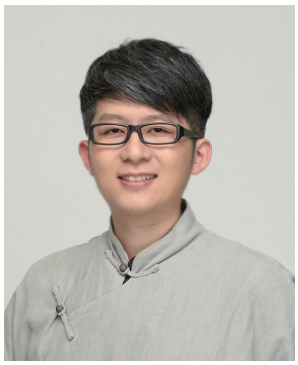

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精子鞭毛轴丝结构相关基因异常与弱精子症

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摘要 精子鞭毛轴丝是精子运动的主要动力来源, 参与鞭毛组装和运动调控的基因变异可导致精子活力降低, 从而引起弱精子症(asthenozoospermia, ASZ)。常见的弱精子症包括两大类: (1) 精子鞭毛在光学显微镜下无明显畸形, (2) 精子鞭毛多发形态异常(multiple morphological abnormalities of the sperm flagella, MMAF)。弱精子症主要由轴丝组分编码基因变异所致, 在过去的十年里, 在揭示致病基因方面取得了显著进展。在MMAF的遗传研究领域, 中国和法国是两个涉及比较广的国家。通过系统文献检索和Meta分析中国和法国关于MMAF的基因变异研究, 纳入1 796名不育男性参与者, 结果表明, 在中国的弱精子症患者中, *DNAH1*基因的突变比例显著高于法国(OR=4.97, 95% CI=[1.70; 14.49], P<0.01)。而*CFAP43*、*CFAP44*、*CFAP251*等基因在两国间未显示显著性差异(P>0.05)。这一发现为理解弱精子症的遗传变异的多样性奠定了基础。

关键词 弱精子症; 精子鞭毛多发形态异常; 中国; 法国; 差异

Abnormal Genes Related to the Structure of Sperm Flagellar Axoneme and Asthenozoospermia

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Abstract Sperm flagellar axoneme is the main power source of sperm motility. Gene mutations involved in flagellar assembly and motility regulation can lead to decreased sperm motility, resulting in ASZ (asthenozoospermia). There are two common types of asthenozoospermia: (1) no obvious deformity of sperm flagella under

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optical microscope; (2) MMAF (multiple morphological abnormalities of the sperm flagella). Asthenozoospermia is mainly caused by mutations in genes encoding axoneme components. In the past decade, significant progress has been made in revealing pathogenic genes. In the field of genetic research of MMAF, China and France are the two most widely involved countries. Through systematic literature search and meta-analysis of MMAF gene mutation studies in China and France, 1 796 infertile male participants were included. The results showed that the proportion of *DNAH1* gene mutation in Chinese asthenozoospermia patients was significantly higher than that in France (OR=4.97, 95% CI=[1.70; 14.49], $P<0.01$). However, *CFAP43*, *CFAP44*, *CFAP251* and other genes showed no significant difference between the two countries ($P>0.05$). This finding lays a foundation for understanding the diversity of genetic variations in asthenozoospermia.

Keywords asthenozoospermia; multiple morphological abnormalities of the sperm flagella; China; France; differences

据世界卫生组织(World Health Organization, WHO)的数据统计, 全球约有1.86亿人口患有不孕不育, 占全球人口的约20%[1-2]。《柳叶刀中国妇幼健康特邀重大报告》显示, 2007—2020年间, 中国的不孕发病率从12%升至18%, 且呈现增加趋势[3]。不孕不育已经成为影响夫妇双方和家庭的全球性健康问题, 有10%~15%的夫妇受到不孕不育的困扰[4]。男性因素是约一半的夫妇中的主要原因或促成原因, 其中80%的原发男性不育症病例与弱精子症有关[5-6]。

《世界卫生组织人类精液检查与处理实验室手册》(第6版)将弱精子症定义为精液中前向运动的精子比例低于参考值下限(32%)[7], 而严重性弱精子症的特征还包括精子完全不具有运动能力, 或者在精液样本中精子活动能力极低, 有研究报道, 精子的不动性与遗传障碍有关, 并且其遗传机制一直尚未被明确解析[8]。引起弱精子症的病因可以被概括为先天性病因和获得性病因两大类, 先天性原因涵盖了精子运动相关基因变异、线粒体基因缺失、膜离子通道蛋白异常、精子鞭毛的结构和功能缺陷等; 而获得性原因则包括其他疾病或外界因素引起的精子损伤, 例如生殖道感染、精索静脉曲张、甲状腺疾病、肥胖、地理环境、生活习惯和心理压力等[9]。在遗传学病因方面, 原发性纤毛运动障碍(primary ciliary dyskinesia, PCD)和精子鞭毛多发形态异常(multiple morphological abnormalities of the sperm flagella, MMAF)以及精子尾部鞭毛的精子环结构缺陷尤为常见。PCD是一种由纤毛和鞭毛运动缺陷引起的常染色体隐性遗传性纤毛运动障碍, 其主要表现为黏液纤毛清除严重受损, 从而出现多种主要影响呼吸系统的临床综合征, 此外, 许多PCD的男性患者存在精子运动障碍和/或附睾管纤毛功能障碍, 从而导致男性不育[10]。

MMAF被定义为由精子鞭毛的形态异常引起的孤立性弱精子症, 这种表型常被描述为“短尾”或“扁尾”, 是导致男性不育的最严重的精子形态缺陷之一。在MMAF患者中, 精子鞭毛的形态异常不仅包括短尾扁尾, 还可能涉及到其他鞭毛的异常, 如不规则、卷曲或缺失。这一异常表型与精子细胞镶嵌有密切关联, 呈现出轴突周围结构的严重紊乱, 其中包括纤维鞘发育的不良。除了鞭毛的外观异常之外, 在超微结构水平上, 可普遍观察到中心对(central pair, CP)、外周微管双联体(doublet microtubule, DMT)或动力蛋白臂(dynein arm, DA)的缺失现象[11]。精子鞭毛作为精子尾部的一种特殊细胞器, 通过规律性的摆动维持精子的活力, 使精子能够在女性生殖道中向卵子游动, 以完成受精过程[12]。轴丝是精子尾部鞭毛的核心结构, 负责细胞的运动和信号传递, 由9个微管二联体(doublet microtubule, DMT)环绕着中央2个单体微管(singlet microtubule)组成[13]。DMT上连接着内侧动力蛋白臂(inner dynein arm, IDA)和外侧动力蛋白臂(outer dynein arm, ODA), 它们作为马达蛋白复合物, 共同调节轴丝的摆动, 维持精子的游动能力[14]。外周二联体通过连接蛋白–动力蛋白调节复合物(nexin-dynein regulatory complex, N-DRC)相互连接[15], 并通过被称为径向辐条(radial spokes, RSs)的多蛋白t形结构与中心双联体连接, 内含微管内蛋白(microtubule inner protein, MIP), 上述组分共同组成经典的“9+2”结构[16-18]。这些蛋白质复合物的结构和功

能对于精子鞭毛的稳定性和运动调控发挥关键作用。在MMAF中，鞭毛结构的缺陷是导致精子运动能力异常的关键因素之一，特别是涉及轴丝、微管以及动力蛋白臂，这些结构的缺陷会对精子的正常游动和受精过程产生影响。

1 光学显微镜下精子鞭毛无明显畸形的弱精子症

第一类光镜下无明显畸形的弱精子症是指精子的形态在光学显微镜下正常，但是精子的运动能力低下，主要由精子鞭毛的微管二联体结构或功能异常所致。微管二联体(doublet microtubule, DMT)的管腔表面高度修饰有微管内蛋白(microtubule inner protein, MIP)，这对DMT的稳定性十分重要，先前对衣藻鞭毛和哺乳动物气管纤毛的冷冻电镜分析表明，在不同系统的DMT中，来自不同生物体的MIP含有物种特异性。光学显微镜下精子鞭毛无明显畸形的弱精子症目前常见的病因主要包括了轴丝组分MIP、动力蛋白臂、N-DRC和RS部分组分的编码基因异常。2023年6月，研究团队解析了小鼠精子的DMT结构，共发现49种蛋白，包括45种与DMT相关的MIP。通过招募精子形态正常，但是精子的运动功能异常并无法完成正常受精的281位非MMAF患者，对其进行外显子测序分析，发现其中32位患者携带了与MIP蛋白相关的突变，并且未携带其他的基因变异，呈17种不同的突变形式，共涉及到10种MIP蛋白。结构分析显示，这些突变位点在精子DMT中的分布较为分散，表明不同区域的DMT异常都可能导致DMT结构被破坏。这一新的亚型被命名为“MIP突变相关弱精子症(MIP variants-associated asthenozoospermia, MIVA)”。该亚型主要以精子运动能力受损，鞭毛摆动异常和轴丝结构受损，但形态无明显的缺陷为特征，类似的表型也可以由动力蛋白编码基因异常导致[19]。此外，N-DRC组分中的*TCTE1*/*DRC5*的双等位基因变异在一例病例中被报道可能是弱精子症的潜在致病基因。光学显微镜下显示携带这些变异的精子数量正常，形态结构正常，但运动能力下降，特别是向前运动能力下降[20]；RS组分中的*LRRC23*在功能缺失的状态下，患者精子运动能力几乎完全丧失，有趣的是其精子鞭毛在光学显微镜下观察并未发现明显的形态异常[21]。

2 鞭毛多发形态异常的弱精子症

为了比较中国和法国的男性在精子鞭毛多发形态异常的弱精子症的致病基因突变方面的差异，我们进行了系统性Meta分析，检索了PubMed和Web of Science数据库中2004年至2023年12月发表的文献，使用了“Asthenozoospermia”、“sperm motility”、“Chinese”、“China”、“France”和“French”等英文关键词，未使用语言过滤器。纳入标准为：研究对象为18岁以上的男性，采用队列研究、病例对照研究或人群调查设计，报告了中国和法国人群中弱精子症患者的总数、基因变异情况以及遗传学基础的观察性研究，发表在中文或英文期刊上，研究对象为中国人和法国人，研究报告了弱精子症的遗传学基础的数据，如基因型、基因表达以及突变率。排除标准为：涵盖其他年龄段或性别的研究对象，其他类型的研究设计，未报告弱精子症数据，发表在非英文或非中文期刊上、干预性研究，未报告遗传学基础数据的研究以及无法获取全文的文章(图1)。

文献质量评价采用Cochrane系统评价手册标准，统计学分析使用R软件(R Core Team 2023, v4.3.1)及其Meta包(版本6.5.0)。效应量以比值比(odds ratio, OR)和95%置信区间(confidence interval, CI)表示，平均值比较采用双尾非配对Student *t*检验或Wilcoxon检验，结果以平均值±SEM呈现，根据I^2值估计异质性程度：I^2>50%表示异质性高[22]。各组之间的显著差异表现为*P<0.05、**P<0.01和***P<0.001。

系统检索后共得到50 714条记录，去重后剩下40 519条。排除了不相关文献类型和进行标题及摘要筛选后，剔除了39 308项研究。剩余的1 211条记录经过全文评估，最终纳入38篇符合条件的研究(30篇来自中国，8篇来自法国)。文献主要因为不符合纳入标准、研究方向不相关或病人招募较少而被排除。纳入文献的基本信息见表1。

图2展示了中国和法国MMAF相关基因的具体定位模式，在这个模式图中，*DRC1*、*DRC2*和*DRC4*位于N-DRC复合体，*CFAP69*、*SPEF2*、*CFAP47*、*CFAP54*、*CFAP65*和*KIF9*位于中央微管，*CEP135*和*DZIP1*位于中心粒，*DNAH5*、*DNAH8*、*DNAH11*和*DNAH17*位于外动力蛋白臂，*DNAH1*、*DNAH2*、*DNAH6*、*DNAH10*和*WDR63*位于内动力蛋白臂。另外，*CFAP251*位于放射辐条，*CFAP43*和*CFAP44*位于

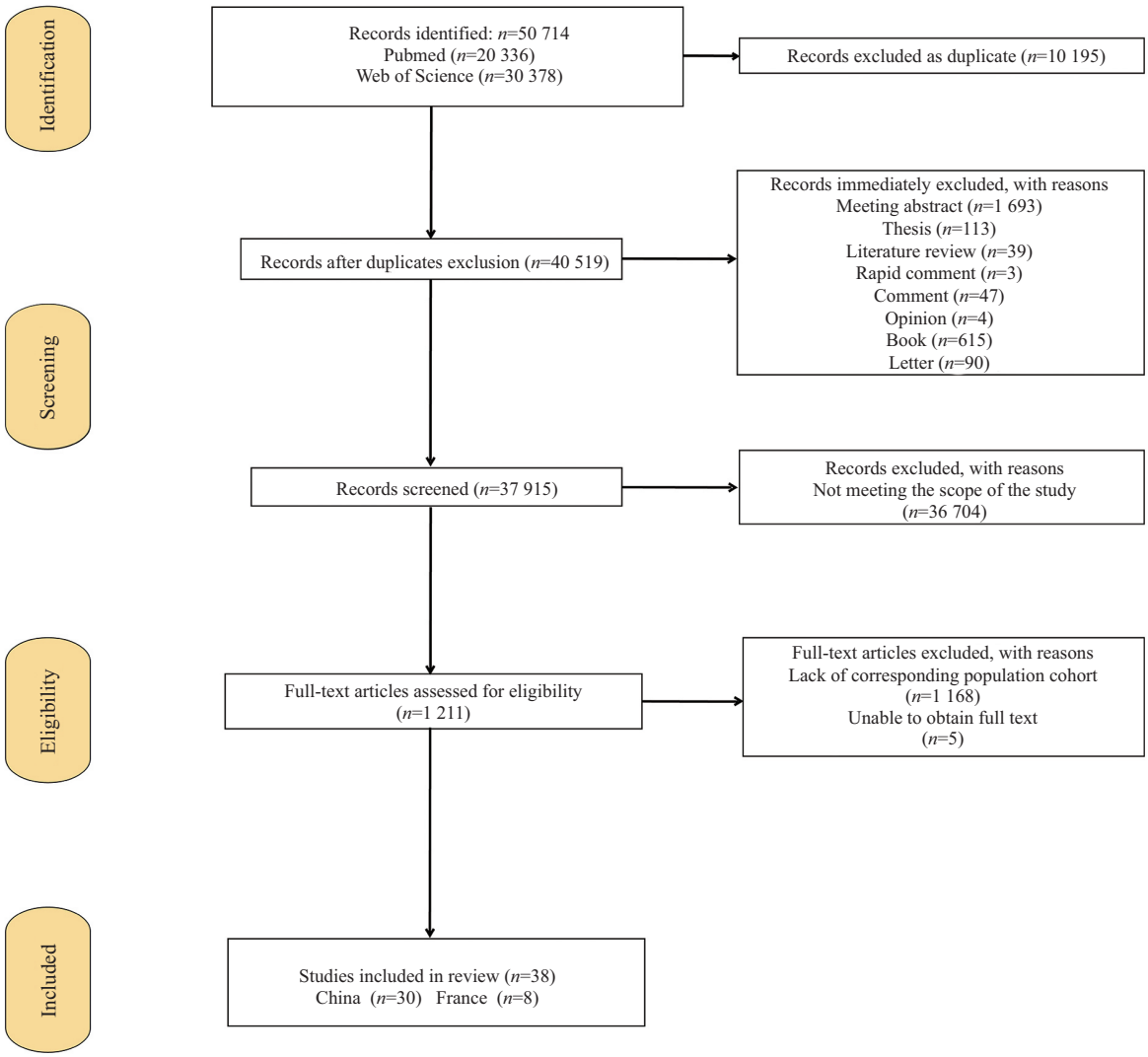


图1 系统性综述的流程图

Fig.1 Flow chart of systematic review

T/TH(tether-tether head)复合体, 此外, 还有一些非轴丝组分, 包括*FSIP2*、*ARMC2*、*DNHD1*、*TTC29*、*AKAP3*、*TTC21A*、*SLC26A8*和*IFT74*等。

如图3和表2所示, 森林图和Meta分析结果表明, 在中国和法国共同研究的9个突变基因中, *DNAH1*在中国的弱精子症患者中的突变率显著高于法国患者(OR=4.97, 95% CI=[1.70; 14.49], $P<0.01$), 然而, *CFAP43*、*CFAP44*、*CFAP251*、*FSIP2*、*ARMC2*、*DNHD1*、*TTC29*以及*CFAP69*等基因的突变率在两个地区之间没有显著差异($P>0.05$)。关于这9个基因在两个国家的纳入队列人数和突变信息, 请参见表3。此外, 我们对在中国或法国单独研究的MMAF相关基因的突变情况进行了总结, 包括突变人数、总人数以及相应的突变率等信息, 我们还将散在报道的未纳入的突变率病例, 例如*DNAH17*和*SLC26A8*等基因, 纳入了我们的研究列表中(表4和表5)。

3 讨论

研究者们在研究MMAF相关变异基因时, 发现了约40个导致精子鞭毛结构和功能异常的基因变异。中国的科学家们鉴定了其中的28个变异基因, 包括*DNAH2*、*CFAP47*、*CEP135*和*SPEF2*等, 法国的科学家们发现了12个变异基因, 包括*IFT74*、*DRC2*、*DRC4*和*TTC29*等。目前, 在中国发现的19个基因包括*DNAH8*、*CFAP47*、*CFAP65*等, 而法国报道的基因有3个, 即*IFT74*、*DRC2*和*DRC4*。此外, 中国和法国共同研究的致病基因包括*DNAH1*、*CFAP43*、*CFAP44*、*CFAP251*、*FSIP2*、*ARMC2*、*DNHD1*、*TTC29*以及*CFAP69*。接下来, 我们分析了这9个基

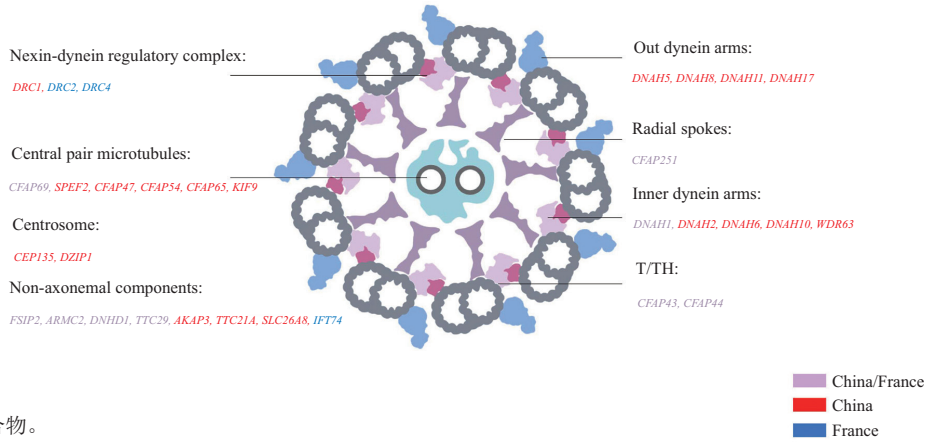
表1 纳入文献的基本特征

Table 1 Basic characteristics of the included literature

年份 Year	作者 Author	标题 Title	纳入标准 Incorporate standards
2017	TANG S, WANG X, LI W, et al[23]	Biallelic mutations in *CFAP43* and *CFAP44* cause male infertility with multiple morphological abnormalities of the sperm flagella	Chinese patients 3/30 *CFAP43* 1/30 *CFAP44*
2018	YANG X, ZHU D, ZHANG H, et al[24]	Associations between *DNAH1* gene polymorphisms and male infertility	Chinese patients 6/287 *DNAH1*
2018	DONG FN, AMIRI-YEKTA A, MARTINEZ G, et al[25]	Absence of *CFAP69* causes male infertility due to multiple morphological abnormalities of the flagella in human and mouse	French patients 2/78 *CFAP69*
2018	COUTTON C, VARGAS AS, AMIRI-YEKTA A, et al[26]	Mutations in *CFAP43* and *CFAP44* cause male infertility and flagellum defects in Trypanosoma and human	French patients 10/78 *CFAP43* 6/78 *CFAP44*
2018	MARTINEZ G, KHERRAF ZE, ZOUARI R, et al[27]	Whole-exome sequencing identifies mutations in *FSIP2* as a recurrent cause of multiple morphological abnormalities of the sperm flagella	French patients 4/78 *FSIP2*
2019	HE X, LI W, WU H, et al[28]	Novel homozygous *CFAP69* mutations in humans and mice cause severe asthenoteratospermia with multiple morphological abnormalities of the sperm flagella	Chinese patients 2/35 *CFAP69*
2019	ZHU D, ZHANG H, WANG R, et al[29]	Association of *DNAH11* gene polymorphisms with asthenozoospermia in Northeast Chinese patients	Chinese patients 1/87 *DNAH11*
2019	LIU W, HE X, YANG S, et al[30]	Bi-allelic mutations in *TTC21A* induce asthenoteratospermia in humans and mice	Chinese patients 3/65 *TTC21A*
2019	LORES P, DACHEUX D, KHERRAF Z E, et al[31]	Mutations in TTC29, encoding an evolutionarily conserved axonemal protein, result in asthenozoospermia and male infertility	French patients 5/167 TTC29
2019	LIU C, HE X, LIU W, et al[32]	Bi-allelic mutations in *TTC29* cause male subfertility with asthenoteratospermia in humans and mice	Chinese patients 3/80 *TTC29*
2019	COUNTTON C, MARTINEZ G, KHERRAF Z E, et al[33]	Bi-allelic mutations in *ARMC2* lead to severe astheno-teratozoospermia due to sperm flagellum malformations in humans and mice	French patients 4/162 *ARMC2*
2019	LI Y, SHA Y, WANG X, et al[34]	*DNAH2* is a novel candidate gene associated with MMAF (multiple morphological abnormalities of the sperm flagella)	Chinese patients 4/38 *DNAH2*
2020	HE J, LI L, YU Y, et al[35]	Two mutations in the axonemal dynein heavy chain gene 5 in a Chinese asthenozoospermia patient	Chinese patients 1/145 *DNAH5*
2020	LIU C, TU C, WANG L, et al[36]	Deleterious variants in X-linked *CFAP47* induce asthenoteratozoospermia and primary male infertility	Chinese patients 3/331 *CFAP47*
2020	LIU C, MIYATA H, GAO Y, et al[37]	Bi-allelic *DNAH8* variants lead to multiple morphological abnormalities of the sperm flagella and primary male infertility	Chinese patients 2/90 *DNAH8*
2020	HE X, LIU C, YANG X, et al[38]	Bi-allelic loss-of-function variants in *CFAP58* cause flagellar axoneme and mitochondrial sheath defects and asthenoteratozoospermia in humans and mice	Chinese patients 5/90 *CFAP58*
2020	TU C, NIE H, MENG L, et al[39]	Novel mutations in *SPEF2* causing different defects between flagella and cilia bridge: the phenotypic link between MMAF and PCD	Chinese patients 4/45 *SPEF2*
2020	LV M, LIU W, CHI W, et al[40]	Homozygous mutations in *DZIP1* can induce asthenoteratospermia with severe MMAF	Chinese patients 2/65 *DZIP1*
2020	LI W, WU H, LI F, et al[41]	Biallelic mutations in *CFAP65* cause male infertility with multiple morphological abnormalities of the sperm flagella in humans and mice	Chinese patients 6/88 *CFAP65*
2020	LIU C, MIYATA H, GAO Y, et al[37]	Bi-allelic *DNAH8* variants lead to multiple morphological abnormalities of the sperm flagella and primary male infertility	Chinese patients 2/90 *DNAH8*

续表1

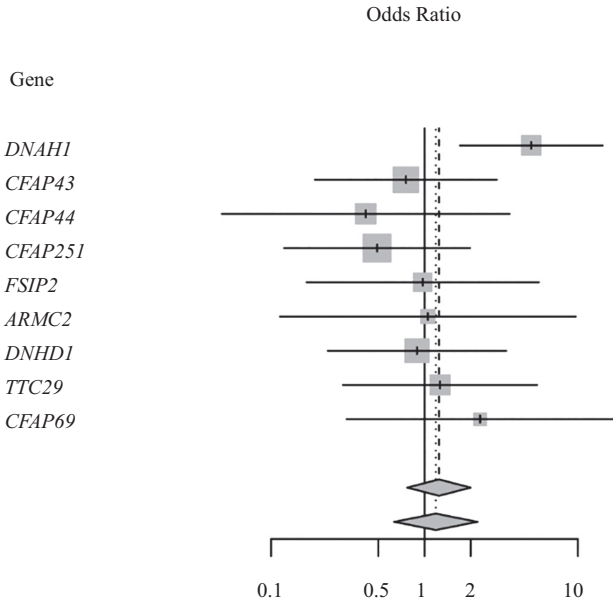
年份 Year	作者 Author	标题 Title	纳入标准 Incorporate standards
2021	LU S, GU Y, WU Y, et al[42]	Bi-allelic variants in human *WDR63* cause male infertility via abnormal inner dynein arms assembly	Chinese patients 1/243 *WDR63*
2021	GAO Y, TIAN S, SHA Y, et al[43]	Novel bi-allelic variants in *DNAH2* cause severe asthenoteratozoospermia with multiple morphological abnormalities of the flagella	Chinese patients 3/90 *DNAH2*
2021	TU C, CONG J, ZHANG Q, et al[25]	Bi-allelic mutations of *DNAH10* cause primary male infertility with asthenoteratozoospermia in humans and mice	Chinese patients 5/643 *DNAH10*
2021	TAN C, MENG L, LÜ M, et al[44]	Bi-allelic variants in *DNHD1* cause flagellar axoneme defects and asthenoteratozoospermia in humans and mice	Chinese patients 8/497 *DNHD1*
2022	LIU C, SHEN Y, TANG S, et al[45]	Homozygous variants in *AKAP3* induce asthenoteratozoospermia and male infertility	Chinese patients 2/150 *AKAP3*
2023	TIAN S, TU C, HE X, et al[46]	Biallelic mutations in *CFAP54* cause male infertility with severe MMAF and NOA	Chinese patients 3/334 *CFAP54*
2023	MENG Z, MENG Q, GAO T, et al[47]	Identification of bi-allelic *KIF9* loss-of-function variants contributing to asthenospermia and male infertility in two Chinese families	Chinese patients 2/92 *KIF9*
2023	MA J, LONG S H, YU H B, et al[48]	Patients with MMAF induced by novel biallelic *CFAP43* mutations have good fertility outcomes after intracytoplasmic sperm injection	Chinese patients 4/30 *CFAP43*
2023	SHAO Z M, ZHU Y T, GU M, et al[49]	Novel variants in *DNAH6* cause male infertility associated with MMAF (multiple morphological abnormalities of the sperm flagella) and ICSI outcomes	Chinese patients 3/375 *DNAH6*
2023	MENG L, LIU Q, TAN C, et al[50]	Novel homozygous variants in *TTC12* cause male infertility with asthenoteratozoospermia owing to dynein arm complex and mitochondrial sheath defects in flagella	Chinese patients 3/314 *TTC12*
2023	MARTINEZ G, BARBOTIN A L, CAZIN C, et al[51]	New mutations in *DNHD1* cause multiple morphological abnormalities of the sperm flagella	French patients 3/167 *DNHD1*
2023	SHA Y, LIU W, LI S, et al[52]	Deficiency in *AK9* causes asthenozoospermia and male infertility by destabilising sperm nucleotide homeostasis	Chinese patients 5/165 *AK9*
2023	KHERRAF Z E, BARBOTIN A L, MARTINEZ G, et al[53]	A splice donor variant of *GAS8* induces structural disorganization of the axoneme in sperm flagella and leads to nonsyndromic male infertility	French patients 1/92 *GAS8*
2023	JREIJIRI F, CAVAROCCHI E, AMIRI-YEKTA A, et al[54]	*CCDC65*, encoding a component of the axonemal Nexin-Dynein regulatory complex, is required for sperm flagellum structure in humans	French patients 2/167 *CCDC65*



T/TH: 系链–系链头复合物。
T/TH: tether-tether head.

图2 中国和法国的MMAF相关基因的定位模式图

Fig.2 Mapping patterns of MMAF-related genes in China and France



OR: 比值比。
OR: odd ratio.

图3 中国和法国中9个MMAF突变基因的森林图

Fig.3 Forest plot of nine MMAF mutant genes between China and France

表2 中国和法国中9个MMAF突变基因的Meta分析

Table 2 Meta-analysis of nine MMAF mutant genes between China and France

基因 Gene	突变数(中国) Number of mutations (China)	总人数 Total	突变数(法国) Number of mutations (France)	总人数 Total	比值比 OR	95%置信区间 95% CI	权重(固定) Weight (common)	权重(随机) Weight (random)
DNAH1	12	41	6	78	4.97	[1.70; 14.49]	9.7%	17.5%
CFAP43	3	30	10	78	0.76	[0.19; 2.96]	16.7%	13.3%
CFAP44	1	30	6	78	0.41	[0.05; 3.59]	10.7%	6.8%
CFAP251	3	65	7	78	0.49	[0.12; 1.98]	20.2%	12.9%
FSIP2	2	40	4	78	0.97	[0.17; 5.56]	8.6%	9.5%
ARMC2	1	40	4	168	1.05	[0.11; 9.67]	5.0%	6.5%
DNHD1	8	497	3	167	0.89	[0.23; 3.41]	14.7%	13.6%
TTC29	3	80	5	167	1.26	[0.29; 5.42]	10.4%	12.2%
CFAP69	2	35	2	78	2.30	[0.31; 17.05]	3.9%	7.7%

固定效应模型1.24[0.77; 2.00]; 随机效应模型1.19[0.63; 2.21]; 异质性: I^2 =23%, τ^2=0.2818, P=0.24; CI: 置信区间; OR: 比值比。
Common effect model 1.24[0.77; 2.00]; random effects model 1.19[0.63; 2.21]; heterogeneity: I^2 =23%, τ^2=0.2818, P=0.24; CI: confidence interval; OR: odd ratio.

因的突变率差异, Meta分析的结果显示, 在由中国和法国共同研究的MMAF相关突变基因中, *DNAH1*在中国的突变率高于法国, 然而, *CFAP43*、*CFAP44*、*CFAP251*等基因在中、法两国患者中并未显示出统计学上的差异, 这表明导致男性不育的基因变异在不同地区存在多样性。目前, 卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI)是MMAF患者最常用的辅助生殖技术, 但其临床效果因不同的致病基因而异。在生育力结局中, 如表3~表5所示, *DNAH1*[55]、*CFAP43*[48]、*TTC29*[32]、*FSIP2*[56]、*DNHD1*[44]、*DNAH2*[43]、*DNAH8*[37]、*DNAH10*[25]、*CFAP47*[36]、*CFAP54*[46]、*DRC2*[54]、*AKAP3*[45]以及*WDR63*[42]等基因经过ICSI治疗后的临床结局较好, 研究报道, 经过ICSI后*DNAH1*变异患者的受精率和囊胚形成率均在80%以上, 总体预后较好[55,58]。而*ARMC2*[33]、*DNAH6*[57]、*CEP135*[59]、*CFAP65*[60]以及*DNAH17*[61]的生育结局差, 显示不可生育, 这些基因的分子机制仍然有待被阐明。中心体蛋白在

表3 中国和法国共同研究的9个MMAF相关基因变异的汇总比例

Table 3 Summary proportion of nine MMAF-related gene mutations studied jointly by China and France

基因 Gene	国家 Country	突变人数 Number of mutants	总人数 Total	突变率 Mutation rate	ICSI结果 ICSI outcomes
DNAH1	China	12	41	0.293	P (10/15)
	France	6	78	0.077	N/A
CFAP43	China	3	30	0.100	P (3/3)
	France	10	78	0.128	N/A
CFAP44	China	1	30	0.033	N/A
	France	6	78	0.077	N/A
CFAP251	China	3	65	0.046	N/A
	France	7	78	0.090	N/A
FSIP2	China	2	40	0.050	P (2/2)
	France	4	78	0.051	P (4/4)
ARMC2	China	1	88	0.011	P (0/1)
	France	4	168	0.024	P (0/4)
DNHD1	China	8	497	0.016	P (4/7)
	France	3	167	0.018	N/A
TTC29	China	3	80	0.038	P (3/3)
	France	5	167	0.030	N/A
CFAP69	China	2	35	0.057	N/A
	France	2	78	0.026	N/A

ICSI: 卵胞质内单精子注射; P: 怀孕的; N/A: 无可用数据。

ICSI: intracytoplasmic sperm injection; P: pregnant; N/A: not available.

表4 中国单独研究的MMAF相关基因变异信息和ICSI结局

Table 4 MMAF-associated gene mutation information and ICSI outcomes of separate studies in China

基因 Gene	突变人数 Number of mutants	总人数 Total	突变率 Mutation rate	ICSI结果 ICSI outcomes
DNAH2	3	90	0.033	P (2/3)
DNAH5	1	143	0.007	N/A
DNAH6	3	375	0.008	P (0/3)
DNAH8	2	90	0.022	P (1/2)
DNAH10	5	643	0.008	P (2/3)
DNAH11	1	87	0.011	N/A
CFAP47	3	331	0.009	P (3/3)
CFAP54	3	334	0.009	P (2/2)
CFAP65	3	47	0.064	P (0/3)
CEP135	1	38	0.026	P (0/1)
TTC21A	3	65	0.046	N/A
SPEF2	4	45	0.089	N/A
DZIP1	2	65	0.031	N/A
KIF9	2	92	0.022	N/A
AKAP3	2	150	0.013	P (1/2)
WDR63	1	243	0.004	P (1/1)
DRC1	1	N/A	N/A	N/A
DNAH17	4	N/A	N/A	P (0/4)
SLC26A8	2	N/A	N/A	N/A

ICSI: 卵胞质内单精子注射; P: 怀孕的; N/A: 无可用数据。

ICSI: intracytoplasmic sperm injection; P: pregnant; N/A: not available.

表5 法国单独研究的MMAF相关基因变异信息和ICSI结局

Table 5 MMAF-associated gene mutation information and ICSI outcomes of separate studies in France

基因 Gene	突变人数 Number of mutants	总人数 Total	突变率 Mutation rate	ICSI结果 ICSI outcomes
DRC2	2	167	0.012	P (1/1)
DRC4	1	92	0.011	N/A
IFT74	2	167	0.012	N/A

ICSI: 卵胞质内单精子注射; P: 怀孕的; N/A: 无可用数据。

ICSI: intracytoplasmic sperm injection; P: pregnant; N/A: not available.

受精后持续存在, 与轴突蛋白不同, 是胚胎发育所必需的, 中心粒/中心体功能障碍可能导致胚胎发育过程中的卵裂不规则或染色体畸变, 从而导致疾病, 如*CEP135*或*DNAH17*, 它们都参与中心粒/中心体的形成和稳定, 但在某些情况下, 它们可能发生突变或表达失调, 影响中心粒/中心体的功能[59]。通过研究两个国家的基因变异率差异, 可以为辅助生殖治疗提供指导意义, 这有助于我们了解不同的遗传因素如何影响MMAF的发病率和治疗效果, 从而为MMAF患者提供更个性化和有效的辅助生殖方案。

当在弱精子症中观察到相同基因携带的基因变异时, 不同的表型可能同时出现, 其中包括光学显微镜下精子鞭毛无明显畸形和精子鞭毛多发形态异常。在此前的MIVA的281个病例中, 除了32例个体(约占11.4%)存在MIP变异体外, 值得注意的是, 第二大类别中也存在动力蛋白臂的异常, 同时有研究报道, 动力蛋白臂组分的基因如*DNAH1*[11]、*DNAH6*[62]等异常也会导致精子鞭毛多发形态异常。而这种现象的来源可能来自于相同基因不同的遗传变异位点, 例如, 携带双等位基因*DNAH8*变异的受影响男性精子活力下降, 精子鞭毛畸形, 从而导致MMAF[37]。另一项研究表明, 携带纯合子剪接变异c.6311-2A>G的患者也表现出较差的精子活力, 然而, 该患者出现异常头部而非尾部缺陷的精子比例很高[63]。此外, 携带*MNS1*纯合无义突变p.Q203*的患者显示鞭毛活力降低, 伴有精子鞭毛多发形态异常[64], 而带有*MNS1*移码突变p.Q203Afs*5的患者精子形态未见明显异常[19]。之前的研究也指出, 哺乳动物轴丝组分*DRC1*突变导致脑积水的表型是存在严重个体差异的[65], 这些结果均提示, 轴丝结构和功能异常可能受遗传背景的影响, 但其背后的机制仍然有待研究。

4 结论与展望

本文综述了两种精子鞭毛结构轴丝异常导致的弱精子症的亚型: 即在光学显微镜下无明显畸形的精子鞭毛的弱精子症和精子鞭毛多发形态异常的弱精子症。同时比较了中国和法国MMAF患者的常见遗传病因和基因变异情况, 发现MMAF遗传变异在地域上呈现多样性。不同的基因变异与ICSI治疗的成功率和胚胎质量有关。这些发现为MMAF的遗传诊断和遗传咨询提供了新的依据, 也为ICSI治疗的方案选择和风险评估提供了新的指标。

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