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# Review of research progresses in genetics related to myopia

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## 近视相关的遗传学研究进展

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**摘要**

近视是极为常见的眼屈光不正状态,近视发病率逐年上升且发病年龄趋于提前,已成为危害人们视觉健康的重大公共卫生问题。研究表明,近视是遗传因素和环境因素及基因-环境交互作用影响的多因素复杂疾病。遗传学包括经典的遗传学和表观遗传学。表观遗传学研究的出现为近视基础研究开拓了新视角。近年来不断有研究者提出近视发生可能与表观遗传学有关联,而且有越来越多的实验研究也证明了该观点。近视的遗传研究通过使用连锁法和全基因组关联方法,现已鉴定出高度近视以及近视的多个近视基因和候选基因,极大地加深了对近视遗传学基础的认识。本文就近年来近视在经典遗传学和表观遗传学两个方面的研究进行综述。

**关键词**:近视;经典遗传学;表观遗传学

## Abstract

• Myopia is an extremely common state of refractive error, and the incidence of myopia is increasing year by year and the age of onset is usually earlier. It has grown up to be a major public health problem that endangers people's visual health. Studies have demonstrated that myopia is a multi-factor complex disease which affected by genetic factors, environmental factors and gene-environment interaction. Genetics includes classical genetics and epigenetics. The emergence of epigenetic research has opened a new perspective of basic research on myopia. In recent years, the researchers have proposed that the occurrence of myopia may be related to epigenetics, and more and more experimental studies have also proved this view. The genetic study of myopia has identified several myopia genes and candidate genes for high myopia and myopia by using linkage and genome-wide association methods, which greatly deepened the understanding of the genetic basis of myopia. This article reviews the research on classical genetics and epigenetics of myopia in recent years.

• KEYWORDS: myopia; classical genetics; epigenetics
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## INTRODUCTION

Myopia is a part of the most common eye diseases in the world. The current global prevalence of myopia is about 28.3%. It is expected that by 2050, 50% of the global population will be affected, and the prevalence of high myopia will reach 10%[1-2]. The situation in our country is not optimistic. It has turned into an area with a high incidence of myopia. High myopia is easy to cause blinding complications equally, such as retinal detachment and macular degeneration, *etc*[3]. Complications may require surgery and medical treatment, leading to high social costs. Therefore, it is urgent to actively explore the pathogenesis of myopia, so as to combat myopia more effectively.

Myopia is considered to be a multi-factor complex disease, genomic factors and environmental or behavioral factors and their interaction play pivotal roles[4-5]. The genomic research of myopia has identified multiple myopia genes and candidate genes for high myopia and myopia through the use of linkage methods and genome-wide association methods, which greatly deepen the understanding of the genetic basis of myopia[6-8].

Genetics includes classic genetics and epigenetics. The emergence of epigenetic research has called to order a new perspective for basic research on myopia. In recent years, researchers have continuously proposed that the occurrence of myopia may be linked to epigenetics, more and more experimental studies have also proved this view. In this article, we consider the classical genetics and epigenetics related to myopia.

**Classical Genetics** Classical genetics believes that the molecular basis of biological inheritance is nucleic acid. Various hereditary information of an organism is stored in the DNA sequence of nucleic acid. Changes in the DNA sequence will cause changes in gene expression levels, which will result in changes in the phenotype of organisms. And this phenotypic change can be stably inherited to the next generation.

**Genes Associated with Myopia** The occurrence of myopia are the result of multiple factors such as genetics and environment. Through genome-wide association studies (GWASs) and exon sequencing, more than 150 polymorphic loci have been found that may be related to myopia. At present, 25 myopia linkage sites (MYP1-25) have been identified[9-10]. Exon sequencing found 10 genes related to high myopia, 4 of which were autosomal dominant inheritance (ZNF644: Gene ID 84146, OMIM 614159; SLC39A5: Gene ID 283375, OMIM 608730; SCO2: Gene ID 9997, OMIM 604272; P4HA2: Gene ID 8974, OMIM 600608), 3 were autosomal recessive inheritance (LRPAP1: Gene ID 4043, OMIM 104225; LEPREL1: Gene ID 55214, OMIM 610341; CTSH: Gene ID 1512, OMIM 116820), 2 were X chromosome linked inheritance (OPN1LW: Gene ID 5956, OMIM 300822 and ARR3: Gene ID 407, OMIM 301770), 1 was inherited by spontaneous mutation (BSG: Gene ID 682, OMIM 10948). ZNF644[11], CCDC111[12], LRPAP1[13], SLC39A5[14] have been defined as myopia-causing genes.

In addition, several myopic susceptibility bases were found through GWASs and repeatability validation studies. For example, PAX6, located on MYP7, is thought to be related to high myopia[15-17], but there are also inconsistent results[18-19]. TGIF is abundantly expressed in the retina, sclera and the optic nerve, and it is also considered to be a susceptibility gene for high myopia. It is involved in the transcription factor TGF-β signaling pathway[20], but no studies have shown that single nucleotide polymorphisms (SNPs) on the TGIF gene are related to high myopia[21-22]. The rs4455882 and rs6469937 polymorphic sites on the SNTB1 gene have been shown to be associated with extreme myopia, and the expression of SNTB1 protein in the myopia mouse model is significantly down-regulated compared to the control group[23].

**Genes Related to the Length of the Eye Axis** The length of the eye axis is an important factor to affect the refractive power of the eyeball, so 16 statistically significant sites were found through GWASs. Among them, studies have revealed that the genes related to the length of the eye axis are: SNP rs4373767 ($P=2.69\times10^{-10}$) located on the ZC3H11B gene, RSPO1, C3orf26, LAMA2, ZNRF3[24].

**Genes Associated with Scleral Remodeling** GJD2, PRSS56, BMP3, KCNQ5, LAMA2, TOX, TJP2, RDH5, ZIC2, RASGRF1, RBFOX1, SHISA6 and other candidate genes are widely involved in neurotransmission, ion transport, retinoic acid metabolism, extracellular matrix remodeling and eye development. They deal with a wide range of cell cycle and growth pathways, such as signal pathways leading to refractive errors, namely TGF-β, mitogen-activated protein kinase (MAPK) and SMAD pathways[24].

Studies have shown that the expression of bone morphogenetic protein (BMP) gene can mediate eye development and remodeling of retinal tissue[25], gene research shows that the frequency of the A allele in its 1379 G/A (rs2288255) polymorphism is significantly different between the case group and the normal control group[26].

Fibroblast growth factor-10 (FGF-10) can govern the expression of extracellular matrix-related genes, suggesting that FGF-10 may be a gene susceptible to myopia. Hsi *et al*[27] showed that the SNP rs339501 G allele of FGF-10 gene is associated with human super-high myopia (*OR* = 1.58), and has higher gene expression in the luciferase assay. It is speculates that FGF-10 may participated in the occurrence and development of myopia.

When looking into the correlation between myopia and genetic polymorphisms, problems such as population differences and linkage disequilibrium should be avoided. With the improvement of genetic polymorphism detection technology and the in-depth study of disease correlation, people will have a deeper and more comprehensive understanding of the pathogenesis of myopia, and more reliable susceptibility markers will be identified, so as to find the prevention and the effective treatment of myopia will make a due contribution to human health.

**Epigenetics** Epigenetics mainly refers to changes in gene expression levels based on changes in non-gene sequences, that is, studying the effects of environmental and behavioral factors on genetic factors. This kind of change refers to a mutation that is not defined by the DNA sequence itself, and can be stably transmitted during cell proliferation and biological development, affecting gene expression or cell phenotype variation. The essence of epigenetics is epigenetic modification, which mainly includes DNA methylation, histone modification and non-coding RNA regulation[28].

**DNA Methylation and Myopia** DNA methylation refer to the reaction in which the methyl group is transferred to the 5' carbon atom of cytosine under the catalysis of DNA methyltransferase to form 5-methylcytosine. CpG dinucleotide accounts for about 1% of the human genome and is the main

site of DNA methylation in mammals. Methylation of CpG islands can change the configuration of related genes in a variety of ways, and methylation can cause gene transcription inactivation, affect the transcription of transcription factors, and thus affect gene expression[29]. The final target organ for the development of myopia is the sclera. Remodeling of the scleral extracellular matrix (ECM) leads to the changes in the axial length and refractive state of the eye, which is an important feature of myopia[30]. In mice and other mammalian models of sclera, collagen accounts for 90% of the dry weight[31], which is mainly type I collagen (COL1A1). In the progress of myopia, COL1A1 plays an important role in the pathological changes of the sclera and the occurrence of myopia[32]. Studies have found that the loss of COL1A1 function can lead to osteogenesis imperfect and thinning of the sclera. The occurrence of other system diseases and myopia[33], the hypermethylation of the promoter of COL1A1/CpG site of exon 1 at the scleral transcription level of myopia may be the basis for the decrease of collagen synthesis at the scleral transcription level of myopia. COL1A1 contain α1 chain (collagen type I α1,COL1α1) and α2 chain (collagen type I α2,COL1α2). Ji[34] compared mouse form-deprivation myopia with normal control eyes, suggesting that DNA methylation may be involved in regulation of scleral COL1α1 transcription, which suggests that DNA methylation may play a role in myopic scleral remodeling important role. The results show that the higher the DNA methylation level of the COL1A1 promoter, the more likely it is to inhibit the synthesis of scleral collagen, thereby promoting the development of myopia. Other studies have shown that the decrease in the expression of COL1α2 mRNA has nothing to do with the DNA methylation of the CpG island in the promoter region of its gene and the DNA methylation of the CpG island in the retina Pax6 promoter region[35].

**Uncoded RNA and Myopia** In the progression of myopia, both coding and non-coding RNA expression changes are involved. Non-coding RNAs are functional RNAs that are not converted into proteins. Among them, miRNAs have become a research hotspot in epigenetics. It is a class of endogenous RNA molecules which largely present in eukaryotic organisms. Most miRNAs are highly conserved, sequence in gene expression, and tissue specific. MiRNA can regulate gene expression in a variety of ways. The principal mechanism of action is to complement mRNA, promote or inhibit mRNA translation, thereby regulating gene expression at the gene level and chromosome level, in cell signal transduction, cell proliferation and apoptosis. Tissue morphogenesis and biological development sequence play important roles[36-37]. Studies have revealed that a variety of miRNAs are expressed differently in the sclera and retina of humans and animals. The results of micro array analysis showed that a total of 54 miRNAs in the sclera showed significant differential expression (24 miRNAs were up-regulated and 30 miRNAs were down-regulated), and a total of 261 mRNA expressions were significantly changed (177 showed up-regulation and 84 showed down-regulation); The qPCR results suggest that the expression changes of Let-7a, miR-16, Peripherin 2 (Prph2) and guanine nucleotide binding protein are statistically significant, supporting miRNA to participate in the formation of myopia[38]. Mei[39] screened 8 miRNAs that co-exist in the retina and whole eye tissues in form-deprived myopia. These miRNAs are miR-468, miR-16-1, miR-466h-5p, miR-466j, miR-699e, miR-15a, miR-466c-5p and miR-294, suggesting that they may be associated with the progression of myopia. Their regulatory effects may be obtained through the regulation of target genes such as REEP3, MAPK10 and INO80D and interference with multiple cellular pathways or biological processes, thus playing a role in the development of myopia. Among them, miR-466h-5p and miR-466j also have a strong synergistic effect. Zhao[40] found that miR-29 was markedly up-regulated in the sclera of form-deprived myopic guinea pigs. After miR-29 transfection, human sclera fibrosis the proliferation of cells (humanization fibroblasts, HSF) is inhibited, and there is a decrease in the expression of type I collagen in HSF cells. Therefore, miR-29 may be associated with the development of myopia. Another study by Metlapally *et al*[41] found that some age-related miRNAs expression patterns, that is, some miRNAs are more in the fast-growing fetal sclera, which increases the understanding of scleral remodeling and may provide strategies for the treatment of myopia. Because low levels of the Pax6 gene are a risk factor for myopia, Chen *et al*[42] studied the relationship among PAX6 SNPRs 662702, myopia development, miR-328 and retinoic acid, that is, retinoic acid-mediated signaling pathways may directly regulate miR-328. The expression of miR-328, SNPRs 662702 can affect the combination of miR-328 and PAX6, and the miR-328 will reduce the expression of PAX6. Therefore, reducing miR-328 and/or retinoic acid may be a strategy for myopia treatment.

**Histone Modification and Myopia** Histone modification is another important modification method in epigenetics. There are numerous modifications of histone in the mammalian genome. Histones are structural proteins that available in the chromatin of eukaryotic cells, including H1, H2A, H2B, H3 and H4. Among them, H1 acts as a link between nucleosomes and H2, H3, H4 are functional histones. Modifications such as methylation and demethylation, acetylation and deacetylation, phosphorylation and dephosphorylation, ubiquitousness and deubiquitination, and adenosine diphosphate tribulation of histone ends under the action of related enzymes. During the process, the positions and types of these modifications constitute the histone code, and thus regulate the specific expression and function of genes. The

regulation of histone modification on gene expression mainly includes two ways: by influencing the binding ability of histone in the nucleosome with DNA double strands to change the compact or loose state of chromatin structure; Or by influencing structural gene promoters and transcription factors the affinity of the gene to play a role in gene regulation[43]. Park *et al*[44] found that the expression levels of histone deaconesses HDAC2 and HDAC3 in Koreans were lower than those in Caucasians, while acetylated histone H3 was increased. The promoter regions of LOXL2, elastin and fribrilllin1 genes in Korean LC were reduced. Highly acetylated, the corresponding gene expression is significantly higher than that of Caucasians. This difference may identify the susceptibility to eye diseases such as myopia. Histone acetylation affects the expression of elastin and fibrillate, the main components of ECM, so it is speculated that acetylation is involved in the occurrence and development of myopia.

## DISCUSSION

The pathogenesis of myopia is just so complicated. So it is difficult to use a single candidate gene or simply from the genetic perspective to fully clarify the genetic principles of myopia pathogenesis. We are required to gene-environment interaction factors, that is, we need to combine classical genetics with epigenetics. Therefore, a lot of exploratory research is still required. Looking for numerous myopia susceptibility genes and study their potential interaction mechanisms. The application of whole genome scanning, exon sequencing, epigenetic research and other strategies will helpus to further search for more genes and their complex mechanisms of action. Thus revealing the genetic mechanism of myopia and laying the foundation for breakthroughs in the prevention and control of myopia.

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