Genetic Influence in Disc Degeneration - Systematic Review of Literature

A influência genética na degeneração discal – Revisão sistemática da literatura

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Abstract

Disc degeneration is a condition that compromises the intervertebral disc functions, which can lead to several important pathological processes, such as disc herniation and canal stenosis. Although its etiology is still unknown, more and more studies have demonstrated the preponderant role of genetic factors to the detriment of environmental factors. Aiming to review the current knowledge about the genes associated with intervertebral disc degeneration, we have performed a narrative review based on the medical literature in the English language from the last 10 years regarding this subject. We have concluded that several genes have been associated with disc degeneration in humans, including the genes for collagen I α-1 (COL1A1), collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2), interleukin 6 (IL-6), aggrecan (AGC1), vitamin D receptor (VDR), and matrix metalloproteinase 3 (MMP-3), in addition to microRNAs. Therefore, the present review emphasizes the latest advancements in the association of genes with specific phenotypes of degenerated discs, single-nucleotide polymorphisms, heritage and genetic-environmental interactions in relation to disc degeneration to help future reviews regarding the genetic mechanisms underlying these processes.

Keywords

► intervertebral disc degeneration
► intervertebral disc genetics
► polymorphism, genetic

Resumo

A degeneração discal é uma condição que compromete as funções do disco intervertebral, podendo levar a vários processos patológicos importantes, como hérnias discais e estenoses de canal. Apesar de sua etiologia ainda ser desconhecida, cada vez mais estudos têm demonstrado o papel preponderante de fatores genéticos em detrimento de fatores ambientais. Com o objetivo de revisar o conhecimento atual sobre os genes associados à degeneração do disco intervertebral, foi realizada uma revisão narrativa da literatura inglesa nos últimos 10 anos sobre o tema. Concluímos que há uma série de...
Introduction

Degenerative disc disease, or simply disc degeneration (DD), is a condition that leads to the impairment of the functions of the vertebral disc, especially shock absorption. It is characterized by a decrease in disc height and elasticity, eventually resulting in the loss of the capacity of impact absorption. These features multiply the chances of fibrous annulus wall ruptures, allowing the extravasation of the nucleus pulposus and the compression of neurological structures.\(^1,2\)

The degenerative process may be a natural evolution of aging, and, therefore, does not cause persistent pain. However, it may also be the cause of very prevalent clinical entities, such as herniated discs and canal stenosis. These conditions chronically lead to pain, especially low back pain, one of the costliest disorders for worldwide health systems.\(^3\)

More than 80% of adults report back pain at some point during their lives, and this is the most common cause of work absenteeism in people < 45 years old. Its costs are estimated at between 50 and 100 billion dollars per year and tend to increase due to the aging of the population.\(^4\)

There is no consensus on the cause for disc degeneration. Several factors have been identified as determinants, including age, compressive loads, vibratory forces, trunk posture at the front of the gravity line, and environmental and genetic factors; in addition, traumatic lesions, deformities, and preexisting diseases may be involved.\(^1,2\) Moreover, aggravating factors, such as obesity, occupation, smoking, alcohol consumption, and diabetes, are all somehow implicated in the origin of DD, leading to the belief that this is a multifactorial process.\(^4,5\)

However, recent studies have pointed out that the genetic influence is the main determinant in the development of degenerative DDs, while environmental factors lost some of their importance.\(^6\) Studies with twins, for example, have shown the genetic involvement in up to 74% of the cases.\(^7-10\)

It is extremely important to spread this knowledge among us, mainly because of the attempts by patients, experts, labor courts, and even medical assistants to relate labor issues to causes of low back pain.

The search for genes and genetic variations that cause degenerative disorders has been influenced by the advances in molecular genetic technology and in the human genome mapping. These genes regulate the intervertebral disc physiology, acting on its structure, homeostasis, and regeneration, which are the mechanisms of disc structural maintenance.\(^11\)

Knowledge of these genes may help to define the patients who are more susceptible to DD, allowing earlier interventions, and, more importantly, the development of more effective therapies.

As such, the present study aims to review the literature on the main genes and genetic mechanisms related to the etiology of DD. Due to the high personal and economic cost attributable to DD, and to the exponential increase in research focused on the elucidation of its etiology during the last 10 years, it is necessary to know the genetic advances that influence this condition, so the attending physician can understand the new diagnostic methods and therapies developed from this information.

Methods

A narrative review of the literature was carried out in the following databases: Medline, Scielo, Web of Science, and Cochrane systematic reviews. Only reviews published between January 2007 and December 2017, written in the English language, were included. This inclusion was carried out by two independent researchers, in addition to a third one, who solved any disagreement. The following descriptors were used: intervertebral disc degeneration, degenerative disc disease, genetics, and polymorphism. Only reviews using gene correlation, genetic variation or genetic polymorphism related to disc structure, to homeostasis or to regeneration, and directly influencing DD, were included. Repeated papers, dissertations, theses, validation papers, and those with no full text available or that did not detail the evaluation method were excluded. Reviews describing degenerative spinal alterations directly related to genetic mechanisms were selected. All of the abstracts were initially evaluated by two independent reviewers, and, after a process of criteria adaptation, the complete versions of the selected papers were obtained. These papers were critically read, and their respective references were checked for additional data to refine the research initially performed. The present study is a literature review, and it does not involve patients, thus not requiring the approval of an ethics committee.
We have found 403 papers, including 21 reviews qualified for analysis (►Fig. 1). The following data were extracted: year of publication, authors, country of study, candidate gene, gene name, chromosome location, and pathophysiological mechanism related to disc degeneration. Among the reviews analyzed (►Table 1), there were several genes associated with DD in humans. However, only some of these genes seemed well-established in the literature, and they were the main genes analyzed in the selected reviews as directly related to DD genesis; therefore, these genes will be the focus of the present study. These genes include those for collagen I α-1 (COL1A1), collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2), interleukin 6 (IL-6), aggrecan (AGC1), vitamin D receptor (VDR) and matrix metalloproteinase 3 (MMP-3), which were the most analyzed and showed their direct influence on DD.

For the other genes not specified in the present study, there is no agreement yet on their direct influence on DD. Some environmental factors, gene-gene, environment-gene and gene-age interactions may exist, but with no strong

Table 1  Review articles selected for analysis

| Candidate gene | Gene name | Chromosomal location | Study | Country |
|----------------|-----------|----------------------|-------|---------|
| COL1A1         | Collagen I α-1 | 17q21.3-q22          | Kalichman et al., 2008 | United States |
|                |           |                      | Zhang et al., 2008 | China |
|                |           |                      | Kalb et al., 2012 | United States |
|                |           |                      | Kepler et al., 2013 | United States |
|                |           |                      | Mayer et al., 2013 | United States |
|                |           |                      | Hanaei et al., 2015 | Iran |
|                |           |                      | Toktas et al., 2015 | Turkey |
|                |           |                      | Martirosyan, 2016 | United States |
| COL9A2         | Collagen IX α-2 | 1p33-p32.3          | Kalichman et al., 2008 | United States |
|                |           |                      | Zhang et al., 2008 | China |
|                |           |                      | Kalb et al., 2012 | United States |
|                |           |                      | Kepler et al., 2013 | United States |
|                |           |                      | Mayer et al., 2013 | United States |
|                |           |                      | Janezko et al., 2014 | Poland |
|                |           |                      | Hanaei et al., 2015 | Turkey |
|                |           |                      | Toktas et al., 2015 | Iran |
|                |           |                      | Martirosyan, 2016 | United States |

(Continued)
| Candidate gene | Gene name     | Chromosomal location | Study                                      | Country      |
|----------------|---------------|----------------------|--------------------------------------------|--------------|
| COL9A3         | Collagen IX α-3 | 20q13.3              | Kalichman et al., 2008                     | United States|
|                |               |                      | Zhang et al., 2008                         | China        |
|                |               |                      | Kalb et al., 2012                          | United States|
|                |               |                      | Kepler et al., 2013                        | United States|
|                |               |                      | Mayer et al., 2013                         | United States|
|                |               |                      | Janeczko et al., 2014                      | Poland       |
|                |               |                      | Toktas et al., 2015                        | Turkey       |
|                |               |                      | Hanaei et al., 2015                        | Iran         |
|                |               |                      | Martirosyan, 2016                          | United States|
| COL11A2        | Collagen XI α-2 | 6p21.3               | Kalichman et al., 2008                     | United States|
|                |               |                      | Kalb et al., 2012                          | United States|
|                |               |                      | Mayer et al., 2013                         | United States|
|                |               |                      | Janeczko et al., 2014                      | Poland       |
|                |               |                      | Hanaei et al., 2015                        | Iran         |
|                |               |                      | Martirosyan, 2016                          | United States|
|                |               |                      | Walker et al., 2016                        | United States|
| IL6            | Interleukin-6  | 7p21                 | Kalichman et al., 2008                     | United States|
|                |               |                      | Kalb et al., 2012                          | United States|
|                |               |                      | Mayer et al., 2013                         | United States|
|                |               |                      | Risbud and Shapiro, 2014                   | United States|
|                |               |                      | Hanaei et al., 2015                        | Iran         |
|                |               |                      | Martirosyan et al., 2016                   | United States|
|                |               |                      | Rigal et al., 2017                         | France       |
| VDR            | Vitamin D receptor | 12q12-q14          | Kalichman et al., 2008                     | United States|
|                |               |                      | Zhang et al., 2008                         | China        |
|                |               |                      | Kalb et al., 2012                          | United States|
|                |               |                      | Colombini et al., 2013                     | Italy        |
|                |               |                      | Kepler et al., 2013                        | United States|
|                |               |                      | Mayer et al., 2013                         | United States|
|                |               |                      | Hanaei et al., 2015                        | Iran         |
|                |               |                      | Chen et al., 2016                          | China        |
|                |               |                      | Martirosyan, 2016                          | United States|
|                |               |                      | Pabalan et al., 2016                       | Philippines  |
|                |               |                      | Jiang et al., 2016                         | China        |
|                |               |                      | Walker et al., 2016                        | United States|
| AGC1           | Aggrencan     | 15q26                | Kalichman et al., 2008                     | United States|
|                |               |                      | Kalb et al., 2012                          | United States|
|                |               |                      | Kepler et al., 2013                        | United States|
|                |               |                      | Mayer et al., 2013                         | United States|
|                |               |                      | Sivan et al., 2014                         | Israel       |
|                |               |                      | Hanaei et al., 2015                        | Iran         |
|                |               |                      | Martirosyan, 2016                          | United States|
Collagen
Collagen plays a primordial structural role in the intervertebral disc (IVD), particularly in the fibrous annulus (FA), where collagen I creates a fiber network that retains the nucleus pulposus (NP) and distributes the compressive load. At the same time, the NP contains reticulated collagen IX fibers and type II collagen fibers to provide optimal stability, forming a complex and highly organized network. 

The various polypeptides that make up the several types of collagen have proper encoding genes. Each mature collagen molecule contains three polypeptide chains. These chains are set up in a triple helix arrangement in at least one region of the collagen molecule. Since this complex arrangement is genetically determined, genetic defects involving collagen may play a role in the etiopathogenesis of DD.

Collagen I
The COL1A1 gene encodes a part of collagen I, which is the main protein in bone, skin and, especially, the outer layer of the FA. It is a heterotrimeric protein, consisting of two similar α-1 chains and of a different third chain, α-2, encoded by the collagen type I α-2 Chain (COL1A2) gene. The genes encoding collagen I, COL1A1 and COL1A2, are present in both NP and FA, although they are much more abundant in FA. Polymorphisms of the COL1A1 gene have been reported as a factor increasing the risk of DD. The Sp1 (TT/GT/GG) polymorphism at the COL1A1 gene intron 1 is highlighted, with a guanine (G) replaced by a thymine (T) at the +1245 position. 

Nucleotide changes increase COL1A1 mRNA expression and, consequently, the expression of proteins encoded by it. The imbalance between COL1A1 and COL1A2 expression leads to an instability in collagen fibers, which is associated with low mineral density, increased bone loss, increased bone turnover, and increased risk of fracture, especially vertebral fracture.

Collagen IX
Collagen IX is a heterotrimeric protein composed by three genetically distinct chains: α-1 (IX), α-2 (IX), and α-3 (IX), encoded by the genes collagen type IX α-1 chain (COL9A1), collagen type IX α-2 chain (COL9A2), and collagen type IX α-3 chain (COL9A3), respectively. Collagen IX has a bridging function between collagens and proteins that are not collagenic in tissues. Both AF and NP contain small amounts of this type of collagen. Since type IX collagen plays an important role in the constitution of IVD, the genes encoding it are suitable candidate genes.

Sequence variations in the COL9A2 gene, which encodes IVD-expressed collagen IX α-2 (IX) chain, were detected in individuals with DD. The substitution of tryptophan for glutamine at the codon 326 impairs the formation of collagen II, IX and XI heterotrimers and may render the IVD more fragile. Studies show that individuals who have a COL9A3 allele with tryptophan (Trp) 3 substitution have a three-fold increased risk of DD compared with individuals without Trp 3. However, this effect was not confirmed in the presence of another allele, called IL-1βff, suggesting that the genetic effect of COL9A3 can be modified by the genetic polymorphism of other alleles that are still unknown.

Collagen XI
Collagen XI is important for the composition and organization of the cartilage-specific extracellular matrix and the formation of cartilage fibrils. It is composed by three chains: α-1 (XI), α-2 (XI), and α-3 (II), which are encoded by the COL11A1, COL11A2 and COL11A3 genes, respectively. It also participates in the formation of fibrils with other cartilage-specific collagens (collagen II and IX), and regulates the diameter of cartilaginous collagen fibrils.

Because of the interaction with collagen II and IX, which are present in the IVD, collagen XI and its encoding genes have been identified as possible contributors to DD. Studies have identified a strong association between polymorphisms in the COL11A1 gene and lumbar disc hernia.
The genetic polymorphism of COL11A1 is the replacement of thymine (T) by cytosine (C) at the position 4603 of the nucleotide chain. The association between this polymorphism and lumbar disc herniation was identified in the Japanese population. In 3 studies, 130/179, 359/286, and 334/379 patients (case and control groups, respectively) were recruited. The frequency of the c.4603T allele was ~1.5 times higher in the case group compared with the control group.12,15

Interleukin 6
Several inflammatory mediators, including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α), have been implicated in the etiopathogenesis of DD. Interleukin 6 is an important inflammatory mediator, and it is involved with lumbar disc herniation. Nevertheless, the exact role of IL-6 in DD has not been fully elucidated.16 One study documented a single nucleotide polymorphism (SNP) at the IL-6 gene that was significantly associated with DD (with a 4.4-fold higher risk of DD development). It is hypothesized that this polymorphism leads to an imbalance of proinflammatory cytokines, thus accelerating inflammation.14

Vitamin D receptor
The vitamin D receptor (VDR) is a member of the nuclear steroid hormones–receptor family. Like other members of this family, VDR plays a role in normal bone mineralization and remodeling, and its genetic polymorphisms are thought to contribute to disorders such as osteoporosis, osteoarthritis and DD; perhaps, these are the most known and studied polymorphisms.20 1,25-Dihydroxyvitamin D3 is an active vitamin D metabolite that regulates local calcium and phosphorus homeostasis and aggrecan synthesis through a VDR-dependent mechanism.22 The VDR gene is expressed in the NP and FA cells. Thus, the VDR gene may affect the disc calcium and phosphorus metabolism and possibly plays a role in the etiology of DD.16,24,25

Matrix Metalloproteinase 3
One of the important steps in DD is the disc extracellular matrix degradation of the by enzymes, such as matrix metalloproteinases (MMPs). Matrix metalloproteinase-3 (MMP-3) is a potent proteoglycan degrading enzyme that plays an important role in the IVD degeneration. Expression of MMP-3 is induced in response to local conditions, such as mechanical pressure and inflammation, and the DD resulting from MMP-3 expression may, therefore, increase over time.19,28

Matrix metalloproteinases are the main IVD catabolic enzymes and the primary mediators of extracellular matrix degradation, thus allowing normal remodeling and contributing to the destruction of pathological tissue.28 The expression of most MMPs is low in nondegenerate discs, whereas the increased expression of different MMPs, such as matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), is observed in human degenerated disc tissue.13 There is a strong correlation between the degree of histologic degeneration and MMP-3, which is significantly increased in severely degenerate NPs.22,27

Aggrecan
Aggrecan is a major aggregating proteoglycan. Its main function is water binding, which is influenced by the negative charge of glycosaminoglycans. As such, aggrecan helps the IVD action as a shock absorber to support and distribute axial forces and loads. Interacting with hyaluronate, aggrecan forms large aggregates that are responsible for tissue resistance to compressive loads. This function is related to aggrecan structure and, in particular, the large number of chondroitin sulfate chain within its core protein.26 The variable number of tandem repeats (VNTR) polymorphisms in the CS1 gene domain, located in exon 12, results in variant aggrecan structures19 and, just like in joint cartilages, the loss of aggrecan is an early event in the degenerative cascade of the IVD tissue.27

microRNAs
Since the last decade, it has become increasingly recognized that small ribonucleic acids (RNAs) are important components of gene regulatory networks. Among them, microRNAs (miRNAs) are a class of small, noncoding, small-stranded RNAs of 18 to 22 nucleotides that act as gene post-transcriptional regulatory elements.32 These miRNAs are expressed differently between the various tissues and cells of the degenerate IVD. Changes in miRNA regulation seem to be involved in DD development, mainly inducing apoptosis, extracellular matrix degradation, cell proliferation, and inflammatory responses.31,32

Discussion
The research on the pathobiology of DD progressed from the classic environmental and physical wasting involvement to a complex disease with multiple causes and an intercorrelated molecular and genetic basis. The preponderance of genetic factors has been increasingly demonstrated, whereas environmental factors relatively lost their importance.

With the Genome Project and the new developments in genetics, genetic analysis studies emerged and led to the discovery of multiple DD-related genes. Candidate genes, the targets of all genetic association studies, were based on the recent understanding of IVD biology and probable degenerative mechanisms. The study of genetic factors implicated in DD remains challenging due to the large number of different genes that contribute to the progression of this complex disease, which does not share a common definition or a fully enlightened pathogenesis. The distinction between genetic and environmental factors requires well-defined samples in similar conditions, which are often difficult to isolate or to characterize. The frequency of genetic associations with degeneration is also different in various parts of the world, hindering the replication and the validation of genetic risk factors among populations. The lack of a clear DD definition further confuses the genetic analysis because of the variability of phenotypes used in multiple studies on the same subject. Therefore, continuous efforts in identifying new candidate domains will be required. However, it is evident that polymorphisms in the COL11A1, COL9A2, COL11A1, VDR,
and AGC1 genes, in addition to polymorphisms in the MMP-3, IL-1 and IL-6 genes, establish a more promising pathway for the broad association of genetic factors with DD, since they were validated in more than one ethnicity and population. Each gene plays an essential role in the development and maintenance of a healthy matrix, and each individual polymorphism can cause loss of structural integrity, loss of pressure status, or an advanced state of proinflammation resulting in potentially painful conditions.

Genetics is involved in the pathology of DD and will soon be integrated into the clinical evaluations to consequently provide opportunities for the development of new diagnoses, as well as preventive and therapeutic capabilities, to manage this disabling disease.

**Conclusion**

A number of genes have been associated with DD in humans, including those encoding collagen I (COL1A1), collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2), IL-6, aggrecan (AGC1), VDR and MMP-3.

**Conflict of Interests**

The authors have no conflict of interests to declare.

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