·脑出血研究进展·

遗传性结缔组织病与颅内动脉瘤发生与破裂相关研究进展

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【摘要】 颅内动脉瘤发生及破裂机制复杂,可能涉及多种环境因素与遗传因素的相互作用。颅内动脉瘤的发生发展与结缔组织病具有相关性,罹患遗传性结缔组织病的患者合并颅内动脉瘤等多种脑血管病的风险明显增加,这些遗传性结缔组织病的某些关联基因突变与颅内动脉瘤的发生发展密切相关。本文重点综述常见颅内动脉瘤相关遗传性结缔组织病及其关联基因位点。

【关键词】 颅内动脉瘤; 结缔组织疾病; 遗传性疾病,先天性; 基因; 突变; 综述

Advances in related research about hereditary connective tissue diseases and the occurrence and rupture of intracranial aneurysm

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【Abstract】 The mechanism of occurrence and rupture of intracranial aneurysm is complex and may involve various environmental and genetic factors. Histopathological studies of intracranial aneurysm suggest a possible relationship between intracranial aneurysm and connective tissue diseases. Clinical studies have shown that patients suffering from hereditary connective tissue diseases are at significantly increased risk of multiple cerebrovascular diseases such as intracranial aneurysm. Further studies have found that mutations in associated gene loci involved in these hereditary diseases are closely related to the occurrence and development of intracranial aneurysm. Based on previous literatures, this study aims to review intracranial aneurysm related hereditary connective tissue diseases and important gene loci involved.

【Key words】 Intracranial aneurysm; Connective tissue diseases; Genetic diseases, inborn; Genes; Mutation; Review

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颅内动脉瘤是临床常见的脑血管病,高峰发病年龄为40~60岁,动脉瘤破裂后导致的蛛网膜下腔出血(SAH)或颅内出血(ICH)是神经外科急危重症,病残率和病死率极高[1]。颅内动脉瘤的发生与破裂机制十分复杂,涉及多种环境因素和遗传因素的相互作用,组织病理学研究提示其发生发展可能与结缔组织病相关[2]。罹患Marfan综合征(MS)、Ehlers-Danlos综合征(EDS)、1型神经纤维瘤病(NF1)、Loeys-Dietz综合征(LDS)、常染色体显性遗传性多囊肾(ADPKD)等遗传性结缔组织病的患者合并颅内动脉瘤等脑血管病的风险显著增加[3-4]。这些结缔组织病通过影响细胞外基质(ECM)重要结构蛋白的合成,破坏血管壁的稳定性,导致颅内动脉瘤的发生与发展[5],遗传学机制可能在其中发挥重要作用[6]。本文拟从颅内动脉结缔组织结构成分和功能特点角度,对常见颅内动脉瘤相关遗传性结缔组织病及其关联基因位点进行综述,以探究遗传性结缔组织病与颅内动脉瘤发生发展的关系。

一、颅内动脉的结缔组织

1.颅内动脉结缔组织的主要成分 颅内动脉包括内膜、中膜、外膜共3层膜性结构,围绕在各层细胞间的细胞外基质是血管结缔组织的主要成分,对

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血管壁结构和功能的稳定性具有重要作用[7]。颅内动脉结缔组织的主要成分是胶原纤维和弹性纤维，前者主要起细胞框架支撑作用，后者为血管提供弹性张力[8]。(1)胶原纤维：胶原纤维系由甘氨酸、脯氨酸和羟脯氨酸等多种氨基酸构成的纤维复合物，其核心结构为胶原蛋白。血管胶原蛋白主要由内皮细胞、平滑肌细胞和纤维母细胞合成，包含α1、α2和α3共3条肽链，迄今已发现27种不同亚型；其中，1型和3型胶原蛋白占血管胶原蛋白总量的80%～90%，为血管弹性骨架网的核心成分，主要作用是稳定血管[9]。颅内动脉含少量4型、5型和6型胶原蛋白，虽然这些胶原蛋白含量较少，但对维持细胞外基质，以及血管壁结构和功能稳定性具有重要作用。(2)弹性纤维：弹性纤维的主要成分是弹性蛋白，该蛋白具有卷曲特性，分子之间通过共价键交联成网并在细胞外基质中形成固有弹性膜，是血管结缔组织中承担压力负荷的重要结构，同时对血管平滑肌的拉伸和回缩产生协同作用[10]。颅内动脉分叉部常出现内弹性膜先天性缺陷或薄弱，此为颅内动脉瘤好发于分叉部的重要病理生理学基础[11]。

2.颅内动脉瘤相关遗传性结缔组织病　结缔组织对维持颅内动脉结构和功能的完整性具有重要作用。罹患遗传性结缔组织病的患者结缔组织重要结构蛋白破坏，其合并颅内动脉瘤等多种脑血管病的风险明显增加[5]。(1)Marfan综合征：患病率为2～6.50/万，是较为常见的常染色体显性遗传性疾病，与位于第15号染色体q21.1的*FBN1*基因突变有关，该基因编码的肌原纤维蛋白-1(fibrillin-1)是结缔组织的重要结构蛋白[12]。肌原纤维蛋白-1除在结缔组织中对细胞起支撑作用，还通过与转化生长因子-β(TGF-β)结合抑制其对血管平滑肌发育和细胞外基质其他结构蛋白的破坏。由此可见，Marfan综合征的病理生理学机制为肌原纤维蛋白-1表达异常及其导致的过量TGF-β聚集致全身性结缔组织病[13]。既往研究显示，Marfan综合征与颅内动脉瘤相关[14]，其合并颅内动脉瘤的风险高达13.56%[5]。2018年，Kim等[3]对13 883例Marfan综合征患者的出院诊断分析发现，颅内动脉瘤的诊断率高于其他住院患者[0.24%(33/13 883)对0.06%(9/13 883)，$P=0.002$]，由于这些患者中仅少数完成脑血管影像学筛查，故Marfan综合征合并颅内动脉瘤的实际风险可能更高。亦有学者得出不同结果：van den Berg等[15]经长期随访并未发现Marfan综合征与颅内动脉瘤的确切关系；Conway等[16]的尸检结果显示，Marfan综合征合并颅内动脉瘤的发生率与非Marfan综合征无显著差异。迄今仍缺乏Marfan综合征合并颅内动脉瘤患病率的确切流行病学统计数据，二者之间持相关性有待进一步证实。(2)Ehlers-Danlos综合征：是一种全身性结缔组织病，人群发病率约为1/5000，发病机制为基因突变所致胶原蛋白生成缺陷，引发结缔组织结构和功能异常[17]。主要包括Ⅰ～Ⅵ共6种亚型，每种均有独立的遗传学特征，其中Ⅳ型具有突出的神经血管病理表现，致病基因定位于2q31的*COL3A1*基因[18]，此类患者的血管组织学形态可见血管内膜和中膜胶原纤维排列紊乱、弹性纤维异常聚集，与Ⅲ型胶原蛋白合成障碍有关，后者作为细胞外基质的主要结构蛋白对维持血管壁结构和功能稳定具有重要作用[19]。因此，Ⅲ型胶原蛋白异常表达可能是Ⅳ型Ehlers-Danlos综合征患者出现血管并发症的重要原因。多项研究显示，Ehlers-Danlos综合征可合并颅内动脉瘤[18,20]，同时还可合并动脉夹层、颈内动脉海绵窦瘘等脑血管并发症，提示Ehlers-Danlos综合征作为遗传性疾病对血管结缔组织影响广泛。文献报道的Ehlers-Danlos综合征合并颅内动脉瘤发生率差异较大，为1.4%～11%[21-23]，可能是由于各项研究中并非所有患者均接受血管影像学筛查，因此该结果并不能真实地反映Ehlers-Danlos综合征合并颅内动脉瘤的风险，二者之间的关系待进一步研究。(3)1型神经纤维瘤病：亦称为von Recklinghausen病，是一种常见的常染色体显性遗传性神经纤维瘤病，全球发病率约为1/2500～1/3000，其遗传学机制为第17号染色体*NF1*基因突变，导致神经纤维蛋白结构改变或功能异常[24]。临床主要表现为全身多发性神经纤维瘤，其他合并症有视神经胶质瘤及其他恶性肿瘤、高血压、骨性病变和血管病变等[25]。对人体血管内皮细胞的体外培养发现其表达神经纤维蛋白，后者作为重要的结缔组织蛋白，对维持血管内皮细胞和平滑肌细胞结构和功能的完整性具有重要作用[4]。因此认为，*NF1*基因突变致神经纤维蛋白异常可能是导致1型神经纤维瘤病合并血管病变的关键机制[26]。二者的相关性研究呈现较明显差异：Schievink等[27]的MRI研究显示，与性别和年龄相匹配的对照者相比，1型神经纤维瘤病患者颅内动脉瘤发生率显著高于对照组[9.09%(2/22)对0(0/526)，$P<0.005$]；一项脑血管影像学筛查研究结果显示，1型神经纤

维瘤病合并颅内动脉瘤的发生率约为10.64%(5/47)[5];但据Rosser等[28]统计,1型神经纤维瘤病合并颅内动脉瘤的发生率仅为0.32%(1/316)。值得注意的是,上述研究中的大多数患者虽然均行头部MRI检查,但仅少数接受过MRA检查,可能存在颅内动脉瘤漏诊,故实际发生率可能高于文献报道。Conway等[29]对25例1型神经纤维瘤病患者进行尸检,无一例合并颅内动脉瘤。基于上述异质性研究结果,二者之间的相关性尚待进一步研究加以证实。(4)Loeys-Dietz综合征:是常染色体显性遗传性结缔组织病,目前尚无流行病学资料。多种遗传学机制可能参与其病理生理学机制,相关致病基因包括*TGFβR1*、*TGFβR2*、*SMAD3*等,上述基因突变影响全身结缔组织和细胞外基质功能,进而出现血管、皮肤、骨骼、头面部等多系统受累表现[30]。针对TGF-β信号转导通路的调控是Loeys-Dietz综合征引起结缔组织病的主要机制,TGF-β与受体(TGFβR)结合形成大分子复合体,后者通过调控特定基因的表达活性,影响细胞增殖周期和细胞分化潜能,同时参与细胞外基质结构蛋白合成[31]。Loeys-Dietz综合征可增加颅内动脉瘤的发生风险,其合并颅内动脉瘤的发生率为10%~32%,高于正常人群的3.20%[5,32-33]。由于目前相关研究较少,Loeys-Dietz综合征合并颅内动脉瘤的确切流行病学数据待进一步揭示。(5)常染色体显性遗传性多囊肾:是一种常见的遗传性结缔组织病,人群发病率为1/3000~1/8000[34],其遗传学机制涉及*PKD1*和*PKD2*基因突变,*PKD1*基因定位于第16号染色体,约占总病例数的85%;*PKD2*基因定位于第4号染色体,约占15%。除常见的肾积液、肾囊肿等肾病表现外,还可见于全身多发性结缔组织病[35]。血管病变是常染色体显性遗传性多囊肾的主要肾外合并症,*PKD1*和*PKD2*基因编码的多囊蛋白是血管结缔组织的重要功能蛋白,参与细胞间粘附和信号转导,对维持血管结构和功能的稳定具有重要作用[35],*PKD1*和*PKD2*基因突变可致多囊蛋白功能异常,通过影响细胞外基质稳定导致血管并发症的发生。此外,*PKD1*和*PKD2*基因还具有调控细胞内钙离子通道作用,基因突变导致钙离子通道异常引起的血压变化也是血管并发症的重要发生机制[36]。多项临床研究显示,常染色体显性遗传性多囊肾与颅内动脉瘤相关,患者年龄一般较小,合并多发性动脉瘤的风险较高[37-38],约10%(149/1490)[39]或12.39%(44/355)[40]的患者可合并颅内动脉瘤。

二、颅内动脉瘤相关基因突变位点

1.胶原蛋白基因*COL1A2*和*COL3A1* 胶原蛋白作为血管壁细胞外基质的重要成分,对于维持血管壁结构和功能的稳定具有重要作用,其合成障碍是多种颅内动脉相关遗传性结缔组织病的重要病理生理学机制[5]。Ⅰ型和Ⅲ型胶原蛋白是颅内血管胶原蛋白的主要类型,其编码基因*COL1A2*和*COL3A1*被认为是颅内动脉瘤的候选关联基因[41]。(1)*COL1A2*基因:定位于染色体7q21,是Ⅰ型胶原蛋白主要肽链的编码基因。有文献报道,该基因单核苷酸多态性(SNP)位点rs42524多态性与颅内动脉瘤的发生发展相关[42]。一项纳入6项临床研究计1542例颅内动脉瘤患者和1424例正常对照者的Meta分析显示,rs42524位点的4种遗传模式与颅内动脉瘤的易感性相关,进一步亚组分析结果提示,亚洲人群该位点多态性与颅内动脉瘤的相关性强于白种人[43]。(2)*COL3A1*基因:定位于染色体2q31,是Ⅲ型胶原蛋白主要肽链的编码基因。Kuivaniemi等[44]发现,*COL3A1*基因突变通过改变蛋白质空间螺旋结构的稳定性影响其功能。目前多项研究支持*COL3A1*基因多态性与颅内动脉瘤的发生相关:Meng等[45]和Hua等[46]均认为,*COL3A1*基因rs180025多态性与中国人群颅内动脉瘤的发生相关;Brega等[47]采用AvaⅡ限制性内切酶处理*COL3A1*基因后得到两个大小不同的片段(Allele A和Allele B),发现颅内动脉瘤患者Allele B片段的概率是对照组的4.5倍。然而,亦有研究未得出阳性结果,van den Berg等[48]对*COL3A1*基因多个单核苷酸多态性位点进行测序分析,并未发现其多态性与颅内动脉瘤的发生及破裂相关。上述研究提示,*COL3A1*基因多态性与颅内动脉瘤之间的关系可能存在人群差异,该基因序列中与颅内动脉瘤相关的单核苷酸多态性位点尚待进一步探究。

2.弹性蛋白*ELN*基因 除胶原蛋白外,弹性蛋白也是血管壁细胞外基质的重要成分,主要参与构成结缔组织弹性纤维并赋予血管抗张力强度,对维持血管壁结构和功能的稳定性具有重要作用。因此,弹性蛋白异常可能影响血管壁的正常收缩功能,进而影响其稳定性并最终导致颅内动脉瘤的发生与发展[49]。弹性蛋白编码基因*ELN*被认为是颅内动脉瘤的重要候选关联基因,但相关性研究尚未得出一致性结论。Onda等[50]对日本人群*ELN*基因

进行测序，发现该基因内含子多个位点单核苷酸多态性与颅内动脉瘤的发生相关；Jeon等[51]基于韩国人群的调查也得出一致性结论。Paterakis等[52]的Meta分析进一步证实，*ELN*基因内含子20 1315T>C突变可增加颅内动脉瘤的风险，但亚组分析显示二者之间的关系可能存在人群差异。Hofer等[53]对来自欧洲的30例家族性颅内动脉瘤、175例散发性颅内动脉瘤和235例正常对照者的*ELN*基因进行测序分析，未发现*ELN*基因多态性与颅内动脉瘤发生及破裂的确切关系。Krex等[54]基于高加索人群的研究也提示，*ELN*基因多个单核苷酸多态性位点及其单倍体型与颅内动脉瘤并无关联性。上述研究显示，*ELN*基因与颅内动脉瘤的关联性可能存在人群差异，尤以亚洲人群显著。

3.*LOX*基因　赖氨酰氧化酶（LOX）是相对分子质量为32×10^3的糖蛋白，目前发现5种亚型，相应编码基因分别定位于第5、15、8、2和10号染色体。LOX通过催化胶原蛋白和弹性蛋白的氧化脱氨基反应，使后两者从可溶性单体转变为稳定性较强的不溶性纤维[55]。因此，LOX表达正常对结缔组织细胞外基质结构和功能的稳定具有重要作用。*LOX*基因缺陷致细胞外基质结构蛋白破坏是血管结缔组织损伤的重要机制。Rodríguez等[56]在*LOX*基因敲除小鼠的血管组织中观察到弹性纤维破碎、内皮细胞与基膜分离等结缔组织改变。Mäki等[57]的动物实验显示，*LOX*基因失活小鼠颅内动脉瘤发生率显著升高。因此认为，*LOX*基因是颅内动脉瘤的候选关联基因，但大多数临床研究并未得出相应阳性结果。Onda等[50]对颅内动脉瘤和正常对照者*LOX*基因的4个单核苷酸多态性位点进行测序，发现两组患者基因多态性无显著差异。Hofer等[58]在25个德国颅内动脉瘤家系中发现*LOX*基因单核苷酸多态性位点的4种遗传模式，但是未发现这些变异与颅内动脉瘤具有明确关联性。Ruigrok和Rinkel[59]对荷兰人群中的44个潜在颅内动脉瘤候选基因进行测序，并未发现*LOX*基因与颅内动脉瘤有关。Sathyan等[60]基于印度人群的研究亦未得出*LOX*基因多态性与颅内动脉瘤的确切关系。然而，2017年Hong等[61]发表的一项基于韩国人群的研究，对比分析颅内动脉瘤与正常对照者*LOX*基因多个单核苷酸多态性位点的多态性差异，发现rs2303656、rs3900446和rs763497共3个位点可能与颅内动脉瘤的发生相关。目前*LOX*基因与颅内动脉瘤的相关研究较少，二者之间的确切关系待进一步证实。

4.*MMP*基因　基质金属蛋白酶（MMPs）是钙依赖性含锌内肽酶，目前已发现近30种不同亚型，根据结构和底物特性分为胶原酶、明胶酶、弹性蛋白酶等多种类别，主要生理作用为分解各种细胞外基质结构蛋白，包括胶原蛋白和弹性蛋白，其中弹性蛋白对维持血管壁结构和功能的稳定性具有重要作用[62]。血管壁细胞外基质破坏是颅内动脉瘤发生发展的重要机制，组织学形态可见纤维性内膜增厚、内弹力层断裂、网状胶原纤维破坏等细胞外基质退行性变，而基质金属蛋白酶活性增强在其中发挥重要作用[63]，因此*MMP*基因可能是颅内动脉瘤的候选关联基因。Bruno等[64]认为，MMP-2可能参与颅内动脉瘤的发生及破裂。Kim等[65]的研究则提示，MMP-9表达水平升高可能在颅内动脉瘤的形成过程中发挥重要作用。值得注意的是，与未破裂颅内动脉瘤相比，破裂颅内动脉瘤基质金属蛋白酶表达水平更高，表明基质金属蛋白酶不仅参与颅内动脉瘤的发生，还可能在其破裂过程中发挥重要作用[66]。然而Krex等[67]基于高加索人群（40例颅内动脉瘤患者和44例正常对照者）*MMP-9*基因部分兴趣位点测序分析并未发现二者位点多态性差异。上述研究结果提示，*MMP*基因与颅内动脉瘤的关联性可能存在人群差异。

5.*α1-AT*基因　α1-抗胰蛋白酶（α1-AT）是一种重要的蛋白酶抑制剂，参与机体90%以上的蛋白酶抑制反应，保护正常细胞和器官免受蛋白酶酶解损伤。弹性蛋白酶与α1-抗胰蛋白酶是一对相互拮抗的组合，二者动态平衡对维持细胞外基质结构和功能的完整性具有重要作用[68]。Baker等[69]的研究显示，颅内动脉瘤患者弹性蛋白酶/α1-抗胰蛋白酶比值是非颅内动脉瘤患者的2倍，而后者该比值减小与*α1-AT*基因表达异常有关。目前关于*α1-AT*基因与颅内动脉瘤关系的相关报道较少，Marzatico等[70]发现，破裂颅内动脉瘤患者*α1-AT*基因突变率高于、α1-抗胰蛋白酶活性低于未破裂动脉瘤患者。Schievink等[71]对比分析颅内动脉瘤患者与正常人群的*α1-AT*基因表型，结果显示，前者*α1-AT*基因突变率显著高于后者。上述研究表明*α1-AT*基因突变在颅内动脉瘤发生发展过程中发挥重要作用。但Yoneyama等[72]并未获得相同结果，对384例破裂颅内动脉瘤患者和289例非颅内动脉瘤患者*α1-AT*基因表型的直接测序分析显示，7个单核苷酸多态性

位点均无明显差别。由于目前关于*α1-AT*基因与颅内动脉瘤关系的研究较少、样本量较小，尚待更多、更大样本量的研究进一步阐明*α1-AT*基因与颅内动脉瘤发生及破裂的关系。

6. *FBN2*基因　*FBN2*基因定位于染色体5q23，编码的原纤维蛋白-2是弹性纤维的重要成分，后者作为细胞外基质的重要结构蛋白，其表达水平降低可影响血管壁细胞外基质的结构和功能，导致颅内动脉瘤的发生发展[73]。目前*FBN2*基因与颅内动脉瘤关系的研究较少，Ruigrok等[74]对382例荷兰颅内动脉瘤患者和609例正常对照者的44个候选关联基因测序分析发现，*FBN2*基因突变可能与颅内动脉瘤的发生发展相关。然而，一项针对日本人群的*FBN2*基因表型分析研究显示，172例颅内动脉瘤患者和192例非颅内动脉瘤神经外科住院患者5个单核苷酸多态性位点与颅内动脉瘤的发生发展均无关联性[75]。上述研究提示，*FBN2*基因与颅内动脉瘤的关联性可能存在人群差异，由于目前相关研究较少、样本量较小，二者之间的相关性尚待进一步研究。

综上所述，颅内动脉瘤的发生与破裂机制十分复杂，涉及遗传、环境、病理生理学等多种因素的相互作用。结缔组织病致血管壁细胞外基质破坏与颅内动脉瘤的发生发展密切相关。血管壁细胞外基质的主要成分包括胶原蛋白、弹性蛋白等大分子复合物，二者对于维持血管壁强度、韧性和弹性抗张力具有重要作用，其重要结构蛋白的破坏是Marfan综合征、Ehlers-Danlos综合征、1型神经纤维瘤病、Loeys-Dietz综合征和常染色体显性遗传性多囊肾等多种遗传性结缔组织病患者颅内动脉瘤风险增加的重要机制。潜在候选致病基因包括*COL1A2*、*COL3A1*、*LOX*、*MMP*、*α1-AT*、*FBN2*等，其编码产物通过直接或间接影响细胞外基质结构蛋白的合成而在颅内动脉瘤的发生发展过程中发挥重要作用。

由于人类基因组数量庞大，目前对疾病相关基因组学的研究仍在不断探索中。近年多项新技术的发展使得对颅内动脉瘤发生发展相关的遗传学机制有了更深入的了解。但迄今仅发现数个相关候选致病基因，且相关研究并未在不同人群中获得一致性结果，因此尚待更多、更大样本量的研究探寻颅内动脉瘤相关致病基因。这些新的致病基因和相关信号转导通路的发现，有望为颅内动脉瘤的诊断、治疗与预后判断提供新的思路。

利益冲突　无

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