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Genetic Predictors of Intervertebral Disc Degeneration: Pilot Study

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Abstract: Intervertebral disk degeneration (IVDD) is a dystrophic multifactorial, chronic, recurrent disease, its associated pain and neurological syndromes are among the most important problems in modern medicine. The etiology of IVDD includes both endogenous and exogenous risk factors. Genetic studies conducted to date have not identified a single gene responsible for the development of IVDD. A pilot study examined the allele and genotypic frequencies of single-nucleotide variants in the genome that play a role in the development of IVDD, depending on the pathophysiological mechanisms underlying its development. The study examined genes encoding fibrillar collagens, which are associated with cartilage mechanical stability, as well as genotypes of proinflammatory mediators, which influence IVD damage and increase the risk of herniation. The study involved 80 patients (40 men and 40 women) with chronic pain in the lower back and the presence of signs of degeneration of intervertebral discs at the lumbar level according to MRI aged 18 to 75 years (mean age 52.2 ± 2.3 years). Real-time polymerase chain reaction was used to detect single nucleotide variants (SNVs): rs1107946 of the *COL1A1* gene, rs1799983 and rs2070744 of the *NOS3* gene, rs1800795 of the *IL6* gene. Genotyping of patients with a traumatic-extrusion phenotype of IVDD was performed in comparison with a degenerative-protrusive phenotype as a control. A pilot study led to the hypothesis that the studied variants of the *NOS3* gene (rs1799983, rs2070744) and the *IL6* gene (rs1800795), encoding inflammatory mediators, may be associated with an increased risk of traumatic-extrusion phenotype of IVDD, as well as the studied variant of the *COL1A1* gene (rs1107946). Genetic testing of patients with various phenotypes of IVDD to identify the carriage of risk alleles of these genetic variants, and the study of their association with the rate of progression of IVDD is promising for the development of a personalized strategy for the diagnosis and dispensary observation of the patients.

Keywords: *intervertebral disk degeneration; genetic risk; genetic predisposition; candidate genes; collagen 1 type; proinflammatory mediator; SNV.*

1. INTRODUCTION

Degenerative-dystrophic changes in the spine are a dystrophic multifactorial, chronic, recurrent disease that begins with the nucleus pulposus of the intervertebral disc, spreading to the fibrous ring, then to other elements of the vertebral motor segment, manifested under certain conditions by polymorphic (reflex, compression, compression-reflex and reflex-compression) neurological syndromes. Intervertebral disc degeneration (IVDD) and its associated pain and neurological syndromes are among the most important problems in modern medicine. This is a common reason for patients to consult a neurologist. It often affects working-age patients and recurrent course leads to unsatisfactory results with conservative and surgical treatment [1]. The new International Classification of Diseases, 11th revision (ICD-11), has a separate coding block for discogenic pathology: FA80 "Intervertebral disc degeneration with or without nervous system involvement"[2].

The etiology of IVDD includes both endogenous predictors (hereditary, genetic) and exogenous risk factors (stress, diet, static and physical loads on the spine, injuries, etc.). Genome-wide association studies on large cohorts of patients with IVDD have significantly expanded our understanding of the genetic predictors of this disease. However, genetic studies conducted to date have not identified a single gene responsible for the development of IVDD. A literature review was conducted, identifying and systematizing candidate genes that contribute to the development of IVDD, depending on the pathophysiological mechanisms of its development. Currently, genes encoding fibrillar collagens associated with cartilage mechanical stability, as well as genotypes of inflammatory mediators that influence damage to the intervertebral disc and increase the risk of herniation, are being actively studied [3, 4].

In 2015, Ma XL [5] introduced a new pathological classification of IVDD, developed to determine the optimal treatment strategy for patients. According to this classification, IVDD was divided into two main phenotypes: degenerative-protrusive and traumatic-extrusive, taking into account clinical, radiographic, pathological characteristics, optical microscopic, and immunohistochemical data. A sequestered disc herniation (traumatic-extrusive phenotype) is a type of intervertebral disc herniation in which the material that has protruded from the disc loses its connection with the disc.

The aim was to study the genetic predictors of variable IVDD phenotypes in adult patients of Caucasian origin living in St. Petersburg.

2. MATERIALS AND METHODS

The study was approved by the Ethics Committee of V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology No. EC-I-6.24 dated 03.28.2024. The study was conducted on 80 patients (40 men and 40 women) from neurological and neurosurgical hospitals in St. Petersburg with chronic pain in the lower back and the presence of signs of degeneration of intervertebral discs at the lumbar level according to magnetic resonance imaging data, aged 18 to 75 years (mean age 52.2 ± 2.3 years). At the randomization stage, 80 patients were divided into 2 groups depending on the identified variative phenotype of IVDD. Patients underwent a somatic and neurological examination; pain and disability were assessed using scales and questionnaires (Visual Analog Scale, Oswestry Quality of Life Questionnaire version 2.1a); laboratory data were assessed (clinical and biochemical blood tests).

Molecular genetic testing was used: real-time polymerase chain reaction (RT-PCR) (to detect single nucleotide variants (SNVs): rs1107946 of the *COL1A1* gene, rs1799983 and rs2070744 of the *NOS3* gene, rs1800795 of the *IL6* gene). Genotyping of patients with a traumatic-extrusion phenotype of IVDD was performed in comparison with a degenerative-protrusive phenotype as a control.

Statistical data processing was performed using the STATISTICA version 13 (Stat Soft, USA), while values at p-value < 0.05 were considered statistically significant.

3. RESULTS

3.1 SNV rs1107946 of the *COL1A1* gene

Since type 1 collagen is an important structural component of the IVD, determining its elastic properties [6], genotyping of patients was carried out and the frequencies of alleles and genotypes of the SNV rs1107946 of the *COL1A1* gene (Table 1). The human *COL1A1* gene located on chromosome 17 at cytogenetic band 17q21.33. Specifically, the gene is found between base pairs 50,184,101 and 50,201,632 on the reverse strand of chromosome 17 in the GRCh38 human genome assembly. The SNV rs1107946 is located in the proximal promoter region of the *COL1A1* gene. It is at position -1997 relative to the transcription start site of the gene, which is responsible for coding for the alpha-1 chain of type I collagen.

Table 1. The frequencies of alleles and genotypes of the SNV rs1107946 of the *COL1A1* gene

Allele/ genotype	Group 1 (traumatic-extrusive phenotype), n (%)	Group 2 (degenerative-protrusive phenotype), n (%)	Total n
C	56 (82.35)	72 (78.26)	
A	12 (17.64)	20 (21.74)	
CC	23 (64.64)	28 (60.86)	51
CA	10 (29.41)	16 (34.78)	26
AA	1 (2.95)	2 (4.36)	3
Total	34	46	

The genotype frequency distribution in both groups conformed to the Hardy-Weinberg law (*p*-value = 0.94 for group 1 and p-value = 0.88 for group 2), allowing us to calculate genetic risk using multiplicative, additive, dominant, and recessive inheritance models. The risk of developing traumatic-extrusive IVDD was independent of carriage of the minor (variative type) A allele and the major (wild type) C allele, as well as homozygous and heterozygous genotypes for the minor and major alleles (between-group differences in the pilot study did not reach statistical significance).

When assessing the general inheritance model (Table 2), it is noteworthy that the risk of rupture of a degenerated IVD and the development of a traumatic-extrusive phenotype of IVDD is higher in carriers of the homozygous genotype for the major C allele (genotype CC), compared to homozygous and heterozygous carriers of the minor A allele.

Table 2. General model of inheritance of the SNV rs1107946 of the *COL1A1* gene

Genotype	Group 1 (traumatic-extrusive phenotype)	Group 2 (degenerative-protrusive phenotype)	X^2	*p*-value	OR	
	n = 34	n = 46			Sign.	95%Cl
CC	0.676	0.609	0.42	*0.81*	1.34	0.53-3.41
CA	0.294	0.348			0.78	0.30-2.03
AA	0.029	0.043			0.67	0.06-7.67

3.2 SNVs rs1799983 and rs2070744 of the *NOS3* gene

Two SNVs of the *NOS3* gene encoding endothelial nitric oxide synthase were also studied (Table 3 and 4), since (NO) is a free oxygen radical that is involved in the development of oxidative stress and IVDD. Excess oxidants cause a decrease in antioxidants, which in turn leads to a redox imbalance in the human body. A deficiency in the antioxidant system leads to oxidative stress, characterized by elevated levels of reactive oxygen species [7]. Oxidative stress and increased local NO level can initiate the development of IVDD and contribute to its progression [8]. The *NOS3* gene is located on chromosome 7 in humans, specifically within the 7q35-7q36 region. More precisely, in the Ensembl human genome browser (GRCh38 build), the gene is found at the band 7q36.1 with coordinates from 150,991,017 to 151,014,588. The rs1799983 genetic variant is located in exon 7 of the *NOS3*

gene. This variant is known as the Glu298Asp (G894T) missense mutation, and it results in the substitution of glutamic acid with aspartic acid in the endothelial nitric oxide synthase protein. The SNV rs2070744 is located in the promoter region of the *NOS3* gene on chromosome 7 in humans. This SNV involves a T to C substitution at position -786 in the promoter.

Table 3. The frequencies of alleles and genotypes of the SNV rs1799983 of the *NOS3* gene

Allele/ genotype	**Group 1 (traumatic-extrusive phenotype), n (%)**	**Group 2 (degenerative-protrusive phenotype), n (%)**	**Total, n**
G	48 (70,59)	73 (79,35)	
T	20 (29,41)	19 (20,65)	
GG	18 (52,94)	29 (63,05)	47
GT	12 (35,30)	15 (32,61)	27
TT	4 (11.76)	2 (4,34)	6
Total	34	46	

The genotype frequency distribution in both groups conformed to the Hardy-Weinberg law (p-value = 0.38 for group 1 and p-value = 0.97 for group 2), allowing us to calculate genetic risk using multiplicative, additive, dominant, and recessive inheritance models. The risk of developing traumatic-extrusive IVDD was independent of carriage of the minor T allele and the major G allele, as well as homozygous and heterozygous genotypes for the minor and major alleles (between-group differences in the pilot study did not reach statistical significance).

Table 4. The frequencies of alleles and genotypes of the SNV rs2070744 of the *NOS3* gene

Allele/ genotype	**Group 1 (traumatic-extrusive phenotype), n (%)**	**Group 2 (degenerative-protrusive phenotype), n (%)**	**Total, n**
T	39 (57.35)	59 (64.13)	
C	29 (42.65)	33 (35.87)	
TT	12 (35.29)	17 (36.95)	29
TC	15 (44.11)	25 (54.35)	40
CC	7 (20.60)	4 (8.70)	11
Total	34	46	

The genotype frequency distribution in both groups conformed to the Hardy-Weinberg law (p-value = 0.57 for group 1 and p-value = 0.22 for group 2), allowing us to calculate genetic risk using multiplicative, additive, dominant, and recessive inheritance models. The risk of developing traumatic-extrusive IVDD was independent of carriage of the minor C allele and the major T allele, as well as homozygous and heterozygous genotypes for the minor and major alleles (between-group differences in the pilot study did not reach statistical significance (p-value > 0.05).

When assessing the general inheritance model (Table 5 and 6), it is noteworthy that the risk of rupture of a degenerated IVD and the development of a traumatic-extrusive phenotype of IVDD is higher in carriers of the homozygous genotype for the minor allele T (genotype TT) and C (genotype CC), compared with homozygous and heterozygous carriers of the major allele (G and T) - for both SNVs, despite the fact that the intergroup differences in the pilot study did not reach statistical significance (p-value > 0.05).

Table 5. General model of inheritance of the SNV rs1799983 of the *NOS3* gene

Genotype	Group 1 (traumatic-extrusive phenotype)	Group 2 (degenerative-protrusive phenotype)	X^2	p	OR	
	n = 34	n = 46			Sign.	95%Cl
GG	0.529	0.630			0.66	0.27-1.62
GT	0.353	0.326	1.82	*0.4*	1.13	0.44-2.87
TT	0.118	0.043			2.93	0.50-17.04

Table 6. General model of inheritance of the SNV rs2070744 of the *NOS3* gene

Genotype	Group 1 (traumatic-extrusive phenotype)	Group 2 (degenerative-protrusive phenotype)	X^2	p-value	OR	
	n=34	n=46			Sign.	95%Cl
TT	0.353	0.370			0.93	0.37-2.34
TC	0.441	0.543	2.44	*0.3*	0.66	0.27-1.62
CC	0.206	0.087			2.72	0.73-10.19

3.3 SNV rs1800795 SNP of the *IL6* gene

Cytokines are important components of the immune system. Their physiological role in inflammation and pathological role in systemic inflammatory conditions are now well understood. Imbalances in cytokine production or cytokine receptor expression and/or dysregulation of cytokine balance contribute to various pathological disorders, including IVDD. Interleukin 6 (IL-6) plays an important role as a proinflammatory cytokine in the development of IVDD by promoting the degradation of the intracellular matrix [9]. The SNV rs1800795 of the *IL6* gene encoding proinflammatory cytokine IL-6 was also studied (Table 7). The *IL6* gene is located on chromosome 7p15.3 in humans. More specifically, it resides within the genomic region 7:22,725,884-22,732,002 on the short (p) arm of chromosome 7. The SNV rs1800795 is located in the promoter region of the *IL6* gene. It's a single nucleotide change from C to G at position -174 relative to the gene's transcription start site.

The genotype frequency distribution in both groups conformed to the Hardy-Weinberg law (p-value = 0.99 for group 1 and p-value = 0.14 for group 2), allowing us to calculate genetic risk using multiplicative, additive, dominant, and recessive inheritance models. The risk of developing traumatic-extrusive IVDD was independent of carriage of the minor G allele and the major C allele, as well as homozygous and heterozygous genotypes

for the minor and major alleles (between-group differences in the pilot study did not reach statistical significance, *p*-value > 0.05).

When assessing the general inheritance model (Table 8), it is noteworthy that the risk of rupture of a degenerated IVD and the development of a traumatic-extrusive phenotype of IVDD is higher in carriers of the heterozygous genotype CC, as well as in homozygous carriers of the major high-yielding allele C, associated with hyperproduction of the cytokine IL6.

Table 7. The frequencies of alleles and genotypes of the SNV rs1800795 of the *IL6* gene

Allele/ genotype	**Group 1 traumatic-extrusive phenotype), n (%)**	**Group 2 (degenerative-protrusive phenotype), n (%)**	**Total, n**
C	35 (51.47)	44 (47.83)	
G	33 (48.53)	48 (52.17)	
CC	9 (26.47)	13 (28.26)	22
CG	17 (50.00)	18 (39.14)	35
GG	8 (23.53)	15 (32.60)	23
Total	34	46	

Table 8. General model of inheritance of the SNV rs1800795 of the *IL6* gene

Genotype	**Group 1 (traumatic-extrusive phenotype)**	**Group 2 (degenerative-protrusive phenotype)**	**X^2**	***p*-value**	**OR**	
	n = 34	n = 46			Sign.	95%Cl
CC	0.265	0.283	1.11	*0.57*	0.91	0.34-2.47
CG	0.500	0.391			1.56	0.64-3.81
GG	0.235	0.326			0.64	0.23-1.74

4. DISCUSSION

A pilot study led to the hypothesis that the studied *NOS3* rs1799983 (G>T), rs2070744 (T>C), and *IL6* rs1800795 (C>G) gene mutations, encoding inflammatory mediators, may be associated with an increased risk of ruptures of degenerated IVDs, leading to the development of a traumatic-extrusion phenotype of IVDD.

The studied *COL1A1* rs1107946 (C>A) gene mutation encoding structural fibrillar collagen type 1 is associated with IVDD in general and may be of equal interest in increasing the risk of ruptures of degenerated IVDs.

A limitation of this study is the small sample size. However, this was a pilot study, and recruitment is ongoing. Increasing the number of patients studied may reveal promising candidate genes.

5. CONCLUSION

Genetic testing of patients with various phenotypes of IVDD to identify the carriage of risk alleles of SNVs of genes encoding fibrillar collagens (*COL1A1*), proinflammatory mediators (*IL6, NOS3*), and the study of their association with the rate of progression of IVDD, hernia formation, and the development of chronic back pain in adults is promising for the development of a personalized strategy for the diagnosis and dispensary observation.

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