

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, metalloproteinase-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

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 XI 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 (*COL1A1*) 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 metalloproteinase-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 metalloproteinase-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-1 α (*IL1A*), IL-1 β (*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 *PTGS2* -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* 1585V leads to an amino acid substitution from isoleucine to valine. 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 marijuana 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 serotonergic 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 sacroiliac 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						
<i>COL9A2</i>	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 <i>COL9A2</i> variants		21	Lumbar disc disease	Increased	[21]
<i>COL9A3</i>	ENSSNP1927949C>T, Arg103Trp, 'Trp3 allele'	Exon 5	12.2/4.7 Case/control	Lumbar disc disease	Increased	[10]
<i>COL11A1</i>	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]
<i>COL11A2</i>	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]
<i>COL1A1</i>	rs1107946G>T	5'UTR	18	Lumbar disc disease, osteoporosis	Increased	[24, 29, 30]
<i>VDR</i>	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]
<i>ACAN</i>	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					
<i>CILP</i>	rs2073711T>4C	Exon 8	24.6/16.9 Case/control	Lumbar disc disease	Increased	[45]
<i>MMP3</i>	rs3025058 6A>5A ins/del	5'UTR	~20 (5A)	Lumbar disc disease	Increased	[47, 48]
<i>MMP9</i>	rs17576A>G	Exon 6		Lumbar disc herniation	Increased	[50]
<i>THBS2</i>	rs9406328C>T	Intron 10		Lumbar disc herniation	Increased	[50]
Genes associated with inflammation						
<i>IL1RN</i>	rs2234677G>A	Intron 8	26	Lumbar disc disease, Low back pain	Increased	[4]
<i>IL1A</i>	rs1800587C>T	5'UTR	38.2	Lumbar disc disease, Low back pain	Increased	[57]
<i>IL1B</i>	rs1143634C>T	Intron 1	31	Lumbar disc disease, Low back pain	Increased	[4]
<i>IL6</i>	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
<i>IL6</i>	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						
<i>GCH1</i>	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 <i>GCH1</i> SNPs		15.4	Chronic low back pain with radicular pain; heat, ischemic and pressure pain,	Decreased	
			14.7	Inflammatory hyperalgesia	Decreased	[71]
<i>COMT</i>	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 <i>COMT</i> SNPs		-	Cold pain intensity	Changed	[90]
<i>MC1R</i>	rs1805007C>T,rs1805008C>T,rs1805009G>C and other)	<i>E.g.</i> exon 1	~2	Electrical pain tolerance	Decreased	[87]
<i>TRPV1</i>	rs8065080A>G	Exon 12	36.8	Cold pain withdrawal time	Decreased	[118]
<i>TRPA1</i>	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 CO ₂ pulses	Decreased	[102]
OPRD1	rs1042114T>G ⁻	Exon 1	10.9	Heat pain intensity	Decreased or unchanged	[118]
			35.6	Heat pain intensity	Increased	
FAAH	rs932816G>A	5'UTR	19	Cold pain intensity	Increased	[90]
			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].

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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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