

## Review Article

# Pharmacogenetics of Chronic Pain and Its Treatment

**Svatopluk Světlík, Karolína Hronová, Hana Bakhouche,  
Olga Matoušková, and Ondřej Slanař**

*Institute of Pharmacology, First Faculty of Medicine, Charles University Prague, Albertov 4, 12800 Prague, Czech Republic*

Correspondence should be addressed to Ondřej Slanař; oslan@lf1.cuni.cz

Received 30 January 2013; Accepted 12 April 2013

Academic Editor: Metoda Lipnik-Stangelj

Copyright © 2013 Svatopluk Světlík et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This paper reviews the impact of genetic variability of drug metabolizing enzymes, transporters, receptors, and pathways involved in chronic pain perception on the efficacy and safety of analgesics and other drugs used for chronic pain treatment. Several candidate genes have been identified in the literature, while there is usually only limited clinical evidence substantiating for the penetration of the testing for these candidate biomarkers into the clinical practice. Further, the pain-perception regulation and modulation are still not fully understood, and thus more complex knowledge of genetic and epigenetic background for analgesia will be needed prior to the clinical use of the candidate genetic biomarkers.

## 1. Introduction

It is well recognized that pain perception as well as pain relief after analgesic treatment display large interindividual variability in the population that affects selection of analgesics and their dosing in the population. Age, gender, ethnicity, and actual level of stress, mood, or diseases may modify individual pain perception. This alters also the response to drug treatment, which represents a complex interaction between analgesic medication and organism. Several mechanisms may be involved in the pain relief either as drug targets or as drug metabolizing enzymes/transporters, and the genetic variability in these processes influence the analgesic efficacy in individual patients. This review is focused on highlighting the genetic variability reported to affect chronic pain treatment efficacy. This paper does not provide exhaustive list of polymorphisms reported but focuses on the current status of the most recognized pharmacogenetic areas and variables in the treatment of chronic pain.

## 2. Neurotransmitters

At least 100 substances can act as neurotransmitters, some of them being released after stimulation of sensory receptors, for example, catecholamines, GABA, and serotonin.

Genes associated with synthesis, release, or target proteins for these pain neurotransmitters all represent candidate genes for chronic pain treatment variability. Variation in these pain-associated genes may result not only in variable pain perception but also in variable drug efficacy. Chronic pain and its association with gene polymorphism involved in neurotransmission have been widely studied in animal models. So far, 371 candidate genes have been identified in mice (<http://www.jbldesign.com/jmogil/enter.html>, accessed in December 2012), and some of them have been also shown to be of clinical relevance for man. Overview of major recently studied pain-associated genes in humans is presented in Table 1. However, the clinical data suggesting possible routine use of all these genetic biomarkers is unconvincing. Studies describing an association of various neurotransmission-related gene polymorphisms with variability of drug response in the treatment of chronic pain are listed in Table 2.

Recently, Klepstad et al. analyzed 112 SNPs in 25 candidate genes involved in opioid neurotransmission (OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat6, ABCB1, COMT, HRH1, ADRA2A, MC1R, TACR1, GCH1, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3D, HTR3E, HTR1, and CNR1) in a large cohort of oncologic patients [22]. No association of these SNPs with opioid dosing (oxycodone, morphine, and fentanyl) was observed. However, haplotypes

TABLE 1: Overview of recently released (2010–2012) studies assessing the influence of various gene polymorphisms on pain perception in humans.

Gene	Refrence	Polymorphisms	Populations	Results
	Hocking et al., 2010 [1]	Totally 11 SNPs	$n = 8572$ , 1958 British birth cohort (83% Caucasians)	No associations of either chronic widespread pain or pain status with COMT genotypes or haplotypes
	Finan et al., 2010 [2]	rs4680	$n = 46$ female fibromyalgia patients (93.0% Caucasians)	Individuals with met/met genotype experienced a greater decline in positive effect on days when pain was elevated more than did either val/met or val/val individuals, <i>COMT</i> genotype contributing 1% of variance over and above the effect of pain on PA
	Fijal et al., 2010 [3]	rs6269, rs4633, rs4818, rs4680, and haplotypes	$n = 159/93$ female/male Caucasians with major depressive disorder	Associations between a haplotype created using rs6269, rs4633, rs4818, and rs4680, and the proportion of female patients with “Pain While Awake” and “Overall Pain” at baseline. No association was found in males
	Fernandez-de-las-Penas et al., 2011 [4]	rs4680	$n = 70$ children with chronic tension type headache, $n = 70$ healthy children	Children with chronic tension type headache (CTTH) met/met genotype-longer headache history compared with met/val ( $P = 0.001$ ) or val/val ( $P = 0.002$ ), children with CTTH, met/met genotype showed lower pressure pain test score over upper trapezius and temporalis muscles than children with CTTH with met/val or val/val genotype.
COMT	Barbosa et al., 2012 [5]	rs4680 and rs4818	$n = 112$ fibromyalgia patients $n = 110$ healthy individuals	SNP rs4818, the frequency of variant genotype CC was 73.21 and 39.09% for patients with FS and controls, respectively, Fibromyalgia Impact Questionnaire score was higher in patients with the homozygous variant genotype for SNPs rs4680 (87.92 points) and rs4818 (86.14 points) met/met subjects exhibited stronger pain-related fMRI signals than val/val in several brain structures, including the periaqueductal gray matter, lingual gyrus, cerebellum, hippocampal formation, and precuneus
	Loggia et al., 2011 [6]	rs4680	$n = 54$ healthy subjects	rs4633 T allele—greater improvement in ODI (Oswestry disability index) score 1 year after surgery ATCA haplotype-APS-average pain sensitivity (9.3% in the study population)—greater improvement in ODI. The greatest mean improvement in ODI-ATCA-homozygotes
	Dai et al., 2010 [7]	rs6269, rs4633, rs4818, rs4680, and haplotypes	$n = 69$ patients with low back pain who underwent an intervention	Association of rs4633 and rs4680 with posttreatment improvement in VAS, for better improvement among heterozygous patients compared to the homozygous ones, no association was observed for the analysis of the common haplotypes
	Omair et al., 2012 [8]	rs4633, rs4680, rs4818, rs6269, rs2097603, and haplotypes	$N = 93$ patients with low back pain	Fibromyalgia individuals with the met/met genotype (Val158Met SNP) or the high- and average-pain sensitivity-associated haplotypes showed higher sensitivity to thermal and pressure pain stimuli than patients carrying the LPS haplotype or val alleles (Val158Met SNP)
	Martinez-Jauand et al., 2013 [9]	rs6269, rs4633, rs4818 rs4680, and haplotypes	$N = 113$ fibromyalgia patients $n = 65$ healthy controls	Brief pain inventory average pain scores higher in AG heterozygotes
OPRM1	Klepstad et al., 2004 [10] Olsen et al., 2012 [11]	A118G (rs1799971)	$N = 99$ Caucasians $N = 258$ patients with lumbar disc herniation and sciatic pain, Caucasians	*/G women had 2.3 times as much pain as the */G men 12 months after the disc herniation, while A/A women and A/A men had almost exactly the same recovery rate

TABLE 1: Continued.

Gene	Refrence	Polymorphisms	Populations	Results
OPRM1	Menon et al., 2012 [12]	A118G	<i>n</i> = 153 chronic migraine females, Caucasians	G118 allele carriers were more likely to be high pain sufferers compared to homozygous carriers of the A118 allele (OR = 3.125, 95% CI = 1.41, 6.93, <i>P</i> = 0.0037)
	Finan et al., 2010 [2]	A118G	<i>n</i> = 46 female patients with fibromyalgia 93.0% Caucasians	Patients with an 118G allele reported higher positive affect score across diary days than those homozygous for 118A
	Janicki et al., 2006 [13]	A118G	<i>n</i> = 121 chronic, non-cancer pain patients, <i>n</i> = 101 opioid-naïve subjects with acute postoperative pain, Caucasians	The frequency of 118G is significantly lower in the subjects with chronic pain than in the group with acute postoperative pain—0.079 versus 0.158; <i>P</i> = 0.009
GCH1	Heddini et al., 2012 [14]	rs8007267 rs3783641 rs10483639	<i>n</i> = 98 women with provoked vestibulodynia, healthy controls <i>n</i> = 102	Significant interaction effect of GCH1 gene polymorphism and hormonal contraceptive therapy on coital pain among patients with current treatment ( <i>n</i> = 36)
TRPV1	Carreno et al., 2012 [15]	rs222741	<i>n</i> = 1040 cases—Caucasians, 1037 controls	Association of rs222741 with the overall migraine group
SCN9A	Reeder et al., 2013 [16]	rs6746030	<i>n</i> = 53 biopsy specimens, <i>n</i> = 26 control specimens	AA or AG genotypes were present in 39.6% patients with cystitis/bladder pain syndrome—statistically significant difference compared with the controls: 11.5%
KCNS1	Costigan et al., 2010 [17]	rs734784	<i>n</i> = 1359 six independent cohorts	rs734784 significantly associated with higher pain scores in five of six independent patient cohorts, lumbar back pain with disc herniation—association with greater pain outcome in homozygote patients. The combined <i>P</i> value for pain association in all six cohorts
CACNG2	Nissenbaum et al., 2010 [18]	Totally 12 SNPs	<i>n</i> = 549 breast cancer patients: <i>n</i> = 215 control group <i>n</i> = 334	rs4820242, rs2284015, rs2284017, rs2284018, and rs1883988 showed significant association with chronic pain
ADRB2	Diatchenko et al., 2006 [19]	Totally 8 SNPs and their haplotypes H1, H2, and H3	<i>n</i> = 181 cohort of females (Caucasians)	H1/H2 and/or H1/H3—lowest temporomandibular disorder incidence—1.3%, H1/H1 elevated risk of developing temporomandibular disorder (RR = 8.0, 95% CI = 1.2–52.2, 99% CI = 0.815–79.7), H3/H3, H2/H3, and H2/H1 H1 elevated risk of developing temporomandibular disorder (RR = 11.3, 95% CI = 1.95–67.9, and 99% CI = 1.38–102)
	Hocking et al., 2010 [1]	rs12654778 and rs1042713	<i>n</i> = 8572, 1958 British birth cohort (82.6% Caucasians)	ADRB2 SNPs rs12654778 and rs1042713 were associated either with chronic widespread pain alone or with pain status
HTR2A	Nicholl et al., 2011 [20]	Totally 47 SNPs	<i>n</i> = 164, control group <i>n</i> = 172	rs12584920T (T/*, T/T) increased likelihood of having chronic widespread pain (OR) = 1.64, 95% confidence interval (95% CI) = 1.01–2.60 ( <i>P</i> = 0.03) in the discovery cohort, and OR = 1.46, 95% CI = 1.07–2.00 ( <i>P</i> = 0.018) in the validation cohort, similar association between rs17289394 and the maximum number of pain sites reported in both cohorts

VAS: visual analogue scale, OR: odds ratio, RR: relative risk, CI: confidence interval, SNP: single-nucleotide polymorphism, fMRI: functional magnetic resonance. GCH1: GTP cyclohydrolase 1, the rate limiting enzyme in the biosynthesis of tetrahydrobiopterin is an essential cofactor in the synthesis of serotonin, nitric oxide, and catecholamines. These neurotransmitters are known to modulate pain perception. TRPV1: transient receptor potential cation channel, subfamily V, member 1, acts as an integrator of multiple painful stimuli in chronic pain conditions. SCN9A: sodium channel, voltage-gated, type IX, alpha subunit encodes the voltage-gated sodium channel. Homozygotes with 2 loss-of-function alleles are congenitally indifferent to pain without other neurological deficit. KCNS1: voltage-gated potassium channel 1. CACNG2: calcium channel, voltage-dependent, gamma-subunit 2, encodes the gamma-2 transmembrane AMPA receptor protein (TARP) stargazin. This protein is known to be involved in the modulation of the ion channel function of glutamatergic AMPA receptors. ADRB2-beta2-adrenergic receptor is a target for epinephrine. HTR2A: 5-hydroxytryptamine (serotonin) receptor 2A. P2X7: cAMP responsive element binding protein 1.

TABLE 2: Trials assessing the influence of gene polymorphisms associated with neurotransmission on drug response in humans.

Gene	References	Drugs	Polymorphisms	Populations	Results
	Laugsand et al., 2011 [21]	Opioids (morphine, oxycodone, fentanyl, others)	rs4680, rs4633	n = 1579 cancer patients (European Caucasians) from the cohort of [22]	C allele of rs165722, the T allele of rs4633 and the G allele of rs4680 had less nausea/vomiting
	Reyes-Gibby et al., 2007 [23]	Morphine	rs4680	n = 207 cancer	Carriers of val/val and val/met genotype required 63% and 23%, respectively, higher morphine dose compared to carriers of met/met genotype
	Lötsch et al., 2009 [24]	Various opioids		n = 352 patients with chronic pain of various origin	No association
COMT	Klepstad et al., 2011 [22]	Morphine (n = 830), oxycodone (n = 446), fentanyl (n = 699), or other opioids (n = 234)	112 SNPs in the 25 candidate genes including OPRM1 A118G	n = 2294 cancer patients, European Caucasians	None of SNPs in the candidate genes OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat6, ABCB1, COMT, HRH1, ADRA2A, MCIR, TACR1, GCH1, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3D, HTR3E, HTR1, or CNR1 showed significant associations with opioid dose
	Rakvåg et al., 2008 [25]	Morphine	11 SNP and haplotypes, including rs4680, rs4633 not included	n = 197 Caucasian cancer patient cohort receiving oral morphine treatment for cancer pain	The most frequent haplotype (34.5% rs2075507, rs37866, rs7287550R, rs5746849, rs740603, rs6269, rs2239393, rs4818, rs4680 (Val158Met) rs174699, rs165728 GACAAAACATT) associated with lower morphine doses, with a reduction factor of 0.71
	Ross et al., 2008 [26]	Morphine	13 SNPs, rs4818 not included	n = 228 cancer patients on morphine	Haplotype in intron 1 (AATTGAAATAATT) and 4873G genotype (10% is strongly associated with somnolence), hallucinations and confusion after treatment with morphine (protective effect). ABCB1 genotypes and haplotypes investigated in the study as well allele 21/2677G and 12/1236C associated with somnolence, hallucinations, and confusion after treatment with morphine (protective effect)
OPRM1	Reyes-Gibby et al., 2007 [23]	Morphine	A118G	n = 207 cancer patients, Caucasians	GG genotype required 93% higher morphine dose compared to carriers of AA genotypes ( $P = 0.012$ )
	Klepstad et al., 2004 [10]	Morphine	A118G	n = 99 cancer patients, Caucasians	No association with the intensities of symptoms such as fatigue, nausea and vomiting, dyspnea, sleep disturbance, loss of appetite, and constipation were similar between the three cohorts. The serum concentrations of morphine, M6G, and M3G were higher in patients homozygous for the 118G allele
	Campa et al., 2008 [27]	Morphine	A118G	n = 145 Italian Caucasians	Significant association of pain relief after treatment with morphine with the allele. The association improved with the combination of the allele and polymorphism in ABCB1 detection of three groups: strong responders, responders, and nonresponders, sensitivity → → 100%, specificity > 70%
	Lötsch et al., 2009 [24]	Various opioids	A118G	n = 352 patients with chronic pain of various origin	Tendency towards increased pain in dose-dependent manner with the $\mu$ -opioid receptor variant 118G. Daily opioid doses significantly decreased in a gene dose-dependent manner with the P-glycoprotein variant ABCB1 3435C>T

TABLE 2: Continued.

Gene	References	Drugs	Polymorphisms	Populations	Results
Liu and Wang 2012 [28]		Acetaminophen/ tramadol	A118G	<i>n</i> = 96 patients with adenocarcinoma of the colon or rectum ( <i>n</i> = 84), or stomach ( <i>n</i> = 12) who developed oxaliplatin-induced painful neuropathy	The requirement for rescue analgesia higher for patients with G allele, AA genotype-better analgesic effect than G allele variants (AG or GG genotypes). Pretreatment and posttreatment VAS scores for patients with G allele variants were 3.1 and 2.6, respectively; for patients with AA genotype, pretreatment and posttreatment VAS scores were 3.0 and 0.9
OPRM1 Janicki et al., 2006 [13]	Morphine		A118G	<i>n</i> = 121 chronic, noncancer pain patients, Caucasians	The mean opioid dose is significantly larger in the homozygous carriers of the wild-type 118A allele when compared with the carriers of the variant allele
Klepstad et al., 2011 [22]	Morphine ( <i>n</i> = 830), oxycodone ( <i>n</i> = 446), fentanyl ( <i>n</i> = 699), or other opioids ( <i>n</i> = 234)		112 SNPs in the 25 candidate genes including OPRM1 A118G	<i>n</i> = 2294 cancer patients, European Caucasians	None of SNPs in the candidate genes OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat6, ABCB1, COMT, HRH1, ADRA2A, MC1R, TACR1, GCH1, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3D, HTR3E, HTTR, or CNRI showed significant associations with opioid dose
Droney et al., 2013 [29]	Morphine		A118G	<i>n</i> = 264 cancer patients taking oral morphine	Genetic factors only accounted for 12% of variability in residual pain on morphine and 3% of variability in central side effects
CREB1 Nishizawa et al., 2012 [30]	Opioids				rs2952768 was associated with more analgesic requirements, and consistent results were obtained in patients who underwent abdominal surgery
HTR3B Laugsand et al., 2011 [21]	Opioids (morphine, oxycodone, fentanyl, and others)		rs1176744, rs3782025 rs1672717	<i>n</i> = 1579 cancer patients (European Caucasians)	G allele of rs1176744, the T allele of rs3782025, and the T allele of rs1672717 were associated with less nausea/vomiting
CHRM3 Laugsand et al., 2011 [21]	Opioids (morphine, oxycodone, fentanyl, and others)		rs10802789 rs685550	<i>n</i> = 1579 cancer patients (European Caucasians)	T allele of rs10802789 associated with more nausea/vomiting
KCNJ6 Lötsch et al., 2010 [31]	Methadone		rs2070995	<i>n</i> = 352 opioid-treated chronic pain patients	The daily methadone substitution doses during the first therapy year were larger in the rs2070995 AA genotype ( <i>n</i> = 4, $119.7 \pm 49.6$ mg/day) than in other rs2070995 genotypes ( $77.5 \pm 26.2$ mg/day, $P = 0.003$ )
DRD4 Ho et al., 2008 [32]	Heroin		-521C/T	<i>n</i> = 43 current heroin users, 66 controls	TT control subjects had lower pain threshold versus CC/CT controls and versus TT addicts
HTR2C Brash-Andersen et al., 2011 [33]	Escitalopram		rs6318	<i>n</i> = 34 patients with peripheral neuropathic pain	rs6318 (Cys23Ser) in the HTR2C gene showed significant association with treatment response in men, with 75% carrying the C allele being responders. The same tendency was seen in women

VAS: visual analogue scale. CREB1: cAMP responsive element binding protein 1 encodes a transcription factor, a member of the leucine zipper family of DNA binding proteins. HTR3B: 5-hydroxytryptamine (serotonin) receptor 3B encodes subunit B of the type 3 receptor for serotonin (neurotransmitter, hormone, and mitogen). Activation of the receptor leads to fast depolarizing responses in neurons. Penta heteromeric complex with subunit A (HTR3A) displays the full functional features of this receptor. HTR2C encodes the 2C subtype of serotonin receptor. CHRM3: the muscarinic cholinergic receptor 3, G-protein-coupled receptor controls smooth muscle contraction, and its stimulation increases secretion of glandular tissue. KCNJ6: gene for potassium inwardly rectifying channels, subfamily J, member 6 (Kir3.2, GIRK2). This G channel is important for opioid receptor transmission and is involved in opioid effects on postsynaptic inhibition [34]. DRD4: dopamine receptor D4 belongs to the dopamine receptor D2-like family, which mediates reward and reinforcement effects (e.g., of heroin) [35].

were not analyzed in this study. Laugsand et al. analyzed 96 single-nucleotide polymorphisms (SNPs) in 16 candidate genes related to opioid or nausea/vomiting signaling pathways (ABCB1, OPRM1, OPRK1, ARRB2, STAT6, COMT, CHRM3, CHRM5, HRH1, DRD2, DRD3, TACR1, HTR3A, HTR3B, HTR3C, and CNR1) for the association with nausea and vomiting in the same cohort of cancer patients. Totally 8 SNPs in 3 genes, COMT, HTR3B, CHRM3 (rs1176744, rs3782025, rs1672717, rs165722, rs4680, rs4633, rs10802789, rs685550), were significantly associated with the interindividual differences in nausea and vomiting among cancer patients treated with opioids [21].

Two candidate genes have been clinically studied most widely so far (OPRM1 and COMT).

**2.1. OPRM1.** The  $\mu$ -opioid receptor gene, OPRM1, is the most widely studied gene in association with different aspects of chronic pain. Probable effect of its polymorphism A118G (rs1799971, Asn-40 → Asp) is recognized. In 1998, Bond et al. demonstrated that Asp substitution on the extracellular N-terminal of the receptor determines the same binding affinity for endo- and exogenous opioids (morphine, fentanyl, methadone, naloxone, and met- and leu-enkephalins) with one exception;  $\beta$ -endorphin showed higher affinity to the receptor in the 118G variant carriers [68]. This finding allowed the authors to propose a hypothesis that there is a possible connection between the allele and addiction. Somewhat later, Zhang et al. found a 2-fold higher expression of  $\mu$ -opioid receptor in brains of 118G heterozygotes [69]. In the study by Oertel et al., a significant reduction in effectiveness of subsequent signaling pathways after the binding of a specific agonist DAMGO was observed. Rate of G-protein coupling in carriers of the G allele reached only 57% in comparison with AA homozygotes [70]. Recently, 4-fold increase in inhibition of Ca channels in the carriers of G-allele was also demonstrated [71]. Contrary to the preclinical data, the results of conducted clinical trials provide unconvincing evidence only. Recent meta-analysis and in particular large-scale cohort study found no evidence for an effect of this polymorphism on opioid dose (oxycodone, morphine, and fentanyl) in oncologic patients [22], although less frequent nausea and vomiting were associated with the polymorphism in the meta-analysis [72].

**2.2. COMT.** Catechol O-methyl transferase plays a central role in extracellular inactivation of catecholamine neurotransmitters, including dopamine and norepinephrine, in the central nervous system. Val158Met variant (rs4680, G1947A) showed higher enzymatic activity compared to wild type in postmortem human brains [113]. It is associated with a three-to-four-fold variation in COMT enzyme activity and also with individual variation in COMT thermal instability. Lower dopamine levels in carriers of this polymorphism were associated with lower levels of enkephalins in animal models, which in turn lead to downregulation of  $\mu$ -opioid receptor [114, 115]. However, the clinical relevance of these findings is still questionable. Polymorphism rs4680 did not result in variable opioid dosing in the treatment of pain in

oncologic patients [22]. Meta-analysis studying rs4680 in different types of chronic pain demonstrated that fibromyalgia or chronic widespread pain could be influenced by the presence of the variant allele. No association was observed with migraineous headache or chronic musculoskeletal pain conditions. According to systematic review of the literature, low COMT activity enhances opioid analgesia and adverse effects in some cancer pains via increasing the absolute amount of opioid receptors [116]. Reyes-Gibby et al. observed significantly lower doses of morphine in cancer patients, carriers of OPRM1 118AA and COMT rs4680 met/met ( $P < 0.012$ ) [23].

Three haplotypes (containing alleles rs6269, rs4633, rs4818, and rs4680) which accounted for 96% of all haplotypes observed in the Caucasian population have been identified [79, 117]. Some haplotypes were associated with different phenotypes: low-pain sensitivity, average-pain sensitivity, and high-pain sensitivity, while the risk of developing temporomandibular disorder could be predicted by a single haplotype in this study [79]. Surprisingly, both the low- and high-pain sensitivity-associated haplotypes possessed the val variant of rs4680. According to Nackley et al., interaction of rs4680 with other SNPs (silent mutations: rs6269, rs4633, and rs4818) determines the changes in the secondary structure of the messenger RNA, and these may modify the protein translation and the real *in vivo* activity of the enzyme [118]. The average-pain sensitivity-associated haplotype was modestly associated with greater improvement on a long-term VAS 1 year after lumbar surgery in patients with disc herniation [8]. In another recent study, high-pain sensitivity associated haplotype was associated with moderate or severe headache and moderate or severe dizziness in patients after motor vehicle collision [119]. However, Nicholl et al. found no correlation between COMT “pain sensitivity” haplotypes (rs6269, rs4633, rs4818 and rs4680 alleles) and chronic wide spread pain in two case-control studies (cases  $n_1 = 164$ ,  $n_2 = 172$ ; controls  $n_1 = 204$ ,  $n_2 = 935$ ) [120].

**2.3. Candidate Genes in New Drug Development.** With regard to the preclinical studies, TRPV1 gene product (transient receptor potential cation channel, subfamily V, member 1) appears to be the most promising as a potential target for therapeutic intervention. It is a polymodal nociceptor, the expression of which is upregulated in several painful disorders. Analysis of its function (including knockout mice) revealed that it plays a crucial role in integrating multiple painful stimuli in chronic pain conditions [121]. TRPV1 gene polymorphism might be an underlying cause of the inter-subject variability in pain sensation and response to TRPV1 antagonists [15]. TRPV1 antagonists are undergoing clinical trials in patients with chronic pain at present (reviewed in [122]).

### 3. Proinflammatory Cytokines

Peripheral nociceptors are sensitized by proinflammatory cytokines that are produced by inflammatory cells (CD4+ and CD8+ T cells) in response to disease as cancer or

TABLE 3: Impact of genetic variability in genes for proinflammatory cytokines.

Gene product	Genetic variability	Effect	Reference
TNFR2	TNFR2(–/–) mice	Attenuated hyperalgesia	[36]
TNF $\alpha$	A allele in –308G/A (rs1800629)	Higher pain severity	[37–39]
	G allele in –308G/A (rs1800629)	Anti-inflammatory treatment success with phytotherapy	[40]
LTA	Variant allele in rs5275	Lower pain scores	[41]
COX 2	CC in rs5275	Lower risk of severe pain	[39]
	G allele in rs5277	Higher pain scores	[41]
IL-1 $\alpha$	C889-T (rs1800587)	Pain intensity	
IL-1 $\beta$	C3954-T (rs1143634)	Occurrence of low back pain, the number of days with pain, and the number of days with limitations in daily activities due to pain	[42]
IL-1RN	G1812-A		
IL1-receptor 1	Variant allele in rs2110726	Less frequent breast pain	[43]
IL-4	Varant allele in rs2243248	More frequent pain	[44]
IL-6	–174G/G (rs1800795)	Pain	[45]
	–174C/C (rs1800795)	Higher opioid dosage	[37, 38]
IL-8	T allele in 251T/A (rs4073)	More frequent severe pain	[46]
	251T/T (rs4073)	Least frequent severe pain	[37]

its treatment, that is, cytostatics. This is one of the direct mechanisms leading to hyperalgesia in chronic diseases [123]. Therefore, the research attributed to the polymorphisms in genes coding for these cytokines and their relationship to various diseases including pain and its treatment arises [124–129].

Summary of known implications of genetic variability in genes for proinflammatory cytokines is given in Table 3.

**3.1. TNF- $\alpha$ .** TNF- $\alpha$  is known to contribute to hyperalgesia associated with chronic illness. After administration of bacterial endotoxin, hyperalgesia can be blocked by functional antagonists of TNF- $\alpha$ , for example, TNF- $\alpha$  binding protein [130]. Deletion of the tumor necrosis factor receptor type 2 (TNFR2) gene attenuated heat hyperalgesia in tumor-bearing mice, whereas TNFR1 gene deletion played only a minor role [36]. There are few clinical trials suggesting that TNF  $\alpha$ -308 G/A (rs1800629) is associated with chronic pain perception and treatment success. Variant alleles in TNF  $\alpha$ -308 G/A were significantly associated with higher pain severity in a study with 140 Caucasians newly diagnosed with nonsmall cell lung cancer [37, 38], and this has been confirmed in another study in newly diagnosed non-Hispanic Caucasian lung cancer patients ( $n = 667$ ) [39]. Higher chance for success of anti-inflammatory phytotherapy treatment in TNF  $\alpha$ -308 wild-type allele carriers with chronic pelvic pain syndrome has been also proposed in a small study [40].

**3.2. LTA.** Lymphotoxin-alpha (LTA), also known as TNF- $\beta$ , as a member of TNF family is also an important inflammatory marker. In a recent study with lung cancer patients, variant allele in rs5275 was associated with lower pain scores in patients surviving for more than 5 years [41].

**3.3. COX-2.** Cyclooxygenase 2, a product of prostaglandin-endoperoxide synthase 2 (PTGS2), is an enzyme responsible for the production of prostaglandins and represents the target for NSAIDs. As such, it plays a significant role in inflammation and chronic, particularly cancer, pain [131, 132].

Two recent studies reported an association between PTGS2 polymorphisms and pain. In study [39], CC genotypes for rs5275 were at lower risk for severe pain. Close SNP rs5277 was found to predict pain intensity in 1149 Caucasian lung cancer patients in the Mayo Clinic Lung Cancer Epidemiology Project. People carrying one or two minor (G) alleles reported higher pain scores [41].

**3.4. IL-1.** IL-1 is a family of 11 members produced during neuropathic pain and inflammation [133, 134]. Its involvement with pain mediation is undisputable as its, IL-1 $\beta$  to be precise, intrathecal injection produces hyperalgesia [135, 136].

Polymorphisms in their genes, as well as in genes of their receptor, have been reported to affect nociceptive response. It was shown that the IL-1 $\alpha$  (C889-T) (rs1800587) and IL-1 $\beta$  (C3954-T) (rs1143634) [137, 138] polymorphisms, and an 86-base pair repeat (VNTR polymorphism) in the IL-1 receptor antagonist (IL-1Ra) [139] genes are associated with the regulation of the IL-1 and IL-1Ra production. Association between IL-1 $\alpha$  (C889-T) polymorphism with pain intensity was revealed in study in Finnish men ( $n = 1832$ ) with low back pain. Moreover, it was implicated that IL-1 $\beta$  (C3954-T) and the IL-1RN (G1812-A) polymorphisms, and their composite genotype, are related to the 12-month occurrence of low back pain, the number of days with pain, and the number of days with limitations in daily activities due to pain [42]. Carriers of variant allele in IL1-receptor 1 (rs2110726) were less likely to report breast pain prior to surgery in a study with 398 women [43].

TABLE 4: The principal polymorphic DMEs involved in the metabolism of drugs used for chronic pain.

Enzymes	Important gene variants	Influenced drug group	Proven effect on PK or efficacy/safety in clinical trials	References
CYP2D6	CYP2D6*1-wt	TCA Opioids SSRI	Opioids (codeine, tramadol, hydrocodone, and oxycodone), TCA (amitriptyline, nortriptyline, imipramine, and desipramine), and SSRI (fluoxetine, paroxetine, and citalopram)	[47, 48]
	CYP2D6*3			
	2549A>del			
	CYP2D6*4			
	1846G>A			
	CYP2D6*5			
	CYP2D6*6			
	1707T>del			
CYP2C9	MxN	NSAIDs SSRIs SNRIs	Coxibs (celecoxib)	[48–50]
	CYP2D6*10			
CYP2C19	CYP2C9*1-wt			
	CYP2C9*2 (Cys144Arg)			
	CYP2C9*3 (Leu359Iso)			
	CYP2C9*5			
CYP2C19	CYP2C19*1-wt	NSAID Antidepressants	SSRI (citalopram)	[48, 51, 52]
	CYP2C19*2			
	CYP2C19*3			
CYP2C8	CYP2C19*17-Ums	NSAID	NSAID (ibuprofen and diclofenac)	[48, 53–55]
	CYP2C8*1-wt			
	CYP2C8*2 (Ile269Phe)			
CYP3A4	CYP2C8*3 (Arg139Lys, Lys399Arg)	Opioids	Opioids (methadone and fentanyl)	[48, 56–58]
	CYP3A4*1 (2023G>A)			
	CYP3A4*2			
	CYP3A4*10			
UGT1A6	CYP3A4*17	NSAIDs, anticonvulsants	NSAID (acetylsalicylic acid)	[59, 60]
	UGT1A6*1			
UGT2B7	UGT1A6*2	Opioids Anticonvulsants	Opioids (morphine) and anticonvulsants (lamotrigine and valproic acid)	[61–65]
	UGT2B7*2 (802C>T, H268Y), 161C>T			
UGT1A1	UGT1A1*28	Paracetamol Opioids	Paracetamol	[62, 66]
SULT1A1	SULT1A1*2 (G638A; Arg213His)	Paracetamol	Paracetamol	[67]
	SULT1A1*3 (A667; Met223Val)			

3.5. *IL-4*. IL-4 is produced by T cells, mast cells, eosinophils, and basophiles [140]. It coregulates the inflammatory response by suppressing TNF- $\alpha$  and IL-1 expressions [141] and by modulating B cells to undergo Ig isotype switching to IgE [142]. Homozygotes for variant allele (rs2243248) in the gene coding for this anti-inflammatory cytokine were found to be more likely in patients with high degree of depression and pain in a recent study with oncology patients ( $n = 168$ ) and their family caregivers ( $n = 85$ ) [44].

3.6. *IL-6*. IL-6 has a role in the regulation of inflammatory response. IL-6 knockout mice have had significantly higher levels of other cytokines in response to endotoxin [143]. In patients with juvenile rheumatoid arthritis, IL-6 genotype -174G/G (rs1800795) was positively correlated with pain [45]. Homozygous carriers of the IL-6 -174C allele required 4.7 times higher dose of opioids for pain relief relative as compared with GG and GC newly diagnosed patients with nonsmall cell lung cancer [37, 38].

3.7. *IL-8*. IL-8 attracts the neutrophiles to the site of infection or injury [144]. Its elevated concentrations are found in various diseases, particularly associated with inflammation, such as rheumatoid arthritis [145]. There are however very few discrepant data on SNP IL8-251T/A (rs4073), where wild-type allele was a predictor for severe pain in 168 Caucasian patients—TT or AT subjects had more than a threefold risk (OR = 3.23, 95% CI = 1.4, 4.7) for severe pain compared to the AA patients [46]; while in another study, TT homozygotes had the least frequency of severe pain [37].

#### 4. Drug Metabolism

The pharmacokinetics of drugs is subject to a large interindividual variability, which is important cause for adverse drug reactions and lack of drug response. In therapy of pain, numerous genetic polymorphisms affecting pharmacokinetics of drugs have been shown to contribute in part to interindividual variability in drug efficacy

TABLE 5: Drugs used in pain treatment and its major DMEs emphasizing FDA recommendations for genetic testing [73–75].

Drug class	Drug	Major enzymes			FDA drug labels including pharmacogenetics information
		CYPs	UGBTs	SULTs	
Analgesic/ antipyretics	Paracetamol	3A4, 2E1, 2A6, 1A2, 2D6, 2C19, 2C9, 2E1, 2A6	1A6, 1A9	1A1	In combination with tramadol CYP2D6
	Ibuprofen	2C9, 2C8, 3A4, 2C19, 2C9, 2C8, 3A4, 2C19	2B7, 1A9, 1A3, 2B4		
NSAIDs	Diclofenac	2C9, 2C8, 3A4, 2C19	2B7, 2B4, 1A3, 1A9		
	Naproxen	2C9, 1A2			
	Ketoprofen		2B7		
	Meloxicam	2C9, 3A4			
Coxibs	Celecoxib	2C9, 3A4			CYP2C9
	Etoricoxib	3A4, 2C9, 2D6, 1A2, 2C19			
TCAs	Amitriptyline	2C19, 2C8, 2C9, 1A2, 2D6, 3B6, 3A4	1A3, 1A4		CYP2D6
	Nortriptyline	2D6, 3A4			CYP2D6
	Imipramine	2D6, 2C19, 1A2			CYP2D6
	Desipramine	2D6			CYP2D6
SNRIs	Duloxetine	2D6, 1A2			
	Venlafaxine	2D6, 2C19, 2C9			CYP2D6
SSRIs	Fluoxetine	2C9, 3A4, 2D6, 2C19, 1A2			In combination with olanzapine, and CYP2D6
	Paroxetine	2D6			CYP2D6
	Citalopram	3A4, 2C19, 2D6			CYPs 2C19, and 2D6
Antiepileptics	Carbamazepine	3A4, 2C8	2B7		
	Valproate		2B7, 1A6, 1A9		
Opioids	Buprenorphine	3A4, 2C8	1A1, 2B7, 1A3		
	Codeine	2D6, 3A4	2B7, 2B4		CYP2D6
	Dihydrocodeine	2D6, 3A4	2B7		
	Morphine	3A4, 2C8	2B7, 1A8, 1A1, 1A3, 1A10, 1A6, 1A1		
	Oxycodone	2D6, 3A4	2B7		
	Pethidine	3A4, 2B6, 2C19			
	Tilidine	3A			
	Tramadol	3A4, 2B6			In combination with paracetamol CYP2D6

and safety [146]. The most important drug metabolizing enzymes for pain treatment are cytochromes P450 (P450), UDP-glucuronyltransferases (UGTs), and sulfotransferases (SULTs) [59, 147]. Table 4 summarizes the principal polymorphic DMEs with its most important genetic variants involved in the metabolism of drugs used for chronic pain. Table 5 shows the drugs used in pain treatment and its major DMEs emphasizing FDA recommendations. An example in which pharmacogenetic testing of DMEs could be clinically relevant is P450 and UDP-glucuronyltransferase [59].

Recently, comprehensive and in-depth monography concerning drug metabolism (including impact of genetic polymorphisms) was published [73].

**4.1. P450.** Cytochrome P450 (P450) consists of heme-containing monooxygenase enzymes located on the smooth endoplasmic reticulum membranes of liver hepatocytes and along the mucosal surface of the intestinal tract and several other tissues including kidney, heart, and brain. Research on human P450 polymorphisms began in the 1970s and continues till now [73]. Actual information concerning P450 polymorphisms is compiled on the website <http://www.cypalleles.ki.se/>.

**4.2. CYP2D6.** CYP2D6 accounts for 2–5% of the total hepatic P450 enzymes; however, it is involved in the metabolism of 25% of all drugs administered in clinical practice [47].

It is also important for many drugs used in pain and palliative medicine as it is responsible for metabolizing certain analgesics as opioids (codeine, tramadol, hydrocodone, oxycodone), neuroleptics, and antidepressants; see Table 5. CYP2D6 plays an important role not only in the metabolism of exogenous opioids but also in the endogenous morphine synthesis pathway. CYP2D6-metabolized drugs exhibit nonlinear saturable kinetics owing to the low capacity of CYP2D6. The existence of almost 80 CYP2D6 allelic variants is known to lead to phenotype diversity within populations [148]. Approximately 7–10% of people may be classified as poor metabolizers (PM) and 3% as ultrarapid metabolizers (UM) in the Caucasian populations [149, 150]. An example in which pharmacogenetic testing of CYP2D6 is clinically relevant is codeine. Codeine as a prodrug requires *O*-demethylation catalyzed by CYP2D6 to be converted into morphine and become analgesic. This metabolite pathway accounts for 10% of codeine clearance in EMs but is much more pronounced in UMs and far less pronounced in PMs; so PMs suffer from a lack of analgesia, while UMs have been shown to be more likely to experience side effects and have 50% higher plasma concentration of morphine compared to EMs [151]. Codeine as a weak opioid was believed to be a relatively safe analgesic. However, after the death of breastfed neonate through morphine overdose by his mother taking codeine, the safety profile of codeine was reevaluated and FDA published a warning on codeine use in nursing mothers [152]. It is suggested that codeine should be avoided in breastfeeding mothers, who are extensive metabolizers (EMs) or UMs of CYP2D6 [153, 154]. The European Medicines Agency started a review of codeine-containing medicines on October 3, 2012, as well [155]. Young and obese children with history of sleep apnea are also at higher risk of developing severe opioid-related respiratory depression. The adverse outcomes of codeine treatment could be avoided and the safety of pain management could be improved by CYP2D6 genetic testing before prescribing the drug (tramadol, hydrocodone, or oxycodone) or by using alternative analgesics [156]. Another analgesic agent which is metabolized by CYP2D6 and where genetic examination is proposed is tramadol. The main metabolite is *O*-desmethyltramadol; (+)-*O*-desmethyltramadol has 300–400 times greater affinity for  $\mu$ -opioid receptors than tramadol, whereas (-)-*O*-desmethyltramadol mainly inhibits norepinephrine reuptake [157]. Production of *O*-desmethyltramadol through mono-*O*-demethylation is mediated by polymorphic CYP2D6. As consequence, PMs need approximately 30% higher tramadol doses compared to EMs, and UMs are at greater risk to develop adverse effects of tramadol [47, 158]. Genetic testing of variants CYP2D6 is commercially available [159].

**4.3. CYP2C.** The group of CYP2C subfamily consists of four members: CYP2C8, CYP2C9, CYP2C18, and CYP2C19. These enzymes metabolize approximately 20% of clinically available drugs. Their genes are tandemly located at 10q24 and there is a linkage between them. Genetic variants in CYP2C8, CYP2C9, and CYP2C19 have been shown to have clinical

consequences. Among pain treatment, NSAIDs represent typical substrates for CYP2C enzymes; however, the relative role of CYP2C enzymes in primary metabolism differs among different NSAIDs.

Common CYP2C8 and CYP2C9 polymorphisms were studied by Blanco et al. in a cross-sectional study, involving 134 NSAID-related bleeding patients and 177 patients receiving NSAID with no adverse effects [160]. Among patients with bleeding after NSAID (CYP2C8/9 substrates), the frequencies of variant allele carriers versus control patients were 0.50 versus 0.23 (odds ratio (OR); 95% confidence interval (CI) = 3.4; 1.5–7.5;  $P$  = 0.002), 0.48 versus 0.26 (OR; 95% CI = 2.7; 1.2–5.8;  $P$  = 0.013), and 0.24 versus 0.20 (OR; 95% CI = 1.3; 0.5–3.1;  $P$  = 0.578) for CYP2C8\*3, CYP2C9\*2, and CYP2C9\*3, respectively. These findings were not influenced by gender, age, smoking, or drinking habits. Among bleeding patients receiving NSAID that are not extensively metabolized by CYP2C8/9, no differences in genotypes or allele frequencies were observed as compared to control patients. Similar findings have been shown by other authors; individuals carrying the gene variants CYP2C8\*3 (rs11572080; rs10509681), CYP2C9\*2 (rs1799853), or CYP2C9\*3 (rs1057910) show increased risk of developing acute gastrointestinal bleeding during the use of NSAID that are CYP2C8 or CYP2C9 substrates [161, 162].

**4.4. CYP2C19.** Totally 36 alleles of gene CYP2C19 have been identified and described so far [48]. CYP2C19 is responsible for the metabolism of several clinically important drugs as citalopram, barbiturates, diazepam, and other drugs [52]. The roles of the cytochrome P450 2C19 enzyme and cytochrome P450 2D6 enzyme in citalopram metabolism were studied [163]. The inactive CYP2C19\*2 (rs4244285) allele was associated with lower odd ratios for tolerance. The estimated dose adjustments for CYP2C19 poor metabolizers suggest using approximately 60% of the standard dose of citalopram [164]. Also the allelic variant CYP2C19\*3 (rs4986893 or rs57081121) influences the total concentration of the active compounds venlafaxine and its active metabolite *O*-desmethylvenlafaxine. Thus, CYP2C19 genotypes (together with CYP2D6 genotypes) should be considered for dose alterations of venlafaxine [165].

**4.5. CYP2C9.** The pharmacokinetics of ibuprofen is strongly related to CYP2C8 and CYP2C9 genotypes. The effect of CYP2C8\*3 (rs10509681 or rs11572080) on ibuprofen clearance is prominent; heterozygous and homozygous carriers of this variant allele display clearance reduced to approximately 62% and 10% as compared to individuals lacking any variants within CYP2C8 and CYP2C9 genes [166]. Although initial findings indicated association of CYP2C9\*2 (rs1799853) genotypes with ibuprofen clearance, it has been shown that CYP2C9\*2 alone, when it is not linked to CYP2C8\*3, does not translate into a major impairment of ibuprofen clearance. Clearance values in subjects heterozygous and homozygous for CYP2C9\*2 not carrying any other mutations are 96 and 84%, respectively, as compared to individuals lacking any mutations in CYP2C8 and CYP2C9 genes. Individuals

carrying CYP2C9\*3 (rs1057910) variant alleles display a mean reduction of clearance of ~65% and 17% for heterozygous and homozygous individuals, respectively [167].

Studies with tenoxicam have indicated that oral clearance among carriers of CYP2C9\*2 and CYP2C9\*3 decreases to ~70 and 55% [168]; however, efficacy or safety data are not available yet.

**4.6. CYP2C8.** CYP2C8 comprises 7% of the total hepatic CYP content and plays an important role in the metabolism of a diverse number of exogenous (e.g., NSAIDs, carbamazepine, diltiazem, methadone, morphine, and zopiclone) and endogenous compounds (e.g., arachidonic acid) [55]. A number of common SNPs have been identified including CYP2C8\*2 (Ile269Phe and rs1572103), CYP2C8\*3 (linked polymorphism Arg139Lys and Lys399Arg, rs10509681, or rs11572080), and CYP2C8\*4 (Ile264Met and rs1058930). One of the drugs implicated as CYP2C8 substrate is methadone. *In vitro*, CYP2C8 was shown to metabolize both the R- and S-enantiomers of methadone, with a greater selectivity for R-enantiomer [169]. Considering that the R-enantiomer is the more pharmacologically active form *in vivo*, the potential influence of CYP2C8 polymorphism on the metabolism of the R-enantiomer may be clinically significant and warrants further studies.

Allelic variants of CYP2C8, UGT2B7, and ABCC2, which may predispose for the formation and accumulation of reactive diclofenac metabolites, are associated with diclofenac hepatotoxicity [55]. Daly et al. showed that UGT2B7\*2 allele (rs7439366) was more common in patients with diclofenac-induced hepatotoxicity when compared with hospital controls (OR, 8.5,  $P = 0.03$ ) or healthy controls (OR, 7.7,  $P = 0.03$ ). Further, the ABCC2 C-24T (rs717620) variant was more common in patients with hepatotoxicity compared with hospital (OR 5.0,  $P = 0.005$ ) and healthy controls (OR 6.3,  $P = 0.0002$ ). Haplotype distributions for CYP2C8 were different between patients and hospital controls ( $P = 0.04$ ).

**4.7. CYP3A4.** CYP3A4, coded by the gene located on chromosome 7q21.1, is involved in the oxidation of the largest range of substrates of all the CYPs. CYP3A4 plays a role in the metabolism of some opioids as fentanyl, oxycodone, and methadone along with the other CYPs [148]. There is little conclusive information about the importance of genetic variation in the CYP3A pathway, but some studies of postmortem forensic toxicology propose pharmacogenomics of CYP3A4 as a kind of molecular autopsy in the analysis of pain-medications-related deaths. In studies of fentanyl-, oxycodone- or methadone-related deaths, the PM status was a clear risk factor [170–172].

**4.8. UDP-Glucuronyltransferase.** Glucuronidation is an important pathway of human metabolism that leads to the formation of water soluble glucuronides. The substrates for glucuronidation include both endogenous substances, such as bilirubin, steroid hormones, and bile acids, and exogenous substances such as morphine, antidepressants, or nonsteroidal anti-inflammatory drugs. The human genome

codes for at least 19 different UDP-glucuronosyltransferases (UGTs) classified within three subfamilies, UGT1A, 2A, and 2B [173]. Genetic polymorphisms have been reported in virtually every UGT family member and many of them have potential clinical consequences. For example, morphine undergoes extensive metabolism by glucuronidation to form morphine-3-glucuronide and morphine-6-glucuronide which possess significant analgesic activity. The ability to glucuronidate morphine varies substantially between individuals. The major enzyme responsible for glucuronidation of morphine is UGT2B7. The variant homozygotes for T/T802 (Y/Y268) displayed the strongest catalyzing abilities toward morphine, and this genotype has been considered as one of the possible causes of interindividual variability in therapeutic response to morphine [174].

A small cross-sectional study observed faster *in vivo* conjugation of salicylic acid in patients genotyped UGT1A6\*2/\*2 (rs2070959) than in the wild-type carriers. The faster conjugation may subsequently influence the therapeutic response to aspirin [175].

## 5. Drug Transport

There are many families of transporters and some of them are known to be interacting with pathways of pain-transporting analgesics, prostaglandins [22]. So far the most known and best studied transporter is P-glycoprotein (Pgp), the first-studied member of ATP-binding cassette (ABC) superfamily. In humans, Pgp consists of two isoforms with 78% amino acid homology. Overexpression of isoform I (ABCB1) in cancer cells was linked with resistance to multiple drugs, hence the name for this transporter multidrug resistance protein 1 (MDR1). Isoform II (MDR2/ABCB4) transports phosphatidylcholine into the bile and is not involved in drug transport [176, 177].

Summary of known implications of genetic variability in genes for drug and neurotransmitter transporters is given in Tables 6 and 7, respectively.

**5.1. MDR1/ABCB1.** Pgp is known to show extremely broad substrate specificity, including peptides, steroids, therapeutic drug from very large and complex ones as paclitaxel [178] to relatively simple as phenytoin, opioids, and other analgesics [179] or even ions [180–186]. Substrates are often, but not always (e.g., colchicine), amphipathic and relatively hydrophobic. Planar aromatic ring and tertiary amino group were also proposed as required structure elements, but many peptides do not have them, and yet they are substrates of Pgp [187].

In addition to this broad substrate specificity, Pgp is also very abundant in the body as it can be found in most tissues [188], although in significantly larger amount on the apical surface of the endothelial cells lining the small intestine, colon, kidney, adrenal gland, bile ductules, thus in the tissues with excretory (or absorptive) function in general. In addition, also in cells with “barrier” function, that is, cells in blood brain [189], blood testis [190], blood

TABLE 6: Impact of genetic variability in genes for drug transporters.

Transporter	Drug	Genetic variability	Effect	Reference
MDR1/ABCB1	Methadone	61 (rs9282564), 1199 (rs2229109), 1236 (rs1128503), 2677 (rs2032582), and 3435 (rs1045642)	Lower dosage	[76]
		C1236 (rs1128503)	Higher dosage	[77]
		61A (rs9282564) : 1199G (rs2229109) : 1236C (rs1128503) : 2677T (rs2032582) : 3435T (rs1045642)	Higher dosage	[78]
		61A (rs9282564) : 1199G (rs2229109) : 1236C (rs1128503) : 2677T (rs2032582) : 3435T (rs1045642)	Lower through concentrations	[78]
		61G (rs9282564) and 3435T (rs1045642)	Lower through concentrations	[79]
		3435T (rs1045642)	Higher dosage	[80]
		C3435T (rs1045642)	Pain relief	[27]
		3435TT (rs1045642)	Higher CSF concentrations	[81]
	Morphine	CC3435 (rs1045642)	Higher CSF concentrations of morphine glucuronides	[81]
	Fentanyl	GG2677 (rs2032582) and CC3435 (rs1045642)	Fewer side effects	[82]
		G2677 (rs2032582) and C3435 (rs1045642)	Vomiting	[61]
		3435T (rs1045642)	Less frequent pain scores >6	[83]
		3435T (rs1045642)	Suppression of respiratory rate	[84]
MRP2/ABCC2	Tramadol	3435TT (rs1045642)	Higher $C_{max}$	[85]
	Oxycodone	3435T, 2677A (rs2032582)	Fewer side effects	[86]
		2677A (rs2032582)	Better analgesic activity	[86]
	Lamotrigine	C1236 (rs1128503)	Higher dose corrected concentrations	[87]
	Gabapentin	2677T/A (rs2032582)	Trend towards higher AUC(0–1.5 h)	[88]
		CC1236 (rs1128503)	Significantly lower clearance	[89]
	Carbamazepine	CC3435 (rs1045642)	Lowest plasma levels	[90]
		3435TT (rs1045642)	Decreased plasma levels	[91]
	Venlafaxine	MDR1/ABCB1(–/–) mice	Higher plasma levels	[92–94]
	Venlafaxine's metabolites	MDR1/ABCB1(–/–) mice	Higher plasma levels	
MRP3/ABCC3	Venlafaxine	TT in rs2232583	Higher plasma levels	[95]
	Trimipramine	MDR1/ABCB1(–/–) mice	Higher plasma levels	[96]
	Amitriptyline	MDR1/ABCB1(–/–) mice	Higher plasma levels	[97, 98]
	Diclofenac	MRP2/ABCC2(–/–) mice	Impaired clearance	[99]
	Diclofenac	24T (rs717620)	Hepatotoxicity	[55]
MRP4/ABCC4	Carbamazepine	AA + AG in rs2273697	Higher clearance	
		AA + AG in rs4148386	Higher clearance	[89]
	—	rs2756109	Pain	[100]
MRP3/ABCC3	Morphine	MRP3/ABCC3(–/–) mice	Increase in plasma levels of its glucuronides	[101]
	—	MRP4/ABCC4(–/–) mice	Decreased pain responsiveness	[102]
		rs9524885	Pain	[100]

TABLE 7: Impact of genetic variability in genes for transporters of neurotransmitters.

Transporter	Drug	Genetic variability	Effect	Reference
5-HTT	Remifentanil	Triallelic 5-HTTLPR	Better analgesic effect	[103]
		Low 5-HTT-expressing	Higher pain thresholds	[104, 105]
		Tandem-repeat polymorphism 2.10	Lesser temporomandibular joint pain and dysfunction	[106, 107]
		10/12 and 10/10 STin2.12 alleles	Protective effect against migraine	[108]
		14/14 sequence repeats	Higher frequency of abdominal pain	[109]
DAT	—	DAT*10	More frequent in fibromyalgia patients More frequent in migraine-without-aura-group	[110] [111]
EAAT2	Analgesics	A allele in -181A/C	Higher usage	[112]

mammary tissue [191], blood inner ear barrier [192], and in placenta [193], protecting respective tissues (or fetus [194]) from toxins in the blood. Recent studies show that this may not be the only one physiological function of Pgp or even the crucial one. It seems that Pgp is involved in the inhibition of apoptosis induced by a number of factors as tumor necrosis factor and ultraviolet and gamma radiations [195]. Further, it was shown that blocking Pgp by antibodies induced apoptosis of activated lymphocytes in peripheral blood, and MDRI/ABCB1 seems to regulate even stem cells [196]. Secretion of various cytokines (interleukin 2 and 4, interferon  $\gamma$ ) is mediated by Pgp [197].

Pgp is a product of the ATP-binding cassette, subfamily B (MDR/TAP), member 1 gene (*ABCB1*), gene of 209617 bp with 29 exons of total length 4872 bp located on chromosome 7q21.12. There are 1425 known SNPs to date with average distance of 161 bp; 46 of them are nonsynonymous: two of them in introns and 46 in coding sequence of exons [198]. The synonymous SNPs and SNPs in promoter regions could influence the expression level of MDRI/ABCB1, for protein activity, that is, its substrate binding, ATP hydrolysis and folding, are most important probably the nonsynonymous SNPs [195]. Because of the important role of Pgp in drug disposition, it seems as a fair presumption that such SNPs could have clinical importance in drug pharmacokinetics and, by extension, in pharmacodynamics (and even direct impact on PD in tumor cells with overexpression of MDRI/ABCB1). Campa et al. found that variability of pain relief in 145 patients on morphine treatment was significantly associated with SNP C3435T (rs1045642). The association was stronger; when C3435T was combined with A80G in OPRM1 SNPs were taken into account [27]. There were significant C3435T-dependent differences in morphine concentrations in cerebrospinal fluid (CSF) with the highest levels in CSF in TT carriers of SNP C3435T and the highest morphine-6- and 3-glucuronide concentrations in CSF in wild-type homozygotes [81]. Response to morphine was dependent on SNP C3435T in children in a recent study using Faces Pain Scale (FPS). Scores >6 were more frequent in 11 checks during 24 hours after orthopedic or abdominal surgery in carriers for the wild-type alleles (adjusted risk ratio = 4.5; 95% confidence

interval (CI), 1.5–13.4; corrected CI for multiple comparisons, 0.98–20.55) [83].

For fentanyl, variability in suppression of respiratory rate (significant only for C3435T and diplootype) and need for oxygen (increased in carriers of 1236T (rs1128503) and 3435T alleles,  $P = 0.0847$ ) were observed, and significant differences in the level of respiratory suppression were found in patients with linked 3435T and 2677T (rs2032582) alleles [84].

The atypical opioid tramadol was proposed to be a subject of P-glycoprotein-dependent transport, as there were significant differences in its  $C_{max}$  and borderline significant differences in  $AUC_{0-24}$  amongst different genotypes for MDRI/ABCB1 in CYP2D6 poor metabolizers [85]. Conversely, no significant differences among MDRI/ABCB1 subgroups with regards of pain difference, drug consumption, reporting of adverse reactions, need for rescue analgesic medication, or verbal description of pain were observed [158]. For oxycodone, strong associations between variant alleles 3435T and 2677A and less adverse drug reactions and better analgesic effect and variant 2677A were found in study with 33 healthy volunteers and experimental pain [86].

Apart from opioids, Pgp is believed to transport several antiepileptic drugs (AED), for example, lamotrigine, gabapentin, topiramate, valproic acid, and carbamazepine and its ketoanalog oxcarbazepine, although there is no consensus about this and studies with positive [199–201] or negative results [202–204] may be found. The efflux may play facilitatory role in refractory epilepsy [205–207], although contradictory results are also available [208]. These agents are widely used in the treatment of neuropathic pain. There are only pharmacogenetic studies in epilepsy in association with MDRI/ABCB1 polymorphisms, but their results could give some guidance about the impact of SNPs in MDRI/ABCB1 in the treatment of neuropathic pain.

In the case of lamotrigine, homozygotes for the C allele in C1236T have had significantly higher lamotrigine dose corrected concentrations ( $0.068 \mu\text{mol} \cdot \text{l}^{-1} \cdot \text{mg}^{-1}$ ) than subjects with CT or TT ( $0.053 \mu\text{mol} \cdot \text{l}^{-1} \cdot \text{mg}^{-1}$ ). Furthermore, 1236C-2677G-3435C carriers have had higher lamotrigine concentrations than 1236T-2677G-3435T carriers ( $P < 0.001$ ), followed by 1236T-2677T-3435C carriers ( $P < 0.001$ ) [87].

Change in gabapentin's disposition due to 2677T/A MDRI/ABCB1 alleles was less pronounced resulting only in trend toward higher values of the absorptive phase characterized by the AUC (0–1 h) and AUC (0–1.5 h) [88].

SNP C3435T did not influence disposition of valproic acid as its serum concentrations of the patients with CT, TT and CC genotypes were  $72.92 \pm 20.55$ ,  $80.47 \pm 14.01$ , and  $68.29 \pm 12.17 \mu\text{g/mL}$ , respectively, and there was no significant difference [209].

Carbamazepine appears to be subject of Pgp transport, its clearance was associated with rs1128503, being significantly lower in subjects with alleles CC versus CT + TT [89]. The median total carbamazepine plasma levels were the lowest in CC ( $20 \mu\text{mol/L}$ ) homozygotes followed by CT ( $23 \mu\text{mol/L}$ ) and TT ( $29 \mu\text{mol/L}$ ) carriers of SNP 3435 [90]. However, Meng et al. suggested that ABCB1 3435TT is associated with decreased plasma carbamazepine levels in Chinese patients with epilepsy [91]. On the other hand, Hung et al. did not find any difference in carbamazepine levels among genotype groups for SNPs C1236T, G2677T/A, and C3435T in MDRI/ABCB1 [210]. Moreover, some studies did not find any association between C3435T and epilepsy treatment response [211] or with dosage [212].

Speaking of neuropathic pain, even tricyclic antidepressant drugs, such as amitriptyline, nortriptyline, desipramine, and SNRI (venlafaxine and duloxetine), are being used for treating this condition, all of which are subject to the Pgp mediated efflux [213–219], which was implicated to be associated with refractory depression [220].

In knockout mice, venlafaxine and its three demethylated metabolites reached significantly higher concentrations than in wild-type mice [92–94]. Similar results were obtained with trimipramine [96] and amitriptyline [97, 98].

Case study was reported in which SNP rs2232583 in MDRI/ABCB1 apparently resulted in excessive plasma levels of venlafaxine and its metabolite desmethylvenlafaxine in the patient [95].

**5.2. MRP.** Multidrug resistance-associated proteins (MRP) also belong to the ABC transporters family, subfamily ABCC, which consists of 12 members, nine of them are MRPs. Similar to MDRI/ABCB1, they utilize ATP but share only 24% of amino acid sequence homology [221]. Thus, there are distinct substrate specificity, inhibitors, and tissue distribution as compared to P-glycoprotein. Mainly, three of MRPs are known to interact with the pathways of pain: MRP2/ABCC2, which transfers diclofenac's metabolites [55, 99], MRP3/ABCC3, which was shown to transfer morphine [101], and diclofenac's glucuronides [99], and MRP4/ABCC4, which transports most prostaglandins [222] (even proposed as prostanoid export pump [223, 224]) and acetylsalicylic acid [225, 226].

As for MRP2/ABCC2, genetic variability could lead to impaired clearance of diclofenac and its glucuronides and hence to hepatotoxicity, as it was shown with knockout mouse [99]. One SNP (C24T, rs717620) in 5'-untranslated region was associated with decreased mRNA expression [227, 228], although many other SNPs have been found [229, 230]. Allele 24T was found to be more prevalent in patients with

hepatotoxicity as compared with patients taking diclofenac for 0.3–20 years ( $n = 48$ ) without hepatotoxicity (OR 5.0,  $P = 0.005$ ) and healthy controls (OR 6.3,  $P = 0.0002$ ) [55].

Carbamazepine appears to be subject of ABCC2 transport, as its clearance was significantly higher in subjects with alleles AA + AG versus GG in rs2273697 and rs4148386 [89]. Ufer et al. strengthen this assumption since in their study carriers of the ABCC2 1249G>A (rs934847) variant were more frequently classified as responders to treatment and this impact was even more pronounced among 64 patients receiving carbamazepine or oxcarbazepine [231].

Involvement of MRP4/ABCC4 in export of prostanoids could have significant clinical implication for nociception and analgesia, as was shown in MRP4/ABCC4 knockout mice in study by Lin et al., where disruption of MRP4/ABCC4 resulted in decreased pain responsiveness [102]. Further, recent study associated SNP rs9524885 in MRP4/ABCC4 (as well as rs2756109 in MRP2/ABCC2) with pain in nonsmall-cell lung cancer patients [100].

**5.3. SLC22A6.** Another drug transporter known to transport analgesics, particularly NSAIDs [232], is SLC22A6, human organic anion transporter 1. However, the clinical relevance for chronic pain treatment of its variation has not been clarified yet.

**5.4. SLCO1B1.** SLCO1B1, also known as OATP2, was shown to transport opioid peptides across blood brain barrier [233] therefore, it is possible that genetic variability may have influence on the pain perception. This has not been clinically assessed yet, but immunofluorescence microscopy and uptake measurements were used to study localization and transport properties. The polymorphisms SLC21A6\*1b and SLC21A6\*4 have been associated with altered transport of cholytaurine and 17 beta-glucuronosyl estradiol [234].

**5.5. 5-HTT.** Genetic polymorphism of serotonin transporter (5-HTT) has also been associated with alteration of pain pathways. For example, study with 43 healthy volunteers found that subjects with the triallelic 5-HTTLPR genotype coding for low 5-HTT expression gained better analgesic effect of remifentanil compared to those homozygous for the 5-HTTLPR LA allele, although the baseline sensitivity to heat pain was not affected by the triallelic 5-HTTLPR polymorphism [103]. Low 5-HTT-expressing group compared to the high 5-HTT-expressing group exhibited significantly increased pressure pain and heat-pain thresholds [104], while contradicting results have been described by Aoki et al. [235]. Association between inferred low 5-HTT expression and elevated thresholds to thermal pain was found in 44 healthy nondepressed individuals [105]. Similarly, homozygotes for variable-number tandem-repeat polymorphism 2/10 suffered less from temporomandibular joint pain and dysfunction [106, 107]. Two recent meta-analyses found that non-STin2.12 alleles possess protective effect compared to STin2.12 alleles, respectively, 10/12 and 10/10 genotypes compared to the 12/12 genotype against migraine among populations of European descent [108],

while no overall association between the SLC6A4 5-HTTLPR polymorphism and migraine among Europeans and Asians was found, though gender and migraine aura status may have modifying roles among Europeans [236].

Repeat variation polymorphism in 5-HTT gene consists of a short (s) variation of 14 repeats of a sequence and a long (l) variation of 16 repeats. Subjects with irritable-bowel syndrome with s/s genotype for 5-HTT have suffered more often from abdominal pain than l/s and l/l [109]. A significantly higher frequency of the s/s genotype of the serotonin transporter promoter region was found in fibromyalgia patients (31%) compared with healthy controls (16%) in study with 62 patients and 110 healthy controls [110], but this was later contradicted in different study with 53 mentally healthy subset of fibromyalgia patients and 60 healthy controls [237].

**5.6. Others.** Dopamine transporter (DAT, SLC6A3) and glutamate transporter protein excitatory amino acid transporter 2 (SLC1A2, EAAT2) polymorphisms have also been reported to affect pain perception. Allele DAT\*10 was significantly underrepresented in patients with chronic daily headache associated with drug abuse when compared with the migraine-without-aura group [111] and A allele carriers of -181 A/C in EAAT2 polymorphism used significantly more analgesics than non-A carriers in migraine patients with chronic daily headache [112].

## 6. Conclusion

There is number of candidate genes whose genetic variability may translate in either individual variation of chronic pain perception or treatment response. The clinical data from pharmacogenetic studies is still very limited and heterogeneous as a result of various methodologies used in different studies, generally small sample sizes and heterogenous patient populations. Therefore, there is still a need for further clarifications of the clinical importance for all these findings, but the recent research in the field that encompasses larger studies and larger-scale genome perspectives may bring more promising findings in the future.

## Abbreviations

CYP:	Cytochromes P450
DME:	Drug-metabolizing enzyme
EM:	Extensive metabolizer
FDA:	Food and drug administration
IM:	Intermediate metabolizer
NSAID:	Nonsteroidal anti-inflammatory drug
PK:	Pharmacokinetics
PM:	Poor metabolizer
SNP:	Single-nucleotide polymorphism
SNRI:	Serotonin-norepinephrine reuptake inhibitor
SSRI:	Selective serotonin reuptake inhibitor
SULT:	Sulfotransferase
TCA:	Tricyclic antidepressant
UGT:	UDP-glucuronyltransferase
UM:	Ultraparid metabolizer.

## Acknowledgments

This study has been supported by IGA MZ CR Grant no. NT11324-3/2010 and Charles University Project PRVOUK P25/LFI/2.

## References

- [1] L. J. Hocking, B. H. Smith, G. T. Jones, D. M. Reid, D. P. Strachan, and G. J. Macfarlane, "Genetic variation in the beta2-adrenergic receptor but not catecholamine-O-methyltransferase predisposes to chronic pain: results from the 1958 British Birth Cohort Study," *Pain*, vol. 149, no. 1, pp. 143–151, 2010.
- [2] P. H. Finan, A. J. Zautra, M. C. Davis, K. Lemery-Chalfant, J. Covault, and H. Tennen, "Genetic influences on the dynamics of pain and affect in fibromyalgia," *Health Psychology*, vol. 29, no. 2, pp. 134–142, 2010.
- [3] B. Fijal, R. H. Perlis, A. N. Heinloth, and J. P. Houston, "The association of single nucleotide polymorphisms in the catechol-O-methyltransferase gene and pain scores in female patients with major depressive disorder," *Journal of Pain*, vol. 11, no. 9, pp. 910–915, 2010.
- [4] C. Fernandez-de-las-Penas, S. Ambite-Quesada, I. Rivas-Martinez et al., "Genetic contribution of catechol-O-methyltransferase polymorphism (Val158Met) in children with chronic tension-type headache," *Pediatric Research*, vol. 70, no. 4, pp. 395–399, 2011.
- [5] F. R. Barbosa, J. B. Matsuda, M. Mazucato et al., "Influence of catechol-O-methyltransferase (COMT) gene polymorphisms in pain sensibility of Brazilian fibromyalgia patients," *Rheumatology International*, vol. 32, no. 2, pp. 427–430, 2012.
- [6] M. L. Loggia, K. Jensen, R. L. Gollub, A. D. Wasan, R. R. Edwards, and J. Kong, "The catechol-O-methyltransferase (COMT) val158met polymorphism affects brain responses to repeated painful stimuli," *PLoS One*, vol. 6, no. 11, Article ID e27764, 2011.
- [7] F. Dai, I. Belfer, C. E. Schwartz et al., "Association of catechol-O-methyltransferase genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease," *Spine Journal*, vol. 10, no. 11, pp. 949–957, 2010.
- [8] A. Omair, B. A. Lie, O. Reikeras, M. Holden, and J. I. Brox, "Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: a prospective genetic association study," *BMC Musculoskeletal Disorders*, vol. 13, article 76, 2012.
- [9] M. Martinez-Jauand, C. Sitges, V. Rodriguez et al., "Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene," *European Journal of Pain*, vol. 17, no. 1, pp. 16–27, 2013.
- [10] P. Klestad, T. T. Rakvåg, S. Kaasa 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 Anaesthesiologica Scandinavica*, vol. 48, no. 10, pp. 1232–1239, 2004.
- [11] M. B. Olsen, L. M. Jacobsen, E. I. Schistad et al., "Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction," *Journal of Neuroscience*, vol. 32, no. 29, pp. 9831–9834, 2012.
- [12] S. Menon, R. A. Lea, B. Roy et al., "The human mu-opioid receptor gene polymorphism (A118G) is associated with head

- pain severity in a clinical cohort of female migraine with aura patients," *Journal of Headache and Pain*, vol. 13, no. 7, pp. 513–519, 2012.
- [13] P. K. Janicki, G. Schuler, D. Francis 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," *Anesthesia and Analgesia*, vol. 103, no. 4, pp. 1011–1017, 2006.
- [14] U. Heddini, N. Bohm-Starke, A. Gronbladh, F. Nyberg, K. W. Nilsson, and U. Johannesson, "GCH1-polymorphism and pain sensitivity among women with provoked vestibulodynia," *Molecular Pain*, vol. 8, article 68, 2012.
- [15] O. Carreno, R. Corominas, J. Fernandez-Morales et al., "SNP variants within the vanilloid TRPV1 and TRPV3 receptor genes are associated with migraine in the Spanish population," *The American Journal of Medical Genetics*, vol. 159, no. 1, pp. 94–103, 2012.
- [16] J. E. Reeder, T. K. Byler, D. C. Foster et al., "Polymorphism in the SCN9A voltage-gated sodium channel gene associated with interstitial cystitis/bladder pain syndrome," *Urology*, vol. 81, no. 1, pp. 210.e1–210.e4, 2013.
- [17] M. Costigan, I. Belfer, R. S. Griffin et al., "Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1," *Brain*, vol. 133, no. 9, pp. 2519–2527, 2010.
- [18] J. Nissenbaum, M. Devor, Z. Seltzer et al., "Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2," *Genome Research*, vol. 20, no. 9, pp. 1180–1190, 2010.
- [19] L. Diatchenko, A. D. Anderson, G. D. Slade et al., "Three major haplotypes of the  $\beta$ 2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder," *The American Journal of Medical Genetics*, vol. 141, no. 5, pp. 449–462, 2006.
- [20] B. I. Nicholl, K. L. Holliday, G. J. MacFarlane et al., "Association of HTR2A polymorphisms with chronic widespread pain and the extent of musculoskeletal pain: results from two population-based cohorts," *Arthritis and Rheumatism*, vol. 63, no. 3, pp. 810–818, 2011.
- [21] E. A. Laugsand, T. Fladvad, F. Skorpen et al., "Clinical and genetic factors associated with nausea and vomiting in cancer patients receiving opioids," *European Journal of Cancer*, vol. 47, no. 11, pp. 1682–1691, 2011.
- [22] P. Klepstad, T. Fladvad, F. Skorpen et al., "Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients," *Pain*, vol. 152, no. 5, pp. 1139–1145, 2011.
- [23] C. C. Reyes-Gibby, S. Shete, T. Rakvåg et al., "Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene," *Pain*, vol. 130, no. 1-2, pp. 25–30, 2007.
- [24] J. Lötsch, N. von Hentig, R. Freyhagen et al., "Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers," *Pharmacogenetics and Genomics*, vol. 19, no. 6, pp. 429–436, 2009.
- [25] T. T. Rakvåg, J. R. Ross, H. Sato, F. Skorpen, S. Kaasa, and P. Klepstad, "Genetic variation in the Catechol-O-Methyltransferase (COMT) gene and morphine requirements in cancer patients with pain," *Molecular Pain*, vol. 4, article 64, 2008.
- [26] J. R. Ross, J. Riley, A. B. Taegtmeyer 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*, vol. 112, no. 6, pp. 1390–1403, 2008.
- [27] D. Campa, A. Gioia, A. Tomei, P. Poli, and R. Barale, "Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief," *Clinical Pharmacology and Therapeutics*, vol. 83, no. 4, pp. 559–566, 2008.
- [28] Y. C. Liu and W. S. Wang, "Human mu-opioid receptor gene A118G polymorphism predicts the efficacy of tramadol/acetaminophen combination tablets (ultracet) in oxaliplatin-induced painful neuropathy," *Cancer*, vol. 118, no. 6, pp. 1718–1725, 2012.
- [29] J. M. Droney, S. K. Gretton, H. Sato et al., "Analgesia and central side-effects: two separate dimensions of morphine response," *British Journal of Clinical Pharmacology*, vol. 75, no. 5, pp. 1340–1350, 2013.
- [30] D. Nishizawa, K. Fukuda, S. Kasai et al., "Genome-wide association study identifies a potent locus associated with human opioid sensitivity," *Molecular Psychiatry*, 2012.
- [31] J. Lötsch, H. Prüss, R. W. Veh, and A. Doehring, "A KCNJ6 (Kir3.2, GIRK2) gene polymorphism modulates opioid effects on analgesia and addiction but not on pupil size," *Pharmacogenomics and Genomics*, vol. 20, no. 5, pp. 291–297, 2010.
- [32] A. M. C. Ho, N. L. S. Tang, B. K. L. Cheung, and A. Stadlin, "Dopamine receptor D4 gene -521C/T polymorphism is associated with opioid dependence through cold-pain responses," *Annals of the New York Academy of Sciences*, vol. 1139, pp. 20–26, 2008.
- [33] C. Brasch-Andersen, M. U. Moller, L. Christiansen et al., "A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C)," *European Journal of Clinical Pharmacology*, vol. 67, no. 11, pp. 1131–1137, 2011.
- [34] I. Mitrovic, M. Margita-Mitrovic, S. Bader, M. Stoffel, L. Y. Jan, and A. I. Basbaum, "Contribution of GIRK2-mediated postsynaptic signaling to opiate and  $\alpha$ 2-adrenergic analgesia and analgesic sex differences," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 1, pp. 271–276, 2003.
- [35] T. Li, Z. H. Zhu, X. Liu et al., "Association analysis of polymorphisms in the DRD4 gene and heroin abuse in Chinese subjects," *The American Journal of Medical Genetics*, vol. 96, no. 5, pp. 616–621, 2000.
- [36] C. E. Constantin, N. Mair, C. A. Sailer et al., "Endogenous tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) requires TNF receptor type 2 to generate heat hyperalgesia in a mouse cancer model," *Journal of Neuroscience*, vol. 28, no. 19, pp. 5072–5081, 2008.
- [37] C. C. Reyes-Gibby, M. Spitz, X. Wu 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 Epidemiology Biomarkers and Prevention*, vol. 16, no. 12, pp. 2745–2751, 2007.
- [38] C. C. Reyes-Gibby, B. El Osta, M. R. Spitz 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 Epidemiology Biomarkers and Prevention*, vol. 17, no. 11, pp. 3262–3267, 2008.
- [39] C. C. Reyes-Gibby, M. R. Spitz, S. Yennurajalingam et al., "Role of inflammation gene polymorphisms on pain severity

- in lung cancer patients," *Cancer Epidemiology Biomarkers and Prevention*, vol. 18, no. 10, pp. 2636–2642, 2009.
- [40] D. A. Shoskes, Q. Albakri, K. Thomas, and D. Cook, "Cytokine polymorphisms in men with chronic prostatitis/chronic pelvic pain syndrome: association with diagnosis and treatment response," *Journal of Urology*, vol. 168, no. 1, pp. 331–335, 2002.
- [41] S. M. Rausch, B. D. Gonzalez, M. M. Clark et al., "SNPs in PTGS2 and LTA predict pain and quality of life in long term lung cancer survivors," *Lung Cancer*, vol. 77, no. 1, pp. 217–223, 2012.
- [42] S. Solovieva, P. Leino-Arjas, J. Saarela, K. Luoma, R. Raininko, and H. Riihimäki, "Possible association of interleukin 1 gene locus polymorphisms with low back pain," *Pain*, vol. 109, no. 1–2, pp. 8–19, 2004.
- [43] B. McCann, C. Miaskowski, T. Koetters et al., "Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery," *Journal of Pain*, vol. 13, no. 5, pp. 425–437, 2012.
- [44] J. Illi, C. Miaskowski, B. Cooper et al., "Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression," *Cytokine*, vol. 58, no. 3, pp. 437–447, 2012.
- [45] K. Oen, P. N. Malleson, D. A. Cabral et al., "Cytokine genotypes correlate with pain and radiologically defined joint damage in patients with juvenile rheumatoid arthritis," *Rheumatology*, vol. 44, no. 9, pp. 1115–1121, 2005.
- [46] C. C. Reyes-Gibby, S. Shete, S. Yennurajalingam et al., "Genetic and nongenetic covariates of pain severity in patients with adenocarcinoma of the pancreas: assessing the influence of cytokine genes," *Journal of Pain and Symptom Management*, vol. 38, no. 6, pp. 894–902, 2009.
- [47] W. Leppert, "CYP2D6 in the metabolism of opioids for mild to moderate pain," *Pharmacology*, vol. 87, no. 5–6, pp. 274–285, 2011.
- [48] M. A. Smith, A. M. Marinaki, and J. D. Sanderson, "Pharmacogenomics in the treatment of inflammatory bowel disease," *Pharmacogenomics*, vol. 11, no. 3, pp. 421–437, 2010.
- [49] G. P. Aithal, C. P. Day, J. B. S. Leathart, and A. K. Daly, "Relationship of polymorphism in CYP2C9 to genetic susceptibility to diclofenac-induced hepatitis," *Pharmacogenetics*, vol. 10, no. 6, pp. 511–518, 2000.
- [50] T. S. Tracy, J. Matthew Hutzler, R. L. Haining, A. E. Rettie, M. A. Hummel, and L. J. Dickmann, "Polymorphic variants (CYP2C9\*3 and CYP2C9\*5) and the F114L active site mutation of CYP2C9: effect on atypical kinetic metabolism profiles," *Drug Metabolism and Disposition*, vol. 30, no. 4, pp. 385–390, 2002.
- [51] J. E. Wyatt, W. L. Pettit, and S. Harirforoosh, "Pharmacogenetics of nonsteroidal anti-inflammatory drugs," *Pharmacogenomics Journal*, vol. 12, no. 6, pp. 462–467, 2012.
- [52] T. Hirota, S. Eguchi, and I. Ieiri, "Impact of genetic polymorphisms in CYP2C9 and CYP2C19 on the pharmacokinetics of clinically used drugs," *Drug Metabolism and Pharmacokinetics*, vol. 28, no. 1, pp. 28–37, 2013.
- [53] E. García-Martín, C. Martínez, B. Tabarés, J. Frías, and J. A. Agúndez, "Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms," *Clinical Pharmacology and Therapeutics*, vol. 76, no. 2, pp. 119–127, 2004.
- [54] X. Durrmeyer, S. Hovhannisyan, Y. Médard et al., "Are cytochrome P450 CYP2C8 and CYP2C9 polymorphisms associated with ibuprofen response in very preterm infants?" *PLoS One*, vol. 23, no. 5, Article ID 12329, 2010.
- [55] A. K. Daly, G. P. Aithal, J. B. S. Leathart, R. A. Swainsbury, T. S. Dang, and C. P. Day, "Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes," *Gastroenterology*, vol. 132, no. 1, pp. 272–281, 2007.
- [56] M. T. Smith and A. Muralidharan, "Pharmacogenetics of pain and analgesia," *Clinical Genetics*, vol. 82, no. 4, pp. 321–330, 2012.
- [57] C. Chen, S. C. Wang, H. H. Tsou et al., "Genetic polymorphisms in CYP3A4 are associated with withdrawal symptoms and adverse reactions in methadone maintenance patients," *Pharmacogenomics*, vol. 1210, no. 10, pp. 1397–1406, 2011.
- [58] R. Yuan, X. Zhang, Q. Deng, Y. Wu, and G. Xiang, "Impact of CYP3A4 1G polymorphism on metabolism of fentanyl in Chinese patients undergoing lower abdominal surgery," *Clinica Chimica Acta*, vol. 412, no. 9–10, pp. 755–760, 2011.
- [59] S. C. Sim, M. Kacevska, and M. Ingelman-Sundberg, "Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects," *Pharmacogenomics Journal*, vol. 13, no. 1, pp. 1–11, 2012.
- [60] A. Shiotani, T. Sakakibara, M. Nomura et al., "Aspirin-induced peptic ulcer and genetic polymorphisms," *Journal of Gastroenterology and Hepatology*, vol. 25, supplement 1, pp. S31–S34, 2010.
- [61] K. I. Fujita, Y. Ando, W. Yamamoto et al., "Association of UGT2B7 and ABCB1 genotypes with morphine-induced adverse drug reactions in Japanese patients with cancer," *Cancer Chemotherapy and Pharmacology*, vol. 65, no. 2, pp. 251–258, 2010.
- [62] M. Holthe, P. Klepstad, K. Zahlsen et al., "Morphine glucuronide-to-morphine plasma ratios are unaffected by the UGT2B7 H268Y and UGT1A1\*28 polymorphisms in cancer patients on chronic morphine therapy," *European Journal of Clinical Pharmacology*, vol. 58, no. 5, pp. 353–356, 2002.
- [63] P. Joly, M. C. Gagnieu, C. Bardel, A. Francina, C. Pondarre, and C. Martin, "Genotypic screening of the main opiate-related polymorphisms in a cohort of 139 sickle cell disease patients," *The American Journal of Hematology*, vol. 87, no. 5, pp. 534–536, 2012.
- [64] M. B. Sánchez, J. L. Herranz, C. Leno et al., "Genetic factors associated with drug-resistance of epilepsy: relevance of stratification by patient age and aetiology of epilepsy," *Seizure*, vol. 19, no. 2, pp. 93–101, 2010.
- [65] C. C. Hung, J. L. Ho, W. L. Chang et al., "Association of genetic variants in six candidate genes with valproic acid therapy optimization," *Pharmacogenomics*, vol. 12, no. 8, pp. 1107–1117, 2011.
- [66] Y. Mimura, Y. Maruo, Y. Ohta, H. Sato, and Y. Takeuchi, "Effect of common exon variant (p.P364L) on drug glucuronidation by the human UDP-glucuronosyltransferase 1 family," *Basic and Clinical Pharmacology and Toxicology*, vol. 109, no. 6, pp. 486–493, 2011.
- [67] J. Fortuny, M. Kogevinas, M. Garcia-Closas et al., "Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain," *Cancer Epidemiology Biomarkers and Prevention*, vol. 15, no. 9, pp. 1696–1702, 2006.
- [68] C. Bond, K. S. Laforge, M. Tian et al., "Single-nucleotide polymorphism in the human mu opioid receptor gene alters  $\beta$ -endorphin binding and activity: possible implications for opiate addiction," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 16, pp. 9608–9613, 1998.

- [69] Y. Zhang, D. Wang, A. D. Johnson, A. C. Papp, and W. Sadée, "Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G," *Journal of Biological Chemistry*, vol. 280, no. 38, pp. 32618–32624, 2005.
- [70] B. G. Oertel, M. Kettner, K. Scholich et al., "A common human  $\mu$ -opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain," *Journal of Biological Chemistry*, vol. 284, no. 10, pp. 6530–6535, 2009.
- [71] E. J. Lopez Soto and J. Raingo, "A118G Mu Opioid Receptor polymorphism increases inhibitory effects on CaV2.2 channels," *Neuroscience Letters*, vol. 523, no. 2, pp. 190–194, 2012.
- [72] C. Walter and J. Lötsch, "Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment," *Pain*, vol. 146, no. 3, pp. 270–275, 2009.
- [73] P. Anzenbacher and U. M. Zanger, Eds., *Metabolism of Drugs and Other Xenobiotics*, Wiley-VCH, Weinheim, Germany, 1 edition, 2012.
- [74] Food and Drug Administration, "Pharmacogenomic biomarkers in drug labels," 2012, <http://www.fda.gov/drugs/science-research/researchareas/pharmacogenetics/ucm083378.htm>.
- [75] PharmGKB, "Drug labels," 2012, <http://www.pharmgkb.org/search/labelList.action>.
- [76] J. K. Coller, D. T. Barratt, K. Dahlen, M. H. Loennechen, and A. A. Somogyi, "ABCB1 genetic variability and methadone dosage requirements in opioid-dependent individuals," *Clinical Pharmacology and Therapeutics*, vol. 80, no. 6, pp. 682–690, 2006.
- [77] O. Levran, K. O'Hara, E. Peles et al., "ABCB1 (MDRI) genetic variants are associated with methadone doses required for effective treatment of heroin dependence," *Human Molecular Genetics*, vol. 17, no. 14, pp. 2219–2227, 2008.
- [78] D. T. Barratt, J. K. Coller, R. Hallinan et al., "ABCB1 haplotype and OPRM1 118A > G genotype interaction in methadone maintenance treatment pharmacogenetics," *Journal of Pharmacogenomics and Personalized Medicine*, vol. 5, pp. 53–62, 2012.
- [79] L. Diatchenko, G. D. Slade, A. G. Nackley et al., "Genetic basis for individual variations in pain perception and the development of a chronic pain condition," *Human Molecular Genetics*, vol. 14, no. 1, pp. 135–143, 2005.
- [80] C. C. Hung, M. H. Chiou, B. H. Huang et al., "Impact of genetic polymorphisms in ABCB1, CYP2B6, OPRM1, ANKK1 and DRD2 genes on methadone therapy in Han Chinese patients," *Pharmacogenomics*, vol. 12, no. 11, pp. 1525–1533, 2011.
- [81] I. Meineke, S. Freudenthaler, U. Hofmann et al., "Pharmacokinetic modelling of morphine, morphine-3-glucuronide and morphine-6-glucuronide in plasma and cerebrospinal fluid of neurosurgical patients after short-term infusion of morphine," *British Journal of Clinical Pharmacology*, vol. 54, no. 6, pp. 592–603, 2002.
- [82] L. Coulbault, M. Beaussier, C. Verstuift et al., "Environmental and genetic factors associated with morphine response in the postoperative period," *Clinical Pharmacology and Therapeutics*, vol. 79, no. 4, pp. 316–324, 2006.
- [83] C. Mamie, M. C. Rebsamen, M. A. Morris, and A. Morabia, "First evidence of a polygenic susceptibility to pain in a pediatric cohort," *Anesthesia and Analgesia*, vol. 116, no. 1, pp. 170–177, 2013.
- [84] H. J. Park, H. K. Shinn, S. H. Ryu, H. S. Lee, C. S. Park, and J. H. Kang, "Genetic polymorphisms in the ABCB1 gene and the effects of fentanyl in Koreans," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 4, pp. 539–546, 2007.
- [85] O. Slanar, M. Nobile, J. Kvetina, O. Matouskova, J. R. Idle, and F. Perlik, "Pharmacokinetics of tramadol is affected by MDRI polymorphism C3435T," *European Journal of Clinical Pharmacology*, vol. 63, no. 4, pp. 419–421, 2007.
- [86] S. T. Zwislter, T. P. Enggaard, L. Noehr-Jensen 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," *Fundamental and Clinical Pharmacology*, vol. 24, no. 4, pp. 517–524, 2010.
- [87] M. Lovric, N. Bozina, S. Hajnsek et al., "Association between lamotrigine concentrations and ABCB1 polymorphisms in patients with epilepsy," *Therapeutic Drug Monitoring*, vol. 34, no. 5, pp. 518–525, 2012.
- [88] H. A. Kang, H. Y. Cho, and Y. B. Lee, "The effect of MDRI G2677T/A polymorphism on pharmacokinetics of gabapentin in healthy Korean subjects," *Archives of Pharmacal Research*, vol. 30, no. 1, pp. 96–101, 2007.
- [89] Y. G. Puranik, A. K. Birnbaum, S. E. Marino et al., "Association of carbamazepine major metabolism and transport pathway gene polymorphisms and pharmacokinetics in patients with epilepsy," *Pharmacogenomics*, vol. 14, no. 1, pp. 35–45, 2013.
- [90] Z. Sterjev, G. K. Trencavska, E. Cvetkovska et al., "The association of C3435T single-nucleotide polymorphism, Pgp-glycoprotein gene expression levels and carbamazepine maintenance dose in patients with epilepsy," *Neuropsychiatric Disease and Treatment*, vol. 8, pp. 191–196, 2012.
- [91] H. Meng, G. Guo, J. Ren, H. Zhou, Y. Ge, and Y. Guo, "Effects of ABCB1 polymorphisms on plasma carbamazepine concentrations and pharmacoresistance in Chinese patients with epilepsy," *Epilepsy and Behavior*, vol. 21, no. 1, pp. 27–30, 2011.
- [92] L. Karlsson, C. Hiemke, B. Carlsson et al., "Effects on enantiomeric drug disposition and open-field behavior after chronic treatment with venlafaxine in the P-glycoprotein knockout mice model," *Psychopharmacology*, vol. 215, no. 2, pp. 367–377, 2011.
- [93] L. Karlsson, U. Schmitt, M. Josefsson et al., "Blood-brain barrier penetration of the enantiomers of venlafaxine and its metabolites in mice lacking P-glycoprotein," *European Neuropsychopharmacology*, vol. 20, no. 9, pp. 632–640, 2010.
- [94] M. Uhr, M. T. Grauer, and F. Holsboer, "Differential enhancement of antidepressant penetration into the brain in mice with abcblab (mdrlab) P-Glycoprotein gene disruption," *Biological Psychiatry*, vol. 54, no. 8, pp. 840–846, 2003.
- [95] M. C. Rosenhagen and M. Uhr, "Single nucleotide polymorphism in the drug transporter Gene ABCB1 in treatment-resistant depression clinical practice," *Journal of Clinical Psychopharmacology*, vol. 30, no. 2, pp. 209–211, 2010.
- [96] M. Uhr and M. T. Grauer, "abcblab P-glycoprotein is involved in the uptake of citalopram and trimipramine into the brain of mice," *Journal of Psychiatric Research*, vol. 37, no. 3, pp. 179–185, 2003.
- [97] M. Uhr, M. T. Grauer, A. Yassouridis, and M. Ebinger, "Blood-brain barrier penetration and pharmacokinetics of amitriptyline and its metabolites in p-glycoprotein (abcblab) knock-out mice and controls," *Journal of Psychiatric Research*, vol. 41, no. 1-2, pp. 179–188, 2007.
- [98] M. Uhr, T. Steckler, A. Yassouridis, and F. Holsboer, "Penetration of amitriptyline, but not of fluoxetine, into brain is enhanced in mice with blood-brain barrier deficiency due to Mdr1a P-glycoprotein gene disruption," *Neuropsychopharmacology*, vol. 22, no. 4, pp. 380–387, 2000.

- [99] J. S. Lagas, R. W. Sparidans, E. Wagenaar, J. H. Beijnen, and A. H. Schinkel, "Hepatic clearance of reactive glucuronide metabolites of diclofenac in the mouse is dependent on multiple ATP-binding cassette efflux transporters," *Molecular Pharmacology*, vol. 77, no. 4, pp. 687–694, 2010.
- [100] J. A. Sloan, M. de Andrade, P. Decker et al., "Geneic variations and patient-reported quality of life among patients with lung cancer," *Journal of Clinical Oncology*, vol. 30, no. 14, pp. 1699–1704, 2012.
- [101] N. Zelcer, K. van de Wetering, M. Hillebrand et al., "Mice lacking multidrug resistance protein 3 show altered morphine pharmacokinetics and morphine-6-glucuronide antinociception," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 20, pp. 7274–7279, 2005.
- [102] Z. P. Lin, Y. L. Zhu, D. R. Johnson et al., "Disruption of cAMP and prostaglandin E2 transport by multidrug resistance protein 4 deficiency alters cAMP-mediated signaling and nociceptive response," *Molecular Pharmacology*, vol. 73, no. 1, pp. 243–251, 2008.
- [103] E. Kosek, K. B. Jensen, T. B. Lonsdorf, M. Schalling, and M. Ingvar, "Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid Remifentanil in humans," *Molecular Pain*, vol. 5, article 37, 2009.
- [104] F. Lindstedt, J. Berrebi, E. Greayer et al., "Conditioned pain modulation is associated with common Polymorphisms in the serotonin transporter gene," *PLoS ONE*, vol. 6, no. 3, Article ID e18252, 2011.
- [105] F. Lindstedt, T. B. Lonsdorf, M. Schalling, E. Kosek, and M. Ingvar, "Perception of thermal pain and the thermal grill illusion is associated with polymorphisms in the serotonin transporter gene," *PLoS ONE*, vol. 6, no. 3, Article ID e17752, 2011.
- [106] H. Herken, E. Erdal, N. Mutlu et al., "Possible association of temporomandibular joint pain and dysfunction with a polymorphism in the serotonin transporter gene," *The American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 120, no. 3, pp. 308–313, 2001.
- [107] S. Potvin, A. Larouche, E. Normand et al., "No relationship between the ins del polymorphism of the serotonin transporter promoter and pain perception in fibromyalgia patients and healthy controls," *European Journal of Pain*, vol. 14, no. 7, pp. 742–746, 2010.
- [108] M. Schürks, P. M. Rist, and T. Kurth, "STin2 VNTR polymorphism in the serotonin transporter gene and migraine: pooled and meta-analyses," *The Journal of Headache and Pain*, vol. 11, no. 4, pp. 317–326, 2010.
- [109] S. Kumar, P. Ranjan, B. Mittal, and U. C. Ghoshal, "Serotonin transporter gene (SLC6A4) polymorphism in patients with irritable bowel syndrome and healthy controls," *Journal of Gastrointestinal and Liver Diseases*, vol. 21, no. 1, pp. 31–38, 2012.
- [110] M. Offenbaecher, B. Bondy, S. de Jonge et al., "Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region," *Arthritis and Rheumatism*, vol. 42, no. 11, pp. 2482–2488, 1999.
- [111] S. Cevoli, M. Mochi, C. Scapoli et al., "A genetic association study of dopamine metabolism-related genes and chronic headache with drug abuse," *European Journal of Neurology*, vol. 13, no. 9, pp. 1009–1013, 2006.
- [112] H. E. Shin, S. J. Han, K. S. Lee, and J. W. Park, "Polymorphism of the glutamate transporter protein EAAT2 and migraine transformation into chronic daily headache," *Journal of Clinical Neurology*, vol. 7, no. 3, pp. 143–147, 2011.
- [113] J. Chen, B. K. Lipska, N. Halim et al., "Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mrna, protein, and enzyme activity in postmortem human brain," *The American Journal of Human Genetics*, vol. 75, no. 5, pp. 807–821, 2004.
- [114] J. F. Chen, V. J. Aloyo, and B. Weiss, "Continuous treatment with the D2 dopamine receptor agonist quinpirole decreased D2 dopamine receptors, D2 dopamine receptor messenger RNA and proenkephalin messenger RNA, and increases mu opioid receptors in mouse striatum," *Neuroscience*, vol. 54, no. 3, pp. 669–680, 1993.
- [115] H. Steiner and C. R. Gerfen, "Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior," *Experimental Brain Research*, vol. 123, no. 1-2, pp. 60–76, 1998.
- [116] A. Tammimaki and P. T. Mannisto, "Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis," *Pharmacogenet Genomics*, vol. 22, no. 9, pp. 673–691, 2012.
- [117] L. Diatchenko, A. G. Nackley, G. D. Slade et al., "Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli," *Pain*, vol. 125, no. 3, pp. 216–224, 2006.
- [118] A. G. Nackley, K. S. Tan, K. Fecho, P. Flood, L. Diatchenko, and W. Maixner, "Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both  $\beta 2$ - and  $\beta 3$ -adrenergic receptors," *Pain*, vol. 128, no. 3, pp. 199–208, 2007.
- [119] S. A. McLean, L. Diatchenko, Y. M. Lee et al., "Catechol O-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision," *Journal of Pain*, vol. 12, no. 1, pp. 101–107, 2011.
- [120] B. I. Nicholl, K. L. Holliday, G. J. Macfarlane et al., "No evidence for a role of the catechol-O-methyltransferase pain sensitivity haplotypes in chronic widespread pain," *Annals of the Rheumatic Diseases*, vol. 69, no. 11, pp. 2009–2012, 2010.
- [121] M. Tominaga, M. J. Caterina, A. B. Malmberg et al., "The cloned capsaicin receptor integrates multiple pain-producing stimuli," *Neuron*, vol. 21, no. 3, pp. 531–543, 1998.
- [122] N. Khairatkar-Joshi and A. Szallasi, "TRPV1 antagonists: the challenges for therapeutic targeting," *Trends in Molecular Medicine*, vol. 15, no. 1, pp. 14–22, 2009.
- [123] H. Junger and L. S. Sorkin, "Nociceptive and inflammatory effects of subcutaneous TNF $\alpha$ ," *Pain*, vol. 85, no. 1-2, pp. 145–151, 2000.
- [124] R. Ramonda, M. Lorenzin, V. Modesti et al., "Serological markers of erosive hand osteoarthritis," *European Journal of Internal Medicine*, vol. 24, no. 1, pp. 11–15, 2013.
- [125] M. Miyashita, T. Ito, M. Sakaki et al., "Genetic polymorphism in cyclooxygenase-2 promoter affects hepatic inflammation and fibrosis in patients with chronic hepatitis C," *Journal of Viral Hepatitis*, vol. 19, no. 9, pp. 608–614, 2012.
- [126] W. T. Loo, L. J. Bai, C. B. Fan et al., "Clinical application of human beta-defensin and CD14 gene polymorphism in evaluating the status of chronic inflammation," *Journal of Translational Medicine*, vol. 10, Supplement 1, p. S9, 2012.
- [127] M. O. Guzman-Ornelas, E. Chavarria-Avila, J. F. Munoz-Valle et al., "Association of ADIPOQ +45T > G polymorphism with body fat mass and blood levels of soluble adiponectin and inflammation markers in a Mexican-Mestizo population," *Diabetes, Metabolic Syndrome and Obesity*, vol. 5, pp. 369–378, 2012.

- [128] N. K. Vikram, S. P. Bhatt, B. Bhushan et al., "Associations of -308G/A polymorphism of tumor necrosis factor (TNF)-alpha gene and serum TNF-alpha levels with measures of obesity, intra-abdominal and subcutaneous abdominal fat, subclinical inflammation and insulin resistance in Asian Indians in north India," *Disease Markers*, vol. 31, no. 1, pp. 39–46, 2011.
- [129] A. Sen, S. K. Paine, I. H. Chowdhury et al., "Impact of interleukin-6 promoter polymorphism and serum interleukin-6 level on the acute inflammation and neovascularization stages of patients with Eales' disease," *Molecular Vision*, vol. 17, pp. 2552–2563, 2011.
- [130] L. R. Watkins, E. P. Wiertelak, L. E. Goehler, K. P. Smith, D. Martin, and S. F. Maier, "Characterization of cytokine-induced hyperalgesia," *Brain Research*, vol. 654, no. 1, pp. 15–26, 1994.
- [131] T. Hussain, S. Gupta, and H. Mukhtar, "Cyclooxygenase-2 and prostate carcinogenesis," *Cancer Letters*, vol. 191, no. 2, pp. 125–135, 2003.
- [132] P. W. Mantyh, D. R. Clohisy, M. Koltzenburg, and S. P. Hunt, "Molecular mechanisms of cancer pain," *Nature Reviews Cancer*, vol. 2, no. 3, pp. 201–209, 2002.
- [133] T. A. Samad, K. A. Moore, A. Sapirstein et al., "Interleukin-1  $\beta$ -mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity," *Nature*, vol. 410, no. 6827, pp. 471–475, 2001.
- [134] D. Hildeman and D. Muller, "Immunopathologic weight loss in intracranial LCMV infection initiated by the anorexigenic effects of IL-1 $\beta$ ," *Viral Immunology*, vol. 13, no. 3, pp. 273–285, 2000.
- [135] S. S. Choi, K. J. Han, J. K. Lee et al., "Antinociceptive mechanisms of orally administered decursinol in the mouse," *Life Sciences*, vol. 73, no. 4, pp. 471–485, 2003.
- [136] A. J. Reeve, S. Patel, A. Fox, K. Walker, and L. Urban, "Intrathecally administered endotoxin or cytokines produce allodynia, hyperalgesia and changes in spinal cord neuronal responses to nociceptive stimuli in the rat," *European Journal of Pain*, vol. 4, no. 3, pp. 247–257, 2000.
- [137] T. L. McDowell, J. A. Symons, R. Ploski, O. Førre, and G. W. Duff, "A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 $\alpha$  polymorphism," *Arthritis and Rheumatism*, vol. 38, no. 2, pp. 221–228, 1995.
- [138] F. Pociot, J. Molvig, L. Wogensen, H. Worsaae, and J. Nerup, "A TaqI polymorphism in the human interleukin-1 $\beta$  (IL-1 $\beta$ ) gene correlates with IL-1 $\beta$  secretion in vitro," *European Journal of Clinical Investigation*, vol. 22, no. 6, pp. 396–402, 1992.
- [139] J. K. Tarlow, A. I. F. Blakemore, A. Lennard et al., "Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat," *Human Genetics*, vol. 91, no. 4, pp. 403–404, 1993.
- [140] D. Voehringer, K. Shinkai, and R. M. Locksley, "Type 2 immunity reflects orchestrated recruitment of cells committed to IL-4 production," *Immunity*, vol. 20, no. 3, pp. 267–277, 2004.
- [141] R. de Waal Malefyt, C. G. Figdor, R. Huijbens et al., "Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes: comparison with IL-4 and modulation by IFN- $\gamma$  or IL-10," *Journal of Immunology*, vol. 151, no. 11, pp. 6370–6381, 1993.
- [142] J. Punnonen, G. Aversa, B. G. Cocks et al., "Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 8, pp. 3730–3734, 1993.
- [143] Z. Xing, J. Gauldie, G. Cox et al., "IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses," *Journal of Clinical Investigation*, vol. 101, no. 2, pp. 311–320, 1998.
- [144] K. Matsushima, K. Morishita, T. Yoshimura et al., "Molecular cloning of a human monocyte-derived neutrophil chemotactic factor (MDNCF) and the induction of MDNCF mRNA by interleukin 1 and tumor necrosis factor," *Journal of Experimental Medicine*, vol. 167, no. 6, pp. 1883–1893, 1988.
- [145] M. Seitz, B. Dewald, N. Gerber, and M. Baggolini, "Enhanced production of neutrophil-activating peptide-1/interleukin-8 in rheumatoid arthritis," *Journal of Clinical Investigation*, vol. 87, no. 2, pp. 463–469, 1991.
- [146] P. J. Jannetto and N. C. Bratanow, "Pain management in the 21st century: utilization of pharmacogenomics and therapeutic drug monitoring," *Expert Opinion on Drug Metabolism and Toxicology*, vol. 7, no. 6, pp. 745–752, 2011.
- [147] S. B. Smith, D. W. Maixner, R. B. Fillingim et al., "Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia," *Arthritis and Rheumatism*, vol. 64, no. 2, pp. 584–593, 2012.
- [148] M. Allegri, M. de gregori, T. Niebel et al., "Pharmacogenetics and postoperative pain: a new approach to improve acute pain management," *Minerva Anestesiologica*, vol. 76, no. 11, pp. 937–944, 2010.
- [149] H. Buzkova, K. Pechanova, O. Slanar, and F. Perlik, "Frequency of single nucleotide polymorphisms of CYP2D6 in the Czech population," *Cell Biochemistry and Function*, vol. 26, no. 1, pp. 76–81, 2008.
- [150] J. Sistonen, A. Sajantila, O. Lao, J. Corander, G. Barbujani, and S. Fuselli, "CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure," *Pharmacogenetics and Genomics*, vol. 17, no. 2, pp. 93–101, 2007.
- [151] L. Poulsen, K. Brøsen, L. Arendt-Nielsen, L. F. Gram, K. Elbæk, and S. H. Sindrup, "Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects," *European Journal of Clinical Pharmacology*, vol. 51, no. 3–4, pp. 289–295, 1996.
- [152] G. Koren, J. Cairns, D. Chitayat, A. Gaedigk, and S. J. Leeder, "Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother," *The Lancet*, vol. 368, no. 9536, p. 704, 2006.
- [153] R. Landau, L. A. Bollag, and J. C. Kraft, "Pharmacogenetics and anaesthesia: the value of genetic profiling," *Anaesthesia*, vol. 67, no. 2, pp. 165–179, 2012.
- [154] Food and Drug Administration, "Information for healthcare professionals: use of codeine products in nursing mothers," 2007.
- [155] European Medicines Agency, "Review of codeine-containing medicines started," 2012.
- [156] S. Sadhasivam and C. M. Myer, "Preventing opioid-related deaths in children undergoing surgery," *Pain Medicine*, vol. 12, no. 7, pp. 982–983, 2012.
- [157] M. J. Garrido, M. Valle, M. A. Campanero, R. Calvo, and I. F. Trocóniz, "Modeling of the in vivo antinociceptive interaction between an opioid agonist, (+)-O-desmethyltramadol, and a monoamine reuptake inhibitor, (-)-O-desmethyltramadol, in rats," *Journal of Pharmacology and Experimental Therapeutics*, vol. 295, no. 1, pp. 352–359, 2000.

- [158] O. Slanar, P. Dupal, O. Matouskova, H. Vondrackova, P. Pafko, and F. Perlik, "Tramadol efficacy in patients with postoperative pain in relation to CYP2D6 and MDRI polymorphisms," *Bratislava Medical Journal*, vol. 113, no. 3, pp. 152–155, 2012.
- [159] N. Fleeman, C. Martin Saborido, K. Payne et al., "The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review," *Health Technology Assessment*, vol. 15, no. 33, pp. 1–102, 2011.
- [160] G. Blanco, C. Martínez, J. M. Ladero et al., "Interaction of CYP2C8 and CYP2C9 genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding," *Pharmacogenetics and Genomics*, vol. 18, no. 1, pp. 37–43, 2008.
- [161] J. H. Martin, E. J. Begg, M. A. Kennedy, R. Roberts, and M. L. Barclay, "Is cytochrome p450 2c9 genotype associated with NSAID gastric ulceration?" *British Journal of Clinical Pharmacology*, vol. 51, no. 6, pp. 627–630, 2001.
- [162] J. A. G. Agúndez, E. García-Martín, and C. Martínez, "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 Opinion on Drug Metabolism and Toxicology*, vol. 5, no. 6, pp. 607–620, 2009.
- [163] D. A. Mrazek, J. M. Biernacka, D. J. O'Kane et al., "CYP2C19 variation and citalopram response," *Pharmacogenetics and Genomics*, vol. 21, no. 1, pp. 1–9, 2011.
- [164] J. Kirchheimer, K. Nickchen, M. Bauer et al., "Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response," *Molecular Psychiatry*, vol. 9, no. 5, pp. 442–473, 2004.
- [165] D. E. McAlpine, J. M. Biernacka, D. A. Mrazek et al., "Effect of cytochrome P450 enzyme polymorphisms on pharmacokinetics of venlafaxine," *Therapeutic Drug Monitoring*, vol. 33, no. 1, pp. 14–20, 2011.
- [166] C. Martínez, E. García-Martín, G. Blanco, F. J. G. Gamito, J. M. Ladero, and J. A. G. Agúndez, "The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects," *British Journal of Clinical Pharmacology*, vol. 59, no. 1, pp. 62–68, 2005.
- [167] U. Yasar, E. Eliasson, C. Forslund-Bergengren et al., "The role of CYP2C9 genotype in the metabolism of diclofenac in vivo and in vitro," *European Journal of Clinical Pharmacology*, vol. 57, no. 10, pp. 729–735, 2001.
- [168] R. Vianna-Jorge, J. A. Perini, E. Rondinelli, and G. Suarez-Kurtz, "CYP2C9 genotypes and the pharmacokinetics of tenoxicam in Brazilians," *Clinical Pharmacology and Therapeutics*, vol. 76, no. 1, pp. 18–26, 2004.
- [169] Y. Wang, D. Zhou, B. Wang et al., "A kindling model of pharmacoresistant temporal lobe epilepsy in Sprague-Dawley rats induced by Coriaria lactone and its possible mechanism," *Epilepsia*, vol. 44, no. 4, pp. 475–488, 2003.
- [170] M. Jin, S. B. Gock, P. J. Jannetto, J. M. Jentzen, and S. H. Wong, "Pharmacogenomics as molecular autopsy for forensic toxicology: genotyping cytochrome P450 3A4\*1B and 3A5\*3 for 25 fentanyl cases," *Journal of Analytical Toxicology*, vol. 29, no. 7, pp. 590–598, 2005.
- [171] S. H. Wong, M. A. Wagner, J. M. Jentzen et al., "Pharmacogenomics as an aspect of molecular autopsy for forensic pathology/toxicology: does genotyping CYP 2D6 serve as an adjunct for certifying methadone toxicity?" *Journal of Forensic Sciences*, vol. 48, no. 6, pp. 1406–1415, 2003.
- [172] P. J. Jannetto, S. H. Wong, S. B. Gock, E. Laleli-Sahin, B. C. Schur, and J. M. Jentzen, "Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases," *Journal of Analytical Toxicology*, vol. 26, no. 7, pp. 438–447, 2002.
- [173] N. Hakooz, S. Alzubiedi, A. M. Yousef et al., "UDP-glucuronosyltransferase 1A4 (UGT1A4) polymorphisms in a Jordanian population," *Molecular Biology Reports*, vol. 39, no. 7, pp. 7763–7768, 2012.
- [174] M. B. Sawyer, F. Innocenti, S. Das et al., "A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine," *Clinical Pharmacology and Therapeutics*, vol. 73, no. 6, pp. 566–574, 2003.
- [175] Y. Chen, G. E. Kuehl, J. Bigler et al., "UGT1A6 polymorphism and salicylic acid glucuronidation following aspirin," *Pharmacogenetics and Genomics*, vol. 17, no. 8, pp. 571–579, 2007.
- [176] S. Ruett and P. Gros, "Phosphatidylcholine translocase: a physiological role for the mdr2 gene," *Cell*, vol. 77, no. 7, pp. 1071–1081, 1994.
- [177] A. van Helvoort, A. J. Smith, H. Sprong et al., "MDR1 P-glycoprotein is a lipid translocase of broad specificity, while MDR3 P-glycoprotein specifically translocates phosphatidylcholine," *Cell*, vol. 87, no. 3, pp. 507–517, 1996.
- [178] H. Yamaguchi, T. Hishinuma, N. Endo et al., "Genetic variation in ABCB1 influences paclitaxel pharmacokinetics in Japanese patients with ovarian cancer," *International Journal of Gynecological Cancer*, vol. 16, no. 3, pp. 979–985, 2006.
- [179] A. C. Allabi, J. L. Gala, and Y. Horsmans, "CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population," *Pharmacogenetics and Genomics*, vol. 15, no. 11, pp. 779–786, 2005.
- [180] R. Callaghan and J. R. Riordan, "Synthetic and natural opiates interact with P-glycoprotein in multidrug-resistant cells," *Journal of Biological Chemistry*, vol. 268, no. 21, pp. 16059–16064, 1993.
- [181] R. Bouer, L. Barthe, C. Philibert, C. Tournaire, J. Woodley, and G. Houin, "The roles of P-glycoprotein and intracellular metabolism in the intestinal absorption of methadone: in vitro studies using the rat everted intestinal sac," *Fundamental and Clinical Pharmacology*, vol. 13, no. 4, pp. 494–500, 1999.
- [182] A. J. Sadeque, C. Wandel, H. He, S. Shah, and A. J. Wood, "Increased drug delivery to the brain by P-glycoprotein inhibition," *Clinical Pharmacology and Therapeutics*, vol. 68, no. 3, pp. 231–237, 2000.
- [183] S. J. Thompson, K. Koszdin, and C. M. Bernards, "Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein," *Anesthesiology*, vol. 92, no. 5, pp. 1392–1399, 2000.
- [184] M. Rodriguez, I. Ortega, I. Soengas, E. Suarez, J. C. Lukas, and R. Calvo, "Effect of P-glycoprotein inhibition on methadone analgesia and brain distribution in the rat," *Journal of Pharmacy and Pharmacology*, vol. 56, no. 3, pp. 367–374, 2004.
- [185] J. S. Wang, Y. Ruan, R. M. Taylor, J. L. Donovan, J. S. Markowitz, and C. L. DeVane, "Brain penetration of methadone (R)- and (S)-enantiomers is greatly increased by P-glycoprotein deficiency in the blood-brain barrier of Abcb1a gene knockout mice," *Psychopharmacology*, vol. 173, no. 1, pp. 132–138, 2004.
- [186] T. Nanovskaya, I. Nekhayeva, N. Karunaratne, K. Audus, G. D. V. Hankins, and M. S. Ahmed, "Role of P-glycoprotein in transplacental transfer of methadone," *Biochemical Pharmacology*, vol. 69, no. 12, pp. 1869–1878, 2005.

- [187] G. You and M. E. Morris, *Drug Transporters : Molecular Characterization and Role in Drug Disposition*, Wiley-Interscience, Hoboken, NJ, USA, 2007.
- [188] F. Thiebaut, T. Tsuruo, H. Hamada, M. M. Gottesman, I. Pastan, and M. C. Willingham, "Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 84, no. 21, pp. 7735–7738, 1987.
- [189] E. Beaulieu, M. Demeule, L. Ghitescu, and R. Beliveau, "P-glycoprotein is strongly expressed in the luminal membranes of the endothelium of blood vessels in the brain," *Biochemical Journal*, vol. 326, no. 2, pp. 539–544, 1997.
- [190] N. Melaine, M. O. Liénard, I. Dorval, C. Le Goascogne, H. Lejeune, and B. Jégou, "Multidrug resistance genes and P-glycoprotein in the testis of the rat, mouse, guinea pig, and human," *Biology of Reproduction*, vol. 67, no. 6, pp. 1699–1707, 2002.
- [191] J. E. Edwards, J. Alcorn, J. Savolainen, B. D. Anderson, and P. J. McNamara, "Role of P-glycoprotein in distribution of nelfinavir across the blood-mammary tissue barrier and blood-brain barrier," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 4, pp. 1626–1628, 2005.
- [192] T. Saito, Z. J. Zhang, H. Tsuzuki et al., "Expression of P-glycoprotein in inner ear capillary endothelial cells of the guinea pig with special reference to blood-inner ear barrier," *Brain Research*, vol. 767, no. 2, pp. 388–392, 1997.
- [193] S. Gil, R. Saura, F. Forestier, and R. Farinotti, "P-glycoprotein expression of the human placenta during pregnancy," *Placenta*, vol. 26, no. 2-3, pp. 268–270, 2005.
- [194] G. M. Kalabis, A. Kostaki, M. H. Andrews, S. Petropoulos, W. Gibb, and S. G. Matthews, "Multidrug resistance phosphoglycoprotein (ABCB1) in the mouse placenta: fetal protection," *Biology of Reproduction*, vol. 73, no. 4, pp. 591–597, 2005.
- [195] K. Jamroziak and T. Robak, "Pharmacogenomics of MDRI/ABCB1 gene: the influence on risk and clinical outcome of haemotological malignancies," *Hematology*, vol. 9, no. 2, pp. 91–105, 2004.
- [196] S. Gollapudi and S. Gupta, "Anti-P-glycoprotein antibody-induced apoptosis of activated peripheral blood lymphocytes: a possible role of P-glycoprotein in lymphocyte survival," *Journal of Clinical Immunology*, vol. 21, no. 6, pp. 420–430, 2001.
- [197] A. Pawlik, M. Baskiewicz-Masiuk, B. Machalinski, M. Kurzawski, and B. Gawronska-Szklarz, "Involvement of C3435T and G2677T multidrug resistance gene polymorphisms in release of cytokines from peripheral blood mononuclear cells treated with methotrexate and dexamethasone," *European Journal of Pharmacology*, vol. 528, no. 1–3, pp. 27–36, 2005.
- [198] U. O. F. Alberto Riva, "CHIP Bioinformatics Tools," 2012, <http://snpper.chip.org>.
- [199] C. Luna-Tortós, M. Fedrowitz, and W. Löscher, "Several major antiepileptic drugs are substrates for human P-glycoprotein," *Neuropharmacology*, vol. 55, no. 8, pp. 1364–1375, 2008.
- [200] H. Potschka, M. Fedrowitz, and W. Löscher, "P-Glycoprotein-mediated efflux of phenobarbital, lamotrigine, and felbamate at the blood-brain barrier: evidence from microdialysis experiments in rats," *Neuroscience Letters*, vol. 327, no. 3, pp. 173–176, 2002.
- [201] C. Luna-Tortós, B. Rambeck, U. H. Jurgens, and W. Loscher, "The antiepileptic drug topiramate is a substrate for human P-glycoprotein but not multidrug resistance proteins," *Pharmaceutical Research*, vol. 26, no. 11, pp. 2464–2470, 2009.
- [202] F. Rivers, T. J. O'Brien, and R. Callaghan, "Exploring the possible interaction between anti-epilepsy drugs and multidrug efflux pumps; in vitro observations," *European Journal of Pharmacology*, vol. 598, no. 1–3, pp. 1–8, 2008.
- [203] A. Crowe and Y. K. Teoh, "Limited P-glycoprotein mediated efflux for anti-epileptic drugs," *Journal of Drug Targeting*, vol. 14, no. 5, pp. 291–300, 2006.
- [204] S. Baltes, M. Fedrowitz, C. L. Tortós, H. Potschka, and W. Löscher, "Valproic acid is not a substrate for P-glycoprotein or multidrug resistance proteins 1 and 2 in a number of in vitro and in vivo transport assays," *Journal of Pharmacology and Experimental Therapeutics*, vol. 320, no. 1, pp. 331–343, 2007.
- [205] M. Ufer, I. Mosyagin, H. Muhle et al., "Non-response to antiepileptic pharmacotherapy is associated with the ABCC2-24C>T polymorphism in young and adult patients with epilepsy," *Pharmacogenetics and Genomics*, vol. 19, no. 5, pp. 353–362, 2009.
- [206] C. Brandt, K. Bethmann, A. M. Gastens, and W. Löscher, "The multidrug transporter hypothesis of drug resistance in epilepsy: proof-of-principle in a rat model of temporal lobe epilepsy," *Neurobiology of Disease*, vol. 24, no. 1, pp. 202–211, 2006.
- [207] M. A. Summers, J. L. Moore, and J. W. McAuley, "Use of verapamil as a potential P-glycoprotein inhibitor in a patient with refractory epilepsy," *Annals of Pharmacotherapy*, vol. 38, no. 10, pp. 1631–1634, 2004.
- [208] D. W. Kim, M. Kim, S. K. Lee, R. Kang, and S. Y. Lee, "Lack of association between C3435T nucleotide MDRI genetic polymorphism and multidrug-resistant epilepsy," *Seizure*, vol. 15, no. 5, pp. 344–347, 2006.
- [209] G. Turgut, E. Kurt, C. Sengul et al., "Association of MDRI C3435T polymorphism with bipolar disorder in patients treated with valproic acid," *Molecular Biology Reports*, vol. 36, no. 3, pp. 495–499, 2009.
- [210] C. C. Hung, W. L. Chang, J. L. Ho et al., "Association of polymorphisms in EPHX1, UGT2B7, ABCB1, ABCC2, SCN1A and SCN2A genes with carbamazepine therapy optimization," *Pharmacogenomics*, vol. 13, no. 2, pp. 159–169, 2012.
- [211] G. O. Ozgon, N. Bebek, G. Gul, and N. Cine, "Association of MDRI (C3435T) polymorphism and resistance to carbamazepine in epileptic patients from Turkey," *European Neurology*, vol. 59, no. 1-2, pp. 67–70, 2007.
- [212] S. K. Tate, C. Depondt, S. M. Sisodiya et al., "Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 15, pp. 5507–5512, 2005.
- [213] C. Bundgaard, C. J. Jensen, and M. Garmer, "Species comparison of in vivo P-glycoprotein-mediated brain efflux using mdrla-deficient rats and mice," *Drug Metabolism and Disposition*, vol. 40, no. 3, pp. 461–466, 2012.
- [214] F. E. O. 'Brien, G. Clarke, P. Fitzgerald, T. G. Dinan, B. T. Griffin, and J. F. Cryan, "Inhibition of P-glycoprotein enhances transport of imipramine across the blood-brain barrier: microdialysis studies in conscious freely moving rats," *British Journal of Pharmacology*, vol. 166, no. 4, pp. 1333–1343, 2012.
- [215] A. Y. Abaut, F. Chevanne, and P. Le Corre, "Influence of efflux transporters on liver, bile and brain disposition of amitriptyline in mice," *International Journal of Pharmaceutics*, vol. 378, no. 1–2, pp. 80–85, 2009.

- [216] P. Gareri, P. De Fazio, L. Gallelli et al., "Venlafaxine-propafenone interaction resulting in hallucinations and psychomotor agitation," *Annals of Pharmacotherapy*, vol. 42, no. 3, pp. 434–438, 2008.
- [217] A. Y. Abaut, F. Chevanne, and P. Le Corre, "Oral bioavailability and intestinal secretion of amitriptyline: role of P-glycoprotein?" *International Journal of Pharmaceutics*, vol. 330, no. 1-2, pp. 121–128, 2007.
- [218] T. B. Ejsing, J. Hasselstrøm, and K. Linnet, "The influence of P-glycoprotein on cerebral and hepatic concentrations of nortriptyline and its metabolites," *Drug Metabolism and Drug Interactions*, vol. 21, no. 3-4, pp. 139–162, 2006.
- [219] T. B. Ejsing and K. Linnet, "Influence of P-glycoprotein inhibition on the distribution of the tricyclic antidepressant nortriptyline over the blood-brain barrier," *Human Psychopharmacology*, vol. 20, no. 2, pp. 149–153, 2005.
- [220] S. Wikinski, "Pharmacokinetic mechanisms underlying resistance in psychopharmacological treatment. The role of P-glycoprotein," *Vertex*, vol. 16, no. 64, pp. 438–441, 2005.
- [221] M. Dean and T. Annilo, "Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates," *Annual Review of Genomics and Human Genetics*, vol. 6, pp. 123–142, 2005.
- [222] S. I. Akanuma, K. I. Hosoya, S. Ito, M. Tachikawa, T. Terasaki, and S. Ohtsuki, "Involvement of multidrug resistance-associated protein 4 in efflux transport of prostaglandin E2 across mouse blood-brain barrier and its inhibition by intravenous administration of cephalosporins," *Journal of Pharmacology and Experimental Therapeutics*, vol. 333, no. 3, pp. 912–919, 2010.
- [223] M. Rius, W. F. Thon, D. Keppler, and A. T. Nies, "Prostanoid transport by multidrug resistance protein 4 (MRP4/ABCC4) localized in tissues of the human urogenital tract," *Journal of Urology*, vol. 174, no. 6, pp. 2409–2414, 2005.
- [224] G. Reid, P. Wielinga, N. Zelcer et al., "The human multidrug resistance protein MRP4 functions as a prostaglandin efflux transporter and is inhibited by nonsteroidal anti inflammatory drugs," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 16, pp. 9244–9249, 2003.
- [225] J. W. Eikelboom and G. J. Hankey, "Overexpression of the multidrug resistance protein-4 transporter in patients undergoing coronary artery bypass graft surgery: a cause of aspirin resistance?" *Journal of the American College of Cardiology*, vol. 58, no. 7, pp. 762–764, 2011.
- [226] T. Mattiello, R. Guerriero, L. V. Lotti et al., "Aspirin extrusion from human platelets through multidrug resistance protein-4-mediated transport: evidence of a reduced drug action in patients after coronary artery bypass grafting," *Journal of the American College of Cardiology*, vol. 58, no. 7, pp. 752–761, 2011.
- [227] L. E. Jensen, A. M. Wall, M. Cook et al., "A common ABCC2 promoter polymorphism is not a determinant of the risk of spina bifida," *Birth Defects Research Part A*, vol. 70, no. 6, pp. 396–399, 2004.
- [228] S. Haenisch, U. Zimmermann, E. Dazert et al., "Influence of polymorphisms of ABCB1 and ABCC2 on mRNA and protein expression in normal and cancerous kidney cortex," *Pharmacogenomics Journal*, vol. 7, no. 1, pp. 56–65, 2007.
- [229] S. Ito, I. Ieiri, M. Tanabe, A. Suzuki, S. Higuchi, and K. Otsubo, "Polymorphism of the ABC transporter genes, MDR1, MRP1 and MRP2/cMOAT, in healthy Japanese subjects," *Pharmacogenetics*, vol. 11, no. 2, pp. 175–184, 2001.
- [230] M. Hirouchi, H. Suzuki, M. Itoda et al., "Characterization of the cellular localization, expression level, and function of SNP variants of MRP2/ABCC2," *Pharmaceutical Research*, vol. 21, no. 5, pp. 742–748, 2004.
- [231] M. Ufer, C. von Stulpnagel, H. Muhle et al., "Impact of ABCC2 genotype on antiepileptic drug response in Caucasian patients with childhood epilepsy," *Pharmacogenet Genomics*, vol. 21, no. 10, pp. 624–630, 2011.
- [232] S. A. Eraly, K. T. Bush, R. V. Sampogna, V. Bhatnagar, and S. K. Nigam, "The molecular pharmacology of organic anion transporters: from DNA to FDA?" *Molecular Pharmacology*, vol. 65, no. 3, pp. 479–487, 2004.
- [233] B. Gao, B. Hagenbuch, G. A. Kullak-Ublick, D. Benke, A. Aguzzi, and P. J. Meier-Abt, "Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier," *Journal of Pharmacology and Experimental Therapeutics*, vol. 294, no. 1, pp. 73–79, 2000.
- [234] C. Michalski, Y. Cui, A. T. Nies et al., "A naturally occurring mutation in the SLC21A6 gene causing impaired membrane localization of the hepatocyte uptake transporter," *Journal of Biological Chemistry*, vol. 277, no. 45, pp. 43058–43063, 2002.
- [235] J. Aoki, K. Ikeda, O. Murayama, E. Yoshihara, Y. Ogai, and K. Iwahashi, "The association between personality, pain threshold and a single nucleotide polymorphism (rs3813034) in the 3'-untranslated region of the serotonin transporter gene (SLC6A4)," *Journal of Clinical Neuroscience*, vol. 17, no. 5, pp. 574–578, 2010.
- [236] M. Schürks, P. M. Rist, and T. Kurth, "5-HTTLPR polymorphism in the serotonin transporter gene and migraine: a systematic review and meta-analysis," *Cephalgia*, vol. 30, no. 11, pp. 1296–1305, 2010.
- [237] S. Gursoy, "Absence of association of the serotonin transporter gene polymorphism with the mentally healthy subset of fibromyalgia patients," *Clinical Rheumatology*, vol. 21, no. 3, pp. 194–197, 2002.

