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

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- degeneração do disco intervertebral
- disco intervertebral
- genética
- polimorfismo genético

genes que foram associados à degeneração discal em seres humanos, incluindo genes codificando colágeno I α-1 (*COL1A1*), colágeno IX (*COL9A2* e *COL9A3*), colágeno XI (*COL11A2*), interleucina 6 (*IL-6*), agrecano (*AGC1*), receptor de vitamina D (*VDR*), metaloproteinase de matriz 3 (*MMP-3*), além de microRNAs. Dessa forma, a presente revisão enfatiza os últimos avanços na associação de genes com fenótipos de discos degenerados específicos, polimorfismos de nucleotídeos únicos, hereditariedade e interações genético-ambientais em relação à degeneração discal, com o intuito de permitir ao clínico entender esse mecanismo de degeneração e estar preparado para as novas terapêuticas que estão por vir baseadas na genética.

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.

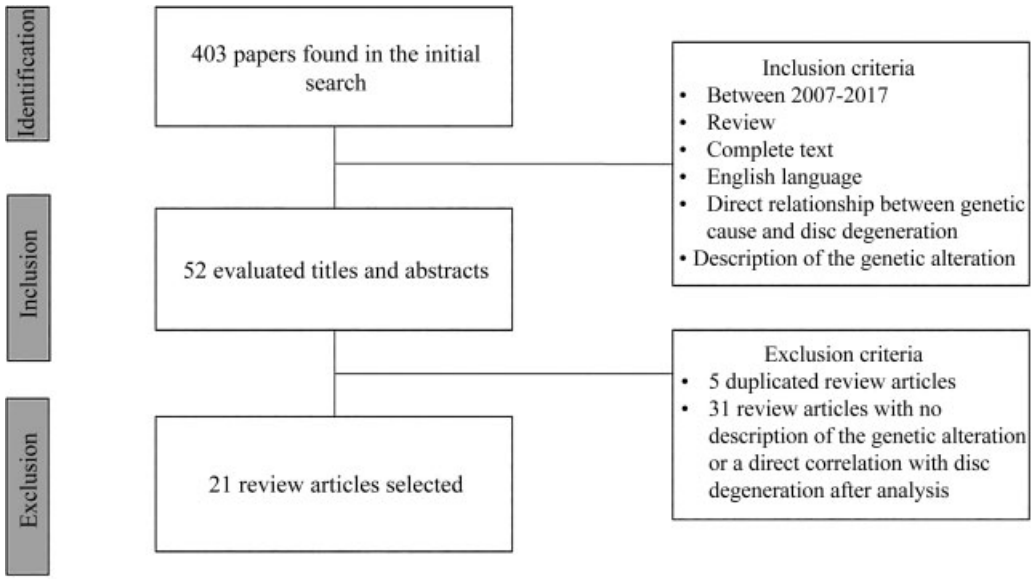

Fig. 1 Organization chart describing the search strategy resulting in the 21 selected review articles.

Results

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**),[6,11–32] 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
			Janeczko et al., 2014	Poland
			Hanaei et al., 2015	Turkey
			Toktas et al., 2015	Iran
			Martirosyan, 2016	United States

(*Continued*)

Table 1 (*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	Aggrecan	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

Table 1 (*Continued*)

Candidate gene	Gene name	Chromosomal location	Study	Country
MMP-3	Matrix metalloproteinase3	11q22.3	Kalichman et al., 2008	United States
			Zhang et al., 2008	China
			Vo et al., 2012	United States
			Kepler et al., 2013	United States
			Mayer et al., 2013	United States
			Hanaei et al., 2015	Iran
			Wang et al., 2015	China
			Eser et al., 2016	Turkey
			Martirosyan, 2016	United States
microRNAs			Li et al., 2015	China
			Wang et al., 2015	China
			Chen et al., 2016	China

evidence, because the studies have limitations in detecting the genetic basis of the disease, requiring a better localization of known binding regions.[33]

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.[12]

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.[13]

Collagen I

The *COLIA1* 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.[13] 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.[14] Nucleotide changes increase *COL1A1* mRNA expression and, consequently, the expression of proteins encoded by it.[34] 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.[15,16]

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.[14,17]

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.[18] 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-1βT, suggesting that the genetic effect of *COL9A3* can be modified by the genetic polymorphism of other alleles that are still unknown.[12,17]

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.[14]

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.[18]

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 $\sim$ 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, aggregan helps the IVD action as a shock absorber to support and distribute axial forces and loads. Interacting with hyaluronate, aggregan forms large aggregates that are responsible for tissue resistance to compressive loads. This function is related to aggregan 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 structures[19] 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 pathophysiology 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 *COL1A1*, *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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