

GENETIC INFLUENCE ON INTERVERTEBRAL DISC DEGENERATION

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SUMMARY

Disorders affecting musculoskeletal system affect hundreds of millions individuals worldwide and are one of the most common causes of disability and chronic suffering. The degenerative vertebral disease is an exacerbation of the aging process, and genetic and environmental factors, as well as traumatic injuries, deformities and pre-existent diseases may be involved. Much has been discussed about the many factors involved on disc degen-

eration, but its etiology remains unclear. Nevertheless, today, the role played by genetics seems to be much more relevant than it was previously suspected. In this article, the participation and role of some genes in the disc degeneration process are addressed for a better understanding of this disease's etiopathogenesis and how to improve its treatment.

Keywords: *Genetic polymorphism, Intervertebral disc degeneration, Predisposing genes.*

INTRODUCTION

Current knowledge about degenerative diseases suggests a multifactorial etiopathogenesis, where genetics plays a primary role, guiding pathologic events, as well as determining marked differences in disease phenotype from patient to patient. Genes may act as susceptibility and predisposing factors, increasing the risks of disease development, or may act as regulating factors, modulating the magnitude and severity of a pathogenic process, as well as the response to drug therapy⁽¹⁾.

Diseases affecting musculoskeletal system affect hundreds of millions of people worldwide and are among the most common causes of disability and chronic suffering. Those conditions are considered as the major responsible for the leading position in the number of disabilities in people younger than 45 years old, resulting in economical losses exceeding 90 billion dollars a year in the United States⁽²⁾.

The intervertebral disc remains of great interest, once its degeneration may influence a variety of structures and processes that are believed to participate in the source of pain. Similarly, the disc serves as a focus to numerous intervention treatments, either conservative or surgical, for symptoms related to the spine⁽³⁾.

The intervertebral disc contains plenty of proteoglycans and collagen extracellular matrix. The outer layer, the fibrous ring, is basically constituted by collagen I, while the inner structure of the disc, called pulpy nucleus, is constituted of about 50% proteoglycans, particularly aggrecan, and 20% collagen II. Both contain small amounts of collagen IX⁽⁴⁾.

Definitions for degenerative joint disease are not uniform due to the lack of a thorough understanding about this phenomenon. Conceptually, disc degeneration is a byproduct of the life-long degradation, combined with a synchronized remodeling of the disc and adjacent vertebrae, including the simultaneous adjustment of disc structures to changes on body weight and eventual injuries healing, with cicatricial tissue formation⁽⁵⁾.

Disc degeneration has been attributed to the accumulation of environmental effects, primarily aggressions and traumas, lifestyle, smoking habits, atherosclerosis, added by changes that occur during aging process. Recent findings, however, demonstrate that those effects have little influence on disc degeneration, which reinforces the importance of genetic factors participation in this process^(3,5).

The Role of Genetics in Disc Degeneration

There are many variations in reports about the prevalence of spine degeneration, which cannot be completely explained by aging or other identifiable risk factors. Researches conducted in the last decade provided a better understanding about disc degeneration and its etiology, and, thereby, the role of genetics has become clear, which turned to be stronger in the disc degeneration process than it was previously suspected^(3,5). The genetic component has been determined in studies with twins and family predisposition^(6,7,8,9,10), as well as in detecting genetic polymorphisms related to its onset^(4,11,12,13,14).

Although clinical studies have provided elucidation on its prevalence and treatment approach, a better understanding of how genetic mutations may contribute to discopathies development it is attributed to recent advancements in molecular mechanisms⁽¹⁰⁾.

The first step in genetic epidemiology studies is to determine whether familial predisposition to the condition or disease of interest occurs or not, suggesting a genetic influence. Two of the first systematic analyses of familial predisposition focusing the intervertebral disc degeneration were conducted in pairs of monozygotic twins^(8,15). Results of those studies show a significant familial predisposition regarding extension and location of the discopathy.

A study conducted in adult patients with intervertebral disc degeneration showed that those individuals presented a two-fold increased likelihood of familial history to the disease, with women

Study conducted by the Molecular Epidemiology Laboratory - Paulista State University- UNESP, São José do Rio Preto Campus.

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being mostly affected if compared to men⁽⁹⁾. Such results are corroborated by others⁽¹⁶⁾, reporting the significant presence of the disease in those whose close relatives have been submitted to surgical procedures in a herniated disc. No significant differences were found among groups exposed to risky activities, such as load carriers, motorcycle riders, or those performing tasks with vibrating equipment or in people who stay in a seated position for long periods. Epidemiologic studies previously performed^(17,18) similarly confirm a higher prevalence of discogenic disease in immediate members of families with such diagnosis when compared to control individuals.

Familial predisposition suggests that the intervertebral disc of those individuals have singular aspects. The expression of those inherited factors leads to disc structural or biochemical-medium changes, causing it to be more susceptible to injuries and, subsequently, to herniation. This process may act in synergy with other factors, such as, for example, carrying heavy loads in an upright position, but specific activities, both job- and sports-related, seem to not influence much. In other words, the natural progression of the disc degeneration, genetically determined, is modified, to a certain degree, by behavioral and environmental factors⁽⁹⁾. Similarly, the genetic factor contributes to disc degeneration in adolescents⁽¹⁹⁾, being family history of herniation an effective risk factor to the development of this disease in individuals younger than 21 years old. Similarly, previous surgery procedures in family members have a significant implication on the evolution of the disease in teenagers⁽²⁰⁾.

Another interesting study⁽²¹⁾ differentiated two sources of familial similarity, that is, the biological factors (genetic) and the social factors (cultural inheritance), involving 86 pairs of monozygotic twins and 154 pairs of dizygotic twins. As mentioned before, there was a substantial genetic component in the presence of disc degeneration.

Aggrecan Genes and Vitamin-D Receptor in Disc Degeneration

Aggrecan Gene

The aggrecan gene is the major structural gene in cartilage, expressed in high levels only in this kind of tissue. Aggrecan is formed by two kinds of structural elements, a central expanded nucleus and three globular, flanking domains⁽²²⁾.

Aggrecan codifies to a protein at the proteoglycan nucleus, with an extension of the central domain carrying the glycosaminoglycan, flanked by globular domains at each end. The central region consists of long extensions of aminoacids repetitions, which serve as bonding sites for glycosaminoglycans, such as chondroitin and keratan sulphates; the terminal globular domains interact with other cartilage components. The genomic DNA test of a non-relative population has shown that the repeated sequences block exists in a multiple allelic form, distinguished by the variable number of tandem repetitions (VNTR) in this codification site in each allele. This polymorphism seem to be restricted to humans and results in the production of different lengths of proteins with an aggrecan nucleus, carrying various numbers of potential bonding sites for chondroitin sulphate⁽¹¹⁾.

As previously noted, the intervertebral disc consists mainly of proteoglycans and collagens, the former being responsible for "supporting the load" of the disc. Thus, it is assumed that genes codifying to proteoglycans significantly act to disc degeneration. Aware of the existence of VNTRs, it is known that this polymorphism results in proteins with different lengths of aggrecan nucleus, which may lead to changes on cartilage's functional properties.

Thus, the aggrecan gene was selected as a candidate marker for the association between gene polymorphism and disc disease⁽¹³⁾ under study, where 64 young women, with or without back problems and 15 additional cases of patients submitted to lumbar

spine surgery. Individuals involved in heavy physical work, as well as smokers, have been excluded. The degeneration degree was determined according to Schneiderman's classification, meaning: grade 1 (normal), 2 (intermediate, reduced intensity of heterogeneous sign), 3 (marked, diffuse loss of sign), 4 (absent, null sign). Disc herniation was evaluated according to the criteria by MacNab as normal or protrusion, extrusion and herniated disc sequestration types. The study revealed that individuals with severe disc degeneration in multiple levels had a short-length aggrecan gene in tandem repetition numbers (VNTR). These findings suggest that those individuals present a significant risk of disc degeneration, despite being young.

The mechanism by which the shortened aggrecan gene is related to the early onset of this disease seems to be reasonable, once the aggrecan protein nucleus is modified by glycosaminoglycans chains, including keratan sulphate and chondroitin sulphate. The high osmotic pressure of the aggrecan is attributed, mainly, to the polyelectrolytic nature of those glycosaminoglycans chains. Thus, such chain shortening provides a reduced ability of the disc to store water, resulting in the anticipation of the degenerative process.

Vitamin-D Receptor Gene

Vitamin-D regulates calcium homeostasis and bone mineralization and its action is mediated by the Vitamin D Receptor (VDR) belonging to the steroid hormones receptors family, activated to transcription factors⁽²³⁾.

The hormonal form of Vitamin D (1.25-2-hydroxy vitamin D3) is necessary for bone mineralization process, calcium absorption by bowel, calcium control, phosphorus homeostasis and regulation of parathyroidal hormone. Vitamin D receptors are intracellular polypeptides specifically bonding to 1.25-2-hydroxy vitamin D3 and interact with target-cells nuclei in order to produce a number of biological effects.

The VDR gene contains many intragenic polymorphisms associated to bone density and osteophyte formation. In the polymorphism Fok I, the transition from thymine to cytosine (ATG to ACG) occurs in the first of the two potential initiating sites at the exon II. Individuals with the allele C (determined by F) initiate the transcription at the second ATG site and do not have the three NH2-terminal aminoacids all through VDR protein's extension, that is to say, the protein is shorter in three aminoacids. The absence of the polymorphic site FokI indicated that the translation of the protein started at the first ATG site, and, therefore, individuals carrying this genotype (ff) synthesize the protein in all its 427-aminoacid extension. This structural difference can affect the VDR function and consequently influence remodeling and bone mineral density. There are evidences suggesting that the longest allele f may be less active, acting with reduced efficiency⁽¹²⁾.

In addition to mineral metabolism, this gene promotes the action of other genes expressed in connective tissues. For example, the osteocalcin synthesis, the most abundant non-collagenous protein in bones, is induced by the hormonal form of vitamin D, through the VDR and a specific responsive element in vitamin D in the osteocalcin promoter gene. Due to this activity in the regulation function in vitamin D metabolic steps, the mechanisms by which the presence of polymorphic variations affect bone, cartilage and disc degeneration may result in variation of the expression either of structural components often found in connective tissues, or of tissue-specific proteins⁽²³⁾.

Recent studies show that VDR specific alleles are associated to disc degeneration, which supports the existence of genetic determinants in this disease^(3,14).

By taking the knowledge that bone and cartilage are partially formed by the same connective tissues of the intervertebral discs, an association of the VDR polymorphisms with disc degeneration was studied, determined by the quantitative measurement of sign

intensity and by the qualitative determination of the sign intensity, protrusion and disc height in magnetic resonance images⁽⁹⁾. The participants of this study were selected from a population of Finnish twins, because Finland is the country having all pairs of twins born before 1958 still alive in 1975.

Results show that the two intragenic polymorphisms detected by Fok I and Taq I, separated by approximately 35 kilobases in the VDR gene, are associated to the findings regarding intervertebral disc degeneration. The quantitative analysis of sign intensity in thoracic and lumbar vertebrae for polymorphism Taq I showed the highest degree of degeneration in T6-S1 intervertebral discs of individuals with recessive homozygote genotype (tt), an intermediate degree for carriers of the heterozygote genotype (Tt) and the lowest degeneration degree in those with dominant homozygote genotype (TT). Equally, a similar pattern was found for polymorphism Fok I. No associations were found between Taq I genotypes and the qualitative aspects assessed. Nevertheless, the same did not happen with Fok I genotypes, since FF individuals presented with the least qualitative degeneration in sign intensity, protrusion, and disc height, while these aspects were worse of Ff and ff individuals.

Thus, this study provides evidences substantiating the existence of genetic determinants in lumbar intervertebral disc degeneration. Not surprisingly, the association was stronger when degeneration measurements, more sensible and more reproducible, were used for phenotype definition. Those findings emphasize the significance of an accurate determination of clinical phenotypes when investigating this complex disease.

The association between the polymorphism TaqI and lumbar disc degeneration was equally evaluated⁽¹⁴⁾, with findings reinforcing the increased risk of severe and multiple-levels degeneration, as well as the presence of herniation in young individuals, carrying the mutant genotype.

Other important genes

The collagen type IX is found in the nucleus and in the disc fibrous ring, as well as in terminal vertebral plates. It is believed that this kind of collagen accounts for the mechanical support of tissues,

acting as a bridge between molecules⁽²⁴⁾. The COL9A2 gene codifies to one of the polypeptide chains of the collagen IX, expressed in the intervertebral disc. A variation in the sequence of collagen IX [alpha]-2 chain, identified as allele Trp2, was associated to the dominant inheritance of the lumbar disc disease⁽⁴⁾.

Similarly, inflammatory cytokines have been recognized as participants in the discogenic process, especially the interleukin-1, for inducing the activity of enzymes destroying proteoglycans and for being involved in the process of pain. An association was found between interleukin-1 polymorphisms and disc degeneration aspects in magnetic resonance imaging tests of Finnish workers (machinery operators, carpenters and clerks). The presence of this polymorphism was related to a three-fold increased risk of disc bowing and probably interfered in the effects of the physical load on the disease⁽²⁵⁾.

Associative studies on genetic epidemiology are difficult to reproduce and should always consider the population under study, due to the ethnical variation in the occurrence of specific polymorphisms. However, promising results have emerged in the last few years. Thus, a positive familial history can strengthen clinical diagnostic and also provide efficient methods for identifying individuals at higher risk, who can be benefited from preventive strategies, as vocational counseling, changing work-related behaviors and lifestyles, and promoting the adoption of preventive exercises for strengthening and stance education.

The potential to prevent those diseases is obvious, as well as the importance of a multidisciplinary research, employing genetic markers combined to clinical follow-up, as accurate tools to better understand the etiology of such disease.

Thus, the union of efforts shall yield options for effective prevention and diagnostic programs, detection of risk factors and treatment designs, thus expanding the scope for cure. It is worthy to highlight here that, currently, all modalities of discopathies treatment, including the surgical approach, have not shown efficient and definitive outcomes. Therefore, the combination of the information about the genetic condition of affected individuals to the clinical findings should largely help to prevent those conditions, as well to establish treatment protocols with specific and customized medication.

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