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Genetic variability of pain perception and treatment – clinical pharmaco- logical implications

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Abstract

Evidence of a genetic control of pain has led to efforts to exploit genotyping information from pain patients for the development of analgesics and for the selection of pharmacological approaches to pain. Translating the genetic bases of familial insensitivity to pain research has contributed to the discovery of crucial molecular pathways of pain and to the identification of new analgesic targets (e.g., sodium channels $\text{Na}_v1.7$, neurotrophic tyrosine kinase receptors or the nerve growth factor).

Moreover, human genetic variants leading to enhanced or reduced function of molecular pathways

are employed as substitutes for lacking modulator molecules usable in humans. This allows early studying of nociceptive or anti-nociceptive pathways in humans before drug development. Translational approaches also served to verify the human importance of experimentally discovered pain pathways, such as in GTP cyclohydrolase 1 and the potassium channel $\text{K}_v9.1$. Besides these uses of

genetics as a research tool, an individualized pharmacological therapy based on the patient's genotype has been attempted.

For the actual analgesics, such guidance has only marginally become available. For upcoming analgesics targeting, for example, $\text{Na}_v1.7$ or TRPA1, the genotype may provide a selective cure for syndromes caused by increased-function mutations in the coding genes. The implementation of human genetics may accelerate analgesic drug development while reducing its cost because the clinical success may be partly anticipated by including the information of functional genetic variants that mimic the action of future analgesics, showing that genotyping information from pain patients plays a role in the clinical pharmacology of pain.

Key words: Pain, analgesics, pain genetics, pharmacogenetics, drug targets, new drugs, investigational drugs, personalized medicine

Introduction

A relation between a patient's genotype and pain phenotype has been suggested about 50 years ago

[1]. In that early report, genetics was used for basic research to show that the risk of migraine is hereditarily transmitted, emphasizing underlying molecular mechanisms. With increasing sophistication of genetic research, genotyping has become an effective scientific tool to identify the particu-

lar molecular causes underlying the susceptibility to pain, its intensity or clinical development toward either disappearance or chronification up to neuropathic pain. The risk or protective mechanisms provide primary candidate targets of new pharmacological approaches to pain treatment.

Besides concluding a molecular mechanism of pain from the identification of its genetic cause, translational approaches are being used to verify and quantitatively estimate the human importance

of a molecular mechanism found in basic research. Functional genetic variants may serve as substitutes for unavailable drugs modulating the newly discovered molecular mechanism. This provides support for the successful development of pharmacological treatments targeting the identified mechanism.

While associating genotypes with phenotypes of pain patients has proved its scientific value in drug development, genotyping information is also expected to provide clinical guidance for the individual pharmacological approach to pain. However, this had so far only limited success [2] and a genotype based pain therapy has not yet emerged. Nevertheless, there is an imminent chance that this might improve with the approval of analgesics addressing new targets that are currently in the clinical phases of development.

Successful applications of genotyping pain patients are summarized in the following. The focus is on

a key role in analgesic drug development or use. This excludes several observations of genetic modulations of pain or analgesia without this particular application, which are extensively summarized elsewhere [3]. It further excludes candidate genes that from the analgesic's pharmacology are likely

to contribute to the pharmacogenetics of the particular analgesic but for which neither evidence nor

scientific utility has been proven, which has been previously covered [4]. Pharmacogenetic information obtained from pain patients has its main clinical pharmacological utility so far in drug development and in evidence based rather than merely possible modulations of drug therapy.

Genotyping and phenotyping in the development process of analgesics

Discovery of analgesic targets

The carriers are not pain patients but the opposite, but the molecular causes of their particular phenotype characterized by absent pain provide primary candidate targets of analgesics. Six very rare hereditary sensory and autonomic neuropathy (HSAN) syndromes have been described [5]. They dif-

fer by their genetic causes, consisting of several loss-of-function mutations in the genes *SPTLC1*,

WNK1, *IKBKAP*, *NTRK1*, *NGFB* and *SCN9A*, and by their association with neurological failures (Table

1). The molecular targets of the last three of these symptoms, i.e., TRK1 (tyrosine kinase 1), NGF (nerve growth factor) and Na_v1.7, are being employed as targets of analgesic drugs under development.

The nerve growth factor (NGF) is a small protein belonging to the class of neurotrophins and identified originally as a survival factor for sensory and sympathetic neurons in the developing nervous system [6]. NGF binds at the p75 low affinity nerve growth factor receptor and at the transmembrane tyrosine kinase receptor, the latter being associated with neurodegenerative disorders. NGF is not required for survival in adults but plays a crucial role in the generation of pain and hyperalgesia

[6]. The expression of NGF is high in injured and inflamed tissues, and activation of the NGF recep-

tor tyrosine kinase A on nociceptive neurons triggers and enhances nociceptive signalling by multi-

ple mechanisms [7]. Members of a Swedish family carrying a hereditary insensitivity to pain were homozygous for a coding 661C>T SNP (R211W) in the *NGFB* gene, which affects a highly conserved region of the protein [8]. These findings have triggered the development of a new class of analge-

sics including the monoclonal NGF-inhibiting antibody tanezumab which is an effective analgesic as

shown for osteoarthritic pain [9, 10].

The tyrosine kinase, TRK, is the receptor for NGF. As mice lacking the gene encoding the NGF recep-

tor tyrosine kinase (*trk1*) display similar phenotypic features as patients with congenital insensitiv-

ity to pain with anhidrosis [11], mutations in the human *NTRK1* gene have been studied as candi- date causes. Three mutations (1726delC with a premature translational stop, IVS15+3A>C with al- tered splicing, 1795 G>C with G571R amino acid substitution) in three unrelated subjects were iden- tified as the molecular basis of HSAN-IV [12]. Up-to-date, 37 different variations of the *NTRK1* gene

in families affected by CIPA are known (for a comprehensive review see [13]).

Among the at least 10 known subtypes of voltage-gated sodium channels responsible for action po- tential creation and propagation [14], Na_v1.7, 1.8 and 1.9 are expressed almost exclusively at noci- ceptive neurons. The complete inability to sense pain in otherwise healthy members of three con- sanguineous families from Pakistan was mapped as an autosomal recessive trait caused by a loss-of-

function variant in the *SCN9A* gene [15]. This gene encodes the -subunit of the voltage-gated so- dium channel, Na_v1.7. In the three families, three distinct homozygous *SCN9A* nonsense mutations

(S459X, I767X and W897X) were identified. In whole-cell voltage clamp experiments in HEK293 cells

expressing mutant Na_v1.7, voltage-gated⁺ currents were not greater than the background Na level.

Additional very rare *SCN9A* variants have been added to the causes of this extreme phenotype [16].

Also rare, but not completely insensitive to pain, are carriers of a C1719R Na_v1.7 variant channel

[17], i.e., a genotype conferring residual channel function and therefore leading to a less extreme pain phenotype.

Verification of analgesic targets

Genetics plays a key role in identifying analgesic targets in laboratory animals [18]. In a translational approach, variants in identified pain associated genes can be employed to test whether a molecular pathway identified in laboratory animals is relevant in humans. Moreover, human genetic variants leading to enhanced or reduced function of molecular pathways can be employed as substi-

tutes for lacking modulator molecules applicable to humans. This allows early studying of nociceptive or anti-nociceptive pathways in humans before drug development.

A genetic association was used as a tool for a proof-of-concept in assessments where the mechanism had been already identified without a major human genetics approach (Table 2). For example, the role of the enzyme guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1) activity for pain was found in laboratory animals and subsequently, its relevance for human pain was verified using a genetic approach [19]. GCH1 catalyzes the conversion of GTP to dihydroneopterin triphosphate, which is further metabolized to tetrahydrobiopterin (BH₄) by the enzymes 6-pyruvoyltetrahydro-

pterin synthase and sepiapterin reductase [20]. BH₄ is an essential co-factor for the three isoforms of

nitric oxide synthase catalyzing the synthesis of nitric oxide and citrulline from arginine, and for tyrosine-, tryptophan- and phenylalanine hydroxylases [21] that catalyze the production of biogenic amines (noradrenaline, dopamine, adrenaline), the production of serotonin, and the degradation of phenylalanine to tyrosine, respectively. Inhibiting the de novo BH₄ synthesis in rats attenuated

neuropathic and inflammatory pain whereas administering BH₄ intrathecally exacerbated pain [19].

After peripheral inflammation, BH₄ concentrations also increased in dorsal root ganglia due to enhanced GCH1 enzyme activity [19].

Because rate limiting for BH₄ synthesis, GCH1 is a key modulator of peripheral neuropathic and inflammatory pain [19]. Human *GCH1* genetic variants in non-coding and non-splicing regions of the *GCH1* gene were found to decrease the risk or intensity of chronic pain. They have allelic frequencies

of approximately 15 – 20% in Caucasians and decrease enzyme up-regulation and tetrahydrobiopter-

in production at the molecular level. Specifically, a particular *GCH1* haplotype comprising 15 *GCH1*

SNPs was associated with an improved outcome in patients with chronic neuropathic pain [19], and with reduced sensitivity to experimental pain [22, 23]. Moreover, in a cross-sectional observational study, carriers of this *GCH1* haplotype were found to have been shorter on specialized therapy of chronic pain of various etiologies than non-carriers [24].

We interpreted this as a prophylactic role

of decreased GCH1 upregulation delaying the need for pain therapy. This hypothesis could subse-

quently be verified by showing that indeed the interval between cancer diagnosis and opioid therapy initiation was significantly longer in homozygous carriers of these *GCH1* variants (78 ± 65.2 months) than in heterozygous and non-carriers (< 40 months) [25]. This suggested a future possibility of using partial GCH1 blockade or BH₄ inhibition to prevent or delay cancer pain.

Considering the shown molecular relevance of GCH1 for pain, negative findings such as lack of association with pain following dental surgery [26]) or in chronic pancreatitis [27] do not necessarily substantially jeopardize GCH1 as an analgesic target. However, a cardiovascular association of a *GCH1* variant with similar molecular consequences has to be considered during drug development. Specifically, the c.*243C>T SNP (dbSNP rs841 in the 3'UTR) was associated with decreased nitric oxide excretion in urine, mildly increased blood pressure and heart rate and dysfunction of the baro-receptor reflex in homozygous carriers [28]. Moreover, this variant is carried by most people who also carry the variants associated with decreased or delayed pain [29]. This draws the attention at potential cardiovascular problems due to inhibition of BH₄ production.

The involvement of potassium channels in pain pathology has also benefitted from a genetic support. Specifically, the potassium voltage-gated channel, delayed-rectifier, subfamily S, member 1 (*KCNS1*, K_v9.1) has been found in rodents to be a putative pain gene down-regulated following nerve

injury by that facilitating the transition to chronic neuropathic pain [30]. These potassium channels

are co-regulated in several pain models. K_v9.1 is expressed in naive rats at high levels in a subset of dorsal root ganglia neurons [30]. The association with pain was subsequently verified in humans. In

151 lumbar discectomy patients, the *KCNS1* coding variant rs734784 (Ile489Val) and the synonymous variant rs13043825 were associated with greater pain and with a higher risk to fail 1-year pain improvement [30]. The functional association of the first variant was also

found in 199 amputees with phantom limb pain and in two further cohorts with neuropathic pain [30]. These first results may suggest agonism at $K_v9.1$ as a possible pharmacological strategy to prevent the development of chronic pain.

Genotyping and phenotyping patients receiving analgesics

With the popularity of genotyping and first successes in other fields such as cancer therapy, where the FDA has considered [31] advising *UGT1A1* (uridine diphosphate glucuronosyltransferase) genotyping for irinotecan treatment safety [32] and *TPMT* (thiopurin methyl transferase) [33] genotyping

for 6-mercaptopurine treatment safety [33]) [31], genotyping information has been expected [3, 34-

36] to also provide a major basis of personalized pain therapy. While in drug discovery the identification of the analgesics' pharmacodynamic targets plays the main role, in individualized therapy both pharmacodynamics and pharmacokinetics of available analgesics may be subject to individual genetically caused modulations.

Pharmacodynamics of analgesics

Pharmacodynamic genetic modulations have been identified for the few primary targets of current analgesics and their downstream signalling i.e., for μ -opioid receptors [37] and Kir3.2 potassium channels [38], and for COX-2 [39].

The most often addressed μ -opioid receptor variant is *OPRM1* 118 A>G (rs1799971), leading to an amino acid exchange N40D. Molecular evidence suggests that it causes a decreased receptor signalling in the pain-relevant secondary somatosensory brain area (S2) [40] and was also reported to decrease-opioid receptor expression throughout the human brain, [41], however, not in S2 [40]. From the altered receptor function or density, a decreased opioid potency can be predicted. From the first in-vitro [42] and in-vivo [43] reports of its functionality, frequent reports from experimental settings controlling for many confounders and in various clinical studies [37] found such roles. A decreased net opioid potency was also repeatedly found in clinical settings. However, a general association of the rs1799971 variant with reduced opioid effects and increased opioid dos-

ing demands did not withhold a meta-analysis [44]. A practical prospective guidance for opioid dos-

ing by this variant has not been obtained. Testing pain patients, who require extremely high opioid

doses, for the *OPRM1* variant rs1799971 is supported by a case report about a patient carrying the *OPRM1* 118G variant allele and needing more than 2 g daily morphine for cancer pain relief [45]. However, a systematic assessment has not yet been published. In addition, the protection from respiratory depression conferred by homozygous presence of the *OPRM1* rs1799971 variant [46] cannot

be used to neglect the supervision of patients under postoperative opioid analgesia although it might provide reassurance to clinicians to administer high opioid doses to these patients. Therefore, the clinical utility of rs1799971 is unclear. A recently discovered *OPRM1* SNP, rs563649 C>T causing alternative splicing of opioid receptors with the appearance of 6-transmembrane segment receptors

[47] that produce increased cAMP concentrations after opioid binding [48], is possibly involved in hyperalgesic opioid effects. This might open an opportunity to predict this unwanted therapy course; however, it is so far not more than a clinical extrapolation from an in-vitro observation of the SNP's functional consequence.

The expression of opioid receptors seems modulated by the variant V158M catechol-O-methyl transferase coded by the 472G>A polymorphism (rs4680) of the *COMT* gene [49, 50]. It causes decreased enzyme activity leading to chronic dopaminergic upregulation, which in turn causes enkephalinergic down-regulation. Finally, this results in a compensatory upregulation of μ -opioid receptors due to downregulation of endorphins, and patients carrying the V158M variant needed less morphine than non-carriers carrying this variant [51].

Downstream signalling of opioid receptors involves potassium channels. Among others (see above) the potassium inwardly-rectifying channel, subfamily J, member 6, (Kir3.2, GIRK2) is

listed in the PainGenes database [52] at <http://www.jbldesign.com/jmogil/enter.html>, a collection of nociceptive and pharmacological genetic association information obtained in

rodents, as modulating opioid effects. This G protein coupled channel is important for opioid receptor transmission and is involved in opioid effects on postsynaptic inhibition [53] and mediating a significant component of analgesia [54, 55]. Two genetic variants in *KCNJ6* (rs6517442 and rs2070995) have been shown to increase opioid requirements in Japanese patients after abdominal surgery [38]. The same tendency toward

higher opioid doses in carriers of rs2070995 was seen in chronic pain patients in outpatient care. In former heroin addicts average daily methadone substitution doses during the first therapy year were comparatively larger in carriers than in non-carriers of rs2070995 [56].

However, these findings (Table 3) have not entered broad clinical practice. Genetic guidance of the choice of analgesics is so far only marginally possible, such as for the selection of μ -opioid agonists being more effective in women carrying certain variants in the melanocortin1 receptor gene conferring a red-hair-fair-skin phenotype [57]. Selective cyclooxygenase (COX) 2 inhibitors might not be chosen for treatment of inflammatory pain in carriers of *PTGS2* variants observed to be associated with decreased COX-2 upregulation following injury [39], although this requires reproduction due to a contrasting finding [58].

Regarding the upcoming new analgesics (Table 3) involving many new targets [59], pharmacogenetics of pain and analgesia may be employed as a guidance for the choice of the optimum analgesic. Pharmacogenetic information may therefore be of great value in choosing the optimum analgesics, along non-genetic, for example disease-specific, guidance factors. Upcoming analgesics targeting Na_v1.7 sodium channels [60] or voltage-gated transient receptor potential channels [61] could be

used for the first time to cure pain syndromes caused by genetically caused exaggerated excitability

of these targets selectively. That is, increased-function mutations of Na_v1.7 cause the rare phenotypes of erythromelalgia [62, 63] consisting of episodic symmetrical red congestion, vasodilatation and burning pain in the feet and lower legs. A child with severe pain had a Na_v1.7 I234T mutation

that induces a shift of -18 mV in the voltage-dependence of activation, accelerated time-to-peak,

slowed deactivation and enhanced responses to slow ramp depolarizations, with a -21 mV shift in the voltage-dependence of slow-inactivation [64]. Besides these very rare genotypes,

more frequent functional variants may modulate the pain phenotype of average carriers. The variant alleles *SCN9A* rs6746030 A [65] (frequency in Caucasians 17.6% [66]) and rs41268673 T [67] (frequency 1.4%) were reported as associated with higher than average pain sensitivity. These genotypes will likely respond to Na_v1.7 inhibitors.

A point mutation in the *TRPA1* gene, leading to an N855S amino acid exchange in the 4th transmembrane segment of TRPA1 receptors that increased the inward current on activation at normal resting potentials by 5-fold [68], was associated with an autosomal-dominant familial syndrome of episodes

of debilitating upper body pain, triggered by fasting and physical stress. For carriers of those *TRPA1* mutations, TRPA1 antagonists are an especially promising useful therapy. The TRP family comprises several non-selective cation channels [69] expressed at nociceptors and excited by diverse stimuli (chemical, thermal, mechanical) and enabling or inhibiting the transmembrane transport of several ions. TRPA1 is excited by cold stimuli below 15°C [70] and pungent chemicals such as horseradish, mustard, cinnamon and garlic [61] or cannabinoids [71], TRPM8 channels are stimulated by cold between 8 and 28°C [72] and cooling compounds such as menthol [73]. TRPV1 mediates pain induced by noxious heat (>43°C), capsaicin or protons. TRPV3, activated at temperatures of 22 – 40°C, is also expressed at sensory nerve endings [74]. Several new analgesics are being developed for TRP channels, and future discoveries of pain syndromes caused by increased-function variants may benefit from this upcoming selection of analgesics.

Pharmacokinetics of analgesics

Functional *CYP2D6* variants alter the effects of codeine [75] and tramadol [76] via absent or exaggerated production of their active metabolites. The latter have been presented in the worst cases as the causes of deaths following codeine administrations [77-80]. Single cases of exaggerated fatal opioid effects after codeine administration were explained by the *CYP2D6* ultrafast metabolizer genotype (summarized in [81]), i.e., carrying three or more copies of the *CYP2D6* gene leading to increased enzyme expression. For example, a 33-year old woman took 60 mg codeine prophylactically to avoid pain due to tooth extraction. Within 30 min she experienced euphoria, dizziness

and difficulties in recognizing details in a TV program [82]. Twelve hours after a last codeine dose, consciousness of a 62-year old patient deteriorated and he became unresponsive [83]. Both patients

were identified as carriers of the CYP2D6 ultra-rapid metabolizer types. Codeine is a weak opioid

analgesic and the genotyping effort before therapy initiating has not become a clinical priority, although rare cases of codeine toxicity might benefit but not all of the patients at risk [81].

Besides drug metabolism, drug distributional changes may cause altered opioid effects. For example, variants in *ABCB1*, coding for P-glycoprotein, increase the brain concentrations of various opioids via altering their outward transport across the blood brain barrier [84-87]. However, despite statistically significant association, a clinical utility of these genotyping has not emerged (Table 3).

Addiction potential

Among classical analgesics, opioids are associated with potential addiction and clinical pharmacological expertise may be clinically queried to estimate the risk for drug dependence in pain patients.

As the main target of opioid analgesics, the μ -opioid receptor has been primarily assessed for variants that modulate the addiction to opioids. The *OPRM1* 118>G variant has been repeatedly reported

to increase the risk, mostly based on its higher frequency in addicts than in non-addicted subjects

[88-90] but lack of such association was similarly often found [42, 91, 92]. The *OPRM1* 17C>T SNP showed also a tendency toward higher frequency in substance abusers [42, 93], and *OPRM1* haplotypes were further suggested to be associated with a modified addiction risk [88, 89, 91, 94]. However, none of the *OPRM1* genetic findings in the context of addiction has achieved a clinical utility. This applies to variants in other genes such as a modulation of methadone demands in former heroin addicts by dopamine 2 receptor (*DRD2*) polymorphisms [95, 96]. Furthermore, a protective effect from heroin addiction was found for European Americans carrying a *HTR1B* (5-Hydroxytryptamine (serotonin)-

1B receptor) haplotype [97]. In Hispanics, an association of the minor allele of the *MC2R* (melanocortin receptor type 2) SNP rs2186944 and for an *MC2R* haplotype with a protective effect from the development of heroin addiction was shown [98]. In addition to a modulation of the risk for addiction [99], which is a multigenetic trait not specific to opioid analgesics, further pharmacogenetic influences on opioid addiction are modulating their pharmacokinetics by drug metabolism or transport such as P-glycoprotein variants [86].

Conclusions

In the clinical setting, where genotyping information was viewed with high expectations, genetics have so far only reluctantly been included, which led to a general questioning of their utility [100]. Despite positive results such as *CYP2D6* related codeine toxicity, *PTGS2* related COX-2 inhibitor ineffectiveness, or *OPRM1* variant associated safety of high opioid doses, cross sectional assessments show that in average pain patients analgesic therapy shows only dim traces of a genetic influence

[101]. Moreover, most of the here presented positive findings are contrasted by negative reports about the same variants. In addition, many genetic variants, summarized elsewhere [3, 34, 102], may influence analgesic therapy by modifying the disease rather than the pharmacology of the cure. However, with the future availability of new analgesics addressing new targets [103], the clinical utility of genotyping and phenotyping of pain patients may become equal with its scientific utility

in the clinical pharmacological context up to providing specific cures for pain syndromes caused by particular enhanced-function mutations of targets that will be soon possible to be inhibited.

From a clinical pharmacological point of view, genotyping and phenotyping of pain patients has proven its use so far mainly for drug discovery and development. Human genetics may serve both directions, i.e., identifying analgesic drug targets or, in the classical translational sense, verifying the human relevance of targets found in basic research. The intelligent implementation of human genetics may accelerate analgesic drug development while reducing its cost because the clinical success may be partly anticipated by including the information of functional genetic variants that mimic the action of future analgesics.

Therefore, genotyping and phenotyping pain patients have their main utility as a research tool for discovery or proof-of-concept of analgesics' targets.

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Table 1: Familial syndromes with absent pain and their genetic basis.

Gene	Gene product	Syndrome	Additional symptoms	Reference
<i>SPTLC1</i>	Serine palmitoyltransferase, long chain base	HSAN-I	Sensory deficit in lower extremities, ulcerations of	[104-106]
<i>WNK1</i>	WNK lysine deficient protein kinase 1	HSAN-II		[107, 108]
<i>IKBKA P</i>	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	HSAN-III (dysautonomia, Riley-Day syndrome)	Sensory and variable autonomic dysfunction, poor temperature and motor incoordination, reduced or absent tears, absent corneal	[109, 110]
<i>NTRK1</i>	Neurotrophic tyrosine kinase, receptor, type	HSAN-IV (congenital insensitivity)	Anhidrosis, episodes of hyperthermia	[12, 111]
<i>NGFB</i>	Nerve growth factor (beta polypeptide)	HSAN-V	Partial anhidrosis	[8]
<i>SCN9A</i>	Na(v)1.7 (alpha-subunit of the voltage-	Channelopathy associated insen-	Anosmia	[15, 112]

Table 2: Genes that played an important role in analgesic drug discovery.

Gene	Gene product	Functional change [#]	Genetically caused pheno-type	Pharmacological implications	Reference
<i>NTRK1</i>	Neurotrophic tyrosine kinase receptor 1	---	Absent pain	Identification of TRK1 as an analgesic target	[113]
<i>NGF1</i>	Nerve growth factor	---	Absent pain	Identification of NGF as	[8]
<i>SCN9A</i>	Na _v 1.7 sodium channel	---	Absent pain	Identification and verification of Na _v 1.7 as an analgesic target	[15, 112]
		- +++ ++	Reduced pain Increased pain		[62, 63]
<i>GCH1</i>	GTP cyclohydrolase 1	-	Reduced or delayed pain	Verification of GCH1 as pain relevant and a	[19]
<i>KCNS1</i>	Kv1.9 potassium channel	-	Increased risk of pain chronification	Verification of KCNS1 as pain relevant and agonists being	[30]

[#] Genetically caused functional change: --- to +++: The degree of genetically caused changes in the net function of the gene product, achieved by either modulation of the expression or function of the protein, is gradually displayed from absent function, “---”, to highly increased function, “+++”.

Table 3: Genes and example variants that might provide comparatively important genotyping information to guide analgesic therapy.

Gene	Gene product *	Variant	Functional change [#]	Genetically caused pheno-	Clinical pharmacologica	Reference
Classical analgesics						
<i>OPRM1</i>	μ -opioid receptor *	rs1799971	-	Decreased opioid effects	Increased opioid dosages	[84, 114]
				Increased therapeutic range of opioids	Opioid safety	[43, 46]
<i>COMT</i>	Catechol-O-methyl transferase	rs4680	-	Increased μ -opioid receptor expression	Reduced opioid requirements	[51]
<i>MC1R</i>	Melanocortin-1 receptor	rs1805007, rs1805008, rs1805009 and other	-	Red hair fair skin	Indication for μ -opioids in women	[57]
<i>KCNJ6</i>	Kir3.2 potassium channel	rs2070995	-	Reduced opioid receptor signalling	Increased opioid requirements	[38, 56]
<i>ABCB1</i>	P-glycoprotein	rs1045642	-	Reduced brain clearance of opioid molecules	Reduced opioid dosing requirements	[84]
<i>CYP2D6</i>	Cytochrome P450 2D6	2 nonfunctional alleles	---	Reduced or absent morphine formation from codeine	Contraindication for codeine	[82]
		> 2 functional alleles	+++	Exaggerated morphine formation from codeine		[75, 77, 80]
<i>PTGS2</i>	Cyclooxygenase 2 *	rs20417	-	Decreased COX-2 expression	Ineffectiveness of selective COX-2 inhibitors	[39]
Future analgesics (currently under clinical development)						
<i>SCN9A</i>	Na _v 1.7 sodium channel *	rs6746030 rs41268673	++	Increased pain	Therapy selection of Na _v 1.7 inhibitors	[62, 63]
<i>TRPA1</i>	Transient receptor potential channel, subfamily A, member 1	c.2564A>G	++	Increased pain	Therapy selection of TRPA1 inhibitors	[68]

[#] Genetically caused functional change: --- to +++: The degree of genetically caused changes in the net function of the gene product, achieved by either modulation of the expression or function of the protein, is gradually displayed from absent function, “---”, to highly increased function, “+++”.

*: Analgesic drug target