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REVIEW ARTICLE/BRIEF REVIEW

Genetics of chronic post-surgical pain: a crucial step toward personal pain medicine

Génétique de la douleur chronique post chirurgicale: une étape cruciale vers une médecine personnalisée de la douleur

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Abstract

Purpose *Most patients who undergo surgery or experience a traumatic injury suffer from acute pain that subsides once tissues heal. Nevertheless, the pain remains in 15-30% of patients, sometimes for life, and this chronic post-surgical pain (CPSP) can result in suffering, depression, anxiety, sleep disturbance, physical incapacitation, and an economic burden. The incorporation of genetic knowledge is expected to lead to the development of more effective means to prevent and manage CPSP using tools of personalized pain medicine. The purpose of this review article is to provide an update on the current state of CPSP genetics and its future potential.*

Principle findings *The large variability in CPSP amongst patients undergoing similar surgery suggests that individual factors are significant contributors to CPSP, raising the possibility that CPSP is influenced by genetic determinants. Heritability estimates suggest that about half of the variance in CPSP levels is attributable to genetic variation. These estimates suggest that identifying the genetic underpinnings of CPSP may lead to significant improvements in treatment. Analyzing patients' DNA sequences, blood and salivary pain biomarkers, as well as their analgesic responses to medications will facilitate developing insights into CPSP pathophysiology and inform predictive algorithms to determine a patient's likelihood of developing CPSP even prior to surgery. These algorithms could facilitate effective treatment regimens that will protect against the transition to chronicity in traumatically injured patients or those scheduled for surgery and lead to better therapy for patients who have already developed CPSP.*

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Conclusions *Pharmacogenomic technologies and strategies provide an opportunity to expand our knowledge in CPSP treatment that may manifest in a personalized approach to diagnosis, prevention, and therapy. Capitalizing on this genomic knowledge will necessitate the analysis of many tens of thousands of study patients. This will require an international coordinated effort to which anesthesiologists and surgeons can contribute substantially.*

Résumé

Objectif *La plupart des patients qui subissent une chirurgie ou une blessure traumatique souffrent de douleurs aiguës qui s'apaisent après la guérison des tissus. Néanmoins, la douleur persiste chez 15 % à 30 % des patients, parfois à vie, et cette douleur chronique post chirurgicale (DCPC) peut provoquer dépression, anxiété, troubles du sommeil, handicap physique et fardeau économique. On s'attend à ce que l'inclusion de connaissances génétiques débouche sur l'apparition de moyens de prévention et de gestion plus efficaces de la DCPC grâce aux outils de traitements personnalisés de la douleur. L'objectif de cette synthèse est de fournir une mise à jour sur l'état actuel de la génétique dans le domaine de la DCPC et sur son possible avenir*

Constatations principales *La grande variabilité de la DCPC parmi les patients subissant une chirurgie similaire suggère que des facteurs individuels y contribuent de façon significative, soulevant la possibilité d'une influence de déterminants génétiques sur la DCPC. Des estimations sur son caractère héréditaire suggèrent qu'environ la moitié de l'écart entre les niveaux de DCPC peut être attribuée à une variation génétique. Ces estimations suggèrent que l'identification des éléments génétiques sous-jacents à la DCPC pourrait conduire à des améliorations significatives de son traitement. L'analyse des séquences ADN des patients, de leurs biomarqueurs sanguins et salivaires, ainsi que de leur réponse aux médicaments analgésiques facilitera l'élaboration de connaissances sur la physiopathologie de la DCPC et enrichira des algorithmes prédictifs visant à déterminer la probabilité de développement d'une DCPC chez un patient, même avant la chirurgie. Ces algorithmes pourraient faciliter la mise au point de protocoles thérapeutiques efficaces qui protégeraient contre le passage à la chronicité de patients ayant subi des lésions traumatisantes ou chez lesquels on planifie une intervention chirurgicale et ils déboucheraient sur un meilleur traitement pour les patients souffrant déjà d'une DCPC installée.*

Conclusions *Les technologies et stratégies de pharmacogénomique nous fournissent une possibilité d'élargir nos connaissances sur le traitement de la DCPC et aboutir à une approche personnalisée de son diagnostic, de sa prévention et du traitement. Il faudra, pour pouvoir capitaliser sur cette connaissance du génome, analyser plusieurs dizaines de milliers de patients dans des études. Cela nécessitera un effort international coordonné auquel les anesthésiologistes et les chirurgiens pourront contribuer de manière significative.*

Overview

Chronic pain affects many adults worldwide, with overall prevalence estimates that range from 20-35% and even higher among women and the elderly.[1-3] Chronic pain syndromes are represented by a vast array of disorders, including chronic post-surgical pain (CPSP), post-traumatic pain, back pain, migraine, as well as chronic pain caused by osteoarthritis, autoimmune diseases, diabetes, shingles, cancer, HIV/AIDS, and stroke.[4] Exposure to certain toxins and chemotherapeutic medications can also lead to the development of chronic pain.[5] Erythromelalgia is a neuropathic pain condition associated with a specific mutation in the *SCN9A* gene that encodes DNA for alpha subunits of the NaV1.7 voltage gated sodium channels;[6] however, for other chronic pain entities, such as fibromyalgia, no etiology (genetic or otherwise) has yet been identified.[7]

All patients who undergo surgery or sustain a traumatic injury suffer from acute pain for a relatively short period of time following tissue injury. This pain generally subsides within days to weeks, concurrent with wound healing. Furthermore, modern medicine has developed effective means of minimizing this type of pain. Nevertheless, CPSP develops in a significant proportion of patients.[8-10] Chronic post-surgical pain is defined as pathological pain that persists for longer than two months following surgery.[11] Several patient-related and surgical factors have been linked to the development of CPSP.[10] In one study, almost 25% of more than 5,000 patients referred to tertiary pain care centres presented with CPSP.[2] Considering the number of patients worldwide who undergo surgery each year, it is problematic that up to 10% of all surgical patients report severe disabling pain at one year.[12] The development of CPSP represents only the *tip of the iceberg* of overall chronic pain conditions in the general population, and therefore, CPSP is part of a larger unsolved health problem.

The cost of chronic pain to the economy in general is greater than the combined costs of cardiovascular diseases and cancer. In North America alone, chronic pain accounts for more than $670 billion annually in direct healthcare

costs, absenteeism from work, lost productivity, and compensation.[13] Despite modest advances in the management of pain, > 60% of patients undergoing surgery still report moderate to severe pain long after their wounds have healed.[8] Recent estimates suggest that persistent postoperative pain can incur annual direct costs of up to $12,000 per patient and indirect annual losses (i.e., lost income) of $30,000 per patient.[14] Therefore, it is imperative to develop strategies aimed at decreasing the development of CPSP.

Current state of chronic pain management

Clinicians cannot predict which analgesic will be most efficacious for an individual pain patient or which drug will be associated with the fewest adverse side effects. The process of finding the appropriate treatment regimen for chronic pain often involves either escalating doses of a particular analgesic until a satisfactory level of pain control is achieved or switching to another medication.[15] Unlike the management of acute pain, the process of finding an appropriate treatment regimen for chronic neuropathic pain requires taking medications over many weeks to determine efficacy. Treatment strategies that implement physiotherapy, psychological and psychosocial interventions are often required in combination with analgesic medications; however, these are often not readily available or affordable for patients.[16] It is common for patients to realize only partial pain relief at the expense of unpleasant adverse effects, which then results in patients ceasing to take their medication.

Despite the increased need for novel analgesic agents and the economic burden caused by chronic pain, in recent years, pharmaceutical companies have reduced their financial investment in the research and development (R&D) of therapeutics aimed at chronic pain. This is partly because analgesic targets have been depleted.[17,18] The development of pharmacological treatment strategies for chronic pain has been largely serendipitous; pain clinicians have tried medications not initially marketed for chronic pain (e.g., antidepressants, anticonvulsants and antiarrhythmics) with mixed success. Although medications now used as first-line treatments for various chronic pain conditions (i.e., serotonin and norepinephrine re-uptake inhibitors, anticonvulsants and tricyclic antidepressants) confer some analgesic efficacy, they are not without adverse effects.[18] This state of affairs constitutes the prevailing treatment paradigm in chronic pain that is unable to prevent chronic pain from developing and cannot cure it among those in whom it has developed.

Chronic pain as a complex heritable trait

Recent reviews in pain genetics have evaluated data from twin studies and human pedigrees and have estimated heritability in animal models of acute and chronic pain, including their responses to analgesics. These studies indicate that chronic pain has heritability ranging from 30-70% (median ~ 45%).[19,20] Heritability estimates attempt to assess the relative contributions of genetic and non-genetic factors to the total phenotypic variation in a population.[21] While mutation in a single gene is causal for the disorder in monogenic diseases (by definition), complex disorders such as chronic pain do not have a single genetic cause but are the result of the interaction of many genes (each having a small effect on the trait variance) with several environmental factors.[22] Recognizing that chronic pain is a complex disorder produced by multiple mechanisms thus implies that a variety of genetic variants combine to control the risk of a transition from acute to chronic pain after surgery, injury, or disease and furthermore contribute to its continuation over time. Such variants may be located mostly within exons, the coding regions within genes, but they may also be situated outside, between genes, along the vast spans of the DNA.

While estimates suggest that genetic factors account for up to half of the variance in the population, it is not yet possible to ascertain the extent that genetic and/or environmental factors contribute to chronic pain in an individual. Furthermore, heritability of a pain syndrome does not inform about the genetic "architecture" of an individual, i.e., which combination of variants creates the predisposition for a specific type of pain and to what extent pain chronicity is caused by many genes with small effects (each of which may be neither necessary nor sufficient for manifestation of the phenotype) or by variants conferring moderate or larger effects. Strategies to identify those variants at an individual's DNA include genome-wide association studies and sequencing. Nevertheless, prior to implementing these methods in clinical practice, pain geneticists would need to identify all pain genes and other intergenic pain variants throughout the span of the DNA, i.e., for every pain syndrome, sex, and ethnic origin, as described in the following section.

Pain genetics: the candidate gene approach

The genome comprises a sequence of four nucleotides, adenine (A), thymine (T), cytosine (C), and guanine (G), along the two strands of the DNA. This sequence is largely fixed in humans, with most people in a population carrying one of these nucleotides (i.e., the major allele). However,

this sequence varies in one of about 1,000 nucleotides such that fewer people carry another variant (i.e., the minor allele). If such single nucleotide polymorphisms (SNPs) are located in a critical position, e.g., within a gene or its regulatory regions, they can affect trait levels. Therefore, it is important to determine the sequence of SNPs in the genome in order to discover the genetic architecture that influences the heritable risk for chronic pain. For example, patients carrying the hypofunctional His270 allele, encoded by the SNP *rs7958311* on the *P2RX7* gene, have less chronic pain; likewise, carrying this allele has been associated with less osteoarthritic pain levels.[23]

Recent studies have identified a number of candidate genes for chronic pain, including a few for post-surgical and post-traumatic pain. These genes encode proteins involved in ion channels, catabolizing enzymes of neurotransmitters, receptors, transporters, transcription factors, and hormone receptors that increase the risk for pain chronicity.[23-27] Several investigative groups, including our own, have identified candidate pain genes using several unbiased approaches for genetic mapping in rodent models of neuropathic pain. These genes include *KCNS1*[24] (encoding the s1 subunit of a voltage-dependent potassium channel) and *CACNG2*[26] (encoding the gamma subunit 2 of a voltage-gated calcium channel). Using the same strategy, we identified the *P2RX7* gene as implicated in pain patients and rodent chronic pain models. This gene encodes the P_2X_7 purinergic receptor (P_2X_7R), a family member of ionotropic adenosine-triphosphate-gated receptors that operate in purinergic synapses in the central nervous system. Following partial hindpaw denervation from nerve injury, mice carrying a variant *P2rx7* sequence with impaired pore formation have less allodynia than mice carrying the normal pore-forming *P2rx7* alleles.[23] Variations within the coding sequence of these three genes are significantly associated with increased levels of chronic pain in humans with traumatic- and post-surgical chronic pain (i.e., phantom limb pain in leg amputees and post-surgical pain in women who had breast surgery to remove a malignant growth).[23,24,26]

Pain genetics: genome-wide approach

The candidate gene approach that interrogates one gene (or a few) at a time has shown to be useful in some cases. It relies on *a priori* knowledge of the potential role that these genes (or their products) may play in chronic pain. Nevertheless, this approach is not designed to identify hitherto unknown genes, which in turn would allow the discovery of new pathways and insight into novel mechanisms. The expectation is that a genome-wide association study (GWAS), which compares the identity of SNPs positioned in short intervals throughout the genome in chronic pain patients with those of matched controls free of chronic pain, will enable the identification of many new variants. Mismatched SNPs found in the compared subgroups call the investigators' attention to the causative gene wherein they are located or to a gene in their vicinity. Following this discovery phase, a replication study in another cohort is then needed to validate the finding by genotyping only the mismatched SNP. If successful, re-sequencing this gene in a smaller number of pain patients *vs* controls would identify the actual causative loci within that gene. Follow-up experiments are then carried out to elucidate the mechanism by which the causative SNPs lead to the pain trait. This usually involves animal models of chronic pain.

The marker loci on the microarrays used in a GWAS typically identify SNPs that are common ($> 1\%$) in the general population. Other methods focus on the genotyping of rare SNPs (see below). To date, only a few GWASs have been reported on pain-related traits, including widespread musculoskeletal pain, inflammatory bowel disease, migraine, and the analgesic efficacy of morphine shortly after surgery.[28,29] Many other relevant pain syndromes still remain to be genotyped using GWAS methods. The methodology for carrying out a GWAS has been available for about a decade and has been used in a few thousand genetic analyses regarding a substantial number of human diseases and traits. A major reason for the slow progress in implementing the methodology in pain research has been the challenge of assembling large enough study cohorts. As described below, however, this gap will soon close with the assembly of several properly powered large-scale study cohorts. Moreover, in the past few years, so-called next-generation sequencing (NGS) of DNA has become available. While a GWAS microarray interrogates only up to a few million SNPs out of the 3 billion SNPs that comprise the human DNA, NGS technology identifies all SNPs on the genome or on selected segments of the genome such as the coding regions of the genes (i.e., the exons).[30] This means that, using NGS technology, the identity of all the nucleotides along an individual's DNA can be discovered, common or rare. Because it is still costly to carry out a full genome sequencing, this method has been largely used in recent years to sequence SNPs only in exons (hence the term "exome analysis") of all genes throughout the genome (there are $\sim$180K exons in the genome).[31] While the exome comprises only about 1% of the genome ($\sim$ 30 million nucleotides out of the 3 billion in genomic DNA), SNPs in exons are involved causally in more than two-thirds of human diseases.[32] The obvious reason for this disproportion is that variants in coding regions can directly or indirectly affect the structure

and function of encoded gene products. But the ultimate goal in genetics is to use this method to carry out a full genome sequencing of all SNPs in the genome, including the intra- and intergenic spans of the DNA.[33] As the price of NGS analysis drops, we anticipate that it will soon be implemented in the advancement of pain treatment.

Pain genetics: ongoing studies

Several research groups are currently analyzing the genetics of human chronic pain in a systematic manner. The National Institutes of Health (NIH)-funded Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) project studies the genetics of temporomandibular pain disorder (TMD).[34] Temporomandibular pain disorder is the most prevalent chronic orofacial pain condition affecting about 450 million adults worldwide, mainly females ages 20-50 yr. It manifests in spontaneous and movement-induced pain in the temporomandibular region involving the jaw, temple, and neck muscles, resulting in limitation of jaw movements and occasionally accompanied by temporomandibular joint (TMJ) clicking sounds which indicate that the TMJ disk and muscles are out of coordination. In addition, patients with TMD have allodynia and hyperalgesia to natural stimuli applied to the TMJ regions. Patients with TMD show structural and functional brain changes, which may reflect maladaptive neuroplasticity as manifested by an increased volume of gray matter in regions related to antinociception and cognitive and limbic functions. They also have increased functional magnetic resonance imaging activity in brain areas associated with attention and emotional processing as well as in the primary sensory and motor cortices. The current model of the susceptibility for developing TMD includes anatomical, neuromuscular, and psychological factors that operate in parallel, reflecting the concerted effects of genetic and non-genetic etiological factors.[35-38]

The OPPERA project began by recruiting 3,300 healthy women who were followed up for five years with the expectation that about 10% would develop TMD over the course of the study. By having participants respond to psychological questionnaires, questionnaires that describe various aspects of TMD pain, and a number of psychophysical and cardiovascular assays, this project identified non-genetic risk factors for TMD. In the second phase of the study, the team recruited another 1,000 women who had already developed TMD for a genetic analysis. Together, these two cohorts provided sufficient statistical power to carry out an analysis of candidate TMD genes and a GWAS. Indeed, a few candidate genes for TMD have already been identified. Thus far, SNPs and haplotypes (i.e., a set of jointly inherited SNPs located on the same chromosome) of *HTR2A* and *COMT* were documented as associated with TMD.[38] The OPPERA study revealed additional genes as risk factors for TMD, including *NR3C1, CAMK4, CHRM2, IFRD1,* and *GRK5*.[38] A GWAS analysis is now underway with that study cohort. As described above, this GWAS is geared toward identifying some of the common genetic variants that confer part of the heritable risk for TMD. The next analytical step following the GWAS analysis would be to conduct an exome sequencing analysis, followed, when financially feasible, by a full genetic sequence (FGS) analysis, to identify rare TMD-causing variants that would hopefully enable the researchers to explain most of the allelic variance.

A study of trigeminal neuralgia (TN) is another chronic pain genetics project that is still at its formative stages. This project is funded by the Facial Pain Research Foundation (FPRF), and its first goal is to collect 500 carefully diagnosed TN cases throughout North America and England and carry out a GWAS and exome analysis. Trigeminal neuralgia is considered one of the most excruciating pain syndromes that a human can suffer. The syndrome is rare, with an incidence of 4.5/100,000 and a peak occurrence in the fifth decade of life. Trigeminal neuralgia manifests as unilateral paroxysmal pain limited to one or two divisions of the trigeminal nerve. The pain is triggered typically by low-threshold inputs anywhere in the orofacial region. In most TN cases, brain imaging will show a blood vessel juxtaposed with the trigeminal nerve root, and surgical decompression relieves TN pain in most of these situations. Nevertheless, it is less known that this congenital malformation occurs in about 17% of the general population but is asymptomatic. Since TN is familial in some cases, it has been suggested that symptomatic cases carry genetic variants for the development of neurovascular compression as well as genetic variants that cause the compression to become painful. More on this project may be found on the FPAF webpage (http://www.facingfacialpain.org).

Our research group has selected to study CPSP by focusing on neuropathic pain, mainly following nerve injury due to traumatic or surgical limb amputation, but also after other surgical procedures such as cardiothoracic surgery and mastectomy. The rationale for this selection is that the inciting event in these cohorts is similar and the timing and extent of the injury can be recorded precisely, considerably better than in other chronic pain syndromes. By collecting data on intraoperative and early postoperative treatments, we hope to identify genetic loci controlling the effect of analgesics used perioperatively on the transition to CPSP. The pathophysiology after peripheral nerve injury is far better characterized than for other chronic pain syndromes. This approach facilitates

analysis of mechanism-based phenotypes for genetic association studies. Such phenotypes could comprise good "intermediate phenotypes" (or "endophenotypes"), which are considered to offer a better chance at finding pain genes than the main pain outcome of "having *vs* not having" chronic pain.[39]

Limb amputation produces three types of pain types: phantom limb pain, i.e., feeling of pain in the missing body part; stump pain in the remaining part of the limb; and to a lesser extent, mirror-image pain in the contralateral intact side of the body. The degree to which these three entities mechanistically and genetically overlap (i.e., the extent to which they represent three unique pathophysiological entities and potentially three unique groups of genes) is not clear. Collecting these phenotypes in the same amputees enables the study of this issue. For example, we and others have studied the genetics of CPSP following nerve injuries in mice.[23,24,26,40] Currently, we continue to map the entire mouse genome for sequence variations controlling chronic pain following nerve injury. In addition, we and others have studied the changes in gene expression levels in the dorsal root ganglia and in the spinal cord after nerve injury.[41-59] When the human genome is mapped for genes controlling CPSP, these comparative studies will facilitate identifying conserved loci for CPSP in mice and humans. This knowledge will become important when developing novel analgesics in mice, which share CPSP genetic "architecture" similar to that in humans.

Similar to the OPPERA project, we also broadly phenotyped the participants in our various study cohorts by collecting data on sociodemographics, ethnicity, family structure, education, socioeconomics, other family members with chronic pain, and detailed medical history comprising other instances of chronic pain prior to the inciting event that produced the present syndrome. We collected details about the etiology of the nature of the inciting event and about treatments for early postoperative/traumatic pain, and we also compiled particulars about the post-amputation pain, including traits related to the plasticity of the central nervous system and the treatments that were tried and their effects. In addition, we collected psychological tests that included: the effects of the pain on the quality of life and participation in daily activities, life with pain (i.e., daily activities that ease or worsen the pain, including use of the prosthesis), pain catastrophizing, affective aspects of coping with pain, cardiovascular tests, and a few acute pain tests. We are currently dissecting these rich datasets in search of risk factors for CPSP as well as identifying specific endophenotypes as outcomes with which to carry out the genetic association analyses.

We are in the midst of conducting an exome analysis in a sample of 3,840 amputees (i.e., 2,700 Cambodian and 1,140 German amputees) and a separate GWAS on 1,056 of these Cambodian amputees. The analyses of these data will be integrated with findings from our animal studies and those from the literature and public databases. As a next step, we will sequence the most promising regions to identify rare variants with large effects.

Other ongoing chronic pain genetics projects include fibromyalgia/widespread musculoskeletal pain, atypical odontalgia, and osteoarthritis. As these projects are beyond the scope of this review, we refer interested readers to reports that describe these cohorts.[60,61]

Pain genetics: expected outcomes

Presently, it is not possible to predict which individuals may well be susceptible to developing chronic pain if exposed to an inciting event such as surgery. One of the goals of pain genetics is to enable anesthesiologists and surgeons to predict preoperatively which patients are at high risk of developing chronic pain following surgery. This could help to determine which drugs are best suited for the type of surgery and the individual patient and even which surgical choices a patient should consider given the genetic risk. This information will empower patients to make more informed decisions regarding whether or not to undergo invasive surgery *vs* a less aggressive alternative treatment. Knowledge about individual patient risk for CPSP may also facilitate the development of preventive analgesic regimens prior to, during, and immediately after surgery for high-risk patients. Similar algorithms based on genomes could be developed for the treatment of patients who have sustained trauma. Individuals who have already developed CPSP could also benefit from such an approach to personalized pain medicine guided by pharmacogenomic knowledge, which could minimize adverse effects and improve analgesic efficacy by stratifying targeted therapies. Finally, identifying the genetic underpinnings of chronic pain in rodent models of neuropathy that target genes identical to those of human chronic pain will greatly expand our understanding of pain mechanisms and very likely lead to new targeted drugs and other forms of therapy by serving as R&D platforms.[62]

Based on the biopsychosocial conceptual framework of human diseases, the likelihood of chronic pain (LCP) is the sum of genetic, psychological, epigenetic, and other non-genetic risk and protective factors that control the transition of pain from acute to sub-acute to chronic, and its maintenance thereafter.[10,63-66] Given that many psychological risk and protective factors are heritable, a simplified equation of LCP can be presented as the arithmetic sum of genetic and non-genetic protective and risk factors. Currently, the contribution of most heritable

protective and risk factors is largely unknown. But unlike the genetics of chronic pain, which is a young research field, the psychology of chronic pain has made significant strides in discovering and reporting on protective and risk factors.[67-69] When the contribution of genetic and non-genetic protective and risk factors becomes known, a mathematical equation that models the LCP as a predictive algorithm can be formulated, including the relative weight assigned to each element, for greater accuracy. Furthermore, genetic data will allow calculating the proportion of risk genes shared with specific pain phenotypes as well as with comorbid mental disorders such as depression. As mentioned earlier, estimates place the heritable risk for developing chronic pain at a median value of ~45%, depending on the syndrome, race and ethnicity, sex, age, and other biopsychosocial and non-genetic factors such as the time after the inciting event and its original severity.[19] Assessing whether a patient is likely to benefit from a novel treatment will necessitate an evaluation of the individual patient's level of risk for developing chronic pain from various surgery types and the likelihood of favourable responses to various classes of drugs. In addition to evaluating the heritable risk, a predictive algorithm will have to include the possible effects of non-genetic risk and protective factors. Such a comprehensive assessment would make it possible for patients and their caregivers to be presented with a comprehensive estimation of the LCP.

Personalization of pain treatments

There is a view that the currently limited approaches to treatment for chronic pain could be enhanced with knowledge garnered from pain genetics. This new knowledge could contribute greatly to personalized pain treatment, moving from the current reactive and symptom-focused approach to an emphasis on a preventive approach that pushes back the timeframe of treatment to the perioperative period and soon after trauma or exposure to certain drugs, toxins, or diseases known to cause chronic pain.[10,66]

Research in rodent models of chronic pain indicates that the pathophysiological mechanisms underlying spontaneous pain, stimulus-induced allodynia and hyperalgesia, as well as spread of pain are specific for that symptom. This would suggest that a unique pool of genes controls the phenotypic expression of each symptom.[62,65] Accordingly, a treatment solution for a symptom in one pain syndrome may not be effective in treating other symptoms in the same syndrome or even the same symptom in another pain syndrome. Therefore, treatment solutions based on genomic knowledge will necessitate the identification of the genetic "architecture" of each chronic pain symptom. This information would need to be obtained by studying clinically uniform cohorts of the same chronic pain syndrome.[19,65,66]

Conclusions

There are strong indications that chronic pain and specifically CPSP are heritable traits and that genetic variation accounts for about half of the variance in pain levels. Genetic advances will enable a major paradigm shift toward personalized pain medicine. This shift will be based on the following advances, some of which have already been accomplished: (1) the development of accurate and relatively low-cost methods for sequencing the whole genome and software capable of analyzing the resulting genetic datasets; (2) development of powerful bioinformatics programs and databases that enable us to use gene ontogeny and pathway analysis; (3) assays for rapidly validating candidate genes flagged by the initial sequence analysis; (4) availability of sufficiently large cohorts of chronic pain and specifically CPSP, with adequate statistical power for a FGS analysis and replication; (5) ongoing phenomic analysis that will result in the identification of robust phenotypes and endophenotypes to strengthen the power of genetic association analyses; (6) the available and growing body of knowledge on the pathophysiology of CPSP that will become invaluable when building mechanistic models to explain how variations in the sequence of genes associated with chronic pain alter pain levels; and (7) availability of animal models of CPSP that are useful for identifying chronic pain genes and can be used to test and refine personalized pain treatments for patients.

While these advances present great opportunities for reducing CPSP and chronic post-traumatic pain, they are large scale (tens to hundreds of thousands of patients needed), and the still non-trivial cost of genotyping so many subjects means that the cost of conducting such research is inevitably large. A major budgetary investment will be needed if we are to deliver the full potential of benefits of personalized pain medicine for our patients.

Key points

- Chronic post-surgical pain (CPSP) makes up a considerable portion of the overall health problem of chronic pain that is estimated to affect one in three to five people worldwide in their lifetime.

- Heritability (i.e., the proportion of variance among individuals of a population explained by genetic factors) estimates of different forms of chronic pain range from 30-70%, with a median of about 45%.
- The complex manifestations of chronic pain and the large variability in presentation of symptoms amongst chronic pain patients suggest that many pathophysiological mechanisms combine to produce CPSP and that the genetic risk for developing such pain is conferred by genetic variation in many genes.
- An understanding of the heritability of CPSP could be useful in developing predictive algorithms to assess the preoperative risk for developing CPSP.
- Pharmacogenomic approaches could potentially be used to stratify patients genetically for treatments that minimize the development of CPSP in those at risk and to treat patients who have already developed CPSP.
- A number of candidate genes for CPSP and chronic post-traumatic pain have already been identified and validated, but the individual (and cumulative) effect size is small, indicating that many more genetic variants await discovery.
- Sample size is an important factor to enable the successful identification of risk genes, and large and multinational well-phenotyped cohorts have been assembled and await funding for large-scale analysis to map common and rare genetic variants relevant to CPSP.
- The expected advances in the knowledge of CPSP genetics are a necessary next step toward personalized mechanisms-based pain treatments that focus not only on better management of the chronic pain patient but also on preventive analgesic strategies.

Conflicts of interest None declared.

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References

1. *Macrae WA*. Chronic pain after surgery. Br J Anaesth 2001; 87: 88-98.
2. *Macrae WA*. Chronic post-surgical pain: 10 years on. Br J Anaesth 2008; 101: 77-86.
3. *Ohayon MM*, *Schatzberg AF*. Chronic pain and major depressive disorder in the general population. J Psychiatr Res 2010; 44: 454-61.
4. *Johannes CB*, *Le TK*, *Zhou X*, *Johnston JA*, *Dworkin RH*. The prevalence of chronic pain in United States adults: results of an internet-based survey. J Pain 2010; 11: 1230-9.
5. *Seretny M*, *Currie GL*, *Sena ES*, *et al*. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain 2014; 155: 2461-70.
6. *Wu MT*, *Huang PY*, *Yen CT*, *Chen CC*, *Lee MJ*. A novel SCN9A mutation responsible for primary erythromelalgia and is resistant to the treatment of sodium channel blockers. PloS One 2013; 8: e55212.
7. *Clauw DJ*. Fibromyalgia: a clinical review. JAMA 2014; 311: 1547-55.
8. *Apfelbaum JL*, *Chen C*, *Mehta SS*, *Gan TJ*. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97: 534-40.
9. *Costigan M*, *Scholz J*, *Woolf CJ*. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 2009; 32: 1-32.
10. *Katz J*, *Seltzer Z*. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009; 9: 723-44.
11. *Macrae W*, *Davies H*. Chronic post surgical pain. In: Crombie IK, Linton SJ, Croft PR, Von Knorff M, Leresche L, editors. Epidemiology of Pain. Washington, USA: IASP Press; 1999. p. 125-42.
12. *Johansen A*, *Romundstad L*, *Nielsen CS*, *Schirmer H*, *Stubhaug A*. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. Pain 2012; 153: 1390-6.
13. *Institute of Medicine of the National Academies*. Relieving Pain in America: a blueprint for transforming prevention, care, education, and research. Committee on Advancing Pain Research, Care, and Education, June 2011. Available from URL: http://www.iom.edu/~/media/Files/ReportFiles/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research/PainResearch2011ReportBrief.pdf (accessed October 2014).
14. *Parsons B*, *Schaefer C*, *Mann R*, *et al*. Economic and humanistic burden of post-trauma and post-surgical neuropathic pain among adults in the United States. J Pain Res 2013; 6: 459-69.
15. *Sarzi-Puttini P*, *Vellucci R*, *Zuccaro SM*, *Cherubino P*, *Labianca R*, *Fornasari D*. The appropriate treatment of chronic pain. Clin Drug Investig 2012; 32(Suppl 1): 21-33.
16. *Gatchel RJ*, *McGeary DD*, *McGeary CA*, *Lippe B*. Interdisciplinary chronic pain management: past, present, and future. Am Psychol 2014; 69: 119-30.
17. *Borsook D, Hargreaves R, Bountra C, Porreca F*. Lost but making progress - Where will new analgesic drugs come from? Sci Transl Med 2014; 6: 249sr3.
18. *Moulin DE*, *Clark AJ*, *Gilron I*, *et al*. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007; 12: 13-21.
19. *Seltzer Z, Mogil JS*. Pain and genetics. *In*: Sessle BJ, Lavigne GJ, Lund JP, Dubner R (Eds). Orofacial Pain - From Basic Science to Clinical Management. The Transfer of Knowledge in Pain Research to Education, Second Edition. Hanover Park, Illinois: Quintessence Publishing; 2008: 69-75.
20. *Young EE*, *Lariviere WR*, *Belfer I*. Genetic basis of pain variability: recent advances. J Med Genet 2012; 49: 1-9.
21. *Visscher PM*, *Hill WG*, *Wray NR*. Heritability in the genomics era–concepts and misconceptions. Nat Rev Genet 2008; 9: 255-66.
22. *Schoeps A*, *Rudolph A*, *Seibold P*, *et al*. Identification of new genetic susceptibility loci for breast cancer through consideration of gene-environment interactions. Genet Epidemiol 2014; 38: 84-93.

23. *Sorge RE*, *Trang T*, *Dorfman R*, *et al*. Genetically determined P2X7 receptor pore formation regulates variability in chronic pain sensitivity. Nat Med 2012; 1: 595-9.
24. *Costigan M*, *Belfer I*, *Griffin RS*, *et al*. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain 2010; 133: 2519-27.
25. *Maher BH*, *Griffiths LR*. Identification of molecular genetic factors that influence migraine. Mol Genet Genomics 2011; 285: 433-46.
26. *Nissenbaum J*, *Devor M*, *Seltzer Z*, *et al*. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res 2010; 20: 1180-90.
27. *Waxman SG*, *Dib-Hajj S*. Erythermalgia: molecular basis for an inherited pain syndrome. Trends Mol Med 2005; 11: 555-62.
28. *Anttila V*, *Winsvold BS*, *Gormley P*, *et al*. Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet 2013; 45: 912-7.
29. *Oertel B*, *Lotsch J*. Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics 2008; 9: 179-94.
30. *Rizzo JM*, *Buck MJ*. Key principles and clinical applications of "next-generation" DNA sequencing. Cancer Prev Res (Phila) 2012; 5: 887-900.
31. *Koboldt DC*, *Steinberg KM*, *Larson DE*, *Wilson RK*, *Mardis ER*. The next-generation sequencing revolution and its impact on genomics. Cell 2013; 155: 27-38.
32. *Marian AJ*, *Belmont J*. Strategic approaches to unraveling genetic causes of cardiovascular diseases. Circ Res 2011; 108: 1252-69.
33. *Kilpinen H*, *Dermitzakis ET*. Genetic and epigenetic contribution to complex traits. Hum Mol Genet 2012; 21: R24-8.
34. *Slade GD*, *Fillingim RB*, *Sanders AE*, *et al*. Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: implications and future directions. J Pain 2013; 14(12 Suppl): T116-24.
35. *Fillingim RB*, *Ohrbach R*, *Greenspan JD*, *et al*. Psychological factors associated with development of TMD: the OPPERA Prospective Cohort Study. J Pain 2013; 14(12 Suppl): T75-90.
36. *Greenspan JD*, *Slade GD*, *Bair E*, *et al*. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain 2011; 12(11 Suppl): T61-74.
37. *Ohrbach R*, *Fillingim RB*, *Mulkey F*, *et al*. Clinical findings and pain symptoms as potential risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 2011; 12(11 Suppl): T27-45.
38. *Smith SB, Mir E, Bair E, et al.* Genetic variants associated with development of TMD and its intermediate phenotypes: the genetic architecture of TMD in the OPPERA Prospective Cohort Study. J Pain 2013; 14(12 Suppl): T91-T101 e3.
39. *Ertekin-Taner N*. Gene expression endophenotypes: a novel approach for gene discovery in Alzheimer's disease. Mol Neurodegener 2011; 6: 31.
40. *Seltzer Z*, *Wu T*, *Max MB*, *Diehl SR*. Mapping a gene for neuropathic pain-related behavior following peripheral neurectomy in the mouse. Pain 2001; 93: 101-6.
41. *Costigan M*, *Befort K*, *Karchewski L*, *et al*. Replicate high-density rat genome oligonucleotide microarrays reveal hundreds of regulated genes in the dorsal root ganglion after peripheral nerve injury. BMC Neurosci 2002; 3: 16.
42. *Coyle DE*. Spinal cord transcriptional profile analysis reveals protein trafficking and RNA processing as prominent processes regulated by tactile allodynia. Neuroscience 2007; 144: 144-56.
43. *Griffin RS*, *Costigan M*, *Brenner GJ*, *et al*. Complement induction in spinal cord microglia results in anaphylatoxin C5a-mediated pain hypersensitivity. J Neurosci 2007; 27: 8699-708.
44. *Kim DS*, *Figueroa KW*, *Li KW*, *Boroujerdi A*, *Yolo T*, *Luo ZD*. Profiling of dynamically changed gene expression in dorsal root ganglia post peripheral nerve injury and a critical role of injury-induced glial fibrillary acidic protein in maintenance of pain behaviors [corrected]. Pain 2009; 143: 114-22.
45. *Kim Y*, *Remacle AG*, *Chernov AV*, *et al*. The MMP-9/TIMP-1 axis controls the status of differentiation and function of myelin-forming Schwann cells in nerve regeneration. PloS One 2012; 7: e33664.
46. *Ko J*, *Na DS*, *Lee YH*, *et al*. cDNA microarray analysis of the differential gene expression in the neuropathic pain and electroacupuncture treatment models. J Biochem Mol Biol 2002; 35: 420-7.
47. *Lacroix-Fralish ML*, *Tawfik VL*, *Tanga FY*, *Spratt KF*, *DeLeo JA*. Differential spinal cord gene expression in rodent models of radicular and neuropathic pain. Anesthesiology 2006; 104: 1283-92.
48. *Liu T*, *Gao YJ*, *Ji RR*. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull 2012; 28: 131-44.
49. *Mechaly I*, *Bourane S*, *Piquemal D*, *et al*. Gene profiling during development and after a peripheral nerve traumatism reveals genes specifically induced by injury in dorsal root ganglia. Mol Cell Neurosci 2006; 32: 217-29.
50. *Nesic O*, *Lee J*, *Johnson KM*, *et al*. Transcriptional profiling of spinal cord injury-induced central neuropathic pain. J Neurochem 2005; 95: 998-1014.
51. *Persson AK*, *Gebauer M*, *Jordan S*, *et al*. Correlational analysis for identifying genes whose regulation contributes to chronic neuropathic pain. Mol Pain 2009; 5: 7.
52. *Persson AK*, *Thun J*, *Xu XJ*, *et al*. Autotomy behavior correlates with the DRG and spinal expression of sodium channels in inbred mouse strains. Brain Res 2009; 1285: 1-13.
53. *Rodriguez Parkitna J, Korostynski M, Kaminska-Chowaniec D, et al.* Comparison of gene expression profiles in neuropathic and inflammatory pain. J Physiol Pharmacol 2006; 57: 401-14.
54. *Stam FJ*, *MacGillavry HD*, *Armstrong NJ*, *et al*. Identification of candidate transcriptional modulators involved in successful regeneration after nerve injury. Eur J Neurosci 2007; 25: 3629-37.
55. *Sun H, Xu J, Della Penna KB, et al.* Dorsal horn-enriched genes identified by DNA microarray, in situ hybridization and immunohistochemistry. BMC Neurosci 2002; 3: 11.
56. *Valder CR*, *Liu JJ*, *Song YH*, *Luo ZD*. Coupling gene chip analyses and rat genetic variances in identifying potential target genes that may contribute to neuropathic allodynia development. J Neurochem 2003; 87: 560-73.
57. *Vega-Avelaira D*, *Geranton SM*, *Fitzgerald M*. Differential regulation of immune responses and macrophage/neuron interactions in the dorsal root ganglion in young and adult rats following nerve injury. Mol Pain 2009; 5: 70.
58. *Wang H, Sun H, Della Penna K, et al.* Chronic neuropathic pain is accompanied by global changes in gene expression and shares pathobiology with neurodegenerative diseases. Neuroscience 2002; 114: 529-46.
59. *Xiao HS*, *Huang QH*, *Zhang FX*, *et al*. Identification of gene expression profile of dorsal root ganglion in the rat peripheral axotomy model of neuropathic pain. Proc Nat Acad Sci U S A 2002; 99: 8360-5.
60. *Arnold LM*, *Fan J*, *Russell IJ*, *et al*. The fibromyalgia family study: a genome-wide linkage scan study. Arthritis Rheum 2013; 65: 1122-8.
61. *arcOGEN Consortium; arcOGEN Collaborators; Zeggini E, Panoutsopoulou K, Southam L, et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 2012; 380: 815-23.
62. *Salter MW*. Cellular signalling pathways of spinal pain neuroplasticity as targets for analgesic development. Curr Top Med Chem 2005; 5: 557-67.

63. *Maixner W*, *Greenspan JD*, *Dubner R*, *et al*. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. Pain 2011; 12(11 Suppl): T75-91.
64. *Max MB*, *Stewart WF*. The molecular epidemiology of pain: a new discipline for drug discovery. Nat Rev Drug Discov 2008; 7: 647-58.
65. *Seltzer Z, Diehl SR, Clarke H, Katz J*. The human chronic pain phenome: mapping nongenetic modifiers of the heritable risk. In: Belfer I, Diatchenko L, editors. Pain Genetics: Basic to Translational Science. Wiley-Blackwell; 2014. p. 161-77.
66. *Seltzer Z*, *Dorfman R*. Identifying genetic and environmental risk factors for chronic orofacial pain syndromes: human models. J Orofacial Pain 2004; 18: 311-7.
67. *Clarke H*, *Woodhouse LJ*, *Kennedy D*, *Stratford P*, *Katz J*. Strategies aimed at preventing chronic post-surgical pain: comprehensive perioperative pain management after total joint replacement surgery. Physiother Can 2011; 63: 289-304.
68. *Pinto PR*, *McIntyre T*, *Ferrero R*, *Almeida A*, *Araujo-Soares V*. Predictors of acute postsurgical pain and anxiety following primary total hip and knee arthroplasty. J Pain 2013; 14: 502-15.
69. *Theunissen M*, *Peters ML*, *Bruce J*, *Gramke HF*, *Marcus MA*. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012; 28: 819-41.