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Current evidence for a modulation of low back pain by human genetic variants

Irmgard Tegeder *, Jörn Lötsch

pharmazentrum Frankfurt/ZAFES, Klinikum der Goethe-Universität Frankfurt am Main, Theodor-Stern-Kai, Frankfurt am Main, Germany

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Abstract

The manifestation of chronic back pain depends on structural, psychosocial, occupational and genetic influences. Heritability estimates for back pain range from 30% to 45%. Genetic influences are caused by genes affecting intervertebral disc degeneration or the immune response and genes involved in pain perception, signalling and psychological processing. This inter-individual variability which is partly due to genetic differences would require an individualized pain management to prevent the transition from acute to chronic back pain or improve the outcome. The genetic profile may help to define patients at high risk for chronic pain. We summarize genetic factors that (*i*) impact on intervertebral disc stability, namely Collagen IX, *COL9A3*, *COL11A1*, *COL11A2*, *COL1A1*, *aggrecan (AGAN)*, cartilage intermediate layer protein, vitamin D receptor, metalloproteinsase-3 (*MMP3*), *MMP9*, and thrombospondin-2, (*ii*) modify inflammation, namely interleukin-1 (IL-1) locus genes and IL-6 and (*iii*) and pain signalling namely guanine triphosphate (GTP) cyclohydrolase 1, catechol-O-methyltransferase, μ opioid receptor (*OPMR1*), melanocortin 1 receptor (*MC1R*), transient receptor potential channel A1 and fatty acid amide hydrolase and analgesic drug metabolism (cytochrome P450 [CYP]2D6, CYP2C9).

Keywords: back pain • intervertebral disc • neuropathic pain • polymorphism • analgesics • extracellular matrix

Introduction

The manifestation of back pain is contributed by structural, psychosocial and occupational influences [1]. Biochemical and inflammatory factors contribute to the transition of acute towards chronic pain and genetic factors may modulate any of these factors. Research has been mainly focused on genes that determine bone and cartilage structure and are accompanied by morphological signs in magnetic resonance imaging (MRI). Genetic associations were found for disc height narrowing and different definitions of back pain, such as duration of the worst back pain episode and hospitalization for back problems [2]. The heritability estimates for these back pain variables ranged from 30% to 45% [2].

However, only a minority of the genetic influences was caused by genes affecting disc degeneration suggesting that genes involved in pain perception, signalling and psychological processing [3] and genetic variants of immune genes [4] contribute to the proportion of heritability of chronic back pain. Individuals vary widely in their sensation and experience of pain [5, 6] and the risk of developing chronic back pain. This inter-individual variability which is partly due to genetic differences in pain signalling molecules would require an individualized pain management which is hampered by the still limited pharmacological treatment options. The genetic variability in the pharmacodynamic and kinetic effects of analgesic agents further contribute to the variable risk of developing chronic back pain because it may interfere with treatment strategies or cause unexpected drug toxicity. In this review, we will summarize genetic factors that specifically modify intervertebral

*Correspondence to: Irmgard TEGEDER, M.D.,
Pharmazentrum Frankfurt/ZAFES, Institut für Klinische Pharmakologie,
Universitätsklinikum Frankfurt am Main, Theodor-Stern-Kai 7,
D-60590 Frankfurt am Main, Germany.
Tel.: +49-69-6301-7621; Fax: +49-69-6301-7636
E-mail: Tegeder@em.uni-frankfurt.de

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disc stability, pain signalling and analgesic drug metabolism that may independently impact on the risk of developing chronic back pain.

Genetic polymorphisms associated with intervertebral disc disease (IDD)

IDD is characterized by disc degeneration and herniation and is often associated with low back pain and lumbar radicular pain due to nerve root compression or inflammation. Sensory neurons and sensory fibres from multiple spinal cord levels innervate intervertebral discs [7] explaining the often widespread back pain. An increased risk of low back pain was found in relation to all signs of disc degeneration [8, 9]. However, morphological signs alone are of limited predictive value for chronic back pain. Genetic variants of the genes encoding molecules of extracellular matrix proteins and other structural proteins have been associated with MRI correlates of degenerative disc disease [10–15] and with chronic low back pain with lumbar radicular pain [16–18]. Collagen is a major component of the extracellular matrix and regulates cartilage fibril formation within intervertebral discs. It is a heterotrimeric protein consisting of three α-chains. Polymorphisms in the gene coding for the α_2 and α_3 chains of collagen IX, *COL9A2* and *COL9A3* were associated with alterations in the mechanical properties of human intervertebral discs and contribute to the susceptibility for lumbar disc herniation and back pain [10, 16, 17, 19–21]. Several IDD associated *COL9A2* alleles were identified. The so called Trp2 allele representing a Gln326Trp amino acid exchange in the α_2 chain was associated with premature disc degeneration and back pain in Finnish, Japanese and Chinese populations [11, 16, 17, 19]. The Trp2 variant however, was not detected in Germans [20] or Greek [18] but a high relapse rate of lumbar disc disease after surgery was detected in carriers of the Gln326Arg variant of collagen IX (*COL9A2*) [20]. The *COL9A3* variant associated with lumbar disc disease is also characterized by an amino acid exchange from arginine to tryptophan, the so-called Trp3 variant [10, 13, 14], suggesting that the variant tryptophan as the most hydrophobic amino acid in either the α_2 or α_3 chain of collagen IX disrupts the collagen IX triple helix or the assembly with type XI and II collagens. In addition to the Trp2 allele, a splice site mutation of *COL9A2* was detected in a patient with lumbar disc stenosis leading to the generation of a truncated protein [22]. Presumably the variants reduce the stability of cartilage collagen and thereby increase the risk of disintegration of the extracellular matrix resulting in disc degeneration and herniation. However, the exact functional consequences are still unknown.

Type X1 collagen is expressed in the annulus fibrosus and nucleus pulposus. It is a minor component of human cartilage but important for the formation of cartilage collagen. It is composed of three α-chains, α_1(XI), α_2(XI) and α_3(II), which are encoded by *COL11A1*, *COL11A2* and *COL2A1*, respectively. The three chains fold into triple-helical heterotrimers to form procollagen, which is secreted into the extracellular matrix, where it participates in fibril formation with the other cartilage-specific collagens, type II and IX collagens. Type XI collagen regulates the diameter of cartilage collagen fibrils by limiting further apposition. Genetic variants in *COL11A1* were associated with an increased risk of lumbar disc herniation in a Japanese cohort [23]. A single nucleotide polymorphism (c.4603C>T) in the coding region of *COL11A1* showed the strongest association with disc herniation. The transcript of the disease-associated T allele had reduced stability and the expression level was inversely correlated with the severity of disc degeneration [23]. In a Finnish population, carriers of the A allele of a deletion splice site variant of *COL11A2* (IVS6-4A/- or A/T) encoding the α_2(XI) chain had a lower risk for degenerative spinal stenosis with radicular pain than carriers of the T allele (T/- or T/T) [22]. Exon 6 and exon 8 were skipped in the presence of the T allele [22] but functional consequences have not been analysed.

Carriers of the Sp1 variant of the α_1 chain of type one collagen (*COLI1A1*) were at risk of developing lumbar disc degeneration [24] and have bone mineral density with osteoporotic bone fractures particularly in postmenopausal women [24–28]. The Sp1 variant is a promoter polymorphism (−1997 G/T) of *COL1A1* that interferes with the binding of the transcription factor Sp1. As a result, COL1A1 expression is reduced in carriers of this variant [29, 30]. This polymorphism was most frequently linked with reductions of bone mineral density and osteoporosis [24, 29–32] that represents a major cause of chronic low back pain [33]. Polymorphisms of various other genes such as transforming growth factor-β (TGF-β) [34, 35], oestrogen receptor [36], the vitamin D receptor [37, 38] and the low density lipoprotein genes *LRP5* and *LRP6* [39, 40] contribute to the pathogenesis of osteoporosis and may therefore also contribute to the development of back pain. Polymorphisms affecting bone mineral density have been summarized in, *e.g.* [41, 42].

IDD was also associated with 'variable number of tandem repeat' (VNTR) polymorphisms in the coding region of the human aggrecan gene (*AGAN)* [43]. Thirteen different alleles have been identified, with repeat numbers ranging from 13 to 33. This polymorphism is apparently restricted to human beings, of several species examined. The polymorphism results in individuals with differing length aggrecan core proteins, bearing different numbers of potential attachment sites for chondroitin sulphate. Magnetic resonance imaging (MRI) in healthy volunteers revealed the association of *ACAN* polymorphisms with MRI signs of IDD [43]. A study in young Japanese women who presented to the orthopaedic department for low back pain MRI scans revealed that multilevel and severe disc degeneration was present in the patients with shorter VNTR length of the aggrecan gene whereas >25 repeats had protective effects [44]. The core aggrecan protein accounts for the tight collagen fibril network of the discs and short variants may affect the resistance to compressive loads predisposing to disc degeneration at an early age [44].

Variants of the gene coding for the cartilage intermediate layer protein (CILP) [12, 45] were recently reported to affect the extracellular matrix of joint cartilage [46]. In a case–control study a functional single nucleotide polymorphism (SNP) in exon 8 of *CILP* (T1184C) was shown to be associated with intervertebral

disc degeneration [45]. CILP was expressed abundantly in intervertebral discs, and its expression increased during progression of disc degeneration. CILP colocalized with TGF-β_1 in clustering chondrocytes and directly inhibited both the TGF-β_1 mediated induction of cartilage matrix genes and the inhibition of metalloproteinase transcription. The aberrantly increased inhibitory effects of CILP attributed to the susceptible allele probably perturb the balance of TGF-β control over chondrocyte metabolism and intervertebral disc tissue maintenance, leading to an increased susceptibility to lumbar disc disease because intervertebral disc cells respond inadequately to injury and mechanical stress.

A single adenine insertion/deletion polymorphism (6A/5A) in the metalloproteinsase-3 (*MMP3* 11716A>5A) promoter region was associated with modic changes in endplates of lumbar vertebral bodies in MRI scans in Finnish male workers, particularly if carriers of the *MMP3* variant had additional polymorphisms in interleukin-1 (IL-1) locus genes [47]. In a cohort of Japanese middle-aged women *MMP3* genotypes with at least one 5-adenine allele (5A5A and 5A6A) were associated with degenerative changes in lumbar intervertebral discs [48]. The mechanism of this association has been suggested by *in vitro* studies of promoter activity. The 5A promoter had higher activity compared to that of the 6A allele in both cultured fibroblasts and vascular smooth muscle cells. Thus, persons with the 'slow-promoter' 6A6A genotype would be predicted to have lower expression and activity of *MMP3*. However, the higher transcriptional activity associated with the 5A allele required an inflammatory stimulus not occurring during basal conditions suggesting that additional predisposing factors will enhance the impact of this variant. As MMP-3 was recently found to play a major role in the inflammatory response in the spinal cord following peripheral nerve injury and to contribute to the development of neuropathic pain [49] this variant may additionally increase the susceptibility to radicular sciatic pain in addition to low back pain.

In addition to *MMP3*, a single missense polymorphism in metallaoproteinase-9 (*MMP9*) causing a change from glutamine to arginine at position 279 in MMP-9 protein was strongly associated with lumbar disc herniation in two independent Japanese cohorts [50]. This polymorphism showed a combinatorial effect with an intronic variant of the thrombospondin-2 gene (*THBS2*: IVS10–8C>T) that itself was also significantly associated with lumbar disc herniation. This *THBS2*-SNP is located in a polypyrimidine tract upstream of the 3′ splice site of intron 10 and exerts allelic differences on exon 11 skipping rates in vivo, with increased skipping in the variant allele. Skipping of exon 11 results in decreased thrombospondin-2 interaction with *MMP2* and *MMP9* [50] probably increasing the activity of these MMPs. *MMP9* also plays a major role in the manifestation of neuropathic pain following nerve injury [49] suggesting that variants in thrombospondin and *MMP9* may also increase the risk of chronic pain in carriers of these variants.

Carriers of some variants of the vitamin D receptor gene may also be at a higher risk for IDD and osteoporosis. A common C to T polymorphism in exon 2 of the vitamin D receptor gene (*VDR*) introduces a new translation start site and in a protein that differs in length by three amino acids and was identified with the restriction enzyme FokI. Some studies suggest that the longer variant is correlated with lower bone mineral density in some populations [37] and lumbar disc degeneration [15, 51, 52]. A further 'restriction site' variant was identified with the enzyme Taq1 [53]. It was also associated with lumbar disc disease [53].

As extracellular matrix protein polymorphisms increase the susceptibility to degeneration of discs and/or bone of the spine they may increase the risk for chronic back pain. However, these genetic variants do not directly affect pain sensation or signalling or adaptations of peripheral and central pain circuits. A prospective trial in a cohort of 100 patients with structural and psychosocial risk factors revealed that the development of serious disability due to low back pain was strongly predicted by baseline psychosocial variables but only weakly by baseline structural MRI variables suggesting that the degree of structural changes does not allow to predict the intensity and frequency of low back pain [54]. The risk conferred by genetic variants of extracellular matrix (ECM) genes is further contributed by the risk conferred by inflammatory and pain signalling genes discussed below.

Polymorphisms in pro-inflammatory genes

Inflammation plays a major role in the development of IDD [55]. The extent and resolution of inflammation is modified by genetic variants in cytokine genes. Particularly, polymorphisms in the IL-1 gene locus were suspected to contribute to the development of low back pain because single nucleotide variants of IL-1α (*IL1A*), IL-1β (*IL1B*) and IL-1 receptor antagonist (*IL1RN*) modify bone mineral density [56] and promote IDD [14, 57]. Herniated discs produce several inflammatory mediators such as IL-1, IL-6 and tumour necrosis factor-α (TNF-α) which maintain the inflammatory process and sensitize nociceptors that innervate the affected discs or the surrounding tissue [58, 59]. In a Finnish study in middle-aged men carriers of the IL-1 receptor antagonist G1821>A allele had an increased risk of low back pain [4]. In addition, carriers of this allele in combination with the *IL1A* C889>T allele or *IL1B* C3954>T variant had a higher risk of developing low back pain than non-carriers, and reported more days with pain and higher intensities of low back pain [4]. The results suggest that IL-1 gene locus polymorphisms promote or prolong low back pain, supported by a recent study that evaluated MRI changes in endplates of lumbar vertebral bodies and their association with chronic low back and sciatic pain [60]. Vertebral endplate changes in MRI, so called modic changes, were interpreted as a morphological marker for inflammatory degenerative IDD. Affected sites showed an enhanced number of sensory nerve fibres and TNF-expressing immune cells explaining the associated back pain syndrome [61]. Out of various pro-inflammatory genes combined polymorphisms in *IL1A* and the 5-adenine promoter polymorphism of metalloproteinase-3 were associated with such modic changes [47]. In addition

to *IL1*, polymorphisms in the *IL6* gene were associated with IDD in patients with discogenic lumbar radicular pain [62]. The *IL6* promoter variations G-597A and G-174C and the T15A polymorphism in exon 5 were increased in Finnish patients with IDD, compared with non-affected controls [62]. Several other pro-inflammatory gene polymorphisms including variants of *IL2*, *TNF*α, *IL4* and interferon-γ were evaluated in this study but had almost identical allele frequencies in low back pain patients and controls [62]. The *IL6* promoter polymorphisms increase the transcription and secretion of *IL6*. This will probably enhance the inflammatory response or interfere with the resolution of inflammation.

Polymorphisms in the *PTGS2* gene coding for cyclooxygenase 2 may modulate the development of inflammation as well as the response to treatment with inhibitors of cyclooxygenases. This has been proposed for the *PTGS* -765G>C SNP, which was reported to be associated with a more than twofold decrease in COX-2 expression [63]. By altering a putative Sp1 binding site [64], the *PTGS2* gene variant decreased the promoter activity by 30% [65] and resulted in a net decrease in COX-2 function, quantified by prostaglandin E2 production from peripheral blood monocytes after stimulation with bacterial LPS [63]. This polymorphism was found to cause a failure of rofecoxib analgesia in carriers of the -765C variant allele [66]. However, neither the -765G>C associated lower COX-2 expression nor reduced effect of COX-2 inhibitors were reproduced in a subsequent study in healthy volunteers having received celecoxib [67].

Polymorphisms associated with subtle modulations of pain sensitivity

MRI signs of bone and cartilage structure are weakly predictive for chronic back pain suggesting that genetic variants in genes modifying pain sensation and signalling also contribute to the relative high heritability estimates for chronic back pain. Only recently it has been increasingly recognized that some frequent genetic polymorphisms are associated with modulations of pain sensitivity or the development of hyperalgesia. These frequent polymorphisms are not the cause of serious diseases but may change the risk for chronic pain including chronic back pain. Associations between candidate genes and chronic back pain and lumbar root pain were evaluated in patients following lumbar disc surgery to remove herniated discs [68]. The patients suffered from serious long lasting back and sciatic pain before surgery. In the first 2 years after surgery pain scores for frequency and intensity at rest and during walking were recorded every 3 months. The statistical analysis revealed that patients with a defined set of single nucleotide polymorphisms in the gene of the GTP cyclohydrolase 1 (*GCH1*) had consistently less pain than non-carriers and a significantly better outcome after surgery [68]. The polymorphisms in *GCH1* that were associated with reduced pain constitute a certain haplotype, referred to as 'pain-protective' haplotype of *GCH1*, with a frequency of about 16% in the Caucasian population. The GTP cyclohydrolase is the rate-limiting enzyme in the synthesis of the enzyme cofactor, tetrahydrobiopterin which is essential for the production of biogenic amines, namely noradrenaline, dopamine and serotonin [69] and the synthesis of nitric oxide [70]. It has been confirmed in further studies that the 'pain-protective' haplotype is associated with a reduction of the sensitivity to mechanical and heat stimulation and particularly the development of inflammatory hyperalgesia [71]. Functionally, this haplotype prevents the up-regulation of *GCH1* and overproduction of tetrahydrobiopterin that normally occurs upon pro-inflammatory stimulation or peripheral nerve injury. Subsequently, the overproduction of the downstream products, particularly nitric oxide, is also prevented [68]. Nitric oxide has long been considered as a pain mediator because it contributes to the manifestation of neuronal hyperexcitability upon ongoing nociceptive stimulation [72, 73].

Other genetic polymorphisms have been associated with reduced pain sensitivity [74] but most studies did not specifically address chronic back pain. However, it appears reasonable to hypothesize that polymorphisms that modulate other types of chronic pain may also impact on the liability of developing chronic back pain. Such pain-modulating gene variants were found for catechol-O-methyltransferase (*COMT*), transient receptor potential channel A1 (*TRPA1*), melanocortin-1 receptor (*MC1R*), fatty acid amide hydrolase (*FAAH*) and the μ-opioid receptor (*OPRM1*). COMT modulates specific aspects of human pain perception and the risk for developing complex pain conditions including migraine [75]. COMT metabolizes catecholamines and modifies thereby the transmission of dopaminergic, adrenergic and noradrenergic pathways in the brain. Noradrenaline and serotonin are mediators in inhibitory pain pathways originating in the brainstem [76, 77] but also neurotransmitters in excitatory tracts and peripheral nociceptive neurons [78, 79]. A single nucleotide exchange in the coding region of *COMT* leads to an amino acid substitution of valine to methionine at position 158 (V158M), with impaired translation of *COMT* mRNA, reduction of its enzyme activity and reduced thermostability [75]. The V158M genotype was primarily associated with the rate of temporal summation of heat pain [75]. Other SNPs of *COMT* exert a greater influence on baseline nociceptive sensitivity and are inversely correlated with enzyme activity and the risk of developing myogenous temporomandibular joint disorder (TMD) [80]. TMD is a common musculoskeletal pain condition with a prevalence of about 10% and 3:1 female to male ratio and is often associated with chronic back pain [81, 82]. Genetic factors are likely to contribute to the development of TMD such as *COMT*, *MC1R* and *OPRM1* [81, 82]. Interestingly, patients carrying the V158M variant of *COMT* show an up-regulation of opioid receptor expression [83]. This may be due to a compensatory mechanism. It was proposed that the V158M polymorphism indirectly regulates μ-opioid receptor function [84] because carriers of this variant showed increased sensitivity to analgesic effects of morphine [85, 86] presumably because of the receptor up-regulation. However, the exact link between COMT and opioid receptors is still elusive.

Variants of the *MC1R* gene were reported to reduce pain sensitivity [87] although a reproduction of this single finding, which paralleled a similar finding in mice [87], was not reproduced in

another human cohort [88]. Nevertheless, in volunteers with a red hair, fair skin phenotype, which is the visible phenotype associated with non-function variants in the *MC1R* gene, the analgesic efficacy of μ-opioid agonists, namely of the active morphine metabolite, morphine-6-glucuronide, was increased in men and women as well as in a respective mouse model as compared to carriers of functional MC1R [87]. In contrast to μ-opioid agonists, κ-opioid agonists, namely pentazocine, showed a sex-specific increased analgesic activity in female carriers of non-functional MC1R but not in males [89].

These studies verify that pain modulation in the two sexes involves neurochemically distinct substrates. Interestingly, female but not male carriers of a genetic variant of the cold receptor, TRPA1 had increased sensitivity to cold-induced pain compared to carriers of the wild-type allele [90]. TRPA1 is mainly activated by noxious cold, chemical and endogenous irritants such as formalin [91–93], bradykinin [94] and 4-hydroxynonenal [95]. It is also a sensor for oxidative stress [96]. The genetic variant *TRPA1* I585V leads to an amino acid substitution from isoleucin to valin. The functional consequence is unknown.

The sensitivity to pain and to opioid analgesia and side effects is known to be modulated by variants in opioid receptors [97]. The μ-opioid receptor, encoded by the *OPRM1* gene (*OPRM1*), is the primary site of action of endogenous and of the most potent exogenous common clinical opioid analgesics such as morphine, fentanyl or methadone. A large number of polymorphisms have been identified in the promoter region, in exons and introns of *OPRM1* [97, 98]. So far, most information has been accumulated about the *OPRM1* 118A>G SNP in exon 1 leading to an amino acid substitution from asparagine to aspartate at position 40 of the protein thereby deleting a putative extracellular glycosylation site. This SNP is highly prevalent in the population with an allele frequency of approximately 16% in Caucasians. At the molecular level, it is thought to either decrease μ-opioid receptor expression [99] or, in a brain-region specific manner, agonist-stimulated receptor signalling [100]. With respect to pain sensitivity, carriers of this variant displayed higher pain thresholds [101] or lower cortical responses to experimental pain stimuli [102]. This fits to neither of the above-mentioned molecular mechanisms and is best explained with an earlier molecular finding of increased binding affinity of β-endorphin at the variant μ-opioid receptors [103], which, however, had not been reproduced [104, 105]. With respect to pain treatment with exogenous opioids, the 118A>G SNP significantly reduced the potency of morphine-6-glucuronide [106, 107], morphine [107] or levomethadone [108] in experimental studies in healthy volunteers that evaluated pupil constrictory effects of the opioids [106]. The *OPRM1* 118A>G polymorphism reduced both analgesic [74, 109] and respiratory depressive [109] effects of alfentanil suggesting that the efficacy of various μ-opioid receptor agonists is affected by this variant. Moreover, two to four times greater alfentanil requirements to achieve the same degree of analgesia in homozygous carriers as compared to wild-type patients was accompanied by 10–12 times greater dose requirements to achieve the same degree of respiratory depression suggesting that the *OPRM1* 118G variant somewhat protects against opioid induced side effects [109], as previously already proposed for morphine-6-glucuronide [110]. However, this might not be the case in heterozygous carriers, in whom in two independent studies an increased therapeutic range, analgesia *versus* respiratory depression, was not observed [109, 111]. In the clinical setting, carriers of the *OPRM1* 118A>G polymorphism required significantly higher doses of morphine in the early post-operative period following knee surgery [112], abdominal hysterectomy [113] or other major abdominal surgical interventions [114]. Cancer patients homozygous for the 118 G allele also needed higher morphine doses to achieve pain control [115], further modulated when these patients had the wild-type COMT Val/Val genotype [86] or the wild-type *ABCB1* (P-glycoprotein) 3435C allele of the 3435C>T SNP of this transporter gene [116]. Thus, except for a single opposite report [117] the *OPRM1* 118A>G polymorphism appears to be well established as a functional variant decreasing the effects of exogenous opioids and possibly also moderately decreasing pain sensitivity.

A single experimental pain study reported a weak association between heat and cold pain sensitivity and genetic variants of the δ-opioid receptor gene (*OPRD1*) in male but not female healthy individuals [118]. However, mostly δ-opioid receptor gene polymorphisms were associated with substance dependence [119] or psychiatric disorders [120].

Endogenous cannabinoids (CBs), cannabis and its congeners reduce pain and modify emotional components of pain through agonistic action at peripheral and central CB-1 receptors [121, 122]. CBs additionally modify the immune response through CB-2 receptors. The immune modulation by CBs ameliorates inflammatory processes including neuro-immune responses that contribute to the manifestation and chronicity of neuropathic pain [123, 124]. Tetrahydrocannabinol, one of the constituents of marihuana has the potential to reduce serious neuropathic pain in patients with multiple sclerosis or other neuropathic pain syndromes [125]. However, polymorphisms in the CB-1 gene *CNR1* have not been associated with specific pain phenotypes, but were found to be associated with obesity [126, 127], schizophrenia or efficacy of neuroleptic treatment [128, 129] and drug and alcohol dependence [130–132]. Polymorphisms in the CB-2 gene *CNR2* play a role in osteoporosis [133] and thereby possibly chronic back pain that is often caused by osteoporosis of the spine with and without vertebral fractures. Genetic variances in *CNR2* might also modulate the susceptibility to autoimmune disorders [134]. The endocannabinoid anandamide is rapidly re-uptaken through a CB transporter and then metabolized by FAAH [135]. Inhibitors of FAAH prolong the half-life of anandamide and other endocannabinoids and potently reduce pain in rodent models [136, 137]. Polymorphisms in the *FAAH* gene [138] cause an amino acid exchange from proline to threonine at position 129 and result in decreased FAAH enzyme catalytic activity [90]. This P129T *mutation* was associated with slightly reduced sensitivity to cold pain in experimental settings in healthy volunteers [90]. The potential modulation of the susceptibility to chronic back pain has not been addressed. However, considering the functions of endocannabinoids on bone formation and density and pain signalling [139, 140] it is likely that alterations in their metabolism affect the susceptibility to chronic back pain.

Polymorphisms contributing to chronic widespread musculoskeletal pain

Chronic back pain is often associated with widespread pain in complex musculoskeletal pain syndromes such as fibromyalgia [141], TMD [142] and chronic fatigue syndrome [143]. Fibromyalgia is a generalized widespread chronic pain disorder characterized by diffuse muscle pain throughout the body, most often including chronic back and neck pain, muscle weakness, fatigue, increased negative mood, sleep disturbance [141] and comorbidity with anxiety and depression [144]. Chronic widespread pain is common in the general population. The precise role of genetic factors in the etiopathology is still unclear but polymorphisms in genes of the serotoninergic and catecholaminergic systems have been associated with an increased risk of fibromyalgia and chronic fatigue syndrome. Polymorphisms in the monoamine oxidase A (*MAOA*) which is one of the enzymes metabolizing serotonin were reported to affect the rate of serotonin degradation and may therefore impact on the risk of psychopathological symptoms which are associated with fibromyalgia, other chronic widespread pain syndromes and chronic back pain [145]. *COMT* polymorphisms may further contribute to the pathogenesis because approximately 74% of fibromyalgia patients had low or intermediate COMT activity resulting in low catecholamine degradation [146, 147] and Spanish fibromyalgia patients carrying a haploype of COMT associated with high pain intensity (rs6269, rs4818 and rs4680) had a higher risk for fibromyalgia and showed higher pain intensities [148].

Polyarthropathic diseases such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis or systemic lupus erythematosus cause inflammatory back pain due to arthritis of the small intervertebral or sacroiliacal joints and myositis. Polymorphisms in the major histocompatibility complex molecules contribute to the development of these diseases [149, 150]. However, several other immune genes such as immunoglobulin receptors, TNF receptor, transcription factors such as Stat4, various cytokines and chemokines were shown to be associated with the risk of developing these chronic inflammatory autoimmune diseases and to modify the response to pharmacologic treatments with, *e.g.* anti-TNF monoclonal antibodies or immunosuppressive agents. Genetic susceptibility to autoimmune disorders have been summarized in, *e.g.* [151–153].

Polymorphisms causing complex syndromes with a loss of pain perception

Several hereditary maladies with complete loss of pain sensitivity have been genetically defined. Although the molecular mechanisms differ among them, all syndromes are characterized by an interruption of transmission or processing at key points of the nociceptive system (for full details, see the 'Online Mendelian Inheritance in Man' database: http://www.ncbi.nlm.nih.gov/sites/entrez?db = omim) [74]. This includes (*i*) the channelopathy associated insensitivity to pain, which is based on loss-of-function mutations of the α-subunit of the voltage-gated sodium channel, Na(v)1.7 [154, 155], (*ii*) the hereditary sensory and autonomic neuropathy type I (HSAN-I), caused by mutations in the serine palmitoyltransferase, long chain base subunit 1 gene [156–158], (*iii*) the HSAN-II, based on mutations in the hereditary sensory neuropathy, type II′ [159, 160]; [161, 162], (*iv*) the HSAN-III due to mutations in the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein gene [163–165], (*v*) the HSAN-IV, also called congenital insensitivity to pain with anhidrosis and based on mutations in the neurotrophic tyrosine kinase, receptor, type 1 gene [166, 167] and (*vi*) the HSAN-V caused by mutations in the nerve growth factor, β polypeptide gene [168]. All these syndromes are very rare, affecting a few families. Therefore, their specific association with back pain has not been shown but it is reasonable to assume that patients with these syndromes will not develop back pain.

Polymorphisms modulating the metabolism of analgesics

Early effective and safe pain therapy may help to prevent the transition to chronic pain [169] and drug-related secondary problems. Polymorphisms in drug metabolizing enzymes may therefore be important for the long-term outcome of back problems. The cytochrome P450 (CYP) isoenzyme 2D6 metabolizes some opioid analgesics, most importantly codeine and tramadol, but also amitriptyline that is often used as a co-analgesic in patients with neuropathic pain and might have some limited usefulness in lumbar root pain [170, 171]. Codeine ineffectiveness is partly caused by the lack of formation of its active metabolite morphine, which has a 200-times higher affinity and intrinsic activity at μ-opioid receptors than codeine itself [172, 173] and is therefore considered the active principle of codeine despite some evidence that codeine or codeine-6-glucuronide contribute to the pharmacodynamic effects [174–178]. In approximately 7% of the Caucasian population, the CYP2D6 enzyme catabolizing codeine O-demethylation to morphine [179] is known to be inactive for genetic reasons [180], with differences in other ethnicities [181], and in these individuals codeine fails to produce relevant clinical analgesia [182, 183]. On the other hand, also in approximately 7% of the Caucasian population, CYP2D6 is extremely active [181, 184] leading to very high morphine formation from codeine. This challenges the safety of codeine therapy as indicated by reported clinical cases of codeine-caused euphoria, dizziness, blurred vision [185], severe deterioration of consciousness [186], apnea with subsequent brain damage [187] up to fatal poisoning of breastfed infants [188]. Tramadol metabolism by CYP2D6 also produces an

Table 1 Evidence for statistically significant genetic modulation of intervertebral disc disease and pain sensation

Gene	SNP with reference ID (minor allele right)†	Gene position	Minor allele frequency (%)	Kind of pain or lumbar disc disease (LDD)	Increased or decreased pain or LDD with minor allele	References
Genes associated with cartilage structure and stability						
COL9A2	rs7533552C>T (c.976C>T; Gln326Trp) 'Trp2 allele'	Exon 19	1.9	Lumbar disc disease with radicular pain	Increased	[19]
	rs12077871A>G (c.976A>G, Gln326Arg)	Exon 19	25.5	Lumbar disc disease	Increased	[19, 20]
	Haplotype from 3 COL9A2 variants		21	Lumbar disc disease	Increased	[21]
COL9A3	ENSSNP1927949C>T, Arg103Trp, 'Trp3 allele'	Exon 5	12.2/4.7 Case/control	Lumbar disc disease	Increased	[10]
COL11A1	rs1676486C>T	Exon 62	35/26 Case/control	Lumbar disc herniation	Increased	[23]
	rs2229783 C>T	Exon 63	41/32 Case/control	Lumbar disc herniation	Increased	[23]
	rs3753841T>C	Exon 52	37/28 Case/control	Lumbar disc herniation	Increased	[23]
COL11A2	rs1799907T>A	Intron 6 splice site IVS6 (−4)T>A	7/28 Case/control	Lumbar disc disease with stenosis and radicular pain	Decreased A allele protective	[22]
COL1A1	rs1107946G>T	5′UTR	18	Lumbar disc disease, osteoporosis	Increased	[24, 29, 30]
VDR	rs10735810C>T additional transcription start site, additional three amino acids	Exon 2	~30	Lumbar disc disease, osteoporosis	Increased	[37, 51, 52]
	rs731236T>C	Exon 9	~25	Lumbar disc disease	Increased	[53]
ACAN	Variable number of tandem repeats (VNTR)	Exon 12	~7	Lumbar disc disease	Increased with short VNTRs	[43, 44]
	LDD associated with 18–22 TRs, protective effect of >25 TRs					
CILP	rs2073711T>4C	Exon 8	24.6/16.9 Case/control	Lumbar disc disease	Increased	[45]
MMP3	rs3025058 6A>5A ins/del	5′UTR	~20 (5A)	Lumbar disc disease	Increased	[47, 48]
MMP9	rs17576A>G	Exon 6		Lumbar disc herniation	Increased	[50]
THBS2	rs9406328C>T	Intron 10		Lumbar disc herniation	Increased	[50]
Genes associated with inflammation						
IL1RN	rs2234677G>A	Intron 8	26	Lumbar disc disease, Low back pain	Increased	[4]
IL1A	rs1800587C>T	5′UTR	38.2	Lumbar disc disease, Low back pain	Increased	[57]
IL1B	rs1143634C>T	Intron 1	31	Lumbar disc disease, Low back pain	Increased	[4]
IL6	rs2069860T>A	Exon 5	1.2	Lumbar disc disease, radicular pain	Increased	[62]

Continued

Table 1 Continued

Gene	SNP with reference ID (minor allele right)†	Gene position	Minor allele frequency (%)	Kind of pain or lumbar disc disease (LDD)	Increased or decreased pain or LDD with minor allele	References
IL6	rs2069826 -597*G>A	Promoter	45	Lumbar disc disease, radicular pain	Increased	[62]
	rs3087226 -174*G>C	Promoter	45	Lumbar disc disease, radicular pain	Increased	[62]
Genes associated with pain signalling						
GCH1	rs8007267G>A	5′UTR	17	Chronic low back pain with radicular pain; heat, ischemic and pressure pain	Decreased	
	rs3783641A>T	Intron 1	19		Decreased	
	rs8007201T>C	Intron 3	28		Decreased	
	rs4411417A>G	Intron 3	19		Decreased	
	rs752688G>A	Intron 5	19		Decreased	
	Haplotype from 15 *GCH1* SNPs		15.4	Chronic low back pain with radicular pain; heat, ischemic and pressure pain,	Decreased	
			14.7	Inflammatory hyperalgesia	Decreased	[71]
COMT	rs4646312T>C	Promoter	33	Cold pain intensity	Decreased	[90]
	rs6269A>G	Intron 1	44	Cold pain intensity	Decreased or increased	
	rs4633T>C	Exon 3	49	Pressure pain, thermal pain	Decreased	[76]
	rs4680 G>A	Exon 4	-	Muscle pain due to hypertonic saline	Increased	[84]
	rs4680 G>A	Exon 4	-	Muscle pain due to hypertonic saline	Increased	[84]
				Heat pain temporal summation	Increased	[75, 199]
	rs6269G/rs4633C/rs4818G/rs4680G		36.5	Pressure pain, thermal pain	Low	[76]
	rs6269A/rs4633T/rs4818C/rs4680A		48.7		Average	
	rs6269A/rs4633C/rs4818C/rs4680G		10.7		High	
	Haplotypes from 6 COMT SNPs		-	Cold pain intensity	Changed	[90]
MC1R	rs1805007C>T,rs1805008C>T, rs1805009G>C and other)	*E.g.* exon 1	~2	Electrical pain tolerance	Decreased	[87]
TRPV1	rs8065080A>G	Exon 12	36.8	Cold pain withdrawal time	Decreased	[118]
TRPA1	rs11988795G>A	Intron 20	41	Cold pain withdrawal time	Increased	[90]
	Haplotypes from rs13255063T>A and rs11988795G>A		-	Cold pain withdrawal time, heat pain intensity	Changed	

Continued

Table 1 Continued

Gene	SNP with reference ID (minor allele right)†	Gene position	Minor allele frequency (%)	Kind of pain or lumbar disc disease (LDD)	Increased or decreased pain or LDD with minor allele	References
OPRM1	rs1799971 A>G	Exon 1	11.2	Pressure pain threshold	Increased	[101]
			10	Intensity of trigeminal pain evoked by gaseous 200 ms CO2 pulses	Decreased	[102]
OPRD1	rs1042114T>G¯	Exon 1	10.9	Heat pain intensity	Decreased or unchanged	[118]
	rs2234918T>C¯	Exon 3	35.6	Heat pain intensity	Increased	
FAAH	rs932816G>A	5′UTR	19	Cold pain intensity	Increased	[90]
	rs4141964T>C	Intron 1	49	Cold pain intensity	Increased	[90]
				Cold pain withdrawal time	Increased	
	rs2295633G>A	Intron 8	43	Cold pain intensity	Increased	[90]

active metabolite, O-desmethyltramadol [189]. Since in contrast to codeine, tramadol has considerable agonist activity at opioid receptors by itself, its analgesic effects in CYP2D6 poor metabolizers were reduced but not abolished [190–192]. However, increased opioid effects in a single clinical case have also been interpreted as an indication for the occurrence of tramadol induced toxicity in a CYP2D6 ultra rapid metabolizer [193].

Genetic variants in *CYP2C9* associated with reduced function (*CYP2C9* alleles *2 and *3) [194] may decrease the metabolic clearance of CYP2C9 substrates, such as some non-steroidal anti-inflammatory drugs (NSAIDs). However, probably due to the wide therapeutic range of NSAIDs, increased plasma concentrations of celecoxib, diclofenac or ibuprofen observed in CYP2C9 poor metabolizers [195, 196] appear not to impact the anti-inflammatory or analgesic effects of these drugs. Nevertheless, a case–control study suggested an increased risk of gastroduodenal bleeding in patients with a poor metabolizer CYP2C9 phenotype when they were treated with NSAIDs metabolized by CYP2C9 [197]. Finally, *CYP2C8* polymorphisms have been proposed to enhance the formation of reactive metabolites of diclofenac that were associated with an increased risk of diclofenac-evoked liver toxicity [198].

Summary

Several genetic factors contribute to the risk for chronic back pain and widespread pain syndromes (Table 1). The experience of pain results from a complex interaction between several genetic variants involved in different steps of neuronal processing of nociceptive information with additional contribution of other genetic, structural, environmental and psychosocial factors. The investigation of interactions between genetic variants that modify pain signalling and the variants affecting bone and intervertebral cartilage and the identification of the molecular consequences of functional variants are further required to understand the genetics of pain and specially to identify genetic predictors of chronic back pain.

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References

1. **Hartvigsen J, Christensen K, Frederiksen H, *et al.*** Genetic and environmental contributions to back pain in old age: a study of 2,108 Danish twins aged 70 and older. *Spine.* 2004; 29: 897–901.
2. **Battie MC, Videman T, Levalahti E, *et al.*** Heritability of low back pain and the role of disc degeneration. *Pain.* 2007; 131: 272–80.
3. **Foulkes T, Wood JN.** Pain genes. *PLoS Genet.* 2008; 4: e1000086; 1–9.
4. **Solovieva S, Leino-Arjas P, Saarela J, *et al.*** Possible association of interleukin 1 gene locus polymorphisms with low back pain. *Pain.* 2004; 109: 8–19.
5. **Kim SR, Lee da Y, Chung ES, *et al.*** Transient receptor potential vanilloid subtype 1 mediates cell death of mesencephalic dopaminergic neurons *in vivo* and *in vitro*. *J Neurosci.* 2005; 25: 662–71.
6. **Lötsch J, Geisslinger G.** Current evidence for a modulation of nociception by human genetic polymorphisms. *Pain.* 2007; 132: 18–22.

7. **Zhang Y, Kerns JM, Anderson DG, *et al.*** Sensory neurons and fibers from multiple spinal cord levels innervate the rabbit lumbar disc. *Am J Phys Med Rehabil.* 2006; 85: 865–71.
8. **Luoma K, Riihimaki H, Luukkonen R, *et al.*** Low back pain in relation to lumbar disc degeneration. *Spine.* 2000; 25: 487–92.
9. **Sakai Y, Matsuyama Y, Hasegawa Y, *et al.*** Association of gene polymorphisms with intervertebral disc degeneration and vertebral osteophyte formation. *Spine.* 2007; 32: 1279–86.
10. **Paassilta P, Lohiniva J, Goring HH, *et al.*** Identification of a novel common genetic risk factor for lumbar disk disease. *JAMA.* 2001; 285: 1843–9.
11. **Higashino K, Matsui Y, Yagi S, *et al.*** The alpha2 type IX collagen tryptophan polymorphism is associated with the severity of disc degeneration in younger patients with herniated nucleus pulposus of the lumbar spine. *Int Orthop.* 2007; 31: 107–11.
12. **Kalichman L, Hunter DJ.** The genetics of intervertebral disc degeneration. Associated genes. *Joint Bone Spine.* 2008; 75: 388–96.
13. **Solovieva S, Lohiniva J, Leino-Arjas P, *et al.*** COL9A3 gene polymorphism and obesity in intervertebral disc degeneration of the lumbar spine: evidence of gene-environment interaction. *Spine.* 2002; 27: 2691–6.
14. **Solovieva S, Lohiniva J, Leino-Arjas P, *et al.*** Intervertebral disc degeneration in relation to the COL9A3 and the IL-1ss gene polymorphisms. *Eur Spine J.* 2006; 15: 613–9.
15. **Virtanen IM, Karppinen J, Taimela S, *et al.*** Occupational and genetic risk factors associated with intervertebral disc disease. *Spine.* 2007; 32: 1129–34.
16. **Aladin DM, Cheung KM, Chan D, *et al.*** Expression of the Trp2 allele of COL9A2 is associated with alterations in the mechanical properties of human intervertebral discs. *Spine.* 2007; 32: 2820–6.
17. **Jim JJ, Noponen-Hietala N, Cheung KM, *et al.*** The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. *Spine.* 2005; 30: 2735–42.
18. **Kales SN, Linos A, Chatzis C, *et al.*** The role of collagen IX tryptophan polymorphisms in symptomatic intervertebral disc disease in Southern European patients. *Spine.* 2004; 29: 1266–70.
19. **Annunen S, Paassilta P, Lohiniva J, *et al.*** An allele of COL9A2 associated with intervertebral disc disease. *Science.* 1999; 285: 409–12.
20. **Knoeringer M, Reinke A, Trappe AE, *et al.*** Absence of the mutated Trp2 allele but a common polymorphism of the COL9A2 collagen gene is associated with early recurrence after lumbar discectomy in a German population. *Eur Spine J.* 2008; 17: 463–7.
21. **Seki S, Kawaguchi Y, Mori M, *et al.*** Association study of COL9A2 with lumbar disc disease in the Japanese population. *J Hum Genet.* 2006; 51: 1063–7.
22. **Noponen-Hietala N, Kyllonen E, Mannikko M, *et al.*** Sequence variations in the collagen IX and XI genes are associated with degenerative lumbar spinal stenosis. *Ann Rheum Dis.* 2003; 62: 1208–14.
23. **Mio F, Chiba K, Hirose Y, *et al.*** A functional polymorphism in COL11A1, which encodes the alpha 1 chain of type XI collagen, is associated with susceptibility to lumbar disc herniation. *Am J Hum Genet.* 2007; 81: 1271–7.
24. **Pluijm SM, van Essen HW, Bravenboer N, *et al.*** Collagen type I alpha1 Sp1 polymorphism, osteoporosis, and intervertebral disc degeneration in older men and women. *Ann Rheum Dis.* 2004; 63: 71–7.
25. **Ashford RU, Luchetti M, McCloskey EV, *et al.*** Studies of bone density, quantitative ultrasound, and vertebral fractures in relation to collagen type I alpha 1 alleles in elderly women. *Calcif Tissue Int.* 2001; 68: 348–51.
26. **MacDonald HM, McGuigan FA, New SA, *et al.*** COL1A1 Sp1 polymorphism predicts perimenopausal and early postmenopausal spinal bone loss. *J Bone Miner Res.* 2001; 16: 1634–41.
27. **Nguyen TV, Esteban LM, White CP, *et al.*** Contribution of the collagen I alpha1 and vitamin D receptor genes to the risk of hip fracture in elderly women. *J Clin Endocrinol Metab.* 2005; 90: 6575–9.
28. **Ralston SH, Uitterlinden AG, Brandi ML, *et al.*** Large-scale evidence for the effect of the COLIA1 Sp1 polymorphism on osteoporosis outcomes: the GENOMOS study. *PLoS Med.* 2006; 3: e90; 0515–23.
29. **Grant SF, Reid DM, Blake G, *et al.*** Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I alpha 1 gene. *Nat Genet.* 1996; 14: 203–5.
30. **Uitterlinden AG, Burger H, Huang Q, *et al.*** Relation of alleles of the collagen type Ialpha1 gene to bone density and the risk of osteoporotic fractures in postmenopausal women. *N Engl J Med.* 1998; 338: 1016–21.
31. **Yamada Y, Ando F, Niino N, *et al.*** Association of a -1997G–>T polymorphism of the collagen Ialpha1 gene with bone mineral density in postmenopausal Japanese women. *Hum Biol.* 2005; 77: 27–36.
32. **Yazdanpanah N, Rivadeneira F, van Meurs JB, *et al.*** The -1997 G/T and Sp1 polymorphisms in the collagen type I alpha1 (COLIA1) gene in relation to changes in femoral neck bone mineral density and the risk of fracture in the elderly: the Rotterdam study. *Calcif Tissue Int.* 2007; 81: 18–25.
33. **Schneider S, Mohnen SM, Schiltenwolf M, *et al.*** Comorbidity of low back pain: representative outcomes of a national health study in the Federal Republic of Germany. *Eur J Pain.* 2007; 11: 387–97.
34. **Dick IM, Devine A, Li S, *et al.*** The T869C TGF beta polymorphism is associated with fracture, bone mineral density, and calcaneal quantitative ultrasound in elderly women. *Bone.* 2003; 33: 335–41.
35. **Langdahl BL, Carstens M, Stenkjaer L, *et al.*** Polymorphisms in the transforming growth factor beta 1 gene and osteoporosis. *Bone.* 2003; 32: 297–310.
36. **Kung AW, Lai BM, Ng MY, *et al.*** T-1213C polymorphism of estrogen receptor beta is associated with low bone mineral density and osteoporotic fractures. *Bone.* 2006; 39: 1097–106.
37. **Morrison NA, Qi JC, Tokita A, *et al.*** Prediction of bone density from vitamin D receptor alleles. *Nature.* 1994; 367: 284–7.
38. **Hustmyer FG, Peacock M, Hui S, *et al.*** Bone mineral density in relation to polymorphism at the vitamin D receptor gene locus. *J Clin Invest.* 1994; 94: 2130–4.
39. **Richards JB, Rivadeneira F, Inouye M, *et al.*** Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. *Lancet.* 2008; 371: 1505–12.
40. **van Meurs JB, Trikalinos TA, Ralston SH, *et al.*** Large-scale analysis of association between LRP5 and LRP6 variants and osteoporosis. *JAMA.* 2008; 299: 1277–90.
41. **Carbonell Sala S, Masi L, Marini F, *et al.*** Genetics and pharmacogenetics of osteoporosis. *J Endocrinol Invest.* 2005; 28: 2–7.
42. **Ralston SH.** Genetic determinants of osteoporosis. *Curr Opin Rheumatol.* 2005; 17: 475–9.
43. **Solovieva S, Noponen N, Mannikko M, *et al.*** Association between the aggrecan

gene variable number of tandem repeats polymorphism and intervertebral disc degeneration. *Spine.* 2007; 32: 1700–5.

44. **Kawaguchi Y, Osada R, Kanamori M, *et al.*** Association between an aggrecan gene polymorphism and lumbar disc degeneration. *Spine.* 1999; 24: 2456–60.
45. **Seki S, Kawaguchi Y, Chiba K, *et al.*** A functional SNP in CILP, encoding cartilage intermediate layer protein, is associated with susceptibility to lumbar disc disease. *Nat Genet.* 2005; 37: 607–12.
46. **Lorenzo P, Bayliss MT, Heinegard D.** A novel cartilage protein (CILP) present in the mid-zone of human articular cartilage increases with age. *J Biol Chem.* 1998; 273: 23463–8.
47. **Karppinen J, Daavittila I, Solovieva S, *et al.*** Genetic factors are associated with modic changes in endplates of lumbar vertebral bodies. *Spine.* 2008; 33: 1236–41.
48. **Takahashi M, Haro H, Wakabayashi Y, *et al.*** The association of degeneration of the intervertebral disc with 5a/6a polymorphism in the promoter of the human matrix metalloproteinase-3 gene. *J Bone Joint Surg Br.* 2001; 83: 491–5.
49. **Kawasaki Y, Xu ZZ, Wang X, *et al.*** Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. *Nat Med.* 2008; 14: 331–6.
50. **Hirose Y, Chiba K, Karasugi T, *et al.*** A functional polymorphism in THBS2 that affects alternative splicing and MMP binding is associated with lumbar-disc herniation. *Am J Hum Genet.* 2008; 82: 1122–9.
51. **Videman T, Leppavuori J, Kaprio J, *et al.*** Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. *Spine.* 1998; 23: 2477–85.
52. **Videman T, Gibbons LE, Battie MC, *et al.*** The relative roles of intragenic polymorphisms of the vitamin d receptor gene in lumbar spine degeneration and bone density. *Spine.* 2001; 26: E7–12.
53. **Kawaguchi Y, Kanamori M, Ishihara H, *et al.*** The association of lumbar disc disease with vitamin-D receptor gene polymorphism. *J Bone Joint Surg Am.* 2002; 84-A: 2022–8.
54. **Carragee EJ, Alamin TF, Miller JL, *et al.*** Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain. *Spine J.* 2005; 5: 24–35.
55. **Battie MC, Videman T, Gibbons LE, *et al.*** 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine.* 1995; 20: 2601–12.
56. **Kim JG, Lim KS, Ku SY, *et al.*** Relations between interleukin-1, its receptor antagonist gene polymorphism, and bone mineral density in postmenopausal Korean women. *J Bone Miner Metab.* 2006; 24: 53–7.
57. **Solovieva S, Kouhia S, Leino-Arjas P, *et al.*** Interleukin 1 polymorphisms and intervertebral disc degeneration. *Epidemiology.* 2004; 15: 626–33.
58. **Hoyland JA, Le Maitre C, Freemont AJ.** Investigation of the role of IL-1 and TNF in matrix degradation in the intervertebral disc. *Rheumatology.* 2008; 47: 809–14.
59. **Le Maitre CL, Freemont AJ, Hoyland JA.** The role of interleukin-1 in the pathogenesis of human intervertebral disc degeneration. *Arthritis Res Ther.* 2005; 7: R732–45.
60. **Kuisma M, Karppinen J, Niinimaki J, *et al.*** Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. *Spine.* 2007; 32: 1116–22.
61. **Ohtori S, Inoue G, Ito T, *et al.*** Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and modic type 1 or type 2 changes on MRI. *Spine.* 2006; 31: 1026–31.
62. **Noponen-Hietala N, Virtanen I, Karttunen R, *et al.*** Genetic variations in IL6 associate with intervertebral disc disease characterized by sciatica. *Pain.* 2005; 114: 186–94.
63. **Cipollone F, Toniato E, Martinotti S, *et al.*** A polymorphism in the cyclooxygenase 2 gene as an inherited protective factor against myocardial infarction and stroke. *JAMA.* 2004; 291: 2221–8.
64. **Hernandez MR, Tonda R, Pino M, *et al.*** Evaluation of effects of rofecoxib on platelet function in an in vitro model of thrombosis with circulating human blood. *Eur J Clin Invest.* 2004; 34: 297–302.
65. **Papafili A, Hill MR, Brull DJ, *et al.*** Common promoter variant in cyclooxygenase-2 represses gene expression: evidence of role in acute-phase inflammatory response. *Arterioscler Thromb Vasc Biol.* 2002; 22: 1631–6.
66. **Lee YS, Kim H, Wu TX, *et al.*** Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther.* 2006; 79: 407–18.
67. **Skarke C, Reus M, Schmidt R, *et al.*** The cyclooxygenase 2 genetic variant -765G>C does not modulate the effects of celecoxib on prostaglandin E2 production. *Clin Pharmacol Ther.* 2006; 80: 621–32.
68. **Tegeder I, Costigan M, Griffin RS, *et al.*** GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med.* 2006; 12: 1269–77.
69. **Blau N, Niederwieser A.** GTP-cyclohydrolases: a review. *J Clin Chem Clin Biochem.* 1985; 23: 169–76.
70. **Gross SS, Levi R.** Tetrahydrobiopterin synthesis. An absolute requirement for cytokine-induced nitric oxide generation by vascular smooth muscle. *J Biol Chem.* 1992; 267: 25722–9.
71. **Tegeder I, Adolph J, Schmidt H, *et al.*** Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. *Eur J Pain.* 2008.
72. **Meller ST, Lewis SJ, Bates JN, *et al.*** Is there a role for an endothelium-derived relaxing factor in nociception? *Brain Res.* 1990; 531: 342–5.
73. **Meller ST, Cummings CP, Traub RJ, *et al.*** The role of nitric oxide in the development and maintenance of the hyperalgesia produced by intraplantar injection of carrageenan in the rat. *Neuroscience.* 1994; 60: 367–74.
74. **Oertel B, Lotsch J.** Genetic mutations that prevent pain: implications for future pain medication. *Pharmacogenomics.* 2008; 9: 179–94.
75. **Diatchenko L, Nackley AG, Slade GD, *et al.*** Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* 2006; 125: 216–24.
76. **Diatchenko L, Slade GD, Nackley AG, *et al.*** Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet.* 2005; 14: 135–43.
77. **Lu Y, Perl ER.** Selective action of noradrenaline and serotonin on neurones of the spinal superficial dorsal horn in the rat. *J Physiol.* 2007; 582: 127–36.
78. **Suzuki R, Dickenson A.** Spinal and supraspinal contributions to central sensitization in peripheral neuropathy. *Neurosignals.* 2005; 14: 175–81.
79. **Oliveira MC, Pelegrini-da-Silva A, Parada CA, *et al.*** 5-HT acts on nociceptive primary afferents through an indirect mechanism to induce hyperalgesia in the subcutaneous tissue. *Neuroscience.* 2007; 145: 708–14.

80. **Slade GD, Diatchenko L, Bhalang K, *et al.*** Influence of psychological factors on risk of temporomandibular disorders. *J Dent Res.* 2007; 86: 1120–5.
81. **Oakley M, Vieira AR.** The many faces of the genetics contribution to temporomandibular joint disorder. *Orthod Craniofac Res.* 2008; 11: 125–35.
82. **Stohler CS.** TMJD 3: a genetic vulnerability disorder with strong CNS involvement. *J Evid Based Dent Pract.* 2006; 6: 53–7.
83. **Berthele A, Platzer S, Jochim B, *et al.*** 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.* 2005; 28: 185–93.
84. **Zubieta JK, Heitzeg MM, Smith YR, *et al.*** COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science.* 2003; 299: 1240–3.
85. **Rakvag TT, Klepstad P, Baar C, *et al.*** The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain.* 2005; 116: 73–8.
86. **Reyes-Gibby CC, Shete S, Rakvag T, *et al.*** Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain.* 2007; 130: 25–30.
87. **Mogil JS, Ritchie J, Smith SB, *et al.*** Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet.* 2005; 42: 583–7.
88. **Liem EB, Joiner TV, Tsueda K, *et al.*** Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology.* 2005; 102: 509–14.
89. **Mogil JS, Wilson SG, Chesler EJ, *et al.*** The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci USA.* 2003; 100: 4867–72.
90. **Kim H, Mittal DP, Iadarola MJ, *et al.*** Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *J Med Genet.* 2006; 43: e40.
91. **McNamara CR, Mandel-Brehm J, Bautista DM, *et al.*** TRPA1 mediates formalin-induced pain. *Proc Natl Acad Sci USA.* 2007; 104: 13525–30.
92. **Bautista DM, Movahed P, Hinman A, *et al.*** Pungent products from garlic activate the sensory ion channel TRPA1. *Proc Natl Acad Sci USA.* 2005; 102: 12248–52.
93. **Macpherson LJ, Dubin AE, Evans MJ, *et al.*** Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. *Nature.* 2007; 445: 541–5.
94. **Bandell M, Story GM, Hwang SW, *et al.*** Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. *Neuron.* 2004; 41: 849–57.
95. **Trevisani M, Siemens J, Materazzi S, *et al.*** 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. *Proc Natl Acad Sci USA.* 2007; 104: 13519–24.
96. **Andersson DA, Gentry C, Moss S, *et al.*** Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress. *J Neurosci.* 2008; 28: 2485–94.
97. **Lotsch J, Geisslinger G.** Are mu-opioid receptor polymorphisms important for clinical opioid therapy? *Trends Mol Med.* 2005; 11: 82–9.
98. **Ikeda K, Ide S, Han W, *et al.*** How individual sensitivity to opiates can be predicted by gene analyses. *Trends Pharmacol Sci.* 2005; 26: 311–7.
99. **Zhang Y, Wang D, Johnson AD, *et al.*** Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. *J Biol Chem.* 2005; 280: 32618–24.
100. **Oertel BG, Preibisch C, Wallenhorst T, *et al.*** Differential opioid action on sensory and affective cerebral pain processing. *Clin Pharmacol Ther.* 2008; 83: 577–88.
101. **Fillingim RB, Kaplan L, Staud R, *et al.*** The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain.* 2005; 6: 159–67.
102. **Lotsch J, Stuck B, Hummel T.** The human mu-opioid receptor gene polymorphism 118A > G decreases cortical activation in response to specific nociceptive stimulation. *Behav Neurosci.* 2006; 120: 1218–24.
103. **Bond C, LaForge KS, Tian M, *et al.*** Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Acad Sci USA.* 1998; 95: 9608–13.
104. **Beyer A, Koch T, Schroder H, *et al.*** Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. *J Neurochem.* 2004; 89: 553–60.
105. **Kroslak T, Laforge KS, Gianotti RJ, *et al.*** The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. *J Neurochem.* 2007; 103: 77–87.
106. **Lotsch J, Skarke C, Grosch S, *et al.*** The polymorphism A118G of the human mu-opioid receptor gene decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. *Pharmacogenetics.* 2002; 12: 3–9.
107. **Skarke C, Darimont J, Schmidt H, *et al.*** Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. *Clin Pharmacol Ther.* 2003; 73: 107–21.
108. **Lotsch J, Skarke C, Wieting J, *et al.*** Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. *Clin Pharmacol Ther.* 2006; 79: 72–89.
109. **Oertel BG, Schmidt R, Schneider A, *et al.*** The mu-opioid receptor gene polymorphism 118A > G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. *Pharmacogenet Genomics.* 2006; 16: 625–36.
110. **Lotsch J, Zimmermann M, Darimont J, *et al.*** Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity? *Anesthesiology.* 2002; 97: 814–9.
111. **Romberg RR, Olofsen E, Bijl H, *et al.*** Polymorphism of mu-opioid receptor gene (OPRM1:c.118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. *Anesthesiology.* 2005; 102: 522–30.
112. **Chou WY, Yang LC, Lu HF, *et al.*** Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand.* 2006; 50: 787–92.
113. **Chou WY, Wang CH, Liu PH, *et al.*** Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. *Anesthesiology.* 2006; 105: 334–7.
114. **Hayashida M, Nagashima M, Satoh Y, *et al.*** Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. *Pharmacogenomics.* 2008; 9: 1605–16.
115. **Klepstad P, Rakvag TT, Kaasa S, *et al.*** The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in

patients with pain caused by malignant disease. *Acta Anaesthesiol Scand.* 2004; 48: 1232–9.

116. **Campa D, Gioia A, Tomei A, *et al.*** Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. *Clin Pharmacol Ther.* 2008; 83: 559–66.
117. **Landau R, Kern C, Columb MO, *et al.*** Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain.* 2008; 139: 5–14.
118. **Kim H, Neubert JK, San Miguel A, *et al.*** Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. *Pain.* 2004; 109: 488–96.
119. **Zhang H, Kranzler HR, Yang BZ, *et al.*** The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. *Mol Psychiatry.* 2008; 13: 531–43.
120. **Brown KM, Bujac SR, Mann ET, *et al.*** Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. *Biol Psychiatry.* 2007; 61: 367–73.
121. **Agarwal N, Pacher P, Tegeder I, *et al.*** Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci.* 2007; 10: 870–9.
122. **Manning BH, Merin NM, Meng ID, *et al.*** Reduction in opioid- and cannabinoid-induced antinociception in rhesus monkeys after bilateral lesions of the amygdaloid complex. *J Neurosci.* 2001; 21: 8238–46.
123. **Racz I, Nadal X, Alferink J, *et al.*** Interferon-gamma is a critical modulator of CB(2) cannabinoid receptor signaling during neuropathic pain. *J Neurosci.* 2008; 28: 12136–45.
124. **Racz I, Nadal X, Alferink J, *et al.*** Crucial role of CB(2) cannabinoid receptor in the regulation of central immune responses during neuropathic pain. *J Neurosci.* 2008; 28: 12125–35.
125. **Svendsen KB, Jensen TS, Bach FW.** Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *Bmj.* 2004; 329: 253–60.
126. **Aberle J, Flitsch J, Beck NA, *et al.*** Genetic variation may influence obesity only under conditions of diet: analysis of three candidate genes. *Mol Genet Metab.* 2008; 95: 188–91.
127. **Russo P, Strazzullo P, Cappuccio FP, *et al.*** Genetic variations at the endocannabinoid type 1 receptor gene (CNR1) are associated with obesity phenotypes in men. *J Clin Endocrinol Metab.* 2007; 92: 2382–6.
128. **Ujike H, Takaki M, Nakata K, *et al.*** CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Mol Psychiatry.* 2002; 7: 515–8.
129. **Hamdani N, Tabeze JP, Ramoz N, *et al.*** The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene for schizophrenia. *Eur Neuropsychopharmacol.* 2008; 18: 34–40.
130. **Zhang PW, Ishiguro H, Ohtsuki T, *et al.*** Human cannabinoid receptor 1: 5′ exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. *Mol Psychiatry.* 2004; 9: 916–31.
131. **Zuo L, Kranzler HR, Luo X, *et al.*** CNR1 variation modulates risk for drug and alcohol dependence. *Biol Psychiatry.* 2007; 62: 616–26.
132. **Agrawal A, Wetherill L, Dick DM, *et al.*** Evidence for association between polymorphisms in the cannabinoid receptor 1 (CNR1) gene and cannabis dependence. *Am J Med Genet B Neuropsychiatr Genet.* 2008; [Epub ahead of print]. DOI: 10.1002/ajmg.b.30881.
133. **Karsak M, Cohen-Solal M, Freudenberg J, *et al.*** Cannabinoid receptor type 2 gene is associated with human osteoporosis. *Hum Mol Genet.* 2005; 14: 3389–96.
134. **Sipe JC, Arbour N, Gerber A, *et al.*** Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: possible risk for autoimmune disorders. *J Leukoc Biol.* 2005; 78: 231–8.
135. **Thomas EA, Cravatt BF, Danielson PE, *et al.*** Fatty acid amide hydrolase, the degradative enzyme for anandamide and oleamide, has selective distribution in neurons within the rat central nervous system. *J Neurosci Res.* 1997; 50: 1047–52.
136. **Lichtman AH, Leung D, Shelton CC, *et al.*** Reversible inhibitors of fatty acid amide hydrolase that promote analgesia: evidence for an unprecedented combination of potency and selectivity. *J Pharmacol Exp Ther.* 2004; 311: 441–8.
137. **Jayamanne A, Greenwood R, Mitchell VA, *et al.*** Actions of the FAAH inhibitor URB597 in neuropathic and inflammatory chronic pain models. *Br J Pharmacol.* 2006; 147: 281–8.
138. **Doehring A, Geisslinger G, Lotsch J.** Rapid screening for potentially relevant polymorphisms in the human fatty acid amide hydrolase gene using Pyrosequencing. *Prostaglandins Other Lipid Mediat.* 2007; 84: 128–37.
139. **Ofek O, Karsak M, Leclerc N, *et al.*** Peripheral cannabinoid receptor, CB2, regulates bone mass. *Proc Natl Acad Sci USA.* 2006; 103: 696–701.
140. **Tam J, Trembovler V, Di Marzo V, *et al.*** The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB J.* 2008; 22: 285–94.
141. **Arnold BS, Alpers GW, Suss H, *et al.*** Affective pain modulation in fibromyalgia, somatoform pain disorder, back pain, and healthy controls. *Eur J Pain.* 2008; 12: 329–38.
142. **Wiesinger B, Malker H, Englund E, *et al.*** Back pain in relation to musculoskeletal disorders in the jaw-face: a matched case-control study. *Pain.* 2007; 131: 311–9.
143. **Meeus M, Nijs J, Meirleir KD.** Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. *Eur J Pain.* 2007; 11: 377–86.
144. **Thieme K, Turk DC, Flor H.** Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. *Psychosom Med.* 2004; 66: 837–44.
145. **Tadic A, Rujescu D, Szegedi A, *et al.*** Association of a MAOA gene variant with generalized anxiety disorder, but not with panic disorder or major depression. *Am J Med Genet B Neuropsychiatr Genet.* 2003; 117B: 1–6.
146. **Gursoy S, Erdal E, Herken H, *et al.*** Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int.* 2003; 23: 104–7.
147. **Tander B, Gunes S, Boke O, *et al.*** Polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase genes: a study on fibromyalgia susceptibility. *Rheumatol Int.* 2008; 28: 685–91.
148. **Vargas-Alarcon G, Fragoso JM, Cruz-Robles D, *et al.*** Catechol-O-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. *Arthritis Res Ther.* 2007; 9: R110.
149. **Brown MA, Kennedy LG, Darke C, *et al.*** The effect of HLA-DR genes on susceptibility to and severity of ankylosing spondylitis. *Arthritis Rheum.* 1998; 41: 460–5.
150. **Brown MA, Pile KD, Kennedy LG, *et al.*** A genome-wide screen for susceptibility loci

in ankylosing spondylitis. *Arthritis Rheum.* 1998; 41: 588–95.

151. **Gutierrez-Roelens I, Lauwerys BR.** Genetic susceptibility to autoimmune disorders: clues from gene association and gene expression studies. *Curr Mol Med.* 2008; 8: 551–61.
152. **Lettre G, Rioux JD.** Autoimmune diseases: insights from genome-wide association studies. *Hum Mol Genet.* 2008; 17: R116–21.
153. **Fu Y, Nathan DM, Li F, *et al.*** Defective major histocompatibility complex class I expression on lymphoid cells in autoimmunity. *J Clin Invest.* 1993; 91: 2301–7.
154. **Cox JJ, Reimann F, Nicholas AK, *et al.*** An SCN9A channelopathy causes congenital inability to experience pain. *Nature.* 2006; 444: 894–8.
155. **Goldberg YP, MacFarlane J, MacDonald ML, *et al.*** Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet.* 2007; 71: 311–9.
156. **Dawkins JL, Hulme DJ, Brahmbhatt SB, *et al.*** Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. *Nat Genet.* 2001; 27: 309–12.
157. **Bejaoui K, Wu C, Scheffler MD, *et al.*** SPTLC1 is mutated in hereditary sensory neuropathy, type 1. *Nat Genet.* 2001; 27: 261–2.
158. **Verhoeven K, Timmerman V, Mauko B, *et al.*** Recent advances in hereditary sensory and autonomic neuropathies. *Curr Opin Neurol.* 2006; 19: 474–80.
159. **Lafreniere RG, MacDonald ML, Dube MP, *et al.*** 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.* 2004; 74: 1064–73.
160. **Riviere JB, Verlaan DJ, Shekarabi M, *et al.*** A mutation in the HSN2 gene causes sensory neuropathy type II in a Lebanese family. *Ann Neurol.* 2004; 56: 572–5.
161. **Roddier K, Thomas T, Marleau G, *et al.*** Two mutations in the HSN2 gene explain the high prevalence of HSAN2 in French Canadians. *Neurology.* 2005; 64: 1762–7.
162. **Cho HJ, Kim BJ, Suh YL, *et al.*** Novel mutation in the HSN2 gene in a Korean patient with hereditary sensory and autonomic neuropathy type 2. *J Hum Genet.* 2006; 51: 905–8.
163. **Slaugenhaupt SA, Gusella JF.** Familial dysautonomia. *Curr Opin Genet Dev.* 2002; 12: 307–11.
164. **Anderson SL, Coli R, Daly IW, *et al.*** Familial dysautonomia is caused by mutations of the IKAP gene. *Am J Hum Genet.* 2001; 68: 753–8.
165. **Leyne M, Mull J, Gill SP, *et al.*** Identification of the first non-Jewish mutation in familial Dysautonomia. *Am J Med Genet A.* 2003; 118A: 305–8.
166. **Indo Y, Tsuruta M, Hayashida Y, *et al.*** Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet.* 1996; 13: 485–8.
167. **Miura Y, Mardy S, Awaya Y, *et al.*** 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.* 2000; 106: 116–24.
168. **Einarsdottir E, Carlsson A, Minde J, *et al.*** A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. *Hum Mol Genet.* 2004; 13: 799–805.
169. **Hummel M, Lu P, Cummons TA, *et al.*** The persistence of a long-term negative affective state following the induction of either acute or chronic pain. *Pain.* 2008; 140: 436–45.
170. **Khoromi S, Cui L, Nackers L, *et al.*** Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain.* 2007; 130: 66–75.
171. **Atkinson JH, Slater MA, Williams RA, *et al.*** A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain.* 1998; 76: 287–96.
172. **Mignat C, Wille U, Ziegler A.** Affinity profiles of morphine, codeine, dihydrocodeine and their glucuronides at opioid receptor subtypes. *Life Sci.* 1995; 56: 793–9.
173. **Schmidt H, Vormfelde SV, Walchner-Bonjean M, *et al.*** The role of active metabolites in dihydrocodeine effects. *Int J Clin Pharmacol Ther.* 2003; 41: 95–106.
174. **Eckhardt K, Li S, Ammon S, *et al.*** Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain.* 1998; 76: 27–33.
175. **Lotsch J, Skarke C, Schmidt H, *et al.*** Evidence for morphine-independent central nervous opioid effects after administration of codeine: contribution of other codeine metabolites. *Clin Pharmacol Ther.* 2006; 79: 35–48.
176. **Vree TB, van Dongen RT, Koopman-Kimenai PM.** Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract.* 2000; 54: 395–8.
177. **Srinivasan V, Wielbo D, Simpkins J, *et al.*** Analgesic and immunomodulatory effects of codeine and codeine 6-glucuronide. *Pharm Res.* 1996; 13: 296–300.
178. **Srinivasan V, Wielbo D, Tebbett IR.** Analgesic effects of codeine-6-glucuronide after intravenous administration. *Eur J Pain.* 1997; 1: 185–90.
179. **Dayer P, Desmeules J, Leemann T, *et al.*** Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P-450 dbl/bufl). *Biochem Biophys Res Commun.* 1988; 152: 411–6.
180. **Lovlie R, Daly AK, Molven A, *et al.*** Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. *FEBS Lett.* 1996; 392: 30–4.
181. **Cascorbi I.** Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. *Eur J Clin Invest.* 2003; 33: 17–22.
182. **Sindrup SH, Brosen K, Bjerring P, *et al.*** Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther.* 1990; 48: 686–93.
183. **Caraco Y, Sheller J, Wood AJ.** Pharmacogenetic determination of the effects of codeine and prediction of drug interactions. *J Pharmacol Exp Ther.* 1996; 278: 1165–74.
184. **Sachse C, Brockmoller J, Bauer S, *et al.*** Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet.* 1997; 60: 284–95.
185. **Dalen P, Frengell C, Dahl ML, *et al.*** Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. *Ther Drug Monit.* 1997; 19: 543–4.
186. **Gasche Y, Daali Y, Fathi M, *et al.*** Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med.* 2004; 351: 2827–31.
187. **Voronov P, Przybylo HJ, Jagannathan N.** Apnea in a child after oral codeine: a genetic variant – an ultra-rapid metabolizer. *Paediatr Anaesth.* 2007; 17: 684–7.
188. **Madadi P, Ross C, Hayden M, *et al.*** Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther.* 2008.
189. **Dayer P, Collart L, Desmeules J.** The pharmacology of tramadol. *Drugs.* 1994; 47: 3–7.

190. **Collart L, Luthy C, Favario-Constantin C, *et al.*** Duality of the analgesic effect of tramadol in humans. *Schweiz Med Wochenschr.* 1993; 123: 2241–3.
191. **Poulsen L, Arendt-Nielsen L, Brosen K, *et al.*** The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther.* 1996; 60: 636–44.
192. **Stamer UM, Lehnen K, Hothker F, *et al.*** Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain.* 2003; 105: 231–8.
193. **Stamer UM, Stuber F, Muders T, *et al.*** Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg.* 2008; 107: 926–9.
194. **Steward DJ, Haining RL, Henne KR, *et al.*** Genetic association between sensitivity to warfarin and expression of CYP2C9*3. *Pharmacogenetics.* 1997; 7: 361–7.
195. **Kirchheiner J, Brockmoller J.** Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin Pharmacol Ther.* 2005; 77: 1–16.
196. **Kirchheiner J, Meineke I, Steinbach N, *et al.*** Pharmacokinetics of diclofenac and inhibition of cyclooxygenases 1 and 2: no relationship to the CYP2C9 genetic polymorphism in humans. *Br J Clin Pharmacol.* 2003; 55: 51–61.
197. **Pilotto A, Seripa D, Franceschi M, *et al.*** Genetic susceptibility to nonsteroidal antiinflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. *Gastroenterology.* 2007; 133: 465–71.
198. **Daly AK, Aithal GP, Leathart JB, *et al.*** Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes. *Gastroenterology.* 2007; 132: 272–81.
199. **Diatchenko L, Anderson AD, Slade GD, *et al.*** Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2006; 141: 449–62.