ADH1B基因启动子区多态性和结直肠癌易感性关联分析

杜淑娇¹, 胡晓雯¹, 蒋婕¹, 孙嘉仪¹, 崔高平¹, 杨添淇¹, 张娟¹, 师咏勇¹, 贺林¹,
万春玲^{1*}, 闫晓梅^{2*}

1. 上海交通大学Bio-X研究院, 上海市精神卫生中心, 上海 200030;

2. 上海交通大学生命科学技术学院, 上海 200240

* 联系人, E-mail: clwan@sjtu.edu.cn; xmyan@sjtu.edu.cn

收稿日期: 2017-02-13; 接受日期: 2017-03-15; 网络发表日期: 2017-04-08

国家重点研发计划(批准号: 2016YFC1306802, 2016YFC1306900)和国家自然科学基金(批准号: 81421061, 81361120389)资助

摘要 乙醇脱氢酶在酒精代谢中发挥着氧化乙醇的作用. 以往的许多研究发现, 乙醇脱氢酶家族中的成员乙醇脱氢酶-1B(ADH1B)的蛋白表达量在多种肿瘤组织中呈现下降的趋势. 为了探讨中国汉族人群中ADH1B基因启动子区多态性与结直肠癌易感性的关系, 本研究在92例结直肠癌患者的癌旁组织中对ADH1B基因转录起始位点上游大小为2444 bp的启动子区进行了一代测序扫描, 并结合千人基因组数据库中的208例中国汉族人群数据分析了ADH1B基因启动子区的多态性与结直肠癌易感性之间的关系. 本研究组在该区域内共检测到8个多态位点, 其中rs3811802位点与结直肠癌的易感性表现出极强的相关性(OR=2.136; 95% CI=1.2~3.7; P=0.006). 本研究认为, 位于ADH1B基因启动子区的多态位点rs3811802是中国汉族人群中结直肠癌的风险位点.

关键词 乙醇脱氢酶-1B, 结直肠癌, 单核苷酸多态性

结直肠癌(colorectal carcinoma, CRC)是世界上第三大常见的恶性肿瘤, 其发病率和死亡率都在逐年增加^[1,2]. 作为一种复杂疾病, 结直肠癌的发病风险受到环境和遗传因素的共同作用. 相关研究表明, 在不同人种中遗传因素对结直肠癌的发生发展均发挥着重要作用^[3-5].

流行病学研究认为酒精代谢异常与多种肿瘤的发生相关, 例如, 口腔癌、咽癌、喉癌、食道癌、肝癌、结直肠癌和乳腺癌等^[6,7]. 乙醇脱氢酶(alcohol dehydrogenase, ADH)和乙醛脱氢酶(aldehyde dehydro-

genase, ALDH)是人体内代谢酒精的主要酶类^[8]. 乙醇进入体内经过乙醇脱氢酶氧化为乙醛, 进而被乙醛脱氢酶代谢为乙酸^[9]. 乙醇脱氢酶家族共有5种亚型, 其中ADH1A, ADH1B和ADH1C属于I类, ADH4属于II类, ADH5属于III类, ADH7属于IV类, ADH6属于V类^[9,10]. 乙醇脱氢酶的I类同工酶是酒精代谢中氧化乙醇的主要酶类^[11]. 许多研究表明, ADH1B基因的蛋白表达在多种肿瘤中均存在下调的趋势^[12-18]. 与正常组织相比, 结直肠癌肿瘤组织中ADH1B基因的mRNA水平较低^[19,20].

引用格式: 杜淑娇, 胡晓雯, 蒋婕, 等. ADH1B基因启动子区多态性和结直肠癌易感性关联分析. 中国科学: 生命科学, 2017, 47: 369-376
Du S J, Hu X W, Jiang J, et al. An association between single nucleotide polymorphisms in the promoter region of alcohol dehydrogenase 1B and the risk of developing colorectal carcinoma in the Chinese Han population. Sci Sin Vitae, 2017, 47: 369-376, doi: 10.1360/N052017-00081

研究发现, 位于*ADH1B*基因外显子区的位点rs1229984 A>G的多态性与结直肠癌易感性有很强的关联, 携带*ADH1B* rs1229984 G等位基因型的人群具有较高的结直肠癌发病风险^[21~23]。在人类HepG2细胞系中, 位于*ADH1B*基因启动子区的多态位点rs1229982等位基因从C到A的变化会导致启动子活性提高1.4倍^[24]。然而, 目前仍缺乏对*ADH1B*基因启动子区多态性与结直肠癌易感性之间关系的研究。本研究通过在结直肠癌患者的癌旁组织中筛查*ADH1B*基因上游大小为2444 bp的启动子区多态性, 研究*ADH1B*基因与中国汉族人群中结直肠癌的关联。

1 材料与方法

1.1 研究对象

本研究的病例组样本取自浙江大学医学院附属第二医院。样本为92例经病理学确诊为结直肠癌的患者的癌旁组织, 其中男性57例, 女性35例(表1)。本研究得到上海交通大学伦理委员会和相关管理机构的支持, 受试者本人或其法定监护人均已签署知情同意书。对照组的基因测序数据来自千人基因组数据库的中国汉族人群(www.1000genomes.org), 共208例正常人, 其中男性98例, 女性110例。

1.2 方法

(1) 基因组DNA抽提。 取结直肠癌患者癌旁组

织20~30mg, 使用DNeasy Blood & Tissue Kit (QIAGEN GmbH, 德国)抽提基因组DNA。提取的DNA样本使用超微量分光光度计NanoDrop 2000 (Thermo Scientific, 美国)进行质量控制。

(2) 引物的设计。 运用引物设计软件PRIMER 5进行PCR引物设计, 由上海捷瑞生物工程有限公司合成PCR引物(表2)。

(3) 基因扩增和扩增产物基因测序。 PCR总反应体系为25 μ L, 其中包括模板DNA 20 ng, Pfu PCR MasterMix 1.25 U (2 $\times$, Tiangen, 北京)以及正反向引物各10 pmol。在GeneAmp PCR system 9700(Applied Biosystems, 美国)上进行PCR扩增, 热循环条件采用Touchdown方式, 具体反应程序如下: 94 $^{\circ}$ C预变性5 min; 94 $^{\circ}$ C变性30s, 64 $^{\circ}$ C退火30 s, 每个循环降低0.5 $^{\circ}$ C, 72 $^{\circ}$ C延伸1 min, 14个循环; 后接94 $^{\circ}$ C变性30 s, 57 $^{\circ}$ C退火30 s, 72 $^{\circ}$ C延伸1 min, 30个循环; 最后72 $^{\circ}$ C延伸10 min。扩增结束后PCR产物经1.5%琼脂糖凝胶电泳和FR-980A生物电泳图像分析系统(上海复日科技有限公司)检测。将PCR产物送至赛默飞世尔科技(中国)有限公司经虾碱性磷酸酶(Roche, 瑞士)和核酸外切酶(NewEngland BioLabs, 美国)纯化, 反应条件: 37 $^{\circ}$ C消化45 min, 85 $^{\circ}$ C灭活20 min。随后采用BigDye Terminator version 3.1 Cycle Sequencing kit (Applied Biosystems)和ABI 3730全自动测序仪(Applied Biosystems)进行Sanger测序。测序结果用DNASar中的SeqMan软件进行人工判读。

(4) 统计学分析。 运用SHEsis遗传分析软件(<http://>

表1 研究对象的临床信息^{a)}

变量	病例组(n=92)		对照组(n=208)		P
	样本数量	百分比	样本数量	百分比	
性别					
男	57	62.0%	98	47.1%	0.024
女	35	38.0%	110	52.9%	
年龄(岁)	62.3 $\pm$ 11.7				
< 60	40	43.5%	n/a	—	
$\geq$ 60	52	56.5%	n/a	—	
Duke分期					
A	10	10.9%	—	—	
B	35	38.0%	—	—	
C	36	39.1%	—	—	
D	10	10.9%	—	—	
n/a	1	1.1%	—	—	

a) n/a: 缺失值

表 2 本实验中PCR的引物序列^{a)}

引物编号	引物序列 (5'→3')	退火温度(°C)	PCR扩增区域(bp)
1	F: GGCTATAATTCCCTGAAATGCT	57.6	-2444~ -1945
	R: CCTTTATGTTAGGACACGCACT	56.7	
2	F: AAGGCTTCCTCATTCTCAAATTAG	58.7	-2260~ -1732
	R: ACTTCTTTCCATCCCTGTCATAC	56.9	
3	F: TCTTCTGGATTATGGGACTGC	56.8	-1997~ -1404
	R: CCAATAGAAAGCAAAGGAGGT	55.9	
4	F: AAACCACAGGAGGGATGCTAG	58.4	-1775~ -1332
	R: GCCAAGGGAACATTTCACTAAG	58.5	
5	F: TATCTTCTTTCCGTCATACCTTTC	57.1	-1425~ -776
	R: TTTTGCCTTAATTTCTTATCTGT	57.3	
6	F: TGTTCCCAAAGCATTAACTGAC	57.3	-1042~ -373
	R: CGTTCTGCCTTGTATTCCTT	57.0	
7	F: TGCTGTGACTAATTGGGTGTCT	57.3	-538~+14
	R: CCTGCTGTGCTCATGTCGT	57.1	

a) 转录起始点为+1

analysis.bio-x.cn)进行哈迪-温伯格平衡检验、连锁不平衡系数计算、单倍型分析、相对风险度(odds ratios, ORs)计算和95%置信区间(confidence intervals, CIs)计算. 采用统计分析软件SPSS Statistics 17.0(IBM, 美国)进行统计学分析. 运用卡方检验对各个多态位点的等位基因频率和基因型频率在两组样本间的差异进行统计学分析, 并进行Bonferroni校正^[25]. 当 $P<0.05$ 时表示差异具有统计学意义.

2 结果与分析

2.1 ADH1B基因启动子区多态位点扫描

通过对ADH1B基因转录起始位点上游2444 bp进行双脱氧核苷酸终止子测序, 进而和NCBI数据库中参考序列(GRCh37)对比, 在此批结直肠癌患者的癌旁组织中共发现8个单核苷酸多态位点(single-nucleotide polymorphisms, SNPs). 这些多态位点在基因上的位置以及PCR产物的扩增区域如图1所示.

2.2 等位基因和基因型差异分析

本研究组在目标区域共检测到8个多态位点. 表3展示了这些位点的等位基因频率和基因型频

率在结直肠癌患者以及千人基因组的中国汉族人群之间的差异. 发现ADH1B多态位点rs3811802(-1733C>T)的等位基因C在结直肠癌患者中的频率是14.7%, 而该位点在千人基因组数据库中中国汉族人群中的频率是7.5%. 该位点与结直肠癌易感性表现出较强的相关性($OR=2.136$; 95% $CI=1.2\sim3.7$; $P=0.006$), 且在经过Bonferroni校正后仍具有统计学意义(校正后 $P=0.048$). 另外7个多态位点 rs3811801(-1831C>T), rs1229982(-1444A>C), rs28913903(-992C>G), rs6810842(-957A>C), rs2070897(-822C>T), rs2070898(-809C>T) 和 rs1159918(-521T>G)并未发现和结直肠癌的发生有明显关联. 除了rs3811802外, 其余SNP位点均符合哈温平衡.

2.3 连锁不平衡系数和单倍型分析

表4展示了本研究中连锁不平衡系数 $D'>0.8$ 的位点和在病例组与对照组中频率 >0.3 的单倍体型. 统计分析结果显示, 单倍体型h3'CTCCCTTG'与结直肠癌的发病风险显著相关($OR=0.451$; 95% $CI=0.27\sim0.76$; $P=0.002$)(表5).

表3 等位基因频率及基因型频率与结直肠癌易感性的风险估计

SNP位点	等位基因		P	P(校正后)	OR (95%CI)	基因型			P	P(校正后)	哈迪-温伯格平衡
rs3811801	C(%)	T(%)				C C(%)	C T(%)	T T(%)			
	病例组	71(0.386)	113(0.614)	0.309	1.000	0.832 (0.584~1.1860)	病例组	11 (0.120) 49 (0.533) 32 (0.348)	0.554	1.000	0.235
	对照组	179(0.430)	237(0.570)				对照组	33 (0.159) 113 (0.543) 62 (0.298)			0.119
rs3811802	C(%)	T(%)				C C(%)	C T(%)	T T(%)			
	病例组	27(0.147)	157(0.853)	0.006	0.046	2.136 (1.2346~3.696)	病例组	9 (0.098) 9 (0.098) 74 (0.804)	0.000	0.000	0.000
	对照组	31(0.075)	385(0.925)				对照组	0 (0.000) 31 (0.149) 177 (0.851)			0.246
rs1229982	A(%)	C(%)				A A(%)	A C(%)	C C(%)			
	病例组	14(0.076)	170(0.924)	0.079	0.634	1.933 (0.932~4.010)	病例组	0 (0.000) 14 (0.152) 78 (0.848)	0.079	0.634	0.430
	对照组	17(0.041)	399(0.959)				对照组	1 (0.005) 15 (0.072) 192 (0.923)			0.248
rs28913903	C(%)	G(%)				C C(%)	C G(%)	G G(%)			
	病例组	159(0.864)	25(0.136)	0.776	1.000	0.929 (0.557~1.548)	病例组	67 (0.728) 25 (0.272) 0 (0.000)	0.719	1.000	0.132
	对照组	363(0.873)	53(0.127)				对照组	156 (0.750) 51 (0.245) 1 (0.005)			0.138
rs6810842	A(%)	C(%)				A A(%)	A C(%)	C C(%)			
	病例组	33(0.179)	151(0.821)	0.434	1.000	1.202 (0.758~1.907)	病例组	3 (0.033) 27 (0.293) 62 (0.674)	0.548	1.000	0.977
	对照组	64(0.154)	352(0.846)				对照组	3 (0.014) 58 (0.279) 147 (0.707)			0.306
rs2070897	C(%)	T(%)				C C(%)	C T(%)	T T(%)			
	病例组	35(0.190)	149(0.810)	0.268	1.000	1.292 (0.820~2.035)	病例组	4 (0.043) 27 (0.293) 61 (0.663)	0.282	1.000	0.650
	对照组	64(0.154)	352(0.846)				对照组	3 (0.014) 58 (0.279) 147 (0.707)			0.306
rs2070898	C(%)	T(%)				C C(%)	C T(%)	T T(%)			
	病例组	40(0.217)	144(0.783)	0.321	1.000	1.243 (0.809~1.910)	病例组	3 (0.033) 34 (0.370) 55 (0.598)	0.587	1.000	0.409
	对照组	76(0.183)	340(0.817)				对照组	5 (0.024) 66 (0.317) 137 (0.659)			0.367
rs1159918	G(%)	T(%)				G G(%)	G T(%)	T T(%)			
	病例组	148(0.804)	36(0.196)	0.266	1.000	0.775 (0.495~1.215)	病例组	60 (0.652) 28 (0.304) 4 (0.043)	0.279	1.000	0.751
	对照组	350(0.841)	66(0.159)				对照组	145 (0.697) 60 (0.288) 3 (0.014)			0.246

图 1 单核苷酸多态位在染色体上的位置

扩增子是由各对引物经过PCR反应后产生的扩增序列; ATG: 转录起始子

表 4 连锁不平衡分析

	rs3811802	rs1229982	rs28913903	rs6810842	rs2070897	rs2070898	rs1159918
rs3811801	0.669	0.999	0.999	1.000	0.959	0.967	0.960
rs3811802	—	0.841	0.775	0.399	0.393	0.599	0.388
rs1229982		—	0.998	1.000	0.941	0.936	1.000
rs28913903			—	0.999	0.997	0.998	0.999
rs6810842				—	0.979	0.977	1.000
rs2070897					—	0.978	0.959
rs2070898						—	0.937
rs1159918							—

表 5 单倍体型组合在病例组 and 对照组中的分布^{a)}

编号	单倍体型	频率(%)		OR (95%CI)	P
		病例组	对照组		
h1	CCACACCT	4.8	3.8	1.437 (0.537~3.845)	0.468
h2	CTCCACCT	8.8	7.2	1.419 (0.680~2.963)	0.350
h3	CTCCCTTG	14.0	29.0	0.451 (0.268~0.758)	0.002
h4	TTCCTTG	46.8	44.3	1.420 (0.932~2.166)	0.103
h5	TTCGCTTG	10.0	10.5	1.068 (0.559~2.089)	0.817

a) 单倍体型的多态位点排列为rs3811801-rs3811802-rs1229982-rs28913903-rs6810842-rs2070897-rs2070898-rs1159918

3 讨论

流行病学研究显示, 结直肠癌在中国的发生率和死亡率一直居高不下^[26,27]. 基因变异可能导致基因表达或者活性发生改变, 进而影响到结直肠癌的发生. 为了分析ADH1B基因启动子区的变异, 曾有研究关注细胞系中ADH1B基因转录因子前约1.5 kb的启动子区^[24]. 本项研究在更大范围内分析了ADH1B基因启

动子区的多态性与结直肠癌易感性之间的关系. 本研究发现, 位于ADH1B启动子上游1733 bp处的多态位点rs3811802 (C>T)与中国人结直肠癌的易感性显著相关.

一些转录因子, 如CCAAT /增强子结合蛋白、特异性蛋白1、肝细胞核因子-1和激活蛋白-1, 均有可能通过结合到ADH1B启动子区的某些特定位置而影响

基因转录的调节^[28]。*ADH1B*基因启动子区的两个多态位点-887C>A和-739C>T位于转录调控区附近,它们的变异将直接影响负转录调控因子的结合进而影响基因的表达^[29]。而多态位点rs3811802的功能尚不明确。在目前的研究中,*ADH1B*基因的多态性与肿瘤内在机制之间的关系仍然存在争议,可能是通过酒精代谢中能抑制DNA合成和修复的乙醛的积累进而影响肿瘤的发生和发展。一项荟萃分析研究显示,*ADH1B*, *MGMT*, *SOD2*, *XPC*和*PPARG*基因均可能与结直肠癌易感性相关^[30]。

本研究发现,*ADH1B*多态位点rs3811802(-1733C>T)的C等位基因频率在中国汉族结直肠癌患者中显著高于正常人,说明该位点是中国人结直肠癌的风险位点。通过对比千人基因组数据库(www.1000genomes.org),发现该位点的C等位基因的

频率在东亚人群、非洲人群、美洲人群、欧洲人群和南非人群中分别是9.23%, 51.44%, 34.44%, 46.92%和26.58%,这一数据显示rs3811802 C>T多态位点在不同地域人群中的频率差异较大。而已有研究表明,结直肠癌发病率在不同地区存在明显差异,在欧美地区的发病率较高,在东亚地区发病率相对较低^[31~33]。不同地区结直肠癌发病率的差异提示,其与*ADH1B*多态位点rs3811802的C等位基因的频率之间可能存在相关的趋势,本研究组认为该位点与结直肠癌的关系值得在不同地区的人群中进行更多的研究。

本研究表明,*ADH1B*基因启动子区的多态位点rs3811802在中国汉族人群中与结直肠癌患病风险密切相关。关于*ADH1B*基因启动子区多态性及其生物学功能,以及二者与结直肠癌之间的关系值得进一步研究。

参考文献

- 1 Favoriti P, Carbone G, Greco M, et al. Worldwide burden of colorectal cancer: a review. *Updates Surg*, 2016, 68: 7-11
- 2 Bode A M, Dong Z, Wang H. Cancer prevention and control: alarming challenges in China. *Nat Sci Rev*, 2016, 3: 117-127
- 3 Seitz H K, Becker P. Alcohol metabolism and cancer risk. *Alcohol Res Health*, 2007, 30: 38-47
- 4 Druesne-Pecollo N, Tehard B, Mallet Y, et al. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. *Lancet Oncol*, 2009, 10: 173-180
- 5 Zeng C, Matsuda K, Jia W H, et al. Identification of susceptibility loci and genes for colorectal cancer risk. *Gastroenterology*, 2016, 150: 1633-1645
- 6 Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol*, 2006, 7: 149-156
- 7 Guo J, Yu W, Su H, et al. Genomic landscape of gastric cancer: molecular classification and potential targets. *Sci China Life Sci*, 2017, 60: 126-137
- 8 Shen Y C, Fan J H, Edenberg H J, et al. Polymorphism of *ADH* and *ALDH* genes among four ethnic groups in China and effects upon the risk for alcoholism. *Alcohol Clin Exp Res*, 1997, 21: 1272-1277
- 9 Duester G, Farrés J, Felder M R, et al. Recommended nomenclature for the vertebrate alcohol dehydrogenase gene family. *Biochem Pharmacol*, 1999, 58: 389-395
- 10 Zuo L, Gelernter J, Kranzler H R, et al. *ADH1A* variation predisposes to personality traits and substance dependence. *Am J Med Genet*, 2010, 453B: 376-386
- 11 Jelski W, Zalewski B, Chrostek L, et al. The activity of class I, II, III, and IV alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in colorectal cancer. *Dig Dis Sci*, 2004, 49: 977-981
- 12 Giordano T J, Thomas D G, Kuick R, et al. Distinct transcriptional profiles of adrenocortical tumors uncovered by DNA microarray analysis. *Am J Pathol*, 2003, 162: 521-531
- 13 Kaur H, Mao S, Li Q, et al. RNA-Seq of human breast ductal carcinoma *in situ* models reveals aldehyde dehydrogenase isoform 5A1 as a novel potential target. *PLoS ONE*, 2012, 7: e50249
- 14 Hansel D E, Zhang Z, Petillo D, et al. Gene profiling suggests a common evolution of bladder cancer subtypes. *BMC Med Genomics*, 2013, 6: 42
- 15 Yu M C, Lee Y S, Lin S E, et al. Recurrence and poor prognosis following resection of small hepatitis B-related hepatocellular carcinoma lesions are associated with aberrant tumor expression profiles of glypican 3 and osteopontin. *Ann Surg Oncol*, 2012, 19: 455-463
- 16 Han S S, Kim W J, Hong Y, et al. RNA sequencing identifies novel markers of non-small cell lung cancer. *Lung Cancer*, 2014, 84: 229-235
- 17 Ahn W S, Kim K W, Bae S M, et al. Targeted cellular process profiling approach for uterine leiomyoma using cDNA microarray, proteomics and

- gene ontology analysis. *Int J Exp Pathol*, 2004, 84: 267–279
- 18 Ye H, Yu T, Temam S, et al. Transcriptomic dissection of tongue squamous cell carcinoma. *BMC Genomics*, 2008, 9: 69
- 19 Kropotova E S, Zinovieva O L, Zyryanova A F, et al. Altered expression of multiple genes involved in retinoic acid biosynthesis in human colorectal cancer. *Pathol Oncol Res*, 2014, 20: 707–717
- 20 Chiang C P, Jao S W, Lee S P, et al. Expression pattern, ethanol-metabolizing activities, and cellular localization of alcohol and aldehyde dehydrogenases in human large bowel: association of the functional polymorphisms of *ADH* and *ALDH* genes with hemorrhoids and colorectal cancer. *Alcohol*, 2012, 46: 37–49
- 21 Wu M, Chang S C, Kampman E, et al. Single nucleotide polymorphisms of *ADH1B*, *ADH1C* and *ALDH2* genes and esophageal cancer: a population-based case-control study in China. *Int J Cancer*, 2013, 132: 1868–1877
- 22 Lao-Sirieix P, Caldas C, Fitzgerald R C. Genetic predisposition to gastro-oesophageal cancer. *Curr Opin Genet Dev*, 2010, 20: 210–217
- 23 Matsuo K, Wakai K, Hirose K, et al. A gene-gene interaction between *ALDH2* Glu487Lys and *ADH2* His47Arg polymorphisms regarding the risk of colorectal cancer in Japan. *Carcinogenesis*, 2006, 27: 1018–1023
- 24 Pochareddy S, Edenberg H J. Variation in the *ADH1B* proximal promoter affects expression. *Chem Biol Interact*, 2011, 191: 38–41
- 25 Sang J, Jia L, Zhao B, et al. Association of three single nucleotide polymorphisms at the *SIX1-SIX6* locus with primary open angle glaucoma in the Chinese population. *Sci China Life Sci*, 2016, 59: 694–699
- 26 Sung J J, Lau J Y, Goh K, et al. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol*, 2005, 6: 871–876
- 27 Hu X, Yang H, He J, et al. The cancer genomics and global cancer genome collaboration. *Sci Bull*, 2015, 60: 65–70
- 28 van Ooij C, Snyder R C, Paepers B W, et al. Temporal expression of the human alcohol dehydrogenase gene family during liver development correlates with differential promoter activation by hepatocyte nuclear factor 1, CCAAT/enhancer-binding protein alpha, liver activator protein, and D-element-binding protein. *Mol Cell Biol*, 1992, 12: 3023–3031
- 29 Pershing L K, Chen Y, Tkachuk A N, et al. Coding and non-coding polymorphisms in alcohol dehydrogenase alters protein expression and alcohol-associated erythema. *J Invest Dermatol*, 2008, 128: 616–627
- 30 Chen C, Wang L, Liao Q, et al. Association between six genetic polymorphisms and colorectal cancer: a meta-analysis. *Genet Test Mol Biomarkers*, 2014, 18: 187–195
- 31 齐鲁, 丁彦青. 大肠癌患者生存相关基因的筛选与网络调控分析. 中国科学: 生命科学, 2014, 44: 481
- 32 Hagggar F A, Boushey R P. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg*, 2009, 22: 191–197
- 33 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 2015, 136: E359–E386

An association between single nucleotide polymorphisms in the promoter region of alcohol dehydrogenase 1B and the risk of developing colorectal carcinoma in the Chinese Han population

DU ShuJiao¹, HU XiaoWen¹, JIANG Jie¹, SUN JiaYi¹, CUI GaoPing¹, YANG TianQi¹, ZHANG Juan¹, SHI YongYong¹, HE Lin¹, WAN ChunLing¹ & YAN XiaoMei²

1 Shanghai Mental Health Center, Bio-X Institutes, Shanghai Jiao Tong University, Shanghai 200030, China;

2 School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai 200240, China

Alcohol dehydrogenase 1B (ADH1B) functions as an oxidase that is involved in the conversion of ethanol to acetaldehyde. Previous studies have shown that ADH1B expression levels are lower in tumor tissues than in adjacent normal tissues in many cancer types. Therefore, the aim of our study was to evaluate the potential association between single nucleotide polymorphisms (SNPs) in the promoter region of ADH1B and the risk of developing colorectal carcinoma (CRC) in the Chinese Han population including 92 CRC patients and 208 controls. The promoter region (−2444 to +14 bp of transcription start site) was sequenced via Sanger sequencing in 92 non-cancerous tissues adjacent to tumor tissues from patients diagnosed with CRC. Eight SNPs were identified in this region and the allele frequencies were compared with that of the Chinese Han population in the 1000 Genomes Project. There was difference in the allele frequency of rs3811802 between the patients with CRC and healthy controls ($P=0.006$). Subjects carrying allele C had a significant 2.136-fold (95% CI=1.2–3.7) increased risk of developing CRC. Therefore, we suggested that the rs3811802 polymorphism in ADH1B is associated with susceptibility to CRC in the Chinese Han population.

alcohol dehydrogenase-1B, colorectal carcinoma, single nucleotide polymorphism

doi: [10.1360/N052017-00081](https://doi.org/10.1360/N052017-00081)