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Pharmacogenetics of analgesic drugs

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Summary points

- Individual variability in pain perception and differences in the efficacy of analgesic drugs are complex phenomena and are partly genetically predetermined.
- Analgesics act in various ways on the peripheral and central pain pathways and are regarded as one of the most valuable but equally dangerous groups of medications.
- While pharmacokinetic properties of drugs, metabolism in particular, have been scrutinised by genotype–phenotype correlation studies, the clinical significance of inherited variants in genes governing pharmacodynamics of analgesics remains largely unexplored (apart from the μ-opioid receptor).
- Lack of replication of the findings from one study to another makes meaningful personalised analgesic regime still a distant future.
- This narrative review will focus on findings related to pharmacogenetics of commonly used analgesic medications and highlight authors' views on future clinical implications of pharmacogenetics in the context of pharmacological treatment of chronic pain.

Keywords
Pharmacogenetics, pharmacogenomics, analgesics, polymorphism, metabolism, genetic screening, genetic association studies, inter-individual variability, pain, single-nucleotide polymorphism, pain perception, pharmacokinetics, pharmacodynamics, phenotype

Introduction

The aim of any medical treatment is to individualise therapy, boosting the efficacy and minimising potential toxicity. It is estimated that response to over 25% of common medications, including analgesics, is influenced by some type of genetic variation, knowledge of which could be useful to prescribers. Furthermore, variation in drug efficacy may vary from 2- to 10-fold or even 100-fold among members of the same family.[1–3] A similar pattern emerges when considering the frequency and intensity of side effects.[4]

The completion of the Human Genome and HapMap projects, together with advances in high-throughput genotyping, has revolutionised our understanding of the importance of genetic predisposition and environmental variables, such as diet and general state of health, in individual drug responses.

According to the recent National Centre for Health Statistics report, analgesics constitute the most dangerous group of medications used legally. Opioids alone attribute to more than 15,000 fatalities annually with 343,000 emergency medicine (EM) department attendances in the United States alone due to drug overdose.

Pharmacogenetics is commonly defined as the study of genetic variation that gives rise to differing responses to drugs. More recently, another term has been

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introduced, *pharmacogenomics*, which covers the broader application of genomic technologies to new drug discoveries and the further characterisation of older drugs. Some authors use those two terms interchangeably; therefore, a clear distinction, as well as consensus definitions, needs to be agreed upon.[5] Behind the emergence of pharmacogenetics as a separate specialty lies our desire to understand how heritability affects the difference in responsiveness of different people to therapeutic agents.

Molecular genetics

The amino acid sequence of every protein is encoded by nucleotides, which form deoxyribonucleic acid (DNA).[6] Clearly identified DNA regions function as templates for the synthesis of messenger RNA (mRNA), and this process is called transcription. Messenger RNA leaves nucleus and is transported to the ribosome. Here, the RNA sequence is translated into a specific amino acid. Later, during the process of folding, the polypeptide chain of amino acids is transformed into an active molecule and then trafficked towards its final destination. A detailed description of the genetic code and the central dogma of molecular biology[7] is beyond the scope of this review but can be easily found elsewhere.[8–10]

Genetic polymorphism

A genetic polymorphism occurs when two or more distinct genotypes exist in the same population of a species. Polymorphism is also a main driver of natural selection and evolution. A single-nucleotide polymorphism (SNP) is a variation in the sequence of DNA when a single nucleotide (adenine (A), guanine (G), thymine (T) or cytosine (C)) differs between members of the same species. In human population genetics, it has been noted that the prevalence of certain SNPs can differ substantially between different ethnicities. SNPs can be inherited or occur de novo. Within a gene, an SNP may occur in intronic, non-coding regions or exonic, coding regions, where the change may be synonymous (no difference in amino acid sequence) or non-synonymous (alters the amino acid sequence). A non-synonymous SNP may lead to protein truncation (nonsense mutation) or affect folding or biophysical properties (missense mutations) and therefore may have important functional consequences. The Online Mendelian Inheritance in Man (OMIM) database defines the relationship between polymorphisms and diseases.[11] The Single Nucleotide Polymorphism Database (dbSNP) gathers information about minor genetic variation in the growing list of species.[12] In 2012, dbSNP contained over 187,000,000 SNPs in humans.

SNP nomenclature

At least three different ways of identifying genetic polymorphisms exist. All changes can be reported at the coding DNA-level (cDNA). For example, the *SCN9A* abbreviation c.2572C>T identifies a C to T substitution at position 2572 of the *SCN9A* gene in exon 15.[13] This is an example of the missense mutation, which leads to the replacement of leucine with phenylalanine in the alpha-subunit of the $Na_v1.7$ sodium channel at amino acid position 858 (p. 858 Leu > Phe). The same SNP can be referred to by its dbSNP allocation number (*rs80356476*). In addition, nomenclature of all of the wild-type P450 enzymes is different. By convention, *CYP2C9*, for example, identifies three different variants labelled accordingly as *CYP2C9*1, CYP2C9*2* and *CYP2C9*3*. Subjects may be homozygous or heterozygous for a particular allele; their genotype can be recorded as *CYP2C9*3/*3* (homozygous) or *CYP2C9*1/*3* (heterozygous).

Copy-number variations

Copy-number variation (CNV) is an example of a more significant alteration in the genetic code. Deletions, insertions and inversions are some other possible alterations that can occur. CNVs may involve an abnormal number of copies of the same gene or a complete deletion of the region. This is very common and up to 0.4% of the genome of two individuals differs with respect to CNVs.[14] The P450 2D6 enzyme gene *CYP2D6* CNV, for example, can produce a complete *CYP2D6* gene deletion (*CYP2D6*5*) or duplication (*CYP2D6*x2*), which can result in the reduced or increased metabolism of many xenobiotics.[15]

Heritability of pain traits

Heritability estimates derived from inbred strains of laboratory animals suggest that up to 30–76% of the variance in pain behaviour can be explained by genetic influences.[16,17] A variety of chronic pain conditions, including sciatica, irritable bowel syndrome and mechanical back pain have been studied utilising human twin-studies. Some important initial estimates of trait variants attributed to the inherited genes were made based on this work.[18–20] Individual variability attributed to the genetic factors in twins was further studied with experimental pain induced by a variety of noxious thermal and chemical stimuli in twins. Up to 50% of variability in experimental pain sensitivity was

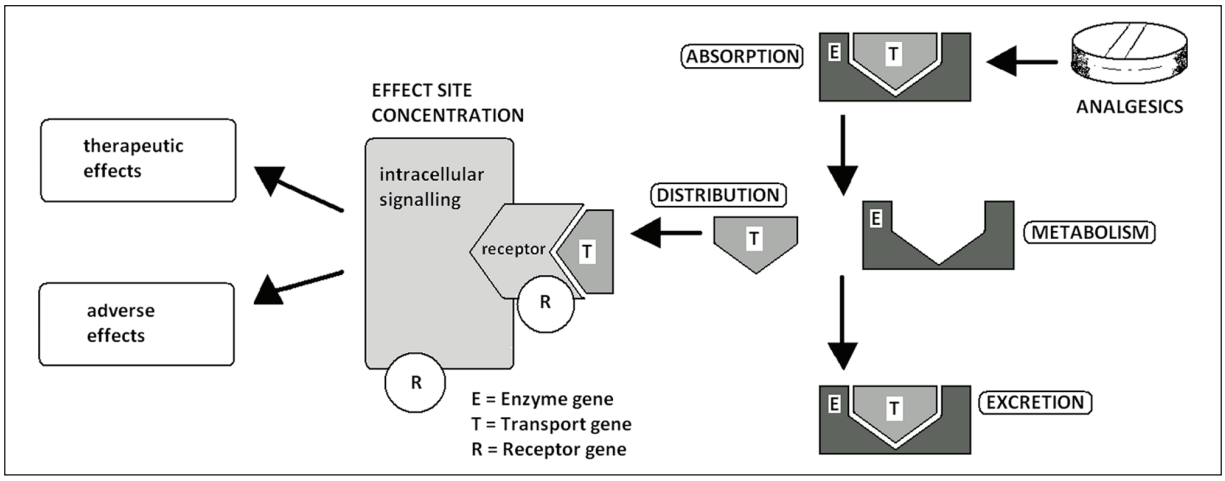

Figure 1. Heritable factors influencing drug–organism interaction.
Source: American Society of Anesthesiologists, Inc.[39] (p. 302).

attributed to inherited factors.[21] In normal individuals, as well as chronic pain sufferers, it is not easy to correlate one cohort of twin subjects to the other, as it appears that the influence of genetic variables cannot be generalised from one pain state to another. The same generalisation can equally apply to data extracted from the experimental pain modalities.

The development of chronic pain is a good example of gene and environment interaction. Only a small minority of all individuals exposed to a noxious event, such as inflammatory or traumatic nerve tissue injury, actually develop chronic pain.[22,23] Once the acute or chronic pain has occurred, pain severities,[24,25] as well as responses to analgesics, can also be very variable among sufferers.[26,27] Both experimental and clinical twin and family studies in humans have contributed to our understanding of altered pain behaviour and variability in the intensity of response to the same stimulus.[28,29]

An overview of peripheral pain circuitry and genes responsible for the variety of anatomical entities has been well described.[30]

Pain genes

Association and linkage human studies have identified a number of genes responsible for heritable conditions involving dramatic alterations in pain perception. The hereditary sensory and autonomic neuropathies I–IV (HSANs I–V) are examples of a family of syndromes in which pain perception and responses are reduced or absent as the result of single point mutations.[31] More recent scientific discoveries have confirmed a pivotal role for the sodium channel $Na_v1.7$ in a growing range of human familial and de novo gain-of-function and loss-of-function pain syndromes.[32,33] Gain-of-function lesions in *SCN9A* were identified in three distinct disorders: primary erythromelalgia (PEM), paroxysmal extreme pain disorder (PEPD) and idiopathic small fibre neuropathy (SFN).[33–35] To date, 14 PEM mutations have been identified, most of which map to the first three domains of $Na_v1.7$[36] Human monogenic pain syndromes provide important insights into the molecular mechanisms that underlie normal and pathological pain states.[37] Gene mapping of human mutants carrying an extremely altered pain phenotype spectrum, ranging from a complete loss of pain[32,38] as well as severe gain-of-function variants, such as inherited erythromelalgia,[33] has provided an exceptional opportunity to study key molecular mechanisms that are involved in the regulation of pain signalling. The knowledge thus obtained may be used towards a better understanding of the wider patient population affected by numerous chronic pain conditions.

Pharmacological concepts applied on pharmacogenetics

Figure 1 schematically portrays the function of different genes in influencing pharmacokinetic and pharmacodynamic properties.

Pharmacodynamics is the study of the effects of a drug on the human body. When describing different analgesic classes, the pharmacodynamics section of this article will focus on the polymorphisms in amino acid sequence variations of cell-surface proteins such as receptor and ion channels as well as SNPs in genes coding for various intracellular signalling pathway structures. *Pharmacokinetics* is supplementary to pharmacodynamics and is the study of drug absorption, distribution, metabolism and drug excretion. The aim of metabolism is to make molecules more water

soluble and ready for renal or other excretion. Corresponding sections will look into how gene variations affect the metabolism of various pro-drugs as well as active metabolites. It will also investigate what effect genes have on the development of side effects of commonly used analgesics. We will start our review with the strongest and arguably most valuable group of analgesic drugs available – opioids.

Pharmacogenetics of opioid analgesics

Opioids are routinely used in the treatment of moderate or severe acute and chronic pain. There are several alternative strong opioids available, for example, morphine, oxycodone, hydromorphone and fentanyl, each with comparable efficacy at a population level.[40] At an individual level, however, there is wide variation in opioid analgesic efficacy and side effects, the reasons for which are not fully understood, but may in part be genetic. In cancer-related pain, up to 30% of patients do not respond well to morphine, either due to inadequate pain relief and/or intolerable side effects. The majority of these morphine 'non-responders' achieve a better clinical outcome when given an alternative opioid.[41,42] Common adverse events evoked by opioids include nausea and vomiting, drowsiness, confusion and hallucinations.

Pharmacodynamics

Opioid receptors. Opioid receptors belong to the family of G-protein-coupled receptors (GPCRs). There are three types of classical opioid receptor: mu (μ), kappa (κ) and delta (δ). Structurally similar, they contain an extracellular N-terminus, seven transmembrane domains and an intracellular C-terminus, and each share a high degree of homology. Most variation is found in the N-terminal domain and extracellular loops.[43,44] The extracellular loops determine ligand binding and are therefore particularly important. Splice variation of opioid receptor mRNA has been shown to produce receptor subtypes, which may be of functional importance.[45]

Gene knockout studies in mice have demonstrated that analgesic response to opioids is primarily mediated by the μ-opioid receptor.[46] Genetic variation in the human μ-opioid receptor gene (*OPRM1*) has been associated with opioid response in several different clinical settings, including acute post-operative pain,[47–49] chronic non-cancer pain[50,51] and cancer-related pain.[2,52]

The non-synonymous exonic SNP c.*118A>G* (*rs1799971*) is the most consistently reported example of association between genetic variation in *OPRM1* and opioid response. This SNP results in an asparagine-to-aspartic acid change at position 40, a putative *N*-glycosylation site in the important extracellular N-terminal region; however, the functional significance remains uncertain.[50] The variant G allele of c.*118A>G* has been associated with increased dose requirements of morphine in cancer patients[2,52] and patients following surgery.[47–49] Similarly, the common A allele has been associated with improved analgesia from morphine in cancer-related pain.[52] Nevertheless, when these opioid pain studies were combined in meta-analysis, no association with increased pain was found, and only a weak association with increased morphine dose requirements in homozygous carriers of the variant G allele.[53] c.*118A>G* has also been associated with the opioid-related side effects. In one post-operative study of patients receiving morphine, carriers of the variant G allele had less sedation and less nausea.[54] Another post-operative study of intrathecal morphine and one of tramadol for osteoarthritis also reported an association with the variant G allele with less nausea/vomiting.[49,54,55] The c.*118A>G* genotype was, however, not associated with fentanyl-induced post-operative nausea and vomiting in another study of post-operative pain.[56] The pattern of less analgesia, in addition to less side effects (upper gastrointestinal and central), suggests reduced receptor sensitivity to opioids.

Other SNPs from *OPRM1* and the other classical opioid receptor genes, including *OPRK1* and *OPRD1*, have been tested, for example, in the European Pharmacogenetic Opioid Study (EPOS). EPOS is the largest genetic association study of opioid response to date, with 2294 patients taking opioids for cancer-related pain. A total of 112 SNPs in 25 genes, including *OPRM1, OPRK1* and *OPRD1*, were investigated for relationship to oral equivalent morphine dose requirements. However, no association was identified with any of the SNPs tested in both development and validation analyses.[57]

When morphine response phenotypes were mathematically determined by principal component analysis in one cancer-related pain study (n = 207), two main components were identified: analgesia and central side effects. Multivariate regression analysis was used to combine clinical and genetic factors (*ORPM1, OPRD1* and *OPRK1* SNPs) to predict response. A total of 16% of variability in analgesic response was predicted by a model, including the *OPRK1* SNP *rs7824175*, two types of concomitant medication: beta-blockers, and anti-emetic and daily morphine dose. A total of 10% of variability in central side effects for morphine was predicted by two SNPs, *OPRM1 rs2075572* and *OPRK1 rs10504151*, including concomitant use of steroid medications, and a diagnosis of sarcoma

Table 1. Selected post-operative and chronic pain studies assessing polymorphisms in opioid receptor genes and opioid response.

Opioid	Gene	Variant	Study population	Route	Results	Reference
Experimental pain studies						
Morphine	*OPRM1*	A118G	102 surgical patients	IV/PCA	No difference in pain scores or dose requirement. Decreased sedation and nausea.	54
Morphine	*OPRM1*	A118G	80 female surgical patients	IV/PCA	Increased morphine dose requirements. No difference in pain scores	47
Morphine	*OPRM1*	A118G	120 surgical patients	IV/PCA	Increased dose requirements. No difference in pain scores	48
Morphine	*OPRM1*	A118G	588 female surgical patients	IV/PCA	Increased dose requirements and pain scores. Decreased nausea/vomiting	49
Fentanyl	*OPRM1*	A118G	189 surgical patients	IV/PCA	Increased dose requirements. No difference in nausea and vomiting scores	59
Clinical pain studies						
Morphine	*OPRM1*	A118G, -172G>T, IVS2+31G>A, IVS2-291G>C	207 (99) cancer patients	NA	Increased dose requirements (A118G only)	2
Morphine	*OPRM1*	A118G	137 cancer patients	Various	Decreased pain relief	52
Various	*OPRM1*, *OPRK1* and *OPRD1*	Various	2294 cancer patients	Various	No difference in opioid dose requirements	57
Tramadol	*OPRM1*	A118G	160 patient with pain from knee osteoarthritis	Oral	Decreased nausea and vomiting	55

OPRM1: μ-opioid receptor gene; *OPRK1*: κ-opioid receptor gene, *OPRD*: δ-opioid receptor gene, NA: not available; PCA: patient-controlled analgesia; IV: intravenous.

malignancy. This is an innovative way of defining phenotypes and involving both clinical and genetic factors[58] (Table 1).

STAT6. *STAT6* is an important transcription factor involved in the regulation of *OPRM1* expression by T_H2 cytokines such as interleukin 4 (IL-4).[59] Polymorphisms in *STAT6* have been associated with overall response to morphine in cancer-related pain and opioid switching.[60]

β-arrestin 2. β-arrestin 2 is an intracellular protein that is integral to μ-opioid receptor inactivation and internalisation.[61] On binding, opioid receptor agonists differentially trigger receptor phosphorylation and recruitment of β-arrestin 2.[62,63] Knockout studies have shown that mice lacking the β-arrestin 2 (*ARRB2*) gene exhibit prolonged analgesia from morphine treatment at lower doses.[64] It is worth noting, however, that prolonged analgesia in mice lacking β-arrestin 2 may also be due to a combination of more complex effects transduced by multiple GPCRs in the knockout animal model. Polymorphisms in *ARRB2* have been associated with overall response to morphine and opioid switching.[60]

Pharmacokinetics

Opioid metabolism. Different enzymes in phase 1 and/or phase 2 metabolism are important for the metabolism of different opioids (Figure 2).

Phase I metabolism

Cytochrome P450 2D6. The cytochrome P450 enzyme 2D6 (*CYP2D6*) is central to the metabolism of several different opioids, including codeine, tramadol and oxycodone, all of which have active metabolites. Over 70 *CYP2D6* alleles have been described which have the potential to alter enzyme function, including SNPs, deletions, insertions and copy CNVs.[65] The overall phenotype produced has been classified into four major groups based on function: poor metabolisers, intermediate metabolisers, extensive metabolisers and ultra-rapid metabolisers, for which, tests are

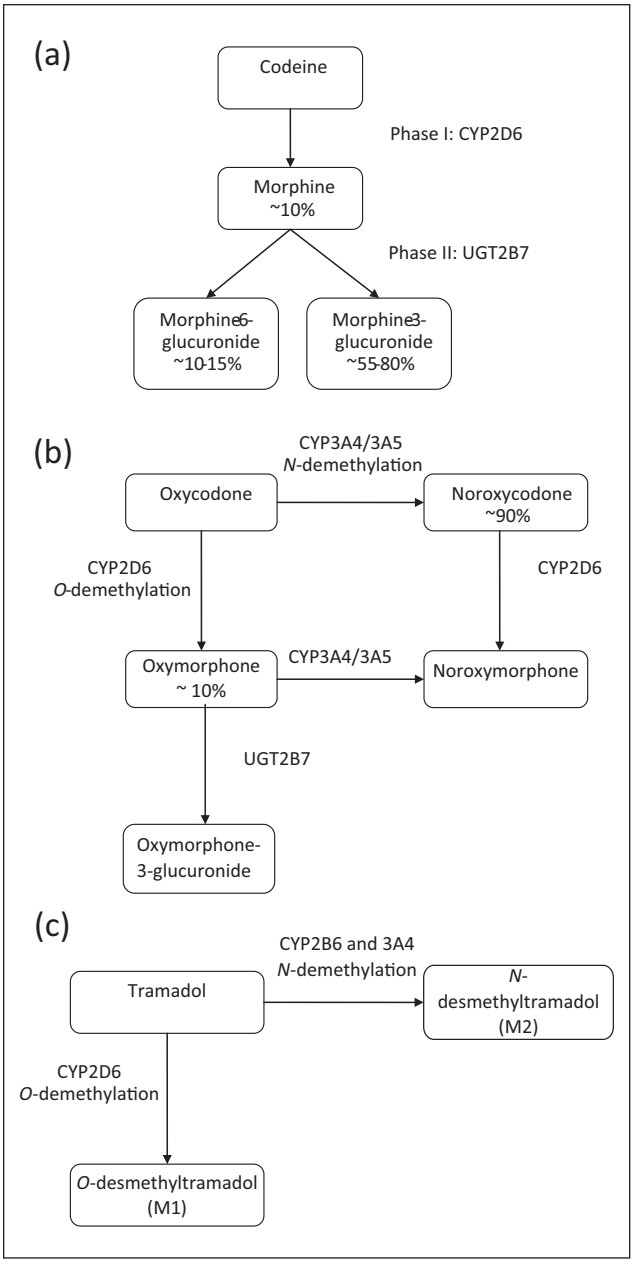

Figure 2. Major metabolic pathways for (a) codeine and morphine, (b) oxycodone and (c) tramadol.

available commercially. In Caucasians, approximately 10% of the population are poor metabolisers and 3% are ultra-rapid metabolisers.[66] A small but significant proportion of codeine (10%) is metabolised to morphine by *CYP2D6*.[67] In response to codeine treatment, poor metabolisers experience little analgesia[68,69] and ultra-rapid metabolisers have a higher incidence of side effects.[1] In addition, there have been cases reported of fatal neonatal opioid toxicity in children breastfed by *CYP2D6* ultra-rapid metabolising mothers taking codeine.[70]

Oxycodone has two main metabolites: noroxycodone (CYP3A4/5) and oxymorphone (CYP2D6), which account for approximately 90% and 10% of metabolites, respectively. Oxymorphone is reported to have greater analgesic potency compared to oxycodone, whereas noroxycodone is inactive.[71,72] Oxymorphone subsequently is rapidly *O*-glucuronidated to form oxymorphone-3-β-glucuronide by uridine 5′-diphospho-glucuronosyltransferase-2B7 (UGT2B7) and is excreted so its overall analgesic contribution is probably minimal.

It is currently unclear whether variation in *CYP2D6* activity significantly alters the efficacy of oxycodone; experimental studies showing a relationship have not been replicated in the clinical setting.[73–75] In experimental pain, it has been demonstrated that ultra-rapid metabolisers experience a 1.5- to 6-fold increase in the analgesic effects of oxycodone as compared with extensive metabolisers, and poor metabolisers had a 2- to 20-fold reduction of the analgesic effects as compared to extensive metabolisers.[74] However, a large study of patients receiving oxycodone for cancer-related pain (n = 450) showed that, although CYP2D6 metaboliser status influenced oxycodone metabolite ratios as expected, there was no clinically measurable difference in terms of analgesia or side effects (nausea or sedation).[76]

Two post-operative pain studies have found that poor metabolisers use more tramadol when given as patient-controlled analgesia compared to other phenotypes (extensive metabolisers or intermediate metabolisers).[77,78] *CYP2D6* metaboliser status has also been linked to tramadol-related side effects, specifically nausea/vomiting. In Korean patients, taking tramadol for osteoarthritis of the knee, *CYP2D6* intermediate metabolisers experienced less nausea/vomiting than extensive metabolisers[55] (Table 2).

Cytochrome P450 3A. The CYP450 3A superfamily of enzymes is involved in the metabolism of 50% of all known drugs. Some 3A substrates, including opioids, for example, oxycodone and fentanyl, can be metabolised equally by 3A4 or 3A5; therefore, a defect in one enzyme may be compensated for by the other. The interaction between 3A4 and 3A5 genetic polymorphisms was studied in Chinese women with post-operative pain following gynaecological surgery. Results showed that while 3A5 variation was not independently important, interactions between 3A4 and 3A5 polymorphisms were additive and significant.[79]

Phase 2 metabolism

UGT2B7. The hepatic isoenzyme UGT2B7 is primarily responsible for morphine metabolism. In vitro work has suggested that functional genetic variants in

Table 2. Selected clinical pain studies assessing polymorphisms in *CYP2D6* and opioid response.

Opioid	Gene	Variant	Study population	Route	Results	Reference
Post-operative pain studies						
Codeine	*CYP2D6*	PM and EM	11 female surgical patients	IV/PCA	PM poor analgesia	69
Tramadol	*CYP2D6*	PM and EM	271 surgical patients	IV/PCA	Increased dose requirements (PM > IM/EM)	78
Tramadol	*CYP2D6*	PM, IM, EM and UM	177 surgical patients	IV/PCA	Increased dose requirements (PM > IM/EM)	79
Clinical pain studies						
Tramadol	*CYP2D6*	IM and EM	160 patients, with knee osteoarthritis	Oral	IM decreased nausea/ vomiting	55
Oxycodone	*CYP2D6*	PM, EM and UM	450 patients with cancer	Oral/ SC/IV	No difference in pain intensity between phenotypes	77

CYP: cytochrome P450; IV: intravenous; PCA: patient-controlled analgesia; SC: subcutaneous, PM: poor metaboliser; IM: intermediate metaboliser; EM: extensive metaboliser; UM: ultra-rapid metaboliser.

UGT2B7 are linked to altered levels of mRNA expression[80,81] and enzyme activity with differential metabolite production.[81] The main metabolites of morphine: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) account for approximately 50% and 10% of metabolites, respectively.[82] M3G binds poorly to opioid receptors and may be responsible for neuroexcitatory effects such as hyperalgesia, allodynia and myoclonic jerks.[83] M6G, however, has been used as an analgesic agent in its own right.[84] Clinical studies have linked genetic variation to differences in morphine/metabolite ratios,[85] but not to overall clinical response to morphine.[86]

Multi-drug resistance gene. The multi-drug resistance gene or adenosine triphosphate (ATP)-binding cassette subfamily B, member 1 (*MDR1* or) encodes P-glycoprotein. P-glycoprotein is a membrane transporter with a central role in the regulation of drugs crossing the blood–brain barrier, and actively removes drugs from the central nervous system (CNS). Heterozygosity for the *ABCB1 3435T* allele has been associated with decreased morphine equivalent daily dose in a mixed chronic pain population[51] and increased pain relief from morphine in cancer-related pain.[52] Side effects have also been associated with *ABCB1* polymorphisms with conflicting results. In an experimental pain study, the variant alleles *2677A* and *3453T* were protective against nausea and vomiting.[87] However, in a post-operative pain study, use of anti-emetics for morphine-related nausea and vomiting was decreased in patients who were homozygous for the *2677GG/3435CC* diplotype.[88] The presence of the A allele at position *2677* of *ABCB1* has been reported to be protective of central side effects, that is, drowsiness and confusion, in patients treated with morphine for cancer-related pain.[89] Functional variants changing transporter activity may influence drug concentrations and parent drug/metabolite ratios in the CNS and consequently adverse reactions; *G2677T/A* has been shown to be linked to altered expression of P-glycoprotein in vivo[90,91] (Table 3).

Modifying systems

Catechol-O-methyltransferase. The enzyme catechol-*O*-methyltransferase (COMT) metabolises catecholamines, such as noradrenaline and dopamine; therefore, changes in activity may influence neurotransmission. The most commonly studied SNP in the *COMT* is p.158V>M (*rs4680*), which results in the substitution of valine to methionine at amino acid position 158. This change has functional consequences as enzyme activity is reduced by between three- and four-fold. The p.158V>M polymorphism has been associated with increased morphine dose requirements in cancer-related pain.[92] Genetic variation in *COMT* has also been associated with opioid-related side effects in patients treated for cancer-related pain. In a subgroup analysis of EPOS, *COMT* polymorphism was associated with severity of nausea and vomiting (n = 1579).[93] Three *COMT* SNPs were found to be weakly associated with less nausea/vomiting: *rs165722C, rs4633T* and *rs4680G*, although the significance was lost after correcting for multiple testing.[93] COMT metabolises dopamine, which is an important neurotransmitter in the area postrema and vomiting centre. In cancer patients receiving morphine, the common G allele at position *-4873* (*rs740603*) of *COMT* has been reported as protective of central side effects.[89] The effect of this allele was independent of and additive to the *ABCB1 2677A* allele (*rs2032582*), which demonstrates the

Table 3. Selected pain studies assessing polymorphisms in drug transporter (*ABCB1*) gene and opioid response.

Opioid	Gene	Variant	Study population	Route	Results	Reference
Post-operative pain studies						
Morphine	*ABCB1*	C3435T and G2677T/A	74 patients	IV/PCA	No difference in pain scores and dose requirements. 2677GG/3435CC diplotype decreased nausea and vomiting	89
Clinical pain studies						
Morphine	*ABCB1*	C3435T	137 patients with cancer	NA	Increased pain relief	52
Morphine	*ABCB1*	C-129T, C139T, C1236T, C3435T and G2677T/A	228 patients with cancer	NA	No difference in pain scores. 2677A protective of central side effects	90
Various	*ABCB1*	C3435T	352 patients with pain of various origin	NA	Decreased dose requirements. No difference in pain scores	51
Various	*ABCB1*	Various	2294 cancer patients	Various	No difference in dose requirements	57

ABC: ATP-binding cassette; IV: intravenous; NA: not available; ATP: adenosine triphosphate.

importance of considering interactions between multiple genes.

HTR3B. Activation of 5-HT_3 (serotonin) receptors in the gastrointestinal tract or chemoreceptor trigger zone is pro-emetic. Three SNPs in the 5-HT receptor 3B gene (*HTR3B*) have been associated with opioid-related nausea/vomiting in cancer patients in a large study: carriers of *rs1176744G, rs3782025T* and *rs1672717T* were found to suffer from less nausea/vomiting.[93] Notably, the association with the G allele of *rs1672717* remained significant when corrected for multiple testing.

Cytokines. Cytokines are vital to the co-ordination of the immune system and the inflammatory response. Cytokines may be broadly classified as pro-inflammatory (tumour necrosis factor α (TNFα), IL-6, IL-8) or anti-inflammatory (IL-10, IL-4, transforming growth factor beta β (TGFβ)). Spinal administration of morphine in animal models stimulates the release of pro-inflammatory cytokines by CNS glial cells, and has been shown to inhibit acute opioid analgesia and induce opioid tolerance after repeated administration.[94,95] In cancer-related pain studies, SNPs in several cytokine gene promoters (*IL-8, IL-6* and *TNF*) have been associated with pain severity and morphine dose requirements.[96,97] Polymorphisms in the promoter region may influence transcription factor binding sites, thereby modifying gene expression.

Pharmacogenetics of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed painkillers in the world, as many of them are easily accessible over the counter; these also possess anti-inflammatory and antipyretic properties. Annual National Health Service (NHS) prescriptions for all causes have reached 25 million in 2012. They are associated with 12,000 hospital admissions per year in order to treat side effects, and they reportedly contribute to 2600 deaths in the United Kingdom per annum.[98,99]

Pharmacodynamics

Cyclooxygenase enzymes. The molecular target of NSAIDs is blockade of the cyclooxygenase (COX) enzymes in the arachidonic acid cascade. Inhibition of COX-1 accounts for most of the side effects,[100,101] while COX-2 inhibition produces therapeutic effects.[102,103] Current literature describes variability in the genetic expression of these COX isoforms with functional and sometimes clinically relevant results.[104,105] For instance, carriers of the COX-1 c.1676- >T (*rs1330344*) allele were found to have a significant risk of non-malignant gastric ulcers when using NSAIDs,[106] while the COX-1 c.50C>T polymorphism was linked to an impaired inhibitory effect on aspirin,[107] although it failed to demonstrate risk of peptic ulcer bleeding.[108]

The main COX-2 functional polymorphism is c.765G>C and is associated with a reduced risk of myocardial infarction and stroke,[109] and of developing Crohn's disease.[110] However, adverse effects have also been identified and include increased monocyte prostaglandin production causing a more severe course of asthmatic disease, reflected by the need for oral corticotherapy,[111] and a significant association with poor outcome in stroke patients from its effect on aspirin resistance.[112]

Pharmacokinetics

CYP2C9 is one of the most abundant P450 cytochromes in the liver and works in the phase 1 metabolism of approximately 15% of clinically useful drugs, including various NSAIDs.[113,114]

Common polymorphisms of the *CYP2C9* gene exist, with three main alleles: *CYP2C9*1, CYP2C9*2* and *CYP2C9*3*.[115] These have been shown to affect cytochrome activity. For example, the allele *CYP2C9*3*, in which isoleucine 359 is changed to leucine (p.359I>L), shows a marked decrease in *CYP2C9* activity, and individuals carrying the homozygous genotype *CYP2C9*3/*3* were shown to have between 5- and 10-fold reduced activity depending on the study design.[115–117] The allelic variants *CYP2C9*2, CYP2C9*1/*2* and *CYP2C9*1/*3* were also associated with a slower metabolism in a number of drug substrates with up to 50% reduction in the V_{max}/K_m ratio.[118,119] NSAID pharmacological activity is almost exclusive to the S(−) enantiomer,[120] and *CYP2C9* contributes to its metabolism.[121] Studies indicate that NSAID-induced common adverse reactions are probably related to inherited impairment of the *CYP2C9* genotype activity.[122] Individuals carrying the gene variants *CYP2C8*3* (*rs11572080; rs10509681*), *CYP2C9*2* (*rs1799853*) or *CYP2C9*3* (*rs1057910*) show an increased risk of developing acute gastrointestinal bleeding following the use of NSAIDs.[123] Similar research revealed that the highest bleeding risk from NSAID use was in patients who possessed both the *CYP2C8*3* and *CYP2C9*2* alleles.[122] While *CYP2C9* contributes to the metabolism of most NSAIDs, recent data show that *CYP2C8* polymorphisms may influence inter-individual variability in the pharmacokinetics of some NSAIDs, namely, ibuprofen and diclofenac.[124] Individuals who are homozygous or double-heterozygous for *CYP2C8*3* and *CYP2C9*3* variant alleles (8% of the population) had extremely low ibuprofen clearance rates, with values ranging from 7% to 27% of the mean clearance rates among non-carriers of mutations.[125]

Voltage-gated sodium channel modulators

Voltage-gated sodium channels (VGSCs) expressed at the terminals of nociceptive poly-sensors act as downstream targets in the process of stimulation, and their activation leads to the initiation of action potentials that are propagated from the periphery to the CNS.[126] The VGSC family consists of nine proteins ($Na_v1.1$–$Na_v1.9$) that are expressed on the membrane of excitable cells and allow intermittent passage of Na^+ ions into these cells. Three isoforms – $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ – are predominantly expressed in the peripheral nervous systems, both somatic as well as autonomic.[127] $Na_v1.7$ is thought to serve a 'threshold channel' function, so when activated, $Na_v1.7$ (and $Na_v1.9$ in some cells) is likely to bring the neuron towards the threshold, and $Na_v1.8$ is largely responsible for the overshooting action potential.[128,129] In addition to classic local anaesthetic (LA) molecules, sodium channels seem to be modulated by a range of other heterogeneous drugs such as carbamazepine, mexiletine, amitriptyline, ketamine and alcohol, all used as analgesics in clinical practice. These modulators interact with the channel on the molecular level in many different ways.[130]

Pharmacodynamics

Mutations within the family of sodium channel genes are known to correlate with varied binding characteristics and clinical actions of the LAs. An example of inherited drug-resistance is demonstrated by the p.395N>K mutation in the *SCN9A* gene, which produces an increased resistance to lidocaine.[131] Inherited conditions, altering electrogenesis by prolonging fast inactivation of VGSCs, such as PEPD, are known to be preferentially responsive to carbamazepine.[34]

SNPs causing the development of inherited erythromelalgia (PEM), leading to the enhancement of channel activation, can be better controlled with oral mexiletine.[132] Treatment of both of these gain-of function sodium channelopathies (PEM and PEPD) with systemic non-selective VGSC blockers has been proven to be rather disappointing overall.[133]

In addition to the involvement of *MC1R* in pain modulation,[134] it appears that red-haired individuals were less affected by the anaesthetic effect of subcutaneous lidocaine, as measured by the pain perception and tolerance thresholds.[135] The *MC1R* gene is not known to be expressed at the periphery, around the nerve fibres,[136] and it is unclear what association there is between the sodium channel blockade in the periphery and melanocortin-1 G-protein–coupled receptor gene. Interaction at the higher, pain modulatory level could play a role in this mechanism.[137] It remains to be studied how other more subtle variations in pain perception phenotypes, such as the recently described association between the A allele of p.1150R>W (*rs6746030*) and altered pain

threshold,[138] are affected by pharmacological modulation of the sodium channel.

Pharmacokinetics

Ester and amide LAs undergo quite different metabolic processes in humans. Most esters are broken down rapidly by plasma esterases to inactive compounds and are excreted renally. Similar to diamorphine, cocaine breakdown is catalysed by pseudocholinesterases human liver carboxylesterase (hCE) 1 and 2.[139,140] It is well known that polymorphism in the pseudocholinesterase peptide is related with apnoea following administration of the muscle relaxant succinylcholine.[141] What is less known is the fact that individuals who carry an inactive copy of this enzyme are also unable to hydrolyse diamorphine to its active metabolite, morphine, and those who have only partially active pseudocholinesterase do so to a much lesser extent than carriers of a fully active isoform.[142] Xie et al.[143] in 1999 examined how variants of human cholinesterase affect cocaine breakdown and found that the substitution of aspartic acid with glycine at position 70 of the enzyme led to a 10-fold lower binding efficiency for cocaine and 10-fold lower catalytic efficiency. It has long been proposed that individuals who demonstrate this abnormality should wear a medical alert bracelet or a similar identifier in order to highlight the risk of death or permanent damage when exposed to ester-type LAs.[144] While a small amount of ester-type LAs may be administered to atypical homozygotes, as a general rule, these compounds are best avoided. Amide-type LAs should be used instead.

Amide LAs are metabolised by the phase 1 modification process of hydrolysis (by amidases) and oxidation (by CYP450 oxidase system) in the liver. Both of these pathways are slower than plasma ester hydrolysis, so these molecules have a higher tendency to accumulate in human circulation. The authors are not aware of any evidence linking polymorphisms in the genes coding for amidase and LA metabolism, unlike in the cytochrome P450 system, where variations in drug metabolism can occur in up to 30% of people in certain ethnic groups with up to 30-fold magnitude of difference.[145] The main CYP isoforms involved in the oxidation of LAs are CYP3A4 for lidocaine and bupivacaine and CYP1A2 in case of ropivacaine. Activity assays of CYP3A4 reveal 10- to 100-fold interindividual differences.[146] One C>T SNP in particular, located in intron 6 of the *CYP3A4* gene (*rs35599367* or *CYP3A4*22* variant), was found to significantly affect the metabolism of xenobiotics, which depend on this enzyme.[147] The cytochrome P450 enzyme CYP1A2 metabolises 5–10% of medications in clinical consumption, including ropivacaine and paracetamol.[148] As with any other enzymatic process, there is considerable variation in 1A2 metabolic activity primarily due to three variables: genetic factors, environmental factors and drug–drug interference. The wild-type allele is conventionally labelled as *CYP1A2*1*. Two functional SNPs have been identified in this gene. G3860A (*CYP1A2*1C* type) is associated with decreased metabolic activity in the enzyme produced when compared with the control carriers. The *CYP1A2*1F* allele is the result of a single point mutation (C163A) and is linked to a hypermetabolic phenotype, particularly under the influence of environmental nicotine when compared with the *CYP1A2*1A* variant.[149,150] (Table 4). Carriers of the 1A2 hyperinduction phenotype, mostly those of Japanese, Egyptian or Caucasian origin, account for up to 45% of the population.[149,151] Commercially available kits testing for these 1A2 variants using polymerase chain reaction (PCR), allele-specific primer extension and subsequent hybridisation using immobilised nucleic acid probes enabling fluorescent detection already exist.

Other analgesics

Paracetamol

Paracetamol (*N*-(4-hydroxyphenyl)-acetamide) is one of the most widely used over-the-counter analgesics. Many studies indicate that paracetamol can offer rapid pain relief for acute pain.[152,153] In chronic pain, paracetamol can be effectively used in treating migraine pain[154] and osteoarthritis.[155] The pharmacodynamic properties of paracetamol, as well as the newly described active metabolite AM404 molecule,[156] are inadequately explained and may involve a diverse range of pathways which include transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors via inhibition of the reuptake of the endogenous cannabinoid/vanilloid anandamide, modulation of VGSC currents,[157] 5-HT receptors[158] or the COX system.[159] Candidate genes involved in these biological systems, with time, are likely to reveal a degree of interindividual differences.

Paracetamol hepatotoxicity is the most common cause of acute liver failure in the United Kingdom.[160] Under normal conditions, paracetamol is extensively conjugated with glucuronic acid and sulphate as part of phase 2 metabolism in order to make it water soluble, preceding its excretion via the kidneys. A total of 5% of the remaining drug undergoes phase 1 oxidation in the liver via the CYP system. Cytochrome P450 2E1 and 3A4 convert paracetamol to a toxic intermediary metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which is instantly cleared by conjugation with glutathione to form cysteine and other conjugates.[161] This

Table 4. Selected experimental and chronic pain studies assessing polymorphisms in genes involved in action of sodium channel blockers.

Drug	Gene	Variant	Study population	Route	Results	Reference
Pharmacodynamics						
Clinical studies:						
LA class	*SCN9A*	Recessive variant R1150W	1277 people in total	NA	An altered pain threshold and the effect mediated through C-fiber activation	139
Lidocaine	*MC1R*	Recessive alleles R151C, R160W, D294H		SC	Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy	136

Biophysical and pharmacological ex vivo characterisation of most significant phenotypic alterations:

Drug	Gene	Variant	Study design	Results	Reference
Lidocaine	*SCN9A*	N395K	Ex vivo	Reduced sensitivity to LAs	132
Ranolazine	*SCN9A*	L858H	Ex vivo	Current normalisation	185
Mexiletine	*SCN9A*	L858F and V872G	Ex vivo	Corrects altered channel activation kinetics and frequency dependence	186, 187
Carbamazepine	*SCN9A*	V400M	Ex vivo	Corrects altered channel inactivation kinetics	178
Carbamazepine	*SCN9A*	R996C, V1298D, F1462V, M1627K, V1298F	Ex vivo	Corrects altered channel inactivation kinetics and reduces the persistent sodium current	34
Lacosamide	*SCNxA* (TTX-s)	Wild type	Ex vivo	Selectively enhances slow inactivation	188

Pharmacokinetics

Clinical Studies:

Drug	Gene	Variant	Study population	Results	Reference
Lidocaine and bupivacaine	*CYP3A4*	T20070C (L293P)	72	Increased activity	189
Ropivacaine	*CYP1A2*	C163A		Hypermetabolic phenotype	150, 151
Ropivacaine	*CYP1A2*	G3860A		Decreased metabolic activity in the enzyme produced	150, 151

Biophysical and pharmacological ex vivo characterisation of most significant phenotypic alterations:

Drug	Gene	Variant	Study design	Results	Reference
Cocaine	*BChE*	D70G and A328Y	Ex vivo	Altered binding efficiency for cocaine and deranged catalytic efficiency	144

LA: local anaesthetic; *SCN9A*: $Na_v1.7$ is a sodium ion channel gene; *MC1R*: melanocortin 1 receptor gene; TTX-s: sodium channels sensitive to tetrodotoxin; *BChE*: butyrylcholinesterase (pseudocholinesterase) gene; CYP: cytochrome P450; NA: not available; IV: intravenous; SC: subcutaneous.

glucuronidation process was first noted to be impaired in sufferers from the inherited bilirubin disglucuronidation condition called Gilbert's syndrome, increasing the risk of paracetamol toxicity in affected individuals.[162] Furthermore, evidence, collected by Patel et al.[163] indicated that up to 33% of Oriental subjects displayed relatively extensive glucuronidation with clinically relevant lower incidence of a fulminant liver failure in patients belonging to this ethnic group who ingested large amounts of paracetamol.[164] Activity of CYP2E1 can be decreased by variety of environmental factors such as liver cirrhosis, chronic alcohol abuse and so on.[165]

Ketamine

Ketamine is metabolised to several phase 1 metabolites, including alkylhydroxy-ketamine, nor-ketamine and dihydro-norketamine. CYP enzymes involved in this process are 3A4 (>60% metabolism), 2C9 and 2B6.[166] Norketamine subsequently undergoes phase I liver processing with the aid of 2B6 and 2A6.[167] When tested in a Swedish Caucasian population, 3A4 normal and slow metabolisers demonstrated no difference in overall pharmacokinetic parameters or in ketamine-related side effects.[168]

Tricyclic antidepressants

Amitriptyline belongs to the tricyclic antidepressant (TCA) group of drugs. It has been a first-line treatment for neuropathic pain and fibromyalgia for many years.[169,170] Disappointingly, however, there is still little robust evidence for a beneficial outcome in treating of these chronic pain states.[171] Amitriptyline acts as a combined serotonin–norepinephrine reuptake inhibitor as well as a sodium channel blocker. Descending noradrenergic inhibitory mechanisms are augmented by this class of drugs, and this is thought to be the main mechanism of the anti-neuropathic action of amitriptyline.[172] The norepinephrine transporter (NET) is a peptide that is encoded by the *SLC6A2* gene. *SLC6A2* polymorphism seems to be associated with altered pain thresholds in humans.[173] The influence of SNPs in *SLC6A2* on the efficacy and TCAs in patients suffering with neuropathic pain has not yet been studied.[174]

Carbamazepine

An anticonvulsant carbamazepine is used in postherpetic and trigeminal neuralgias as well as autoimmune-mediated pain states such as Guillain–Barré syndrome.[175] Rare heritable severe pain conditions such as PEPD and some forms of inherited erythromelalgia are treated with this drug as well.[176] Characterisation of sodium current alterations caused by p.1627M>K, p.1464T>I mutations affecting *SCN9A* gene have revealed that the likely mechanism of action of carbamazepine is via a normalisation of voltage dependence of inactivation and activation in VGSC action.[177–179]

Carbamazepine is mainly metabolised by the CYP3A4 enzyme to carbamazepine-10,11-epoxide. This drug has been linked to severe, type B (idiosyncratic, dose-independent) adverse cutaneous and systemic reactions varying from Stevens–Johnson syndrome (SJS) to toxic epidermal necrolysis (TEN).[180,181] There is an association of the development of both TEN and SJS in carriers of the human leukocyte antigen (HLA) *HLA-B*1502* allele. This is observed explicitly in Asians who are prescribed carbamazepine. More recently, both *HLA*3101* and *HLA*1511* alleles have also been identified as potentially contributory to the increased risk of development of these reactions.[182–184] As a result, the Food and Drug Administration (FDA) recommends that before introducing carbamazepine, all Asian patients be genotyped for the *HLA-B*1502* allele.

Discussion

Pharmacogenetics has the potential to provide clinical guidance on drug dosing and timing in order to reach maximum efficacy and minimum side effects and complications. However, with the vast scope of genetic variables likely to contribute to pain phenotypes, 'bedside' clinically available kits have limited applicability.[185]

There have been two main approaches to population-based genetic association studies: candidate gene studies and, more recently, genome-wide association (GWA) studies. Candidate gene studies tend to focus on a small set of SNPs in genes, which are hypothesised to have biological relevance to the condition being studied. In analgesic response studies, these have mainly been in key genes from either pharmacodynamic or pharmacokinetic pathways. The SNPs selected usually include functional SNPs, which may have direct causal relevance. GWA arrays can type as many as one million SNPs across the genome to provide the highest possible coverage of common genetic variation. Associations generated from GWA studies may not have any direct causal relevance and are more likely to be in linkage disequilibrium with underlying causative variants. This approach may also identify novel contributing genes previously unidentified in our current understanding of pain pathways and represents an exciting technique for future investigations.

Population-based genetic association studies, which aim to correlate genotype to phenotype in complex traits, including pain and analgesic response, have had variable success; the reproducibility of results has

remained low. Twin studies demonstrate that up to 60% of the observed variability in response to painful stimuli is genetically determined. However, genetic and environmental factors known to contribute to pain experience are only moderately correlated across different pain modalities, which suggests that different genes influence different types of pain. In pain of mixed aetiology, such as cancer-related pain, genetic influences may therefore not be clearly identified in clinical studies.[186]

The majority of genetic association studies that investigate inter-individual variability in analgesic response have used relatively small sample sizes. There are several factors which contribute to the required sample size, including the prevalence of disease/trait in the general population, the frequency of the susceptibility allele and its effect size and the number of SNPs to be tested. The lower the frequency of the susceptibility allele and lower the effect size, the larger the sample size required. Complex traits are likely to be influenced by multiple genetic variables, all with small or modest effect sizes. Any variant strongly associated with a disease or trait is likely to be rare.[187] Therefore, large sample sizes, possibly of many thousands, are generally preferable in the study of complex traits. The sample sizes in the studies described in this narrative review are generally small and therefore many associations, particularly with small effect sizes, may not have been identified.

The candidate gene approach used to study rare dramatic human phenotypes has identified a variety of promising therapeutic targets. *NTRK1, SCN9A* and *P2X* family of genes have been the focus of drug development for the last decade with some molecules reaching phase 3 clinical trials. Undesirable side effects and idiosyncratic reactions aside, as a proof of concept, these examples greatly encourage more work and research to be done in order to identify more potential drug targets. A recent review article produced by Lotsch and Geisslinger[188] has explored this particular area further.

Pain experience and analgesic response are complex traits, and as such are likely to be influenced by a host of gene–gene and gene–environment interactions. A few studies have started to investigate interactions between polymorphisms from more than one gene; however, so far, this has been limited to two candidate SNPs at once.[90,189] Environmental and patient variables such as compliance, concomitant medications, diet and psychosocial issues also contribute to the ultimate endpoint of analgesic response. The exploration of potential gene–gene/gene–environment interactions or epistasis provides a huge challenge for future pharmacogenomic research, both practical and analytical. Such work requires exponential increases in sample size and focused phenotype definitions.

Other variations besides the DNA sequence may influence phenotype in epigenetic processes, for example, histone modifications and DNA methylation. The purpose of this complex process seems to be the activation or silencing of specific genes. The inherited phenotypic change may be achieved without any alteration in the DNA sequence.[190,191] This phenomenon has already been associated with many other neural functions, including plasticity of synaptic transmission and memory. In the context of peripheral nerve injury, animal studies have revealed epigenetic changes, down-regulating the expression of some members of both the opioid and sodium channel expressing family of genes.[192] This is achieved via the neuron-restrictive silencer factor (NSRF), which is a transcriptional repressor of genes expressed in the peripheral C-fibres. Nociceptor-related targets include OPRM1, SCN10A and KCND3.[193] It remains to be seen if coding polymorphisms of the NSRF complex and related neuron-restrictive silencer element (NRSE) in any way influence our pain perception and alter the way analgesic drugs interact with humans.

The majority of the human genome is transcribed into non-protein coding RNA (ncRNA) molecules, which seem to play a part in genetic adjustments of our traits.[194] Other molecules, 20- to 30-base-pair-long RNAs called microRNAs (miRNAs), target specific sites and alter phenotypes by regulating expression of the whole cluster of genes in a tissue-specific manner. We have only just started to appreciate their influential role on nociceptor-related gene expression patterns and regulation of pain signalling.[195] How to utilise this knowledge of miRNA represents an exciting new chapter of drug discovery.

Any further implementation of pharmacogenetic assays into day-to-day pain management practice faces many obstacles such as ethical, legal and social issues, a lack of readily available resources, as well as the scientific quality of information itself.[196]

Conclusion

Phenotypic differences in pain perception and its pharmacological modulation are significantly dependent on human genetic factors. Knowledge about genes governing pharmacodynamic and pharmacokinetic processes involving analgesic molecules is gaining more consideration among prescribers. Lack of robustness and reproducibility in pain pharmacogenetics correlation studies is one of many significant limitations in development of readily available bedside genotyping devices. Personalised drug selection and dosing for individual patients with acute or chronic pain is still a long way off.

Conflict of interest

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References

1. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* 2007; 7(4): 257–265.
2. Klepstad P, Rakvåg TT, Kaasa S, et al. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiol Scand* 2004; 48(10): 1232–1239.
3. Lalovic B, Kharasch E, Hoffer C, et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* 2006; 79(5): 461–479.
4. Williams DG, Patel A and Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; 89(6): 839–845.
5. Meyer UA. Pharmacogenetics – five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet* 2004; 5(9): 669–676.
6. Watson JD and Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 1953; 171(4356): 737–738.
7. Crick F. Central dogma of molecular biology. *Nature* 1970; 227(5258): 561–563.
8. Frueh FW, Amur S, Mummaneni P, et al. Pharmacogenomic biomarker information in drug labels approved by the United States food and drug administration: prevalence of related drug use. *Pharmacotherapy* 2008; 28(8): 992–998.
9. Li GW and Xie XS. Central dogma at the single-molecule level in living cells. *Nature* 2011; 475(7356): 308–315.
10. Passaro E Jr, Hurwitz M, Samara G, et al. Molecular biology: an overview. *Am J Surg* 1992; 164(2): 146–152.
11. Hamosh A, Scott AF, Amberger JS, et al. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res* 2005; 33(Database issue): D514–D517.
12. Sherry ST, Ward M and Sirotkin K. dbSNP-database for single nucleotide polymorphisms and other classes of minor genetic variation. *Genome Res* 1999; 9(8): 677–679.
13. Han C, Rush AM, Dib-Hajj SD, et al. Sporadic onset of erythermalgia: a gain-of-function mutation in $Na_v1.7$. *Ann Neurol* 2006; 59(3): 553–558.
14. Kidd JM, Cooper GM, Donahue WF, et al. Mapping and sequencing of structural variation from eight human genomes. *Nature* 2008; 453(7191): 56–64.
15. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. *Clin Pharmacokinet* 2009; 48(11): 689–723.
16. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception II. 'Types' of nociception revealed by genetic correlation analysis. *Pain* 1999; 80(1–2): 83–93.
17. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. *Pain* 1999; 80(1–2): 67–82.
18. Livshits G, Popham M, Malkin I, et al. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis* 2011; 70(10): 1740–1745.
19. Williams FM, Spector TD and MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. *Rheumatology* 2010; 49(9): 1753–1755.
20. Hartvigsen J, Nielsen J, Kyvik KO, et al. Heritability of spinal pain and consequences of spinal pain: a comprehensive genetic epidemiologic analysis using a population-based sample of 15,328 twins ages 20-71 years. *Arthritis Rheum* 2009; 61(10): 1343–1351.
21. Norbury TA, MacGregor AJ, Urwin J, et al. Heritability of responses to painful stimuli in women: a Classical Twin Study. *Brain* 2007; 130(Pt 11): 3041–3049.
22. Kehlet H, Jensen TS and Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367(9522): 1618–1625.
23. Mogil JS. Pain genetics: past, present and future. *Trends Genet* 2012; 28(6): 258–66.
24. Young EE, Lariviere WR and Belfer I. Genetic basis of pain variability: recent advances. *J Med Genet* 2012; 49(1): 1–9.
25. Kim H, Neubert JK, San Miguel A, et al. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. *Pain* 2004; 109(3): 488–496.
26. Aubrun F, Langeron O, Quesnel C, et al. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. *Anesthesiology* 2003; 98(6): 1415–1421.
27. Walker JS, Sheather-Reid RB, Carmody JJ, et al. Nonsteroidal antiinflammatory drugs in rheumatoid arthritis and osteoarthritis: support for the concept of 'responders' and 'nonresponders'. *Arthritis Rheum* 1997; 40(11): 1944–1954.
28. MacGregor AJ, Andrew T, Sambrook PN, et al. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. *Arthritis Rheum* 2004; 51(2): 160–167.
29. Turk DC, Flor H and Rudy TE. Pain and families. I Etiology, maintenance, and psychosocial impact. *Pain* 1987; 30(1): 3–27.
30. Foulkes T and Wood JN. Pain genes. *PLoS Genet* 2008; 4(7): e1000086.
31. Auer-Grumbach M, Mauko B, Auer-Grumbach P, et al. Molecular genetics of hereditary sensory neuropathies. *Neuromolecular Med* 2006; 8(1–2): 147–158.

32. Cox J, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006; 444(7121): 894–898.
33. Yang Y, Wang Y, Li S, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genet* 2004; 41(3): 171–174.
34. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* 2006; 52(5): 767–774.
35. Faber CG, Hoeijmakers JG, Ahn HS, et al. Gain of function $Na_v1.7$ mutations in idiopathic small fiber neuropathy. *Ann Neurol* 2012; 71(1): 26–39.
36. Lampert A, O'Reilly AO, Reeh P, et al. Sodium channelopathies and pain. *Pflugers Arch* 2010; 460(2): 249–263.
37. Kremyer B, Lopera F, Cox JJ, et al. A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome (FEPS). *Neuron* 2010; 66(5): 671–680.
38. Einarsdottir E, Carlsson A, Minde J, et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. *Hum Mol Genet* 2004; 13(8): 799–805.
39. American Society of Anesthesiologists, Inc. *58th annual refresher course lectures and basic science reviews*, 1st edn. Park Ridge, IL: American Society of Anesthesiologists, Inc., 2007, 515 pp.
40. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; 13(2): e58–e68.
41. Mercadante S and Bruera E. Opioid switching: a systematic and critical review. *Cancer Treat Rev* 2006; 32(4): 304–315.
42. Riley J, Ross JR, Rutter D, et al. No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. *Support Care Cancer* 2006; 14(1): 56–64.
43. Meng F, Xie GX, Thompson RC, et al. Cloning and pharmacological characterization of a rat kappa opioid receptor. *Proc Natl Acad Sci U S A* 1993; 90(21): 9954–9958.
44. Wang JB, Imai Y, Eppler CM, et al. mu opiate receptor: cDNA cloning and expression. *Proc Natl Acad Sci U S A* 1993; 90(21): 10230–10234.
45. Dietis N, Rowbotham DJ and Lambert DG. Opioid receptor subtypes: fact or artifact? *Br J Anaesth* 2011; 107(1): 8–18.
46. Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature* 1996; 383(6603): 819–823.
47. Chou WY, Wang CH, Liu PH, et al. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. *Anesthesiology* 2006; 105(2): 334–337.
48. Chou WY, Yang LC, Lu HF, et al. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand* 2006; 50(7): 787–792.
49. Sia AT, Lim Y, Lim EC, et al. A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. *Anesthesiology* 2008; 109(3): 520–526.
50. Janicki PK, Schuler G, Francis D, et al. A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. *Anesth Analg* 2006; 103(4): 1011–1017.
51. Lotsch J, von Hentig N, Freynhagen R, et al. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. *Pharmacogenet Genomics* 2009; 19(6): 429–436.
52. Campa D, Gioia A, Tomei A, et al. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. *Clin Pharmacol Ther* 2008; 83(4): 559–566.
53. Walter C and Lotsch J. Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. *Pain* 2009; 146(3): 270–275.
54. Kolesnikov Y, Gabovits B, Levin A, et al. Combined catechol-O-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. *Anesth Analg* 2011; 112(2): 448–453.
55. Kim E, Choi CB, Kang C, et al. Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants. *Ann Rheum Dis* 2010; 69(10): 1889–1890.
56. Zhang W, Yuan JJ, Kan QC, et al. Study of the OPRM1 A118G genetic polymorphism associated with postoperative nausea and vomiting induced by fentanyl intravenous analgesia. *Minerva Anestesiol* 2011; 77(1): 33–39.
57. Klepstad P, Fladvad T, Skorpen F, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. *Pain* 2011; 152(5): 1139–1145.
58. Droney JM, Gretton SK, Sato H, et al. Analgesia and central side-effects: two separate dimensions of morphine response. *Br J Clin Pharmacol* 2013; 75(5): 1340–1350.
59. Quelle FW, Shimoda K, Thierfelder W, et al. Cloning of murine Stat6 and human Stat6, Stat proteins that are tyrosine phosphorylated in responses to IL-4 and IL-3 but are not required for mitogenesis. *Mol Cell Biol* 1995; 15(6): 3336–3343.
60. Ross JR, Rutter D, Welsh K, et al. Clinical response to morphine in cancer patients and genetic variation in candidate genes. *Pharmacogenomics J* 2005; 5(5): 324–336.

61. Steele AD, Szabo I, Bednar F, et al. Interactions between opioid and chemokine receptors: heterologous desensitization. *Cytokine Growth Factor Rev* 2002; 13(3): 209–222.
62. Zaki PA, Keith DE Jr., Brine GA, et al. Ligand-induced changes in surface mu-opioid receptor number: relationship to G protein activation? *J Pharmacol Exp Ther* 2000; 292(3): 1127–1134.
63. Zhang Y, Xiong W, Lin X, et al. Receptor trafficking induced by mu-opioid-receptor phosphorylation. *Neurosci Biobehav Rev* 2009; 33(8): 1192–1197.
64. Bohn LM, Lefkowitz RJ, Gainetdinov RR, et al. Enhanced morphine analgesia in mice lacking beta-arrestin 2. *Science* 1999; 286(5449): 2495–2498.
65. Leandro-Garcia LJ, Leskelä S, Montero-Conde C, et al. Determination of CYP2D6 gene copy number by multiplex polymerase chain reaction analysis. *Anal Biochem* 2009; 389(1): 74–76.
66. Bernard S, Neville KA, Nguyen AT, et al. Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. *Oncologist* 2006; 11(2): 126–135.
67. Lotsch J. Opioid metabolites. *J Pain Symptom Manage* 2005; 29(Suppl. 5): S10–S24.
68. Persson K, Sjöström S, Sigurdardottir I, et al. Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* 1995; 39(2): 182–186.
69. Sindrup SH, Brøsen K, Bjerring P, et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1990; 48(6): 686–693.
70. Madadi P, Koren G, Cairns J, et al. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* 2007; 53(1): 33–35.
71. Heiskanen T, Olkkola KT and Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* 1998; 64(6): 603–611.
72. Thompson CM, Wojno H, Greiner E, et al. Activation of G-proteins by morphine and codeine congeners: insights to the relevance of O- and N-demethylated metabolites at mu- and delta-opioid receptors. *J Pharmacol Exp Ther* 2004; 308(2): 547–554.
73. Gronlund J, Saari TI, Hagelberg NM, et al. Exposure to oral oxycodone is increased by concomitant inhibition of CYP2D6 and 3A4 pathways, but not by inhibition of CYP2D6 alone. *Br J Clin Pharmacol* 2010; 70(1): 78–87.
74. Samer CF, Daali Y, Wagner M, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol* 2010; 160(4): 919–930.
75. Samer CF, Daali Y, Wagner M, et al. The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. *Br J Pharmacol* 2010; 160(4): 907–918.
76. Andreassen TN, Eftedal I, Klepstad P, et al. Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study. *Eur J Clin Pharmacol* 2012; 68(1): 55–64.
77. Stamer UM, Lehnen K, Höthker F, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* 2003; 105(1–2): 231–238.
78. Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin Pharmacol Ther* 2007; 82(1): 41–47.
79. Zhang W, Yuan JJ, Kan QC, et al. Influence of CYP3A5*3 polymorphism and interaction between CYP3A5*3 and CYP3A4*1G polymorphisms on post-operative fentanyl analgesia in Chinese patients undergoing gynaecological surgery. *Eur J Anaesthesiol* 2011; 28(4): 245–250.
80. Duguay Y, Báár C, Skorpen F, et al. A novel functional polymorphism in the uridine diphosphate-glucuronosyltransferase 2B7 promoter with significant impact on promoter activity. *Clin Pharmacol Ther* 2004; 75(3): 223–233.
81. Innocenti F, Liu W, Fackenthal D, et al. Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene. *Pharmacogenet Genomics* 2008; 18(8): 683–697.
82. Andersen G, Christrup L and Sjogren P. Relationships among morphine metabolism, pain and side effects during long-term treatment: an update. *J Pain Symptom Manage* 2003; 25(1): 74–91.
83. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol* 2000; 27(7): 524–528.
84. Kilpatrick GJ and Smith TW. Morphine-6-glucuronide: actions and mechanisms. *Med Res Rev* 2005; 25(5): 521–544.
85. Sawyer MB, Innocenti F, Das S, et al. A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine. *Clin Pharmacol Ther* 2003; 73(6): 566–574.
86. Rutter D. *The pharmacogenetics of morphine metabolism*. London: University of London, 2008.
87. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. *Fundam Clin Pharmacol* 2010; 24(4): 517–524.
88. Coulbault L, Beaussier M, Verstuyft C, et al. Environmental and genetic factors associated with morphine response in the postoperative period. *Clin Pharmacol Ther* 2006; 79(4): 316–324.
89. Ross JR, Riley J, Taegetmeyer AB, et al. Genetic variation and response to morphine in cancer patients: catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. *Cancer* 2008; 112(6): 1390–1403.

90. Green H, Söderkvist P, Rosenberg P, et al. mdr-1 single nucleotide polymorphisms in ovarian cancer tissue: g2677T/A correlates with response to paclitaxel chemotherapy. *Clin Cancer Res* 2006; 12(3 Pt 1): 854–859.
91. Tanabe M, Ieiri I, Nagata N, et al. Expression of P-glycoprotein in human placenta: relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther* 2001; 297(3): 1137–1143.
92. Rakvag TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain* 2005; 116(1–2): 73–78.
93. Laugsand EA, Fladvad T, Skorpen F, et al. Clinical and genetic factors associated with nausea and vomiting in cancer patients receiving opioids. *Eur J Cancer* 2011; 47(11): 1682–1691.
94. Hutchinson MR, Coats BD, Lewis SS, et al. Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. *Brain Behav Immun* 2008; 22(8): 1178–1189.
95. Watkins LR, Hutchinson MR, Ledeboer A, et al. Norman Cousins Lecture. Glia as the 'bad guys': implications for improving clinical pain control and the clinical utility of opioids. *Brain Behav Immun* 2007; 21(2): 131–146.
96. Reyes-Gibby CC, Spitz M, Wu X, et al. Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-alpha-308 G/A IL6-174G/C and IL8-251T/A. *Cancer Epidemiol Biomarkers Prev* 2007; 16(12): 2745–2751.
97. Reyes-Gibby CC, El Osta B, Spitz MR, et al. The influence of tumor necrosis factor-alpha -308 G/A and IL-6 -174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiol Biomarkers Prev* 2008; 17(11): 3262–3267.
98. Blower AL, Brooks A, Fenn GC, et al. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Aliment Pharmacol Ther* 1997; 11(2): 283–291.
99. Hawkey CJ, Cullen DJ, Greenwood DC, et al. Prescribing of nonsteroidal anti-inflammatory drugs in general practice: determinants and consequences. *Aliment Pharmacol Ther* 1997; 11(2): 293–298.
100. Moncada S, Gryglewski R, Bunting S, et al. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976; 263(5579): 663–665.
101. Whittle BJ, Boughton-Smith NK, Moncada S, et al. Actions of prostacyclin (PGI2) and its product, 6-oxo-PGF1alpha on the rat gastric mucosa in vivo and in vitro. *Prostaglandins* 1978; 15(6): 955–967.
102. Kurumbail RG, Stevens AM, Gierse JK, et al. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. *Nature* 1996; 384(6610): 644–648.
103. Riendeau D, Percival MD, Brideau C, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther* 2001; 296(2): 558–566.
104. Ulrich CM, Bigler J, Sibert J, et al. Cyclooxygenase 1 (COX1) polymorphisms in African-American and Caucasian populations. *Human Mutat* 2002; 20(5): 409–410.
105. Sansbury LB, Millikan RC, Schroeder JC, et al. COX-2 polymorphism, use of nonsteroidal anti-inflammatory drugs, and risk of colon cancer in African Americans (United States). *Cancer Causes Control* 2006; 17(3): 257–266.
106. Arisawa T and Hirata I. Genetic polymorphism of COX-1 gene and NSAID-induced ulcer. *Nihon Rinsho* 2007; 65(10): 1885–1889.
107. Clappers N, van Oijen MG, Sundaresan S, et al. The C50T polymorphism of the cyclooxygenase-1 gene and the risk of thrombotic events during low-dose therapy with acetyl salicylic acid. *Thromb Haemos* 2008; 100(1): 70–75.
108. Van Oijen MG, Laheij RJ, Koetsier M, et al. Effect of a specific cyclooxygenase-gene polymorphism (A-842G/C50T) on the occurrence of peptic ulcer hemorrhage. *Dig Dis Sci* 2006; 51(12): 2348–2352.
109. Cipollone F, Toniato E, Martinotti S, et al. A polymorphism in the cyclooxygenase 2 gene as an inherited protective factor against myocardial infarction and stroke. *JAMA* 2004; 291(18): 2221–2228.
110. De Vries HS, te Morsche RH, van Oijen MG, et al. The functional -765G–>C polymorphism of the COX-2 gene may reduce the risk of developing Crohn's disease. *PloS One* 2010; 5(11): e15011.
111. Szczeklik W, Sanak M and Szczeklik A. Functional effects and gender association of COX-2 gene polymorphism G-765C in bronchial asthma. *J Allergy Clin Immunol* 2004; 114(2): 248–253.
112. Sharma V, Kaul S, Al-Hazzani A, et al. Association of COX-2 rs20417 with aspirin resistance. *J Thromb Thrombolysis* 2013; 35(1): 95–99.
113. Ali ZK, Kim RJ and Ysla FM. CYP2C9 polymorphisms: considerations in NSAID therapy. *Curr Opin Drug Discov Devel* 2009; 12(1): 108–114.
114. Goldstein JA and de Morais SM. Biochemistry and molecular biology of the human CYP2C subfamily. *Pharmacogenetics* 1994; 4(6): 285–299.
115. Stubbins MJ, Harries LW, Smith G, et al. Genetic analysis of the human cytochrome P450 CYP2C9 locus. *Pharmacogenetics* 1996; 6(5): 429–439.
116. Kidd RS, Straughn AB, Meyer MC, et al. Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9*3 allele. *Pharmacogenetics* 1999; 9(1): 71–80.
117. Sullivan-Klose TH, Ghanayem BI, Bell DA, et al. The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. *Pharmacogenetics* 1996; 6(4): 341–349.
118. Yamazaki H, Inoue K, Chiba K, et al. Comparative studies on the catalytic roles of cytochrome P450 2C9 and its Cys- and Leu-variants in the oxidation of warfarin, flurbiprofen, and diclofenac by human liver microsomes. *Biochem Pharmacol* 1998; 56(2): 243–251.
119. Crespi CL and Miller VP. The R144C change in the CYP2C9*2 allele alters interaction of the cytochrome

P450 with NADPH:cytochrome P450 oxidoreductase. *Pharmacogenetics* 1997; 7(3): 203–210.
120. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin Pharmacokinet* 1998; 34(2): 101–154.
121. Hamman MA, Thompson GA and Hall SD. Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. *Biochem Pharmacol* 1997; 54(1): 33–41.
122. Martinez C, Blanco G, Ladero JM, et al. Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. *Br J Pharmacol* 2004; 141(2): 205–208.
123. Agundez JA, Garcia-Martin E and Martinez C. Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine? *Expert Opin Drug Metab Toxicol* 2009; 5(6): 607–620.
124. Daily EB and Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. *Pharmacogenomics* 2009; 10(9): 1489–1510.
125. Garcia-Martin E, Martínez C, Tabarés B, et al. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clin Pharmacol Ther* 2004; 76(2): 119–127.
126. Eijkelkamp N, Linley JE, Baker MD, et al. Neurological perspectives on voltage-gated sodium channels. *Brain* 2012; 135(Pt 9): 2585–2612.
127. Toledo-Aral JJ, Moss BL, He ZJ, et al. Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons. *Proc Natl Acad Sci U S A* 1997; 94(4): 1527–1532.
128. Cummins TR, Howe JR and Waxman SG. Slow closed-state inactivation: a novel mechanism underlying ramp currents in cells expressing the hNE/PN1 sodium channel. *J Neurosci* 1998; 18(23): 9607–9619.
129. Rush AM, Cummins TR and Waxman SG. Multiple sodium channels and their roles in electrogenesis within dorsal root ganglion neurons. *J Physiol* 2007; 579(Pt 1): 1–14.
130. Catterall WA. Molecular properties of brain sodium channels: an important target for anticonvulsant drugs. *Adv Neurol* 1999; 79: 441–456.
131. Sheets PL, Jackson JO II, Waxman SG, et al. A $Na_v1.7$ channel mutation associated with hereditary erythromelalgia contributes to neuronal hyperexcitability and displays reduced lidocaine sensitivity. *J Physiol* 2007; 581(Pt 3): 1019–1031.
132. Kuhnert SM, Phillips WJ and Davis MD. Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999; 135(12): 1447–1449.
133. Cregg R, Laguda B, Werdehausen R, et al. Novel mutations mapping to the fourth sodium channel domain of $Na_v1.7$ result in variable clinical manifestations of primary erythromelalgia. *Neuromolecular Med* 2013; 15(2): 265–278.
134. Mogil JS, Wilson SG, Chesler EJ, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci U S A* 2003; 100(8): 4867–4872.
135. Liem EB, Joiner TV, Tsueda K, et al. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology* 2005; 102(3): 509–514.
136. Abdel-Malek ZA. Melanocortin receptors: their functions and regulation by physiological agonists and antagonists. *Cell Mol Life Sci* 2001; 58(3): 434–441.
137. Xia Y, Wikberg JE and Chhajlani V. Expression of melanocortin 1 receptor in periaqueductal gray matter. *Neuroreport* 1995; 6(16): 2193–2196.
138. Reimann F, Cox JJ, Belfer I, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. *Proc Natl Acad Sci U S A* 2010; 107(11): 5148–5153.
139. Dean RA, Christian CD, Sample RH, et al. Human liver cocaine esterases: ethanol-mediated formation of ethylcocaine. *FASEB J* 1991; 5(12): 2735–2739.
140. Brzezinski MR, Abraham TL, Stone CL, et al. Purification and characterization of a human liver cocaine carboxylesterase that catalyzes the production of benzoylecgonine and the formation of cocaethylene from alcohol and cocaine. *Biochem Pharmacol* 1994; 48(9): 1747–1755.
141. Kalow W and Staron N. On distribution and inheritance of atypical forms of human serum cholinesterase, as indicated by dibucaine numbers. *Can J Biochem Physiol* 1957; 35(12): 1305–1320.
142. Lockridge O, Mottershaw-Jackson N, Eckerson HW, et al. Hydrolysis of diacetylmorphine (heroin) by human serum cholinesterase. *J Pharmacol Exp Ther* 1980; 215(1): 1–8.
143. Xie W, Altamirano CV, Bartels CF, et al. An improved cocaine hydrolase: the A328Y mutant of human butyrylcholinesterase is 4-fold more efficient. *Mol Pharmacol* 1999; 55(1): 83–91.
144. Zsigmond EK and Eilderton TE. Survey of local anesthetic toxicity in the families of patients with atypical plasma cholinesterase. *J Oral Surg* 1975; 33(11): 833–837.
145. Watkins PB. Cyclosporine and liver transplantation: will the midazolam test make blood level monitoring obsolete? *Hepatology* 1995; 22(3): 994–996.
146. Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994; 270(1): 414–423.
147. Wang D, Guo Y, Wrighton SA, et al. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. *Pharmacogenomics J* 2011; 11(4): 274–286.
148. Lewis DF, Lake BG and Dickins M. Substrates of human cytochromes P450 from families CYP1 and CYP2: analysis of enzyme selectivity and metabolism. *Drug Metabol Drug Interact* 2004; 20(3): 111–142.
149. Aklillu E, Carrillo JA, Makonnen E, et al. Genetic polymorphism of CYP1A2 in Ethiopians affecting

induction and expression: characterization of novel haplotypes with single-nucleotide polymorphisms in intron 1. *Mol Pharmacol* 2003; 64(3): 659–669.
150. Faber MS and Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharm Ther* 2004; 76(2): 178–184.
151. Hamdy SI, Hiratsuka M, Narahara K, et al. Genotyping of four genetic polymorphisms in the CYP1A2 gene in the Egyptian population. *Br J Clin Pharmacol* 2003; 55(3): 321–324.
152. Barden J, Edwards J, Moore A, et al. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database Syst Rev* 2004; 1: CD004602.
153. Moore A, Collins S, Carroll D, et al. Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997; 70(2–3): 193–201.
154. Prior MJ, Cooper KM, May LG, et al. Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. *Cephalalgia* 2002; 22(9): 740–748.
155. Zhang W, Jones A and Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004; 63(8): 901–907.
156. Hogestatt ED, Jönsson BA, Ermund A, et al. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem* 2005; 280(36): 31405–31412.
157. Köfalvi A. Alternative interacting sites and novel receptors for cannabinoid ligands. In: Köfalvi A (ed.) *Cannabinoids and the brain*. New York: Springer, 2008, pp. 131–160.
158. Pickering G, Loriot MA, Libert F, et al. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* 2006; 79(4): 371–378.
159. Hinz B, Cheremina O and Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* 2008; 22(2): 383–390.
160. Ryder SD and Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Other causes of parenchymal liver disease. *BMJ* 2001; 322(7281): 290–292.
161. Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 2008; 359(3): 285–292.
162. De Morais SM, Uetrecht JP and Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. *Gastroenterology* 1992; 102(2): 577–586.
163. Patel M, Tang BK and Kalow W. Variability of acetaminophen metabolism in Caucasians and Orientals. *Pharmacogenetics* 1992; 2(1): 38–45.
164. Marzilawati AR, Ngau YY and Mahadeva S. Low rates of hepatotoxicity among Asian patients with paracetamol overdose: a review of 1024 cases. *BMC Pharmacol Toxicol* 2012; 13(1): 8.
165. Lauterburg BH and Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. *Gut* 1988; 29(9): 1153–1157.
166. Sinner B and Graf BM. Ketamine. *Handb Exp Pharmacol* 2008; 182: 313–333.
167. Aroni F, Iacovidou N, Dontas I, et al. Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol* 2009; 49(8): 957–964.
168. Persson J, Hasselström J, Maurset A, et al. Pharmacokinetics and non-analgesic effects of S- and R-ketamines in healthy volunteers with normal and reduced metabolic capacity. *Eur J Clin Pharmacol* 2002; 57(12): 869–875.
169. Onghena P and Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; 49(2): 205–219.
170. Fishbain D. Evidence-based data on pain relief with antidepressants. *Ann Med* 2000; 32(5): 305–316.
171. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012; 12: CD008242.
172. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* 1997; 340(2–3): 249–258.
173. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Mol Pain* 2006; 2: 24.
174. Muralidharan A and Smith MT. Pain, analgesia and genetics. *J Pharm Pharmacol* 2011; 63(11): 1387–1400.
175. Walling AD and Dickson G. Guillain-Barre syndrome. *Am Fam Physician* 2013; 87(3): 191–197.
176. Choi JS, Boralevi F, Brissaud O, et al. Paroxysmal extreme pain disorder: a molecular lesion of peripheral neurons. *Nat Rev Neurol* 2011; 7(1): 51–55.
177. Theile JW and Cummins TR. Inhibition of Na_vbeta4 peptide-mediated resurgent sodium currents in Na_v1.7 channels by carbamazepine, riluzole, and anandamide. *Mol Pharmacol* 2011; 80(4): 724–734.
178. Fischer TZ, Gilmore ES, Estacion M, et al. A novel Na_v1.7 mutation producing carbamazepine-responsive erythromelalgia. *Ann Neurol* 2009; 65(6): 733–741.
179. Dib-Hajj SD, Estacion M, Jarecki BW, et al. Paroxysmal extreme pain disorder M1627K mutation in human Na_v1.7 renders DRG neurons hyperexcitable. *Mol Pain* 2008; 4: 37.
180. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996; 135(1): 6–11.
181. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994; 102(6): 28S–30S.
182. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 2011; 364(12): 1134–1143.
183. Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson

syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 2010; 51(12): 2461–2465.
184. Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 2011; 20(5): 1034–1041.
185. Ma JD, Lee KC and Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract* 2012; 25(4): 417–427.
186. Nielsen CS, Stubhaug A, Price DD, et al. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain* 2008; 136(1–2): 21–29.
187. Zondervan KT and Cardon LR. The complex interplay among factors that influence allelic association. *Nat Rev Genet* 2004; 5(2): 89–100.
188. Lotsch J and Geisslinger G. Pharmacogenetics of new analgesics. *Br J Pharmacol* 2011; 163(3): 447–460.
189. Reyes-Gibby CC, Shete S, Rakvåg T, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain* 2007; 130(1–2): 25–30.
190. Feinberg AP. Genome-scale approaches to the epigenetics of common human disease. *Virchows Arch* 2010; 456(1): 13–21.
191. Borrelli E, Nestler EJ, Allis CD, et al. Decoding the epigenetic language of neuronal plasticity. *Neuron* 2008; 60(6): 961–974.
192. Uchida H, Ma L and Ueda H. Epigenetic gene silencing underlies C-fiber dysfunctions in neuropathic pain. *J Neurosci* 2010; 30(13): 4806–4814.
193. Uchida H, Sasaki K, Ma L, et al. Neuron-restrictive silencer factor causes epigenetic silencing of Kv4.3 gene after peripheral nerve injury. *Neuroscience* 2010; 166(1): 1–4.
194. Mattick JS, Amaral PP, Dinger ME, et al. RNA regulation of epigenetic processes. *Bioessays* 2009; 31(1): 51–59.
195. Zhao J, Lee M-C, Momin A, et al. Small RNAs control sodium channel expression, nociceptor excitability, and pain thresholds. *J Neurosci* 2010; 30(32): 10860–10871.
196. Lee KC, Ma JD and Kuo GM. Pharmacogenomics: bridging the gap between science and practice. *J Am Pharm Assoc* 2010; 50(1): e1–e14; quiz e15–e17.