

莱伯遗传性视神经病变“三重打击”致病机制研究进展

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[摘 要] 莱伯遗传性视神经病变(LHON)是一种典型的线粒体遗传性视神经疾病,主要累及视网膜神经节细胞,导致不可逆性视力损伤。单一线粒体 DNA(mtDNA)原发突变虽构成疾病发生基础,但无法充分解释其不完全外显、男性高发及临床异质性。基于家系遗传分析和功能研究,本文归纳 LHON 的“三重打击”致病机制:第一重打击为 mtDNA 原发突变,如 m.11778G>A、m.14484T>C 和 m.3460G>A,主要损伤呼吸链复合体 I 功能并削弱线粒体能量代谢;第二重打击为 mtDNA 修饰变异、mtDNA 单倍群遗传背景和核修饰基因变异,降低发病阈值并影响 mtDNA 原发突变携带者外显率;第三重打击为非遗传性诱因,包括外源性暴露(如吸烟、饮酒、线粒体毒性药物暴露等)和内源性个体生理状态异常(如性激素水平相关的线粒体保护差异等),进一步削弱线粒体代偿能力,最终促使视网膜神经节细胞损伤。本文为理解 LHON 的致病机制提供了一个整合性框架,以期为 LHON 高危个体筛查、遗传咨询、风险预测和机制驱动的临床研究提供参考。



[关键词] 莱伯遗传性视神经病变;线粒体 DNA;母系遗传;线粒体病;综述

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“Triple-hit” pathogenic mechanism of Leber hereditary optic neuropathy

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[**Abstract**] Leber hereditary optic neuropathy (LHON) is a typical mitochondrial genetic optic neuropathy predominantly affecting retinal ganglion cells and leading to irreversible visual damage. Although a single primary mitochondrial DNA (mtDNA) mutation provides the basis for the disease, it cannot fully explain its incomplete penetrance, male predominance, and clinical heterogeneity. Based on familial genetic analysis and functional studies, this review summarizes the “triple-hit” pathogenic mechanism of LHON. The first hit consists of primary mtDNA mutations, such as m.11778G>A, m.14484T>C, and m.3460G>A, which primarily impair respiratory chain complex I function and weaken mitochondrial energy metabolism. The second hit involves mtDNA modifier variants, mtDNA haplogroup backgrounds, and nuclear modifier gene variants, which lower the threshold for disease onset and affect the penetrance in primary mtDNA mutation carriers. The third hit consists of non-genetic triggers, including exogenous exposures (such as smoking, alcohol consumption, and exposure to mitochondrial-toxic drugs) and endogenous physiological abnormalities (such as sex hormone-related differences in mitochondrial protection), which further weaken mitochondrial compensatory capacity and ultimately precipitate retinal ganglion cell damage. This review provides an integrated framework for understanding the pathogenic mechanism of LHON, aiming to serve as a reference for the screening of high-risk individuals, genetic counseling, risk prediction, and mechanism-driven clinical research of LHON.

[**Key words**] Leber hereditary optic neuropathy; Mitochondrial DNA; Maternal inheritance; Mitochondrial disorder; Review

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[**缩略语**] 莱伯遗传性视神经病变 (Leber hereditary optic neuropathy, LHON); 线粒体 DNA (mitochondrial DNA, mtDNA); NADH 泛醌氧化还原酶 (NADH-ubiquinone oxidoreductase, ND); 腺苷三磷酸 (adenosine triphosphate, ATP); 转运 RNA (transfer RNA, tRNA)

LHON 是一种典型的遗传性线粒体疾病, 主要累及视网膜神经节细胞, 造成双眼视力不可逆损伤。LHON 总体患病率较低, 但在遗传性视神经病变中较为常见。该病好发于青少年男性, 患者平均发病年龄约为 21 岁^[1], 在儿童及 65 岁以上老年人中亦有报道^[2-3]。流行病学研究显示, 不同地区 LHON 患病率存在差异, 如在我国河北邢台地区患病率约为 1.09/10 万^[4]; 在欧洲, 基于多项临床研究的荟萃分析估算患病率约为 2.23/

10 万^[5]。该病还具有明显的性别倾向性, 男性发病率明显高于女性, 男女患者比例通常在 3:1 至 5:1 之间^[1]。

LHON 多表现为急性或亚急性、无痛性的双眼视力丧失, 双眼视力丧失通常先后发生, 间隔数周至数月。早期眼底检查可见视神经乳头充血、视网膜神经纤维层水肿及微血管扩张; 慢性期则表现为颞侧或弥漫性视神经萎缩^[6]。多数患者仅表现为视力障碍, 但部分患者可伴有运动障

碍等其他神经系统异常^[7]。目前该病尚无根治方案和有效预防手段,患者预后差异较大,仅少数患者视力可自发恢复,多数遗留长期视功能损害^[8-9]。

中国大规模队列研究显示,LHON平均外显率约为20%^[10],超过半数患者无明确家族史,且相同致病性mtDNA突变者的发病年龄、外显率、性别偏倚和表型严重程度存在差异,传统“单一mtDNA突变—母系遗传”理论难以完全解释疾病发生规律。本文通过系统梳理LHON相关mtDNA原发突变谱、遗传修饰因素、非遗传性诱因,总结归纳LHON“三重打击”致病机制,以期为该病的机制解析、遗传咨询、风险预测及高危个体管理提供参考。

1 线粒体DNA原发突变造成基础性线粒体功能缺陷

目前已报道40多种与LHON发病相关的mtDNA突变^[7],其中m.11778G>A、m.14484T>C和m.3460G>A是LHON的主要致病位点^[11],基因检测这三种突变是LHON分子诊断的基石。

1988年,Wallace等^[12]通过北美家系研究首次鉴定出ND4基因m.11778G>A突变,该突变导致复合体I的ND4亚基第340位精氨酸替换为组氨酸,损害了复合体I结构和功能完整性。生化功能研究显示,m.11778G>A突变可导致复合体I依赖性呼吸受损^[13],破坏电子传递并降低氧化磷酸化效率^[14]。该突变还消除了野生型序列中原有的限制性内切酶SfaNI识别位点,使酶切后的DNA片段长度发生改变,因此早期可通过聚合酶链反应—限制性片段长度多态性分析对m.11778G>A突变进行检测。

1991年,Howell等^[15]和Huoponen等^[16]均发现ND1基因m.3460G>A突变,该突变导致复合体I的ND1亚基第52位丙氨酸替换为苏氨酸,可造成复合体I功能缺陷,影响电子传递和ATP生成,并增加氧化应激风险,导致视网膜神经节细胞能量代谢失衡和凋亡。

1992年,Johns等^[17]发现ND6基因m.14484T>C突变,该突变导致ND6亚基第64位甲硫氨酸被缬氨酸取代,影响质子转位。与其他原发突变不同,m.14484T>C突变常以同质性状态出现,但外显率较低。与m.11778G>A突变(约4%)^[18]或m.3460G>A突变(约20%)^[19]比较,m.14484T>C突

变相关的LHON患者视力自发恢复率更高(约37%)^[20],可能与其对复合体I相关的最大呼吸速率的影响相对较轻有关^[13]。

中国与欧美国家LHON患者mtDNA突变分布存在差异。在高加索LHON患者中,原发突变m.11778G>A、m.14484T>C和m.3460G>A总体检出率约为90%^[7];但在中国LHON患者中,其总体检出率相对较低(约为46.5%)^[11]。从上述三种原发突变的内部构成来看,m.11778G>A突变在中国LHON患者中占绝对优势。在346例携带三种原发突变的中国LHON先证者的家系中,m.11778G>A、m.14484T>C和m.3460G>A的占比分别为90.17%、8.67%和1.16%^[21];而在1512例三种原发突变阳性的欧美国家LHON患者中,上述三种突变的占比分别为69%、17%和13%^[1]。

部分LHON患者还可携带其他LHON相关mtDNA基因变异(表1),这些变异主要集中在ND1、ND4、ND6等基因^[22-33]。

表1 与莱伯遗传性视神经病变相关的罕见线粒体DNA变异位点及其所在基因

Table 1 Rare mtDNA variants and their corresponding genes associated with Leber hereditary optic neuropathy

变异位点	基 因	变异位点	基 因
m.3394T>C ^[22]	ND1	m.3700G>A ^[28]	ND1
m.4171C>A ^[23]	ND1	m.12338T>C ^[29]	ND5
m.3472T>C ^[24]	ND1	m.3733G>C ^[30]	ND1
m.10197G>A ^[25]	ND3	m.14459G>A ^[31]	ND6
m.3635G>A ^[26]	ND1	m.3866T>C ^[32]	ND1
m.10663T>C ^[27]	ND4L	m.14502T>C ^[33]	ND6

ND:NADH泛醌氧化还原酶。

2 遗传修饰因素降低莱伯遗传性视神经病变发病阈值

尽管LHON一直被视为母系遗传疾病,但其遗传特征呈现复杂性:多数家系为散发,仅单个成员发病;而具有母系聚集倾向的家系往往同时携带多个mtDNA突变或存在其他遗传修饰因素^[29]。这些发现提示单一原发突变通常不足以决定疾病外显,多因素叠加可进一步降低疾病发病阈值,从而使家系更易表现出母系遗传特征。

2.1 mtDNA修饰变异

原发突变与修饰变异共同存在时可进一步增加LHON发病风险。表2总结了多种线粒体

修饰变异及其作用,这些线粒体修饰变异的发现为阐明 LHON 长期存在的不完全外显的分子机制提供了关键线索^[34-41]。例如,线粒体 *ND1* 基因 m.3394T>C 可与 m.11778G>A 等 mtDNA 原发突变协同作用改变疾病临床表现^[34]。具体而言, m.3394T>C 变异单独存在时的外显率较低(约为 13.5%),线粒体功能缺陷仅为轻度;其与原发突变共同存在时可破坏复合体 I 的组装和稳定性,加重呼吸链缺陷、减少 ATP 合成及增加活性氧产生,使外显率上升至 34.5% 以上。Qu 等^[35]发现在一个高外显率的中国 LHON 家系中 m.11778G>A 突变与 m.4435A>G 变异共同存在,后者位于线粒体 *tRNA^{Met}* 反密码子相邻的保守第 37 位。与仅携带 m.11778G>A 者比较,同时携带 m.11778G>A 和 m.4435A>G 者中 *tRNA^{Met}* 表达水平显著下降,提示 m.4435A>G 变异可通过影响线粒体 tRNA 代谢加重 m.11778G>A 突变所致的线粒体功能障碍,从而提高 LHON 的外显率并加重表型。

2.2 mtDNA 单倍群遗传背景

原发突变所处的线粒体遗传背景也会影响 LHON 的外显率和表型严重程度。线粒体单倍群是由一组共同母系遗传的 mtDNA 多态性位点构成的遗传背景^[42],可通过影响氧化磷酸化效率、活性氧生成水平和线粒体代偿能力调节原发突变的致病效应。因此,同一 LHON 相关原发突变在不同 mtDNA 单倍群遗传背景下可能呈现不同的外显率、发病年龄和临床预后。这种影响在不同人群中存在差异:在欧洲国家 LHON 患者中,单倍群 J 会显著提高携带 m.11778G>A、m.14484T>C 等原发突变者的 LHON 外显率,是主要的危险因素^[43];而在中国 LHON 患者中,单倍群 D4j、M7b1'2

和 M10 会显著增加 LHON 易感性^[39, 44-45]。

2.3 核修饰基因变异

核修饰基因变异也是影响 LHON 外显率的重要因素。线粒体蛋白质组中绝大多数蛋白质由核基因编码,因此线粒体的呼吸链组装、蛋白质翻译、氧化磷酸化及抗氧化应激等核心过程均高度依赖这些核基因产物^[46]。核修饰基因变异可与 mtDNA 原发突变协同作用,调节疾病易感性和表型严重程度。X 连锁核修饰基因 *PRICKLE3* c.157C>T 变异见于多个 LHON 家系,该变异可影响线粒体 ATP 合酶组装、稳定性及功能,导致线粒体能量代谢异常,并与 m.11778G>A 突变协同加重线粒体功能障碍^[47]。*YARS2* 编码线粒体酪氨酰-tRNA 合成酶,催化酪氨酸与对应 tRNA 结合,对线粒体蛋白质合成至关重要。研究发现, *YARS2* c.572G>T 变异与 m.11778G>A 突变协同作用导致细胞内 ATP 水平低于维持正常生理功能所需的临界阈值^[48],触发个体从无症状转变为严重病变。上述研究明确了线粒体突变与核修饰基因变异在 LHON 发病中的协同作用,既解释了疾病临床表现的异质性,也提示核修饰基因可能成为 LHON 干预的新靶点。

3 非遗传性诱因削弱线粒体代偿能力

LHON 原发突变主要造成复合体 I 功能受损、ATP 生成不足和氧化应激增强;外界暴露或个体生理状态异常则可加重线粒体能量代谢障碍,进一步削弱线粒体代偿储备并加速代偿失衡,使视网膜神经节细胞更易发生不可逆损伤^[7]。吸烟是目前证据较充分的危险因素,研究显示其与 LHON 携带者视力丧失相关且可能具有剂量效

表 2 部分已报道的线粒体 DNA 修饰变异及其作用

Table 2 Selected reported mtDNA modifier variants and their reported effects

基 因	修饰变异	协同作用的原发突变	可能的修饰作用	参考文献
<i>ND1</i>	m.3394T>C	m.11778G>A	加重 m.11778G>A 突变相关线粒体功能缺陷	[34]
<i>tRNA^{Met}</i>	m.4435A>G	m.11778G>A	增加家系中 LHON 的外显风险和表型严重程度	[35]
<i>tRNA^{Thr}</i>	m.15951A>G	m.11778G>A	影响 m.11778G>A 突变相关 LHON 表型严重程度	[36]
<i>tRNA^{Glu}</i>	m.14693A>G	m.14484T>C	通过影响线粒体 tRNA 功能和线粒体稳态提高 LHON 外显率	[37]
<i>ND1</i>	m.3866T>C	m.11778G>A	破坏复合体 I 的组装和稳定性,降低其活性	[38]
<i>ND4</i>	m.11696G>A	m.11778G>A	线粒体单倍群 D4j 相关变异	[39]
<i>ND6</i>	m.14502T>C	m.11778G>A	进一步损伤复合体 I 功能和线粒体能量代谢	[40]
<i>12S rRNA</i>	m.1555A>G	m.11778G>A	影响 LHON 外显率	[41]

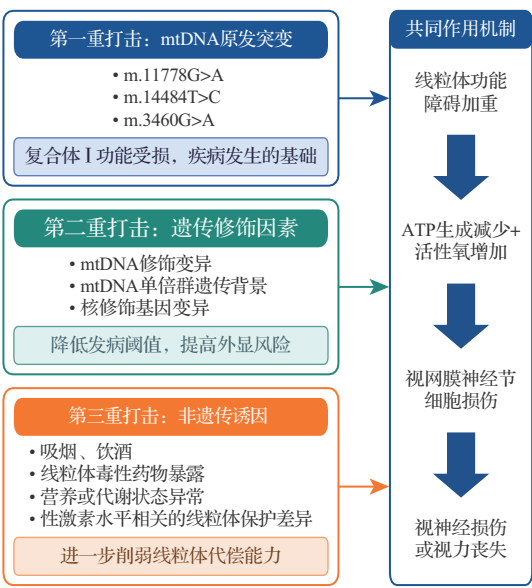
ND: NADH 泛醌氧化还原酶; tRNA: 转运 RNA; Met: 甲硫氨酸; LHON: 莱伯遗传性视神经病变; Thr: 苏氨酸; Glu: 谷氨酸; rRNA: 核糖体 RNA。

应^[49],其机制可能涉及降低 mtDNA 拷贝数,抑制氧化磷酸化并削弱活性氧清除能力,进而加重线粒体功能障碍^[50]。饮酒、头部外伤、工业毒物和线粒体毒性药物也可能诱导 LHON 发病^[51-52],但相关证据多来自病例报道或回顾性研究,证据强度弱于吸烟,或可作为潜在促发因素。这些因素可能通过加重氧化应激、干扰线粒体呼吸链功能和减少 ATP 生成,使已存在复合体 I 缺陷的视网膜神经节细胞更易发生代偿失衡。此外,个体生理状态亦可影响 LHON 外显率和表型严重程度。雌激素对线粒体具有显著保护作用,可改善线粒体能量代谢并减轻氧化应激损伤,这可能部分解释了 LHON 的性别差异(男性高发、女性外显率较低)^[53-54]。眼压升高可能增加视网膜神经节细胞轴突运输和能量代谢负担,在遗传易感背景下进一步加重视神经损伤^[55]。

4 结 语

LHON 的发病过程并非由单一 mtDNA 原发突变决定,更可能是原发突变、遗传修饰因素以及非遗传性诱因共同作用的结果。基于大样本家系研究和功能实验资料,本文整理归纳提出 LHON 的“三重打击”致病机制(图 1):第一重打击为 mtDNA 原发突变,主要包括 m.11778G>A、m.14484T>C 和 m.3460G>A 等经典致病突变。此类突变主要影响呼吸链复合体 I 功能,导致 ATP 生成减少、氧化应激增强及视网膜神经节细胞能量代谢障碍增加,是 LHON 发生的基础条件。第二重打击为遗传修饰因素,包括 mtDNA 修饰变异、mtDNA 单倍群遗传背景和 *PRICKLE3*、*YARS2* 等核修饰基因变异。这些因素可进一步影响线粒体翻译、呼吸链组装、氧化磷酸化效率和细胞抗应激能力,从而降低 LHON 发病阈值并提高突变携带者的外显率。第三重打击为非遗传性诱因,包括外源性暴露(如吸烟、饮酒、线粒体毒性药物暴露等)和内源性个体生理状态异常(如性激素水平差异引起的线粒体保护效应强弱不同)。这些因素均可能在遗传易感背景下进一步削弱线粒体代偿能力,最终促进视网膜神经节细胞损伤和视神经病变发生。

“三重打击”致病机制提示 LHON 的防治应同时针对线粒体功能和遗传缺陷开展。当前的治疗策略围绕线粒体功能修复和遗传缺陷校正



mtDNA:线粒体 DNA;ATP:腺苷三磷酸。
图 1 莱伯遗传性视神经病变“三重打击”致病机制示意图
Figure 1 The “triple-hit” pathogenic mechanism of Leber hereditary optic neuropathy

两大方向,形成覆盖疾病不同阶段的多维度干预体系。药物治疗是 LHON 最常用的临床干预方式,其核心目标是改善线粒体功能和缓解氧化应激。艾地苯醌可激活替代能量通路发挥视神经保护作用,但其疗效高度依赖早期干预,若视网膜神经节细胞发生不可逆损伤,视觉获益的概率将相应降低^[56];补充维生素 A 可能调节视网膜代谢和线粒体功能^[57],为 LHON 治疗提供了新方法。精准基因治疗利用腺相关病毒载体将正常基因 *ND4* 或 *ND6* 递送至受损视网膜神经节细胞,如针对 *ND4* 基因突变的 LHON 腺相关病毒载体基因疗法 LUMEVOQ[®] 在 m.11778G>A 突变的患者中显示长期视觉获益,但其中载体转运、治疗时机和疗效评估仍存在挑战^[58]。碱基编辑技术(DdCBE、TALED)可直接修复 mtDNA 原发突变^[59-60],实现原位修复,但眼部递送效率和长期安全性尚待优化。线粒体捐赠联合植入前遗传学检测虽可阻断致病基因代际传递^[61],但该策略仍面临技术和伦理双重瓶颈,目前尚停留在基础研究阶段。总之,LHON 干预策略涵盖代谢支持、基因替代、突变修复和遗传阻断,未来需突破临床转化瓶颈以实现更精准、高效且有根治潜力的治疗。

综上,LHON 的发病机制具有多因素叠加特征。mtDNA 原发突变构成疾病发生的遗传基础,

mtDNA 修饰变异、mtDNA 单倍群遗传背景及核修饰基因变异可进一步影响外显率和表型严重程度,而吸烟、线粒体毒性药物暴露和个体生理状态异常等非遗传因素可能削弱线粒体代偿能力,共同加剧视网膜神经节细胞损伤及视力丧失。未来研究应重点解析 mtDNA 与核修饰基因相互作用、线粒体单倍群遗传背景及非遗传诱因对疾病外显的调控机制,进一步建立可量化的疾病易感阈值模型,并结合多组学和大样本家系临床资料提高高危个体识别、遗传咨询和风险预测的准确性。

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数据可用性 本研究未生成任何新数据集,所有分析数据均已公开,并已在文中明确标引

Data Availability This study did not generate any new datasets, all data analyzed are publicly available, and have been properly cited

医学伦理 本研究不涉及人体或动物实验

Ethical Approval This study does not contain any studies with human participants or animals performed by any of the author

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