·前沿进展·

结节性硬化症的遗传学研究进展

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【摘要】 结节性硬化症（TSC）是指多个系统受累的神经皮肤综合征，可累及脑、肾、皮肤、心、肺、肝、眼睛等，主要临床特征为面部皮脂腺瘤、癫痫发作和智力减退。TSC是一种常染色体显性遗传病，主要有两个缺陷基因（TSC1和TSC2）。近年来，TSC的基因突变筛查、诊断、治疗等取得了一定进展，为TSC的基因诊断和治疗打下了坚实基础。本文综述了TSC的遗传学研究进展，以期为临床有效诊治TSC提供参考。

【关键词】 结节性硬化症；遗传学；综述

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Genetic Research Progress on Tuberous Sclerosis Complex

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【Abstract】 Tuberous sclerosis complex (TSC) means neurocutaneous syndrome that involved systems, such as brain, kidney, skin, heart, lung, liver and eyes, mainly performed as facial sebaceous adenoma, epileptic seizure and cognitive disabilities. TSC is one kind of autosomal dominant inherited disorders, mainly including two defect genes (TSC1 and TSC2). In recent years, gene mutation screening, diagnosis and treatment of TSC achieved some progress and laid a solid foundation for genetic diagnosis and treatment of TSC. This paper reviewed the genetic research progress on TSC, to provide a reference for clinical effective diagnosis and treatment of TSC.

【Key words】 Tuberous sclerosis; Genetics; Review

结节性硬化症（TSC）是一种常染色体显性遗传病，是多个神经系统受累的神经皮肤综合征，其发病率为1/10 000～1/6 000[1]。1880年法国神经病学家Désiré-Magloire Bourneville对TSC进行了系统描述，TSC是一种良性非侵袭性肿瘤样病变（被称为错构瘤），可累及脑、肾、皮肤、心、肺、肝、眼睛等[2]，主要临床特征为面部皮脂腺瘤、癫痫发作和智力减退。2012年，国际结节性硬化症共识会议上提出心脏与皮肤病变通常是发现TSC的第一线索[2]。近年来，临床在TSC基因突变筛查、疾病诊断及治疗等方面取得一定进展[3]。本文综述了TSC的遗传学研究进展，以期指导临床更好地掌握其发病机制，进而为临床诊治提供参考。

1　TSC1和TSC2基因

TSC有两个缺陷基因（TSC1和TSC2），分别位于9q34和16p13.3。目前，已发现TSC1和TSC2基因存在8种突变类型，300多种突变方式。TSC1和TSC2基因中任何一个发生突变引起的临床表现均是可变的，即使有相同的基因突变也可以显示出多种临床表现。研究表明，65%～75%的TSC患者是自发突变[4]。也有研究表明，存在TSC1或TSC2基因致病性突变即可诊断为TSC[2]。因此，明确TSC患者基因诊断，并了解其发病机制具有重要意义。

1.1　TSC1基因突变　TSC1基因包含23个外显子，其中第1个和第2个外显子为非编码区，第3个至第23个外显子为编码区，从第222个核苷酸起开始转录，其基因产物为错构瘤蛋白。TSC1基因突变类型多为无义突变、移码突变及剪接突变，而错义突变及基因大片段缺失或重排较少见[5-6]。SLEGTENHORST等[7]研究表明，TSC1基因突变大多数位于外显子15和17，且家系患者和散发患者的基因突变率无明显差异。GAN等[8]研究表明，TSC1第403～787位氨基酸残基有一个粘着斑激酶家族互作蛋白（FIP200）结合区域，FIP200可通过与TSC1第403～787位氨基酸区域相互作用而调控TSC1-TSC2复合体功能，上调S6激酶的磷酸化水平，调节细胞大小。FIP200作为一种新的TSC1互作蛋白，能负性调节TSC1功能。MURPHY等[9]报道了1例由TSC1缺失导致散发淋巴管平滑肌瘤患者的病例资料，但并未排除其存

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在嵌合体突变的可能。既往研究表明，行为变异型额颞叶痴呆（bvFTD）是由 TSC1 基因新移码突变引起 TSC1/ 错构瘤蛋白转录提前终止所致，TSC1/ 错构瘤蛋白是哺乳动物雷帕霉素靶蛋白（mTOR）上游抑制剂，能调节细胞生长和蛋白质降解[10-11]。TSC1 基因突变的 TSC 患者临床表现轻于 TSC2 基因突变者，可能与 TSC1 基因“二次打击”发生率低于 TSC2 基因有关[12-14]。1971 年，克努森提出“二次打击”假说[15]，其是由正常等位基因大片段缺失引发，可通过筛选杂合性丢失（LOH）进行评估。研究表明，错构瘤或皮质结节发生机制可能与“二次打击”有关[16-17]。

1.2 TSC2 基因突变 TSC2 基因包含 42 个外显子，其中 41 个外显子通过 5.4 kb 的 mRNA 编码马铃薯球蛋白，其基因产物为结节蛋白[18-19]。研究表明，结节蛋白与鸟苷三磷酸酶激活蛋白（GAP）高度同源[20-21]。TSC2 基因突变形式多样，其中剪接突变、无义突变、移码突变及错义突变较多，而大片段基因缺失或重排较少。研究表明，与 TSC1 基因相比，TSC2 基因突变发生率较高[4]。NELLIST 等[22]研究表明，TSC2 异亮氨酸残基 820 缺失、TSC2 的 C244R、L1511H 和 Y598H 氨基酸替代会导致 TSC 的发生；而 TSC2 的 R1771C、T993M、S132C、F143L、A196T 替代是罕见的基因多态性，不能抑制 TSC1-TSC2 功能，不会引发 TSC。QIN 等[23]对 46 个 TSC 皮质结节样本的 TSC1、TSC2 和 KRAS 基因进行高通量测序，发现 TSC1、TSC2 和 KRAS 基因“二次打击”广泛分布于同一侧大脑半球，且发生率达 10%。MONTEIRO 等[24]对 35 例 TSC 患者进行研究，结果发现 TSC2 基因突变者占 58.3%。JONES 等[12]研究表明，TSC2 基因突变的 TSC 患者临床表现较严重、并发症较多、智力减退发生率较高。

1.3 TSC1 和 TSC2 基因突变检出情况 TSC 患者基因突变检出率为 69% ~ 89%。AU 等[25]研究表明，325 例 TSC 患者基因突变检出率为 72%，其中 TSC1 突变占 20%，TSC2 突变占 80%；另外，TSC1 15 号外显子和 TSC2 16 号外显子突变发生率较高。SANCAK 等[26]研究表明，276 例 TSC 患者基因突变检出率为 85%，其中 TSC2 基因突变检出率：TSC1 基因突变检出率为 3.4∶1.0。DABORA 等[27]研究表明，224 例 TSC 患者基因突变检出率约为 83%，其中无义突变占 29%，缺失突变占 27%，错义突变占 19%，剪接位点突变占 17%，插入突变占 8%。也有研究发现，TSC 患者中 TSC1 基因突变占比较低，基因突变形式及位点各异，且无热区分布[27-29]。分析其原因可能为：（1）基因突变位点位于未能检测到的内含子或其他非编码区，如启动子区等；（2）存在其他基因突变位点（如 TSC3、TSC4 等）；（3）可能为嵌合体突变；（4）目前检测技术无法检测出复杂的基因大范围缺失或重排；（5）检测技术灵敏度不高或发生漏检等。

2 TSC 发病机制

TSC1 基因编码的错构瘤蛋白是一种 130 kDa 跨越 1 164 个氨基酸的蛋白质；TSC2 基因编码的马铃薯球蛋白是一种 200 kDa 跨越 1 807 个氨基酸的蛋白质[30]。错构瘤蛋白和马铃薯球蛋白在细胞内形成异二聚体，通过 TSC-Rheb-TORS6K1/4EBP1 途径调节细胞增殖，参与细胞黏附等[31-33]。TSC1 或 TSC2 基因突变会导致 mTOR 信号级联活性增高，引起细胞生化异常（包括转录、翻译、细胞周期调控、代谢水平等）。mTOR 信号级联〔磷脂酰肌醇 3- 激酶（PI3Ks）/ 蛋白激酶 B（Akt）/mTOR 通路〕在正常细胞生长、增殖和存活中发挥着重要作用[11]。mTOR 可形成 mTORC1 和 mTORC2 两种多蛋白复合体，主要通过相互作用物、底物选择性、对西罗莫司及其类似物依维莫司的敏感性不同进行区分[34-35]。mTORC1 下游效应包括基因转录、蛋白翻译、细胞增殖和存活、血管新生；mTORC2 可调节细胞骨架信号通路[35]。近年研究发现，HMGA2 通路可参与 TSC 患者肿瘤形成[36]。

3 治疗方法

西罗莫司与依维莫司通过与 FK506 结合蛋白 12（FKBP12）结合形成复合物而抑制 mTORC1 分泌[37]。依维莫司已被美国食品药品监督管理局（FDA）批准用于治疗不能进行手术的室管膜下巨细胞星形细胞瘤（SEGAs）或肾血管平滑肌脂肪瘤（AML）患者，也适用于治疗存在皮肤表现、癫痫、肺淋巴管肌瘤病的 TSC 患者[38]。BISSLER 等[39]研究表明，依维莫司可有效缩小 TSC 患者肿瘤体积。HINTON 等[40]研究表明，西罗莫司可有效缩小 TSC 患者血管平滑肌脂肪瘤体积，并改善患者肺功能，但停药 12 个月后肿瘤体积和肺功能接近治疗前。

4 小结

近年来，随着生物技术飞速发展，TSC 的研究取得了突破性进展，为 TSC 的基因诊断和治疗打下了坚实基础。目前，以 TSC1 及 TSC2 基因突变为基础的病理变异和自然病程变化机制尚不完全明确，且新的检测技术有待开发，相信随着研究的不断深入，人类终将实现 TSC 的基因治疗。

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