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Novel diagnostic and prognostic methods for disc degeneration and low back pain

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Introduction

Low back pain (LBP) is the world's leading debilitating condition [1]. It is estimated that 80% of the general population in the United States will develop LBP at one point in time [2,3]. Such pain can lead to diminished daily function and quality of life and work disability [4,5]. Not surprisingly, spine surgery to address LBP is one of the top five surgeries performed in the United States [6] where approximately 90-billion US dollars in health-care expenses are used annually to treat LBP [7]. As data indicate, LBP is clearly related with detrimental socioeconomic and health-care consequences that motivate efforts to identify LBP risk factors to develop improved prevention and treatment strategies.

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Although the etiology of LBP is multifaceted, disc degeneration (DD) has been suggested to be one of the most prominent risk factors [8–11]. However, whether DD is synonymous with LBP continues to be a topic of immense controversy. In this article, we review the current data regarding pain generating pathways and epidemiological evidence associating DD with LBP. In further support of this association, we review novel disc imaging techniques that may increase LBP diagnostic sensitivity and specificity. Finally, we discuss relevant aspects of the field of pain genes that may shed further light as to the links between DD and pain.

Pain generators

A tissue or organ can generate pain only if it is innervated. The intervertebral disc is innervated mainly by the sinuvertebral nerve although it receives direct branches in its posterolateral aspect from the ramus communicans or the ventral ramus [12]. In a healthy lumbar disc, nerve endings can be found only in the periphery of the outer annulus fibrosus (AF) and throughout the end plate with varying densities: no nerves are normally present in the inner AF or nucleus pulposus (NP) [13–17]. These nerves are mainly nociceptive, respond to neurotrophins, such as nerve growth factor, and are implicated in disc pain transmission [18]. However, in highly degenerated discs, these nerves can penetrate into the NP [19,20].

All the tissues that surround the spinal motion segment (vertebra plus adjacent discs) are innervated and thus have the potential to cause pain. In clinical practice, we can, however, neglect muscles as major chronic back pain generators as pain from muscles is of lesser intensity and tends to subside within days of symptom initiation [21]. The facet joints are extensively innervated synovial joints that lie posterior to the disc. They function synergistically with the disc to constrain spine motion. Reduced disc height associated with DD can lead to facet overloading and subsequent facet degeneration and pain [22]. Facet pain can be exacerbated by increased compression from spinal extension. However, the fact that facet degeneration and pain are not always associated with DD motivates further investigation with large-scale studies to identify other facet degeneration triggers, such as morphology.

The disc is typically assumed to be the major cause of nonspecific LBP [23–25]. Consistent with innervation patterns, discographic studies have shown that only annular ruptures that extend to the outer AF associate with provocation of a patients' typical pain [26]. In support of their clinical significance, a cadaveric study related radial tears with a history of frequent LBP [27]. As a clinical rule of thumb, LBP of young subjects is more likely discogenic in nature, whereas in older subjects, the likelihood of facet joint-related pain increases [23]. This clinical observation supports the notion that DD most likely precedes facet degeneration and the significance of radial tears that are reported to occur in a young age group (11–16 years) [28]. Yet, although discography has been used widely to localize painful discs and is regarded as the gold standard in the diagnosis of discogenic pain, this procedure is invasive and may even enhance progression of DD itself [29]. Unfortunately, none of the standard clinical tests can differentiate discogenic from nondiscogenic pain [25,30].

Epidemiological studies

For the past two decades, magnetic resonance imaging (MRI) has been the gold standard in assessing DD severity (Fig. 1) [31–33]. In the T2-weighted MRI sequences, water content is correlated positively with signal intensity; therefore, the healthy NP is bright on T2 MRI because it contains a large amount of proteoglycan (PG) that attracts water. In DD, PG degradation results in a secondary reduction in water content, and consequently, the NP signal darkens on T2 MRI. Therefore, the loss of MRI “signal intensity” has become synonymous with DD and is often used as a marker to relate DD with LBP. However, we must be mindful that grades of DD based on imaging may not always correlate with the true gold-standard histology [34].

In 1990, Boden et al. [35] assessed the sagittal MRIs of 67 asymptomatic subjects. Because most subjects exhibited lumbar DD, the authors concluded that DD is not synonymous with pain. Since then, numerous groups have tested this association using larger sample sizes, the results of which provide some evidence that DD is associated with LBP [8,9,11,36,37]. In fact, both global severity [10,11] and patterning [38] of lumbar DD are associated with increased risk of LBP. For example, a large-scale 4-year prospective study among asymptomatic Southern Chinese adults by Samartzis et al. [39] has reported that baseline patterns of DD may predict future development of first-time LBP episodes. This indicates that although overall DD may not be synonymous with LBP, perhaps, specific degeneration patterns and severity may foretell a pain risk profile. However, it is important to note that currently we usually do not know how these population studies on DD imaging can be applied to an individual patient because degeneration is frequently observed in asymptomatic subjects [11,35,40,41].

Although DD on MRI imaging may not provide the locus of pain, other imaging findings may be clinically useful. High-intensity zone lesions have been described as markers of painful internal disc disruption [42,43], but this view has been lately questioned [44–46]. Radial tears may be better indicators of pain (as discussed previously), but controversial data on their diagnostic role have been presented [47,48]. However, both these phenotypes have not been thoroughly investigated and demand further attention. Alternatively, recent evidence has stressed that the vertebral end plate is an important pain generator, and defects/abnormalities at this anatomic site may have clinical relevance [16,17,49].

In support of the end plate’s clinical relevance, the most promising MRI phenotype of discogenic pain are the so-called Modic changes, originally described by Modic et al. in 1980 (Fig. 1) [50]. Modic changes are vertebral bone marrow MRI signal intensity changes that are attributed to various etiological determinants (eg, abnormal biomechanics, bacterial infection, lifestyle factors, and so forth). Several studies have noted an association between Modic changes and LBP [30,51–54], although negative findings have also been reported [55]. Type I Modic changes, with low signal intensity on T1-weighted and high signal intensity on T2-weighted images, consistently show stronger association with LBP than Type II lesions (ie, fatty infiltration) [53,54]. This may be because of the inflammatory etiology of Type I changes [50,56]. However, reliable identification of Modic changes can be confounded by technical factors, such as MRI field strength [57]. In addition, there are other

more fundamental issues that limit consensus between population studies that attempt to link LBP to imaging findings. First, phenotypic definitions of spinal findings (eg, stages/ interpretation of DD, end-plate lesions, Modic types, and so forth) are heterogenic between studies and the current classification schemes do not fully depict the underlining pathobiology. This fact may necessitate reclassification or standardization between investigators [58]. Second, because of individual variation pain perception, large sample sizes are needed to support robust conclusions regarding imaging findings and pain. Third, the pain phenotype and patient reports of the findings can vary widely, in particular between ethnicities [59]. Fourth, statistical analysis is oftentimes limited. As such, standardization of “more sensitive” imaging modalities that are more closely linked to the pain profile or pain genetics are needed to clarify what distinguishes physiologic nonpainful degeneration from pathologic painful degeneration.

Imaging

Imaging technologies have proven useful for surgical planning and to categorize patients with various spinal disorders, such as radiculopathy and stenosis [60]. However, most chronic LBP patients fall into a third category, non-specific LBP, where no specific pathology can be identified and the use of advanced imaging has not been shown to improve outcomes [61]. At the same time, advanced imaging can increase the identification of incidental findings that can trigger a cascade of diagnostic procedures or treatments that can be costly and may pose risks to the patient [62,63]. Consequently, current consensus recommends against the routine use of advanced imaging except in cases of suspected serious pathology and when conservative care is unsuccessful [64,65].

Mixed pathologies are common in DD, challenging the clinician’s ability to distinguish the dominant pathology responsible for the patient’s pain. Consequently, there is a need for improved imaging techniques that discriminate between pain generators and incidental degenerative findings. Success in this regard relies on matching the fundamental principles of imaging technologies with mechanisms of pathologic pain. Doing so will increase diagnostic certainty, particularly during the initial stage of DD, and provide information about disease activity that can be used to measure treatment efficacy in clinical trials.

Radiographic detection of DD via the Thompson grading scale is the most common clinical method in use but is limited to detection of gross morphologic deformities [66]. It does not depict soft tissues clearly and requires the injection of contrast to detect subtle internal disc abnormalities, such as fissures. Computed tomography (CT) discography has been used to improve patient selection and consequently surgical outcome [67]. However, CT discography is problematic by being invasive because of radiation exposure and placement of a needle through the annular fibers for contrast injection and by the high incidences of false positives [68]. Although CT can accurately visualize disc morphology, it fails to distinguish findings that are symptomatic from those that are incidental. Hence, CT fails to demonstrate the cause of pain in patients without obvious nerve root compression. “Dynamic” CT can be employed to accurately measure spinal motion when a load or torque is applied, in vivo. This technique is made possible because of the advent of the high-speed

capability and image processing tools in CT scanners [69]. However, this is also limited by uncertainty regarding intervertebral movement patterns that are specific to painful levels.

Magnetic resonance imaging with its exquisite soft-tissue contrast has tremendous potential for characterizing disc matrix quality through morphologic and functional parameters. In conventional (T2-weighted) MR images, the NP appears bright and the AF is invisible because of its short T2 in the normal disc. Disc degeneration can be qualitatively graded by quantifying reduction in signal intensity of the NP [70], whereas in advanced stages of degeneration, there is no clear distinction between NP and AF. The widely used classification system of Pfirrmann et al. [31] (based on T2-weighted MR images) provides an integer grade (between I and V) based on structural morphology (eg, homogeneity within the NP, distinction between the NP and AF, signal intensity, and disc height). Although this classification system is among the most widely accepted and used [71] and provides excellent detection of advanced stage degeneration, integer-based classification systems cannot discriminate among early degenerative changes [72,73]. Moreover, integer classification systems are qualitative, susceptible to observer bias, and are not specific for disc substructures. It is not surprising, therefore, that there is little correlation between integer classification of DD with the presence or severity of clinical symptoms. This limits the value of integer-based systems (Pfirrmann and Thompson grades) in clinical decision making.

Consequently, although traditional MRI methods can effectively detect morphologic changes in the disc, they lack sensitivity to the early stages of DD and other subtle changes of key pain generator phenotypes. Hence, newer MRI-based methods are being developed to detect and quantify the biochemical composition of the disc extracellular matrix because subtle changes in the NP and AF composition and structure are the earliest changes in DD. The following methods have evolved over the last few years from several research groups that are specifically working in developing protocols for eventual application in the clinical setting.

T1_ρ MRI

T1_ρ(T1-rho) MRI is an alternative to conventional T1 and T1 MRI [74] in which a long-duration low-power radiofrequency (RF) referred to as “spin-lock” pulse is applied to the magnetization in the transverse plane (Fig. 2). Here, the magnetization undergoes relaxation in the presence of the field (B_1) in the rotating frame, a situation analogous to that of the longitudinal magnetization in the main magnetic (B_0) field, but $B_1 \ll B_0$. The spin-locked magnetization will relax with a time constant T1_ρ, called the spin-lattice relaxation in the rotating frame [74]. Spin locking attenuates the effect of signal loss mechanisms on the MRI signal and for this reason: T1_ρ is always greater than T2. Images obtained by performing T1_ρ MRI with four to five different SL pulse durations, while keeping the amplitude fixed, can be used to obtain quantitative “T1_ρ maps” of tissues, such as the disc. T1_ρ MRI has recently been used as a biomarker for DD with a low T1_ρ value correlating with higher disc changes, low PG content, low swelling pressure in the NP, and the presence of pain (as verified by discography) [75–78].

Chemical exchange saturation transfer MRI

Chemical exchange saturation transfer (CEST) is a method to directly detect exchangeable solute protons in tissues by constant irradiation and saturation of their chemically shifted magnetization (Fig. 3) [79]. The CEST signal is detected as a reduction in the water signal after the saturated spins undergo chemical exchange with water [80], provided the exchange is more rapid than the T₁ of either site. The asymmetric distribution of labile protons around the central water peak in cartilage is readily detected in the difference image obtained after saturating symmetrically on either side of the water. A very homogeneous B₀ is necessary for a robust estimation of the difference signal. Furthermore, care must also be taken to avoid the direct saturation of the water peak because of the close resonances of labile species of interest.

In spite of these stringent requirements, solutes in the nanomolar to millimolar range have been reliably detected using this approach in vitro [81] and in vivo [82]. The feasibility of CEST MRI to reliably detect glycosaminoglycan in vivo was recently demonstrated in the cartilage of the knee joint [83] by comparing it with sodium MRI of the same joint. With regard to the disc, Kim et al. [84] used a new water frequency mapping approach, called “water saturation shift referencing,” which provides a more accurate quantification of CEST effects. However, CEST MRI suffers from poor signal to noise and, hence, has reduced sensitivity compared with other novel MRI methods.

Ultrashort time-to-echo MRI

The vertebral end plate is a composite of bony and cartilaginous layers. The end plate has a significant role in disc metabolism by being the route for transport of nutrients to, and waste products from, the avascular disc [85]. The end plate also plays an important biomechanical role of resisting significant spinal compressive forces. Because it has previously been hypothesized that changes in disc mechanics may be initiated by damage to the end plate [86], the visualization of end-plate defects may provide clues to the cause of DD. Furthermore, because end-plate defects are highly innervated, their quantification may provide a sensitive and specific index of disc pain risk [17,87].

Unfortunately, end-plate integrity is not discernible by conventional T₂ MRI because it appears dark on T₂ because of a strong dipolar interaction experienced by protons in water bound to collagen, which results in short T₂s (~1 to 10 ms). The ultrashort time-to-echo (UTE) MRI pulse sequence overcomes this impediment by either selecting the short T₂ components with special RF pulses or combining images acquired at different echo times to effectively produce an MRI of only the short T₂ species (Fig. 4) [88]. This allows for the potential to characterize end-plate morphology and biochemistry [89]. There are several approaches to perform UTE MRI on clinical scanners. In one instance, a narrow bandwidth excitation RF pulse selectively destroys magnetization from long T₂ components by using dephasing gradients, leaving the short T₂ components largely unaffected [90]. Other methods combine pairs of images obtained by a half RF excitation with and without gradient reversal followed by radial imaging [91]. The latter method has been employed to visualize the collagen-rich AF in human intervertebral disc [92] in which patients with the most severe DD show irregular signal from the end plates compared with normal; however, the

reason for this observation is unclear. In a recent study by Law et al. [93] assessing the utility of UTE MRI in human subjects in vivo, the authors noted that cartilaginous end-plate defects were more common in the lower lumbar spine and associated with an increase severity of DD compared with those with no end-plate defects.

Sodium MRI

Osmotic attraction of water is a fundamental attribute of the disc nucleus that is required for proper biomechanical function. Osmotic tissue swelling is facilitated by a negative fixed charge density (FCD) of the nucleus matrix. Maroudas et al. [94] have shown that the FCD is correlated to PG in the extracellular matrix. Fixed charge density is decreased in disc tissues [95,96] causing the dark nucleus that is characteristic of DD on T2 MRI as noted previously. Because FCD is counterbalanced by the Na^+ ions, there is interest in sodium imaging as a means to assess the functional competency of the disc nucleus.

Although nonquantitative sodium MRI of the spine has been reported [97], Wang et al. [98] recently employed a quantitative method to image sodium in the bovine disc, the results of which were significantly correlated to a gold-standard PG biochemical measure (dimethyl methylene blue assay, Fig. 5). Subsequent preliminary application of sodium MRI to human discs in vivo suggest that this technique may differentiate discs between asymptomatic and LBP patients. However, sodium MRI is in limited use because of the requirement for special hardware modifications to the conventional MRI scanner. The short T2 of ^{23}Na (about few milliseconds) means that sodium MRI has to be performed with MRI pulse sequences with ultra-short echo times. Furthermore, due low sodium concentrations in tissues, sodium MRI requires field strengths $\geq 3\text{T}$ to obtain quality images to enable accurate quantification of FCD and PG. Sodium MRI requires four times stronger gradients to obtain images with identical resolution to that of proton MRI. Because of these constraints, sodium MRI is currently infeasible for routine clinical use.

Pain genes

Pain is often times regarded as the body's protective mechanism, eliciting warnings from impending or actual tissue injury that stems from thermal, chemical, disease, or mechanical forces. Pain is multimodal in nature, and significant interindividual variability has been noted to be present. Such variation has been evident with regard to heritability, response of analgesic use, susceptibilities to pain stimuli and chronic pain syndromes, and cancer-induced pain [99,100], suggesting that pain sensitivity may be under genetic control. This variability in an individual's pain response to pathology further complicates the establishment of generalizable LBP diagnostic criteria. Furthermore, because of the continued challenges to "image pain" and the complexities of pain perception/experience in individuals, "pain genetics" may shed light in understanding an individual's pain profile (Table).

In the past decade, it has become increasingly evident that genetics plays a substantial role in the development of numerous medical conditions, such as Alzheimer's disease, macular degeneration, diabetes, obesity, and various cancers. With regard to spine-related conditions, genetic factors have also been implicated in the development of scoliosis [101], ankylosing

spondylitis [102], and DD among others [10,36,103–111]. Recent evidence has also suggested that genetics plays a role in shaping the cortical thickness and structure of the brain [112] and the predisposition to various psychological disorders/behaviors and even intelligence [113]. Such evidence that genetic factors may affect higher brain systems and neural networking further lend credence to the notion that processing of pain sensation, perception, and tolerance may be under genetic influence.

Based on a twin study from the United Kingdom, the susceptibility for genetic factors accounts for 68% of neck pain and 35% of LBP [114]. Mutations associated with the *SCN9A* gene affect the voltage-gated sodium channels causing channelopathy syndromes that can lead to complete insensitivity to pain or extreme pain sensation [115]. Genetic polymorphisms in the *HSAN* gene may also lead to sensory and autonomic neuropathies that can affect myelination of nerve fibers and supporting glial cells, which may affect pain [116]. Pain tolerance has been noted in red-headed individuals because of a mutation in the melanocortin-1 gene, the nonmutated gene causing an increase in pain sensitivity [117]. Guanosine triphosphate cyclohydrolase 1 is an enzyme that synthesizes catecholamine neurotransmitters. This enzyme is encoded by the *GCHI* gene, which modulates pain sensitivity [118]. Catechol-*O*-methyltransferase (*COMT*) catabolizes catecholamine neurotransmitters. Polymorphisms in the *COMT* gene modulate the pain experience by affecting higher cognitive and emotional processes of the brain, which can affect low to high levels of pain sensitivity [119].

In recent years, the identification of more than 100 “pain genes” (eg, *OPRD1*, *FAAH*, *NTRK1*, *OPRM1*, *ABCB1*, *GCHI*, *TRPV1*, and *COMT*) have advanced tremendously our understanding of how pain is modulated, perceived, experienced, and tolerated. Studies in several patient cohorts have noted that pain genes may play a role in postoperative outcomes; however, studies addressing patients undergoing spine surgery are limited. Recent studies based on a US cohort of 69 patients who underwent spinal fusion for DD have suggested that polymorphisms in the *GCHI* [120] and *COMT* [121] genes predict postoperative disability and that such genes may be “pain protective” and potential markers for successful outcomes in spine surgery. However, these studies consisted of a small sample size and the populations were heterogeneous, which may introduce bias that may affect the pain outcome [122,123]. Furthermore, studies did not address gene-environment interactions, the analyses were limited, and the presence and interaction of additional known pain genes were not addressed. As such, the true role of pain genes in spine surgery patients needs further exploration in larger more homogenous populations with more extensive analysis of various modifiable and nonmodifiable factors and outcome parameters. Recent studies by Olsen et al. [124] and Jacobsen et al. [125] from Norway have indicated that specific pain genes may predict pain intensity, long-lasting sciatica, and disability after surgery for lumbar disc herniation; however, such studies suffer from similar limitations as those that have preceded. Moreover, other factors that were recently identified as modifiers or modulators of genetic effects on pain (eg, sex and stress) should be considered. For example, a recent association study revealed the influence of the vasopressin-1A receptor gene (*AVPR1A*) on pain levels but only in male subjects reporting stress at the time of testing [126]. A cross-sectional study of LBP in 371 monozygotic and 698 dizygotic twin pairs showed that genetic background and lumbar DD are main risk factors of severe and

disabling LBP in females [127]. This study also showed a significant genetic correlation between DD and LBP outcomes, suggesting that approximately 11% to 13% of the genetic effects are shared by the aforementioned conditions. Therefore, one's susceptibility to pain as mediated by pain genes may explain why some individuals with different stages of DD on MRI may exhibit varying degrees of LBP, which may not oftentimes be expected.

Other genetic factors contributing to LBP may be shared with musculoskeletal pain disorders, such as chronic widespread pain (CWP) and fibromyalgia, and/or painful joint disorders, such as osteoarthritis (OA). A prospective population-based cohort study on persistent CWP found association with genetic variation in hypothalamic-pituitary-adrenal (HPA) axis genes [128]. Another large population-based study on CWP found that functional variants in the beta-2 adrenergic receptor gene (*ADRB2*) are involved in regulating pain status at a population level [128]. This is in line with previously reported data on the role of *ADRB2* polymorphism in other chronic musculoskeletal pain conditions—temporomandibular joint disorder [129] and fibromyalgia [130]—leading to the suggestion that this gene might influence LBP through overlapping mechanisms. Interesting findings have been reported in the genetic studies of OA [131] that may be relevant to LBP because chronic LBP is a frequent comorbid condition. These genes are of top priority for future genetic association studies on DD and LBP, to investigate common biological mechanisms and shared genetic background. Upcoming genome-wide association studies of persistent LBP, CWP, temporomandibular joint disorder, and OA will provide more comprehensive unbiased approach to study genetics of these disorders by identification of novel genes and pathways contributing to interpatient variability in symptoms and their severity.

Conclusions

The association between DD and LBP is often debated. Although some studies demonstrate significant degeneration in asymptomatic subjects, large-scale epidemiological studies suggest that DD severity or specific patterning of MRI phenotypes may predict LBP occurrence. Yet, although epidemiological studies may shed light on cause-and-effect relationships, they provide little help with the clinical management of individual patients. This may be attributed to a variety of methodological limitations, inconsistencies, and ill-defined degeneration phenotypes that need to be redefined, reclassified, and standardized. Importantly, poor correspondence between DD phenotypes and LBP highlights the need for more sensitive and quantitative imaging tools that assess disc and end-plate integrity beyond the traditional T2-weighted MRI sequences [58,132,133].

Various novel MRI approaches have been introduced to detect subtle chemical changes of the disc matrix that may have important clinical value (eg, T1ρ, CEST, UTE, and sodium MRI). However, indications for use are currently not agreed on because prospective studies that validate the utility of these techniques, both in terms of LBP diagnosis and improved clinical outcomes, have not been extensively performed. Success in this regard may require statistical and machine-learning algorithms that combine multiple imaging biomarkers into a tractable classification scheme [134,135] to address several objectives, such as which approach gives the most timely, reliable, and accurate measurement of the pathologic

changes because of DD. As such, a multiparametric imaging platform may be needed to fully assess the motion segment and its clinical implications.

Advances in pain genetics have also broadened our understanding of LBP. As such, a more personalized approach to understanding the interplay between DD and LBP may be warranted. Pain genetics may further expand on our knowledge as to factors that distinguish physiologic from pathologic DD, progression and severity of pain, and outcome after treatments. Such information, coupled with novel imaging to help localize and “image pain,” may further aid in understanding the DD and pain profiles of an individual and identifying ideal candidates for biological therapies for disc regeneration/repair and pain alleviation. Therefore, a concerted effort for global consortiums, such as the International Spine and Pain Consortium, is needed to bring together a multidisciplinary group of spine and pain specialists to address such burning concerns and further refine the understanding of DD and LBP.

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Fig. 1. Sagittal T2-weighted magnetic resonance imaging of the lumbar spine. (Left) Normal hydrated discs manifesting as high signal intensity in an asymptomatic subject. (Right) Loss of disc signal intensity, with multiple levels of decreased disc height, Modic changes, end-plate abnormalities, disc displacement, and loss of lumbar lordosis in an individual with low back pain.

Fig. 2.

Representative proton T2 magnetic resonance imaging (gray scale) and corresponding T1ρ maps (in color overlaid on gray-scale T1ρ-weighted image) of the lumbar discs from (Left) a 52-year-old female and (Middle) a 35-year-old male patients diagnosed with low back pain and from (Right) an asymptomatic 38-year-old man. Average T1ρ (in milliseconds) was measured in the disc nucleus and is displayed below each disc, followed by the opening pressure (in psi) and whether discs were painful (P) or nonpainful (N), both determined by discography are indicated in the lower back pain patients [136].

Fig. 3.

A glycosaminoglycan map of the intervertebral disc is determined using the magnetic resonance imaging glycosaminoglycan chemical exchange saturation transfer (gagCEST) method in two subjects: (Top) a 25-year-old woman at L5–S1 and (Bottom) a 54-year-old man at L5–S1. The nucleus pulposus is delineated from the annulus fibrosus (AF) region by the dotted oval in the 1.5-ppm images. The gagCEST maps are shown at different frequency offsets relative to water at 0 ppm. In both subjects, the gagCEST effect is highest in the 0.75- to 1-ppm range of frequency offsets [84].

Fig. 4.
(Left) T2-weighted magnetic resonance imaging (MRI) of the lumbar spine and its corresponding (Right) ultrashort time-to-echo MRI.

Fig. 5. Representative proton T2-weighted magnetic resonance imaging (gray scale) and corresponding sodium maps (color) obtained in vivo. (Top) A 22-year-old man with lower lumbar trauma that resulted in chronic low back pain. (Bottom) A 26-year-old asymptomatic man [98].

Table

Pain genes and their function

Gene	Protein	Mutation	Phenotype	Reference
<i>ABCB1</i>	ATP-binding cassette, B1	Multiple SNPs	Altered morphine sensitivity	Campa et al. [137] Bastami et al. [138] Rhodin A et al. [139]
<i>ADRB2</i>	Beta-2 adrenergic receptor	SNP	Increased pain sensitivity	Skouen et al. [140]
<i>CACNA2D2</i> *	Calcium channel complex subunit	SNP	Increased opioid sensitivity	Rhodin A et al. [139]
<i>COMT</i> *	Catechol- <i>O</i> -methyltransferase	Multiple SNPs	Increased/decreased pain sensitivity	Dai et al. [121] Diatchenko et al. [141] Rut et al. [142] Jacobsen et al. [125]
<i>CYP2D6</i>	Cytochrome P450 2D6	Multiple SNPs	Altered analgesic efficacy	Stamer et al. [143]
<i>FAAH</i>	Fatty acid amide hydrolase	Multiple SNPs	Increased pain sensitivity	Kim et al. [144]
<i>GCH1</i> *	GTP cyclohydrolase	Multiple SNPs	Partial analgesia	Kim et al. [120]; Tegeder et al. [118]
<i>HTR2A</i>	Serotonin receptor 2A	SNP	Increased pain sensitivity and increased number of painful sites	Bondy et al. [145] Gursoy et al. [14]
<i>5-HTR3B</i>	Serotonin receptor 3B	SNP	Pain catastrophizing	Horjales-Araujo et al. [146]
<i>IL1-B</i>	Interleukin-1beta	SNP	Increased pain sensitivity	Oliveira et al. [147]
<i>IL18RAP, IL18R1, IL1A</i>	Interleukin 18 receptor accessory protein, interleukin 18 receptor 1, and interleukin 1A	Haplotype association	Decreased pain sensitivity	Omair et al. [148]
<i>IL-6</i> *	Interleukin-6 GGGA haplotype	SNP	Increased pain sensitivity	Karppinen et al. [149]
<i>KCNJ6 (GIRK2)</i>	G-protein-coupled inwardly rectifying potassium (GIRK) channel 2	Multiple SNPs	Increased pain sensitivity	Bruehl et al. [150]
<i>MC1R</i>	Melanocortin-1 receptor	Loss of function SNPs	Partial analgesia and increased analgesic responsiveness	Mogil et al. [117]
<i>MMP1</i> *	Metalloproteinase 1	SNP	Increased pain sensitivity	Jacobsen et al. [151]
<i>MMP3</i> *	Matrix metalloproteinase 3	SNP	Decreased pain sensitivity	Omair et al. [148]
<i>OPRD1</i>	Opioid receptor δ 1	Multiple SNPs	Increased/decreased pain sensitivity	Kim et al. [152]
<i>OPRM1</i> *	Opioid receptor μ 1	Multiple SNPs	Increased/decreased pain sensitivity and decreased opioid analgesia	Fillingim et al. [153] Solak et al. [154]

Gene	Protein	Mutation	Phenotype	Reference
<i>P2RX7</i> *	ATP-gated ion channel P2X7	Multiple SNPs	Increased pain sensitivity	Olsen et al. [124] Rhodin A et al. [139] Ursu et al. [155]
<i>SCN9A</i> *	A-subunit voltage-gated Na (v) 1.7	Multiple SNPs	Increased/decreased pain sensitivity	Reimann et al. [156] Yang et al. [157]
<i>SERPINA1</i>	Alpha-1 antitrypsin	SNP	Increased number of painful sites	Holliday et al. [158]
<i>TRPA1</i>	Transient receptor potential A1	Multiple SNPs	Increased pain sensitivity	Kim et al. [152]
<i>TRPV1</i>	Transient receptor potential V1	SNP	Decreased pain sensitivity	Kim et al. [152]
<i>UGT2B7</i>	UDP glucuronosyltransferase 2 family, polypeptide B7	SNP	Altered morphine sensitivity	Bastami et al. [138]

ATP, adenosine triphosphate; GTP, guanosine triphosphate; SNP, single-nucleotide polymorphism; UDP, uridine 5'-diphosphoglucuronosyltransferase. This list is not inclusive of all pain genes.

* Asterisk denotes reported investigation in spine patients.