·综述·

大动脉粥样硬化型缺血性卒中易感基因研究进展

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【摘要】 脑卒中是严重威胁人类健康的疾病之一，具有高发病率、高病残率和高病死率等特点。遗传因素在脑卒中发病中发挥重要作用，动脉粥样硬化、高血压、糖尿病、高脂血症和心脏病等是脑卒中的危险因素，均与遗传因素相关。脑卒中易感基因是目前国内外研究的热点之一，本文拟就大动脉粥样硬化型缺血性卒中易感基因研究进展进行综述。

【关键词】 卒中；　脑缺血；　动脉粥样硬化；　基因；　综述

Research progress of susceptibility genes associated with large artery atherosclerotic ischemic stroke

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【Abstract】 Stroke is one of the serious threats to human health, with high incidence, morbidity and mortality. Studies have shown that genes play an important role in the pathogenesis of stroke. Atherosclerosis, hypertension, diabetes, hyperlipidemia and heart disease are risk factors for stroke, and are associated with inheritance. Stroke susceptibility gene is one of the hotspots at home and abroad. This article reviews the progress of susceptibility genes in large artery atherosclerotic ischemic stroke.

【Key words】 Stroke;　Brain ischemia;　Atherosclerosis;　Genes;　Review

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脑卒中是严重威胁人类健康的疾病之一，居全球病死原因第2位，亦是成人主要病残原因[1]。脑卒中是遗传因素和环境因素共同作用的结果，其中遗传因素在发病机制中起重要作用。近年来，缺血性卒中候选基因研究已成为脑卒中遗传学机制的研究重点。根据TOAST分型，缺血性卒中可以分为5种类型，即大动脉粥样硬化型（LAA型）、心源性栓塞型（CE型）、小动脉闭塞型（SAO型）、其他明确病因型（SOD型）和不明病因型（SUD型），其中，LAA型缺血性卒中系脑血管造影证实与缺血性卒中神经功能缺损相对应的颅内或颅外大动脉狭窄率＞50%或闭塞，且符合动脉粥样硬化改变。动脉粥样硬化是以脂质代谢障碍、血管内皮细胞功能障碍、炎性细胞浸润致炎症反应、动脉粥样硬化斑块破裂、最终形成血栓为特点的复杂慢性病理生理学过程[2]。基于上述发病机制探寻LAA型缺血性卒中基因治疗靶点，近年国内外学者已经进行大量研究揭示LAA型缺血性卒中的遗传易感性，并结合其他危险因素（如高血压、糖尿病、高脂血症和心脏病等）进行评价，对指导临床医师建立更佳、更新的诊断与治疗方法具有积极意义。本文拟对目前研究较多的LAA型缺血性卒中易感基因研究进展进行简要综述。

一、*ApoE*基因

载脂蛋白E（ApoE）是包含299个氨基酸的磷脂糖蛋白，主要存在于血液乳糜颗粒（CM）、极低密度脂蛋白（VLDL）、中密度脂蛋白（IDL）和部分高密度脂蛋白（HDL）中，对脂质代谢和心血管相关疾病有决定性作用。*ApoE*基因定位于染色体19q13.2，由3597个核苷酸组成，含4个外显子和3个内含子。

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ApoE是多态性蛋白质，包含3个常见异构体即E2、E3和E4，分别编码3种亚型即ApoE2、ApoE3和ApoE4。ApoE各亚型与不同脂蛋白受体相互作用，通过乳糜颗粒和极低密度脂蛋白与肝脏不同酶类结合，调节吸收和分解代谢过程以改变血清胆固醇水平。*ApoE*基因型与高密度脂蛋白和胆固醇水平密切相关，可以影响动脉进展和动脉疾病进程。研究显示，*E2*等位基因是低回声和溃疡型颈动脉斑块的独立危险因素[3]；与其他基因型相比，*E3/E3*基因型是脑卒中保护因素，特别是女性患者，*E3*等位基因可能具有潜在的神经保护作用[4]。根据LAA型缺血性卒中与*ApoE*基因之间的相关性评价其对颈动脉内-中膜厚度（IMT）的作用，共纳入22项临床试验计30 879例存在血管病或血管危险因素的患者进行Meta分析，其结果显示，*ApoE2*基因型患者颈动脉内-中膜厚度最低，*ApoE3*基因型患者适中，*ApoE4*基因型患者最高，提示颈动脉内-中膜厚度增加与*ApoE*基因特异性表达有关，尤其与*ApoE4*基因型有关，并与环境因素（如高血压、吸烟等）相互作用，增加脑卒中发病风险[5]。马飞煜等[6]在LAA型缺血性卒中患者中发现，含*E4*等位基因的患者血清低密度脂蛋白（LDL）水平显著高于含*E3*等位基因的患者；LAA型缺血性卒中患者*E4*等位基因和*E3/E4*基因型频率高于对照组，*E3*等位基因和*E3/E3*基因型频率低于对照组；*E4*等位基因可以升高血清低密度脂蛋白水平，与LAA型缺血性卒中相关，而与其他类型缺血性卒中无明显关联性。

二、*MMP-12*基因

基质金属蛋白酶（MMPs）是一组依赖金属离子作为辅助因子催化降解细胞外基质（ECM）的酶群。基质金属蛋白酶-12（MMP-12）是基质金属蛋白酶家族成员，可降解细胞外基质蛋白，并在动脉粥样硬化中有关键作用。研究显示，*MMP-12* mRNA高表达可以促进巨噬细胞侵袭[7]和血管新生[8]，并在斑块中活性增强[9]。*MMP-12*基因多态性对脑卒中的作用可能通过脂质代谢、遗传因素、环境因素或炎症反应机制介导。*MMP-12*基因除降解细胞外基质外，还可通过激活肿瘤坏死因子-α（TNF-α）或调节促炎性因子如单核细胞趋化蛋白-1（MCP-1），促使巨噬细胞募集至血管壁[10]。Traylor等[11]进行全基因组相关性研究（GWAS）发现，*MMP-12*基因在颈动脉斑块中呈明显过表达，*MMP-12*基因rs660599多态性与LAA型缺血性卒中有关，这种易感基因增加早发性缺血性卒中发病风险[12]。基于转基因兔模型的动物实验证实，*MMP-12*基因可以促进动脉粥样硬化的发生，刺激脂肪条纹形成至纤维斑块的进展[13]。Johnson等[14]予*ApoE*基因敲除小鼠模型选择性MMP-12抑制剂RXP470.1，结果显示，RXP470.1可以延缓动脉粥样硬化进展，究其原因，RXP470.1通过增加平滑肌细胞/巨噬细胞比例，减少巨噬细胞凋亡，增加纤维帽厚度，减少坏死核心，降低钙化，从而增加斑块稳定性。*MMP-12*基因表达变化与颈动脉斑块进展、破裂[15]和晚期发育有关[16]，其转录水平影响颈动脉斑块稳定性。基于中国汉族人群的研究显示，*MMP-12*基因可能并非颈动脉斑块的危险因素[17]。

三、*HDAC9*基因

组蛋白去乙酰化酶9（HDAC9）是对染色体结构修饰和基因表达调控发挥重要作用的蛋白质。*HDAC9*基因定位于染色体7p21.1，表达于动脉内膜和平滑肌细胞、颅内血管、颈动脉和冠状动脉等。研究显示，*HDAC9*基因可以导致血管内皮细胞损伤，是将脑损伤与表观遗传修饰相关联的信号转导通路的关键组成部分之一[18]。HDAC9蛋白可以抑制肌细胞生成，参与心脏发育，通过改变脑组织缺血性反应增加脑卒中发病风险，并对神经元存活有影响。*HDAC9*基因敲除可以导致脂质平衡基因增加、炎症基因减少，巨噬细胞在ATP结合盒转运子A1（*ABCA1*）、ATP结合盒转运子G1（*ABCG1*）和过氧化物酶增殖物激活受体γ（*PPARγ*）基因启动子处通过H3和H3K9乙酰化，组蛋白聚集，促进巨噬细胞向M2型转化。*HDAC9*基因表达上调可抑制胆固醇外排和活化巨噬细胞产生，促进动脉粥样硬化[19]。2012年，英国和德国等欧洲国家进行的一项全基因组相关性研究确定*HDAC9*基因与LAA型缺血性卒中的关系，此后多项国际多中心全基因组相关性研究均证实*HDAC9*基因多态性与LAA型缺血性卒中相关[20-22]。Markus等[23]发现，*HDAC9*基因rs11984041和rs2107595多态性与无症状性颈动脉斑块和颈动脉内-中膜厚度增加相关，*HDAC9* mRNA在颈动脉斑块中表达上调，这与加速动脉粥样硬化进展机制相一致，而少见于其他动脉，可能是通过加快斑块进展、促进斑块不稳定，增加缺血性卒中发病风险。研究业已证实*HDAC9*基因是心肌梗死、冠心病的主要风险基因[24-25]。故推测*HDAC9*基因靶向抑制剂有可能预防动脉粥样硬化，成为LAA型

缺血性卒中的有效治疗药物[19,24]。*HDAC9*基因rs2107595多态性与欧洲人群LAA型缺血性卒中相关，但中国南方汉族人群脑卒中与rs2107595多态性无关联性，而与血清总胆固醇和甘油三酯（TG）相关，可能是由于rs2107595位点的等位基因频率不同造成欧洲和中国人群脑卒中风险差异[26]。第二军医大学附属长海医院共纳入279例脑卒中患者和984例正常对照者，基因检测显示，LAA型缺血性卒中与*HDAC9*基因rs11984041多态性无关联性，而与rs2389995和rs2240419多态性相关[27]。

四、*NINJ2*基因

神经损伤诱导蛋白2（NINJ2）系由142个氨基酸组成、*NINJ2*基因编码的黏附分子，在神经系统发育、分化、再生过程中调节细胞之间或细胞与基质之间的相互作用。*NINJ2*基因是脑损伤修复相关基因，是脑卒中相关单核苷酸多态性（SNP）基因，其产物是神经损伤诱导蛋白，于神经损伤后呈高表达，参与神经修复和再生，表达于成熟感觉神经元，促进神经轴突增生，使受损神经远端施万细胞数目增加[28]。*NINJ2*基因表达变化影响脑组织对缺氧缺血的耐受[29]。*NINJ2*基因启动子（rs3809263 G > A）单核苷酸多态性是功能性的，是LAA型缺血性卒中的生物学标志物[30]。Ikram等[29]的全基因组相关性研究显示，临近*NINJ2*基因染色体12p13区的rs11833579和rs12425791多态性与白种人脑卒中相关，特别是增加LAA型缺血性卒中的发病风险。王锋等[31]对128例LAA型缺血性卒中患者和112例正常对照者进行基因检测，结果显示，*NINJ2*基因rs11833579位点隐性模型（*AA*/*AG*基因型）与LAA型缺血性卒中密切相关，且在后循环动脉粥样硬化中的频率显著高于其他基因型，提示*NINJ2*基因多态性可能与动脉粥样硬化的责任血管有关，而且不同血管发生动脉粥样硬化的概率可能与遗传因素密切相关。基于中国人群的研究显示，*NINJ2*基因染色体12p13区rs11833579和rs12425791多态性与LAA型缺血性卒中密切相关[31-33]，且rs12425791位点*A*等位基因增加脑卒中发病风险[34-35]；亦有少数研究结果显示，rs11833579多态性与脑卒中无关联性[28,36]；在非洲裔美国人群和巴基斯坦人群中，*NINJ2*基因染色体12p13区rs11833579和rs12425791多态性与缺血性卒中无关联性[37]。

五、*CXCL16*基因

CXC型趋化因子配体16（*CXCL16*）基因定位于染色体17p13区，包含5个外显子。CXCL16蛋白是集趋化因子、黏附分子、清道夫受体为一体的免疫因子，与其受体共同表达于血管平滑肌细胞，在诱导大动脉平滑肌细胞增殖、细胞间粘附、脂质累积和基质降解中发挥重要作用[38]。研究显示，*CXCL16*基因通过促动脉粥样硬化因子、干扰素-γ（IFN-γ）以及炎症反应等促进斑块形成[39]和斑块不稳定[40]。*CXCL16* mRNA表达于培养的动脉内皮细胞[41]，不仅可以活化血小板，而且可以促进CXCL16蛋白成为有效的新型血小板黏附配体，诱导血小板粘附至血管壁[42]。Wang等[43]对244例LAA型缺血性卒中患者、153例存在动脉粥样硬化危险因素但未发生脑卒中的患者和167例正常对照者进行聚合酶链反应-限制性片段长度多态性（PCR-RFLP），结果显示，LAA型缺血性卒中患者CXCL16蛋白水平明显升高，而3组患者*CXCL16* p.Ala181Val基因型分布以及等位基因频率差异无统计学意义。刘丹等[44]的研究显示，LAA型缺血性卒中患者*CXCL16* p.Ala181Val的*AA*基因型分布和*A*等位基因频率明显高于正常对照者，多因素Logistic回归分析显示，*AA*基因型是缺血性卒中的独立危险因素，表明*CXCL16* p.Ala181Val多态性与LAA型缺血性卒中遗传易感性相关，*A*等位基因是LAA型缺血性卒中的遗传易感基因之一。亦有研究显示，血清CXCL16蛋白水平与LAA型缺血性卒中和颈动脉粥样硬化相关[43,45]，测定CXCL16蛋白水平不仅有助于识别LAA型缺血性卒中高危患者，且与急性缺血性卒中不良预后相关[38,40]。*CXCL16*基因参与和促进动脉粥样硬化形成和进展，与动脉粥样硬化性疾病如冠心病、颈动脉粥样硬化、脑卒中等的发病密切相关。

六、其他

染色体9p21.3区与LAA型缺血性卒中相关的主要单核苷酸多态性长度约100×10^3 bp，该片段与INK4位点反义非编码RNA（ANRIL）的外显子18～24部分重叠[46]。*ANRIL*基因表达于人类动脉粥样硬化血管和颈动脉内膜，亦表达于血管内皮细胞、单核细胞起源的巨噬细胞以及冠状动脉平滑肌细胞[46]，在动脉粥样硬化中发挥一定作用。染色体9p21.3区的遗传片段不仅与甲硫腺苷磷酸（*MTAP*）基因剪接变体外显子5进一步重叠，而且临近细胞周期蛋白依赖性激酶抑制基因2A/B（CDKN2A/B，分别表达*p16INK4A*和*p15INK4B*基因），上述基因在细

胞增殖、衰老和凋亡中发挥重要作用。相关研究显示，*ANRIL*、*p16INK4A*、*p15INK4B*、染色体9p21.3区共同协调转录[49]。2012年，METASTROKE协作组对多个全基因组相关性研究进行Meta分析，证实染色体9p21.3区与LAA型缺血性卒中相关（$r=1.150$，$P<0.001$）[21]；近年的多项研究均证实二者具有相关性[49-50]。染色体9p21区rs2383206和rs4977574多态性与中国汉族人群颈动脉斑块潜在相关[51]，rs10757278多态性与女性颈动脉斑块呈正相关（$r=2.420$，$P=0.013$）[52]，rs1333035多态性可能与斑块破裂和血栓形成相关[53]。Musunuru等[54]发现，染色体9p21.3区与血小板聚集明显相关（$P<0.001$），推测染色体9p21.3区可能通过调节血小板活性而增加斑块破裂和血栓形成风险，从而导致本身已存在动脉粥样硬化的人群发生LAA型缺血性卒中。未来尚待进一步确定LAA型缺血性卒中与染色体9p21.3区之间的联系是否通过上述基因或其他可能途径进行远距离调节[46]。尽管目前业已证实染色体9p21.3区是冠状动脉疾病和心肌梗死的主要风险基因，但该基因和脑卒中的关系不依赖冠状动脉疾病、心肌梗死或者其他血管危险因素而独立发挥作用[25]。

综上所述，脑卒中是多基因、多因素互相作用疾病。目前与其发病相关的基因研究大部分针对单基因，且国内外报道多不尽一致，究其原因，主要有以下几方面：（1）种族和人群差异。（2）大部分临床研究样本量较小，统计学说服力参差不齐。（3）对多基因遗传性疾病，单一基因作用较小，易受其他基因和环境的影响。（4）不同的入组标准存在选择偏倚。因此，为准确筛选LAA型缺血性卒中候选基因，尚待更大样本量，同时开展遗传流行病学和分子流行病学调查，以及综合考虑多种因素。通过脑卒中易感基因研究，使临床医师可以从遗传学角度筛查脑卒中高危人群，早期预防疾病发生；也可以从遗传学角度对脑卒中进行病因分型，针对不同患者的个体化治疗将是未来脑卒中基因研究的重点。

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