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Study of polymorphic loci of CALCR, COL1A1, VDR, and LCT genes in patients with aseptic necrosis of the femoral head

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Introduction Aseptic necrosis of the femoral head (ANFH) is a multifactorial disease, and genetic predisposition is one of these factors. Considering this circumstance, researchers search for identification of genetic markers of ANFH development. An objective of this research was to study the frequency of alleles and genotypes of polymorphic loci of 1377 C/T gene *CALCR*; -1997G/T, -1663indelT and +1245 G/T (Sp1) of gene COL1A1; -3731 A/G (Cdx2) и +283 G/A (BsmI) of gene *VDR*, and -13910 C/T of gene *LCT* in patients with ANFH and further analyze the association of the molecular-genetic markers under the study with the risk of developing this disease. **Material and methods** Analysis of association of alleles of genes for studying genetic predisposition to ANFH was carried out. Seven polymorphic markers in genes *CALCR, COL1A1, VDR, LCT* were detected by pyrosequencing method using the system of genetic analysis PyroMark Q24. Genotyping of 60 DNA samples of individuals with ANFH was conducted, frequencies of alleles and genotypes were determined. **Results** Genotype A/A of polymorphic locus +283 G/A (BsmI) of gene *VDR* (OR = 2.92; 95 % CI: 1.16–7.35) was associated with the risk of ANFH development as well as the carriage of allele A of this locus (OR = 1.55; 95 % CI: 1.02-2.37). It was also found that genotype G/G of polymorphic locus -3731 A/G (Cdx2) in gene *VDR* increased the risk of ANFH development more than twice (OR = 2.09; 95 % CI: 0.51-8.59); the carriage of the allele G of this polymorphic locus is associated with an elevated risk of ANFH (OR = 1.8; 95 % CI: 1.13-2.86). **Discussion** The results show that the analysis of the polymorphic loci +283 G/A (BsmI) and -3731 A/G (Cdx2) of *VDR* gene enables an early identification of persons at high risk of ANFH and, consequently, a possibility to prevent this disease. However, the involvement of certain genes in ANFH development requires further study, particularly given the sample sizes and ethnic specificity. **Conclusion** The risk of developing ANFH increased more than twice in the presence of genotype G/G of the polymorphic locus -3731 A/G (Cdx2) of VDR gene (OR = 2.09; 95 % CI: 0.51–8.59). Association of genotype A/A of locus +283 G/A (BsmI) of the gene of vitamin D receptor *VDR* with the risk of ANFH was established (OR = 2.92; 95 % CI: 1.16–7.35); it was also found that the A allele carriage was associated with an increased risk of ANFH (OR = 1.55; 95 % CI:1.02–2.37).

Keywords: aseptic necrosis of the femoral head, polymorphic loci, polymorphism of genes *CALCR, COL1A1, VDR, LCT*

INTRODUCTION

Aseptic necrosis of the femoral head (ANFH) accounts for 1.2 to 4.7 % of the total orthopedic hip joint pathology. Studies of its etiopathogenesis point to the multifactorial origin of the disease, and one of the factors is genetic predisposition [1]. The genetic aspect of ANFH etiopathogenesis has not been studied sufficiently to date, therefore, it seems to us that studies aimed at identifying molecular genetic markers of ANFH are relevant. In this work, we analyzed the frequencies of alleles and genotypes of polymorphic variants of candidate genes which products are involved in the processes of bone metabolism and osteogenesis: calcitonin receptor *CALCR* [2]; α1 chains of collagen of type 1 (COL1A1) [3-6]; receptor of vitamin D (*VDR*) [7, 8], as well as lactase (*LCT*) [9]. To our knowledge, such molecular genetic studies have not been conducted in the Russian Federation.

The aim of the research was to study the frequency of alleles and genotypes of polymorphic loci c.1377 C/T of the calcitonin receptor gene *CALCR*; -1997G /T, -1663indelT and +1245 G/T (Sp1) of gene α1 of collagen type 1 (*COL1A1*); -3731 A/G (Cdx2) and +283 G/A (BsmI) of the vitamin D receptor gene (*VDR*), as well as -13910 C/T of lactase gene (*LCT*) in patients with ANFH, followed by the analysis of the associations of molecular genetic markers studied with the risk of developing this pathology.

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MATERIALS AND METHODS

Clinical and genetic study was conducted in 60 patients with ANFH, 31 men and 29 women aged 21-89 years, who applied to the specialized Center for Treatment of Aseptic Necrosis (Limited Liability Company HuangDi Medical Center, Moscow). The average age was 56.29 ± 0.43 years in males and 58.86 ± 0.38 years in females. Ethnogenetic origin of patients was homogeneous; all were of Slavic-Baltic origin (51 Russians, six Ukrainians, one Belarusian, and two Latvians) and were residents of the Central Federal District.

Control sample population consisted of the individuals of Russian origin and was based on the findings taken from the published literature sources.

Patients' age and anthropometric parameters were recorded. Clinical diagnosis of aseptic necrosis and osteoporosis was established using clinical and anamnesis data, laboratory tests, radiography in three projections (supine, prone and Lauenstein positions), computed tomography (CT) and magnetic resonance imaging (MRI) of the hip joints. ANFH grade was established according to the classification criteria of Ficat and Arle and ARCO (Association Research Circulation Osseuos); the functional condition of the joints was assessed using the Harris Hip Score. Assessment of bone tissue density and quality (densitometry) was performed on the radial bone and proximal phalange of the third finger of the non-dominant hand using Sunlight MiniOmni ultrasonic densitometer (BeamMed., LTD, Israel). The results were presented as SOS (speed of sound, m/sec), T and Z - criteria.

Genomic DNA samples isolated from blood leukocytes were used for molecular genetic analysis with the King Fisher Flex automatic station (Thermo Scientific). Determination of polymorphisms in *CALCR, COL1A1, VDR, LCT* genes was carried out by PCR (polymerase and PCR buffer produced by Isogen Lab, amplification primers fabricated by CJSC Eurogen, Russia). PCR was carried out on a thermocycler Eppendorf Mastercycler Nexus Gradient (Germany). Analysis of polymorphic DNA loci was performed by pyrosequencing using the PyroMark Q24 QIAGEN genetic analysis system (Germany) based on a commercial diagnostic laboratory.

The hypothesis that samples belong to one general population (ie, no differences in the distribution of allele frequencies and genotype frequencies between samples) was evaluated with the Pearson χ^2 criterion using the WinPepi application software package (http://www.brixtonhealth.com/pepi4windows. html).

In the case of significant differences between the study group and the population controls, the odds ratio-OR ratio [2] was calculated taking into account 95 % confidence interval (95 % CI).

OR ratio equal to one indicates that there is no association of the DNA marker with the risk of developing the disease; OR more or less than one indicates an increased or decreased risk of developing the disease, respectively. To determine the OR, a statistical calculator for case-control studies was used (http://test. tapotili.ru/calculator or.php).

RESULTS

CALCR gene encodes receptor membrane proteins to calcitonin on osteoclasts, kidney, liver and other tissue cells. It is known that activation of calcitonin receptors results in the inhibition of osteoclast activity and in a decrease in the rate of bone resorption. Disorders in the function of calcitonin receptors can lead to an increase in bone resorption. Polymorphism c.1377 C/T (rs1801197) of the calcitonin gene *CALCR* is a point single nucleotide mutation leading to the replacement of the amino acid in the peptide chain of the enzyme molecule [2].

Analysis of allele frequencies and genotype frequencies of the polymorphic locus c.1377 C/T (rs1801197) of *CALCR* gene in the group of patients with ANFH and in the control sample showed no statistically significant differences (Table 1).

Table 1

Allele and genotype frequencies in polymorphic locus c.1377 C/T (rs1801197) of CALCR gene in ANFH patients and control sample

Group and number of its subjects (n)	Allele frequencies, %		χ^2; df = 1	Genotype frequency, %			χ^2; df = 2
	T	C		TT	TC	CC	
Population sample (84)*	73.7	26.3	0.05; P = 0.82	53.5	40.5	6.0	0.34; P = 0.82
Patients with ANFH(66)	72.3	27.3		53.3	38.3	8.4	

Note: * – literature data [2].

Protein products of *COL1A1* gene expression (collagen type I) are the basis of the connective matrix (up to 25–30 %) and bone (90 %) tissues. *COL1A1* gene is mapped on the long arm of chromosome 17 (17q21.33). In the 5' region of the gene, three polymorphisms are located: in the site of transcription initiation - Spl (+ 1245G / T, rs1800012) and in the promoter (-1997G / T, rs1107946 and -1663IndelT, rs2412298) [10, 11].

Our analysis of the frequencies of alleles and genotypes of the polymorphic loci -1997G / T (rs1107946), 1663IndelT (rs2412298) and +1245 G/T (Sp1) (rs1800012) of *COL1A1* gene in the group of patients with ANFH and in the control sample did not reveal statistically significant differences (Table 2).

VDR gene is mapped on chromosome 12 (12q13.11) and encodes a nuclear receptor that binds the active form of the vitamin (1.25-dihydroxyvitamin D3-1α, 25 (OH) 2D3). Researchers show interest in polymorphic allelic variants of Cdx2 (rs11568820) and BsmI (rs1544410) of the vitamin D receptor gene of *VDR* [15].

Frequencies GG, AG, and AA of genotypes of the polymorphic locus -3731 A/G (Cdx2) of vitamin D receptor gene VDR (rs11568820) in patients with ANFH significantly differed from the population sample (63.6, 33.3, 3.0 %, and 44.9 , 48.9 and 6.2 %, respectively, $\chi^2 = 6.88$, df = 2, p = 0.009) (Table 3). According to the odds ratios, the risk of developing ANFH increases more than 2-fold in the presence of genotype G/G in the *VDR* gene (OR = 2.09, 95 % CI: 0.51-8.59). Carriage of allele G is associated with an increased risk of development of ANFH (OR = 1.8, 95 % CI: 1.13-2.86): among patients with ANGBC, the carriage frequency was 80.3 % which is significantly higher than in the control group – 69, 4 % (p = 0.01, df = 1).

Analysis of the obtained data showed that the frequencies of alleles and genotypes of the polymorphic locus +283 G/A (BsmI) of vitamin D receptor gene *VDR* in the group of ANFH patients and the population sample differed significantly (Table 3): 51.0, 41.7, 7.3 % and 43.3, 38.3, 18.4 %, respectively ($\chi^2 = 3.80$, df = 2, p = 0.05); the risk of ANFH development was increased in the presence of genotype A /A in the *VDR* gene (OR = 2.92, 95 % CI: 1.16-7.35). Carriage of allele A is associated with an increased risk of ANFH (OR = 1.55, 95% CI: 1.02-2.37): among patients with ANFH, the carriage frequency was significantly higher than in the control group, 18.4 % and 7.3 %, respectively (p = 0.04, df = 1).

Table 2

Alleles and genotype frequencies in polymorphic loci of COL1A1 gene in ANFH patients and control samples

Group and number of its subjects (n)	-1997G/T (rs1107946)						
	Alleles		χ^2; df = 1	Genotypes			χ^2; df = 2
	G	T		GG	GT	TT	
Population sample (197)*	81.3	18.7	0.76 P = 0.38	65.3	31.0	3.7	0,70 P = 0,40
Patients with ANFH (66)	77.8	22.2		63.3	28.3	8.4	
	-1663IndelT (rs2412298)						
	I	D	0.18 P = 0.67	II	ID	DD	0.84 P = 0.66
Population sample (n = 197)*	84.8	15.2		71.1	26.5	2.4	
Patients with ANFH (n = 66)	86.4	13.5		75.0	21.7	3.3	
	+1245 G/T (Sp1) (rs1800012)						
	G	T	0.21 P = 0.65	GG	GT	TT	0.41 P = 0.81
Population sample (n = 174)**	83.2	16.8		67.8	29.3	2.9	
Patients with ANFH (n = 66)	84.8	15.2		70.0	28.3	1.7	

Note: * – literature data [12]; ** – [13].

Table 3

Alleles and genotype frequencies in polymorphic locus of *VDR* gene in ANFH patients and control sample

Group and number of its subjects (n)	-3731 A/G (Cdx2) (rs11568820)						
	Alleles		χ^2; df = 1	Genotypes			χ^2; df = 2
	G	A		GG	AG	AA	
Population sample (250)*	69.4	30.6	6.24 P = 0.01	44.9	48.9	6.2	6.88 P = 0.009
Patients with ANFH (66)	80.3	19.7		63.3	33.3	3.3	
	+283 G/A (BsmI) (rs1544410)						
	G	A	4.15 P = 0.04	GG	AG	AA	3.80 P = 0.05
Population sample (197)**	71.4	28.6		51.0	41.7	7.3	
Patients with ANFH (66)	65.1	34.9		43.3	38.3	18.4	

Note: * – literature data [17]; ** – [12]

LCT gene is located on chromosome 2 at the 2q21 locus. Lactase deficiency (hypolactasia) is manifested in the inability to absorb lactose of the whole milk and is genetic.

For direct DNA diagnostics of hypolactasia, an analysis of single nucleotide polymorphism C/T-13910 in the regulatory region of *LCT* gene (rs4988235) which is associated with primary hypolactasia is used [9]. Our analysis of the frequency of alleles and genotypes of the polymorphic locus C/T-13910 of *LCT* gene in groups of patients with ANFH and the population sample showed no significant differences (Table 4).

Table 4

Alleles and genotype frequencies in polymorphic locus of C/T-13910 of LCT gene (rs4988235) in ANFH patients and control sample

Group and number of its subjects (n)	Alleles frequencies, %		χ^2; df = 1	Genotype frequencies, %			χ^2; df = 2
	C	T		CC	CT	TT	
Population sample (n = 112)*	71.4	28.6	1.12; P = 0.29	53.6	38.7	8.0	1.08; P = 0.30
Patients with ANFH (n = 66)	69.6	30.4		46.6	41.7	11.7	

Note: * – literature data [9]

DISCUSSION

The change in the structure of receptors to calcitonin on osteoclasts, kidney, liver, and other tissues reflects their functional activity, which is associated with a high degree of bone resorption in carriers of variant T of polymorphism c.1377 C / T (rs1801197) of calcitonin *CALCR* gene [2]. In the course of the study, differences in the frequencies of genotypes and alleles of this gene between the group of patients with ANFH and control sample were not established.

It is known that the polymorphic loci -1997G/T and -1663IndelT of *COL1A1* gene are bound and are in close disequilibrium with respect to Spl polymorphism and directly affect bone tissue mineral density both separately and in combination with each other [5]. Based on the results of some studies, the allele G of the polymorphic locus -1997G/T is associated with the development of diseases associated with impaired calcium metabolism, rapid loss of bone mineral density and the development of severe osteoporosis [3-5]. In some studies of Sp1 (rs1800012) polymorphism in carriers of allele T (analogue of allele s), both in homozygous and heterozygous states, collagen function disorders and predisposition to osteoporosis were noted [6]. In the course of the studies, no statistically significant differences were found between the frequencies of the alleles and genotypes of polymorphic loci -1997G / T, -1663IndelT and +1245 G / T (Sp1) of *COL1A1* gene in the ANFH group and in the control sample.

It is known that the allele A of the polymorphic locus BsmI (rs1544410) of the gene of the vitamin D receptor VDR is associated with the stimulation of gene expression and increases the serum level of 1α, 25 (OH) 2D3 compared to the G allele [7, 15]. Also, in a number of studies of Cdx2 polymorphism (rs11568820), the protective role of the carriage of the mutant allele A was demonstrated, which is associated with an increase in the ranscription of calcium-carrying proteins: in the conditions of reduced calcium intake, the loss of bone mineral density is prevented [8, 16].

In the course of the study, it was found that the carriage of the G allele of the polymorphic locus -3731 A/G (Cdx2) of the vitamin D receptor gene of *VDR* (rs11568820) is associated with an increased risk of developing ANFH (OR = 1.8, 95 % CI: 1,13-2.86): the carriage was 80.3 % among ANFH patients which is significantly higher than in the control group –69.4 % (p = 0.01, df = 1). It was also shown that in the presence of the genotype G/G, the risk of developing ANFH increases more than 2-fold (OR = 2.09, 95 % CI: 0.51-8.59).

Analysis of the obtained data showed that the risk of developing ANFH was increased in the presence of the genotype A / A of polymorphic locus +283 G/A (BsmI) of the *VDR* gene (OR = 2.92, 95 % CI: 1.16-7.35). Carriage was also associated with an increased risk of developing the disease (OR = 1.55, 95 % CI: 1.02-2.37): among ANFH patients, the carriage was significantly higher than in the control group, 18.4 % and 7, 3%, respectively (p = 0.04, df = 1).

It is known that persons with genotypes CT or TT of the polymorphic locus C/T-13910 of the *LCT* lactase gene (rs4988235) have an increased lactase activity, whereas in the individuals with

CC genotypes a decrease in the activity of the enzyme is observed. In a number of studies, the association of lactase deficiency with a decrease in bone mineral density was found which is associated with alimentary deficiency of milk calcium [9]. In our study, significant differences in the comparison of the frequency distribution of alleles and genotypes of the polymorphic locus C / T-13910 of the *LCT* gene in groups of ANFH patients and the population sample were not established.

CONCLUSION

The results of the study showed that the risk of ANFH increases more than 2-fold in genotype G/G of the polymorphic locus -3731 A/G (Cdx2) in *VDR* gene (OR = 2.09, 95 % CI: 0.51-8.59).

Genotype A/A of locus +283 G/A (BsmI) of vitamin D receptor (*VDR*) gene was found to be associated with the risk of developing ANFH: OR = 2.92; 95 % CI: 1.16-7.35. It was also found that the carriage of allele A is associated with an increased risk of ANFH (OR = 1.55, 95 % CI: 1.02-2.37): its carriage is significantly higher among patients with ANFH than in the control group, 18.4 % and 7.3 %, respectively (p = 0.04, df = 1).

The results of the study testify to the possibility of early detection of persons with a hereditary predisposition to ANFH using molecular-genetic markers and, consequently, administration of possible measures for prevention of this disease.

However, the contribution of certain genes to ANFH requires further study, especially given the size of the samples and ethnic specificity.

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