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Chronic postsurgical pain: is there a possible genetic link?

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Abstract

Persistent or chronic postsurgical pain (CPSP) has been defined as 'pain persisting beyond 2 months'. The cut-off limit of 2 months has been controversial, and some researchers argue for a 3-month period for the definition of CPSP. Multiple mechanisms, including both patient and surgical, have been shown to influence this transition. Patient factors include age, gender, anxiety, depression, somatisation, catastrophising, pre-existing pain anywhere and pain at the site of surgery. The various surgical factors include site and nature of surgery, infection, inflammation and repeat surgery. There is evidence that pre- or post-op chemotherapy and radiotherapy can also contribute towards the chronification of pain after surgery. The question of why pain following surgery or trauma persists long after the normal healing time is not yet fully explained by current evidence. This is frustrating to healthcare providers and intensely disappointing to the patients, many of whom suffer in silence for years. Genetics is now being shown to influence both the onset and the perpetuation of chronic pain in the susceptible patient. The main mechanisms are believed to be 'single nucleotide polymorphisms' (SNPs) and 'epigenetics', both of which will be discussed, with current and ongoing research and evidence, in this review. The influence of SNPs has not been replicated in recent studies and researchers advise caution in interpreting past studies. More research is needed to demonstrate the involvement of epigenetics as well as linking SNPs to the susceptible patient's journey.

Keywords

Chronic postsurgical pain, persistent postsurgical pain, genetics, genome-wide association studies, single nucleotide polymorphisms, epigenetics

Introduction and background to chronic postsurgical pain

Over the past 20 years, persistent pain arising solely as a result of a surgical intervention has been highlighted by several authors and investigators, with incidences varying from 10% to almost 80%.[1,2,3] Patients are very often left suffering in pain, long after their operative procedure is over, with chronic pain interfering with their life and work, sometimes for many years. Clinicians are left frustrated by their inability to explain CPSP in simple terms, as well as not being able to understand the poor response to multiple medication trials. Although several mechanisms have been proposed involving both the patient and the surgical procedure, the link between genetics and CPSP has only been getting the attention of researchers and clinicians in the past 10 years or so.

Acute pain, following surgery or a traumatic event, gives rise to a cascade of events both in the peripheral and central nervous systems, resulting in rapid gene expression profile changes in the ensuing period. This

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is believed to activate over 1000 genes in the dorsal root ganglia (DRG) alone. The genes responsible are believed to be involved in the immunological response/inflammatory cytokine expression, glucocorticoid receptor (GR) function, pain regulatory enzymes and opioid receptor regulation and function.[4] If one takes into consideration the patient's pre-existing psychosocial profile, epigenetic factors can be considered to influence the development of CPSP at any stage of the patient's journey, well before the proposed surgical intervention. Anxiety, depression, somatisation, catastrophising and so on have been shown by various authors, in several studies, to be some of the consistent predictive factors for the development of CPSP.[5] Multiple stressors have the potential to change the 'epigenetic landscape' in the vulnerable patient and influence his or her response to further stress as in surgery, with pain persisting in varying intensity and duration.[6] Other patient-related factors include concurrent or past pain,[7] as well as fear of pain following the surgery.[8] Both single nucleotide polymorphisms (SNPs – subtle changes in the nucleotide sequences in the genome, which can lead to abnormal protein synthesis and/or function of receptors leading to downstream consequences) and epigenetics (change in the function of DNA, without any change in the core structure. Can affect various functions in the processing, inflammatory, corticosteroid/stress response as well as involving the pain matrix (both bottom to top and top to bottom regulation)) have been shown to influence the progression of acute pain to chronicity, at various stages of the susceptible patient's journey.

This article will try to trace the 'vulnerable' patient's journey and will try to link genetic factors, either SNPs or epigenetics or both, at each stage, with an attempt to explain the development of chronic postsurgical pain (CPSP).

Despite extensive knowledge of the mechanisms linking inflammation, peripheral and central sensitisation and pain, in both human and animal models, as well as advances in understanding the human genetic code, we are still not fully able to answer why some patients are prone to develop CPSP, why one incision becomes painful or indeed why a repeat operation becomes more painful.[9] Several studies over the past few years have demonstrated the growing evidence of the influence of anxiety, depression,[10,11] catastrophising, somatisation[12–14] as well as pre-existing pain and pain from previous surgeries on the development of CPSP. Various investigators have shown the impact of chemo/radiotherapy in the chronification of pain, either given pre- or post-operatively, with the possible involvement of mitochondrial RNAs in chemotherapy following cancer surgery.[15–18] Studies in patients developing CPSP after total knee replacement have shown that the presence of chronic widespread pain, depression, higher body mass index (BMI), younger age, and female gender were all risk factors.[19] In a study looking at the predictive values of patient coping and expectations about recovery after traumatic tibial fracture and the subsequent development of CPSP, high Somatic Pre-Occupation and Coping (SPOC) questionnaire scores at 6 weeks following the fracture were associated with significant pain interference at 1 year.[20] Many patients coming in for a surgical procedure could already have widespread pain due to long-term opioids, resulting in the well-recognised phenomenon of 'opioid induced hyperalgesia', and this can make post-operative pain control difficult and can possibly lead to CPSP.[21]

The perioperative period

A number of surgical factors have been shown to be associated with CPSP, by various investigators. These include size, site as well as the number of incisions, including the complexity of operations. Other factors such as increased duration of surgery, low versus high volume surgical units, open surgical versus laparoscopic techniques, intra-costal versus peri-costal stitches and intraoperative nerve damage have also been highlighted as potential risk factors for developing CPSP.[7]

The intraoperative use of opioids, especially remifentanil, and excessive use of opioids both peri- and post-operatively, could possibly contribute to CPSP.[22] Some patients who are already on long-term opioids could have developed opioid-induced hyperalgesia, resulting in poorly controlled postsurgical pain, with increased opioid requirements and a risk of developing CPSP. A recent review by Fletcher and Martinez[23] on opioid-induced hyperalgesia in post-operative patients suggests that high intraoperative doses of remifentanil are associated with small but significant increases in acute pain after surgery. Another systematic review on the intraoperative use of remifentanil by Kim et al.[24] also urged caution and recommended further studies to investigate the contribution of remifentanil-induced hyperalgesia to the chronicity of pain.

The post-operative period

Several factors such as poor post-operative pain control,[25] presence of drains, post-operative infection[3] and delay in introducing established anti-neuropathic medications (patient's regular medication) have all been shown to influence the development of CPSP.[26] The presence of post-operative infection, with raised inflammatory markers or raised C-reactive protein (CRP), poorly controlled postsurgical pain especially

Table 1. Frequently studied and well-documented SNPs involved in pain modulation in humans.

Gene	Function	References
COMT	Neurotransmission	Kim et al.[41]
SCN9A	Neurotransmission	Edwards[42]
GCH1	Metabolism	Edwards[42]
IL10 and IL1R2	Immune response	Stephens et al.[43]
KCNS1	Neurotransmission	Edwards[42], Costigan et al.[44], Young et al.[45]
OPRM1	Neurotransmission	Kolesnikov et al.[46]
P2RX7	Neurotransmission	Foulkes and Wood[47]
CACNG2 'Stargazin' gene	Neurotransmission	Nissenbaum et al.[48]

SCN9A: gene coding for voltage-gated sodium channel subtype 1.7; *KCNS1*: gene coding for potassium channel; *CACNG2*: gene coding for the ç2 subunit of the voltage dependent Ca^{2+}channel; *COMT*: catechol-*O*-methyltransferase.

Table 2. Pain-related genes associated with neurotransmitter (NT) systems.[49]

Gene name	NT system affected	Pain phenotype
GCH1	Serotonin, dopamine, nor-epinephrine, epinephrine, nitric oxide	↓ Sensitivity to experimental pain ↓ Postsurgical pain
COMT	Serotonin	Varying response

GCH1: gene encoding cyclohydrolase 1; *COMT*: catechol-*O*-methyltransferase.

in patients on long-term opioids,[27] prolonged hospitalisation and increased post-operative opioid use[28] have also been shown to influence the development of CPSP by different genetic mechanisms.[29]

Postsurgical exposure to chemotherapeutic medications has been shown to cause painful neuropathy and, in vulnerable patients, worsen the already developing CPSP.[30]

The genetic links in CPSP

The transition of acute pain to chronic is a complex process involving multiple steps including recent evidence of glial cell activation in the central nervous system (CNS), and as yet, there is no single genetic cause identified.[31] It is believed to be a complex interaction between multiple genetic factors,[32] involving SNPs and epigenetics.[33] The epigenetic mechanisms involve DNA methylation, histone modifications and micro RNA interference. Advances in genome-wide association studies (GWAS – it identifies the genetic locations (SNPs) that differ significantly between cases and controls for a specific phenotype),[34] as well as the success in the selective breeding of rodents with different 'pain traits' in recent years by several labs, are giving us more clues into the complex interaction between genetics and pain.[35,36]

SNPs and their role in CPSP

SNP is a DNA sequence variation that occurs when a single nucleotide (Adenine, Thymine, Cytosine or Guanine) in the genome sequence is altered. The vast majority of human genetic association studies linking pain (both acute and chronic) have been on a few SNPs.[37] It is important to realise that rather than directly causing a chronic pain disease, most of the studied SNPs modulate susceptibility to it.[38] Although approximately 100 genes have been linked to possible modification of pain, only a handful have been studied in humans using GWAS.

Gain of function and loss of function by SNPs

SNPs are considered to alter pain experience by modulation – either by increasing postsurgical pain levels or by lowering pain levels, the so-called 'gain of function' or 'loss of function' modulation. There have been numerous candidate genes studies in the pain literature, including a few on CPSP, to date.[39] Most of the well-investigated SNPs have been known to have complex interactions (Tables 1–3).[40]

In a recently published GWAS study in patients complaining of neuropathic pain following total knee replacement, a variant in the protein-kinase C alpha gene (*PRKCA*) was reported by Warner et al.[57] This finding could be of relevance, as the *PRKCA* gene has been associated with long-term potentiation, synaptic plasticity, chronic pain and memory in the literature.

However, a recent study by Montes et al. could not replicate many of the previous studies linking various well-established SNPs and outcomes (both favourable

Table 3. Pain-related genes associated with ion channel function.[49]

Gene name	Channel type affected	Pain phenotype
SCN9A[50]	Voltage-gated Na^+ channels	↑ Chronic pain in a mixed cohort (phantom limb, post-lumbar discectomy
KCNS1	Voltage-gated K^+ channels	↑↑ Post-amputation pain
CACNA2D3	Voltage-gated Ca^{2+} channels	↓ Chronic postsurgical pain (discogenic)
CACNG2	Voltage-gated Ca^{2+} channels	↑ Chronic postsurgical pain (post mastectomy)

SCN9A: gene coding for voltage gated sodium channel subtype 1.7; KCNS1: gene coding for potassium channel; CACNA2D3: gene coding for α2δ3 subunit of voltage dependent Ca^{2+}channel; CACNG2: gene coding for the ς2 subunit of the voltage dependent Ca^{2+}channel.

Table 4. Epigenetic mechanisms in CPSP and proposed sites.

Mechanism	Site	References
DNA methylation	General	Doehring et al.[28]
	Prefrontal cortex	Tajerian et al.[51]
Histone modification	Brain stem nucleus	Zhang et al.[52]
	Spinal cord	Imai et al.[53]
miRNA involvement	Spinal cord	Shi et al.[54]
	Spinal cord	Lutz et al.[55]
	PNS, spinal cord and brain	Bali and Kuner[56]

CPSP: chronic postsurgical pain; PNS: peripheral nervous system.

and unfavourable). Their aim was to identify CPSP risk factors and functional genetic polymorphisms to predict the risk of developing CPSP. The authors conclude by suggesting the systematic use of clinical factors for predicting and managing the risk for CPSP until equivocal genetic predictors are identified.[58] In another study, where the investigators tried to link the association of genetic and psychological factors with persistent pain after cosmetic thoracic surgery in previously pain-free patients, common genetic variants previously associated with, or functionally related to, pain perception could not 'significantly' predict the development of CPSP.[59] The investigators looked at the relative contribution of several SNPs in pain-related genes for post-surgical pain chronification. Recently, Liu et al. evaluated the association between spinal cathepsin G (*CTSG*) polymorphisms and the risk of developing CPSP in 1152 surgical patients. Patients with polymorphisms in the *CTSG* gene had a 'lower risk' for CPSP.[60]

Epigenetics and its influence on CPSP

Epigenetics is a term first defined by Conrad Waddington in 1942,[61] and is used to describe modifications to the function of a gene which do not alter the sequence of the gene itself. There is increasing evidence, mostly from rodent models, in the involvement of epigenetics in modifying acute pain and leading to the development of CPSP (Table 4).[62]

A variety of factors are known to initiate epigenetic processes in the peripheral nervous system, spinal cord and brain, which include drugs, toxins, diet and psychological stressors.[63] The principal mechanisms involved are DNA methylation, histone modification and miRNA interference (RNA – directed gene silencing). These multiple layers of regulatory mechanisms are functionally interrelated to 'activate' a gene or 'silence' a gene[4] (switching on and off). Possible sites of epigenetic influence during and after nerve injury could include immunological and inflammatory cytokine expression, GR function, pain regulatory enzymes and opioid receptor regulation and function as these are all known to be under epigenetic control.[64] GR function and expression have been implicated in long-lasting epigenetic changes very early in life (poor maternal care and grooming, diet and early life stresses as the 'nurturing' mechanisms), possibly predisposing vulnerable individuals to develop chronic pain states later in life, especially in the context of surgery. GR dysfunction is also proposed to play a role in development of chronic fatigue, chronic pain states and the syndrome of fibromyalgia, thus providing a potential link between injury, environmental stressors and severity of chronic pain. Perhaps these cohorts of patients have a higher risk of developing CPSP since we have current evidence that pre-existing pain elsewhere and patient factors like anxiety, depression and other stressors have a strong association with development of CPSP.

Epigenetic changes following acute and persistent injury or inflammation can occur anywhere in the pain matrix, including areas involved in synaptic plasticity, learning and memory. These changes, especially in the 'top-down' regulatory brain regions, such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), periaqueductal grey (PAG) and rostroventral medial thalamus (RVM) could then lead to alterations in the balance of pain messages causing stimuli-induced activation, when there is no ongoing injury.[65] Gene expression changes caused by epigenetic changes have been noticed in interneurones and glial cells in the spinal cord and brain, potentially leading to long-lasting pain syndromes.[66]

Chronicity of pain is currently known to induce well-characterised changes in the neurones and microglia. Basic researchers and clinicians have been faced with one question though – Why do these changes persist well after the initial injury has healed? The role of microglial enhancers as a hypothesis for the genomic memory of pain, chronicity of pain and the emerging role for the involvement of epigenetics in the spinal cord, has been recently highlighted by Denk et al.[67]

Glutamic acid decarboxylase 65 (GAD65) expression and its role in mediating persistent pain,[52] monocyte chemotactic protein 3 and its role in chronic neuropathic pain,[53] and spinal CXCR2 signalling in incisional hypersensitivity[68] have all been linked to epigenetics and CPSP by various research groups.

There is current evidence that peripheral inflammation and nerve injury can cause changes in the expression of non-coding RNAs like microRNAs and Kcna2 antisense RNA in pain-related regions, especially in the DRG. Peripheral noxious stimuli induce these changes and possibly contribute to the development and maintenance of chronic pain.[55]

Current challenges and the future

Research in the genetics of pain is still a very young but rapidly expanding field, especially in the field of epigenetics. SNPs are fixed in the genome, which are not easily altered, but with the advent of drugs which interfere with methylation, histone modification and miRNA interference, one can optimistically hope for safer, 'epigenetically-targeted' drugs to be available in future. There are, of course, several unanswered questions.

Can we prevent the development of CPSP with currently available drugs or pre-emptive techniques? Is there a role of histone deacetylase (HDAC) or DNA methyltransferase (DNMT) inhibitors in treating CPSP? This could involve targeting epigenetic processes with the use of HDAC or DNMT inhibitors to prevent the progression of acute to chronic pain. These, and the use of other 'epigenetic modifying' drugs, have been reviewed recently.[4]

If there are changes in the spinal cord and brain, how early does this transition happen and how long do the changes persist? One of the mechanisms proposed in the progression of acute pain to persistent pain is '*hyperalgesic priming*'. Hyperalgesic priming is a preclinical model of this transition due to neuroplastic changes in nociceptors produced by inflammatory or neuropathic insults. A distinctive feature is the prolonged (about 72 hours) delay from the acute painful stimulus that induces 'priming' to the development of the long-lasting 'primed' state which, interestingly, can last for as long as 2 months. Detailed mechanisms of pain getting 'imprinted' in the memory of the pain matrix and possible mechanisms to erase these memories have been recently reviewed.[69–71] Yukhananov and Kissin[72] have shown that a long-lasting imprint of acute pain in the CNS may contribute to the transition of acute pain to chronicity by a mechanism of persistent changes in spinal cord gene expression long after recovery from inflammatory hyperalgesia.

Currently, there is a lack of well-documented and confirmative genetic factors, in the form of either SNPs or epigenetic markers, which can realistically predict the transition from acute to chronic pain.[41,73] Polymorphisms of various pain modifying genes have not been replicated in recent studies, although some studies have also shown that various SNPs may interact and modify the effect of each other.[39,43,45] As mentioned previously, a recent study by Montes et al., could not find a strong association between functional variants of common 'pain genes' as a predictive factor for developing CPSP. Belfer et al. recently described four factors which were independently found to correlate with CPSP in the setting of post-herniotomy pain. These were preoperative pain intensity, preoperative pain response to heat, intraoperative nerve injury and post-operative pain intensity.[74]

We still have to rely on well-evaluated and robust clinical scoring factors, which include procedure, age, preoperative quality of life and past or present experience of pain.[75]

Several researchers have shown the main predictors for developing CPSP to be female sex, age, psychosocial factors, pain in the same site or anywhere else, procedural type, nerve damage or injury and intensity of post-operative pain.[76] Preoperative anxiety and catastrophising have been identified as strong pain phenotypes in their association with the development of CPSP.[77] Many chronic pain syndromes such as fibromyalgia, interstitial cystitis, musculoskeletal pain, chronic pelvic pain, irritable bowel syndrome, migraine and temporomandibular joint disorders are known to have shared genetic factors[78] and these patients could

be assumed to be at a high risk of developing CPSP as they are already primed by their pain experience. Multiple areas of the brain which network for pain as well as its inhibition are involved in the chronification of pain, and attempting to target one or several of these areas with currently available drugs is not possible.[51]

The study by Liu et al.[60] concluded that spinal CTSG is a pro-nociceptive mediator in both animal models and human studies, suggesting that CTSG represents a new target for pain control and a potential marker for the prediction of CPSP. There is increasing evidence in the role of miRNAs in persisting pain as well as their potential for early markers in predicting CPSP.[54,56,79]The use of perfusion magnetic resonance imaging as a reproducible cerebral representation of ongoing surgical pain[80] has been proposed by Howard and his group. Various genetic polymorphisms and their association with the prevalence and severity of CPSP have been reviewed recently with suggestions to conduct large scale GWAS studies on CPSP.[81]

It is also worthwhile remembering that CPSP, similar to other chronic pain syndromes, is multi-faceted, with a complexity of sensory-discriminative, affective-emotive and cognitive-evaluative variables.[82,83] In the light of current knowledge of epigenetics, all these processes could be changing dynamically, influenced by past experiences, the immediate environment and analgesics (especially opioids). Considering chronicity of pain as a complex disorder of the brain, the study of pain epigenetics could be a promising paradigm for its better understanding and appropriate management.[84,85] Finally, most epigenetic studies have been done on rodent models and extrapolation to human subjects and their interpretation has to be cautious for obvious reasons.

Conflict of interest

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References

1. Werner MU and Kongsgaard UE. Defining persistent post-surgical pain: is an update required? *Br J Anaesth* 2014; 113(1): 1–4.
2. Kalso E. Persistent post-surgical pain: research agenda for mechanisms, prevention and treatment. *Br J Anaesth* 2013; 111(1): 9–12.
3. Lirk P, Fiegl H, Weber NC, et al. Epigenetics in the perioperative period. *Br J Pharmacol* 2015; 172: 2748–2755.
4. Buchheit T, Van de Ven T and Shaw A. Epigenetics and the transition from acute to chronic pain. *Pain Med* 2012; 13: 1474–1490.
5. Belfer I. Nature and nurture of human pain. *Scientifica* 2013; 2013: 415279.
6. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 2008; 105(44): 17046–17049.
7. Katz J and Seltzer Z. Transition from acute to chronic post-surgical pain: risk factors and protective factors. *Expert Rev Neurother* 2009; 9(5): 723–744.
8. Turk DC and Wilson HD. Fear of pain as a prognostic factor in chronic pain: conceptual models, assessment and treatment implications. *Curr Pain Headache Rep* 2010; 14(2): 88–95.
9. Crow M, Denk F and McMahon SB. Genes and epigenetic processes as prospective pain targets. *Genome Med* 2013; 5(2): 12.
10. Flor H. New developments in the understanding and management of persistent pain. *Curr Opin Psychiatry* 2012; 25(2): 109–113.
11. Wylde V, Hewlett S, Learmonth ID, et al. Persistent pain after joint replacement: prevalence, sensory qualities and postoperative determinants. *Pain* 2011; 152(3): 566–572.
12. Khan RS, Ahmed K, Blakeway E, et al. Catastrophizing: a predictive factor for postoperative pain. *Am J Surg* 2011; 201: 122–131.
13. Riddle DL, Wade JB, Jiranek WA, et al. Pre-operative pain catastrophising predicts pain outcome after knee arthroplasty. *Clin Orthop Relat Res* 2010; 468: 798–806.
14. Pavlin DJ, Sullivan MJ, Freund PR, et al. Catastrophising: a risk factor for postsurgical pain. *Clin J Pain* 2005; 21: 83–90.
15. Ishiyama H, Niino K, Hosoya T, et al. Results of a questionnaire survey for symptoms of late complications caused by radiotherapy in breast conserving therapy. *Breast Cancer* 2006; 13: 197–201.
16. Podratz JL, Knight AM, Ta LE, et al. Cisplatin induced mitochondrial DNA damage in dorsal root ganglion neurons. *Neurobiol Dis* 2011; 41(3): 661–668.
17. Dropcho EJ. Neurotoxicity of radiation therapy. *Neurol Clin* 2010; 28: 217–234.
18. Andersen KG and Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. *J Pain* 2011; 12: 725–746.
19. Belfer I, Greco CM, Lokshin A, et al. The design and methods of genetic studies on acute and chronic postoperative pain in patients after total knee replacement. *Pain Med* 2014; 15(9): 1590–1602.
20. Khan JS, Devereaux PJ, LeManach Y, et al. Patient coping and expectations about recovery predict the development of chronic postsurgical pain after traumatic tibial fracture repair. *Br J Anaesth* 2016; 117(3): 365–370.
21. Parsadaniantz SM, Rivat C, Rostène W, et al. Opioid and chemokine receptor cross talk: a promising target for pain therapy? *Nat Rev Neurosci* 2015; 16(2): 69–78.
22. Koppert W and Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract Res Clin Anaesthesiol* 2007; 21(1): 65–83.

23. Fletcher D and Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014; 112(6): 991–1004.
24. Kim SH, Stoicea N, Soghomonyan S, et al. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front Pharmacol* 2014; 5: 108.
25. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain* 1996; 12(1): 50–55.
26. Kinney MA, Jacob AK, Passe MA, et al. Increased risk of postthoracotomy pain syndrome in patients with prolonged hospitalization and increased postoperative opioid use. *Pain Res Treat* 2016; 2016: 7945145.
27. Liang D, Li X and Clark JD. Epigenetic regulation of opioid-induced hyperalgesia, dependence, and tolerance in mice. *J Pain* 2013; 14(1): 36–47.
28. Doehring A, Oertel BG, Sittl R, et al. Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain. *Pain* 2013; 154(1): 15–23.
29. Liang DY, Sun Y, Shi XY, et al. Epigenetic regulation of spinal cord gene expression controls opioid induced hyperalgesia. *Mol Pain* 2014; 10: 59.
30. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence and predictors of chemo-therapy induced peripheral neuropathy: a systematic review and meta-analysis. *Pain* 2014; 155(12): 2641–2670.
31. Ji RR, Berta T and Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain* 2013; 154: S10–S28.
32. Young EE, Lariviere WR and Belfer I. Genetic basis of pain variability: recent advances. *J Med Genet* 2012; 49: 1–9.
33. Stone LS and Szyf M. The emerging field of pain epigenetics. *Pain* 2013; 154(1): 1–2.
34. Visscher PM, Brown MA, McCarthy MI, et al. Five years of GWAS discovery. *Am J Hum Genet* 2012; 90: 7–24.
35. Seltzer Z. Nothing in pain makes sense except in the light of genetics. *Pain* 2014; 155(5): 841–842.
36. Mogil JS. Pain genetics: past, present and future. *Trends Genet* 2012; 28(6): 258–266.
37. Clarke H, Katz J, Flor H, et al. Genetics of chronic postsurgical pain: a crucial step toward personal pain medicine. *Can J Anaesth* 2015; 62: 294–303.
38. Smith SB, Reenilä I, Männistö PT, et al. Epistasis between polymorphisms in COMT, ESR1 and GCH1 influences COMT enzyme activity and pain. *Pain* 2014; 155(11): 2390–2399.
39. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005; 14(1): 135–143.
40. Rut M, Machoy-Mokrzyńska A, Ręcławowicz D, et al. Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: a report on 176 cases. *Acta Neurochir* 2014; 156(2): 245–252.
41. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Mol Pain* 2006; 2: 24.
42. Edwards RR. Genetic predictors of acute and chronic pain. *Curr Rheumatol Rep* 2006; 8(6): 411–417.
43. Stephens K, Cooper BA, West C, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *J Pain* 2014; 15(2): 169–180.
44. 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(9): 2519–2527.
45. Young EE, Lariviere WR and Belfer I. Genetic basis of pain variability: recent advances. *J Med Genet* 2011; 49(1): 1–11.
46. Kolesnikov Y, Gabovits B, Levin A, et al. Chronic pain after lower abdominal surgery: do catechol-O-methyl transferase/opioid receptor μ-1 polymorphisms contribute? *Mol Pain* 2013; 9: 19.
47. Foulkes T and Wood JN. Pain genes. *PLoS Genet* 2008; 4(7): 1–9.
48. Nissenbaum J, Devor M, Seltzer Z, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. *Genome Res* 2010; 20(9): 1180–1190.
49. James S. Human pain and genetics: some basics. *Br J Pain* 2013; 7(4): 171–178.
50. Bennett DL and Woods CG. Painful and painless channelopathies. *Lancet Neurol* 2014; 13(6): 587–599.
51. Tajerian M, Alvarado S, Millecamps M, et al. Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PLoS ONE* 2013; 8(1): e55259.
52. Zhang Z, Cai YQ, Zou F, et al. Epigenetic suppression of GAD65 expression mediates persistent pain. *Nat Med* 2011; 17(11): 1448–1455.
53. Imai S, Ikegami D, Yamashita A, et al. Epigenetic transcriptional activation of monocyte chemotactic protein 3 contributes to long-lasting neuropathic pain. *Brain* 2013; 136: 828–843.
54. Shi G, Shi J, Liu K, et al. Increased miR-195 aggravates neuropathic pain by inhibiting autophagy following peripheral nerve injury. *Glia* 2013; 61(4): 504–512.
55. Lutz BM, Bekker A and Tao YX. Noncoding RNAs: new players in chronic pain. *Anesthesiology* 2014; 121: 409–417.
56. Bali KK and Kuner R. Noncoding RNAs: key molecules in understanding and treating pain. *Trends Mol Med* 2014; 20(8): 437–448.
57. Warner SC, van Meurs JB, Schiphof D, et al. Genome-wide association scan of neuropathic pain symptoms post total knee replacement highlights a variant in the protein-kinase C gene. *Eur J Hum Genet* 2017; 25(4): 446–451.
58. Montes A, Roca G, Sabate S, et al. Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy and thoracotomy: a two year multicenter cohort study. *Anaesthesiology* 2015; 122(5): 1123–1141.
59. Dimova V, Lötsch J, Hühne K, et al. Association of genetic and psychological factors with persistent pain

after cosmetic thoracic surgery. *J Pain Res* 2015; 8: 829–844.
60. Liu X, Tian Y, Meng Z, et al. Up-regulation of Cathepsin G in the development of chronic postsurgical pain: an experimental and clinical genetic study. *Anesthesiology* 2015; 123(4): 838–850.
61. Waddington CH. The epigenotype (*Endeavour* 1942; 18–20). *Int J Epidemiol* 2012; 41(1): 10–13.
62. Burma NE, Leduc-Pessah H, Fan CY, et al. Animal models of chronic pain: advances and challenges for clinical translation. *J Neurosci Res* 2017; 95(6): 1242–1256.
63. Seo S, Grzenda A, Lomberk G, et al. Epigenetics: a promising paradigm for better understanding and managing pain. *J Pain* 2013; 14(6): 549–557.
64. Anacker C, O'Donnell KJ and Meaney MJ. Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. *Dialogues Clin Neurosci* 2014; 16(3): 321–333.
65. Tracy I and Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron* 2007; 55(3): 377–391.
66. Descalzi G, Ikegami D, Ushijima T, et al. Epigenetic mechanisms of chronic pain. *Trends Neurosci* 2015; 38(4): 237–246.
67. Denk F, Crow M, Didangelos A, et al. Persistent alterations in microglial enhancers in a model of chronic pain. *Cell Rep* 2016; 15(8): 1771–1781.
68. Sun Y, Sahbaie P, Liang DY, et al. Epigenetic regulation of spinal CXCR2 signalling in incisional hypersensitivity in mice. *Anesthesiology* 2013; 119: 1198–1208.
69. Ferrari LF, Bogen O, Reichling DB, et al. Accounting for the delay in the transition from acute to chronic pain: axonal and nuclear mechanisms. *J Neurosci* 2015; 35(2): 495–507.
70. Alvarado S, Tajerian M, Suderman M, et al. An epigenetic hypothesis for the genomic memory of pain. *Front Cell Neurosci* 2015; 9: 88.
71. Géranton SM and Tochiki KK. Could targeting epigenetic processes relieve chronic pain states? *Curr Opin Support Palliat Care* 2015; 9: 138–146.
72. Yukhananov R and Kissin I. Persistent changes in spinal cord gene expression after recovery from inflammatory hyperalgesia: a preliminary study on pain memory. *BMC Neurosci* 2008; 9: 32.
73. Kraft P and Hunter DJ. Genetic risk prediction- are we there yet? *N Eng J Med* 2009; 360(17): 1701–1703.
74. Belfer I, Dai F, Kehlet H, et al. Association of functional variations in COMT and GCH1 genes with postherniotomy pain and related impairment. *Pain* 2015; 156(2): 273–279.
75. Theunissen M, Peters ML, Bruce J, et al. Preoperative anxiety and catastrophizing- a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain* 2012; 28: 819–841.
76. Perez AM. Genetics and pain. *Tech Reg Anesth Pain Manage* 2015; 18(3): 79–86.
77. Vehof J, Zavos HM, Lachance G, et al. Shared genetic factors underlie chronic pain syndromes. *Pain* 2014; 155(8): 1562–1568.
78. Denk F, McMahon SB and Tracey I. Pain vulnerability: a neurobiological perspective. *Nat Neurosci* 2014; 17(2): 192–200.
79. Niederberger E, Kynast K, Lötsch J, et al. MicroRNAs as new players in the pain game. *Pain* 2011; 152(7): 1455–1458.
80. Howard MA, Krause K, Khawaja N, et al. Beyond patient reported pain: perfusion magnetic resonance imaging demonstrates reproducible cerebral representation of ongoing post-surgical pain. *PLoS ONE* 2011; 6(2): e17096.
81. Hoofwijk DM, van Reij RR, Rutten BP, et al. Genetic polymorphisms and their association with the prevalence and severity of chronic postsurgical pain: a systematic review. *Br J Anaesth* 2016; 117(6): 708–719.
82. Szyf M. Epigenetics, a key for unlocking complex CNS disorders? Therapeutic implications. *Eur Neuropsychopharmacol* 2015; 25(5): 682–702.
83. Deumens R, Steyaert A, Forget P, et al. Prevention of chronic post-operative pain: cellular, molecular and clinical insights for mechanism-based treatment approaches. *Prog Neurobiol* 2013; 104: 1–37.
84. Bonasio R, Tu S and Reinberg D. Molecular signals of epigenetic states. *Science* 2010; 330(6004): 612–616.
85. McEwen BS and Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann NY Acad Sci* 2010; 1186: 190–222.