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REVIEW

Pharmacogenetics of new analgesics

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Patient phenotypes in pharmacological pain treatment varies between individuals, which could be partly assigned to their genotypes regarding the targets of classical analgesics (*OPRM1*, *PTGS2*) or associated signalling pathways (*KCNJ6*). Translational and genetic research have identified new targets, for which new analgesics are being developed. This addresses voltage-gated sodium, calcium and potassium channels, for which *SCN9A*, *CACNA1B*, *KCNQ2* and *KCNQ3*, respectively, are primary gene candidates because they code for the subunits of the respective channels targeted by analgesics currently in clinical development. Mutations in voltage gated transient receptor potential (TRPV) channels are known from genetic pain research and may modulate the effects of analgesics under development targeting TRPV1 or TRPV3. To this add ligand-gated ion channels including nicotinic acetylcholine receptors, ionotropic glutamate-gated receptors and ATP-gated purinergic P2X receptors with most important subunits coded by *CHRNA4*, *GRIN2B* and *P2RX7*. Among G protein coupled receptors, δ-opioid receptors (coded by *OPRD1*), cannabinoid receptors (*CNR1* and *CNR2*), metabotropic glutamate receptors (mGluR5 coded by *GRM5*), bradykinin B_1 (*BDKRB1*) and 5-HT_{1A} (*HTR1A*) receptors are targeted by new analgesic substances. Finally, nerve growth factor (*NGFB*), its tyrosine kinase receptor (*NTRK1*) and the fatty acid amide hydrolase (*FAAH*) have become targets of interest. For most of these genes, functional variants have been associated with neuro-psychiatric disorders and not yet with analgesia. However, research on the genetic modulation of pain has already identified variants in these genes, relative to pain, which may facilitate the pharmacogenetic assessments of new analgesics. The increased number of candidate pharmacogenetic modulators of analgesic actions may open opportunities for the broader clinical implementation of genotyping information.

Abbreviations

AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; COX-2, prostaglandin endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase); FAAH, fatty acid amide hydrolase; Il-1, interleukin 1; MAO, monoamine oxidase; mGluR5, metabotropic glutamate receptor 5; nAChR, neuronal nicotinic acetylcholine receptors; Na_v, voltage-gated sodium channels; NGF, nerve growth factor; NMDA, N-methyl-D-aspartic acid; NR2B, NR2B Subunit of the NMDA receptor; P2X7, purinergic receptor P2X, ligand-gated ion channel, 7; TRPV1, transient receptor potential cation channel, subfamily V, member 1; TRPV3, transient receptor potential cation channel, subfamily V, member 3

Introduction

The phenotype of patients receiving pain therapy displays a large inter-individual variability that could be partly assigned to the patients' genotype (Lötsch and Geisslinger, 2006; Lötsch *et al.*, 2009a). Pharmacogenetic influences affecting the pharmacodynamic actions of marketed analgesics have been mainly found among the genes coding for their main targets (*OPRM1*, *PTGS2*) or components of their respective signalling pathways (*KCNJ6*), in a few additional genes (*COMT*, *MC1R*) partly affecting the function of the main analgesic targets, and in genes important for the pharmacokinetics of some classical analgesics (*CYP2D6*, *ABCB1*) (Lötsch *et al.*, 2009a).

With the targets of classical analgesics, that is, opioid receptors and cyclooxygenases, and of substances labelled as co-analgesics, that is, the $\alpha_2\delta$ subunit of voltage gated calcium

channels, NMDA channels, sodium channels, noradrenaline or 5-HT transporters, there have been remarkable successes in treating pain. However, chronic pain has remained a primary healthcare problem listed by the World Health Organisation. Consistent with the multifactorial nature of pain (Julius and Basbaum, 2001), translational and genetic research have identified several new analgesic targets (Backonja and Woolf, 2010), for which analgesics are being developed (Table 1). From a pharmacogenetic point of view, this will increase the number of candidate genetic modulators of clinical analgesic actions, opening a chance of broader clinical use of genotyping information for pre-selection of analgesics.

The present overview summarizes potential pharmacogenetic modulators of those new analgesic targets for which substances have reached at least the clinical development phase 1. This avoids an inflated set of all possible targets that have not yet left basic research and their pharmacogenetic implementations are not yet acute. A complete set of all targets of analgesics that are presently considered as promising can, therefore, be found elsewhere (Marchand *et al.*, 2009; Rodger, 2009). Due to corporate strategies and partially pending results, this survey does not provide a uniform picture of which compounds will be chosen for further development. Other new analgesics targeting the same structures as classic analgesics are excluded because this pharmacogenetic information has been discussed elsewhere (Lötsch *et al.*, 2009a). Several novel analgesics were identified by a survey of online sources, including the http://www.clinicaltrials.gov database, company websites, presentations and press releases. As most of the new analgesics are nevertheless not yet broadly available, direct information about a pharmacogenetic modulation of their actions is often lacking. Nevertheless, pharmacogenetics can start from knowledge gathered in other context, often neuro-psychiatric disorders, where functional variants in the same genes have been already identified.

Pharmacogenetics of pain and analgesia in clinical practice

Pharmacogenetics are often expected to provide guidance for clinical drug therapy. This has been successful in several fields such as cancer therapy (Gonzalez-Angulo *et al.*, 2010) or anticoagulation (Caraco *et al.*, 2008), but pain therapy is not yet among them. The utility of genotyping information in clinical analgesia has been viewed from being broadly optimistic (Argoff, 2010) to pessimistic (Mogil, 2009); however, even most promising results on a modulation of common human analgesia are presently unable to provide a comprehensive prediction of individual analgesic response in the clinical setting (Lötsch *et al.*, 2009c; Walter and Lötsch, 2009). Often, phenotypes could be only retrospectively associated with genotypes. This qualifies genotypes as risk factors and provides explanations for extreme phenotypes.

However, a prospective clinical utility has not been proven, as for example for *CYP2C9* genotyping for warfarin anticoagulation (Caraco *et al.*, 2008), neither are genotype-based analgesic therapy plans broadly used in clinical practice. Currently, most genotyping information has been associated with opioid requirements. Since opioids can be adequately efficiently titrated in most patients, there is no major advantage of genotyping information, beyond explanations for extreme dosing demands.

With the new, in-development, analgesics involving many new targets, the pharmacogenetics of pain and analgesia may be employed as guidance for the choice of the optimum analgesic. This is currently only marginally possible, as for example basing the non-selection of codeine on the *CYP2D6* genotype (Eckhardt *et al.*, 1998), the selection of a κ-opioid agonist on the *MC1R* genotype and sex (Mogil *et al.*, 2005) and the non-selection of a coxib on the *PTGS2* genotype (Lee *et al.*, 2006). Most of the new drugs are being developed against neuropathic pain and it is unlikely that a patient would receive all of these. Pharmacogenetic information may, therefore, be of great value in choosing the optimum analgesics, along with non-genetic, for example disease-specific, guidance.

Targets of new analgesics and their genetic modulation

Ion channels

Ion channels are integral membrane proteins that contain pathways through which ions can flow (Di Resta and Becchetti, 2010). They are considered likely targets in the treatment of pain (Mathie, 2010).

Voltage-gated sodium channels. Voltage-gated Na^+ (NaV) channels are key mediators of neuronal function and essential for neuronal excitability (Mantegazza *et al.*, 2010). They are the main targets of local anaesthetics. From a genetic perspective, the 1.7 subunit seems to play a major role in pain. Specifically, the complete inability to sense pain in otherwise healthy members of three consanguineous families from northern Pakistan was mapped as an autosomal recessive trait caused by a loss-of-function variant in the *SCN9A* gene (Cox *et al.*, 2006). This gene encodes the α-subunit of the voltage-gated sodium channel, $Na_v1.7$. In the three families, three distinct homozygous *SCN9A* nonsense mutations (S459X, I767X and W897X) were identified. In accompanying whole-cell voltage clamp experiments in HEK293 cells expressing mutant $Na_v1.7$, voltage-gated Na^+ currents were no greater than the background level. Additional very rare *SCN9A* variants have been added to the causes of this extreme phenotype (Nilsen *et al.*, 2009).

The same gene also exhibits increased-function mutations, which cause the rare opposite phenotype erythromelalgia (Norbury *et al.*, 2007; Choi *et al.*, 2010) consisting of episodic symmetrical red congestion, vasodilatation and burning pain in the feet and lower legs. For example, 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, slower deactivation and enhanced responses to slow ramp depolarizations, with a −21 mV shift in the voltage-dependence of slow-inactivation (Ahn *et al.*, 2010). Aside from these very rare genotypes, more frequent functional variants may modulate the pain phenotype of average carriers. The variant alleles rs6746030 A (Reimann *et al.*, 2010) (frequency in Caucasians 9.7%) and rs41268673 T (Samuels *et al.*, 2008) (frequency 1.4%) were reported as being associated with higher than average pain sensitivity.

Table 1

Compounds for which analgesia is the main clinical target, or at least among clinical indications, and which address a molecular target that has not been addressed by classical available analgesics or co-analgesics, or only as a pleiotropic effect, and which have reached at least clinical phase 1 in their development. The molecular targets and their coding genes are given as derived from publicly available information. Most substances are being developed for neuropathic pain

Compound	Company	Target	Gene	Comments
Ralfinamide	Newron	$Na_v1.7$, (and N-type calcium channels, NMDA)	*SCN9A (CACNA1B, see below)*	Missed primary endpoint (5/2010)
Lacosamide	UCB	$Na_v1.8$, 1.7 and 1.3	*SCN10A, SCN9A, SCN3A*	
MK-6721 / NMED160	Neuromed	N-type calcium channels	*CACNA1B*	Suspended in 2007
Ziconotide	Azur Pharma			Approved in 2004
ACV1	Metabolic Pharmaceuticals			
Retigabine	Valeant	KCNQ/Kv7 potassium channels	*KCNQ2, KCNQ3*	
NGD8243 (MK-2294)	Ligand	TRPV1 channel	*TRPV1*	
GRC-6211	Glenmark			Partner suspended trial in 2008
AMG986	Amgen			
AMG8562 (back-up)	Amgen			
AZD1386	AstraZeneca			
NGX-4010	NeurogesX			
ABT 102	Abbott			
SB 705498	GlaxoSmithKline			
NGX-1998	NeurogesX			
MK2295 (BGD8243)	Neurogen/Merck			
NGX-4010	NeurogesX			
adlea	Anesiva			
GRC-15300	Glenmark	TRPV3 channel	*TRPV3*	
Tezampanel / NGX426 = oral prodrug)	TorreyPines/Raptor	AMPA/kainate receptors	*GRIA1-4/GRIK1-5*	
Indantadol (CHF-3381, V-3381)	Vernalis	NMDA receptor, MAO	*GRIN1, GRIN2A-D, GRINA, MAOB*	Suspended 5/2010
CNS-5161	Paion/ERGOMED	NMDA receptor	*GRIN1, GRIN2A-D, GRINA*	Suspended 12/2009
RGH-896	ForestLabs	NR2B receptor subunit	*GRIN2B*	Phase 2 failed 6/2010
TC6499	Targacept/GSK	nAChR (α_4/β_2) receptor	CHRNA4	
ABT-594	Abbott			
ABT-894	Abbott/NeuroSearch			Discontinued 2009
EVT 401	Evotec	P2X7 receptor	*P2RX7*	
CE-224	Pfizer			
CE-535	Pfizer			
GSK1482160	GSK			
ADL5859	Adolor/Pfizer	δ–opioid receptor	*OPRD1*	Failed in phase 2
ADL5747	Adolor/Pfizer			Failed in phase 2
PF-4856880	Pfizer			
PF-4856881	Pfizer			

Table 1

Continued

Compound	Company	Target	Gene	Comments
IP751	Endo (Former Indevus)	CB_1 receptor/COX-2/Il-1	*CNR1, PTGS2, IL1A, IL1B*	
KDS2000	Kadmus (aquired by Organon)	$CB_{1/2}$ receptor	*CNR1, CNR2*	
AZD1940	AstraZeneca			Discontinued
Sativex	GW Pharmaceuticals /Otsuka			Approved
SAD 448 /SAD 378	Novartis			
GRC-10693	Glenmark	CB_2 receptor	*CNR2*	
GW842166	GlaxoSmithKline			
PRS-211,375 (Cannabinor)	Pharmos			
ADX10059	Addex	mGluR5 receptor	*GRM5*	Terminated 12/2009 due to liver toxicity
AZD2066	Astra Zeneca			
AZD2516	AstraZeneca			
LY545694	Lilly			
SSR 240612	Sanofi-Aventis	Bradykinin B_1 receptor	*BDKRB1*	
F-13640 / Befiradol	Pierre Fabre	5-HT_{1A} receptor	*HTR1A*	
Tanezumab	Pfizer	NGF	*NGFB*	Suspended 6/7, 2010
REGN 475	Regeneron/sanofi			
MEDI-578	AstraZeneca/MedImmune			
PG110	PanGenetics/Abbott			
losmapimod	GSK	p38 kinase	*MAPK14*	
PF-4457845	Pfizer	FAAH	*FAAH*	
V158866	Vernalis			

While these genetic changes have attracted the interest of pain researchers so far, the translation of the results of genetic research into drug development makes them immediate candidate variants for a pharmacogenetic modulation of $Na_v1.7$ blocking analgesics. Carriers of increased-function variants might particularly benefit from $Na_v1.7$ inhibitors because this would be a selective cure for paroxysmal pain (Fertleman *et al.*, 2006). The consequences of carrying decreased-function variants are theoretically possible in both directions but could be easily assessed.

Voltage-gated calcium channels. Members of this ion channel family contain $\alpha_2\delta$, β and γ subunits, and play a role in neuronal excitation. The $\alpha_2\delta$ subunit of L-type calcium channels is the target of the established co-treatments for neuropathic pain, gabapentin and pregabalin (Perret and Luo, 2009). Newer developments such as ziconotide (Schmidtko *et al.*, 2010), the synthetic form of the hydrophilic conopeptide ω-$MV_{II}A$ found in the venom of the Pacific fish-hunting snail *Conus magus* (Olivera, 2006), target, with high affinity, the α_{1B} subunit of N-type voltage-sensitive calcium channels. These calcium channels are also key players in chronic pain (Swayne and Bourinet, 2008). They are coded by the *CACNA1B* gene and expressed at the presynaptic terminals of primary afferent neurons that end in the dorsal horn of the spinal cord (Gohil *et al.*, 1994), an area playing a key role in nociceptive signal transmission. *CACNA1B* gave an above-threshold signal in a genome-wide association study of the risk of schizophrenia (Moskvina *et al.*, 2009), and the gene was deleted in 16 cases of schizophrenia (Glessner *et al.*, 2010).

Voltage-gated potassium channels. The inwardly rectifying potassium channel $K_{IR}3.2$, a two-transmembrane-one-pathway potassium channel, is involved in opioid signalling on postsynaptic inhibition (Mitrovic *et al.*, 2003) and mediates a significant component of analgesia (Marker *et al.*, 2004). Delayed rectifying neuronal KCNQ channels ($KCNQ_{2\text{-}5}$) have homologies with cardiac channels involved in long QT syndrome and play a role in benign idiopathic neonatal epilepsy or congenital deafness (Gribkoff, 2008). These slowly inactivating channels are also expressed at the postsynaptic membrane of small diameter nociceptive nerve endings (Brown and Passmore, 2009) and play a key role in the control of the excitability of nociceptors (Passmore *et al.*, 2003). Potassium channels are considered as targets in several CNS diseases that involve neuronal hyperexcitability such as migraine, epilepsy or neuropathic pain (Wua and Dworetzky, 2005). $KCNQ_{2/3}$ are not new analgesic targets as the well-known flupirtine has been recognized primarily to exert its analgesic actions via opening of these potassium channels

(Ilyen *et al.*, 2002). The principle has been recently taken up for the development of new analgesics (Fritch *et al.*, 2010). Flupirtine has not yet been analysed for pharmacogenetic variability. Genetic modulations regarding *KCNQ2* or *KCNQ3* are known as channelopathies causing hereditary epilepsy (Schroeder *et al.*, 1998; Singh *et al.*, 1998).

Voltage-gated transient receptor potential (TRPV) channels. Members of this cation channel superfamily play critical roles in sensory physiology such as in vision, thermosensation, olfaction, hearing and touch (Montell, 2005). These receptors are activated by capsaicin (the pungent ingredient of hot peppers), protons and heat (>43°C), and are expressed at nociceptors and in pain relevant brain areas (Steenland *et al.*, 2006). This stimuli are employed in experimental pain models using either directly heat and capsaicin (Petersen and Rowbotham, 1999) or producing protons via short pulses of gaseous CO_2 applied to the nasal mucosa, where protons are generated by the action of carbonic anhydrase (Kobal, 1985). A further family member, TRPV3, activated at temperatures of 22–40°C, is also expressed at sensory nerve endings (Eid and Cortright, 2009). Aside from these heat receptors, the TRP family includes cold receptors, among which TRPA1 and M8 have been most often associated with pain. TRPA1 is excited by cold stimuli below 15°C (Story *et al.*, 2003), whereas TRPM8 channels are stimulated by cold between 8 and 28°C (McKemy *et al.*, 2002). TRPM8 is also activated by cooling compounds such as menthol (Peier *et al.*, 2002), while TRPA1 channels are additionally activated by pungent chemicals such as isothiocyanates (horseradish, mustard), cinnamaldehyde (cinnamon) and allicin (garlic) (Patapoutian *et al.*, 2009) or cannabinoids (Jordt *et al.*, 2004). New analgesics are either antagonists at the TRPV1 or TRPV3 nociceptors, or agonists (TRPV1) including capsaicin and chemically derived developments, which act via nociceptor desensitization (Novakova-Tousova *et al.*, 2007).

Because of their involvement in pain sensations, *TRPV1*, *A1* and *M8* genotypes have been studied for modulation of the pain phenotype. Genetic associations have been reported about a single subject insensitive to capsaicin, who carried seven intronic *TRPV1* polymorphisms and had only 50% of the mRNA and protein expression levels of normally sensing subjects (Park *et al.*, 2007). In 17 European-American women carrying the *TRPV1* variant rs8065080 G (I585V), cold withdrawal time was 1.6 times longer than in 136 non-carriers (Kim *et al.*, 2004). This was surprising because TRPV channels are stimulated by heat and, therefore, heat pain was the phenotype expected to be modulated, while for a modulation of cold pain, variants in *TRPM8* or *TRPA1* would have been primary candidates. The authors hinted at properties in the three-dimensional structure of the engaged *TRPA1* haplotype for explanation (Kim *et al.*, 2004). In the same gene, a point mutation leading to an N855S amino acid exchange in the S4 transmembrane segment of TRPA1 receptors increased the inward current on activation at normal resting potentials fivefold (Kremeyer *et al.*, 2010). This was associated with an autosomal-dominant familial episodic pain syndrome characterized by episodes of debilitating upper body pain, triggered by fasting and physical stress. For carriers of such *TRPA1* mutations, TRPA1 antagonists are an especially promising therapy.

Ligand-gated ion channels. Targets of this kind addressed with new analgesics include ionotropic glutamate-gated receptors, nicotinic cholinoceptors and ATP-gated purinergic P2X receptors.

Glutamatergic ion channels. Ionotropic receptors directly gate ion channels and are divided into three major subclasses: AMPA, Kainate and NMDA (Petrenko *et al.*, 2003). Several NMDA antagonists have been available for a long time, such as amantadine, dextromethorphan, ketamine, memantine, nitrous oxide, phencyclidine, riluzole or tiletamine, some of them being used in pain treatment, others in treatment of neurological diseases or as substances of abuse. New NMDA or AMPA modulators often target ion channel subunits to obtain higher selectivity for pain. One of these targets is the NMDA receptor 2b subunit coded by the *GRIN2B* gene. The *GRIN2B* 2664C>T polymorphism plays a role in Huntington pathology where it appears to modulate neuronal response inhibition (Beste *et al.*, 2010) and has been associated with Parkinson's disease (Tsai *et al.*, 2002). Another variant, *GRIN2B* 366C>G, was more frequent in Parkinson patients displaying impulse control and related behaviours than in non-affected patients (Lee *et al.*, 2009). The *GRIN2B* rs10845840 variant has been associated with the temporal lobe volume in Alzheimer's disease patients (Beste *et al.*, 2010). A *GRIN2B* haplotype has been associated with variation in memory performance (de Quervain and Papassotiropoulos, 2006). In addition, the *GRIN2B* rs1019385 polymorphism was associated with higher glutamate concentrations in the anterior cingulum and was involved in obsessive-compulsive disorder (Lee *et al.*, 2009) and schizophrenia (Hokyo *et al.*, 2010). Finally, rs2284411 showed associations with symptom dimensions of attention deficit hyperactivity disorder (Dorval *et al.*, 2007).

The antagonist at kainate receptors currently developed as a new analgesic, tezampanel, has selectivity toward the GluK1 (GluR5) subtype and coded by the *GRIK1* gene. Variants in this gene are known from associations with alcoholism (Kranzler and Edenberg, 2010) or autism (Haldeman-Englert *et al.*, 2010).

Neural nicotinic receptors. Nicotine exerts antinociceptive effects by interacting with one or more of the subtypes of nicotinic cholinoceptors (nAChRs) present throughout neuronal nociceptive pathways (Marubio *et al.*, 1999), for example forming capsaicin-sensitive and -insensitive nociceptors expressed at dorsal root ganglia (Rau *et al.*, 2005). Therefore, new analgesic compounds target certain subtypes (Gao *et al.*, 2010) of neuronal nAChRs to circumvent the narrow therapeutic window between analgesic efficacy and toxicity of non-selective nicotinic agonists (Vincler, 2005). Specifically, mice lacking the α_4 subunit of the neuronal nAChR displayed reduced antinociceptive effects of nicotine (Marubio *et al.*, 1999). However, these newer analgesics, such as ABT-594, are not without side effects, such as nausea, dizziness, vomiting, abnormal dreams and asthenia, reported in patients with diabetes-induced peripheral neuropathic pain (Rowbotham *et al.*, 2009).

Functional variants in the *CHRNA4* gene, which codes for this receptor subunit, have been associated with epilepsy (Steinlein and Bertrand, 2010). In addition, the *CHRNA4*

polymorphisms rs4603829 and rs4522666 were reported to modulate financial and psychological risk behaviours (Roe *et al.*, 2009), *CHRNA4* rs1044396 was associated with novelty seeking (Etter *et al.*, 2009), whereas rs2236196, rs1044396 and rs2236196 were associated with nicotine dependence (Breitling *et al.*, 2009). More severe consequences have some rare loss-of-function variants associated with the occurrence of amyotrophic lateral sclerosis (Sabatelli *et al.*, 2009). However, as for several other candidate variants, a direct association with pain or analgesia has not yet been shown and possibly not even been studied because they have played, so far, no role in analgesia.

Purinergic receptors. Purinergic receptors have been reported to be involved in pain (Jarvis and Khakh, 2009; Jarvis, 2010). One mechanism by which ATP evokes acute pain is the interaction with P2X receptors that are also involved in the pathophysiology of chronic inflammatory and neuropathic pain (Kennedy, 2005). P2X3 receptors are expressed in capsaicin-sensitive small-sized dorsal root ganglion neurons where they contribute to the generation of rapidly desensitizing inward currents, which are involved in evoking nocifensive behaviours and thermal hyperalgesia. A P2X receptor-mediated excitatory postsynaptic current was also found in pyramidal neurones of the somatosensory cortex (North, 2003; Pankratov *et al.*, 2003). P2X4 receptors induced in spinal microglia mediate tactile allodynia after nerve injury (Tsuda *et al.*, 2003).

Genetic variation in purine receptors has been studied less frequently. *P2RX7* rs1718119 was associated with severity scores in the panic- and agoraphobia scale (Erhardt *et al.*, 2007) and the loss-of-function mutations *P2RX7* 568N (rs1653624), 307Q (rs28360457) and a null allele (splice site mutation, rs35933842) tended to be over-represented among patients who needed a surgical revision after total hip arthroplasty (Mrazek *et al.*, 2010), which had been related to the involvement of P2X7 receptors in inflammation. In addition, a role in the development of depression has been suggested for the *P2RX7* rs2230912 G allele (Nagy *et al.*, 2008).

G protein coupled receptors

G-protein coupled receptors have seven transmembrane segments and sense external molecules triggering activation of internal signalling pathways.

δ–opioid receptors. δ–opioid receptors are the natural targets of enkephalins and mediate several biological functions including antinociception. Although the action of most current opioid analgesics is simply described as μ-opioid receptor agonism, it is well known that they also bind at other opioid receptors (Mignat *et al.*, 1995). Therefore, a δ-opioid component is part of the action of most clinically used opioid analgesics (Gharagozlou *et al.*, 2002). More selective δ-opioid agonists have not been broadly established clinically, despite demonstrations of better side effect profiles and a proposal of their use to selectively antagonize μ-opioid receptor associated respiratory depression (Su *et al.*, 1998). Selective δ-opioid agonists are being under development as analgesics.

In *in vitro* transfection experiments, the W284L variant of the δ-opioid receptor selectively reduced the affinity of some but not all of the tested δ-opioid agonists (Hosohata *et al.*, 2001). *In vivo*, most polymorphisms in the δ-opioid receptor gene (*OPRD1*) have been associated with substance dependence (Zhang *et al.*, 2008) and other psychiatric disorders (Brown *et al.*, 2007). For example, *OPRD1* rs569356 may enhance transcription factor binding and increase δ -opioid receptor expression and was associated with substance addiction (Zhang *et al.*, 2010). *OPRD1* variants have also already shown to play a role in pain. Thus, men carrying the rs1042114T>G variant (allelic frequency 10.9%) had lower heat pain sensitivity than carriers of the rs2234918T>C variant (allelic frequency 35.6%) (Kim *et al.*, 2004).

Cannabinoid receptors. The involvement of the cannabinoid system in a number of important physiological processes including the regulation of neurotransmitter release, pain and analgesia, energy homeostasis, and control of immune cell function is mediated by CB_1 and CB_2 receptors (Graham et al., 2009). They are activated by endocannabinoids, which are arachidonic acid derived lipids such as anandamide and 2-arachidonoyl-glycerol, plant cannabinoids such as tetrahydrocannabinol and synthetic cannabinoids including substances under development as analgesics. The two main receptor subtypes, CB_1 and CB_2, are primarily located in the CNS or in the periphery, respectively, although this separation is not strict, as, for example, the CB_1 receptor is expressed also in the lungs, liver and kidneys (Graham *et al.*, 2009). Cerebral endocannabinoid signalling is involved in antinociception (Wilson and Nicoll, 2002). However, the peripheral CB_2 receptor has also been proposed to play a key role in cannabinoid-mediated analgesia (Agarwal *et al.*, 2007). Exogenous cannabinoids have been suggested to decrease the subjective intensity estimates of pain alone or in synergy with opioids (Naef *et al.*, 2003; Roberts *et al.*, 2006) but hyperalgesic cannabis actions on electric experimental pain stimuli in healthy volunteers have also been reported (Kraft *et al.*, 2008). A cannabis formulation has been approved in Canada since 2005 for the treatment of neuropathic pain.

Polymorphisms in the CB_1 gene *CNR1* have not yet been associated with pain phenotypes. So far, functional associations were found with obesity (Russo *et al.*, 2007; Aberle *et al.*, 2008), schizophrenia (Ujike *et al.*, 2002; Chavarría-Siles *et al.*, 2008; Hamdani *et al.*, 2008), drug (Proudnikov *et al.*, 2010) and alcohol dependence (Zhang *et al.*, 2004; Zuo *et al.*, 2007; Agrawal *et al.*, 2009). Polymorphisms in the CB_2 gene *CNR2* play a role in osteoporosis (Karsak *et al.*, 2005) and might also modulate the susceptibility to autoimmune disorders (Sipe *et al.*, 2005).

Metabotropic glutamate receptors. These G_q or G_i protein coupled receptors transmit glutamatergic excitatory signals (Swanson *et al.*, 2005), are expressed at nociceptive neurons and involved in sensitization processes to noxious stimulation (Coderre, 1993). Analgesics are being tested that inactivate the mGluR5 receptor, which is coupled with a G_q protein. Via phospholipase C activation and inositoltriphosphate/diacylglycerol signalling, activation of this receptor leads to liberation of calcium from the endoplasmic reticulum into the intracellular space and to activation of

protein kinase C. *GRM5* variants were associated with schizophrenia (Devon *et al.*, 2001; Choi *et al.*, 2009) or attention-deficit hyperactivity disorder (Elia *et al.*, 2009).

Bradykinin receptors. Bradykinin B_1 receptors (Marceau *et al.*, 1998) mediate hyperalgesia due to kininin up-regulation (Gabra *et al.*, 2006). In a diabetic neuropathic rodent model, blocking of B_1 receptors reversed tactile and cold allodynia (Dias *et al.*, 2007). A variant in *BDKRB1* (-699 G>C) was slightly associated with progression of polycystic kidney disease (Tazón-Vega *et al.*, 2007) but also with the risk of inflammatory bowel disease (Bachvarov *et al.*, 1998). *BDKRB1* variants were also reported in the context of hypertension (Cui *et al.*, 2005).

5-HT receptors. 5-HT receptors are expressed in the central and peripheral nervous systems where they mediate both excitatory and inhibitory neurotransmission (Hoyer *et al.*, 1994). They exert many physiological and pathophysiological functions and some of their subtypes play a role in nociception. Several 5HT receptor subtypes are involved in nociception (Xu *et al.*, 1994), such as spinal 5-HT_1, 5-HT_2 and 5HT_3 receptors (Alhaider *et al.*, 1991; Danzebrink and Gebhart, 1991; Giordano, 1997). Human polymorphisms of their genes have been associated with several pathophysiological functions (Hannon and Hoyer, 2008) leading to a complex knowledge of the genetics and pharmacogenetics of the serotonergic system. Currently, only the 5-HT_{1A} receptor is being studied as the target of an analgesic, F-13640/befiradol, that has entered the clinical phase of development. Besides several other biological functions in the regulation of blood pressure and penile erection, mood, addiction and memory, the 5-HT_{1A} receptor subtype has been described to play a role in nociception (Nadeson and Goodchild, 2002; Pucadyil *et al.*, 2005). An agonist at these receptors possessed anti-allodynic and anti-hyperalgesic properties (Bardin *et al.*, 2003) including efficiency in neuropathic pain models in laboratory animals (Deseure *et al.*, 2007). The *HTR1A* -1019C>G polymorphism was associated with schizophrenia, substance abuse disorder, panic attack and antidepressant response in mood disorders (Huang *et al.*, 2004), attention deficit hyperactivity disorder (Shim *et al.*, 2010), and has been suggested to be linked to frontal brain electrical asymmetry (Bismark *et al.*, 2010).

Signalling messengers

Nerve growth factor (NGF). 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 (Fiore *et al.*, 2009). The expression of NGF is high in injured and inflamed tissues, and activation of the NGF receptor tyrosine kinase A (trkA) on nociceptive neurons triggers and enhances pain signalling by multiple mechanisms (Hefti *et al.*, 2006).

trkA is a catalytic receptor being approached as an analgesic's target, (Wang *et al.*, 2009), but the candidate compound has not yet entered phase 1 clinical trial. NGF signalling plays a role in the generation of pain and hyperalgesia (Levi-Montalcini *et al.*, 1996; Fiore *et al.*, 2009) also because the local production of inflammatory cytokines up-regulates NGF (Hefti *et al.*, 2006).

Due to the signal transduction pathway, the actions of NGF targeting dugs may be genetically modulated both at *NGFB* level, the gene coding for NGF β, and at *NTRK1* level, the gene coding for trkA receptors. Loss-of-function variants in the *NGFB* gene have been identified as the causes of extreme pain phenotypes consisting of complete congenital insensitivity to pain. Since NGF and its receptor trkA are involved in nervous system development and homoeostasis, the genetic variants are associated with other neurological deficits. Thus, the hereditary sensory and autonomic neuropathy type V (HSAN-V) is characterized by a loss of pain perception, impaired temperature sensitivity, ulcers, and sometimes self-mutilation, with variable autonomic involvement (Hilz, 2002). All three affected members of a Swedish family were homozygous for a coding 661C>T SNP (R211W) in the *NGFB* gene encoding NGF-β, which affects a highly conserved region of the protein (Einarsdottir *et al.*, 2004).

Variants in the *NTRK1* gene coding for the trkA receptor have been identified as the causes of the extreme pain phenotype congenital insensitivity to pain with anhidrosis (CIPA), also called hereditary sensory and autonomic neuropathy type IV (HSAN-IV). It is an autosomal-recessive disorder characterized by recurrent episodes of unexplained fever, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behaviour and mental retardation. Since mice lacking the gene encoding the trkA receptor (*ntrk1*) for NGF display similar phenotypic features as CIPA patients (Smeyne *et al.*, 1994), mutations in the human *NTRK1* gene have been studied as candidate causes. Three mutations (1726delC with premature translational stop, IVS15 + 3A > C with altered splicing, 1795 G > C with G571R amino acid substitution) in three unrelated subjects were identified as the molecular basis of HSAN-IV (Indo *et al.*, 1996). Several further mutations have been found in these patients (Indo, 2001), most of them only once but 1726delC was found in more than 50% of Japanese CIPA families (Miura *et al.*, 2000), and 1926–1927insT found in 16 of 19 unrelated CIPA families from Israeli Bedouins (Shatzky *et al.*, 2000).

Interleukin-1. Interleukin (IL)-1 is a pro-inflammatory cytokine. Antagonists are developed for the treatment of inflammatory rheumatic and low back pain. Genetic modulations in IL-1-related genes have been found in 131 middle-aged men, among whom carriers of the IL1 receptor antagonist (*IL1RN*) variant rs2234677 had an increased risk for low back pain. When present with the IL-1α genetic variant *IL1A* rs1800587 or the IL-1β gene (*IL1B*) variant rs1143634, a higher risk and more days with low back pain was identified (Solovieva *et al.*, 2004). Higher pain incidence was associated with the *IL1A* rs1800587 and *IL1RN* rs2234677 variants and the simultaneous presence of *IL1A* rs1800587 and *IL1RN* rs2234677 was associated with increased number of days with pain (Solovieva *et al.*, 2004). The functional variants were associated with IL-1 up-regulation at RNA and cytokine levels (Pociot *et al.*, 1992; Dominici *et al.*, 2002). This makes antagonists primary choices for patients carrying variants that enhance the algesic activity of IL-1.

P38 MAP kinase. P38 MAP kinases respond to stress stimuli, such as pro-inflammatory cytokines and cytokines and cellular stresses (Ashwell, 2006). P38 MAP kinases play a role in the

pathogenesis of neuropathic pain. In microglial signal transduction under chronic pain states, downstream effects of p38 produce inflammatory mediators (Ji and Suter, 2007). Selective p38 inhibitors are being clinically evaluated for the treatment of chronic inflammatory disorders including those involving pain (Cottrell *et al.*, 2009). The *MAPK14* gene coding for p38 (named MAP kinase 14) has so far not been positively reported from association studies.

Enzymes involved in the production of nociceptive or inflammatory mediators

FAAH. The fatty acid amide hydrolase (FAAH) is one of the endocannabinoid metabolizing enzymes. It degrades the fatty acid amide family of endogenous signalling lipids including the endogenous cannabinoid anandamide (Bisogno *et al.*, 2005), which among many other functions has been implicated in the suppression of pain. Lack of FAAH has been associated with a cannabinoid related hypoalgesic phenotype in mice (Lichtman *et al.*, 2004). Moreover, FAAH has been implicated in the antinociceptive effects of paracetamol (Högestätt *et al.*, 2005; Mallet *et al.*, 2008) and other analgesics such as R-flurbiprofen (Ates *et al.*, 2003; Bishay *et al.*, 2010) affecting prostaglandin production and therefore, its polymorphisms may modulate the action of classical and new analgesics.

In pain, a tendency towards increased pain sensitivity associated with frequent *FAAH* alleles was seen in a cohort of 935 subjects. Cold pain intensity was up to 1.4-fold increased in men carrying the variant *FAAH* alleles rs932816 A, rs4141964 C and rs2295633 A, and carriers of the rs4141964 C allele had shorter (0.8-fold) cold withdrawal time than non-carriers (Kim *et al.*, 2006). This would be compatible with increased enzyme activity leading to accelerated endocannabinoid degradation but the molecular consequences of these variants have not yet been assessed.

Future directions of the pharmacogenetics of analgesia

Pharmacogenetics of pain and analgesia as a research tool

The genetics of pain and analgesia has proven its value as a superior research tool to discover the role of molecular pathways in human nociception and analgesia. Quantitative sensory trait techniques in rodents (Abiola *et al.*, 2003) have been successfully employed to identify molecular pathways of nociception leading to an increased understanding of pain and in some cases to the identification of new analgesic drug targets. Information about pain pathways from human research employed genotyping of patients with rare and extreme pain phenotypes, thus identifying indispensable components of the human nociceptive system (Oertel and Lötsch, 2008).

Variants in pain-associated genes can be employed to test whether a molecular pathway identified in laboratory animals is relevant in humans. Without modulator molecules that can be applied to humans, genetic variants functionally altering components of the pathway can be taken as a substitute. This requires, however, the demonstration of a molecular consequence of the genetic variant to avoid overinterpretation of an accidental positive association. A genetic association was used as a tool for a proof-of-concept in assessments where genetics was not in the focus. For example, the role of GTP cyclohydrolase (GCH1) activity in pain, first found in laboratory animals, was proven in humans using *GCH1* genetic variants shown to decrease enzyme up-regulation and tetrahydrobiopterin production at the molecular level (Tegeder *et al.*, 2006).

Genetic association studies can also be used as a tool to generate hypotheses but this requires molecular proof and replications of the findings. Genetics has also contributed to identify functionally relevant portions of the gene product, as for example for the μ-opioid receptor (Wolf *et al.*, 1999). Importantly, a demonstrable molecular effect or at least a reproduction of positive associations in an independent cohort has become a scientific standard on which pharmacogenetics results may be based. This has not yet been shown for all so far known polymorphisms affecting pain or other clinical symptoms related to the present drug targets.

Further pharmacogenetically modulated analgesic targets

The present overview addressed those analgesics targets for which substances are closest to clinical use. It excluded targets for which no drug has so far reached clinical development, such as the GCH1 that may be used to delay the development of pain (Lötsch *et al.*, 2009b). Similarly, T-type voltage gated calcium channels have been shown to play a key role in nociception (Bourinet *et al.*, 2005; Zamponi *et al.*, 2009). Furthermore, hyperpolarization-activated, cyclic nucleotide-modulated (HCN) 'pacemaker' channels play a role in the pathogenesis of neuropathic pain (Chaplan *et al.*, 2003; Papp *et al.*, 2006) rendering them possible further future targets of analgesics. Moreover, acid-sensing ion channels (ASICs) are activated by extracellular protons and can trigger acid-induced pain during inflammation or metabolic stress (Deval *et al.*, 2010). They may be addressed with an existing experimental pain model employing administration of gaseous carbon dioxide to the nasal mucosa where via carbonic anhydrase, protons are generated and, along with TRPV1 activation, stinging pain is evoked (Kobal, 1985).

A further potential target is the inducible microsomal PGE_2 synthase 1 (mPGES-1) that catalyses the formation of prostaglandin E_2 (PGE_2) from PGH_2, a cycloxygenase product from arachidonic acid. PGE_2 represents an important pain mediator and its pain signalling effects are translated mostly via peripheral prostanoid EP_1 receptors and spinal EP_2 receptors (Vanegas and Schaible, 2001). mPGES-1-deficient mice showed a reduced pain hypersensitivity and inflammation in some but not all models (Kamei *et al.*, 2004). It therefore qualifies as a target of anti-inflammatory and analgesic drugs, although it is not clear for which diseases such treatment would provide a particular advantage (Rörsch *et al.*, 2010). The *PTGES2* gene polymorphism rs13283456 (R298H enzyme) has been found to reduce the risk of type 2 diabetes mellitus (Lindner *et al.*, 2007; Nitz *et al.*, 2007), perhaps through contribution of a lowered body mass index (Fischer *et al.*, 2009).

This overview also excluded new analgesics that are innovative improvements of classic principles but do not add new

targets. For example, tapentadol is an opioid and noradrenaline re-uptake inhibitor, but its pharmacogenetics may be primarily deduced from known pharmacogenetic associations of *OPRM1*, *KCNJ6* and *COMT*. Some further variants may be added in genes coding for targets of analgesics that have reached phase 2 without a publicly disclosed mechanism of action, such as the 'small molecule' AGN-209323. Candidate genes additional to the present variants affecting the pharmacodynamics of analgesics, may be found in drug metabolizing enzymes or transmembrane transporters potentially affecting the analgesic's pharmacokinetics. However, from the present selection, those variants will be dropped for which the whole target fails clinical development. It is relevant to note that pain drugs under clinical development have failed, for example, ADX10059, RGH-896, ralfinamide and tanezumab. Whether pharmacogenetic reasons played a role in these failures is not known.

Conclusions

For several genes coding for the targets of new analgesics (Table 1), functional modulations by genetic variants are already known. They have so far been found mainly in neuropsychiatric disorders and need to be tested for a possible role in analgesia. However, intensive research on the genetic modulation of pain has provided already substantial knowledge that may serve as a start point. That is, many targets have analysed in terms of pain genetics (Lötsch and Geisslinger, 2007), rather than analgesic genetics (Lötsch and Geisslinger, 2006), and may now be transferred from pain genetic research to pain *pharmaco*genetic research. Variants modulating the pharmacokinetics of new analgesics will possibly increase the number of candidates.

Several new analgesics will soon increase the choice of targets addressed for control of pain. This broader selection of analgesic targets and genetic modulators (Table 1) may increase the clinical utility of genotyping information in pain treatment, which so far with mainly opioid related proposed applications is modest (Lötsch and Geisslinger, 2010). The already considerable specific knowledge of functional variants, summarized here, may allow for specific hypothesis testing and help improving the statistical power of association studies that without a narrow selection of candidate variants would require large samples. Greater benefits of genotyping in pain therapy could be seen in the possibility to choose the individual optimum analgesic before the start of therapy. The chances for a genetics-based individualized pain therapy increase with an increasing number of targets. However, the challenge remains to compile this into clinically feasible guidance to therapy that provides additive value to therapy decisions made without genetics information.

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Conflicts of interest

The authors declare no conflict of interest.

References

Aberle J, Flitsch J, Beck NA, Mann O, Busch P, Peitsmeier P *et al.* (2008). Genetic variation may influence obesity only under conditions of diet: analysis of three candidate genes. Mol Genet Metab 95: 188–191.

Abiola O, Angel JM, Avner P, Bachmanov AA, Belknap JK, Bennett B *et al.* (2003). The nature and identification of quantitative trait loci: a community's view. Nat Rev Genet 4: 911–916.

Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ *et al.* (2007). Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 10: 870–879.

Agrawal A, Wetherill L, Dick DM, Xuei X, Hinrichs A, Hesselbrock V *et al.* (2009). Evidence for association between polymorphisms in the cannabinoid receptor 1 (CNR1) gene and cannabis dependence. Am J Med Genet B Neuropsychiatr Genet 150B: 736–740.

Ahn H, Dib-Hajj S, Cox JJ, Tyrell L, Elmslie FV, Clarke AA *et al.* (2010). A new Nav1.7 sodium channel mutation I234T in a child with severe pain. Eur J Pain 14: 944–950.

Alhaider AA, Lei SZ, Wilcox GL (1991). Spinal 5-HT3 receptor-mediated antinociception: possible release of GABA. J Neurosci 11: 1881–1888.

Argoff CE (2010). Clinical implications of opioid pharmacogenetics. Clin J Pain 26 (Suppl. 1): S16–S20.

Ashwell JD (2006). The many paths to p38 mitogen-activated protein kinase activation in the immune system. Nat Rev Immunol 6: 532–540.

Ates M, Hamza M, Seidel K, Kotalla CE, Ledent C, Gühring H (2003). Intrathecally applied flurbiprofen produces an endocannabinoid-dependent antinociception in the rat formalin test. Eur J Neurosci 17: 597–604.

Bachvarov DR, Landry M, Houle S, Paré P, Marceau F (1998). Altered frequency of a promoter polymorphic allele of the kinin B1 receptor gene in inflammatory bowel disease. Gastroenterology 115: 1045–1048.

Backonja M, Woolf CJ (2010). Future directions in neuropathic pain therapy: closing the translational loop. Oncologist 15 (Suppl. 2): 24–29.

Bardin L, Tarayre JP, Malfetes N, Koek W, Colpaert FC (2003). Profound, non-opioid analgesia produced by the high-efficacy 5-HT(1A) agonist F 13640 in the formalin model of tonic nociceptive pain. Pharmacology 67: 182–194.

Beste C, Baune BT, Domschke K, Falkenstein M, Konrad C (2010). Dissociable influences of NR2B-receptor related neural transmission on functions of distinct associative basal ganglia circuits. NeuroImage 52: 309–315.

Bishay P, Schmidt H, Marian C, Häussler A, Wijnvoord N, Ziebell S *et al.* (2010). R-flurbiprofen reduces neuropathic pain in rodents by restoring endogenous cannabinoids. PloS ONE 5: e10628.

Bismark AW, Moreno FA, Stewart JL, Towers DN, Coan JA, Oas J *et al.* (2010). Polymorphisms of the HTR1a allele are linked to frontal brain electrical asymmetry. Biol Psychol 83: 153–158.

Bisogno T, Ligresti A, Di Marzo V (2005). The endocannabinoid signalling system: biochemical aspects. Pharmacol Biochem Behav 81: 224–238.

Bourinet E, Alloui A, Monteil A, Barrère C, Couette B, Poirot O *et al.* (2005). Silencing of the Cav3.2 T-type calcium channel gene in sensory neurons demonstrates its major role in nociception. EMBO J 24: 315–324.

Breitling LP, Dahmen N, Mittelstrass K, Rujescu D, Gallinat J, Fehr C *et al.* (2009). Association of nicotinic acetylcholine receptor subunit alpha 4 polymorphisms with nicotine dependence in 5500 Germans. Pharmacogenomics J 9: 219–224.

Brown DA, Passmore GM (2009). Neural KCNQ (Kv7) channels. Br J Pharmacol 156: 1185–1195.

Brown KM, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE (2007). Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. Biol Psychiatry 61: 367–373.

Caraco Y, Blotnick S, Muszkat M (2008). CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther 83: 460–470.

Chaplan SR, Guo H, Lee DH, Luo L, Liu C, Kuei C *et al.* (2003). Neuronal hyperpolarization-activated pacemaker channels drive neuropathic pain. J Neurosci 23: 1169–1178.

Chavarría-Siles I, Contreras-Rojas J, Hare E, Walss-Bass C, Quezada P, Dassori A *et al.* (2008). Cannabinoid receptor 1 gene (CNR1) and susceptibility to a quantitative phenotype for hebephrenic schizophrenia. Am J Med Genet B Neuropsychiatr Genet 147: 279–284.

Choi J, Cheng X, Foster E, Leffler A, Tyrrell L, Te Morsche RH *et al.* (2010). Alternative splicing may contribute to time-dependent manifestation of inherited erythromelalgia. Brain 133: 1823–1835.

Choi KH, Zepp ME, Higgs BW, Weickert CS, Webster MJ (2009). Expression profiles of schizophrenia susceptibility genes during human prefrontal cortical development. J Psychiatry Neurosci 34: 450–458.

Coderre TJ (1993). The role of excitatory amino acid receptors and intracellular messengers in persistent nociception after tissue injury in rats. Mol Neurobiol 7: 229–246.

Cottrell JA, Meyenhofer M, Medicherla S, Higgins L, O'Connor JP (2009). Analgesic effects of p38 kinase inhibitor treatment on bone fracture healing. Pain 142: 116–126.

Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K *et al.* (2006). An SCN9A channelopathy causes congenital inability to experience pain. Nature 444: 894–898.

Cui J, Melista E, Chazaro I, Zhang Y, Zhou X, Manolis AJ *et al.* (2005). Sequence variation of bradykinin receptors B1 and B2 and association with hypertension. J Hypertens 23: 55–62.

Danzebrink RM, Gebhart GF (1991). Evidence that spinal 5-HT1, 5-HT2 and 5-HT3 receptor subtypes modulate responses to noxious colorectal distension in the rat. Brain Res 538: 64–75.

Deseure K, Bréand S, Colpaert FC (2007). Curative-like analgesia in a neuropathic pain model: parametric analysis of the dose and the duration of treatment with a high-efficacy 5-HT(1A) receptor agonist. Eur J Pharmacol 568: 134–141.

Deval E, Gasull X, Noel J, Salinas M, Baron A, Diochot S *et al.* (2010). Acid-Sensing Ion Channels (ASICs): pharmacology and implication in pain. Pharmacol Ther [Epub ahead of print].

Devon RS, Anderson S, Teague PW, Muir WJ, Murray V, Pelosi AJ *et al.* (2001). The genomic organisation of the metabotropic glutamate receptor subtype 5 gene, and its association with schizophrenia. Mol Psychiatry 6: 311–314.

Di Resta C, Becchetti A (2010). Introduction to ion channels. Adv Exp Med Biol 674: 9–21.

Dias JP, Ismael MA, Pilon M, de Champlain J, Ferrari B, Carayon P *et al.* (2007). The kinin B1 receptor antagonist SSR240612 reverses tactile and cold allodynia in an experimental rat model of insulin resistance. Br J Pharmacol 152: 280–287.

Dominici R, Cattaneo M, Malferrari G, Archi D, Mariani C, Grimaldi LM *et al.* (2002). Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1 alpha. Immunogenetics 54: 82–86.

Dorval KM, Wigg KG, Crosbie J, Tannock R, Kennedy JL, Ickowicz A *et al.* (2007). Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. Genes Brain Behav 6: 444–452.

Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M (1998). Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. Pain 76: 27–33.

Eid SR, Cortright DN (2009). Transient receptor potential channels on sensory nerves. Handb Exp Pharmacol 194: 261–281.

Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G *et al.* (2004). A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Hum Mol Genet 13: 799–805.

Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT *et al.* (2009). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry 15: 637–646.

Erhardt A, Lucae S, Unschuld PG, Ising M, Kern N, Salyakina D *et al.* (2007). Association of polymorphisms in P2RX7 and CaMKKb with anxiety disorders. J Affect Disord 101: 159–168.

Etter J, Hoda J, Perroud N, Munafò M, Buresi C, Duret C *et al.* (2009). Association of genes coding for the alpha-4, alpha-5, beta-2 and beta-3 subunits of nicotinic receptors with cigarette smoking and nicotine dependence. Addict Behav 34: 772–775.

Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B *et al.* (2006). SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron 52: 767–774.

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

Fischer A, Grallert H, Böhme M, Gieger C, Boomgaarden I, Heid I *et al.* (2009). Association analysis between the prostaglandin E synthase 2 R298H polymorphism and body mass index in 8079 participants of the KORA study cohort. Genet Test Mol Biomarkers 13: 223–226.

Fritch PC, McNaughton-Smith G, Amato GS, Burns JF, Eargle CW, Roeloffs R *et al.* (2010). Novel KCNQ2/Q3 agonists as potential therapeutics for epilepsy and neuropathic pain. J Med Chem 53: 887–896.

Gabra BH, Berthiaume N, Sirois P, Nantel F, Battistini B (2006). The kinin system mediates hyperalgesia through the inducible bradykinin B1 receptor subtype: evidence in various experimental animal models of type 1 and type 2 diabetic neuropathy. Biol Chem 387: 127–143.

Gao B, Hierl M, Clarkin K, Juan T, Nguyen H, van der Valk M *et al.* (2010). Pharmacological effects of nonselective and subtype-selective nicotinic acetylcholine receptor agonists in animal models of persistent pain. Pain 149: 33–49.

Gharagozlou P, Demirci H, Clark JD, Lameh J (2002). Activation profiles of opioid ligands in HEK cells expressing delta opioid receptors. BMC Neurosci 3: 19.

Giordano J (1997). Antinociceptive effects of intrathecally administered 2-methylserotonin in developing rats. Brain Res Dev Brain Res 98: 142–144.

Glessner JT, Reilly MP, Kim CE, Takahashi N, Albano A, Hou C *et al.* (2010). Strong synaptic transmission impact by copy number variations in schizophrenia. Proc Natl Acad Sci U S A 107: 10584–10589.

Gohil K, Bell JR, Ramachandran J, Miljanich GP (1994). Neuroanatomical distribution of receptors for a novel voltage-sensitive calcium-channel antagonist, SNX-230 (omega-conopeptide MVIIC). Brain Res 653: 258–266.

Gonzalez-Angulo AM, Hennessy BT, Mills GB (2010). Future of personalized medicine in oncology: a systems biology approach. J Clin Oncol 28: 2777–2783.

Graham ES, Ashton JC, Glass M (2009). Cannabinoid receptors: a brief history and 'what's hot'. Front Biosci 14: 944–957.

Gribkoff VK (2008). The therapeutic potential of neuronal K V 7 (KCNQ) channel modulators: an update. Expert Opin Ther Targets 12: 565–581.

Haldeman-Englert CR, Chapman KA, Kruger H, Geiger EA, McDonald-McGinn DM, Rappaport E *et al.* (2010). A de novo 8.8-Mb deletion of 21q21.1-q21.3 in an autistic male with a complex rearrangement involving chromosomes 6, 10, and 21. Am J Med Genet A 152A: 196–202.

Hamdani N, Tabeze J, Ramoz N, Ades J, Hamon M, Sarfati Y *et al.* (2008). The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene for schizophrenia. Eur Neuropsychopharmacol 18: 34–40.

Hannon J, Hoyer D (2008). Molecular biology of 5-HT receptors. Behav Brain Res 195: 198–213.

Hefti FF, Rosenthal A, Walicke PA, Wyatt S, Vergara G, Shelton DL *et al.* (2006). Novel class of pain drugs based on antagonism of NGF. Trends Pharmacol Sci 27: 85–91.

Hilz MJ (2002). Assessment and evaluation of hereditary sensory and autonomic neuropathies with autonomic and neurophysiological examinations. 12 (Suppl. 1): I33–I43.

Hokyo A, Kanazawa T, Uenishi H, Tsutsumi A, Kawashige S, Kikuyama H *et al.* (2010). Habituation in prepulse inhibition is affected by a polymorphism on the NMDA receptor 2B subunit gene (GRIN2B). Psychiatr Genet 20: 191–198.

Hosohata Y, Varga EV, Stropova D, Li X, Knapp RJ, Hruby VJ *et al.* (2001). Mutation W284L of the human delta opioid receptor reveals agonist specific receptor conformations for G protein activation. Life Sci 68: 2233–2242.

Hoyer D, Clarke D, Fozard J, Hartig P, Martin G, Mylecharane E *et al.* (1994). International Union of Pharmacology classification of receptors for 5- hydroxytryptamine (Serotonin). Pharmacol Rev 46: 157–203.

Huang Y, Battistuzzi C, Oquendo MA, Harkavy-Friedman J, Greenhill L, Zalsman G *et al.* (2004). Human 5-HT1A receptor C(–1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol 7: 441–451.

Högestätt ED, Jönsson BA, Ermund A, Andersson DA, Björk H, Alexander JP *et al.* (2005). Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem 280: 31405–31412.

Ilyen VI, Carlin KP, Hodges DD, Robledo S, Woodward RM (2002). Flupirtine – a positive modulator of heteromeric KCNQ2/3 channels. Soc. Neurosci. Abstr. 758: 10.

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: 462–471.

Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T *et al.* (1996). Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 13: 485–488.

Jarvis MF (2010). The neural-glial purinergic receptor ensemble in chronic pain states. Trends in neurosciences 33: 48–57.

Jarvis MF, Khakh BS (2009). ATP-gated P2X cation-channels. Neuropharmacology 56: 208–215.

Ji R, Suter MR (2007). p38 MAPK, microglial signaling, and neuropathic pain. Molecular pain 3: 33.

Jordt S, Bautista DM, Chuang H, McKemy DD, Zygmunt PM, Högestätt ED *et al.* (2004). Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 427: 260–265.

Julius D, Basbaum AI (2001). Molecular mechanisms of nociception. Nature 413: 203–210.

Kamei D, Yamakawa K, Takegoshi Y, Mikami-Nakanishi M, Nakatani Y, Oh-Ishi S *et al.* (2004). Reduced pain hypersensitivity and inflammation in mice lacking microsomal prostaglandin e synthase-1. J Biol Chem 279: 33684–33695.

Karsak M, Cohen-Solal M, Freudenberg J, Ostertag A, Morieux C, Kornak U *et al.* (2005). Cannabinoid receptor type 2 gene is associated with human osteoporosis. Hum Mol Genet 14: 3389–3396.

Kennedy C (2005). P2X receptors: targets for novel analgesics? Neuroscientist 11: 345–356.

Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ *et al.* (2004). Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain 109: 488–496.

Kim H, Mittal DP, Iadarola MJ, Dionne RA (2006). Genetic predictors for acute experimental cold and heat pain sensitivity in humans. J Med Genet 43: e40.

Kobal G (1985). Pain-related electrical potentials of the human nasal mucosa elicited by chemical stimulation. Pain 22: 151–163.

Kraft B, Frickey NA, Kaufmann RM, Reif M, Frey R, Gustorff B *et al.* (2008). Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 109: 101–110.

Kranzler HR, Edenberg HJ (2010). Pharmacogenetics of alcohol and alcohol dependence treatment. Curr Pharm Des 16: 2141–2148.

Kremeyer B, Lopera F, Cox JJ, Momin A, Rugiero F, Marsh S *et al.* (2010). A Gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron 66: 671–680.

Lee J, Lee EK, Park SS, Lim J, Kim HJ, Kim JS *et al.* (2009). Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Mov Disord 24: 1803–1810.

Lee Y, Kim H, Wu T, Wang X, Dionne RA (2006). Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 79: 407–418.

Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A (1996). Trends Neurosci 19: 514–520.

Lichtman AH, Shelton CC, Advani T, Cravatt BF (2004). Mice lacking fatty acid amide hydrolase exhibit a cannabinoid receptor-mediated phenotypic hypoalgesia. Pain 109: 319–327.

Lindner I, Helwig U, Rubin D, Fischer A, Marten B, Schreiber S *et al.* (2007). Prostaglandin E synthase 2 (PTGES2) Arg298His polymorphism and parameters of the metabolic syndrome. Mol Nutr Food Res 51: 1447–1451.

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

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

Lötsch J, Geisslinger G (2010). A critical appraisal of human genotyping for pain therapy. Trends Pharmacol Sci 31: 312–317.

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

Lötsch J, Klepstad P, Doehring A, Dale O (2009b). A GTP cyclohydrolase 1 genetic variant delays cancer pain. Pain.

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

Mallet C, Daulhac L, Bonnefont J, Ledent C, Etienne M, Chapuy E *et al.* (2008). Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. Pain 139: 190–200.

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 Neurol 9: 413–424.

Marceau F, Hess JF, Bachvarov DR (1998). The B1 Receptors for Kinins. Pharmacol Rev 50: 357–386.

Marchand F, Jones NG, McMahon SB (2009). Future treatment strategies for neuropathic pain. Handb Exp Pharmacol 194: 589–615.

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: 2806–2812.

Marubio LM, del Mar Arroyo-Jimenez M, Cordero-Erausquin M, Léna C, Le Novère N, de Kerchove d'Exaerde A *et al.* (1999). Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. Nature 398: 805–810.

McKemy DD, Neuhausser WM, Julius D (2002). Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 416: 52–58.

Mathie A (2010). Ion channels as novel therapeutic targets in the treatment of pain. J Pharm Pharmacol 62: 1089–1095.

Mignat C, Wille U, Ziegler A (1995). Affinity profiles of morphine, codeine, dihydrocodeine and their glucuronides at opioid receptor subtypes. Life Sci 56: 793–799.

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: 271–276.

Miura Y, Mardy S, Awaya Y, Nihei K, Endo F, Matsuda I *et al.* (2000). Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. Hum Genet 106: 116–124.

Mogil JS (2009). Are we getting anywhere in human pain genetics? Pain 146: 231–232.

Mogil JS, Ritchie J, Smith SB, Strasburg K, Kaplan L, Wallace MR *et al.* (2005). Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. J Med Genet 42: 583–587.

Montell C (2005). Drosophila TRP channels. Pflugers Arch 451: 19–28.

Moskvina V, Craddock N, Holmans P, Nikolov I, Pahwa JS, Green E *et al.* (2009). Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. Mol Psychiatry 14: 252–260.

Mrazek F, Gallo J, Stahelova A, Petrek M (2010). Functional variants of the P2RX7 gene, aseptic osteolysis, and revision of the total hip arthroplasty: a preliminary study. Hum Immunol 71: 201–205.

Nadeson R, Goodchild CS (2002). Antinociceptive role of 5-HT1A receptors in rat spinal cord. Br J Anaesth 88: 679–684.

Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain 105: 79–88.

Nagy G, Ronai Z, Somogyi A, Sasvari-Szekely M, Rahman OA, Mate A *et al.* (2008). P2RX7 Gln460Arg polymorphism is associated with depression among diabetic patients. Prog Neuropsychopharmacol Biol Psychiatry 32: 1884–1888.

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

Nitz I, Fisher E, Grallert H, Li Y, Gieger C, Rubin D *et al.* (2007). Association of prostaglandin E synthase 2 (PTGES2) Arg298His polymorphism with type 2 diabetes in two German study populations. J Clin Endocrinol Metab 92: 3183–3188.

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: 3041–3049.

North RA (2003). P2X3 receptors and peripheral pain mechanisms. J Physiol 554: 301–308.

Novakova-Tousova K, Vyklicky L, Susankova K, Benedikt J, Samad A, Teisinger J *et al.* (2007). Functional changes in the vanilloid receptor subtype 1 channel during and after acute desensitization. Neuroscience 149: 144–154.

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

Olivera BM (2006). Conus peptides: biodiversity-based discovery and exogenomics. J Biol Chem 281: 31173–31177.

Pankratov Y, Lalo U, Krishtal O, Verkhratsky A (2003). P2X receptor-mediated excitatory synaptic currents in somatosensory cortex. Mol Cell Neurosci 24: 842–849.

Papp I, Szucs P, Holló K, Erdélyi F, Szabó G, Antal M (2006). Hyperpolarization-activated and cyclic nucleotide-gated cation channel subunit 2 ion channels modulate synaptic transmission from nociceptive primary afferents containing substance P to secondary sensory neurons in laminae I-IIo of the rodent spinal dorsa. Eur J Neurosci 24: 1341–1352.

Park JJ, Lee J, Kim MA, Back SK, Hong SK, Na HS (2007). Induction of total insensitivity to capsaicin and hypersensitivity to garlic extract in human by decreased expression of TRPV1. Neurosci Lett 411: 87–91.

Passmore GM, Selyanko AA, Mistry M, Al-Qatari M, Marsh SJ, Matthews EA *et al.* (2003). KCNQ/M currents in sensory neurons: significance for pain therapy. J Neurosci 23: 7227–7236.

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

Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM *et al.* (2002). A TRP channel that senses cold stimuli and menthol. Cell 108: 705–715.

Perret D, Luo ZD (2009). Targeting voltage-gated calcium channels for neuropathic pain management. Neurotherapeutics 6: 679–692.

Petersen KL, Rowbotham MC (1999). A new human experimental pain model: the heat/capsaicin sensitization model. Neuroreport 10: 1511–1516.

Petrenko AB, Yamakura T, Baba H, Shimoji K (2003). The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg 97: 1108–1116.

Pociot F, Molvig J, Wogensen L, Worsaae H, Nerup J (1992). A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion *in vitro*. Eur J Clin Invest 22: 396–402.

Proudnikov D, Kroslak T, Sipe JC, Randesi M, Li D, Hamon S *et al.* (2010). Association of polymorphisms of the cannabinoid receptor (CNR1) and fatty acid amide hydrolase (FAAH) genes with heroin addiction: impact of long repeats of CNR1. Pharmacogenomics J 10: 232–242.

Pucadyil TJ, Kalipatnapu S, Chattopadhyay A (2005). The serotonin1A receptor: a representative member of the serotonin receptor family. Cell Mol Neurobiol 25: 553–580.

de Quervain DJ, Papassotiropoulos A (2006). Identification of a genetic cluster influencing memory performance and hippocampal activity in humans. Proc Natl Acad Sci U S A 103: 4270–4274.

Rau KK, Johnson RD, Cooper BY (2005). Nicotinic AChR in subclassified capsaicin-sensitive and -insensitive nociceptors of the rat DRG. J Neurophysiol 93: 1358–1371.

Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP *et al.* (2010). Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A 107: 5148–5153.

Roberts JD, Gennings C, Shih M (2006). Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. Eur J Pharmacol 530: 54–58.

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

Roe BE, Tilley MR, Gu HH, Beversdorf DQ, Sadee W, Haab TC *et al.* (2009). Financial and psychological risk attitudes associated with two single nucleotide polymorphisms in the nicotine receptor (CHRNA4) gene. PloS ONE 4: e6704.

Rowbotham MC, Duan WR, Thomas J, Nothaft W, Backonja M (2009). A randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of ABT-594 in patients with diabetic peripheral neuropathic pain. Pain 146: 245–252.

Russo P, Strazzullo P, Cappuccio FP, Tregouet DA, Lauria F, Loguercio M *et al.* (2007). Genetic variations at the endocannabinoid type 1 receptor gene (CNR1) are associated with obesity phenotypes in men. J Clin Endocrinol Metab 92: 2382–2386.

Rörsch F, Wobst I, Zettl H, Schubert-Zsilavecz M, Grösch S, Geisslinger G *et al.* (2010). Nonacidic inhibitors of human microsomal prostaglandin synthase 1 (mPGES 1) identified by a multistep virtual screening protocol. J Med Chem 53: 911–915.

Sabatelli M, Eusebi F, Al-Chalabi A, Conte A, Madia F, Luigetti M *et al.* (2009). Rare missense variants of neuronal nicotinic acetylcholine receptor altering receptor function are associated with sporadic amyotrophic lateral sclerosis. Hum Mol Genet 18: 3997–4006.

Samuels ME, te Morsche RH, Lynch ME, Drenth JP (2008). Compound heterozygosity in sodium channel Nav1.7 in a family with hereditary erythermalgia. Mol Pain 4: 21.

Schmidtko A, Lötsch J, Freynhagen R, Geisslinger G (2010). Ziconotide for treatment of severe chronic pain. Lancet 375: 1569–1577.

Schroeder BC, Kubisch C, Stein V, Jentsch TJ (1998). Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K+ channels causes epilepsy. Nature 396: 687–690.

Shatzky S, Moses S, Levy J, Pinsk V, Hershkovitz E, Herzog L *et al.* (2000). Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies. Am J Med Genet 92: 353–360.

Shim S, Hwangbo Y, Kwon Y, Jeong H, Lee B, Hwang J *et al.* (2010). A case-control association study of serotonin 1A receptor gene and tryptophan hydroxylase 2 gene in attention deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry 34: 974–979.

Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R *et al.* (1998). A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat Genet 18: 25–29.

Sipe JC, Arbour N, Gerber A, Beutler E (2005). Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: possible risk for autoimmune disorders. J Leukoc Biol 78: 231–238.

Smeyne RJ, Klein R, Schnapp A, Long LK, Bryant S, Lewin A *et al.* (1994). Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature 368: 246–249.

Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimaki H (2004). Possible association of interleukin 1 gene locus polymorphisms with low back pain. Pain 109: 8–19.

Steenland HW, Ko SW, Wu LJ, Zhuo M (2006). Hot receptors in the brain. Mol Pain 2: 34.

Steinlein OK, Bertrand D (2010). Nicotinic receptor channelopathies and epilepsy. Pflugers Arch 460: 495–503.

Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR *et al.* (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112: 819–829.

Su Y, McNutt RW, Chang K (1998). Delta-opioid ligands reverse Alfentanil-induced respiratory depression but not antinociception. J Pharmacol Exp Ther 287: 815–823.

Swanson CJ, Bures M, Johnson MP, Linden A, Monn JA, Schoepp DD (2005). Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 4: 131–144.

Swayne LA, Bourinet E (2008). Voltage-gated calcium channels in chronic pain: emerging role of alternative splicing. Pflugers Arch 456: 459–466.

Tazón-Vega B, Vilardell M, Pérez-Oller L, Ars E, Ruiz P, Devuyst O *et al.* (2007). Study of candidate genes affecting the progression of renal disease in autosomal dominant polycystic kidney disease type 1. Nephrol Dial Transplant 22: 1567–1577.

Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H *et al.* (2006). GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 12: 1269–1277.

Tsai S, Liu H, Liu T, Cheng C, Hong C (2002). Association analysis for genetic variants of the NMDA receptor 2b subunit (GRIN2B) and Parkinson's disease. J Neural Transm 109: 483–488.

Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW *et al.* (2003). P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature 424: 778–783.

Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M *et al.* (2002). CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. Mol Psychiatry 7: 515–518.

Vanegas H, Schaible HG (2001). Prostaglandins and cyclooxygenases [correction of cycloxygenases] in the spinal cord. Prog Neurobiol 64: 327–363.

Vincler M (2005). Neuronal nicotinic receptors as targets for novel analgesics. Expert Opin Investig Drugs 14: 1191–1198.

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

Wang T, Yu D, Lamb ML (2009). Trk kinase inhibitors as new treatments for cancer and pain. Expert Opin Ther Pat 19: 305–319.

Wilson RI, Nicoll RA (2002). Endocannabinoid signaling in the brain. Science 296: 678–682.

Wolf R, Koch T, Schulz S, Klutzny M, Schroder H, Raulf E *et al.* (1999). Replacement of threonine 394 by alanine facilitates internalization and resensitization of the rat mu opioid receptor. Mol Pharmacol 55: 263–268.

Wua Y, Dworetzky SI (2005). Recent developments on KCNQ potassium channel openers. Curr Med Chem 12: 453–460.

Xu W, Qiu XC, Han JS (1994). Serotonin receptor subtypes in spinal antinociception in the rat. J Pharmacol Exp Ther 269: 1182–1189.

Zamponi GW, Lewis RJ, Todorovic SM, Arneric SP, Snutch TP (2009). Role of voltage-gated calcium channels in ascending pain pathways. Brain Res Brain Res Rev 60: 84–89.

Zhang H, Kranzler HR, Yang B, Luo X, Gelernter J (2008). The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. Mol Psychiatry 13: 531–543.

Zhang H, Gelernter J, Gruen JR, Kranzler HR, Herman AI, Simen AA (2010). Functional impact of a single-nucleotide polymorphism in the OPRD1 promoter region. J Hum Genet 55: 278–284.

Zhang P, Ishiguro H, Ohtsuki T, Hess J, Carillo F, Walther D *et al.* (2004). Human cannabinoid receptor 1: 5′ exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. Mol Psychiatry 9: 916–931.

Zuo L, Kranzler HR, Luo X, Covault J, Gelernter J (2007). CNR1 variation modulates risk for drug and alcohol dependence. Biol Psychiatry 62: 616–626.