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综 述

后 GWAS 时代结直肠癌致病 SNP 功能机制的研究进展

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摘要： 结直肠癌(colorectal cancer, CRC)是受遗传与环境因素共同影响的复杂疾病，其中遗传因素发挥重要作用。至今，全基因组关联研究(genome-wide association studies, GWAS)已经发现了大量与结直肠癌风险相关的遗传变异。随之而来的后 GWAS 时代，越来越多的研究侧重于利用多组学数据和功能实验对潜在的致病位点进行解析。分析表明绝大多数风险单核苷酸多态性(single nucleotide polymorphism, SNP)位于非编码区，可能通过影响转录因子结合、表观遗传修饰、染色质可及性、基因组高级结构等，调控靶基因表达。本文对后 GWAS 时代结直肠癌致病位点的机制研究进行综述，阐述了后 GWAS 对于理解结直肠癌分子机制的重要意义，并探讨了结直肠癌 GWAS 的应用和前景，为实现 GWAS 成果转化提供参考。

关键词： 结直肠癌；后全基因组关联研究；单核苷酸多态性；致病变异

Progress on functional mechanisms of colorectal cancer causal SNPs in post-GWAS

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Abstract: Colorectal cancer (CRC) is caused by genetic and environmental factors, and the genetic component plays a significant role in CRC development. Currently, genome-wide association studies (GWAS) have identified a large number of genetic loci associated with CRC risk. In the post-GWAS era, more and more efforts focus on deciphering the biological mechanisms behind these potential causal variants by using multi-omics data and functional experiments. Many analyses have revealed that most risk single nucleotide polymorphisms (SNPs) are located in non-coding regions and these variants may regulate the expression of target genes by altering the transcription factor-binding motif, epigenetic modification,

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chromatin accessibility or 3D genome conformation. Results obtained from post-GWAS era have highlighted the possibility of moving from association to function. In this review, we summarize the current status of CRC post-GWAS studies and discusses the clinical application as well as future directions of CRC GWAS, in order to better gain insight into the molecular basis of CRC and provide evidence for prevention.

Keywords: colorectal cancer; post-GWAS; SNP; casual variant

结直肠癌(colorectal cancer, CRC)是常见的恶性肿瘤之一，严重威胁人类健康。据统计，2018 年全球 CRC 新发病例超过 180 万，死亡病例约 86 万；位居发病瘤谱第 3 位，死亡瘤谱第 2 位[1]。在我国，2015 年 CRC 新发病例估计有 38.76 万例，死亡病例 18.71 万例；位列发病瘤谱第 4 位，死亡瘤谱第 5 位[2,3]。吸烟、缺乏锻炼、不健康的饮食习惯等环境因素均会增加 CRC 患病风险[3]；此外，遗传因素也影响着 CRC 的发生，大型双生子研究表明 CRC 的遗传力约占 35%[4]。可见，CRC 受遗传与环境因素共同作用。随着人类基因组计划等大型项目的开展以及测序技术的进步，利用全基因组关联研究(genome-wide association studies, GWAS)发现了大量结直肠癌易感位点，为了解和防治结直肠癌提供信息。

GWAS 被认为是探索常见遗传变异主要是单核苷酸多态性(single nucleotide polymorphism, SNP)与复杂疾病相关性的“万能钥匙”[5]，广泛应用于癌症、糖尿病和精神分裂症等疾病[6,7]。自 2007 年 GWAS 研究发现 8q24.2, 18q21.1 区域上的多态位点与结直肠癌风险显著相关[8~10]后，越来越多的位点被鉴定，然而由于连锁不平衡的存在以及基因与环境之间复杂的相互作用，GWAS 识别的标签 SNP 不一定是真正的致病变异，因此迫切需要对 GWAS 结果进行深入解读。早前，Freedman 等[11]和 Edwards 等[12]提出后 GWAS(post-GWAS)研究策略，旨在筛选功能位点并阐明其潜在的分子机制(图 1)。至今已有相当数量的研究对结直肠癌风险 SNP 进行功能解析。为了更好地理解功能 SNP 在结直肠癌发生发展过程中的作用，本文总结了致病位点的功能机制，并期望促进 GWAS 成果的临床转化，为疾病的预防、诊断寻找可靠的生物标志物和高效的治疗方法。

1 结直肠癌风险位点

截至到 2020 年 11 月，GWAS Catalog (http://www.genome.gov/gwastudies/)数据库收录了 70 多篇结直

图 1 后 GWAS 研究策略

Fig. 1 Post-GWAS approach

GWAS-SNP 功能研究的一般策略是：(1)对结直肠癌相关位点进行基因型填补，获得连锁不平衡区域内的所有位点；(2)整合转录组、表观遗传等多组学数据对相关位点进行注释，筛选潜在功能位点并对候选位点做进一步的功能注释。如 ENCODE、Roadmap 等数据库提供了甲基化、组蛋白修饰、染色质开放程度等信息；表达数量性状基因座(expression quantitative trait loci, eQTL)数据有助于识别 SNP 可能影响的靶基因；Cistrome、JASPAR 等数据库可用于预测 SNP 是否影响转录因子结合等；(3)利用体内外实验阐明风险位点的致病机制。常见的实验方法有：荧光素酶报告基因实验、ChIP-seq、染色体构象捕获技术、基因敲除等。参考文献[5]绘制。

肠癌 GWAS 研究，共鉴定到 821 个相关位点，其中 584 个为非重复位点，241 个 SNP 与结直肠癌风险显著相关($P<5\times10^{-8}$)，绝大部分位于内含子、基因间等非编码区(表 1)。从人群上看，影响东亚人群患病风险的 SNP 约有 38 个，与欧洲人群相关的 SNP 超过 100 个[14]。组学数据的累积、样本数量的增加和分析方法的改善，促进了新的风险位点不断被发现，这些位点包括位于已知风险位点上的新变异(rs6584283, 10q24.2[15])，甚至是一些稀有、低频变异(rs145364999, 频率为 0.3%[16])。然而，这些变异的风险预测效应较弱(OR<1.5)，但大部分 SNP 所在或邻近基因参与 TGF-β/BMP (如 *BMP2*、*SMAD7*、*CCND2*)、Wnt (如 *CTNNB1*、*TCF7L2*)等信号通路以及维持端粒生物功能(如 *TERC*、*TERT*)，暗示这些变异的功能效应赋予疾病易感性[17,18]。因此，有必要对风险变异进行进一步的功能分析。

2　结直肠癌后 GWAS 研究

2.1　功能注释

2.1.1　编码区 SNP

位于编码区的 SNP 可分为同义和非同义突变，同义突变虽然不影响蛋白质的氨基酸序列，但可能通过影响转录后修饰、翻译速率等过程，改变蛋白的表达；而非同义 SNP (non-synonymous SNP, nsSNP)会引起氨基酸的替换，造成蛋白结构、理化性质(稳定性、溶解性等)和功能发生改变。那些对蛋白结构和功能影响较大的非同义突变往往会在自然选择中被淘汰，推测剩下的非同义突变功能效应可能较小，这给 nsSNP 的研究带来一定的挑战。目前，已有大量的生物软件(如 MUpro、INPS-MD、ModPred 等)可用于预测 nsSNP 对蛋白结构和功能的影响，相较而言，nsSNP 的功能机制相对简单，因此相关的研究也较多[19~22]。结合全外显子分析发现多个与结直肠癌发展相关的编码区 SNP，如位于 *SH2B3* 重要结构域上的错义突变 rs3184504 (p.Trp263Arg)可能改变该蛋白对细胞分裂的调节功能；还有些编码变异可能影响可变剪切(rs16888728, *UTP23*)[23]。

表 1　GWAS 鉴定的 SNP 的类型

Table 1　The genomic context of identified SNPs

变异类型	数量	比例(%)
内含子	137	57
基因间	85	35
3′非翻译区	4	~1
5′非翻译区	2	~1
同义编码	3	~1
错义变异	4	~2
非编码 RNA	4	~2
剪接受体	1	~0.5
获得性终止子	1	~0.5

2.1.2　非编码区 SNP

目前 GWAS 发现的结直肠癌风险相关位点主要位于非编码区，这些位点可能参与基因转录、转录后加工、翻译和翻译后修饰等过程调控基因表达。在研究非编码区 SNP 时，首先需要明确这类 SNP 的靶基因，常用的方法是利用表达数量性状基因座(expression quantitative trait loci, eQTL)检测 SNP 与基因表达的关系，基于此策略，已发现大量非编码 SNP 可能影响的靶基因，包括 *CTNNB1*、*GREM1*、*ATF1* 等以及一些与结直肠癌关系尚不明确的基因(如 *TNS3*、*FUT2*)。非编码 SNP 可以通过近距离顺式或远距离反式作用调控靶基因的转录，研究发现这类风险 SNP 所在区域的组蛋白修饰特别丰富，尤其是与启动子、增强子活性相关的修饰(H3K4me3、H3K4me1、H3K27ac)；并预测大部分 SNP 会破坏特定转录因子的结合基序，如 rs6983267 可能会改变与 MYC、CTCF、TCF7L2 等转录因子的结合[18]。有些非编码 SNP 可能影响增强子活性，通过远距离增强子与启动子相互作用改变靶基因的表达[14]。此外，基因组的 3D 结构在基因表达调控等过程中发挥重要作用[24,25]，整合 Hi-C 等数据发现，一些非编码 SNP 所在区域与靶基因启动子区存在显著的染色质环相互作用[14,18,26]，因此在对非编码 SNP 进行功能解析时，常常需要考虑染色质相互作用等。

非编码 SNP 功能多样，可参与到基因表达调控的各个进程中，可能位于不同的调控区，如 miRNA 种子序列结合位点区、可变剪切位点区等，还可以出现在非编码 RNA 上，包括长链非编码 RNA 和 miRNA 等。功能注释发现位于 *DOK3* 非翻译区的

rs2279398 可能改变与 miRNA 的结合效率[27]；目前也识别到大量非编码 RNA 上的 SNP，如 rs2632159 (*lncRNA-PCAT1*)、rs6505162 (*miR-423*)等[28~31]；位于 *hsa-mir-146a* 的 rs1052918 可能会引起 Wnt 信号通路的持续激活，导致细胞增殖失控和肿瘤发生[32]。可见，非编码 SNP 功能机制十分复杂，有待系统、深入的研究。

2.2 功能 SNP 机制的实验证据

2.2.1 编码区 SNP 的潜在功能机制

编码区 SNP 影响患病风险的机制离不开其所在基因编码蛋白的功能。由于这类 SNP 发生的频率相对较低，研究者往往聚焦在特定信号通路/基因或某种感兴趣的修饰方式，如 N^6-甲基腺嘌呤(N^6-Methyladenosine, m^6A)修饰，进行全外显子关联分析以发现效应较大的编码 SNP。对参与 TGFβ 信号通路的 12 个基因进行外显子测序和关联性分析，筛选到 *SMAD7* 上的低频错义变异 rs3764482 与中国汉族人群的结直肠癌风险显著相关，SMAD7 能够抑制 R-SMAD 的磷酸化并在该通路中发挥负调控作用，鉴于此功能而设计的体外实验表明，该 SNP 通过影响 R-SMAD 磷酸化，改变 TGFβ 信号活性[33]。类似地，rs3750050 (*PTPN12*, p.Thr573Ala)、rs149418249 (*TPP1*, p.Pro507Leu)通过破坏蛋白功能、蛋白与蛋白的相互作用，分别引起 Ras/MEK/ERK 通路和端粒功能异常，导致结直肠患病风险升高[34,35]。

编码区 SNP 还可能影响基因或蛋白的修饰。如 m^6A 修饰主要发生在 RNA 上，参与 mRNA 稳定性的维持、mRNA 前体剪切、翻译调控等过程，是近些年的研究热点。通过分析 m^6A 相关 SNP 与结直肠癌风险的关系，发现在 m^6A 编辑器的参与下，发生在 *ANKLE1* 外显子区的 rs8100241[A]等位基因能够增加 *ANKLE1* 的 m^6A 修饰水平和转录效率，促进该潜在抑癌蛋白的表达[36]。

值得注意的是，编码区 SNP 可能与其他 SNP 存在相互作用[23,37]，发挥更强的功能效应。如：位于转录因子 *TCF7L2* 外显子区的 rs138649767[A]等位基因，能激活含有 rs6983267[G]的 *MYC* 增强子，促进 *MYC* 的表达[38]；发生在 *SMAD7* 外显子和内含子上的 SNP 可能存在调控与被调控的关系，也可能共同影响 SMAD7 的功能和 TGFβ 信号通路[33]。因此，在研究编码区 SNP 时，可以考虑 SNP 之间的相互作用，以更好的解析其功能机制。

2.2.2 非编码区 SNP 调控基因表达

结直肠癌风险 SNP 主要位于非编码区[39]，根据所处位置发挥不同的机制，其所在区域可以是近端(启动子、增强子或超级增强子)或远端(基因间或基因内)应答元件。非编码 SNP 往往通过改变转录因子结合位点(transcription factor-binding site, TFBS)、表观遗传修饰和/或染色质结构，影响基因转录水平(表 2，图 2)。SNP 造成的序列变化可能会产生新的 TFBS 或破坏已存在的 TFBS，影响与转录因子(如 SP1, NF1, GATA3; MYC, NFATC2, YY1 等[40~44])的结合，调控靶基因的转录，参与细胞增殖、凋亡、迁移侵袭等过程。

(1)影响启动子活性。启动子区上的 SNP 一般通过影响与转录因子的结合，发挥调控作用。如：rs13278062 和 rs2243828 分别位于 *DR4* 和 *MPO* 启动子区，体内体外实验表明，这两个 SNP 的[T]等位基因在结直肠癌发展中有着不同的作用，前者抑制克隆形成，后者促进细胞增殖，但它们的分子机制相似，都是通过增加与转录因子(Sp1/NF1、AP-2α)的结合亲和力，使 DR4 和 MPO 表达增加[40,47]。

(2)影响增强子活性。内含子区的 SNP 常位于增强子元件，也会改变与转录因子的结合，主要发挥远距离调控作用。发生在 *CDH1* 内含子区的 rs7198799 能够靶向转录因子 NFATC2，远距离增强 *ZFP90*(距离致病位点超过 200 kb)的表达，通过 NFATC2-ZFP90-BMP4 通路促进癌症发生[43]；类似地，rs174575 可以在转录因子 E2F1 的参与下，作为 *FADS2* 和 *lncRNA-AP002754.2* 位点特异的远距离增强子[50]，有趣的是后者又能够促进 FADS2 的表达，形成环路，影响结直肠癌发生[50]。

单个 SNP 的效应可能较小，但是多个致病 SNP 对 TFBS 产生的累积效应可能对靶基因表达的影响很大。例如，rs61926301 和 rs7959129 是分别发生在 *ATF1* 启动子区和内含子区上的 SNP，这两个 SNP 的[T]风险等位基因能够分别增加与转录因子 SP1 和 GATA3 的结合能力，通过启动子与增强子相互作用的方式促进潜在癌基因 *ATF1* 的转录，影响细胞增殖、

表 2　后 GWAS 实验性研究阐明的非编码 SNP 作用机制

Table 2　Mechanisms of non-coding SNPs based on post-GWAS experimental reports

功能	SNP	位置	靶基因	实验	参考文献
影响与转录因子的结合	rs13278062	*DR4* 启动子区	*DR4*	CRISPR/Cas9、ChIP、流式分析等实验	[40]
	rs11777210	*KBTBD11* 内含子区	*KBTBD11*	凝胶迁移、荧光素酶报告基因等实验	[42]
	rs55829688	*lncRNA-GAS5*	*GAS5*	荧光素酶报告基因、凝胶迁移、流式分析、迁移侵袭等实验	[44]
	rs2238126	*ETV6* 内含子区	*ETV6*	荧光素酶报告基因、凝胶迁移实验、ChIP	[45]
	rs27437	*SLC22A5* 上游	*SLC22A5*	荧光素酶报告基因实验	[46]
	rs2333227	*MPO* 启动子区	*MPO*	ChIP、CRISPR/Cas9、克隆形成、侵袭迁移、裸鼠体内成瘤等实验	[47]
	rs420038	*SLC22A3* 内含子区	*SLC22A3*	荧光素酶报告基因、流式分析、细胞增殖等实验	[48]
影响启动子增强子相互作用	rs61926301	*ATF1* 启动子区	*ATF1*	荧光素酶报告基因、凝胶迁移、ChIP、3C、裸鼠异种移植体外等实验	[41]
	rs7959129	*ATF1* 内含子区			
	rs7198799	*CDH1* 内含子区	*ZFP90*	荧光素酶报告基因、凝胶迁移、ChIP、4C 测序、3C-qPCR、小鼠实验等	[43]
	rs12263636	*ZMIZ1* 内含子区	*RPS24*	荧光素酶报告基因实验	[49]
	rs174575	*FADS2* 内含子区	*FADS2*, *AP002754.2*	荧光素酶报告基因、凝胶迁移、3C、裸鼠体内异种移植等实验	[50]
作为绝缘子发挥远距离调控作用	rs6702619	*LPPR4* 与 *PALMD* 基因间	*GNAS* 等	ChIP、增强子阻断、3C 测序等实验	[51]
影响与 miRNA 的结合	rs11169571	*ATF1* 3′UTR	*ATF1*	荧光素酶报告基因实验	[38]
	rs3814058	*PXR* 3′UTR	*PXR*	荧光素酶报告基因实验	[52]
	rs12915554	*GREM1* 3′UTR	*GREM1*	荧光素酶报告基因实验	[53]
	rs1062044	*LAMC1* 3′UTR	*LAMC1*	荧光素酶报告基因实验	[54]
	rs5030740	*RPA1* 3′UTR	*RPA1*	荧光素酶报告基因、细胞增殖、流式分析等实验	[55]
	rs6504593	*IGF2BP1* 3′UTR	*IGF2BP1*	荧光素酶报告基因、细胞增殖、流式分析等实验	[56]
	rs1590	*TGFBR1* 3′UTR	*TGFBR1*	荧光素酶报告基因	[57]
	rs1317082	*CCSlnc362*	*CCSlnc362*	荧光素酶报告基因、细胞增殖、流式分析等实验	[58]
	rs664589	*lncRNA-MALAT1*	*MALAT1*	荧光素酶报告基因实验	[59]
	rs12982687	*lncRNA-UCA1*	*UCA1*	荧光素酶报告基因、细胞增殖、侵袭迁移等实验	[60]
影响与靶基因的结合	rs35301225	*miR-34*	*E2F1*	荧光素酶报告基因、细胞增殖等实验	[61]

ChIP (chromatin immunoprecipitation)：染色质免疫沉淀；3C (chromosome conformation capture)：染色体构象捕获；4C (circular chromosome conformation capture)：环形染色体构象捕获； UTR (untranslated region)：非翻译区。

抑制细胞凋亡；基因表达的调控与染色质的高级结构密切相关，分析发现这两个 SNP 所在的区域富集活跃的组蛋白修饰峰和开放的染色质可及性[41]。

(3)其他。miRNA 能够靶向基因 3′非翻译区(untranslated region, UTR)，沉默基因表达。如，发生在 *IGF2BP1* 3′UTR 区的 rs6504593 突变位点减弱

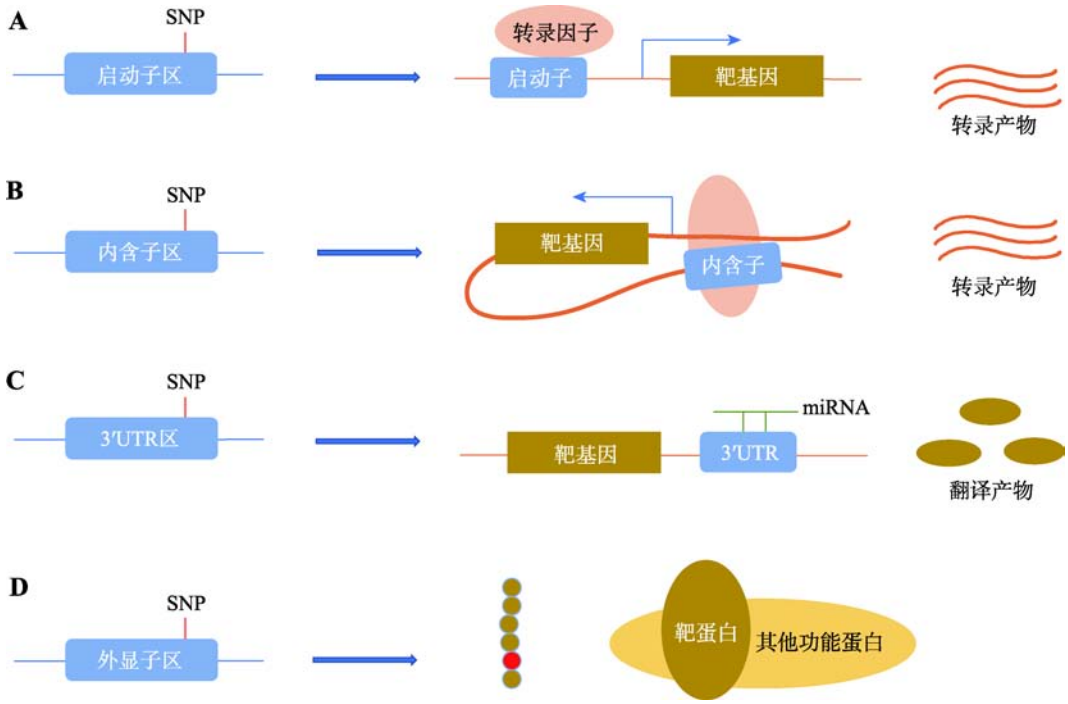

图 2　致病 SNP 潜在功能机制总结

Fig. 2　Summary of the potential functional mechanisms of causal SNPs

A：启动子区 SNP 的潜在功能机制。通过影响与转录因子的结合，调控靶基因的表达，影响结直肠癌发生；B：内含子区 SNP 的潜在功能机制。常在转录因子的参与下，通过远距离启动子增强子相互作用，影响靶基因表达；C：3′UTR 区 SNP 的潜在功能机制。往往通过改变与 miRNA 的结合，影响靶基因转录后水平；D：外显子区 SNP 的潜在功能机制。可能通过改变氨基酸序列，影响蛋白与蛋白之间的相互作用。

了 *miR-21* 与该区域的结合，使 *IGF2BP1* 表达上调，引起结直肠癌发生[56]。发挥类似机制的还有位于 *GREM1*、*LAMC1*、*ATF1* 等基因 3′UTR 区的 SNP[38,53,54]，此外，长链非编码 RNA 上的一些 SNP 也能通过改变与 miRNA 的结合发挥作用，如 rs1317082、rs664589、rs12982687[58~60]等。若 SNP 发生在 miRNA 上，同样会影响其与靶基因的结合亲和力[61]。

3　结直肠癌 GWAS 的应用

GWAS 和后 GWAS 研究不仅可以帮助人们更好地在遗传水平上理解结直肠癌的发病机制，也有助于筛查预防、风险分层和临床治疗等。

3.1　风险预测

通过组合已发现的结直肠癌风险位点计算遗传风险评分(genetic risk score, GRS)是 GWAS-SNP 重要的公共卫生价值之一[62]，该方法对每个 SNP 的微弱效应进行叠加，大大提高了对疾病风险的预测能力，有潜力成为药物治疗、行为矫正的基础。基于 37 个已知 CRC 风险变异的 GRS 表明，与人群中位数相比，得分排在前 1%的个体患 CRC 的风险增加了 2.9 倍[63]；在中国南方汉族人群中，GRS 结合传统风险因素构建的风险模型预测能力优于传统风险因素模型[64]。随着风险位点的数量不断增加，基于此建立的 GRS 风险模型的预测效能也将不断提高，有望实现肿瘤精准预防。

3.2　预后分析

rs5030740、rs9939049、rs11196172 等结直肠癌风险 SNP 与患者的生存期显著相关，有可能发展成为可靠的预后标志物[55,65~67]。其中，rs5030740 能够调控 *RPA1* 的表达，而 *RPA1* 低表达增加了结直肠癌细胞对奥沙利铂的敏感性，抑制了奥沙利铂治疗后的细胞增殖[55]；另外，在接受贝伐单抗一线化疗的结直肠癌患者中开展的试验表明，携带 rs699947-AA

(*VEGF-A*)和 rs1799969-GA (*ICAM-1*)基因型的患者总生存期比其他患者更长[68]。上述研究表明风险 SNP 可用于分析预后、指导用药,实现个体化治疗。

4　结语与展望

尽管 GWAS 研究已经发现了大量结直肠癌风险相关位点，但大部分 SNP 的功能效应较小，更多高效力的位点有待发掘。相信随着测序技术的进步、人群研究规模的扩大、分析水平的提高，新的结直肠癌易感位点(包括一些低频、稀有变异)将会不断被发现[15,69~71]。目前，对结直肠癌潜在功能变异的筛选稍显不足，对其进行机制探索的实验更是屈指可数。各种组学、基因组结构等数据的涌现，以及孟德尔随机化的应用，为筛选潜在致病变异提供了可靠信息[72,73]；实验技术的发展为阐明致病变异的生物学功能提供更可靠的证据，如：CRISPR/Cas9 使单碱基编辑成为可能，染色体构象捕获及其衍生技术可探究 SNP 的远距离调控机制等等，相信未来将会有更多致病变异的分子机制被阐明。此外，已有研究表明几个不同区域的 SNP 同时突变时，结直肠癌的患病风险大大增加[38,49]；SNP 还与多种因素(如阿司匹林的服用、吸烟等)存在交互作用，影响结直肠癌风险[74,75]。可见癌症作为复杂疾病，遗传与遗传、遗传与环境之间的相互作用不可忽视[76]。因此在研究风险 SNP 的功能时，需要更多的关注 SNP 与 SNP 以及 SNP 与环境之间的作用。相信随着后 GWAS 研究的开展和深入，将会帮助我们更好地认识变异与结直肠癌发生发展之间的关系，推动个体化预防和精准治疗的发展。

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