

胃癌相关基因研究进展

于尚睿, 黄晓俊, 张亚萍

于尚睿, 黄晓俊, 张亚萍, 兰州大学第二医院消化科 甘肃省兰州市 730030

于尚睿, 主要从事消化系统肿瘤方面的研究.

作者贡献分布: 本文由于尚睿与张亚萍完成; 黄晓俊审校.

通讯作者: 黄晓俊, 教授, 主任医师, 博士生导师, 730030, 甘肃省兰州市城关区萃英门80号, 兰州大学第二医院消化内科. huangxj62@163.com
电话: 0931-8942731

收稿日期: 2016-09-01

修回日期: 2016-09-13

接受日期: 2016-09-25

在线出版日期: 2016-11-18

Gastric cancer related genes

Shang-Rui Yu, Xiao-Jun Huang, Ya-Ping Zhang

Shang-Rui Yu, Xiao-Jun Huang, Ya-Ping Zhang, Department of Gastroenterology, the Second Hospital of Lanzhou University, Lanzhou 730030, Gansu Province, China

Correspondence to: Xiao-Jun Huang, Professor, Chief Physician, Department of Gastroenterology, the Second Hospital of Lanzhou University, 80 Cuiying Door, Chengguan District, Lanzhou 730030, Gansu Province, China. huangxj62@163.com

Received: 2016-09-01

Revised: 2016-09-13

Accepted: 2016-09-25

Published online: 2016-11-18

Abstract

Gastric cancer is one of the most common malignant tumors. In addition to environmental, socioeconomic, and dietary factors, hereditary factors also play an important role in the development of gastric cancer. Although some

driver genes have been identified in gastric cancer, the molecular compositions of gastric cancer have not been fully understood. Genome-wide association studies, copy number variations and next-generation sequencing provide systematic methods to identify all genetic alterations in the cancer genome, especially in the field of mutation detection. Here we make a brief review of the current status of research on gastric cancer genetics.

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Key Words: Gastric cancer; Genetic studies; Genome-wide association studies; Copy number variations; Next-generation sequencing

Yu SR, Huang XJ, Zhang YP. Gastric cancer related genes. *Shijie Huaren Xiaohua Zazhi* 2016; 24(32): 4381-4388 URL: <http://www.wjgnet.com/1009-3079/full/v24/i32/4381.htm> DOI: <http://dx.doi.org/10.11569/wcjd.v24.i32.4381>

摘要

胃癌是世界最常见恶性肿瘤之一,除了与环境、饮食、社会经济等因素有关外,遗传因素也起着重要的作用. 尽管有些基因在胃癌中已经确定,但胃癌的遗传因素尚未得到充分的认识. 全基因组关联分析、拷贝数变异分析、二代基因测序技术提供了系统化的方法来识别癌症基因组所有的基因变异,特别是在突变检测领域. 本文就胃癌目前遗传学研究现状作一简要综述.

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

■背景资料
胃癌是世界最常见恶性肿瘤之一,每年新发人数约为952000人(占所有恶性肿瘤的7%),死亡人数约为723000(占所有恶性肿瘤9%),70%-85%的患者死于诊断的5年内. 研究胃癌的相关发病基因对胃癌的诊断、治疗、预防有重大意义.

■同行评议者
李正荣,副教授,副主任医师,南昌大学附属第一医院胃肠外科(普六病区);邱江锋,主任医师,上海交通大学医学院附属仁济医院胃肠外科

研究前沿

胃癌的发生是一个多因素参与的过程, 目前除已经明确部分基因与胃癌的发病有关, 胃癌的遗传相关性仍未阐明, 通过对其相关基因研究, 有助于提高对胃癌发病机制的认识, 进而其诊断与治疗也将迈上新台阶。

关键词: 胃癌; 遗传学研究; 全基因组关联分析; 拷贝数变异分析; 二代基因测序技术

核心提要: 胃癌的遗传因素在胃癌的发生中起着重要的作用。尽管有些基因在胃癌中已经确定, 但胃癌的遗传因素尚未得到充分的认识。全基因组关联分析、拷贝数变异分析、二代基因测序技术提供了系统化的方法来识别癌症基因组的基因变异, 特别是在突变检测领域。

于尚睿, 黄晓俊, 张亚萍. 胃癌相关基因研究进展. 世界华人消化杂志 2016; 24(32): 4381-4388 URL: <http://www.wjgnet.com/1009-3079/full/v24/i32/4381.htm> DOI: <http://dx.doi.org/10.11569/wjcd.v24.i32.4381>

0 引言

胃癌是世界最常见恶性肿瘤之一, 每年新发人数约为952000人(占有恶性肿瘤的7%), 死亡人数约为723000(占有恶性肿瘤9%), 70%-85%的患者死于诊断的5年内^[1,2]。幽门螺杆菌是胃癌的明确危险因素, 吸烟、盐渍饮食也可增加胃癌风险, 与此同时遗传因素已经被视为胃癌发病的重要组成部分。到目前为止, 与胃癌相关的确切遗传因素一直没能完全明确。在过去几年中, 通过易感基因研究、全基因组关联分析(genome-wide association studies, GWAS)、拷贝数变异分析(copy number variations, CNVs)、二代基因测序技术(next-generation sequencing, NGS)等方法, 我们对胃癌研究有了更进一步的认识。

1 常见易感基因

1.1 E-钙粘蛋白基因 1998年, Guilford等^[3]研究了3个新西兰毛利血统家系共98人, 其中28人患有胃癌, 通过遗传学分析首次揭示遗传性弥漫性胃癌(hereditary diffuse gastric cancer, HDGC)呈现常染色体显性遗传且与E-钙粘蛋白(E-cadherin, CDH1)基因突变密切相关。CDH1基因位于16号染色体的长臂上, 即16q22.1, 其全长约100 kb, 包含16个外显子, 转录生成4.5 kb mRNA, 最终编码E-钙黏蛋白^[4]。E-钙黏蛋白是一种钙依赖性蛋白, 是I型钙黏蛋白超家族的跨膜糖蛋白分子, 主要是表达在上皮细胞基底外侧膜, 由3部分组成: 胞内区、跨膜区以及胞外区, 其主要功能是介导细胞间黏连和抑制入侵^[5]。该基因的突变主要影响胞内与胞外蛋白质, 进而影响蛋白质完整性, 导

致上皮组织细胞-细胞黏连受到干扰, 增加细胞运动性并对肿瘤浸润与转移能力起到加强作用^[6]。2010年国际胃癌联合会证实, 对数百位满足HDGC的诊断标准的先证者进行了CDH1突变测试, 其中大约40%被发现携带的遗传基因发生改变。目前已明确CDH1基因突变与HDGC相关。

1.2 MAP3K6基因 促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)级联由一个激酶模块构成: MAPK、MAPK激酶(mitogen-activated protein kinase kinase, MKK)及MKK激酶(mitogen-activated protein kinase kinase kinase, MAP3K)。MAPK级联中信号从细胞表面到达细胞核, 从而形成基因转录。MAP3K6是c-Jun氨基末端激酶(c-jun n-terminal kinase, JNK)与p38信号级联的组成部分, 主要表达于皮肤、胃肠道及肺^[7,8]。MAP3K6与其同源的MAP3K5形成异聚复合体, 通过他们的卷曲螺旋域, 阻止MAP3K6降解并促进其自身磷酸化和活化^[7]。在氧化应激与活性氧诱导下, 活化磷酸化的MAP3K6激活JNK和p38信号级联并促进细胞凋亡, MAP3K6的促凋亡、抑制肿瘤的作用和MAP3K5的促炎/抗凋亡作用保持严格的平衡^[7-9]。所以MAP3K6突变可能使个体易患胃癌^[10]。虽然MAP3K6突变在胃癌中作用尚不十分明确, 但越来越多的研究证明MAP3K6在癌症发病机制中起重要作用。

1.3 SMAD4基因 1996年Hahn等^[11]发现SMAD4基因, 其位于18号染色体, 即18q22.1, 包括11个外显子, 其功能在调节转化生长因子-β(transforming growth factor-β, TGF-β)转录活性中起着关键作用。SMAD4是TGF-β信号转录所需的常见SMAD蛋白^[12]。SMAD4的突变失活可导致TGF-β反应迟钝, Kim等^[13]指出, 在T细胞中的SMAD4依赖性信号的选择性丧失导致小鼠胃肠道自发上皮癌, 而结肠、直肠、十二指肠、胃及口腔肿瘤与大量浆细胞浸润相关。SMAD4可能参与HDGC, Takaku等^[14]敲除位于小鼠SMAD4上的一个等位基因, 从而在小鼠的胃黏膜组织中可见印戒细胞癌巢, Caspase 10为胃癌的另一候选基因, 其突变可能导致凋亡功能的丧失。有报告^[15]表明在HDGC患者中发现该基因编码区突变以及杂合性缺失分别为3%和15%。上述结果提示SMAD4与Caspase 10可能与胃癌存在一定相关性。

1.4 其他相关基因 家族性胃癌除了可能与

上述基因相关外, 有报道表明 β -环连蛋白基因、*HPPI*基因、*BRCA2*基因、*MET*基因、*RUNX3*基因的改变也与胃癌相关^[16]。

2 全基因组关联发现的有意义的胃癌易感位点和/或区域

2.1 染色体8q24的SNP位点rs6983267以及rs2294008 染色体8q24是一个已经被确认与包括胃癌在内的多器官癌症相关的风险基因位点, 其与前列腺癌、乳腺癌、膀胱癌、肾细胞癌、葡萄胎、胰腺癌、结肠直肠癌的发病相关^[17,18]。研究^[19]表明, 染色体8q24的一个功能性SNP位点rs6983267和MYC之间存在功能链接, 其影响Wnt信号调节转录因子7-like 2(transcription factor 7-like 2, TCF7L2), 且rs6983267变体是一个转录增强子, 其不仅能差异结合TCF7L2, 而且该危险区域可以与MYC原癌基因相互作用。染色体8q24上的增强子可以与MYC形成一个染色质环。MYC增强区域可以与非编码RNA *CARLO-5*启动子的活性调节区相互作用, 从而调控*CARLO-5*的表达^[20], 上述研究表明rs6983267等位基因与癌症易感性的增加相关。此外, 前列腺干细胞抗原 (prostate stem cell antigen, *PSCA*)基因定位于常染色体8q24上, 其编码的*PSCA*多肽是一种含123个氨基酸残基的糖基磷脂酰肌醇锚定的细胞表面蛋白。GWAS研究^[21]发现*PSCA*基因的一个功能性SNP位点rs2294008(C/T)影响*PSCA*的转录活性, 该rs2294008决定翻译起始密码子的位置, 基因突变导致起始密码子位置的变化。研究^[22]表明, rs2294008的T等位基因与胃癌相关, 而C等位基因增加十二指肠溃疡风险。此外, 有研究^[23]表明*PSCA*基因rs2294008多态性与白种人胃癌发病风险无统计学意义, 但与亚洲胃癌发病明显相关。

2.2 染色体1q22的SNP位点rs12904 *EFNA1*是糖基磷脂酰肌醇锚定的配体, 定位于染色体1q22上, 由205个氨基酸构成, 其细胞-细胞接触时优先结合到受体酪氨酸激酶(the receptor tyrosine kinase, RTK)的EphA2上, 他们在发育过程中发挥重要作用, 并且参与许多不同类型的肿瘤的发生、发展^[24]。GWAS研究^[25]发现*EFNA1*基因的一个功能性SNP位点rs12904(G/A)与胃癌发病风险密切相关。研究^[25]表明, rs12904位于*EFNA1*基因的3'UTR, 从G到A的

突变可导致在荧光素酶表达下的miR-200c(是miR-200家族中最重要组成部分, 在抑制在上皮-间充质转化与肿瘤细胞的黏附、侵袭、转移中发挥关键作用)的调控改变, 并且基因表达分析表明胃癌组织中, rs12904基因型突变改变了*EFNA1*的表达水平。此外, ICSNPPathway分析表明, *EFNA1*基因与肝配蛋白受体结合途径可能在增加胃癌易感性上发挥重要作用^[26]。这些研究结果为研究癌症发病机制及*EFNA1*的生理病理功能开辟了新的道路。

2.3 染色体1q21的SNP位点rs4072037 全基因组关联研究报道定位于染色体1q21上*MUC1*基因的一个功能性SNP位点rs4072037与胃癌发生密切相关。*MUC1*基因编码的MUC1多肽是黏蛋白家族中的一种膜结合蛋白, 可分为N-末端和C-末端两个亚基, 两个亚单位由非共价结合并定位于细胞膜顶侧上皮细胞, 他可以阻挡外源损伤, MUC1-N存在于细胞表面上具有多个糖基化位点, 对细胞起保护作用, MUC1-C具有跨膜结构域和胞质尾, 其涉及细胞信号转导, 目前MUC1一直被认为是一个癌蛋白^[27]。该SNP rs4072037位于MUC1第二外显子, 并且A等位基因与MUC1的生理功能减低有关, 其引起第二外显子5'区的选择性剪接, 从而导致胃黏膜的生理保护功能降低, 胃癌易感性增加^[28,29]。

2.4 其他相关位点 近年来通过GWAS和高通量遗传分析已经确定了与胃癌相关的几个位点, 如3q13.31、5p13.1、10q23及20p13等。

3 基因CNVs下发现的有意义的常见基因

3.1 染色体8q24上MYC及TNFRSF11B 最近的研究^[30]显示位于染色体8q24上的基因拷贝数增加是胃癌多级发病的早期事件, 并且与胃癌患者低生存率相关。研究^[31]表明使用基于芯片的比较基因组杂交技术加上患者的临床资料发现染色体8q24的MYC和TNFRSF11B在胃癌患者中出现明显扩增。MYC是某些原发性肿瘤发生的原癌基因^[32], 且与迟发性肠型晚期肿瘤和胃癌远处转移相关^[33]。TNFRSF11B位于染色体8q24, 其编码的骨保护素(osteoprotegerin, OPG), 是肿瘤坏死因子受体超家族的一员, OPG已被认为是多种癌症的一个预后标志物。大量的研究^[34]表明, OPG保护肿瘤细胞免受肿瘤坏死因子相关凋亡诱导配体影响, 并且可

□相关报道 近年来随着分子生物学发展, 全基因组关联分析(genome-wide association studies, GWAS)、拷贝数变异分析(copy number variations, CNVs)、二代基因测序技术(next-generation sequencing, NGS)等技术越来越多地应用于肿瘤突变基因检测上, 与胃癌相关的许多位点被发现, 为胃癌遗传学的进一步研究提供了方向。

创新视点
本文综述了GWAS、CNVs、NGS等不同检测方式下的常见突变基因。

以通过Wnt/ β -联蛋白途径驱动OPG的表达促进癌变和肿瘤细胞产生. 此外统计分析表明, MYC和TNFRSF11B的共同增益与肿瘤深度浸润、淋巴结转移和TNM分期密切相关^[31].

3.2 染色体7q21上MET 定位于7q21染色体的MET编码肝细胞生长因子受体, 肝细胞生长因子/MET途径在胃癌及其他癌症中可见功能障碍, MET通路的激活主要是由于MET扩增, 从而增强的肿瘤细胞的生长、入侵^[35,36]. 此外, 最近的报告^[37]显示MET基因扩增与mRNA过表达以及胃癌患者低生存率显著相关. MET基因拷贝数扩增也与肿瘤的浸润、转移相关, 表明其可以作为预后指标比蛋白质过表达更有价值^[38]. MET扩增的临床影响与MET作为胃癌的功能性驱动基因相关. MET CNVs可以用作选择标记, 作为MET抑制剂治疗, 但仍需进一步探索^[35].

3.3 染色体17p13.1上TP53 TP53基因是目前研究最为广泛的抑癌基因之一, 位于17p13.1上, 通过影响细胞的应激调控机制以诱导细胞周期阻滞、细胞凋亡、衰老、DNA修复或代谢变化^[39]. 在胃癌致癌过程中, TP53基因座的缺失是这一基因功能障碍最常见的机制, 其频繁见于胃癌组织中^[40,41]. 有研究^[32]表明, 胃癌组织样本相比非肿瘤性胃样本, TP53 mRNA水平大幅下降, 杂合性丢失和突变可能导致Tp53功能的丧失. 此外研究表明, TP53缺失和胃癌癌前病变显著相关, 上述研究表明TP53 CNV可以是胃癌的早期分子事件^[42].

3.4 染色体20q13上AURKA与20q13上C20orf11 中心体相关极光激酶A(aurora kinase A, AURKA)基因位于20q13染色体基因座上, 其编码的AURKA蛋白被广泛表达, 具有调节细胞周期(S期晚期-M期)的功能^[43]. 此外, AURKA过度表达可以激活多个致癌途径, 包括PI3K/AKT、 β -catenin、NF- κ B及JAK2-STAT3^[44]. 多项研究^[45,46]表明, AURKA基因拷贝数增加及过表达常见于胃癌组织中且其与恶性程度相关. AURKA扩增和肿瘤发展相关表明AURKA可能具有预后意义^[35]. 研究^[35,47]表明位于20q13.33染色体上的C20orf11基因的扩增可区分低分化胃癌和中度分化胃癌, 其在中分化胃癌中过表达, 并且C20orf11 CNV与TNM分期和胃癌的组织学亚型相关.

3.5 其他与胃癌相关基因 有报道表明染色体

1q、5p、7、8、13、20的扩增和染色体1p、3p、4、5q、9p、17p、18q、19p、21、22.41的缺失与胃癌相关, 同时, 许多基因的扩增或缺失也与胃癌相关, 如PIK3CA、TNK2、APC、HER2、KRAS、FGFR2等基因^[40,48-55].

4 NGS发现的胃癌相关基因或途径

4.1 RTK RTK超家族对生长发育的调节至关重要, RTK信号通路的异常激活涉及到包括胃癌在内的许多癌症的发展, PLK通路是RTK通路的一主要下游通路, PI3K蛋白是激活配体和下游信号的关键分子^[56]. PI3K蛋白由两个亚基构成: 催化亚基主要由PIK3CA编码, 调节亚基主要由PIK3R1编码^[57]. PIK3CA突变广泛存在于多种人类癌症^[58]. 谷氨酸542赖氨酸, 谷氨酸545赖氨酸, 和组氨酸1047精氨酸是三种最常见的突变, 比野生型PIK3CA具有更强的激酶活性和致癌性^[57,59]. 人第10号染色体缺失的磷酸酶(phosphatase and tensin homolog deleted on chromosome ten, PTEN)是PIK通路的负性调节因子. PTEN基因失活突变常见于胃癌^[58,60]. 研究^[61]表明, PIK通路抑制剂对于癌症有一定缓解作用.

4.2 RHOA RHOA属于的Rho GTP酶家族, 该家族几乎参与每一个生物学过程, 最主要的是调控肌动蛋白骨架^[62,63]. RHOA编码小GTP酶能加速肌动蛋白聚合, 促进细胞周期^[63]. 在胃癌相关研究中, 发现存在RHOA基因突变, 其突变率为6.5%-25.3%^[48,62,64]. RHOA被报道参与包括胃癌在内的许多肿瘤的发生和发展^[63]. 在胃癌中RHOA的突变热点主要为精氨酸5、甘氨酸17、酪氨酸42和亮氨酸57, 这些突变分布在RHOA与GTP结合区^[48,62]. RHOA野生型细胞不影响细胞的生长, 而在RHOA突变细胞中RHOA的基因沉默显著抑制细胞增殖^[62]. 此外, 细胞RHOA酪氨酸42亮氨酸或亮氨酸57缬氨酸突变多表达有较强的抗失巢凋亡能力^[48]. 有研究发现野生型RHOA抑制增殖和Jurkat细胞的G₁-S期细胞周期, 而RHOA甘氨酸17缬氨酸突变型则无此作用, 并且有研究还发现, 与RHOA甘氨酸17缬氨酸, 酪氨酸42亮氨酸, 或亮氨酸57缬氨酸突变型与GTP结合能力比野生型RHOA更弱, 说明存在RHOA信号缺陷^[62,65-67]. 但RHOA如何参与胃癌发生和发展有待进一步研究.

4.3 其他与胃癌相关基因 DNA的甲基化, JAK2、PD-L1和PD-L2的扩增, PKHD1、CTNNA2、BRCA2均有报道与胃癌相关^[68-71].

5 结论

目前除已经明确部分基因与胃癌的发病有关, 胃癌的遗传相关性仍未阐明, 其发病机制还需进一步研究. 所以通过对其相关基因进行研究, 以期能够达到早期诊断及早期治疗的目的. 相信随着分子生物学的发展, 胃癌遗传学基础及具体发病机制终将被揭示, 其诊断与治疗也将迈上新台阶.

6 参考文献

- 1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374-1403 [PMID: 23485231 DOI: 10.1016/j.ejca.2012.12.027]
- 2 Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. *Lancet Oncol* 2015; 16: e60-e70 [PMID: 25638682 DOI: 10.1016/S1470-2045(14)71016-2]
- 3 Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scouler R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998; 392: 402-405 [PMID: 9537325 DOI: 10.1038/32918]
- 4 Bex G, Staes K, van Hengel J, Molemans F, Bussemakers MJ, van Bokhoven A, van Roy F. Cloning and characterization of the human invasion suppressor gene E-cadherin (CDH1). *Genomics* 1995; 26: 281-289 [PMID: 7601454 DOI: 10.1016/0888-7543(95)80212-5]
- 5 Vermeulen S, Van Marck V, Van Hoorde L, Van Roy F, Bracke M, Mareel M. Regulation of the invasion suppressor function of the cadherin/catenin complex. *Pathol Res Pract* 1996; 192: 694-707 [PMID: 8880870 DOI: 10.1016/S0344-0338(96)80091-4]
- 6 Mateus AR, Simões-Correia J, Figueiredo J, Heindl S, Alves CC, Suriano G, Lubert B, Seruca R. E-cadherin mutations and cell motility: a genotype-phenotype correlation. *Exp Cell Res* 2009; 315: 1393-1402 [PMID: 19268661 DOI: 10.1016/j.yexcr.2009.02.020]
- 7 Takeda K, Shimozono R, Noguchi T, Umeda T, Morimoto Y, Naguro I, Tobiume K, Saitoh M, Matsuzawa A, Ichijo H. Apoptosis signal-regulating kinase (ASK) 2 functions as a mitogen-activated protein kinase kinase kinase in a heteromeric complex with ASK1. *J Biol Chem* 2007; 282: 7522-7531 [PMID: 17210579 DOI: 10.1074/jbc.M607177200]
- 8 Iriyama T, Takeda K, Nakamura H, Morimoto Y, Kuroiwa T, Mizukami J, Umeda T, Noguchi T, Naguro I, Nishitoh H, Saegusa K, Tobiume K, Homma T, Shimada Y, Tsuda H, Aiko S, Imoto I, Inazawa J, Chida K, Kamei Y, Kozuma S, Taketani Y, Matsuzawa A, Ichijo H. ASK1 and ASK2 differentially regulate the counteracting roles of apoptosis and inflammation in tumorigenesis. *EMBO J* 2009; 28: 843-853 [PMID: 19214184 DOI: 10.1038/emboj.2009.32]
- 9 Eto N, Miyagishi M, Inagi R, Fujita T, Nangaku M. Mitogen-activated protein 3 kinase 6 mediates angiogenic and tumorigenic effects via vascular endothelial growth factor expression. *Am J Pathol* 2009; 174: 1553-1563 [PMID: 19246638 DOI: 10.2353/ajpath.2009.080190]
- 10 Gaston D, Hansford S, Oliveira C, Nightingale M, Pinheiro H, Macgillivray C, Kaurah P, Rideout AL, Steele P, Soares G, Huang WY, Whitehouse S, Blowers S, LeBlanc MA, Jiang H, Greer W, Samuels ME, Orr A, Fernandez CV, Majewski J, Ludman M, Dyack S, Penney LS, McMaster CR, Huntsman D, Bedard K. Germline mutations in MAP3K6 are associated with familial gastric cancer. *PLoS Genet* 2014; 10: e1004669 [PMID: 25340522 DOI: 10.1371/journal.pgen.1004669]
- 11 Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, Weinstein CL, Fischer A, Yeo CJ, Hruban RH, Kern SE. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science* 1996; 271: 350-353 [PMID: 8553070 DOI: 10.1126/science.271.5247.350]
- 12 Shioda T, Lechleider RJ, Dunwoodie SL, Li H, Yahata T, de Caestecker MP, Fenner MH, Roberts AB, Isselbacher KJ. Transcriptional activating activity of Smad4: roles of SMAD hetero-oligomerization and enhancement by an associating transactivator. *Proc Natl Acad Sci USA* 1998; 95: 9785-9790 [PMID: 9707553 DOI: 10.1073/pnas.95.17.9785]
- 13 Kim BG, Li C, Qiao W, Mamura M, Kasprzak B, Anver M, Wolfrum L, Hong S, Mushinski E, Potter M, Kim SJ, Fu XY, Deng C, Letterio JJ. Smad4 signalling in T cells is required for suppression of gastrointestinal cancer. *Nature* 2006; 441: 1015-1019 [PMID: 16791201 DOI: 10.1038/nature04846]
- 14 Takaku K, Miyoshi H, Matsunaga A, Oshima M, Sasaki N, Taketo MM. Gastric and duodenal polyps in Smad4 (Dpc4) knockout mice. *Cancer Res* 1999; 59: 6113-6117 [PMID: 10626800]
- 15 Park WS, Lee JH, Shin MS, Park JY, Kim HS, Lee JH, Kim YS, Lee SN, Xiao W, Park CH, Lee SH, Yoo NJ, Lee JY. Inactivating mutations of the caspase-10 gene in gastric cancer. *Oncogene* 2002; 21: 2919-2925 [PMID: 11973654 DOI: 10.1038/sj/onc/1205394]
- 16 Carneiro F, Oliveira C, Suriano G, Seruca R. Molecular pathology of familial gastric cancer, with an emphasis on hereditary diffuse gastric cancer. *J Clin Pathol* 2008; 61: 25-30 [PMID: 17513507 DOI: 10.1136/jcp.2006.043679]
- 17 Taeb J, Asgari M, Abolhasani M, Farajollahi MM, Madjd Z. Expression of prostate stem cell antigen (PSCA) in prostate cancer: a tissue microarray study of Iranian patients. *Pathol Res Pract* 2014; 210: 18-23 [PMID: 24183365 DOI: 10.1016/j.prp.2013.09.012]
- 18 Tarleton HP, Chang SC, Park SL, Cai L, Ding B, He N, Hussain SK, Jiang Q, Mu LN, Rao J, Wang H, You NC, Yu SZ, Zhao JK, Zhang ZF. Genetic variation at 8q24, family history of cancer, and

应用要点

本文就近年来常见胃癌基因进行归纳, 使读者在胃癌基因研究方面有进一步的了解.

■名词解释

单核苷酸多态性 (SNP): 是分子遗传标记; 全基因组关联分析(GWAS): 是应用基因组中数以百万计的SNP, 进行全基因组水平上的对照分析或相关性分析, 通过比较发现影响复杂性状的基因变异的一种新策略.

- upper gastrointestinal cancers in a Chinese population. *Fam Cancer* 2014; 13: 45-56 [PMID: 24030569 DOI: 10.1007/s10689-013-9673-4]
- 19 Pomerantz MM, Ahmadiyeh N, Jia L, Herman P, Verzi MP, Doddapaneni H, Beckwith CA, Chan JA, Hills A, Davis M, Yao K, Kehoe SM, Lenz HJ, Haiman CA, Yan C, Henderson BE, Frenkel B, Barretina J, Bass A, Tabernero J, Baselga J, Regan MM, Manak JR, Shivdasani R, Coetzee GA, Freedman ML. The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nat Genet* 2009; 41: 882-884 [PMID: 19561607 DOI: 10.1038/ng.403]
- 20 Kim T, Cui R, Jeon YJ, Lee JH, Lee JH, Sim H, Park JK, Fadda P, Tili E, Nakanishi H, Huh MI, Kim SH, Cho JH, Sung BH, Peng Y, Lee TJ, Luo Z, Sun HL, Wei H, Alder H, Oh JS, Shim KS, Ko SB, Croce CM. Long-range interaction and correlation between MYC enhancer and oncogenic long noncoding RNA CARLo-5. *Proc Natl Acad Sci USA* 2014; 111: 4173-4178 [PMID: 24594601 DOI: 10.1073/pnas.1400350111]
- 21 Saeki N, Ono H, Sakamoto H, Yoshida T. Genetic factors related to gastric cancer susceptibility identified using a genome-wide association study. *Cancer Sci* 2013; 104: 1-8 [PMID: 23057512 DOI: 10.1111/cas.12042]
- 22 Cho SJ, Choi IJ, Kim CG, Kook MC, Lee JY, Kim BC, Ryu KH, Nam SY, Kim YW. Risk factors associated with gastric cancer in patients with a duodenal ulcer. *Helicobacter* 2010; 15: 516-523 [PMID: 21073608 DOI: 10.1111/j.1523-5378.2010.00805.x]
- 23 Gu X, Zhang W, Xu L, Cai D. Quantitative assessment of the influence of prostate stem cell antigen polymorphisms on gastric cancer risk. *Tumour Biol* 2014; 35: 2167-2174 [PMID: 24146278 DOI: 10.1007/s13277-013-1287-9]
- 24 Pasquale EB. Eph receptors and ephrins in cancer: bidirectional signalling and beyond. *Nat Rev Cancer* 2010; 10: 165-180 [PMID: 20179713 DOI: 10.1038/nrc2806]
- 25 Li Y, Nie Y, Cao J, Tu S, Lin Y, Du Y, Li Y. G-A variant in miR-200c binding site of EFNA1 alters susceptibility to gastric cancer. *Mol Carcinog* 2014; 53: 219-229 [PMID: 23065816 DOI: 10.1002/mc.21966]
- 26 Lee JH, Kim Y, Choi JW, Kim YS. Genetic variants and risk of gastric cancer: a pathway analysis of a genome-wide association study. *Springerplus* 2015; 4: 215 [PMID: 25992311 DOI: 10.1186/s40064-015-1005-8]
- 27 Gendler SJ. MUC1, the renaissance molecule. *J Mammary Gland Biol Neoplasia* 2001; 6: 339-353 [PMID: 11547902]
- 28 Zheng L, Zhu C, Gu J, Xi P, Du J, Jin G. Functional polymorphism rs4072037 in MUC1 gene contributes to the susceptibility to gastric cancer: evidence from pooled 6,580 cases and 10,324 controls. *Mol Biol Rep* 2013; 40: 5791-5796 [PMID: 24072653 DOI: 10.1007/s11033-013-2682-4]
- 29 Kupcinskas J, Wex T, Link A, Bartuseviciute R, Dedelaite M, Kevalaite G, Leja M, Skieceviciene J, Kiudelis G, Jonaitis L, Kupcinskas L, Malfertheiner P. PSCA and MUC1 gene polymorphisms are associated with gastric cancer and pre-malignant gastric conditions [corrected]. *Anticancer Res* 2014; 34: 7167-7175 [PMID: 25503145]
- 30 Kang JU. Chromosome 8q as the most frequent target for amplification in early gastric carcinoma. *Oncol Lett* 2014; 7: 1139-1143 [PMID: 24944681 DOI: 10.3892/ol.2014.1849]
- 31 Wang X, Liu Y, Shao D, Qian Z, Dong Z, Sun Y, Xing X, Cheng X, Du H, Hu Y, Li Y, Li L, Dong B, Li Z, Wu A, Wu X, Bu Z, Zong X, Zhu G, Ji Q, Wen XZ, Zhang LH, Ji JF. Recurrent amplification of MYC and TNFRSF11B in 8q24 is associated with poor survival in patients with gastric cancer. *Gastric Cancer* 2016; 19: 116-127 [PMID: 25618371 DOI: 10.1007/s10120-015-0467-2]
- 32 Calcagno DQ, Freitas VM, Leal MF, de Souza CR, Demachki S, Montenegro R, Assumpção PP, Khayat AS, Smith Mde A, dos Santos AK, Burbano RR. MYC, FBXW7 and TP53 copy number variation and expression in gastric cancer. *BMC Gastroenterol* 2013; 13: 141 [PMID: 24053468 DOI: 10.1186/1471-230X-13-141]
- 33 de Souza CR, Leal MF, Calcagno DQ, Costa Sozinho EK, Borges Bdo N, Montenegro RC, Dos Santos AK, Dos Santos SE, Ribeiro HF, Assumpção PP, de Arruda Cardoso Smith M, Burbano RR. MYC deregulation in gastric cancer and its clinicopathological implications. *PLoS One* 2013; 8: e64420 [PMID: 23717612 DOI: 10.1371/journal.pone.0064420]
- 34 De Toni EN, Thieme SE, Herbst A, Behrens A, Stieber P, Jung A, Blum H, Göke B, Kolligs FT. OPG is regulated by beta-catenin and mediates resistance to TRAIL-induced apoptosis in colon cancer. *Clin Cancer Res* 2008; 14: 4713-4718 [PMID: 18676739 DOI: 10.1158/1078-0432.CCR-07-5019]
- 35 Liang L, Fang JY, Xu J. Gastric cancer and gene copy number variation: emerging cancer drivers for targeted therapy. *Oncogene* 2016; 35: 1475-1482 [PMID: 26073079 DOI: 10.1038/onc.2015.209]
- 36 An X, Wang F, Shao Q, Wang FH, Wang ZQ, Wang ZQ, Chen C, Li C, Luo HY, Zhang DS, Xu RH, Li YH. MET amplification is not rare and predicts unfavorable clinical outcomes in patients with recurrent/metastatic gastric cancer after chemotherapy. *Cancer* 2014; 120: 675-682 [PMID: 24804300 DOI: 10.1002/cncr.28454]
- 37 Ha SY, Lee J, Kang SY, Do IG, Ahn S, Park JO, Kang WK, Choi MG, Sohn TS, Bae JM, Kim S, Kim M, Kim S, Park CK, Ignatius Ou SH, Kim KM. MET overexpression assessed by new interpretation method predicts gene amplification and poor survival in advanced gastric carcinomas. *Mod Pathol* 2013; 26: 1632-1641 [PMID: 23807774 DOI: 10.1038/modpathol]
- 38 Teng L, Lu J. cMET as a potential therapeutic target in gastric cancer (Review). *Int J Mol Med* 2013; 32: 1247-1254 [PMID: 24141315 DOI: 10.3892/ijmm.2013.1531]
- 39 Wang J, Qian J, Hu Y, Kong X, Chen H, Shi Q, Jiang L, Wu C, Zou W, Chen Y, Xu J, Fang JY. ArhGAP30 promotes p53 acetylation and function in colorectal cancer. *Nat Commun* 2014; 5: 4735 [PMID: 25156493 DOI: 10.1038/ncomms5735]
- 40 Sonoda A, Mukaisho K, Nakayama T, Diem VT, Hattori T, Andoh A, Fujiiyama Y, Sugihara H. Genetic lineages of undifferentiated-type gastric carcinomas analysed by unsupervised clustering

- of genomic DNA microarray data. *BMC Med Genomics* 2013; 6: 25 [PMID: 23866769 DOI: 10.1186/1755-8794-6-25]
- 41 Fassin M, Simbolo M, Bria E, Mafficini A, Pilotto S, Capelli P, Bencivenga M, Pecori S, Luchini C, Neves D, Turri G, Vicentini C, Montagna L, Tomezzoli A, Tortora G, Chilosi M, De Manzoni G, Scarpa A. High-throughput mutation profiling identifies novel molecular dysregulation in high-grade intraepithelial neoplasia and early gastric cancers. *Gastric Cancer* 2014; 17: 442-449 [PMID: 24272205 DOI: 10.1007/s10120-013-0315-1]
 - 42 Karaman A, Kabalar ME, Binici DN, Öztürk C, Pirim I. Genetic alterations in gastric precancerous lesions. *Genet Couns* 2010; 21: 439-450 [PMID: 21290973]
 - 43 Dar AA, Goff LW, Majid S, Berlin J, El-Rifai W. Aurora kinase inhibitors--rising stars in cancer therapeutics? *Mol Cancer Ther* 2010; 9: 268-278 [PMID: 20124450 DOI: 10.1158/1535-7163.MCT-09-0765]
 - 44 Katsha A, Arras J, Soutto M, Belkhiri A, El-Rifai W. AURKA regulates JAK2-STAT3 activity in human gastric and esophageal cancers. *Mol Oncol* 2014; 8: 1419-1428 [PMID: 24953013 DOI: 10.1016/j.molonc.2014.05.012]
 - 45 Katsha A, Soutto M, Sehdev V, Peng D, Washington MK, Piazzuelo MB, Tantawy MN, Manning HC, Lu P, Shyr Y, Ecsedy J, Belkhiri A, El-Rifai W. Aurora kinase A promotes inflammation and tumorigenesis in mice and human gastric neoplasia. *Gastroenterology* 2013; 145: 1312-1322.e1-e8 [PMID: 23993973 DOI: 10.1053/j.gastro.2013.08.050]
 - 46 Özdemir M, Öznur M, Çiftçi E, Durak Aras B, Aslan H, Saygili H, Öner KS, Erkasap SM, Özakyol A, Paşaoğlu Ö, Çilingir O, Artan S. Detection of kinase amplifications in gastric adenocarcinomas. *Turk J Med Sci* 2014; 44: 461-470 [PMID: 25558650 DOI: 10.3906/sag-1303-139]
 - 47 Cheng L, Wang P, Yang S, Yang Y, Zhang Q, Zhang W, Xiao H, Gao H, Zhang Q. Identification of genes with a correlation between copy number and expression in gastric cancer. *BMC Med Genomics* 2012; 5: 14 [PMID: 22559327 DOI: 10.1186/1755-8794-5-14]
 - 48 Wang K, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, Siu HC, Deng S, Chu KM, Law S, Chan KH, Chan AS, Tsui WY, Ho SL, Chan AK, Man JL, Foglizzo V, Ng MK, Chan AS, Ching YP, Cheng GH, Xie T, Fernandez J, Li VS, Clevers H, Rejto PA, Mao M, Leung SY. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* 2014; 46: 573-582 [PMID: 24816253 DOI: 10.1038/ng.2983]
 - 49 Tsai PC, Huang SW, Tsai HL, Ma CJ, Hou MF, Yang IP, Wang YS, Juo SH, Wang JY. The association between DNA copy number aberrations at chromosome 5q22 and gastric cancer. *PLoS One* 2014; 9: e106624 [PMID: 25210923 DOI: 10.1371/journal.pone.0106624]
 - 50 Takahashi N, Yamada Y, Taniguchi H, Fukahori M, Sasaki Y, Shoji H, Honma Y, Iwasa S, Takashima A, Kato K, Hamaguchi T, Shimada Y. Clinicopathological features and prognostic roles of KRAS, BRAF, PIK3CA and NRAS mutations in advanced gastric cancer. *BMC Res Notes* 2014; 7: 271 [PMID: 24774510 DOI: 10.1186/1756-0500-7-271]
 - 51 Das K, Gunasegaran B, Tan IB, Deng N, Lim KH, Tan P. Mutually exclusive FGFR2, HER2, and KRAS gene amplifications in gastric cancer revealed by multicolour FISH. *Cancer Lett* 2014; 353: 167-175 [PMID: 25086186 DOI: 10.1016/j.canlet.2014.07.021]
 - 52 Shinmura K, Kiyose S, Nagura K, Igarashi H, Inoue Y, Nakamura S, Maeda M, Baba M, Konno H, Sugimura H. TNK2 gene amplification is a novel predictor of a poor prognosis in patients with gastric cancer. *J Surg Oncol* 2014; 109: 189-197 [PMID: 24178904 DOI: 10.1002/jso.23482]
 - 53 Yang Q, Shao Y, Shi J, Qu Y, Wu K, Dang S, Shi B, Hou P. Concomitant PIK3CA amplification and RASSF1A or PAX6 hypermethylation predict worse survival in gastric cancer. *Clin Biochem* 2014; 47: 111-116 [PMID: 24505629 DOI: 10.1016/j.clinbiochem.2013.10.014]
 - 54 Sheng WQ, Huang D, Ying JM, Lu N, Wu HM, Liu YH, Liu JP, Bu H, Zhou XY, Du X. HER2 status in gastric cancers: a retrospective analysis from four Chinese representative clinical centers and assessment of its prognostic significance. *Ann Oncol* 2013; 24: 2360-2364 [PMID: 23788757 DOI: 10.1093/annonc/mdt232]
 - 55 Matsuoka T, Yashiro M. Recent advances in the HER2 targeted therapy of gastric cancer. *World J Clin Cases* 2015; 3: 42-51 [PMID: 25610849 DOI: 10.12998/wjcc.v3.i1.42]
 - 56 Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004; 10: 789-799 [PMID: 15286780 DOI: 10.1038/nm1087]
 - 57 Samuels Y, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, Willson JK, Markowitz S, Kinzler KW, Vogelstein B, Velculescu VE. High frequency of mutations of the PIK3CA gene in human cancers. *Science* 2004; 304: 554 [PMID: 15016963 DOI: 10.1126/science.1096502]
 - 58 Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal* 2013; 6: p11 [PMID: 23550210 DOI: 10.1126/scisignal.2004088]
 - 59 Bader AG, Kang S, Vogt PK. Cancer-specific mutations in PIK3CA are oncogenic in vivo. *Proc Natl Acad Sci USA* 2006; 103: 1475-1479 [PMID: 16432179 DOI: 10.1073/pnas.0510857103]
 - 60 Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012; 2: 401-404 [PMID: 22588877 DOI: 10.1158/2159-8290.CD-12-0095]
 - 61 Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, Tsimberidou AM, Stepanek VM, Moulder SL, Lee JJ, Luthra R, Zinner RG, Broaddus RR, Wheler JJ, Kurzrock R. Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. *Cell Rep* 2014; 6: 377-387 [PMID: 24440717 DOI: 10.1016/

□ 同行评价
本文综述了近年来发现的部分基因在胃癌发生发展中的作用, 有一定的参考意义。

- j.celrep.2013.12.035]
- 62 Kakiuchi M, Nishizawa T, Ueda H, Gotoh K, Tanaka A, Hayashi A, Yamamoto S, Tatsuno K, Katoh H, Watanabe Y, Ichimura T, Ushiku T, Funahashi S, Tateishi K, Wada I, Shimizu N, Nomura S, Koike K, Seto Y, Fukayama M, Aburatani H, Ishikawa S. Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. *Nat Genet* 2014; 46: 583-587 [PMID: 24816255 DOI: 10.1038/ng.2984]
 - 63 Karlsson R, Pedersen ED, Wang Z, Brakebusch C. Rho GTPase function in tumorigenesis. *Biochim Biophys Acta* 2009; 1796: 91-98 [PMID: 19327386 DOI: 10.1016/j.bbcan.2009.03.003]
 - 64 Wong SS, Kim KM, Ting JC, Yu K, Fu J, Liu S, Cristescu R, Nebozhyn M, Gong L, Yue YG, Wang J, Ronghua C, Loboda A, Hardwick J, Liu X, Dai H, Jin JG, Ye XS, Kang SY, Do IG, Park JO, Sohn TS, Reinhard C, Lee J, Kim S, Aggarwal A. Genomic landscape and genetic heterogeneity in gastric adenocarcinoma revealed by whole-genome sequencing. *Nat Commun* 2014; 5: 5477 [PMID: 25407104 DOI: 10.1038/ncomms6477]
 - 65 Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, Kim SC, Lee B, Rho K, Lee JE, Cho KH, Kim W, Ju H, Kim J, Kim SJ, Kim WS, Lee S, Ko YH. A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. *Nat Genet* 2014; 46: 371-375 [PMID: 24584070 DOI: 10.1038/ng.2916]
 - 66 Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, Muto H, Tsuyama N, Sato-Otsubo A, Okuno Y, Sakata S, Kamada Y, Nakamoto-Matsubara R, Tran NB, Izutsu K, Sato Y, Ohta Y, Furuta J, Shimizu S, Komeno T, Sato Y, Ito T, Noguchi M, Noguchi E, Sanada M, Chiba K, Tanaka H, Suzukawa K, Nanmoku T, Hasegawa Y, Nureki O, Miyano S, Nakamura N, Takeuchi K, Ogawa S, Chiba S. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet* 2014; 46: 171-175 [PMID: 24413737 DOI: 10.1038/ng.2872]
 - 67 Palomero T, Couronné L, Khiabani H, Kim MY, Ambesi-Impiomato A, Perez-Garcia A, Carpenter Z, Abate F, Allegretta M, Haydu JE, Jiang X, Lossos IS, Nicolas C, Balbin M, Bastard C, Bhagat G, Piris MA, Campo E, Bernard OA, Rabadan R, Ferrando AA. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet* 2014; 46: 166-170 [PMID: 24413734 DOI: 10.1038/ng.2873]
 - 68 Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; 513: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]
 - 69 Lin Y, Wu Z, Guo W, Li J. Gene mutations in gastric cancer: a review of recent next-generation sequencing studies. *Tumour Biol* 2015; 36: 7385-7394 [PMID: 26364057 DOI: 10.1007/s13277-015-4002-1]
 - 70 Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; 1: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]
 - 71 Chen K, Yang D, Li X, Sun B, Song F, Cao W, Brat DJ, Gao Z, Li H, Liang H, Zhao Y, Zheng H, Li M, Buckner J, Patterson SD, Ye X, Reinhard C, Bhatena A, Joshi D, Mischel PS, Croce CM, Wang YM, Raghavakaimal S, Li H, Lu X, Pan Y, Chang H, Ba S, Luo L, Cavenee WK, Zhang W, Hao X. Mutational landscape of gastric adenocarcinoma in Chinese: implications for prognosis and therapy. *Proc Natl Acad Sci USA* 2015; 112: 1107-1112 [PMID: 25583476 DOI: 10.1073/pnas.1422640112]

编辑: 闫晋利 电编: 胡珊





Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton,
CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
<http://www.wjgnet.com>



ISSN 1009-3079

