

*Theory and practice*

## Molecular and genetic mechanisms of predisposition to osteoporosis

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### Abstract

Osteoporosis is a systemic metabolic disease of the skeleton characterized by low bone mass and microarchitectural damages of bone tissue, leading to an increase in bone fragility and in risk of fractures. Homeostasis of bone tissue during lifetime is mainly maintained by balance of bone resorption and formation, resulting from the combined action of multiple genes and environmental factors. Identification of genes responsible for predisposition to osteoporosis will let to recognize persons of high-risk and pursue the most effective measures of prophylaxis, diagnostics and treatment allowing reducing disability and mortality. This review is focused on the molecular and genetic diagnostics of predisposition to osteoporosis as one of the most common multifactorial diseases, and on the peculiarities of allelic polymorphism of bone metabolism genes. The analysis of published data indicates that the greatest contribution into the development of osteoporosis belongs to *VDR*, *COL1A1*, *ER* and *LCT* genes.

### Key words:

osteoporosis, predisposition, prevention, candidate genes

### Introduction

Osteoporosis is a systemic metabolic disease of the skeleton characterized by low bone mass and microarchitectural damages of bone tissue, leading to an increase in bone fragility and in risk of fractures. Homeostasis of bone tissue during lifetime is mainly maintained by balanced processes of bone resorption and formation, resulting from the combined action of multiple genes and environmental factors. Identification of gene variants, responsible for susceptibility to this disease, will let separate groups of high-risk persons and pursue the most effective measures of prophylaxis, diagnostics and treatment for such patients allowing to avoid complications and reduce mortality and disability.

The project “Human Genome” determined the rapid development of molecular medicine and similarly of information about the existence of “susceptibility genes” and their active implementation into the medical practice. Susceptibility genes are those, which mutated alleles are compatible with the birth and postnatal life, but which may contribute to the development of a disease under certain

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adverse conditions [1]. Such diseases are called multifactorial (MFDs). The development of MFDs (diabetes, atherosclerosis, coronary heart disease, asthma, osteoporosis, endometriosis, some mental diseases and cancer) to a large extent depends on the provocative action of unfavourable environmental factors specific to a particular disease.

This review is focused on the molecular and genetic diagnostics of predisposition to osteoporosis (one of the most common MFDs) and on the peculiarities of allelic polymorphism of bone metabolism genes.

According to the WHO definition, osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural damages of bone tissue, leading to an increase in bone fragility and in risk of fractures [2]. The disease affects all age and racial groups and it is typical for men and women. Usually osteoporosis is diagnosed in elderly age. According to the World Health Organization, osteoporosis now is the fourth most significant non-infectious disease after cardiovascular disorders, cancer, and diabetes.

The great interest in osteoporosis as an important medical and social problem is primarily related to rising attention to the elderly people in the developed countries due to increasing their lifespan and long-stay creative activity. High social importance of this disease is determined by its prevalence, severity of outcomes, especially vertebral or femoral neck fractures, and loss of ability to self-service.

Bone tissue constantly renovates. New bone tissue totally replaces the old one every 10 years. In children and adolescents formation of new bone tissue proceeds more rapidly than resorption, and bone density increases, reaching a peak by the age of 18. Then balance between bone formation and resorption sets, rates of these processes become equal. By about the age of 40 age-related bone loss starts, and resorption gradually begins to dominate over the increase in bone mineral density [3].

The likelihood of developing osteoporosis in women is higher than in men: 80% of all osteoporosis cases are diagnosed for women. With age, women lose important bone “protectors”, i. e. estrogens, and at menopause their bone resorption rate increases drastically. It was calculated that an average of 40% of postmenopausal women experience at least one fracture due to osteoporosis [4].

### **Multifactorial nature of osteoporosis**

Variations of osteoporosis in the population are associated with the interaction between genotype and en-

vironment. In rare cases, osteoporosis is inherited as a monogenic disease and sometimes it can be hardly distinguished from mild forms of osteogenesis imperfecta caused by dominant mutations of type I collagen genes – *COL1A1* and *COL1A2*. Thus, it is not surprising that about 2% of these mutations are associated with osteoporosis. The development of osteoporosis depends on the human lifestyle – physical activity, nutrition, addictions (smoking, alcohol abuse), medications and comorbidities. Age, sex, racial and geographic disparities in the incidence and progression of osteoporosis also testify for multifactorial nature of this disease. The above-named facts suggest that the evaluation of the molecular and genetic causes of osteoporosis is quite an actual task.

The main area of studies in osteoporosis genetics is investigation of peak bone mass formation, its inheritance, loss with age, family susceptibility to fractures and bone metabolism. Investigation of the role of genetic factors is important for the determination of phenotypic characteristics in the population and for the identification of their job in the development of osteoporosis. There are several approaches for assessing the contribution of particular candidate gene to the pathogenesis of osteoporosis. One of them is to determine the degree of correlation between allelic polymorphism of the candidate gene and the factors provoking the development of the disease (population-associative model). For this purpose, frequencies of suspected candidate genes alleles are compared in patients with osteoporosis and in those whose bone mineral density (BMD) is normal.

Bone mass, without doubt, belongs to one of the genetically modulable parameters. Study [5] revealed increased risk for osteoporosis in children of subjects, whose BMD was below the normal range: for the son of male patient with low BMD it was 4 times and for the female patient's daughter – even 5 times higher than in general population. Now it is clearly proven, that low peak bone mass can be considered as a predictor of osteoporosis and osteoporotic fractures [6].

There is shown the specificity of the peak bone mass formation depending on gender [7]. Studies performed have confirmed unquestionable role of genetic factors, but environmental factors are also necessary to consider [8]. A wide range of diseases (such as malabsorption, renal dystrophy, rheumatoid arthritis, respiratory and immunological disorders, blood diseases, immobilization etc) can act as an impulse for the disturbances in peak bone mass formation and for the development of

osteoporosis. The high contribution of heredity in bone tissue characteristics manifests at the eighth decade of life [9] and varies depending on gender [10].

Susceptibility to bone fractures is also genetically predetermined [11]. For example, a study [12] revealed that hip fractures in parents doubles the risk of femoral neck fracture in their children, irrespective of BMD. The contribution of heredity in the wrist fracture varies from 23 to 54% and is also independent of BMD [13]. Family and hereditary nature of fractures irrespective of BMD suggests that genetic factors influence the risk of fracture in ways as distinct from those that control bone density.

One of hereditary risk factors for osteoporosis is the feature of the patients' constitution, inherited from their parents. Persons of low height and fragile physique are proved to be at increased risk of this disease [14]. Anatomical features of bone structure also are genetically predisposed. Some variants of the bone structure and configuration can be considered as risk factors for fractures (in particular, the length of the femoral neck and of the femoral bone itself) [15]. Reliable information about the features of bone mass and BMD inheritance can be obtained from studies of twins. This is a convenient genetic model, as 100% of the alleles in monozygotic twins are the same, and in dizygotic ones the part of identical alleles is 50%. The BMD differences are proved to be less in monozygotic twins than in dizygotic [16].

One of the main reasons for bone loss in women is estrogen deficiency at the period of menopause. Some studies also revealed genetic predetermination of the menopause age [17]. Determination of genetic predisposition to osteoporosis in accordance with BMD encouraged investigations with the purpose to identify candidate genes involved in the process of bone tissue formation. In this case the main problem in choosing candidate gene is the large number and variety of proteins involved in skeletal biology and bone formation, thus, all the genes, encoding these proteins, may be potential candidates. In this connection, the number of possible candidate genes is quite large and it is constantly growing due to introduction of new technologies of gene expression analysis. Polymorphic alleles of candidate genes can be considered genetic risk factors only if their rates in cohorts of patients are significantly higher than control levels.

Currently, huge amount of information about the genetic determination of bone mineral density have been accumulated. Assessment of the BMD heritability varies depending on the characteristics of the analyzed cohort and reaches quite a high values – from 45 to 80%, what is obvious evidence of genetic determination of osteoporosis. Over 100 candidate genes associated with BMD and with the risk of osteoporosis have already been identified [18]. The main ones that make the greatest contribution to the development of osteoporosis are analyzed in this review (Table).

**Table.** The polymorphisms of genes that have the greatest impact on the development of osteoporosis

Gene	Polymorphism	Reference SNP #	Favorable allele	Risk allele
VDR	BsmI	rs1544410	b	B
	ApaI	rs7975232	a	A
	TaqI	rs731236	T	t
	FokI	rs2228570	F	f
	Cdx2	rs11568820	G	A
ER	PvuII	2234693	T	C
	XbaI	rs9340799	A	G
	(TA) <sub>n</sub>		> 15	< 15
COL1A1	104 - 441G> T	rs1800012	G	T
LCT	c.-13910C> T	rs4988235	T	On

### Vitamin D receptor (*VDR*) gene

Currently, *VDR* gene is best studied one of the set of found candidate genes that determine the development of osteoporosis. Vitamin *D* as a part of endocrine system has pleiotropic effects on immune modulation, regulation of skeletal metabolism and cellular proliferation and differentiation. Prolonged deficiency of vitamin *D*3 in chil-

dren leads to rickets and in adults – to osteomalatia. *VDR* gene is a central endocrine system regulator and acts as a candidate gene determining the characteristics of the human's growth.

Vitamin D receptor gene has polymorphism at the 9th exon. The sequence of *VDR* gene was revealed to be polymorphic in different individuals. Five polymorphisms

of restriction fragments length (*Bsm I*, *Apa I*, *Taq I*, *Fok I*, and *Cdx2*) are known in this gene. *Bsm I* marker has the greatest informativeness.

*Bsm I* polymorphism contains restriction site marked as *b* allele. If such a site is absent, allele is designated as allele *B*. Up to 16% of Caucasians are homozygote for a functionally defective allele of this gene (*B/B*) and are at risk of osteoporosis and osteoporotic fractures.

It was demonstrated that in persons with *B/B* genotype the risk of vertebral fractures appeared 11 years earlier than in those with *b/b* genotype. Risk of femoral neck fractures in *B/B* group is four times higher than in people with normal genotype [19]. The study of twins of different ages revealed smaller BMD differences in pairs of monozygotic twins with a matching *VDR* genotype than in dizygotic ones [19]. The analysis of twins' groups demonstrated the highest BMD in subjects with *b/b* genotype. BMD value in *B/b* heterozygotes approximately corresponds to the average value observed in *b/b* and *B/B* groups, i. e. an effect of gene dose takes place. A comparative analysis of the results of 16 studies on the correlation between BMD and *Bsm I* polymorphism frequency revealed on the average 1.5–2.5% lower BMD *B/B* genotype compared with carriers of *b/b* genotype [20].

The association between vitamin *D* receptor gene polymorphisms and the occurrence of vertebral and non-vertebral fractures was investigated by P. Garnero et al. [21]. Overall 589 postmenopausal women over the age of 60 were examined in this study. Association between the increase in the *B* allele rate and the frequency of fractures was found. The relative risk of such fractures in women with *B/b* genotype was 1.5 times and in women with *B/B* genotype – 2.1 times higher in comparison with female carriers of the *b/b* genotype. There was no difference in demographic characteristics, constitution, individual and family history of fractures or calcium absorption level between women in the study groups. Bone mineral density level in the spine, femur, radius, as well as reduced bone tissue density in the radius, did not affect the association of genotype with the occurrence of fractures.

*Apa I* and *Taq I* polymorphisms (*A* and *a*, *T* and *t* alleles, respectively) are other common variants of the *VDR* gene. Multiple studies revealed higher values of bone mineral density in association with *Ttbaa*-genotype [22]. Low BMD level in carriers of the *A/A* genotype of *Apa I* polymorphism and *B/B* genotype of *Bsm I* polymorphism compared with owners of *a/a* and *b/b* genotypes

was observed in a study of prepubescent girls [23]. Investigation performed [24] revealed that the maximal BMD correlates with *Apa I*, *Bsm I* and *Taq I* polymorphisms. Another study [25] analyzing *Taq I* polymorphism of *VDR* gene revealed higher BMD in carriers of *T/T* genotype compared with the owners of other genotypes.

*Bsm I*, *Apa I* and *Taq I* polymorphisms are located in the 3'-regulatory region of the *VDR* gene, so they often are marked as one haplotype. The area 3'UTR of *VDR* gene is involved in the expression regulation, primarily through the regulation of mRNA stability *BAt* and *baT* variations are common and frequently analyzed haplotypes (Figure) [19].

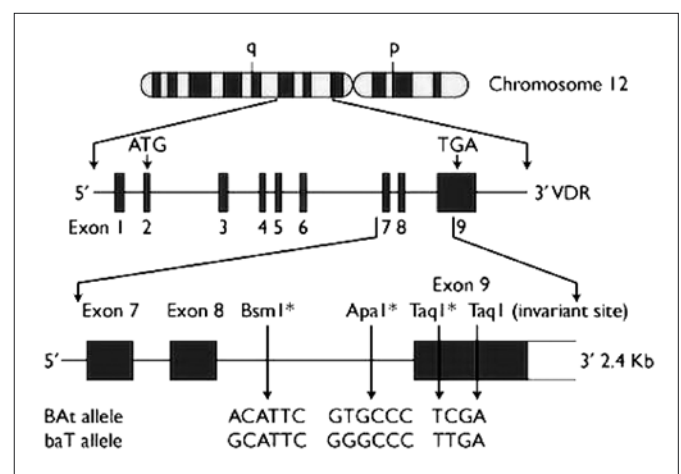


Figure. Localization of *Bsm I*, *Apa I* and *Taq I* polymorphisms of *VDR* gene

*Fok I* polymorphism. It was found that 12.8% increased rates of low BMD values were observed in women with *f/f* genotype of *Fok I* polymorphism in the *VDR* gene compared to those with *F/F* genotype. Comparative analysis of white premenopausal women with *F/F* and *f/f* genotypes also showed the increased rates of low BMD values (4.3% higher in the total body and 12.1% higher in the femoral neck) for carriers of *f/f* genotype than in owners of *F/F* genotype [26].

*Cdx2* polymorphism. A number of papers devoted to the study of polymorphism, resulting in *A* → *G* replacement at -3731 position from the site of the *VDR* gene transcription initiation appeared recently. Functional analysis of polymorphism site was performed on a model line of intestinal cells. It was shown that the presence of *Cdx2* polymorphism contributes to the activation of *VDR* gene transcription [27]. Results of this study allowed the authors to suggest an important role of *Cdx2* in the regulation of *VDR* gene.



Association between *Cdx2* polymorphism and BMD was investigated in 261 Japanese women [27]. It was shown that in case of low calcium intake BMD in the lumbar spine for patients with *A/A* genotype was significantly higher than in those with *G/G* genotype. At higher calcium intake BMD of the femoral neck in women with *A/A* genotype was lower in than those with the *G/G* and *G/A* genotypes [28]. Thus, women with *A/A* genotype had higher BMD in case of low calcium intake, whereas in case of its higher intake, the situation was completely the opposite. This fact is fully compatible with the Eisman's theory, postulating that the interaction of environmental factors (for example, food) and the BMD differs for each genotype, so that a low impact of the environmental factor gives the advantage for one genotype, and impact at a higher level – for other [29]. Performed studies demonstrated that the presence of *Cdx2* polymorphism 20% reduces the risk of vertebral fracture, regardless of subject's gender [30].

#### **Type I collagen (*COL1A1*) gene**

Type I collagen is the major bone tissue protein, it is forming organic matrix of the bone. The gene encoding this protein can be considered as a candidate gene in the pathogenesis of osteoporosis. Collagen consists of three intertwined protein strands: two strands of alpha 1 collagen and a single strand of alpha 2 collagen. *COL1A1* gene encodes a major component of type I collagen. Nine types of collagen molecules encoded by at least 17 genes are known currently. Fibrous collagen is the major component of cartilage and is also included in most types of connective tissue. Mutations in this gene are associated with the development of osteogenesis imperfecta, Ehlers-Danlos syndrome, and idiopathic osteoporosis.

In 1996, Grant et al. firstly described *G>T* polymorphism of the *COL1A1* gene in the site of binding with *SP1* transcription factor [31]. This polymorphism is located in the first intron of the gene and it is significantly associated with osteoporotic fractures. Association of this polymorphism with bone mineral density (BMD) decrease and with rising of osteoporotic fractures number was demonstrated in study of 299 British women. *G/T* and *T/T* genotypes were more common in patients with severe osteoporosis and vertebral fractures (54% of all cases), compared with the control group (27%). The relative risk of vertebral fracture in mutant *T* allele carriers was 2.97. These results were confirmed later by Uitter-

linden et al. on a group of 1778 postmenopausal women [32].

Studies performed with blood samples of Danish population in order to determine the relationship between the variants of *COL1A1* gene, bone density and biochemical markers of bone remodeling revealed *T/T* genotype to be an independent marker for predicting the risk of osteoporotic fractures in both genders. Consequently, its definition can be of great clinical value in identifying individuals having high risk for developing of osteoporosis, regardless of gender [33].

One more study [34] revealed increased risk of fractures (by 40%) in individuals with *T/T* genotype of *COL1A1* gene polymorphism in comparison to those with *G/G* genotype. Investigation of *G/T* polymorphism of *COL1A1* gene revealed disbalance of type 1 and 2 collagen proteins in carriers of *T* allele leading to a decrease in bone growth in length, to the reduction of bone mass and disturbance of its mineralization [35]. These studies demonstrate an association between *COL1A1* gene polymorphism and decreased BMD what may predispose to accidental fractures in postmenopausal women. Retrospective meta-analysis of the results of published data [36] revealed relation between the presence of *T* allele of *Sp1* polymorphism and decreased BMD at the lumbar spine, femoral neck and vertebral fractures.

#### **Estrogen receptor (*ER*) gene**

Estrogens play an important role in the regulation of bone homeostasis and in BMD maintenance. The age-related loss of estrogens leads to marked disruptions in the structure of both compact and spongy bone. Estrogens act as an irreversible link in the complex of factors impacting the ossification of bone growth areas in young women [37] and they also contribute to the preservation of bone mass in mature women [38]. The analysis of the relationship between BMD and estrogen receptor (*ER*) gene is not accidental as these receptors are presented on osteoblasts. Effects of estrogens on the skeletal structures are mediated through their binding to two types of receptors encoded by *ER-α* and *ER-β* genes. Both of these receptors are expressed in large quantity in the bone tissue [39].

*PvuII*, *XbaI* polymorphisms in the 1<sup>st</sup> intron and *TA-repetitions* in the promoter area of the *ER-α* gene were intensively investigated. Polymorphism of *TA-repetitions* is considered to have an effect on BMD by altering the

production and stability of mRNA, whereas functional role of *PvuII* and *XbaI* polymorphisms is not fully clarified [40]. The relationship between *PvuII* and *XbaI* polymorphisms of the *ER-α* gene and BMD was analyzed in 2230 Japanese subjects aged from 40 to 79 years [41]. A reliable correlation between these polymorphisms and femoral neck BMD was found in women over 60 years. Correlation between spine BMD and the genotype of the *XbaI* polymorphism was noted in another study [42].

Relationship of *ER* gene polymorphisms with spine BMD and fracture incidence was studied in 2042 elderly Dutch subjects by Vann Meurs et al. [43]. Statistically significant correlation between the frequency of *CG/CG* homozygotes, small number of *TA-repetitions* and low lumbar spine BMD in comparison with the homozygous carriers of the wild-type alleles was noted in women. Moreover, the incidence of fractures was higher in the carriers of *PvuII* and *XbaI* polymorphisms (RR was 2.2) in combination with the small number of *TA-repetitions* in the *ER-α* gene (RR was 2.0). Relationship between the frequency of osteoporotic fractures and newly-found polymorphism *rs1801132* of *ER-α* gene was revealed in the study of 6752 white women [44]. Further investigations are necessary to confirm the influence of *ER-α* and *ER-β* genes polymorphism on the risk of osteoporosis.

In general, influence of the *ER* gene on the development of osteoporosis, as well as for the *VDR* gene, is confirmed. The aim of ongoing studies is to determine molecular mechanisms of the contribution of this gene to the susceptibility of osteoporosis and the possibility of substitutional therapy.

### Lactase (*LCT*) gene

*LCT* gene encodes the amino acid sequence of the enzyme lactase. This enzyme is produced in the small intestine and takes part in the lactose hydrolysis. Lactase is usually present in children, but in adult people with certain genotype its production stops. Usage of dairy products in this case leads to intestinal disorders (such as flatulence, burp, abdominal spasms and diarrhea) due to lactose intolerance. From 10 to 18% of the general population in Germany, 20–25% in Austria and 20–40% in Switzerland suffer from this type of metabolic disorder. As a rule, exclusion of milk and other lactose-containing products from meals leads to the normalization of health condition during 2–3 weeks in the majority of people with lactase deficiency.

Intentional or non-intentional avoidance by adults of

using milk and dairy products which are an important source of calcium, can lead to the development of calcium deficiency. It is extremely unfavorable for postmenopausal women as calcium deficiency after menopause contributes to the development of osteoporosis.

Described symptoms are seen in people who have *-13910 T>C*, certain genetic variant of the *C/C* polymorphism in the lactase (*LCT*) gene. People with genetic predisposition to lactose intolerance are at higher risk of bone mass loss and of non-vertebral fractures. This relationship is apparently caused by the change in calcium metabolism due to its deficiency. Normal variant of *C* polymorphism is associated with decreased lactase synthesis in adulthood, and mutant *T* variant determines preservation of high lactase activity in this period of life. Thus, homozygous carriers of *C* variant lose the ability to digest lactose in adulthood (the level of lactase gene mRNA synthesis in these patients is reduced and varies from 2 to 22% of its initial activity), whereas homozygous owners of *T* variant assimilate lactose easily and tolerate dairy products well. The functional role of *-13910 T>C* polymorphism of *LCT* gene in this gene transcription regulation was evaluated in one more study [45]. By the result of this experiment, activity of this gene was reduced 2.2 times in case of *-13910C* variant.

Obermayer-Pietsch et al. [46] demonstrated that *-13910 T>C* polymorphism of *LCT* gene affects susceptibility to fractures in postmenopausal women indirectly, through reduction of alimentary calcium entry, due to decreased lactose tolerance. In this study presence or absence of this polymorphism was determined for 258 postmenopausal women. The object of investigation was the influence of this genotype on milk tolerance, calcium absorption in the intestine, bone tissue density and non-vertebral fractures rate. *C/C* genotype and hereditary lactose intolerance were found in 24% of the total number of study participants. A significant reduction ( $p = 0.04$ ) of bone tissue density in total hip for *C/C* genotype (7% decrease) and in spine in case of *C/C* and *T/C* genotypes (11% decrease) was revealed by statistical analysis. In addition, reliable association between fractures frequency and *C/C* genotype was found. In *C/C* genotype carriers calcium assimilation from milk was reduced 55% ( $p = 0.004$ ), and 16.6% ( $p = 0.01$ ) of these women experienced subjective disgust to milk. However, influence of this polymorphism on the total calcium assimilation from food, not only from milk, was not revealed.

Thus, the determination of *-13910 T>C* polymor-

phism of *LCT* gene is important evaluating individual risk of osteoporosis due to reduced lactose digestion in postmenopausal women.

### Conclusion

The analysis of published data indicates that the greatest contribution into the development of osteoporosis belongs to *VDR*, *COL1A1*, *ER* and *LCT* genes. Currently, doctors of various specialties, for their successful practice, must have complete knowledge about the influence of the polymorphisms in human genes on the development of pathological processes. Thus, such studies are important for more rational organization of diseases prevention and treatment at early, pre-symptomatic stages.

In case of identifying of described polymorphisms in a patient, a serious attention should be paid to diet, supplementation of calcium and vitamin D and usage of natural or artificial insolation in rational doses.

Identification of risk groups can enable to perform preventive measures in a timely manner and also to improve treatment effectiveness, avoid complications, reduce disability and mortality of these patients, as well as cut down the treatment costs.

Investigations carried by the project "Relationship of genetic, clinical and biochemical markers of bone remodeling in case of severe postmenopausal osteoporosis" were initiated in Laboratory of Human Genetics at the Institute of Genetics and Cytology of Belarusian National Academy of Science in conjunction with the City center for osteoporosis prevention (Minsk) and in collaboration with State Research Institute Centre for Innovative Medicine (Vilnius) and National Osteoporosis Center (Vilnius). The aim of this project is to analyze the frequency of homozygous and heterozygous carriers of *VDR*, *COL1A1*, *ER* and *LCT* genes polymorphisms and BMD results in patient with severe postmenopausal osteoporosis, compared with the control group of Belarusian and Lithuanian populations.

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## POLINKIO OSTEOPOROZEI MOLEKULINIAI IR GENETINIAI MECHANIZMAI

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### Santrauka

Osteoporozė – tai sisteminė griaučių liga, kuriai būdinga maža kaulų masė ir kaulinio audinio mikroarchitektūros pokyčiai, lemiantys padidėjusį kaulų trapumą ir lūžių riziką. Gyveni-

mo eigoje kaulinio audinio apykaitą nulemia kaulinio audinio rezorbcijos ir formacijos procesai, kuriuos įtakoja daugelis genų ir aplinkos veiksnių. Atsakingų už polinkį kaulų retėjimui genų nustatymas padeda identifikuoti asmenis su didele rizika sirgti osteoporozė ir sudaro prielaidas imtis veiksmingų profilaktikos, diagnostikos bei gydymo priemonių, sumažinančių segančiųjų šia liga negalią ir mirtingumą.

Šioje literatūros apžvalgoje yra nagrinėjami molekuliniai ir genetiniai veiksniai, įtakojantys polinkį sirgti osteoporozė, bei genų, nulemiančių kaulinio audinio metabolizmą, alelių polimorfizmo savitumai. Mokslinių publikacijų analizė rodo, kad osteoporozę labiausiai nulemia *VDR*, *COL1A1*, *ER* ir *LCT* genai.

### Raktažodžiai:

osteoporozė, polinkis, prevencija, kandidatiniai genai