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述评 EDITORIAL

炎症性肠病易感基因研究进展

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Research progress in susceptible genes of inflammatory bowel disease

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Abstract
The mechanism of inflammatory bowel disease (IBD) is partially understood, but it is certain that a genetic predisposition, through the inheritance of a number of contributory genetic polymorphisms, contributes to the pathogenesis of IBD. These variant forms of genes may be associated with an abnormal response to normal luminal bacteria. Those genes that have been consistently associated with IBD thus far primarily fall into one of three classes: those affecting bacterial recognition, those affecting immune response, and a third group affecting mucosal transport polarity or mucosal transporter function. This article reviews the IBD related genes mentioned above.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Susceptibility genes

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摘要
炎症性肠病(inflammatory bowel disease, IBD)的发生与基因多态性所致的遗传易感性相关, 目前研究已发现许多IBD相关基因及易感突变位点. 这些基因可能与机体针对肠腔正常菌群产生异常免疫反应有关, 大致可分为细菌识别相关基因、免疫应答相关基因以及黏膜转运和极性相关基因3类. 本文将就这些基因与IBD遗传易感性关系的研究进展作一介绍.

关键词: 炎症性肠病; 溃疡性结肠炎; 克罗恩病; 易感基因

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0 引言
炎症性肠病(inflammatory bowel disease, IBD)是胃肠道慢性非特异性炎症性疾病, 主要包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD). 过去欧洲和北美人群中IBD发病率较高, 亚洲人群发病率较低, 然而近20年来IBD在亚洲人群中的发病呈现明显增高趋势. IBD的病因和发病机制尚未完全明确, 目前认为IBD的发病是由环境、遗传、感染和免疫等多种因素相互作用所致. 同卵双生子高共患病率, IBD的家族聚集现象和IBD发病的种族差异性提示遗传因素在其发病中的重要作用. 近年来研究表明肠黏膜屏障功能异常与IBD发病关系密切[1]. 肠腔表面积很大, 由上皮细胞紧密连接而成, 长期暴露于各种食物成分、共生菌及病原菌. 肠道上皮有重要的屏障功能, 在多数情况下, 上皮细胞对各种损伤稳定应答, 炎症处于限制状态. IBD发生时, 肠黏膜屏障功能障碍, 黏膜通透性增高, 导致肠腔内细菌、抗原等物质移位至黏膜固有层而激活免疫细胞, 诱导黏膜过度免疫反应的发生, 继而进一步破坏肠黏膜屏障, 加重黏膜异常免疫反应. 自从2001年Hugot *et al*[2]发现CARD15/NOD2与CD发病显著相关以来, 现在已有许多有关基因与IBD相关性

■背景资料
过去欧洲和北美人群中IBD发病率较高, 亚洲人群发病率较低, 然而近20年来IBD在亚洲人群中的发病呈现明显增高趋势. IBD的病因和发病机制尚未完全明确, 目前认为IBD的发病是由环境、遗传、感染和免疫等多种因素相互作用所致. 同卵双生子高共患病率, IBD的家族聚集现象和IBD发病的种族差异性提示遗传因素在其发病中的重要作用.

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■研发前沿
位于人类6号染色体短臂上的主要组织相容性复合体基因, 因其在免疫应答和免疫调节中的重要作用成为近十几年来遗传学和免疫学的研究热点.

的报道, 其中大约有9个基因位点经相关性研究得到证实. 根据其功能大致可分为以下3类: 细菌识别相关基因、免疫应答相关基因以及黏膜转运和极性相关基因. 本文将分别予以阐述.

1 细菌识别相关基因

1.1 CARD15/NOD2 胱冬酶吸引域家族成员15(caspase-activation recruitment domain 15, CARD15)/核苷酸结合寡聚域2(nucleotide-binding oligomerization domain 2, NOD2)是第一个被发现的CD易感基因, 位于16号染色体着丝粒旁的IBD1位点. 他主要在巨噬细胞及小肠腺特有的潘氏细胞中表达, 负责编码NOD2蛋白. 其基本功能包括激活Casepase介导细胞凋亡, 诱导NF-κB活化引发炎症反应和作为细菌胞壁成分胞乙酰二聚肽(muramyl dipeptide, MDP)的受体识别细菌, 从而刺激抗菌肽(antimicrobial peptide)如α-防御素等的分泌以保护宿主免受侵犯. 目前该基因上已有3个突变明确为CD发病的独立危险因子[3], 其中2个为单核苷酸改变, 即rs2066844(p. R702W)和rs2066845(p. G908R), 另1个系在11外显子的3020核苷酸处插入1个胞嘧啶(3020insC), 导致1007密码子的第2个核苷酸移码突变, 发生Leu1007Pro氨基酸改换(Leu1007fs), 终止密码子提前, 使其编码的蛋白质丢失最后33个氨基酸导致NF-κB活性的降低, 机体先天性低反应, 从而诱导机体对肠道细菌异常强烈的免疫反应引起CD发生. 对爱尔兰[4]及欧洲犹太人群[5]的研究提示CARD15的另外2个突变rs2066842(p. P268S)及IVS8^{+158}(JW1)可能与CD相关, 但是否导致编码的NOD2蛋白功能发生改变及是否与其他基因单核苷酸多态性(single nucleotide polymorphism, SNP)位点存在不平衡连锁尚有待进一步研究. 虽然前3种突变已被证明与CD相关, 但在不同人种中, 其出现频率及与疾病相关程度不同. 德系和西班牙系犹太人CD患者中3种主要突变频率均显著增高, 前者3种突变携带率明显高于后者[6]. 荷兰人群[7]中CD发病与G908R和Leu1007fs有关. 瑞典人群[8]中CD发病与R702W和G908R突变有关, 而与Leu1007fs无关, 相反在丹麦人群[9]中Leu1007fs为主要突变型. 捷克人群[10]中CD患者1007fs、G908R和P268S 3种突变频率明显高于对照组, 回归分析提示1007fs、G908R、R702W分别与CD密切相关, 而P268S与CD没有独立的关联. 对土耳其人群[11]的研究未发现上述5种突变与IBD发病相关. 对日本[12]及我国香港[13]、浙江[14]、湖北[15]和广东[16]等地区人群的研究未发现上述3个西方人常见的CARD15/NOD2基因多态性位点与亚洲人IBD发病相关. 最近, 龙靖华 *et al*[17]发现我国人群CD患者中存在CARD15/NOD2基因P268S突变, 且与患者的发病年龄、病变部位和并发症相关. 目前国外研究多认为CARD15基因型与临床表型相关. Lesage *et al*[18]、Ahmad *et al*[19]、Vermeire *et al*[20]的研究均提示CARD15基因突变与早年发病及回肠受累关系密切. 近年来, CARD15与其他易感基因的关系也逐渐受到关注, Linderson *et al*[21]研究发现CARD15/NOD2与另一个重要的IBD易感基因TNF-α的启动子的基因多态性间存在关联, 二者相互作用, 影响TNF-α的表达. Gazouli *et al*[22]认为CARD15/NOD2和TLR4或CD14之间的相互作用可增加IBD尤其是CD的发病危险性. 最近Beynon *et al*[23]研究发现CARD15的基因型影响外周血单核细胞包括TNF-α, IL-10, IL-1β和IL-12 p40等在内的多种MDP相关的细胞因子的表达水平. 在今后的研究中弄清CARD15/NOD2与其他因子之间相互作用的机制将是非常重要的.

1.2 ATG16L1 自噬相关16样1(autophagy-related 16-like 1, ATG16L1)基因位于2q37.1, 主要表达于肠上皮细胞和CD4$^+$、CD8$^+$、CD19$^+$淋巴细胞, 其编码的ATG16L1蛋白是一种涉及处理细胞内细菌的自噬小体代谢途径的蛋白, 该蛋白在处理胞内细菌感染时发挥重要作用, 如他可抑制巨噬细胞内结核分枝杆菌的生长, 敲除ATG16L1基因会降低HeLa细胞对沙门氏菌的吞噬作用[24]. Hampe *et al*通过全基因组扫描及回归分析筛选出与CD相关的ATG16L1基因SNP位点rs2241880(Thr300Ala, p. T300A), 并通过大样本量的实验证实欧洲人此位点的多态性与CD易感性相关, 与UC无关; 且此突变导致CD的发病风险与CARD15显著相关[25-26]. 目前该位点与CD的关系已在西方人群中得到反复验证[27-31]. 对日本人群[32]及我国人群[33]的研究均未发现该多态性位点与CD相关. 最近Fowler *et al*[34]研究发现此突变与UC的发生负相关. 在澳大利亚[34]及北欧[26,35]人群中的研究显示T300A突变与回肠型CD显著相关.

1.3 HBD-2、HBD-3和HBD-4 近来, 抗菌肽(antimicrobial peptide)作为固有免疫系统的一分子在抵御微生物中的作用越来越受到重视. 防御素(defensin)是哺乳动物体内发现的、在

宿主防御中起重要作用的一类广谱抗菌肽. 根据其基因及蛋白水平结构特点分为α和β两型, 后者又分为4个亚型, 即人类β防御素1, 2, 3和4(human beta defensins B1, B2, B3 and B4, HBD-1, HBD-2, HBD-3和HBD-4), 其中HBD-2是一种低相对分子质量富含半胱氨酸的抗菌肽. 近年研究表明, HBD-2是第一个在防御应答时于转录水平有所上调的防御素, 且在宿主防御特别是在黏膜表面抵御革兰阴性菌和真菌方面具有重要作用. 携带突变型CARD15基因的CD患者回肠Paneth细胞中, α-防御素水平特异性偏低, 最近, 人们发现在IBD患者结肠中, β-防御素的表达水平也是下调的. 可以推测, 这些抗菌肽的缺失会促进IBD患者的炎症反应. 在IBD患者肠道黏膜上皮中β-防御素的编码基因HBD-2, HBD-3和HBD-4存在着不同水平的表达[36-37]. 他们表达水平的差异并非由各自基因的突变所致, 在人类8号染色体的防御素位点上广泛存在着DNA拷贝数的多态性[38], 这可能是β-防御素表达水平不同的发生机制. 最近有研究显示β-防御素位点上HBD-2基因拷贝数减少者更易患结肠型CD, UC患者结肠浆细胞大量聚集且HBD表达水平明显高于正常对照[39], 因此我们可以推测上述基因的低拷贝导致了防御素低水平表达, 减弱了结肠黏膜屏障的抗菌能力, 促进了IBD的发生.

2 免疫应答相关基因

2.1 MHC 位于人类6号染色体短臂上的主要组织相容性复合体(major histocompatibility complex, MHC)基因, 因其在免疫应答和免疫调节中的重要作用成为近十几年来遗传学和免疫学的研究热点. MHC区域目前被认为与多种免疫系统疾病的发生、发展相关. 早期研究提示该区域内的一些基因的变异与IBD发病相关. 一项对于2004年间研究的IBD相关基因的Meta分析[40]发现包含了MHC基因的IBD3位点(6p21)与IBD, 尤其是UC关系最为恒定. 在与哺乳动物免疫防御和自身免疫密切相关的基因组中, MHC所含基因最为密集, 这一复合体可分为Ⅰ、Ⅱ、Ⅲ 3个亚群, 具高度多态性. 在MHC基因中, 研究最多的是编码细胞表面抗原呈递蛋白的4种MHC基因, 即MHC-A、B、C和D. MHC-A、B、C属于MHC-Ⅰ, MHC-D属于MHC-Ⅱ.

近年一些研究发现靠近MHC-B的非经典Ⅰ类基因, 如MHC-Ⅰ类相关基因A(MHC class Ⅰ chain-related gene A, MICA)和MHC-Ⅰ类相关基因B(MHC class Ⅰ chain-related gene B, MICB), 与IBD存在关联[41-45], 但另一些研究却未能得出类似结论[46-47]. Orchard *et al*[43]研究发现在英国人中, MIC-A×007与UC易感性相关. 对我国人群的研究亦证实MICA-A5.1和MICB-CA18[45]与国人UC有相关性. 而Glas *et al*[30]在德国人群中所作的研究未发现此关系. 与健康对照相比, 日本UC患者中MICA基因5号外显子微卫星多态性等位基因A6的出现频率较高[42], 但他们随后进行的研究显示这一差异是由于其与MHC-B52连锁不平衡所致[46]. 正常情况下, MICA和MICB分子与其表达于NK细胞、T细胞和巨噬细胞上的受体NKG2D结合, 共同激发上述细胞的活性, 当细菌或病毒感染时表达增加. Perera *et al*[41]研究发现UC患者肠黏膜上皮细胞MICA/MICB表达缺失. 因此, 两者部分基因的突变, 可能通过与受体结合能力的改变影响免疫系统的活性.

与MHC-Ⅰ类基因相比, MHC-Ⅱ类基因与IBD关系更为密切. MHC-Ⅱ主要包含MHC-DQ、DP、DR, 属于免疫球蛋白超基因家族, 对T细胞免疫应答及B细胞产生抗体均有重要作用. Stokkers *et al*[48]就HLA-DR和HLA-DQ与IBD的关系进行了Meta分析, 发现他们与IBD尤其是UC密切相关. 这一关系已在许多不同人群中得到验证[49-52]. 另外, Silverberg *et al*[53]研究发现MHC-DRB1×0103与CD累及结肠有关. 但MHC-Ⅱ类基因区DR、DP和DQ 3个与IBD相关的位点, 在MHC-Ⅱ类基因上紧密连锁, 而非独立存在, 哪个为初级, 哪个为次级相关尚待进一步研究.

同样位于IBD3区的MHC-Ⅲ编码另外一些免疫因子, 包括补体C3、C4, B因子和其他一些促进细胞因子生成的免疫因子, 如TNF-α. TNF-α基因启动区域的6个单核苷酸多态性(TNF-1031T/C、-863C/A、-857C/T、-380G/A、-308G/A、-238G/A)与IBD遗传易感性的关系在人群中报道不一. van Heel *et al*[54]在457个北欧高加索家族中研究了4种SNPs(-1031T/C、-863C/A、-857C/T、-308G/A)与IBD、UC和CD的关系, 遗传不平衡法分析显示, 在不携带CARD15 3种易感突变的患者中, -857C/T与UC和CD相关, 然而van Heel *et al*[54]亦发现此SNP与其他易感基因存在不平衡连锁, 尚不能确定为致病因素. Cucchiara *et al*[55]在意大利IBD患者中发现TNF-308G/A与CD及UC均显著相关, 而TNF-

■相关报道
自从2001年Hugot *et al*发现CARD15/NOD2与CD发病显著相关以来, 现在已有许多有关基因与IBD相关性的报道, 其中大约有9个基因位点经相关性研究得到证实.

■应用要点
全基因组扫描法与传统方法相结合用以探索基因变异与发病风险的关系已使人们对于IBD的发生发展的认识有了很大提高.

857C/T与之无相关性. 部分人群, 如土耳其[56]及印度人群[57]中研究提示TNF-α基因多态性与IBD并无明确关联. 宋瑛 *et al*[58]及曹倩 *et al*[59]对我国人群的研究发现UC患者TNF-308A基因型频率和等位基因频率显著高于健康对照, 但同时有研究未能得出相同结果[60]. 捷克人群[61]中的研究提示TNF-308G/A与CD病情活动指数, 并发症的出现等临床表现型有关. Levine *et al*[62]发现TNF-863A与病变累及回肠呈反相关, 与孤立性结肠炎及家族聚集性正相关.

2.2 IL-23R 白介素23受体(interleukin-23 receptor, IL-23R)基因位于1p31区, 编码炎症细胞因子IL-23的受体的亚单位. 在一项全基因组关联分析(genome wide association, GWA)的研究中, Duerr *et al*[63]发现该基因编码区一个不常见的变异(rs11209026, p. Arg381Gln)对IBD易感性有保护作用. 最近, 世界各研究中心进行的实验中, 在欧洲儿童[64-66]和成人IBD[27,29,31,50,67-71]患者中均验证了IL-23R与IBD, 尤其是CD的相关性.

IL-23是一个由亚单位*p19*和白介素12(IL-12)的组成部分*p40*通过二硫键形成的异源二聚体分子, 是IL-12细胞因子家族的新成员. IL-23除了与IL-12共用受体亚单位IL-12Rβ1外, 还有一个自身特有的受体亚单位即IL-23R. IL-23对于T-辅助细胞的分化有重要作用, 在CD中发挥主导调节作用[72-73]. 在T细胞缺失小鼠上, IL-23通过固有免疫参与肠道炎症的发生, 并与IL-12相互作用. 因此, Neurath[72]提出IL-23能够激活并维持肠道的固有免疫反应和T细胞介导的免疫反应, 致病的T细胞可能因为某一导致IL-23R失活的功能性SNP而未被激活, 削弱的IL-23信号传导可能降低固有免疫的效力, 从而使炎症反应受到抑制, 避免IBD发生. 临床上IL-12/IL-23亚单位的抗体的试验也有效地减少了CD的症状[74], 进一步说明了IL-23通路在CD发生过程中的重要作用.

2.3 Toll样受体 Toll样受体(Toll-like receptors, TLRs)是近年来发现的重要的免疫受体, 他通过识别病原体, 能立即启动先天性免疫, 并通过信号传导启动获得性免疫. 目前已发现至少11个TLR家族成员, 他们分布于各个脏器, 针对不同的病原体独立或联合发挥其识别作用, 调节免疫反应. 不同TLR之间胞内区相似而胞外区同源性较差, 胞外区结构的差异决定了他们各自有特征性的配体. TLR4主要识别G$^-$菌的胞壁脂多糖(lipopolysaccharide, LPS); TLR9则感应细菌DNA中的未甲基化CpG. 目前LPS激活TLR4的过程部分明确, 配体诱导TLR4二聚体形成进而激活至少2条信号通路: 通过MyD88-或TRAF6-依赖途径激活NF-κB和/或干扰素调节因子3(interferon regulatory factor 3, IRF3).

TLR4基因定位于染色体9q区. 与其他候选基因不同, 全基因组扫描并未有该基因片段与IBD相关的提示. 在一项病例对照研究中, Franchimont *et al*[75]发现Asp299Gly(869C/T)的多态性与CD和UC存在明显相关. 这一结果尚未得到很好的重复[76-78], 但许多在高加索人群[75,78-83]中所进行的研究都显示在CD与UC患者中, 299Gly的出现频率高于对照组. Browning *et al*[84]的研究及Meta分析亦支持TLR4与IBD相关. 我国湖北人群[85]中的研究未发现此SNP与IBD易感性相关. TLR9基因定位于3p21.3区. 与TLR4类似, 这一基因也并未在全基因组扫描的研究中有阳性发现. 在一个小样本量的研究中发现TLR9基因上的1237C/T和2848A/G 2个SNP与IBD相关. Török *et al*[86]人在德国人群中的研究认为1237C/T与CD相关而与UC无关. Hong *et al*[78]在新西兰高加索人群中的研究未能得出上述结论, 但他们所作的Meta分析支持1237C/T与CD相关. van Hell *et al*[87]在英国高加索人群中选取7例携带野生型CARD15的健康对照和19例携带CARD15突变纯合子的CD患者进行研究, 发现TLR9对CpGDNA(TLR9配体)的应答取决于CARD15基因的多态性.

3 黏膜转运和极性相关基因

3.1 SLC22A4和SLC22A5 IBD5区域(5q31-q33)与成人患CD关系密切, 溶质携带物家族22A4和22A5(solute carrier family 22A4/22A5, SLC22A4/22A5)即存在于这一区域. SLC22A4/22A5基因的主要功能是转运肠道中的l-肉毒碱和清除肠道中的阳离子药物. Peltekova *et al*[88]对IBD5中的5个基因进行测序, 鉴定出10个SNP, 其中的2个分别存在于SLC22A4(1672C/T)和SLC22A5(207G/C), 二者存在不平衡连锁. 但其他研究[89]并未有类似发现. 已有许多研究[87,90-92]证实这两种SNP与白种人CD发病相关, 但在日本[93]及我国[94]人群中的研究未发现上述基因变异. Mirza *et al*[95]报道对于至少含一个CARD15易感突变的患者, IBD5基因与CD发病相关, 而在没有CARD15易感突变者, IBD5基因的变异没有此效应.

白种人中CD患者的5q31区存在基因的易感突变的证据由来已久. 一些学者[88-96]认为这2个SNP就是致病的基因突变, 然而后续的研究[89]又认为1672C/T与207G/C与CD发病无关或者5q31区的其他位点的变异也与CD发生有关.

3.2 ABCB1 ATP结合盒转运子B1(ATP-binding cassette subfamily B member 1, ABCB1)位于7q21.1(含49-587 bp不等的28个外显子, cDNA全长4.5 kb, 基因全长210 kb), 又被称为多药耐药基因1(multidrug resistance gene 1, MDR1). 他编码一种ATP依赖的转运蛋白(P-糖蛋白或P-gp). P-gp在包括肠上皮在内的多种组织高表达, 可将进入胞内的药物, 细菌毒素和化学物质等主动泵出细胞, 保护上皮免受有毒物质侵犯. 其表达具有个体差异性, 从而影响个体对药物的耐受能力. 在这一基因片段上已发现了不下300个SNPs, 其中一部分SNP与多种癌症, HIV感染, 高胆固醇血症和帕金森病的易感性相关, 亦有一些SNP与IBD有关[97]. 研究发现P-gp表达缺失的mdr1a$^{-/-}$小鼠肠上皮通透性增加[98], 且此类小鼠可作为理想的IBD动物模型. IBD患者肠上皮P-gp表达亦有下降[99]. 目前已发现3个SNP位点[100-102]即外显子21上的G2677T/A, 26上的C3435T和1B上的T129C与P-gp低水平表达有关. 高加索人G2677T/A与C3435T基因存在连锁不平衡[97].

2项基因连锁扫描和有关Meta分析提示IBD与7q区相关[40,103]. Onnie *et al*[97]针对二者之间关系进行了Meta分析, 发现了较强的支持ABCB1与UC相关的依据. C3435T的统计学意义最大, G2677A/T次之. Annese *et al*[104]所作的Meta分析提示3435T等位基因和3435TT基因型与UC显著相关, 而与CD无关, 亦未发现G2677T/A与IBD相关. Fiedler *et al*[105]的研究提示G2677T/A与C3435T的多态性与UC早年发病有关.

3.3 DLG5 人类DLG5(drosophila discs large homologue 5)是果蝇dlg基因的同源基因, 定位于10q23, 202 kDa, 广泛表达于肠道、心脏、胎盘等组织. 他属于编码参与胞内信号传导的蛋白的骨架的MAGUK(membrane associated guanylate kinase homologs)家族. 作为该家族的一个典型成员, DLG5有4个PDZ(PSD-95/Discs large/zona occludens)结构域, 1个SH3(Scr homology 3), 1个GUK(guanylate kinase)结构域. 结构域多提示DLG5蛋白与其他蛋白相互作用的潜力. Nakamura *et al*[106]人发现他与红细胞膜蛋白P55的GUK结构域相作用, 二者在胞膜上结合形成异二聚体, 聚集胞内分子保持上皮细胞结构, 并且可以传递胞外信号至胞膜. 因此, 此蛋白与上皮完整性与极性的保持有关.

IBD特征之一是肠上皮屏障功能受损(肠泄漏). 现有关于DLG5的数据提示该基因可能为IBD易感基因. SNP G113A能导致氨基酸替换(R30Q), 可能通过阻止DLG5骨架形成[107]进而损伤肠道屏障功能. 最近, Friedrichs *et al*[108]发现DLG5亦属于CARD蛋白家族, 可能通过NF-κB或Casepase途径参与CD的发生.

Stoll小组[107]对DLG5单体型作分析发现其有4个较普遍的单体型, 分别为A、B、C、D, 在早期关于DLG5的研究中, 人们通常关注以下3种变异: (1)非同义编码SNP G113A(R30Q), 即D单体型的标签SNP(haplotypetag SNP, htSNP), 在高加索人中发生率约10%[107]; (2)出现率相对较少的非同义编码SNP P1371Q[110]; (3)A单体型的8个htSNP[107]. Slovak *et al*[100]研究发现前两种使CD发病风险增加而A单体型与低发病风险相关.

早期曾有2个家庭的病例研究和1项病例对照研究证实上述关系. 在随后的1项病例对照研究和家庭病例研究中上述结果得到了重复[107,109]. 然而后来的一系列试验都未能验证R30Q增加发病风险, A单体型降低风险这一结论[110-118]. P1371Q与CD的关系只在1项研究中得到了验证[117], 另外4项均未能[109,94,114-115]. 新西兰人群[119]中的研究显示rs2289311变异(A单体型的htSNP)可全面降低IBD发病风险, 小组分析显示在有IBD家族史和有肠外表现的UC患者中, 这一关系尤为明显. 然而未发现R30Q和P1371Q与IBD的关系, 关于R30Q病例对照研究的Meta分析也未能发现其与IBD相关. Friedrichs *et al*[120]、Tenesa *et al*[121]、Biank *et al*[122]及Browning *et al*[123]的研究提示R30Q对CD患者易感性的影响存在性别差异, 突变型的携带可能降低女性患CD的危险性, 而增加男性的患病风险. 这可能是上述实验的结果不一致的原因, 对性别进行分层分析可能有助明确DLG5与CD发病的关系. Yamazaki *et al*[93]在日本人群中的研究发现DLG5存在其他SNP, 如rs3758462与CD相关. 在我国人群中所作研究尚未发现上述与白种人IBD相关的DLG5变异.

4 结论

遗传因素是IBD发病过程中的一个重要因素. 全基因组扫描法与传统方法相结合用以探索基因

■同行评价

本文立题有依据, 目的明确, 重点突出, 文字简洁, 参考文献引用合理, 为IBD发病机制提供理论依据, 对临床IBD的防治有积极参考意义.

变异与发病风险的关系已使人们对于IBD的发生发展的认识有了很大提高. 自第1个CD易感基因CARD15/NOD2明确以来, 已相继发现了许多与IBD发病相关的易感基因和易感SNP位点, 有关基因型与临床表型的关系也有大量报道. 可以明确的是IBD是一种复杂的多基因疾病, 其易感性涉及多个基因位点, 且有着显著的种族差异性. 具体的发病机制及如何将其运用于IBD患者的诊断、治疗尚待进一步研究. 迄今为止还没有找到与我国乃至亚洲IBD人群明显相关的基因和SNP位点, 因此有必要在亚洲人群中展开大规模的易感基因及易感突变位点的筛查.

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• 消息 •

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本刊讯 本刊栏目设置包括述评, 基础研究, 临床研究, 焦点论坛, 文献综述, 研究快报, 临床经验, 病例报告, 会议纪要. 文稿应具科学性、先进性、可读性及实用性, 重点突出, 文字简练, 数据可靠, 写作规范, 表达准确.
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