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New Insights into Functional Implication of Genetic Variation in Association with Cancer

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Abstract

Investigations of the genetic basis of cancers have identified hundreds of robust risk loci associated with cancers using large-scale, case-control, candidate gene studies as well as genome-wide association studies (GWASs) during the past ten years. Most leading single nucleotide polymorphisms (SNPs) associated with cancer sensitivity lie in non-protein-coding regions, suggesting the potentially regulatory functions as targets for susceptible variants. That is a critical question to understand the molecular mechanisms and causality within cancer susceptible loci. In this short review, the latest findings about functional implications of genetic variants in cancer etiology were summarized on the basis of genetics, epigenetics and environmental factors. Several helpful directions in post-GWAS functional determinants of cancer-associated polymorphisms were also previewed.

Keywords

Genetic polymorphism, Cancer risk locus, Chromatin interaction, QTL, Methylation, Non-Coding RNA

Introduction

Recent advances in genome-wide association studies (GWASs) and fine-mapping analyses have yielded a plethora of common and rare loci associated with diverse cancers and other complex diseases [1-3]. These different penetrant risk loci together substantially unveil the heritable fraction of diseases [4]. Due to the majority of cancer risk variants reside in intronic or intergenic regions of unknown function, how to effectively understand their molecular mechanisms has become a challenging but critical question in post-GWAS research [5]. Several pioneering studies have revealed some promising molecular evidences at both transcriptional and regulatory levels for cancer genetic variants [6,7], and the contributions are continuously underway, especially in the area of gene expression and regulation.

Thanks to the development of diverse of high-throughput technologies, particularly next-generation sequencing (NGS) technologies, genome-scale large data sets — including genomic, epigenomic, transcriptomic and proteomic information, are now freely accessible from large collaborative projects, including Encyclopedia of DNA Elements (ENCODE) [8,9], NIH Epigenomics Roadmap [10], The Cancer Genome Atlas (TCGA) [11], Genotype-Tissue Expression (GTEx) [12]. Concomitantly, an integrative genomic approach [13] has increasingly adopted to interrogate whether genetic variants of interest are the causal potential. More recently, Ward *et al.* [14] and Edwards *et al.* [15] depicted a systematic flowchart for functional prediction of genetic variants by integrating publicly accessible functional genomic data, including expression quantitative trait loci (eQTLs), chromatin modification and states across diverse cell types and disease relevant tissues/cells, transcription factors binding motif. This short article will review the latest findings about functional implications of cancer genetic loci focusing on QTLs and epigenetic regulation, as well as the interactions of cancer-associated variants with environmental and nutritional factors. The summary might help to comprehensively understand the cancer pathogenesis, and provide an additional direction for future cancer genetic studies.

Quantitative Trait Loci

DNA methylation QTL: Numerous studies have revealed a common profile of a global DNA hypomethylation and local DNA hypermethylation associated with tumorigenesis [16-19], which provides a clue to determine the functional feature of identified common and rare genetic variants associated with cancer risk. A growing attention has focused on the correlation between cancer-risk variants and DNA methylation levels, a definition referring to as the methylation quantitative trait loci (meQTL) [20,21]. Heyn *et al.* first conducted [22] a comprehensive meQTL analyses via integrating genome-wide DNA methylation profiles with 109 GWAS-SNPs in 13 solid cancer types. They found 23 *cis*-meQTLs, accounting for approximately one-quarter of interrogated cancer risk polymorphisms. Several other studies also found several cancer-associated meQTLs in lung cancer [17], prostate cancer [23], myeloma [24], etc. Thus, screening the genomic variants and epigenomic modifications at high resolution could elucidate a direct functional implication of the underlying genetic genotypes associated with DNA methylation at specific sites.

The Infinium Human Methylation 450 and Human Methylation 27 Bead Chips [22-25] are two popular platforms to measure DNA methylation profiles [26]. At present, the measurement of DNA methylation levels for meQTL analyses also largely depend on these platforms. Nonetheless, a large proportion of human genomic CpG sites are still uncovered in the design of DNA methylation chips in current microarray-based meQTL studies. It causes that the meQTLs accounting for cancer risk variants are far less discovered. So it is possible to conduct fine-scale mapping of meQTLs associated with

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cancer risk by employing genome-wide bisulfite sequencing or targeted bisulfite-sequencing technologies [27,28] in single CpG site resolution.

Apart from methylation on cytosine (5-mC) at CpG sites, recent studies have discovered several newtypes of DNA modifications [29-32], including 5-Hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC), 5-carboxylcytosine (5-caC), andN^6-adenine methylation (N^6-methyladenine, 6mA). QTL analysis with these DNA modifications may help to reveal novel molecular phenotypes for genetic effects on cancer risk.

Expression QTL: Expression QTL analysis has been widely used to detect the regulatory feature of genetic variants that influence the expression level of genes in cis and trans [15]. Recent works did more deep exploration in the study of expression QTLs for cancer-associated genetic variants. One of the most powerful approaches to perform eQTL analyses in cancer genetic studies is the Li *et al.* developed method [33], which directly works through the TCGA data sets. The method did a residual linear regression test with tumor gene expression adjusted by somatic copy-number alternation and CpG methylation. This method shows considerably robust in functional annotation of cancer-associated variants. For example, Cai et al. applied this model to examine eQTLs for novel discovered breast cancer risk variants [34]. Based on this model, Wong *et al.* also identified thousands of expression-associated somatic single nucleotide variants (eSNVs) in endometrial cancer [35].

It should be also noted that the non-coding RNAs, including long non-coding RNAs (lncRNAs), piRNAs, endogenous siRNAs, snoRNAs, have been reported to show aberrant expression in tumors [36-38]. However, there are still less findings about whether cancer-associated genetic variants could functionally control the expression of the non-coding RNAs. Studies in other diseases or human traits have implicated the relationship between the expression of lncRNAs and genetic variants. In the study of Kumar *et al.* [39], they found that the majority of lncRNAs-eQTLs were specific to lncRNA alone and did not affect the expression of neighboring protein-coding genes in blood. Brown *et al.* proposed that the most promising molecular phenotype for genetic risk variants is cancer-relevant tissue or cell type specific eQTLs [40]. Due to high tissue-restricted expression pattern for most lncRNAs, exploring the lncRNA-eQTL association for cancer risk loci could be conducted to understand the specificity of cancer-associated genetic variants. In Addition, relative to genetically steady eQTLs, some eQTLs are probably inducible [41], another missing layer involved in disease predisposition.

Transcriptional regulation by genetic variants is involved in allelic imbalance. The allelic specificity on gene expression is a phenomenon where two alleles for heterozygous SNPs show significantly biased expression [42]. Recent studies have showed the allelic biased expression for cancer risk loci. For example, two breast cancer risk loci (rs2046210 at 6q25 and rs418269 at 8q24) are significantly associated with allelic specific expression of *ESR1* and *MYC*, respectively [33]. Due to the transcriptomic complexity and fine-tune regulation at both transcriptional and post-transcriptional levels, genetic variants associated with gene expression could be comprehensively analyzed, so as to maximize the understanding of cancer risk loci as regulators.

Protein-level QTL: At the translational level, many studies and reviews reported the regulatory effects of cancer genetic variants by transcription factors (TFs) focused on the difference of binding affinity on genetic variants in *trans* regulation [15,43-45]. Several *in vitro* and *in vivo* functional assays are developed to determine the binding affinity difference at two alleles of a locus of interest, including Electrophoretic Mobility Shift Assay (EMAS), gene reporter assays, chromatin immune-precipitation followed by quantitative PCR (ChIP-qPCR), and the rest [43,44,46,47]. Here one newly discovery of the functional relationship of genetic variants with protein abundance, termed as protein quantitative trait loci (pQTLs), was first reported in the study of Wu *et al.* [48]. Interestingly, some pQTLs could not be detected as eQTLs, providing a new layer for genetic variants in molecular phenotypic regulation. Similarly, another study identified that the SNP rs6834 was significantly correlated with DIDO1 protein levels relevant for cancer chemotherapy [49]. Thus, combining genomic and proteomic quantification data could be considered for cancer risk variants.

Epigenetic regulation

Although several studies have manifested that cancers and other diseases associated causal non-coding variants function as enhancer or other *cis*-regulatory roles [50-52], how to establish the functional interaction between *cis*-regulatory elements and gene regulation becomes a critical issue. The latest studies have made some efforts on the chromatin architecture scale.

Chromosome conformation capture (3C) and its derived methods are the high-throughput molecular biology techniques used to analyze the topology of chromosomal regions in viable cells [53]. With 3C technology, it is possible to identify the physically local or distal interaction between regulatory elements and genetic variants. For example, 3C followed by real-time PCR (3C-qPCR) has been successfully utilized in determining whether the two pre-defined genomic regions are physically interacted [6,33,43,54-56]. More recently, the development of targeted 3C and relevant technologies [57-60] further allow for a high-resolution survey of the whole genome for potential interactions with multiple regions of interest simultaneously. With these targeted chromosome architecture technologies, several studies have found both intra-chromosomal and inter-chromosomal physical interactions in high precision for cancer genetic variants. For example, Jager *et al.* found a regulatory network about the looping interactions between *CCAT2*, *CCAT1* and *MYC*, at 8q24 risk locus associated with colorectal cancer [61]. Another study also discovered the strongest long-range interaction was not at intra-chromosomal locus 8q24 but at inter-chromosomal locus 3q13 associated with prostate cancer [57]. Therefore, for a given cancer risk locus, it may function as a regulatory hub by physical interactions with multiple genes important for carcinogenesis, implicating the multiple-directional regulation probably exists at specific risk loci.

There are still some issues for current epigenomic assays to link the chromosome-level DNA looping with cancer risk loci, because most chromosome-capturing assays are carried out in well-established cell lines. Due to the potential difference of genetic background between cell lines and patient-derived tissues or cells, it will be attractive to develop patient-derived cell/tissue system to characterize the personalized chromatin interaction landscape for cancer genetic studies. In addition, combining with single-cell based genomic and epigenomic sequencing technologies [62-64], experiments on the patient-derived *ex vivo* cells could provide a deeper knowledge about the genetic and etiologic susceptibility of cancers.

Environmental factors

Besides the genetic and epigenetic implications for cancer risk loci, a few studies reported other potential non-(epi)genetic factors in association with cancer susceptibility, including gene-trait interaction [65,66], gene-nutrition interaction [67,68], genetic-microbiome interaction [69], as well as electronic medical record (EMR)-based genetic integrative analysis [70].Taking one as an example, Ramagopalan *et al.* [71] reported that the vitamin D receptor (VDR) binding sites were significantly enriched near cancer and autoimmune disease associated genes. Biochemical study demonstrated that the chromatin remodeler *JMJD3* was regulated by vitamin D in colon cancer cells [72]. Clinical surveys also demonstrated that a higher vitamin D level was significantly associated with a lower colorectal cancer risk [73,74], suggesting that cancer risk variants could be also implicated in the interaction with vitamins and other nutrients.

Conclusions and Prospects

In this review, the latest progression in the molecular phenotypes for cancer risk variants at multiple levels is summarized. We expect that these discussions will provide additional understanding of

cancer molecular genetics in post-GWAS functional characterization. Undoubtedly, future advances in exploring the gene expression and regulation will identify more molecular genetic evidences for cancer susceptibility.

References

1. Welter D, MacArthur J, Morales J, Burdett T, Hall P, et al. (2014) The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res 42: D1001-1006.
2. Ruark E, Snape K, Humburg P, Loveday C, Bajrami I, et al. (2013) Mosaic PPM1D mutations are associated with predisposition to breast and ovarian cancer. Nature 493: 406-410.
3. Zhang Y, Long J, Lu W, Shu XO, Cai Q, et al. (2014) Rare coding variants and breast cancer risk: evaluation of susceptibility Loci identified in genome-wide association studies. Cancer Epidemiol Biomarkers Prev 23: 622-628.
4. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, et al. (2009) Finding the missing heritability of complex diseases. Nature 461: 747-753.
5. Lewis A, Tomlinson I (2012) The utility of mouse models in post-GWAS research. Science 338: 1301-1302.
6. Pomerantz MM, Ahmadiyeh N, Jia L, Herman P, Verzi MP, et al. (2009) The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. Nat Genet 41: 882-884.
7. Ahmadiyeh N, Pomerantz MM, Grisanzio C, Herman P, Jia L, et al. (2010) 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. Proc Natl Acad Sci U S A 107: 9742-9746.
8. Consortium EP (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489: 57-74.
9. Consortium EP (2011) A user's guide to the encyclopedia of DNA elements (ENCODE). PLoS Biol 9: e1001046.
10. Bernstein BE, Stamatoyannopoulos JA, Costello JF, Ren B, Milosavljevic A, et al. (2010) The NIH Roadmap Epigenomics Mapping Consortium. Nat Biotechnol 28: 1045-1048.
11. Cancer Genome Atlas Research N, Weinstein JN, Collisson EA, Mills GB, Shaw KR, et al. (2013) The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet 45: 1113-1120.
12. Consortium GT (2015) Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 348: 648-660.
13. Hawkins RD, Hon GC, Ren B (2010) Next-generation genomics: an integrative approach. Nat Rev Genet 11: 476-486.
14. Ward LD, Kellis M (2012) Interpreting noncoding genetic variation in complex traits and human disease. Nat Biotechnol 30: 1095-1106.
15. Edwards SL, Beesley J, French JD, Dunning AM (2013) Beyond GWASs: illuminating the dark road from association to function. Am J Hum Genet 93: 779-797.
16. Hon GC, Hawkins RD, Caballero OL, Lo C, Lister R, et al. (2012) Global DNA hypomethylation coupled to repressive chromatin domain formation and gene silencing in breast cancer. Genome Res 22: 246-258.
17. Leng S, Liu Y, Weissfeld JL, Thomas CL, Han Y, et al. (2015) 15q12 variants, sputum gene promoter hypermethylation, and lung cancer risk: a GWAS in smokers. J Natl Cancer Inst 107: pii: djv035.
18. Hiltunen MO, Koistinaho J, Alhonen L, Myohanen S, Marin S, et al. (1997) Hypermethylation of the WT1 and calcitonin gene promoter regions at chromosome 11p in human colorectal cancer. Br J Cancer 76: 1124-1130.
19. Wu W, Bhagat TD, Yang X, Song JH, Cheng Y, et al. (2013) Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, AFAP1-AS1, in Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 144: 956-966.
20. Gibbs JR, van der Brug MP, Hernandez DG, Traynor BJ, Nalls MA, et al. (2010) Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. PLoS genetics 6: e1000952.
21. Shoemaker R, Deng J, Wang W, Zhang K (2010) Allele-specific methylation is prevalent and is contributed by CpG-SNPs in the human genome. Genome Res 20: 883-889.
22. Heyn H, Sayols S, Moutinho C, Vidal E, Sanchez-Mut JV, et al. (2014) Linkage of DNA methylation quantitative trait loci to human cancer risk. Cell Rep 7: 331-338.
23. Berndt SI, Wang Z, Yeager M, Alavanja MC, Albanes D, et al. (2015) Two susceptibility loci identified for prostate cancer aggressiveness. Nat Commun 6: 6889.
24. Johnson DC, Weinhold N, Mitchell JS, Chen B, Kaiser M, et al. (2016) Genome-wide association study identifies variation at 6q25.1 associated with survival in multiple myeloma. Nat Commun 7: 10290.
25. Naumov VA, Generozov EV, Zaharjevskaya NB, Matushkina DS, Larin AK, et al. (2013) Genome-scale analysis of DNA methylation in colorectal cancer using Infinium HumanMethylation450 BeadChips. Epigenetics 8: 921-934.
26. Rakyan VK, Down TA, Balding DJ, Beck S (2011) Epigenome-wide association studies for common human diseases. Nat Rev Genet 12: 529-541.
27. Deng J, Shoemaker R, Xie B, Gore A, LeProust EM, et al. (2009) Targeted bisulfite sequencing reveals changes in DNA methylation associated with nuclear reprogramming. Nat Biotechnol 27: 353-360.
28. Lee EJ, Luo J, Wilson JM, Shi H (2013) Analyzing the cancer methylome through targeted bisulfite sequencing. Cancer Lett 340: 171-178.
29. Luo GZ, Blanco MA, Greer EL, He C and Shi Y (2015) DNA N(6)-methyladenine: a new epigenetic mark in eukaryotes? Nat Rev Mol Cell Biol 16: 705-710.
30. Huang S, Chen D (2015) N6-methyladenine: a potential epigenetic mark in eukaryotes. Oncotarget 6: 15744-15745.
31. Song CX, Yi C, He C (2012) Mapping recently identified nucleotide variants in the genome and transcriptome. Nat Biotechnol 30: 1107-1116.
32. Song CX, Szulwach K, Dai Q, Fu Y, Mao SQ, et al. (2013) Genome-wide Profiling of 5-Formylcytosine Reveals Its Roles in Epigenetic Priming. Cell 153: 678-691.
33. Li Q, Seo JH, Stranger B, McKenna A, Pe'er I, et al. (2013) Integrative eQTL-based analyses reveal the biology of breast cancer risk loci. Cell 152: 633-641.
34. Cai Q, Zhang B, Sung H, Low SK, Kweon SS, et al. (2014) Genome-wide association analysis in East Asians identifies breast cancer susceptibility loci at 1q32.1, 5q14.3 and 15q26.1. Nat Genet 46: 886-890.
35. Wong HS, Juan YS, Wu MS, Zhang YF, Hsu YW, et al. (2016) Integrative bioinformatic analyses of an oncogenomic profile reveal the biology of endometrial cancer and guide drug discovery. Oncotarget 7: 5909-5923.
36. Muller S, Raulefs S, Bruns P, Afonso-Grunz F, Plotner A, et al. (2015) Next-generation sequencing reveals novel differentially regulated mRNAs, lncRNAs, miRNAs, sdRNAs and a piRNA in pancreatic cancer. Mol Cancer 14: 94.
37. Ravo M, Cordella A, Rinaldi A, Bruno G, Alexandrova E, et al. (2015) Small non-coding RNA deregulation in endometrial carcinogenesis. Oncotarget 6: 4677-4691.
38. Su H, Xu T, Ganapathy S, Shadfan M, Long M, et al. (2014) Elevated snoRNA biogenesis is essential in breast cancer. Oncogene 33 1348-1358.
39. Kumar V, Westra HJ, Karjalainen J, Zhernakova DV, Esko T, et al. (2013) Human disease-associated genetic variation impacts large intergenic non-coding RNA expression. PLoS genetics 9: e1003201.
40. Brown CD, Mangravite LM, Engelhardt BE (2013) Integrative modeling of eQTLs and cis-regulatory elements suggests mechanisms underlying cell type specificity of eQTLs. PLoS genetics 9: e1003649.
41. Fairfax BP, Humburg P, Makino S, Naranbhai V, Wong D, et al. (2014) Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. Science 343: 1246949.
42. Pastinen T (2010) Genome-wide allele-specific analysis: insights into regulatory variation. Nat Rev Genet 11: 533-538.
43. Meyer KB, O'Reilly M, Michailidou K, Carlebur S, Edwards SL, et al. (2013) Fine-scale mapping of the FGFR2 breast cancer risk locus: putative functional variants differentially bind FOXA1 and E2F1. Am J Hum Genet 93: 1046-1060.
44. Cowper-Sal lari R, Zhang X, Wright JB, Bailey SD, Cole MD, et al. (2012) Breast cancer risk-associated SNPs modulate the affinity of chromatin for FOXA1 and alter gene expression. Nat Genet 44: 1191-1198.
45. Zeron-Medina J, Wang X, Repapi E, Campbell MR, Su D, et al. (2013) A polymorphic p53 response element in KIT ligand influences cancer risk and has undergone natural selection. Cell 155: 410-422.
46. Meyer KB, Maia AT, O'Reilly M, Ghoussaini M, Prathalingam R, et al. (2011) A functional variant at a prostate cancer predisposition locus at 8q24 is associated with PVT1 expression. PLoS Genet 7: e1002165.
47. Zhang X, Cowper-Sal lari R, Bailey SD, Moore JH and Lupien M (2012) Integrative functional genomics identifies an enhancer looping to the SOX9 gene disrupted by the 17q24.3 prostate cancer risk locus. Genome Res 22: 1437-1446.
48. Wu L, Candille SI, Choi Y, Xie D, Jiang L, et al. (2013) Variation and genetic control of protein abundance in humans. Nature 499: 79-82.
49. Stark AL, Hause RJ, Gorsic LK, Antao NN, Wong SS, et al. (2014) Protein quantitative trait loci identify novel candidates modulating cellular response to chemotherapy. PLoS Genet 10: e1004192.
50. Corradin O, Scacheri PC (2014) Enhancer variants: evaluating functions in common disease. Genome Med 6: 85.

51. He H, Li W, Liyanarachchi S, Srinivas M, Wang Y, et al. (2015) Multiple functional variants in long-range enhancer elements contribute to the risk of SNP rs965513 in thyroid cancer. Proc Natl Acad Sci U S A 112: 6128-6133.

52. Parker SC, Stitzel ML, Taylor DL, Orozco JM, Erdos MR, et al. (2013) Chromatin stretch enhancer states drive cell-specific gene regulation and harbor human disease risk variants. Proc Natl Acad Sci U S A 110: 17921-17926.

53. de Wit E, de Laat W (2012) A decade of 3C technologies: insights into nuclear organization. Genes Dev 26: 11-24.

54. French JD, Ghoussaini M, Edwards SL, Meyer KB, Michailidou K, et al. (2013) Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet 92: 489-503.

55. Wright JB, Brown SJ, Cole MD (2010) Upregulation of c-MYC in cis through a large chromatin loop linked to a cancer risk-associated single-nucleotide polymorphism in colorectal cancer cells. Mol Cell Biol 30: 1411-1420.

56. Ghoussaini M, Edwards SL, Michailidou K, Nord S, Cowper-Sal Lari R, et al. (2014) Evidence that breast cancer risk at the 2q35 locus is mediated through IGFBP5 regulation. Nat Commun 4: 4999.

57. Du M, Yuan T, Schilter KF, Dittmar RL, Mackinnon A, et al. (2015) Prostate cancer risk locus at 8q24 as a regulatory hub by physical interactions with multiple genomic loci across the genome. Hum Mol Genet 24: 154-166.

58. Martin P, McGovern A, Orozco G, Duffus K, Yarwood A, et al. (2015) Capture Hi-C reveals novel candidate genes and complex long-range interactions with related autoimmune risk loci. Nat Commun 6: 10069.

59. Dryden NH, Broome LR, Dudbridge F, Johnson N, Orr N, et al. (2014) Unbiased analysis of potential targets of breast cancer susceptibility loci by Capture Hi-C. Genome Res 24: 1854-1868.

60. de Vree PJ, de Wit E, Yilmaz M, van de Heijning M, Klous P, et al. (2014) Targeted sequencing by proximity ligation for comprehensive variant detection and local haplotyping. Nature biotechnology 32: 1019-1025.

61. Jager R, Migliorini G, Henrion M, Kandaswamy R, Speedy HE, et al. (2015) Capture Hi-C identifies the chromatin interactome of colorectal cancer risk loci. Nat Commun 6: 6178.

62. Swami M (2015) Technology: Dropping in on single-cell epigenetic profiles. Nat Rev Genet 16: 684-685.

63. Hashimshony T, Wagner F, Sher N, Yanai I (2012) CEL-Seq: single-cell RNA-Seq by multiplexed linear amplification. Cell Rep 2: 666-673.

64. Smallwood SA, Lee HJ, Angermueller C, Krueger F, Saadeh H, et al. (2014) Single-cell genome-wide bisulfite sequencing for assessing epigenetic heterogeneity. Nat Methods 11: 817-820.

65. Usset J, Fridley B, Goode E, Schildkraut J and Pharoah P (2015) Assessment of multifactor gene-environment interactions and ovarian cancer risk: SNPs, obesity, and hormone-related risk factors. Cancer research 75: 4684.

66. Rudolph A, Chang-Claude J, Schmidt MK (2016) Gene-environment interaction and risk of breast cancer. Br J Cancer 114: 125-133.

67. Andersen V and Vogel U (2014) Interactions between meat intake and genetic variation in relation to colorectal cancer. Genes & Nutrition 10: 1-14.

68. Andersen V, Egeberg R, Tjønneland A, Vogel U (2012) Interaction between interleukin-10 (IL-10) polymorphisms and dietary fibre in relation to risk of colorectal cancer in a Danish case-cohort study. BMC Cancer 12: 1-9.

69. Blekhman R, Goodrich JK, Huang K, Sun Q, Bukowski R, et al. (2015) Host genetic variation impacts microbiome composition across human body sites. Genome Biol 16: 191.

70. Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, et al. (2013) The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. Genetics in medicine : official journal of the American College of Medical Genetics 15: 761-771.

71. Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, et al. (2010) A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. Genome Res 20: 1352-1360.

72. Pereira F, Barbáchano A, Silva J, Bonilla F, Campbell MJ, et al. (2011) KDM6B/JMJD3 histone demethylase is induced by vitamin D and modulates its effects in colon cancer cells. Hum Mol Genet 20: 4655-4665.

73. Jung S, Qian ZR, Yamauchi M, Bertrand KA, Fitzgerald KC, et al. (2014) Predicted 25(OH)D score and colorectal cancer risk according to vitamin D receptor expression. Cancer Epidemiol Biomarkers Prev 23: 1628-1637.

74. Chandler PD, Buring JE, Manson JE, Giovannucci EL, Moorthy MV, et al. (2015) Circulating Vitamin D Levels and Risk of Colorectal Cancer in Women. Cancer Prev Res 8: 675-682.