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Review Article

Genetic polymorphisms and their association with the prevalence and severity of chronic postsurgical pain: a systematic review

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Abstract

Background: Although several patient characteristic, clinical, and psychological risk factors for chronic postsurgical pain (CPSP) have been identified, genetic variants including single nucleotide polymorphisms have also become of interest as potential risk factors for the development of CPSP. The aim of this review is to summarize the current evidence on genetic polymorphisms associated with the prevalence and severity of CPSP in adult patients.
Methods: A systematic review of the literature was performed, and additional literature was obtained by reference tracking. The primary outcome was CPSP, defined as pain at least 2 months after the surgery. Studies performed exclusively in animals were excluded.
Results: Out of the 1001 identified studies, 14 studies were selected for inclusion. These studies described 5269 participants in 17 cohorts. A meta-analysis was not possible because of heterogeneity of data and data analysis. Associations with the prevalence or severity of CPSP were reported for genetic variants in the *COMT* gene, *OPRM1*, potassium channel genes, *GCH1*, *CACNG*, *CHRNA6*, *P2X7R*, cytokine-associated genes, human leucocyte antigens, *DRD2*, and *ATXN1*.
Conclusions: Research on the topic of genetic variants associated with CPSP is still in its initial phase. Hypothesis-free, genome-wide association studies on large cohorts are needed in this field. In addition, future studies may also integrate genetic risk factors and patient characteristic, clinical, and psychological predictors for CPSP.

Key words: chronic pain; pain; postoperative; polymorphism, genetic

Chronic postsurgical pain (CPSP) is a common problem that can occur after any type of surgery.[1 2] The prevalence of moderate to severe CPSP varies between 10 and 60%.[1 3 4] Chronic postsurgical pain not only has a negative influence on the quality of life of the patient, but it also has major socioeconomic consequences.[5 6] Several studies have been performed to determine the risk factors for the development of CPSP, and a number of patient characteristic, clinical, and psychological risk factors have already been identified.[1 2 7–9] However, these studies have also demonstrated that a substantial amount of the variance in CPSP cannot be explained by these predictors.[1 2 9]

Recently, polymorphisms of several genes have also become of interest as potential risk factors for the prevalence and severity of CPSP. It is suspected that some genes predispose to CPSP, whereas others are associated with a protective effect. Data from twin studies and human pedigrees estimate that the heritability of chronic pain ranges from 30 to 70%.[10] Research has focused on variants in genes that encode for proteins involved in nerve conduction and transmission, opioid receptor signalling, and inflammatory processes.[11–15]

The lack of ability of patient characteristic, clinical, and psychological factors to explain all the variance in the prevalence and severity of CPSP, coupled with the interest in genetic polymorphisms as predictors of other chronic pain states, leads to two questions. Are genetic polymorphisms associated with the prevalence and severity of CPSP? If this is the true, does adding these polymorphisms to the existing prediction models improve their accuracy?

Therefore, the objective of this systematic review is to summarize the current evidence with respect to genetic polymorphisms as predictors for the prevalence (i.e. the number of patients in the study population that develop CPSP) and severity of CPSP after any type of surgery in adult patients. Finding consistent and reliable genetic predictors might improve the understanding of the molecular mechanisms underlying the development of CPSP and reveal therapeutic targets, and might also improve preoperative prediction models and thus offer surgeons and anaesthetists the possibility to identify patients at risk for developing CPSP.

Methods

Search strategy

This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. A systematic literature review was conducted, using the databases of PubMed, Embase and PsychINFO. The final search strategy was as follows: ("Pain, Postoperative"[Mesh] OR ("persistent pain" AND surgery) OR ("chronic postsurgical pain") OR ("chronic post surgical pain") OR cpsp OR ("persistent postoperative pain") OR ("chronic postoperative pain") OR ("chronic pain" AND surgery)) AND (genetic* OR gene OR genes OR snp OR snps OR polymorphism*) NOT "pain treatment" NOT "pain therapies" NOT "pain management" NOT "pain control". Electronic searches were limited to the availability of abstracts and to studies published in the English, French, German, or Dutch language. Additional searches were carried out by reference tracking and expert consultation.

Study selection and inclusion criteria

Studies eligible for inclusion were observational cohort studies, case–control studies, and randomized controlled trials, performed in adult patients undergoing any type of surgical procedure. Conference abstracts and case reports were excluded, as were studies performed exclusively in animals. Studies were included if the study population had already undergone surgery and the follow-up time was at least 2 months. This time frame was chosen in line with the definition of CPSP.[16] Pain had to be the primary outcome parameter, but the method by which pain was measured was not a specific inclusion or exclusion criterion. All included studies had to measure genetic polymorphisms directly. Indirect measurement, via the analysis of gene products, resulted in exclusion of the study. The abstracts retrieved from the search were all read and assessed independently by two authors (D.M.N.H. and R.R.I.v.R.). If an abstract fulfilled all inclusion criteria or if any aspect of the abstract was unclear, the full text was obtained and assessed by the two reviewers (D.M.N.H. and R.R.I.v.R.). Differences in opinion were resolved through structured discussion.

Data extraction and data analysis

The following information was extracted from each study: reporting author, publication year, study design, number of participants, ethnicity of participants, type of surgery, primary and secondary outcome measures, follow-up time, polymorphisms studied, and type of statistical analyses used. The quality of the studies was assessed using an eight-item checklist (scores 0–8), based on the Critical Appraisal Checklist for Cohort/Case Control of the Joanna Briggs Institute[17] and the checklist for measuring study quality developed by Downs and Black.[18] The quality of each study was assessed independently by two authors (D.M.N.H. and R.R.I.v.R.) This eight-item checklist was used in previous research, where substantial agreement between raters was demonstrated.[8] An explanation of this quality checklist is available elsewhere.[8] We considered performing a meta-analysis for polymorphisms that were reported by more than one study. Unfortunately, an accurate and reliable meta-analysis could not be performed because only a few polymorphisms were reported by more than one study. Furthermore, study design (e.g. included surgical procedures, definition of CPSP, follow-up time), the statistical analysis, and the manner of reporting the results [e.g. odds ratios (ORs) *vs* only *P*-values] varied too much between authors.

Results

The systematic search and reference tracking resulted in 1002 publications (Fig. 1). Of these initial 1002 articles, 49 duplicates were removed and 920 articles were excluded after screening of the abstracts. Most of these 920 articles were either conference abstracts or animal studies. Hence, a total of 33 full-text articles were screened, of which 18 were excluded (in four articles pain was not an outcome parameter, 12 articles did not measure CPSP, two articles did not include genetic analyses, and one article included patients younger that 18 yr old). A total of 14 articles, including 5269 participants in 17 cohorts, were finally used for the analyses.

The characteristics of the patient cohorts are summarized in Table 1. The most common surgical procedures were breast surgery and inguinal hernia repair. In all studies, CPSP was measured at 3 months or more after the surgical procedure. Seven of the cohorts studied a Caucasian population, three cohorts studied an Israeli population (of Ashkenazi and non-Ashkenazi descent), one cohort studied a Chinese population, and the remaining studies included participants of diverse ethnicities or did not report the ethnicity of the participants. The sample size of the included cohorts varied between 42 and 1005 participants. The relatively low sample size of many studies, combined with the number of polymorphisms investigated, resulted in low statistical power in most studies. Moreover, the statistical analyses used in the studies differed considerably; one study used multiple testing corrections by the Bonferroni method,[11] two other studies chose not to correct for multiple testing because they considered their investigation to be of exploratory nature, and the remaining studies did not report whether they performed multiple testing correction.[13 15] The quality of the studies varied between four and seven points on the eight-item