REVIEW ARTICLE

Genetic factors in intervertebral disc degeneration

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Abstract
Low back pain (LBP) is a major cause of disability and imposes huge economic burdens on human society worldwide. Among many factors responsible for LBP, intervertebral disc degeneration (IDD) is the most common disorder and is a target for intervention. The etiology of IDD is complex and its mechanism is still not completely understood. Many factors such as aging, spine deformities and diseases, spine injuries, and genetic factors are involved in the pathogenesis of IDD. In this review, we will focus on the recent advances in studies on the most promising and extensively examined genetic factors associated with IDD in humans. A number of genetic defects have been correlated with structural and functional changes within the intervertebral disc (IVD), which may compromise the disc’s mechanical properties and metabolic activities. These genetic and proteomic studies have begun to shed light on the molecular basis of IDD, suggesting that genetic factors are important contributors to the onset and progression of IDD. By continuing to improve our understanding of the molecular mechanisms of IDD, specific early diagnosis and more effective treatments for this disabling disease will be possible in the future.

Abbreviations: LBP, low back pain; IDD, intervertebral disc degeneration; IVD, intervertebral disc; NP, nucleus pulposus; AF, annulus fibrosus; EP, endplate; ECM, extracellular matrix; MRI, magnetic resonance imaging; SNP, single-nucleotide polymorphism; MMPs, matrix metalloproteinases; VDR, vitamin D receptor.

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Introduction

Low back pain (LBP) is a leading cause of disability worldwide and has tremendous effects on the economy and quality of life of the patients.\(^1\)\(^-\)\(^4\) LBP imposes an economic burden similar to or even greater than that of coronary heart disease and other major health problems such as diabetes, Alzheimer’s disease and kidney diseases.\(^1\)\(^-\)\(^4\) As the second most common cause of doctor visits in the USA, LBP treatment costs $20–100 billion in direct care spending and contributes $100–200 billion each year in total economic burden, according to studies about the direct and indirect costs of LBP published in English from 1997 to 2007.\(^2\)\(^,\)\(^6\)\(^-\)\(^10\)

Among many causes of LBP, intervertebral disc degeneration (IDD) is the most common diagnosis and target for intervention. IDD plays a critical role in LBP and correlates strongly with structural breakdown and dysfunction of the intervertebral disc (IVD).\(^11\)\(^,\)\(^12\) The etiology of IDD is complex and multifactorial, in which aging, certain diseases and injuries, and genetic factors are involved. Since the mechanisms of IDD are still not completely understood, current treatment is largely limited to symptomatic relief using non-steroidal or steroidal anti-inflammatory medication and surgical intervention for late-stage IDD with severe neurological symptoms caused by herniation of IVD.\(^6\) A better understanding of IDD will enable more targeted and less invasive therapies while keeping people mobile and functional.\(^3\)\(^,\)\(^8\)\(^,\)\(^9\) This review article will focus on the recent advances in understanding the genetic mechanisms of IDD. The first section is a brief review of the basic structural and functional characteristics of IVD; the second section summarizes the recent studies on the most promising and extensively examined genetic factors associated with IDD in humans.

Structural and functional characteristics of IVD

The IVD is a fibrocartilaginous tissue connecting two adjacent vertebral bodies in the spine.\(^13\) IVD is an elastic structure and functions as a weight-bearing cushion which plays a major role in maintaining flexibility and stability of the spine.\(^1\) The IVD is composed of the external annulus fibrosus (AF) and the inner gel-like center, the nucleus pulposus (NP). The central NP consists of a water-based gel-like avascular substance rich in proteoglycans and a small amount of collagen type II and elastin fibers; the function of the elastic NP is to distribute hydraulic pressure in all directions within each disc under compressive loads.\(^7\)\(^,\)\(^11\) The outer region AF encloses the NP with a type I collagen-based concentric lamellar structure.\(^8\)\(^,\)\(^11\) Within each lamella, the collagen fibers are aligned approximately 30° with respect to the transverse plane of the vertebral endplates (EP). There are two thin EPs, which extend superiorly and inferiorly over the inner AF and NP and supply nutrients to discs by diffusion. The EPs consist of osseous and hyaline-cartilaginous layers and connect the intervertebral disc to the vertebral bodies. Only NP and the inner AF are covered by the cartilaginous endplates. The collagen fibers of the outer AF anchor directly into the bone of the apophyseal ring. There is no distinct border between the NP and the inner AF.\(^11\)

There are different cell types located in various regions of the IVD. The cartilaginous EPs contain rounded chondrocytes, similar to the hyaline cartilage in other locations. The cells in the outer AF are elongated and fibroblast-like, whereas in the most inner zone of AF and the NP, the cells become more spheroidal and chondrocyte-like. The NP contains a relatively small number of fibroblasts and more numerous chondrocyte-like cells (Fig. 1A). The cell types of cartilaginous EP and AF remain relatively constant throughout their life. However, the NP goes through substantial cell type changes early in life.\(^7\)\(^,\)\(^14\) Cells in NP at birth are largely of notochordal origin, but in most humans, the number of notochordal cells decreases rapidly after birth and eventually becomes undetectable at about 4–10 years of age.\(^15\) At the same time, the NP is gradually populated with chondrocyte-like cells, probably originating and migrating from the cartilaginous EPs and the inner AF.\(^7\) Although the detailed mechanism of this cell type transition is still unknown, it has been assumed that Fas, a member of the tumor necrosis factor receptor family, plays a role in this process. Apoptosis induced by an autocrine or paracrine Fas-mediated counterattack may be important in this transition.\(^9\)\(^,\)\(^14\) Human notochordal cells gradually disappear with aging, which correlates with disc degeneration. These observations suggest that the notochordal cell population may be involved in maintenance and regeneration of IVD.\(^17\)

However, the transplantation of notochordal cells into IVD to reverse degeneration is not feasible clinically, because it relies on the removal of notochordal cells at an early age. The use of soluble factors produced by notochordal cells may be more practical than cell transplantation.\(^3\)\(^,\)\(^8\)\(^,\)\(^14\)

The extracellular matrix (ECM) composition is very important for IVD structure and function because changes in ECM can eventually contribute to IDD.\(^3\) Type I and II collagens are the main components of IVD. Peripheral AF ECM contains mostly type I collagen with relatively low proteoglycan and water content. ECM of the inner AF becomes higher in type II collagen and proteoglycans. In general, collagens account for approximately 60% of the AF dry weight whereas proteoglycans account for approximately 25%. Other collagen types, such as type XI and type IX collagens, which play a role in assembly of type II collagen fibrils and formation of crosslinks between the adjacent collagen fibrils, comprise a small portion of ECM. In comparison with the AF, the ECM in NP contains more type II collagen and proteoglycans, the function of which is to maintain water content and to withstand conductive pressure. Aggrecan, the most common proteoglycan, constitutes up to 50% of NP dry weight and is responsible for osmotic properties and helps maintain disc height and ability to withstand compression.\(^3\)\(^,\)\(^9\)

During the course of growth and skeletal maturation, under the influence of both intrinsic and extrinsic factors, the boundary between NP and AF becomes less obvious. The nucleus generally becomes more fibrotic and less gel-like, while the annular lamellae become irregular with disorganized collagen and elastin networks. During the progression of IDD, cleft formation with fissuring is usually seen within the disc, especially in the nucleus. Degeneration of the AF allows the NP to push out towards the outer AF causing disc bulge (Fig. 1B). Complete rupture of the AF allows the NP to protrude beyond the boundary of the disc.
(herniation of IVD/NP) and pressure on the spinal cord and/or nerve root depending on the location of disc herniation. In addition, nerve and blood vessel formation, cell proliferation, and cell death can also be found in and around the degenerated IVD.6

Genetic factors involved IDD

Current therapeutic strategies to alleviate low back pain resulting from IDD generally lie in conservative treatments, which include physiotherapy and anti-inflammatory medication. Although these conservative strategies are often effective to relieve symptoms, actual causes of the degeneration are not addressed. To enable more targeted and less invasive therapies, it is imperative to have a more thorough understanding about the etiology and pathogenetic mechanisms of IDD. Though huge efforts have been put into IDD research and substantial progress has been made, the real cause of IDD is still largely unclear. It is believed that IDD and associated degenerative entities such as disc herniation are attributed to many different factors, both biological and environmental. Certain factors, such as aging, injury and spinal deformity, have been proposed and investigated, and their contributions to IDD are acknowledged.6,18,19

New genetic and proteomic tools have begun to promote our understanding of the molecular basis of diseases. Insights gained from several studies suggest that genetic factors are critical contributors to the onset and progression of IDD.9,13,20–22 However, it is still unknown whether a specific gene effect of relatively large magnitude exists or the genetic contribution is due to the sum of small effects of many genes. Identification of specific genetic influences on the development of IDD will provide us key insights into the molecular mechanism of the disease. This review is not intended to cover all of the genes involved in IDD; rather, we will discuss a few most promising and extensively studied gene loci closely associated with the pathogenesis of IDD in humans.

Collagen I

Collagen I (Type I collagen) is an important protein in the skin, ligament, and bone. It is a heterotrimeric protein
composed of 2 identical α chains and a third chain that differs.\textsuperscript{13,23,24} The genes encoding collagen I, \textit{COL1A1} and \textit{COL1A2} are present in both NP and AF. Although the mechanism by which genetic alterations of collagen I influence the development of IDD is not fully understood, polymorphisms of \textit{COL1A1} gene have been reported to increase the risk of IDD in different population studies. In a Dutch population (65- to 85-year-old) with TT genotype of collagen type I α1 (\textit{COL1A1}) Sp1 polymorphism, their risk of disc degeneration was found to be higher than people with GG and GT genotypes,\textsuperscript{23} suggesting (\textit{COL1A1}) Sp1 polymorphism may be a genetic risk factor related to IDD in older people. In another study carried out in Greek military recruits, some young soldiers were diagnosed with early lumbar disc degeneration at the time of their presentation to a military training site. Genetic analyses indicated that 33.3% people in this population with lumbar disc disease had TT genotype polymorphism of \textit{COL1A1} Sp1 binding site; in contrast, no healthy people in the control group had the TT genotype.\textsuperscript{24} In a more recent Twin Spine Study from the population-based Finnish Twin Cohort, a specific IVD phenotype (disc signal intensity on magnetic resonance imaging) was strongly associated with allelic variants of \textit{COL1A1} gene (rs2075555; \(P = 0.005\)).\textsuperscript{25-27} These findings strongly suggest that \textit{COL1A1} is a candidate gene associated with the pathogenesis of disc degeneration.\textsuperscript{28}

Collagen IX

Collagen IX is a heterotrimeric protein consisting of 3 genetically distinct chains, α1, α2 and α3, encoded by the \textit{COL9A1}, \textit{COL9A2}, and \textit{COL9A3} genes, respectively.\textsuperscript{29} Both AF and NP contain small amounts of collagen IX, which is thought to serve as a bridge between collagens and non-collagenous proteins in tissues. Mutations in \textit{COL9} genes are known to affect disc degeneration in both mice and humans. Transgenic mice with an overexpression of mutant \textit{Col9a1} and mice with an inactivated \textit{Col9a1} were found to have accelerated disk degeneration and more herniation than the age-matched control group.\textsuperscript{26,29,30} The \textit{COL9A2} gene, which codes for the α2 chain of collagen IX, was screened for sequence variations in individuals with IDD in a Finnish population. Trp2, a rare \textit{COL9A2} allele that replaces the wild-type arginine with tryptophan, was found in 6 of 157 patients, but absent in 174 controls.\textsuperscript{30} Coinheritance of the Trp2 allele and the phenotype was studied in the families of four original patients. All members who had inherited the allele in those families developed intervertebral disc disease. A large cohort study of 804 Chinese individuals confirmed the above finding. The Trp2 allele was related to a 4-fold increase of annular tears in patients aged from 30 to 39 years, a 2.4-fold increase in disc degeneration defined by magnetic resonance imaging (MRI), and disc herniation in patients aged between 40 and 49. It has been found that one-fifth of Chinese population bear the Trp2 allele.\textsuperscript{31} However, the Trp2 association was not replicated in a German study of 250 patients.\textsuperscript{32}

In relation to the tryptophan allele Trp3 of \textit{COL9A3} gene, a 3-fold risk of IDD with the allele was shown in Finnish studies. The Trp3 allele was found in 24% of patients and 9% of controls in one study\textsuperscript{30} and 12.3% of 171 patients compared with 4.7% of 186 controls in another study (\(P = 0.000013\)).\textsuperscript{33} Solovieva et al. confirmed Trp2 association with disc degeneration and also noted a gene–gene interaction with an IL-1β polymorphism (rs1143634).\textsuperscript{34} Those with the Trp3 allele without the IL-1β polymorphism had an increased risk of signal intensity changes, but there was no effect on the IL-1β polymorphism. This significant change suggests that Trp3 is modified by an additional and seemingly irrelevant polymorphism or that the IL-1β polymorphism is a negative confounder with an unknown single complementary third factor.\textsuperscript{34} In contrast, similar association was not found in Greek patients.\textsuperscript{25,26,33,35} Therefore, further research with distinctive environmental, ethnic, and age factors is needed to establish a realistic association between the Trp alleles in \textit{COL9A2} and \textit{COL9A3} and disc degeneration.

Collagen XI

Type XI collagen is a cartilage-specific ECM protein important for cartilage-collagen fibril formation and for ECM organization. It consists of 3 α chains, which are encoded by \textit{COL11A1}, \textit{COL11A2}, and \textit{COL11A3} genes. The 3 chains fold into triple-helical heterotrimers to form procollagen, which is secreted into the ECM, where it participates in fibril formation with other specific collagens and regulates the diameter of cartilage collagen fibrils. Because of the interaction with collagen type II and IX in IVD, collagen XI and its encoding genes have been targeted as possible contributors to disc diseases. A strong association between the single-nucleotide polymorphism (SNP) in \textit{COL11A1} gene and lumbar disc herniation in Japanese patients with lumbar disease has been identified.\textsuperscript{36} Furthermore, the same study also found that \textit{Col11a1} mRNA was substantially expressed in healthy IVD, whereas its expression in patients with lumbar disc herniation was decreased along with the increase of degeneration severity. This finding suggests that the susceptibility of SNP produces unstable \textit{Col11a1} transcripts. Solovieva et al. found that a sequence variation in Intron 9 of \textit{Col11a2} was associated with an increased risk of disc bulges compared with those people without this polymorphism.\textsuperscript{34} Another large study conducted in 588 Finnish men found that two \textit{Col11a1} and three \textit{Col11a2} polymorphisms were associated with MRI-defined disc bulges and signal intensity. These polymorphisms may play a role in producing unstable transcripts of the disease-associated allele. Instability of gene transcription would cause decreased functional collagen and subsequent disc degeneration.\textsuperscript{27}

Aggrecan

Aggrecan is a proteoglycan that interacts with hyaluronan to form large aggregates, which are responsible for the ability of the tissues to resist compressive loads.\textsuperscript{37} This function is related to the structure of aggrecan, specifically to the large number of chondroitin sulfate chains present on its core protein. The chondroitin sulfate chains are located in two adjacent regions of the aggrecan core protein, termed the CS1 and CS2 domains. The human aggrecan gene (\textit{ACAN}) possesses variable numbers of tandem
repeat polymorphisms in the part of exon 12 encoding the CS1 domain. Alleles have been identified with CS1 repeat numbers ranging from 13 to 33, with 26, 27, or 28 repeats being the most common. This can result in variation in the degree of chondroitin sulfate substitution of aggrecan in different individuals and raise the possibility that the functional properties of aggrecan may vary between individuals. Those people with an inferior aggrecan structure may be more vulnerable to IDD and cartilage degeneration.\textsuperscript{39} Research from Kawaguchi et al. indicated that subjects with shorter variable numbers of tandem repeat length of the ACAN gene are at risk of developing multilevel disc degeneration at an early age.\textsuperscript{39} However, no correlation between ACAN CS1 polymorphism and IDD in 44 patients was established in research from Roughly et al.\textsuperscript{40} Therefore, current data are not sufficient to establish a strong association between the ACAN gene polymorphisms and IDD.

**Interleukin-1 (IL-1)**

IL-1 is a cytokine produced in response to inflammation, injury, or antigenic challenge.\textsuperscript{13,41,42} There are 3 members in IL-1 gene family: IL-1\textalpha, IL-1\textbeta, and IL-1 receptor antagonist (IL-1RN). The first 2 are strong inducers of inflammation, whereas IL-1RN is a suppressor of IL-1 because it competitively inhibits the binding of IL-1 to its receptors. Excessive and/or dysregulated activity of IL-1 is related to tissue destruction. Therefore, its synthesis, secretion, and biological activity are strongly associated with inflammatory disorders. When compared with normal IVDs, degenerated discs spontaneously produce increased amounts of IL-1 cytokines, with an increase in IL-1\textalpha and IL-1\textbeta, without an increase in IL-1RN. Furthermore, IL-1\textbeta has the tendency to upregulate itself, whereas IL-1\textalpha downregulates IL-1RN, further increasing the cytokine expression within the IVD.\textsuperscript{25,26}

IL-1 increases gene expression of MMP-3, MMP-9, and MMP-13, which are ECM degrading enzymes.\textsuperscript{44} At the same time, IL-1 decreases the expression of normal ECM molecule genes.\textsuperscript{45} Cells derived from degenerative discs showed upregulated expression of an aggrecanase ADAMTS-4 in the presence of IL-1.\textsuperscript{25,45} In a study involving 133 Finnish men, evidence has shown the effect of the IL-1 gene polymorphism locus on the risk of lumbar disc degeneration.\textsuperscript{46} A more than 3-fold increase in the risk of disc degeneration was observed in people with 2 IL-1\textalpha T889 alleles, compared to people without them. Additionally, a 2-fold increased risk for disc bulges was found in people carrying IL-1\textalpha C889-T or IL-1\textbeta C3954-T alleles. In another study by Karppinen et al., a 2.5-fold increased risk of endplate “Modic changes” was found in carriers of allele IL-1\textalpha C889-T.\textsuperscript{47} Modic changes are vertebral endplate and adjacent bone marrow changes visible in MRI, which are classified into 3 types: Type I shows a low signal intensity (SI) in T1-weighted images (T1WI) and a high SI in T2-weighted images (T2WI), indicating an ongoing active inflammatory degenerative process. Type II shows a high SI both in T1WI and in T2WI, reflecting fatty degeneration of the bone marrow. Type III shows a low SI both in T1WI and in T2WI, demonstrating a late regenerative process.\textsuperscript{47}

**Interleukin-6 (IL-6)**

Proinflammatory cytokine IL-6 has been correlated with the presence of either lower back pain or sciatica.\textsuperscript{47} A Finnish study showed that the risk allele (A allele) in an IL-6 SNP in Exon 5 (rs13006435) was strongly associated with IDD patients, compared with the controls.\textsuperscript{48} In another study analyzing the other three SNPs of IL-6 (rs1800797, rs1800796, rs1800795), the GCC haplotype was found to be associated with early development of disc degeneration in Danish girls, but not in boys. However, the difference between genders may result from the relatively small sample size.\textsuperscript{49} IDD and associated sciatica is characterized by tissue destruction, inflammation and pain, all of which correspond to the functions of IL-6.

**Matrix metalloproteinase-3 (MMP-3)**

One of the important pathological processes in IDD is the degradation of the disc matrix by enzymes such as matrix metalloproteinases (MMPs).\textsuperscript{50} MMP-3 is a potent proteoglycan-degrading enzyme that plays important role in IDD. Local conditions, such as mechanical loading and inflammation, may induce MMP-3 expression.\textsuperscript{38} Takahashi et al. reported that MMP-3 gene polymorphism (5A/6A) was linked to IDD in an elderly Japanese population (age 64 to 94). Compared with the 6A6A genotype, a significantly larger number of degenerative IVDs was observed in people with 5A5A and 5A6A genotypes.\textsuperscript{51} The association between MMP-3 and IDD was replicated in another study of 720 English women.\textsuperscript{52} In contrast, no association between IDD and MMP-3 was found in the study by Noponen-Hietala et al. of 29 Finnish probands with degenerative spinal stenosis (evaluated by MRI).\textsuperscript{25,26,53} Therefore, more studies are required to confirm the association between MMP-3 polymorphism and IDD.

**Vitamin D receptor (VDR)**

VDR mediates the function of Vitamin D and plays a role in normal bone mineralization and remodeling. Its association with degenerative disc disease has been validated in large populations of different ethnic backgrounds, including Chinese, Japanese, Finnish and English. VDR gene polymorphisms are believed to contribute to specific disorders, such as osteoporosis, osteoarthritis, and degenerative disc disease.\textsuperscript{13,38} The relationship between two VDR polymorphisms (Taql and FokI) and disc degeneration has been studied extensively. The first polymorphism, Taql is located in a noncoding region of Exon 9.\textsuperscript{54} The Tt and the tt genotypes of TaqI polymorphism of VDR gene have been related to disc degeneration. Videman et al. showed that quantitatively assessed signal intensities using MRI in thoracic and lumbar discs in men with TaqI tt and Tt genotype were worse by 12.9% and 4.5%, respectively, than men with the TT genotype.\textsuperscript{55} Comparable findings can be seen in research of Kawaguchi et al. who reported that Tt allele of the VDR gene was found more frequently in Japanese patients with multilevel and more severe disc degeneration than in patients with the TT allele.\textsuperscript{56} In a study of 804 Chinese patients, it was found that individuals with at least 1 t allele
of the VDR gene were 2.6 times more likely to have degenerative disc disease when compared to individuals with the T allele. The second polymorphism, FokI, is located in Exon 2 and appears at the first of the two potential translation initiation sites of VDR cDNA. Individuals with the ff and Ff genotypes had mean signal intensities that were 9.3% and 4.3% lower, respectively, than those with FF genotypes. The summary scores of qualitatively assessed signal intensity, bulging, and disc height were 4.0% and 6.9% worse in individuals with Ff and ff genotypes, compared to those with the FF genotype.

It is not clear how the genetic variants of the VDR gene affect IDD. It was speculated that this polymorphism might alter the structural characteristics of the matrix in IVD. In addition, it is possible that VDR gene polymorphism only functions as a marker for other genes, rather than being directly involved in the pathogenesis of IDD. The type II collagen gene (COL2A1) and insulin-like growth factor (IGF) type-1 gene are located close to VDR gene on chromosome 12. The physical distance between VDR gene and COL2A1 gene is less than 740 kb. IGF is expressed in intervertebral disc tissue, and IGF-1 stimulates proteoglycan synthesis in cells of the NP. Further study of the linkage of the VDR gene and its nearby genes might help the evaluation of the genetic background of IDD.

Other genes

Several other genes, such as IGF-1R, MMP-2, MMP-9, CILP, TIMP1, COX2 and THSD2 that may also be involved in spine degeneration are listed in Table 1.

Conclusions and future directions

Investigations on the origin of IDD have evolved from the classic aging and wear-and-tear theory to a sophisticated multiple-causative disease involving molecular and genetic changes. A number of genetic defects have been correlated with IDD in both animals and humans. Genetic factors with or without the presence of other risk factors (e.g. aging, spine injury, spine deformity) may cause IDD through both mechanical and biological mechanisms. For example, genetic defects may result in structural and functional changes of specific collagens within the IVD, which compromise the disc’s mechanical properties and thus its susceptibility to external stress. Abnormal mechanical properties of the disc tissue may further deteriorate the metabolic changes, such as decreased synthesis (anabolic

| Gene name | References | Population | Comments |
|-----------|------------|------------|----------|
| MMP-2     | Dong et al., 2007 | 162 young Chinese individuals (25.4 ± 3.5 years of age) | 3-fold higher risk for lumbar disc disease in individuals with the MMP-2-1306CC genotype compared with individuals with at least 1 variant T allele |
| MMP-9     | Sun et al., 2009 | 408 individuals with IDD from north China | A 2-fold increased risk of IDD found in individuals with CT/TT genotype compared with individuals with CC genotype |
| IGF-1R    | Urano et al., 2008 | 434 postmenopausal Japanese women | The G allele (GG and GC) of the IGF-1R gene was overrepresented in the population showing more severe disc space narrowing on radiographs |
| CILP      | Seki et al., 2005 | 467 Japanese men and women | CILP plays a role in lumbar disc degeneration by regulating TGF-beta signaling pathway |
| TIMP1     | Valdes et al., 2005 | 700 English women | Polymorphisms of TIMP1, COX2 and THSD2 were associated with progression of IDD |

![Figure 2](https://via.placeholder.com/150) Intervertebral disc degeneration can be attributed to many different factors, including genetic factors as well as aging, injury, spine deformity (e.g. scoliosis and kyphosis). These biological and environmental factors may lead to the spine being susceptible to stress and abnormal gene expression. As a result, increased catabolic activity and decreased anabolic activity may occur in the intervertebral disc, leading to intervertebral disc degeneration.
activity) and increased breakdown (catabolic activity) of the ECM structural proteins, leading to higher incidence of IDD in certain populations relative to others. 63 (Fig. 2).

Recent heredity and linkage studies have certainly improved our understanding of the etiology of IDD; however, the magnitude and mechanism of influence of the genetic factors on the development of IDD are still not fully understood. Some of the genetic studies were based on small cohort sizes, which may lead to false positive and false negative errors. Future genetic studies should combine patient resources and proceed with more focused, directed analyses of susceptibility loci in large patient cohorts. In addition, it would be important to explore genetic defects in more upstream regulators of specific genes associated with IDD. For example, transcription factors SOX9 and NFAT1 regulate the expression of multiple anabolic and catabolic genes and mediate the matrix production in articular cartilage; it would be valuable to further investigate whether genetic alterations in these upstream regulators exist and are involved in the development of IDD. With the advances in imaging technology and molecular and cellular biology including genetic studies, specific early diagnoses and more targeted treatments for this costly and disabling disease will become possible in the future.

Conflicts of interest

All the authors state that they have no conflicts of interests.

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References

1. Lai A, Moon A, Purmessur D, et al. Assessment of functional and behavioral changes sensitive to painful disc degeneration. J Orthop Res. 2015;33:755–764.
2. Sivakamasundari V, Lučkin T. Bridging the gap: understanding embryonic intervertebral disc development. Cell Dev Biol. 2012;1.
3. Wang SZ, Rui YF, Lu J, Wang C. Cell and molecular biology of intervertebral disc degeneration: current understanding and implications for potential therapeutic strategies. Cell Prolif. 2014;47:381–390.
4. Alkhaltib B, Rosenzweig DH, Krock E, et al. Acute mechanical injury of the human intervertebral disc: link to degeneration and pain. Eur Cell Mater. 2014;28:98–110. discussion 110–111.
5. Maetzel A, Li L. The economic burden of low back pain: a review of studies published between 1996 and 2001. Best Pract Res Clin Rheumatol. 2002;16:23–30.
6. Urban JP, Roberts S. Degeneration of the intervertebral disc. Arthritis Res Ther. 2003;5:120–130.
7. Rodrigues-Pinto R, Richardson SM, Hoyland JA. An understanding of intervertebral disc development, maturation and cell phenotype provides clues to direct cell-based tissue regeneration therapies for disc degeneration. Eur Spine J. 2014;23:1803–1814.
8. Weber KT, Jacobsen TD, Maldhof R, et al. Developments in intervertebral disc disease research: pathophysiology, mecha
9. Kepler CK, Ponnappan RK, Tannoury CA, Risbud MV, Anderson DG. The molecular basis of intervertebral disc degeneration. Spine J. 2013;13:318–330.
10. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. Spine J. 2008;8:8–20.
11. Galbusera F, van Rijsbergen M, Ito K, Huyghe JM, Brayda-Bruno M, Wilke HJ. Ageing and degenerative changes of the intervertebral disc and their impact on spinal flexibility. Eur Spine J. 2014;23(suppl 3):S324–S332.
12. Richardson SM, Kalamegam G, Pushparaj PN, et al. Mesenchymal stem cells in regenerative medicine: focus on articular cartilage and intervertebral disc regeneration. Methods. 2015; 99:69–80.
13. Zhang Y, Sun Z, Liu J, Guo X. Advances in susceptibility genetics of intervertebral degenerative disc disease. Int J Biol Sci. 2008;4:283–290.
14. Zhao CQ, Wang LM, Jiang LS, Dai LY. The cell biology of intervertebral disc aging and degeneration. Ageing Res Rev. 2007;6:247–261.
15. lwata M, Alkawa T, Hakozaki T, et al. Enhancement of Runx2 expression is potentially linked to beta-catenin accumulation in canine intervertebral disc degeneration. J Cell Physiol. 2015;230:180–190.
16. Kim KW, Kim YS, Ha KY, et al. An autocrine or paracrine Fas-mediated counterattack: a potential mechanism for apoptosis of notochordal cells in intact rat nucleus pulposus. Spine. 2005;30:1247–1251.
17. Pattappa G, Li Z, Peroglio M, Wismer N, Alini M, Grad S. Diversity of intervertebral disc cells: phenotype and function. J Anat. 2012;221:480–496.
18. Menard AL, Grimard G, Massol E, Londono I, Moldovan F, Villemure I. Static and dynamic compression application and removal on the intervertebral discs of growing rats. J Orthop Res. 2016;34:290–298.
19. Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. Pain Pract. 2008;8:18–44.
20. Pelle DW, Peacock JD, Schmidt CL, et al. Genetic and functional studies of the intervertebral disc: a novel murine intervertebral disc model. PLoS One. 2014;9:e112454.
21. Hanaei S, Abdollahzade S, Khoshnevisan A, Kepler CK, Rezaei N. Genetic aspects of intervertebral disc degeneration. Rev Neurosci. 2015;26:581–606.
22. Wang C, Wang WJ, Yan YG, et al. MicroRNAs: new players in intervertebral disc degeneration. Clin Chim Acta. 2015;450:333–341.
23. Pluirim SM, van Essen HW, Brauvenboer N, et al. Collagen type I alpha1 Sp1 polymorphism, osteoporosis, and intervertebral disc degeneration in older men and women. Ann Rheum Dis. 2004;63:71–77.
24. Tilkeridis C, Bei T, Garantziotis S, Stratakis CA. Association of a COL1A1 polymorphism with lumbar disc disease in young military recruits. J Med Genet. 2005;42:e44.
25. Kalb S, Martirosyan NL, Kalani MY, Broc GG, Theodore N. Genetics of the degenerated intervertebral disc. World Neurosurg. 2012;77:491–501.
26. Kalichman L, Hunter DJ. The genetics of intervertebral disc degeneration. Associted genes. Joint Bone Spine. 2008;75:388–396.
27. Videman T, Saarela J, Kaprio J, et al. Associations of 25 structural, degradative, and inflammatory candidate genes with lumbar disc desiccation, bulging, and height narrowing. Arthritis Rheum. 2009;60:470–481.
28. Kimura T, Nakata K, Tsumaki N, et al. Progressive degeneration of articular cartilage and intervertebral discs. An experimental study in transgenic mice bearing a type IX collagen mutation. Int Orthop. 1996;20:177–181.

29. Boyd LM, Richardson WJ, Allen KD, et al. Early-onset degeneration of the intervertebral disc and vertebral end plate in mice deficient in type IX collagen. Arthritis Rheum. 2008;58:164–171.

30. Annunen S, Paassilta P, Lohiniva J, et al. An allele of COL9A2 associated with intervertebral disc disease. Science. 1999;285:409–412.

31. 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;30:2735–2742.

32. Wrocklage C, Wassmann H, Paulus W. COL9A2 allelotypes in intervertebral disc degeneration. Arthritis Res. 2001;279:398–400.

33. Paassilta P, Lohiniva J, Goring HH, et al. Identification of a novel common genetic risk factor for lumbar disk disease. JAMA. 2001;285:1843–1849.

34. 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;15:613–619.

35. Janeczko L, Janeczko M, Chrzanowski R, Zielinski G. The role of polymorphisms of genes encoding collagen IX and XI in lumbar disc disease. Neurol Neurochir Pol. 2014;48:60–62.

36. 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;81:1271–1277.

37. Sivan SS, Wachtel E, Roughley P. Structure, function, aging and turnover of aggrecan in the intervertebral disc. Biochim Biophys Acta. 2014;1840:3181–3189.

38. Mayer JE, Iatridis JC, Chan D, Qureshi SA, Gottesman O, Hecht AC. Genetic polymorphisms associated with intervertebral disc degeneration. Spine J. 2013;13:299–317.

39. Kawaguchi Y, Osada R, Kanamori M, et al. Association between an aggrecan gene polymorphism and lumbar disc degeneration. Spine. 1999;24:2456–2460.

40. Roughley P, Martens D, Rantakokko J, Alini M, Mwale F, Antoniou J. The involvement of aggrecan polymorphism in degeneration of human intervertebral disc and articular cartilage. Eur Cell Mater. 2006;11:1–7. discussion 7.

41. Wuertz K, Haglund L. Inflammatory mediators in intervertebral disc aging and degeneration. Global Spine J. 2013;3:175–184.

42. Johnson ZI, Schoepflin ZR, Choi H, Shapiro IM, Risbud MV. Disc in flames: roles of TNF-alpha and IL-1beta in intervertebral disc degeneration. Eur Cell Mater. 2015;30:104–116. discussion 116–107.

43. Kang R, Li H, Rickers K, Ringgaard S, Xie L, Bunger C. Expression and regulation of metalloproteinases and their inhibitors in intervertebral disc aging and degeneration. Spine J. 2013;13:331–341.

44. Takahashi M, Haro H, Wakabayashi Y, Kawauchi Y, Tomori H, Shinnomiya K. 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;83:491–495.

45. Valdes AM, Hassett G, Hart DJ, Spector TD. Radiographic progression of lumbar spine disc degeneration is influenced by variation at inflammatory genes: a candidate SNP association study in the Chingford cohort. Spine. 2005;30:2445–2451.

46. 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;62:1208–1214.

47. Cheung KM, Chan D, Karpinnen J, et al. Association of the TaqI allele in vitamin D receptor with degenerative disc disease and disc bulge in a Chinese population. Spine. 2006;31:1143–1148.

48. 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–E12.

49. Kawaguchi Y, Kanamori M, Ishihara H, Ohmori K, Matsu H, Kimura T. The association of lumbar disc disease with vitamin-D receptor gene polymorphism. J Bone Surg Am. 2002;84-A:2022–2028.

50. Arai H, Miyamoto K, Taketani Y, et al. A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women. J Bone Miner Res. 1997;12:915–921.

51. Videman T, Leppavuori J, Kaprio J, et al. Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. Spine. 1998;23:2477–2485.

52. Urano T, Narusawa K, Shiraki M, et al. Association of a single nucleotide polymorphism in the insulin-like growth factor-1 receptor gene with spinal disc degeneration in postmenopausal Japanese women. Spine. 2008;33:1256–1261.

53. Dong DM, Yao M, Liu B, Sun CY, Jiang YQ, Wang YS. Association between the -1306C/T polymorphism of matrix metalloproteinase-2 gene and lumbar disc disease in Chinese young adults. Eur Spine J. 2006;15:1958–1961.

54. Sun ZM, Miao L, Zhang YG, Ming L. Association between the -1562 C/T polymorphism of matrix metalloproteinase-9 gene and lumbar disc disease in the young adult population in North China. Connect Tissue Res. 2009;50:181–185.

55. 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 degeneration. Nat Genet. 2005;37:607–612.

56. Freeman AJ. The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. Rheumatology. 2009;48:5–10.

57. Rodova M, Lu Q, Li Y, et al. Nfat1 regulates adult articular chondrocyte function through its age-dependent expression mediated by epigenetic histone methylation. J Bone Miner Res. 2011;26:1974–1986.

58. Shi S, Wang C, Acton AJ, Eckert GJ, Trippel SB. Role of sox9 in growth factor regulation of articular chondrocytes. J Cell Biochem. 2015;116:1391–1400.