·综　　述·

先天性无眼球和小眼球的遗传学病因及临床对策

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【摘要】 先天性无眼球和小眼球分别指眼球缺失和眼轴长度明显缩短。其中，单纯性小眼球仅眼球体积小于正常，不伴其他眼部畸形。先天性无眼球和小眼球的患病率为 1.18/10 000，病因以遗传缺陷为主，常见的致病基因包括 *SOX2*、*OTX2*、*PAX6*、*RAX*。近年研究结果表明 *MAB21L1*、*EPHA2*、*VPS35L*、*FAT1* 等基因异常也与先天性无眼球和小眼球的发生和发展有关。高龄生育、妊娠期糖尿病和妊娠期吸烟是该病的危险因素。先天性无眼球和小眼球可通过眼部超声或磁共振成像测量眼轴长度和角膜直径确诊。目前，先天性无眼球和小眼球仍以对症治疗为主，其常见并发症包括远视、青光眼、眼眶发育异常和葡萄膜渗漏综合征。本文就先天性无眼球和小眼球的遗传学病因和治疗策略进行综述，以期为其诊治提供新的思路。

【关键词】 先天性无眼球；先天性小眼球；基因；临床表现；治疗
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Genetic etiology and clinical strategies of congenital anophthalmia and microphthalmia

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[**Abstract**] Congenital anophthalmia and microphthalmia refer to the absence of eyeball and a significantly shortened axial length, respectively. Among them, simple microphthalmia only has a smaller eyeball volume than normal without other eye malformations. The prevalence of congenital anophthalmia and microphthalmia is 1.18/10 000 and the etiology of the diseases are dominated by genetic defects, with common causative genes including *SOX2*, *OTX2*, *PAX6* and *RAX*. Recent research results have shown that genetic abnormalities of *MAB21L1*, *EPHA2*, *VPS35L*, *FAT1* are also associated with the occurrence and development of the diseases. Advanced childbearing age, gestational diabetes and smoking during pregnancy are risk factors for the diseases. Congenital anophthalmia and microphthalmia can be diagnosed by ocular ultrasound or magnetic resonance imaging measurement of axial length and corneal diameter. At present, congenital anophthalmia and microphthalmia mainly focus on symptomatic treatment. The common complications of congenital anophthalmia and microphthalmia include hyperopia, glaucoma, orbital dysplasia, and uveal effusion. To provide new ideas for the diagnosis and treatment of congenital anophthalmia and microphthalmia, genetic etiology and treatment are reviewed in this article.

[**Key words**] Congenital anophthalmos; Congenital microphthalmos; Genes; Clinical manifestation; Treatment
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先天性无眼球和小眼球是一种严重的遗传缺陷疾病，在活产婴儿中的患病率为 1.18/10 000[1]。小眼球定义为眼轴长度低于同龄人群眼轴长度均值 2 个标准差[2]。正常新生儿和成人眼轴长度分别约为 17 和 23.8 mm，而小眼球患者通常眼球前后径小于 20 mm，角膜直径小于 10 mm[3]。无眼部残余物则定义为无眼球。先天性小眼球可伴随其他眼部病变，如白内障、青光眼、眼球震颤、视网膜脱离、角膜瘢痕和眼球结构缺损[4]。33%～85%先天性无眼球和小眼球患者伴随其他眼外病变[5-7]。先天性无眼球和小眼球相关的危险因素包括母亲有流产史、糖尿病、孕早期吸烟、高龄生育等[5,7]。一般认为先天性无眼球和小眼球与胚胎发生期间视裂闭合失败，眼形态发生紊乱有关。眼的发育需要精确的基因网络调控，而关键基因的缺

陷将导致先天性无眼球和小眼球。20%～40%的先天性无眼球和小眼球患者可筛查出已知的致病基因变异，涉及 100 多个基因[8-9]。由于缺乏有效治疗手段，临床上仍以改善视力、促进眼眶发育、预防和治疗并发症为主。本文就先天性无眼球和小眼球的遗传学病因和治疗策略进行综述，以期为其诊治提供新的思路。

1　真性小眼球

仅眼球体积小于正常，不伴其他眼部畸形称为单纯性小眼球。根据眼球前后节长度，单纯性小眼球可分为真性小眼球和部分性小眼球。眼前节和眼后节均缩短称为真性小眼球[10]。与正常人相比，真性小眼球患者角膜较小、眼轴较短、晶状体更厚，眼球壁弥漫性增厚，眼前后段结构均狭窄[11]。真性小眼球巩膜和视网膜发育不协调可导致黄斑皱襞，中心凹无血管区缩小或缺如可能导致中心凹发育不良，引起视力下降[12]。此外，真性小眼球还可能存在视盘拥挤，外观类似假性视盘水肿，可能与视神经轴突密集排列穿过巩膜管有关[13]。

2　先天性无眼球和小眼球的遗传学病因

SOX2、*OTX2*、*PAX6*、*RAX* 基因是先天性无眼球和小眼球常见的致病基因，以下将介绍这些基因变异所导致的先天性无眼球和小眼球的流行病学特征和临床表现，并总结新近发现的相关致病基因。

2.1　*SOX2* 基因变异

SOX2 基因位于 3 号染色体上的 q26.3-27，编码 HMG 盒转录因子[14]。*SOX2* 基因变异是先天性无眼球和小眼球常见的病因，4.6%～14.3%病例存在 *SOX2* 基因变异[15-16]。在小鼠的研究中发现，*Sox2* 基因表达低于正常 40%可导致无眼球和小眼球[17]。

SOX2 基因在中枢神经系统早期发育过程中发挥重要调控作用，故 *SOX2* 基因变异导致的先天性无眼球和小眼球通常较为严重，表现出的眼外临床症状可能与神经-内分泌系统功能异常相关。*SOX2* 基因变异患者常见的表现包括小眼球或无眼球、颅面部改变、学习障碍、癫痫、发育迟缓、关节畸形、生殖器异常[15-16,18-19]。*SOX2* 基因变异患者也可出现硬化性角膜、共济失调、听力损伤等表现[16,20-21]。*SOX2* 基因缺失和 3 型小眼综合征（即 AEG 综合症）有关，主要表现为神经系统和生殖系统发育异常、食管闭锁。Ramirez-Botero 等[22]报道了 1 例 AEG 综合征患者，基因测序显示患者存在 *SOX2* 基因的 c.70_89del（p.Asn24Argfs＊65）变异。导致先天性无眼球和小眼球的 *SOX2* 基因变异是多样的，SOX2 蛋白结构和功能的改变可影响其在不同发育时期与其他因子的相互作用，引起不同的临床表现，SOX2 蛋白相同氨基酸位点的不同变异可引起轻度至重度表型[18]。

2.2　*OTX2* 基因变异

OTX2 基因主要在胚胎的垂体后叶、耳、视网膜和下丘脑等部位表达，与眼、颅面和垂体发育有关[23]。*OTX2* 基因变异在先天性无眼球和小眼球患者中占 2%～3%[24]。OTX2 蛋白可调控 *RAX*、*PAX6*、*SIX3* 基因的表达，影响眼发育[25-26]。研究表明，*OTX2* 基因与先天性无眼球和小眼球有关的功能域位于该基因编码的前 220 个氨基酸[23]。OTX2、LHX1 和 FOXA2 共同组成复合物发挥调控作用[27]，OTX2 前 220 个氨基酸包含与 LHX1 或 FOXA2 相互作用的结构域，结构域的缺失可能与先天性无眼球和小眼球相关[28]。

OTX2 基因变异可引起下丘脑-垂体病变，影响机体内分泌功能，从而导致神经运动系统发育迟缓和骨骼畸形[23]。*OTX2* 变异可导致 5 型小眼综合征，症状包括小眼球、无眼球、神经运动发育迟缓、骨骼畸形。此外，耳畸形和听力受损在 *OTX2* 基因变异患者中也很常见[23]。有研究表明，*OTX2* 基因变异存在不完全外显率和可变表型，*OTX2* 基因单倍体不足（p.Q99＊）的同一家系不同成员出现心脏畸形、耳畸形、发育迟缓和小眼球等不同表型[23]。近期研究发现，*OTX2* 基因的缺失与 14q22q23 微缺失综合征（Frias 综合征）的无眼球有关，Pichiecchio 等[29]报道了 1 例 14q22q23 包含 *OTX2* 基因片段缺失无眼球患者。

2.3　*PAX6* 基因变异

PAX6 是眼发育的主要调节因子，在胚眼中广泛表达，此外，胚胎期的端脑、间脑和松果体等部位也有 PAX6 的表达[30]。*PAX6* 基因变异占先天性无眼球和小眼球患者的 0.67%～4%[15,31]。*PAX6* 基因致病突变有高度的遗传异质性，突变类型和表型之间无明确相关性[32]。PAX6 通过促进 *BMP4*、*TGFβ2* 和 *FOXC1* 基因表达参与虹膜的形成[33]。PAX6 可与 SOX2 共同组成分子络合物，启动晶状体发育[34]。PAX2 和 PAX6 相互抑制，影响视杯和视柄的分界[35]。

PAX6 基因变异患者常见的眼部特征包括虹膜发育不全、中央凹发育不全、晶状体病变和角膜病变，部分 *PAX6* 基因变异病例表现为无眼球和小眼球[31,36-37]。Williamson 等[31]提出可根据 PAX6 配对结构域的变化预测患者表型，*PAX6* 基因的 p.Ser54Arg 和 p.Asn124Lys 变异将导致严重的双侧小眼球。既往研究报道了 2 个 *PAX6* 基因变异嵌合体家系，表明需要对健康父母进行全面基因筛查以更准确地评估复发风险[37-38]。

2.4　*RAX* 基因变异

RAX 基因属于同源异形盒基因，在胚胎期的眼、下丘脑、垂体和松果体表达，是眼、下丘脑和垂体发育所必需的基因[39-40]。*RAX* 基因的纯合或杂合变异均可导致先天性无眼球和小眼球，在患者中占 2.6%～5.7%[15,18,41]。*RAX* 基因变异的先天性无眼球和小眼球患者多无其他眼外表现，部分患者神经系统受累，发育迟缓，颚骨异常[15,41-42]。Brachet 等[42]通过敲除小鼠的 *Rax* 基因，证实 *Rax* 基因变异与垂体、颅骨发育异常有关。

2.5　其他基因变异

Harding 等[9]统计了截至 2019 年的 98 个与先天性无眼球和小眼球有关的致病基因，本文总结了在此之后报道的相关致病基因（表 1）。其中，*MAB21L1*、*EPHA2*、*VPS35L*、*FAT1* 基因变异导致的无眼球或小眼球在实验动物模型中得到了进一步验证[43-46]。

表 1　新发现的先天性无眼球和小眼球相关基因及表型特征

基因名称	OMIM#	变异位点	眼部症状	眼外表现	测序方法	参考文献
MAB21L1	601280	c. 152G>T (p. Arg51Leu)	双眼小眼球、小角膜、虹膜缺损、眼球震颤	/	全外显子测序	Seese 等[43]
EPHA2	176946	c. 1751C>T (p. Pro584Leu)	双眼小眼球、白内障、眼球震颤	/	全基因组测序	Harding 等[44]
VPS35L	618981	c. 1097dup (p. Cys366Trpfs * 28); c. 2755G>A (p. Ala919Thr)	左眼小眼球	颅-小脑-心脏发育不良	全外显子测序	Kato 等[45]
FAT1	600976	c. 2207dupT (p. I737NfsX7)	双眼小眼球、视网膜缺损、虹膜缺损、上睑下垂	脚趾畸形,慢性肾脏疾病	全外显子测序	Lahrouchi 等[46]
KIF17	605037	c. 1255C>T (p. Arg419Trp); c. 2554C>T (p. Arg852Cys)	左眼小眼球	发育迟缓	二代测序	Riva 等[47]
FZD5	601723	c. 1181_1246del (p. Asn394_Gly415del)	双侧无眼球	/	二代测序	Aubert-Mucca 等[48]
CRYBB3	123630	c. 467G>A (p. Gly156Glu)	双眼白内障、小眼球、小角膜	/	二代测序	Zin 等[49]
PRR12	616633	c. 5624-2A>G (p. Asp1875Glyfs * 54)	左眼小眼球,Peters 异常	发育迟缓,学习障碍	一代测序	Reis 等[50]
MYRF	608329	c. 3361delC (p. Arg1121GlyfsTer36)	双眼小眼球、青光眼	/	二代测序	Siggs 等[51]
TUBGCP4	609610	c. 1746G>T (p. Leu582=)	双眼小眼球、脉络膜视网膜病变、视网膜穿孔	面部畸形,学习困难,小头畸形	二代测序	Da Palma 等[52]
CAPN15	603267	c. 2905G>A (p. Gly969Ser)	单眼小眼球、晶状体混浊,双眼眼球缺损	喉裂,发声困难,多毛,骶骨凹陷	全外显子测序	Zha 等[53]
PXDN	605158	c. 4085_4086del (p. Gln1362ArgfsTer22)	双眼小眼球、青光眼、角膜混浊	/	全外显子测序,全基因组测序	Zazo-Seco 等[54]
NUP188	615587	c. 287dupA;(p. Tyr96 *)	双眼小眼球、白内障	小头畸形,唇裂,腭裂,心脏室间隔缺损,大脑改变如脑室周围白质丢失、胼胝体变薄和髓鞘化延迟	低起始量靶向序列捕获技术	Sandestig 等[55]
CRYBB1	600929	c. 279C>G (p. S93R)	双眼小眼球、白内障、小角膜	/	全外显子测序	Jin 等[56]
CDK5RAP2	608201	c. 564_565dup (p. Lys189Argfs * 15)	小眼球、视网膜色素沉着不均	小头畸形,语言发育迟缓,皮肤色素沉着,听力异常	二代测序	Nasser 等[57]
CENPF	600236	c. 1744G>T(p. Glu582 *); c. 9280C> T (p. Arg3094 *)	小眼球、Peters 异常、白内障	小头畸形,肠闭锁,输尿管积水,面部畸形	全外显子测序	Alghamdi 等[58]
GJA8	600897	c. 116C>G (p. Thr39Arg)	双眼小眼球、角膜混浊、白内障、眼球震颤,左眼继发性青光眼和严重视盘萎缩	/	一代测序	Ceroni 等[59]
GJA1	121014	c. 119C>T (p. Ala40Val)	小眼球、小角膜、眼压升高和浅前房	面部畸形	靶向测序	Park 等[60]
TMEM67	609884	c. 725A > G (p. Asn242Ser)	双眼小眼球和小角膜,左眼眼球震颤、视网膜下纤维化、视盘前膜	肌张力降低、共济失调、神经发育缺陷	全外显子测序	Elsayed 等[61]
KAT6B	605880	c. 3147G>A (p. P1049P)	双眼小眼球	肌张力降低、发育迟缓、智力障碍	全外显子测序	Davarnia 等[62]
ALDH1A3	600463	c. 874G>T (p. Asp292Tyr); c. 1393A>T (p. Ile465Phe)	双侧无眼球	轻度发育迟缓	全外显子测序,全基因组测序	Kesim 等[63]

注:/:未提及

3　先天性无眼球和小眼球患者的临床诊断和治疗

先天性无眼球和小眼球可通过外观、眼部超声或 MRI 测量眼轴长度、角膜直径确诊，通过染色体微阵列分析、新一代高通量测序技术进一步筛查可能存在的遗传缺陷。已确诊的患者应完善相关结构和功能检查，如视力和眼压测量、眼部超声检查虹膜和晶状体、视网膜电图检查评估视网膜功能、CT 检查评估眼眶畸形情况。结构光三维扫描系统是评估患者眼眶发育的新方法，可更直观地反映小眼球引起的眼眶畸形情况[64]。

先天性无眼球和小眼球尚缺乏有效治疗手段，临床上以提高视力为主要目的，尽可能改善外观。先天性无眼球和小眼球常合并其他系统异常，需多学科综合诊治。先天性无眼球和小眼球常见的眼部并发症包括远视、青光眼、眼眶发育异常和葡萄膜渗漏综合征，治疗策略总结如下。

3.1　远视

小眼球患者眼轴短，角膜曲率大，会导致远视[65]。配戴眼镜可帮助患者矫正屈光不正，小眼球患者远视度数偏高，植入人工晶状体可减少眼镜需矫正的度数。对于小眼球的理想人工晶状体屈光度计算公式全球尚无明确共识，但有报道表明，Hoffer Q 或 Holladay Ⅱ公式更适用于眼轴长度小于 22 mm 的情况[66]。Mohebbi 等[67]采用双联人工晶状体植入术有效改善了小眼球患者的视力。对于眼前节正常的小眼球患者，Elhofi 等[68]首先植入+30 D 人工晶状体，再根据术后实际屈光度行二次手术植入虹膜固定式人工晶状体，治疗效果优于双联人工晶状体植入术。对于无晶状体眼的小眼球患者，Alwohaibi 等[69]采用改良的无缝线巩膜固定人工晶状体植入术，也取得了较满意的效果。

3.2　青光眼

单纯性小眼球患者中青光眼的发生率为 69.23%[70]。小眼球患者瞳孔阻滞房水循环、房水静脉引流受阻和慢性房角阻滞易诱发青光眼[71]。急性青光眼病例通常采用药物治疗，包括抑制房水生成，如碳酸酐酶抑制剂、β 受体阻滞剂，以及高渗脱水剂甘露醇，但缩瞳剂应谨慎使用，以免加重房水循环阻滞[71]。单纯药物治疗效果通常不理想，可采用小梁切除术、巩膜切开术、晶状体切除术等手术干预。Yalvac 等[72]对小眼球的青光眼患者实施小梁切除联合巩膜切开术，有效降低了患者眼压。Zhang 等[73]提出，小眼球患者前房过浅，晶状体与眼球的比值高于正常，为减轻瞳孔阻滞房水流通，可行玻璃体切割联合晶状体摘除术，术后大多数患者眼压可得到控制。

小眼球患者眼前节结构异常可引发青光眼，应尽可能纠正异常结构，可采用睫状体手术以控制眼压。Kanigowska 等[74]报道了 1 例晶状体脱位引发青光眼的小眼球患者，行小梁切除术、晶状体摘除术和晶状体后纤维膜切除术后，患者眼压正常化。虹膜部分缺损患者的虹膜前旋导致虹膜角膜角狭窄，可引发青光眼。Tefon Arıbaş 等[75]对小眼球伴虹膜部分缺损的青光眼患者实施经巩膜二级管激光睫状体光凝术后，患者青光眼得到控制。中央角膜厚度薄是青光眼的危险因素，小眼球患者角膜异常可能引起青光眼[76]。Thompson 等[77]报道了 1 例小眼球伴薄角膜的青光眼患者，采用内窥镜睫状体光凝术治疗后，青光眼得到控制。

3.3　眼眶发育畸形

先天性无眼球和小眼球常伴眼眶发育迟缓，患者可植入框内扩张器、填充材料或义眼促进眼眶发育[78]。具体干预措施的选择取决于眼球畸形的严重程度，需要评估小眼球是否还有视觉潜力。Taha Najim 等[79]建议在患者出生后约 3 个月时开始填充物的治疗。Brandão 等[78]将具有成骨和血管生成潜力的生物硅酸盐应用于临床，有效提高了患者的眼眶容量，植入物定位良好，几乎没有炎症反应，是植入材料的良好选择。由于早期摘除眼球将影响眼眶的生长，采用框内扩张器可达到填充眼眶的效果[80]。Schittkowski 等[81]验证了“可注射自膨胀水凝胶颗粒膨胀剂”修复眼眶的可行性。颗粒膨胀剂由自膨胀水凝胶制成，将扩张剂注射到眼球后组织，可观察到眼眶体积明显增加，观察期间未出现并发症。

3.4　葡萄膜渗漏综合征

小眼球患者的巩膜通透性降低，漩涡静脉受到压迫，易引发葡萄膜渗漏综合征[82]。葡萄膜渗漏综合征是导致小眼球患者视力丧失的常见原因，临床特征是周边部睫状体脉络膜脱离和渗出性视网膜脱离，可通过眼部 B 型超声、MRI 和 CT 等检查对其进行诊断和分型[83]。糖皮质激素治疗对葡萄膜渗漏综合征有效[84]，但目前尚缺乏治疗小眼球患者葡萄膜渗漏综合征的有效性研究。研究显示，广泛的巩膜环形切除术可有效处理小眼球患者的葡萄膜渗漏综合征[85]。此外，眼前节手术可诱发葡萄膜渗漏综合征，预防性巩膜造口术可显著降低葡萄膜渗漏综合征的发生率[86]。

综上，先天性无眼球和小眼球遗传相关性较高，研究先天性无眼球和小眼球的遗传学病因有助于揭示其遗传危险因素及其作用机制，为其筛查和治疗奠定基础。先天性无眼球和小眼球具有显著的遗传异质性和可变的外显率，目前尚缺乏有效治疗手段，建议有眼部畸形家族史的家庭接受遗传咨询。

利益冲突　所有作者均声明不存在利益冲突

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自我刊开通网上投稿以来，作者均采用将 Word 文档从网上在线投稿的方式，但部分来稿中所包含的图片像素较低，这些图片便于网上审稿，并不能用于制版印刷。因为显示器与彩印纸品的色彩形成截然不同，显示器应用红、绿、兰的三原色原理发射光线形成图像，这种色彩形成的原理被称为 RGB 模式；而彩色印刷品是兰、红、黄、黑四色油墨印制在纸制品上来形成彩色图像，这种原理被称为 CMYK 模式。那些在显示器上看起来比较清晰但分辨率较低的图片在实际印刷时不能转换为高质量 CMYK 模式的图片。为了保证论文的刊出质量及本刊的印刷出版质量，如果作者的来稿中附有组织病理图、免疫荧光染色图、免疫组织化学图、细胞图，请作者将原图保存为 TIFF 格式或 JPG 格式，图片的分辨率至少 300 dpi。

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