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·综　述·

高度近视遗传方式和防控手段的研究进展

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摘要：高度近视是一种具有高度群体特异性和遗传异质性的可致盲的眼部疾病，目前尚无有效的治疗方法。近视在东亚人中更为普遍和严重，尤其是在中国。近视及近视临床前期的防控有助于预防其发展为高度近视。目前对分子遗传学和环境因素进行了大量研究，确定导致高度近视的相关基因，以建立近视的多基因风险评估，以期阐明发病机制和通路机制。本文以现代医学与分子遗传学为基础，探讨近年来高度近视相关基因新的基因位点、危险因素及近视防控手段的进展。

关键词：高度近视；*MYP* 基因位点；屈光不正；危险因素；遗传学研究进展

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Research progress on genetic patterns and prevention and control measures for high myopia

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Abstract: High myopia is a highly population-specific and genetically heterogeneous eye disease for which there is no effective treatment. Myopia is more prevalent and severe in east Asians, especially in China. Prevention and control of myopia and preclinical myopia can help prevent its progression to high myopia. Therefore, numerous studies on molecular genetics and environmental factors have been conducted to identify genes associated with high myopia in order to establish a polygenic risk assessment for myopia and to elucidate the pathogenesis and pathway mechanisms. This paper will discuss the recent advances in genetic loci, risk factors, and myopia prevention and control tools based on modern medicine and molecular genetics for high myopia-related genes.

Keywords: High myopia; *MYP* gene locus; Refractive error; Risk factors; Advances in genetics

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近视是世界上最常见的人类眼疾。未矫正的近视是视力障碍的最常见原因，影响 1.08 亿人，也是全球第二大常见失明原因[1]。高度近视定义为屈光度≥6 D 或眼轴长度(AL)>26 mm[2]。高度近视可导致视网膜脱离、黄斑脉络膜变性、早发性白内障和青光眼等相关疾病，增加视力丧失的相关风险。而高度近视患者占全球人口的 0.5% ~ 5.0%[3]，发病率因国家而异。2020 年我国安阳市一项研究发现，儿童近视的发病率从一年级和二年级的 7.8% 上升到五年级和六年级的 25.3%[4]。鉴于目前的趋势，预计到 2050 年，全球受近视影响的人口将显著增加，其中 10% 将发展为高度近视[5]。目前已经证实 *MYP* 相关基因、血管活性肠肽(VIP)、AR33 等基因与高度近视相关[6]。近年来高度近视防控手段飞速发展，但防控手段与相关易感基因的结合却仍然是一大难题。本文将从分子遗传学出发探讨近年来高度近视相关位点、危险因素及防控手段的最新进展。

1　高度近视的危险因素

高度近视的危险因素受多种环境和遗传因素的影响。在长达数十年的研究中已证明高度近视的危险因素包括父母是否近视，患儿是否过早的出现近视以及户外活动时间的长短等[7]。环境因素被认为是近视的主要因素，特别是在学龄儿童中，遗传因素所占比例很小。此外，探索的已知遗传位点仅

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解释了欧洲近视遗传率的不到 20%，东亚儿童甚至更少[8]。但基因研究在提高对与疾病发作、易感性相关基因成分、视力受损的分子机制的理解，以及探究相关治疗手段仍然具有重要意义[9]。

2　屈光状态的决定因素

人眼主要的屈光结构是角膜、晶状体和眼轴。眼轴的延长是近视发生和进展的主要原因，眼轴长度的增长成为近视的基本内表型，且具有高度遗传性[10]。

3　高度近视的遗传方式、研究策略和遗传学研究方法

目前，流行病学研究证实了高度近视的遗传模式，主要有 X-性连锁遗传、常染色体显性遗传和常染色体隐性遗传。各种遗传模式均存在高度遗传异质性。研究者对近视发生机制的研究集中于对高度近视患者候选基因的筛选，并在动物实验中验证其作用。群体研究、双生研究、家系研究被认为是高度近视遗传研究中最常见的研究策略。目前国内外学者通过对众多群体、家系等进行连锁分析、关联研究、全外显子组测序和实验性近视研究确定了许多与近视相关的位点和基因。这些方法应用的遗传标记主要有全基因组关联研究（GWAS）、全外显子组测序（WES）和下一代测序（NGS）等。

4　高度近视的遗传方式和基因位点

自 1990 年基因座 *MYP*1 被报道为第一个与近视相关的基因座以来，现在已经有 20 多个名为 *MYP* 的基因座被国际人类基因命名委员会认可，并在《人类孟德尔遗传学》中编码，部分基因位点见表 1。

表 1　近视相关遗传位点

Tab. 1　Myopia related genetic loci

基因座	位点	代表基因	遗传方式	来源	参考文献
*MYP*1	Xq28	*OPN*1*LW*, *OPN*1*MW*	X-linked	丹麦	[11]
*MYP*2	18p11.31	—	AD	中国/欧洲	[12]
*MYP*3	12q21-q23	—	AD	德国/意大利	[13]
*MYP*6	22q13.33	*SCO*2	AD	犹太人	[14]
*MYP*7	11p13	—	Multifactorial	高加索	[15]
*MYP*11	4q22-q27	—	AD	中国	[16]
*MYP*13	Xq23-q27.2	—	X-linked	中国	[17]
*MYP*14	1q36	—	Multifactorial	犹太人	[18]
*MYP*26	Xq13.1	*ARR*3	X-linked	中国	[19]
*MYP*27	8q24.3	*CPSF*1	AD	中国	[20]

注：AD 为常染色体显性遗传；X-linked 为 X 性连锁隐性遗传基因；Multifactorial 为多因素影响。

4.1　常染色体显性遗传（AD）基因

4.1.1　*MYP*2 基因　1998 年，研究人员利用全基因组连锁研究技术，对 8 个高度近视家系分析找到了 *MYP*2 基因[12]。并将其定位确定于 18p11。多项研究证明定位于 *MYP*2 位点的候选基因对于眼部结缔组织的基本组织结构和功能至关重要，其主要包括 *MYOM*1、*EMILIN*2 位点[21]。并已证明在该位点的基因也在视网膜中表达并影响巩膜的生长，有假说猜测该基因是导致高度近视的原因[22]。

4.1.2　*MYP*5 基因　2003 年，*MYP*5 基因在一个高度近视家庭中被发现，该基因为常染色体显性遗传性，位于遗传标记 D17s787 和 D17s1811 之间[23]。在这个区域发现了一个候选基因 *COL*1*A*1，候选基因的两个 SNP 多态位点分别位于基因的内含区和上游，编码细胞外基质蛋白Ⅰ型胶原并与高度近视有显著关系。

4.2　*MYP*1 基因　该基因为 X 性连锁隐性遗传基因，1990 年第一个近视基因位点 Xq28 被确定。研究者在丹麦一个大型近视家系中发现家族中的高度近视的患病与性别有明显联系，并将其命名为 *MYP*1[11]。2015 年 Li 等[24] 证明定位于 *MYP*1 的 *OPN*1*LW* 基因中独特的单倍型可能是映射到 *MYP*1 高度近视的常见原因。并提出 *OPN*1*LW* 中独特单倍型所导致的 L 和 M 视锥细胞缺陷可能参与高度近视的发展。

4.3　*MYP*26 基因　该基因为 X 连锁-女性限定，Xiao 等[19] 报道早发性高度近视仅限于女性家庭成员，并在其中一个家系中，定位到染色体 Xp11.1-q13.3，全外显子组测序确定 *ARR*3 基因错义突变的杂合性，这些突变通过 Sanger 测序得到证实。

4.4　其他 *MYP* 基因位点及候选基因　除外以上所提及的基因，还有研究发现 *MYP*6、*MYP*7、*MYP*8、*MYP*9、*MYP*10、*MYP*17 与中低度近视遗传相关，*MYP*14 与所有类型的近视遗传相关。而 *MYP*23、*MYP*24、*MYP*25、*MYP*27 基因均被证明与基因的杂合突变有关。

4.5　其他候选基因　*VIP* 已被证明参与不同模式动物在正常眼睛和由形觉剥夺引起的近视眼的屈光特性的发展。并在最新研究中证明在中国高度近视 *VIPR*2 位点中存在两种不同的高风险因果变异。且中国人的高风险位点比欧洲人多[25]，这可能是导致中国人近视的患病率远高于欧洲人的原因之一。

5　近视防控手段

目前，近视的有效治疗方法包括药物手段、物理手段以及手术手段。

5.1　药物手段

5.1.1　阿托品　阿托品是一种非选择性毒蕈碱拮抗剂，在眼科中作为散瞳和睫状肌麻痹药物[26]。研究表明低剂量阿托品对近视进展有抑制作用，1 年内使用 0.01%浓度的阿托品，近视进展了 27%；而 0.025%和 0.05%阿托品的分别使近视进展延迟了 43%和 67%[27]。但同时也在该研究观察到 0.1%和 0.5% 的阿托品在停药后会出现近视反弹、畏光等副作用。

5.1.2　7-甲基黄嘌呤（7-MX）　7-MX 是一种非选择性腺苷受体拮抗剂，可引起巩膜增厚和巩膜胶原纤维直径增加，即引起巩膜变化与近视眼所导致的巩膜变化相反。目前一个临床试验揭示了 7-MX 在近视进展缓慢的受试者中可能抑制约 22% 的近视，而对进展率高的受试者的近视进展没有影响；但在停药后，轴向长度开始正常延长，即药物作用消失[28]。

5.1.3　其他具有抗近视潜力的药理化合物　除以上两种药物外，目前还有毒蕈碱受体拮抗剂吡仑西平，但现在吡仑西平临床试验因安全性较低目前已被叫停[29]。此外 GABAB 和

GABAC 受体拮抗剂(1,2,5,6-四氢吡啶-4 基)甲基膦酸、(3-氨基环戊基)丁基膦酸 (3-ACPBPA)、α 肾上腺素能激动剂,如可乐定和胍法辛(guanfacine)以及溴莫尼定、阿扑吗啡、拉坦前列素、藏红花素等药物均在动物实验中验证可以在一定程度上控制近视进展[30-31],但因暂无临床试验数据,其在人体中的疗效及其副作用仍未可知。

5.2　物理干预

5.2.1　框架眼镜　单光框架眼镜是目前儿童青少年近视最普遍的视力矫正方式,其缺点是单光镜片无法与眼球角膜表面弧度一致,导致周边视网膜出现远视离焦从而造成近视的进展[32]。因此渐进多焦眼镜、周边离焦框架眼镜、多点近视离焦框架眼镜的出现使得光学干预进入近视防控的范围,并更适用于近距离存在内隐斜和明显调节滞后的近视儿童。周边离焦框架眼镜的设计是减少相对周边远视来影响近视进展。临床试验发现周边离焦框架眼镜可将儿童近视平均减缓 30%[33]。而多点正向光学离焦镜片的设计原理是用于矫正屈光不正的中心光学区和围绕中央区的多个持续近视散焦(+3.50 D)段,并基于近视散焦的视觉原理,将其用于近视的控制。相关研究,显示与佩戴 2 年以上单光眼镜片的儿童相比,多点正向光学离焦镜片的近视进展减少 52%,眼轴增长率降低 62%[34]。

5.2.2　角膜塑形镜　角膜塑形镜是一种刚性透气性隐形眼镜,可过夜佩戴,旨在重塑角膜,并暂时矫正中低度近视。它基于近视在周边视网膜上散焦的假设,将角膜形状变为扁圆形,导致外周屈光减少远视散焦。临床研究表明,角膜塑形镜可有效抑制近视的进展,减缓眼轴长度增长的效果范围为 32%~63%,总体治疗效果在 50%左右[35]。

5.2.3　低能量红光治疗仪　做为目前来说较为新兴的近视防控手段,其原理是使用低水平的红光和近红外光。其波长范围 600~1 100 nm,其输出可以达到 500 mW[36]。作为一种光疗手段,其产生足够低的能量以在不改变周围组织温度的情况下诱导组织中的刺激反应。最新研究证实,低能量红光治疗可以有效控制近视,且与 0.01%阿托品相比,红光治疗仪疗法显著减缓轴向伸长和近视进展[37]。但其安全性和光疗能量的稳定性也有待进一步验证。

5.2.4　户外活动　增加户外时间也可以降低近视发展的风险,尤其是在学龄儿童中。随着户外活动的增加,眼部肌肉放松,导致更多的近视散焦效应从而抑制近视发展。此外,户外的高光照条件以及阳光抑制了近视发展。有证据表明,无论近视的近工作时间和父母的近视史如何,白天在户外活动时间长的儿童患近视的可能性较小,近视进展也较少[38]。

5.3　手术干预　激光角膜屈光手术、人工晶状体植入和植入式晶状体等手术干预措施可有效治疗近视,但这些手段并不能停止近视的进展。阻止高度近视进展的最新手术策略包括巩膜下注射间充质干细胞和多巴胺注射[39],而阻止眼轴增长的最有效手术方法是后巩膜加固术(PSR)。PSR 涉及修改巩膜重塑,这导致眼球壁的直接机械加固,可以有效稳定视力,防止眼轴伸长,延缓脉络膜视网膜变性,最终阻止近视的进展[40]。

6　小　结

现有研究已经证明,基因积极或消极的变化成为近视发展的分子基础。全基因组分析技术的发展为系统研究遗传变异与人类近视的相互作用提供了机会。文中所提到的候选基因被证明在引起家族性近视风险中占到很小的一部分,且在大多数所确定的基因中包括了与种族、民族、环境等多重因素对遗传影响的作用,所以尽管进行了相关的蛋白质功能预测以及细胞和动物实验,但目前大多数近视的确切遗传因素在很大程度上是未知的。在这种情况下,要对近视基因相关问题达成共识是很困难的。并且对鉴定新的遗传位点投入的精力往往大过后续的研究。而日益丰富的近视防控手段如何与相关的基因位点相结合,这也是一大问题。因此,明确高度近视的主要致病基因,对鉴定近视新治疗的药物靶点和开发更有效的高度近视治疗方案具有重要意义。

利益冲突　无

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