

Olha Yakovleva<sup>1</sup> , Olha Nikolova<sup>2</sup> <sup>1</sup>National Pirogov Memorial Medical University, Vinnytsya, Ukraine<sup>2</sup>Communal nonprofit enterprise Vinnytsya regional clinical hospital named after N.I. Pirogov by the Vinnytsya Regional Council, Vinnytsya, Ukraine

## Controversial problems of Vitamin D receptor genetic polymorphism in patients with bronchial asthma

For citation: *Bol', sustavy, pozvonočnik.* 2020;10(4):174-180. doi: [10.22141/2224-1507.10.4.2020.220457](https://doi.org/10.22141/2224-1507.10.4.2020.220457)

**Abstract.** The review presents information on variants of Vitamin D receptor's genetic polymorphism, ensuring the direct physiological effects of the Vitamin via stimulation of nuclear cellular mechanisms. The article was aimed at raising awareness of the global scientific advances in the field of Vitamin D receptor's genetic polymorphism and its association with bronchopulmonary pathology in various regions of the planet. The search of scientific references was carried out in the Scopus, Web of Science, The Cochrane Library, Pubmed, ResearchGate, Russian Science Citation Index (RINC) information databases. The regulatory potential of the Vitamin D active hormonal effects in the bronchopulmonary pathology, especially in bronchial asthma (BA), remains unclear in terms of its pathogenetic links. Individual alleles inherent in the receptor genetics were studied, primarily in children with BA across the world. The results were compared as to levels of Vitamin D supplementation, BA symptoms and course. The divergences were found in the four variants of alleles: Fok1, Apal, BsmI, TaqI. Those divergences prevail in the individual ethnic populations, limiting our capacities of drawing unambiguous conclusions, although the relationship between the course of BA and the deficient Vitamin's status remains predominant. It is necessary to widen the database prospectively, to clarify the genetic variants of all the components involved in the metabolism and the Vitamin's effects (transporter proteins, cytochrome P450 and vitamin D receptor) while the research geography is also expanding in the world.

**Keywords:** vitamin D receptor review; genetic polymorphism of receptor; bronchial asthma in children; ethnic differences in polymorphism

### Introduction

The Vitamin D-mediated physiological regulation is an extremely topical issue as it is considered an active hormone with various properties, and the human body requires its optimal supply [1]. The interest towards evidence base on the Vitamin D deficiency and attending disorders' prevalence is ever rising [2].

Apart from an exogenous supplementation of Vitamin D, there are also endogenous pathways of its complex metabolism and transportation to the cellular membranes and nuclei via VDR, a specific Vitamin D receptor, ensuring "an extremely wide range of developmental disorders and diseases" notably among children, according to O. A. Gromova et al. [3]. Due to the nuclear gene stimulation, Vitamin D is regulating the connective and bone tissue, as well as immune system [3]. The VDR gene located on the short arm of chromosome 12 (12q12-q14) is up to 75 kb, contains 11 ex-

ons (among them 8 (2-9) encoding the gene's protein structure). According to the common nomenclature of alleles, the Vitamin D receptor gene's polymorphism is identified by Fok1 (Ff rs2228570), Apal (Aa rs7975232 GT), BsmI (Bb rs1544410 GA), TaqI (Tt rs731236 TC) isoforms [4].

Among numerous pathologies potentially attributed to the vitamin status disorders, the problem of bronchopulmonary conditions remains the most controversial and least researched. It is unconfirmed, for instance, which mechanisms (inflammatory, immune, metabolic, electrolytic) of Vitamin D deficiency may determine the inclination to, development, course and prognosis of both bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) [5]. It is substantiated that the Vitamin D status is associated with the COPD's influence on the skeletal muscle strength: its reduced rates is attributed to the reduced muscle adaptation to power load [6].

© 2020. The Authors. This is an open access article under the terms of the Creative Commons Attribution 4.0 International License, CC BY, which allows others to freely distribute the published article, with the obligatory reference to the authors of original works and original publication in this journal.

Для кореспонденції: Яковлева Ольга Олександрівна, доктор медичних наук, професор, завідувачка кафедри клінічної фармації та клінічної фармакології, Вінницький національний медичний університет ім. М.І. Пирогова, вул. Пирогова, 56, м. Вінниця, 21018, Україна; e-mail: [dr\\_yakovleva@meta.ua](mailto:dr_yakovleva@meta.ua); контактний телефон: +38 (097) 587 06 51.

For correspondence: O. Yakovleva, MD, PhD, Professor, Head of the Department of Clinical Pharmacy and Clinical Pharmacology, National Pirogov Memorial Medical University, Pirogov st., 56, Vinnytsya, 21018, Ukraine; e-mail: [dr\\_yakovleva@meta.ua](mailto:dr_yakovleva@meta.ua); phone: +38 (097) 587 06 51.

Full list of author information is available at the end of the article.

The problem of Vitamin D's supplementation is not thoroughly researched in connection with respiratory diseases, as their scope and pathogenetic links of the leading system (tracheobronchial tree)'s damage and directly-implicated respiratory system (blood–air barrier) may have completely different mechanisms of Vitamin D's regulatory functions [7].

Among the less obvious associations of Vitamin D and respiratory disorders of allergic genesis, there is a BA, namely its juvenile form. Furthermore, it is well-known that the BA prevalence among children has been on the rise during the recent five decades. Today it is one of the most common chronic conditions among adolescents under 18 years, afflicting about 6.3 million subjects across the world. This increase is attributed to a partial extent to the urbanization, microbe changes of the environment, augmented pollution associated with the allergic load of the external element. However, this list may be supplemented by the understanding of Vitamin D's hormonal effects, specification of genetic polymorphism both in terms of Vitamin D turnover and VDR polymorphism [8].

The **aim** of this review is analysis of the international studies into genetic polymorphism of Vitamin D receptor and its association with bronchopulmonary pathology in various regions of the world.

## Materials and methods

The search of academic sources is performed in the online information bases such as Scopus, Web of Science, The Cochrane Library, Pubmed, ResearchGate, Russian Science Citation Index, all of them featuring ethnic properties and genetic discrepancies of Vitamin D receptor of subjects with bronchopulmonary pathologies originating from various countries.

## Results and discussion

The bronchial asthma is one of the topical issues of international healthcare system. According to the statistical data, the BA prevalence is from 1 to 16 %. The large-scale epidemiological study was mediated by the WHO in 70 countries (out of 192); it shows that the diagnosed BA's prevalence among adults is 4.3 %, fluctuating from 0.2 % in China to 21 % in Australia. The BA diagnosed due to wheezing (asthma's marker) is twice as prevalent.

In Ukraine, the statistical data on BA prevalence amount to 0.5 %; this fact does not correspond to the international rates, which is why the BA prevalence figures may be significantly suppressed. The “physician-diagnosed BA” (judging by the respondents) in Ukraine is about 6 times as low (1.25 %) as other symptoms revealed by the screening questionnaire, namely wheezing (7.4 %) (by the CORE international epidemiological study's findings) [9].

However, diagnosing the BA only by the respiratory symptoms may overplay its global prevalence; first and foremost, it concerns the poor-resource countries with their limited access to the healthcare, restricted functional diagnostics and treatment. The recent guidelines stress the BA hypodiagnostics being an acute problem; however, its hyperdiagnostics may also be an issue. The “severe BA” diagnosis

remains unconfirmed in 12-50 % cases further on [9]. This situation reflects a lack of awareness of various clinical and scientific aspects of its course. Among the under-tackled aspects of BA pathogenesis, one should refer to a limited understanding of genetic mechanisms of Vitamin D status' interdependence with BA's development risks. It concerns primarily the role of individual variants of Vitamin D receptor.

It is inevitable that the complex VDR structure should be inclined to the genetic “wrecks”, changes in dome of its domains causing the diverse influences on the efficacy of Vitamin D's physiological regulation involved in various bodily functions.

The number of studies on VDR genetic polymorphism has been on the rise in the recent years, corroborating our published findings [8] in various planetary regions in terms of geographical features of VDR genetic variant prevalence associated with bone turnover, Calcium metabolism and muscle function. Very few studies are targeted at the VDR genetic polymorphisms associated with bronchopulmonary pathologies [8].

The following information clearly suggests that there are very diverse correlations of BA-related genetic alleles in specific countries and regions. For instance, the Chinese study held among children (43 boys and 27 girls aged 5-12 years, mean age being  $8.84 \pm 3.21$  the BA's duration being 1-3 years ( $1.84 \pm 0.57$  years on average)) describes the rs7975232 (Apal) and rs1544410 (BsmI) VDR gene's loci, selected as candidate loci. In 67 % BA-afflicted children there was a registered prevalence of rs1544410 (BsmI) [10].

The evaluation of VDR gene's polymorphism frequency in the BA-afflicted children was at the core of the Ukrainian study (Odessa, 2017). The mean age of children was  $7.6 \pm 1.3$  years (20 boys and 22 girls). The main group involved 22 subjects with BA and excessive body mass (EBM) or obesity, the reference group consisting of 20 subjects with BA and harmonious physical development. The control group was made of 20 healthy children with no somatic pathology. The main group's children had body mass index (BMI) at  $21.00 \pm 1.34$  kg/m<sup>2</sup>, the fat percentage reached  $31.09 \pm 2.64$  %; the reference group had BMI at  $21.10 \pm 1.04$  kg/m<sup>2</sup>, the fat percentage reached  $30.15 \pm 2.55$  %. In the control group, the BMI was  $16.80 \pm 0.22$  kg/m<sup>2</sup> ( $p < 0.05$  compared with the principal group values and reference group values), the fat percentage being  $14.5 \pm 0.5$  % ( $p < 0.05$  for both groups). Out of 42 examined children, the VDR gene mutation (rs1544410) by heterozygote inheritance type (T/T) was found in 64.3 % of those examined and 28.5 % of those sick. The C/T variant had a normal gene distribution (7.2 %). In the control group there were no mutations found, 10 % of healthy children having a heterozygote inheritance type (C/T). That is, 90 % of those examined had a normal gene distribution ( $p < 0.01$ ). The VDR mutation-afflicted children and heterozygote inheritance children had a significantly lower Vitamin D level in blood serum:  $12.10 \pm 0.67$  ng/ml and  $13.53 \pm 0.26$  ng/ml, respectively, than children with a normal gene distribution:  $32.17 \pm 1.05$  ng/ml ( $p < 0.01$ ). That is, the authors revealed an established statistical correlation between the present VDR gene polymorphism

and Vitamin D level. Furthermore, it was confirmed that ionized Calcium rate was higher in children afflicted with Vitamin D deficiency [11].

The study held in the Netherlands reveals association between Vitamin D and the extent of BA control in the examined children: 75 BA patients vs. 227 healthy children; their mean age being 9.1 and 10.3, respectively. The authors did not reveal any significant differences of 25(OH)D level in healthy children and BA-afflicted children. However, there was an association between the Vitamin D and BA status control; there might be an association between the Vitamin D sufficiency and VDR SNP (Single Nucleotide Polymorphism) FokI C allele potentially affecting the BA treatment outcome [12].

In 2017, there was a metaanalysis published on the children BA and VDR gene polymorphism - Apal (rs7975232), Bsm1 (rs1544410), Fok1 (rs2228570) and Taq1 (rs731236). Out of 4 revealed SNPs (Single Nucleotide Polymorphisms) of Apal polymorphism, it was this variant that played a certain role in the BA development in the Asian children. Unlike the above-mentioned variant, the Fok1 polymorphism may be associated with the BA developing in the Caucasian subjects. The Bsm1 polymorphism is insignificantly related with the increased BA risk in children while in case of the Taq1 polymorphism there was no association with BA development risk [13].

Several studies by the Japanese researchers (metaanalysis and randomized trials) discovered associations between the blood serum Vitamin D level and the BA aggravation symptoms in children. For instance, the analysis of 25(OH)D level in the BA-afflicted subjects aged 1 – 4 years, as well as in the healthy children confirmed a significant reduction of Vitamin D level in the BA patients compared to the controls. On the contrary, the group of examined subjects with an adequate Vitamin D level had an aggregate number of complications during the previous year which was significantly lower than the values of sick children with Vitamin D deficiency. It is clear that the likelihood of controlled BA was higher in the adequate Vitamin D level group, confirming the positive association between the Vitamin D level in the blood serum and the BA control [13].

However, there are several studies where the authors did not reveal any evidence on the Vitamin D deficiency and insufficiency promotes an aggravated BA course. 89 Japanese school children aged 6-15 years with the BA diagnosed by the GINA criteria and spirometry had been randomly prescribed Vitamin D (n = 54) or placebo (n = 35). 94 % patients were using inhaled corticosteroids or leukotriene receptor antagonists (LTRA). The initial mean Vitamin D level was 29 ng/ml in the BA patients. In order to evaluate the BA course, the researchers used: the asthma control tests (Childhood Asthma Control Test) and physical load, total and specific IgE, allergic history evaluation. The children with no anti-inflammatory treatment had a mean Vitamin D level of 23 ng/ml. The correlation of Vitamin D level and established values, inflammatory signs and allergic symptoms was not revealed [14].

This is why the World Allergy Organization (WAO) has recently reported no extant support of the hypothesis on the

Vitamin D supplementation reducing the risk of allergy-related conditions developing in children. Furthermore, the WAO does not recommend the Vitamin D supplementation for the pregnant and lactating women as well as for the healthy neonates used as an allergic prevention tool [15].

There are even more issues arising out of the VDR genetic variants correlated with the hormonal therapy. For instance, in Brazil the study involved 77 children aged 7-14 years who were divided into 3 groups: the BA patients using the inhaled corticosteroids (ICS) for over 1 year and those not using them; the no-BA children with no signs of allergy. The study findings prove that there are some discrepancies in the following receptor gene allele distribution: in the BA group - GG – 28.3 %, GA – 48.3 %, AA – 23.3 %, in the control group - GG – 29.4 %, GA – 70.6 %, AA – 0 %. That is, with the BA the AA allele variant's frequency is rising [16].

Another study held in Brazil compared the 25(OH)D supplementation with 3SNP frequency in the children's VDR gene among the BA-afflicted and healthy subjects. The 25(OH)D rate was measured by means of the radioimmunological assay, the clinical anamnesis being analyzed, Single Nucleotide Polymorphisms (SNPs) - FokI, ApaI and TaqI - studied by means of PCR-RFLP-analysis. 75 BA-afflicted children (mean age – 9.1 years) and 227 healthy subjects (mean age – 10.3 years) were examined. In the general group, the share of adequate Vitamin D supplementation made only 14.9 %, while of the insufficiencies - 44 % and deficiencies – 41.1 %. The rate of 25(OH)D supplementation was similar in the BA-afflicted and healthy subjects (p = 0.57). However, the share of Vitamin D supplementation in the BA-afflicted subjects in terms of stages 2,3 and 4 outlined by the Global Initiative for Asthma (GINA) differed to a substantial extent: on the background of the regular controlled therapy – 8.6 %, of the initial supplementation – 16.6 %, of the consistent insufficient control – 43.7 % (p = 0.046), i.e. the deficiencies aggravated the course. All the patients diagnosed with the 4<sup>th</sup> stage of the BA (16/16) were heterozygous in terms of C allele (SNP FokI VDR). The patients with the 2<sup>nd</sup> stage of the disease (30/33), the 3<sup>rd</sup> stage (16/24) and the patients of the control group (45/50) (p=0007), the frequency of C allele turned out to be lower; however, this parameter remained unconfirmed after the data analysis by means of the logistic regression. There were no significant differences in the ApaI and TaqI frequencies; however, there was a likely association found between the Vitamin D status and FokI C allele with a higher therapeutic urgency aimed at the BA control. The above-mentioned facts suggest the possible implication of this variant in the BA treatment response while the VDR variants may also play their role in the determination of 25(OH)D rate in the blood serum [12].

The study held in Pakistan demonstrated an association among polymorphisms in the VDR's intron 8 and exon 9 and the BA's course. 100 BA-afflicted subjects and 100 healthy subjects were examined by means of PCR-RFLP (study of the VDR's intron 8 and exon 9 polymorphisms). By means of the recombinant VDR luciferase gene-reporter, these polymorphisms get connected with the VDR's mRNA

stability. It is suggested that they may influence the immune system by regulating the level of VDR expression. The TaqI-evaluated genotypes are associated with the BA, and it is quite possible that the registered changes of the VDR's mRNA stability are caused by those polymorphisms and may be the reason of immune system's deregulation typical of the BA patients. The study findings demonstrate the statistically relevant differences of TaqI frequencies in the genotypes while comparing the values of the BA-afflicted subjects with respective values of the healthy subjects, which may play an important role in the BA pathogenesis [17].

The association between the gene polymorphism in the Vitamin D FokI-receptor allele and the BA course was researched in the Egyptian children. The structure of VDR's polymorphous variants of FokI gene was specified in 180 children afflicted by the allergic ( $n = 90$ ) and non-allergic generated ( $n = 90$ ) BA and compared with the healthy subjects' values. The rate of general IgE in the blood serum was measured by the enzyme-linked immuno sorbent assay (ELISA). The findings also revealed the FF genotype's frequency was much higher in the healthy subjects (in 90 examined subjects it amounted to 50 %) compared with the BA-afflicted ones ( $n=39$ , only 21.7 %,  $p=0.02$ ). The frequency of ff variant was much higher in the children who had no BA of the allergic genesis (among 27 children - up to 30 %) compared to the subjects afflicted by the BA of the non-allergic genesis (among 12 children – up to 13.4 %,  $p=0.041$ ). The general IgE was significantly different from the three VDR's polymorphous genotypes of FokI gene in the atopic BA-afflicted children ( $p=0.007$ ), while its highest mean rate was determined with ff genotype present [18].

The study held in Turkey involved 80 healthy children (control group) and 100 BA children aged from 5 to 18 years. The VDR genotypes (ApaI, TaqI and FokI) and VDR's mRNA were determined across all groups. The authors did not reveal significant differences of the Vitamin D level in the group of BA-afflicted and healthy children. However, there was an association found between the CC-genotype of TaqI polymorphism and CA-genotype of ApaI polymorphism and the BA risk. By comparing the uninuclear polymorphisms of allele frequencies present in the BA-afflicted and control group, the researchers did not observe any significant association<sup>4</sup> however, compared with the control group, the VDR's mRNA expression decreased in the group of BA-afflicted children with CC and CA ApaI genotypes, TaqI TT- and TC- isoforms ( $p < 0.05$ ). The obtained findings confirm the existing association among the TaqI and ApaI polymorphisms and the BA development [19].

In the recent years, several separate observations completed the understanding of VDR gene allele variability in various countries. For instance, there was the first study evaluating the VDR FokI polymorphism in the Iranian population, making it a biomarker which is used to locate the subjects with a high risk of pronounced clinical BA manifestations and its triggers: environmental factors, prenatal maternal influence, allergens, and respiratory infections, tobacco smoke, contaminating agents, premature birth and dietary factors. There were considerable differences observed in the FokI T > C (rs10735810) polymorphism when

the BA-afflicted subjects were compared with the control ( $p < 0.001$ ). This association was made without consideration of gender and age; however, the study revealed the extant association of BA and FokI SNPs (Single Nucleotide Polymorphisms) compared with the healthy controls, confirming the BA association with SNP FokI polymorphisms. The determination and presentation of this candidate gene may help developing the diagnostic and interventional strategies which are safe, efficient, necessary and customized for the BA-afflicted patients [20].

The detailed study of adolescents held in Cyprus involved 190 BA-afflicted subjects, 69 of them manifesting symptoms of frequent aggravations (general group), and 671 belonging to the control group. The BA-afflicted subjects were assayed for all three VDR genotypes (BsmI, TaqI, ApaI) and 25(OH)D rate in the blood serum. It is confirmed that the distribution of TaqI genotypes significantly fluctuates between the control and main group. The tt genotype was found in 21.3 % of patients compared with 12.9 % of control subjects. On the contrary, there were divergences of the controls and the BA patients in terms of asthmatic wheeze and the BA aggravations on the background of the BsmI and ApaI polymorphous sites. On stratification of the hypovitaminosis D, there was a strong association found between the tt genotype of TaqI polymorphism and the wheeze-attended BA in those subjects who had a normal Vitamin D rate ( $> 20$  ng/ml) though not in those subjects who had a low Vitamin D rate. Those findings reveal the fact that it was the TaqI VDR genotype variant which were associated with the BA. This polymorphism may promote the BA development even under the normal Vitamin D rate ( $> 20$  ng/ml) [21].

In order to understand the correlation of Vitamin D status with the bronchopulmonary and other pathologies, one needs considering the individual metabolic pathways of Vitamin D's active forms arising out of the enzyme range, namely Cytochrome P450 (CYP) and its isoforms. In the Toronto, Canada, pilot study, it was established that the low Vitamin D rate was associated with a grave BA course in children; furthermore, the young Black Americans residing in the big cities had a high hypovitaminosis D rate and the BA frequency. With the BA present and a low Vitamin D rate, there was but one association – with homozygous genotype of CYP2R1 cytochrome (rs10766197,  $p=0.044$ ), SNYP CYP24A1 (rs2248137) ( $p=0.006$ ). The cohort of the BA patients had several meaningful associations between the SNP receptor and the BA symptoms. The VDR SNP FokI (rs2228570) was associated with the higher frequencies of the nighttime BA onsets ( $p = 0.04$ ), lower base rates of spirometric parameters ( $p < 0.05$ ) or the majority of positive tests for the air-allergic skin samples ( $p = 0.003$ ) and increased IgE rates ( $p < 0.001$ ). In their review, the authors emphasize that the gene variants of both Vitamin D metabolism and its receptor are associated with the clinical numerical BA characteristics in the young Black Americans. The range of these associations may be enlarged, manifesting the necessity of a large-scale population genetic study on Vitamin D in this cohort [22].

Another detailed study evaluating the VDR as an element of 12q chromosome analyzed the response to the

VDR polymorphism's association with the BA and atopia in the Quebec founders' population, in Canada. The 28 loci were genotyped in 582 families. Among the examined candidates, the ApaI VDR polymorphism demonstrated an insufficient inheritance of C allele within the range of 4 : 5 ( $p = 0.01$ ). This association was more evident in the girls ( $p = 0.009$ ). There were also gender-specific associations between numerous VDR and IgE polymorphisms ( $p=0.006-0.01$ ). There was a demonstrated association of 4 out of 6 VDR variants with the BA ( $p = 0.02-0.04$ ) in the cohort study (517 of the BA-afflicted females and 519 healthy subjects). These findings also demonstrate the ability of the VDR variants to influence the BA and allergy susceptibility [23].

In Connecticut, the researchers paid attention to the issue of Vitamin D transportation. The potential Vitamin D-associated influences on the inflammatory diseases such as the BA are contradictory; they suggest the Vitamin D insufficiency being associated with the increased BA morbidity. The Vitamin D-binding protein (VDBP) is transporting its metabolites into the blood flow. The unicellular polymorphisms encoding the Vitamin D-binding protein (VDBP) in the GC genes may be attributed to the circulating rate of the Vitamin D metabolite in the healthy neonates and babies. The researchers checked their hypothesis that the single nucleotide polymorphisms encoding the D432E and T436K variants determine the further BA development in the healthy children. The obtained findings demonstrate that the GC genotype was open for the evaluation of 463 subjects; after the primary analysis of all data, their analysis was restricted to the predominantly Latin American population (72.1 %) in order to minimize the potentially convoluted consequences of ethnic background. The bronchial asthma was diagnosed in 87 children (26 %). The subjects with GC genotype encoding the ET/ET (Gc1s/Gc1s) variant had lower chances to develop the BA; which should be interpreted as a side effect, compared with the children having the DT/DT (Gc1f/ Gc1f) variant. The authors made their conclusion that for the Latin American population of New Haven, Connecticut, the ET/ET (Gc1s/Gc1s) genotype of the Vitamin D-binding protein (VDBP) may be the protection against the BA, compared with the wild type of the DT/DT (Gc1f/ Gc1f) genotype [24].

In the Kurdish population, they delved into the Vitamin D's molecular pathways involving the blood serum Vitamin D and the Vitamin D-binding protein (VDBP) as well as the genetic features of VDR and VDBP in the BA-afflicted patients. The serum rate of Vitamin D and the Vitamin D-binding protein (VDBP) was measured by means of immunoenzyme assay. The VDR rs1544410 and rs2228570 and VDBP rs7041 were evaluated by means of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The obtained findings suggest the significant decrease of Vitamin D rate in the blood serum of the BA-afflicted patients compared with the controls ( $16.26 \pm 6.76$  vs.  $23.05 \pm 10.57$  ng/ml,  $p = 0.001$ ). The researchers found the correlation between the Vitamin D rate and the results of patient evaluation (reduction of Vitamin D rate associated

with functional results and involving the reduced FEV1, FVC and their correlation, the extent of BA gravity, while the increased VDBP rate in the blood serum of the BA-afflicted patients is unrelated with these characteristics). The increased VDBP rate in the blood serum of the BA-afflicted patients (rather than of the controls,  $1044.6 \pm 310.82$  vs.  $545.95 \pm 121.73$  mcg/ml,  $p < 0.001$ ) promoted the risk of progressing BA in the VDR rs2228570 CC та VDBP rs7041 GG genotype subjects (the odds ratio (OR) = 3.56,  $p = 0.04$  and OR = 2.58,  $p = 0.01$ , respectively). These findings explain the influence of VDR and VDBP genetic variations on the added dynamics of Vitamin D and VDBP blood concentrations in terms of the BA risk in the Kurdish population [25].

In a similar manner, the VDR rs2228570 turned out the risk factor of the BA susceptibility for the Caucasian children (OR = 1.23, 95 % Confidence interval (CI) = 1.06-1.56,  $p = 0.01$ ) to the same extent as the allele (OR = 1.56, 95 % CI = 1.05–2.4,  $p = 0.03$ ) model in patients, testifying to the FokI polymorphism. However, the ApaI polymorphism is important for the BA-afflicted patients of the Asian continent. The BsmI polymorphism does not promote the BA development in the homozygous children in a significant manner (OR = 1.462, 95 % CI = 1.02-2.11,  $p = 0.04$ ). There is no confirmed association between the TaqI polymorphism and the BA risk in children [13].

To sum up, there are separate features presented of the VDR genetic polymorphism, as well as some enzymes of its metabolism or transporting protein. The studies were performed in various countries and on various ethnic populations. There is a frequent tendency of under-examination of the BA patients, namely of children with various ages, which reduces its informative value and persuasiveness. Those findings are very diverse, and the extant condition promotes further information accumulation for the reduction of controversy surrounding the issue.

## Conclusions

Most facts and studies corroborate the extant associative connection between the insufficient Vitamin D supplementation, BA course and pulmonary function disorder in children following the obstructive type. The results of VDR genetic polymorphism evaluation are significantly different across some ethnic groups, which is why it is impossible to outline the most adverse variant of polymorphism. The features of VDR genetic variants in various Ukrainian regions are unclear.

In the academic perspective, one requires the prolonged extra studies for the final determination of the genetic mechanisms behind the Vitamin D insufficiency; its receptor provoking or aggravating the course and symptoms of the BA-afflicted children.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

**Individual contributions:**

Yakovleva O.O. — concept of study, data analysis, design of the text.

Nikolova O.M. — collection and processing of data.

**References**

1. Povoroznyuk VV, Balatska NI. Deficiency of vitamin D among Ukrainian population: risk-factors of development. *Reproductive endocrinology*. 2013;(13):7-13. <https://doi.org/10.18370/2309-4117.2013.13.7-13>. (in Ukrainian).
2. Yakovleva OA, Konovalova NV, Engel A. Vitamins from the standpoint of evidence-based medicine. *Medix Antiaging*. 2008;(4):31-36. (in Ukrainian).
3. Gromova OA, Torshin IY, Spirichev VB. The genome-wide analysis of the vitamin D receptor binding sites evidences a wide range of potential therapeutic applications of vitamin D. *Meditsinskiy sovet*. 2016;(1):12-21. <https://doi.org/10.21518/2079-701X-2016-1-12-21>. (in Russian).
4. Bhanushali AA, Lajpal N, Kulkarni SS, Chavan SS, Bagadi SS, Das BR. Frequency of fokI and taqI polymorphism of vitamin D receptor gene in Indian population and its association with 25-hydroxyvitamin D levels. *Indian J Hum Genet*. 2009 Sep;15(3):108-113. <https://doi.org/10.4103/0971-6866.60186>.
5. Hopkinson NS, Li KW, Kehoe A, et al. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. *Am J Clin Nutr*. 2008 Feb;87(2):385-390. <https://doi.org/10.1093/ajcn/87.2.385>.
6. Jackson AS, Shrikrishna D, Kelly JL, et al. Vitamin D and skeletal muscle strength and endurance in COPD. *Eur Respir J*. 2013 Feb;41(2):309-316. <https://doi.org/10.1183/09031936.00043112>.
7. Pfeffer PE, Hawrylowicz CM. Vitamin D and lung disease. *Thorax*. 2012 Nov;67(11):1018-1020. <https://doi.org/10.1136/thoraxjnl-2012-202139>.
8. Yakovleva OA, Nikolova OM, Doroshkevych IA, Shcherbeniuk NV. Genetic polymorphism of vitamin D receptor determines its metabolism and efficiency. *Bol', sustavy, pozvanočnik*. 2017;7(2):73-78. <https://doi.org/10.22141/2224-1507.7.2.2017.108699>. (in Ukrainian).
9. Feshhenko YI. New approach to the improvement of bronchial asthma treatment in world practice. *Asthma and allergy*. 2019;(4):56-57. (in Ukrainian).
10. Hou C, Zhu X, Chang X. Correlation of vitamin D receptor with bronchial asthma in children. *Exp Ther Med*. 2018 Mar;15(3):2773-2776. <https://doi.org/10.3892/etm.2018.5739>.
11. Velichko VI, Pichuhina YuA, Bazhora YaI. The correlation between the VDR gene polymorphism and the level of vitamin D in children with bronchial asthma on the background of overweight or obesity. *Zdorov'a suspil'stva*. 2017;6(4):109-112. <https://doi.org/10.22141/2306-2436.6.4.2017.123505>. (in Ukrainian).
12. Einisman H, Reyes ML, Angulo J, Cerda J, López-Lastra M, Castro-Rodriguez JA. Vitamin D levels and vitamin D receptor gene polymorphisms in asthmatic children: a case-control study. *Pediatr Allergy Immunol*. 2015 Sep;26(6):545-550. <https://doi.org/10.1111/pai.12409>.
13. Zhao DD, Yu DD, Ren QQ, Dong B, Zhao F, Sun YH. Association of vitamin D receptor gene polymorphisms with susceptibility to childhood asthma: A meta-analysis. *Pediatr Pulmonol*. 2017 Apr;52(4):423-429. <https://doi.org/10.1002/ppul.23548>.
14. Tachimoto H, Mezawa H, Segawa T, Akiyama N, Ida H, Urashima M. Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebo-controlled trial. *Allergy*. 2016 Jul;71(7):1001-1009. <https://doi.org/10.1111/all.12856>.
15. Yepes-Nuñez JJ, Fiocchi A, Pawankar R, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Vitamin D. *World Allergy Organ J*. 2016 May 17;9:17. <https://doi.org/10.1186/s40413-016-0108-1>.
16. Santos HLBS, Silva SSE, Paula E, Pereira-Ferrari L, Mikami L, Riedi CA, Chong-Neto HJ, Rosário NA. Vitamin D receptor gene mutations and vitamin D serum levels in asthmatic children. *Rev Paul Pediatr*. 2018 Jul-Sep;36(3):269-274. <https://doi.org/10.1590/1984-0462/2018;36;3;00016>.
17. Arababadi MK, Abousaidi H, Hassanshahi G, et al. Polymorphisms within Exon 9, but not Intron 8, of the vitamin D receptor gene are associated with asthma. *IJBMS*. 2011;14(3):225-230. <https://dx.doi.org/10.22038/ijbms.2011.4995>.
18. Nabih ES, Kamel TB. Association between vitamin D receptor gene FokI polymorphism and atopic childhood bronchial asthma. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2014;63(3):547-552. <https://doi.org/10.1016/j.ejcdt.2014.02.012>.
19. Kilic M, Ecin S, Taskin E, Sen A, Kara M. The Vitamin D Receptor Gene Polymorphisms in Asthmatic Children: A Case-Control Study. *Pediatr Allergy Immunol Pulmonol*. 2019 Jun 1;32(2):63-69. <https://doi.org/10.1089/ped.2018.0948>.
20. Bijanzadeh M, Sharifbakhsh S, Keshavarzi F, Mohammadi-Asl J. Vitamin D receptor gene polymorphism and asthma in Southern Iran. *Current Respiratory Medicine Reviews*. 2018;14(3):156-160. <https://doi.org/10.2174/1573398X15666181224102151>.
21. Papadopoulou A, Priftis KN. Vitamin D and Vitamin D Receptor in Asthma and Allergy. *Mini Rev Med Chem*. 2015;15(11):880. <https://doi.org/10.2174/138955751511150702124617>.
22. Pillai DK, Iqbal SF, Benton AS, et al. Associations between genetic variants in vitamin D metabolism and asthma characteristics in young African Americans: a pilot study. *J Invest Med*. 2011 Aug;59(6):938-946. <https://doi.org/10.2310/jim.0b013e318220df41>.
23. Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med*. 2004 Nov 15;170(10):1057-1065. <https://doi.org/10.1164/rccm.200404-447oc>.
24. Navas-Nazario A, Li FY, Shabanova V, et al. Effect of vitamin D-binding protein genotype on the development of asthma in children. *Ann Allergy Asthma Immunol*. 2014 Jun;112(6):519-524. <https://doi.org/10.1016/j.anai.2014.03.017>.
25. Nasiri-Kalmarzi R, Abdi M, Hosseini J, Tavana S, Morkarizadeh A, Rahbari R. Association of vitamin D genetic pathway with asthma susceptibility in the Kurdish population. *J Clin Lab Anal*. 2020 Jan;34(1):e23039. <https://doi.org/10.1002/jcla.23039>.

Received 14.08.2020

Revised 01.09.2020

Accepted 05.10.2020 ■

**Information about authors**

O. Yakovleva, MD, PhD, Professor, Head of the Department of Clinical Pharmacy and Clinical Pharmacology, National Pirogov Memorial Medical University, Vinnytsia, Ukraine; e-mail: dr\_yakovleva@meta.ua; phone: +38 (097) 587 06 51; <http://orcid.org/0000-0001-8171-7414>.

O. Nikolova, PhD student of third year study, Department of Clinical Pharmacy and Clinical Pharmacology, National Pirogov Memorial Medical University, Vinnytsia, Ukraine; physician, doctor of admission department, Communal nonprofit enterprise Vinnytsya regional clinical hospital named after. N.I. Pirogov Vinnytsya Regional Council. e-mail: Dr.Nikolova@ukr.net; phone number: +38 (097) 996 39 08; <http://orcid.org/0000-0003-2146-5109>.

**Яковлева О.О.<sup>1</sup>, Ніколова О.М.<sup>2</sup>**

<sup>1</sup>*Вінницький національний медичний університет імені М.І. Пирогова, м. Вінниця, Україна*

<sup>2</sup>*Комунальне некомерційне підприємство «Вінницька обласна клінічна лікарня імені М.І. Пирогова Вінницької обласної ради», м. Вінниця, Україна*

## Дискусійні проблеми генетичного поліморфізму рецептора вітаміну D при бронхіальній астмі

**Резюме.** В огляді подано інформацію щодо варіантів генетичного поліморфізму рецептора вітаміну D, який забезпечує безпосередньо фізіологічні впливи вітаміну через стимуляцію ядерних клітинних механізмів. Метою статті було ознайомлення з науковими досягненнями в світі щодо генетичного поліморфізму рецептора вітаміну D і його асоціацій із бронхолегеневою патологією в різних регіонах планети. Пошук наукової літератури здійснено в інформаційних базах даних Scopus, Web of Science, The Cochrane Library, PubMed, ResearchGate, РИНЦ. Регуляторні можливості активного гормонального впливу вітаміну D у бронхолегеневій патології, особливо при бронхіальній астмі, залишаються нез'ясованими патогенетичними ланками. У різних країнах світу досліджено окремі алелі, притаманні генетиці рецепто-

ра, переважно при бронхіальній астмі (БА) у дітей. Результати зіставляли з рівнями забезпеченості вітаміном D, симптомами та перебігом БА. Вони відрізняються за чотирма варіантами алелей: FokI, ApaI, BsmI, TaqI. Різноманітність даних у окремих етнічних популяціях переважає, що не дозволяє отримати однозначні висновки, хоча зв'язок перебігу БА з дефіцитними станами вітаміну D домінує. Необхідне перспективне збільшення бази даних, уточнення генетичних варіантів метаболізму вітаміну D та його рецептора, білків-транспортів, CYP450, з проведенням популяційних досліджень.

**Ключові слова:** рецептор вітаміну D; генетичний поліморфізм рецептора; бронхіальна астма, діти, етнічні відмінності поліморфізму; огляд

**Яковлева О.А.<sup>1</sup>, Ніколова О.М.<sup>2</sup>**

<sup>1</sup>*Вінницький національний медичний університет імені Н.І. Пирогова, г. Вінниця, Україна*

<sup>2</sup>*Коммунальное некоммерческое предприятие «Винницкая областная клиническая больница имени Н.И. Пирогова Винницкого областного совета», г. Винниця, Украина*

## Дискуссионные проблемы генетического полиморфизма рецептора витамина D при бронхиальной астме

**Резюме.** В обзоре представлена информация о вариантах генетического полиморфизма рецептора витамина D, который обеспечивает непосредственные физиологические эффекты через рецепторы, локализованные в клеточном ядре. Целью статьи было ознакомление с научными достижениями в мире по поводу генетического полиморфизма рецептора витамина D и ассоциаций его полиморфизмов с бронхолегочной патологией в различных регионах планеты. Поиск научной литературы осуществлен в информационных базах данных Scopus, Web of Science, The Cochrane Library, PubMed, ResearchGate, РИНЦ. Регуляторные возможности активного гормонального влияния витамина D при бронхолегочной патологии, особенно при бронхиальной астме (БА), остаются среди неизученных патогенетических звеньев. В разных странах мира исследованы отдельные аллели, присущие ге-

нетике рецептора, преимущественно при БА у детей. Результаты сопоставлялись с уровнями обеспеченности витамином D, симптомами и течением БА. Они отличаются по четырем вариантам аллелей: FokI, ApaI, BsmI, TaqI. Разнообразие данных в отдельных этнических популяциях преобладает, что не позволяет получить однозначные выводы, хотя связь течения БА с дефицитным статусом витамина доминирует. Необходимо перспективное увеличение базы данных, уточнение генетических вариантов всех задействованных в метаболизме и эффектах витамина составляющих (белков-транспортёров, цитохрома P450 и рецептора витамина D), с расширением географии исследований в мире.

**Ключевые слова:** рецептор витамина D; генетический полиморфизм рецептора; бронхиальная астма, у детей; этнические различия полиморфизма; обзор