中南大学学报(医学版) 2013, 38(12) 1208-1216 DOI: 10.3969/j.issn.1672-7347.2013.12.002 ISSN: 1672-7347 CN: 43-1427/R

论著

中国汉族人群BSG基因SNPs发掘与连锁不平衡分析

郑杰[1], 李慕鹏[2], 孙涛[1], 呼晓雷[2], 李元建[1], 陈小平[1,2]

1. 中南大学药学院药理学系, 长沙 410078;
2. 中南大学临床药理研究所, 长沙 410078

摘要:

目的：探讨健康中国汉族人群中basigin（BSG）基因的单核苷酸多态性（single nucleotide polymorphisms，SNPs）发生情况。方法：随机收集48例健康、无亲缘关系的中国汉族人外周血液并提取基因组DNA，设计引物对所有个体BSG基因的启动子区、外显子区和外显子内含子交界区的序列进行PCR扩增和正反向测序，通过判读测序峰图，明确SNPs的发生情况及其频率；通过Hardy-Weinberg平衡分析、单倍型推测和连锁不平衡分析，确定BSG基因位点的单倍型标签SNPs（haplotype tag SNPs，htSNPs）；中性理论检验查明该基因位点SNPs频率分布是否符合选择中性。结果：共发现19个SNPs，其中包括2个新发现的SNPs；所有SNPs位点基因型分布均符合Hardy-Weinberg平衡。该基因位点共推测出4种常见单倍型域，确定9个SNPs为htSNPs。中性理论检验结果提示健康中国汉族人群BSG基因的SNPs分布符合中性进化假说。结论：首次对中国健康汉族人群BSG基因的SNPs进行了发掘，确定了其9个单倍型标签SNPs，为在汉族人群中研究该基因的遗传多态性与疾病易感性或药物反应性个体差异奠定了基础。

关键词： BSG/CD147 单核苷酸多态性（SNPs） 单倍型标签SNPs（tagSNPs） 连锁不平衡（LD） 中国汉族人群

SNPs discovery and linkage disequilibrium analysis of BSG in Chinese Han population

ZHENG Jie[1], LI Mupeng[2], SUN Tao[1], HU Xiaolei[2], LI Yuanjian[1], CHEN Xiaoping[1,2]

1. Department of Pharmacology, School of Pharmaceutical Sciences, Central South University, Changsha 410078, China;
2. Institute of Clinical Pharmacology, Central South University, Changsha 410078, China

Abstract:

Objective: To identify BSG single nucleotide polymorphisms (SNPs) in Chinese Han population. Methods: Peripheral blood samples were collected from 48 unrelated healthy Chinese Han subjects. Sequences at the BSG locus, including the promoter region, all exons and exon-intron boundaries were amplified, sequenced and followed by Hardy-Weinberg equilibrium test and linkage disequilibrium (LD) analysis. Results: A total of 19 SNPs were identified, 2 of which two were novel. Genotype distributions of all SNPs were consistent with Hardy-Weinberg equilibrium. Four haplotype blocks were constructed throughout the gene locus, and 9 haplotype tag SNPs (htSNPs) were inferred. Distribution of SNPs was in accordance with the neutrality theory in Chinese Han population. Conclusion: For the first time, systematic identification of BSG SNPs in the Chinese Han population has been done, and 9 htSNPs are identified. Our study has provided basis for further genetic association studies for related diseases as well as pharmacogenetics study for drug response in Chinese Han population.

Keywords: Basigin (BSG/CD147) single nucleotide polymorphisms (SNPs) haplotype tag SNPs (htSNPs) linkage disequilibrium (LD) Chinese Han population

收稿日期 2013-09-23 修回日期 网络版发布日期

DOI: 10.3969/j.issn.1672-7347.2013.12.002

基金项目:

国家自然科学基金（81170091）；湖南省自然科学基金（13JJ1010）；湖南省科技项目（2020FJ3085）；中南大学研究基金（2011JQ016）。

通讯作者: 陈小平，Email: chenxp74@hotmail.com

作者简介: 郑杰，博士研究生，讲师，主要从事心血管药理学研究。

作者Email: chenxp74@hotmail.com

参考文献：

1. Miyauchi T, Masuzawa Y, Muramatsu T. The basigin group of the immunoglobulin superfamily: complete conservation of a segment in and around transmembrane domains of human and mouse basigin and chicken HT7 antigen [J] . J Biochem, 1991, 110(5): 770-774.

2. Kaname T, Miyauchi T, Kuwano A, et al. Mapping basigin (BSG), a member of the immunoglobulin superfamily, to 19p13.3 [J] . Cytogenet Cell Genet, 1993, 64(3/4): 195-197.

3. Biswas C, Zhang Y, DeCastro R, et al. The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily [J] . Cancer Res, 1995, 55(2): 434-439.

4. Kasinrerk W, Fiebiger E, Stefanova I, et al. Human leukocyte activation antigen M6, a member of the Ig superfamily, is the species homologue of rat OX-47, mouse basigin, and chicken HT7 molecule [J] . J Immunol, 1992, 149(3): 847-854.

5. Jiang JL, Zhou Q, Yu MK, et al. The involvement of HAb18G/CD147 in regulation of store-operated calcium entry and metastasis of human hepatoma cells [J] . J Biol Chem, 2001, 276(50): 46870-46877.

6. Seulberger H, Lottspeich F, Risau W. The inducible blood--brain barrier specific molecule HT7 is a novel immunoglobulin-like cell surface glycoprotein [J] . EMBO J, 1990, 9(7): 2151-2158.

7. Schlosshauer B, Herzog KH. Neurothelin: an inducible cell surface glycoprotein of blood-brain barrier-specific endothelial cells and distinct neurons [J] . J Cell Biol, 1990, 110(4): 1261-1274.

8. Fadool JM, Linser PJ. 5A11 antigen is a cell recognition molecule which is involved in neuronal-glial interactions in avian neural retina [J] . Dev Dyn, 1993, 196(4): 252-262.

9. Fossum S, Mallett S, Barclay AN. The MRC OX-47 antigen is a member of the immunoglobulin superfamily with an unusual transmembrane sequence [J] . Eur J Immunol, 1991, 21(3): 671-679.

10. Altruda F, Cervella P, Gaeta ML, et al. Cloning of cDNA for a novel mouse membrane glycoprotein (gp42): shared identity to histocompatibility antigens, immunoglobulins and neural-cell adhesion molecules [J] . Gene, 1989, 85(2): 445-451.

11. Nehme CL, Cesario MM, Myles DG, et al. Breaching the diffusion barrier that compartmentalizes the transmembrane glycoprotein CE9 to the posterior-tail plasma membrane domain of the rat spermatozoon [J] . J Cell Biol, 1993, 120(3):687-694.

12. Weidle UH, Scheuer W, Eggle D, et al. Cancer-related issues of CD147 [J] . Cancer Genomics Proteomics, 2010, 7(3):157-169.

13. Zhong WD, Liang YX, Lin SX, et al. Expression of CD147 is associated with prostate cancer progression [J] . Int J Cancer, 2012,130(2):300-308.

14. Kong LM, Liao CG, Chen L, et al. Promoter hypomethylation upregulates CD147 expression through increasing Sp1 binding and associates with poor prognosis in human hepatocellular carcinoma [J] . J Cell Mol Med, 2011, 15(6):1415-1428.

15. Igakura T, Kadomatsu K, Taguchi O, et al. Roles of basigin, a member of the immunoglobulin superfamily, in behavior as to an irritating odor, lymphocyte response, and blood-brain barrier [J] . Biochem Biophys Res Commun, 1996, 224(1):33-36.

16. Ochrietor JD, Moroz TP, Clamp MF, et al. Inactivation of the Basigin gene impairs normal retinal development and maturation [J] . Vision Res, 2002, 42(4):447-453.

17. Saxena DK, Oh-Oka T, Kadomatsu K, et al. Behaviour of a sperm surface transmembrane glycoprotein basigin during epididymal maturation and its role in fertilization in mice [J] . Reproduction,2002, 123(3): 435-444.

18. Igakura T, Kadomatsu K, Kaname T, et al. A null mutation in basigin, an immunoglobulin superfamily member, indicates its important roles in peri-implantation development and spermatogenesis [J] . Dev Biol,1998, 194(2): 152-165.

19. Pushkarsky T, Zybarth G, Dubrovsky L, et al. CD147 facilitates HIV-1 infection by interacting with virus-associated cyclophilin A [J] . Proc Natl Acad Sci USA, 2001, 98(11): 6360-6365.

20. Muramatsu T, Miyauchi T. Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion [J] . Histol Histopathol, 2003,18(3): 981-987.

21. Gabison EE, Hoang-Xuan T, Mauviel A, et al. EMMPRIN/CD147, an MMP modulator in cancer, development and tissue repair [J] . Biochimie, 2005, 87(3/4): 361-368.

22. Schmidt R, Bultmann A, Ungerer M, et al. Extracellular matrix metalloproteinase inducer regulates matrix metalloproteinase activity in cardiovascular cells: implications in acute myocardial infarction [J] . Circulation, 2006, 113(6): 834-841.

23. Levick SP, Brower GL. Regulation of matrix metalloproteinases is at the heart of myocardial remodeling [J] . Am J Physiol Heart Circ Physiol, 2008, 295(4): H1375-H1376.

24. Yong A, Pennings G, Wong C, et al. Intracoronary upregulation of platelet extracellular matrix metalloproteinase inducer (CD147) in coronary disease [J] . Int J Cardiol, 2013, 166(3): 716-721.

25. Zhu W, Khachi S, Hao Q, et al. Upregulation of EMMPRIN after permanent focal cerebral ischemia [J] . Neurochem Int, 2008, 52(6):1086-1091.

26. Hu Z, Wu C, Shi Y, et al. A genome-wide association study identifies two new lung cancer susceptibility loci at 13q12.12 and 22q12.2 in Han Chinese [J] . Nat Genet, 2011, 43(8): 792-796.

27. Adeyemo A, Gerry N, Chen G, et al. A genome-wide association study of hypertension and blood pressure in African Americans [J] . PLoS Genet, 2009, 5(7): e1000564.
28. Rosin G, Hannelius U, Lindstrom L, et al. The dyslexia candidate gene DYX1C1 is a potential marker of poor survival in breast cancer [J] . BMC Cancer, 2012, 12: 79.
29. Sinner MF, Pfeufer A, Akyol M, et al. The non-synonymous coding IKr-channel variant KCNH2-K897T is associated with atrial fibrillation: results from a systematic candidate gene-based analysis of KCNH2 (HERG) [J] . Eur Heart J, 2008, 29(7): 907-914.
30. Guo H, Majmudar G, Jensen TC, et al. Characterization of the gene for human EMMPRIN, a tumor cell surface inducer of matrix metalloproteinases [J] . Gene, 1998, 220(1/2): 99-108.
31. Wu LS, Li FF, Sun LD, et al. A miRNA-492 binding-site polymorphism in BSG (basigin) confers risk to psoriasis in central south Chinese population [J] . Hum Genet, 2011, 130(6): 749-757.
32. Koho NM, Mykkanen AK, Reeben M, et al. Sequence variations and two levels of MCT1 and CD147 expression in red blood cells and gluteus muscle of horses [J] . Gene, 2012, 491(1): 65-70.
33. Barrett JC, Fry B, Maller J, et al. Haploview: analysis and visualization of LD and haplotype maps [J] . Bioinformatics, 2005, 21(2): 263-265.
34. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data [J] . Am J Hum Genet,2001, 68(4): 978-989.
35. Librado P, Rozas J. DnaSP v5: a software for comprehensive analysis of DNA polymorphism data [J] . Bioinformatics, 2009, 25(11): 1451-1452.
36. Tajima F. Statistical method for testing the neutral mutation hypothesis by DNA polymorphism [J] . Genetics, 1989, 123(3): 585-595.
37. Fu YX, Li WH. Statistical tests of neutrality of mutations [J] . Genetics,1993, 133(3): 693-709.
38. Sauna ZE, Kimchi-Sarfaty C. Understanding the contribution of synonymous mutations to human disease [J] . Nat Rev Genet, 2011,12(10): 683-691.
39. Ho PA, Kopecky KJ, Alonzo TA, et al. Prognostic implications of the IDH1 synonymous SNPs rs11554137 in pediatric and adult AML: a report from the Children's Oncology Group and SWOG [J] . Blood,2011, 118(17): 4561-4566.
40. Levy D, Ehret GB, Rice K, et al. Genome-wide association study of blood pressure and hypertension [J] . Nat Genet, 2009, 41(6): 677-687.
41. Barrett JC, Cardon LR. Evaluating coverage of genome-wide association studies [J] . Nat Genet, 2006, 38(6): 659-662.
42. Dong X, Zhong T, Xu T, et al. Evaluating coverage of exons by HapMap SNPs [J] . Genomics, 2013, 101(1): 20-23.
43. Chen X, Wang H, Zhou G, et al. Molecular population genetics of human CYP3A locus: signatures of positive selection and implications for evolutionary environmental medicine [J] . Environ Health Perspect, 2009, 117(10): 1541-1548.
44. Fumagalli M, Cagliani R, Pozzoli U, et al. Widespread balancing selection and pathogen-driven selection at blood group antigen genes [J] . Genome Res, 2009, 19(2): 199-212.
45. Hao K, Chudin E, McElwee J, et al. Accuracy of genome-wide imputation of untyped markers and impacts on statistical power for association studies [J] . BMC Genet, 2009, 10: 27.

本刊中的类似文章