Pharmacogenomics and Pain

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Abstract

Currently, chronic pain studies are gaining high evidence, outcoming the increased incidence of oncologic and osteoarticular degenerative disorders.

Pain perception is a complex multifactoral process which is still not completely known. Genetic factors are related to the susceptibility to develop some chronic pain conditions and, furthermore, to drug metabolism, being responsible for different reactions to therapy among individuals.

In this review the author discusses the novel and recent knowledge in pain management. It is also stressed out the significance of pharmacogenomic studies either in the diversity of reaction to pain therapy or in the underlying causes of different chronic conditions.

Pharmacogenomics is an imperative field in pain research and there have been major achievements during the last years related to increased knowledge and technological progression. A pharmacogenomics approach will contribute significantly to a new perspective on pain management and future directions point towards a more detailed medical diagnosis and an adjusted prescription with better accomplishments.

The most promising genes for pharmacogenomic analysis of pain are COMT, OPRM1, CYP450, MC1R and SLC6A4, according to the existing facts and to the knowledge of pain physiology. Pharmacogenomics approach represents a powerful tool to the management of both chronic and acute pain, in order to improve patients' quality of life.

Key Words

Pharmacogenomic; Chronic pain; Genetic polymorphisms; *COMT*; *OPRM1*; *CYP450* family*; MC1R; SLC6A4*

"We certainly cannot succeed as a culture by continuing to deny and ignore pain, as if we could silence it beneath a mountain of pills."

David Morris

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INTRODUCTION

Currently, people live according to different standards in life but everyone ambitious to live with some quality.

The ageing process is associated to the appearance of different chronic pathologies, being oncologic and degenerative diseases the most important ones.

One of the various signs of illness is pain. This is one of the most unpleasant symptoms and, for most patients, it is the primarily reason to look for clinical intervention.

Frequently, pain is the reflection of an underlying process and it disappears with treatment. However acute pain occasionally evolves to a chronic situation, producing a new clinical condition with huge impact in patients' daily life.

Pain is a society problem that is responsible for long-term disability. The decrease in work productivity of employees with pain is responsible for an amount of days of medical leave leading to enormous costs.

In addition, treatments are expensive and not always efficient. The reason for such unsuccessful achievement is the lack of acknowledge of pain's perception mechanisms. However, the recent capacity to use imaging techniques to perform research in humans had contributed to new advances in this field.

It is well known that pain's perception is subjective and its assessment is complex. It is not only a sensory perception but also an emotional experience. Although multifactoral, heredity has been shown to play an important role in pain disclosure. Some chronic painful processes are determined through genetic basis. Some genetic polymorphisms account for susceptibility

to develop disease. Furthermore, drug metabolism are also determined by genetic factors reproducing different reactions to therapy among individuals.

Pharmacogenomics is the result of the observation of this genetic influence. It has contributed to novel achievements in pain management. Pharmacogenomic studies revealed the involvement of genetic variants in some chronic conditions, such as migraine and fibromyalgia. It has also allowed to observe that genetic diversity accounts for different degrees of drug metabolism, with significant impact on the clinical approach. Given the possibility to distinguish individuals from a population using a genetic diagnosis, it will be feasible to achieve a therapeutic approach based on genetic characteristics of small groups.

The emergent need for original advances in pain is evident. The recent advances in genetics and proteomics will contribute to the clarification of mechanisms involved in pain and to the possibility for the development of innovative drug targets.

In this review the author discusses the novel and recent knowledge in pain management. It is also stressed out the significance of pharmacogenomic studies either in the drug metabolism or in the underlying causes of some chronic conditions.

ANATOMY AND PHYSIOLOGY OF PAIN

Pain perception is an intricate response from body to stimuli. It is a multidimensional phenomenon that encompasses sensory-discriminative, affective-motivational and cognitive-emotional components mediated by different mechanisms and processed in a complex neural network (Dickenson 2008) The entire process of how human body reacts to pain has still unrevealed mechanisms. The idea that sensory perception is shaped by previous pain experiences and beliefs has gained increasing credibility among scientists. Our ability to modulate pain perception is evident in placebo analgesia, in which the belief that one is receiving an effective analgesic treatment can reduce pain (Wager et al. 2004).

The conventional model discriminates four components of pain, that interact so closely that are impossible to set apart (Calvino and Grilo 2006).

1. The sensory-discriminative component, that decode the intensity, duration and location of the nociceptive stimulus;
2. The emotional-affective component, which connects the nociceptive stimulus to related environmental conditions;
3. The cognitive component, to attain pain perception;
4. The behavioral component, which includes the verbal and nonverbal behaviors in response to nociceptive stimulus.

Until very recently, human studies of pain perception were almost impossible. The use of non-invasive brain image, as functional magnetic resonance imaging (fMRI) and positron

emission tomography (PET), allowed to access the inside of brain functioning and contributed to a large footstep in the understanding of pain's perception mechanism (Brooks and Tracey 2005).

The persistent pain which accompanies inflammatory tissue damage and/or nerve injury is generally characterized by: its spontaneous nature (not elicited by extrinsic stimuli), and by the presence of hyperalgesia (an increase in the pain elicited by a noxious stimulus) and/or allodynia (pain elicited by normally innocuous stimuli). Prolonged/chronic pain is regarded as fulfilling no physiological purpose (Serpell 2005; Diatchenko et al. 2007).

The pathways of pain generation can be modulated at three levels: the peripheral nociceptor, the spinal (dorsal horn of the cord), and the supraspinal (brain) (Serpell 2005).

Primary step on nociceptive information

Peripheral nociception is originated in tissue injury (Figure 1), which causes the release of inflammatory mediators. The propagation of pain initiates with the activation of physiological receptors, called nociceptors, which are widely distributed (Di Patti and Fanelli 2010).

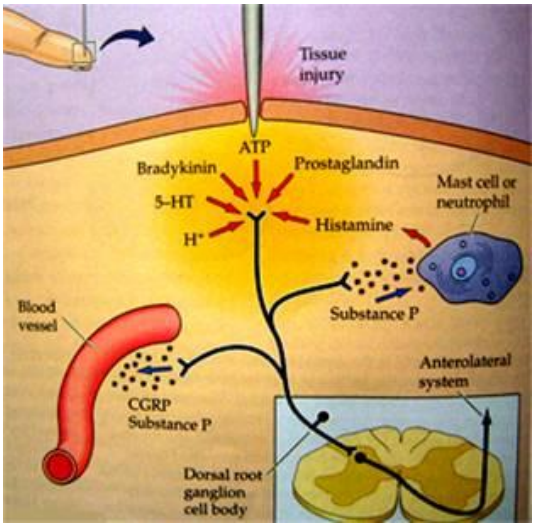

Figure 1 Injury stimulates peripheral nociception with the release of inflammatory mediators. Adapted from www.pacifu.edu

Some mediators (e.g. ATP, protons, serotonin) act on receptors that are linked directly to ion channels. Others (e.g.

bradykinin) act indirectly through receptors linked to second messenger systems and in this way modulate the activity of ion channels and either activate or sensitize the neurons (Rang et al. 1991).

The transmission of peripheral stimuli is made by the cutaneous primary afferent fibers. These can be classified essentially into three types on the basis of their diameter, structure and conduction velocity: (1) C-fiber (thin, unmyelinated and slow), (2) Aδ-fiber (medium, myelinated and intermediate velocity) and (3) Aβ-fiber (large, myelinated and fast). Although all three classes of cutaneous fibers can transmit non-nociceptive information, under normal circumstances, only C and Aδ, but not Aβ, fibers transmit nociceptive information (Millan 1999; Serpell 2005).

In an acute stage, nociceptor endings cause a generator potential, which leads to an action potential in C and Aδ fibers. These action potentials are then conducted to higher centers in the central nervous system (CNS) via neurotransmitter release and are followed by a variety of responses, including withdrawal reflexes, conscious perception of pain, and emotional effects (Ueda 2008).

A set of local factors can contribute to peripheral nociception. For example, it has been shown that low pH had influence on pain intensity, as it has been demonstrated in animal studies. A high proportion of C-fibers are activated by pH 6.0 of lactic acid *in vitro* (Kang and Brennan 2009). Increased chemosensitivity of c-nociceptors to lactic acid after incision, further supports the possibility that cofactors, such as lactate or others, might facilitate nociceptor activation by low pH and contribute to postsurgical pain (Kang and Brennan 2009).

At the level of the peripheral nerve, drugs that act on particular sodium channels may target only pain-related activity. Agents acting on some of the peripheral mediators of pain may control peripheral nerve activity (Besson 1999).

REGULATORS OF PAIN

Neuropeptides include a diverse group of chemically distinct molecules, contained in and released from a range of sensory nerves. They are involved in the formation, transmission, modulation and perception of all types of pain (physiological, neuropathic and inflammatory). These neurotransmitters connect to receptors and according to their activity they can be called excitatory or inhibitory neuropeptides (Besson 1999). Glutamate is the most prevalent excitatory neurotransmitter facilitating the transmission of noxious sensory signals while γ-aminobutyric acid (GABA) and glycine inhibit it (Dickenson et al. 1997).

Sensory neurons, at periphery, express opioid receptors and opioid peptides, and the function of these neurons can be modulated by endogenous opioids derived from immune cells or by opioid drugs (Paassilta et al. 2001).

Pain system

The primary afferent fibers reach the spinal cord via the dorsal horn of at each cervical, thoracic, lumbar and sacral level, where they establish synapses with second-order neurons. Pain fibers from head reach brain stem through the cranial nerve pairs V, VII, IX and X (Sessle 2005).

Before synapsing with second-order neuron, pain fibers can ascend or descend one or two spinal cord segments making part of the posterolateral tract (Lissauer Tract). The second-order neurons are distributed along the dorsal horn of the spinal cord and are organized according to the Rexed laminae (Almeida et al. 2004) (Figure 2).

At the dorsal horn, neurons are either ascending tract neurons or interneurons that are part of segmental motor or vegetative reflex pathways. Most ascending axons constitute the spinothalamic tract, which activates the thalamocortical system. This tract sends fibers to thalamus, reticular formation, raphe nucleus and the periaqueductal gray matter; it can be divided into lateral and medial tracts. The lateral, also called neospinothalamic tract, projects to vento-postero-lateral thalamus. The medial, paleospinothalamic, projects for medial thalamus (Xie et al. 2009). The lateral thalamocortical system consists of relay nuclei in the lateral thalamus and the primary (SI) and secondary (SII) somatosensory cortices in the postcentral gyrus. These are responsible for perception and discrete localization of pain. The medial thalamocortical system is responsible for the affective component of pain sensation. This consists on nuclei in the central and medial thalamus and the anterior cingulate cortex (ACC), the insula, and the prefrontal cortex (PFC) (Schaible 2004; Xie et al. 2009).

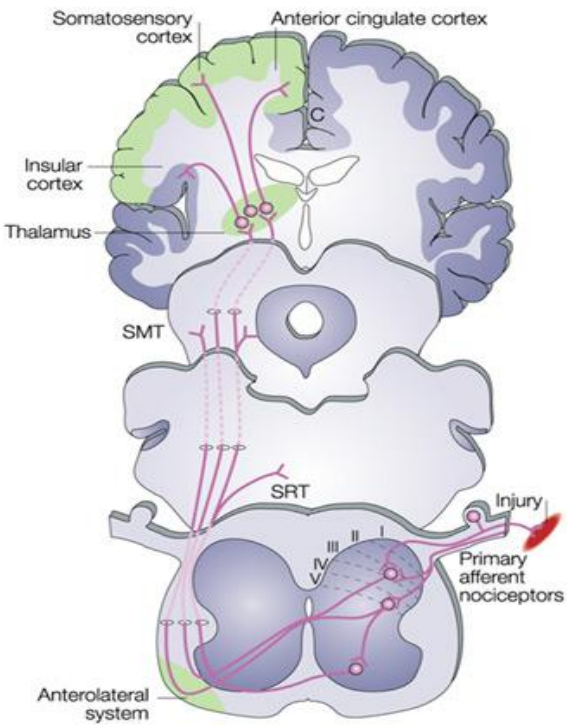

Figure 2 Transmission of nociceptive stimulus through dorsal horn of spinal cord to cortical regions. SRT spinoreticular tract, SMT spinomesencephalic tract. Adapted with authors permission from Nature Reviews Neuroscience 2004, 5:565-575

The role of supraspinal structures in pain process remains unknown. Neuroimaging studies, as a non-invasive method, contributed to a progressive unraveling of the neuroanatomical structures and brain network involved in pain perception (Brooks and Tracey 2005).

LATERAL PAIN SYSTEM

Lateral pain system includes the cortices SI and SII. In these areas, the characteristics of the nociceptive signal are deciphered, leading to the genesis of pain perception (quality, location, intensity, and duration) (Calvino and Grilo 2006).

Reports in amputees describing phantom limb pain demonstrate a positive correlation between pain intensity and the amount of SI reorganization. In spinal cord injuries, it was also demonstrated that the amount of SI reorganization significantly correlated with on-going pain intensity levels (Wrigley et al. 2009).

Studies revealed that activations in SII were significantly correlated with scores for the sensory-discriminative component during mechanical impact pain, thus SII may play an important role in the sensory-discriminative dimension of pain (Maihöfner et al. 2006).

It has been proposed that the SI cortex is involved mainly in discriminative aspects of pain, whereas the SII cortex seems to have an important role in recognition, learning, and memory of painful events (Xie et al. 2009).

MEDIAL PAIN SYSTEM

The ACC mainly collects projections from mediodorsal thalamic nucleus and mostly connects with important regions of the descending modulation system, including periaqueductal gray matter (PAG) (Xie et al. 2009).

The ACC is connected to brain structures that influence the emotional component of thought, autonomic and visceral responses, and mood regulation (Ro Hemodynamic responses in ACC, reflect simultaneously the sensory, cognitive and affective dimension of pain. ACC activation was found in noxious cutaneous / intramuscular stimuli of chronic regional pain patients (Xie et al. 2009).

The activation of the ACC in response to thermal and mechanical pain was shown in human fMRI studies in healthy volunteers (Seifert et al. 2007). Single photon emission computed tomography demonstrated reduced blood flow in the ACC of patients with chronic pain conditions (Honda et al. 2007).

Studies approaching placebo-induced analgesia revealed that placebo treatment has widespread effects on endogenous opioid activity in cortical and subcortical regions, which are critical for the determination of affective value and context-based control of pain (Wager et al. 2007). PET studies showed that both opioid and placebo analgesia are associated with increased activity in rostral ACC, that may play a key role in the cortical control of the brainstem during opioid analgesia through fiber tracts projecting directly to the PAG or across of the medial thalamic nucleus (Petrovic et al. 2002).

The involvement of ACC in nociception modulation may be associated with the activities of variety of a neurotransmitters, including glutamate, dopamine and opioids. Activation of μ-opioid receptor significantly inhibited the glutaminergic excitatory postsynaptic currents in the ACC neurons, which was attained through the suppression of presynaptic glutamate release (Zheng 2010).

ACC is associated with both visceral and somatic pain (Xie et al. 2009). The ACC nociceptive transmission is mediated by glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in normal circumstances. In viscerally

hypersensitive rats, the synaptic transmission in the ACC neurons is enhanced. This enhancement is mediated mainly by N-methyl D-aspartate (NMDA) receptor activation (Wu et al. 2008).

Another element important for medial pain system is the insular cortex. It is often bilaterally activated during noxious somatosensory stimulation and has been suggested that it plays a relevant role in pain processing (Coghill et al. 2001).

The insular cortex receives sensory information from the thalamus and sends efferent fibers to the amygdale, lateral hypothalamus, dorsal raphe, PAG, pericerulear region, rostroventral medulla, parabrachial nuclei, and the nucleus accumbens. The insular cortex has extensive reciprocal cortico-cortical connections with the orbital, infralimbic, ACC and with the contralateral insular cortex (Xie et al. 2009). The strategic position of insular cortex, to both send and receive information from essential areas in sensory processing, as well as memory retrieval, attention, and affection, allows its contribution to the formation of a unique signature/fingerprint of pain experience for each individual (Starr et al. 2009).

Activation of the insular cortex has been correlated with the intensity of noxious stimulation, suggesting that this structure may play a role in pain intensity coding (Derbyshire et al. 1997) The insula has also been proposed to be involved in autonomic reactions to noxious stimuli and in pain-related learning and memory (Ploner and Schnitzler 2004; Xie et al. 2009).

Central pain augmentation resulting from enhanced excitatory and/or decreased inhibitory neurotransmission is a suggested mechanism underlying the pathophysiology of functional pain syndromes. Multiple fMRI studies implicate the insula as a region of heightened neuronal activity in this condition (Harris et al. 2009).

PFC as part of medial pain system is thought to have a role in mediating analgesic effect during the cognitive modulation of pain (Bingel and Tracey 2008). A placebo-induced

analgesia fMRI study revealed that activation of PFC reflects a form of externally elicited top-down control that modulates the experience of pain (Wager et al. 2004).

A network of seventeen distinct anatomical areas specifically activated during heat allodynia showed the bilateral PFC to be exclusively negatively correlated with perceived intensity and/or unpleasantness (Lorenz et al. 2003).

Sakai et al. (2002) proposed that PFC may protect the maintenance of momentary behavioral goals, by rendering working memory operations resistant to distractive stimuli.

VENTROLATERAL ORBITAL CORTEX SYSTEM

The ventrolateral orbital (VLO) cortex system receives ascending afferent fiber from the submedius nucleus, PAG and the dorsal raphe nucleus (Li et al. 1993). The combined effects of submedius nucleus, VLO and PAG may constitute one nociception modulation pathway that regulates nociceptive information input at the terminal/spinal cord level (Xie et al. 2009).

The VLO contains a considerable number of μ-opioid receptor subtype 1-like immunoreactive neurons and GABAergic neurons that also express μ-opioid receptors (Huo et al. 2005). Xie et al (2009) propose the hypothesis that opioid-induced antinociception in the VLO might be produced by opioid, via the μ-opioid receptor subtype 1. This receptor exerts inhibitory effects on GABAergic inhibitory neurons and leading to activation of the VLO-PAG brainstem descending pain control system, to depress the nociceptive inputs, at the trigeminal/spinal cord level. The mechanism of this hypothetic pathway needs further confirmation by other investigation studies.

MOTOR CORTEX SYSTEM

The role of motor cortex system in pain modeling comes mainly from clinical studies.

Motor cortex stimulation (MCS) has been proposed as a treatment for chronic, drug-resistant neuropathic pain of various origins. The indication of MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain (Rasche et al. 2006; Lefaucheur et al. 2008). MCS is effective not only to treat pain, but also improves the sympathetic changes in complex regional pain syndrome (Velasco et al. 2009).

Unilateral repetitive transcranial magnetic stimulation of the motor cortex induces a long-lasting decrease in chronic widespread pain and may therefore constitute an effective alternative analgesic treatment for fibromyalgia (Passard et al. 2007).

A case report demonstrated that MCS could restore tactile and thermal sensory loss, resulting from peripheral nerve injury (Fontaine et al. 2009).

A PET study showed that MCS may act in part through descending (top-down) inhibitory controls that involve prefrontal, orbitofrontal and ACC, as well as basal ganglia, thalamus and brainstem (Peyron et al. 2007).

Opioid receptors blockade by naloxone abolished the increase in nociceptive threshold induced by MCS, which demonstrate that epidural electrical MCS elicits a substantial and selective antinociceptive effect mediated by opioids (Fonoff et al. 2009).

SPINAL CORD RECEPTORS

The vast majority of excitatory neurotransmission are mediate by the ionotropic glutamate receptors, which are ligand-gated ion channels. These can be stimulated by AMPA, NMDA and kainate neuropeptides. The inhibitory receptors are constituted mainly by γ-aminobutyric acid (GABA) and glycine receptors (Dingledine et al. 1999; Colvin 2005).

Descending control of pain

The spinal cord is under the influence of descending tracts that reduce or facilitate the nociceptive processing (Schaible and Richter 2004). The descending control of pain, through its pro- and anti-nociceptive components, is an important part of pain mechanism. As important as pain transmission, to control tissue damage, it is also imperative to control the consequence of these signals in the nervous system. Selective suppression of nociception allows a properly reaction to a life-threatening situation without the distraction or counterproductive motor responses that might be evoked by noxious input (Heinricher et al. 2009). The key problem appears when there is a disruption between these normal regulatory processes that can account for vulnerability for the development and maintenance of chronic pain (Bingle and Tracey 2008).

Some authors have show that the PAG has an important role on descending influences on spinal nociceptive processing (Calvino and Grilo 2006; Bingle and Tracey 2008), essentially on the rostral ventromedial medulla (RVM). Neurons in the RVM project along the spinal dorsolateral funiculus (DLF) to terminate in the dorsal horn, where they cause inhibition of nociceptive transmission (Vanegas and Schaible 2004; Calvino and Grilo 2006). RVM is known for its pronociceptive and antinociceptive effects (Tavares and Lima 2007). Anatomical, electrophysiological, and behavior studies reveal a primary role for the dorsal reticular nucleus in facilitating pain processing (Lima and Almeida 2002).

On an inflammatory pain model, descending inhibition generally predominates over descending facilitation in the primary pain, while the descending facilitation predominates over descending inhibition in the secondary pain. In opposition, the primary hyperalgesia and

allodynia of the neuropathic syndrome also depend on facilitation from the RVM, while secondary neuronal pools are under descending inhibition that is partly supported from the PAG (Vanegas and Schaible 2004).

Descending control of pain is yielded by serotonergic, noradrenergic and opioidergic systems, which interact by an intricate manner (Tavares and Lima 2007).

Serotonergic is an antinociceptive system that acting through the activation of RVM, which has been demonstrated by the reduction of RVM analgesic effect by intrathecal administration of serotonin antagonists (Schmauss et al. 1983). However, apparently the serotonergic system can act separately from the noradrenergic system (Lima and Almeida 2002).

The noradrenergic system has a peripheral pronociceptive effect associated with injured tissues. Therefore, in the spinal cord, noradrenaline release from descending pathways, suppresses pain by inhibitory action on α2A- adrenoceptors on central terminals of primary afferent nociceptors (presynaptic inhibition), by direct α2-adrenergic action on pain-relay neurons (postsynaptic inhibition), and by α1-adrenoceptor-mediated activation of inhibitory interneurons (Pertovaara 2006).

The pathways conveying the opioidergic antinociceptive actions descend in the dorsolateral fasciculus, as revealed by the suppression of antinociception produced by either focal electrical stimulation and injection of morphine in the PAG, or systemic administration of morphine following bilateral lesioning of that spinal tract (Lima and Almeida 2002). Exogenous opiates imitate endogenous opioids and induce analgesia by acting upon PAG and RVM, in addiction to the spinal dorsal horn (Vanegas and Schaible 2004).

The placebo effect

Placebo analgesia, in analogy to Pavlovian conditioning, is a prime example of cognitive modulation of pain. The unexplained success of fake analgesics is supported by the underlying mechanism of expectation-induced placebo analgesia, which involves a top down activation of endogenous analgesic activity via the descending modulatory system (Bingel and Tracey 2008) Studies revealed that placebo can reduce pain by both opioid and non-opioid system (Colloca and Benedetti 2005). The placebo activated opioid system acts not only at pain modulation but also in the respiratory and cardiovascular systems. Placebo administration can be followed by manifestation of respiratory depression, decreased heart rate and β-adrenergic response (Benedetti et al. 2005).

The placebo–induced analgesia has a cumulative effect as it increases the analgesic effect of a treatment when the patient is aware of it. Colloca and Benedetti (2005) demonstrated that patients who previously knew their pain treatment and had expectations on the outcome, had higher analgesic efficacy than those who did not. Petrovic et al. (2002) showed, using PET studies, that both opioid and placebo analgesia were associated with increased activity in the rostral ACC. It was also demonstrated that there was a covariation between the activity in the rostral ACC and the brainstem during both opioid and placebo analgesia but not during pain-only condition.

Functional MRI studies revealed a decreased brain activity in thalamus, insula and ACC related to placebo analgesia during painful heat stimulus. These were also associated with increased activity during anticipation of pain in the PFC, providing evidence that placebo alter the experience of pain (Wager et al. 2004).

THE IMPACT OF PHARMACOGENOMIC IN THE TREATMENT OF PAIN

Pain's perception, as mention above, is a complex interaction of many features. There is a distinctive interindividual response to pain related to sensory, affective and cognitive interactions.

Environmental factors, such as early exposure to acute painful stimuli, can determine nociceptive thresholds in both animals and humans. A good example is the experience of a child to circumcision's pain, which has been established to increase sensitivity to pain in latter life (Taddio et al. 1995). Although former experiences can influence our physiological response to a painful stimulus, it is also determined by individual genetics. It has been suggested that genetic predisposition can explain a significant part of the variability observed in the perception of pain, sensitivity to painful stimuli and development of chronic pain (Neumann and Buskila 2003).

The multifactoral nature of pain perception brings problems to the genetic research related to pain sensitivity. The use of animal models has been helpful in the increasing knowledge about mechanisms involved in pain (Kambur et al. 2008; Hedlung 2009). Models of inflammatory and neuropathic pain have been also well-described, and may have more relevance to human clinical conditions than assays of acute pain (Foulkes and Wood 2008).

Association analysis approaches have been used to examine the genetic involvement in human pain perception (Janicki et al. 2006). Heritability studies using sensory testing of twins could identify the importance of genetic contributions to pain traits, and single nucleotide polymorphism (SNP) association studies allowed the finding of several genes correlating with

altered pain "behavior"(Foulkes and Wood 2008). In contrast, some rare recessive conditions found in populations undergoing consanguineous mattings led to alterations in pain thresholds, and the genes underlying this effect are of most interest (Verhoeven et al. 2006).

Although acute pain treatment has been studied by many researchers, chronic pain has not been explored in such detail mainly due to its morbidity and association to oncology. Therefore, novel pharmacogenetic approaches are emerging and this is a promising research field.

Chronic pain syndromes affect a significant portion of the general population, 10-11% of the subjects presented this symptom any time during their lifetime (Buskila 2007).

The complete genetic information, that is produced every year, from different research groups, has contributed to increasing knowledge on the physiological mechanisms and genetic variants associated to pain's perception. However, much is still unknown and further studies will allow new advances in the understanding of pain.

The design of future genetic studies will be shaped by future insights into fundamental questions about pain, such as whether subtypes of skeletal, neuropathic, and visceral pain are processed by mostly similar or differing mechanisms.

Pharmacogenetics or pharmacogenomics analyses the role of inter-individual genomic variation in drug response (Weinshilboum and Wang 2004). The aim is to disclose influences of specific genetic variations on pharmacological responses and the possible interference of drug efficacy and side effects. The final goal of pharmacogenomics is the possibility that knowledge of DNA sequence might be used to improve therapy in order to maximize efficacy. Accordingly this approach allows to target drugs for patients that are likely to respond best and to avoid adverse drug reactions, minimizing toxicity (Tsai and Hoyme 2002; Roden et al. 2006)

The concept that genetic features might influence individual response to drug treatments or to physiological events emerged in the middle of the XX century. Although the conception of genetic tests was not the same from the present time, it was possible to observe individual genetic differences by an indirect approach. Studies of drug metabolism involved the measurement of diverse parameters: plasma drug concentrations, urinary drug excretion, peak plasma levels, drugs half-life, among others (Weinshilboum and Wang 2004).

A good example of pharmacogenetic approach are the several studies found in literature related to variations in genes coding enzymes of the Cytochrome P450 family and the phenotypic variations in the pharmacokinetics of drugs (Evans et al. 1960). More than 80 distinct allelic variants, mostly polymorphisms, were discovered and it is presently known that they influence drug therapy response (Daly et al. 1996; Merez et al. 1997).

Currently, there have been rapid changes in genomic science, most significantly the accomplishment of the human genome project. These recent informations, together with the development of novel and more efficient technical tools, it is even more prompt to genotype a large number of individuals, allowing major advances in pharmacogenomics studies.

The major challenge of Pharmacogenomics studies is the development of genetic tests that are part of the therapeutic decision tools. The concept of translational science, "from the bench to the bedside", fits this goal. However, this will be achievable only when the genetic tests show to have strong scientific evidence of clinical utility.

From the possibility to distinguish genetic groups in a population, using a diagnostic genetic database, it will be feasible to achieve an adjusted therapeutical approach. When reading that point, a concerted effort must be conducted and directed to upbringing of health professionals and patients (Weinshilboum and Wang 2004).

The costs and benefits of a pharmacogenomics approach

The generalized access to a diagnostic genetic database and to most recent technologies heralds an era in which professionals will use pharmacogenomics approaches to perform patients care. Most likely, genotyping all population in order to adjust therapy to individuals with a specific genotype will be costly (Philips and Bebber 2005).

Despite the huge investment in recent years, pharmacogenomics did not fullfil the promise of defining diagnostic markers for a more rationale drug therapy, in order to maximize drug efficacy and reduce adverse events (Halapi and Hakonarson 2005).

Most pharmacogenomic strategies relay on enhancing novel treatments and reduce drug side effects. It is likely to be cost effective when the polymorphism under consideration is prevalent in the population and has a high degree of penetrance, or if the disease state involves outcomes with significant morbidity or mortality if left untreated. This approach is useful also if the treatment involves significant outcomes and/or costs that can be impacted by genotype-individualized therapy (flowers and Veenstra 2004).

Epidemiological studies point out the importance of evaluating the benefits of genomic research for public-health application, because of the large resources that have been devoted to this area and the urgent need to find its utility in the clinical practice (Merikangas and Risen 2003).

Fishbain et al. (2004) determined the imminent clinical relevance of genomic testing related to drug metabolism enzymes in the practice of Pain Medicine. These authors concluded that these genomic tests have significant potential for providing the efficacy of drug treatments and reduced adverse drug reactions. Therefore, at the present time, genomic tests may not be

cost effective if one is not using or planning to use a drug with differential previously demonstrated effects according to genotypes.

Biomedical science has significantly improved our understanding of pain in recent decades, but few novel genetic data addressing fundamental pain mechanisms have been included in the clinic practice, despite the dramatic increase in pharmaceutical investment (Woodcock et al. 2007).

Presently, we are facing an emergent need of novel drugs for pain therapy. On the last decades, the analgesics that have been produced derived from opioids or aspirin-like drugs. The knowledge of addicional data concerning pain's perception and the establishment of new pain's treatment approach stands as a significant challenge in pain genetic research. Genomics and proteomics have been identifying targets that could be validated to selectively modify pathways of pain and inflammation (Sery et al. 2005).

Research on receptors involving the transduction, transmission and modulation of nociceptive information is clearly one of the most exciting and rapidly advancing areas in the field of pain research (Govoni et al. 2008).

PAIN GENES

COMT

Catechol–O–methyltransferase (COMT) is an enzyme responsible for the inactivation, through O-methylation, of catecholamines such as dopamine, adrenaline and noradrenaline (Bunker et al. 2008). These neurotransmitters are involved in pain conduction and thus variations in COMT activity can contribute to differences in pain sensitivity and response to analgesics. This likely involvement of COMT in the regulation of pain perception has been shown in recent reports (Zubieta et al. 2003; Diatchenko et al. 2006, Rakvag et al. 2008).

There are two forms of COMT protein: the soluble COMT (S-COMT) and the membrane bound COMT (MB-COMT). MB-COMT is more effective in metabolizing dopamine and noradrenaline, while S-COMT is more effective in metabolizing adrenaline (Mannisto and Kaakkola 1999).

The foremost studied SNP in the *COMT* gene is the rs4680, also known as Val158Met. This polymorphism causes an amino acid substitution from valine (Val) to methionine (Met), at position 158, leading to a three- to four-fold reduced activity of the enzyme (Tiihonen et al. 1999).

The alleles are codominant, so that individuals with the Val/Val genotype have the highest activity of COMT, those with the met/met genotype present the lowest activity of COMT, and heterozygous individuals have intermediate activity (Vandenbergh et al. 1997).

Additionally, Diatchenko et al. (2005) identified three haplotypes of the *COMT* gene that determine enzymatic activity. The LPS haplotype is associated with low pain sensitivity, APS with average and HPS with high pain sensitivity. Together, these three haplotypes include approximately 96% of the human population.

Several authors compared *COMT* genotype and individual response to pain. Zubieta et al. (2003) revealed that different levels of catecholamine metabolism induced by Val158Met polymorphism are associated with downstream alterations in the functional responses of the μ-opioid neurotransmitter system and compensatory changes in μ-opioid receptor binding. These authors demonstrated that individuals homozygous for the Met allele showed diminished regional μ-opioid system response to pain compared with heterozygotes. These effects were followed by higher sensory and affective ratings of pain and a more negative internal affective state. These results suggest that reduction in COMT activity, associated with the met variant enzyme, result in chronic over-stimulation of dopamine receptor 2 (D2). It is located on enkephalin-containing neurons and therefore in prolonged elevations of synaptic dopamine that lead to the depletion of enkephalins. The depletion of releasable enkephalins results in increased sensitivity to sustained noxious stimuli and is associated with a compensatory increase in μ-opioid receptor binding (Diatchenko et al. 2006). However, more recent studies are not in agreement with these facts. It was demonstrated that the amount of opioid peptide mRNA was not reduced in any of the brain regions studied, except for the caudate nucleus (Berthele et al. 2005). In another study the amount of opioid peptide mRNA was reduced only in the shell region of the nucleus accumbens but not in other regions (Nikoshkov et al. 2008).

Rakvåg et al. (2008) tested the variation in the *COMT* gene and morphine requirements in cancer patients with pain. They suggest that *COMT* genetic variability (14 haplotypes with 11

SNP) influences the efficacy of morphine treatment in cancer patients. It was shown that cancer patients carrying haplotype 1 required lower morphine doses to relieve pain than other patients. Regarding the Val158Met polymorphism, cancer patients with the Val/Val genotype needed more morphine when compared to the other two genotypes (Rakvåg et al. 2005). Another study (Reyes-Gibby et al. 2007) explored the joint effect of *COMT* and the genes coding for the μ-opioid receptor (OPRM1) namely the polymorphisms 118A>G and the Val158Met in the effectiveness of morphine therapy in cancer patients. This study showed that carriers of Met/Met and AA genotype in the COMT and OPRM1 gene, respectively, needed lower morphine dose for adequate control of pain.

Diatchenko et al. (2006) demonstrated an association between thermal stimuli and *COMT* diplotypes. According to the results Val158Met polymorphism was associated with the rate of temporal summation of heat pain but not with the resting nociceptive sensitivity. According to the authors, a subject with Met containing form of MB-COMT and/or haplotypes that produce reduced levels of S-COMT (HPS and APS haplotypes) may have an increased risk of developing persistent pain conditions.

Jensen et al. (2009) suggest that the initial response of the pain system is not influenced by the COMT Val158Met polymorphism but when the pain defense system is challenged repeatedly, this specific genotype based difference become apparent. A possible clinical implication of this finding may be that the COMT Val158Met polymorphism related differences may be more expressed in individuals where the inhibitory system is already challenged and the individual is sensitive already from start, such like patients with chronic pain.

Contrasting with the above mentioned data, Armero et al. (2005) in their study in the Spanish population have not found association between COMT activity and individual susceptibility to neuropathic pain.

The role of COMT in central nervous system has previously been demonstrated in several other neurological/psychiatric disorders, such as anxiety (Azzan and Mathews 2003) and schizophrenia (Glatt et al. 2003). In a preliminary study, George et al. (2008) suggested that high pain catastrophizing and low COMT activity were associated with higher pre-operative pain ratings, and an increased probability of experiencing persistent pain following arthroscopic shoulder surgery. This study is one of the first that considers a possible psychological and genetic interaction in pain.

Further studies will carry on revealing COMT genetic variability and its interaction with enzymatic activity along with its involvement in psychological pain perception.

OPRM1

Opioids are the class of drugs that cause pain relieve by binding to specific receptors located in the brain and spinal cord. Opioid receptors are essential drug targets in pain treatment. The μ - opioid receptor, which is coded by the *OPRM1* gene, is a primary candidate for the pharmacogenetic studies since it is the site of action of most opioids established in clinical practice (Lötsch and Geisslinger 2005). Recent findings associate *OPRM1* mutations to altered clinical opioid effects and to the susceptibility for drug addiction (Haile et al. 2008). Furthermore, it is expected that these studies will have an important contribute for pain therapy.

The most common SNP of *OPRM1* is the 118A>G that results from an exchange of aspargine for aspartate at position 40. A study in healthy volunteers (Lötsch and Geisslinger 2006) revealed a frequency of 10-14% of this SNP.

The clinical consequences of SNP 118A>G have been extensively evaluated. Several studies shown that the carriers of 118G allele need more alfentanil (Caraco et al. 2001) and morphine (Chou et al. 2006; Tan et al. 2009) for postoperative analgesia, as well as higher doses (twice than wild-type) of morphine for cancer pain relief (Klepstad et al. 2004). This SNP was also associated with higher pain scores, an increased requirement of morphine for analgesia still with lower nausea score (Tan et al. 2009).

The influence of gender on the association of 118A>G polymorphism and pain sensitivity was also established. In disagreement with previously mention results, another study on labor pain demonstrated that women carrying 118G allele were more sensitive to analgesic effect of intrathecal fentanyl (Laudau 2010). These findings suggest that the presence of 118A>G polymorphism is related to a lower effect of opioid analgesia. However, an homozygous carrier of the 118G allele, with renal failure, receiving morphine for analgesic treatment, tolerated the accumulated plasma levels of morphine-6-glucuronide M6G surprisingly well (Lötsch et al. 2002) It seems that these carriers are more protected from opioid side effects.

An association study demonstrated that the frequency of the minor allele 118G of the *OPRM1* gene was significantly decreased in the group of patients with chronic pain and opioid-treated, when compared to the opioid-naïve acute postoperative group without chronic pain (Janicki et al. 2006).

It was also reported that 118A>G SNP is significantly associated with alcohol addiction (Bart et al. 2005), methamphetamine (Ide et al. 2004) and heroin abuse (Tan et al. 2003). On the other hand, several groups reported lack of association between this genetic variant and alcohol or heroin abuse (Franke et al. 2001).

CYP Family

The cytochrome P450 (CYP) is a family of enzymes, highly expressed in liver, that play an important role in drug metabolism and exhibit considerable interindividual genetic variability correlating with their catalytic activity (Stamer and Stüber 2007; Allengaert and Anker 2008). Among high number of enzymes, CYP2D6 is one of the most interesting concerning genetic variability (Patti et al. 2008). The existence of more than 80 distinct allelic variants of *CYP2D6* correlated with a variety of metabolic capacity and phenotypes within the population (Daly et al. 1996; Marez et al. 1997).

There are at least fifteen alleles that encode nonfunctional gene products resulting from SNPs, gene deletion, aberrant splicing or premature translation termination (Mikus and Weiss 2005)

If an individual carries both nonfunctional alleles he has a severely impaired CYP2D6 activity and he is classified as a poor metabolizer (PM). In the other hand, if an individual carries at least one functional allele, he has normal CYP2D6 activity and thus he is called extensive metabolizer (EM). Among Caucasians, 5-10% are PMs, and present higher risk of developing toxic side effects to CYP2D6 drugs, compared to extensive metabolizers (Lundqvist et al. 1999), and 10-15% show impaired residual activity of CYP2D6, the so called intermediate metabolizers (IMs) (Mikus and Weiss 2005). In the Caucasian population, 1-5% of the subjects have a duplication or multiduplication of the *CYP2D6* gene, leading to the phenotype of ultra rapid metabolizers (UMs) (Lundqvist et al. 1999).

In other populations, such as Chinese or Japanese and African Americans, CYP2D6 alleles are differently distributed compared with Caucasians (Gaedigk et al. 2002; Ji et al. 2002). The prevalence of the PM phenotype in Asians ranges from 0–2% and from 1–2% are UMs.

This genetic predisposition for drug metabolism variability has important consequences on clinical results to pain therapy. As a portion of individuals is predisposed to drug inefficacy, others are prone to excessive side effects.

Tramadol and Codeine are commonly used as analgesics. They belong to the group of drugs metabolized by CYP2D6 and, consequently, the genetic variation mentioned previously influences their metabolism and efficacy on pain's treatment.

TRAMADOL

Tramadol is a synthetic opioid commonly used in the treatment of acute and chronic pain, which is known to be metabolized by CYP2D6 (Patti et al. 2008). Its mechanism of action is not fully understood, but it is known that CYP2D6 metabolizes tramadol to eleven desmethylated compounds, from which, O-desmethyltramadol (M1) predominates and has analgesic properties (Stamer et al. 2003).

Tramadol is used as a racemic mixture of two enantiomers: (+)-tramadol and (-)-tramadol. (+)-M1 is largely responsible for μ-opioid receptor mediated analgesia: it has 200 times higher affinity than the original compound, whereas (+)-tramadol and (-)-tramadol inhibit reuptake of neurotransmitters, such as serotonin and noradrenalin (Stamer and Stüber 2007). A study preformed in healthy volunteers (Enggaard et al. 2006) demonstrated that the (+)-M1 has a major impact on the analgesic effect of tramadol. However, the monoaminergic effect of tramadol itself seems to create an analgesic effect.

Research work on the efficacy of tramadol in postoperative analgesia showed that PMs consume higher doses of tramadol and require rescue medication, when compared to carriers of at least one wild-type allele (Stamer et al. 2003; Wang et al. 2006).

Clinical results were confirmed by analysis of serum concentration of (+)-M1 in different *CYP2D6* genotypes (Stamer et al. 2007). The PMs had negligible concentrations of this active metabolite, compared to heterozygous individuals, EM and UM. Non response rate to tramadol increased four-fold in PMs and a significantly higher number of patients were not satisfied with pain treatment.

CODEINE

Codeine is an anti-tussive and analgesic drug, which main metabolite is morphine that results from CYP2D6 metabolism (Kirchheiner et al. 2007). O-demethylation of codeine into morphine by CYP2D6 represents a minor pathway of codeine metabolism (accounting for less than 10 percent of codeine clearance) but is essential for its opioid activity (Dayer et al. 1988). More than 80 percent of codeine clearance (to inactive compounds) results from N-demethylation of codeine into norcodeine by CYP3A4 and the glucuronidation of codeine (Gasche et al. 2005).

In PM patients, codeine is an ineffective analgesic. Tyndale et al. (1997) has suggested that these individuals may have protection against opiate addiction, since they are unable to form active metabolites acting on μ-opioid receptors.

UM patients are prone to develop toxic effects, some of them lethal, after codeine administration (Gasche et al. 2005). Several clinical cases report intoxication related to codeine consumption. Voronov et al. (2007) describes a case of narcosis and apnea in a 29 month old child, two days after an uneventful minor surgery, to whom was administer codeine for pain treatment. This child was found out later to be an UM. Another child, a breastfed 13 days old neonate, died because his mother was taking codeine and he was a UM (Dayer et al. 1988). Respiratory depression was reported after administration of small dose of codeine in an

UM patient with an additional inhibition of CYP3A4 activity by other medication and transient reduction in renal function (Gasche et al. 2005) (Figure 3).

The *CYP2D6* genotype predicting UM resulted in about 50% higher plasma concentrations of morphine and its glucuronides compared to EM (Kirchheiner et al. 2007).

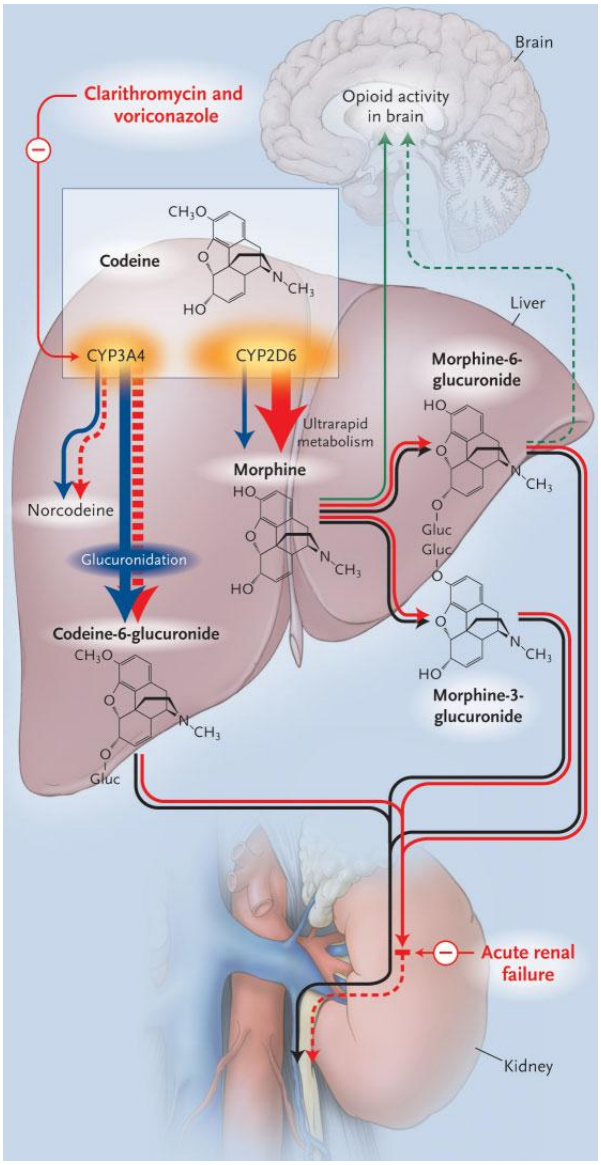

Figure 3 Codeine's metabolism. Cause of respiratory depression after acute renal failure. Adapted with permission from New England Journal

ADDITIONAL OPIOIDS

Other opioids like fentanyl (Tateishi et al. 1996) alfentanil (Klees et al. 2005), methadone and buprenorphine (Elkader and Sproule 2005) are among the drugs metabolized by CYP3A4 (Armstrong et al. 2009).

Meperidine is a synthetic opiate analgesic in which N-demethylation is catalized by CYP2B6 and 3A4, with 2C19 playing a minor role (Armstrong et al. 2009).

Genetic polymorphisms in *CYP3A4* have been identified (Gellner et al. 2001). Perera et al. (2009) found an haplotype tagging SNP 141689, located −7206 base pairs upstream of the *CYP3A4* gene, which significantly affects the transcriptional activation and enzyme activity. Clopidogrel (an antiplatelet agent) response variability is associated to CYP3A4 gene

IVS10+12G>A polymorphism which modulates its activity (Dominick et al. 2006). As SNPs in transcription factors regulating *CYP3A4* are still undisclosed it is likely that they are important contributors to human variation in CYP3A4 activity (Perera et al. 2009).

NON-OPIOID ANALGESICS

Non-opioid analgesics are commonly used in persistent mild pain or in association with opioid therapy in moderate to severe pain.

Non-steroidal anti-inflammatory drugs are metabolized by CYP2C9. Individuals with several variant alleles (*CYP2C9*2* and *CYP2C9*3*) have demonstrated decreased metabolic clearance compared with the ones carrying the wild-type allele (*CYP2C9*1*) (Ali et al. 2009). The allele *CYP2C9*2* is frequent among caucasians with approximately 1% of the population being homozygous carriers and 22% heterozygous (Zhou et al. 2009).

MC1R

The gene coding for melanocortin 1 receptor (*MC1R*) variants present supplementary appealing evidence of the potential for highly targeted analgesia based on sex and other differences (Webster 2008). *MC1R* is usually associated to red hair and fair skin in humans. Non function variants of the MC1R were associated with an increase analgesic response to κ receptor-mediated opioid analgesia (Diatchenko et al. 2007). Mogil et al. (2003) found that red – headed women with two *MC1R* variant required lower doses of the κ-opioid pentazocine to reach a specific level of analgesia, compared with all the other groups. In opposing, the authors also found that red-headed men did not experienced this increased analgesia rising the evidence for a gene-by-sex interaction in pain genetics (Diatchenko et al. 2007).

SLC6A4

Serotonergic neurons of the CNS are localized in clusters within the raphe nuclei, central grey and reticular formation. Nerve fibers arising from the caudal groups of serotonergic neurons form a descending system directly to the spinal cord and also project to cerebellum, pontine and midbrain structures, whereas ascending fibers originate from the rostral groups of serotonergic neurons and innervate almost all brain areas (Ciranna 2006).

The human serotonin (5-hydroxytryptamine, 5-HT) transporter (5-HTT) is encoded by one single gene, *SLC6A4*, which contains several known polymorphisms in its promoter region that affect the transcriptional efficacy of the 5-HTT coding gene (e.g. 5-HTTLPR, 5-HTT linked polymorphic region) (Kosek et al. 2009). The 5-HTTLPR consists of a 43-bp insertion/deletion yielding a short (S) allele and a long (L) allele. The short-allele reduces the transcriptional efficiency of the *SLC6A4* gene promoter, resulting in decreased 5-HTT expression and availability.

Kosek et al. (2009) found that the triallelic 5-HTTLPR was associated with individual differences in analgesic response to an opioid drug in healthy subjects.

As it will be mentioned further on the present review, the less active short allele of *SLC6A4* gene may be involved in the etiology of some clinical pain syndromes, such as migraine with aura and fibromyalgia.

PHARMACOGENOMICS OF PAIN AND CLINICAL SYNDROMES

Migraine

Migraine is a chronic and sometimes progressive disorder characterized by recurrent episodes of headache, which last from 4 to 72h, and associated symptoms (nausea / vomiting, photophobia / phonophobia) (Lipton and Bigal 2005). It affects people particularly during their productive years. Worldwide, according to the World Health Organization (WHO), migraine alone is 19th among all causes of years lived with disability.

Marziniak et al. (2005) disclosed that the frequency of the less active short allele of 5-HTT was increased in migraineurs with aura, but not in migraineurs without aura in comparison with control population. This indicates that the *SLC6A4* may be involved in the polygenic etiology of migraine with aura.

Several epidemiology studies reveal that migraine frequently runs in families (Honkasalo et al. 1995; Russel and Olesen 1995; Gervil et al. 1999; Ulrich et al. 1999). A rare type of migraine is familial hemiplegic migraine (FHM), which appears to be transmitted by an autossomal dominant mode of inheritance (Gardener 2006). FHM is associated to a mutation in *CACNL1A4* gene, located to chromosome 19p13 (Ophoff et al. 1996). As *CACNL1A4* gene encodes a brain-specific P/Q-type Ca^{2+} channel α1 subunit, FHM can be considered as a cerebral ion channel disorder. It is expressed in the cell bodies, dendrites and presynaptic neurons, most prominent in the cerebellar Purkinje cells (Jee-Young and Kim 2005).

Identification of FHM as channelopathy opens new avenues for the development of prophylactic treatment (Ophoff et al. 1996).

Complementary works explore the association between dopaminergic system and migraine. Although there is some contradiction most of the authors agreed in the association of dopamine D2 receptor coding gene (*DRD2*) and migraine. Peroutka et al. (1997) were one of the first groups studying this association. They had demonstrated that individuals with migraine with aura had an increased frequency (0.84) of the *DRD2* NcoI C allele when compared with controls, suggesting that activation of the D2 receptor could play a modifying role in the pathophysiology of migraine with aura.

De Sousa et al. (2007) found that a seven-repeat allele of the dopamine D4 receptor coding gene (*DRD4*) located at exon 3 variable number tandem repeat (VNTR) may have a protective factor for migraine without aura.

Recently, a mutation in the *SLC1A3* (glutamate-aspartate transporter) gene encoding the glutamate transporter EAAT1 (excitatory amino acid transporters) was identified in a patient with severe episodic and progressive ataxia, seizures, alternating hemiplegia, and migraine headache (Jen et al. 2005). This study may be important in introducing decreased glutamate uptake as a potential pathogenic mechanism for neuronal hyperexcitability and a potential pharmacological target in migraine (Montagma 2007).

Several new reports of linkage or genetic association are also available for migraine. Russo et al. (2005) reported a new locus of genetic determination for migraine with aura at 15q11 – q13, a region that contains 3 genes for GABA-A receptors.

Although all of these findings seem very attractive, the underlying pathophysiology mechanisms of migraine remain unknown (Gladstone 2007).

Migraine treatment develops along strategies, mostly based on empirical grounds (Montagma et al. 2005). Several drugs used for the treatment of attacks are unspecific, such as paracetamol (acetaminophen), a non-steroidal anti-inflamatory drugs. Only some drugs, like triptans, are more specific for migraine treatment (Ophoff et al. 2001; Tfelt-hansen and Brosen 2008). Triptans are 5-$HT_{1B/1D}$ agonists and are regarded as very effective acute migraine treatment. Eletriptan is metabolized by CYP3A4. Sumatriptan, rizatriptan and almotriptan are metabolized by monoamino-oxidase (MAO)-A. Zolmitriptan is metabolized by CYP 1A2 and the active metabolite by MAO-A (Tfelt-hansen and Brosen 2008). Genotyping for the genes coding for these three enzymes is not relevant for clinical practice, because the prediction of the phenotype is poor (Tfelt-hansen and Brosen 2008).

Low Back pain

Low back pain is a leading motive to job-related disability and is a frequent cause of chronic pain. Besides many possible causes, deterioration of spine and intervertebral discs are commonly mentioned. Physicians frequently considered these deteriorations as mechanical, but recent findings suggests the implication of genetic and biochemical mechanisms. A large population study in China exposed the association of *TRP2* allele polymorphism of *COL9A2* gene and degenerative disc disease (Jim et al. 2005). This allele codes for α2 chain of collagen IX and it was recently again indicated as one of the risk factors for the development and severity of degenerative disc disease in a Chinese Han population (Song et al. 2010).

Another study using finish population discovered that the presence of at least one *TRP3* allele increases the risk of lumbar disk disease for about threefold (Paassilta et al. 2001).

Fibromyalgia

Fibromyalgia is part of a group of psychiatric and medical disorders, generally named affective spectrum disorder (ASD), which commonly co-occur in individuals and coaggregate within families (Hudson et al. 2004; Bradley 2009). It is a syndrome characterized by widespread pain and diffuse tenderness and is considered to be a multifactoral disorder.

American college of rheumatology defined fibromyalgia as a chronic disorder characterized by the presence of widespread pain of at least 3 months duration followed by tenderness upon palpation of at least 11 of 18 predefined tender points throughout the skeletal system (Wolfe et al. 1990) (Table 1).

LOCALIZATION OF TENDER POINT	
Occiput	2 - at the suboccipital muscle insertions.
Low cervical	2 - at the anterior aspects of the intertransverse spaces at C5-C7.
Trapezius	2 - at the midpoint of the upper border.
Supraspinatus	2 - at origins, above the scapula spine near the medial border.
Second rib	2 - upper lateral to the second costochondral junction.
Lateral epicondyle	2 - 2 cm distal to the epicondyles.
Gluteal	2 - in upper outer quadrants of buttocks in anterior fold of muscle.
Greater trochanter	2 - posterior to the trochanteric prominence.
Knee	2 - at the medial fat pad proximal to the joint line.

Table 1 Localization of tender points in fibromyalgia diagnosis

Pain and tenderness are thus the defining features of the fibromyalgia syndrome. This central feature is currently attributed to an increase in central pain processing (Ablin et al. 2008).

It is now well established that fibromyalgia aggregates in families. Arnold et al. (2004) demonstrated, using 533 relatives of 78 probands with fibromyalgia, that fibromyalgia and reduced pressure pain threshold aggregates in families, and that fibromyalgia coaggregates with major mood disorders in families. Raphael et al. (2004) studied the comorbidity of fibromyalgia and major depressive disorder. They have found increasing rates of depression among women with fibromyalgia, establishing that this association was mainly due to an hereditary mediated risk for depression among those members affected with fibromyalgia.

A large study with twins performed in Sweden (Kato et al. 2006), concluded that genetic factors accounted for 48-54% of the total variance in chronic widespread pain. Furthermore, they observed no sex differences in either the type or magnitude of genetic influences.

Studies that have addressed the possible linkage of fibromyalgia to human leukocyte antigens (HLA) are rare. One study found an excessive representation of DR4 antigen: 64% versus 30% in healthy controls (Burda et al. 1986). Subsequent studies confirmed the existence of a possible gene for fibromyalgia that was linked with HLA region (Yunus et al. 1999) However, an additional study failed to support this association (Biasi et al. 1994).

The neurotransmitter serotonin has also been implicated in the pathophysiology of fibromyalgia syndrome. Genotypes' analysis of the promoter region of SLC6A4 gene in patients with fibromyalgia showed a higher frequency of the homozygous genotype for the shorter allele, compared with healthy controls. This subgroup exhibited higher mean levels of depression and psychological distress. These results support the notion of altered serotonin metabolism in at least a subgroup of patients with fibromyalgia (Offenbaecher et al 1999; Gürsoy et al. 2001).

It was further was suggested that there was another polymorphism associated with fibromyalgia at position 102 in the 5-HT2A receptor coding gene, 5HT2A102T>C (Gürsoy et al. 2001). The proportion of T/T genotype that was significantly correlated with the lowest pain threshold was not increased in fibromyalgia patients. The authors concluded that this polymorphism of *5-HT2A* gene was not associated with the etiology of fibromyalgia, but the T/T genotype could be responsible for psychiatric symptoms of fibromyalgia syndrome.

Additional studies investigated the association of serotonin receptors coding genes, *5HT3A* and 5*HT3B* in fibromyalgia patients (Frank et al. 2004). Mutation analysis of *5HT3A* revealed one novel in addition to five known sequence variations; analysis of 5*HT3B* showed seven formerly described mutations and one novel alteration. The authors suggested that future pharmacogenomic studies would help to determine possible relevant associations.

The possible association between *COMT* and fibromyalgia was studied by Gursöy et al. (2001). They concluded that *COMT* Val158Met polymorphism could be involved in the pathogenesis of fibromyalgia and therefore have a potential pharmacological importance in the treatment of fibromyalgia patients.

Further studies by Tander et al. (2008), in contrast to what has been presented above showed no association between fibromyalgia patients and *5HT2A* and *COMT* genes.

Neurophysiological studies (Wood et al. 2007) revealed that the disrupted dopaminergic reactivity in fibromyalgia patients could be a critical factor underlying the widespread pain and discomfort in fibromyalgia and thus therapeutic effects of dopaminergic treatments should be explored. Buskila (2004) and Neumann (2005) reported an association between fibromyalgia and the *DRD4* gene exon 3 repeat polymorphism and its relationship to novelty seeking personality traits. It was shown that dopaminergic, rather than serotoninergic

neurotransmission, is altered in fibromyalgia, suggesting increased sensitivity or density of D2 dopamine receptors in fibromyalgia patients (Malt et al. 2003).

As substance P levels have been clearly shown to be elevated in the cerebral spinal fluid of fibromyalgia patients, an attempt has been made to find an association between the tachykinin NK1 substance P receptor and fibromyalgia. A trend towards an increase frequency of the G>C substitution at position 1354 in the 3' untranslated region of the NK1 receptor coding gene was identified, but without reaching statistical significance (Ablin et al. 2008).

All the polymorphisms mentioned may contribute to the etiology, expression or response to treatment in Fibromyalgia patients and therefore they may contribute to a better understanding of the disease and be relevant in therapeutic intervention..

CONCLUSION

Pharmacogenomics is an imperative field in pain research and there have been major achievements during the last years related to increased knowledge and technological progression. Studies showed a firm association between pain and genetic markers, including polymorphisms.

It has been revealed that response to drug therapy depends on individual genetic variability and, in some circumstances, it can be predicted. Genetic discrimination approach will increase the effectiveness of pain treatment.

Some chronic pain conditions are also associated to genetic factors, which can be useful for diagnosis. Furthermore, it may be essential to understand the pathophysiology of each disease and to the development of novel drug targets.

The capacity to predict chronic pain condition development and drug response allows the improvement of pain management.

A pharmacogenomics approach will contribute significantly to a new perspective on pain management and future directions point towards a more detailed medical diagnosis and an adjusted prescription with better accomplishments.

The most promising genes for pharmacogenomic analysis of pain are *COMT, OPRM1, CYP450* family, *MC1R* and *SLC6A4*, according to the existing facts and to the knowledge of pain physiology. However, we cannot exclude that other genetic factors may be involved.

Although contradictory results have been produced and more advances must be achieved, pharmacogenomics approach represents a powerfull tool to the management of both chronic and acute pain, in order to improve patients quality of life.

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Abbreviations' list

5-HT	5- hydroxytryptamine
5 – HTT	serotonin transporter
5 – HTTPR	serotonin transporter linked polymorphic region
ACC	anterior cingulate cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	adenosine triphosphate
ASD	affective spectrum disorder
APS	average pain sensitivity
CNS	central nervous system
COMT	catechol – O – methyltransferase
CYP	cytochrome P450
D2	dopamine receptor 2
DLF	dorsolateral funiculus
EM	extensive metabolizer
FHM	familial hemiplegic migraine
fMRI	functional magnetic resonance
GABA	γ-aminobutyric acid
HLA	human leukocyte antigen
HPA	high pain sensitivity
IM	intermediate metabolizer
LPS	low pain sensitivity
M1	O-desmethyltramadol
M6G	morphine-6-glucuronide

MAO	monoamino-oxidase
MB – COMT	membrane bound catechol – O – methyltransferase
MC1R	melanocortin 1 receptor
MCS	motor cortex stimulation
Met	methionine
mRNA	messenger ribonucleic acid
NMDA	N-methyl D-aspartate
OPRM	opioid receptor μ
PAG	periaqueductal gray matter
PET	positron emission tomography
PFC	prefrontal cortex
PM	poor metabolizer
RVM	rostral ventromedial medulla
S – COMT	soluble atechol – O – methyltransferase
SI	primary somatosensory
SII	secondary somatosensory
SNP	single nucleotide polymorphism
UM	ultra rapid metabolizer
Val	valine
VLO	ventrolateral orbital
VNTR	variable number tandem repeat
WHO	world health organization

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