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Review

Pain, analgesia and genetics

Arjun Muralidharan and Maree T. Smith

The University of Queensland, Centre for Integrated Preclinical Drug Development and School of Pharmacy, Steele Building, St Lucia Campus, Brisbane, Queensland, Australia

Abstract

Objectives In the clinical setting, there is marked intersubject variability in the intensity of pain reported by patients with apparently similar pain states, as well as widely differing analgesic dosing requirements between individuals to produce satisfactory pain relief with tolerable side-effects. Genetic and environmental factors as well as their interaction are implicated, and these are discussed in this review.

Key findings Pioneering work undertaken in mice more than a decade ago, showed a strong genetic contribution to levels of nociception/hypersensitivity as well as levels of antinociception produced by commonly available analgesic agents. To date more than 300 candidate 'pain' genes have been identified as potentially contributing to heritable differences in pain sensitivity and analgesic responsiveness in animals and humans, with this information available in a publicly accessible database http://www.jbldesign.com/jmogil/enter.html. Since then, many genetic association studies have been conducted in humans to investigate the possibility that single nucleotide polymorphisms (SNPs) in an individual gene may explain drug inefficacy or excessive toxicity experienced by a small subset of the whole population who have the rare allele for a particular SNP.

Summary Despite the fact that SNPs in more than 20 genes that affect pain sensitivity or contribute to interindividual variability in responses to analgesic medications have been identified in the human genome, much of the data is conflicting. Apart from deficiencies in the design and conduct of human genetic association studies, recent research from other fields has implicated epigenetic mechanisms that facilitate dynamic gene-environment communication, as a possible explanation.

Keywords analgesia; genetic association studies; interindividual variability; pain; single nucleotide polymorphism (SNP)

Introduction

Globally, the prevalence of chronic pain is high at 15–20% of the adult population, with pain severity ratings given by patients encompassing not only the intensity of the nociceptive stimulus but also the individual's affective/emotional response to that stimulus.[1] This in turn results in marked interindividual variability in reported levels of pain intensity for apparently similar pain states.

Despite great advances in our understanding of the neurobiology of chronic pain in the last two decades, translation of the vast wealth of basic science information into new analgesic agents for clinical use has been painstakingly slow. For this reason, the medications currently available for prescribing by frontline clinicians for alleviation of pain in patients remain similar to those available a decade or more ago.

Adding to the challenge of clinical pain management is the widely differing analgesic drug dosing requirements to evoke satisfactory pain relief with tolerable side-effects in individuals. This marked intersubject variability is underpinned by interacting genetic and environmental factors (Figure 1) with the latter including age, sex, status of hepatic and renal function, lifestyle variables (e.g. smoking and alcohol consumption), co-morbidities and other concurrent medications.[2,3] In addition, interindividual differences in genetic traits not only affect pain sensitivity but also the pharmacokinetics and pharmacodynamics of medications used to alleviate pain.[3]

Based on the assumption that suitably robust genetic associations could be identified between levels of pain reported and analgesic drug dosing requirements, and particular genetic profiles in patients, the prospect of point-of-care genotyping to assist clinicians to

Correspondence: Maree T. Smith, The University of Queensland, Centre for Integrated Preclinical Drug Development and School of Pharmacy, St Lucia Campus, Brisbane, Queensland 4072, Australia.
E-mail: maree.smith@uq.edu.au

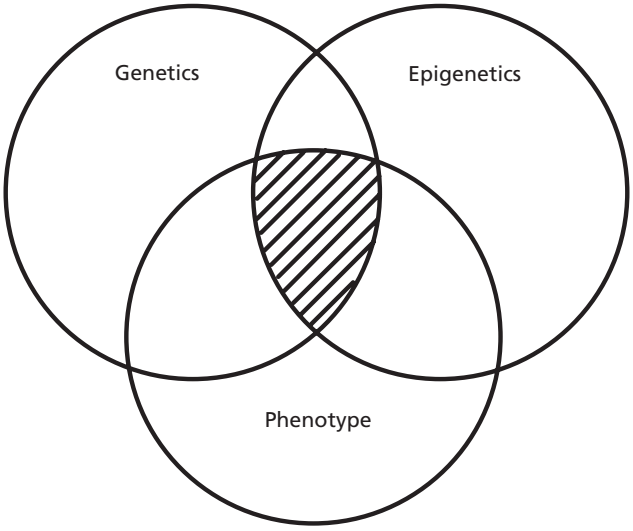

Figure 1 Schematic diagram illustrating that gene-environment communication via epigenetic mechanisms has the potential to influence the observed phenotype.

individually tailor analgesic drug therapy, was predicted to become routine. However, this is currently not the case and the underlying issues are addressed herein.

In the following sections, an overview of findings from heritability studies of pain (nociception) and analgesia (antinociception) in laboratory animals as well as those of human genetic association studies conducted over the last decade, is presented as a means of gaining insight into the marked interpatient variability in analgesic dosing requirements. A brief overview of insights from recent research in other fields that shed light on mechanisms underpinning gene-environment communication (epigenetics) is presented also.

Rodent Studies and Pain Genetics

Pioneering work by Mogil *et al*.[4] just over a decade ago using quantitative sensory trait analysis in 11 different mouse strains across 12 different testing modalities, showed clear heritability of pain-related traits when assessed using thermal, mechanical and chemical measures of nociception. Their findings were characterized by marked between-strain differences in each pain test with a 1.2–54-fold range in nociceptive sensitivity.[4] Subsequent work by the same laboratory extended these findings to measures of hypersensitivity after induction of inflammatory and neuropathic pain states in mice.[5,6] Impressively, they found a 30–76% genetic contribution to levels of nociception/hypersensitivity in their mouse studies.[4,5] Between-strain differences in sensitivity to the antinociceptive effects of morphine in mice were also shown.[7] Since then, multiple groups have identified candidate genes potentially underlying these heritable differences.[3] To date, studies using animal pain models have identified 334 'pain' genes with this information available in a publicly accessible database (http://www.jbldesign.com/jmogil/enter.html; accessed May 20th 2011).[8] This database has proven an invaluable resource for identifying genes for investigation in genetic association studies of pain and analgesia in humans.[3]

In mouse studies, between-study environmental differences including cage density, experimenter, housing, humidity, habituation to the testing procedures, season, time of day, all have the potential to interact with genotype to alter the observed phenotype.[9] Hence, by extrapolation, between-study differences in environmental factors will potentially influence the outcomes of studies designed to investigate relationships between genotype and pain phenotypes in humans, and the impact of the gene-environment interaction should not be underestimated.

Single Nucleotide Polymorphisms in Target Genes

In humans, a single nucleotide polymorphism (SNP) is a DNA sequence variation at a specific location in the genome, occurring when a single nucleotide (A, T, C or G) differs between individuals at a frequency of more than 1% in the normal population, such that for each SNP there will be two possible alleles. The possibility that individual SNPs may explain lack of efficacy or excessive toxicity of a medication in those individuals with the rare allele for a particular SNP, has given rise to the field of pharmacogenetics. Although SNPs have been identified in more than 20 genes that affect pain sensitivity and/or contribute to interindividual variability in responses to analgesic medications, much of the data are conflicting.[2] Several examples are outlined in the following sections.

Genetics and Pain in Humans

Rare monogenic pain-related disorders

Pain insensitivity: loss of function mutations

The complete inability of a person to sense pain is a very rare phenotype (Table 1), encompassing both hereditary sensory neuropathies whereby patients have an impaired nociceptive signalling system or a channelopathy-associated inability to sense pain.[10–25] Individuals with these monogenic pain-related disorders often die in childhood as they fail to recognize/report pain associated with injury and infection, observations that underscore the role of physiological pain as an important survival mechanism.[18,21] These rare pain phenotypes involve loss-of-function mutations in individual genes including *SCN9A, SPTLC1*, *WNK1/HSN2*, *IKBKAP*, *NTRK1* and *NGFB* (Table 1) that encode ion channels, enzymes, transcription factors and neurotrophins.[2,3,26]

Pain sensitivity: gain of function mutations

Gain-of-function mutations in the $Na_v1.7$ gene (*SCN9A*) that increase the excitability of dorsal root ganglia neurons are linked to two clinically-distinct familial pain syndromes (Table 1), viz inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD).[27] Patients with IEM report intermittent burning pain and skin redness in the hands and feet that is triggered by warmth or mild exercise, whereas PEPD is characterized by skin flushing and episodes of ocular, mandibular and rectal pain that is triggered by bowel movement and perianal stimulation.[27] Additionally, mutations in

Table 1 Genes implicated in monogenic pain-related disorders in humans

Disorder	Gene; Inh	Protein	Clinical features; AAO
Insensitivity to pain: loss of function mutations			
HSAN type I	*SPTLC1;* AD	Serine palmitoyl-transferase, long chain 1	Loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement[12–14]
HSAN type II	*WNK1/HSN2;* AR	With-no-lysine(kinase)-1 (WNK1)	Prominent sensory loss and mutilations in hands and feet, acropathy[14,15]
HSAN type III	*IKBKAP;* AR	IκB kinase-complex associated protein	Familial dysautonomia, prominent autonomic disturbances and complications, hyperhidrosis, absence of fungiform papillae of tongue, alacrimia[14,16,17]
HSAN type IV	*NTRK1;* AR	Neurotrophic tyrosine kinase receptor	No or reduced response to painful stimuli, anhidrosis, episodic fever, mild mental retardation, skin and cornea lesions, joint deformities[11,13]
HSAN type V	*NGFB;* AR	Nerve growth factor, β	Congenital insensitivity to pain, severe loss of deep pain perception, painless fractures, joint deformities, normal intelligence[11,14]
Channelopathy-associated inability to sense pain	*SCN9A;* AR	$Na_v1.7$ sodium channel	[18,19]
Pain sensitivity: gain of function mutations			
IEM	*SCN9A;* AR	$Na_v1.7$ sodium channel	Intermittent burning pain and skin redness in the feet or hands, triggered by warmth or mild exercise[20]
PEPD	*SCN9A;* AR	$Na_v1.7$ sodium channel	Episodes of rectal, ocular and mandibular pain accompanied with skin flushing, triggered by bowel movement and perianal stimulation[21]
FHM type I	*CACNA1A*	α1-subunit of neuronal Cav2.1 (P/Q-type) voltage-gated calcium channels	Migraine attacks with hemiplegic aura, epilepsy, mild head trauma may be lethal[22,23]
FHM type II	*ATP1A2*	α1-subunit of Na^+-K^+-ATPase	Migraine attacks with hemiplegic aura; childhood convulsions, epilepsy, permanent mental retardation[23,24]
FHM type III	*SCN1A*	α1-subunit of neuronal $Na_v1.1$ voltage-gated sodium channels	Migraine attacks with hemiplegic aura; epilepsy; elicited repetitive transient daily blindness not associated with headache or other neurological symptoms[23,25]

Adapted from Lacroix-Fralish and Mogil[2], Guillemette *et al.*[10] and Einarsdottir *et al.*[11] AAO, age at onset; AD, autosomal dominant; AR, autosomal recessive; FHM, familial hemiplegic migraine; HSAN, hereditary sensory and autonomic neuropathy; IEM, inherited erythromelalgia; Inh, inheritance; PEPD, paroxysmal extreme pain disorder.

genes for three subtypes of familial hemiplegic migraine (FHM Types I–III) have been identified (Table 1).

Quantitative sensory testing: volunteer studies

In volunteer studies, quantitative sensory testing (QST) is used to determine experimental pain thresholds or stimulus response curves for sensory processing across a range of pain modalities, including thermal, mechanical, electrical and chemical stimuli.[28] More sophisticated designs employing QST involve application of these stimuli to a range of tissue types, including skin, muscles and viscera to produce a mosaic of responses.[28] In recent years, QST has been used in volunteer studies to assess the contribution of the genetic component to interindividual variability in pain thresholds.

Does pre-operative quantitative sensory testing have clinical relevance?

In support of the notion that QST assessment of pain thresholds in the experimental setting has clinical relevance, a recent systematic review of 14 studies found that pre-operative QST responses were able to predict 4–54% of the variance in the postoperative clinical pain experience depending upon the stimulation methods and the test paradigm utilized.[29] Hence, it appears that for acute postsurgical pain, pre-operative QST has the potential to identify patients who have enhanced pain sensitivity and who may be at higher risk for development of persistent postoperative pain, thereby enabling more intensive postoperative analgesic regimens to be implemented.[30]

Human twin studies

In a QST study undertaken in 98 pairs of volunteer healthy female twins (51 monozygotic and 47 dizygotic) using a wide range of noxious stimuli, genetic components were able to explain 22–55% of interindividual variability for the majority of painful stimuli assessed, particularly heat and chemical pain thresholds.[31] More recently, in a study involving 53 pairs of monozygotic and 39 pairs of dizygotic twins, QST revealed similar findings in that 60% of the variance in cold pressor pain responses and 26% of the variance in heat pain responses could be explained by genetic factors.[32] Clearly, as cold pressor pain and contact heat pain are distinct phenomena from both the genetic and environmental perspectives, this cautions against generalizing genetic findings from one pain modality to another.[26,32]

Genetic association studies in humans

As already noted, marked interpatient variability in pain sensitivity as well as analgesic drug dosing requirements for apparently similar pain conditions is a hallmark of clinical pain management, with interindividual differences in responses to analgesic agents potentially underpinned by pharmacodynamic and pharmacokinetic factors. In the last decade numerous genetic association studies have been undertaken in patients to assess the impact of genotype for individual target genes of interest not only on reported levels of pain intensity, but also on analgesic dosing requirements and side-effect profiles (Table 2).[33–66] Genes investigated in this way include *CYP2D6, CYP3A4, CYP2C9, CYP2C19* and *UGT2B7* that encode key enzymes in drug metabolism, *ABCB1* that encodes the P-glycoprotein transporter, *HTT* that encodes the serotonin transporter, *SLC6A2* that encodes the noradrenaline transporter, as well those encoding the α-subunit of the $Na_v1.7$ sodium channel (*SCN9A*), the μ-opioid receptor (*OPRM1*), the melanocortin-1 receptor (*MC1R*), the β_2-adrenergic receptor (*ADRB2*), cytokines (*IL-1A/B, IL-6, TNFA, ILIRN, IL10*) and the enzymes catechol-O-methyltransferase (*COMT*) and guanosine triphosphate cyclohydrolase 1 (*GCH1*), to name but a few.[2,3,26,49,53,60,67]

Genetic Association Studies of Pain Sensitivity and Analgesic Drug Pharmacodynamics

Melanocortin-1 receptor (MC1R)

The *MC1R* gene is best known for its role in skin and hair pigmentation (redheads). In 2005, Mogil *et al*.[57] reported that people with two or more inactivating variants of the *MC1R* gene had a 1.3-fold higher tolerance to electrical pain stimuli. However, Liem *et al*.[59] found seemingly opposite results in that redheaded women were more sensitive to thermal pain stimuli than control study participants.[56,57,59] Together, these findings highlight the dangers in extrapolating findings from one pain phenotype to another. *MC1R* variants have been shown to modulate opioid analgesia in a sex-specific manner such that women with two nonfunctional *MC1R* alleles experienced a stronger analgesic effect from pentazocine (κ-opioid agonist) relative to women with either one or no *MC1R* variants, or to men with two inactivating *MC1R* variants.[58]

Guanosine triphosphate cyclohydrolase 1 (GCH1)

The enzyme, GTP cyclohydrolase (GCH1), reportedly has a key role in modulating pain sensitivity as it regulates the production of tetrahydrobiopterin (BH4), an essential cofactor in the synthesis of nitric oxide, serotonin and catecholamines.[68] In support of this notion, SNPs in *GCH1*, the gene encoding GCH1 were significantly correlated with altered responses to noxious stimuli in healthy humans and appeared to predict the susceptibility of individual patients to development of neuropathic and inflammatory pain.[55] Specifically, in study participants heterozygous or homozygous for the pain-protective *GCH1* haplotype, there was reduced upregulation of the *GCH1* transcript, resulting in lower levels of BH4.[53] In a subsequent study involving assessment of the clinical pain responses of 221 patients after a third molar extraction, as well as the thermal and cold pain sensitivities of a cohort of 735 healthy volunteers, associations between GCH1 genetic variations and pain sensitivity were reportedly weak or negligible.[54] More recently however, data from 251 cancer patients showed that for individuals with a reduced-function haplotype in *GCH1* leading to decreased BH4 expression, there was a significantly ($P = 0.002$) longer mean period (78 months) in homozygous carriers of non-coding and non-splice site GCH1 variants, between cancer diagnosis and initiation of opioid therapy relative to heterozygous individuals (37 months) and non-carriers (30 months).[56]

SCN9A ($Na_v1.7$ sodium channel)

The analgesic effects of local anaesthetics (e.g. lidocaine) and anti-arrhythmics (e.g. mexiletine) are produced via blockade of voltage-gated sodium channels in sensory nerves. However, these agents also produce many side-effects including motor block, cardiac conduction block and neurotoxicity due to inhibition of sodium channels located in motor nerves, cardiac tissue and the brain. Of the nine sodium channel subtypes identified to date, $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ are mainly expressed in sensory nerves and so novel analgesics targeted to these sodium channel subtypes may potentially have more favourable adverse event profiles whilst retaining analgesic efficacy.[69–71] $Na_v1.7$, encoded by *SCN9A*, is predominantly expressed in dorsal root ganglion neurons that are nociceptive.[72,73] A recent genetic association study has found a significant association between the *SCN9A* SNP, rs6746030 (G/A substitution), and pain perception.[60] Observations that individuals with nonsense mutations in *SCN9A* are unable to sense pain, whereas those with rare gain-of-function mutations suffer from familial pain syndromes, provide human data validating $Na_v1.7$ as a target suitable for modulation by molecules in development as potential novel analgesic agents.[27]

OPRM1 (μ-opioid receptor)

Morphine, the prototypic strong opioid analgesic that is widely used for the management of moderate to severe pain, produces its analgesic effects primarily by acting as an agonist at the μ-opioid receptor (MOP-R).[74] The human MOP-R gene, *OPRM1* (chromosome 6q24-q25) spans over 200 kb with at least nine exons and 19 different splice variants under the control of multiple promoters.[75] Of the large number of polymorphisms that have been identified in the promoter, the most commonly investigated is the 118A > G SNP (N40D variant), with its rare allele occurring in approximately 20–30% of the population.[76] Initial genetic association studies suggested functional importance of the N40D variant.[77] There is also accumulated evidence that the *OPRM1* A118G variant causes a decrease in opioid potency by a factor of 2 to 3, providing a rationale for increased doses in selected patients.[78] Though several studies have shown positive association between the A118G SNP and opioid dosing, a recent meta-analysis has questioned the relevance of the *OPRM1* A118G genetic variant for clinical pain management due to inconsistent association between *OPRM1* A118G genotypes and most of the phenotypes.[49] Hence, the value of *OPRM1* A118G genotyping for individualizing opioid analgesic treatment is not supported by current knowledge.

Table 2 The outcomes of genetic association studies for genes implicated in the modulation of pain and analgesia are often conflicting

Gene	Gene product	Genotype	Study population*	Study outcomes
COMT	Catechol-O-methyl transferase	COMT 158	EXP	No significant association between the val158met polymorphism and sensitivity to cold pain[33] Individuals homozygous for the *met158* allele showed diminished μ-opioid responses when compared with heterozygotes. The opposite effects were observed for *val158* homozygotes[34]
			CLIN	COMT polymorphisms did not appear to be implicated in the genetic liability to migraine or to increase susceptibility to neuropathic pain[35,36] There was no significant association between Val158Met polymorphism and migraine. For women with the Val/Val genotype, nonmigrainous headache tended to be less likely than for those with other genotypes[37] 2 × Significant associations with comparable results Individuals with Val/Val and Val/Met genotypes required 63% and 23% higher morphine doses, respectively, relative to carriers of the Met/Met genotype[38,39]
		COMT 158 and haplotypes	EXP	3 × Significant associations Following application of thermal, mechanical and ischaemic experimental pain stimuli to healthy female study participants, three major COMT haplotypes (LPS, APS and HPS) encompassing 96% of the examined genotypes were identified that appeared to determine COMT enzymatic activity[40] (a) The LPS, APS and HPS haplotypes were associated with low, average and high pain sensitivity, respectively. The LPS haplotype was associated with much higher levels of COMT activity compared with the APS and HPS haplotypes.[40,41] Individuals with low COMT activity appeared to have an increased risk of developing chronic pain[40] (b) The Val158Met genotype was associated with the rate of temporal summation of heat but not other types of pain[42] (c) Presence of a single LPS haplotype diminished the risk of developing myogenous temporomandibular joint disorder by 2.3-fold[40]
		13 SNPs from COMT	EXP	There were no differences among Val/Val, Val/Met, and Met/Met populations in contrast to earlier findings of Zubieta *et al*.[34] and Diatchenko *et al*.[40] who reported higher pain ratings for Met/Met homozygotes and that levels of pain sensitivity were correlated with LPS, APS and HPS haplotypes, respectively[43]
		15 SNPs from COMT	CLIN	SNPs in intron 1 of the COMT gene at positions −4873G and −4871G appeared to be protective against morphine-related drowsiness, confusion and hallucinations. However, there was no association between COMT genotype and morphine dose or serum morphine or metabolite concentrations[44]
OPRM1	μ-opioid receptor	OPRM1 118 A > G	EXP	4 × Significant associations (a) This SNP was associated with higher thermal pain thresholds in men, lower thermal pain thresholds in women and higher mechanical pain thresholds in both men and women.[45] (b) Individuals carrying the *OPRM1* 118GG genotype required 2–4-fold higher alfentanil plasma concentrations to achieve analgesia and 10–12-fold higher alfentanil concentrations to evoke respiratory depression, when compared with individuals not carrying this genotype[46]
			CLIN	No significant association between this SNP and opioid dose for relief of acute post operative pain[47] Major allele (A118) in patients with chronic pain was associated with higher opioid dosages[47] Individuals sharing at least one G allele and those homozygous for the A/A allele were poor and good morphine responders, respectively. The A118G polymorphism appeared to significantly affect morphine responsiveness[48] 4 × Significant associations with apparently similar findings showing that individuals homozygous for G118 required higher morphine doses compared with those who were homozygous A118 or heterozygotes. Clinical relevance is questioned by findings of a meta-analysis showing an inconsistent association between A118G genotypes and most pain phenotypes[39,49–52]
GCH1	Guanosine triphosphate cyclohydrolase 1	GCH1 SNPs and haplotypes	EXP	Decreased GCH1 function as a result of genetic polymorphism offers protection against pain[53] Weak or negligible association between thermal and cold pain responses and GCH1 genetic polymorphism in healthy volunteers[54]
			CLIN	Role of GCH1 polymorphism in nociceptive pain after 3rd molar surgery is weak or negligible.[54] 2 × Significant associations Pain protective haplotype (a) Shows high threshold to mechanical pain[55] (b) Longer time between cancer diagnosis and opioid initiation therapy for homozygous carriers[56]
MC1R	Melanocortin-1 receptor	MC1R (R151C, R160W, D294H) (red hair phenotype)	EXP	Significant associations with apparent contradictory findings (a) Nonfunctional MC1R associated with decreased electrical pain sensitivity and increased μ-opioid analgesia[57] (b) MC1R genotype significantly associated with higher levels of pentazocine analgesia in women but not men[58] (c) MCR1 genotype more sensitive to thermal pain and resistant to the analgesic effects of lignocaine[59]
SCN9A	$Na_v1.7$ sodium channel	rs6746030	EXP	Significant association between SCN9A polymorphism and experimental pain measures evoked by C-fibre activation[60]
			CLIN	Significant association between SCN9A polymorphism and pain perception in patients with five different chronic pain conditions[60]
HTR1A and *HTR2A*	Serotonin receptor 1A and 2A	SNPs from HTR1A and HTR2A	CLIN	No association between SNPs in genes encoding the serotonin receptor and pain[61]
SERT	Serotonin transporter	5-HTTLPR and STin2 of SCL6A4	CLIN	No association between 5-HTTLPR polymorphism and migraine. A meta-analysis of 10 studies concluded no association between migraine and 5-HTTLPR polymorphism in Europeans and Asians[62] No association between 5-HTTLPR polymorphism and migraine in paediatric patients[63] A meta-analysis of five studies suggested a protective effect of the 10/12 and 10/10 STin2 genotypes c.f. the 12/12 genotype for migraine in people of European descent.[64] There was a higher frequency of the 12/12 STin2 genotype in patients with migraine who did not respond to triptans relative to those who did[65]
MAO A and *MAO B*	Monoamine oxidase	SNPS from MAO A and MAO B	CLIN	In women only, there was a weak association between relief of postoperative pain and SNPs in *MAO A* but not *MAO B*[66]

*CLIN, clinical pain; EXP, experimental pain.

Serotonin receptor

Serotonin (5-hydroxytryptamine, 5-HT) is the endogenous agonist for seven 5-HT receptor families (5-$HT_{1–7}$) that modulate multiple physiological and pathophysiological processes in the brain and spinal cord, with spinal 5-HT_1, 5-HT_2 and 5-HT_3 receptors implicated in nociception.[79] Triptans are medications that alleviate migraine by acting as agonists at 5-HT1B/1D receptors to induce cranial vasoconstriction and to inhibit pro-nociceptive neurotransmitter release from perivascular trigeminal neurons as well as in the spinal dorsal horn.[80] Although SNPs in the genes encoding 5-HT1B/1D receptors may contribute to interpatient variability in response to triptans, genetic association studies have failed to show significant relationships between clinical response for a range of disorders and three common SNPs (T-261G, A-161T and G861C) in the *HTR1B* gene that encodes the 5-HT1B receptor.[81–83]

Catecholamine neurotransmitters and pain

The endogenous catecholamine neurotransmitters, noradrenaline, serotonin and dopamine have key roles in the physiological modulation of nociception, analgesia and mood.[67] Their neurotransmitter function is terminated primarily by re-uptake from the synapse into presynaptic nerve terminals via specific transporters, e.g. the noradrenaline transporter (NET), the serotonin transporter (SERT) and the dopamine transporter (DAT), respectively.[84] A lesser mechanism involves metabolism by catchol-O-methyl transferase (COMT) and monoamine oxidase (MAO).[85,86] Thus, SNPs in one or more of these transporters or enzymes has the potential to modulate nociception as well as analgesic drug outcomes, with the net effect difficult to predict.

SERT

SERT is encoded by the *5HTT* gene (also known as *SERT* or *SLC6A4*) with acute pain responses in the postoperative setting reportedly weakly associated with SNPs in this gene.[66] The *5HTT* gene has two main functional variants, viz 5-HTTLPR and STin2 VNTR.[80] The 5-HTTLPR involves a 44-bp insertion/deletion in the 5' promoter region yielding a short (s) and a long allele (l).[87] The s-allele results in decreased SERT expression and prolonged serotonin responses due to reduced re-uptake into nerve terminals.[88] 5-HTTLPR polymorphisms are reportedly associated with a higher risk for painful conditions such as fibromyalgia, tension-headache and migraine.[89–92] Although several studies suggested a role for 5-HTTLPR polymorphism in the pathophysiology of migraine, a recent large cohort study showed that migraine frequency was not significantly correlated with 5-HTTLPR polymorphism.[93–96] Furthermore, a systematic review and meta-analysis of 10 studies concluded that there is no overall association between migraine and 5-HTTLPR polymorphism among Europeans and Asians.[62] However, a sex-specific link between 5-HTTLPR polymorphisms and the emotional response to nociception has recently been suggested.[87] The STin2 VNTR is a 17 bp variable number of tandem repeats located in intron 2 of the *5HTT* gene, resulting in alleles carrying 9-, 10- or 12-repeats.[80] Although a recent study found no significant correlation between migraine susceptibility and STin2 VNTR polymorphisms, a recent meta-analysis of five studies suggested a protective effect of the 10/12 and 10/10 genotypes cf. the 12/12 genotype for migraine in people of European descent.[64,97] Moreover, there was a higher frequency of the 12/12 genotype in patients who did not respond to triptans relative to those who did.[65] In paediatric patients, no association was found between 5-HTTLPR polymorphism and migraine headache, whereas a significant increase in the frequency of the 12/12 genotype of STin2 was observed in patients with migraine and aura.[63]

NET

In postoperative patients, SNPs in the NET (*SLC6A2*) appear to be weakly associated with acute pain responses.[66] Although tricyclic antidepressants (TCAs) and selective noradrenaline re-uptake inhibitors (SNRIs) alleviate neuropathic pain by acting as NET inhibitors to produce analgesia by augmenting descending noradrenergic inhibitory mechanisms in the brain, the influence of SNPs in *SLC6A2* on levels of pain relief produced by these drugs in patients with neuropathic pain, has not been investigated yet.[98]

COMT

COMT is an enzyme that plays a key role in catecholamine (dopamine, adrenaline and noradrenaline) metabolism.[67] A functional valine-to-methionine SNP at position 158 (V158M) in COMT (called rs4680) has been associated with increased sensitivity to painful stimuli and the requirement for lower doses of morphine to attain satisfactory relief of cancer pain.[34,38] A haplotype of four SNPs of the COMT gene including rs4680 was reportedly associated with experimental pain and the prospective risk of temporomandibular joint disorders.[40] However, subsequent studies failed to show a genetic association with either experimental pain or postsurgical pain.[66,99] A large cohort study of chronic widespread pain also failed to find any association with rs4680 alone and there was no association of this genotype with cold pressor pain.[33,37] More recently, another large cohort study showed no associations of either chronic widespread pain or self-reported pain status with COMT genotypes, including that encoding rs4680.[67]

MAO

There are two isoforms of the enzyme, monoamine oxidase (MAO), known as MAO-A and MAO-B that differ significantly in their substrate specificity, cellular localization and regulation.[66] These two enzymes are encoded by the genes *MAOA* and *MAOB*, respectively.[66] For acute postoperative pain, a weak association was found between the relief of postoperative pain and SNPs in *MAOA*, but not *MAOB*.[66] More work is required in other patient populations, before definitive conclusions can be drawn.

Genetic association studies and analgesic drug pharmacokinetics

Following systemic administration, analgesic agents may be metabolized by a range of enzymes present in the gastrointestinal mucosa or the liver. Although these enzymes have evolved as endogenous detoxification mechanisms, some

molecules such as codeine undergo metabolic activation, and others such as morphine and tramadol have active metabolites.[100] Apart from genetic polymorphisms in drug metabolizing enzymes contributing to interpatient variability in responses to analgesic agents, induction or inhibition of drug metabolizing enzymes may mimic genetic defects.[101]

Cytochrome P450 enzymes

Cytochrome P450 (CYP 450) is a superfamily of Phase I drug metabolizing enzymes that oxidize a broad range of endogenous substances as well as xenobiotics.[102] In the human genome, there are 57 functional *CYP* genes and 58 CYP pseudogenes within 18 families (i.e. CYPs 1–5, 7, 8, 11, 17, 19–21, 24, 26, 27, 39, 46 and 51).[103] However, only six of these CYPs play significant roles in the metabolism of clinically utilized medications: CYP1A2, CYP2D6, CYP2C9, CYP3A4, CYP2E1 and CYP2A6.[104] Most CYP families are polymorphic with variants resulting in altered protein expression or activity (see http://www.cypalleles.ki.se/). Genetic polymorphism in the genes encoding CYPs produces one of four main phenotypes, viz poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM) and ultrarapid metabolizers (UM), with the corresponding genotypes being two nonfunctional (null) alleles (PMs), at least one reduced functional allele (IM), at least one functional allele (EMs i.e. normal individuals) and multiple copies of a functional allele and/or an allele where the mutation confers increased gene transcription (UMs).[105–107] Individuals with the PM phenotype for a particular enzyme would be expected to have higher circulating plasma concentrations after standard doses of drugs that are substrates for that enzyme.[108] Many analgesic agents are metabolized by CYPs and so their apparent pain-relieving potency is potentially modulated by SNPs in the genes encoding these enzymes.

CYP2D6 (cytochrome P450 2D6)

CYP2D6 has a significant role in the metabolism of ~25% of currently used medications, despite this enzyme being a minor constituent (2–4%) of hepatic CYP proteins in humans.[109] SNPs in the *CYP2D6* gene influence pain relief outcomes in patients for many analgesic agents including codeine, tramadol, tricyclic antidepressants, venlafaxine and antiarrythymics, as well as other agents such as anti-emetics (e.g. ondansetron), tamoxifen and the antipsychotics (e.g. risperidone).[3,105]

In humans, more than 80 genetic variants of CYP2D6 have been identified resulting in marked phenotypic diversity within populations characterized by considerable differences between ethnic groups.[105,110,111] Approximately 7–11% of the Caucasian population has the poor metabolizer (PM) phenotype and they do not metabolize codeine to morphine resulting in poor analgesic efficacy.[3] By contrast, up to 7% of the Caucasian population has the ultrafast metabolizer (UM) phenotype resulting in very high levels of morphine being formed from codeine with the risk of toxicity being observed.[3] Particular caution is required with breastfeeding mothers due to the potential for excessive CNS depression and fatal respiratory depression in infants of UM mothers administered codeine due to the high levels of metabolically-derived morphine produced.[112] Based on the findings of a recent case-controlled study, it was recommended that codeine not be prescribed to breastfeeding mothers.[113] Similarly, caution is required in the use of hydrocodone in the paediatric population where a combination of PM phenotype and drug–drug interactions has the potential to result in toxic plasma concentrations with fatal consequences.[114]

The analgesic effects of tramadol are mediated in part by its O-demethylated metabolite, O-desmethyltramadol (M1), a potent μ-opioid receptor agonist, whose formation is catalysed by CYP2D6.[115] Hence, CYP2D6 PMs would be expected to experience less analgesia after standard doses and to have higher tramadol dosing requirements to achieve satisfactory pain relief compared with EMs.[116,117] After oral administration of tramadol in humans, plasma M1 concentrations are higher in EMs relative to PMs whereas there is increased M1 formation in UMs who are at higher risk for developing opioid-related side-effects.[118,119] In neonates and infants, there is a complex interplay between CYP2D6 polymorphisms, renal excretion and age-dependent maturation (ontogeny) in terms of phenotypic variability with respect to circulating plasma concentrations of tramadol and its analgesically active M1 metabolite, both of which contribute to analgesic outcomes.[120]

Following systemic administration of mexiletine, it is metabolized extensively to mainly inactive metabolites with the formation of hydroxymethylmexiletine and parahydroxymexiletine catalysed predominantly by CYP2D6.[105] Mexiletine has a very narrow therapeutic index with target plasma concentrations in the range 0.5–2 μg/ml and so standard doses need to be reduced in PMs relative to EMs to avoid toxicity.[105]

CPY3A (cytochrome P450 3A)

In humans, the *CYP3A* gene encodes two major CYP3As expressed in human liver, viz CYP3A4 and CYP3A5,[121] whose activity is characterized by marked variability between individuals and between ethnic groups due to both genetic and non-genetic factors.[121–125]

CYP3A4 (cytochrome P450 3A4) and CYP3A5 (cytochrome P450 3A5)

CYP3A4 catalyses the metabolism of >60% of all clinically utilized medications in humans with ~10-fold variability in the metabolism of CYP3A4 substrates.[126,127] Common allelic variants in Asian populations include *CYP3A4*1G, CYP3A4*4*, *CYP3A4*5* and *CYP3A4*18*, whereas the *CYP3A4*2*, *CYP3A4*10* and *CYP3A4*17* variants are common in Caucasian populations.[128–132] The strong opioid analgesic, fentanyl, is widely used for postoperative pain management as well as for the relief of chronic cancer pain.[133] Postoperatively, there is marked interpatient variability in fentanyl dosing requirements to produce satisfactory pain relief.[134] As fentanyl is primarily cleared from the systemic circulation by CYP3A4-catalysed N-demethylation, SNPs in CYP3A4 have the potential to contribute, at least in part, to this variability.[135] In support of this notion, two recent studies undertaken in Chinese Han women administered intravenous fentanyl via patient-controlled analgesia following gynaecological surgery, showed a significant correlation

between fentanyl dosing requirements and the *CYP3A4*1G* genotype (2023 G > A) with GG homozygotes requiring significantly lower ($P < 0.05$) doses at 2, 4 and 24 h compared with patients who were AA homozygotes.[136,137] By contrast, the *CYP3A5*3* variant (6986A > G) that is a frequent SNP of *CYP3A5* in the Chinese population, did not contribute significantly to interindividual variability in the doses of fentanyl to produce satisfactory pain relief in Chinese Han women following abdominal gynaecological surgery.[138] More research in other patient populations as well as diverse ethnic groups is required before general conclusions can be made.

CYP2C9 (cytochrome P450 2C9)

CYP2C9 metabolizes ~15% of drugs used clinically and it is one of the most abundant CYP enzymes in the human liver accounting for ~20% of total hepatic CYP content.[139] CYP2C9 is highly polymorphic with at least 35 variants having been identified to date (http://www.imm.ki.se/CYPalleles, access date: 28 May 2011).[139] Although many nonsteroidal anti-inflammatory drugs (NSAIDs) are metabolized by CYP2C9 (e.g. diclofenac, ibuprofen, ketoprofen, suprofen, naproxen, flurbiprofen, indometacin, meloxicam, piroxicam and tenoxicam), the significance of this pathway to metabolic clearance varies from one NSAID to another in the range 5 to >90%.[139,140] Apart from NSAIDs, other analgesics that are CYP2C9 substrates include selective cyclooxygenase-2 (COX_2) inhibitors (e.g. celecoxib, lumiracoxib, etoricoxib and valdecoxib) as well as the strong opioid analgesics, methadone and hydromorphone.[141,142] For multiple NSAIDs including flurbiprofen, *R*-ibuprofen, piroxicam and tenoxicam as well as the COX_2 inhibitor, celecoxib, the CYP2C9 genotype appears to be a significant predictor of metabolic clearance such that individuals with the CYP2C9*3 genotype have significantly higher systemic exposure compared with individuals that have the wild-type *1 genotype.[139,140,143–148] For celecoxib, similar findings were observed in paediatric patients homozygous for *CYP2C9*3* whereby systemic exposure was 8–9-fold higher compared with that of extensive metabolizers with the *CYP2C9*1/*1* or **1/*2* genotypes.[149] Thus, it is plausible that for these analgesics, the dosing requirements for individuals with the CYP2C9*3 allele would be lower than for individuals with wild-type alleles.

CYP2C19 (cytochrome P450 2C19)

CYP2C19 metabolizes ~10% of drugs used clinically.[105] The *CYP2C19* gene is highly polymorphic with >25 SNPs resulting in marked phenotypic differences between individuals and between ethnic groups.[105,106,150] Individuals homozygous for the *CYP2C19*2* and *CYP2C19*3* alleles are considered to be PMs whereas people with at least one *CYP2C19*1* allele are classified as EMs.[151] Tricyclic antidepressants, such as amitriptyline and imipramine that are widely used for the symptomatic relief of neuropathic pain, are challenging to use in the clinical setting due to their narrow therapeutic index and the 50-fold intersubject variability in circulating plasma concentrations after a standard dose.[152] The major metabolic pathway for systemic clearance of amitriptyline and imipramine involves CYP2C19-catalysed N-demethylation to form nortriptyline and desipramine, respectively, with these metabolites being antidepressants in their own right.[105,152,153] These active metabolites are further metabolized by CYP2D6 to inactive metabolites that are subsequently glucuronidated and eliminated via the kidney.[105,152,153] The risk of adverse events is particularly high in patients who have both CYP2C19 EM and CYP2D6 IM/PM phenotypes.[153]

Phase 2 drug metabolizing enzymes: the uridine diphosphoglucuronosyl transferase superfamily

Phase 2 metabolism of parent drug or Phase 1 metabolite is catalysed by members of the uridine diphosphoglucuronosyl transferase (UGT) superfamily of enzymes to form water-soluble glucuronide conjugates, thereby facilitating termination of drug action and renal excretion.[10,154] There are two major UGT enzyme classes in humans, viz UGT1A and UGT2 with at least eight isoforms of UGT1A (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9 and 1A10) and seven isoforms of UGT2 (UGT2A1, 2B4, 2B7, 2B10, 2B11, 2B15 and 2B17) identified to date.[155] UGT2B7 in particular, has a major role in the metabolism of NSAIDs, opioid analgesics (e.g. morphine and hydromorphone), and anticonvulsants with abundant expression of this enzyme in the gastrointestinal mucosa and the liver.[156,157] In humans, UGT2B7 is the major isoform that catalyses the metabolism of morphine to its pharmacologically active 3- and 6-glucuronides, and it is subject to genetic polymorphism.[158] Although the common 802C/T missense polymorphism in exon 2 of *UGT2B7* results in an H268Y change, the extent of variability in the M3G/morphine (16-fold), M6G/morphine (42-fold), and M3G/M6G (7-fold) plasma concentration ratios in patients receiving morphine for cancer pain management did not differ significantly ($P > 0.05$) between the UGT2B7 H/H, H/Y and Y/Y genotypes.[154,158] Although a large number of variants in *UGT* genes have been identified there is considerable complexity, making interpretation difficult with respect to impact on analgesic outcomes.[10]

Drug transporters in the blood–brain barrier

Efflux drug transporters residing in the blood–brain barrier (BBB) such as P-glycoprotein (P-gp) have evolved to protect the brain from exposure to toxins of environmental and dietary origin. Most efflux transporters belong to the superfamily of ATP-binding cassette (ABC) membrane proteins that influence the intracellular concentration of a broad array of molecules.[159] To date, the ABC-transporter family has been subdivided into seven subfamilies, A–G, comprising 49 members (http://nutrigene.4t.com/humanabc.htm).[159,160]

P-gp (ABCB1) is the best characterized human ABC-transporter with >50 SNPs and several insertion/deletion polymorphisms in the *ABCB1* gene having been identified.[159] The three most studied *ABCB1* SNPs are C1236T, G2677T|A and C3435T, and several studies have examined their influence on opioid analgesic outcomes. In one study, interindividual variability in levels of analgesia produced by morphine in patients with cancer was significantly associated with the C3435T SNP.[48] In the experimental pain setting, a reduction in oxycodone-related adverse events was significantly correlated with the variant allele, 3453T, whereas enhanced antinociception was found for individuals with the variant 2677T.[161] In 32 Japanese patients with cancer pain, those

with the T/T genotype at 1236 or the TT/TT diplotype at 2677 and 3435 in the *ABCB1* gene, reported reduced fatigue compared with other patients.[162] In the same study, the frequency of morphine-induced vomiting was higher in patients with one GC allele at 2677 and 3435 in the *ABCB1* gene cf. other patients.[162] However, this latter finding contradicts earlier work that found patients with the GC/GC diplotype at 2677 and 3435 in the ABCB1 gene had a lower incidence of morphine-induced vomiting.[163]

Although efflux of many drugs used to treat clinical pain including opioids and tricyclic antidepressants, is mediated by P-gp in the BBB, between-study variability in the influence of a particular SNP in the *ABCB1* gene on pharmacokinetic or pharmacodynamic outcomes makes it difficult to draw conclusions.[159,164]

Genetic association studies and pain – overview

Despite initially promising results, most genetic association studies performed over the past decade to assess genetic contributions to pain phenotypes in patients, have either failed to replicate or have been only partially replicated (see reviews by Lacroix-Fralish and Mogil[2], Kim *et al*.[26] and Belfer and Dai[165]. Possible reasons include considerable between-study variability in their design (underpowered studies), execution problems (heterogenous study populations, poor phenotyping, genotyping errors), unsuitable choice of statistical methods (failure to correct for multiple comparisons), as well as between-study differences in interacting environmental factors that affect pain phenotypes.[165] More recently, a study of genetic variability in a large population of 2294 patients with cancer pain using a confirmatory validation population methodological approach, showed that none of the 112 SNPs in 25 candidate genes examined, showed significant associations with the dose of opioid required to produce satisfactory pain relief.[166] The inability to replicate results from human genetic association studies and pain phenotypes between research groups over the last decade, argues against the potential value of point-of-care genotyping to identify 'at risk' individuals for particular pain phenotypes, in clinical decision making with regard to pain management optimization.[166]

Genome-wide association studies: insights from other fields

Over the past two years, a number of genome-wide association studies (GWAS) for complex diseases such as diabetes have been undertaken, resulting in more than 250 genetic loci in which common genetic variants appear to be reproducibly associated with polygenic traits.[167] However, the effect sizes for common variants, both individually and in combination, are modest, likely contributing less than 1% of phenotypic variation.[167] Even with highly heritable phenotypes such as height (heritability estimates at ~90%), the most significant SNP from a GWAS of ~5000 individuals followed by extensive genotyping with ~20 000 people could only explain 0.3% of the interindividual variation.[26] Hence, by extrapolation, it is likely that a GWAS in the pain field would produce broadly similar results, with a large number of genes each contributing a small amount to interindividual variability in pain sensitivity and analgesic dosing requirements.

Gene environment communication: epigenetics and RNA-editing

In the pain genetics field to date, the primary focus has been on assessing the impact of SNPs on protein-coding regions of the genome, which in total account for only 2% of the mammalian genome.[168] However, many SNPs also occur in non-protein coding regions and recent research from other fields sheds light on this emerging dimension of pain genetics.

Epigenetics

Epigenetic processes involve the modification of histone proteins associated with DNA in the chromatin structure to activate or silence particular genes; the phenotypic changes so produced may be inherited without a change in the underling DNA sequence.[169,170] Two recent studies in mice showed that epigenetic mechanisms appear to have a key role in neuronal plasticity secondary to peripheral nerve injury.[169,171] In nerve-injured mice, there was epigenetic silencing of *OPRM1*, *SCN10A* and *KCND3* genes in dorsal root ganglia to produce long-lasting downregulation of expression levels of the corresponding protein products, viz μ-opioid receptors, $Na_v1.8$ sodium channels and $K_v4.3$ potassium channels, respectively, all of which have key roles in pain modulation.[172,173] These changes were mediated by a common epigenetic mechanism involving neuron-restrictive silencer factor (NSRF) that is a transcriptional repressor of genes including *OPRM1*, *SCN10A* and *KCND3* that contain neuron-restrictive silencer element (NRSE).[172,173] Clearly, SNPs in either NSRF or NRSE have the potential to simultaneously affect expression levels of multiple receptors and ion channels in response to nerve injury, revealing this additional level of complexity in the pain genetics field.

RNA editing

In mammals, although only 2% of the genome encodes mRNAs, the remainder is abundantly transcribed to long and short nonprotein-coding RNAs (ncRNAs).[168,174] Recent findings from other fields show that a major function of long ncRNAs appears to be epigenetic regulation of genes encoding proteins such as receptors, enzymes and ion channels.[168] Additionally, allele-specific SNPs in microRNA (miRNA) target sites regulate hundreds of genes in a tissue-specific manner and miRNA disruption has been implicated in many diseases.[168] Thus, regulation of gene-environment communication appears to be highly complex with RNA editing a possible fine control mechanism facilitating dynamic interplay between the transcriptome, the environment and the epigenome such that hardwired genetic information may be altered in animals in response to environmental changes.[174]

Conclusions

Interindividual variability in pain sensitivity and analgesic drug responsiveness in the clinical setting appears to be underpinned by complex interactions between an array of genetic and environmental factors. Recent research from other fields implicates epigenetic mechanisms including RNA editing as a means for facilitating dynamic gene-environment communication.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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