015, rs2284017	A-C-C	1.65			**0.01**		
Hickey 2011	COMT	rs4680		A: 11% vs. 39% AA; 37.5% vs 37.5% AG	NR	-	-	0.06	**NR**	Covariates not reported. No ancestry
	GCH1		rs8007267, rs10483639, rs3783641	ATG	NR	-	-	1		
Lee 2011	COMT GCH1	rs4680, rs4818, rs6269		A, G, G T	-	-	-	NS	NR	Psychological and clinical covariates; no ancestry*Relative risk
	OPRM1	rs8007267 rs1799971		G						
	CACNA2D2	rs5030977		GG (72.3% vs 70.2%)	1.14*	0.66	2	0.603	R	

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
	GRIK	rs6691840		TT (59.6% vs 51.8%)	1.16*	0.7	1.92	0.247	R	
	BDNF	rs6265		GG (63.8% vs 62.3%)	0.96*	0.58	1.61	0.34	R	
	OPRM1	rs1799971		AA (70.2% vs 70.2%)	0.98*	0.57	1.68	0.935	R	
Sorge 2012	P2X7R	rs208294		A	1.17	Beta values of regression with pain intensity reported		**0.003**	**NR**	age at surgery, and time since the operation, which robustly affected pain traits in this cohort); no ancestry
		rs208296		T	−1.21			**0.003**		
		rs7958311		A	−1.19			**0.006**		
			rs208294 rs208296 rs7958311	p.H155Y, c.533+630C> T, p.R270H						
				ATA	1.58			0.186		
				GTA	−0.71			**0.003**		
				ACA	−0.48			0.354		
				GCA	0.08			0.922		
				GTG	−0.41			0.211		
				ACG	0.7			**0.001**		
				GCG	0.06			0.803		
Hegarty 2012	GCH1	rs3783641		T (72% vs 75%)	0.07	Pearson's chi square values reported		0.77	Allelic or genotype model	Unadjusted. No ancestry
				TT/AA/AA	0.14			0.93		
		rs8007627		T (22% vs 44%)	4.86			**0.02**		
				CC/CT/TT	4.23			0.12		
		rs10483639		C (77% vs 36%)	0.8			0.37		
				GG/CG/CC	0.92			0.63		
	OPRM1	rs1799971		A (72% vs 57%)	0.29			0.58		
				AA/AG/GG	0.23			0.88		
	COMT	rs4680		G (28% vs. 43%)	1.85			0.17		
				AA/AG/GG	3.7			0.15		
	CYP2D6	rs3892097		T (13% vs. 23%)	1.63			0.2		
				CC/CT/TT	2.13			0.34		
Lebe 2013	5HTR1A	rs6295		G	3.909#	# main genetic effect in interaction model		<0.05		age, pain intensity, and depression; no ancestry
	5HTR2A	rs6311		G	0.047#			**NS**		

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
Kolesnikov 2013	COMT	rs4680		A: 10/35 AA, 16/35 AG vs 12/67 AA, 39/67 AG	-	-	-	0.74, 0.44, 0.79	A, D, R	age, sex, and baseline pain score; no ancestry
	OPRM1	rs1799971		G: 4/35 (AG +GG) vs 14/67	-	-	-	0.31, 0.22, 0.95		
Dominguez 2013	HLA-DRB1	1		14% vs 13%	1.11	0.62	1.99	NS		Age, smoking, treatment status; No ancestry
		3		10% vs 17%	0.53	0.29	0.98	NS		
		4		24% vs 12%	2.28	1.32	3.96	**0.004**	**D**	
		7		8% vs 8%	0.94	0.45	1.97	NS		
		8		6% vs 2%	2.89	0.9	9.24	NS		
		9		1% vs 2%	0.5	0.09	2.76	NS		
		11		2% vs 4%	0.42	0.11	1.66	NS		
		12		2% vs 3%	0.67	0.19	2.4	NS		
		13		15% vs 14%	1.06	0.6	1.87	NS		
		14		4% vs 3%	1.19	0.39	3.6	NS		
		15		14% vs 19%	0.72	0.42	1.24	NS		
		16		0% vs 2%	0.25	0.03	2.25	NS		
	DQB1*03:02			20% vs 7%	3.24			**<0.003**	**D**	
			DQB1⁄03:02 – DRB1⁄04		3.16	1.61	6.22	<0.001		
Stephens 2014	IFNG1	rs2069727		G	FE			**0.025**	**R**	[^]Chi-square genomic estimates of and self-reported race/ethnicity (ie, white, black, Asian, Hispanic/ mixed ethnic background/ other), occurrence of pain in the affected breast prior to surgery, and severity of average postoperative pain
		rs2069718		T	10.09[^]			**0.006**	**A**	
			HapA5		6.58[^]			**0.037**		
	IL1R1	rs3917332		T	FE			**0.037**	**D**	
	IL1R2	rs11674595		C	FE			**0.041**	**R**	
	IL4	rs2243248		G	FE			**0.033**	**D**	
	IL10	rs3024498		G	FE			**0.015**	**D**	
		rs1878672		C	FE			**0.029**	**D**	
		rs3024491		T	FE			**0.035**	**D**	
			HapA8		6.39[^]			**0.041**		
	IL13	rs1881457		C	FE			**0.043**	**D**	
		rs1800925		T	FE			**0.007**	**D**	
		rs1295686		A	FE			**0.014**	**D**	
		rs20541		T	7.81[^]			**0.017**	**A**	
			HapA1		8.7[^]			**0.013**		

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
	NFKB1	rs4648141		A	FE			**0.041**	**R**	
	IL1R2	rs11674595		C: TT +TC>CC	36.07	2.02	643.37	0.015	D	
			HapA8: rs3024505-rs3024498-rs3024496-rs1878672-rs1518111-rs1518110-rs3024491	0, 1, or 2 doses of the C-G-C-G-A-T-T haplotype	0.21	0.05	0.91	0.037		
Rut 2014	COMT	rs4680		A: GG vs GA+AA (MAF NR)				0.053	R	Age, sex, change in pain score; no ancestry; p-value for pain score change for back pain from preoperative to postoperative is reported.
		rs4680		A: AA vs GG+GA				0.87	D	
		rs4818		T: TT vs AT+AA				0.27	R	
		rs4818		T: AA vs AT+TT				0.08042	D	
		rs4633		T: GG vs GC+CC				0.91	R	
		rs4633		T: CC vs GC+GG				**0.053**	**D**	
		rs6269		G: AA vs AG+GG				**0.16**	**D**	
		rs6269		G: GG vs AG+AA				**0.0042**	R	
		Multiple regression model								
		rs4680		A	−1.2			**0.046**	D	
			Haplotype L (rs6269, rs4633, rs4818, rs4680)	A_C_C_G	−1.3			0.014		
		rs4633		T	−1.45			**0.0032**	R	
Liu 2015	Cathepsin (CTSG)	rs2236742		A: (GG 22.6%, GA 20.4%, AA 6.4% in cases; controls NR)	0.34	0.21	0.98	0.043	Genotype model	age, sex, smoking habit, employment history, education level, prior pain syndrome, and severity of acute pain after index surgery; no ancestry
		rs2070697		AA (GG 22.3%, GA 24.1%, AA 15.3% cases)	0.67	0.26	0.99	0.044		
Belfer 2015	COMT		rs6269, rs4633, rs4818	GCG	0.57	0.35	0.95	**0.031**		surgical treatment (open vs laparoscopic), preoperative AAS score, preoperative pain response to the 47°C heat stimuli, difference (postoperative 2 preoperative) of warmth detection
				ATC	1.66			**0.041**		
				ACC	0.67	0.25	1.82	0.431		
	GCH1		rs3783641, rs8007267	AT	0.53	0.27	1.07	0.076		
				AC	0.46	0.1	2.11	0.321		
				TC	1.94			**0.043**		

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
	COMT	rs6269		G (30% vs 40.3%)	0.59	0.37	0.96	**0.034**	**A**	in groin, preoperative HADS anxiety score, preoperative HADS depression score, and Pain Catastrophizing Scale score; No ancestry.
		rs4633		C (35.5% vs 47.3%)	0.53	0.32	0.88	**0.014**	**A**	
		rs4818		G (30.9% vs 39.8%)	0.63	0.39	1.03	0.063	A	
	GCH1	rs3783641		A (14.5% vs 22.1%)	0.57	0.31	1.07	0.079	A	
	GCH1	rs8007267		T (13% vs 23.2%)	0.51	0.26	1.02	0.057	A	
Montes 2015	OPRD1	rs1042114		G	1.2	0.93	1.55	0.1636	different inheritance models were tested in autosomic SNPs by comparing each genotype against the combination of the remaining two	Age, SF-12 = Short Form Health Survey-12 physical and mental summary scores, preoperative pain score; No ancestry
		rs533123		C	1	0.8	1.25	0.9907		
	GRIK3	rs6691840		A	1.04	0.85	1.27	0.7091		
	FAAH/ NSUN4	rs932816		A	1.16	0.96	1.41	0.1251		
	FAAH	rs4141964		G	1.02	0.85	1.22	0.8462		
		rs2295633		C	1	0.83	1.21	0.9675		
	Unknown gene			A	1.11	0.92	1.33	0.2757		
	PTGS2	rs5275		C	1.03	0.85	1.24	0.8001		
	IL19/IL10	rs1800896		A	1.04	0.87	1.24	0.675		
	POMC	rs934778		T	1.03	0.86	1.24	0.7558		
	SCN9A	rs6746030		A	1.01	0.78	1.32	0.9196		
		rs6747673		A	1.08	0.9	1.28	0.4144		
		rs9646771		C	1.04	0.86	1.25	0.6842		
	GABRA4	rs7678338		T	1.05	0.86	1.27	0.6507		
		rs7689605		A	1.08	0.78	1.49	0.6494		
	GABRB1	rs10028945		A	1.01	0.84	1.23	0.8924		
	SLC6A3/ CLPTM1L	rs12516948		G	1.04	0.87	1.24	0.6565		
	SLC6A3	rs40184		A	1.01	0.85	1.2	0.9359		
		rs403636		G	1.17	0.92	1.47	0.1926		
		rs6350		C	1.13	0.81	1.57	0.4853		
	GABRB2/ GABRA6	rs3816596		T	1.05	0.87	1.26	0.6129		
	GABRA1/ LOC100287123	rs12658835		G	1.05	0.86	1.28	0.6454		
	ATXN1	rs179997		A	1.2	1	1.44	**0.0473**		
	TNF/LTA	rs1800629		G	1.14	0.87	1.5	0.3355		

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						LL	UL			
	OPRM1	rs1799971		A	1.12	0.89	1.41	0.337		
		rs563649		A	1.04	0.72	1.5	0.8261		
	OPRK1	rs702764		T	1.04	0.81	1.33	0.7637		
		rs997917		C	1.09	0.9	1.33	0.3819		
	PENK	rs3839874		T	1.11	0.93	1.32	0.2525		
		rs1975285		C	1.19	0.96	1.47	0.1082		
	TRPA1	rs11988795		C	1.01	0.84	1.22	0.8807		
	BDNFOS	rs6265		G	1.12	0.91	1.37	0.295		
	BDNF	rs2049046		T	1.14	0.96	1.36	0.1426		
	KIF18A/ BDNF	rs908867		G	1.28	0.93	1.77	0.127		
	DRD2	rs6277		T	1.04	0.87	1.24	0.6926		
		rs1076560		C	1.08	0.83	1.41	0.5758		
		rs2734837		G	1.03	0.85	1.24	0.7506		
		rs11608185		T	1.03	0.85	1.24	0.7529		
		rs4936272		C	1.02	0.85	1.21	0.864		
		rs4648317		T	1.35	1.05	1.74	**0.0186**		
		rs4322431		T	1.09	0.9	1.33	0.3671		
	TMPRSS5/ DRD2	rs1799978		A	1.03	0.69	1.53	0.8962		
	TMPRSS5/ DRD2	rs12364283		G	1.58	1.11	2.23	**0.0102**		
	Unknown gene *	rs6693882		T	1.17	0.97	1.4	0.1005		
	SLCO1B3	rs4149117		G	1.09	0.84	1.41	0.5382		
	SLCO1A2	rs11568563		A	1.23	0.87	1.74	0.2388		
	NFKBIA	rs8904		T	1.21	1.01	1.44	**0.0394**		
	SAMD4A/ GCH1	rs10483639		C	1.24	0.98	1.57	0.0713		
	SAMD4A/ GCH1	rs7142517		C	1.09	0.9	1.31	0.3649		
	GCH1	rs752688		T	1.27	1	1.6	0.0514		
		rs4411417		C	1.27	1	1.62	**0.0458**		
		rs9671371		T	1.18	0.97	1.44	0.1016		
		rs12147422		T	1.17	0.87	1.57	0.3107		
		rs8004445		G	1.19	0.88	1.6	0.2536		
		rs998259		C	1	0.82	1.22	0.9864		
		rs3783641		A	1.23	0.97	1.56	0.0807		

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						LL	UL			
	WDHD1	rs8007267		T	1.15	0.9	1.47	0.2502		
	SLC6A2	rs40434		C	1.15	0.96	1.38	0.139		
	SLC6A2	rs36024		C	1.12	0.94	1.34	0.2056		
	SLC6A2	rs36017		G	1.14	0.96	1.36	0.141		
	TRPV1	rs8065080		C	1	0.84	1.2	0.9945		
	CCDC55	rs1979572		C	1.02	0.86	1.22	0.7896		
	SLC6A4	rs4325622		T	1	0.84	1.2	0.9607		
	SLC6A4	rs140701		G	1.05	0.88	1.26	0.557		
	SLC6A4	rs2066713		C	1.07	0.89	1.29	0.4839		
	MC4R/ LOC728115	rs9966412		C	1.11	0.86	1.44	0.4191		
	Unknown	rs2562456		C	1.1	0.9	1.35	0.3402		
	B9D2/ TGFB1	rs1800469		C	1.05	0.88	1.27	0.5785		
	COMT	rs4646312		C	1.09	0.91	1.3	0.3568		
		rs6269		G	1.06	0.89	1.27	0.5077		
		rs4680		G	1.05	0.88	1.25	0.6067		
	MAOA	rs3788862		A	1.1	0.85	1.42	0.4551		
		rs2283724		G	1.08	0.85	1.37	0.5271		
		rs1800659		C	1.03	0.8	1.31	0.8307		
		rs979606		G	1.03	0.8	1.33	0.8108		
		rs979605		T	1.03	0.8	1.33	0.7978		
Wieskopf JS	CHRNA6	rs7828365		TT (8/325 vs 0.12% in general population)	12	SEM 1.1		**0.03**	**D**	patients' age, surgery type, and activity assessment scale (AAS) score (0% if no pain-related activity impairment was reported, and 100% for maximum impairment) at baseline; no ancestry
Langford 2015	Multiple regression model									
	KCND2	rs17376373			0.12	0.017	0.814	0.030	D	population substructure (ie, race/ethnicity), occurrence of pain in the affected breast before surgery, hardness in affected breast
	KCNJ3		HapA2 rs3111020 - rs11895478	G-A	0.11	0.027	0.438	0.002		
	KCNJ6	rs2835925		C	19.28	3.299	112.713	0.001	G	

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						LL	UL			
	KCNK9	rs2014712		T	9.85	1.099	88.268	0.041	R	before surgery, and reexcision or mastectomy performed within 6 mo after the initial surgery for breast cancer
	Univariate regression				X2			p-value		
	KCNA1	rs4766311		T	1.02			0.601	A	
	KCND2	rs17376373		G	FE			**0.009**	D	
		rs702414		C	FE			**0.023**	R	
		rs802340		T	8.74			**0.013**	A	
		rs12706292		G	FE			**0.03**	D	
		rs1072198		G	1.09			0.58	A	
	KCNS1	rs734784		G	0.73			0.693	A	
			HapB1		0.73			0.693		
	KCNJ3	rs6435329		T	FE			**0.005**	D	
		rs11895478		T	FE			**0.001**	D	
		rs3106653		C	FE			**0.004**	D	
		rs3111006		T	FE			**0.012**	R	
		rs12471193		G	6.11			**0.047**	A	
		rs7574878		G	FE			**0.01**	D	
		rs12995382		C	FE			**0.031**	D	
		rs13398937		G	1.63			0.444	A	
		rs2591157		G	0.02			0.992	A	
		rs17641121		C	1.99			0.37	A	
		rs4467223		A	1.26			0.533	A	
			HapA2		11.69			**0.003**		
			HapB1		9.3			**0.01**		
			HapB4		7.83			**0.02**		
			HapC5		6.11			**0.047**		
	KCNJ6	rs860795		C	1.47			0.481		
		rs857967		A	3.9			0.142		
		rs858010		A	3.93			0.14		
		rs858003		T	3.65			0.161		
		rs2835914		C	0.02			0.99		
		rs858035		C	3.03			0.22		
		rs2835925		G	12.62			**0.002**	**A**	

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
			HapB2		3.9			0.142		
			HapC3		3.93			0.14		
			HapE2		6.39			**0.041**		
			HapE7		13.18			**0.001**		
	KCNK3	rs1662988		T	FE			**0.023**	**R**	
		rs7584568		A	FE			**0.004**	**D**	
			HapB1		9.92			**0.007**		
			HapB4		6.27			**0.043**		
	KCNK9	rs2542424		G	0.74			0.69	A	
		rs2014712		T	FE			**0.041**	R	
		rs2545457		C	3.71			0.156	A	
		rs888349		C	3.14			0.208	A	
Thomazeau 2016	COMT	rs4680		A: 83.3% vs 63.5%	-			0.047		patient characteristics (gender, high school diploma, physical activity), pain intensity and consequences, Pain Matcher, anesthetic procedure; no ancestry
	OPRM1	rs1799971		G: 16.7% vs 17.6%	-	-	-	0.912		
	COMT	Rs4680		A	3.42	0.93	12.51	0.63	D	
George 2016	ADRB2	rs1042713			R^2 increment				NR	age, sex, race, and preoperative status, and psychological factors, and interactions; no ancestry
				A	0.001			0.863		
	AVPR1A	rs1042615		C	0.01			0.338		
	TNF/LTA	rs2229094		C	0.009			0.368		
	IL6	rs1800797		A	0.002			0.793		
	IL6	rs2069840		C	0.001			0.867		
Kalliomaki 2016	TNF-α	rs1800629		GG (78% vs 58.8%)	1.93*	1.03	3.61	**0.036**	**R**	NR. No ancestry
	CACNA2D2	rs5030977		GG (72.3% vs 70.2%)	1.14*	0.66	2	0.603	R	
	GRIK	rs6691840		TT (59.6% vs 51.8%)	1.16*	0.7	1.92	0.247	R	
	BDNF	rs6265		GG (63.8% vs 62.3%)	0.96*	0.58	1.61	0.34	R	
	OPRM1	rs1799971		AA (70.2% vs 70.2%)	0.98*	0.57	1.68	0.935	R	
Warner 2017	PRKCA	rs887797		A	2	1.48	2.7	**4.29×10^{-6}**		Unadjusted

Author/ Year	Gene	SNP	Haplotype SNPs	Reference Allele/ genotype Frequency (Cases versus (vs) controls) when reported	OR	95% CI		p-value	Genetic model	Covariates and ancestry
						LL	UL			
	CDH18	rs4866176		A	2.86	1.76	4.66	**1.19×10^{-5}**		
	TG	rs1133076		A	1.66	1.23	2.24	**3.41×10^{-4}**		
	MAT2B	Rs7734804		A	4.64	2.26	9.53	**5.25 × 10^{-6}**		
	GPD2	Rs298235		A	6.72	2.67	16.92	**3.41 × 10^{-6}**		
	FOXL1	Rs12596162		A	2.05	1.51	2.79	**3.53 × 10^{-6}**		
	Meta-analysis									
	PRKCA	Rs887797		A	1.48	1.23	1.75	**1.65 × 10^{-5}**	**A**	
	PRKCA	Rs887797		A	2.41	1.74	3.34	**1.29 × 10^{-7}**	**R**	

Values are provided if reported in the study or deducible from the information provided in the study.

* RR: Relative risk; FE: Fisher's Exact

^ X2: chi-square test

OR: Odds ratio; CI: confidence interval; LL: lower limit; UL: upper limit; NR: Not reported; NS: Not significant, Gene names are reported in Table 1. Genetic model A: Additive, D: Dominant; R: Recessive.

Bolded p-values represent nominal significance (0.05) for CPSP variant association

Studies included in the meta-analysis are shaded in gray color.

Table 3:

Results of the meta-analysis: genetic models

Gene	SNP	Reference Alleles	Number of Studies	Genetic model	Effect size			Heterogeneity	
					OR	95% CI	p-value	I^2 (%)	p_Q
OPRM1	rs1799971	G (minor)	5 (T, Ko, M, Ka, H)	dominant	1.052	(0.856, 1.294)	0.630	0	0.669
GCH1	rs3783641	A (minor)	3 (B, M, H)	additive	1.123	(0.908, 1.390)	0.285	60.7	0.079
COMT	rs4680	A (minor)	5 (Hi, T, Ko, M, H)	additive	1.012	(0.855, 1.198)	0.888	65.9	0.019
COMT	rs4680	A (minor)		dominant	1.028	(0.862, 1.228)	0.757	50.9	0.086
COMT	rs4680	A (minor)		recessive	1.058	(0.884, 1.264)	0.541	64.0	0.025
COMT	rs6269	G (minor)	2 (B, M)	additive	0.993	(0.845, 1.169)	0.935	79.7	0.026
KCNS1	rs734784	G (minor)	2 (L, C)	additive	1.511	(1.000, 2.284)	0.050	0	0.344
TNF-alpha/ TNFA	rs1800629	G (major)	2 (M, Ka)	allelic	1.240	(0.963, 1.597)	0.096	73.2	0.054

I^2: ratio of excess heterogeneity (observed total variation – expected variation) to total variation in observed effects; OR: odds ratio; CI: confidence interval

p_Q: p-value of the Q statistics, weighted sum of squares of the deviation of each observed effect size from the mean effect size.

T: Thomazeau 2016, Ko: Kolesnikov 2013, M: Montes 2015, Ka: Kaliomaki 2016; H: Hegarty 2012, Hi: Hickey 2011; B: Belfer 2015; L: Langford 2015, C: Costigan 2010.