国际遗传学杂志 2006 29 (05): 325-335 ISSN: 1673-4386 CN: 23-1536/R

论著

beta-纤维蛋白原基因启动子区单体型与缺血性脑卒中的关联分析

邢宏运; 廖小平; 肖锋1;梁亮;孙川;黄仕雄;陈晓丹;文国强;汤小兰;刘国勋;程爽;蔡望伟

1.海南医学院生物化学教研室
2.广东医学院附属医院血液研究室
3.海南省人民医院神经内科
4.海南医学院附属医院检验科
5.海南医学院流行病学教研室
6.海南医学院分子生物学实验室
7.泸州医学院附属医院血液内科

收稿日期 修回日期 网络版发布日期:

摘 要 目的 研究b -纤维蛋白原（b -Fg）基因启动子区单体型与缺血性脑卒中的关系。方法 用比浊法测定160例缺血性脑卒中患者和130例健康对照个体的血浆纤维蛋白原浓度，采用聚合酶链反应-限制性片段长度多态性法（PCR-RFLP）、等位基因特异聚合酶链反应及核苷酸序列测定法分析b -Fg基因启动子区的－1420G/A、-993C/T、-854G/A、－455G/A、-249C/T、-148C/T单核苷酸多态性(SNPs)和基因型，用EH+程序分析核苷酸多态性的连锁不平衡关系及单体型，用卡方检验分析病例组和对照组之间的基因型频率、等位基因频率及单体型频率的差异，用MatInspector 程序预测序列中的顺式作用元件。结果 缺血性脑卒组中，-455(GA+AA)、-148(CT+TT)基因型携带者急性期的血浆 Fg水平比-455(GG)、-148(CC)基因型携带者高(P<0.05)；脑卒中组与对照组之间的-993C/T、－455G/A、-148C/T 三个位点的基因型频率和等位基因频率存在显著性差异（p< 0.01），由－1420G、-993C、-854G、－455G、-249C、-148C构成的单体型H1在对照组中的频率高于病例组（P<0.05），由－1420A、-993T、-854G、－455A、-249T、-148T构成的单体型H14在病例组中的频率高于对照组（P<0.01）；野生型序列存在6个不同于突变型的顺式作用元件，突变型序列出现9个不同于野生型的顺式作用元件。结论 海南汉族人群中-455G/A、-148C/T多态性与缺血性脑卒中急性期血浆Fg升高相关，单体型H14可能是与缺血性脑卒中相关的危险因素，单体型H1可能是降低缺血性脑卒中发生风险的保护性因素，单体型与缺血性脑卒中的相关性可能是由于顺式作用元件改变所致。

关键词 纤维蛋白原 单核苷酸多态性 缺血性脑卒中 连锁不平衡分析 单体型

分类号

Haplotypes in the promoter region of betab -fibrinogen gene and their relationship to ischemic stroke in Hainan Han population

XING Hongyun1,2;LIAO Xiaoping3;XIAO Feng1,2;LIANG Liang1,2;SUN Chuan1,2; HUANG Shixiong3;CHEN Xiaodan4;WEN Guoqiang3;TANG Xiaolan5; LIU Guoxun2;CHENG Shuang2; CAI Wangwei1,6

1.Department of Biochemistry, Hainan Medical College, Xueyuan Road No.2,Haikou, Hainan, P.R.China，571101
2. Laboratory of Hematology, Guangdong Medical College, People Avenue No.57,Xiashan, Zhanjiang, Guangdong, P.R.China,524001
3. Department of Neurology, The People Hospital of Hainan Province, Xiuhua Road No.19, Haikou, Hainan, P.R.China，570311
4. Clinical Laboratory, The Affiliated Hospital, Hainan Medical College, Longhua Road No.33, Haikou, Hainan, P.R.China, 570102.
5. Department of Epidemiology, Hainan Medical College, Xueyuan Road No.2, Haikou, Hainan, P.R.China,571101.
6. Laboratory of Molecular Biology, Hainan Medical College, Xueyuan Road No.2,Haikou, Hainan, P.R.China, 571101.
7. Department of Hematology, Luzhou Medical College, Taiping Road No.25, Luzhou, Sichuan, 64600.

- 文国强
- 汤小兰
- 刘国勋

Abstract Objective To analyze the haplotypes in promoter region of beta-fibrinogen gene and their relationship to with ischemic stroke(IS). Method Plasma fibrinogen level of the IS patient and control individuals was measured by turbidimetric assay in 160 cases with ischemic stroke and 130 healthy individuals from Hainan Han population. Genotypes were determined by PCR-RFLP, allelic specific-PCR and sequencing at polymorphisms -1420G/A、-993C/T、-854G/A、-455G/A、-249C/T、-148C/T in the promoter region of beta-fibrinogen gene. Pairwise linkage disequilibrium was calculated and haplotypes were estimated by the EH+ program. Statistical differences of allele, genotype and haplotype frequencies were obtained by Chi square test. Cis-elements were predicted by MatInspector program. Results In the IS group, the Fg level of plasma is higher in the patients with -455(GA+AA),-148(CT+TT) genotype than in the patients with -455GG, -148CC genotype($P<0.05$). There were highly significant differences in genotype frequencies and allelic frequencies at polymorphisms -993C/T、-455G/A、-148C/T between the IS group and control($P<0.01$). The frequency of haplotype H1 with -1420G、-993C、-854G、-455G、-249C and -148C were higher in the control than in the IS group ($P<0.05$), whereas haplotype H14 with 1420A、-993T、-854G、-455A、-249T and -148T were higher in the IS group than in the control($P<0.01$). Six cis-elements absent in the mutant sequences were found in the wild type sequence and nine cis-elements absent in the wild type sequences were found in the mutant sequence. Conclusion The results indicated that the elevation of Fg level was associated with -455(GA+AA),-148(CT+TT) genotype in the acute phase of IS. Haplotype H14 may be a risk factor associated with IS and haplotype H1 a protective factor in reducing the risk of ischemic stroke in Hainan Han population. The association of haplotype with IS may be due to the change of cis-elements in the promoter region.

Key words Fibrinogen Single nucleotide polymorphism Ischemic stroke Linkage disequilibrium Haplotype

DOI

通讯作者 蔡望伟 caiww@hainmc.edu.cn