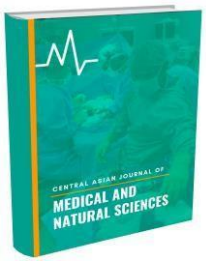

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Article

Prediction of the Development of Osteoarthritis of the Hip Joint Based on Distribution of the Gene Encoding 5-Factor Gdf5 Growth Differentiations

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Abstract: Medical research confirms that inherited genetic tendencies strongly increase coxarthrosis development as a degenerative disease mainly targeting the hip joint. Searchers have determined Single Nucleotide Polymorphisms (SNPs) as major genetic elements that help initiate this disease process. Research findings show that SNPs act as direct contributors to coxarthrosis development by actively affecting the disease pathogenesis in addition to being non-random associations. SNPs have a substantial effect on cellular and molecular mechanisms which control the structural well-being and operational competence of articular cartilage together with subchondral bone. Genetic studies show SNPs enable control over signaling pathway and metabolic processes including those concerning extracellular matrix (ECM) and chondrocytes and osteocytes. The pathways control essential processes which include collagen production along with proteoglycan regulation and mechanical pressure and inflammatory response of cells. The abnormalities triggered by particular polymorphisms create problems with ECM remodeling alongside enhanced cartilage breakdown while producing bone structural modifications that are core elements of coxarthrosis. The deterioration of joint tissue caused by abnormal signaling between chondrocytes and osteocytes becomes worse because of SNP-related signaling dysfunctions. Research on genetic variants helps explain coxarthrosis origin while creating individualization strategies for both diagnostics and disease monitoring procedures and therapeutic options for reducing its progression.

Keywords: Idiopathic osteoarthritis, post-COVID osteoarthritis, genetic marker, genotype.

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1. Introduction

According to genome-wide association studies (GWAS), the influence of the most common genetic polymorphisms on the development of coxarthrosis is insignificant, while, on the contrary, rarer genetic variants can play a key role in triggering the molecular mechanisms of disease formation[1].

Among the polymorphic genetic variants that can generate joint destruction, researchers are particularly interested in studying the genes encoding growth differentiation factor 5 (GDF5 - G/A) and the protein α-1 chain of type I collagen (COL1A1 - C/A) [4]. Despite the accumulated evidence that genetic factors play a key role in the development of coxarthrosis, the results of existing studies are not unambiguous[2]. At the same time, it is known that the GDF5 gene, located on chromosome 20q11.22, plays a key role in the prenatal and postnatal development of synovial joints[3].

It has been proven that mutations in the GDF 5 gene are associated with abnormal bone development in humans [5]. Moreover, the GDF5 marker is currently considered a key pathogenic gene leading to the formation of hip dysplasia[4]. The main component of connective tissue is collagen, which is one of the main markers of early degeneration of cartilage tissue and reflects the mechanical properties of the hip joint[5].

J. Chen et al ., (2018) found that cartilage tissue consisting of chondroid tissue and collagen fibers expresses type I collagen , consisting of the proteins alpha-1-chain of type I collagen (COL 1 A 1) and alpha-2-chain of type I collagen (COL 1 A 2), which are encoded by the type I collagen gene located on chromosome 17 q 21.3- q 22.1[6]. The COL1A1 gene is one of the key regulatory genes that affects the formation of collagen fibers. In studies by foreign authors, it was found that a decrease in gene expression, leading to the loss of collagen fibers and fibroblasts in the hip joint capsule, is associated with its relaxation[7]. Taking these data into account, it is assumed that mutational changes in the COL1A1 gene lead to various degenerative changes in the hip joint[8].

2. Materials and Methods

Object: to improve methods of early diagnosis and prognosis of disease outcome based on the distribution of genotypes of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A in patients with idiopathic and post-COVID osteoarthritis of the hip joints.

In order to evaluate the structural features of the polymorphic genetic marker encoding the growth differentiation factor 5 (GDF5 - G/A) to determine its significance in the development of pathology, 86 patients with coxarthrosis who were treated in the cardiorheumatology department at the Samarkand City Medical Association and 78 individuals in the control group were examined.

3. Results and discussion

The nature of the differences in the distribution of actually detected (Ho) and expected (He) genotype frequencies of the genetic marker encoding the growth differentiation factor 5 (GDF5 - G/A) within the Hardy-Weinberg equilibrium in the control and main groups was analyzed (Table 1).

Table 1.

Differences in the distribution of genotypes of the genetic marker encoding growth differentiation factor 5 in RHV - GDF5 - G/A

Control group, n= 78			
Genotype frequencies	G/ G	G/A	A/A
H_o	0.4	0.45	0.15
H_e	0.39	0.47	0.14
Reliability indicator	$\chi^2 = 0.16$; P=0.653; df=1		
Main group with coxarthrosis, n = 86			
Genotype frequencies	G/ G	G/A	A/A
H_o	0.27	0.53	0.2
H_e	0.29	0.50	0.21
Reliability indicator	$\chi^2 = 0.48$; P = 0.464; df = 1		

In the control group Ho and He genotype frequencies were distributed with no statistically significant differences between them (χ 2 = 0.16; P = 0.653; df = 1). In parallel, in the main group, no significant results were found between similar indicators (χ 2 = 0.48; P = 0.464; df = 1). In addition, when calculating the heterozygosity index based on the differences between the H o and He frequencies of heterozygotes among the control sample (D = -0.05), a slight deficiency of He was determined. whereas in the group with coxarthrosis (D=0.08) an insignificant excess of them was determined.

In the structure of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A In the control group, a higher frequency of the major allele G (62.2%) was found with a lower frequency of the weakened variant A (37.8%), which shows the dominant favorable effect of the major variant. However, in the distribution of genotypes, a higher frequency of the heterozygous locus GA was found (44.9%), followed by the frequency of the major homozygous locus GG (39.7) and the mutant locus AA (15.4) (Table 2).

Table 2.

Frequency of loci of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A among examined patients

Genetic loci frequency		Group			
		Control (CG), n=78	Primary with coxarthrosis, n=86	Idiopathic coxarthrosis (IC), n=42	Post-Covid coxarthrosis (PC) n=44
G	%/ n	62.2/97	53.5/92	53.6/45	53.4/47
A	%/ n	37.8/59	46.5/80	46.4/39	46.6/59
GG	%/ n	39.7/31	26.7/23	26.2/11	27.3/12
GA	%/ n	44.9/35	53.5/46	54.8/23	52.3/23
AA	%/ n	15.4/12	19.8/17	19.0/8	20.4/9

At the same time, in the distribution of allelic variants in the main group with coxarthrosis, the highest incidence of the main variant G (53.3%) and a lower incidence of the weakened variant A (46.5%) were also found. Meanwhile, from the data presented in Table 2 it is evident that in the main group, than in the control group, the weakened allele A was determined with a higher frequency, which indicates an increase in its activity in coxarthrosis. Moreover, an increase in the expression of unfavorable genotypic frequencies was also characteristic of the main group of patients with coxarthrosis, where the incidence of the heterozygous locus GA and the mutant locus AA increased, respectively, from 44.9% to 53.5% and from 15.4% to 19.8%, while the frequency of the main homozygous locus GG decreased from 39.7% to 26.7% (Table 2) .

As in the main group, among patients with idiopathic and post-COVID coxarthrosis, with a higher incidence of the main allelic variant G , a decrease in their frequencies was observed compared to their control level to 53.6% and 53.4%. Meanwhile, the weakened allele A among these patients increased to 46.4% and 46.6%, respectively[9].

Similar to the allelic variants, with IR and PC, in comparison with the control, the main GG locus decreased to 26.2% and 27.3%, while the proportion of heterozygous GA and mutant AA loci increased to 54.8% and 52.3%, as well as to 19.0% and 20.4% (Table 2).

Reduction in the frequency of the main allele (G) and genotype (GG) for the GDF5 marker - G/A among patients with coxarthrosis indicate a decrease in the activity of their protective effect in relation to the likelihood of the onset of the disease, while the opposite increase in the expression of unfavorable loci (A, GA and AA) of the studied gene shows an increase in their unfavorable influence, laying the foundation for the formation of coxarthrosis[10].

Assessing the significance of differences in the structure of the genetic marker encoding the growth differentiation factor 5 - GDF5 - G/A among those examined, it was found that, in comparison with the control values, in the MG with coxarthrosis there was a weak tendency to increase the frequency of the mutant allele A by 1.4 times (χ 2 = 2.5; P = 0.2; OR = 1.4; 95% CI: 0.92-2.22) (Table 3) .

In addition, a pronounced tendency towards a decrease in the protective effect of the main GG locus was observed in the OG (χ 2 = 3.1; P = 0.1; 95% CI: 0.29-1.07). Meanwhile, in the frequencies of heterozygous GA (χ 2 = 1.2; P = 0.3; OR = 1.4; 95% CI: 0.76-2.61) and mutant homozygous AA (χ 2 = 0.5; P = 1.3; OR = 1.4; 95% CI: 0.6-3.05) loci, an increase was recorded in relation to similar ones in the control group by 1.4 times without statistically significant significance (Table 3) .

Table 3.

Differences in the structure of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A among subjects with coxarthrosis and the control group

Loci	Group				χ^2	R	RR	95%CI	OR	95% CI
	PG, n=86		CG, n=86							
	n	%	n	%						
G	92	53.5	97	62.2	2.5	0.2	0.9	0.58-1.28	0.7	0.45-1.09
A	80	46.5	59	37.8	2.5	0.2	1.2	0.73-1.85	1.4	0.92-2.22
G/G	23	26.7	31	39.7	3.1	0.1	0.7	0.34-1.33	0.6	0.29-1.07
G/A	46	53.5	35	44.9	1.2	0.3	1.2	0.67-2.12	1.4	0.76-2.61
A/A	17	19.8	12	15.4	0.5	0.5	1.3	0.65-2.54	1.4	0.6-3.05

The obtained calculations of differences in the frequencies of the loci of the genetic marker encoding the 5-factor of growth differentiation - GDF5 - G/A between the groups of patients with coxarthrosis and the control indicate a tendency to decrease the favorable protective effect of the main homozygote GG (χ 2 = 3.1; P = 0.1) in relation to an increase in the likelihood of coxarthrosis, emphasizing the role of the GDF5 - G/A gene as a marker that increases the risk of the disease[11].

In the structure of the genetic marker encoding the growth differentiation factor 5 - GDF5 - G/A differences between patients with idiopathic coxarthrosis and healthy individuals were also characterized by the presence of a weak tendency to increase the frequency of the mutant allele A by 1.4 times (χ 2 = 1.7; P = 0.2; OR = 1.4; 95% CI: 0.83-2.44) and a decrease in the activity of the protective homozygote GG (χ 2 = 2. 2 ; P = 0.2; 95% CI: 0.24-1.22).

At the same time, in the frequencies of heterozygous GA and mutant homozygous AA loci, when they increased in relation to similar ones in the control group by 1.5 (χ 2 = 1.1; P = 0.4; OR = 1.5; 95% CI: 0.7-3.16) and 1.3 (χ 2 = 0.3; P = 0.7; OR = 1.3; 95% CI: 0.48-3.46) times, they did not reach a reliable significant value (Table 4) .

Table 4.

Differences in the structure of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A among examined patients with idiopathic coxarthrosis and the control group

Loci	Group				χ^2	R	R.R.	95%CI	OR	95% CI
	IC, n= 42		CG, n=86							
	n	%	n	%						
G	45	53.6	97	62.2	1.7	0.2	0.9	0.44-1.69	0.7	0.41 - 1.2
A	39	46.4	59	37.8	1.7	0.2	1.2	0.79 - 1.7	1.4	0.83-2.44
G/G	11	26.2	31	39.7	2.2	0.2	0.7	0.21-2.04	0.5	0.24-1.22
G/A	23	54.8	35	44.9	1.1	0.4	1.2	0.47-3.19	1.5	0.7-3.16
A/A	8	19.0	12	15.4	0.3	0.7	1.2	0.38-4.03	1.3	0.48-3.46

Thus, according to the results obtained between patients with idiopathic coxarthrosis and healthy individuals, no statistically significant differences were found in the frequencies of the loci of the genetic marker encoding the 5-factor of growth differentiation - GDF5 - G/A (χ 2 <3.84; P>0.5). In turn, this shows that the polymorphic gene GDF5 - G/A does not have an independent significant role in increasing the likelihood of developing idiopathic coxarthrosis[12].

Calculating the degree of differences between the loci of the genetic marker encoding the growth differentiation factor 5 - GDF5 - G/A in the group of patients with post-COVID coxarthrosis in comparison with the frequencies of loci in the healthy group, a weak tendency to increase the frequency of the mutant allele A by 1.4 times was observed (χ 2 = 1.8; P = 0.2; OR = 1.4; 95% CI: 0.85 - 2.43), accompanied by an insignificant decrease in the activity of the protective homozygote GG (χ 2 = 1.9; P = 0.2; 95% CI: 0.26 - 1.26)[13].

Moreover, among patients with post-COVID coxarthrosis, an increase in the frequencies of unfavorable heterozygous GA and mutant homozygous AA loci was found compared to their control values by 1.3 (χ 2 = 0.6; P = 0.5; OR = 1.3; 95% CI: 0.64 - 2.82) and 1.4 (χ 2 = 0.5; P = 0.5; OR = 1.3; 95% CI: 0.54 - 3.67) times. However, between these groups, the differences in the given loci were not significant (Table 5).

Table 5.

Differences in the structure of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A among examined patients with post-COVID coxarthrosis and the control group

Loci	Group				χ^2	R	R.R.	95%CI	OR	95% CI
	PC, n= 44		CG, n=86							
	n	%	n	%						
G	47	53.4	97	62.2	1.8	0.2	0.9	0.45-1.65	0.7	0.41 - 1.18
A	41	46.6	59	37.8	1.8	0.2	1.2	0.79-1.72	1.4	0.85 - 2.43
G/G	12	27.3	31	39.7	1.9	0.2	0.7	0.23-2.02	0.6	0.26 - 1.26
G/A	23	52.3	35	44.9	0.6	0.5	1.2	0.46-2.94	1.3	0.64 - 2.82
A/A	9	20.5	12	15.4	0.5	0.5	1.3	0.44-4.0	1.4	0.54 - 3.67

Thus, according to the results of the analysis obtained between patients with post-COVID coxarthrosis and healthy individuals in the frequencies of the loci of the genetic marker encoding the 5-factor of growth differentiation - GDF5 - G / A, no statistically significant differences were found, as in relation to idiopathic coxarthrosis (χ 2 <3.84; P> 0.5). This means that the studied genetic variant GDF5 - G / A does not independently participate in the mechanisms that increase the likelihood of the formation of post-COVID coxarthrosis[14].

No less interesting was the study of the nature of differences in the loci of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A between groups of patients with idiopathic and post-COVID coxarthrosis[15].

The results of statistical analysis showed that the differences in none of the loci of the studied gene reached statistically significant values, because allele frequencies (G - χ 2 <3.84; P=0.99; OR=1.0; 95% CI: 0.55 – 1.83 and A - χ 2 <3.84; P=0.99; OR=1.0; 95% CI: 0.55 - 1.81) and genotypes (GG - χ 2 <3.84; P=0.95; OR=0.9; 95% CI: 0.36 - 2.46 ; GA - χ 2 <3.84; P=0.9; OR=1.1; 95% CI: 0.47 - 2.58 and AA - χ 2 <3.84; P=0.9; OR=0.9; 95% CI: 0.32 - 2.65) of this markers in the examined groups were close in their values (Table 6) .

Table 6.

Differences in the structure of the genetic marker encoding growth differentiation factor 5 - GDF5 - G/A among examined patients with idiopathic and post-COVID coxarthrosis

Loci	Group				χ^2	R	R.R.	95%CI	OR	95% CI
	IC, n= 42		PC, n= 44							
	n	%	n	%						
G	45	53.6	47	53.4	0.0	0.99	1.0	0.55-1.83	1.0	0.55 - 1.83
A	39	46.4	41	46.6	0.0	0.99	1.0	0.56-1.77	1.0	0.55 - 1.81
G/G	11	26.2	12	27.3	0.0	0.95	1.0	0.36-2.53	0.9	0.36 - 2.46
G/A	23	54.8	23	52.3	0.1	0.90	1.0	0.45-2.46	1.1	0.47 - 2.58
A/A	8	19.0	9	20.5	0.0	0.90	0.9	0.31-2.78	0.9	0.32 - 2.65

The results of statistical comparison of the frequencies of the loci of the genetic marker encoding the 5-factor of growth differentiation - GDF5 - G/A between patients with idiopathic and post-COVID coxarthrosis did not differ in the presence of reliable significant differences (χ 2 <3.84; P> 0.5), which proved the absence of an increase in the chance of developing coxarthrosis associated with the independent influence of the studied genetic marker GDF5 - G/A.

4. Conclusion

Thus, based on the conducted molecular genetic analysis, which included the study of the distribution pattern of polymorphic loci of the genetic marker encoding the 5-factor of growth differentiation - GDF5 - G/A among patients with coxarthrosis in a comparative aspect with a healthy control group, a tendency to a decrease in the favorable protective effect of the main homozygote GG was found (χ 2 = 3.1; P = 0.1). The discovered fact proves the possible participation of the GDF5 - G/A gene in creating conditions for an increased chance of coxarthrosis formation.

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