

Lumbar degenerative disc disease: all in the genes?

Lumbar degenerative disc disease is a common ailment that causes patients significant pain, disability and psychologic distress, in addition to its large socioeconomic impact on society. The etiology of disc degeneration has been extensively studied, but our understanding remains incomplete. Increased age and male gender are risk factors for radiographic and histologic changes associated with disc degeneration. Smoking and mechanical stress have also been evaluated as causative agents, but their impact on disease development has proven to be very small. The largest influence on degeneration has been shown to come from an inherited element. Twin studies, case-control studies and large population-based studies have confirmed that a familial predisposition exists. However, the underlying genetic cause of this heritable risk remains unknown. Variations in collagens and other extracellular matrix components likely play a role, but we remain in the infancy of our understanding of this complex genetic process.

KEYWORDS: degenerative disc disease ■ familiarity ■ genetics ■ low back pain ■ lumbar spine

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Back pain is the second most common reason for patients to seek medical care in the USA [1]. Low back pain is estimated to occur in up to 84% of individuals at some point in their life, and lumbar disc degeneration is one of the most common findings in the work-up of low back pain [2]. Owing to its prevalence, it is not surprising that the diagnosis and treatment of low back pain has a large socioeconomic impact. The total cost of back pain, including lost wages and reduced productivity, is estimated to exceed 100 billion dollars per year in the USA [3]. This staggering societal cost is paralleled by the individual patient's burden of pain, disability and psychological distress. This enormous impact underscores the importance of developing improved methods to prevent, diagnose and treat these disorders.

With lumbar disc degeneration, herniation of the disc can occur leading to leg pain or neurogenic symptoms, in addition to back pain. The term lumbar degenerative disc disease (LDD) lacks a standard definition, but includes the entire spectrum of disease from disc desiccation ('black disc disease') to osteophyte formation or frank disc herniation. Despite its prevalence, the etiology of LDD is incompletely understood. In many situations, the sole presence of degenerative disc disease may or may not correlate with low back pain symptoms. Studies have suggested a multifactorial etiology including contributions from mechanical stresses [4,5], nutritional factors [6], age-dependent disc degeneration [7],

biochemical factors [8] and genetics [9,10]. In this article, we hope to dissect the available data to evaluate the current understanding of the causes of LDD and low back pain.

The difficulties of studying LDD

Asymptomatic individuals have been found to have radiographic disc degeneration at such high rates that the correlation between disc disease and clinical symptoms has been called into question [11]. Further, the radiographic findings of disc degeneration (e.g., disc narrowing, osteophyte formation, decreased signal on T₂ MRI and disc herniation) have not been definitively linked to pain production. One possible explanation of this disconnect between radiographic and clinical findings is the variation in pain perception and sensitivity. A recent study has shown an association between a known genetic marker of pain perception (catechol-*O*-methyltransferase [COMT]) and surgical outcomes following low back pain surgery [12]. Another cause for this disconnect is variation in methodology within the literature on LDD.

Etiologic studies vary in their definition and measurement of the disease, and, therefore, it is not surprising that they vary in their findings as well. The lack of a standardized definition of LDD stems from an incomplete understanding of the disease process itself. The terms degenerative disc disease, disc degeneration and LDD will be used interchangeably for the purpose of this article. Battié and Videman

have described LDD conceptually and operationally [9]. Conceptually, LDD is the process of degradation and remodeling of the disc and neighboring vertebrae in response to the physical loads and occasional injuries common in life. Operationally, LDD is defined by the method of evaluation – histologic, biochemical or radiographic. By far the most common operational definition has been based upon a combination of MRI findings such as signal intensity loss, disc space narrowing, osteophyte formation, annular tears, endplate sclerosis and disc bulging [9]. Although these findings are correlated to some degree, combination scores used in genetic studies may mask the effect on individual aspects of the degenerative process.

Another difficulty in the study on LDD is the variation of pathology seen at the five disc levels of the lumbar spine. Although it is known that degenerative conditions are more common at the lower levels of the lumbar spine, and Schmorl's nodes are more common in the upper levels of the lumbar spine, most studies group all lumbar disc disease together. This makes it virtually impossible to detect level-specific influences of etiologic factors on disease development.

Risk factors

■ Age & sex

Lumbar degenerative disc disease is more common as we age and is likely part of the aging process to some degree. Pathologic studies have looked for histologic evidence of LDD using Nachemson's grading scheme that considers fibrosis of the nucleus pulposus, fissures of the annulus fibrosis and marginal osteophyte formation [13]. In the largest meta-analysis of these pathologic studies, Miller *et al.* found that disc degeneration can occur as early as the second decade of life in males and the third decade of life in females and is present to some degree in 97% of individuals by the sixth decade of life [14]. They also reported that male lumbar discs degenerate approximately 10 years earlier than female discs. To explain this gender discrepancy, they suggested that increased compression loading and longer avascular nutritional pathways of the male disc may contribute to its earlier degeneration. This theory has yet to be proven, but the tendency of LDD to affect males earlier and more severely has been accepted.

■ Lifestyle

Environmental influences have long been thought to contribute to the development of low back pain, and specifically to LDD. The exposures

most commonly linked to LDD include smoking and mechanical stresses imparted to the spine. True measurements of these exposures are impossible, and thus self-reported exposures have been used to approximate their influence.

Self-reported smoking status has been linked to poor surgical outcomes from spine surgery and higher infection rates; it has also been suggested as a minor contributor to the development of LDD. Monozygotic twin studies have varied in their results on this issue, but the study with the largest discordance between twins in lifetime smoking history found that this exposure only accounted for 2% of the variance in disc degeneration between the twins [15]. Another twin study found that smoking also had little to no effect on the radiologic progression of the degenerative process [16].

The impact of heavy physical loading on disc degeneration has been evaluated in many epidemiologic studies [17,18]. However, these studies are difficult to interpret because of the high risk of confounding variables and the variable dose–response relationships that have been suggested. Owing to the weaknesses of these studies, identical twin studies were conducted to minimize confounding variables and thus isolate the effect of mechanical stress on disc disease. The studies on monozygotic twins with large variations in exposure to mechanical stress revealed a minimal effect on the development of disc degeneration. In one of the largest twin studies with the longest follow-up, Videman *et al.* looked at the influence of self-reported resistance training and occupational physical loading on the development of radiographic LDD [16]. In this study of 75 pairs of twins (150 individuals) followed for over 5 years, both of these mechanical stresses together explained only 2–10% of the degenerative findings on MRI and had little effect on progression of the degeneration. A similar study examined 45 sets of monozygous twins that had significant self-reported exposure to motorized vehicles and associated whole-body vibration. They concluded that driving-associated vibration had no significant effect on the development of LDD [19].

■ Genetics

The twin studies failed to find environmental exposures that had large effects on disc degeneration, but did reveal considerable similarity in lumbar disc disease among the co-twins. Battié *et al.* evaluated the lumbar spine MRIs of 40 identical twins (20 pairs) and found that 26–72% of the variance in the imaging

studies could be attributed to their genetics [20]. In a more recent study, Battié *et al.* reported that genetic influences were responsible for 29–54% of disc degeneration in a study of 300 twin pairs [21]. In the previously mentioned Videman study [16], MRIs were obtained at baseline and again 5 years later. They found that 47–66% of the variability in the progression of degenerative changes could be attributed to an inheritable risk. To further support the idea of familial aggregation, a case–control study was performed to evaluate the impact of a self-reported family history of intervertebral disc disease [22]. It revealed that while less than one third of control patients will self-report a family history, nearly half of patients (47%) requiring surgery for disc herniation will report a positive family history. In an effort to evaluate if an inheritable factor effects the severity of disc herniations, Matsui *et al.* performed a similar study [23]. They found that the disc herniations were more severe in the patients with a positive family history than those without ($p < 0.03$).

Although these case–control and twin studies suggested a familial predisposition to LDD, they failed to prove that relationship. Despite attempts to minimize confounding variables, the fact remains that twins are likely to have very similar environmental exposures. Most of the twin studies also focused on radiographic definitions of LDD, and were unable to comment on the inheritability of the clinical diagnosis. Further, both the twin and case–control studies were hindered by recall and ascertainment bias. To avoid these bias and ascertainment issues, and study more distant relationships, a population-based, multigenerational study was performed to evaluate the familial clustering of LDD. By combining a unique genealogy database with data on over 2 million individuals and a hospital-based diagnosis database, Patel *et al.* were able to definitively prove the contribution of heritable factors to LDD [10]. Using a well-established metric for genetic studies (Genealogical Index of Familiability test), they revealed significant excess relatedness of affected individuals. The relative risk of disease in relatives was also estimated and showed that this genetic influence was present in not only near relatives with similar environmental influences, but also in more distant relatives (e.g., cousins) who are unlikely to share those exposures.

■ Associated genes

The understanding that there is a heritable predisposition to the development of LDD has led to research into the genetic cause of this

effect. The first gene associated with an increased risk of degenerative disc disease was published in 1998. Videman *et al.* found that *TaqI* and *FokI* of the vitamin D receptor gene were associated with low MRI signal intensity, disc bulging and loss of disc height [24].

More recently, Eser *et al.* have reported associations between polymorphisms of the vitamin D receptor gene and severe radiographic disc degeneration [25]. Transgenic mice studies and evaluation of human mutations suggested that extracellular matrix genes likely impact the development of lumbar disc disease. Further, biomechanical and histologic studies revealed that the intervertebral disc has a very structured matrix to resist mechanical forces. The highly oriented collagens of the annulus fibrosis provide tensile strength and the hydrated proteoglycans of the nucleus pulposus resists compression. Researchers theorized that any change in the components of these structures would lead to increased load across the disc and increased degeneration. Thus, many recent studies have focused on the genetic variation of types of collagen found in the disc. Similar studies have evaluated other components of the extracellular matrix, such as aggrecan, as well as proteins involved in the degradation of the extracellular matrix, such as matrix metalloproteinases. These biochemical studies have shown an association between LDD and genes that encode: type XI collagen [26], type IX collagen [27], matrix metalloproteinase-2 [28], aggrecan [29] and multiple other intervertebral disc proteins.

Another protein found in the intervertebral disc is the cartilage intermediate layer protein. It interacts with TGF- β 1, aggrecan and collagen II. Polymorphisms of the cartilage intermediate layer protein have been associated with lumbar disc degeneration in collegiate male athletes, but not in female athletes [30]. This brings up an important issue of group variability when evaluating the influence of genes on disease development in individuals. Gender and ethnic differences may substantially change the role of individual genes in the formation of disc disease.

In an attempt to investigate the role of structural, degenerative and inflammatory genes in lumbar disc disease, Videman *et al.* utilized MRI and genetic data on 588 twins [31]. In this study 25 candidate genes were evaluated, including an aggrecan gene, 12 collagen genes, eight interleukin genes and four matrix metalloproteinase genes. They found that allelic variants of the aggrecan, collagen and

interleukin genes were significantly associated with MRI findings of disc degeneration. This large study served to shed further light on possible mechanisms of disc degeneration and support a polygenic influence on disease development.

Owing to the variability in clinical symptoms among individuals with radiographic evidence of LDD, some experts have suggested that symptomatic LDD is as much a chronic pain condition as it is a biomechanical failure. Within this context, variation of the genes associated with pain sensitivity and response to pain medications have been evaluated in patients treated for LDD. One such gene is *COMT*, which encodes an enzyme that is critical in the breakdown of pain causing neurotransmitters such as dopamine and epinephrine [32]. A recent study found significant improvement in functional outcome scores after surgical treatment for LDD in patients with certain *COMT* alleles. Further, patients homozygous for the allele had larger postoperative improvements than patients that were heterozygous for the allele. *GCHI* is another gene identified to have a major role in pain modulation. It encodes a protein critical in the nitric oxide synthesis pathway and has been shown to modulate neuropathic and inflammatory pain. In a recent study, Kim *et al.* evaluated the frequencies of 14 single nucleotide polymorphisms (SNPs) within the *GCHI* gene and found that one SNP (minor T allele) was associated with significantly improved functional and pain outcomes [33].

The advances in our genetic understanding of the development of LDD have provided insight into the molecular mechanism of disc degeneration. Beyond proving a genetic component to LDD, this insight may also have an impact in the diagnosis and treatment of disc degeneration. The proteins associated with LDD have shown encouraging regenerative effects *in vivo* in animal studies and *in vitro* in human studies [34]. However, such effects are limited by the proteins half-lives (<1 h). Gene therapy has the potential to overcome this limited effect duration by transferring the genes to the intervertebral disc cells for longer term local production. Successful *in vivo* transfer of therapeutic genes to target cells in animal models exemplifies the progress being made in this exciting field [35]. However, important questions regarding the efficacy in high-order animals, safety in humans and the indications and timing of treatment need to be answered before human clinical trials can begin [36].

■ Mechanisms & methodologies

As we have detailed above, there are many possible mechanisms by which the observed heritability of LDD may be transmitted. Several of these mechanisms have been studied, such as the genes that code for proteins in the intervertebral disc and genes involved in the pain perception pathways. However, genes involved in the formation of the spinal column, the metabolism of the intervertebral disc and vertebral bodies, the response to disc injury and the vascular supply to the disc may also have roles. Further, the genetic influence may be modified by gene–gene interactions or gene–environment interactions that would obviously complicate the study of the genetic influence.

There are several different methodologies to determine the mechanism of inheritability of lumbar disc disease. Using basic knowledge of the disease process, individual candidate genes can be selected based upon an understanding of their function and individually compared in cases and in controls. For example, sequence variations that cause single amino acid substitutions within a single chain of a molecule (e.g., α -2 chain of type IX collagen) can be studied by looking at the presence of the allele within large groups of individuals with and without the disease. The advantage to this methodology is that it allows a group to quickly and relatively inexpensively test many candidate genes. However, the number of genes that might affect the inheritability of LDD is potentially endless. The candidate gene method has identified genes that appear to predispose to the development of disease, but we have no way of knowing if these are the largest or the smallest contributors to the observed inheritability.

A more general approach that makes no assumptions based on knowledge of candidate genes would be a genome-wide association study that would similarly compare cases to controls for 1–5 million SNPs representing the entire genome. With a large enough sample size to provide power, the SNP variants identified at significantly different frequencies among cases compared with controls could then be tested in an independent population of cases to confirm true associations.

Another genetic study by which to identify the genes responsible for predisposition to disc degeneration is a linkage study. In a linkage study the DNA of affected members of pedigrees identified to be high-risk is analyzed to identify regions of chromosomes that are

inherited from a common affected ancestor. A statistical measure of the probability of all affected family members sharing the same small region of a chromosome can be made to support evidence that a predisposition gene must lie in the region. Through genome-wide genotyping, and observation of the segregation of the chromosomes with LDD, the chromosomal regions likely to be involved with disease predisposition can be localized. This serves to identify a region of the genome, on a single haplotype, in which all genes/variants present can be considered candidates. Depending on how many affected individuals are in a pedigree, and how many high-risk pedigrees show linkage to a region, and the density of the markers used for genotyping, the region can be quite small, and thus the number of candidate genes can be greatly reduced.

It was through linkage analysis that the *BRCA1*, *BRCA2* and *p16* genes were identified as significant risk factors for the development of breast and ovarian cancer, and melanoma [37–39]. The advantage of linkage analysis is that it allows researchers to concentrate on relatively small areas of the genome and to focus on an appropriate set of affected individuals (the LDD patients in the pedigree who carry the same haplotype) to screen for genetic mutations. This method is not widely used because it requires the ability to identify informative high-risk pedigrees from large numbers of individuals within high-risk family pedigrees.

Conclusion

Lumbar degenerative disc disease is a common condition that causes patients significant

disability and places a large economic burden on society. The etiology of disc degeneration has been extensively studied, revealing multiple risk factors for disease. Increased age and male gender are risk factors for radiographic and histologic changes associated with disc degeneration, while smoking and mechanical stress have a relatively small impact on disease development. Twin studies, case–control studies and large population-based studies have confirmed that the largest influence on disease development is hereditary. The underlying genetic cause of this heritable risk remains unknown, but variations in the collagens and other extracellular matrix components likely play a role.

Future perspective

The etiology of LDD has been proven to have a strong genetic component in addition to smaller influences from environmental exposures such as smoking and mechanical loading. In the coming decade, we anticipate an improved understanding of the mechanism by which this heritable predisposition occurs. This insight will arise through DNA studies of high-risk family pedigrees, by genome-wide association studies of case sets and by biochemical assays of genes known to be associated with the components of the intervertebral disc. Further research into the perception of pain will help to explain the differences seen between radiographic and symptomatic degenerative disc disease. This improved knowledge about the etiology of the disease will hopefully lead to improved screening, counseling as well as interventions to disrupt the development of symptomatic disc degeneration.

Executive summary

Difficulties of studying lumbar degenerative disc disease

- Radiographic lumbar degenerative disc disease (LDD) does not always correlate with symptomatic LDD.
- There are variable definitions of LDD.
- There are also confounding variables such as levels of lumbar spine and exposures.

Risk factors

- Age and gender:
 - Males have earlier onset of degenerative changes (~10 years) and more severe disease at any given age.
- Smoking:
 - Only has a small impact.
- Mechanical stress:
 - Has little to no impact.
- Genetics:
 - Has a large impact on the development and progression of disease.
 - Genes thought to be involved include those that encode intervertebral disc proteins and genes involved in pain perception.

Future perspective

- Increased understanding of the genetic mechanism responsible for inheritability leading to improvements in prevention, diagnosis and treatment of LDD.

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