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## Abstract

Human pain causes untold misery and suffering, with major impact on functioning and resources. Recent advances in genetics have revealed that subtle changes in DNA could partly explain the variation in individual differences in pain. Various genes encoding for receptors are now known to play a major role in the sensitivity, perception and expression of pain. The fields of epigenetics and proteomics hold promises in the way pain could be treated and managed in future.

## Keywords

Chronic pain, fibromyalgia, hereditary sensory and autonomic neuropathies, musculoskeletal pain, nociceptive pain, genetics, pain, post-operative, pain insensitivity, congenital, pain perception, temporomandibular joint dysfunction syndrome

## Introduction

Pain is one of the commonest reasons patients seek medical attention. There is a high degree of individual variation in pain, very likely due to complex environmental and multiple genetic factors. There is growing evidence that a number of genes play a critical role in determining pain sensitivity, pain reporting and susceptibility to developing chronic pain and their response to surgical outcomes primarily, pain.<sup>1</sup> The study of pain in humans is very challenging, as pain is a very complex trait influenced by race, ethnicity,<sup>2</sup> gender<sup>3</sup> and the social context and interpretation<sup>4</sup> of the pain experience.

There are well-reported inter-individual differences in pain reporting as well as varying responses to treatment and management.<sup>5,6</sup> The past decade has revealed to us the established role of genetics in pain, with significant advances in the fields of 'genome wide association studies' (GWAS), 'single nucleotide polymorphisms' (SNPs) and the role of epigenetics in the modulation of pain (Table 1).

## Useful terminologies

*Polymorphism.* Genetic variants that occur in the population.

*Genome.* The entire hereditary information of an organism. It is encoded either in the DNA, or for many types of virus, in the RNA. The genome includes both the genes and the non-coding sequences of the DNA/RNA<sup>8</sup>

*SNP.* A DNA sequence variation that occurs when a single nucleotide (A, T, C or G) in the genome sequence is altered. SNPs can act as biological markers, helping to locate genes that are faulty or associated with disease. They can also be used to track the inheritance of diseases within families.

*Epigenetics.* This term is conventionally used to describe how the reading of the genetic information can be influenced by the non-DNA coded, often environmental factors.

*Human Genome Project.* The International Human Gene Sequencing Consortium published the complete sequence of the human genome in 2003.

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**Table 1.** Historical landmarks in genetics.

Year	Discovery	Team/work
1953	DNA structure	Watson, Crick, Franklin and Wilkins
1961	Genetic code	Nirenberg – he also explained the ‘codons’ <sup>a</sup>
1975	DNA sequencing	Sanger, Maxam and Gilbert
2000	First draft of the human genome sequenced	
2003	Completion of human genome sequencing	HGSC and Celera
2005	Launch of the International HapMap (haplotype map) Project <sup>7</sup>	
2007	Human genome SNP map reported	3.1 million SNPs

HGSC: Human Genome Sequencing Consortium; SNP: single nucleotide polymorphism.

<sup>a</sup>Codon: a codon is a sequence of three bases of the DNA (adenine, guanine, cytosine and thymine) that specify each of the 20 amino acids.

**GWAS.** Study, which involves identifying regions of the human genome, where genetic influences on disease(s) may reside.

**Haplotype.** A combination of alleles (DNA sequences) at adjacent loci on a chromosome that are inherited together.

**Alleles (allelomorph).** One member of a pair of genes that is located at a specific position on a specific gene.

## Is there a ‘pain gene’?

A pain gene has been described as ‘a gene for which there are one or more polymorphisms that affect the expression or the functioning of its protein product in a way that affects pain response’.<sup>9</sup> Pain genes are discovered either by the study of large families termed ‘linkage analysis’ or by the study of large cohorts of matched, but unrelated, individuals with and without the condition – known as ‘association analysis’. Yet, another method used by geneticists and basic scientists is studying pain behaviour in twins. One of the first twin studies (experimental, female only) by Norbury et al.<sup>10</sup> showed a statistically significant genetic component (varying between 22% and 55%) in pain sensitivity. In another twin study by William et al.,<sup>11</sup> looking at musculoskeletal pain from different sites, there was a significant similarity among monozygotic (MZ) twins, compared to dizygotic (DZ) twins in reporting pain. In both studies mentioned above, MZ twins showed a strong correlation to both experimental and musculoskeletal pain, compared to DZ twins, demonstrating a strong genetic component to pain heritability.

## The role of ion-channels in pain modulation

Ion-channels are membrane-spanning proteins, with the principal task of selectively transporting ions into

or out of the cell. These channels can be divided broadly into two groups – *voltage gated* and *ligand gated*. The human genome is known to contain over 400 channel genes.<sup>8</sup>

### Voltage-gated channels

Voltage-gated sodium and calcium channels are closely related members of the so-called ion-channel super family.<sup>12</sup> Among all the ion-channels, the voltage-gated sodium-channels (Na<sub>v</sub>) are the most widely distributed and most investigated. Nine voltage-gated sodium-channel subtypes have been identified to date. Of these, Na<sub>v</sub>1.3, Na<sub>v</sub>1.7, Na<sub>v</sub>1.8 and Na<sub>v</sub>1.9 are expressed primarily in sensory nerves.<sup>13</sup> Unfortunately, because of their complex chemical structure, wide distribution and important functions, they can be subject to a wide variety of mutations – inherited and SNPs – and this can in turn cause rare conditions of hypo-/hyper-excitability in the context of pain-related syndromes.<sup>14,15</sup> Changes in Na<sup>+</sup> channels in neuropathic pain involve a complex pattern of both upregulation and downregulation, both in damaged and undamaged fibres.

### Sodium-channel mutation and small fibre neuropathy

Patients with small fibre neuropathy (SFN) present with neuropathic pain and autonomic dysfunction. The pathology is believed to be selective injury to the thinly myelinated A-delta and un-myelinated C fibres. Common conditions that cause SFN are diabetes mellitus, impaired glucose tolerance, alcohol abuse, toxins like arsenic and drugs like metronidazole, statins, vincristine, paclitaxel and cisplatin, to name a few. Diseases like coeliac disease, sarcoidosis, HIV and Fabry’s disease have also been described as causing SFN.<sup>16</sup> Single amino acid substitutions in the *SCN9A* gene (gene encoding the voltage-gated Na Channel

**Table 2.** Genes affecting ion-channel function.

Encoding gene	Risk of pain	Site/condition
<i>SCN9A</i> (gene encoding for Na <sup>+</sup> Channel)	Increased	Sciatica, OA, pancreatitis, post-lumbar discectomy and phantom limb pain
<i>KCNS1</i> (gene encoding for K <sup>+</sup> Channel)	Increased	Sciatica, lumbar pain, amputation, phantom pain and experimental pain
<i>CACNA2D3</i> (alpha 2 delta 3 subunit of voltage-dependent Ca <sup>2+</sup> channel)	Reduced	Acute noxious heat as well as chronic back pain following disc surgery
<i>CACNG2</i> (gene encoding for the gamma 2 subunit of voltage-dependent Ca <sup>2+</sup> channel, also known as 'stargazin')	Increased	Development of chronic post-surgical pain after full or partial mastectomy

OA: osteoarthritis.

1.7), resulting in a gain-of-function change in the Na<sub>v</sub>1.7 channel, have been implicated in two cohorts of patients with idiopathic SFN.<sup>17</sup> A gain-of-function mutation in the Na<sub>v</sub>1.8 channel, causing painful peripheral neuropathy, has been described recently by Faber et al.<sup>18</sup>

### Sodium-channelopathy and post-operative pain sensitivity

A recent study by Duan et al.<sup>19</sup> showed that a SNP lesion in *SCN9A* may decrease post-operative pain sensitivity in a cohort of patients (Table 2).

### Pain conditions inherited as a 'Mendelian' trait

Sometimes, the relationship between a specific gene and a pain condition can be quite direct and informative – as in rare Mendelian inherited painful conditions. Although very rare, both congenital insensitivity to pain (*loss-of-function mutation*) and amplification of pain (*gain-of-function mutation*) have been described. The study of certain individuals/families with extremely rare, altered pain conditions has helped basic scientists unravel mutations in a sodium-channel, the Na<sub>v</sub> 1.7, which is preferentially expressed within the dorsal root ganglion (DRG) neurons, particularly nociceptive cells, and sympathetic ganglion cells. Other rare pain conditions affecting genes encoding for the Ca<sup>2+</sup> channel, Na<sup>+</sup>/K<sup>+</sup> ATPase pump, among others, have also been described, which include familial hemiplegic migraine (FHM) type 1 and FHM type 2, respectively.

### Insensitivity to pain

This is inherited as a *loss of function* mutation in Na<sub>v</sub>1.7 channel, resulting in a congenital insensitivity to pain. The gene affected is the *SCN9A* (voltage-gated sodium-channel) gene, and is inherited as an autosomal

recessive trait. Recently, 10 new variants of the *SCN9A* gene have been identified which cause the 'channelopathy-associated insensitivity to pain' or 'congenital indifference to pain' (Table 3).<sup>20,21</sup>

### Amplification of pain

1. *Primary erythromelalgia*. This is described as a 'chronic inflammation/burning pain due to a *gain of function*' mutation of Na<sub>v</sub>1.7 channel. This is an autosomal dominant disorder with symptoms typically including episodes of burning pain and erythema, primarily in the extremities, triggered by exercise or heat. To date, a total of 14 *SCN9A* mutations have been linked to this disorder. They are all *gain-of-function mutations*.<sup>22</sup>
2. *Paroxysmal extreme pain disorder (PEPD)*. Mandibular, ocular and rectal pain due to an impaired Na<sub>v</sub>1.7 channel inactivation. This is an autosomal dominant painful neuropathy, with most cases linked to having a *gain-of-function mutation* in *SCN9A*.<sup>23</sup>
3. *FHM* – types 1–3

*FHM 1*. The FHM 1 gene *CACNA1A* (gene for the P/Q type of calcium channel) is associated with voltage-gated neuronal calcium channel. Functionally, FHM1 mutations exhibit a gain-of-function character.

*FHM 2*. The FHM2 gene *ATP1A2*, encodes the alpha-2 subunit of a sodium–potassium ATPase exchange pump. There is a loss of function of Na/K ATPase activity, in which the pump is less effective at transporting Na<sup>+</sup> and K<sup>+</sup> ions across the cell membrane.

*FHM 3*. The FHM3 gene *SCN1A* encodes the pore-forming alpha subunit of Na<sub>v</sub>1.1, a neuronal voltage-gated sodium-channel.

*FHM4 and sporadic hemiplegic migraine (SHM)*. A rare and novel type of FHM. The SHM is also extremely rare.

**Table 3.** Rare chronic pain conditions due to Mendelian inheritance – Mendelian inheritance with absent or reduced perception/response to pain

Condition	Mode of inheritance	Encoding gene
HSAN I	Autosomal dominant	<i>SPTLC1</i>
HSAN II	Autosomal recessive	<i>HSN2</i>
HSAN III	Autosomal recessive	<i>IKBKAP</i>
HSAN IV (congenital insensitivity to pain with anhidrosis-CIPA)	Autosomal recessive	<i>NTRK1</i>
HSAN V (congenital insensitivity to pain with partial anhidrosis)	Autosomal recessive	<i>trkA</i>

HSAN I–V: hereditary sensory and autonomic neuropathy types I–V; SPTLC1: serine palmitoyltransferase; HSN2: hereditary sensory neuropathy type 2, IKBKAP-I: kappa B kinase complex-associated protein; NTRK1: neurotropic tyrosine kinase receptor type 1; trkA: tyrosine kinase A.

## Non-Mendelian inherited pain conditions

### *Altered pain perceptions/processing associated with SNPs*

Catecholamines which include nor-adrenaline, adrenaline and dopamine have complex and multiple functions in the brain and spinal cord, which include pain perception and processing, as well as increasing/decreasing sensitivity to pain.<sup>24</sup> Catechol-*O*-methyltransferase, encoded by the *COMT* gene in humans, is one of several enzymes that degrade dopamine, nor-adrenaline and adrenaline. We now know that genes encoding for catechol-*O*-methyltransferase (*COMT*), guanosine triphosphate (GTP) cyclohydrolase 1 (*GCH1*) and the voltage-gated sodium-channels, especially Na<sub>v</sub>1.9, play a significant role in human pain perception, including cancer pain.<sup>25–27</sup>

Na<sub>v</sub>1.9 is believed to be an effector of the hypersensitivity produced by multiple inflammatory mediators, on nociceptive peripheral terminals and therefore plays a key role in mediating peripheral sensitization. Polymorphism of the *SCN1A* (Na channel, voltage-gated, type II alpha) gene, which encodes for the Na<sub>v</sub>1.9, has been shown to alter thermal, but not mechanical, hypersensitivity in experimental mouse models.<sup>28</sup>

*Fibromyalgia.* With an estimated prevalence of 2–4%, and a reported higher incidence in females, it has been one of the commonest ‘pain conditions’ which has been studied. Patients with fibromyalgia (FM) typically report widespread aches and pains, poor concentration, memory and often broken, unrefreshing sleep. Functional abnormalities in the central nervous system processing of pain and other sensory stimuli is believed to play a key role in FM. Irritable bowel syndrome (IBS), temporomandibular joint disorder (TMJD), chronic fatigue syndrome (CFS), interstitial cystitis and tension and migraine headache are other common conditions which are

believed to share similar mechanisms as in FM.<sup>29</sup> Specific genetic polymorphisms involving the serotonin 5-HT<sub>2A</sub> receptor, serotonin transporter, dopamine 4 receptor and *COMT* polymorphisms have been reported more frequently in patients with FM.<sup>30</sup>

But, what exactly is the proposed role of *COMT* in pain transmission? Recently, several SNPs and haplotypes composed of SNPs, among genes involved in catecholamine metabolism have been identified.<sup>5</sup> Zubieta et al.<sup>31</sup> showed that the Val158Met polymorphism in the *COMT* gene was responsible for differential pain sensitivity in humans, in part by modulating opioidergic activity. In addition to modulation of opioidergic activity, it has also been shown by Nackley et al.<sup>32</sup> that *COMT* acts by mediating effects on β<sub>2</sub> and β<sub>3</sub> adrenergic receptors. *COMT* inhibition increases pain sensitivity through activation of adrenergic receptors β<sub>2</sub> and β<sub>3</sub>. In experimental animals, depressed *COMT* activity resulted in increased mechanical and thermal pain sensitivity, and this was completely blocked by propranolol (non-selective β antagonist) or by the combined administration of selective β<sub>2</sub> and β<sub>3</sub> antagonists. Administration of β<sub>1</sub>, α adrenergic or dopaminergic receptor antagonists failed to alter *COMT*-dependent pain pathways. Interestingly, in a 1958 British Birth Cohort Study, Hocking et al.<sup>33</sup> reported that genetic variation in the β<sub>2</sub> adrenergic receptor, not *COMT*, predisposes to chronic pain states. The knowledge of these genetic polymorphisms may help clinicians to sub-group patients with FM and associated disorders and help to design better pharmacologic treatment approaches.

*GCH1 (gene encoding GTP cyclohydrolase).* GTP cyclohydrolase is the rate-limiting enzyme for tetrahydrobiopterin (BH<sub>4</sub>) synthesis. This is an essential cofactor in the biosynthesis of biogenic amines and nitric oxide (NO). SNPs of the *GCH1* gene have been shown to be associated with varying conditions like decreased persistent low back pain after discectomy, decreased response to heat, ischaemic and

**Table 4.** Genes encoding the neurotransmitter systems and their role in pain.

Encoding gene	Nature of pain	Site
<i>GCH1</i> (gene encoding cyclohydrolase 1)	Decreased risk	Experimental and post-discectomy pain Decreased pain reporting and decreased specialized pain therapy following diagnosis of cancer
<i>SLC6A4</i> (serotonin transporter gene)	Increased risk	Chronic widespread pain and emotional modulation of pain
<i>ADRB2</i> (gene coding for $\beta$ 2 adrenergic receptor)	Increased risk	Chronic widespread pain and self-reporting for the extent and duration of pain.
<i>HTR2A</i> (gene coding for serotonin receptor 2A)	Increased risk	Chronic widespread pain and post-surgical pain

pressure pain and reduced incidence of low back pain.<sup>34</sup> A rare loss-of-function mutation of the *GCH1* coding regions has been shown to cause ‘hereditary, progressive levodopa responsive dystonia’, a severe neurologic disease (Table 4).<sup>35</sup>

### Pain and the *OPRM1* gene (opioid receptor, mu 1)

The opioids, both endogenous and exogenous, are ligands at the opioid receptors. Of these, the mu receptor, encoded by the gene *OPRM1*, has been shown to have several variants, of which, the 118 A>G (adenine to guanine) has been studied extensively.

Genetic variations in the mu-opioid receptor gene have been associated with variation in opioid requirement/response, in diverse settings. These include acute post-operative pain, cancer pain and chronic non-cancer pain.<sup>36</sup>

In cancer pain patients with the *OPRM1* (gene coding for mu-opioid receptor) 118GG genotype, a higher dose of morphine was required, compared to carriers of the AA genotypes. The 118GG genotype is believed to decrease the effects of opioids on pain-related activation, mainly in those regions of the brain involved with processing the intensity of pain, rather than the affective response by the patient.<sup>37</sup> In both animal models and humans, studies have shown that mu-opioid receptor agonists produce a bimodal response – an initial brief period of intense analgesia followed by a delayed onset of persistent and widespread hyperalgesia.<sup>38,39</sup> Polymorphisms in *OPRM1* and *COMT* gene, in combination, may also be important modulators of opioid efficacy, as shown by Reyes-Gibby et al.<sup>37</sup>

### Pain reporting and SNPs

There is some evidence that SNPs in critical genes can play a role in the reporting of pain by patients as described below.

### *CASP9* (aspartic acid specific protease) (caspase 9)

A SNP within this gene has been shown to increase self-reporting of pain, without effects on the progress of the disease itself.<sup>40</sup>

### *IL16* gene encoding for *IL16* (Interleukin 16)

Reporting of pain in females diagnosed with endometriosis has been shown to be higher in a polymorphism in the *IL16* gene. The gene has also been linked to a higher incidence of endometriosis (Table 5).<sup>42</sup>

### Epigenetics

This term is used to describe the link between the ‘gene’ and the ‘environment’. Factors implicated are age, nutrition, environmental chemicals, social context and so on. There is growing evidence that epigenetic mechanisms can silence the expression of pro- or anti-nociceptive genes. Processes such as histone modifications and DNA methylation have been known to be associated with altering many neural functions, including synaptic plasticity, memory and learning.<sup>43</sup> Epigenetic mechanisms have also been implicated in the transition from acute to chronic pain, as well as its role in the development of chronic post-surgical neuropathic pain.<sup>44</sup> Epigenetic, as well as genetic, mechanisms have been implicated for diverse pain conditions like ‘human bladder pain syndrome’, as well as primary headaches, migraine and cluster headache.

### Challenges in pain genetics

The breakthrough in mapping the whole human genome along with GWAS<sup>45</sup> has led to rapid advances in the knowledge of human diseases and causative factors, especially the genetic basis of disease.

**Table 5.** Summary of genes and effect on pain/analgesia.

Genes facilitating/ amplifying pain	Genes which confer protection/decrease in pain	Genes involved in the modulation of analgesic efficacy
<i>KCNS1</i>	<i>COMT</i>	<i>COMT</i>
<i>SCN9A</i>	<i>OPRM1</i>	<i>MC1R</i>
<i>ADRB2</i>	<i>TRPV1*</i>	<i>OPRM1</i>
<i>H2TRA</i>	<i>MC1R</i>	<i>CYP2D6</i>
<i>CACNG2</i>	<i>GCH1</i>	<i>ABCB1</i>
<i>IL16</i>	<i>CACNA2D3</i>	

Source: Binder et al.<sup>41</sup>

*KCNS1*: voltage-gated potassium channel; *H2TRA*: serotonin; *ADRB2*:  $\beta$  2 subtype adrenergic receptor; *COMT*: catechol-*O*-methyl transferase; *MC1R*: melanocortin receptor; *GCH1*: GTP cyclohydrolase.

\*TRPV1: the 1911 A>G polymorphism was significantly associated with altered heat pain thresholds.

In pain medicine, this has led to the identification of ‘pain genes’ (as described earlier) – genes that influence pain behaviour, prediction of post-operative drug requirement and persistence of pain and possible ‘gene therapy’ for neuropathic pain conditions.

In humans, pain is a complex trait – a personal experience – with multiple, complex interplay between genetic, neurobiological, psychosocial and environmental influences. A single disease itself can have varying, confounding influences in its ‘cause and effect’. A common condition like chronic low back pain can have a bewildering array of genetic influences as well as SNPs.<sup>46</sup> Till date, GWAS has been limited in pain medicine. This is due to the complexity of finding a large number of subjects with identical pathology and a corresponding, matched control.

Nevertheless, improved techniques in breeding rodents and association studies have already identified the *CACNG2* as a ‘neuropathic pain susceptibility gene’.<sup>47</sup> The discovery that genes encoding for mu-opioid receptors, serotonergic systems and voltage-gated ion-channels are also involved in pain processing/modulation takes us ever closer to developing a simple blood test, which one day will predict which patient is prone/less prone to develop pain after surgery, as well as a patient’s response to drug(s). The AmpliChip® is such a device which is used to determine the genotype of a patient in terms of two cytochrome P<sub>450</sub> enzymes – 2D6 and 2C19. This has been used to detect metabolism of drugs that include codeine, anti-depressants and anti-psychotics.<sup>48</sup> Goldberg et al.<sup>49</sup> reported a successful trial of XEN402 (a novel Na<sub>v</sub>1.7 antagonist), in patients with the inherited erythromelalgia syndrome, compared to placebo, in four patients.

### Advances in gene therapy for pain – are we there yet?

Gene therapy has made great strides in cancer treatment since the late 1990s. Pain treatment with gene(s) is

unique – it might involve initiating ‘de novo’ expression of an ‘anti-nociceptive’ gene that is not normally present in the target cell or, decreasing the expression of an active ‘pro-nociceptive’ gene in those cells. Gene therapy for pain still remains in its infancy, but there are several agents being trialled, looking at the various voltage-gated channels for future therapy. Novel experimental therapies using viral vectors, including adenoviral, adeno-associated viral, lentiviral and herpes simplex virus (HSV) vectors have been tried for cancer pain.<sup>50,51</sup> Gene therapy-based approaches to treat neuropathic cancer pain have been trialled.<sup>52</sup> Phase I clinical trial of NP2 (NP2 is a replication-defective, HSV-based vector, expressing human pro-enkephalin (PENK)) has been completed.<sup>53</sup> This was a relatively small study involving 10 subjects, with no placebo control, all who had intractable focal pain caused by cancer. Subjects receiving the low dose of NP2 (NP2 was injected intra-dermally into the dermatome corresponding to the radicular distribution of pain) reported no substantive change in pain, whereas subjects in the middle- and high-dose cohorts reported pain relief, as assessed by the Numerical Rating Scale (NRS) and Short Form McGill Pain Questionnaire (SF-MPQ). A phase II study has been ongoing since January 2011, with an estimated study completion date of November 2013.<sup>54</sup>

Advances in stem cell research and regenerative medicine may hold keys for future pain treatments. Treatment of painful neuropathy by using neuronal stem cells has been shown in an animal model recently.<sup>55</sup> Gene therapy-based strategies could soon evolve as a novel approach to pain management, not only for cancer but for pain associated with a number of other disorders.

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## Conflict of interest

The author declares that there is no conflict of interest.

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