PERSPECTIVES

The Etiology of Intervertebral Disc Degeneration

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Abstract

Intervertebral discs are pads of fibrocartilage having the capacity to maintain stability under a wide variety of loading conditions, while permitting intersegmental motion of the spine and showing degenerative and aging changes earlier than any other connective tissue in the body. Disc degeneration may manifest as disc space narrowing, disc bulging, protrusion, extrusion, sequestration, annular tears, reduced signal intensity on magnetic resonance imaging, Schmorl's nodes and vertebral rim osteophytes. It is believed to be clinically important since disc degeneration has been found to be associated with back pain. This *Perspective* describes how disc degeneration can be distinguished from normal disc aging and reviews factors associated with intervertebral disc degeneration, with a focus on genetic factors in particular. *IBMS BoneKEy*. 2010 November;7(11):388-405.
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Introduction

Intervertebral discs (IVDs) are unique structures with the capacity to maintain stability under a wide variety of loading conditions, while permitting intersegmental motion of the spine (1). Degenerative changes in lumbar IVDs are multifarious. Disc space narrowing, disc bulging, protrusion, extrusion, sequestration, annular tears, reduced signal intensity on magnetic resonance imaging (MRI), Schmorl's nodes and vertebral rim osteophytes are all manifestations of intervertebral disc degeneration (IDD). MRI studies have shown that IDD can begin as early as the second decade and increases linearly with age; hence at 70 years of age, 80% of all lumbar discs are abnormal (2-4). Moreover, by the age of 50, 85-95% of adults show evidence of IVD degeneration on autopsy.

Most recent publications have tried to distinguish between aging and IDD, although there seems to be a correlation between the two processes. Disc degeneration due to normal aging is a product of lifelong degradation with synchronized remodeling of discs and neighboring vertebrae, including simultaneous adaptation of the disc structures to changes in physical loading and responses to the occasional injury (4). Adams and Roughley (5) defined the IVD degenerative process as corresponding mainly to pathological changes, stating that the IDD process is an aberrant, cell-mediated response to progressive structural failure. IDD is the response of the disc to secondary injury and inflammation whereas disc aging represents a normal progression of the maturation process, with associated cellular and molecular changes. A degenerate disc is one with structural failure combined with accelerated or advanced signs of aging. A degenerate disc that is also painful should be referred to as degenerative disc disease.

Imaging Methods of IDD Evaluation

Plain radiographs are still widely used today, as they are accessible and cheap. On a standard x-ray, disc space narrowing and vertebral body shapes can be recognized easily (Fig. 1). Initially, disc space narrowing was perhaps the most commonly used specific finding indicating IDD in clinical imaging. Severe disc space narrowing is an obvious sign of IDD, and single-level severe

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Fig. 1. An x-ray of the lateral lumbar spine with intervertebral disc narrowing and anterior osteophytes at L3-L4 and L4-L5 spinal levels.
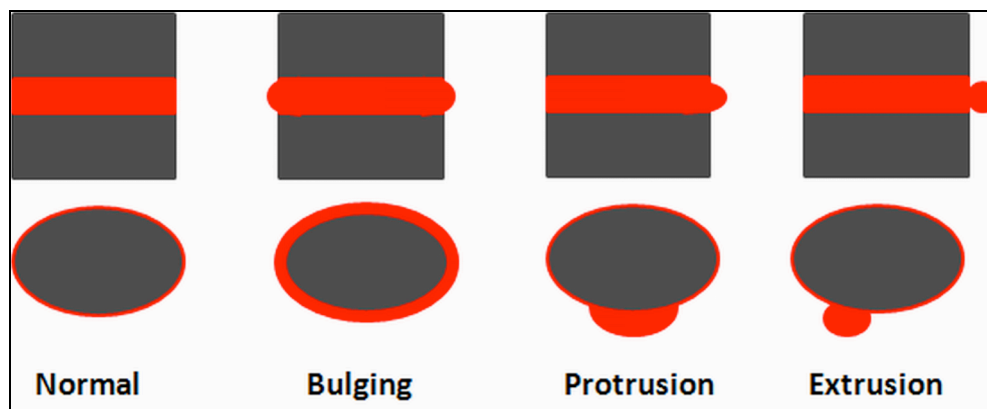

Fig. 2. Schematic representation of a morphological nomenclature based on a two-dimensional assessment of the disc contour. *Normal disc:* absence of DEBIT. *Bulging disc:* circumferential, symmetric DEBIT. *Protrusion:* focal or asymmetric DEBIT; the base against the parent disc is broader than any other diameter of the protrusion. *Extrusion:* focal, obvious DEBIT; the base against the parent disc is narrower than the diameter of the extruded material itself, or there is no connection with the parent disc. DEBIT = disc extension beyond the interspace.

narrowing is thought more likely to reflect a traumatic or biomechanical etiology than a systemic one. Vertebral rim osteophytosis has also been used frequently as an indicator of IDD. Computed tomography (CT) scanning can detect the shape of the discs. Use of this technology has led to the development of new nomenclature for disc lesions based on assessment of the disc contour (6) or more specifically, the observed "disc extension beyond the interspace" (DEBIT). Discs are classified as normal, bulging, protruding or extruding (Fig. 2 and Fig. 3). At present, MRI is the preferred method of IDD evaluation (Fig. 4), since it allows simultaneous evaluation of various phenomena, such as disc space narrowing, bulging, protrusion or extrusion of discs, signal intensity changes in the disc and the vertebral body marrow adjacent to the endplates of the degenerated discs (Modic (7) changes), etc. Table 1, modified and adopted from Milette (8), summarizes the parameters that may differentiate a
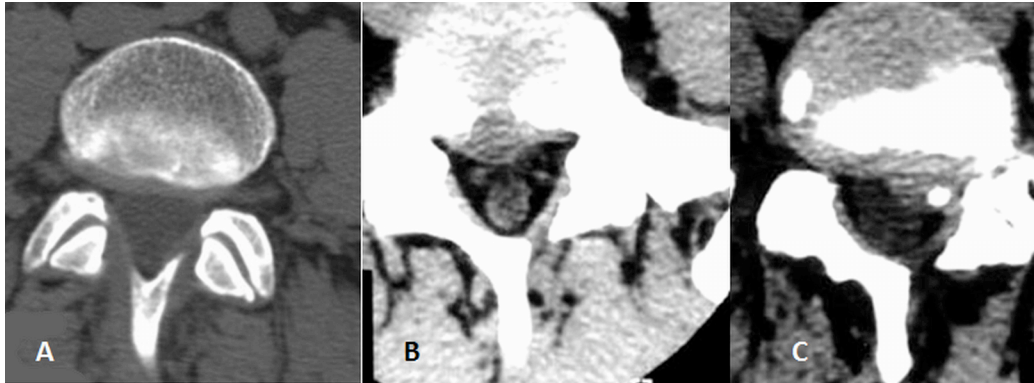
Fig. 3. Examples of intervertebral disc bulging (A), protrusion (B) and extrusion (C) on axial CT images.

Fig. 4. A midsagittal T2-weighted MRI illustrating early imaging signs of disc degeneration (reduced brightness of T2-signal sometimes called a "dark disc" and the presence of disc bulging) at L4-5 and L5-S1.

normal aging disc from a pathologically degenerated one. In addition to the imaging studies, information gained from microscopic, histological, or biochemical analysis, as well as surgical and autopsy samples can provide a macroscopic measurement of disc degeneration (9).

Disc Aging

Matrix synthesis decreases steadily throughout life but occasionally increases again in old and severely disrupted discs (10). IVD cells are continuously subjected to hypoxia, low pH, low nutrition, and high pressure (11). The concentration of cells in the disc declines with age, especially in the annulus (12;13). They are subject to senescence, lose their ability to proliferate and may induce degeneration by decreased anabolism or increased catabolism (14;15). The appearance of necrotic and apoptotic cells is also very common. Trout et al. found that > 50% of adult disc cells are necrotic (13).

The rate of proteoglycan synthesis decreases with age, both in the annulus and nucleus (16;17). Furthermore, the proteoglycans produced are smaller (18;19) and less aggregated (17). The concentration of chondroitin sulphate lessens with

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Table 1. Differentiating features of the normal aging disc and the pathologically changed disc*.

Criterion	Normal disc aging	Pathological changes
Clinical		
Age	> 40	All ages
Symptoms	None	Frequent
History of LBP	Probable	Frequent
History of inciting event	None	Probable
X-ray and CT		
Disc space height	Normal or uniformly decreased	Decreased at the pathologic level/s
Posterior disc margin	Regular	Irregular
Vertebral bodies	Normal or with osteoporotic signs	Sclerosis of end-plates
Osteophytes	Anterolateral	All directions
Intradiscal gas	None or anterolateral	Central
Number of affected discs	All	Variable
MRI		
Vertebral body marrow	Normal for age group	Type 2 or 3 Modic (7) changes
Central disc signal intensity	Slight decrease	Marked decrease

*Adopted with modification from Milette PC (8). LBP = low back pain.

increasing age, resulting in a rise in the keratan sulphate to chondroitin sulphate ratio (20). The collagen content of the nucleus increases and changes from type II to type I (16;21;22), rendering the nucleus more fibrous (23). The non-collagenous proteins in the nucleus also increase (24;25). Increased collagen and increased collagen-proteoglycan binding leave fewer polar groups of the proteoglycans available to bind water (22). The nucleus becomes progressively more solid, dry and granular (26), with cracks appearing in the desiccated, fibrous nucleus (23). The collagen lamellae of the annulus increase in thickness and become further fibrillated (27); cracks and cavities may develop within (16).

Characteristics of the Degeneration Process

Advanced IDD is associated with vertebral body osteophytes, increased bone density or sclerosis of the vertebral bodies adjacent to the disc, and facet joint osteoarthritis (Fig. 1). IVD narrowing has previously been considered one of the signs of lumbar spine aging (26;28), however, post-mortem studies have shown that lumbar discs do not narrow with age. Similarly, although pathologists regard annulus tears as a degenerative change (23;26), it has been shown that radial tears do not correlate with age (29). These fissures are probably indicative of the degenerative process.

Juvenile Disc Degeneration

Scheuermann in 1921 (30) and later Schmorl (31) described changes in the vertebral endplates and disc space that occur during the growing years (mostly in boys) and can thus lead to kyphosis in the thoracic spine (Scheuermann's disease or juvenile kyphosis). They also described adolescent degenerative disc disease

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(juvenile disc disorder or lumbar Scheuermann's disease) where the endplates are not strong enough to withstand the pressures generated within the disc spaces, thus leading to disc herniations into the vertebral bodies (Schmorl's nodes), causing back pain at an early age. This condition is very similar to IDD in the adult population, but the degeneration begins at a much earlier age and usually involves most of the lumbar spine discs (as opposed to only one or two typically involved in adult IDD) (32).

Association with Pain

Degenerative changes in IVDs can contribute to the development of low back pain (LBP) and acute lumbar radiculopathy associated with disc herniation (4;16;33;34). In their systematic review of observational studies, van Tulder *et al*. suggested an association between lumbar IDD and LBP with odds ratios varying between 1.3 and 3.2 (35). Back pain is associated with disc prolapse (36) and radial fissures (29;37), especially when reaching the disc exterior, *i.e*., disc extrusion (38). Internal disc disruption, with inward collapse of the annulus was also found to be associated with pain (39). Several studies have reported back pain due to disc narrowing (37;40-44), with increasing severity of the disc narrowing (41;44;45). Endplate fracture, Schmorl's nodes (46), disc bulging (36;37;46;47) and disc signal intensity on MRI (37) showed little if any relationship to pain.

Normal IVDs are poorly innervated and supplied only by sensory and sympathetic perivascular nerve fibers. Most of the studies performed in different animal species, including in humans, have demonstrated that nerve fibers in IVDs are found mostly on the periphery (1-3 mm) of the annulus fibrosus (48). Endplate innervation is centrally concentrated, adjoining the nucleus (49). Pain provocation studies associate severe LBP with relatively innocuous mechanical stimulation of the outer posterior annulus and endplate (50). Interestingly, in humans and animal models of IDD, the number of nerve fibers in the disc increases (51;52), however, the

mechanisms responsible for nerve growth and hyperinnervation of the degenerated disc have not been fully elucidated.

Factors Associated with Disc Degeneration

Age, heavy physical loading, injury, vibration, infection and smoking have been reported as risk factors (53-55) for IDD. However, results of recent studies suggest that genetic factors/heredity play a dominant role in IDD (56). A review article by Battié *et al*. (57) concluded with the statement that "the genetically determined 'natural progression of disc degeneration' is modified to some degree by behavioral and environmental factors." Adams and Roughley (5) defined the underlying cause of IDD as tissue weakening occurring primarily from genetic inheritance, aging, nutritional compromise, and loading history. Modic and Ross (58) suggested that many interactive factors such as mechanical, traumatic, nutritional, genetic and environmental factors may play a role in the disc degeneration cascade, albeit to variable degrees in different individuals.

Hereditary factors could affect IDD through several mechanisms, *i.e.*, through an influence on size and shape of spinal structures, which then affect the spine's mechanical properties and thus producing vulnerability to external forces. Biological processes associated with the synthesis and breakdown of the disc's structural and biochemical constituents could be genetically predetermined. Identification of specific genetic influences may eventually provide key insights into underlying mechanisms.

With this dramatic change in the current view of risk factors for IDD from one where age and mechanical factors were paramount, to the current theory that genetic risk factors are predominant, the remainder of this *Perspective* reviews the mechanical and nutritional factors, and the genetic influences, on IDD, beginning with familial aggregation and heritability estimation and concluding with specific studies of genes associated with IDD.

Age, Sex and Body Weight

The association between age and IDD has been well-established. Utilizing 600 autopsy specimens from 273 cadavers, Miller *et al.* estimated that the prevalence of IDD increases from 16% at age 20 to about 98% at age 70 (59). The authors also noted that lumbar IDD first appeared in 11- to 19-year-old males and approximately 10 years later in females. Numerous recent studies used different modalities for IDD definition, confirming the association between age and IDD (40;60-64).

Miller *et al.* (59), in an autopsy study, found that male discs were more degenerated than female discs at most ages. Similar results were described in MRI (65) and surgical (66) studies. On the other hand, several recent imaging studies found no association between sex and IDD (63;67).

A number of studies have described the association between obesity and increased risk of disc degeneration (68-70). A recent large study of twins (71) showed that adjusting for age, sex, zygosity, and relatedness of twins, an independent effect of body mass index on IDD summary score was attributable to significant contributions from both disc signal intensity and disc height.

Mechanical Load and Injury

For many years, abnormal mechanical loads and injury, often work-related, were considered major contributors to IDD. It was thought that these injuries lead to IDD, clinical symptoms and LBP (72-74). However, recent studies using MRI scanning to identify IDD classifications have shown that although factors such as occupation, psychosocial factors, benefit payments and environment are linked to disabling LBP (75), contrary to previous assumptions, these factors have little influence on the pattern of IDD itself (76;77).

Regardless, it is difficult to disregard the numerous epidemiological studies that have found associations between physical loading and the development of LBP and IDD. These studies have found heavy physical work, baseball and swimming activities during youth (78), lifting (70), professional driving (79-81), frequent bending (81) and obesity (68;82) to be risk factors for IDD. The association between physical loading and IDD was supported by animal models (83;84). Eck *et al.* found that abnormal mechanical forces in IDD cause disc levels adjacent to a fused segment to degenerate rapidly (85).

IVDs are constantly subjected to compression loads, but normally can withstand this pressure. However, these compression forces might influence disc cell metabolism. Depending on the duration, magnitude, and type (static or cyclic) of compressive loads, reversible or irreversible degeneration occurs (86). Torsion load – resulting from rotational movements – can also lead to endplate damage or annulus tear, which leads to IDD (87). It has been suggested that mechanical factors produce endplate damage, the antecedent to IDD (73). There is a strong association between degeneration and defects in the endplate from Schmorl's nodes (46;88), Scheuermann's disease (89) and fractures (90), with an increased incidence of disc prolapse, particularly at the lower lumbar levels (46).

Nutritional Pathways to Disc Degeneration

One of the causes of IDD is thought to be failure of the nutrient supply to the disc cells (91). The disc is large and avascular. The cells receive the nutrients and remove metabolic waste through the blood vessels at the disc margins (92). The nucleus cells are supplied virtually entirely by capillaries originating in the vertebral bodies, penetrating the subchondral plate and terminating just above the cartilaginous endplate (93). This source of nutrition is at great risk in the aging disc, as the permeability of the endplate diminishes with advancing age (91;93). A detrimental effect of decreased blood supply from the endplate results in tissue breakdown, starting in the nucleus. A recent study has shown that this process may begin early in the second decade of life (94).

Scant information is available regarding the association between nutrient supply and IDD. There is some evidence that nutrient transport is affected in IDD *in vivo* (95). The importance of normal blood flow to the homeostatic nutritional process in the IVD complex has been suggested as an explanation for the association of atherosclerosis and aortic calcification with increased IDD and subjective LBP (96).

The association between smoking and IDD, noted in several studies (62;97-99), may also be attributed to nutritional deficiencies. Smoking causes constriction of arterioles, resulting in anoxia to cells induced by carboxyhemoglobin (100). This theory is supported by animal studies, which have demonstrated that nicotine facilitates IDD by decreasing the blood supply to the disc (101). Finally, even if the blood supply remains undisturbed, nutrients may not reach the disc cells if the cartilaginous end-plate calcifies (91;102). A loss of water volume within the nucleus pulposus results in decreased disc pressure and reduced disc height (16). Thus, although there is as yet little direct evidence, it seems apparent that a decrease in nutrient supply will eventually lead to IDD.

Genetic Factors in Disc Degeneration

Recent studies have suggested that genes play a crucial role in IDD. Assessing a genetic influence usually starts with a familial aggregation evaluation. The next step is to distinguish between genetic and environmental sources of familial aggregation as well as to estimate the heritable proportion of IDD variability. Finally, specific gene effects, gene-gene interactions, and gene-environment interactions need to be evaluated.

Familial Predisposition and Heritability Estimation

The first descriptions of familial predisposition for lumbar IDD were found in juvenile and adolescent populations (103-106). The study of juvenile lumbar disc herniation is especially interesting since in young patients, normal disc aging and risk factors such as occupation, smoking and

comorbidities have little, if any, influence on disease predisposition. Numerous studies have also provided solid evidence of the existence of a familial predisposition to IDD in adults (82;107-110). Results from a study of healthy volunteer male monozygotic (MZ) twin pairs (111) demonstrated substantial familial aggregation of lumbar IDD. Whereas smoking status and age explained 0-15% of the variability in the various degenerative findings in the discs, 26-72% of the variability was explained with the addition of a variable representing co-twin status. These results suggest a substantial familial influence on lumbar disc height narrowing, bulging or herniation, and disc desiccation.

In a retrospective cohort study of 115 pairs of male MZ twins, lumbar MRIs were assessed to investigate the relative effects of environmental exposures, age and familial aggregation on disc bulging, height narrowing, and disc desiccation (60). In a multivariate analysis of the T12-L4 region, physical loading explained 7% of the variance in IDD summary scores; an additional 9% was explained by age and another 61% by familial aggregation. The observations and studies in juveniles and adults provide convincing evidence for familial predisposition in two different, but related phenotypes: 1) in individuals who underwent surgery of the lower spine due to lumbar intervertebral disc herniation, *i.e.*, those who suffer from a severe degenerative condition and 2) in a sample of healthy volunteers, *i.e.*, as distinct from symptomatic subjects who may represent different ends of the IDD spectrum.

Heritability estimations performed in one classic twin study (112) and two cohort studies (62;113) found a high heritable component for IDD: H = 0.73-0.75. Results of a segregation analysis (62) showed that the model of inheritance assuming a major gene effect and Mendelian transmission of susceptibility to multiple disc herniations was rejected, indicating a more complex mode of intergenerational transmission.

Associated Genes

There are a number of genes that have been associated with IDD in humans,

including the genes coding for collagen I (*COL1A1*) (114;115), collagen IX (*COL9A2 and COL9A3*) (116-126), collagen XI (*COL11A2*) (120;124), interleukin-1 (*IL-1*) (127;128), interleukin-6 (*IL-6*) (120), vitamin D receptor (*VDR*) (129-134), aggrecan (*ACAN*) (135-138), SRY (sex determining region Y)-box 9 (*SOX9*) (139;140), matrix metalloproteinase 3 (*MMP-3*) (120;131;141) and cartilage intermediate-layer protein (*CILP*) (128;142). At present, only the associations of *COL1A1*, *COL9A2*, *ACAN*, *MMP-3* and *VDR* with IDD have been verified in different ethnic populations. Among the possible reasons for replication deficiency is the complexity of the IDD process, the different phenotypes used in genetic studies, and the different sample sizes. For example, an association between *COL9A3* and IDD was found in a Finnish population by two different research groups (121;124) using MRI to define the phenotype of IDD. However, in a study performed in a Greek population (118), x-rays and/or back surgery were used as an IDD phenotype, and no association was found. In this case, we cannot be sure if the reason for a lack of association was the different ethnicity of the subjects studied or the different phenotypes used. Another factor that needs to be considered is the subjects' ages. It is possible that a particular gene is associated with IDD only at a certain age. Takahashi *et al*. (141) found that the *5A5A* and *5A6A* genotypes of *MMP-3* in the elderly were associated with a significantly larger number of degenerative IVDs than the *6A6A* genotype (p < 0.05), but there was no significant difference in young individuals. The products of these genes probably affect the quality of the skeletal tissues. Their systemic effects may explain the association between disc degeneration and osteoarthritis (40) or, on the other hand, a positive, genetically-mediated association between lumbar disc degeneration and hip bone mineral density (BMD) (143). It is worth mentioning that all candidate gene studies have demonstrated only a modest level of association. A risk still exists that these associations are false positives. Until new studies showing a high level of association ($P < 5 \times 10^{-8}$ is commonly accepted in genetic studies) are performed,

these findings need to be discussed with a great degree of caution.

An important but extremely complicated aspect of understanding the genetics of IDD is gene-gene and gene-environment interactions. Solovieva *et al*. (123) presented evidence suggesting that the effect of weight on lumbar disc degeneration was modified by *COL9A3* polymorphisms in Finnish men; 45 to 71% of disc degeneration among persistently obese individuals with the *Trp3* allele could be attributed to the synergism of *COL9A3* polymorphisms and persistent obesity. Another example of gene-environment interaction was demonstrated in a later study by Solovieva *et al*. (127) suggesting that *IL-1* cluster polymorphisms modified the effect of occupation on disc bulges. The negative effect of physical workload on IDD for carpenters was exaggerated by the presence of a minor allele of the polymorphism in all studied genes. For machine drivers, the effect of occupational load on bulges was modified only by the presence of the $IL\text{-}1\alpha T^{889}$ allele. A recent study from China (144) showed additive and multiplicative interaction between the aggrecan gene variable number of tandem repeat (VNTR) polymorphisms and smoking in symptomatic IDD.

There is also evidence for gene-gene interaction (124). Multivariate logistic regression analysis showed that the carriage of *COL9A3* in the absence of the *IL-1β-T(3954)* allele increased the risk of dark nucleus pulposus (OR 7.0, 95% CI: 1.3-38.8). There was no effect of *COL9A3* on disc degeneration in the presence of the *IL-1β-T(3954)* allele. These results suggest that the effect of the *COL9A3* polymorphism on IDD might be modified by the *IL-1β* polymorphism.

Candidate gene association studies have limitations in detecting the genetic basis of the disease because this approach relies on predicting the correct genes based on biological hypotheses or the location of the known linkage regions. The genome-wide association approach has no assumptions regarding the location of the causal variants and represents an unbiased yet fairly

comprehensive approach even in the absence of knowledge of the function or location of the causal genes (145). Additional studies, including linkage analyses and whole genome scan studies in different populations, are required in order to improve our understanding of the influence of the aforementioned genes on IDD and to identify novel genes.

Conclusions

IDD is a very prevalent condition with various manifestations such as disc space narrowing, disc bulging, protrusion, extrusion and sequestration, annular tears, reduced signal intensity on MRI, Schmorl's nodes and vertebral rim osteophytes, causing LBP and acute lumbar radiculopathy associated with disc herniation. To facilitate the study of IDD, it is important to distinguish between age-related disc changes and manifestation of pathological IDD. Age, heavy physical loading, injury, vibration, failure of the nutrient supply to the disc cells, infection and smoking have been reported to be risk factors for IDD. However, the results of recent studies suggest that genetic factors/heredity play a dominant role in IDD.

Familial history must be an essential part of the medical history of individuals suffering from LBP and can strengthen a clinical diagnosis of IDD. Family history may provide a cost-effective means of identifying high-risk individuals who could benefit from aggressive preventative strategies (109). There are a number of genes associated with IDD in humans, including genes coding for collagen I, collagen IX, collagen XI, IL-1, IL-6, VDR, aggrecan, SOX9, MMP-3 and CILP. Additional studies, including linkage analyses and whole-genome scan studies in different populations, are required to improve our understanding of the influence of the aforementioned genes on IDD and to identify novel genes.

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

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