Genetics of the Degenerated Intervertebral Disc

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Key words
- Aggrecan
- Collagens
- Degeneration
- Genetics
- Interleukins
- Intervertebral disc
- Matrix-degrading enzymes
- Vitamin D receptor

Abbreviations and Acronyms
AF: Annulus fibrosus
CS: Chondroitin sulfate
ECM: Extracellular matrix
FasL: Fas ligand
GAG: Glycosaminoglycans
IGF-1: Insulin-like growth factor
IGF-1R: Insulin-like growth factor receptor
IL: Interleukin
IVD: Intervertebral disc
IVDD: Intervertebral disc degeneration
MMP: Matrix metalloproteinase
MRI: Magnetic resonance imaging
NGF: Neutrophin nerve growth factor
NP: Nucleus pulposus
SNP: Single-nucleotide polymorphism
THBS: Thrombospondins
TIMP: Tissue inhibitors of matrix metalloproteinase
Trp: Tryptophan
VDR: Vitamin D receptor

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BACKGROUND: **Given the genetic and proteomic advances of the past decade, understanding of the molecular etiopathogenesis of several complex diseases is increasing. Intervertebral disc disease (IVDD) is no different from other complex diseases where both environmental and genetic constituents are considered causes. This concept has challenged the traditional view that age, occupation, smoking, obesity, and primarily wear and tear are the only sources of disc degeneration.**

METHODS: **We conducted a systematic Medline review of the most current articles related to gene involvement in the development of IVDD in humans.**

RESULTS: **Candidate gene linkage and association studies involving the functional components of the intervertebral disc, including collagen I, collagen IX, collagen XI, aggrecan, extracellular matrix-degrading enzymes, inflammatory cytokines (IL-1, IL-6, and TNFα), Fas/FasL and vitamin D receptors, have had promising results.**

CONCLUSIONS: **This review emphasizes the latest advances in gene association with specific degenerated disc phenotypes, single nucleotide polymorphisms, disease heredity, and gene-environmental interactions in relation to IVDD to help improve future studies related to the genetic mechanisms underlying IVDD.**

INTRODUCTION

New genetic and proteomic tools are beginning to refine our understanding of the molecular basis of disease. Insight gained from studies suggests that genetic factors are major contributors to the onset and progression of intervertebral disc degeneration (IVDD) (7, 65). As our understanding of disease processes has progressed, we have begun to understand how genetic factors contribute to the role of environmental factors such as smoking, occupational and recreational exposures, as well as chronic inflammatory states to cause and exacerbate IVDD and other diseases.

The first organ-level change in disc degeneration appears to be a functional compromise in the ability of the nucleus pulposus (NP) to imbibe water, leading to a decrease in intradiscal pressure (64). Biomechanically, the consequences of a swollen nucleus are to alter the transfer of load and to create hydrostatic pressure in the center of the disc. The distinct biomechanical functions of the annulus fibrosus (AF) and NP are confirmed by their respective constituents. The NP is proteoglycan-rich with type II collagen, which provides the osmotic properties necessary for optimal disc hydration. The AF is mostly ligamentous fibrocartilage with type I collagen optimized for resisting tensile load (**Figure 1**). Alterations in the extracellular matrix (ECM) of the NP involving a decrease in synthesis and accumulation of proteoglycans, increased accumulation of aggrecan fragments (50), decreased synthesis and accumulation of type II collagen, increased synthesis of collagen I, and a decreased glycosaminoglycan/hydroxyproline ratio are present at the degenerated disc (21, 52). Furthermore, the activity of matrix-degrading enzymes (matrix metalloproteinases [MMPs] and a disintegrin and metalloproteinase with thrombospondin motifs); their regulators (the tissue inhibitors of matrix metalloproteinases [TIMPs] and thrombospondins [THBS]); inflammatory molecules such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α; and the anabolic insulin-like growth factor (IGF-1) and its receptor (IGF-1R) has been genetically associated with IVDD (52).

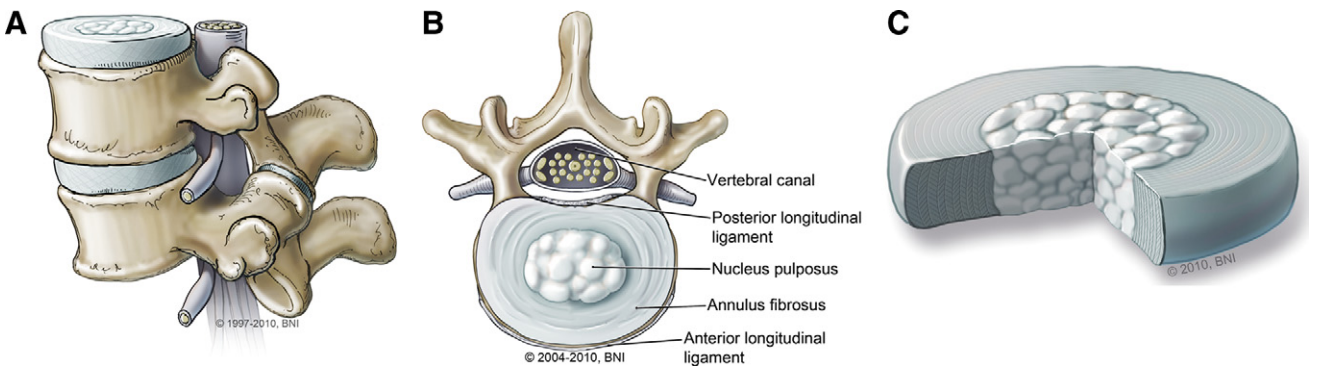

Figure 1. (**A**) Sagittal illustration of a normal intervertebral disc (IVD). (**B**) Axial illustration of a normal IVD showing its contents. (**C**) Magnified illustration of an IVD. Used with permission from Barrow Neurological Institute.

Increasing evidence suggests that heredity plays an important role in the pathophysiology of IVDD (5-7, 35, 44, 51, 53). Reported heritability estimates have ranged from 29% to 74% (7, 51), and familial aggregation (representing genetic and other familial influences) has been found to account for 61% of variance in disc degeneration in the upper lumbar region and 34% in the lower lumbar region (5). Annunen et al. identified specific inherited disease-causing genetic sequence variations in patients with symptomatic IVDD (3). Of 157 studied cases of sciatica, 6 had an alteration in the [α]2 chain of collagen IX (COL9A2) that converted a codon for glutamine or arginine to one for tryptophan. None of 174 control subjects had this alteration. Concurrently, family members in 4 of the 6 cases also were studied. All 20 such subjects carrying the tryptophan (Trp2) allele were examined clinically and with imaging studies and were found to have IVDD (27). Although this landmark study established the role of genetics in IVDD, the underlying pathophysiology remains poorly understood.

The most recent research on occupational, constitutional, or age-related factors correlated with genetics include a study by Virtanen et al. (63), in which whole-body vibration among Finnish train engineers with IVDD was linked to a single polymorphism in IL1A–889 (25). The Trp2 allele of COL9A2 gene (collagen IX), which is present in 20% of the population of Southern China, is associated with IVDD exclusively in individuals in the 40 to 49 age group with no influence on any other age group (25). Finally, Solovieva et al. (54) found that obesity, a traditional risk factor for disc overloading and degeneration, acted synergistically with Trp3 allele of the COL9A3 gene increasing the risk of posterior disc bulging, dark NP signaling, and diminished disc height at the L4/L5 level, as well as posterior disc bulging at the L3/L4 level. Interestingly, in the same study, obesity had no effect in the disc when the Trp3 allele was absent, strongly supporting the theory of the interconnection between environmental components and genes as causes of disease. This evidence leaves behind the traditional view in which a single factor such as age, occupation, smoking, obesity, and mainly wear and tear were considered the sole source of disc degeneration.

GENE POLYMORPHISMS ASSOCIATED WITH IVDD

Table 1 summarizes the current genetic polymorphisms shown to be associated with the development of IVDD in humans.

Collagens

Collagens are extracellular matrix molecules used by cells throughout the body for structural integrity and other functions, including tissue scaffolding, cell adhesion, cell migration, angiogenesis, tissue morphogenesis, and tissue repair (26). Each mature collagen molecule contains 3 polypeptide (β) chains (**Figure 2**). These polypeptide α chains are used to build trimeric molecules that are woven together into a triple helix in at least 1 region (18). The various collagen polypeptides have their own genes, and at least 28 different collagens have been identified in vertebrates (26).

In the intervertebral disc (IVD), collagen plays a major structural role, particularly at the AF where type I collagen creates a network of fibers that functions as a retainer of the NP and distributes the compressive load. At the same time, the NP contains collagen IX fibers that are cross-linked to collagen type II fibers to provide optimal stability (14). Because of this highly organized network of fibril-forming collagens present at the IVD and the wide spectrum of diseases clearly related to collagen with or without genetic variations, it is reasonable to assume that genetic defects involving collagen play a role in the etiopathogenesis of IVDD.

Collagen I

Type I collagen is the major protein in skin, ligaments, and bone. It is a heterotrimeric protein consisting of 2 identical α chains and a third chain that differs [α1(2) α2]. The genes encoding collagen I, COL1A1 and COL1A2, are present in both the NP and AF, although they are much more abundant at the annulus (4). How genetic alterations of collagen I influence the development of disc degeneration is still unclear. However, polymorphisms of the COL1A1 gene have been reported to increase the risk for disc degeneration in 2 separate population studies. In a study of a Dutch population (65 to 85 years old) with the TT genotype of collagen type I α1 (COL1A1) Sp1 polymorphism, Pluijm et al. (49) found a higher risk of disc degeneration than in subjects with the GG and GT genotypes. Tilkerdis et al. (58) showed that 33.3% of Greek military re-