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pharmazentrum frankfurt/ZAFES, Institute of Clinical Pharmacology, Goethe - University, Frankfurt am Main, Germany

Address for correspondence: *pharmazentrum frankfurt*/ZAFES, Institute of Clinical Pharmacology, Goethe - University, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany; e-mail: j.loetsch@em.uni-frankfurt.de, Phone: +49-69-6301 4589, Fax: +49-69-6301 4354

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 $Na_v1.7$, 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. Transla- tional approaches also served to verify the human importance of experimentally discovered pain pathways, such as in GTP cyclohydrolase 1 and the potassium channel $K_v9.1$. Besides these uses of

genetics as a research tool, an individualized pharmacological therapy based on the patient's geno-

type has been attempted. For the actual analgesics, such guidance has only marginally become available. For upcoming analgesics targeting, for example, $Na_v1.7$ or TRPA1, the genotype may pro- vide 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 func- tional genetic variants that mimic the action of future analgesics, showing that genotyping infor-

mation from pain patients plays a role in the clinical pharmacology of pain.

Key words: Pain, analgesics, pain genetics, pharmacogenetics, drug targets, new drugs, investiga- tional 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 sophistica- tion 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 to- ward either disappearance or chronification up to neuropathic pain. The risk or protective mecha- nisms 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 substi- tutes 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 modu- lations 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 infor- mation obtained from pain patients has its main clinical pharmacological utility so far in drug de- velopment 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 phe- notype 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 develop- ment.

The nerve growth factor (NGF) is a small protein belonging to the class of neurotrophins and identi- fied 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 transmem- brane 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 analgesics including the monoclonal NGF-inhibiting antibody tanezumab which is an effective analgesic as shown for ostheoarthritic pain [9, 10].

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

tor tyrosine kinase (*ntrk1*) 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 Na^+ currents were not greater than the background 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 transla- tional 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 nocicep- tive 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 (BH_4) by the enzymes 6-pyruvoyltetrahydrop-

terin synthase and sepiapterin reductase [20]. BH_4 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 BH_4 synthesis in rats attenuated

neuropathic and inflammatory pain whereas administering BH_4 intrathecally exacerbated pain [19].

After peripheral inflammation, BH_4 concentrations also increased in dorsal root ganglia due to en- hanced GCH1 enzyme activity [19].

Because rate limiting for BH_4 synthesis, GCH1 is a key modulator of peripheral neuropathic and in- flammatory 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 BH_4 inhibition to prevent or delay cancer pain.

Considering the shown molecular relevance of GCH1 for pain, negative findings such as lack of asso- ciation 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 BH_4 production.

The involvement of potassium channels in pain pathology has also benefitted from a genetic sup- port. 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 synony- mous 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) geno- typing 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 identifi- cation 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 signallin[redacted] i.e., for -opioid receptors [37] and Girk3.2 potassium channels [38], and for COX-2 [39].

The most often addressed [redacted]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 signal- ling in the pain-relevant secondary somatosensory brain area (S2) [40] and was also [redacted]ported 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 experi- mental 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 res- piratory 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 de- creased enzyme activity leading to chronic dopaminergic upregulation, which in turn causes enkephalinergic down-regulation. Finally, this results in a compensatory upregulation of -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 nocicep- tive 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, [redacted]ch as for the selection of -opioid agonists being more effective in women carrying certain variants in the melanocortin1 receptor gene confer- ring 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], pharmacogene- tics 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 pheno- types 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 transmem- brane 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 in- duced 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 exag- gerated 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 gen- otype (summarized in [81]), i.e., carrying three or more copies of the *CYP2D6* gene leading to in- creased 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 diffi- culties in recognizing details in a TV program [82]. Twelve hours after a last codeine dose, con- sciousness 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 statisti- cally 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 pharmaco- logical expertise may be clinically queried to estimate the risk for drug dependence in pain patients.

As the main target of opioid analgesics, t[redacted]-opioid receptor has been primarily assessed for vari- ants 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* haplo- types were further suggested to be associated with a modified addiction risk [88, 89, 91, 94]. How- ever, 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 phar- macogenetic influences on opioid addiction are modulating their pharmacokinetics by drug metabo-

lism 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 inef- fectiveness, 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.

References

1 Godinova AM (1967) [Phenotypic manifestations and genetic features of migraine]. Zh
Nevropatol Psikhiatr Im S S Korsakova 67 (7): 1002-1007

2 Lötsch J, Geisslinger G (2010) A critical appraisal of human genotyping for pain therapy.
Trends Pharmacol Sci (in press)

3 Lötsch J, Geisslinger G, Tegeder I (2009) Genetic modulation of the pharmacological treatment of pain. Pharmacol Ther 124 (2): 168-184

4 Lötsch J, Skarke C, Liefhold J, Geisslinger G (2004) Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. Clin Pharmacokinet 43 (14): 983-1013

5 Oertel B, Lötsch J (2008) Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics 9 (2): 179-194

6 Fiore M, Chaldakov GN, Aloe L (2009) Nerve growth factor as a signaling molecule for nerve cells and also for the neuroendocrine-immune systems. Reviews in the neurosciences 20:
133-145

7 Hefti FF, Rosenthal A, Walicke PA, Wyatt S, Vergara G, Shelton DL, Davies AM (2006) Novel class of pain drugs based on antagonism of NGF. Trends in pharmacological sciences 27: 85-
91

8 Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, Holmgren G, Holmberg D, Holmberg M (2004) A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Hum Mol Genet 13 (8): 799-805

9 Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, Brown MT (2010) Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 363 (16):
1521-1531

10 Schnitzer TJ, Lane NE, Birbara C, Smith MD, Simpson SL, Brown MT (2011) Long-term open- label study of tanezumab for moderate to severe osteoarthritic knee pain. Osteoarthritis Cartilage

11 Smeyne RJ, Klein R, Schnapp A, Long LK, Bryant S, Lewin A, Lira SA, Barbacid M (1994) Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature 368 (6468): 246-249

12 Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, Mitsubuchi H, Tonoki H, Awaya Y, Matsuda I (1996) Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 13

(4): 485-488

13 Indo Y (2001) Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA):
mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Hum Mutat 18 (6): 462-471

14 Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M (2010) Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. The Lancet Neurology 9: 413-424

15 Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, Al-Gazali L, Hamamy H, Valente EM, Gorman S, Williams R, McHale DP, Wood JN, Gribble FM, Woods CG (2006) An SCN9A channelopathy causes congenital inability
to experience pain. Nature 444 (7121): 894-898

16 Nilsen KB, Nicholas AK, Woods CG, Mellgren SI, Nebuchennykh M, Aasly J (2009) Two novel
SCN9A mutations causing insensitivity to pain. Pain 143 (1-2): 155-158

17 Staud R, Price DD, Janicke D, Andrade E, Hadjipanayis AG, Eaton WT, Kaplan L, Wallace MR (2010) Two novel mutations of SCN9A (Nav1.7) are associated with partial congenital insensitivity to pain. Eur J Pain

18 Lariviere WR, Mogil JS (2010) The genetics of pain and analgesia in laboratory animals.
Methods Mol Biol 617: 261-278

19 Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas
SJ, Carlezon WA, Parsegian A, Lötsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB,
Woolf CJ (2006) GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 12 (11): 1269-1277

20 Auerbach G, Nar H (1997) The pathway from GTP to tetrahydrobiopterin: three-dimensional structures of GTP cyclohydrolase I and 6-pyruvoyl tetrahydropterin synthase. Biol Chem 378
(3-4): 185-192

21 Thony B, Auerbach G, Blau N (2000) Tetrahydrobiopterin biosynthesis, regeneration and functions. Biochem J 347 Pt 1: 1-16

22 Tegeder I, Adolph J, Schmidt H, Woolf CJ, Geisslinger G, Lötsch J (2008) Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. Eur J Pain 12 (8):
1069-1077

23 Campbell CM, Edwards RR, Carmona C, Uhart M, Wand G, Carteret A, Kim YK, Frost J, Campbell JN (2009) Polymorphisms in the GTP cyclohydrolase gene (GCH1) are associated with ratings of capsaicin pain. Pain 141 (1-2): 114-118

24 Doehring A, Freynhagen R, Griessinger N, Zimmermann M, Sittl R, Hentig N, Geisslinger G, Lötsch J (2009) Cross-sectional assessment of the consequences of a GTP cyclohydrolase 1 haplotype for specialized tertiary outpatient pain care. Clin J Pain 25 (9): 781-785

25 Lötsch J, Klepstad P, Doehring A, Dale O (2010) A GTP cyclohydrolase 1 genetic

variant delays cancer pain. Pain

26 Kim H, Dionne RA (2007) Lack of influence of GTP cyclohydrolase gene (GCH1) variations on pain sensitivity in humans. Mol Pain 3: 6

27 Lazarev M, Lamb J, Barmada Pitt Edu MM, Dai F, Anderson MA, Max MB, Whitcomb DC (2008) Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? Mol Pain 4 (1): 58

28 Zhang L, Rao F, Zhang K, Khandrika S, Das M, Vaingankar SM, Bao X, Rana BK, Smith DW, Wessel J, Salem RM, Rodriguez-Flores JL, Mahata SK, Schork NJ, Ziegler MG, O'Connor DT (2007) Discovery of common human genetic variants of GTP cyclohydrolase 1 (GCH1) governing nitric oxide, autonomic activity, and cardiovascular risk. J Clin Invest 117 (9): 2658-2671

29 Doehring A, Antoniades C, Channon KM, Tegeder I, Lötsch J (2008) Clinical genetics of functionally mild non-coding GTP cyclohydrolase 1 (GCH1) polymorphisms modulating pain and cardiovascular risk. Mutat Res 659 (3): 195-201

30 Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, Wu T, Kiselycznyk C, Poddar M, Lu Y, Diatchenko L, Smith S, Cobos EJ, Zaykin D, Allchorne A, Shen PH, Nikolajsen L, Karppinen J, Mannikko M, Kelempisioti A, Goldman D, Maixner W, Geschwind DH, Max MB, Seltzer Z, Woolf CJ (2010) Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain 133 (9): 2519-2527

31 Maitland ML, Vasisht K, Ratain MJ (2006) TPMT, UGT1A1 and DPYD: genotyping to ensure safer cancer therapy? Trends Pharmacol Sci 27 (8): 432-437

32 Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ (2004) Genetic variants in the UDP- glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22 (8): 1382-1388

33 Relling MV, Hancock ML, Rivera GK, Sandlund JT, Ribeiro RC, Krynetski EY, Pui CH, Evans WE (1999) Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S- methyltransferase gene locus. J Natl Cancer Inst 91 (23): 2001-2008

34 Kim H, Dionne RA (2005) Genetics, Pain, and Analgesia. Pain: Clinical updates (International Association for the Study of Pain) 8 (3)

35 Kim H, Clark D, Dionne RA (2009) Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. J Pain 10 (7): 663-693

36 Lötsch J, Geisslinger G (2006) Current evidence for a genetic modulation of the response to analgesics. Pain 121 (1-2): 1-5

37 Lötsch J, Geisslinger G (2005) Are mu-opioid receptor polymorphisms important for clinical opioid therapy? Trends Mol Med 11 (2): 82-89

38 Nishizawa D, Nagashima M, Katoh R, Satoh Y, Tagami M, Kasai S, Ogai Y, Han W, Hasegawa

J, Shimoyama N, Sora I, Hayashida M, Ikeda K (2009) Association between KCNJ6 (GIRK2) gene polymorphisms and postoperative analgesic requirements after major abdominal surgery. PLoS One 4 (9): e7060

39 Lee YS, Kim H, Wu TX, Wang XM, Dionne RA (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 79 (5): 407-418

40 Oertel BG, Kettner M, Scholich K, Renne C, Roskam B, Geisslinger G, Schmidt PH, Lötsch J (2009) A Common Human mu-Opioid Receptor Genetic Variant Diminishes the Receptor Signaling Efficacy in Brain Regions Processing the Sensory Information of Pain. J Biol Chem
284 (10): 6530-6535

41 Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W (2005) Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 280 (38): 32618-
32624

42 Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L (1998) Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. ProcNatlAcadSciUSA 95 (16): 9608-9613

43 Lötsch J, Zimmermann M, Darimont J, Marx C, Dudziak R, Skarke C, Geisslinger G (2002) Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6- glucuronide toxicity? Anesthesiology 97 (4): 814-819

44 Walter C, Lötsch J (2009) Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. Pain 146 (3): 270-275

45 Hirota T, Ieiri I, Takane H, Sano H, Kawamoto K, Aono H, Yamasaki A, Takeuchi H, Masada
M, Shimizu E, Higuchi S, Otsubo K (2003) Sequence variability and candidate gene analysis
in two cancer patients with complex clinical outcomes during morphine therapy. Drug Metab
Dispos 31 (5): 677-680

46 Oertel BG, Schmidt R, Schneider A, Geisslinger G, Lötsch J (2006) The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenet Genomics 16 (9): 625-636

47 Shabalina SA, Zaykin DV, Gris P, Ogurtsov AY, Gauthier J, Shibata K, Tchivileva IE, Belfer I, Mishra B, Kiselycznyk C, Wallace MR, Staud R, Spiridonov NA, Max MB, Goldman D, Fillingim RB, Maixner W, Diatchenko L (2009) Expansion of the Human mu-Opioid Receptor Gene Architecture: Novel Functional Variants. Hum Mol Genet

48 Gris P, Gauthier J, Cheng P, Gibson DG, Gris D, Laur O, Pierson J, Wentworth S, Nackley AG, Maixner W, Diatchenko L (2010) A novel alternatively spliced isoform of the mu-opioid receptor: functional antagonism. Molecular pain 6: 33

49 Berthele A, Platzer S, Jochim B, Boecker H, Buettner A, Conrad B, Riemenschneider M, Toelle
TR (2005) COMT Val108/158Met genotype affects the mu-opioid receptor system in the human brain: evidence from ligand-binding, G-protein activation and preproenkephalin mRNA expression. Neuroimage 28 (1): 185-193

50 Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D (2003) COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 299 (5610): 1240-1243

51 Rakvag TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan HE, Skorpen F (2005) The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 116 (1-2): 73-78

52 Lacroix-Fralish ML, Ledoux JB, Mogil JS (2007) The Pain Genes Database: An interactive web browser of pain-related transgenic knockout studies. Pain 131 (1-2): 3 e1-4

53 Mitrovic I, Margeta-Mitrovic M, Bader S, Stoffel M, Jan LY, Basbaum AI (2003) Contribution
of GIRK2-mediated postsynaptic signaling to opiate and alpha 2-adrenergic analgesia and analgesic sex differences. Proc Natl Acad Sci U S A 100 (1): 271-276

54 Kobayashi T, Ikeda K, Kojima H, Niki H, Yano R, Yoshioka T, Kumanishi T (1999) Ethanol opens G-protein-activated inwardly rectifying K+ channels. Nature neuroscience 2: 1091-
1097

55 Marker CL, Stoffel M, Wickman K (2004) Spinal G-protein-gated K+ channels formed by GIRK1 and GIRK2 subunits modulate thermal nociception and contribute to morphine analgesia. J Neurosci 24 (11): 2806-2812

56 Lötsch J, Prüss H, Veh RW, Doehring A (2010) A KCNJ6 (Kir3.2, GIRK2) gene polymorphism modulates opioid effects on analgesia and addiction but not on pupil size. Pharmacogenet Genomics 20 (5): 291-297

57 Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV, Lariviere WR, Groce MK, Wallace MR, Kaplan L, Staud R, Ness TJ, Glover TL, Stankova M, Mayorov A, Hruby VJ, Grisel JE, Fillingim RB (2003) The melanocortin-1 receptor gene mediates female-specific mechanisms
of analgesia in mice and humans. Proc Natl Acad Sci U S A 100 (8): 4867-4872

58 Skarke C, Reus M, Schmidt R, Grundei I, Schuss P, Geisslinger G, Lötsch J (2006) The cyclooxygenase 2 genetic variant -765G>C does not modulate the effects of celecoxib on prostaglandin E2 production. Clin Pharmacol Ther 80 (6): 621-632

59 Rodger IW (2009) Analgesic targets: today and tomorrow. Inflammopharmacology 17: 151-
161

60 Clare JJ (2010) Targeting voltage-gated sodium channels for pain therapy. Expert opinion on investigational drugs 19: 45-62

61 Patapoutian A, Tate S, Woolf CJ (2009) Transient receptor potential channels: targeting pain
at the source. Nat Rev Drug Discov 8 (1): 55-68

62 Choi J-S, Cheng X, Foster E, Leffler A, Tyrrell L, {Te Morsche} RHM, Eastman EM, Jansen HJ, Huehne K, Nau C, Dib-Hajj SD, Drenth JPH, Waxman SG (2010) Alternative splicing may contribute to time-dependent manifestation of inherited erythromelalgia. Brain : a journal
of neurology 133: 1823-1835

63 Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB (2007) Heritability of responses to painful stimuli in women: a classical twin study. Brain 130 (Pt 11): 3041-3049

64 Ahn H-S, Dib-Hajj S, Cox JJ, Tyrell L, Elmslie FV, Clarke AA, Drenth JPH, Woods CG, Waxman
SG (2010) A new Nav1.7 sodium channel mutation I234T in a child with severe pain. Eur J Pain

65 Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP, Drenth JP, Dai F, Wheeler
J, Sanders F, Wood L, Wu TX, Karppinen J, Nikolajsen L, Mannikko M, Max MB, Kiselycznyk C, Poddar M, Te Morsche RH, Smith S, Gibson D, Kelempisioti A, Maixner W, Gribble FM, Woods

CG (2010) Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad
Sci U S A

66 Estacion M, Harty TP, Choi J-S, Tyrrell L, Dib-Hajj SD, Waxman SG (2009) A sodium channel gene SCN9A polymorphism that increases nociceptor excitability. Annals of neurology 66:
862-866

67 Samuels ME, te Morsche RHM, Lynch ME, Drenth JPH (2008) Compound heterozygosity in sodium channel Nav1.7 in a family with hereditary erythermalgia. Molecular pain 4: 21

68 Kremeyer B, Lopera F, Cox JJ, Momin A, Rugiero F, Marsh S, Woods CG, Jones NG, Paterson KJ, Fricker FR, Villegas A, Acosta N, Pineda-Trujillo NG, Ramirez JD, Zea J, Burley MW, Bedoya G, Bennett DL, Wood JN, Ruiz-Linares A (2010) A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron 66 (5): 671-680

69 Montell C (2005) Drosophila TRP channels. Pflügers Archiv : European journal of physiology
451: 19-28

70 Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR, Earley TJ, Hergarden AC, Andersson DA, Hwang SW, McIntyre P, Jegla T, Bevan S, Patapoutian A (2003) ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell
112 (6): 819-829

71 Jordt S-E, Bautista DM, Chuang H-H, McKemy DD, Zygmunt PM, Högestätt ED, Meng ID, Julius D (2004) Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 427: 260-265

72 McKemy DD (2005) How cold is it? TRPM8 and TRPA1 in the molecular logic of cold sensation. Mol Pain 1 (1): 16

73 Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, Patapoutian A (2002) A TRP channel that senses cold stimuli and menthol. Cell 108 (5): 705-715

74 Eid SR, Cortright DN (2009) Transient receptor potential channels on sensory nerves.
Handbook of experimental pharmacology: 261-281

75 Poulsen L, Brosen K, Arendt-Nielsen L, Gram LF, Elbaek K, Sindrup SH (1996) Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. EurJClinPharmacol 51 (3-4): 289-295

76 Collart L, Luthy C, Favario-Constantin C, Dayer P (1993) Duality of the analgesic effect of tramadol in humans. SchweizMedWochenschr 123 (47): 2241-2243

77 Madadi P, Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder JS, Teitelbaum R,

Karaskov T, Aleksa K (2007) Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. Can Fam Physician 53 (1): 33-35

78 Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ (2006) Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 368 (9536): 704

79 Ferreirós N, Dresen S, Hermanns-Clausen M, Auwaerter V, Thierauf A, Müller C, Hentschel R, Trittler R, Skopp G, Weinmann W (2009) Fatal and severe codeine intoxication in 3-year-old twins--interpretation of drug and metabolite concentrations. International journal of legal medicine 123: 387-394

80 Voronov P, Przybylo HJ, Jagannathan N (2007) Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth 17 (7): 684-687

81 Lötsch J, Rohrbacher M, Schmidt H, Doehring A, Brockmöller J, Geisslinger G (2009) Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? Pain 144 (1-2): 119-124

82 Dalen P, Frengell C, Dahl ML, Sjoqvist F (1997) Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. TherDrug Monit 19 (5): 543-544

83 Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J (2004) Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 351 (27): 2827-
2831

84 Campa D, Gioia A, Tomei A, Poli P, Barale R (2008) Association of ABCB1/MDR1 and OPRM1
gene polymorphisms with morphine pain relief. Clin Pharmacol Ther 83 (4): 559-566

85 Skarke C, Jarrar M, Schmidt H, Kauert G, Langer M, Geisslinger G, Lötsch J (2003) Effects of ABCB1 (multidrug resistance transporter) gene mutations on disposition and central nervous effects of loperamide in healthy volunteers. Pharmacogenetics 13 (11): 651-660

86 Coller JK, Barratt DT, Dahlen K, Loennechen MH, Somogyi AA (2006) ABCB1 genetic variability and methadone dosage requirements in opioid-dependent individuals. Clin Pharmacol Ther 80 (6): 682-690

87 Park HJ, Shinn HK, Ryu SH, Lee HS, Park CS, Kang JH (2007) Genetic polymorphisms in the
ABCB1 gene and the effects of fentanyl in Koreans. Clin Pharmacol Ther 81 (4): 539-546

88 Szeto CY, Tang NL, Lee DT, Stadlin A (2001) Association between mu opioid receptor gene polymorphisms and Chinese heroin addicts. Neuroreport 12 (6): 1103-1106

89 Shi J, Hui L, Xu Y, Wang F, Huang W, Hu G (2002) Sequence variations in the mu-opioid receptor gene (OPRM1) associated with human addiction to heroin. Hum Mutat 19 (4): 459-
460

90 Tan EC, Tan CH, Karupathivan U, Yap EP (2003) Mu opioid receptor gene polymorphisms and heroin dependence in Asian populations. Neuroreport 14 (4): 569-572

91 Hoehe MR, Kopke K, Wendel B, Rohde K, Flachmeier C, Kidd KK, Berrettini WH,

Church GM (2000) Sequence variability and candidate gene analysis in complex disease: association of
mu opioid receptor gene variation with substance dependence. HumMolGenet 9 (19): 2895-
2908

92 Crowley JJ, Oslin DW, Patkar AA, Gottheil E, DeMaria PA, Jr., O'Brien CP, Berrettini WH, Grice
DE (2003) A genetic association study of the mu opioid receptor and severe opioid dependence. Psychiatr Genet 13 (3): 169-173

93 Berrettini WH, Hoehe MR, Ferraro TN, Demaria PA, Gottheil E (1997) Human mu opioid receptor gene polymorphisms and vulnerability to substance abuse. Add Biol 2 (3): 303-308

94 Luo X, Kranzler HR, Zhao H, Gelernter J (2003) Haplotypes at the OPRM1 locus are associated with susceptibility to substance dependence in European-Americans. Am J Med Genet 120B (1): 97-108

95 Doehring A, Hentig N, Graff J, Salamat S, Schmidt M, Geisslinger G, Harder S, Lötsch J (2009) Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution. Pharmacogenet Genomics 19 (6): 407-414

96 Barratt DT, Coller JK, Somogyi AA (2006) Association between the DRD2 A1 allele and response to methadone and buprenorphine maintenance treatments. Am J Med Genet B Neuropsychiatr Genet 141 (4): 323-331

97 Proudnikov D, LaForge KS, Hofflich H, Levenstien M, Gordon D, Barral S, Ott J, Kreek MJ (2006) Association analysis of polymorphisms in serotonin 1B receptor (HTR1B) gene with heroin addiction: a comparison of molecular and statistically estimated haplotypes. Pharmacogenet Genomics 16 (1): 25-36

98 Proudnikov D, Hamon S, Ott J, Kreek MJ (2008) Association of polymorphisms in the melanocortin receptor type 2 (MC2R, ACTH receptor) gene with heroin addiction. Neurosci Lett 435 (3): 234-239

99 Goldman D, Oroszi G, Ducci F (2005) The genetics of addictions: uncovering the genes. Nat Rev Genet 6 (7): 521-532

100 Mogil JS (2009) Are we getting anywhere in human pain genetics? Pain 146 (3): 231-232

101 Lötsch J, von Hentig N, Freynhagen R, Griessinger N, Zimmermann M, Doehring A, Rohrbacher M, Sittl R, Geisslinger G (2009) Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. Pharmacogenet Genomics 19 (6): 429-436

102 Lötsch J, Geisslinger G (2007) Current evidence for a modulation of nociception by human genetic polymorphisms. Pain 132 (1-2): 18-22

103 Lötsch J, Geisslinger G (2010) Pharmacogenetics of new analgesics. Britisch Journal of Pharmacology accepted

104 Nicholson GA, Dawkins JL, Blair IP, Kennerson ML, Gordon MJ, Cherryson AK, Nash J, Bananis T (1996) The gene for hereditary sensory neuropathy type I (HSN-I) maps to chromosome 9q22.1-q22.3. Nat Genet 13 (1): 101-104

105 Bejaoui K, Wu C, Scheffler MD, Haan G, Ashby P, Wu L, de Jong P, Brown RH, Jr. (2001) SPTLC1 is mutated in hereditary sensory neuropathy, type 1. Nat Genet 27 (3): 261-262

106 Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach M, Nicholson GA (2001) Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. Nat Genet 27 (3): 309-312

107 Lafreniere RG, MacDonald ML, Dube MP, MacFarlane J, O'Driscoll M, Brais B, Meilleur S, Brinkman RR, Dadivas O, Pape T, Platon C, Radomski C, Risler J, Thompson J, Guerra-Escobio AM, Davar G, Breakefield XO, Pimstone SN, Green R, Pryse-Phillips W, Goldberg YP, Younghusband HB, Hayden MR, Sherrington R, Rouleau GA, Samuels ME (2004) Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the Study of Canadian Genetic Isolates. Am J Hum Genet 74 (5): 1064-1073

108 Riviere JB, Verlaan DJ, Shekarabi M, Lafreniere RG, Benard M, Der Kaloustian VM, Shbaklo Z, Rouleau GA (2004) A mutation in the HSN2 gene causes sensory neuropathy type II in a Lebanese family. Ann Neurol 56 (4): 572-575

109 Blumenfeld A, Slaugenhaupt SA, Axelrod FB, Lucente DE, Maayan C, Liebert CB, Ozelius LJ, Trofatter JA, Haines JL, Breakefield XO, et al. (1993) Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. Nat Genet 4 (2): 160-164

110 Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, Liebert CB, Chadwick B, Idelson M, Reznik L, Robbins C, Makalowska I, Brownstein M, Krappmann D, Scheidereit C, Maayan C, Axelrod FB, Gusella JF (2001) Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 68 (3): 598-605

111 Houlden H, King RH, Hashemi-Nejad A, Wood NW, Mathias CJ, Reilly M, Thomas PK (2001) A novel TRK A (NTRK1) mutation associated with hereditary sensory and autonomic neuropathy type V. Ann Neurol 49 (4): 521-525

112 Goldberg YP, MacFarlane J, MacDonald ML, Thompson J, Dube MP, Mattice M, Fraser R, Young
C, Hossain S, Pape T, Payne B, Radomski C, Donaldson G, Ives E, Cox J, Younghusband HB, Green R, Duff A, Boltshauser E, Grinspan GA, Dimon JH, Sibley BG, Andria G, Toscano E, Kerdraon J, Bowsher D, Pimstone SN, Samuels ME, Sherrington R, Hayden MR (2007) Loss-of- function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. Clin Genet 71 (4): 311-319

113 Miura Y, Hiura M, Torigoe K, Numata O, Kuwahara A, Matsunaga M, Hasegawa S, Boku N, Ino
H, Mardy S, Endo F, Matsuda I, Indo Y (2000) Complete paternal uniparental isodisomy for chromosome 1 revealed by mutation analyses of the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with congenital insensitivity to pain with anhidrosis. HumGenet 107 (3): 205-209

114 Klepstad P, Rakvag TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F (2004) The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 48 (10): 1232-1239

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

Gene	Gene product	Syndrome	Additional symptoms	Reference
SPTLC 1	Serine palmitoyltransferase, long chain base	HSAN-I	Sensory deficit in lower extremities, ulcerations of	[104-106]
WNK1	WNK lysine deficient protein kinase 1	HSAN-II		[107, 108]
IKBKA P	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]
NTRK1	Neurotrophic tyrosine kinase, receptor, type	HSAN-IV (congenital insensitivity	Anhidrosis, episodes of hyperthermia	[12, 111]
NGFB	Nerve growth factor (beta polypeptide)	HSAN-V	Partial anhidrosis	[8]
SCN9A	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 phenotype	Pharmacological implications	Reference
NTRK1	Neurotrophic tyrosine kinase receptor 1	---	Absent pain	Identification of TRK1 as an analgesic target	[113]
NGF1	Nerve growth factor	---	Absent pain	Identification of NGF as	[8]
SCN9A	$Na_v1.7$ sodium channel	--- -	Absent pain Reduced pain	Identification and verification of $Na_v1.7$ as an analgesic target	[15, 112]
		+++ ++	Increased pain		[62, 63]
GCH1	GTP cyclohydrolase 1	-	Reduced or delayed pain	Verification of GCH1 as pain relevant and a	[19]
KCNS1	Kv1.9 potassium channel	-	Increased risk of pain chronification	Verification of KCNS1 as pain relevant and agonists being	[30]

[#] Genetically cased 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						
OPRM1	-opioid receptor *	rs1799971	-	Decreased opioid effects	Increased opioid dosages	[84, 114]
				Increased therapeutic range of opioids	Opioid safety	[43, 46]
COMT	Catechol-O-methyl transferase	rs4680	-	Increased -opioid receptor expression	Reduced opioid require- ments	[51]
MC1R	Melanocortin-1 receptor	rs1805007, rs1805008, rs1805009 and other	–	Red hair fair skin	Indication for -opioids in women	[57]
KCNJ6	Kir3.2 potassium channel	rs2070995	-	Reduced opioid receptor signalling	Increased opioid require- ments	[38, 56]
ABCB1	P-glycoprotein	rs1045642	-	Reduced brain clearance of opioid molecules	Reduced opioid dosing requirements	[84]
CYP2D6	Cyptochrome P450 2D6	2 nonfunctional alleles	---	Reduced or absent mor- phine formation from co- deine	Contraindication for co- deine	[82]
		> 2 functional alleles	+++	Exaggerated morphine formation from codeine		[75, 77, 80]
PTGS2	Cyclooxygenase 2 *	rs20417	-	Decreased COX-2 expres- sion	Ineffectiveness of selec- tive COX-2 inhibitors	[39]
Future analgesics (currently under clinical development [108])						
SCN9A	$Na_v1.7$ sodium channel *	rs6746030 rs41268673	++	Increased pain	Therapy selection of $Na_v1.7$ inhibitors	[62, 63]
TRPA1	Transient receptor potential channel, subfamily A, member 1	c.2564A>G	++	Increased pain	Therapy selection of TRPA1 inhibitors	[68]

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

*: Analgesic drug target