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纤毛相关基因在儿童胆汁淤积性疾病中的研究进展

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摘　要

胆汁淤积性肝病是儿科领域重要的肝脏疾病类型，其病程呈持续性进展，可逐步发展为肝纤维化、肝硬化甚至肝衰竭，严重影响患儿长期预后。该病的发生与胆汁生成、胆管分泌、转运及排泄等多个生理环节的功能障碍密切相关，涉及多基因、多通路参与，尤其在儿童患者中，遗传因素常发挥关键作用。近年来研究证实，肝内胆管上皮细胞的初级纤毛作为一类关键的“机械－化学信号传感器”，在感知胆汁流体力学刺激、响应管腔微环境变化、调控胆汁成分以及维持胆管系统稳态中发挥核心作用。纤毛相关基因突变所引发的纤毛结构缺陷或信号转导功能障碍，已被认定为多种胆汁淤积性疾病的重要致病基础。然而，上述过程所涉及的具体分子机制、细胞层面因果联系及病理转化条件仍有待系统阐明。本文系统综述初级纤毛的基本结构与功能，探讨纤毛相关基因突变导致胆汁淤积的致病机制，并总结该领域在发病机理与治疗策略方面的最新研究进展，以期为儿童胆汁淤积性疾病的临床诊断与治疗提供新思路与方向。

关键词

胆汁淤积，初级纤毛，纤毛相关基因，分子机制，治疗

Research Progress on Ciliary-Related Genes in Childhood Cholestatic Diseases

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Abstract

Cholestatic liver disease represents a significant category of pediatric liver disorders, characterized by a progressive course that can evolve into liver fibrosis, cirrhosis, and even hepatic failure, severely impacting long-term prognosis in children. The pathogenesis of cholestasis is closely linked to impairments in multiple physiological processes, including bile synthesis, secretion, transport, and excretion, involving polygenic and multi-pathway interactions, with genetic factors often playing a critical role, especially in pediatric patients. Recent studies have established that the primary cilia of intrahepatic cholangiocytes function as crucial "mechano-chemical signal sensors," playing a central role in sensing bile fluid dynamics, responding to changes in the ductal microenvironment, regulating bile composition, and maintaining biliary system homeostasis. Mutations in ciliary genes leading to structural defects or signaling dysfunction in cilia have been recognized as an important pathogenic basis of various cholestatic diseases. However, the specific molecular mechanisms, cell-level causal relationships, and pathological transition conditions involved in these processes remain to be fully elucidated. This review systematically summarizes the basic structure and function of primary cilia, discusses the pathogenic mechanisms by which ciliary gene mutations contribute to cholestasis, and highlights recent advances in the pathogenesis and therapeutic strategies in this field, aiming to provide new perspectives and directions for the clinical diagnosis and treatment of cholestatic liver diseases in children.

Keywords

Cholestasis, Primary Cilium, Cilia-Related Genes, Molecular Mechanism, Treatment

1. 引言

儿童胆汁淤积性肝病以胆汁生成、分泌或排泄过程障碍为主要特征，导致胆汁酸及其他毒性物质在肝内异常蓄积，进而引发肝细胞损伤、纤维化进展，并可最终发展为肝衰竭，严重降低患者生存质量与长期预后[1]。其发生机制复杂多样，涉及肝细胞转运体功能障碍、胆管上皮损伤、遗传突变以及药物、感染等多种因素[2]，而在儿童患者中，遗传因素常发挥关键作用。近年来，胆管上皮细胞的初级纤毛(cilia)在感知和调节肝内胆汁代谢中的作用日益受到重视。研究发现，初级纤毛能够感知胆汁成分、流体动力学特征及其他生化信号变化，并通过激活特定细胞内信号通路，精密调控胆管上皮细胞的增殖、分泌与吸收功能，因此，编码胆管细胞纤毛的基因若发生突变，可导致纤毛感知与信号转导能力受损，进而引发一系列以胆汁淤积为核心病理特征的肝胆疾病,如胆道闭锁、原发性硬化性胆管炎(PBC)、多囊肝病、胆管癌等[3] [4]。这些研究不仅揭示了初级纤毛在维持胆汁代谢稳态中的重要性，更提示纤毛相关基因突变引起纤毛功能障碍可能是胆汁淤积的关键机制之一。

本文围绕初级纤毛基本结构与功能，聚焦纤毛障碍相关胆汁淤积性疾病的致病基因谱系、分子发病机制研究进展以及治疗新策略研究进展展开综述，旨在为儿童胆汁淤积性疾病的诊疗提供新的理论依据与干预思路。

2. 纤毛的结构、功能与分类

纤毛作为一种膜性细胞器，广泛存在于绝大多数真核细胞表面，其核心结构在进化上高度保守，主

体均由9组双联体微管规则排列组成，结构上可分为4个亚区：基体(Basal body)、过渡区(Transition Zone)、轴丝(Axoneme)和顶端(Ciliary tip) [5]。根据结构和功能的差异，纤毛主要分为两大类，即运动纤毛和初级纤毛。运动纤毛轴丝呈“9 + 2”结构，即9对外周双联体微管围绕两根中央单微管，依赖动力蛋白臂(Dynein arms)驱动摆动。大多数初级纤毛为“9 + 0”结构，无两根中央微管，缺乏动力蛋白臂，无运动功能，也被称为静止纤毛(Immotile cilia) [6]。作为一种特化的细胞器，初级纤毛在感知胞外环境信号中发挥关键作用，其功能类似于“化学–机械感受天线”，能够检测多种外界刺激，并通过启动细胞内信号级联反应，将胞外信息转化为细胞响应。该结构在调控细胞分化、增殖以及维持组织稳态等生理过程中具有重要作用，并且是Hedgehog等关键发育信号通路正常转导所必需的核心结构[6]-[8]。

3. 初级纤毛相关基因在胆汁淤积中发挥的作用和机制

胆管初级纤毛的组装、结构维持和信号转导功能依赖于一系列高度保守的纤毛相关蛋白的精密协同作用。编码此类蛋白的基因若发生突变，可破坏纤毛结构的完整性或损害其信号传导能力，进而引发一类以胆汁淤积与慢性肝损伤为核心病理特征的胆管纤毛病(Cholangiociliopathies) [9]。这类疾病的核心机制在于胆管上皮细胞初级纤毛的机械感知、渗透压感知及化学信号传导能力受损，引起细胞内钙离子稳态紊乱和腺苷酸环化酶(cAMP)信号水平异常，进一步导致胆管上皮细胞异常增殖、胆管结构重塑障碍、胆汁分泌与吸收功能失调，最终造成进行性胆汁淤积及肝损伤[3] [9]。

3.1. PKD1 (Polycystin 1)/PKD2 (Polycystin 2)基因

PKD1和PKD2基因突变可导致多囊性肝病(PLD)，其肝脏病理表型主要包括肝内胆管源性囊肿广泛形成、继发性胆汁淤积及肝纤维化等[10]。PKD1和PKD2分别编码多囊蛋白1 (PC-1)和多囊蛋白2 (PC-2)，两者在胆管上皮细胞初级纤毛上共同组装形成机械敏感性钙离子通道复合体。当胆管腔内流体流动引起纤毛弯曲时，该机械刺激通过PC-1与PC-2的协同感应，触发细胞内钙信号振荡及cAMP水平变化，进而调控胆管上皮细胞的增殖与胆管结构重塑过程，这一机制已得到多项功能研究的证实[11]。因此，当PKD1或PKD2基因突变引起PC-1/PC-2复合体功能丧失，导致胆管上皮细胞异常增殖与囊肿形成。不断扩张的囊肿压迫胆管树，破坏胆汁流动的连续性，最终引发进行性胆汁淤积，构成该类疾病胆汁淤积发生的主要病理基础[12]。

3.2. PKHD1 (Polycystic Kidney and Hepatic Disease 1)基因

PKHD1基因突变可引起常染色体隐性遗传性多囊肾病(ARPKD)和先天性肝纤维化(CHF)，胆汁淤积是其肝脏病变的重要表现之一[13]。PKHD1基因编码的纤维囊素(Fibrocystin/Polyductin, FPC)在肝脏主要表达于胆管上皮细胞的初级纤毛基体及顶端膜，参与细胞内信号转导，是细胞增殖、凋亡和极性维持的关键调节因子[14]。虽然PKHD1突变导致胆汁淤积的确切机制尚不清楚，但有研究表明，PKHD1突变引起FPC蛋白功能缺陷，进而干扰胆管板的正常重塑过程，导致胆管板发育畸形和胆汁排泄受阻[15]。在类器官模型中可以观察到，PKHD1缺陷型胆管细胞无法形成具有正常极性的管腔结构，从而阻碍胆汁的定向输送过程。这一结果进一步证实，PKHD1编码的蛋白产物在胆管腔形态发生及管腔结构的稳定性维持中发挥关键作用[16]。还有研究[17] [18]发现FPC参与调节PC-2的表达和功能及细胞内钙信号传导，从而在胆管上皮细胞增殖和胆管重塑过程中发挥重要作用。

3.3. 其他与胆汁淤积相关的纤毛相关基因

除上述基因外，多种其他纤毛相关基因也被证实参与胆汁淤积发病，其分子机制涉及纤毛结构蛋白、转运复合体或信号分子等。这些基因的突变可导致纤毛组装缺陷、转运功能障碍或信号转导异常，最终

通过干扰胆管上皮稳态引发胆汁淤积。具体基因及相关疾病、重要临床表型详见表 1 (见第 4 节)。

4. 基因型–表型相关性及临床诊断策略

纤毛病相关基因突变常累及多系统，但不同基因所致肝脏病变的起病年龄、严重程度及肝外表现存在显著差异，掌握这些特征对临床鉴别诊断至关重要。

4.1. PKD1/PKD2 基因突变

PKD1/PKD2 突变引起的多囊肝病(PLD)，该病儿童期起病较少，但部分严重突变可致婴幼儿期即出现肝大、胆汁淤积[19]。肝脏表现为多发胆管源性囊肿，压迫胆管树导致胆汁淤积，可伴有肝纤维化。肝外以肾脏多发囊肿、高血压和进行性肾功能下降为特征[20]。影像学(超声、MRI)可见双肾及肝脏多发囊肿，基因检测可明确突变亚型，需与常染色体隐性多囊肾病(ARPKD)鉴别。

4.2. PKHD1 基因突变

PKHD1 突变导致 ARPKD 和先天性肝纤维化(CHF)，常在围产期、婴儿期或儿童期起病。肝脏病变主要为胆管板发育畸形、先天性肝纤维化和 Caroli 综合征，胆汁淤积常见，可伴门脉高压。肾脏表现为双侧增大、集合管扩张，可致肾功能不全[21]。诊断依靠影像学(肾脏髓质导管扩张、肝纤维化征象)及基因检测，需与胆道闭锁、Alagille 综合征等鉴别，后者常伴心脏畸形、蝴蝶椎等特征[22]。

4.3. 其他纤毛相关基因突变

随着基因测序技术的快速发展和相关研究的不断深入，越来越多的纤毛相关基因突变被证实与肝脏胆汁淤积的发生相关。部分已报道的与胆汁淤积相关的纤毛基因信息与临床表型总结见表 1。

Table 1. Ciliary gene information and clinical phenotype related to partial cholestasis
表 1. 部分胆汁淤积相关的纤毛基因信息与临床表型

基因	相关疾病	肝外表型	肝脏表型
BBS 基因家族(BBS1、BBS2 等 20 余个基因)	Bardet-Biedl 综合征	视网膜病变、肥胖、多指/趾畸形、肾功能不全、智力障碍、性腺发育不全等。	肝内胆管扩张、胆汁淤积、肝纤维化[23] [24]。
MKS 基因家族(MKS1 等 10 余个基因)	Meckel-Gruber 综合征	枕部脑膨出、多囊肾、多指/趾畸形、中枢神经系统发育畸形等。	肝内胆管畸形、肝纤维化、胆汁淤积[25]。
NPHP 基因家族	肾单位肾病、肾消耗病	多尿、贫血、进行性肾功能衰竭，视网膜变性、眼球运动异常(部分亚型)等。	肝纤维化、门脉高压、胆汁淤积[26] [27]。
IFT 基因家族(IFT88、IFT140 等)	Jeune 综合征、多囊肾病、Mainzer-Saldino 综合征等	肾囊肿、肾功能不全、胸廓狭窄、短肋、肢端短小等。	胆道发育异常、新生儿胆汁淤积、肝纤维化[28] [29]。
DCDC2	新生儿硬化性胆管炎	肾功能异常(部分病例报道)，无典型多系统受累。	胆汁淤积、黄疸、肝功能损害、肝纤维化、肝硬化、胆管增生狭窄[30] [31]。

续表

ZFYVE19	婴儿胆汁淤积症、进行性家族性肝内胆汁淤积症等	目前报道以肝脏孤立受累为主，无典型肾或视网膜病变。	新生儿期胆汁淤积、门脉高压、肝功能异常、肝纤维化等[32] [33]。
Joubert 综合征相关基因(AHI1、CC2D2A、ARL13B、CEP290、TMEM67 等 20 余个基因)	Joubert 综合征、COACH 综合征(Joubert 综合征亚型)	小脑蚓部发育不良(“臼齿征”)、眼球运动异常、呼吸节律异常、多囊肾、视网膜营养不良等。	肝纤维化、肝囊肿、胆汁淤积[34]。

5. 治疗

近年来，CRISPR-Cas9 等基因编辑技术的问世与迅猛发展，为治疗由单基因突变引起的纤毛疾病开辟了全新的治疗前景。Lakhia 等[35]通过 CRISPR/Cas9 技术恢复 PKD1/2 的 mRNA 翻译，可有效上调 PC-1 蛋白表达。该干预手段在细胞、离体器官及多囊肾小鼠模型中，均展现出显著的囊肿生长抑制效果。然而，基因编辑疗法在临床转化中仍面临技术瓶颈(如脱靶效应精准控制)、伦理争议及高昂成本等挑战。另一方面，围绕小分子药物，Kim 等人[36]的研究表明，在小鼠模型上，类黄酮药物优帕替林(flavonoid Eupatilin)可缓解 CEP290 基因缺失导致的纤毛发生和纤毛受体传递缺陷；此外，还有研究发现胆管细胞中组蛋白去乙酰酶 6 (HDAC6)介导的 α 微管蛋白去乙酰化是驱动纤毛解体的关键途径，使其成为逆转纤毛功能障碍的潜在靶点。基于此，HDAC6 抑制剂在多种疾病模型中已被证实可有效恢复纤毛功能[37]。尽管上述治疗策略多在肾脏纤毛病模型中进行验证，但基于纤毛在胆汁代谢中的关键作用，恢复纤毛功能策略仍被认为是改善胆汁淤积的一种新兴治疗手段，靶向纤毛的治疗方式有望从根本上逆转疾病的病理进程。

6. 展望

对胆管细胞初级纤毛功能的深入探索，结合基因检测技术的革新，持续扩充着与胆汁淤积相关的纤毛病致病基因谱。虽其驱动胆汁淤积的分子病理机制仍未完全阐明，然而，不断累积的证据正逐步揭示“纤毛信号转导异常→胆管稳态失衡→胆汁代谢障碍”这一因果关联，这些发现有望为部分儿童胆汁淤积性疾病从分子诊断到靶向干预的策略提供全新方向。

参考文献

[1] Sutton, H., Karpen, S.J. and Kamath, B.M. (2024) Pediatric Cholestatic Diseases: Common and Unique Pathogenic Mechanisms. *Annual Review of Pathology: Mechanisms of Disease*, **19**, 319-344. https://doi.org/10.1146/annurev-pathmechdis-031521-025623

[2] Chen, H., Wu, S., Hsu, S., Liou, B., Chen, H. and Chang, M. (2018) Jaundice Revisited: Recent Advances in the Diagnosis and Treatment of Inherited Cholestatic Liver Diseases. *Journal of Biomedical Science*, **25**, Article No. 75. https://doi.org/10.1186/s12929-018-0475-8

[3] Pant, K., Peixoto, E. and Gradilone, S.A. (2025) Primary Cilia in Hepatic Biliary Hyperplasia: Implications for Liver Diseases. *Seminars in Liver Disease*, **45**, 348-361. https://doi.org/10.1055/a-2563-9791

[4] Fliegauf, M., Benzing, T. and Omran, H. (2007) When Cilia Go Bad: Cilia Defects and Ciliopathies. *Nature Reviews Molecular Cell Biology*, **8**, 880-893. https://doi.org/10.1038/nrm2278

[5] Szymanska, K. and Johnson, C.A. (2012) The Transition Zone: An Essential Functional Compartment of Cilia. *Cilia*, **1**, Article No. 10. https://doi.org/10.1186/2046-2530-1-10

[6] Satir, P. and Christensen, S.T. (2007) Overview of Structure and Function of Mammalian Cilia. *Annual Review of Physiology*, **69**, 377-400. https://doi.org/10.1146/annurev.physiol.69.040705.141236

[7] Anvarian, Z., Mykytyn, K., Mukhopadhyay, S., Pedersen, L.B. and Christensen, S.T. (2019) Cellular Signalling by

Primary Cilia in Development, Organ Function and Disease. *Nature Reviews Nephrology*, **15**, 199-219. https://doi.org/10.1038/s41581-019-0116-9

[8] Hilgendorf, K.I., Myers, B.R. and Reiter, J.F. (2024) Emerging Mechanistic Understanding of Cilia Function in Cellular Signalling. *Nature Reviews Molecular Cell Biology*, **25**, 555-573. https://doi.org/10.1038/s41580-023-00698-5

[9] Mansini, A.P., Peixoto, E., Thelen, K.M., Gaspari, C., Jin, S. and Gradilone, S.A. (2018) The Cholangiocyte Primary Cilium in Health and Disease. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1864**, 1245-1253. https://doi.org/10.1016/j.bbadis.2017.06.006

[10] Masyuk, T.V., Masyuk, A.I. and LaRusso, N.F. (2022) Polycystic Liver Disease: Advances in Understanding and Treatment. *Annual Review of Pathology*: *Mechanisms of Disease*, **17**, 251-269. https://doi.org/10.1146/annurev-pathol-042320-121247

[11] Masyuk, A.I., Masyuk, T.V., Splinter, P.L., Huang, B.Q., Stroope, A.J. and LaRusso, N.F. (2006) Cholangiocyte Cilia Detect Changes in Luminal Fluid Flow and Transmit Them into Intracellular Ca^{2+} and Camp Signaling. *Gastroenterology*, **131**, 911-920. https://doi.org/10.1053/j.gastro.2006.07.003

[12] Yokoda, R.T. and Rodriguez, E.A. (2020) Review: Pathogenesis of Cholestatic Liver Diseases. *World Journal of Hepatology*, **12**, 423-435. https://doi.org/10.4254/wjh.v12.i8.423

[13] Burgmaier, K., Kilian, S., Bammens, B., Benzing, T., Billing, H., Büscher, A., *et al.* (2019) Clinical Courses and Complications of Young Adults with Autosomal Recessive Polycystic Kidney Disease (ARPKD). *Scientific Reports*, **9**, Article No. 7919. https://doi.org/10.1038/s41598-019-43488-w

[14] Ma, M. (2021) Cilia and Polycystic Kidney Disease. *Seminars in Cell & Developmental Biology*, **110**, 139-148. https://doi.org/10.1016/j.semcdb.2020.05.003

[15] Awasthi, A., Das, A., Srinivasan, R. and Joshi, K. (2004) Morphological and Immunohistochemical Analysis of Ductal Plate Malformation: Correlation with Fetal Liver. *Histopathology*, **45**, 260-267. https://doi.org/10.1111/j.1365-2559.2004.01945.x

[16] Guan, Y., Enejder, A., Wang, M., Fang, Z., Cui, L., Chen, S., *et al.* (2021) A Human Multi-Lineage Hepatic Organoid Model for Liver Fibrosis. *Nature Communications*, **12**, Article No. 6138. https://doi.org/10.1038/s41467-021-26410-9

[17] Kim, I., Fu, Y., Hui, K., Moeckel, G., Mai, W., Li, C., *et al.* (2008) Fibrocystin/Polyductin Modulates Renal Tubular Formation by Regulating Polycystin-2 Expression and Function. *Journal of the American Society of Nephrology*, **19**, 455-468. https://doi.org/10.1681/asn.2007070770

[18] Nagano, J., Kitamura, K., Hujer, K.M., Ward, C.J., Bram, R.J., Hopfer, U., *et al.* (2005) Fibrocystin Interacts with CAML, a Protein Involved in Ca^{2+} Signaling. *Biochemical and Biophysical Research Communications*, **338**, 880-889. https://doi.org/10.1016/j.bbrc.2005.10.022

[19] Yang, H., Sieben, C.J., Schauer, R.S. and Harris, P.C. (2023) Genetic Spectrum of Polycystic Kidney and Liver Diseases and the Resulting Phenotypes. *Advances in Kidney Disease and Health*, **30**, 397-406. https://doi.org/10.1053/j.akdh.2023.04.004

[20] Mahboobipour, A.A., Ala, M., Safdari Lord, J. and Yaghoobi, A. (2024) Clinical Manifestation, Epidemiology, Genetic Basis, Potential Molecular Targets, and Current Treatment of Polycystic Liver Disease. *Orphanet Journal of Rare Diseases*, **19**, Article No. 175. https://doi.org/10.1186/s13023-024-03187-w

[21] Burgmaier, K., Brinker, L., Erger, F., Beck, B.B., Benz, M.R., Bergmann, C., *et al.* (2021) Refining Genotype-Phenotype Correlations in 304 Patients with Autosomal Recessive Polycystic Kidney Disease and PKHD1 Gene Variants. *Kidney International*, **100**, 650-659. https://doi.org/10.1016/j.kint.2021.04.019

[22] Semenova, N., Kamenets, E., Annenkova, E., Marakhonov, A., Gusarova, E., Demina, N., *et al.* (2023) Clinical Characterization of Alagille Syndrome in Patients with Cholestatic Liver Disease. *International Journal of Molecular Sciences*, **24**, Article 11758. https://doi.org/10.3390/ijms241411758

[23] Shoemaker, A. (2024) Bardet-Biedl Syndrome: A Clinical Overview Focusing on Diagnosis, Outcomes and Best-Practice Management. *Diabetes*, *Obesity and Metabolism*, **26**, 25-33. https://doi.org/10.1111/dom.15494

[24] Branfield Day, L., Quammie, C., Héon, E., Bhan, A., Batmanabane, V., Dai, T., *et al.* (2015) Liver Anomalies as a Phenotype Parameter of Bardet-Biedl Syndrome. *Clinical Genetics*, **89**, 507-509. https://doi.org/10.1111/cge.12684

[25] Hartill, V., Szymanska, K., Sharif, S.M., Wheway, G. and Johnson, C.A. (2017) Meckel-Gruber Syndrome: An Update on Diagnosis, Clinical Management, and Research Advances. *Frontiers in Pediatrics*, **5**, Article 244. https://doi.org/10.3389/fped.2017.00244

[26] Li, J., Su, X., Zhang, H., Wu, W., Li, J., Chen, Y., *et al.* (2022) Genotype and Phenotype Analysis and Transplantation Strategy in Children with Kidney Failure Caused by NPHP. *Pediatric Nephrology*, **38**, 1609-1620. https://doi.org/10.1007/s00467-022-05763-3

[27] Petzold, F., Billot, K., Chen, X., Henry, C., Filhol, E., Martin, Y., *et al.* (2023) The Genetic Landscape and Clinical

Spectrum of Nephronophthisis and Related Ciliopathies. *Kidney International*, **104**, 378-387. https://doi.org/10.1016/j.kint.2023.05.007

[28] Wang, W., Pottorf, T.S., Wang, H.H., Dong, R., Kavanaugh, M.A., Cornelius, J.T., *et al.* (2021) IFT-A Deficiency in Juvenile Mice Impairs Biliary Development and Exacerbates ADPKD Liver Disease. *The Journal of Pathology*, **254**, 289-302. https://doi.org/10.1002/path.5685

[29] Shaheen, R., Alsahli, S., Ewida, N., Alzahrani, F., Shamseldin, H.E., Patel, N., *et al.* (2020) Biallelic Mutations in Tetratricopeptide Repeat Domain 26 (Intraflagellar Transport 56) Cause Severe Biliary Ciliopathy in Humans. *Hepatology*, **71**, 2067-2079. https://doi.org/10.1002/hep.30982

[30] Grammatikopoulos, T., Sambrotta, M., Strautnieks, S., Foskett, P., Knisely, A.S., Wagner, B., *et al.* (2016) Mutations in DCDC2 (doublecortin Domain Containing Protein 2) in Neonatal Sclerosing Cholangitis. *Journal of Hepatology*, **65**, 1179-1187. https://doi.org/10.1016/j.jhep.2016.07.017

[31] Lipiński, P., Ciara, E., Jurkiewicz, D., Mekrouda, M., Cielecka-Kuszyk, J., Jurkiewicz, E., *et al.* (2023) DCDC2-Related Ciliopathy: Report of Six Polish Patients, Novel DCDC2 Variant, and Literature Review of Reported Cases. *Diagnostics*, **13**, Article 1917. https://doi.org/10.3390/diagnostics13111917

[32] Mandato, C., Siano, M.A., Nazzaro, L., Gelzo, M., Francalanci, P., Rizzo, F., *et al.* (2021) A ZFYVE19 Gene Mutation Associated with Neonatal Cholestasis and Cilia Dysfunction: Case Report with a Novel Pathogenic Variant. *Orphanet Journal of Rare Diseases*, **16**, Article No. 179. https://doi.org/10.1186/s13023-021-01775-8

[33] Xue, M., Huang, L., Zhu, Y. and Zheng, Q. (2025) Case Report: ZFYVE19 Gene Mutation Is Associated with Familial Cholestasis. *Frontiers in Medicine*, **11**, Article 1400475. https://doi.org/10.3389/fmed.2024.1400475

[34] Bachmann-Gagescu, R., Dempsey, J.C., Phelps, I.G., O'Roak, B.J., Knutzen, D.M., Rue, T.C., *et al.* (2015) Joubert Syndrome: A Model for Untangling Recessive Disorders with Extreme Genetic Heterogeneity. *Journal of Medical Genetics*, **52**, 514-522. https://doi.org/10.1136/jmedgenet-2015-103087

[35] Lakhia, R., Ramalingam, H., Chang, C., Cobo-Stark, P., Biggers, L., Flaten, A., *et al.* (2022) PKD1 and PKD2 mRNA Cis-Inhibition Drives Polycystic Kidney Disease Progression. *Nature Communications*, **13**, Article No. 4765. https://doi.org/10.1038/s41467-022-32543-2

[36] Kim, Y.J., Kim, S., Jung, Y., Jung, E., Kwon, H.J. and Kim, J. (2018) Eupatilin Rescues Ciliary Transition Zone Defects to Ameliorate Ciliopathy-Related Phenotypes. *Journal of Clinical Investigation*, **128**, 3642-3648. https://doi.org/10.1172/jci99232

[37] Wang, Z., Zhu, X., Huang, Z., Ren, K., Ran, J. and Yang, Y. (2025) Histone Deacetylase 6 (HDAC6) in Ciliopathies: Emerging Insights and Therapeutic Implications (Adv. Sci. 21/2025). *Advanced Science*, **12**, Article ID: 2570163. https://doi.org/10.1002/advs.202570163