VERSITA

Acta Medica Marisiensis 2013;59(4):231-233 DOI: 10.2478/amma-2013-0054

LETTER TO THE EDITOR

# Genetics of Pain

Chiorean MI[1], Chiorean MA[2]

[1] SC Hipocrate 2000 SRL, Tîrgu Mureş, Romania
[2] University of Medicine and Pharmacy, Tîrgu Mureş, Romania

In memoriam Prof. Dr. Livia Chiorean

**Motto**

"Pain is a personal signature, with complex genetic foundations, and very probably, the painkillers are influenced by certain genes."

(V. Dinca [1])

## Introduction

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [2]; it is a common problem, not only for patients, but also for the medical world.

Nociceptive pain has a protective role, a signal role, but if the lesions that caused it persist and are excessive, pain becomes a disease (neuropathic pain).

The partial failure of integrated treatment methods, especially in the case of chronic diseases, determined scientists to turn their attention towards the genetic conditioning of individual pain perception and the effectiveness or adverse reactions of painkillers or neuroleptic medication.

The financial aspect of treating pais is also of great importance: there are immense sums of money spent annually to treat pain: 150 billion USD in the USA, and 200 billion EUR in Europe [3]. Other pain-related aspects, such as depression (22%) and the loss of jobs (25%) also have to be considered [3].

In the following, we will present the genetic implications of pain, according to literature data:

- individual perception of pain;
- individual response to painkillers/co-painkillers;
- adverse reactions to painkillers/co-painkillers;
- therapeutic implications.

## Individual perception of pain [4–7]

Genetic studies on animals and humans, especially those connected to neuropathic pain, have shown certain genes that code the activity of the enzymatic system, or of the proteins belonging to Na and Ca channels in the nervous system, that lead to "phenotypic reactions" of the response towards pain. As a result of this research, in the past two decades over 200 genes, which mediate sensibility in animals and humans, were identified and published in the "Pain Genes Database" [8]. The most common genetic variations are given by a single nucleotide change in the DNA (single nucleotide polymorphism, SNPS), e.g. replacing Citozine (C) with Timine (T).

The most studied genetic variations are linked to the mutations of the following genes:

- *COMT*, gene which codifies cateocol-o-metil-transferase;
- *SCN9A*, which codifies voltage dependent Na channel $Na_V1.7$;
- *CACNL1/A4*, which produces a variation of the voltage dependent Ca channel, $CA_V2.1$;
- *MC1R*, which controls melanin;
- *OPRM1*, with the receptor A118G;
- *TRPV1*, with the receptor trpV1, vaniloid, capsicine;
- *TRPM8*, through protein TRPM8 or CMR1;
- *LPP1*, through protein CD91;
- *PRDM16*, through protein PRDM16;
- *HCN2*, through HCN17, HCN4.

The factors that belong to the genetics of pain are cultural, psychosocial and psychological.

*COMT*, which codifies catechol-o-metil-transferase, a neurotransmitter which modulates nervous cell signals through dopamine, epinephrine and norepinephrine [9,10], was linked with pain from the temporo-mandibular joint, with 3 phenotypes: low intensity pain (36.5%), medium intensity pain (48.7%) and high intensity pain (10.7%). Reduction of the activity of catechol-o-metil-transferase increases sensibility to pain, adding temporary pain. Zubieta et al. [11] suggest that the underlying mechanism is the depletion of enkephalin stock due to the high levels of dopamine, which produces an overregulation of the μ opium receptors and temporarily increases sensitivity to nociceptive stimulation.

*SCN9A(15)*, which codifies voltage dependent Na channel $Na_V1.7$, is associated with 3 rare conditions: congenital insensitivity to pain (CIP), erythermalgia and paroxysmal extreme pain disorder (PEPD) [12,13,14]. Congenital insensitivity to pain [12,15] was described in a boy from Pakistan who, working in a circus, was walking on heated coals or was stabbing his arms with daggers. He died at the age of 14, because he fell from the roof of his house.

Correspondence to: Mircea Chiorean
E-mail: live_med@yahoo.com

SCN9A was found in family members, who's mutation annihilates the Na channels' capacity to transmit pain signals. Erythermalgia, an autosomal dominant disease in which the affected individuals present intermittent burns and redness in the extremities, is triggered by warm signals or exercise. The disease progresses with age, producing complications [15]. Paroxysmal extreme pain disorder (PEPD) is an autosomal dominant disease, which presents rectal pain in infants; it was identified in 11 families [15].

*CACNL1A4* [12], situated on chromosome 19, p3, produces a variation of the voltage dependent Ca channel $Ca_v2.1$. This gene is responsible for familial hemiplegic migraine, where the mechanism of headache remains uncertain. However, there is evidence regarding the implication of the sensitivity of meningeal receptors, as well as central sensitivity of medular neurons from the posterior horn [12]. Recently, 2 more genes were linked with this disease, *FHM2* and *FHM3* [12].

*MC1R* [16,17] is responsible for the production of pigments within the organism, melanocortin-1-receptor (pheomelanin, eumelanin in red-haired women), as well as hormones that stimulate pain receptors in the brain [16]. The mutation of the *MC1R* gene could inhibit eumelanin and increase pheomelanin, with an overproduction of hormones. Therefore, red-haired women need more anesthetics, but with a chance of overdose [16]. The explanation of the disfunction of *MC1R* in some populations from Europe, Asia and Africa remains uncertain [17].

*OPRM1* (micro opioid receptor gene), A118G is involved in the addiction to opioids. The association with OPRD (delta) and OPRK (kappa) is connected to alcohol addiction [18,19,20]. Genes that codify enzymes responsible for morphine production (gene *UGT286*), μ opioid receptors (gene *OPRM*) and morphine transport through DBB (gene *MDR1*) generally influence the response towards opioids in anesthesiology and pain therapy. Additionally, COMT, which degrades cathecolamines, can alter the efficiency of morphine [1].

*TRPV1*, through the trpv1 protein (vaniloid receptor or capsicin-type) is responsible for the detection and regulation of the body's temperature, and also for the detection of burns and pain, as a result of mediated inflammatory overflow (prostaglandins, bradikinin, etc.). The clinical importance is linked to the usage of trpv1 agonists and antagonists, capsicin or endocarabinoid amantadine. The control of trpv1 contributes to the treatment of anxiety and epilepsy [21].

*TRPM8*, which codifies trpm8 or cmr1 (receptors responsible for sickness and menthol), allows through its activation the entrance of Na and Ca inside the cells, producing depolarization and generation of action potential. Activation is realized through low temperature and cooling agents (menthol) [22]. Solutions containing menthol are used for analgesia in case of traumas and itching. The mechanism remains unknown [22]. trpm8, with androgenic regulation, has recently been proposed for the treatmen of prostate cancer.

*LRP1* and *PRDM16*, with no direct connection to pain, could be involved in Alzheimer's disease (*LRP1*) and mieloid leukemia (*PRDM16*) [23,24].

*HCN2* codifies proteins within the ionic channels of nerve endings, playing a central role in inflammatory and neuropathic pain, in conditions such as diabetes and back pain [25,26]. In this field, research is headed towards blocking gene *HCN4*, in order to complete the arsenal against chronic pain.

Genetic influences over pain associated to gender, ethnicity and temperament: *TRPV1*, *ORPD1* and *COMT* were evaluated in a representative number of Caucasian, African, Asian and Hispanic women and men using nociceptive signals, warmth and cold, reaching the conclusion that ethnicity, gender and temperament influence individual sensitivity to pain [27].

## Individual response

Currently, individual response to analgetic and co-analgetic drugs [28,29] is subject to genomics, through which variables from the gene level are examined, that codify individual response to drugs.

Genomic techniques based on gene chips or microarray, which detect over 10.000 SNP's, apart from the detection of drug efficiency, are used for the discovery of new drugs, which are safe for the individual. At the same time, biological tests allow the discovery, by practicing physicians, of the types of adverse reactions of which their patients are suffering.

The existence of the National Center for Biotechnology Information (NCBI) allows the classification and brief description of genomic research data [28].

## Adverse reactions

Adverse reactions to analgetic and co-analgetic drugs are part of pharmacogenetic studies, which refer to genetic differences of the metabolic ways that affect the individual response to drugs, their therapeutic efficiency, as well as their adverse effects [30].

After the first observations of the 50's and the last century regarding the deficit of pseudocolinesterase found in patients with prolonged apnea to succinil-colin, ample studies were devoted to genetic variations involved in drug metabolism have shown that a big part of these drugs (beta blockers, statins, antiaggregants, anticonvulsants, analgetics, co-analgetics, etc) [30,31] are controlled by the liver's P450 2D6 enzymatic system (CYP2D6), polygenically coded by *CYP2D6*, located on chromosome 22.

Based on the type of pharmacogenetic reactions, individuals have been classified in [32]:

- Poor metabolizer (PM), with a low enzyme function;
- Intermediate metabolizer (IM), with a low-extensive power of drug metabolisation;
- Extensive metabolizer (EM), with a normal enzyme functionality;
- Ultra-rapide metabolizer (UM), with a higher enzyme functionality.

In this case, in certain individuals, drug efficiency appears normal, in others inefficient, and in others toxic.

Codeine (betilmorphine), considered to be a "pre-drug" [33], is a low opioid painkiller (connects with μ receptors), being metabolized in the liver it becomes 6-glucuronid-codein (80%) and morphine (5%), through a reaction called O-demetilation, catalyzed by CYP2D6 [32]. In the PM population codein has weak analgetic effects, with increased adverse reactions (sedation, itching, constipation). In UM individuals, by increase of CYP2D6, high quantities of morphine can appear, with respiratory complications, even with respiratory apnea, especially in children (case of an infant, that died from breast feeding)[32].

Tramadol [34], an opioid painkiller, acts as an agonist of μ receptors, as well as through GABA, 5-HT and noradrenaline. High concentrations of these neurotransmitters favor analgesia. CYP2D6 transforms tramadol into an active substance, M1-O-Desmetyltramadol, which acts on the μ receptors. In PM individuals this metabolite does not develop an effective agonist activity, therefore the second mechanism (5HT and noradrenaline), which is not reached, has an efficiency of only up to 30%.

Tricyclic antidepressors [32] are used as co-analgetics in patients with chronic neuropathic pain. CYP2D6 is also involved in their metabolism, generating UM type uncooperative individuals, and the PM type without sedation effects, but with many side effects such as dry mouth, weight gain, tahichardia, sedation.

The presence of adverse reactions that can occur while using drugs that are under the influence of the CYP2D6 enzyme system, leads to the setting of some inhibitors, stronger, normal or weaker, used for clinical therapy.

## Therapeutical implications

If the classic treatment of diseases seeks the correction of functional anomalies of the body, genetic therapy tries to correct its very own mistakes, starting from the DNA [32].

Through genic therapy, functional copies of defective genes are inserted inside the patient's cells, which induce correction of codified proteins and restoration of the whole biochemic path [32]. The most used gene transport method inside the defective genes' core, is the one that uses viral vectors (e.g. herpes simplex). Certain successes were obtained regarding pain, where the deficit of a single nucleotide was involved. Therefore, in neuropathic pain recombined gene transfer, and in cancerous pains "good genes" carried by viruses (herpes simplex type1, hsv1) was tried [32]. In inflammatory pains gene transfer is made for anti-inflamatory citokines (e.g. IL-10).

Until this day, genic therapy is limited by some difficulties such as: polygenic deficits , target error, integration inside the host cell, long-term survival of the transferred gene, possible deterioration of the genes by the host's immune response or reactivation of the viral vector. The last two decades have shown great progress in genic therapy and especially in pain therapy, where research is in full motion.

## References


1. Dinca V. Variabilitatea genetică şi eficacitatea opioidelor. Durerea. 2005;3: 2-5.
2. IASP Taxonomy Working Group. Part III: Pain Terms, A Current List with Definitions and Notes on Usage. In: Merskey H, Bogduk N (eds). Classification of Chronic Pain, Second Edition. IASP Press, Seattle, 1994, 209-214.
3. Mogil JS. The genetics of pain. IASP Press, Seattle, 2004, 174-190.
4. Edwards RR. Genetic predictors of acute and chronic pain. Current Rheumatology Reports. 2006;8(6):411-417.
5. Mogil JS, Ritchie J, Smith S. Melanocortin-1 receptor gene variants affect pain μ opioid analgesia in mice and humans. F. Med. Gen. 2006;42(7): 583-587.
6. Kim Y, Mittal DP, Iadarola MJ, Dionne RA. Genetic predictions for acute experimental cold and loop pain sensitivity in humans. J. Med. Genet. 2006;43:8 e40.
7. Diatchenko L, Slade GD, Nackley AG. Genetic basis for individual variations in pain perception and development of a chronic pain condition. Hum. Mol. Genet. 2005;14(1):135-143.
8. What are single nucleotide polymorphisms (SNPs)? Available online at: http://ghr.nlm.nih.gov/handbook/genomicresearch/snp
9. Catechol-O-methyl transferase. Available online at: http://en.wikipedia.org/wiki/Catechol-O-methyl_transferase
10. Kim H, Lee G, Rowan J. Genetic polimorphisms in monoamine neurotransmuter systems show only weak association with acute post-surgical pain in humans. Molecular Pain. 2006;2:24.
11. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science. 2003;299:1240-1243.
12. Raouf R, Quick K, Wood JN. Pain as a channelopathy. J Clin Invest. 2010;120(11):3745-3752.
13. $Na_v1.7$. Available online at: http://en.wikipedia.org/wiki/Nav1.7
14. Drenth JPY, Waxman SG. Mutation in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J. Clin. Invest. 2007; 117(12):3603-3609.
15. Friedrich MJ. Studii care sugereaza noi strategii ale tratamentelor durerii. JAMA-RO. 2007;5(5):3-5.
16. Foulkes T, Wood JN. Pain Genes. PLoS Genet. 2008;4(7):e1000086.
17. Melanocortin 1 receptor. Available online at: http://en.wikipedia.org/wiki/Melanocortin_1_receptor
18. OPRM1 - opioid receptor, mu 1. Available online at: http://www.wikigenes.org/e/gene/e/4988.html
19. Mu Opiod Receptor. Available online at: http://en.wikipedia.org/wiki/Mu_Opiod_Receptor
20. Filingim RB, Kaplan L, Staud R. The A118G single nucleotide polymorphism of the Mu_opioid receptor, gene (OPRM1), is associated with pressure pains sensitivity in humans. The Journal of Pain. 2005;6(3):159-167.
21. TRPV1. Available online at: http://en.wikipedia.org/wiki/TRPV1
22. TRPM8. Available online at: http://en.wikipedia.org/wiki/TRPM8
23. LRP1. Available online at: http://en.wikipedia.org/wiki/LRP1
24. PRDM16. Available online at: http://en.wikipedia.org/wiki/PRDM16
25. HCN2: A Gene For Chronic Pain? Available online at: http://www.huffingtonpost.com/2011/09/10/chronic-pain-gene-hcn2
26. Gena responsabila pentru reglementarea durerii cronice a fost descoperita. Available online at: http://www.credite-leasing.com/Gena+responsabila+pentru+reglementarea+durerii+cronice+a+fost+descoperita-p6-2816-1.htm
27. Kim H, Neubert JK, San Miguel A. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain. 2004;109(3):488-496.
28. Genomics. Available online at: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics
29. Pharmacogenetics. Available online at: http://en.wikipedia.org/wiki/Pharmacogenetics
30. Chiorean M. Impicațiile geneticii în anestezie terapie intensivă. In: Actualități în anestezie terapie intensivă (Eds. Sanda Maria Copotoiu, L. Azamfirei). University Press, Targu Mures, 2005, 16-45.
31. Madach K. Genetics in the clinical practice. From benchs to bedside: genetics in the intensive care. In: Actualități în anestezie terapie intensivă (Eds. Sanda Maria Copotoiu, L. Azamfirei). University Press, Targu Mures, 2011 213-225.
32. CYP2D6. Available online at: http://en.wikipedia.org/wiki/CYP2D6
33. Codeine. Available online at: http://en.wikipedia.org/wiki/Codeine
34. Tramadol. Available online at: http://en.wikipedia.org/wiki/Tramadol