·专题综述·

基因检测在脑血管病精准医疗中的应用

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【摘要】 精准医疗是以个体化医疗为基础、随着基因检测技术快速进步以及生物学信息和大数据科学交叉应用而发展起来的新型医学概念与医疗模式。基因检测技术是精准医疗的基础。脑血管病是遗传因素和环境因素相互作用的多因素疾病，其中遗传因素发挥重要作用。本文拟从单基因遗传病、基因多态性、药物遗传学研究和精准治疗等方面阐述基因检测在脑血管病精准医疗中的应用。

【关键词】 脑血管障碍；　基因；　综述

Application of gene detection in precision medicine of cerebrovascular disease

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【Abstract】 Precision medicine (PM), a new type of medical concept and model which based on personalized medicine, is developed with the fast progress of genetic detection technology and the cross-application of biological information and large data science. Genetic detection technology is the basis of PM. Cerebrovascular disease is a multifactorial disease, in which genetic factors play an important role in the pathogenesis. This paper intends to discuss the application of gene detection technology in the PM of cerebrovascular disease, including single gene genetic disease, genetic polymorphism, drug genetics research and precision treatment.

【Key words】 Cerebrovascular disorders;　Genes;　Review

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精准医疗（PM）是以个体化医疗为基础，随着基因检测技术迅速进步以及生物学信息和大数据科学交叉应用而发展起来的新型医学概念与医疗模式。精准医疗采用现代遗传技术、分子影像学技术、生物学信息技术，结合患者生活环境和临床数据，实现精准疾病分类与诊断，制定个体化预防、诊断与治疗方案，包括精确预测风险、精确诊断与分类、精确用药、精确评价疗效、精确预测预后等。美国“精准医疗计划”已经明确首期任务是完成数百万个体的基因组测序。因此，基因检测技术作为采集患者信息和精准诊断与治疗的依据，是精准医疗的支撑基础。

《全国第三次死因回顾抽样调查报告》显示，脑血管病已经跃升至我国疾病死因的首位[1]。急性脑血管病是单病种病残率最高的疾病，其高发病率、高病残率和高病死率给社会、家庭和患者带来沉重负担和巨大痛苦。脑血管病是遗传因素和环境因素等相互作用的多因素疾病，遗传因素起重要作用。本文拟从单基因遗传病、基因多态性、药物遗传学研究、精准治疗等方面介绍基因检测在脑血管病精准医疗中的应用。

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表1 单基因遗传性脑血管病[3-5]

Table 1. Monogenic hereditary cerebrovascular disease[3-5]

Syndrome	Gene	Locus	Inheritance	Symptoms	Vascular pathology
CADASIL	*NOTCH3*	19p13.1	AD	Migraine, cognitive problems, depression, seizures, stroke	Small-vessel vasculopathy
CARASIL	*HTRA1*	10q	AR	Spasticity, stroke, cognitive problems, scalp hair loss, back pain	
MELAS	*MTTL1*	mtDNA	Maternal	Muscle weakness, headache episodes, seizures, stroke-like episodes	
Hereditary endotheliopathy with retinopathy, nephropathy and stroke	*TREX1*	3p21.31	AD	Visual loss, cognitive problems, stroke-like episodes, renal dysfunction	
COL4A1-related brain small vessel disease	*COL4A1*	13q34	AD	Epilepsy, loss of vision, dystonia, stroke, migraine, mental disorders and Alzheimer's disease	
Moyamoya disease type 1 Moyamoya disease type 2 Moyamoya disease type 3 Moyamoya disease type 4 Moyamoya disease type 5	— *RNF213* — *BRCA1/2* *MTCP1/MTCP1NB* *ACTA2*	3p24.2–p26 17q25.3 8q23 Xq28 Xq28 10q23.31	AD? AD? AD? XR AD	Progressive, occlusive, cerebrovascular arteriopathy, bilateral progressive stenosis of the distal internal carotid arteries, with particular involvement of the circle of Willis	Large-artery vasculopathy
Fabry's disease	*GLA*	Xq22	XR	Episodes of pain in hands and feet, angiokeratomas, corneal opacity, renal affection, heart affection, stroke	Small and large artery vasculopathy
Marfan's syndrome type 1 and 2	*FBN1* *TGFBR2*	15q21.1–3p24.1	AD	Tall build, long arms, legs, scoliosis, flat feet, fatigue, shortness of breath, heart palpitations, chest pain, partial lens dislocation, spontaneous pneumothorax	Arterial dissection
Ehlers-Danlos syndrome type Ⅳ	*COL3A1*	2q31	AD	Arterial rupture, intestinal rupture, skin irritation, carotid cavernous fistula, intracranial aneurysm, arterial dissection	
Pseudoxanthoma elasticum	*ABCC6*	16p13.1	AD/AR	Papules, loss of vision, high blood pressure	
Hereditary cerebral hemorrhage with amyloidosis of the Dutch type	*APP*	21q21.3	AD	Lobar intracerebral hemorrhage, cerebral microbleeds, cognitive problems	Inherited CAA
Cystatin C-related familial CAA	*CST3*	20p11.21	AD	Intracerebral hemorrhage, stroke and dementia	
Transthyretin-related CAA	*TTR*	18q12.1	AD	Pain, paresthesia, muscular weakness, autonomic dysfunction, sensory and motor polyneuropathy	
Polycystic kidney disease adult type 1 and 2	*PDK1* *PDK2*	16p13.3–4q22.1	AD	Pain in the abdomen, side or lower backhematuria, hypertension, kidney stones recurrent urinary tract infections, loss of kidney function	Cerebrovascular malformations
Cerebral cavernous malformations	*KRIT1* *C7orf22* *PDCD10*	7q21–q22, 7p13–p15, 3q25.2–q27	AD	Some are silent, others cause seizures, hemorrhage or focal neurologic deficit	
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendud disease)	*ENG* *ACVRL1*	9q34.1, 12q11–q14	AD	Telangiactasia, arteriovenous malformations in lungs, brain, liver, intestines, intracerebral hemorrhage, ischemic stroke	
Sickle cell disease	*β-Hemoglobin*	11p15.4	AR	Chronic hemolytic anemia, embolism, erythrocyte sickle change, pain crisis, susceptible to infection	Small and large vascular disease, blood dysfunction
Homocystinuria	*Cystathionine β-Synthase*	21q22.3	AR	Mental retardation, lens ectopic, skeletal malformations, seizures, thrombotic diseases	Small and large vascular disease, cardiac embolism, arterial dissection
Neurofibromatosis type 1	*NF1*	17q11.2	AD	Skin fibroma, lisch nodules, iris hamartoma, glioma, skeletal dysplasia, etc.	Narrow, closed plug, aneurysm, mezzanine, arteriovenous malformations

—，unknown，未知。CADASIL，cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy，常染色体显性遗传性脑动脉病伴皮质下脑梗死和白质脑病；CARASIL，cerebral autosomal recessive arteriopathy with subcortical infarts and leukoencephalopathy，常染色体隐性遗传性脑动脉病伴皮质下脑梗死和白质脑病；MELAS，mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes，线粒体脑肌病伴乳酸血症和卒中样发作；CAA，cerebral amyloid angiopathy，淀粉样脑血管病；AD，autosomal dominant，常染色体显性遗传；AR，autosomal recessive，常染色体隐性遗传；AD?，suspicious AD，可疑常染色体显性遗传；XR，X-linked recessive，X连锁隐性遗传

一、脑血管病相关单基因遗传病

相关研究显示，有30%～40%青年缺血性卒中患者无明确危险因素，其中一部分由单基因遗传病所致[2]。目前已发现多种单基因遗传病可以导致脑血管病（表1）[3-5]。对病因不明或某些特殊类型脑血管病，应行基因检测以明确是否为单基因遗传性脑血管病及其分型，从而制定个体化治疗方案。

二、基因多态性与脑血管病

从遗传因素角度看，绝大多数脑血管病为多基因遗传病，与基因多态性密切相关。如果将脑血管

病遗传因素视为内因，高血压、高脂血症、糖尿病、高同型半胱氨酸血症和血液成分异常等因素即为外因，外因通过内因发挥作用而诱发脑血管病[6]。因此，我们可以从遗传因素角度筛选可能的脑血管病高危人群，通过基因多态性分析，提示何种基因型个体更易发生脑血管病。如果对这些高危人群进行重点预防和早期抗高血压、调脂、控制血糖等治疗，可以有效降低脑血管病发病率。

1. 肾素-血管紧张素基因多态性 （1）血管紧张素转换酶（*ACE*）基因多态性：编码血管紧张素转换酶的基因根据其第16内含子是否存在长度287 bp的片段呈现插入（I）/缺失（D）多态性，即插入纯合子型（*II*型）、缺失纯合子型（*DD*型）和杂合子型（*ID*型）共3种基因型。*D*等位基因频率与缺血性脑血管病发病率呈正相关[7]，在亚洲人群中风险显著增加，增加中国南方人群缺血性卒中易感性，但在白种人中的统计学结果不可靠[8]。（2）血管紧张素原（*AGT*）基因多态性：*AGT*基因编码区由5个外显子和4个内含子组成，当位于第2外显子第704位核苷酸胸腺嘧啶（T）被胞嘧啶（C）替代（c.704T>C），则导致第235位氨基酸由蛋氨酸突变为苏氨酸（p.Met235Thr）。根据等位基因的不同，*AGT*基因分为*TT*型、*MT*型、*MM*型。*T*等位基因可能增加中国北方汉族人群缺血性卒中风险[9]。第174位氨基酸由苏氨酸突变为甲硫氨酸（p.Thr174Met）增加亚洲人群缺血性卒中风险[10]。

2. 载脂蛋白基因多态性 （1）载脂蛋白E（*ApoE*）基因多态性：*ApoE*基因有6种常见基因型，即纯合子型（*E2/2*型、*E3/3*型、*E4/4*型）和杂合子型（*E2/3*型、*E2/4*型、*E3/4*型），其中，*E2*和*E4*等位基因增加亚洲人群出血性脑血管病风险和中国北方汉族人群缺血性卒中风险，且增加高血压易感性[11-12]；*E4*等位基因增加缺血性卒中风险，故亚洲人群缺血性卒中发病率高于高加索人群[13-14]。（2）对氧磷酶（*PON*）基因多态性：对氧磷酶是一种催化水解磷酸酯键的芳香酯酶，由355个氨基酸组成。在*PON1* Gln192Arg多态性中，*R*等位基因增加缺血性卒中风险[15]，尤其增加高加索人群缺血性卒中易感性[16]。*PON1* c.575A>G多态性和*PON1* c.163T>A多态性可能与缺血性卒中风险增加有关[17]。

3. β-纤维蛋白原基因多态性 纤维蛋白原（fibrinogen）是由α，β和γ共3对多肽链组成的糖蛋白，其中β链的合成是整个分子合成的限速步骤。研究显示，*β-fibrinogen*基因突变是导致个体间血浆纤维蛋白原水平差异的重要遗传因素，与脑血管病密切相关。目前已发现β链基因簇存在10个多态性位点。2014年的一项Meta分析显示，*β-fibrinogen* c.455G>T多态性是缺血性卒中的易感因素[18]。2015年的一项关于中国人缺血性卒中的Meta分析显示，*β-fibrinogen* c.148C>T和c.-854G>A多态性可能增加缺血性卒中易感性[19-20]。

4. 同型半胱氨酸相关基因多态性 N5,10-亚甲基四氢叶酸还原酶（MTHFR）主要作用是在叶酸代谢通路中将MTHFR转化为具有生物学功能的5-甲基四氢叶酸。*MTHFR*基因包含12个外显子，编码656个氨基酸残基组成的蛋白质。*MTHFR* c.1298A>C多态性增加缺血性卒中风险，*C*等位基因是缺血性卒中重要危险因素[21]，增加亚洲成年人群脑血管病风险[22]。*MTHFR* c.677C>T多态性增加缺血性卒中风险[23]，亦增加儿童缺血性卒中易感性[24]。*T*等位基因是中国人群缺血性卒中的另一危险因素[25]。胱硫醚β-合成酶（CBS）是同型半胱氨酸代谢关键酶，*CBS* c.833T>C多态性与脑卒中风险增加有关[26]。

5. 纤溶酶原激活物抑制物基因多态性 纤溶酶原激活物抑制物-1（PAI-1）是纤溶酶原系统主要调节因子，与纤溶酶原激活物结合后迅速失活而发挥抗纤溶作用。PAI-1是一种单糖蛋白，包含9个外显子和8个内含子，编码379个氨基酸。2014年的一项Meta分析显示，中国人群*PAI-1 4G/4G*基因型可能是缺血性卒中的危险因素[27]。亦有研究显示，*PAI-1*基因多态性与脑血管病无关联性[28]。

6. 凝血因子和血小板膜糖蛋白基因多态性 凝血因子Ⅴ（FⅤ）*Leiden*基因突变与静脉血栓风险增加有关，但并未增加青年人群缺血性卒中风险[29]。*F*Ⅶ c.807C>T多态性可能增加心房颤动患者脑卒中风险[30]。既往研究显示，*F*Ⅻ基因多态性与脑血管病有关[31]，但最新的Meta分析显示二者无明显关联性，而增加白种人脑出血风险[32]。血小板膜糖蛋白Ⅲa基因第33位氨基酸突变为脯氨酸是心源性和大血管源性缺血性卒中的危险因素[33]。血小板膜糖蛋白Ⅰa c.807C>T多态性[34]和Ⅰb p.Met145Thr多态性和*Koxak* c.-5T>C多态性与缺血性脑血管病相关[32,35]。

7. 内皮型一氧化氮合酶基因多态性 内皮型一氧化氮合酶（eNOS）催化合成的一氧化氮可以通过

对血小板聚集、白细胞黏附、平滑肌细胞增殖和迁移的抑制效应发挥保护作用。*eNOS*基因包含26个外显子和25个内含子，编码1203个氨基酸，基因型主要有：(1)第7外显子c.894G>T突变，导致其编码的第298位氨基酸由谷氨酸突变为天冬氨酸。(2)第4内含子的27个碱基重复序列不一致，重复4次者为*A*等位基因，重复5次者为*B*等位基因。(3)启动子区c.-786T>C突变。2017年的一项Meta分析显示，缺血性卒中与*eNOS* c.894G>T突变和*4b/a*基因多态性相关，而与c.-786T>C突变无显著关联性[36]。亦有研究显示，c.-786T>C突变与亚洲人群缺血性卒中有关[37-38]，而*4b/a*基因多态性与高加索人群缺血性卒中无关联性[39]。

8. 炎症反应相关基因多态性 (1)白细胞介素(IL)：2016年的一项Meta分析显示，*IL-6* c.174G>C和c.572G>C突变并未增加缺血性和出血性卒中易感性[40-41]。*IL-10* c.-1082A>G突变增加亚洲人群缺血性卒中易感性[42]，亦增加大血管病变和小血管病变易感性[22]。肿瘤坏死因子-α(*TNF-α*)c.-238G>A突变与亚洲人群缺血性脑血管病风险增加有关，而c.-308G>A突变与其无关联性[43-44]。亦有相关研究显示，*TNF-α* c.-308G>A突变与青年缺血性卒中相关[45]。E-选择素(E-slection)是黏附分子选择素家族成员之一，在炎症反应、动脉粥样硬化致血栓形成过程中发挥重要作用。*E-slection*基因包含14个外显子和13个内含子，*AC*基因型较*AA*基因型的缺血性卒中易感性更高[46]，c.561A>C突变增加汉族人群缺血性卒中易感性[47]。(2)磷酸二酯酶4D(PDE4D)：主要作用是降解cAMP，而cAMP水平降低可以引起血管平滑肌细胞增殖和迁移，局部炎症反应加剧，促进动脉粥样硬化形成和斑块不稳定性增加，*PDE4D* c.83T>C多态性与中国人群缺血性卒中易感性相关[48]。(3)转化生长因子β1(TGF-β1)：系一种多效细胞因子，在缺血性脑血管病中具有抗炎症反应作用。*TGF-β1* -c.509C>T多态性与转化生长因子β1表达变化相关，*T*等位基因增加转化生长因子β1总蛋白和活性蛋白水平；编码区第10位氨基酸密码子发生c.869T>C突变，使亮氨酸突变为脯氨酸，从而升高转化生长因子β1表达水平。然而Meta分析显示，目前尚无法得出c.869T>C多态性和c.509C>T多态性与缺血性卒中易感性相关的结论[49-50]。(4)脂联素(APN)：系脂肪细胞分泌的细胞因子，干预机体糖和脂肪代谢途径，具有明确的抗炎症反应和抗动脉粥样硬化作用。包含3个外显子和2个内含子，c.45T>G多态性与北方汉族人群缺血性卒中易感性相关，*GG*基因型是北方汉族女性人群缺血性卒中的危险因素[51]。

9. 其他 研究显示，淋巴毒素α(*LTα*)c.-252G>A突变增加高加索人群缺血性卒中易感性[52]，雌激素受体α(*ERα*)c.454-397T>C突变[53]、β2肾上腺素受体(*β2AR*)Gln27Glu多态性与缺血性卒中风险增加有关[54]。

三、脑血管病药物遗传学研究

脑血管病预防药物相关基因突变可能影响药代动力学和药效学，并增加不良事件风险。药物遗传学是脑血管病的重要研究领域。

1. 重组组织型纤溶酶原激活物静脉溶栓治疗 一项纳入497例缺血性卒中患者的重组组织型纤溶酶原激活物(rt-PA)静脉溶栓研究结果显示，*IL-1β*和血管性血友病因子(*vWF*)基因突变均与早期血管再通有关，*vWF*基因突变也与凝血因子Ⅷ(FⅧ)活性相关[55]。α2巨球蛋白(*α2M*)c.669A>G多态性与rt-PA治疗后出血性转化有关[56]。上述研究均表明遗传学信息可能在未来用于预测缺血性卒中rt-PA治疗反应，从而有助于rt-PA静脉溶栓或替代疗法如血管内治疗的决策。

2. 华法林或达比加群抗凝治疗 编码细胞色素P-450酶的*CYP2C9*基因突变影响华法林代谢，编码维生素K环氧化物还原酶的*VKORC1*基因突变影响华法林敏感性[57]。对2944例长期华法林抗凝治疗的患者进行全基因组相关性研究(GWAS)显示，羧酸酯酶1(CES1)次要等位基因与较低活性的达比加群代谢物水平相关，亦与达比加群治疗后低出血风险相关[58]。

3. 抗血小板药治疗 抗血小板药的临床应用存在显著个体差异。有5%~40%的缺血性卒中患者对阿司匹林治疗无反应，4%~30%患者氯吡格雷疗效欠佳[59]。存在阿司匹林抵抗的患者常合并氯吡格雷抵抗。因此，了解基因型并选择适宜药物，可以决定治疗效果。参与阿司匹林作用机制的各种基因发生遗传变异性，可以导致活性药物浓度差异，影响药物疗效。研究显示，环氧合酶-1(*COX-1*)-1676A>G突变[60]和*COX-2* -765G>C突变[61]均与阿司匹林抵抗相关。

4. 他汀类调脂药治疗 他汀类调脂药治疗过程中，低密度脂蛋白胆固醇(LDL-D)每降低1 mmol/L，

脑卒中相对风险降低约20%[62]。肌肉病是他汀类调脂药罕见且严重的并发症,剂量增加或与某些药物同时应用时风险增加。*SLCO1B1*基因突变使他汀类调脂药导致肌肉病的相对风险增加[63]。

5.戒烟 某些基因型与吸烟起止时间、数量和治疗反应相关。某些基因涉及多巴胺再摄取和代谢,与吸烟成瘾性相关或与尼古丁代谢相关[64]。

四、精准医疗中应注意的问题

基因检测有助于检出更多的单基因遗传性脑血管病,有助于发现脑血管病基因多态性易感位点,有助于在脑血管病危险因素出现前更早地预测脑血管病发生和发展机制,药物代谢相关基因单核苷酸多态性(SNP)研究有助于检测脑血管病药物治疗效果,从而提高脑血管病个体化预防、诊断与治疗水平。然而,基因检测仅是实现精准医疗的一种技术支持,要全面实现精准医疗还应注意以下问题:(1)基因检测的临床效度随基因型的不同而异,这些不同基因型的改变可能对致疾病风险有不同的含义,其中一些变异可能有证据支持是明确的致病性突变,一些可能是无义突变,在人群数据库中有超过5%的存在,另一些可能是临床意义不明的突变。基因型与临床表型关系的复杂性影响基因检测的临床效度。对于何种疾病患者应行何种基因检测,最重要的考虑是对检测结果呈阳性的患者能否进行有效干预。(2)随着高通量基因检测设备的广泛应用,近年来检测成本降低,基因数据量呈倍数增加。精准医疗的发展需建立高效、便捷的数据处理和共享系统,还应建立标准化、可重复和可追踪的数据流。(3)目前的高通量基因检测技术可以数字或字母序列形式快捷、准确地提供基因信息,但如何解读基因检测结果仍是绝大多数临床医师的难题。基因检测从人工测序转为数据分析,使很多医师难以处理大规模数据,不能准确探寻基因与疾病、药物选择、患者之间关系。

因此,基因检测只有与生物学信息和临床表型相结合,才能被理解和正确使用。目前由于数据科学到生物学信息和医学的脱节,使得如何解读基因检测结果成为下一步工作的关键[65]。

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·小词典·

中英文对照名词词汇(四)

血小板源性生长因子受体
platelet-derived growth factor receptor(PDGFR)

N5,10-亚甲基四氢叶酸还原酶
N5, 10-methylene tetrahydrofolate reductase(MTHFR)

遗传性痉挛性截瘫 hereditary spastic paraplegia(HSP)

遗传性运动感觉神经病
hereditary motor and sensory neuropathy(HMSN)

乙二胺四乙酸 ethylenediaminetetraacetic acid(EDTA)

乙酰肉碱 acetylcarnitine(C2)

婴儿神经轴索营养不良
infantile neuroaxonal dystrophy(INAD)

荧光原位杂交 fluorescence in situ hybridization(FISH)

原发性家族性脑钙化
primary familial brain calcification(PFBC)

运动神经元病 motor neuron disease(MND)

在线人类孟德尔遗传数据库
Online Mendelian Inheritance in Man(OMIM)

整合素样金属蛋白酶与凝血酶6型
disintegrin and metalloproteinase with thrombospondin motif-6(ADAMTS6)

正常血钾型周期性麻痹
normokalemic periodic paralysis(NormPP)

症状自评量表 Symptom Check List-90(SCL-90)

肢带型肌营养不良症
limb-girdle muscular dystrophy(LGMD)

脂肪酸羟化酶相关性神经变性病
fatty acid hydroxylase-associated neurodegeneration(FAHN)

植入型心律转复除颤器
implantable cardioverter defibrillator(ICD)

中文人类表型标准用语
China Human Phenotype Ontology(CHPO)

周期性麻痹 periodic paralysis(PP)

Andersen-Tawil综合征 Andersen-Tawil syndrome(ATS)

Woodhouse-Sakati综合征
Woodhouse-Sakati syndrome(WSS)