BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Advances in Medicine Science
https://ojs.bilpublishing.com/index.php/jams

Advances in Single Nucleotide Polymorphisms of Vitamin D Metabolic Pathway Genes and Respiratory Diseases

Zhilu Li[1] Honghai Li[1] Saijia Li[1] Yingjing Du[1] Bingxin Xu[1] Yuxuan Wang[2] Yiyu Cai[3]

1. First Clinical College of Hainan Medical University, Haikou, Hainan, 570100, China
2. School of Public Health, Hainan Medical University, Haikou, Hainan, 570100, China
3. School of Tropical Medicine and Laboratory, Hainan Medical University, Haikou, Hainan, 570100, China

ARTICLE INFO

Article history
Received: 24 June 2020
Revised: 1 July 2020
Accepted: 24 July 2020
Published Online: 31 July 2020

Keywords:
Vitamin D metabolic pathway genes
Single nucleotide polymorphisms
Respiratory diseases

ABSTRACT

Vitamin D is a fat-soluble vitamin. It is an essential vitamin for human body. It has a classical effect on regulating calcium and phosphorus metabolism. Participate in cellular and humoral immune processes by regulating the growth, differentiation and metabolism of immune cells. A large number of studies in recent years have shown that vitamin D deficiency increases the incidence of respiratory diseases. Respiratory diseases mainly include bronchial asthma, chronic obstructive pulmonary disease, tuberculosis, acute upper respiratory tract infection and pneumonia. Vitamin D metabolic pathway genes play a very important regulatory role in the transformation of vitamin D into active vitamin D, including *CYP2R1, CYP27B1, CYP24A1, VDBP, VDR* five genes. Genetic polymorphism of genes is the molecular basis of individual differences and disease development. Therefore, this paper summarizes the research on single nucleotide polymorphism of vitamin D metabolic pathway gene and respiratory diseases. In order to provide a new idea for future treatment.

1. Overview

1.1 Sources D Vitamins and Physiological Effects

Vitamin D (VD) is a necessary fat-soluble vitamin, mainly derived from the skin, a small amount from food[1]. In addition to the classical function of regulating calcium and phosphorus metabolism, the role of cell proliferation, anti-infection, and immun-modulation has attracted more and more attention[2].

1.2 VD Genes of Existing Forms and Metabolic Pathways

Various forms of VD are present in the body, including 25-hydroxyvitamin D (25-(OH) D),1,25-dihydroxyvitaminD (1,25-$(OH)_2$D)[3]VD first forms 25-(OH)D in the liver under the hydroxylation of 25- hydroxylase encoded by CYP2R1 gene, and 25-(OH)D is considered to be Biomarkers that can best represent the overall level of VD in human body[4].Then in the kidney through the *CYP27B1* gene encoding 1-αhydroxylase hydroxylated to form 1,25-$(OH)_2$D[5].1,25-$(OH)_2$D is the active form of VD, forming 1,24,25-$(OH)_2$D under the action of 24 hydroxylase encoded by the *CYP24A1* gene)$_3$,24 Hydroxylase can also add 25(OH) D and 1,25-$(OH)_2$D degradation, negative feedback regulation[6]Vitamin D binding protein (VitaminD Binding Protein,*VDBP*), edited by

Fund Project:
National College Student Innovation and Entrepreneurship Training Project (Project No.: 202011810001).

 DOI: https://doi.org/10.30564/jams.v3i3.2322

VDBP genes, binds to vitamin D and promotes vitamin D transport in the liver and kidney. Vitamin D receptor (VitaminD Receptor,*VDR*) edited by *VDR* gene, with 1,25-$(OH)_2$D combination promotes its biological effect. Vitamin D metabolic pathway gene refers to VD conversion to 1,25-$(OH)_2$DThe genes that play a regulatory role in the D process mainly include *CYP2R1*、*CYP27B1*、*CYP24A1*、*VDBP*、*VDR* five genes. The abnormal expression of VD metabolic pathway genes may affect the level of serum VD and thus affect the exertion of biological efficacy[7].

1.3 Single Nucleotide Polymorphisms

Genetic variation is the molecular basis of individual differences and disease development[8].Single nucleotide polymorphisms (SNPs), as the third generation genetic markers, are the most common genetic variants, which are dynamic and relatively stable in diagnosing the relationship between genes and diseases[9].

1.4 VD Effects on Respiratory Health

Respiratory diseases include bronchial asthma, chronic obstructive pulmonary disease, tuberculosis, acute upper respiratory tract infection and pneumonia[10]A study by Song Hang has shown that VD can reduce wheezing diseases in children[11];Huang Tao studies have shown that VD may affect the prognosis of pulmonary tuberculosis[12];Wang Qingqing and other studies have shown that vitamin D supplementation can improve lung function and quality of life of male COPD patients with severe smoking with vitamin D deficiency and reduce the number of acute exacerbation[13]VD can improve respiratory diseases to some extent and ensure respiratory health.

2. Genetic Polymorphism Related to Vitamin D Metabolic Pathway Associated with Respiratory Diseases

2.1 Genetic Polymorphisms Related to Vitamin D Metabolic Pathway and Bronchial Asthma

Bronchial asthma is a chronic respiratory heterogeneity disease controlled by environmental and genetic factors, which is mainly characterized by dyspnea, bronchospasm, airway remodeling and so on. Bu FX and other studies in the Caucasian population found that *CYP2R1* gene rs12794714 locus was associated with serum 25-(OH) D rise, but no association was found with bronchial asthma susceptibility[14]Li Fei and others conducted similar studies in the Han population of northern China and found no correlation with bronchial asthma[15]The possible reason for this speculation is that rs12794714 site (C>T) has undergone synonymous mutations but has not altered its encoded amino acid sequence and has not undergone structural and functional changes. Zhou Xiaoting and others also carried out the same type of research, but obtained the opposite results, the results showed that *CYP2R1* gene polymorphism and bronchial asthma have a certain correlation, vitamin D metabolic dysfunction may affect the occurrence of bronchial asthma[16]Zhang Y et al. study showed that rs4646536 in the *CYP27B1* gene was significantly associated with the development of bronchial asthma in Han children, and that expression of this locus was positively associated with increased risk of bronchial asthma[17]Studies by Oussama L et al on the same type of population in Tunisian adult bronchial asthma show that the rs10877012 genotype of this gene is higher than that of male bronchial asthma population TT and the expression of this locus plays an important role in the development of bronchial asthma[18]Studies such as Yu Mei have shown that rs10877012 in *CYP27B1* genes may not be significantly associated with bronchial asthma in children due to G/T mutations[19]From the above studies, we can see that the expression of different loci of *CYP27B1* gene plays a different role in bronchial asthma.Two common SNP sites in the *VDBP* (*GC*) gene rs4588、rs7041 located in exon XI. Studies have shown that the *GC1* and *GC2* genes encoded by these genes are associated with susceptibility to bronchial asthma, among which *GC1* genes may be protective factors for bronchial asthma[20]Zella LA et al. found that *GC* knockdown could reduce the 25-(OH) D content in human serum[21]At the same time, studies have found a positive correlation between lung function and serum 25-(OH) D levels in patients with bronchial asthma[22]Moria et al. showed that there was no statistical difference in the expression of rs1544410 in *VDR* genes in children in Hunan Province between the bronchial asthma population and the normal population, but the genotype expression analysis of rs7975232 showed that this locus played an important role in the occurrence and development of the bronchial asthma population, but its mechanism needs to be studied[23]Rasoul N K and other studies of the Kurdish population in different countries showed no significant association between *VDR* gene rs1544410 and bronchial asthma, but a case-control meta-analysis by Tizaoui et al found a significant association between homozygous wild-type rs1544410 and bronchial asthma. According to the above studies *VDR* the degree of homozygosity of individual gene loci also affects the development of bronchial asthma in human body[24-25]. To sum up, the single nucleotide polymorphism of vitamin D metabolic pathway gene is associated with the development of

DOI: https://doi.org/10.30564/jams.v3i3.2322

bronchial asthma.

2.2 Genetic Polymorphisms Associated with Vitamin D Metabolic Pathways and Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a common chronic disease characterized by airflow obstruction. Chronic obstructive pulmonary disease, like asthma, may have been associated with vitamin D at an early stage[26]. Studies have shown that chronic obstructive pulmonary disease can be improved by *VD* supplementation[27-29]David AJ et al. conducted a blood sample survey in the London COPD population in the UK and found that *CYP2R1* genes were not associated with COPD and that genetic variation in vitamin D pathways was not associated with vitamin D status or COPD severity[30]. Mathyssen C et al. detected the expression and localization of key enzymes and vitamin D channel receptors in lung tissue of COPD explants. *CYP27B1* was not expressed in vascular endothelial cells, but in bronchial epithelium. *CYP27B1* expression is high in lung endothelial cells, suggesting that vitamin D may be inactivated before reaching epithelial cells and tissue immune cells[31]The polymorphism of *VDBP* gene and the related report of COPD were not found by consulting a lot of literature.1,25-$(OH)_2$Studies such as D regulate gene expression by binding to vitamin D receptors (*VDR*) suggest that VD deficiency is associated with COPD susceptibility[32]The level of serum 25(OH) D in COPD patients was significantly lower than that in the control group[33]These studies suggest that vitamin D deficiency may be associated with the occurrence and development of COPD.

2.3 Genetic Polymorphisms Related to Vitamin D Metabolic Pathway and Tuberculosis

Tuberculosis is one of the most common chronic respiratory diseases in tuberculosis. In recent years, due to the abuse of antibiotics, the drug resistance of Mycobacterium tuberculosis has increased, the prevalence of tuberculosis has increased, and the cure rate of the disease has not increased. The main manifestations are weak body, night sweat, breathing and so on. To explore the occurrence and development of tuberculosis from the genetic aspect has become a research hotspot in recent years. Junaid K studies on Pakistan positive pulmonary tuberculosis showed that the absence of vitamin D increased the prevalence of pulmonary tuberculosis, but there was no significant difference in the genotype distribution of the *CYP2R1* gene in the metabolic pathway between the case group and the control group, and there was no significant correlation with the susceptibility of the population to pulmonary tuberculosis[34]Asadollah M and other studies on the population of tuberculosis in Iran show that there is no significant correlation between the genotype distribution of rs7975232、rs1544410 locus in the *VDR* gene and the risk of tuberculosis, but the polymorphism of its rs7975232、rs1544410 may have some protective significance for tuberculosis in the European population[35] ShihWei L and other studies on the rs7041 and susceptibility to tuberculosis in the *VDBP* genes of the Han population in Taiwan indicate a certain correlation between Gc1F carriers and tuberculosis[36]Wang Xi and other research centers on tuberculosis susceptibility genes in Xinjiang Kazakh population show that most of the T alleles in *VDR* genes are common genes in tuberculosis patients and most of the t alleles are protective genes to protect the population from Mycobacterium tuberculosis[37]The rs731236 study of TB patients in Iran and Yunnan showed that the frequency of "tt" genotypes" in TB patients was low, and that the polymorphism of vitamin D related gene loci might be associated with resistance to TB[35,38].

2.4 Genetic Polymorphisms Related to Vitamin D Metabolic Pathway and Acute Upper Respiratory Infection and Pneumonia

The upper sense is the general term of acute upper respiratory tract (nasal cavity, pharynx or larynx) infection. The immune function is easy to infect the upper sense, but the general prognosis is good. Unlike the upper sense, pneumonia mainly occurs in the lungs, in addition to causing fever, cough and other cold symptoms, severe cases will also appear dyspnea. The David A and others confirmatory experiments in children in Manchester, England, found that the rs10500804、rs2060793、rs10766197 of the three polymorphic loci of the *CYP2R1* gene had no significant correlation with the upper sense, but the frequency of the locus rs12060793 the median gene was increased to a certain extent compared with that of the normal population, suggesting that it may be related to the upper sense, but further research is needed to prove it[39]Tian Huiqin and others analyzed the unrelated Han population in Jiangsu and Anhui regions and found no statistically significant difference in the SNP locus of *CYP27B1* gene rs10877012 susceptibility to nasal infection[40]There was no significant correlation between the SNP locus rs464537 rs4646536 and acute upper respiratory tract infection[41]The SNP locus rs1260 of *CYP27B1* genes is also associated with peripheral blood concentrations, which may influence the development of

 DOI: https://doi.org/10.30564/jams.v3i3.2322

nasal inflammation[42]. Through retrieval, There are no reports α- hydroxylase or its corresponding *CYP27B1* gene polymorphism and pneumonia. Validation experiments in children such as David A in Manchester, England, six SNP sites in the *GC* rs7041,rs4588, rs12512631, rs2070741, rs2298849,rs16846876 Correlation analysis of with acute upper respiratory tract infection[43]. It was found that there was no significant correlation between the above 6 sites and the upper sense, The P rs7041 the site was 0.06, There may be no statistical difference between the two due to insufficient sample size. Jolliffe DA and other studies of American children show that, *VDR*, of 8 SNP sites rs9409929 rs10783219, rs4516035, rs2238136, rs1544410, rs2228570, rs2853559, rs7975232 had no significant correlation with upper sense, The other three *VDR* sites rs4334089, rs11568820, rs7970314 analysis revealed statistical differences, It shows that it has a certain correlation with the upper sense[39]Ren Jing et al. showed that *VDR* gene Fok I loci were associated with RSV susceptibility to pneumonia, and the Taq I loci were less correlated with susceptibility to pneumonia due to synonymous mutations[44]. These studies suggest that single nucleotide polymorphisms in genes associated with vitamin D metabolic pathways may regulate the progression of upper sense and pneumonia.

3. Summary and Prospect

The influence of genetic factors on disease is a hot topic. As the third generation genetic marker, single nucleotide polymorphism can more accurately explore the relationship between genes and diseases. Therefore, this paper summarizes the correlation between single nucleotide polymorphism of vitamin D metabolic pathway gene and respiratory diseases. So far, there have been more studies on this area, but the results are not consistent. The differences in the population and the size of the sample size may affect the results. The prevalence of these problems requires the use of larger samples and the summary analysis of multiple research results in future studies. At the same time, the analysis of single nucleotide polymorphisms of single genes should also consider the comprehensive analysis of multiple gene polymorphisms of different chromosomes. The ultimate goal of this improvement is to explore the relationship between vitamin D metabolic pathway related genes and respiratory diseases more comprehensively. To explore a new diagnosis and treatment plan for clinical treatment.

References

[1] Xie Zhongjian, Cheng Qun, Ding Yue. J]. D Vitamin Metabolism and Effects Chinese Journal of Osteoporosis and Bone Mineral Salt Disease, 2018 (01):26-33.

[2] C hen Xue ,C hen Meng .Vitamin D and childhood asthma [J]. Journal of Nanjing Medical University (Natural Sciences), 2020(03):454-460.

[3] Zeng Qin, Yuan Jingjing, Xie Zhongjian. Research Status of Vitamin D and Thyroid Cancer [J]. Chinese Journal of Endocrine Metabolism,2017(06):525-528.

[4] Wu Lily, Liu Chunli. Vitamin D [J]. Respiratory Infections Chinese Medicine, 2018(02):159-163.

[5] ChenSai-Ming, ZhouXiao-Liu, LIZhi-Lu, et al. Association between the genetic variation of vitamin D binding protein gene and chronic sinusitis of elder in Hainan province[J]. Chinese Journal of Gerontology, 2019(11):2694-2697.

[6] Yu Song Cheng. Relationship between gene polymorphism, copy number and methylation variation of vitamin D metabolic pathway and type 2 diabetes mellitus [D]. Zhengzhou: Zhengzhou University, 2018.

[7] Li Jiaheng. Study on the relationship between vitamin D level and gene expression and embryo quality related to its metabolic pathway [D]. Zhengzhou: Zhengzhou University, 2019.

[8] Wang Hui, Li Zhilu, Zhang Yong, et al. Correlation analysis of single nucleotide polymorphism of ABCG1gene and cerebral infarction in Li nationality of Hainan province[J]. Chinese Journal of Behavioral Medicine and Brain Science, 2019 (08):705-709.

[9] D ai Si-Min, Q in Zhi-Qiang,Lu Chao ,et al. Progress of research on associa ti on between schistosomiasis and single nucleotide polymorphisms [J]. Chinese Journal of Schistosomiasis Control,2018(06):702-704.

[10] Wu Ying, Zeng Huiqing, Huang Qiufen, et al. Advances in the relationship between vitamin D and respiratory diseases [J]. Journal of Clinical Pulmonary Medicine, 2020(06):958-961.

[11] Song Hang, Chen Lei, Zhang Yunfeng, et al. Vitamin D and pediatric asthmatic diseases [J]. China Experimental Diagnostics ,2018(10):1863-1865.

[12] Huang Tao, Tang Xianzhen, Chen Qing, et al. Analysis of serum vitamin D level and clinical characteristics in elderly patients with pulmonary tuberculosis [J]. Chinese Journal of Geriatrics ,2020(06):618-621.

[13] Chronic obstructive pulmonary disease D risk of deterioration or [J]. Reduction Chinese Medical Information Bulletin, 2019(03):9.

[14] Bu FX, Armas L, Lappe J, et al. Comprehensive

DOI: https://doi.org/10.30564/jams.v3i3.2322

association analysis of nine candidate genes with serum 25-hydroxy vitamin D levels among healthy Caucasian Subjects[J]. Hum Genet 2010(128):549-556.

[15] Li Fei. Study on Vitamin D and Bronchial Asthma susceptibility and Related Phenotypes of Han Chinese [D]. Beijing:Northern China Peking Union Medical College, 2011.

[16] Zhou Xiaoting. The Effect of Vitamin D on Expression of Vascular Endothelial Growth Factor and Permeability of Human Bronchial Epithelial Cells [D]. Stimulation Southern Medical University ,2011.

[17] Zhang Y, Wang Z,Ma T. Associations of Genetic Polymorphisms Relevant to Metabolic Pathway of Vitamin D3 with Development and Prognosis of Childhood Bronchial Asthma[J]. DNA Cell Biol. 2017 (08):682-692.

[18] Lahmar O,Salhi M,Kaabachi W,et al.Association Between Vitamin D Metabolism Gene Polymorphisms and Risk of Tunisian Adults'Asthma[J]. Lung.2018 (03):285-295.

[19] in beauty, Ma Zhaoyue. Relationship between RAD50, CDHR3, *CYP27B1* gene polymorphism and susceptibility to asthma in children [J].]1 Shandong Medicine ,2016(13):59-61.

[20] Armaud J,Constans J.Affinity differences for vitamin D metabolites associated with the genetic isoforms of the human serum carrier protein (DBP)[J]. Hum Genet 1993 (02):183-188.

[21] Zella LA,Shevde NK,Hollis BW,et al.Vitamin D-binding protein influences total circulating levels of 1,25-dihydroxyvitamin D3but does not directly modulate the bioactive levels of thehormone in vivo [J]. Endocrinology 2008:3656-3667.

[22] Bosse Y,Maghni K,Hudson TJ.la, 25-Dihydroxy-vitamin D3stimulation of bronchial smoothmuscle cells induces autocrine, contractility and remodelling processes [J]. Physiol Genomics, 2007(29):161-168.

[23] Moria, Deng Yongchao, Huang Caizhi, et al. Study on the correlation between polymorphism of vitamin D receptor gene and asthma in children [J]. Chinese Journal of Child Health, 2015(07):742-744.

[24] Nasiri-Kalmarzi R, Abdi M,Hosseini J, et al .Association of vitamin D genetic pathway with asthma susceptibility in the Kurdish population [J]. J Clin Lab Anal. 2020(01):e23039.

[25] Tizaoui K, Berraies A, Hamdi B, et al .Association of vitamin D receptor gene polymorphisms with asthma risk: systematic review and updated meta-analysis of case-control studies [J]. Lung.2014(06):955-965.

[26] Sootao, Hook. The effect of vitamin D on common respiratory diseases [J]. Hainan Medical Science, 2017(15):2516-2519.

[27] Chen Zhaocong. Re-recognition D Vitamin [J]. Medical Bulletin, 2011 (05):555-560.

[28] N anzer A M,C hambers E S,R yanna K,et al.The effects of calcitriol treatment in glucocorticoid-resistant asthma[J]. J Allergy Clin Immunol, 2014(06):1755-1757.

[29] M artineau A R, J ames W Y, H ooper R L, et al. Vitamin D3supplementation in patients with chronic obstructive pulmonary disease (ViDico): a multicentre, double-blind, randomised controlled trial[J]. Lancet Respir Med .2015(02):120-130.

[30] Jolliffe DA,James WY,Hooper RL,et al.Prevalence,-determinants and clinical correlates of vitamin D deficiency in patients with Chronic Obstructive Pulmonary Disease in London,UK[J]. Steroid Biochem Mol Biol.2018:138-145.

[31] Mathyssen C,Aelbrecht C,Serre J,et al.Local expression profiles of vitamin D-related genes in airways of COPD patients [J]. Respir Res.2020(01):137.

[32] HuG,DongT,WangS,etal .Vitamin D3-vitamin D receptor axis suppresses pulmonaryemp -hysema by maintaining alveolar macrophage homeostasis and function [J]. EBioMedicine. 2019(45):563-577.

[33] Fei J,Fu L,Cao W,et al .Low Vitamin D Status Is Associated with Epithelial-Mesenchymal Tra -nsition in Patients with Chronic Obstructive Pulmonary Disease.J Immunol.2019(06):1428-1435.

[34] Junaid K,Rehman A,Jolliffe DA,et al.Vitamin D deficiency associates with susceptibility to tuberculosis in Pakistan,but polymorphisms in *VDR*,DBP and *CYP2R1*do not[J]. BMC Pulm Med.2016(01):73.

[35] Mohammadi A, Khanbabaei H, Nasiri-Kalmarzi R, et al.Vitamin D receptor ApaI (rs7975232), BsmI (rs1544410), Fok1(rs2228570), and TaqI (rs731236) genepolymorphisms and susceptibility to routine tuberculosis in an Iranian population: A systematic review and meta-analysis [J]. J Microbiol Immunol Infect. 2019(19):30146.

[36] Lee SW, Chuang TY, Huang HH,et al. *VDR* and *VDBP* genes polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population[J]. J Microbiol Immunol Infect. 2016(05):783-787.

[37] Wang Xi, Yang Yuejin, Wu Fang, et al. Case-control study on susceptibility genes to tuberculosis in Kazak population in Xinjiang [J]. China Chinese Journal of Comorbidity, 2011(03):206-211.

[38] Liu Xing, Sun Hui, du Yingrong, et al. The association of *VDR* gene polymorphism with multidrug-re-

 DOI: https://doi.org/10.30564/jams.v3i3.2322

sistant pulmonary tuberculosis [J]. Journal of Kunming Medical University, 2020(03):22-29.

[39] Jolliffe DA,Greiller CL,Mein CA,et al.Vitamin D receptor genotype influences risk of upper respiratory infection [J]. Br J Nutr. 2018(08):891-900.

[40] Tian Huiqin, Wu Zhongfei, Lu Ying, et al. Study on the association of GC and *CYP27B1* gene polymorphisms with persistent allergic rhinitis sensitized by dust mites in Han population [J].Journal of Otolaryngology, Shandong University ,2019 (03):71-78.

[41] Martineau AR,Hanifa Y,Witt KD,et al. Double-blind randomised controlled trial of vitamin D3supplementation for the prevention of acute respiratory infection in older adultsand their carers [J]. Thorax,2015:953–960.

[42] Hypponen E,Berry DJ,Wjst M,et al. Serum 25-hydroxyvitamin D and IgE -a significant but nonlinear relationship[J]. Allergy, 2009(04):613-620.

[43] Jolliffe DA,Griffiths CJ,Martineau AR.Vitamin D in the prevention of acute respiratory infection:systematic review of clinical studies.J Steroid Biochem Mol Biol. 2013(136):321-329.

[44] Ren Jing. Relationship between Vitamin D and Receptor Gene Polymorphism and Susceptibility of Neonatal Respiratory Syncytial Virus Pneumonia [D]. Suzhou: Suzhou University, 2013.

DOI: https://doi.org/10.30564/jams.v3i3.2322