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

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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 immunomodulation 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)2D)[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-α-hydroxylase hydroxylated to form 1,25-(OH)2D[5]. 1,25-(OH)2D is the active form of VD, forming 1,24,25-(OH)3D under the action of 24-hydroxylase encoded by the CYP24A1 gene[6]. 24 Hydroxylase can also add 25(OH) D and 1,25-(OH)2D degradation, negative feedback regulation[6] Vitamin D binding protein (VitaminD Binding Protein, VDBP), edited by

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**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. Li Fei and others conducted similar studies in the Han population of northern China and found no correlation with bronchial asthma. 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. Zhang Y et al. study showed that rs4646536 in the \( CYP2B71 \) 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. 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.

**1.4 VD Effects on Respiratory Health**

Respiratory diseases include bronchial asthma, chronic obstructive pulmonary disease, tuberculosis, acute upper respiratory tract infection and pneumonia. A study by Song Hang has shown that VD can reduce wheezing diseases in children. Huang Tao studies have shown that VD may affect the prognosis of pulmonary tuberculosis; 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. VD can improve respiratory diseases to some extent and ensure respiratory health.

**1.3 Single Nucleotide Polymorphisms**

Genetic variation is the molecular basis of individual differences and disease development. 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.

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),D combination promotes its biological effect. Vitamin D metabolic pathway gene refers to VD conversion to 1,25-(OH),D. The 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.

**1. Genetic Polymorphisms**

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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.\(^{[1,25]}\) \(25-(OH)\)D levels in COPD patients was significantly lower than that in the control group.\(^{[32]}\) 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. Ju-nai 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\(^{[33]}\). 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\(^{[34]}\). 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\(^{[35]}\). 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\(^{[36]}\). The rs731236 study of TB patients in Iran and Yunnan showed that the frequency of “t” genotypes in TB patients was low, and that the polymorphism of vitamin D related gene loci might be associated with resistance to TB\(^{[37,38]}\).

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
nasal inflammation\cite{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\cite{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\cite{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\cite{40}. 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 Vi-


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

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