DOI:10.3724/cbls.2026015 **CSTR**:32203.14.cbls.2026015
文章编号:1004-0374(2026)01-0059-11

Costello综合征的遗传学研究进展

李若冰[1],金介员[2],项 荣[2],程振波[1*]
(1 湖南师范大学附属第一医院(湖南省人民医院)检验科,长沙 410005;2 中南大学生命科学学院,长沙 410013)

摘 要:Costello综合征(Costello syndrome,CS)是一种罕见的常染色体显性遗传病,以心脏缺陷、特殊颅面特征、生长发育迟缓、皮肤异常等为主要表型。*HRAS*是Costello综合征的致病基因,现已报道多种有关*HRAS*的变异。*HRAS*基因变异导致HRAS蛋白的GTP酶活性降低或GDP/GTP交换活性增强,使HRAS蛋白持续处于活化状态,从而引起RAS/MAPK信号通路的异常激活,通过影响细胞内信号转导扰乱正常生理功能,进而导致患者出现多系统的异常表现,如心脏肥大、智力障碍、皮肤病变等。Costello综合征的遗传学研究可为遗传咨询、产前诊断乃至精准医疗提供依据。

关键词:Costello综合征;*HRAS*基因;致病机制;遗传学研究
中图分类号:Q311 **文献标识码**:A

Genetic research progress on Costello syndrome

LI Ruo-Bing[1], JIN Jie-Yuan[2], XIANG Rong[2], CHENG Zhen-Bo[1*]
(1 Department of Clinical Laboratory, Hunan Provincial People′s Hospital, The First Affiliated Hospital of Hunan Normal University, Hunan Normal University, Changsha 410005, China; 2 School of Life Sciences, Central South University, Changsha 410013, China)

Abstract: Costello syndrome (CS) is a rare autosomal dominant genetic disorder characterized by cardiac anomalies, distinctive craniofacial features, growth and developmental delays, as well as cutaneous abnormalities. Given the complexity of its clinical presentation and underlying pathogenic mechanisms, advances in genetic and molecular research are essential for deepening our understanding of CS and improving patient outcomes. This review systematically synthesizes recent progress on the genetics of CS from four interconnected perspectives: clinical manifestations, molecular pathogenesis, current diagnostic and therapeutic strategies, and future research directions. By critically integrating existing evidence, we aim to elucidate the core molecular mechanisms driven by dysregulated HRAS signaling and to consolidate both established and emerging genotype-phenotype correlations, which are critical for prognosis and clinical management. The *HRAS* gene, which encodes a pivotal GTPase in cellular signal transduction, lies at the heart of CS pathogenesis. Through a comprehensive analysis of published *HRAS* mutation data from CS cases worldwide, this review delineates the mutational spectrum, with emphasis on the predominant p.Gly12Ser variant, its functional consequences, and the associated range of clinical phenotypes. We describe how specific germline missense mutations, predominantly affecting codons 12 or 13, impair GTPase activity or accelerate GDP/GTP exchange, leading to constitutive activation of the HRAS protein. This persistent activation results in hyperactivation of the downstream RAS/MAPK signaling pathway, disrupting fundamental cellular processes such as proliferation, differentiation, and apoptosis, ultimately giving rise to the multisystem features of CS, particularly its hallmark cardiac, neurological, and dermatological manifestations. Beyond cataloging genetic variants, this review critically evaluates the translational implications of these findings for clinical practice. It examines how molecular confirmation through *HRAS* sequencing has refined diagnostic criteria, underscores the necessity of proactive, multidisciplinary management involving cardiology, neurology, and oncology, and highlights the importance of individualized genetic counseling for affected families. In conclusion, *HRAS* mutations represent the central molecular drivers of CS, with disease pathogenesis

收稿日期:2025-06-26; **修回日期**:2025-09-08
基金项目:国家自然科学基金项目(82301882);湖南省自然科学基金项目(2025JJ50583)
***通信作者**:Email:zbcheng88hn@163.com

primarily mediated by sustained RAS/MAPK pathway activation. A clear understanding of this genetic basis not only facilitates accurate diagnosis, informed reproductive decision-making, and personalized surveillance but also establishes a robust scientific foundation for advancing prenatal diagnostics and developing targeted therapeutic interventions, including MEK inhibitors, for this complex and heterogeneous disorder.

Key words: Costello syndrome; *HRAS*; pathogenesis; genetic studies

Costello综合征(Costello syndrome,CS;OMIM_218040)是一种罕见的常染色体显性遗传疾病,主要由*HRAS*突变导致,发病率在1/300 000~1/230 000之间,最早由新西兰儿科医生Costello于1971年发现并命名,其主要临床表型包括特殊的颅面特征、生长发育迟缓,且存在皮肤、心脏、肌肉骨骼、神经系统异常以及肿瘤易感性等[1]。近年来还报道了一些罕见表型,如肥厚性幽门狭窄、呼吸系统受累等[2,3]。CS的发病原因及致病机制非常复杂,遗传学研究的推进及相关研究使得对该病的了解更加深入。本文将从临床特征、致病机制、诊疗现状及展望四方面对CS的遗传学研究进展作一综述。

1 Costello综合征的主要临床特征

1.1 特殊的颅面特征

Costello综合征(CS)的特征性颅面特征主要表现为相对或者绝对的大头畸形,面部体征包括前额突出、多毛、耳朵低垂和螺旋肉质、内眦赘皮、睑裂倾斜、鼻梁凹陷、鼻子球状和鼻孔前倾、脸颊饱满、厚嘴唇,具有典型的"粗糙"面容[4]。大部分CS患者检测出弱视以及严重近视[5],少数患者还出现圆锥角膜——一种角膜营养不良,伴有进行性角膜变薄,导致角膜形状异常和散光[6],也有很多CS患者有屈光不正、斜视、眼球震颤、立体视消失等异常眼部特征[7]。近年有文献指出Euryblepharon(一种罕见的眼周异常)也属于CS的表型特征[8]。CS患者具有特征性的牙齿表型,包括前开合和后反咬合的咬合不正、牙釉质矿化不足、牙齿发育和萌出延迟、牙龈增生、牙槽嵴增厚和高腭等[9]。此外,还有患者出现颅缝早闭[10]。

1.2 生长发育迟缓

CS患者表现出显著的生长发育迟缓和吞咽功能障碍。患儿自出生起即存在吞咽与吸吮困难,其体重增长在出生后三年内虽有轻微改善,但仍远低于正常水平[11]。鉴于喂养困难,大多数患儿需借助经鼻胃管或胃造口管进行喂养。进入儿童期后,虽部分个体可经口进食,但生长障碍问题仍未得到根本解决,生长速度依然持续低于同龄正常儿童[12]。

1.3 皮肤

CS患者毛发普遍存在异常,包括波浪形或卷曲的头发和过多的眉毛。肢端皮肤过多、乳头状瘤和角化丘疹、掌跖角化过度、上唇"鹅卵石"状瘤状丘疹和多发性黑色素细胞痣等问题也普遍存在[13]。此外,手脚皮肤松弛、指尖"斑点状"皮纹和黑棘皮也是CS的常见特征[14]。

1.4 心脏

心脏缺陷在CS患者中很常见,60%以上的CS患者至少有一种心脏异常,主要包括以下三类:先天性心脏病、肥厚型心肌病和心律失常[15]。研究表明,约30%的患者存在先天性心血管结构畸形,其中最常见的为肺动脉瓣狭窄(占46%),近年也有报道二尖瓣发育不良的CS患者[16];34%的患者表现为心肌肥厚,其中一半累及左心室;还有33%的患者出现了各种心律失常问题,其中74%为房性心动过速,具体表现为室上性、混乱性、多灶性或异位性等类型[17]。

1.5 肌肉骨骼

CS患者表现出不同程度的骨关节改变,典型症状包括颈部短、手指指间松弛、关节伸展受限和手指尺侧偏斜。CS患者轴向骨骼常出现脊髓弯曲、前胸壁畸形,脊柱后凸、侧凸发生率较高[18];在附肢骨骼异常中,韧带松弛、手指过度伸展、大关节易挛缩、上肢手宽短等表型较为典型,其中足部异常最为普遍,可出现跟腱紧绷等多种病变;先天性或后天性髋关节发育不良、骨质减少或骨质疏松等表型也较为常见[19]。此外,很多CS患者还会出现轻度的肌张力运动障碍,并且在步态过程中表现出异常的轴向姿势,还有手足肌张力障碍性姿势,如足内旋、大脚趾伸展、肌张力障碍性拇指伸展、可复位性腕屈以及各种舞蹈病样和肌张力障碍性手部生涩运动[20]。

1.6 神经系统

CS患者一般存在智力障碍(多在轻度至中度范围内)[21]。在CS患者中,语言发育迟缓普遍存在,有的还出现焦虑、刻板行为[22]。此外,结构性脑病

在CS综合征中也并不罕见，目前已报道了包括轻度脑萎缩[23]、下角和枕角扩张、白质低密度[11]、轻度皮质下萎缩、弥漫性脑异常[24]、小脑异常、额叶发育不全[25]、Chiari 畸形[26]和脊髓空洞症[27]等在内的脑部异常。少数CS患者还有癫痫或痉挛发作史[28]。

1.7 肿瘤易感性

CS患者具有较高的肿瘤易感性。据估计，截至20岁，CS患者患恶性肿瘤的风险为13%[29]。CS中最常见的肿瘤是横纹肌肉瘤[30]，神经母细胞瘤是CS儿童中常见的癌症，而膀胱肿瘤在成年患者中更为常见。值得注意的是，由于CS儿童的癌症风险很高，建议对所有CS儿童进行这些恶性肿瘤的监测[31]。此外，还有少数患者出现心脏肿瘤、纤维肉瘤、节神经母细胞瘤以及两种肝脏肿瘤(一种肝母细胞瘤和一种未具体说明的肝脏肿瘤)。与所有其他变体相比，p.Gly12Ser相关的癌症和死亡率较低，p.Gly12Cys、p.Gly12Asp、p.Gly12Val和p.Gly60Val的死亡率较高，p.Gly12Ala的恶性肿瘤发生率较高[29]。

1.8 其他罕见表型

除上述经典表型，一些罕见的表型也被陆续报道，如Gripp等[2]发现一名患者患有肥厚性幽门狭窄；Waldburg等[3]报道了一名与 CS直接相关的弥漫性肺浸润患者，该患者存在异常胶原和弹性纤维的沉积以及内源性脂质肺炎的发展。部分CS患者也出现内分泌系统疾病，包括低血糖、高胰岛素血症[32]、生长激素缺乏症、促肾上腺皮质激素缺乏症[33]和甲状腺功能减退症[34]。隐睾症、肾结石等泌尿生殖系统疾病近些年也有报道[35]。上述报道充分展示了CS涉及症状的广泛性和表型的异质性，也说明了进一步丰富和总结CS相关表型对临床诊断CS的迫切性。为此，我们总结了已报道的典型病例，汇总了CS患者的典型临床特征(图1)[36-38]以及主要的*HRAS*基因型变异及对应临床表型(表1)。

2 Costello综合征的致病机制

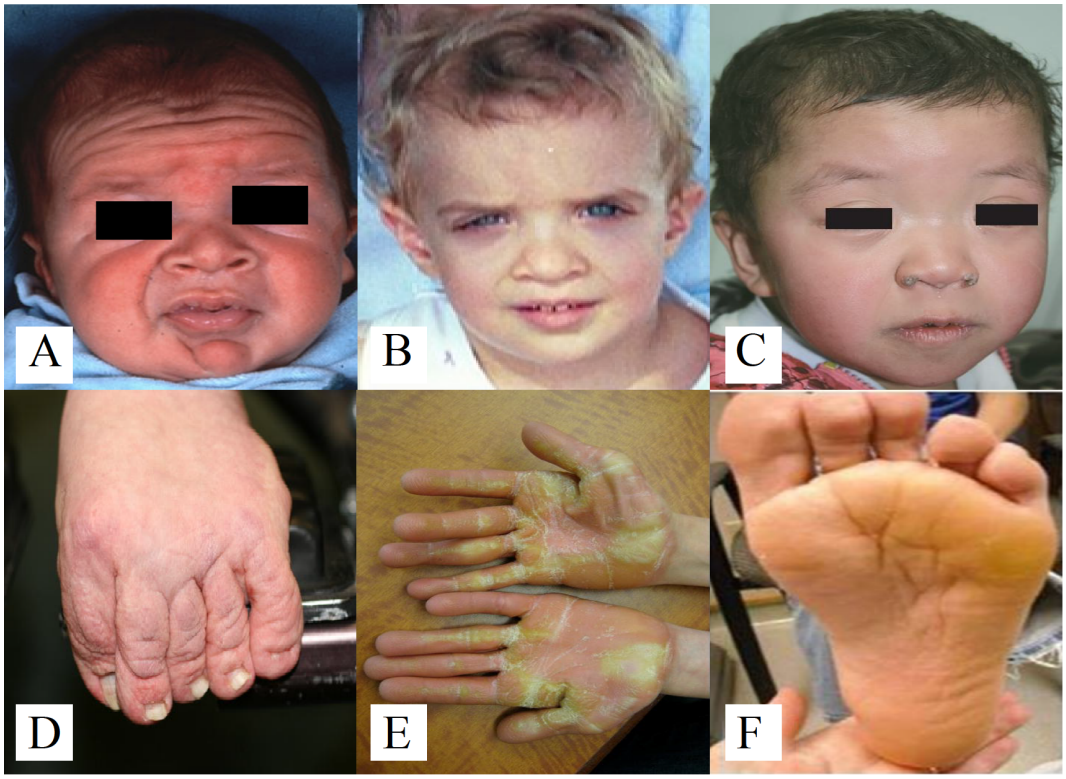

图1 CS患者的典型特征

A：粗糙面容；B：高额头、眦赘皮和轻度上睑下垂、宽嘴和卷发；C：双侧鼻翼及鼻中多发乳头状瘤；D：皮肤松弛；E：手指角化过度；F：足部有老茧和深足底折痕

Figure 1 Clinical phenotype of CS patient

A: coarse face; B: tall forehead, telecanthus and mild ptosis, wide mouth and curly hair; C: multiple papillomas of bilateral nasal wings and nasal septum; D: cutis laxa; E: hyperkeratosis of fingers, F: feet with callouses and deep plantar creases

表1　CS病例*HRAS*基因型及对应表型

Table 1　Summary of reported *HRAS* mutations associated with Costello syndrome

核苷酸变化	蛋白质变化	特殊面容	发育迟缓	皮肤异常	心脏缺陷	肌肉骨骼	神经系统	肿瘤易感	其他
c.34G>A	p.Gly12Ser	+	+	+	+	+	-	+	脊柱侧弯、气道阻塞
c.35G>C	p.Gly12Ala	+	+	+	+	+	-	+	恶性肿瘤风险高
c.35-36GC>TT、c.35_36delinsTA、c.35_36delinsTT	p.Gly12Val	+	+	-	+	+	-	-	严重致死表型、胎儿水肿、肝肿大、羊水过多、白内障
c.35_36delinsAA	p.Gly12Glu	+	+	-	+	+	+	-	高胰岛素血症
c.34G>T	p.Gly12Cys	+	+	-	+	+	-	+	-
c.35G>A	p.Gly12Asp	+	-	+	+	+	-	-	呼吸衰竭
c.34G>C	p.Gly12Arg	+	-	+	-	+	+	-	性早熟、掌跖角化症
c.38G>A	p.Gly13Asp	+	+	+	+	+	+	+	-
c.37G>T	p.Gly13Cys	-	+	+	-	-	+	-	羊水过多
c.64C>A	p.Gln22Lys	+	+		+	+	-	-	低血糖
c.108_110dupAGA、c.110_111dupAGG	p.Glu37dup	+	+	+	-	-	+	-	-
c.164_172dup	p.Ile55_Asp57dup	+	-	+	-	-	-	-	轻微表型
c.173C>T	p.Thr58Ile	+	+	-	+	+	-	-	幽门狭窄、父系传播
c.179G>T	p.Gly60Val	+	+	+	+	-	+	-	-
c.179G>A	p.Gly60Asp	+	+	-	+	+	-	-	轻微表型、母系传播
c.186_206dup	p.Glu62_Arg68dup	+	-	+	-	-	-	-	轻微表型
c.187A>G	P.Glu63Lys	+	-	-	+	+	+	+	呼吸衰竭
c.202C>T	p.Arg68Trp	+	-	-	+	-	+	-	-
c.187_207dup	p.Glu63_Asp69dup	+	+	-	-	-	-	-	轻微表型
c.266C>G	p.Ser89Cys	+	-	+	-	-	-	-	严重水肿
c.350A>G	p.Lys117Arg	+	+	-	+	+	-	-	轻微表型
c.436G>A	p.Ala146Thr	+	+	+	-	+	-	-	轻微表型
c.436G > C	p.Ala146Pro	+	+	-	+	+	+	-	-
c.437C>T	p.Ala146Val	+	+	+	+	+	+	-	-
c.481_490delGG-GACCCTCT	p.Leu163ProfsTer52	+	+	-	+	-	+	+	-

注：“+”：存在症状；“-”：无症。

Note: “+”: symptom present; “-”: symptom absent.

2.1 Costello综合征的遗传模式

Costello综合征(CS)为常染色体显性遗传疾病。然而，绝大多数患者由于新发变异而患病，其父母通常不会表现出相关症状，患者兄弟姐妹患病的概率与正常人一致。也有文献报道过兄弟姐妹同时患病的案例，这可能是由于父母存在胚系嵌合现象。一般而言，患有典型CS的个体通常生育能力受限[39]，因而家系报道罕见。

2.2 Costello综合征的致病机制

2.2.1 *HRAS*与Costello综合征

RAS/MAPK信号通路是细胞内重要的信号转导通路，其在细胞的生长、分化、存活以及凋亡等诸多重要生理过程中发挥关键作用。该通路主要由酪氨酸激酶(RTK)受体、RAS蛋白、RAF蛋白激酶、MEK蛋白激酶以及ERK蛋白激酶等关键组分构成。RAS蛋白作为一类小分子鸟苷核苷酸结合的GTP酶，广泛分布于细胞膜上，能够被与酪氨酸激酶(RTK)受体、G蛋白偶联受体、细胞因子受体以及细胞外基质受体结合的生长因子激活，进而在细胞内发挥关键的信号转导枢纽作用[40]。RAS/MAPK信号通路的异常激活与多种疾病的发生发展密切相关，包括癌症以及RAS信号通路相关综合征(RASopathies)等。

CS是RAS信号通路相关综合征中的一种，主要由*HRAS*基因的胚系突变引起[41]。正常情况下，HRAS结合GTP时处于激活状态，结合GDP时处于失活状态，由鸟嘌呤核苷酸交换因子(GEFs，负责打开)和GTP酶激活蛋白(GAPs，负责关闭)调控。而CS患者的*HRAS*基因变异，导致HRAS蛋白的空间构象等发生改变，如p.Gly12Val引入的大侧链氨基酸形成空间位阻，阻挡GAP结合，使其无法调控关闭，也使得GAP的“精氨酸手指”无法准确定位到催化位点，GTP水解变得缓慢，同时GEF调控打开的功能正常，最终使HRAS蛋白持续处于活化状态；HRAS被激活后，促使Raf(包括ARAF、BRAF和CRAF)进入激活状态，Raf是RAS/MAPK通路中首个MAPK激酶激酶。激活后的Raf会磷酸化并激活MAPK激酶MEK1和

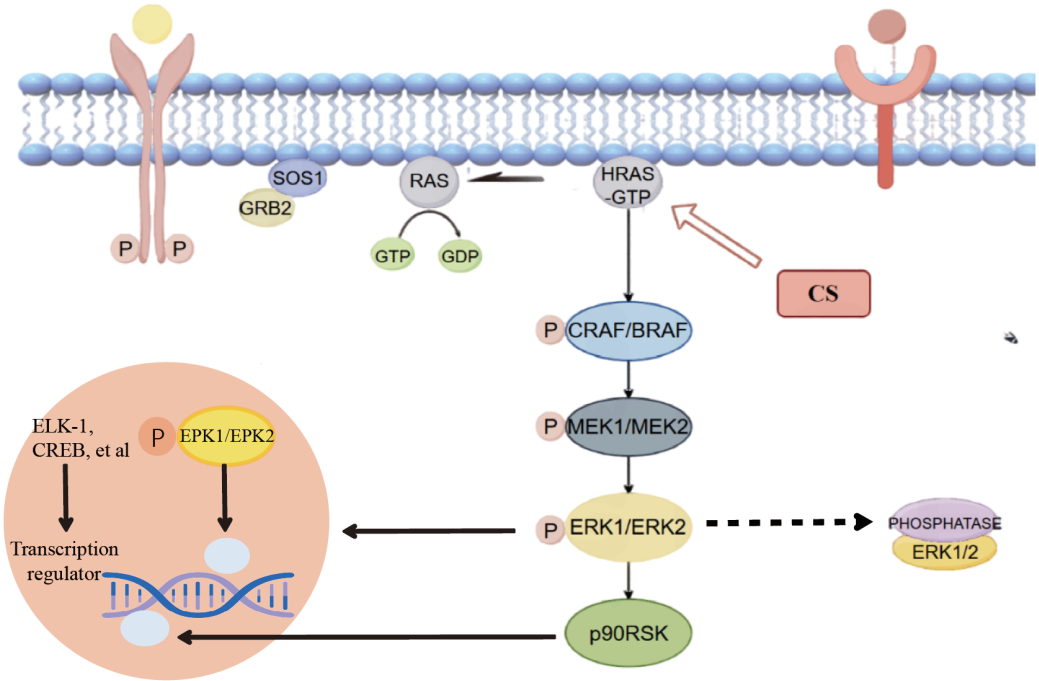

图2 *HRAS*的致病机制图

本图揭示了*HRAS*参与的 RAS/MAPK 信号转导通路机制。HRAS-GTP 激活后，依次磷酸化激活 CRAF/BRAF、MEK1/MEK2、ERK1/ERK2 等信号分子，通过磷酸化修饰(P)传递信号，最终作用于 ELK-1、CREB 等转录调节因子，调控下游基因表达。

Figure 2 Pathogenic mechanism of *HRAS*

This figure elucidates the mechanism of *HRAS* in RAS/MAPK signaling pathway. Upon activation of HRAS-GTP, it sequentially phosphorylates and activates signaling molecules such as CRAF/BRAF, MEK1/MEK2, and ERK1/ERK2. The signal is propagated through phosphorylation modifications (P) and ultimately acts on transcription regulators like ELK1 and CREB, thereby regulating the expression of downstream genes.

(或)MEK2,随后MEK1和(或)MEK2继续磷酸化并激活ERK1和(或)ERK2。ERK1和ERK2作为最终的效应分子,对众多下游分子(既包括细胞核内的分子,也包括细胞质中的分子)发挥作用(图2)。其中,核内底物以转录因子为主,ERK入核后通过磷酸化这些因子直接调控细胞周期、增殖及分化相关基因的表达。例如,ETS家族转录因子Elk1通过其D结构域和DEF结构域与ERK结合,在Thr353、Thr363和Ser383等位点被磷酸化后,DNA结合及转录激活能力增强,进而促进c-Fos等即时早期基因(IEG)的转录;c-Fos作为AP-1转录复合物(c-Fos/c-Jun)的核心组分,其Ser374和Thr325等位点被ERK及下游MAPKAPK(如RSK)磷酸化,不仅可稳定c-Fos蛋白和延长其半衰期,还能促进AP-1复合物组装,并结合于靶基因启动子中的AP-1位点,调控Cyclin D1等细胞周期相关蛋白的表达。Cyclin D1过表达促使细胞从G_1期进入S期,破坏细胞周期调控,为组织过度生长和肿瘤发生提供基础。此外,ERK还可通过磷酸化c-Myc(Ser62)、ATF2(Thr71)和p53(Thr55)等转录因子,分别调控细胞周期进程、应激响应及肿瘤抑制通路。而胞质底物包括三类:MAPKAPK、细胞骨架相关蛋白及凋亡调节因子。MAPKAPK(如RSK、MSK、MNK)被ERK激活后,可分别参与抑制凋亡、调控基因表达、修饰染色质状态或促进蛋白质翻译;而Paxillin等细胞骨架元件被磷酸化,能够调控细胞黏附、铺展及骨架重排;此外,通过磷酸化MCL1、Bim-EL等凋亡相关蛋白,ERK可抑制细胞程序性死亡,从而协同促进细胞增殖与生存[42]。

*HRAS*基因编码的蛋白在机体中广泛表达,如心脏、消化系统、皮肤、神经系统、早期胚胎、肾单位、感觉器官以及牙齿等,因而其变异所引起的症状也是广泛的。具体来说,在皮肤方面,*HRAS*异常会通过持续激活MEK/ERK信号通路,使成纤维细胞增殖加快、细胞外基质合成异常,导致皮肤松弛粗糙[13];在心血管系统中,变异的*HRAS*通过上调心肌细胞中ERK1/2的磷酸化水平,导致心肌细胞异常增殖和肥大,同时干扰心脏神经嵴细胞的迁移,引发心肌肥厚等[43];在骨骼系统内,RAS/MAPK通路过度激活会通过抑制SOX9和RUNX2等转录因子的表达,直接阻碍软骨细胞分化、抑制成骨相关基因的表达以及激活破骨细胞分化因子,导致骨骼畸形、身材矮小[19];在神经系统中,ERK1/2磷酸化水平异常升高导致神经元迁移障碍、突触可塑性损伤及髓鞘形成异常,引发智力发育迟缓、肌张力低下和运动协调缺陷等[44];在视觉系统中,MAPK通路的激活与视网膜色素上皮细胞的氧化应激、炎症反应以及新生血管形成有关,此信号通路增强也会导致角膜上皮愈合延迟,进而引发视网膜和角膜疾病[45]。

*HRAS*基因位于人类第11号染色体上,由6个外显子组成,编码具有 189 个氨基酸的蛋白质[41]。迄今为止,已发现28种可导致CS的*HRAS*基因变异(表1),这些变异主要集中在*HRAS*外显子2(图3)。外显子2中编码氨基酸10至15的G1框P-loop(磷酸结合环)区域包含多个5′-CG-3′(CpG)位点,这些CpG位点的存在,很可能是导致该区域成为变异热点的关键因素[46]。体细胞变异热点是第12和13位甘氨酸以及第61位谷氨酰胺的编码碱基,其中p.Gly12Ser最常见。在涉及第13位甘氨酸的变异中,最常见的氨基酸变化是p.Gly13Cys[47]。除了上述经典变异,还存在一些可能导致CS但尚未经过严格验证的*HRAS*变异,以及一些在CS综合征中症状表现不够典型的*HRAS*变异。例如,Pekeles等[48]报道了一例智力障碍患者,其携带p.Gln150Term变异,但CS特征并不明显;Leach等[49]鉴定了多个*HRAS*变异位点可能与Noonan 综合征相关,这些变异在不同患者中表现出不同的临床特征。因此,*HRAS*基因型与CS表型之间的对应关系还有待进一步研究。同时,还存在一些被认为具有典型Costello表型的个体,但未能检测到*HRAS*变异,其原因可能为:(1)所检测组织中存在低水平的 *HRAS* 致病变异体细胞嵌合现象,这种情况较为罕见[50];(2)存在其他CS致病基因[51]。

2.2.2 其他基因与Costello综合征

除了*HRAS*基因,诸多研究还发现了其他基因的变异与CS存在关联。Zenker等[52]在诊断为CS的患者体内检测到了*KRAS*基因的变异,同时指出这些患者后续可能会呈现出心-面-皮肤综合征(CFC综合征)的特征。Pabari等[53]报道了1例*NRAS*变异的白血病患者,该患者同时也被诊断出患有CS。Nava等[54]针对诊断为CS但未检测出*HRAS*变异的患者展开调查研究,结果发现了*BRAF*、*KRAS*或*MEK1*的变异。此外,Kobayashi 等[55]在 CS 患者中发现了*RAF1*基因的变异。Castellanos等[56]还发现*NF1*、*RASA1*、*LZTR1*变异的患者会出现CS。而Strong等[57]报道了一例*RREB1*基因的变异,患者存在先

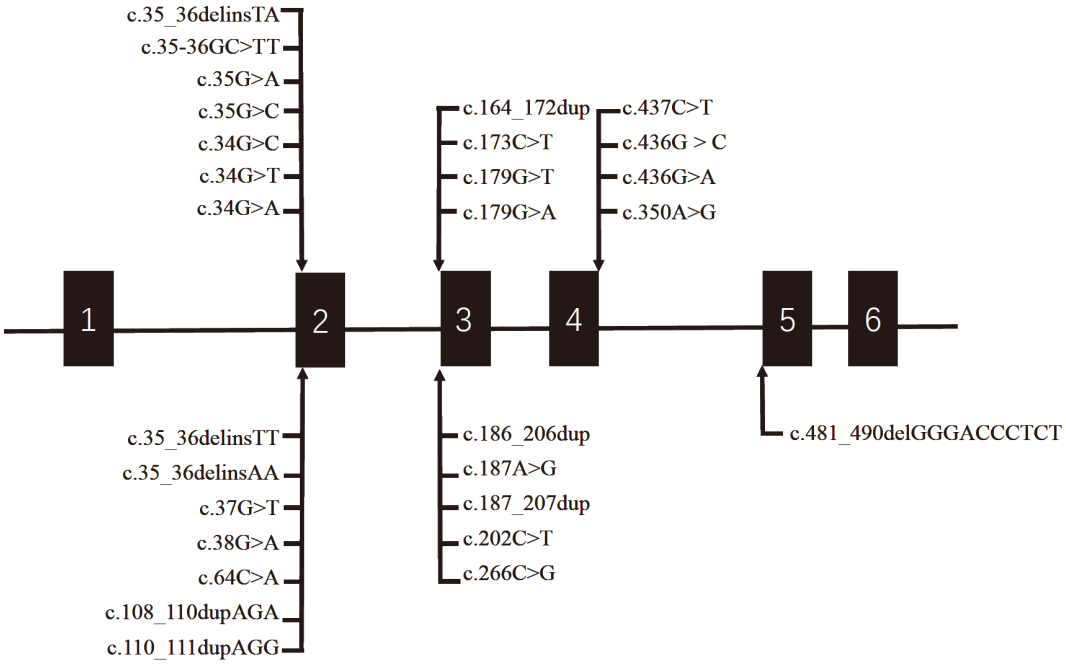

图3 *HRAS*基因变异位置的示意图

HGMD与GeneCards收录的与Costello综合征相关的*HRAS*基因变异分布。

Figure 3 Schematic distribution of *HRAS* gene variants

Distribution of *HRAS* gene variants associated with Costello syndrome recorded in HGMD and GeneCards.

天性心脏病、泌尿生殖系统畸形和生长发育迟缓，与CS患者症状高度重合。然而，Grant等[58]认为，*HRAS*是唯一被认定与 CS 相关的明确临床有效性分类的基因，其他基因的变异与 CS 的关联性仍存在较大争议 。

这些研究表明，CS的发病机制可能并非仅由*HRAS*基因变异单一驱动，其他基因如*KRAS*、*NRAS*、*BRAF*、*MAP2K1*、*RAF1*等的变异，可能通过影响RAS/MAPK信号通路等机制，参与CS的发生发展过程，不过这些基因与 CS之间的确切联系仍有待更多研究进一步明确。

3 Costello综合征的诊疗

3.1 诊断

Costello综合征(CS)目前没有统一的诊断标准，但现有文献通过对已报道病例的系统分析，为CS患者的临床诊断和护理提供了临床管理指南。Gripp等[35]通过对186例经分子确诊的CS患者进行表型分析，制定了包含主要标准(如典型面容、皮肤松弛、发育迟缓)和次要标准(如乳头状瘤、心肌病)的评分系统，为CS的临床诊断和分级管理提供了重要依据。CS的诊断主要基于临床表现，并经分子遗传学检测验证。对于颈部半透明层增加(包括囊性水瘤)、羊水过多、手腕尺侧偏斜、肥厚型心肌病或心动过速的胎儿，应考虑 CS的产前诊断[59]。需要注意的是，CS与另外两种RASopathies——Cardiofaciocutaneous综合征和Noonan综合征存在相似的临床特征，许多胎儿特征和产前超声检查结果重叠[35]，要根据每种综合征独特的临床表现进行鉴别诊断。分子检测是确诊的关键，可对*HRAS*基因进行测序分析，80%~90%的临床诊断患者携带*HRAS*基因的致病错义变异[41]。

3.2 治疗

对CS患者的治疗措施主要是多学科综合管理，针对不同的症状和并发症进行治疗。例如，MEK 抑制剂(曲美替尼等[60])可改善CS患者的心肌病[61]，口服异维A酸可治疗CS患者的黑棘皮病[62]，也可手术改善CS引起的严重脊柱侧凸[63]。而Foussat等[64]聚焦于部分CS患者出现髋关节疼痛这一特性，探索出髋关节囊周围化学去神经支配这种疗法，缓解患者疼痛，最大限度地减少他们的功能丧失。

4 展望

近年来，随着基因组学和外显子组测序技术的

快速发展,Costello综合征(CS)的遗传学研究有显著进展,但其具体致病机制仍有待进一步验证。目前一般认为*HRAS*变异导致HRAS蛋白的GTP酶活性降低或GDP/GTP交换活性增强,使HRAS蛋白持续处于活化状态,从而引起RAS/MAPK信号通路的异常激活,通过影响细胞内信号转导扰乱正常生理功能,进而导致患者出现多系统的异常表现。然而,不同*HRAS*基因变异类型在CS中表现出显著的表型多样性,这可能与以下几个因素相关。首先,不同变异位点对HRAS蛋白功能的影响程度是导致表型差异的重要因素,不同的氨基酸替换对蛋白质结构的干扰程度不同。缬氨酸侧链较大,疏水性强,对GTP酶活性口袋的空间阻碍效应最大,几乎完全废除了GTP水解功能,所以p.Gly12Val突变体存在严重的GTP酶活性缺陷,具有极高的信号激活强度,在体外实验中显示出最强的恶性转化潜能,但其在胚胎期的强效作用可能致死,因此临床上极为罕见。而HRAS蛋白的持续激活型变异(如p.Gly12Ala等)会导致HRAS蛋白无法正常从“开”(GTP结合状态)切换到“关”(GDP结合状态),从而过度激活下游的RAS/MAPK信号通路,引发严重的生长发育异常、心脏缺陷和肿瘤等表型。相比之下,部分功能改变型变异(如p.Gly13Cys)可能仅部分改变HRAS蛋白的功能,导致其活性有所改变但不至于完全失控,从而与较轻的表型相关。其次,体细胞嵌合现象是导致表型变异的另一重要机制。当合子后突变发生时,仅部分机体细胞携带突变,嵌合比例与组织分布直接影响信号通路异常的程度和范围,可导致嵌合个体症状显著减轻或呈局灶性表现,同时也增加了临床检测和诊断的复杂性。另外,遗传修饰因子也可通过影响RAS/MAPK信号通路的调控网络,在一定程度上调节突变*HRAS*的外显率(携带该突变个体的发病比例)和表现度(疾病症状的严重程度差异),进而为CS的表型多样性提供重要遗传基础。除此以外,CS患者的表型在不同年龄阶段也有所变化。一般而言,在婴儿期和幼儿期,患者常出现心脏缺陷、发育迟缓、皮肤异常以及良性肿瘤发生率高;至青少年期,患者部分心脏问题可能有所改善,但肌肉骨骼问题较为突出,开始展现认知和行为异常,而成年后大部分CS患者症状稳定,心脏问题改善,肿瘤风险降低,但仍保持典型的CS外貌特征,这为CS的临床诊断、分阶段干预和治疗提供了重要思路。除*HRAS*外,研究人员也已检测到与CS相关的更多基因,并阐明了这些基因变异影响RAS信号转导的可能机制[52-57]。同时,科学界正积极探索新的治疗策略,以更好地治疗疾病与改善预后,如RAS靶向治疗的新兴策略包括直接靶向RAS蛋白、靶向上游因子或下游效应因子、RNA干扰和靶向代谢过程等[65]。也有研究聚焦*BRAF*等特定基因,证实其突变激活MAPK通路驱动癌变,并验证了靶向*BRAF*联合MEK抑制剂的临床疗效与价值[66]。

对CS的遗传学研究仍在持续中,未来的研究可能会集中在以下几个方向:(1)进一步探究RAS/MAPK信号通路在CS发生发展中的详细作用机制,以便更精确地理解疾病的发生和进展;(2)开发针对性的靶向药物,以干预异常的信号转导途径,从而提高治疗效果,改善患者的生活质量;(3)利用患者的遗传信息来制定个性化的治疗方案。总之,对CS相关遗传学的深入研究有望为遗传咨询、产前诊断乃至精准医疗提供重要依据。

参考文献

[1] Costello JM. A new syndrome: mental subnormality and nasal papillomata. Aust Paediatr J, 1977, 13: 114–8.

[2] Gripp KW, Innes AM, Axelrad ME, et al. Costello syndrome associated with novel germline *HRAS* mutations: an attenuated phenotype? Am J Med Genet A, 2008, 146A: 683–90.

[3] Waldburg N, Buehling F, Evert M, et al. Pulmonary infiltrates in Costello syndrome. Eur Respir J, 2004, 23: 783–5.

[4] Borochowitz Z, Pavone L, Mazor G, et al. New multiple congenital anomalies: mental retardation syndrome (MCA/MR) with facio-cutaneous-skeletal involvement. Am J Med Genet, 1992, 43: 678–85.

[5] Peschiaroli S, Viscogliosi G, Salerni A, et al. Costello syndrome and ophthalmologic issues: unveiling the unseen. Am J Med Genet A, 2025, 197: e64049.

[6] Gripp KW, Demmer LA. Keratoconus in Costello syndrome. Am J Med Genet A, 2013, 161A: 1132–6.

[7] Shankar SP, Fallurin R, Watson T, et al. Ophthalmic manifestations in Costello syndrome caused by Ras pathway dysregulation during development. Ophthalmic Genet, 2022, 43: 48–57.

[8] Alhazmi AM, Alsubaie MA, Alanazi RR. Concurrent presentation of Euryblepharon and Moyamoya syndrome in Costello syndrome: a rare clinical case. Cureus, 2023,

15: e40808.
[9] Goodwin AF, Oberoi S, Landan M, et al. Craniofacial and dental development in Costello syndrome. Am J Med Genet A, 2014, 164A: 1425–30.
[10] Weaver KN, Care M, Wakefield E, et al. Craniosynostosis is a feature of Costello syndrome. Am J Med Genet A, 2022, 188: 1280–6.
[11] Zampino G, Mastroiacovo P, Ricci R, et al. Costello syndrome: further clinical delineation, natural history, genetic definition, and nosology. Am J Med Genet, 1993, 47: 176–83.
[12] Leoni C, Onesimo R, Giorgio V, et al. Understanding growth failure in Costello syndrome: increased resting energy expenditure. J Pediatr, 2016, 170: 322–4.
[13] Bessis D, Bursztejn AC, Morice-Picard F, et al. Dermatological manifestations in Costello syndrome: a prospective multicentric study of 31 *HRAS*-positive variant patients. J Eur Acad Dermatol Venereol, 2024, 38: 1818–27.
[14] Siegel DH, Mann JA, Krol AL, et al. Dermatological phenotype in Costello syndrome: consequences of Ras dysregulation in development. Br J Dermatol, 2012, 166: 601–7.
[15] Siwik ES, Zahka KG, Wiesner GL, et al. Cardiac disease in Costello syndrome. Pediatrics, 1998, 101: 706–9.
[16] Naneishvili T, Yuan M, Mansour M, et al. Dysplastic mitral valve in Costello syndrome. JACC Case Rep, 2024, 29: 102408.
[17] Lin AE, Grossfeld PD, Hamilton RM, et al. Further delineation of cardiac abnormalities in Costello syndrome. Am J Med Genet, 2002, 111: 115–29.
[18] Machida M, Rocos B, Taira K, et al. Costello syndrome-associated orthopaedic manifestations focussed on kyphoscoliosis: a case series describing the natural course. J Pediatr Orthop B, 2023, 32: 357–62.
[19] Fowlkes JL, Thrailkill KM, Bunn RC. RASopathies: the musculoskeletal consequences and their etiology and pathogenesis. Bone, 2021, 152: 116060.
[20] Dileone M, Zampino G, Profice P, et al. Dystonia in Costello syndrome. Parkinsonism Relat Disord, 2012, 18: 798–800.
[21] Axelrad ME, Glidden R, Nicholson L, et al. Adaptive skills, cognitive, and behavioral characteristics of Costello syndrome. Am J Med Genet A, 2004, 128A: 396–400.
[22] Schmetz A, Ballesta-Martínez MJ, Isidor B, et al. Adult syndromology: challenges, opportunities and perspectives: illustrated by the description of four adults with Costello syndrome. Med Genet, 2024, 36: 95–102.
[23] Torrelo A, Lo´pez-Avila A, Mediero IG, et al. Costello syndrome. J Am Acad Dermatol, 1995, 32: 904–7.
[24] Fryns JP, Vogels A, Haegeman J, et al. Costello syndrome: a postnatal growth retardation syndrome with distinct phenotype. Genet Couns, 1994, 5: 337–343.
[25] Di Rocco M, Gatti R, Gandullia P, et al. Report of two patients with Costello syndrome and sialuria. Am J Med Genet, 1993, 47: 1135–40.
[26] Lages Pereira R, Ribeiro A, Saraiva J, et al. An unusual presentation of Costello syndrome in a boy with precocious puberty and chiari I malformation: a case report. Cureus, 2025, 17: e78321.
[27] Delrue MA, Chateil JF, Arveiler B, et al. Costello syndrome and neurological abnormalities. Am J Med Genet A, 2003, 123A: 301–5.
[28] Say B, Guçsavas M, Morgan H, et al. The Costello syndrome. Am J Med Genet. 1993, 47: 163–5.
[29] Astiazaran-Symonds E, Ney GM, Higgs C, et al. Cancer in Costello syndrome: a systematic review and meta-analysis. Br J Cancer, 2023, 128: 2089–96.
[30] Kratz CP, Franke L, Peters H, et al. Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes. Br J Cancer, 2015, 112: 1392–7.
[31] Perrino MR, Das A, Scollon SR, et al. Update on pediatric cancer surveillance recommendations for patients with neurofibromatosis type 1, Noonan syndrome, CBL syndrome, Costello syndrome, and related RASopathies. Clin Cancer Res, 2024, 30: 4834–43.
[32] Alexander S, Ramadan D, Alkhayyat H, et al. Costello syndrome and hyperinsulinemic hypoglycemia. Am J Med Genet A, 2005, 139: 227–30.
[33] Gregersen N, Viljoen D. Costello syndrome with growth hormone deficiency and hypoglycemia: a new report and review of the endocrine associations. Am J Med Genet A, 2004, 129A: 171–5.
[34] Triantafyllou P, Christoforidis A, Vargiami E, et al. Growth hormone replacement therapy in Costello syndrome. Growth Horm IGF Res, 2014, 24: 271–5.
[35] Gripp KW, Morse LA, Axelrad M, et al. Costello syndrome: clinical phenotype, genotype, and management guidelines. Am J Med Genet A, 2019, 179: 1725–44.
[36] Gripp KW, Sol-Church K, Smpokou P, et al. An attenuated phenotype of Costello syndrome in three unrelated individuals with a HRAS c.179G>A (p. Gly60Asp) mutation correlates with uncommon functional consequences. Am J Med Genet A, 2015, 167A: 2085–97.
[37] Morice-Picard F, Ezzedine K, Delrue MA, et al. Cutaneous manifestations in Costello and cardiofaciocutaneous

syndrome: report of 18 cases and literature review. Pediatr Dermatol, 2013, 30: 665–73.

[38] 秦雯, 徐哲, 林志淼, 等. Costello综合征HRAS基因突变研究. 临床皮肤科杂志, 2020, 49: 521–4.
Qin W, Xu Z, Lin ZM, et al. *HRAS* gene mutation in Costello syndrome. J Clin Dermatol, 2020, 49: 521–4.

[39] Gripp KW, Weaver KN. *HRAS*-related Costello syndrome[M]//Adam MP, Feldman J, Mirzaa GM, et al. GeneReviews®[Internet]. Seattle (WA): University of Washington, 1993–2025.

[40] Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell, 2017, 170: 17–33.

[41] Aoki Y, Niihori T, Kawame H, et al. Germline mutations in *HRAS* proto-oncogene cause Costello syndrome. Nat Genet, 2005, 37: 1038–40.

[42] Yoon S, Seger R. The extracellular signal-regulated kinase: multiple substrates regulate diverse cellular functions. Growth Factors, 2006, 24: 21–44.

[43] Rodríguez NA, Patel N, Dariolli R, et al. *HRAS*-mutant cardiomyocyte model of multifocal atrial tachycardia. Circ Arrhythm Electrophysiol, 2024, 17: e012022.

[44] Pan Y, Gu Y, Liu T, et al. Epitranscriptic regulation of *HRAS* by N6-methyladenosine drives tumor progression. Proc Natl Acad Sci U S A, 2023, 120: e2302291120.

[45] Moustardas P, Aberdam D, Lagali N. MAPK pathways in ocular pathophysiology: potential therapeutic drugs and challenges. Cells, 2023, 12: 617.

[46] Gripp KW, Lin AE. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from *HRAS* germline mutations. Genet Med, 2012, 14: 285–92.

[47] Gripp KW, Lin AE, Stabley DL, et al. *HRAS* mutation analysis in Costello syndrome: genotype and phenotype correlation. Am J Med Genet A, 2006, 140: 1–7.

[48] Pekeles H, Accogli A, Boudrahem-Addour N, et al. Diagnostic yield of intellectual disability gene panels. Pediatr Neurol, 2019, 92: 32–6.

[49] Leach NT, Wilson Mathews DR, Rosenblum LS, et al. Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions. Genet Med, 2019, 21: 417–25.

[50] Girisha KM, Lewis LE, Phadke SR, et al. Costello syndrome with severe cutis laxa and mosaic *HRAS* G12S mutation. Am J Med Genet A, 2010, 152A: 2861–4.

[51] Quezada E, Gripp KW. Costello syndrome and related disorders. Curr OpinPediatr, 2007, 19: 636–44.

[52] Zenker M, Lehmann K, Schulz AL, et al. Expansion of the genotypic and phenotypic spectrum in patients with *KRAS* germline mutations. J Med Genet, 2007, 44: 131–5.

[53] Pabari R, Chun K, Naqvi A. The Clinical landscape of *NRAS*-mutated juvenile myelomonocytic leukemia-like myeloproliferation includes children with Costello syndrome. J Pediatr Hematol Oncol, 2023, 45: e401–5.

[54] Nava C, Hanna N, Michot C, et al. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet, 2007, 44: 763–71.

[55] Kobayashi T, Aoki Y, Niihori T, et al. Molecular and clinical analysis of RAF1 in Noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation. Hum Mutat, 2010, 31: 284–94.

[56] Castellanos E, Rosas I, Negro A, et al. Mutational spectrum by phenotype: panel-based NGS testing of patients with clinical suspicion of RASopathy and children with multiple café-au-lait macules. Clin Genet, 2020, 97: 264–75.

[57] Strong A, McKenna C, Stals K, et al. Truncating variants in *RREB1* cause a novel RASopathy syndrome of congenital heart disease, genitourinary malformations, and developmental delay. Am J Med Genet A, 2025, 26: e64119.

[58] Grant AR, Cushman BJ, Cavé H, et al. Assessing the gene-disease association of 19 genes with the RASopathies using the ClinGen gene curation framework. Hum Mutat, 2018, 39: 1485–93.

[59] Smith LP, Podraza J, Proud VK. Polyhydramnios, fetal overgrowth, and macrocephaly: prenatal ultrasound findings of Costello syndrome. Am J Med Genet A, 2009, 149A: 779–84.

[60] Kato AS, Shwaish NS, Hwang EY, et al. Novel use of trametinib for treatment of atrial arrhythmia in absence of cardiomyopathy in a patient with Costello syndrome. Cardiol Young, 2024, 34: 2703–5.

[61] Geddes GC, Parent JJ, Lander J, et al. MEK inhibition improves cardiomyopathy in Costello syndrome. J Am Coll Cardiol, 2023, 81: 1439–41.

[62] Sriboonnark L, Arora H, Falto-Aizpurua L, et al. Costello syndrome with severe nodulocystic acne: unexpected significant improvement of acanthosis nigricans after oral isotretinoin treatment. Case Rep Pediatr, 2015, 2015: 934865.

[63] Grabala P, Kowalski P, Rudziński MJ, et al. The surgical management of severe scoliosis in immature patient with a very rare disease Costello syndrome-clinical example and brief literature review. Life (Basel), 2024, 14: 740.

[64] Foussat E, Geffrier A, Guignans C, et al. Pericapsular hip chemical denervation with phenol: a case report suggesting the interest of this new tool in rehabilitation medicine. Ann Phys Rehabil Med, 2025, 68: 101982.
[65] Chen K, Zhang Y, Qian L, et al. Emerging strategies to target RAS signaling in human cancer therapy. J Hematol Oncol, 2021, 14: 116.
[66] Subbiah V, Baik C, Kirkwood JM. Clinical development of BRAF plus MEK inhibitor combinations. Trends Cancer, 2020, 6: 797–810.