

伴中枢神经系统症状的单基因遗传性肾小球疾病的研究进展

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[摘要] 迄今为止, 已报道约500种单基因遗传性肾脏病, 其中50多个基因与单基因孤立性或综合征性肾病综合征的发病相关, 这些基因大多在肾小球足细胞中表达。神经系统症状为综合征性肾病综合征常见的肾外表现, 各种研究发现足细胞和神经元在形态和功能方面存在联系。该综述总结了同时出现肾小球和中枢神经系统病变的单基因遗传病的遗传学进展及临床特点, 有助于提高临床医生对该类疾病的了解, 认识基因诊断技术对共病筛查的重要性, 降低漏诊、误诊率。

[中国当代儿科杂志, 2024, 26 (6): 652-658]

[关键词] 肾小球疾病; 中枢神经系统; 单基因遗传病

Research progress on monogenic inherited glomerular diseases with central nervous system symptoms

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Abstract: To date, approximately 500 monogenic inherited kidney diseases have been reported, with more than 50 genes associated with the pathogenesis of monogenic isolated or syndromic nephrotic syndrome. Most of these genes are expressed in podocytes of the glomerulus. Neurological symptoms are common extrarenal manifestations of syndromic nephrotic syndrome, and various studies have found connections between podocytes and neurons in terms of morphology and function. This review summarizes the genetic and clinical characteristics of monogenic inherited diseases with concomitant glomerular and central nervous system lesions, aiming to enhance clinicians' understanding of such diseases, recognize the importance of genetic diagnostic techniques for comorbidity screening, and reduce the rates of missed diagnosis and misdiagnosis.

[Chinese Journal of Contemporary Pediatrics, 2024, 26(6): 652-658]

Key words: Glomerular disease; Central nervous system; Monogenic inherited disease

遗传性肾脏病是由遗传物质改变所致的一类肾脏疾病, 占成年慢性肾脏病的5%~30%及儿童慢性肾脏病的30%以上^[1], 根据突变基因作用靶点不同分为先天性肾脏和尿路畸形、纤毛病、遗传性肾小球疾病、遗传性肾小管疾病、遗传代谢性疾病、儿童肾结石; 根据遗传变异方式不同分为染色体异常、拷贝数变异、单基因遗传、复杂或多因素遗传、线粒体基因异常等相关疾病^[2]。现已发现约500种单基因遗传性肾脏病^[3], 其中遗传性肾小球疾病多表现为激素耐药型肾病综合征

(steroid-resistant nephrotic syndrome, SRNS), 已发现50多个基因与肾病综合征(nephrotic syndrome, NS)相关, 这些基因多在肾小球中表达^[4-5]。部分遗传性肾脏病伴有多种肾外器官功能受损, SRNS最常见的肾外症状为神经系统症状、身材矮小和面部畸形^[6]。足细胞与神经元具有相似形状, 均形成特定的细胞间相互作用: 突触间隙和裂孔^[7]。此外, 多种组织特异性蛋白同时在两种细胞中表达, 如Densin蛋白、Synaptopodin蛋白、Rab3a/Rabphilin3a蛋白、Nephrin蛋白、Neph1蛋白、肾

[收稿日期] 2023-12-12; [接受日期] 2024-04-15

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小球上皮蛋白 1/蛋白酪氨酸磷酸酶受体 O^[7]。本文对合并中枢神经系统疾病的遗传性肾小球病的遗传学进展及临床特点作一综述，以便临床医生全面认识和了解该类疾病，减少临床工作中该类疾病的漏诊、误诊。

1 核蛋白基因突变所致 Galloway-Mowat 综合征

Galloway-Mowat 综合征 (Galloway-Mowat syndrome, GAMOS) 是一种罕见的遗传性疾病，自 1968 年 Galloway 和 Mowat^[8] 首次报道以来，迄今为止，已确认 10 种基因与 GAMOS 有关，分别命名为 GAMOS 1~10 型 (表 1)，至今共报道 160 多例 GAMOS，包括 60 多例 GAMOS 1 型^[9-12]、10 例 GAMOS 2 型^[13-17]、49 例 GAMOS 3 型^[13, 18-26]、12 例 GAMOS 4 型^[13, 27-30]、2 例 GAMOS 5 型^[13]、5 例 GAMOS 6 型^[31-32]、9 例 GAMOS 7 型^[33-34]、4 例 GAMOS 8 型^[35]、13 例 GAMOS 9 型^[36]、4 例 GAMOS 10 型^[36-37]，不排除存在部分漏诊、误诊病例。GAMOS 存在遗传异质性及临床异质性，典型临床表现为小头畸形、中枢神经系统病变、SRNS，并伴有其他多个系统不同程度病变。WDR73 基因

在维持细胞结构、细胞存活和微管调节中发挥关键作用^[12]，WDR73 基因突变可导致细胞周期调节蛋白表达异常^[38]、足细胞的局灶性黏附功能损伤^[39]。GON7、LAGE3、OSGEP、TP53RK、TPRKB 蛋白共同组成激酶、内肽酶和其他小尺寸蛋白复合物 (kinase, endopeptidase, and other proteins of small size, KEOPS)^[36]。YRDC 蛋白和 KEOPS 参与转运 RNA (transfer RNA, tRNA) 转录后的苏氨酰氨甲酰腺苷 [N(6)-threonylcarbamoyladenine, t6A] 修饰的生物合成^[5, 7]。YRDC 基因和编码 KEOPS 的基因突变可导致 t6A 水平下降，降低 tRNA 稳定性，影响其功能，从而影响蛋白质的稳定性、翻译效率和保真度^[13, 36]。WDR4 基因编码蛋白为甲基转移酶 1 (methyltransferase 1, METTL1) -WD 重复结构域 4 (WD repeat domain 4, WDR4) 复合物的组成成分，WDR4 蛋白可提高 METTL1 的 7-甲基鸟苷 (7-methylguanosine, m7G) 转移酶活性，促进 tRNA 的 m7G 修饰^[40]。tRNA 的 t6A 或 m7G 修饰异常可能与 GAMOS 发病相关。NUP107 和 NUP133 基因编码的核孔蛋白为核孔复合体的重要组成成分，NUP107 和 NUP133 基因突变导致其编码蛋白表达降低，破坏蛋白之间的相互作用，影响核孔密度^[33, 35]。

表 1 GAMOS 相关基因列表

表型	表型 MIM	基因	基因 MIM	基因染色体定位	遗传方式
GAMOS 1 型	251300	WDR73	616144	15q25.2	AR
GAMOS 2 型	301006	LAGE3	300060	Xq28	XLR
GAMOS 3 型	617729	OSGEP	610107	14q11.2	AR
GAMOS 4 型	617730	TP53RK	608679	20q13.12	AR
GAMOS 5 型	617731	TPRKB	608680	2p13.1	AR
GAMOS 6 型	618347	WDR4	605924	21q22.3	AR
GAMOS 7 型	618348	NUP107	607617	12q15	AR
GAMOS 8 型	618349	NUP133	607613	1q42.13	AR
GAMOS 9 型	619603	GON7	617436	14q32.12	AR
GAMOS 10 型	619609	YRDC	612276	1p34.3	AR

注：[AR] 常染色体隐性遗传；[XLR] X 连锁隐性遗传。

GAMOS 神经系统表现异质性较大，可出现小头畸形 (原发或继发)、发育迟缓、语言障碍、智力障碍、癫痫、肌张力减退、痉挛、共济失调、视觉和听觉障碍 (视神经萎缩、眼球震颤、眼球运动障碍、斜视) 等不同症状。头颅 MRI 可见不同异常，如脑沟脑回异常 (无脑回、简化脑回模式、巨脑回、多小脑回)、小脑发育不全、小脑萎

缩、脑萎缩、皮质萎缩、胼胝体萎缩、脑室扩张、脑软化灶、孔洞脑、髓鞘发育不良、Dandy-Walker 畸形、小脑干等。GAMOS 肾损伤多在婴幼儿期出现，最早可在出生时即出现尿检异常^[13, 27]，肾脏表型为孤立性蛋白尿，多发展为 SRNS，并可迅速发展为终末期肾病 (end-stage renal disease, ESRD)，甚至部分患儿于新生儿期进展为

ESRD^[13, 27], 但个别GAMOS 4型患者6岁时仍未表现出肾损伤^[30]; GAMOS 6型^[31-32]和7型^[33-34]肾脏表型出现较晚, 已报道的病例肾损伤分别在6岁和4岁之后出现。1例GAMOS 6型患儿在糖皮质激素与他克莫司联合治疗后, 尿蛋白减少, 血清白蛋白恢复正常^[31]。目前尚无GAMOS 6型肾衰竭的报道^[31-32]。Fujita等^[35]报道2例GAMOS 8型患儿分别于6岁、8岁接受肾移植手术后NS未复发。部分GAMOS 3型患儿还可出现Fanconi综合征的部分症状、泌尿系统结石、神经源性膀胱功能障碍^[18]。亦有报道携带WDR73基因纯合错义突变的姐弟表现出智力障碍和小脑发育不全, 但无小头畸形, 弟弟30多岁时出现非肾病水平蛋白尿, 姐姐始终未出现肾损伤相关临床表现^[10]。肾组织病理类型主要为局灶节段性肾小球硬化(focal segmental glomerulosclerosis, FSGS)、弥漫性系膜硬化(diffuse mesangial sclerosis, DMS), 伴足突消失, 部分患儿表现为微小病变(minimal change disease, MCD)、系膜增生性肾小球肾炎(mesangial proliferative glomerulonephritis, MsPGN), 伴基底膜异常、肾小管扩张萎缩^[13, 23-25, 35]。GAMOS除神经系统及肾损伤外, 还可表现出其他多系统畸形, 包括面部畸形(前额畸形、面中部小、下颌畸形、下巴外凸、面部衰老)、眼部畸形(眼距过宽、内眦赘皮、小眼畸形、睑裂向下倾斜、眼窝凹陷、眼眶丰满)、耳畸形(大耳、低位耳、厚耳垂)、鼻畸形(朝天鼻、喙鼻、鼻孔前倾)、口腔畸形(宽嘴、嘴角下斜、小齿、牙釉质发育不全、人中光滑、高腭弓)、骨骼畸形(身材矮小、脊柱钙化、脊柱侧凸、漏斗胸、屈曲指、蜘蛛指、拇指分裂、扣拇指、斜指、足畸形、肘外翻/拇趾外翻、髌关节脱位、关节挛缩等)、心脏畸形(室间隔缺损、扩张型心肌病、主动脉狭窄、动脉导管未闭)、消化系统畸形(胆道闭锁、幽门狭窄、膈疝、胃食管反流、胃扭转、肠道旋转不良)及进食困难、宫内生长迟缓、皮肤色素异常、多毛症、毛发粗糙、湿疹、隐睾症、指甲发育不良、甲状腺功能减退、QT间期延长、高钙尿症等异常。GAMOS累及多个系统, 进展快, 大多数无法度过青春期^[12-13, 35-37], 但报道的大多数GAMOS 9型^[36]及所有6型^[31-32]和7型^[33-34]患者为存活状态, 最大存活年龄为32岁^[36]。

2 原发性辅酶Q10缺乏症

辅酶Q10(coenzyme Q10, COQ10)是线粒体呼吸链中的电子载体, 在线粒体代谢、核苷酸合成、细胞凋亡等过程中发挥重要作用^[41-42]。15种基因参与COQ10合成^[43]。其中COQ2、COQ6和PDSS2基因突变可导致神经系统及肾损伤, 均为常染色体隐性遗传。(1)原发性COQ10缺乏症1型由COQ2基因突变所致, 至今约20例患者被报道同时存在神经系统和肾损伤, 肾脏表型为SRNS, 神经系统表型可为脑病、共济失调、癫痫、痉挛、肌张力低下、智力障碍、脑萎缩等, 部分患儿可伴有心肌病、视锥视杆营养不良、视网膜色素变性^[42, 44]。多于婴儿期发病, 可于新生儿期进展为ESRD, 也可十几岁时出现NS^[42]。(2)原发性COQ10缺乏症6型由COQ6基因突变所致, 目前共报道30多例患儿, 发病年龄为0.2~16岁, 肾损伤表现为婴儿期NS, 可伴有感音神经性耳聋、视神经萎缩、共济失调、癫痫、脑白质异常、斜视、发育迟缓、肌张力减退等神经肌肉病变, 面部畸形及肾结石。最早可于5月龄进展为ESRD, 肾脏病理主要为FSGS、DMS^[43, 45]。(3)原发性COQ10缺乏症3型由PDSS2基因突变所致。目前已报道6例同时存在NS及神经系统症状的PDSS2基因突变患者; 肾脏表型均为NS, 病理为DMS; 肾外表现有癫痫、脑病、脑性瘫痪、智力障碍、共济失调、肌张力障碍、运动发育迟缓、皮质失明、视网膜色素变性、视神经萎缩、白内障、耳聋、肥厚性心肌病^[46]。

COQ10缺乏症可以通过测定皮肤成纤维细胞或骨骼肌活检中的COQ10含量进行生化诊断^[46]。早期口服大剂量COQ10可改善部分患者的神经系统及肾脏病变; 但因遗传缺陷不同疗效不同, PDSS2基因突变患者口服大剂量COQ10的疗效较其他类型欠佳^[42, 45-46]。

3 基底膜相关基因突变所致Pierson综合征

Pierson综合征是由LAMB2基因突变所致的常染色体隐性遗传病, 以先天性NS、眼部异常和神经发育缺陷为特点^[47-48]。LAMB2基因编码的层粘连蛋白 $\beta 2$ 存在于全身基底膜中, 其中肾小球基底膜主要为 $\alpha 5\beta 2\gamma 1$ (LM-521)^[47]。Pierson综合征的

肾脏表型多为婴儿型NS，肾脏病理多为DMS、FSGS、MCD。眼部病变存在异质性，主要表现为小瞳孔，其他眼部异常也有报道，如虹膜异常、晶状体形状异常伴白内障、视网膜异常、视神经发育不全等。其他肾外表现包括发育迟缓、肌张力减退、听力缺陷、肌无力、骨骼异常、智力障碍、语言障碍、癫痫等。Pierson综合征预后很差，多数患儿需肾替代治疗和肾移植，大多数在2岁前死亡^[47-49]。注射LM-521可降低*Lamβ2*^{-/-}小鼠足细胞损伤标记蛋白的表达，减少足突消失，延迟蛋白尿的发生，但并不能预防NS^[50]。

4 其他

鞘氨醇磷酸裂解酶不全综合征(sphingosine phosphate lyase insufficiency syndrome, SPLIS)，又称肾病综合征14型，为*SGPL1*基因相关的常染色体隐性遗传病。*SGPL1*基因突变导致其编码蛋白1-磷酸鞘氨醇裂解酶表达下降和功能缺失，鞘脂代谢物1-磷酸鞘氨醇裂解减弱，影响各种生理过程及细胞功能^[51]，从而出现多系统病变，包括SRNS、内分泌系统异常（原发性肾上腺功能不全、肾上腺钙化、甲状旁腺功能亢进、甲状腺功能减退）、神经系统异常（癫痫、发育迟缓、发育退后、听力障碍、小头畸形、巨头畸形、周围/轴突神经病变、肌张力减退、共济失调、舞蹈病、脑积水、上睑下垂）、皮肤异常（鱼鳞病、色素沉着过度、皮肤钙化）和免疫缺陷（淋巴细胞减少、低丙种球蛋白血症）、心脏病（左心室肥厚、室间隔缺损）、斜视、小阴茎和隐睾等。目前报道的近60例患者多在1岁前发病，最迟发病年龄为19岁。该疾病的临床表现存在异质性，从严重的多器官受累至孤立的单器官疾病不等；发病年龄越早病情越重，整体病死率接近47%。肾脏病理主要为：FSGS、MsPGN、DMS、IgM肾病。目前治疗方法以对症支持治疗为主，既往研究发现补充维生素B₆可减少1-磷酸鞘氨醇的积累，但临床疗效不一致，其他可能的治疗正在研究评估中^[51-54]。

2013年Gee等^[55]发现足细胞骨架相关基因*ARHGDIA*基因突变可导致伴有神经系统症状（感音神经性耳聋、智力障碍、癫痫、皮质失明）的SRNS，3岁前进展为ESRD。个别研究发现足细胞裂孔膜相关基因*FAT1*基因变异可导致患儿同时出现肾脏和神经系统疾病；神经系统症状包括智力

障碍、巨脑回、小松果体囊肿、发育迟缓、癫痫、耳聋、眼睑下垂等；肾损伤表现为NS，肾组织病理可见肾小管间质性肾炎、系膜硬化、薄基底膜、微小病变，泌尿系统病变除肾小球肾小管损伤外，也可表现为膀胱输尿管反流、双肾发育不良；另外，可伴有肺动脉狭窄、眼部异常、骨骼异常等其他肾外症状^[56-57]。需要更多的基因型-表型研究来了解*ARHGDIA*和*FAT1*基因突变相关疾病。

5 基因诊断与遗传性肾脏病

基于对目前已报道的遗传性肾脏病的认识，如出现以下情况，可考虑行基因检测：（1）发病年龄早，如1岁以内发病的NS；（2）伴有肾外表现的肾脏病；（3）有肾脏病家族史；（4）SRNS；（5）肾活检病理或影像学检查提示可疑遗传性肾脏病者；（6）不明原因的ESRD^[58]。基因检测方法的选择依赖于临床医师对患者的综合判断；临床症状典型、疑诊特定疾病，选择第一代测序检测目标基因或者选择含靶向基因的panel测序；非典型临床表型疑诊某类疾病，选择含该类疾病致病基因的panel测序或者全外显子组测序；无法确定疾病范围或者多系统损伤者可选择全外显子组测序或全基因组测序。怀疑基因组疾病时可联合染色体微阵列分析技术检测拷贝数变异。通常，为了获得最佳结果，建议受影响的孩子和父母同时检测^[2, 59]。

遗传学诊断可避免有风险的诊断程序（如肾活检）和有潜在不良反应的治疗（如类固醇激素和免疫抑制剂），发现并干预潜在的可治疗的罕见病（如COQ10生物合成途径缺陷），预测预后（如移植后复发），以及提供精确的基因咨询。其次，可以预测和进一步筛查肾外并发症，提前发现并治疗并发症^[1, 60]。

6 总结与展望

通过对以上疾病的遗传学及临床特征分析，有助于提高临床医师对该类疾病的了解，认识基因诊断技术对共病筛查的重要性。神经-肾脏疾病存在异质性，足细胞和神经元之间存在共同的细胞信号通路，蛋白质生物合成异常、肌动蛋白和微管细胞骨架重构可能与肾脏-神经系统损伤有关。需要进一步研究其细胞机制，期待在不久的将来寻找出治疗靶点。

作者贡献声明：王英负责文献检索及文章撰写；何庆南负责拟定写作思路，指导撰写文章。

利益冲突声明：所有作者声明无任何利益冲突。

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