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Published in:
Scandinavian Journal of Pain

DOI (link to publication from Publisher):
[10.1515/sjpain-2022-0086](https://doi.org/10.1515/sjpain-2022-0086)

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Giordano, R., Kjær-Staal Petersen, K., & Arendt-Nielsen, L. (2022). The link between epigenetics, pain sensitivity and chronic pain. *Scandinavian Journal of Pain*, 22(4), 664-666. <https://doi.org/10.1515/sjpain-2022-0086>

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Short Communication

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The link between epigenetics, pain sensitivity and chronic pain

<https://doi.org/10.1515/sjpain-2022-0086>
 Received July 7, 2022; accepted July 18, 2022;
 published online September 26, 2022

Abstract: Increasing evidence suggests an association between gene expression and clinical pain. Epigenetic modifications are the main modulators of gene expression or protein translation in response to environmental stimuli and pathophysiological conditions. Preclinical and clinical studies indicate that epigenetic modifications could also impact the development of pain, the transition from acute to chronic pain, and the maintenance hereof.

Keywords: epigenetic modifications; epigenetic of pain; microRNA.

Main text

Epigenetics can be defined as the study of mechanisms that induce changes in the phenotypes without altering the main sequence of the DNA [1]. Epigenetic processes include three major mechanisms (1) DNA methylation, (2) histone modifications, and (3) the action of non-coding RNA

(ncRNA) [2–4]. The application of epigenetics in pain research is progressing fast and studies have revealed epigenetic mechanisms underlying acute pain [5–7].

One way to assess somatosensory changes and evaluate allodynia, hyperalgesia, hypoesthesia, or hypoalgesia is through standardized quantitative sensory testing (QST) [8]. QST can include a series of tests for detection of thermal and mechanical thresholds, thresholds for pain after several stimuli, suprathreshold pinprick tests and wind-up, plus specific assessment for dynamic mechanical allodynia, paradoxical heat sensation, and the assessments targeting the descending pain inhibitory systems [8]. Accumulating evidence suggests that pre-treatment QST might hold a predictive value for treatment responses to standard pain treatments [9–12]. This summary aims to explain the involvement of epigenetics in pain research and its potential association with QST.

DNA methylation occurs mostly on cytosine-5-carbon at the CpG dinucleotide island site, where the DNA methyltransferase (DNMT) enzyme catalyzes the addition of methyl (CH₃) groups [1], which leads to inhibition and silencing of the gene expression [6, 13, 14]. A preclinical study has shown that reversing methylation responses through intrathecal injection of DNMT inhibitors, reduces mechanical and thermal hyperalgesia in a rat model [15]. Moreover, heat pain sensitivity has been shown to be associated with hypermethylation in the promoter region of the TRPA1 gene expressed in peripheral nociceptors and pain-sensitivity scores in a study with 100 volunteers [16].

Histone modification and chromatin remodeling, are changes that happen at the nucleosome level, which is the basic unit of chromatin, and consist of 140 base pairs of DNA wrapped around a histone octamer (proteins H1/H5, H2A, H2B, H3, and H4) [17]. The terminal portion of histones protrudes from the nucleosome and is the site where post-transcriptional modification such as acetylation and methylation can occur [17]. Preclinical studies have shown that acetylation and methylation of promoter regions of genes that code for the μ -receptor, Nav1.8, and Kv4.3 can either attenuate or induce hyperalgesia [17].

Non-coding RNAs (ncRNAs) include short-ncRNAs such as microRNAs (miRNAs) and long ncRNAs

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(lncRNAs). The main function of ncRNAs is to regulate gene expression at the transcriptional and translational levels and their expression is influenced by environmental or external stimuli, confirming the concept of epigenetic regulation independently from the DNA sequences [4]. Despite many studies highlighting the involvement of miRNAs and lncRNA in pain states [18, 19], this is still an emerging field within pain research that needs further attention [20]. Studies have found that preoperative circulating long- and miRNAs are associated with chronic postoperative pain one year after total knee arthroplasty [21–23], which could indicate that certain long- and miRNA might hold prognostic information. Studies have demonstrated that *in silico* target prediction models can identify pathways of regulations that involved miRNAs and lncRNAs, that are associated with the regulation of interleukin 1 β (IL-1 beta), IL-6, and TNF-alpha [21–23], which are well known pro-inflammatory cytokines involved in the sensitization of nociceptors [24].

The field of epigenetics and pain is an emerging field, which potentially can highlight aspects of how pain is regulated at a transcriptional and translational level. Some studies can link epigenetics to pain sensitivity but more research is needed. Emerging studies indicate that epigenetic markers might hold prognostic value and these findings should be investigated in future large-scale studies.

Research funding: The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Center for Mathematical Modeling of Knee Osteoarthritis (MathKOA), Department of Material and Production, Faculty of Engineering and Science, Aalborg University.

Competing interests: The authors have no conflict of interest to disclose.

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