

◇ 综 述 ◇

Cornelia de Lange 综合征的遗传学与分子机制研究进展

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摘要 Cornelia de Lange 综合征(CdLS)是一种以多系统发育障碍为特征的罕见遗传病,核心致病机制与黏连蛋白复合体功能异常密切相关。整合多组学证据揭示,该复合体功能异常破坏染色质三维结构与表观遗传稳态,引发全基因组转录失调,扰乱 Wnt/ β -catenin、TGF- β /BMP、Sonic Hedgehog(SHH)等信号通路的调控网络,共同驱动神经、心血管、骨骼等多系统表型,为深入理解 CdLS 病理机制、优化分子诊断奠定理论基础。该文综述 CdLS 的遗传学基础(含表观遗传异常机制)、关键发育信号通路失调机制,并探讨分子诊断优化策略。

关键词 Cornelia de Lange 综合征;黏连蛋白复合体;表观遗传;信号通路;分子诊断

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Cornelia de Lange 综合征(Cornelia de Lange syndrome, CdLS)是一种遗传性发育疾病,以特殊面容、生长受限及多系统发育异常为特征^[1]。自1933年首次报道以来,其诊断已从表型观察发展为临床与分子遗传学整合模式,因临床异质性显著,传统诊断易导致轻型及不典型病例误诊漏诊^[2]。黏连蛋白复合体功能异常是 CdLS 核心致病机制,该复合体调控染色质结构、基因转录及 DNA 修复,其功能紊乱可致发育基因表达失调^[3]。现有研究多聚焦于单一基因或通路,缺乏表观遗传与信号通路协同作用的系统性阐释。该文整合遗传学与多组学证据,解析黏连蛋白复合体功能异常如何破坏染色质稳态及信号网络,进而引发多系统发育缺陷的级联机制,探讨分子诊断优化策略,为全面理解 CdLS 分子机制与精准诊断提供理论框架。

1 遗传学基础

1.1 从临床诊断到分子诊断 CdLS 全球发病率约为 1/10 000~1/30 000^[4],因诊断障碍该数据可能被低估。在非洲等医疗资源有限地区,规范诊断更难普及^[5]。此外,CdLS 表型异质性在族群间尤为突

出,连眉、短鼻核心特征虽具普遍性,但头围、鼻翼宽度等指标存在显著差异^[6]。这种源于遗传背景的表型修饰,增加了单纯依赖临床表型诊断的难度。为此,国际 CdLS 共识小组制定了综合性诊断路径,量化临床特征(基本特征 2 分/项,提示性特征 1 分/项),对评分 4~8 分且至少具备 1 项基本特征的疑似病例,需结合分子检测确诊,并鉴别表型重叠疾病^[2]。该策略提升了诊断准确性,凸显了向分子诊断递进的必要性,为理解 CdLS 的遗传异质性及个体化管理奠定了基础。

1.2 致病基因变异与表型关联 CdLS 是一种由黏连蛋白复合体功能缺陷引起的染色质病,该复合体由结构核心亚基[染色体结构维持蛋白 1A (structural maintenance of chromosomes 1A, *SMC1A*), 染色体结构维持蛋白 3 (structural maintenance of chromosomes 3, *SMC3*)]、桥连亚基[*RAD21* 黏连蛋白复合体组分 (RAD21 Cohesin complex component, *RAD21*)]及调节因子[Nipped-B 样蛋白 (nipped-B-like protein, *NIPBL*), 组蛋白去乙酰化酶 8 (histone deacetylase 8, *HDAC8*)]构成,通过形成环状结构包裹 DNA,调控染色质三维构象与基因转录^[3](图 1)。核心基因突变通过影响复合体不同功能,导致 CdLS 表型广泛异质性^[3]。*NIPBL* 作为复合体关键装载因子,其编码的 *NIPBL* 是核心致病基因,突变约占病例的 60%~70%,是 CdLS 经典表型的主要遗传驱动

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因素^[2], *NIPBL* 突变类型与表型严重程度相关^[2,7]。无义、移码或剪接位点突变导致蛋白截断,破坏复合体功能及基因组稳定性,引发转录紊乱,患者常表现为生长迟缓、显著智力障碍及肢体畸形等严重表型,*NIPBL* 表达下调可抑制骨髓间充质干细胞成骨分化,降低下游 *runt* 相关转录因子 2 (*runt*-related transcription factor 2, *RUNX2*) 及骨钙素 (*osteocalcin*, *OCN*) 等成骨标志物水平,佐证骨骼发育异常;错义突变仅致部分功能改变,蛋白保留部分复合体调控功能,患者表型不典型或较轻。不同突变对 *NIPBL* 功能的影响差异,共同阐释了该群体的表型异质性。

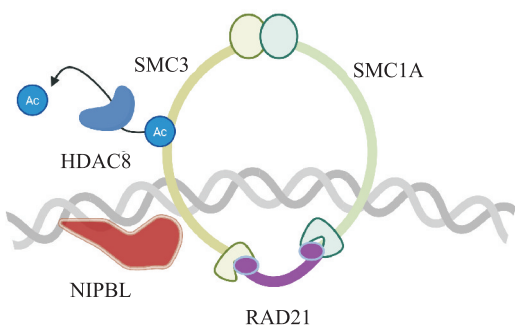


图1 黏连蛋白复合体结构及其与DNA的相互作用

Fig. 1 Cohesin complex structure and its interactions with DNA

SMC1A 与 *SMC3* 是黏连蛋白环核心亚基,通过结构域协作保障复合体与DNA的结合与动态调控,致病性突变频率分别为 5% 和 1%~2%^[8]。二者表型较 *NIPBL* 突变温和,以轻度认知延迟、轻微颅面异常为主,无严重畸形,因突变仅影响DNA结合动力学等局部功能,未完全破坏复合体组装,对发育干扰较轻^[8-9]。*SMC1A* 定位于X染色体,突变以移码

及无义突变为主,心血管异常发生率约 20%,多为房间隔缺损、室间隔缺损等简单畸形,心血管畸形并非其突出特征^[10]。*SMC3* 突变与先天性心脏病 (congenital heart disease, CHD) 的关联显著强于 *SMC1A*, 发生率高达 52.4% 且多见复杂缺陷,差异源于二者调控分工不同:*SMC3* 直接调控心脏关键基因,*SMC1A* 对 CHD 的影响相对间接^[11]。

RAD21 突变率为 1%~2%,表型常与典型 CdLS 重叠 (如特征性面部容貌、生长迟缓),但智力障碍或发育迟缓程度较轻^[2]。*RAD21* 连接 *SMC1A* 与 *SMC3* 头部以维持环状结构稳定,其突变损害复合体完整性,破坏拓扑相关结构域 (topologically associating domains, TADs) 形成,引发染色质三维构象紊乱与全基因组转录失调^[2,12]。

HDAC8 定位于X染色体,突变率不足 5%,编码 I 型组蛋白去乙酰化酶^[13]。与影响黏连蛋白结构的基因不同,其致病核心是干扰复合体动态调控周期:有丝分裂期,*SMC3* 须经 *HDAC8* 去乙酰化才能使黏连蛋白从染色质解离循环,其功能丧失致乙酰化 *SMC3* 异常积累,阻碍循环并降低复合体与染色质亲和力^[13],导致了广泛的临床谱系,涵盖典型 CdLS 特征及眼距过宽等非特异性表现^[13]。半合子男性因仅携带单个突变拷贝,症状通常更重,杂合子女性因X染色体随机或偏斜失活,表型从近乎无症状到重度发育缺陷不等^[13]。

为系统总结 CdLS 核心致病基因,表 1 从功能角色、主要致病机制、主要表型关联及突变频率 4 个维度进行对比分析。

1.3 表观遗传异常机制 CdLS 是典型染色质病,本质是染色质状态失衡导致的先天性缺陷,其致病基因均属调控表观基因,编码蛋白参与染色质修

表 1 CdLS 核心基因功能与表型关联

Tab. 1 Core gene functions and phenotypic correlations in CdLS

Gene	Functional role	Primary pathogenic mechanism	Main phenotypic association	Mutation frequency (%)
<i>NIPBL</i>	Cohesin loader	Disruption of 3D chromatin structure, impaired dynamic loading	Classic severe phenotype: severe growth and intellectual disability, limb abnormalities	60-70
<i>SMC1A</i>	Cohesin core subunit	Reduced stability of the ring structure	Atypical/mild phenotype: craniofacial features, mild developmental delay	5
<i>SMC3</i>	Cohesin core subunit	Abnormal <i>SMC3</i> acetylation/deacetylation cycle	High CHD incidence (predominantly complex defects), overall mild phenotype	1-2
<i>RAD21</i>	Cohesin subunit involved in dissociation	Impaired TAD formation	Atypical/mild phenotype: characteristic facial features, relatively mild intellectual disability	1-2
<i>HDAC8</i>	<i>SMC3</i> deacetylase	Dysfunction of histone deacetylation	Broad phenotypic spectrum: from classic features to nonspecific manifestations, significant sex differences	0-5

饰、重塑或结构维持^[14]。按功能可分为3类:黏连蛋白复合体相关基因(*NIPBL*、*SMC1A*、*SMC3*、*RAD21*)、组蛋白修饰相关基因(*HDAC8*)及其他表观遗传调控基因,包括赖氨酸甲基转移酶2A(lysine methyltransferase 2A, *KMT2A*)、SET结构域蛋白5(SET domain containing 5, *SETD5*)等^[14]。这些基因的功能缺陷共同导致CdLS系统性表观遗传调控紊乱,核心机制如下。

1.3.1 三维染色质结构 黏连蛋白复合体通过介导TADs和染色质环形成,调控增强子-启动子互作,维持染色质三维构象^[3]。复合体基因突变致TADs稳定性下降、染色质环紊乱、阻碍RNA聚合酶II招募并引发全局转录失调^[3],机制上,*NIPBL*负责招募复合体至染色质,其突变直接破坏三维结构稳定性^[3]; *RAD21*变异则干扰黏连蛋白环的形成与解离^[12]。总之,该复合体功能异常通过破坏染色质三维构象,导致发育相关基因转录失调,是CdLS多系统表型的核心分子基础^[12]。

1.3.2 DNA甲基化 CdLS具有独特的基因组DNA甲基化图谱,是染色质病中明确的特异性表观标志物,表观遗传标志(epigenetic signature, Epi-Sign)技术利用机器学习算法比对患者外周血数据,生成甲基化变异致病性(methylation variant pathogenicity, MVP)评分辅助CdLS诊断(>0.5为阳性),结果与基因测序高度一致^[14]。该技术不仅能区分CdLS亚型与其他染色质病、评估变异的临床意义、还能验证基因阴性患者的诊断,特别是对于临床疑似但基因检测阴性的病例,若甲基化图谱符合CdLS 1-4型特征,可作为确诊的重要依据^[14-15]。

1.3.3 组蛋白修饰 组蛋白修饰缺陷是CdLS的关键表观遗传机制,涉及多种酶及效应蛋白的功能异常。*HDAC8*催化*SMC3*去乙酰化以调控黏连蛋白复合体循环,其突变致乙酰化*SMC3*异常积累,加剧染色质结构异常^[13,16]。含溴结构域蛋白2(bromodomain containing 2, *BRD2*)作为乙酰阅读器,其功能紊乱可能破坏其与*NIPBL*的协作,影响基因组稳定,导致类似*NIPBL*突变的DNA修复缺陷,可能参与CdLS的病理过程^[17]。此外,甲基化调控因子*KMT2A*与*SETD5*的突变,分别通过影响H3K4甲基化及H3甲基化稳态,导致神经发育异常或轻度CdLS重叠表型^[18-19]。

1.3.4 非编码RNA的调控 *NIPBL*+/-患者诱导多能干细胞中存在非编码RNA(ncRNA)的表达失调,

伴随表观遗传调控相关基因集的上调以及Wnt信号通路基因的下调^[20],提示ncRNA可能通过影响表观遗传网络及发育通路参与CdLS发病。目前其调控机制尚未完全阐明,但已成为重要研究方向,有待结合转录组学数据进一步解析。

2 关键信号通路及发育异常

黏连蛋白复合体功能异常破坏染色质三维结构,干扰信号通路稳态,驱动多系统发育缺陷。Wnt/ β -catenin、转化生长因子- β /骨形态发生蛋白(transforming growth factor- β /bone morphogenetic protein, TGF- β /BMP)及刺猬信号通路(sonic hedgehog, SHH)作为调控细胞增殖、分化与组织形态发生的核心网络,其失调可导致CdLS神经、心血管及骨骼畸形^[21-23]。鉴于通路间存在复杂互作,系统解析其核心机制与表型关联尤为重要。

2.1 Wnt/ β -catenin信号通路 Wnt/ β -catenin通路通过调控 β -catenin蛋白稳定性介导靶基因转录,是维持神经分化与骨骼稳态的核心网络,功能与染色质构象密切相关^[24]。CdLS中,黏连蛋白突变损害其与CCCTC结合因子(CCCTC-binding factor, CTCF)协同作用,导致印记区域染色质环扰动与基因表达异常,扰乱核心转录程序,表现为Frizzled受体表达抑制,进而影响细胞周期与分化^[24]。通路失调导致两大核心发育异常:神经系统中,磁共振成像(magnetic resonance imaging, MRI)显示约24.5%的CdLS患者存在小脑蚓部发育不良,且与严重认知障碍密切相关^[25];动物模型亦证实,因黏连蛋白缺陷抑制该通路引发的神经异常可被激活剂部分逆转^[25]。骨骼系统则因Wnt通路异常激活引发*RUNX2*表达紊乱,导致腕骨融合、关节强直等缺陷^[26]。

2.2 TGF- β /BMP信号通路 TGF- β 与BMP同属TGF- β 超家族,通过结合细胞表面受体激活Smad依赖或非依赖性信号通路^[27]。黏连蛋白功能异常通过多重机制扰乱通路稳态:*NIPBL*缺陷破坏染色质结构并下调细胞外基质(extracellular matrix, ECM)中TGF- β 隔离蛋白,增加游离TGF- β 生物利用度,引发通路过度激活,诱导细胞衰老并与ECM异常互作,形成病理性正反馈^[23]。TGF- β 信号异常激活致心室肥厚、心肌纤维化等病变,受体抑制剂或通路拮抗剂可改善上述表型^[28-29];在骨骼发育中,TGF- β 经Smad2/3调控成骨基因以维系稳态,通路失调会破坏成骨连接^[30-31]。*NIPBL*缺陷亦降低TGF- β 1及

Smad2/4 表达,抑制骨髓间充质干细胞向软骨分化^[32]。BMP/Smad 通路经 Smad1/5/8 调控成骨与软骨分化,稳态依赖 Smad6 负反馈,通路失调导致分化受阻,引发肢体畸形及软骨异常^[27, 30]。

2.3 SHH 信号通路 SHH 通路由肢体芽后部极化活性区(zone of polarizing activity, ZPA)分泌的 Shh 蛋白启动信号,通过调控胶质瘤相关癌基因同源物 1 (Glioma-associated oncogene homolog 1, Gli1)、Patched 1 蛋白(Patched 1, Ptc1)等关键分子的活性,决定指(趾)数量、形态及肢体长度,参与颅面骨骼、轴骨和神经系统发育^[33-35]。经典机制是 Shh 与受体 Ptc1 结合后解除对激活型跨膜受体(smoothened, Smo)的抑制,促使 Gli 转录因子入核启动转录,参与神经前体细胞增殖分化、神经元存活、成骨前体细胞分化及骨骼发育,同时调控轴突重塑、抗凋亡及认知功能^[34-35]。小鼠模型研究表明, *Nipbl* 单倍体不足或黏连蛋白功能异常破坏 *Shh* 与远端增强子长距互作,抑制 *Shh* 转录、削弱 SHH 信号,该机制与肢体发育缺陷密切相关^[36-38]。通路失调引发表型异质性:SHH 信号异常减弱致肢体缩短、指趾形态异常等畸形,机制涉及肢芽 ZPA 信号紊乱、成骨及

软骨分化受抑;同时通路的抑制也损害神经前体细胞增殖,加剧认知障碍^[34-35];过度激活则通过 *Gli1* 等基因异常表达,引发多指(趾)症^[35, 39]。颅面发育中,通路异常破坏神经嵴细胞稳态,致中面部发育不全、唇腭裂、宽鼻根等畸形^[34, 39]。此外,平滑激动剂(smoothened agonist, SAG)可激活小鼠胚胎腭突间充质细胞 SHH 通路,诱发细胞自噬,部分逆转通路抑制及细胞增殖障碍,为先天性腭裂等面部畸形治疗提供方向^[40]。

2.4 通路间交叉调控 CdLS 表型广泛异质性源于黏连蛋白复合体功能缺陷引发的染色质与基因表达异常,该失调并非局限于单一通路,而是系统性扰乱多个发育信号网络^[2]。各通路间存在复杂的协同与拮抗关系:SHH 与 Wnt 呈功能性拮抗,失衡致颅缝早闭等畸形^[41];而在骨骼发育中, TGF- β /BMP 与 Wnt 通路呈核心拮抗与局部协同关系,即特定发育阶段抑制骨形成,成骨早期协同促进骨形成^[27]。此外, *HDAC8* 或 *SMC3* 突变等表观遗传上游紊乱干扰染色质构象及 DNA 甲基化,放大通路失调,加剧多系统表型异质性^[24, 42]。这种由黏连蛋白缺陷触发的多层次信号网络失调,从根本上解释了 CdLS 表型

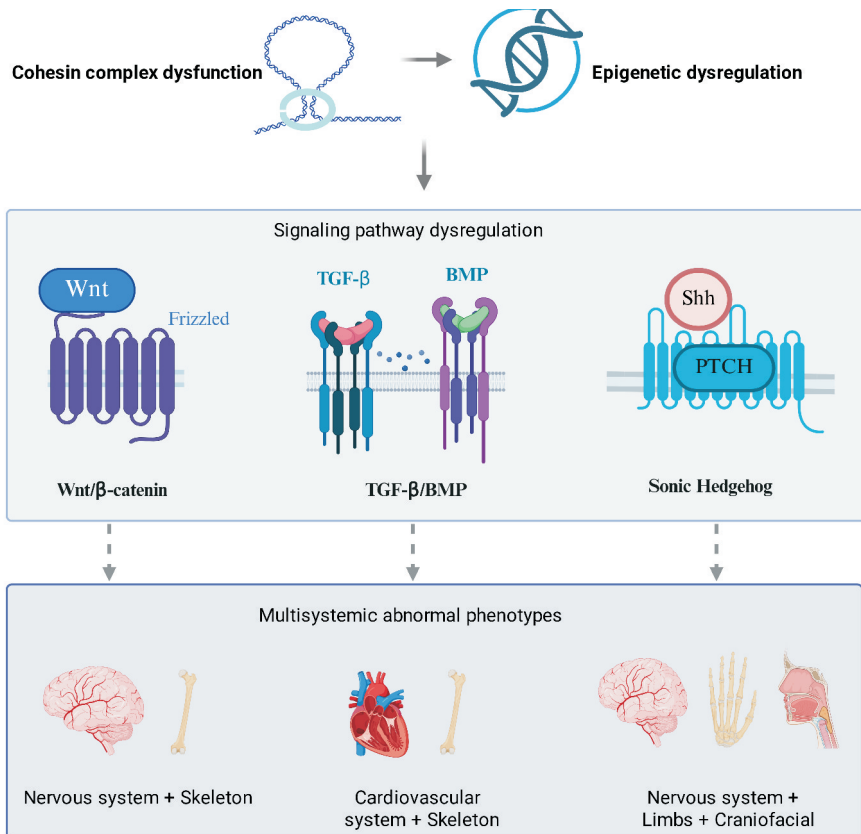


图2 CdLS致病机制示意图:从黏连蛋白功能异常到多系统表型

Fig. 2 Schematic diagram of the pathogenic mechanism of CdLS: from cohesin dysfunction to multisystem phenotypes

的复杂性。

为直观呈现 CdLS 致病级联过程,图 2 整合前述分子机制,展示了从黏连蛋白复合体功能异常到多系统表型的病理网络。

3 分子诊断优化策略

当前 CdLS 诊断已转向基因型-表型整合分析,将下一代测序作为一线检测手段,系统性筛查 *NIPBL*、*SMC1A* 等致病基因,非典型需扩展检测至 *BRD4*、*ANKRD11* 等候选基因^[2]。嵌合突变是经典 CdLS 易漏诊的重要原因,约 15%~20% 的经典表型患者存在 *NIPBL* 基因嵌合突变,其他致病基因罕见报道^[2,43-44]。这类突变因血液细胞中突变细胞比例极低,易被血液 DNA 检测遗漏,对血液全基因组测序(whole-exome sequencing, WES)阴性但临床高度疑似病例,推荐采用皮肤、颊黏膜等多组织联合检测以提高检出率^[2]。临床案例证实,该策略可发现血液未检出的 *NIPBL* 新发突变,部分突变在皮肤组织中的等位基因比例可达 38%,有效弥补血液检测局限^[44]。

4 总结

CdLS 临床异质性源于黏连蛋白复合体功能缺陷,该缺陷破坏染色质三维结构,引发转录与表观遗传紊乱,扰乱 Wnt、TGF- β /BMP 及 SHH 等关键信号通路,导致多系统发育缺陷。诊断需采用基因型-表型整合分析与多组织测序策略。未来可结合染色质构象捕获等技术进一步解析 CdLS 的致病网络,为分子分型、诊断优化及遗传咨询提供精准理论依据。

参考文献

- [1] Kao H J, Wang E H F, Yeh E C, et al. Identification of *de novo* chromosomal translocations disrupting *NIPBL* in a patient with Cornelia de Lange syndrome by full genome analysis [J]. *Mol Genet Genomic Med*, 2025, 13 (6) : e70115. doi: 10.1002/mgg3.70115.
- [2] Kline A D, Moss J F, Selicorni A, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement [J]. *Nat Rev Genet*, 2018, 19 (10) : 649-66. doi: 10.1038/s41576-018-0031-0.
- [3] Gruca-Stryjak K, Doda-Nowak E, Dzierla J, et al. Advancing the clinical and molecular understanding of Cornelia de Lange syndrome: a multidisciplinary pediatric case series and review of the literature [J]. *J Clin Med*, 2024, 13 (8) : 2423. doi: 10.3390/jcm13082423.
- [4] Shao X T, Dai Y X, Zhao Y F, et al. Case Report: a novel intronic variant of *NIPBL* gene detected in a child with Cornelia de Lange syndrome [J]. *Front Genet*, 2025, 16: 1665167. doi: 10.3389/fgene.2025.1665167.
- [5] Seymour H, Feben C, Nevondwe P, et al. Mutation profiling in South African patients with Cornelia de Lange syndrome phenotype [J]. *Mol Genet Genomic Med*, 2024, 12 (1) : e2342. doi: 10.1002/mgg3.2342.
- [6] Dowsett L, Porras A R, Kruszka P, et al. Cornelia de Lange syndrome in diverse populations [J]. *Am J Med Genet A*, 2019, 179 (2) : 150-8. doi:10.1002/ajmg.a.61033.
- [7] 姜德坤, 张惠荣, 潘金勇, 等. 慢病毒介导沉默 *NIPBL* 基因对小鼠骨髓间充质干细胞成骨分化能力的影响 [J]. *安徽医科大学学报*, 2022, 57 (1) : 105-10. doi:10.19405/j.cnki.issn1000-1492.2022.01.020.
- [7] Jiang D K, Zhang H R, Pan J Y, et al. Effect of lentivirus mediated silencing of *NIPBL* gene on osteogenic differentiation of mouse bone marrow mesenchymal stem cells [J]. *Acta Univ Med Anhui*, 2022, 57 (1) : 105-10. doi:10.19405/j.cnki.issn1000-1492.2022.01.020.
- [8] Deardorff M A, Kaur M, Yaeger D, et al. Mutations in cohesin complex members *SMC3* and *SMC1A* cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation [J]. *Am J Hum Genet*, 2007, 80 (3) : 485-94. doi: 10.1086/511888.
- [9] Ansari M, Faour K N W, Shimamura A, et al. Heterozygous loss-of-function *SMC3* variants are associated with variable growth and developmental features [J]. *HGG Adv*, 2024, 5 (2) : 100273. doi:10.1016/j.xhgg.2024.100273.
- [10] Gibellato E, Cianci P, Mariani M, et al. *SMC1A* epilepsy syndrome: clinical data from a large international cohort [J]. *Am J Med Genet A*, 2024, 194 (7) : e63577. doi: 10.1002/ajmg.a.63577.
- [11] Zhang B, Zhu Y, Zhang Z, et al. *SMC3* contributes to heart development by regulating super-enhancer associated genes [J]. *Exp Mol Med*, 2024, 56 (8) : 1826-42. doi: 10.1038/s12276-024-01293-0.
- [12] Cheng H, Zhang N, Pati D. Cohesin subunit *RAD21*: from biology to disease [J]. *Gene*, 2020, 758: 144966. doi: 10.1016/j.gene.2020.144966.
- [13] Fontana A, Cursaro I, Carullo G, et al. A therapeutic perspective of HDAC8 in different diseases: an overview of selective inhibitors [J]. *Int J Mol Sci*, 2022, 23 (17) : 10014. doi:10.3390/ijms231710014.
- [14] Bukowska-Olech E, Majchrzak-Celińska A, Przyborska M, et al. Chromatinopathies: insight in clinical aspects and underlying epigenetic changes [J]. *J Appl Genet*, 2024, 65 (2) : 287-301. doi: 10.1007/s13353-023-00824-1.
- [15] Trajkova S, Kerkhof J, Rossi Sebastiano M, et al. DNA methylation analysis in patients with neurodevelopmental disorders improves variant interpretation and reveals complexity [J]. *HGG Adv*, 2024, 5 (3) : 100309. doi:10.1016/j.xhgg.2024.100309.

- [16] Lui J C. Growth disorders caused by variants in epigenetic regulators: progress and prospects [J]. *Front Endocrinol*, 2024, 15: 1327378. doi:10.3389/fendo.2024.1327378.
- [17] Gothwal S K, Refaat A M, Nakata M, et al. BRD2 promotes antibody class switch recombination by facilitating DNA repair in collaboration with NIPBL [J]. *Nucleic Acids Res*, 2024, 52(8): 4422-39. doi:10.1093/nar/gkae204.
- [18] Castiglioni S, Di Fede E, Bernardelli C, et al. *KMT2A* umbrella gene for multiple diseases [J]. *Genes*, 2022, 13(3): 514. doi:10.3390/genes13030514.
- [19] Luppino G, Wasniewska M, Pepe G, et al. Two years of growth hormone therapy in a child with severe short stature due to overlap syndrome with a novel *SETD5* gene mutation: case report and review of the literature [J]. *Genes*, 2025, 16(8): 859. doi:10.3390/genes16080859.
- [20] Selicorni A, Mariani M, Lettieri A, et al. Cornelia de Lange syndrome: from a disease to a broader spectrum [J]. *Genes*, 2021, 12(7): 1075. doi:10.3390/genes12071075.
- [21] Avagliano L, Grazioli P, Mariani M, et al. Integrating molecular and structural findings: Wnt as a possible actor in shaping cognitive impairment in Cornelia de Lange syndrome [J]. *Orphanet J Rare Dis*, 2017, 12(1): 174. doi:10.1186/s13023-017-0723-0.
- [22] Lopez-Burks M E, Santos R, Kawauchi S, et al. Genetic enhancement of limb defects in a mouse model of Cornelia de Lange syndrome [J]. *Am J Med Genet C Semin Med Genet*, 2016, 172(2): 146-54. doi:10.1002/ajmg.c.31491.
- [23] Hachoud C, Chaabani F, Watrin E, et al. Inhibition of TGF β -induced embryonic cell senescence at the origin of Cornelia de Lange syndrome [J]. *bioRxiv*, 2022. doi:10.1101/2022.07.26.501526.
- [24] Pileggi S, La Vecchia M, Colombo E A, et al. Cohesin mutations induce chromatin conformation perturbation of the H19/*IGF2* imprinted region and gene expression dysregulation in Cornelia de Lange syndrome cell lines [J]. *Biomolecules*, 2021, 11(11): 1622. doi:10.3390/biom11111622.
- [25] Grazioli P, Parodi C, Mariani M, et al. Lithium as a possible therapeutic strategy for Cornelia de Lange syndrome [J]. *Cell Death Discov*, 2021, 7(1): 34. doi:10.1038/s41420-021-00414-2.
- [26] Yi D, Xie R, Zeng D, et al. Loss of Axin1 in limb mesenchymal cells leads to multiple synostoses syndrome-like phenotype in mice [J]. *Innov Med*, 2024, 2(1): 100053. doi:10.59717/j.xinnmed.2024.100053.
- [27] Zhu S, Chen W, Masson A, et al. Cell signaling and transcriptional regulation of osteoblast lineage commitment, differentiation, bone formation, and homeostasis [J]. *Cell Discov*, 2024, 10(1): 71. doi:10.1038/s41421-024-00689-6.
- [28] Kmiec P, Rosenkranz S, Odenthal M, et al. Differential role of aldosterone and transforming growth factor beta-1 in cardiac remodeling [J]. *Int J Mol Sci*, 2023, 24(15): 12237. doi:10.3390/ijms241512237.
- [29] Chen P Y, Qin L, Simons M. TGF β signaling pathways in human health and disease [J]. *Front Mol Biosci*, 2023, 10: 1113061. doi:10.3389/fmolb.2023.1113061.
- [30] Wu M, Wu S, Chen W, et al. The roles and regulatory mechanisms of TGF- β and BMP signaling in bone and cartilage development, homeostasis and disease [J]. *Cell Res*, 2024, 34(2): 101-23. doi:10.1038/s41422-023-00918-9.
- [31] Wang L, Ruan M, Bu Q, et al. Signaling pathways driving MSC osteogenesis: mechanisms, regulation, and translational applications [J]. *Int J Mol Sci*, 2025, 26(3): 1311. doi:10.3390/ijms26031311.
- [32] 马雯晴. NIPBL 基因对小鼠骨髓间充质干细胞成软骨分化能力的影响与 TGF- β 1/Smad 信号通路相关性研究 [D]. 石河子: 石河子大学, 2022.
- [32] Ma W Q. The effect of NIPBL gene on the chondrogenic differentiation ability of mouse bone marrow mesenchymal stem cells and the correlation between TGF- β 1/smard signaling pathway [D]. Shihezi: Shihezi University, 2022.
- [33] Zhu M, Tabin C J. The role of timing in the development and evolution of the limb [J]. *Front Cell Dev Biol*, 2023, 11: 1135519. doi:10.3389/fcell.2023.1135519.
- [34] Li X, Li Y, Li S, et al. The role of Shh signalling pathway in central nervous system development and related diseases [J]. *Cell Biochem Funct*, 2021, 39(2): 180-9. doi:10.1002/cbf.3582.
- [35] Lézet F, Corre I, Morice S, et al. SHH signaling pathway drives pediatric bone sarcoma progression [J]. *Cells*, 2020, 9(3): 536. doi:10.3390/cells9030536.
- [36] Muto A, Ikeda S, Lopez-Burks M E, et al. Nipbl and mediator cooperatively regulate gene expression to control limb development [J]. *PLoS Genet*, 2014, 10(9): e1004671. doi:10.1371/journal.pgen.1004671.
- [37] Kane L, Williamson I, Flyamer I M, et al. Cohesin is required for long-range enhancer action at the Shh locus [J]. *Nat Struct Mol Biol*, 2022, 29(9): 891-7. doi:10.1038/s41594-022-00821-8.
- [38] Paliou C, Guckelberger P, Schöpflin R, et al. Prefomed chromatin topology assists transcriptional robustness of Shh during limb development [J]. *Proc Natl Acad Sci USA*, 2019, 116(25): 12390-9. doi:10.1073/pnas.1900672116.
- [39] Niida Y, Togi S, Ura H. Molecular bases of human malformation syndromes involving the SHH pathway: *GLIA/R* balance and cardinal phenotypes [J]. *Int J Mol Sci*, 2021, 22(23): 13060. doi:10.3390/ijms222313060.
- [40] 廉舒博, 陈珏蓉, 瞿功玲, 等. Shh 信号通路变化对小鼠胚胎腭突间充质细胞自噬的影响 [J]. *重庆医科大学学报*, 2023, 48(4): 375-80. doi:10.13406/j.cnki.cyx.003208.
- [40] Lian S B, Chen J R, Qu G L, et al. The effect of Shh signaling pathway changes on autophagy in mouse embryonic palatal mesenchymal cells [J]. *J Chongqing Med Univ*, 2023, 48(4): 375-80. doi:10.13406/j.cnki.cyx.003208.
- [41] Chen J, Ren C, Mao C, et al. Cranial base synostosis in mice caused by upregulation of Wnt following partial inhibition of Shh [J]. *BMC Biol*, 2025, 23(1): 268. doi:10.1186/s12915-025-

02381-x.

- [42] LaSalle J M. Epigenomic signatures reveal mechanistic clues and predictive markers for autism spectrum disorder[J]. *Mol Psychiatry*, 2023, 28(5): 1890-901. doi:10.1038/s41380-022-01917-9.
- [43] Coursimault J, Cassinari K, Lecoquierre F, et al. Deep intronic NIPBL de novo mutations and differential diagnoses revealed by whole genome and RNA sequencing in Cornelia de Lange syn-

drome patients[J]. *Hum Mutat*, 2022, 43(12): 1882-97. doi:10.1002/humu.24438.

- [44] Tehrani Fateh S, Mohammad Zadeh N, Salehpour S, et al. Comprehensive review and expanding the genetic landscape of Cornelia-de-Lange spectrum: insights from novel mutations and skin biopsy in exome-negative cases[J]. *BMC Med Genomics*, 2024, 17(1): 20. doi:10.1186/s12920-024-01798-7.

Cornelia de Lange syndrome: advances in genetic and molecular mechanisms

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Abstract Cornelia de Lange syndrome (CdLS) is a rare genetic disorder characterized by multisystem developmental abnormalities, with its core pathogenic mechanism closely linked to dysfunction of the cohesin complex. Integrated multi-omics evidence revealed that cohesin dysfunction disrupted three-dimensional chromatin architecture and epigenetic homeostasis, triggered genome-wide transcriptional dysregulation, and perturbed the regulatory networks of signaling pathways such as Wnt/ β -catenin, TGF- β /BMP, and Sonic Hedgehog (SHH). These disturbances collectively drove multisystem phenotypes involving the neurological, cardiovascular and skeletal systems, and laid a theoretical foundation for further understanding of the pathological mechanisms of CdLS and optimizing molecular diagnosis. This review summarized the genetic basis (including epigenetic dysregulation mechanisms) and disruption of key developmental signaling pathways in CdLS, and discussed strategies for optimizing molecular diagnosis.

Key words Cornelia de Lange syndrome; cohesin complex; epigenetics; signaling pathways; molecular diagnosis

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