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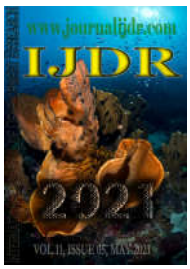

RESEARCH ARTICLE OPEN ACCESS

GENETIC ASPECTS OF DEVELOPMENT OF OSTEOPOROSIS IN PREMENOPASAL PERIOD

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ABSTRACT

XXI century, in many of world community scientists' opinion, is the century of genetics. The direct and most important achievement of genetics was decoding (reading) human genome. The international program "Human Genome" determined the rapid development and active implementation of molecular medicine and the concept of "predisposition genes" existence - genes whose mutant alleles are compatible with birth and life in the postnatal period, but under certain unfavorable conditions can contribute to the development of some diseases, into medical practice. A tendency to multifactorial (combined or complex) diseases (diabetes mellitus, atherosclerosis, ischemic heart disease, bronchial asthma, osteoporosis, endometriosis, some mental and oncological diseases) can also be determined immediately after birth, but their manifestation depends largely on the provoking adverse environmental factors specific to a particular disease. Considering above facts, the determination of molecular genetic causes of osteoporosis is a rather relevant task. There are several approaches to assessing the contribution of a particular candidate gene to the pathogenesis of osteoporosis. One of them is to determine the level of correlation between allele polymorphism of the candidate gene and the factors leading to the development of the disease. For this purpose, a comparison is conducted between allele frequencies of potential candidate genes in patients with osteoporosis and those who do not have this disease and, accordingly, maintain normal bone mineral density.

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INTRODUCTION

Confirmation of the association between genes alleles of bone remodeling and osteoporosis in women in the premenopausal period among Uzbek population will allow using this algorithm to test individuals to identify tendency to this disease. The results of the study are important for a more rational organization of a system for preventing and treating this disease even at the early pre-symptomatic stages of its development. In relation to the above, the search and implementation of osteoporosis markers in premenopausal women is the step without which significant progress in solving modern problems can't be achieved. Screening markers warning about the future development of osteoporosis should be clinically available in order to identify women requiring dynamic check-up during the premenopausal period and preventive therapy before the beginning of clinical manifestation. Bone mass decrease is one of the most significant risk factors for the development of OP and, as shown, can be of genetic nature [3, 11, 14, 15, 16, 22]. The data gathered by researchers [1, 2, 6, 8] indicate that there is a variety of genetic disorders associated with BMD. This indicates a polygenic nature of the inheritance of this indicator.

Therefore, genetic markers that correlate with bone mineral density (BMD) can be used, on the one hand, to predict future fractures, and, on the other hand, to develop a method for differentiated prevention of bone mass loss in osteoporosis.

MATERIAL AND RESEARCH METHODS

For the final confirmation of our hypothesis about the significance of genetic predisposition in the development of OP, we conducted DNA analysis in 170 women aged 40-50 years. The patients were divided into 2 groups depending on BMD. The main group with osteopenic syndrome (main group) consisted of 140 women and 30 women with normal BMD indicators made up the control group. In turn, the main group was divided into 2 subgroups: subgroup A included 57 (40.7%) women with osteoporosis and subgroup B - 83 (59.3%) women with osteopenia.

RESULTS OF THE RESEARCH

Genetic mutations in the main group of patients were detected in 112 (65.9%), and among women with normal BMD indicators - in 8

(4.7%). The study of the structure of markers that cause osteopenic syndrome showed (Fig. 1) that the most frequent polymorphic versions were the rs2228570 versions of the vitamin D receptor gene (VDR), which were found in 44 (39.3%) women with OP. Of these, 33.03% of women with OP were carriers of heterozygous Ff genotype, while homozygous VDR gene mutation was observed in 6.3% of women in the OP group. The second most common form among general population of women with OP was polymorphism of the alpha 1 chain of collagen type 1 (COL1A1) (rs1800012), which was diagnosed in 37 (33.03%), 4 (10.8%) of which had homozygous and 33 (89.2%) - heterozygous form.

Such difference in the distribution of normal genotype within groups are apparently associated with a small range of samples in control group (Table 1). As seen in the table, the frequency of Ff genotype of VDR gene in women with osteopenia and osteoporosis was 35.8% and 28.9%, which was 10.9 and 8.7 times higher than in control group (3.3%). However, there was no statistically significant difference in the indicators of the groups with osteoporosis and osteopenia ($p > 0.05$). In the case of differences in genotypes, this genotype (Ff) was found significantly more often in comparison with ff ($p < 0.01$) and less often in comparison with FF ($p < 0.05$).

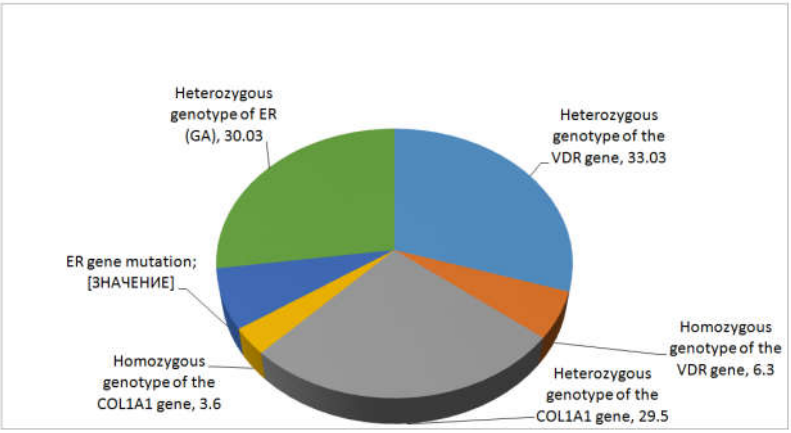

Fig. 1. The structure of markers causing osteopenic syndrome

Table 1. Allele frequency and distribution of polymorphism genotypes (rs2228570) F/f of vitamin D receptor (VDR) gene among patients with osteopenic syndrome

Groups	Number of patients	Allele frequency		Distribution frequency of genotypes					
		F	F	F/F		F/f		f/f	
		%	%	абс.	%	абс.	%	абс.	%
Main group, Of these:	112	93,7	6,3	68	60,7*	37	33,03*	7	6,3
а) osteopenia	67	95,5	4,5	40	59,7*	24	35,8*	3	4,5
б) osteoporosis	45	91,1	8,9*	28	62,2*	13	28,9*	4	8,9
Control group	30	96,7	3,3#	29	96,7#	1	3,3#	-	-

Note: * - statistically significant difference according to Pearson's Chi-square ($p < 0.01$); # - statistically significant difference according to Pearson's Chi-square ($p < 0.05$).

The mutation of estrogen receptor alpha (ESR1) rs2228480 gene, which is rare for Asian population, was detected in only 9 (8.04%) women with OP; they also had a homozygous AA genotype. Indicators of the mutant estrogen receptor gene alpha were not detected in women from the control group. The results of our studymatch with the data of some authors partially [2, 9, 18, 24, 26], according to which the most common genetic factors among Asian population — polymorphism of the COL1A1 gene, VDR gene and ESR1 gene — are found with the same frequency among the examined women. Thus, the high frequency of hereditary form of osteopenic syndrome among the examined women allowed us to consider it as the most important etiopathogenetic factor in the development of OP, which dictates to choose an optimal and safe preventive therapy to compensate genetic disorders.

Analysis of the association of polymorphism 2228570 F/f with the vitamin D receptor gene (VDR) among patients with osteopenic syndrome (Table 1) showed that in both groups there was a dominance of normal F/F allele (normal), while the mutant f allele (homozygous - f / f) was not detected in patients with normal BMD (control).

The frequency of dominant allele (F) was 61.83%, recessive (f) - 38.17%. The observed distribution of alleles and genotypes corresponds to the Hardy – Weinberg principle [4, 10, 28]. The distribution frequency of normal F/F genotype in the group with osteopenic syndrome and control group was respectively 60.7% (68/112) and 96.7% (29/30).

At the same time, the differences in the distribution of allele frequencies in main and control groups turned out to be insignificant, but close to the limits of statistical significance ($\chi 2 = 2.29$; $P = 0.06$; OR = 4.9; 95% CI 0.50-47.56), which does not match withother authors' data. Apparently, this is due to the low frequency of this mutation in studied samples. The distribution of mutant homozygous f/f genotype of this genetic marker among the patients of main group was 6.3% (7/112), and this genotype was not found in women with normal BMD values (0/30). As expected, a rare homozygous f/f mutation of this marker was detected in 8.9% (4/45) women of the group with OP, which is 2 times more often than in the group with osteopenia - 4.5% (3/67). This version of the mutation is rare, which was confirmed by a number of authors [5, 19, 20, 27]. Thus, the ff genotype is prognostically unfavorable in terms of BMD indicators, T-criterion. According to odds ratio (OR), the risk of developing OP increases more than 6 times in the presence of F/f and f/f genotypes. However, despite such an increase in distribution frequency of mutant f allele, no statistically noticeable differences were found inits heterozygous F/f version among women with osteopenia and osteoporosis ($\chi 2 = 0.9$; $P = 0.2$; OR = 2.9; 95% CI 0.29-28.02). This statistical uncertainty in obtained data is possibly associated, as mentioned above, with the different frequency of this mutation in studied groups and relatively small number of those examined in control group.

Analysis of the association of estrogen receptor gene's polymorphism 2228480 (ERα). Family risk factors, such as low estrogen status inherited by daughter from mother, have a certain influence on the development of OP. The state of estrogen receptors

Table 2. Allele frequency and genotype distribution of rs2228480 G/A polymorphism of estrogen receptor gene (ERα) among patients with osteopenic syndrome

Groups	Number of patients	Allele frequency		Distribution frequency of genes					
		G	A	G/G		G/A		A/A	
		%	%	abc.	%	abc.	%	abc.	%
Main group, of these:	112	91,9	27,7	81	72,36*	22	19,6*	9	8,04
a) Osteopenia	67	97,0	16,4	56	83.6*	9	13,4*	2	3,0
b) Osteoporosis	45	84,4	24,4*	25	55,6*	13	28,9*	7	15,6
Control group	30	100	16,7#	25	83.3#	5	16,7#	0	0

Note: * - statistically significant difference according to Pearson's Chi-square (p <0.01); # - statistically significant difference according to Pearson's Chi-square (p <0.05).

Table 3. Differences between alleles and genotypes of polymorphic marker 2228480 G/A of the estrogen receptor gene (ERα) among patients of main and control groups

Allele and genotype	Frequency of alleles and genotypes in groups		Statistic difference
	main, (n=112)	control,(n=30)	
Allele G	91,9	100	χ^2=2,29; P=0,06 OR=4,9; 95% CI 0,50-47,56
Allele A	27,7	16,7	
Genotype GG	72,36	83,3	χ^2=0,9; P=0,1
Genotype GA	19,6	16,7	χ^2=0,9; P=0,2; OR=2,9; 95% CI 0,29-28,02
Genotype AA	8,04	-	

Table 4. Correspondence with Hardy-Weinberg law of genotype distribution of polymorphism G/T of COL1A1 gene

	Observed	frequency	Expected	frequency		
Genotypes of COL1A1 gene polymorphism	abc	%	abc	%	x2	P
GG	75	67,0		67,22	0,04	0,84
GT	33	29,5		29,54		
TT	4	3,6		3,24		

in osteoblasts and their physiological activity effect bone metabolism. The polymorphism of estrogen receptor (ER) genes was proven and the analysis of ER gene mutation in comparison with BMD in the European population was carried out[13, 18]. However, the data obtained in the study of different populations and age groups differ vastly. A close relationship between these indicators was found in the age group of women over 57 years old, but no correlation was found in the groups of women younger than this age [2, 5, 7]. Examination of 512 women in postmenopausal period revealed a limited effect of ER genotype on BMD of the lumbar spine and hip [3, 6, 13, 17]. The study on the relationship between BMD and ER polymorphism in Asian populations of women revealed an effect dependence on existing genetic background, however, in contrast to the results obtained while studying white groups in Asian population, a low level of BMD was associated with the PP genotype according to Pvull- polymorphism and ER gene [17, 25]. Whereas the studies conducted by Azizova [2] did not find the relationship between studied pathology in menopausal women and rs2228480 G/A genotype of the estrogen receptor gene (ERα).

The results of our studies showed reliable differences in the distribution frequency of genotypes G/G, G/A and A/A in women with OP and in women in control group (Table 2). The expression of normal G/G genotype was observed in all the studied groups most frequently, which will allow the use of estrogens for prophylactic and therapeutic purpose in our pathology [12, 21]. In osteopenic syndrome, the presence of the A/A genotype was detected in 8.04% of women, which was 2.4 times less in control group. Whereas, the frequency of heterozygous G/A genotype in women with osteopenic syndrome was 3 times higher than in control group. As can be seen in Table 3, in both groups, the dominance of normal allele G (normal) over the mutant A allele was observed,among the patients of main group respectively in 82.1 and 17.9% and in control group - in 93.3 and 6.7 %. Meanwhile, the differences in the distribution frequencies of allele in general and control groups were inaccurate, but close to the limits of statistical significance ($\chi2$ = 2.29; P = 0.06; OR = 4.9; 95% CI 0.50-47.56), which does not match with other authors' data [8, 9, 23, 29].

Apparently, this is related to the low frequency of this mutation in studied samples. The distribution frequency of the normal GG genotype in main and control groups was respectively 74.1% (83/112) and 83.3% (25/30). Such differences in the distribution of normal genotype in main group also turned out to be statistically inaccurate ($\chi2$ = 0.9; P = 0.1) (Table 3.). The distribution of mutant heterozygous G/A genotype of this genetic marker in patients of main group was 21.4%, and among women with normal BMD - 16.7%. As expected, a rare homozygous mutation A/A of this marker was found only in a group with OP, which was confirmed by a number of authors [2, 23, 29]. According to odds ratio (OR), the risk of developing OP with existence of G/A genotypeincreases by more than 2.9 times (Table 3). However, despite such an increase in distribution of heterozygous G/A genotype frequency among women with OP, no statistically significant differences were found ($\chi2$ = 0.9; P = 0.2; OR = 2.9; 95% CI 0.29- 28.02). This statistical inaccuracy of the difference in obtained data is possibly associated, as mentioned above, with very low frequency of this mutation in studied groups and relatively small number of examined.

A similar genotype distribution of above-mentioned polymorphism was also found among women in Iran [14], Mexico [24], Tunisia [25], Saudi Arabia [17]. The connections of GT and TT genotypes, observed in our work, with low indicators such as BMD, most likely, reflect the possible influence of polymorphic versions of the COL1A1 gene on skeleton system of body. Based on observed associations, it is possible to explain, at least partially, the fact that the root cause of OP syndrome may be the features of COL1A1 gene, which cause changes in basic substance synthesis of connective tissue, simultaneously influencing on the state of skeleton, and, possibly, on other characteristics of human body, including height, weight, body mass index. Along with above mentioned, one should be mentioned that in some studies, associations of the Sp1 polymorphism of COL1A1 gene with the development of osteoporosis and/or the risk of low-energy fractures have not been detected [5, 14]. These discrepancies in obtained results can be associated with the features of study design, differences in examined people's race and ethnicityand an insufficient number of

observations. Undoubtedly, the role of COL1A1 gene polymorphism in bone pathology can be neutralized by other genetic systems activities, since osteoporosis is a polygenic disease [15, 24]. Apart from interaction of various genes with each other, other factors, which are not always taken into account, could influence the result of research. Thus, it is established that women atpremenopausal age with GG genotype of COL1A1 gene polymorphism are associated with a decrease in the levels of bone mineral density and T-score. TT genotype of mentioned polymorphism (p = 0.004) is also associated with a decrease in densitometry indicators. Gathered data can be used to develop criteria for determining the risk of osteoporosis among premenopausal women, early diagnosis of the disease and increasing the effectiveness of therapeutic and prophylactic measures. Significant associations were observed between functionally weakened hetero- and homozygous genotypes with the onset of OP. At the same time, the most distinct association was revealed in the frequency of homozygotes of studied genes. Our results reveal some genetic aspects of osteoporosis and its complications in premenopausal women and indicate the relevance of further study on other genes polymorphism. Summing up this stage of our work, we can conclude that women with osteopenic syndrome have disorders bone metabolism system associated with genetic factors. The significant ones among them are the mutation of the vitamin D receptor gene (39.3%), the alpha 1 collagen receptor gene (33.03%) and the homozygous version of estrogen receptor gene polymorphism (8.04%), leading to a decrease in bone formation and bone tissue resorption, which can be considered as an independent risk factor for the development of OP. Moreover, the simultaneous carriage of mutant alleles of hereditary osteopenia VDR + COL1A1, ER + COL1A1, can be considered as one of the key risk factors for the development of osteoporosis and its complications in the pathogenesis of pathology. Therefore, timely detection of these mutations and the implementation of preventive therapy methods can improve the metabolism processes of bone tissue and reduce the frequency of fractures and disability, and is also the prevention of morbidity and mortality.

CONCLUSION

Significant advances of recent years in the study of genetic regulation of bone remodeling made it possible to identify a large number of genes that affect the structure and morphology of bone tissue, physiological and pathophysiological features of bone metabolism. The studies performed using molecular genetics methods allow to identify a group of genes in which mutations are associated with BMD, the development of OP and, ultimately, the risk of low-energy fractures. Critical importance of these genes in the formation of skeleton and its strength indicates the need for further research in this area and opens up prospects for the practical use of scientific advances in predicting, diagnosing and treating OP.

Conclusion

- Established that the frequency of osteopenic syndrome among women of premenopausal age remains high, in the structure of which osteoporosis constituted 34.9%, osteopenia - 57.1%.
- Among hereditary forms of OP, homozygous mutation rs2228570 (ff) of VDR gene is a dominant risk factor in 33.03% of cases. Homozygous form of ER gene AA mutation is very rare among women with OP (8.04%). Existance of homozygous T/T genotype COL1A1 increases the risk of fractures in OP more than 5.5 times ($\chi 2 = 5.55$; P = 0.01; OR = 5.8; 95% CI 1.134-29.6).

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