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文献综述 REVIEW

# 全基因组关联分析在消化系肿瘤中的研究进展

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■背景资料
近年, 各国科学家运用全基因组关联分析在人类肿瘤, 特别是在消化系肿瘤的研究中取得了一系列重要的研究成果.

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## Progress in genome-wide association study of digestive tract cancers

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## Abstract
Genome-wide association analysis is a new strategy for discovering genetic characteristics affecting the development of complex diseases, which uses human genome single nucleotide polymorphisms (SNPs) as markers. Using high-throughput techniques, genome-wide association analysis permits to genotype whole-genome SNPs and to explore their association with complex disease at one time. Over the past 5 years, genome-wide association studies have been proven to be a powerful approach for screening the susceptibility genes for complex disease. In recent years, a series of important achievements have been made in genome-wide association analysis of human cancers, especially digestive tract cancers. In this paper we will review the progress in genome-wide association study of digestive tract cancers.

Key Words: Genome-wide association study; Esophageal cancer; Gastric cancer; Colorectal cancer

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## 摘要
全基因组关联分析(genome-wide association study, GWAS)是应用人类基因组中单核苷酸多态性(single nucleotide polymorphism, SNP)为标记进行分析, 以期发现影响复杂性疾病发生的遗传特征的一种新策略. 因其可在全基因组范围内进行整体研究, 能够一次性对疾病与基因的关联进行轮廓性概览, 所以在过去的5年中, 全基因组关联研究方法已被证明是研究复杂疾病一种有效手段. 近年, 各国科学家运用全基因组关联分析在人类肿瘤, 特别是在消化系肿瘤的研究中取得了一系列重要的研究成果, 本文将综述消化系肿瘤GWAS研究进展, 并展望GWAS所面临的挑战及可能的解决策略.

**关键词: 全基因组关联分析; 食管癌; 胃癌; 结直肠癌**

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## 0 引言
全基因关联分析(Genome-wide association studies, GWAS)是一种对全基因组范围内的单核苷酸多态性(single nucleotide polymorphism, SNP)进行总体关联分析的方法, 即在全基因组范围内选择遗传变异进行基因分型, 比较病例和对照间每个变异频率的差异, 计算变异与疾病的关联强度, 选出最相关的变异进行验证并最终确认与疾病相关. 2007年4月, 《Nature Genetics》上同时发表了2篇关于前列腺癌的GWAS结果[1,2], 这是GWAS在肿瘤研究领域的首次报道. 迄今为止, 已经开展了对常见恶性肿瘤的多项GWAS研究, 如前列腺癌[3-12]、乳腺癌[13-20]和肺癌[21-25]等. 近年来, 消化系肿瘤的GWAS研究进展迅

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表 1 全基因组关联发现的有意义的食管癌易感位点和(或)区域

| 染色体 | 候选基因 | 位 点 | OR值 | 参考文献 |
|---|---|---|---|---|
| 4q21–23 | ADH1B | rs1229984 | 1.79 | [26] |
| 12q24 | ALDH2 | rs671, rs11066015 | 1.33–1.67 | [26,27] |
| | | rs2074356 | 1.56 | [27] |
| | | rs11066280 | 1.30 | [27] |
| 10q23 | PLCE1 | rs2274223 | 1.34–1.43 | [27–29] |
| 20p13 | C20orf54 | rs13042395 | 0.86 | [28] |
| 5q11 | PDE4D | rs10052657 | 0.67 | [27] |
| 21q22 | RUNX1 | rs2014300 | 0.7 | [27] |
| 6p21 | UNC5CL | rs10484761 | 1.33 | [27] |

**■创新盘点**
本文对消化系肿瘤(胃癌、食管癌及结直肠癌)中GWAS研究进展和GWAS面临的挑战及可能的解决策略做一综述.

速, 并取得了重要的成果, 故本文将对消化系肿瘤(胃癌、食管癌及结直肠癌)中GWAS研究进展和GWAS面临的挑战及可能的解决策略作一综述.

## 1 消化系肿瘤的研究进展

1.1 食管癌 2009年, 日本学者[26]率先报道了日本人群中的食管癌的GWAS研究结果, 随后又有中国[27,28]及美国学者[29]陆续发表了中国人群中食管癌的GWAS研究成果. 至今, 共报道了7个有意义的食管癌易感性位点, 分别位于ADH1B、ALDH2、C20orf54、PLCE1、RUNX1等基因(表1).

ADH1B和ALDH2是最早报道的有意义的食管癌易感基因, 分别位于染色体4q21-23和12q24. Cui等[26]在日本人群中利用2阶段的GWAS研究, 在总数为1 070例日本食管癌病例和2 836例对照人群中, 经过反复的筛选, 最终发现了2个有意义的易感基因ADH1B(OR = 1.79)和ALDH2(OR = 1.67). 这2个基因均编码的是与酒精和烟草代谢相关蛋白, 而吸烟和饮酒是日本人群中最为主要的与生活习惯相关的食管癌的危险因素. 研究者的统计分析表明, 同时具有遗传和生活习惯危险因素的个体, 比二者均无的个体患食管癌的风险高出190倍. 2011-06, Wu等[27]在中国人群中的GWAS食管癌研究结果也发现这个位于12q24染色体的易感位点(OR = 1.33), 与Cui[26]报道的结果一致.

2010年8月, 来自中国[27,28]和美国的研究组[29]同时报道了中国人群食管癌的GWAS研究结果, 并发现了相同的食管癌易感基因—位于染色体10q23的PLCE1. Wang等[28]在中国人群中进行了2阶段GWAS研究(第1阶段: 1 077例食管癌和1 733例对照, 506 666个SNP; 第2阶段: 7 976例食管癌和11 568例对照, 18个SNP), 结果发现了新的有意义的食管癌易感基因-PLCE1(rs2274223, OR = 1.43). 同年同期的Abnet等[29]和随后的Wu等[27]的中国人群食管癌的GWAS研究, 也都报道和证实了该食管癌易感基因的存在(PLCE1, OR = 1.34). PLCE1基因编码的是磷脂酶, 他水解磷脂酰肌醇4, 5-二磷脂盐而参与细胞内信号传导. 而且, PLCE1可结合Ras家族的小G蛋白, 成为GTP酶类的效应器而调节细胞生长、分化、凋亡、血管发生.

值得关注的是, 在Wang等[28]报道中, 还发现了另一个有意义的食管癌易感基因: 位于染色体20p13的C20orf54(rs13042395). C20orf54作为一个人类核黄素转移蛋白2(hRFT2), 编码一个开放读码框蛋白, 其在核黄素的肠吸收中发挥重要作用. 很多文献报道过细胞内稳态中核黄素的作用, 且核黄素缺乏与患食管癌风险性的增加相关, 补充核黄素被证实能够降低患食管癌风险性. 因此, hRFT2很可能通过影响核黄素吸收的作用, 而在食管鳞癌发生中发挥重要的作用.

Wu等[27]在中国人群食管癌的进行的GWAS研究, 结果发现了位于5个区域的7个食管癌的易感性位点(位于染色体5q11的rs10052657, 21q22的rs2014300, 6p21的rs10484761, 10q23的rs2274223和12q24的rs11066015, rs2074356, rs11066280), 证实了已往的研究结果, 即ALDH2(12q24), PLCE1(10q23)是食管癌的易感基因. 此外还有5q11, 6p21和21q22为新发现的有意义的食管癌的易感性区域, 而其涉及的易感基因还有待进一步研究.

1.2 胃癌 胃癌的GWAS研究结果也是日本学者于2008年率先发表, 随后, 中国及美国学者也相继报道了中国人群中的研究结果[28-31](表2).

**■应用要点**
GWAS开创了研究肿瘤遗传易感基因的方法一个新时代, 他是增强人们对肿瘤认识的强而有力的工具, 并对肿瘤发生发展机制的研究提供了新思路和途径.

表 2 全基因组关联发现的有意义的胃癌易感位点和(或)区域

| 染色体 | 候选基因 | 位 点 | OR值 | 参考文献 |
|---|---|---|---|---|
| 8q24 | PSCA | rs2976392 | 1.62 | [30] |
| 1q22 | MUC1 | rs4072037 | 0.72 | [29,31] |
| 10q23 | PLCE1 | rs2274223 | 1.31–1.55 | [28,29,31] |
| 20p13 | C20orf54 | rs13042395 | 0.91 | [28] |

表 3 全基因组关联发现的有意义的结直肠癌易感位点和(或)区域

| 染色体 | 候选基因 | 位 点 | OR值 | 参考文献 |
|---|---|---|---|---|
| 8q23 | EIF3H | rs16892766 | 1.25 | [36] |
| 8q24 | – | rs6983267 | 1.17–1.27 | [32–34,36] |
| 10q14 | – | rs10795668 | 1.11 | [36] |
| 11q23 | – | rs3802842 | 1.12 | [37] |
| 14q22 | BMP4 | rs4444235 | 1.11 | [37] |
| 15q13 | GREM1/SCG5 | rs4779584 | 1.23–1.26 | [35,36] |
| 16q22 | CDH1 | rs9929218 | 1.10 | [38] |
| 18q21 | SMAD7 | rs4939827 | 1.16–1.20 | [34,36] |
| 19q13 | RHPN2 | rs10411210 | 1.15 | [38] |
| 20q12 | – | rs961253 | 1.12 | [38] |

2008年3月, Sakamoto等[30]报道了日本人群胃癌的GWAS研究结果: 位于8q24的前列腺干细胞抗原基因(PSCA)内区的rs2976392(OR = 1.62), 该位点与弥漫型胃癌的相关度远远高于其与肠型胃癌的相关度. 他们发现PSCA在分化的胃上皮细胞中有表达, 并在体外实验中证实有抑制细胞分化的活性, 且其常常在胃癌中表达沉默. 同样的危险等位基因在韩国人群的457例病例390例对照中也证实与弥漫型胃癌显著相关[30](OR = 1.90).

Wang等[28]报道的中国人群中胃-贲门腺癌的GWAS研究中发现2个有意义的易感基因: 位于染色体10q23的PLCE1(OR = 1.55), 20p13的C20orf54(OR = 0.91). 同期, Abnet等[29]也报道了位于染色体10q23的PLCE1为中国人群中有意义的胃腺癌易感基因(OR = 1.31). 2011年, Zhang[31]采用独立的病例-对照研究, 在中国的人群中验证了这几个位点. 他们选取了1 681例胃癌和1 858例对照, 结果发现位于染色体1q22的MUC1(OR = 0.72)和10q23(OR = 1.42)的PLCE1与胃癌的发生有显著的相关性, 且PLCE1与胃癌相关性在女性(OR = 1.86)和胃腺癌(OR = 1.71)中更显著. 他们联合2个多态性评估了其联合作用, 发现随着危险等位基因数目增加, 胃癌的发生危险度明显增加; 且携带2个危险等位基因的个体比未携带危险等位基因的个体患胃癌的风险高出3.28倍. 结果显示, 位于染色体1q22和10q23的易感基因可能被作为易感胃癌的候选标记物. 但他们并没有检测到位于染色体20p13的rs13042395与胃癌有显著相关性.

1.3 结直肠癌 2007年, 结直肠癌的GWAS研究即已开始, 至今, 已有来自英国和加拿大的研究组分别在英国和加拿大等人群中报道了10个有意义的结直肠癌的易感位点[32-38](表3).

2007年7月, Tomliuson[32]和Zanke[33]同时报道了结直肠癌GWAS研究结果, 2个研究组同时发现了相同的结直肠癌易感位点: 位于染色体8q24的rs6983267(OR = 1.27). 此外, Broderick等[34]对英国家族性结直肠肿瘤(627例结直肠癌、313例腺瘤和965例对照)的GWAS研究发现, 除8q24外, 最显著有意义的位点是位于SMAD7(染色体18q21.1)第3内含子的rs4939827; 此后, 该课题组对GWAS数据进一步挖掘并经过多个研究的独立验证发现了另一个有意义的易感基因位于染色体15q13.3的GREM1/SCG5(rs4779584)[35]除了已经确定的3个易感区域(分别位于染色体8q24、18q21.1和15q13.3), 研究者通过更大样本多次验证, 最终确认了位于染色8q23上EIF3H基因的rsl6892766和10q14的rsl0795668是结直肠癌的易感位点[36].

随后, Tenesa等[37]于2008年在苏格兰人群中进行了3个阶段的GWAS研究(第1阶段: 1 012例结直肠癌和1 012例对照, 555 510个SNP; 第2阶段: 2 057结直肠癌和2 111例对照, 15 008个SNP; 第3阶段: 14 500例结直肠癌和13 294例对照, 5个SNP), 最终发现3个有意义的位点(rs7014346、rs4939827和rs3802842)仍然显著. 研究结果不仅验证了以往GWAS结果(位于染色体8q24的rs7014346和18q2l的rs4939827), 还发现了1处新的易感位点位于染色体11q23.19的rs3802842, 该位点具有明显的人群差异, 其效应在日本人群明显低于欧洲人群.

为发现更多低共显性的易感位点, 上述2个GWAS研究组通过Meta分析的方式共享GWAS数据[38], 研究者共获得13 315例研究对象的38 710个SNP信息, 经过8个研究组27 418例研究对象的验证, 最终发现了4个新的结直肠癌易感区域(分别位于染色体14q22.2、16q22.1、19q13.1和20p12.3), 体现了数据共享在肿瘤GWAS研究中的优势.

尽管染色体8q24、10q14、11q23区域缺乏我们已知的基因, 近期2个报道显示[39,40], 位于染色体8q24的易感区域可能可增强Wnt通路的信号, 而这个通路是我们众所周知的致癌机制之一. 将近半数的结直肠癌的易感位点存在连锁不平衡现象, 或是存在与致癌机制中转化生长因子β(TGF-β)信号通路的附近[41,42], 结直肠癌的GWAS研究结果报道的与TGF-β通路相关的基因包括: SMAD7、RHPN2、BMP4和GREM1, 而TGF-β表达的增多会导致结直肠癌的进展和复发.

## 2 GWAS面临的挑战及可能的解决策略

虽然GWAS在肿瘤研究中取得了令人鼓舞的成绩, 发现了大量的易感基因/位点, 但目前GWAS发现的一些变异多位于基因组的非编码区, 所以需更深入的研究肿瘤易感基因的功能. 且目前GWAS确定的易感基因/位点仅能解释一部分肿瘤发生, 仍需采取有效的措施扩大GWAS范围, 提高GWAS发现易感位点的能力. 因此, GWAS结果只提示某些基因与肿瘤具有关联性, 为其机制的研究提供启示, 至于基因如何影响肿瘤的发生发展还将是一个更大的挑战. 我们应该在总结过去GWAS经验的基础上发现存在的问题, 并采取合理的措施应对这些挑战, 以进一步优化GWAS和后续研究, 更好地理解和应用GWAS研究结果.

**2.1 深入分析研究结果** 通过统计分析遗传因素和肿瘤的关系, 确定与肿瘤关联的功能性位点存在一定难度. 很多研究发现, 通过GWAS发现的许多SNP位点的改变, 并不能影响蛋白质中氨基酸, 这为解释SNP位点与肿瘤发生之间的关系造成了一定的困难. 但由于肿瘤发生是多因素的作用结果, SNP位点可能通过影响RNA的转录或翻译效率等, 在基因表达上产生短暂的或依赖时空的多种影响, 刺激调节基因的转录表达或影响其RNA剪接方式. 所以我们需要更加深入的研究和确定易感基因的功能以及在肿瘤发生发展中的作用, 比如进行精细定位研究寻找相关变异、易感基因的功能和结构以及转录调节方面的相关研究. 因此, 我们在找寻某种肿瘤相关变异时, 应同时注意到编码区和调控区位点变异的重要性, 并进一步深入研究其功能影响[43-45].

**2.2 扩大遗传变异研究范围** 目前报道的GWAS所采用的基因分型通量大多可同时检测55万个SNP位点(即550K)或低于这个水准, 为发现更多的遗传易感位点/区域, 新一轮的GWAS可能需要进一步提高标签位点的密度(达到100万个SNP)[46]. 此外, 基因组拷贝数变异(copy number variation, CNV)的研究将是GWAS的一个新的研究点. CNV是人类基因组中存在的多种类型的染色体数目和结构变异, 指的是与参考序列相比基因组中≥1 kb的DNA片段插入、缺失和/或扩增, 及其互相组合衍生的复杂染色体结构变异[47]. 与SNP相似, 部分CNV在不同人群中以不同频率分离并具有显著性差异, 并可能影响基因表达和表型改变, 因此CNV也是可能引起肿瘤发生的一种重要遗传变异[48]. 由于肿瘤相关遗传变异可能分布在不同染色体, 单纯以SNP为基础的关联分析可能无法有效地区分受累个体和健康对照, 而CNV可能通过数量作用和质量作用2种机制引起的基因剂量改变导致表型改变, 所以CNV全基因组关联分析可能更容易检测到致病遗传变异[49]. 因此在进行GWAS时, 联合使用SNP和CNV这2个具有互补性的遗传标志, 将为深入理解复杂疾病的分子机制和鉴定易感基因, 对研究肿瘤的遗传易感机制具有重要意义.

## 3 结论

GWAS开创了研究肿瘤遗传易感基因的方法一个新时代, 虽然该研究需耗费大量的精力和经

**■名词解释**

全基因关联分析: 是一种对全基因组范围内的单核苷酸多态性进行总体关联分析的方法, 即在全基因组范围内选择遗传变异进行基因分型, 比较病例和对照间每个变异频率的差异, 计算变异与疾病的关联强度, 选出最相关的变异进行验证并最终确认与疾病相关.

■同行评价
“全基因组关联分析技术在消化系肿瘤中的研究进展”一文对近年来全基因组关联分析在消化系肿瘤中研究进展作了较好地叙述, 可读性好.

费, 但值得的是我们会得到一个全面的肿瘤相关基因组变异的组图, 他是增强我们对肿瘤认识的强而有力的工具, 并为我们对肿瘤发生发展机制的研究提供了新思路和途径.

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**• 消息 •**

# 《世界华人消化杂志》正文要求

**本刊讯** 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化. A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: $^{a}P<0.05$, $^{b}P<0.01$($P>0.05$不注). 如同一表中另有一套$P$值, 则$^{c}P<0.05$, $^{d}P<0.01$; 第3套为$^{e}P<0.05$, $^{f}P<0.01$. $P$值后注明何种检验及其具体数字, 如$P<0.01$, $t = 4.56$ *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用$t$/min, $c$/(mol/L), $p$/kPa, $V$/mL, $t$/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm×4.5 cm, 必须使用双面胶条粘贴在正文内, 不能使用浆糊粘贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.