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Genetics Of Intervertebral Hernia And Ethnic Features Of Associations Of Col1a1 Col9a2 And Mmp3 Polymorphisms

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Abstract
Degenerative diseases of the spine, including intervertebral hernias (IVH), are a pressing medical and social problem, especially among people of working age. In recent years, interest in the role of genetic factors in the pathogenesis of these conditions has increased.
The article summarizes and analyzes current data on the role of COL1A1 , COL9A2 and MMP3 gene polymorphisms in the development of intervertebral disc herniations with an emphasis on ethnic characteristics and the potential significance of these markers in personalized prevention and therapy.
A review of publications over the past 10 years was conducted, including molecular genetic studies, meta-analyses, population and clinical studies reflecting the relationship of these genes with the risk of MPH.
It has been shown that COL1A1 (rs1800012) polymorphism can reduce the biomechanical strength of the fibrous ring, COL9A2 (Trp2/Trp3) can disrupt the stability of cartilage tissue, and MMP3 (rs3025058, 5A/6A) can enhance the degradation of the extracellular matrix. The frequency of risk-associated alleles varies depending on the population, while in the population of Uzbekistan, data are limited, which emphasizes the need for local studies.
Genetic markers COL1A1 , COL9A2 and MMP3 have potential diagnostic and prognostic value in assessing predisposition to intervertebral disc herniation. Their study is important for the development of personalized prevention and early diagnosis strategies, especially in ethnically heterogeneous regions such as Uzbekistan.

Keywords: Intervertebral disc herniation; COL1A1; COL9A2; MMP3; genetic polymorphism; extracellular matrix; degenerative diseases of the spine; personalized medicine; population differences; Uzbekistan.

Introduction

Degenerative diseases of the spine, including intervertebral disc herniations, are one of the most common causes of chronic back pain and temporary disability in people of working age. According to the World Health Organization, up to 80% of people experience episodes of back pain at least once in their lives, with up to 40% of cases caused by degenerative-dystrophic changes in the intervertebral discs [1].
Intervertebral hernia (IVH) is characterized by prolapse or protrusion of the nucleus pulposus through the fibrous ring, which leads to compression of the nerve roots and the development of pain syndrome. Despite the wide variety of etiopathogenetic factors (physical activity, excess weight, injuries), more and more attention is paid to the role of hereditary predisposition to degenerative changes in the discs [2,3].
A number of studies show that variations in genes encoding extracellular matrix proteins, including collagen and matrix metalloproteinases, may be associated with the vulnerability of vertebral disc structures to degenerative changes [4–6]. Among the most studied genes are COL1A1, COL9A2, and MMP3, associated with the metabolism of collagen types I and IX, as well as the regulation of extracellular matrix remodeling. Polymorphisms of these genes may affect the biomechanical strength of disc tissues and their resistance to microtrauma and inflammatory processes [7–9].
Of particular interest are studies of the association of these genes with the development of MPH in various ethnic populations, including Asian and European countries. However, for the population of Uzbekistan, such data are extremely scarce, which justifies the need for further study [10].
The aim of this review article is to summarize and analyze current data on the role of COL1A1, COL9A2 and MMP3 polymorphisms in the pathogenesis of intervertebral disc herniation, with an emphasis on the identified ethnic characteristics and the potential significance of these markers for personalized prevention and therapy.
Main part. In this part of the article Three key blocks are considered sequentially: molecular genetic characteristics of the COL1A1 gene and their impact on the strength of the fibrous ring of the intervertebral disc; the role of COL9A2 polymorphisms in the structural integrity of cartilage tissue and predisposition to degeneration of the nucleus pulposus; and the significance of the insertion-deletion variant of MMP3 rs3025058 in the regulation of matrix metalloproteinase activity and accelerated destruction of the extracellular matrix. Each section includes a brief overview of the gene function, a description of the most studied SNPs, population

prevalence data and results of association studies, as well as a discussion of clinical and preventive implications for various ethnic groups, with an emphasis on the Uzbek population.

The COL1A1 gene and the structure of type I collagen

The COL1A1 gene is located on chromosome 17q21.33 and encodes the α1 chain of type I collagen, one of the most common proteins of the extracellular matrix, which plays a key role in providing strength and elasticity to connective tissue, including the fibrous ring of intervertebral discs [11]. Type I collagen forms fibers that are resistant to stretching and is involved in maintaining the integrity and stability of the spinal segment.

One of the most studied variants in this gene is the polymorphism in the binding site of the transcription factor Sp1 (rs1800012). This single nucleotide polymorphism (SNP), located in the first intron of COL1A1, can alter the level of gene expression and, as a consequence, disrupt the ratio of α1 and α2 chains in the structure of collagen fibers, which weakens the mechanical properties of tissues [12,13].

Meta-analyses and population studies have shown that the presence of the T allele in the rs1800012 polymorphism is associated with an increased risk of degenerative diseases of the spine, including osteoporosis, kyphosis, and intervertebral disc herniation [14–16]. In particular, studies conducted in China, Italy, and Iran have demonstrated a significant association between the presence of this polymorphism and an increased likelihood of developing disc herniation in young and middle-aged patients [17,18].

Studies in model populations also indicate that carriers of the mutant T allele have reduced levels of mature type I collagen and an increased risk of annular disruption under axial loads, supporting the important role of COL1A1 as a potential marker of genetic predisposition to discogenic diseases [19].

Thus, disruption of the synthesis or structure of type I collagen due to the carriage of certain allelic variants of the COL1A1 gene can reduce the mechanical stability of the intervertebral disc, especially its outer fibrous membrane, which is subject to significant biomechanical loads. This makes the spinal tissues more susceptible to microdamage, degeneration and subsequent formation of protrusions and herniated discs.

Some studies suggest that the presence of COL1A1 genetic variations is particularly significant in patients exposed to prolonged static and vibration loads, such as athletes, drivers, construction workers, and law enforcement officers [20]. In these populations, the rs1800012 polymorphism may act as a predictor of increased risk of developing intervertebral disc disease as early as 25–40 years of age.

Interestingly, in studies conducted among European, Asian and Middle Eastern populations, the frequency of the T allele showed geographical differences: in East Asian countries the frequency was lower than, for example, in the Mediterranean region [21]. This may indicate both differences in genetic predisposition and variations in disease expression under the influence of environmental, lifestyle and occupational factors.

To date, it has been proposed to use the COL1A1 (rs1800012) polymorphism as part of genetic testing panels for early diagnosis of predisposition to degenerative diseases of the spine. This is especially relevant for individuals with a burdened family history, as well as when planning a professional career associated with physical overload. However, for widespread implementation in clinical practice, multicenter studies are required involving various ethnic groups, including the population of Uzbekistan, where similar data are still limited [22].

Thus, the COL1A1 gene and its rs1800012 polymorphism represent an important target for genetic studies of intervertebral pathology and may play a key role in a personalized approach to the prevention and treatment of discogenic diseases.

COL9A2 gene and intervertebral cartilage

The COL9A2 gene is localized on chromosome 1p33-p32 and encodes the α2chain of type IX collagen, a structural component of the extracellular matrix of cartilage tissue, which is especially important for maintaining the architecture and elasticity of intervertebral discs, in particular, their nucleus pulposus [23]. Type IX collagen interacts with collagen II and proteoglycans, providing resistance to compressive loads.

One of the most studied single nucleotide polymorphisms of COL9A2 is the Trp2 allele, which arises from the substitution of arginine for tryptophan at position 103 (Arg103Trp). This variant, as studies have shown, disrupts the structure of collagen fibrils, changing the mechanical properties of intervertebral cartilage and increasing its vulnerability to degeneration [24].

Early studies in Finland found a statistically significant association between the COL9A2 Trp2 polymorphism and lumbar disc herniation in young men [25]. Similar results were obtained in Japanese and Chinese populations, where carriage of the Trp2 allele was associated with more pronounced degenerative changes according to MRI data [26,27].

However, in a number of ethnic groups, including German and Korean populations, such an association was not confirmed, which indicates the presence of ethnic specificity and the possible influence of other modifying genetic or epigenetic factors [28]. In the population of Uzbekistan, studies on this polymorphism have not yet been conducted, but taking into account geographic and genetic differences remains necessary when extrapolating international data.

The COL9A2 gene is also considered as a possible biomarker of discogenic pathology in the context of genetic screening, especially in patients with an adverse heredity and early manifestation of the disease. Since type IX collagen is actively expressed during the period of active skeletal growth, the influence of Trp2 may be especially pronounced in adolescence and young age, which is confirmed by clinical observations [29].

Thus, COL9A2 mutations may have a significant impact on the stability of intervertebral cartilage and predispose to the development of herniated disc protrusion. In the future, it is planned to include the analysis of this polymorphism in the panel of personalized genetic risk.

MMP3 gene and extracellular matrix (ECM) regulation

The MMP3 (matrix metalloproteinase-3) gene, located on chromosome 11q22.2, encodes an enzyme capable of degrading extracellular matrix components, including collagen types II, III, IV, IX, as well as proteoglycans and laminins. This enzyme plays a key role in tissue remodeling and regulation of inflammatory processes, which makes it an important factor in the pathogenesis of degenerative diseases of the intervertebral discs [26,27].

One of the most significant polymorphisms in the promoter region of the MMP3 gene is the 5A/6A insertion-deletion variant (rs3025058). It determines transcriptional activity: the 5A allele is associated with increased expression of MMP3 and, accordingly, with accelerated destruction of the intervertebral disc [28]. The 6A allele, on the contrary, is associated with lower expression and may have a protective value [29].

Studies conducted in various countries have shown that the presence of the 5A allele is associated with an increased risk of degenerative changes in the intervertebral discs, especially in men over 40 years of age and in patients with increased mechanical load on the spine [30,31]. In the Chinese population, a significant association was shown between the 5A/5A genotype and the severity of clinical symptoms in lumbar hernias [32]. European data also confirm these findings, although the frequency of the 5A allele varies from 25 to 40% depending on the region [33].

The first local data from Central Asia (including samples from Uzbekistan) show that the frequency of the 5A allele may be higher than average and amount to 42%, especially in individuals with heavy physical labor or in sports samples. This requires further clinical and genetic studies in national cohorts [34].

Thus, MMP3 polymorphism may act as an independent genetic marker of increased risk of disc destruction and be used in the context of personalized prevention of degenerative spinal diseases.

Below is a summary table of the prevalence of key polymorphisms of the COL1A1 (rs1800012), COL9A2 (Trp2/Trp3), MMP3 (rs3025058) genes in patients with intervertebral disc herniations in different ethnic populations, including data for Uzbekistan (if available), Asia and Europe:

Table 1. Prevalence of COL1A1, COL9A2 and MMP3 polymorphisms in different populations (%)

Gene	Polymorphis m	Allele/Genoty pe	Uzbekistan *	Eas t Asi a	Sout h Asia	Europ e	USA / Europ e (white)	Sourc e
COL1A 1	rs1800012 (Sp1)	T-allele	~11–14%	610 %	9–13%	16–22%	20–25%	[14–18]
COL9A 2	Trp2, Trp3	Trp3 homozygotes	data is limited	3-5%	~6%	8-12%	9–14%	[21–24]
MMP3	rs3025058	5A allele	~42%	36–40 %	30–35%	25–40%	33–38%	[30–34]

Note: Data for Uzbekistan are partly based on small samples or cross-sectional studies and require extensive validation. Data are presented with rounding and may vary by region and gender.

In the population of Uzbekistan, according to preliminary data, the frequency of risk-associated alleles (especially for MMP3 and COL1A1) is at a level comparable to or higher than in East and South Asian countries. Allele 5A of the MMP3 gene, associated with degradation of intervertebral structures, is more common in Uzbek patients than in European samples, which may indicate a population-significant predisposition. Data on COL9A2 in the Central Asian region are extremely limited, which emphasizes the need for further population and association studies in the Uzbek cohort.

Ethnic features of the prevalence of polymorphisms and their clinical significance

Prevalence of gene polymorphisms COL1A1 **,** COL9A2 and MMP3 **,** associated with degenerative diseases of the spine, varies significantly depending on ethnicity, which causes differences in the frequency of intervertebral disc herniation among populations.

rs1800012 polymorphism of the COL1A1 gene is manifested by a higher frequency of the T allele in Europeans (up to 22–25%) than in Asian populations, including Uzbek, where its prevalence is about 11–14% [14–18]. This may explain the higher prevalence of osteoporosis and connective tissue disorders in Europe, but does not exclude its significance for Central Asia, where other factors, including lifestyle and epigenetic mechanisms, may enhance the effect of the gene.

Polymorphic variants Trp2/Trp3 of the COL9A2 gene are associated with weakening of cartilage tissue. These alleles were identified predominantly in the European population (8–12%), but were also found in Asia (3–6%) [21–24]. There is little reliable data for Uzbekistan, but given the mixed gene pool of the region, the presence of these variants in some patients with disc herniations requires further study.

MMP3 gene and its rs3025058 polymorphism **,** which determines the ratio of 5A/6A alleles, regulates the expression level of metalloproteinases that affect intervertebral disc degradation. The 5A allele, associated with higher enzymatic activity and the risk of disc degeneration, has a high prevalence in the population of Uzbekistan

(up to 42%), which is higher than in most European countries [30–34]. These data emphasize the need to take into account ethnic differences when interpreting the results of molecular genetic studies **;** development of regional screening programs for early identification of individuals with a genetic predisposition to disc herniation; inclusion of genetic markers in personalized prevention and rehabilitation protocols.

Conclusion

Analysis of the literature confirms the significant role of genetic factors in the pathogenesis of intervertebral hernias, especially in individuals with a predisposition to metabolic disorders of connective and cartilaginous tissue. Polymorphisms in the genes COL1A1 (rs1800012) , COL9A2 (Trp2/Trp3) and MMP3 (rs3025058) are associated with impaired fiber strength, decreased resistance of intervertebral discs to mechanical stress and accelerated matrix degradation.

The data obtained show that the COL1A1 polymorphism disrupts the balance of collagen α-chains, weakening the fibrous ring of the disc. COL9A2 variants reduce the strength of cartilage tissue, especially in the presence of an amino acid substitution of Trp3. The 5A allele in MMP3 increases the activity of matrix metalloproteinases, contributing to the destruction of intervertebral discs.

The ethnic specificity of the distribution of these polymorphisms is important in the formation of individualized approaches to the diagnosis, prevention and treatment of degenerative diseases of the spine. Given the characteristics of the Uzbek population and the high level of professional physical activity in a number of regions, it is advisable to develop local genetic risk panels integrated into clinical practice.

The introduction of genetic testing into the structure of clinical diagnostic algorithms will allow for early diagnosis and monitoring of high-risk individuals ; personalization of rehabilitation and preventive programs ; and improvement of the effectiveness and social significance of orthopedic and neurosurgical interventions.

Future studies should be aimed at investigating multigene interactions , the involvement of epigenetic mechanisms and gene-environment correlations in the development of intervertebral disc herniation.

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