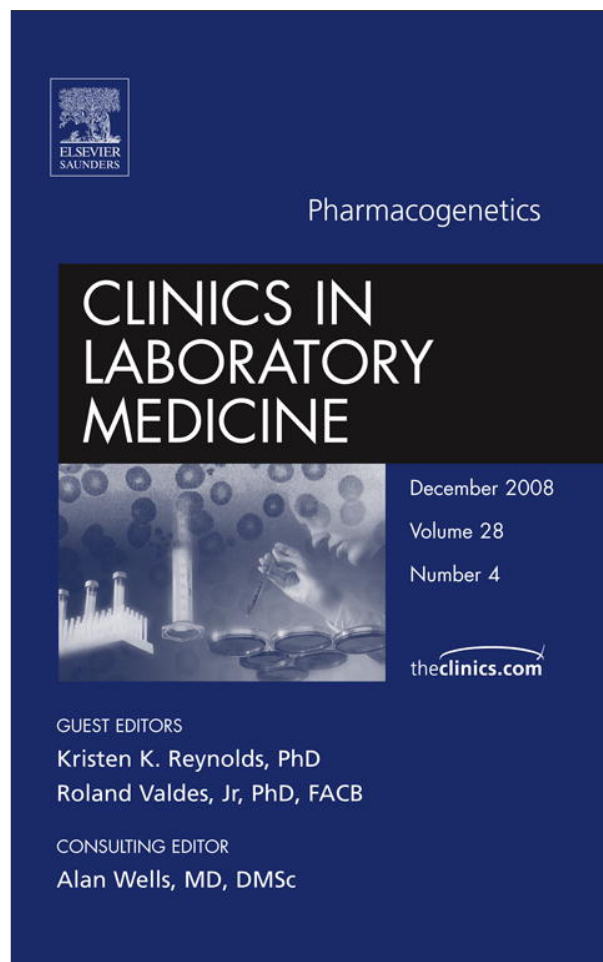


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Pharmacogenetics in Pain Management: the Clinical Need

Lynn R. Webster, MD

*Lifetree Clinical Research and Pain Clinic, 3838 South, 700 East,
Suite 200, Salt Lake City, UT 84106, USA*

Pharmacogenetic therapy in pain patients requires consideration of two different genetic substrates to determine the outcome of pharmacotherapy. The first is the genetic contribution of a variety of different pain types and the second is the genetic influence on drug effectiveness and safety. This article presents evidence of a genetic influence on the prevalence and processing of pain, a discussion of the genetics of drug therapy, and a clinical scenario to illustrate the need to integrate the genetics of pain and pharmacogenetics to achieve the best outcomes.

Genetics of pain

When it comes to nociceptive sensitivity, the stimulus intensity makes a difference and so does the person's experience of pain. Studies to isolate the genetic risk of inheriting a specific pain condition are plentiful, but scientists are only beginning to examine genetic variations that may influence pain processing. If a genetic basis underlies how pain is expressed, including the varying mechanisms of nociceptive, neuropathic, and visceral pain, then the potential exists for new analgesic targets. In the future, the right drug may depend on the patient's genotype.

Financial Disclosures: Advanced Bionic, research-consultant; Alharma Pharmaceuticals and Ameritox, research; Aztra Zenca, research; Cephalon, consultant; CoMentis, research; Covidien, consultant; Durect, research; Elan, research-consultant; Elite, research; Forest, research; GlaxoSmithKline, research; Jazz, research; King Pharmaceutical, research-consultant; LLC, research-consultant; Medtronic, research-consultant; Merck, research; Nektar, research; Nervo, consultant; NeurogesX, research; Pfizer, research; Pain Therapeutics, Inc., research; Purdue, research; QRx, research; Respironics, research; Takeda, research; Torreypines, research; Zars, research.

E-mail address: lynnw@lifetreepain.com

Pain expression is also influenced by environmental factors, such as cultural attitudes, attention, and stress. Fibromyalgia (FM), tension headaches, and irritable bowel syndrome are a few of the functional pain conditions influenced by environmental factors. Environment may sometimes confound efforts to isolate genetic contributions in clinical studies, and these effects should be kept in mind.

Candidate gene studies in pain

The clinical needs in pain management are driven by a broad spectrum of pain sensitivity observed in patients. Clinical observation suggests large interindividual differences in pain sensitivity (Fig. 1), and research confirms that view [1]. Examples of pain conditions that persist in a minority of patients include diabetes with diabetic peripheral neuropathy, herpes zoster with postherpetic neuralgia, lumbar disc degeneration with low back pain, and whiplash injuries with cervicgia [2]. Some of the variance is explained by age, severity of stimulus, and environmental factors, but not all. A genetic influence is suggested by results showing that inbred mouse strains respond differently to the same acute and chronic pain stimuli [3–5].

Allele-based association studies are expected to shed light on the mystery of why pain persists in some patients but not others after nearly identical tissue damage. At present, close to 200 candidate genes have been identified that may be involved in pain processing [2], and there may be thousands more. The 200 molecules have been categorized by their frequency of occurrence in chronic neuropathic pain conditions and further by the strength of evidence, frequency of the specific variant, and likelihood that a genetic polymorphism¹ alters function (Table 1).

Separating genetic from environmental factors is usually best explored through twin studies. Patients with migraine [6–8], back pain [9], and menstrual pain [10] have been studied in twins with estimates of genetic contribution to pain-related traits reported as 39% to 58%, 50%, and 55%, respectively. The following subsections further elucidate findings related to genetics in specific pain conditions.

Low back pain

Low back pain is the leading cause of job-related disability in the United States and second only to headache as the most common neurologic complaint [11]. The causes are many, but degeneration of the spine and intervertebral discs are frequently blamed. Conventional scientific consensus says intervertebral disc degeneration and other spinal abnormalities are largely mechanical, but recent evidence has implicated genetic and biochemical

¹ A polymorphism is a variation in DNA sequencing that occurs in greater than 1% of the population; in contrast, a mutation occurs in less than 1% (Stamer UM, Stüber F. The pharmacogenetics of analgesia. *Expert Opin Pharmacother* 2007;8(14):2235–45).

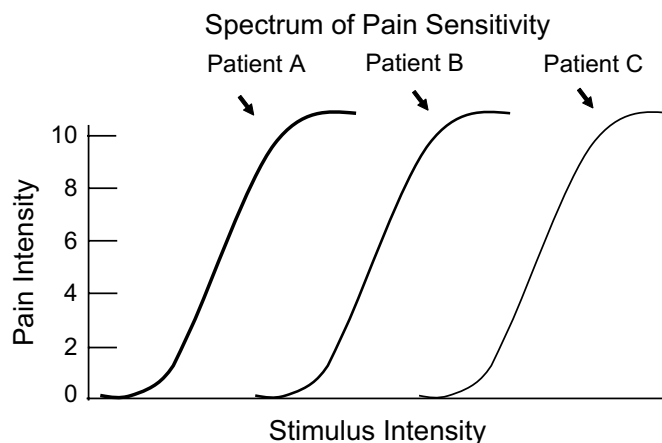


Fig. 1. A simulation of interindividual variability in pain sensitivity: Patient A has increased sensitivity, Patient B has a normal response, and patient C has decreased sensitivity.

mechanisms. In a study of 804 Chinese volunteers, age 18 to 55, investigators found that a polymorphism—the Trp2 allele COL9A2 coding for alpha2 chain of collagen IX—is associated with a fourfold increase in the risk of developing annular tears in people ages 30 to 39 years. The molecule was associated with a 2.4-fold increase in the risk of developing degenerative disc disease and end-plate herniations in people ages 40 to 49 years [12]. In addition, the presence of Trp2 predicted the severity of disc degeneration. The effect was more apparent in some age groups than in others. Boosting evidence that genetic risk factors vary among ethnicities, the Trp3 allele—shown to increase the risk of lumbar disc disease threefold in Finnish patients [13]—was absent in the Chinese population.

Migraine

Migraine is more prevalent in females (17.1%) than in males (5.6%), and evidence points to an X-chromosome link, specifically at the locus of chromosome Xq24-28 [14,15]. High anxiety and certain types of migraines have shown an association with the short (s) allele of the serotonin transporter gene 5HTTLPR polymorphism [16]. Furthermore, hemiplegic migraine is associated with a gene on the 19p13 chromosome, presenting evidence that different types of migraines may be linked to different genetic polymorphisms [17].

Fibromyalgia

Fibromyalgia is a disease characterized by diffuse musculoskeletal pain and generalized tender points. It affects approximately 2% of the general population, and women are more susceptible than men [18]. Studies show FM to be more prevalent within families than in the general population [19,20]; however, the problem of isolating environmental and genetic factors continues. Some evidence exists that FM is autosomal dominant [21]. An

Table 1
High-priority candidate genes for human neuropathic pain

Gene	Molecule	Variant	Location
IL6	Interleukin 6	G 174 C	Promoter
NOS1	Neuronal nitric oxide synthase	AAT VNTR	Intron 20
IL1B	Interleukin 1 β	C 511 T	Promoter
TNF α	Tumor necrosis factor α	G 308 A	Promoter
SLC6A4	Serotonin transporter	5HTTLPR	Promoter
GDNF	Glial-derived nerve factor	(AGG) (n)	3' UTR
BDKRB2	Bradykinin receptor 2	C 58 T	Promoter
COMT	Catechol-O-methyltransferase	Val 158 Met	Exon 3
NOS2A	Inducible nitric oxide synthase	CCTTTn repeat	Promoter
PDYN	Prodynorphin	68 bp repeat	Promoter
OPRM1	μ -opioid receptor	Asn 40 Asp	Exon 1
IL10	Interleukin 10	A 1082 G	Promoter
BDKRB1	Bradykinin receptor 1	G 699 T	Promoter
TH	Tyrosine hydroxylase	Val 81 Met	Exon 3
RET	Protooncogene (tyrosine kinase)	Gly 691 Ser	Exon 11
GRIK3	Kainate (glutamate) receptor	Ser 310 Ala	Coding
IL13	Interleukin 13	Arg 130 Gln	Coding
BDNF	Brain-derived nerve factor	Val 66 Met	Exon 5
ADRA2A	α _{2A} -Adrenergic receptor	C 1291 G	Promoter
CACNA2D2	Calcium channel subunit	G 845 C	Intron 2

Data from Belfer I, Wu T, Kingman A, et al. Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size. Anesthesiology 2004;100(6):1562–72.

association of a gene for FM with human leukocyte antigen has been reported [22] and further supported by research conducted in 40 multicase families with FM [23]. The T102C polymorphism of the 5-HT_{2A} serotonin receptor gene may contribute to nociception in FM, though a link has not been established in FM etiology. An investigation of the T102C allele found that FM patients exhibited a decrease in T/T and an increase in T/C and C/C genotypes when compared with healthy controls [24]. The pain scores for the T/T genotype were significantly higher than for T/C or C/C polymorphisms.

Several disorders associated with fibromyalgia have similar symptoms and also appear to have a similar neuropathology. A large population-based study using the Swedish Twin Registry determined that genetic factors contribute to the co-occurrence of FM with psychiatric disorders, including major depression, generalized anxiety disorder, and eating disorders [25]. Significant co-occurrences were found between FM and chronic fatigue, joint pain, depressive symptoms, and irritable bowel syndrome. Collectively termed “functional somatic syndromes,” these conditions share many clinical features, which point to a shared mechanism for pain sensitivity.

A role has been suggested for polymorphisms of genes in the serotonergic, dopaminergic, and catecholaminergic systems, which are associated with FM and additional comorbid conditions [26]. The polymorphisms

could result in an imbalance of many neurochemicals, leading to the somatic complaints and depression common in FM and related disorders.

Hereditary disorders insensitive to pain

A confirmation of the genetic association to perceived pain is found in the five congenital disorders characterized by defects in normal sensation that have been documented to date (Box 1, [27–31]). Understanding genomic involvement with pain may lead to more precise pain therapies.

Genetics of analgesia

Clinicians who treat pain have always known that the response to opioids varies widely among patients. Differences in bioavailability and pain stimuli explain some of this difference, but genetic makeup is likely a strong factor. Clinicians struggle with finding a consistent response to pain medications because of this tremendous interpatient response. There are several ways genetics influence drug response: through drug metabolism enzymes, drug transporters, opioid or other pain medication receptors, or structures involved in the perception and processing of pain.

Pharmacogenetics describes the effects of polymorphic genes on the enzymes that metabolize drugs. It has been shown that a variation in amino acid sequence replacing an arginine and a serine by a histidine (R265H) and a proline (S268P) residue, respectively, at the mu opioid receptor can change receptor signaling after stimulation with morphine [32]. Ethnic groups are known to vary in response to opioid medications. Caucasians are more prone to sedation and respiratory depression than Asians are, and Native Americans display even more depression of the ventilatory response than do Caucasians [33,34]. Animal studies provide further ballast: in one study, inbred laboratory mice (CXBK) showed no response to levels of morphine that are analgesic for more than 90% of typical mice [35].

What follows is a consideration of research involving certain genetic polymorphisms and their association with increased or reduced drug sensitivity. The evidence, so far, implicates only a few genes in pain processing.

Box 1. Congenital disorders characterized by defects in normal pain processing

Congenital insensitivity to pain with anhidrosis [27]
Familial dysautonomia (also called Riley-Day syndrome or HSAN III) [28]
Lesch-Nyhan syndrome [29]
Tourette's syndrome [30]
De Lange syndrome [31]

Cytochrome P450 2D6 gene

Among the most studied factors in drug metabolism is the CYP2D6, one of the cytochrome P450 enzymes, which are a super-family of drug-metabolizing enzymes that have shown variations in large populations [36]. Researchers have described more than 75 CYP2D6 alleles [36], and further study has found that patients who rapidly metabolize therapeutic drugs have multiple copies of the CYP2D6 gene [37]. Polymorphism of this gene helps explain tremendous individual differences in opioid requirements.

Here, too, research has uncovered notable differences in the frequencies of alleles among different nations and ethnic groups: close to 29% of people in parts of East Africa may have multiple copies of CYP2D6, while the pattern is rare in Northern Europeans [38]. In fact, CYP2D6 gene duplication has been shown to occur in less than 2.6% of Caucasians [39].

OPRM1 118G

The mu-opioid receptor encoded by genetic locus OPRM1 is a prime site of action for endogenous opioid peptides and, thus, of interest to genetic investigators. Laboratory and clinical evidence has shown increased opioid requirements in patients with the OPRM1 118G polymorphism [40–42]. Of 120 patients who underwent total knee arthroplasty, patients who were 118G homozygotes consumed significantly more morphine than did patients who were 118A homozygotes or heterozygotes [41]. A further study found significantly greater opioid consumption to achieve pain control in 118G homozygotes compared with 118A homozygotes for hysterectomy patients during the first 24 hours postsurgery [42].

Catechol-O-methyltransferase gene

Catechol-O-methyltransferase metabolizes catecholamines and is important for dopaminergic and adrenergic/noradrenergic neurotransmission. A common polymorphism at amino acid position 158 (Val158Met) has been shown to impact human pain response [43]. Individuals with a homozygous methionine-158 genotype showed diminished regional mu-opioid system response to pain when compared with heterozygotes, and also demonstrated higher sensory and affective ratings of pain. Cancer patients with the Met/Met genotype also have shown a heightened need for morphine [44]. However, other research has found only a weak association between polymorphisms in the monoamine neurotransmitter systems and postsurgical pain response [45].

Melanocortin-1 receptor gene

The Melanocortin-1 receptor (MC1R) gene variants offer additional interesting evidence of the potential for highly targeted analgesia based on sex and other differences. There is evidence that women, more than men,

respond to kappa-induced analgesia [46], which is mediated by the MC1R [47]. Women carrying two nonfunctional alleles displayed greater pentazocine (kappa agonist) analgesic response compared with women with one or no such alleles, or men [48]. Furthermore, 75% of individuals with red hair and pale skin phenotypes carry two or more inactivating variants of the MC1R [48].

Affect of genotype variants on dose

The opioid dose required for analgesia will be affected by genotype variants. One dose does not fit all. For example, a patient with the variant of OPRM1 may require twice the standard morphine dose to be effective. This variability in clinical effect among patients based on genotype emphasizes the need to perform pharmacogenetic assessments in patients, perhaps leading to the concept of “pharmacogenetic-based dose adaptation” [49].

Joining the genetics of pain and analgesia for clinical utility

Pharmacotherapy for chronic pain will encompass the genetic research on the variability of pain expression and the variations in response to analgesic medications. One clinical scenario that presents difficulty in this regard lies in initiating doses of methadone for pain.

Initiating methadone: a clinical scenario

Unintentional overdose deaths involving methadone are rising. A report by the National Drug Intelligence Center found methadone deaths rose 390% from 1999 through 2004, a higher rate than for any other opioid [50]. A common scenario in these deaths is accumulation of methadone to a toxic level during initiation for pain therapy or addiction treatment because of an overestimation of tolerance and lack of consideration for methadone's long, variable half-life, according to the United States Substance Abuse and Mental Health Services Administration [51]. Because many deaths from methadone occur within the first few weeks of initiating therapy, poor methadone metabolism in a subset of patients may well be a factor.

The cytochrome P450 (CYP) enzyme system is a key player in methadone metabolism, and research is aimed at discovering which isoenzymes have the most influence. Although its metabolism is complex and research is incomplete, methadone appears to be metabolized mainly by CYP2B6 [52–54]. Testing for this isoenzyme may help identify who is at risk for slow metabolism and, therefore, toxicity from drug accumulation.

The spectrum of medication response

Genotyping for CYP2D6 has resulted in classifying morphine recipients as poor metabolizers, extensive metabolizers, intermediate metabolizers,

or ultrarapid metabolizers [55] with consequences for pain sensitivity and opioid consumption. The categorization suggests a spectrum of possible responses from analgesia to lack of efficacy to toxicity after the same doses.

Furthermore, poor metabolism of opioids could compromise the interpretations of urine drug testing administered to ensure compliance with opioid therapy. If genotyping were to reveal poor or ultrarapid opioid metabolizers, clinicians may find quantitative urine drug testing useful in assessing whether patients are consuming their prescriptions as directed or possibly diverting some of them.

Adverse drug reactions

Genetic variations that impact a patient's drug sensitivity can lead to adverse reactions, toxicity, or therapeutic failure [56]. Of 27 drugs frequently cited in adverse drug reaction studies, 59% are metabolized by at least one enzyme with a variant allele known to cause poor metabolism [57]. That compares with 7% to 22% of randomly selected drugs. Tailoring therapy based upon each individual's genotype should yield increased therapeutic effectiveness and minimize adverse effects.

Summary

Each person carries his or her own genetic imprint for pain response and medication sensitivity. How this genetic profile is expressed may be significantly influenced by the environment. Studies of genetic polymorphisms linked to pain syndromes and medication metabolism promise a fresh therapeutic approach where targeted analgesia with fewer side effects may be possible based on genotype.

Acknowledgments

The author would like to thank Beth Dove of Lifetree Clinical Research and Pain Clinic for providing technical writing and manuscript review.

References

- [1] Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci U S A* 1999;96(14):7744–51 [review].
- [2] Belfer I, Wu T, Kingman A, et al. Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size. *Anesthesiology* 2004; 100(6):1562–72.
- [3] 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.
- [4] Lariviere WR, Wilson SG, Laughlin TM, et al. Heritability of nociception. III. Genetic relationships among commonly used assays of nociception and hypersensitivity. *Pain* 2002;97(1–2):75–86.

- [5] Seltzer Z, Wu T, Max MB, et al. Mapping a gene for neuropathic pain-related behavior following peripheral neurectomy in the mouse. *Pain* 2001;93(2):101–6.
- [6] Honkasalo ML, Kaprio J, Winter T, et al. Migraine and concomitant symptoms among 8167 adult twin pairs. *Headache* 1995;35(2):70–8.
- [7] Larsson B, Bille B, Pedersen NL. Genetic influence in headaches: a Swedish twin study. *Headache* 1995;35(9):513–9.
- [8] Ziegler DK, Hur YM, Bouchard TJ Jr, et al. Migraine in twins raised together and apart. *Headache* 1998;38(6):417–22.
- [9] Bengtsson B, Thorson J. Back pain: a study of twins. *Acta Genet Med Gemellol (Roma)* 1991;40(1):83–90.
- [10] Treloar SA, Martin NG, Heath AC. Longitudinal genetic analysis of menstrual flow, pain, and limitation in a sample of Australian twins. *Behav Genet* 1998;28(2):107–16.
- [11] National Institute of Neurological Disorders and Stroke. 2003 Low back pain fact sheet. Office of Communications and Public Liaison. National Institutes of Health. Bethesda (MD): NIH Publication No. 03-5161; Available at: http://www.ninds.nih.gov/disorders/backpain/detail_backpain.htm. Updated January 10, 2008. Last accessed March 6, 2008.
- [12] Jim JJ, Noponen-Hietala N, Cheung KM, et al. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. *Spine* 2005;30(24):2735–42.
- [13] Paassilta P, Lohiniva J, Göring HH, et al. Identification of a novel common genetic risk factor for lumbar disk disease. *JAMA* 2001;285(14):1843–9.
- [14] Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68(5):343–9.
- [15] Nyholt DR, Curtain RP, Griffiths LR. Familial typical migraine: significant linkage and localization of a gene to Xq24-28. *Hum Genet* 2000;107(1):18–23.
- [16] Gonda X, Rihmer Z, Juhasz G, et al. High anxiety and migraine are associated with the s allele of the 5HTTLPR gene polymorphism. *Psychiatry Res* 2007;149(1–3):261–6.
- [17] Joutel A, Boussier MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet* 1993;5(1):40–5.
- [18] Chakrabarty S, Zoorob R. Fibromyalgia. *Am Fam Physician* 2007;76(2):247–54.
- [19] Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum* 2004;50(3):944–52.
- [20] Buskila D, Neumann L, Hazanov I, et al. Familial aggregation in the fibromyalgia syndrome. *Semin Arthritis Rheum* 1996;26(3):605–11.
- [21] Pellegrino MJ, Waylonis GW, Sommer A. Familial occurrence of primary fibromyalgia. *Arch Phys Med Rehabil* 1989;70(1):61–3.
- [22] Burda CD, Cox FR, Osborne P. Histocompatibility antigens in the fibrositis (fibromyalgia) syndrome. *Clin Exp Rheumatol* 1986;4(4):355–8.
- [23] Yunus MB, Khan MA, Rawlings KK, et al. Genetic linkage analysis of multicase families with fibromyalgia syndrome. *J Rheumatol* 1999;26(2):408–12.
- [24] Bondy B, Spaeth M, Offenbaecher M, et al. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. *Neurobiol Dis* 1999;6(5):433–9.
- [25] Kato K, Sullivan P, Evengård B, et al. Chronic widespread pain and its comorbidities: a population-based study. *Arch Intern Med* 2006;166(15):1649–54.
- [26] Buskila D, Sarzi-Puttini P, Ablin JN. The genetics of fibromyalgia syndrome. *Pharmacogenomics* 2007;8(1):67–74.
- [27] Berkovitch M, Copeliovitch L, Tauber T, et al. Hereditary insensitivity to pain with anhidrosis. *Pediatr Neurol* 1998;19(3):227–9.
- [28] Blumenfeld A, Slaugenhaupt SA, Axelrod FB, et al. Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. *Nat Genet* 1993;4(2):160–4.
- [29] Shapira J, Zilberman Y, Becker A. Lesch-Nyhan syndrome: a nonextracting approach to prevent mutilation. *Spec Care Dentist* 1985;5(5):210–2.

- [30] Lowe O. Tourette's syndrome: management of oral complications. *ASDC J Dent Child* 1986;53(6):456–60.
- [31] Shear CS, Nyhan WL, Kirman BH, et al. Self-mutilative behavior as a feature of the de Lange syndrome. *J Pediatr* 1971;78(3):506–9.
- [32] Befort K, Filiol D, Decalliot FM, et al. A single nucleotide polymorphic mutation in the human μ -opioid receptor severely impairs receptor signaling. *J Biol Chem* 2001;276:3130–7.
- [33] Zhou HH, Sheller JR, Nu HE, et al. Ethnic differences in response to morphine. *Clin Pharmacol Ther* 1993;54:507–13.
- [34] Cepeda MS, Farrar JT, Roa JH, et al. Ethnicity influences morphine pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2001;70(4):351–61.
- [35] Schuller AG, King MA, Zhang J, et al. Retention of heroin and morphine-6 beta-glucuronide analgesia in a new line of mice lacking exon 1 of MOR-1. *Nat Neurosci* 1999;2(2):151–6.
- [36] Weinshilboum R. Inheritance and drug response. *N Engl J Med* 2003;348(6):529–37.
- [37] Johansson I, Lundqvist E, Bertilsson L, et al. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci U S A* 1993;90:11825–9.
- [38] Aklillu E, Persson I, Bertilsson L, et al. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. *J Pharmacol Exp Ther* 1996;278:441–6.
- [39] Sachse C, Brockmüller J, Bauer S, et al. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet* 1997;60(2):284–95.
- [40] 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):1232–9.
- [41] 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):787–92.
- [42] 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):334–7.
- [43] Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003;299(5610):1240–3.
- [44] Rakvåg 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):73–8.
- [45] 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.
- [46] Gear RW, Miaskowski C, Gordon NC, et al. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med* 1996;2(11):1248–50.
- [47] 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):4867–72.
- [48] Mogil JS, Ritchie J, Smith SB, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet* 2005;42(7):583–7.
- [49] Lötsch J, Geisslinger G. Current evidence for a genetic modulation of the response to analgesics. *Pain* 2006;121(1–2):1–5.
- [50] Methadone diversion, abuse, and misuse: deaths increasing at alarming rate Product No. 2007-Q0317-001. Johnstown, PA: US Department of Justice, National Drug Intelligence Center; 2007.
- [51] Center for Substance Abuse Treatment. Methadone-associated mortality: report of a national assessment, May 8–9, 2003. Rockville (MD): CSAT Publication No. 28-03; Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. 2004.

- [52] Clark JD. Understanding methadone metabolism: a foundation for safer use. *Anesthesiology* 2008;108(3):351–2.
- [53] Totah RA, Sheffels P, Roberts T, et al. Role of CYP2B6 in stereoselective human methadone metabolism. *Anesthesiology* 2008;108(3):363–74.
- [54] Crettol S, Déglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther* 2006;80(6):668–81.
- [55] Candiotti KA, Yang Z, Curia L, et al. The impact of CYP2D6 genetic polymorphism on postoperative morphine consumption. Presented at the 24th Annual Meeting of the American Academy of Pain Medicine. Orlando (FL) (February 12–16, 2008). [Poster 120].
- [56] Stamer UM, Stüber F. The pharmacogenetics of analgesia. *Expert Opin Pharmacother* 2007; 8(14):2235–45 [review].
- [57] Phillips KA, Veenstra DL, Oren E, et al. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 2001;286(18):2270–9.