**Research Progress on the Relationship between Polymorphism and SLE of Vitamin D Metabolic Pathway Related Gene**

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**[Abstract]:**Vitamin D is a class of hormones necessary to maintain normal physiological activities of the body. A large number of studies have shown that vitamin D, as a fat-soluble vitamin, is not only related to calcium and phosphorus metabolism, but also closely related to immune regulation, humoral regulation, cell cycle and so on.Systemic Lupus erythema-Tosus (SLE) is a specific autoimmune diffuse connective tissue disease that causes tissue and organ damage under the joint action of multiple factors such as environment and heredity.Among many factors, the vitamin D metabolism pathway gene is particularly important for its influence.Several literatures have shown that the genetic polymorphism of vitamin D metabolic pathway genes is correlated with SLE.Therefore, by referring to relevant literature, this paper summarized the progress in the research on the mechanism of genetic polymorphism of vitamin metabolism pathway genes and the development of SLE.  
**[Keywords]:**Vitamin D metabolic pathways;Gene polymorphism;Systemic lupus erythematosus

**[Preface](交李志路、陈晓旭文件夹.zip)**[: Recent studies have shown that serum vitamin D deficiency in patients with SLE[1].Gao et al. conducted a study on the relationship between vitamin D and SLE and found that 62.81% of the patients had vitamin D deficiency and 34.71% had severe vitamin D deficiency, indicating that vitamin D deficiency would significantly increase the incidence of SLE[2].Some animal experiments have also shown that moderate vitamin D can reduce the levels of urine protein, impaired joint function and reduce the damage of renal function in lupus rats[3]. In the study of genetic level, Luo Xiongyan, Liu Junlin et al. further studied the genetic polymorphism of vitamin D metabolic pathway genes and SLE[4-5]In foreign literature, Ozaki, Huang et al also studied the correlation[6-7]. In this paper, we review the research progress on the genetic polymorphism of vitamin D metabolic pathway related to the pathogenesis and development of SLE.](交李志路、陈晓旭文件夹.zip)

**[1. Research progress of systemic lupus erythematosus (SLE)](交李志路、陈晓旭文件夹.zip)**

[1.1 Pathogenesis](交李志路、陈晓旭文件夹.zip)

[Systemic lupus erythematosus (SLE) is an autoimmune disease that often affects women of childbearing age[8], with high incidence, multiple system, multiple organs involved, repeated attacks and other characteristics[9-10].At present, its pathogenesis is not fully understood, mainly including the formation of immune complex which is involved in multiple organ damage, the production of autoantibodies, the over-activation of T cells and B cells and other abnormal regulation of the immune system[11-13].](交李志路、陈晓旭文件夹.zip)

[1.2 Clinical manifestations](交李志路、陈晓旭文件夹.zip)

[The clinical symptoms of SLE are more complex, mainly including respiratory system damage, kidney damage symptoms, fever, facial erythema, joint pain and so on.In mild cases, only arthralgia or facial rashes are present, while in severe cases, early life-threatening severe thrombocytopenia, neuropsychiatric lupus, progressive lupus nephritis, and alveolar bleeding occur[10、14].](交李志路、陈晓旭文件夹.zip)

[1.3 Common treatment methods](交李志路、陈晓旭文件夹.zip)

[The drugs for clinical treatment of SLE mainly include hormones and immunosuppressants, which are known as Stand of Care (SOC). Glucocorticoids are often used in combination with prednisone and metasone. In the acute stage of the onset of SLE, a large amount of glucocorticoids may pull the patient back from the line of life or death, but adverse reactions may occur[15].](交李志路、陈晓旭文件夹.zip)

**[2. Single nucleotide polymorphism and SNP detection techniques](交李志路、陈晓旭文件夹.zip)**

[Single nucleo tide polymorphism (SNP) refers to the transformation, transposition, insertion and deletion of a specific nucleotide position in the DNA of the genome, and the frequency of at least one allele in the population is not less than 1%. Although the genetic code consists of four bases, an SNP is usually just a biallelic, or dimorphic genetic variation, in which two different bases are present at that location. If the four bases mutate randomly, the transversions in the SNP should be twice as much as the transversions, but the chance of four bases mutating is not equal. In fact, the conversion accounts for a higher proportion in the SNP. Through the application of sequencing and gene mutation research technology, a large number of SNPs have been obtained, and a common database has been established. The development of efficient SNP analysis techniques has expanded the scope of the study from a small number of variants associated with a particular disease to genetic markers corresponding to multiple variation types within multiple genes. SNP analysis techniques are mainly divided into two categories according to their research objects, namely: (1) analysis of unknown SNPs, that is, finding unknown SNPs or determining the relationship between an unknown SNP and a genetic disease; ② Analysis of known SNPs, i.e. detection of genetic diversity of SNPs in different populations or genetic diagnosis of genetic diseases with known pathogenic genes in clinical practice. In practical application, many methods for detecting unknown SNPs can also be used to detect known SNPs, and methods for detecting known SNPs can also be used to screen unknown SNPs, and then sequencing method can be used to determine the types and locations of SNP mutations after screening. The following introduction of SNP analysis commonly used method, in addition to the mutation mismatch amplification test (MAMA), SNPshotTM GeneScan and allele specific oligonucleotide fragment analysis (ASO) can only detect known mutations, other methods can be used in the analysis of two kinds of SNP detection, the experimenter can according to their own needs and choose to suit the condition of the experiment equipment, simple and efficient, economy or mass detection method.[16]](交李志路、陈晓旭文件夹.zip)

**[3. Research progress on vitamin D metabolic pathway](交李志路、陈晓旭文件夹.zip)**

[VD occurs in a variety of forms in the body, including 25-hydroxyvitamin D (25-(OH)D) and 1, 25-dihydroxyvitamin D (1,25- (OH)).2D)[17], 25-(OH)D is first formed by the hydroxylation of 25-α-hydroxylase encoded by CYP2R1 gene in liver, and 25-hydroxyvitamin D is considered to be the most representative biomarker of the overall level of VD in human body[18]; After that, it is formed by hydroxylating 1-α hydroxylase encoded by CYP27B1 gene in the kidney[19], 1, 25 - (OH)2D is the active form of VD,1,25-(OH).2D forms 1,24,25-(OH) under the action of 24 hydroxylase encoded by CYP24A1 gene3,24 hydroxylases also combine 25(OH)D and 1,25-(OH).2D degrades and plays a negative feedback regulating role[20]. Vitamind Binding protein (VDBP), edited by VDBP gene, binds to vitamin D and promotes vitamin D transport in the liver and kidney.1, 25 (OH)2D exerts biological effects by binding to the VitaminD receptor (VDR), which is encoded by the VDR gene.The vitamin D pathway gene is the conversion of VD to 1,25-(OH)2The genes that play a regulatory role in the process of D mainly include CYP2R1, CYP27B1, CYP24A1, VDBP and VDR. The abnormal expression of vitamin D metabolic pathway genes may affect the level of vitamin D, thus affecting the play of biological efficacy[21].](交李志路、陈晓旭文件夹.zip)

**4. Vitamin D metabolic pathway gene polymorphism and SLE**

4.1 CYP2R1 gene polymorphism and SLE

CYP2R1 gene is located in human chromosome 11 P15.2, with a span of 15.5 KB and 5 exons[22].CYP2R1 gene encodes the 25-hydroxylase of vitamin D (CYP2R1), which is present in the liver microsomal cytochrome P450. It is a member of the 2 subfamilies of the P450 family and is composed of 501 amino acids[23] . The main role of CYP2R1 is the 25-position hydroxylation of vitamin D in the liver to produce 25-hydroxyvitamin D(25-(0H)D), which is the main product of the vitamin D metabolic cycle.Genome-wide Association Studies (GWAS) determined that CYP2R1 SNPs were associated with vitamin D levels, and some previous Studies also showed a significant Association between CYP2R1 variants and 25-(0H)D levels[24-25]. It was also confirmed by Wang et al that both CYP2R1 and CYP27A1 played a role in the 25-hydroxylation of vitamin D[24], but CYP2R gene plays a dominant role, and CYP27A1 is a secondary factor in the synthesis of 25-(0H)D.

A large number of studies have shown that single nucleotide polymorphisms of CYP2R1 are significantly associated with many diseases.The occurrence of atypical vitamin D deficiency rickets was related to the mutation of CYP2R1 gene. Xu et al. found that CYP2R1 locus rs10766197 was significantly correlated with low serum vitamin D content in Uyghur population[26].Wang et al. confirmed through comparative studies that CYP2R1 locus rs10766197 was significantly correlated with serum 25-(0H)D level in patients with type II diabetes[27]At the same time, CYP2R1 gene polymorphism was found to be significantly associated with the susceptibility to type I diabetes, and the low expression of CYP2R1 may be associated with the decreased 25-(0H)D concentration in blood of patients with type I diabetes.The CYP2R1-induced product 25-(0H)D is associated with susceptibility to a variety of cancers, including pancreatic cancer and breast cancer.Sheng et al. found that the high expression of CYP2R1 gene was significantly correlated with the relapse-free survival rate of breast cancer through a large number of studies and analyses[28].The loci rs10741657, rs2060793 and rs12794714 in CYP2R1 gene are associated with 20% to 30% susceptibility to pancreatic cancer.In GWAS, these SNPs of CYP2R1 were significantly correlated with 25-(0H)D levels.

In addition to being associated with these diseases, a large number of loci of the CYP2R1 gene also indicate an association with 25-(0H)D levels.25-(0H)D is the main form of vitamin D in the blood. At present, the level of vitamin D in the body is mainly measured by detecting serum 225-(0H)D in clinical practice[29]. Studies have shown that there are widespread problems of insufficient or deficient serum 25-(0H)D levels in patients with SLE[30], Squance et al. found that the serum level of 25-(0H)D in SLE patients was significantly lower than that in normal healthy people by comparing the serum of 80 patients with SLE and 41 healthy people with normal physical examination[31]. Serum 25-(0H)D level plays an important role in the pathogenesis of SLE, and is related to the pathogenesis of SLE, and can be used as a clinical indicator to judge the severity of SLE disease[36]. Studies have found that low 25-(0H)D level in patients with SLE is associated with high activation of B cells and high expression of IFN-α signal, as well as high anti-dsDNA and immunoglobulin levels[32]. This finding provides evidence that low 25-(0H)D levels may trigger the production of autoantibodies, thereby increasing an individual's risk of developing autoimmune diseases.On this basis, it can be concluded that CYP2R1 gene further affects SLE by affecting the liver 25 hydroxylation of vitamin D in the vitamin D metabolic pathway, thereby affecting the blood 25-(0H)D level.

4.2 VDBP gene polymorphism and SLE

Vitamin D Binding Protein (VDBP) is encoded by the VDBP gene. VDBP is a plasma Protein that can play a variety of roles and is synthesized in a variety of tissues in the body, but mainly in the liver.It was successfully isolated in 1959 and was originally called group-specific conponent-Gc globulin because of its immunological characteristics[33]. Later, Gc protein and VDBP were found to be the same protein through multiple studies[34].Genes encoding VDBP GC locates to the long arm of chromosome 4 q11 - q12, at present there are more than 2000 SNPS are found the gene, VDBP with vitamin D has a close connection between VDBP in maintaining serum vitamin D levels, adjust the bioavailability of vitamin D, vitamin D activity and end the response to vitamin D plays and important role[35]. Among them, VDBP plays a very important role in vitamin D pinocytosis, and its gene polymorphism will affect vitamin D level and activity[36]. In addition, studies have shown that VDBP also plays a very important role in the vitamin D metabolic pathway, and its polymorphism is related to the immune response and the ability to bind vitamin D and its derivatives.

There are many studies on the association between single nucleotide polymorphism of VDBP gene and disease at home and abroad[37].VDBP is associated with lung disease, liver disease, obesity, bone tissue disease, diabetes and many other diseases[38-40]. At present, domestic and foreign studies on VDBP encoding genes mostly focus on rs2282679(A/C), rs45889(C/A) and rs7041(T/G), and studies have found that rs2282679(A/C) polymorphism is correlated with vitamin D level[41-43], and SNP rs2282679 is associated with bone metabolic diseases, obesity, heart and lung diseases, etc[38].Regulla et al. found that VDBP gene polymorphism was correlated with Graves' disease[44]. Wang Gaoshuai et al. found that the SNP locus rs7041 of VDBP was closely related to obesity[45]. However, at present, the role of VDBP gene polymorphism in the pathogenesis of SLE is still unclear, and there are no large-scale clinical studies and reports on the association between SLE patients and VDBP gene polymorphism, so it still needs to be verified by subsequent experiments.

4.3 CYP27B1 gene polymorphism and SLE

CYP27B1 gene is the encoding gene of 1-α-hydroxylase, which exists on the long arm of human chromosome 12 (12q13.1-q13.3). It consists of 9 exons and 8 introns, and is a single-copy gene.Its full length cDNA is 4.8 KB, encoding 508 amino acid polypeptide[46-47], a member of the P450 family of enzymes, encodes 1-α hydroxylase.

α-hydroxylase catalyzes 25-(0H)D to form 1,25-(0H)2A rate-limiting enzyme of D whose main function is to catalyse the hydroxylation and activation of 25-(0H)D in the proximal convoluted tubules and rectus and convert it to its active form 1,25-(0H).2D[48-50].Panda and Zhang Zengli et al found that the changes of 1-α-hydroxylase activity were correlated with 1,25-(0H) in plasma and local area.2D levels were associated with immune system dysfunction, and no active vitamin D was found in animals targeted with the CYP27B1 gene[51-53]. Multiple literature reports,1,25-(0H)2D has a direct effect on both T and B cells, not only promoting the production of various inflammatory cytokines, but also inducing regulatory T cells to participate in a "off" inflammatory response.On this basis, some studies show that[51]Vitamin D is mainly involved in SLE by increasing the number of regulatory T cells and producing anti-proliferation effects. Therefore, it can be concluded that CYP27B1 single nucleotide polymorphism is closely related to the occurrence and development of SLE.

4.4 Calcium-phosphorus regulation of vitamin D in SLE

Coexistence of vitamin D and vitamin A in cod liver oil, animal tissues and within the human body skin contains cholesterol, A precursor of vitamin D3 7 - dehydrogenation after sunlight into vitamin D, vitamin D with biological activity of 1, 25 - (OH) 2 D3 form play A role, the calcium, phosphorus, and children's bone growth has very important meaning. Studies have reported that the level of 1,25- (OH) 2D3 is positively correlated with bone mineral density in patients with SLE, and the incidence of SLE combined with osteoporosis is 1.4% ~ 68% ［54-46］, the larger span was due to differences in genetic background, ethnicity, age, and disease activity, and postmenopausal women were at higher risk for lumbar osteoporosis. Children with SLE are also at a higher risk of developing osteoporosis, considering that long-term use of hormones may affect the growth of their normal peak bone mass［57］. The causes of osteoporosis in SLE are very complex, including disease factors, drug influencing factors (glucocorticoid) and renal damage, etc., and defective osteogenic differentiation of mesenchymal stem cells in SLE may also lead to osteoporosis［58-59］. 1,25- (OH) 2D3 can regulate calcium and phosphorus levels in patients with SLE through binding with vitamin D receptor (VDR), maintain mineral stability, thus promoting bone metabolism and bone transformation, and reducing the occurrence of osteoporosis in patients with SLE. Vitamin D can also regulate osteoblasts and osteoclasts

4.5 VDR gene polymorphism and SLE

VDR is a nuclear receptor of 50 kDa, belonging to the second class of the steroid receptor family, similar to retinoic acid receptor and thyrotropin[60].1, 25 - (0 h)2D binds to the nuclear VDR genome and determines genomic responses by regulating the transcription of certain genes[56].VDR is synthesized by a gene located at position 12q13.1 on chromosome 12, known as VDR gene[57]. The gene is basically composed of 9 exons distributed in the 5 'promoter and the 3' regulatory region.In the latter region, a long 3 'untranslated region, known as the 3' untranslated region, is involved in the regulation of gene expression, in particular by regulating the stability of messenger RNA.VDR gene showed some polymorphisms in the promoter region between exons 2 and 9 in the 3 'translation region, especially in the promoter region around exons 1, F and C[61]. Polymorphism BSMI located in intron 8 and adenine - guanine replacement results (A-G)[62].*Apai and Taqi polymorphisms were distributed in this region of the 3' gene.*Polymorphic APAI is defined as thymine substitution (T-G) in intron 8, while polymorphic TAQI is defined as cytosine-thymine substitution (C-T), resulting in codon exchange (ATC→ATT), but maintaining the same isoleucine amino acid[63]. Functional correlations of these polymorphisms were associated with increased mRNA stability[64].*Foki polymorphism is caused by the substitution of cytosine-thymine (C-T) at the junction of intron 1 and exon 2, resulting in an additional start codon (ACG→ATG), three codons close to the transcription start site.*This polymorphism can be considered as an independent genetic marker because it does not appear to be in linkage imbalance with other VDR gene polymorphisms. *An occurrence variant of Foki, defined as a mutation in F (Atg codon) resulting in complete production of VDR protein (427 amino acids)*[65]", and the mutation Foki, defined as F (codon GCA), starts translating at a different site to produce a slightly shorter VDR protein containing three fewer amino acids (424 amino acids).In vitro studies have shown that short proteins seem to have higher transcriptional activity than long proteins[66]. This may increase the function of VDR and thus alter the role of vitamin D in different cells and tissues.*The effect of Foki polymorphism on the transcriptional activity of immunospecific transcription factors in lymphocyte proliferation and immunocell protein synthesis suggests that Foki polymorphism is involved in immune regulation and immunoregulatory polymorphism*[67].

*In vitamin D transport and metabolism pathway, the SNP of VDR gene is associated with the susceptibility to severe respiratory syncytial virus infection, tuberculosis, asthma, systemic lupus erythematosus, colorectal tumor, melanoma, periodontitis, renal cell tumor, gout, multiple sclerosis, AIDS, Parkinson's disease and other diseases*[68-70].

A large number of researchers have conducted experiments on the relationship between BSMI polymorphism of VDR gene and SLE.In 2000, a study of 58 Japanese patients with SLE demonstrated a higher incidence of B/B genotypes compared with healthy controls (15.5 vs. 5.7%,p<0.0001).In addition, a higher frequency of genotype B/B was found in nephrotic syndrome (61.5% vs. 35.7%,p<0.0034) in nephrotic patients[67].In 2002, Chinese authors studied 47 patients with systemic lupus erythematosus and 90 healthy controls and found a higher B allele frequency in patients with systemic lupus erythematosus (39.4% vs. 8.3%,OR=0.74, P <0.0001).[71].A study of 101 Thai and 60 Iranian patients in 2006 and 2010, respectively, found no association between BSMI polymorphisms and SLE or clinical and laboratory manifestations of the disease.In 2002, a study assessed FOKI polymorphisms in 52 patients with SLE and 90 healthy controls and found no significant differences in allele and genotype frequencies[72].In 2010, a meta-analysis was published that found no significant Foki polymorphism.However, due to the small number of studies included, these results should be interpreted with caution, and they apply only to European and Asian ethnic groups[73]. A case-control study conducted in Brazil also investigated the association between BSMI and Foki VDR gene polymorphism and susceptibility to SLE in 195 patients of European or African origin and 201 control patients.The results showed no association between BSMI and Foki VDR gene polymorphisms and SLE susceptibility.In this study, the mean serum level of 25-(0H)D in patients with SLE was 25.51±11.43 ng/ml.*25-(0H)D level in F/F genotype patients was significantly higher than that in F/F genotype patients (31.6±14.1 vs 23.0±9.2 ng/ml, P <0.004).*Although there is no significant association between FOKI polymorphism and SLE, the authors suggest that FOKI polymorphism has an important effect on vitamin D metabolism in patients with SLE[71], BSMI and Foki VDR polymorphisms have recently been found in Chinese patients.The frequency of homozygous F/F was higher in SLE patients than in controls (42.8 vs 25.4%, P =0.001).Seritis, anti-dsDNA antibodies, anti-Sm antibodies, and anti-hiprotein antibodies in SLE patients with homozygous F/F and heterozygous F/F were higher than those in SLE patients with homozygous F/F.Patients with SLE show a marked increase in the frequency of the B allele, which is associated with lupus nephritis and with the production of anti-nucleosome antibodies[74].

**5. To summarize**

At present, a large number of studies have explored the relationship between vitamin D deficiency and the occurrence and development of SLE disease, but most of the studies on its mechanism remain at the cellular level, and a few involve genetic level.However, with the deepening of the research on SLE, it is not difficult to find that genetic polymorphism of genes plays a non-negligible role in the occurrence and development of SLE.As an important pathway of vitamin D production, vitamin D metabolic pathway has a direct impact on vitamin D level, which further affects the occurrence and development of some diseases, especially autoimmune diseases (such as SLE).To sum up, in view of the vitamin D in SLE properties of calcium phosphate, immunity adjustment, system and SLE and VDR gene polymorphism, the correlation of atherosclerosis, improve the level of 1, 25 - (OH) 2 d3 to improve SLE patients with osteoporosis, disease activity, atherosclerosis, cardiovascular disease and clinical symptoms may play a role, but the kinds of vitamin D supplements, dose and treatment remains to be more large-scale clinical trials research further defined. It remains to be further investigated whether vitamin D and VDR can reduce or even replace hormone and immunosuppressive therapy, and whether adequate vitamin D supplementation can prevent the occurrence of SLE.[75]

Therefore, the study of genetic polymorphism of SLE gene has become a new hot topic and provides some help for its early prevention and follow-up treatment, which is expected to become a new direction for the research and treatment of SLE.

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