Published in final edited form as:
JAMA. 2008 October 1; 300(13): 1523–1531. doi:10.1001/jama.300.13.1523.

Variants of the Adiponectin (*ADIPOQ*) and Adiponectin Receptor 1 (*ADIPOR1*) Genes and Colorectal Cancer Risk

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Abstract

Context—Current epidemiological evidence suggests an association between obesity, hyperinsulinemia, and colorectal cancer risk. Adiponectin is a hormone secreted by the adipose tissue, and serum levels are inversely correlated with obesity and hyperinsulinemia. While there is evidence of an association between circulating adiponectin levels and colorectal cancer risk, no association between genes of the adiponectin pathway and colorectal cancer have been reported to date.

Objective—To determine the association of 10 haplotype-tagging single-nucleotide polymorphisms (SNPs) of the adiponectin (*ADIPOQ*) and adiponectin receptor 1 (*ADIPOR1*) genes with colorectal cancer risk.

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Financial Disclosures: None reported.

Disclaimer: Dr Pasche is a Contributing Editor for *JAMA* but was not involved in the editorial evaluation or editorial decision making regarding publication of this article.

Obtained funding: Ahsan, Pasche. *Administrative, technical, or material support:* Offit, Baron.

Role of the Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Design, Setting, and Patients—Two case-control studies including patients with a diagnosis of colorectal cancer and controls were recruited between 2000 and 2007. Case-control study 1 included a total of 441 patients with a diagnosis of colorectal cancer and 658 controls; both groups were of Ashkenazi Jewish ancestry and from New York, New York. Case-control study 2 included 199 patients with a diagnosis of colorectal cancer and 199 controls from Chicago, Illinois, matched 1:1 for sex, age, and ethnicity.

Main Outcome Measures—*ADIPOQ* and *ADIPOR1* SNP frequency among cases and controls.

Results—In study 1, after adjustment for age, sex, and SNPs from the same gene, 3 *ADIPOQ* SNPs and 1 *ADIPOR1* SNP were associated with colorectal cancer risk: rs266729 (adjusted odds ratio [AOR], 0.72; 95% confidence interval [CI], 0.55–0.95) and rs822396 (AOR, 0.37; 95% CI, 0.14–1.00) were associated with decreased risk whereas rs822395 (AOR, 1.76; 95% CI, 1.09–2.84) and rs1342387 (AOR, 1.79; 95% CI, 1.18–2.72) were associated with increased risk. In study 2, after adjustment for age, sex, race, and SNPs from the same gene, the *ADIPOQ* SNP rs266729 was associated with a decreased colorectal cancer risk of similar magnitude as in study 1 (AOR, 0.52; 95% CI, 0.34–0.78). Combined analysis of both studies shows an association of rs266729 with decreased colorectal cancer risk (AOR, 0.73; 95% CI, 0.53–0.99).

Conclusion—The SNP rs266729, which tags the 5′ flanking region of the *ADIPOQ* gene, is associated with decreased colorectal cancer risk.

Several epidemiological studies have shown an association between adiposity and the risk of incident colorectal cancer.[1–5] Observational studies also have shown that markers of insulin resistance, such as high circulating levels of C-peptide and insulin-like growth factor–binding protein 1 (IGFBP1), are directly associated with colorectal cancer risk.[6–9]

Adiponectin is a protein secreted by the adipose tissue, and has been found to be an endogenous insulin sensitizer. In contrast to other adipokines such as leptin, adiponectin circulating levels are decreased in obese individuals and in those with diabetes.[10] Given the association of adiponectin with insulin resistance and IGF as well as the association of insulin resistance and IGF with risk of colorectal cancer, we hypothesized that the adiponectin pathway may directly affect colorectal cancer risk.

Several lines of evidence support this hypothesis. Adiponectin and its receptors are expressed in colonic tissue.[11,12] Adiponectin seems to act in preneoplastic colonic lesions to regulate cell growth by activating, altering, or interacting with several pathways including the leptin and the NFκB pathways.[13] Furthermore, we have previously shown that adiponectin levels are inversely associated with risk of colorectal cancer.[14] In a prospective, nested case-control study, men with low adiponectin levels had a higher risk of colorectal cancer compared with men with higher levels. Compared with men in the lowest quintile, men in the highest adiponectin quintile had a 68% lower risk of colorectal cancer (relative risk, 0.42; 95% confidence interval [CI], 0.23–0.78).[14] In addition, the expression levels of ADIPOR1 and ADIPOR2, the 2 adiponectin receptors, are higher in colorectal carcinomas compared with normal colonic epithelium.[12]

Several adiponectin polymorphisms have been shown to influence adiponectin levels and polymorphisms of genes for both the ligand (*ADIPOQ*, Gene ID 9370, GeneBank ID NM_004797) and its type 1 receptor (*ADIPOR1*, Gene ID 51094, Gene-Bank ID NM_015999) have been associated with risk for insulin resistance, cardiovascular disease, and diabetes mellitus.[15–22] The roles of adiponectin receptor 1 (*ADIPOR1)* and adiponectin receptor 2 (*ADIPOR2)* genes in insulin resistance were assessed in several genetic association studies. Crimmins and Martin[22] summarized those findings and found that only 1 *ADIPOR1* single-nucleotide polymorphism (SNP) (rs1342387) was significantly associated with risk for insulin resistance. However, the association of these polymorphisms with colorectal cancer risk has

not been studied. To investigate the association between 2 key genes of the adiponectin pathway and colorectal cancer risk, we genotyped 10 haplotype-tagging SNPs of the *ADIPOQ* and *ADIPOR1* genes in 2 independent case-control studies.

METHODS

Study Participants

The first study was performed to evaluate potential associations between polymorphisms of *ADIPOQ* and *ADIPOR1* with colorectal cancer. The second case-control study was used for replication of the findings from the first.

Case-Control Study 1

As part of the protocols approved by the institutional review board (IRB), we obtained blood samples that had been collected from 441 patients treated at Memorial Sloan-Kettering Cancer (New York, New York) with a diagnosis of colorectal cancer. Collection of consecutive cases occurred in one phase between April 1, 2000, and December 31, 2000, and another phase between October 1, 2005, and February 28, 2006. All colorectal cancer cases were histologically confirmed at Memorial Sloan-Kettering Cancer Center. Information regarding sex, current age, age at colorectal cancer diagnosis, and ethnic status was recorded. A sample of 658 healthy volunteers from New York, New York, was recruited between January 1, 2003, and December 31, 2004, as a subset of the New York Cancer Project, a large cohort study that has been previously described in detail.[23] The response rate was 89%. None of the controls had any personal history of cancer at the time of blood donation, which was ascertained with a questionnaire completed by each healthy volunteer. All participants signed an IRB-approved informed consent. All cases and controls were white and of Ashkenazi Jewish background.

Case-Control Study 2

The second case-control study included 199 matched pairs of colorectal cancer cases and controls from Northwestern University in Chicago, Illinois. Cases and controls were matched 1:1 for age, ethnicity, and sex. Race was included as a variable because colon cancer risk varies among various ethnic groups. Consecutive cases with a biopsy-confirmed diagnosis of colorectal adenocarcinoma were recruited from the medical and surgical oncology clinics affiliated with the Northwestern Medical Faculty Foundation and US Oncology in 2 phases (June 1, 2006, through August 31, 2006, and January 15, 2007, through May 31, 2007). The response rate was 92% and 86% for each phase, respectively, and a blood sample was obtained from each recruited patient. All cases signed an informed consent for genetic studies and the protocol was approved by the IRB of Northwestern University. Controls were chosen from a total of 5578 patients without a diagnosis of cancer at the time of enrollment who were recruited between October 31, 2002, and December 31, 2007. Controls were matched for age within 5 years, sex, and ethnic status. Controls came from the NUgene Project, a biospecimen repository compliant with the Health Insurance Portability and Accountability Act and approved by the IRB, with questionnaire data and longitudinal medical information from participating patients treated at hospitals and outpatient clinics affiliated with Northwestern University.

Potential participants are approached either by a genetic counselor or by a physician. The overall response rate has been 25%. The 2 main reasons for refusal to participate were lack of time and concerns about privacy. The repository represents a clinically diverse population with housing samples and data from healthy individuals and patients with the most common health conditions such as diabetes, cancer, and autoimmune and cardiovascular diseases. Participants signed an IRB-approved informed consent to allow distribution and use of deidentified samples and data for a broad range of research. The ability to regularly update participant health status allows NUgene to provide investigators with the most appropriate samples for their research.

Controls were selected from NUgene participants without any self-reported history of cancer. Participants with *International Classification of Diseases, Ninth Revision* codes indicating a diagnosis of cancer were excluded.

DNA Isolation

DNA from whole blood lymphocytes was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and was stored at −20°C until use for genotyping. All DNA samples underwent whole genome amplification using the Illustra Genomiphi V2 DNA Amplification Kit (GE Healthcare, Waukesha, Wisconsin; catalog No. 25660032). The samples were stored at −20°C.

Selection of SNPs

We selected SNPs capturing variations in the major blocks in each gene. However, we preferentially chose the functionally relevant SNPs among those tagging SNPs and therefore genotyped 10 SNPs that either affect adiponectin levels or are associated with risk for insulin resistance, cardiovascular disease, and diabetes.[15–22] Furthermore, we only selected SNPs with a minimum allele frequency of 10% in whites. The adiponectin gene has more than 10 tagging SNPs[16,21] and 2 linkage disequilibrium blocks with a block boundary between −2049 and −450.[18] We chose to genotype rs266729 (5′ flanking region), rs822395 (intron 1), and rs822396 (intron 1) to tag block 1 and rs1501299 (intron 2) and rs2241766 (exon 2) to tag block 2 because these are the 5 most common SNPs and have been studied more extensively by others regarding their functionality and in relation to diseases such as diabetes mellitus[15–18] (Figure). *ADIPOR1* has more than 28 SNPs in 2 linkage disequilibrium blocks.[20] One block extends from the 5′ flanking region to intron 4 and the other is located at the 3′ end of the gene. Based on this structure, we selected 5 common SNPs for genotyping. For block 1, we selected the following tagging SNPs: rs2232853 (5′ flanking region), rs12733285 (intron 1), and rs1342387 (intron 4). For block 2, we selected rs7539542 (exon 8) and rs10920531 (3′ flanking region). These SNPs were selected because they tag both linkage disequilibrium blocks.

Box. Single-Nucleotide Polymorphisms for *ADIPOQ* and *ADIPOR1*

Primers for *ADIPOQ*

rs266729: TTGCAAGAACCGGCTCAGATCCTGC[C/G]
CTTCAAAAACAAAACATGAGCGTGC

rs822395: TGATCGCACCTATTAGTGGAGAAAT[A/C]
TGTCCATAATACTGAAGTTTGGGGA

rs822396: GTAGGAGAAAGAGATCTTTATTTTT[A/G]
ACAAAGGGGGAGGAGCCAGAAAACT

rs2241766: TTCTACTGCTATTAGCTCTGCCCGG[G/T]
CATGACCAGGAAACCACGACTCAAG

rs1501299: CTACACTGATATAAACTATATGAAG[G/T]
CATTCATTATTAACTAAGGCCTAGA

Primers for *ADIPOR1*

rs2232853: CAAGTGGTAGCAGCAGCTGGGAAT[A/G]
GGTATACTCAGCCTGCCTCAAGCTG

rs12733285: TCATGCTATGCTCAACCCACAAGCA[C/T]
AGTTGAAAGCAACCGGCAATCTAGT

rs1342387: AAAAAAGGGAATGTGTACACTTTGA[C/T]
GGTTGATGTTTTTGAATCAGAGAGC

rs7539542: CATGTGAAATCTTTGAATGCCAAGT[C/G]
TCTTCTGTACTTTCTTTTATTAACA

rs10920531: AAACTTGACTCTTGACATGAACCCA[A/C]
CTTTAACTCAAAAAGACTGCCCTTA

The probes used were VIC and FAM. The primers for the different SNPs for *ADIPOQ* and *ADIPOR1* are shown in the Box.

Genotyping

Genotyping for all 10 SNPs was performed by Taqman SNP allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Forest City, California). Results were ascertained by using the SDS software version 2.3 (Applied Biosystems). All results were automatically called (ie, the device displays the genotypes automatically with a 95% certainty). A total of 5% of samples were genotyped in duplicate and showed 100% concordance.

Statistical Analysis

χ^2 Tests were used to compare genotype frequency and demographic distributions between cases and controls. Univariate and multivariate unconditional logistic regression was used to estimate crude and adjusted odds ratios (ORs). Multivariate logistic regression models for each SNP were adjusted for age, sex, and other SNPs in the same gene. Specifically, for case-control study 1, crude ORs were unadjusted but the other ORs were adjusted for age (continuous), sex (binary), and SNPs from the same gene (categorical). For case-control study 2, crude ORs were adjusted for matching factors of age (continuous), sex (binary), and race (categorical) and other ORs were additionally adjusted for SNPs from the same gene (categorical). For the combined analysis, crude ORs were unadjusted but other ORs were adjusted for age (continuous), sex (binary), race (categorical), and SNPs from the same gene (categorical).

The additive and the dominant models were used for the analysis. In the additive model, each SNP is modeled categorically and separated into 3 categories, 1 for each genotype, with 1 genotype chosen as the reference group. For the dominant model, each SNP is modeled as a dichotomous variable with 1 genotype chosen as the reference group, and the other 2 genotypes combined into 1 category.

All comparisons were 2-sided with a *P* value of .05. Using a prevalence of 0.48 (prevalence of GG/CG for SNP rs266729 in controls), we calculated that the power to detect an OR of 2 is as follows: combined study, power=0.99; matched study (case-control study 2), power=0.93, and unmatched study (case-control study 1), power=0.99. No adjustment for multiple comparisons was conducted in the analysis. All *P* values can be multiplied by 10 to give Bonferroni-adjusted *P* values or the 2-sided significance level can be changed to .005. Statistical analysis was performed using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Demographics

Cases and controls from study 1 were all whites and residents of New York, New York (Table 1). The median age of cases was 64 years (interquartile range [IQR], 55.0–71.0 years) and the median age of controls was 51 years (IQR, 43.0–58.6 years). More cases than controls were men. Individuals in case-control study 2 were matched for ethnicity, age (within 5 years),

geographic location, and sex (Table 1). The median age of cases was 60 years (IQR, 51.0–69.0 years) and the median age of controls was 58 years (IQR, 49.0–67.0 years).

ADIPOQ SNPs and Colorectal Cancer Risk

Table 2 and Table 3 present results under the dominant and additive models, respectively. Analysis under the dominant model showed that 3 haplotype-tagging SNPs were associated with colorectal cancer risk in case-control study 1 (Table 2). The rs266729 GG/CG genotypes were associated with decreased colorectal cancer risk (OR, 0.72; 95% CI, 0.55–0.95). The rs822395 AA/AC genotypes were associated with increased colorectal cancer risk (OR, 1.76; 95% CI, 1.09–2.84) and the rs822396 AA/AG genotypes conferred a decreased colorectal cancer risk (OR, 0.37; 95% CI, 0.14–1.00). In the validation study (case-control study 2), only the rs266729 polymorphism was significantly associated with risk (relative risk for the GG/CG genotypes, 0.52; 95% CI, 0.34–0.78). Combined analysis of the 2 studies under the dominant model is presented in Table 4. The allelic frequencies of rs266729 among controls were comparable between the 2 case-control studies: GG, 6% and 7%; CC, 41% and 51%; and CG, 52% and 41%. After adjustment for age, sex, race, and SNPs of the same gene, rs266729 was associated with a reduced colorectal cancer risk (OR, 0.73; 95% CI, 0.53–0.99). After multivariate adjustment, there is a nonsignificant association between rs822395 with colorectal cancer risk (OR, 0.79; 95% CI, 0.61–1.02; P=.07). Both rs266729 and rs822395 belong to the same haplotype block (Figure). Each SNP associated with colorectal cancer risk fits the Hardy-Weinberg equilibrium among controls.

ADIPOR1 SNPs and Colorectal Cancer Risk

Five haplotype-tagging SNPs of *ADIPOR1* were genotyped. In case-control study 1, rs1342387 CC/TC genotypes were associated with an increased risk of colorectal cancer (OR, 1.79; 95% CI, 1.18–2.72). This association was not confirmed in the validation study (OR, 1.06; 95% CI, 0.68–1.66). Combined analysis of the 2 studies under the dominant model does not show any association of *ADIPOR1* SNPs with colorectal cancer risk (Table 4). Each SNP associated with colorectal cancer risk fits the Hardy-Weinberg equilibrium among controls.

COMMENT

In this clinic-based case-control analysis, we found an association between 1 SNP of the *ADIPOQ* gene (rs266729) and colorectal cancer risk in 2 separate case-control studies, as well as in the combined analysis of both studies after adjustment for age, sex, and other SNPs.

There is considerable emerging evidence pointing to the importance of adiponectin signaling in colorectal carcinogenesis. Colonic tissue expresses both *ADIPOR1* and *ADIPOR2*.[12] Two recent studies have shown an association between serum adiponectin levels and colorectal cancer risk,[12,14] with a 47% reduction in risk in the highest vs the lowest quintile.[14] However, another investigation did not find an association.[24]

The link between adiponectin and colorectal cancer may be the IGF pathway. Hyperinsulinemia reduces circulating levels of IGFBP1, which may lead to higher levels of unbound IGF1. High levels of circulating IGF1, which increase cellular proliferation and inhibit apoptosis,[25,26] have been associated with increased risk of several common cancers, including colorectal cancer.[6,27,28] We also recently reported that high levels of insulin (as reflected by increased C-peptide) or high levels of bioavailable IGF1 (assessed by the ratio of IGF1 to IGFBP3) independently predicted increased risk for colorectal cancer; high levels of both were not associated with higher risk.[9]

In the 2 sets of cases and controls that included a total of 1497 individuals, we observed a consistent association between rs266729 and colorectal cancer risk. More specifically, individuals with the GG/GC genotype have a 27% lower odds of colorectal cancer than those with the CC genotype. It has been shown that the G allele is associated with lower adiponectin levels.[19] The haplotype-tagging SNP rs266729 is located in the 5′ flanking region of the gene at position −11365 within the promoter region. Polymorphisms within the promoter region have been associated with adiponectin levels and risk of diabetes.[21] Furthermore, rs266729 has been associated with the risk of coronary artery bypass graft and percutaneous transluminal coronary angioplasty.[29] Other polymorphisms in this region, including rs2117985 (−18003), rs822387 (−14811), and rs860291 (−12891), also have been significantly associated with adiponectin levels.[17] In addition, individuals with the genotypes rs17300539 (−11391) AA/AG have 64% higher adiponectin levels (*P*=.01).[18] In our current study, we chose to study only 1 polymorphisms of the 5′ flanking region. Our data as well as data from other investigators highlight the importance of this region, both for gene function and as a disease-causing region in the adiponectin gene. Interestingly, combined analysis of the 2 studies presented in this article showed a borderline association between rs822395 and colorectal cancer risk, which suggests that several SNPs within this region may be associated with colorectal cancer risk.

We recently evaluated 10 SNPs of the adiponectin pathway with regard to breast cancer risk.[30] Our findings showed that a different region in the adiponectin gene was an important modifier of breast cancer risk. More specifically, we found that +45 T→G (rs2241766) and +276 G→T (rs1501299) are associated with breast cancer risk. Both polymorphisms belong to block 2; rs2241766 is located in exon 2 whereas rs1501299 is located in intron 2. We also found 1 polymorphism of *ADIPOR1* (+10225 C→G [rs7539542]) to be significantly associated with breast cancer risk. The haplotype-tagging SNPs used in these studies represent genomic regions putatively associated with cancer risk but the functionally significant SNPs and/or mutations are likely different from these haplotype-tagging SNPs. Additional fine mapping studies will be needed to determine if the functional SNPs associated with breast cancer risk are different from the SNPs associated with colorectal cancer risk.

This study has several strengths. Case-control study 1 included a large number of cases and controls (N=1099) with the same ethnic status and from the same geographic area. All cases and controls recruited in case-control study 2 were recruited at the same institution, and were matched for age, sex, and ethnic status. One of the 4 genotypic combinations associated with colorectal cancer in study 1 was confirmed in study 2 despite differences in the age, ethnic status, and proportion of males and females between the 2 studies. The magnitude of the association of rs266729 with colorectal cancer was comparable in the 2 studies. Furthermore, a combined analysis of both studies showed that the significant association of rs266729 with colorectal cancer risk persisted after adjustment for age, sex, race, and SNPs within the same gene. Using prevalence of 0.48 (prevalence of GG/CG for SNP rs266729 in controls), our study had good power to detect an OR of 2 (combined study: power = 0.99; matched study: power = 0.93; unmatched study: power=0.99).

While rs226729 was associated with colorectal cancer risk in both studies, this SNP only represents a genomic region putatively associated with risk. It is likely that the functionally significant SNPs/mutations are different. Additional studies that include resequencing of this genomic region and dense SNP analysis will be needed to identify these SNPs/mutations and determine their impact on the expression levels of *ADIPOQ*.

Our study also has several limitations. The epidemiological design is relatively informal, with possibly different case and control populations. Cases and controls in study 1 differed significantly in sex and age in that the median age of cases was slightly higher than that of controls. It is possible that age differences in cases and controls affected the allele frequencies

observed. Furthermore, inaccurate information with respect to any variable classification would result in nondifferential misclassification, which also would be expected to result in a conservative bias in measures of association. A common limitation to both studies is the absence of information on family history of colorectal cancer as well as other risk factors for colorectal cancer. Another limitation is the difference between the 2 studies as to the patient population included. All cases and controls were white and of Ashkenazi Jewish background in study 1, whereas case-control study 2 included several ethnic groups. The additional SNPs associated with colorectal cancer risk in study 1 may be specific to Ashkenazi Jews, a population with increased colorectal cancer risk. Of note, *APC I1307K*, a gene associated with increased colorectal cancer risk in Ashkenazi Jews,[31] maps to 5q21–22. If 1 or more of the 3 SNPs associated with colorectal cancer in study 1 are validated in another population of Ashkenazi Jews, it will be interesting to study gene-gene interactions between these SNPs and *APC I1307K*. In addition, we did not make any formal adjustment of our results for the multiple comparisons made in the study with 10 SNPs. This adjustment, however, would not have materially changed the conclusions of our study.

To our knowledge, this is the first study reporting an association of polymorphisms of the adiponectin pathway with colorectal cancer risk. Our study did not attempt to provide a comprehensive evaluation of all genes involved in the adiponectin pathway. Our findings, however, suggest that *ADIPOQ* rs266729 is associated with colorectal cancer risk. Importantly, they suggest that the 5′ region of the *ADIPOQ* gene harbor SNPs/mutations susceptible to modify colorectal cancer risk. If these exciting results can be confirmed in other studies, the adiponectin axis may emerge as an important modifier of colorectal cancer risk. Future studies will need to address the potential impact of adiponectin and its SNPs in the prognosis of colorectal cancer and also may be incorporated in genetic risk models for the disease.

Acknowledgements

Funding/Support: This work was supported by the Walter S. Mander Foundation (Chicago, Illinois); grants CA112520, CA108741, DK081913, DK79929, DK 58785 from the National Institutes of Health; the Jeannik M. Littlefield-AACR Grant in Metastatic Colon Cancer Research from the American Institute for Cancer Research; a discretionary grant from Beth Israel Deaconess Medical Center; the Lynn Sage Foundation and the American Society of Clinical Oncology Career Development Award; and the Niehaus Clinical Cancer Genetics Initiative.

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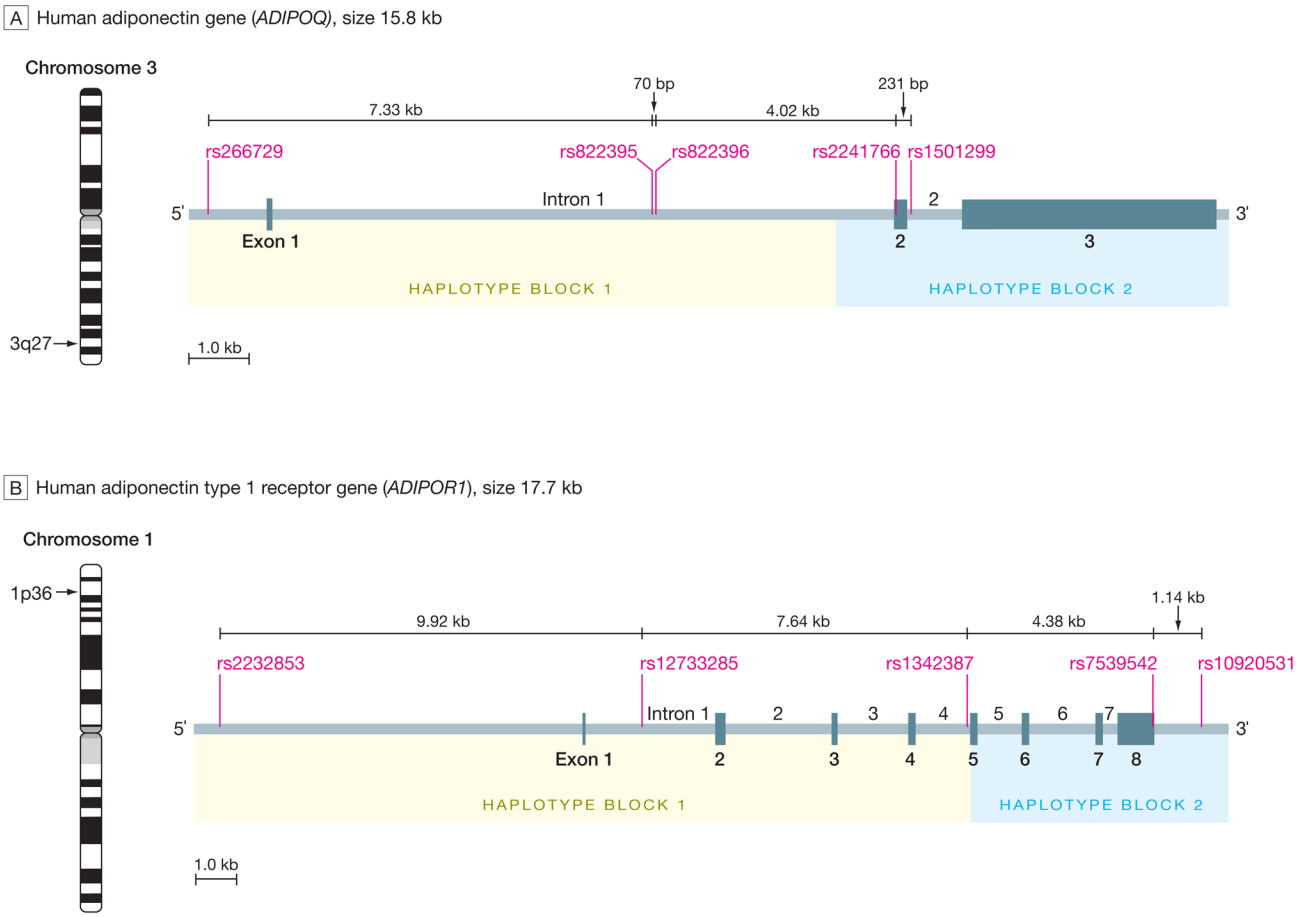

Figure. Adiponectin Gene Haplotypes and Tagging Single-Nucleotide Polymorphisms (SNPs)

A, The adiponectin gene (*ADIPOQ*) maps to 3q27 and has 2 haplotype blocks. Four intronic SNPs and 1 exonic SNP were chosen to genotype these 2 blocks. B, The adiponectin receptor 1 gene (*ADIPOR1*) maps to 1p36 and has 2 haplotype blocks. Four intronic SNPs and 1 exonic SNP were chosen to genotype these 2 blocks. Designation of haplotype blocks in the Figure is approximate.

Table 1
Demographics of the 2 Case-Control Studies

	Case-Control Study 1			Case-Control Study 2		
	Cases, No. (%) (n = 441)	Controls, No. (%) (n = 658)[a]	*P* Value	Cases, No. (%) (n =199)	Controls, No. (%) (n = 199)	*P* Value
Age range, y						
≤40	17 (3.9)	108 (16.9)		16 (8.0)	14 (7.0)	
41-50	50 (11.3)	185 (28.9)		33 (16.6)	42 (21.1)	
51-60	102 (23.1)	220 (34.4)	<.001	58 (29.2)	54 (27.1)	.54
61-70	148 (33.6)	118 (18.4)		48 (24.1)	55 (27.6)	
≥71	124 (28.1)	9 (1.4)		44 (22.1)	34 (17.1)	
Sex						
Male	255 (57.8)	211 (32.1)	.001	104 (52.3)	104 (52.3)	>.99
Female	186 (42.2)	447 (67.9)		95 (47.7)	95 (47.7)	
Ethnicity, No. (%)						
White	441 (100)	658 (100)	>.99	162 (81.4)	162 (81.4)	
Black				31 (15.6)	31 (15.6)	>.99
Hispanic				1 (0.5)	1 (0.5)	
Asian				5 (2.5)	5 (2.5)	

[a]There are 18 controls with missing age.

Table 2

Dominant Model of Crude and Adjusted Odd Ratios (ORs) by *ADIPOQ* and *ADIPOR1* Single-Nucleotide Polymorphism (SNP) Genotypes

		Case-Control Study 1					Case-Control Study 2				
SNP	**Genotype**	**No. of Cases/ No. of Controls**	**Crude OR (95% CI)**	***P* Value**	**Adjusted OR (95% CI)[a]**	***P* Value**	**No. of Cases/ No. of Controls**	**Crude OR (95% CI)**	***P* Value**	**Adjusted OR (95% CI)[a]**	***P* Value**
					ADIPOQ						
rs266729	CC	244/340	1 [Reference]		1 [Reference]		112/82	1 [Reference]		1 [Reference]	
	GG/CG	190/318	0.83 (0.65–1.06)	.14	0.72 (0.55–0.95)	.02	83/115	0.50 (0.33–0.75)	.001	0.52 (0.34–0.78)	.002
rs822395	CC	45/88	1 [Reference]		1 [Reference]		28/22	1 [Reference]		1 [Reference]	
	AA/AC	386/566	1.33 (0.91–1.95)	.14	1.76 (1.09–2.84)	.02	165/174	0.76 (0.42–1.38)	.36	0.58 (0.28–1.21)	.15
rs822396	GG	13/16	1 [Reference]		1 [Reference]		6/9	1 [Reference]		1 [Reference]	
	AA/GA	419/634	0.81 (0.39–1.71)	.59	0.37 (0.14–1.00)	.05	187/184	1.61 (0.56–4.62)	.38	2.52 (0.71–9.00)	.15
rs2241766	TT	279/435	1 [Reference]		1 [Reference]		151/164	1 [Reference]		1 [Reference]	
	GG/TG	161/213	0.73 (0.56–0.96)	.02	0.80 (0.59–1.09)	.17	48/31	1.47 (0.90–2.41)	.12	1.30 (0.78–2.18)	.32
rs1501299	TT	45/58	1 [Reference]		1 [Reference]		15/17	1 [Reference]		1 [Reference]	
	GG/TG	388/578	0.87 (0.57–1.30)	.49	0.83 (0.52–1.33)	.44	183/179	1.11 (0.53–2.30)	.79	1.14 (0.53–2.42)	.74
					ADIPOR1						
rs2232853	GG	261/393	1 [Reference]		1 [Reference]		107/107	1 [Reference]		1 [Reference]	
	AA/GA	167/258	0.98 (0.76–1.25)	.84	0.94 (0.70–1.26)	.68	84/88	0.96 (0.64–1.43)	.83	1.00 (0.65–1.56)	.99
rs12733285	TT	69/105	1 [Reference]		1 [Reference]		19/14	1 [Reference]		1 [Reference]	
	CC/TC	368/547	1.02 (0.74–1.43)	.89	0.62 (0.38–1.01)	.06	176/178	0.76 (0.37–1.57)	.46	0.78 (0.37–1.67)	.53
rs1342387	TT	99/179	1 [Reference]		1 [Reference]		32/32	1 [Reference]		1 [Reference]	
	CC/TC	336/468	1.23 (0.98–1.72)	.07	1.79 (1.18–2.72)	.007	158/160	1.07 (0.69–1.65)	.77	1.06 (0.68–1.66)	.80
rs7539542	GG	44/63	1 [Reference]		1 [Reference]		26/24	1 [Reference]		1 [Reference]	
	CC/GC	388/586	0.95 (0.63–1.42)	.80	0.98 (0.61–1.57)	.93	171/170	0.85 (0.46–1.56)	.60	0.81 (0.42–1.55)	.53
rs10920531	CC	153/236	1 [Reference]		1 [Reference]		79/73	1 [Reference]		1 [Reference]	
	AA/CA	279/409	1.05 (0.82–1.36)	.70	0.89 (0.66–1.19)	.43	112/124	0.90 (0.59–1.36)	.61	0.86 (0.56–1.34)	.51

Abbreviation: CI, confidence interval.

[a]Values adjusted for age, sex, race, and SNPs from the same gene.

Table 3

Additive Model of Crude and Adjusted Odd Ratios (ORs) of Colorectal Cancer by *ADIPOQ* and *ADIPOR1* Single-Nucleotide Polymorphism (SNP) Genotypes

SNP	Genotype	Case-Control Study 1					Case-Control Study 2				
		No. of Cases/ No. of Controls	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value	No. of Cases/ No. of Controls	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
					ADIPOQ						
rs266729	CC	244/340	1 [Reference]		1 [Reference]		112/82	1 [Reference]		1 [Reference]	
	CG	163/271	0.84 (0.65–1.08)	.17	0.73 (0.55–0.98)	.03	77/103	0.50 (0.33–0.77)	.001	0.48 (0.31–0.75)	.001
	GG	27/47	0.80 (0.49–1.32)	.38	0.68 (0.38–1.21)	.19	6/12	0.34 (0.12–0.95)	.04	0.27 (0.09–0.83)	.02
rs822395	CC	45/88	1 [Reference]		1 [Reference]		28/22	1 [Reference]		1 [Reference]	
	AC	202/265	1.49 (1.00–2.23)	.05	1.62 (1.01–2.60)	.05	89/97	0.70 (0.37–1.32)	.27	0.69 (0.35–1.36)	.29
	AA	184/301	1.20 (0.80–1.79)	.39	1.65 (0.97–2.83)	.07	76/77	0.79 (0.41–1.50)	.46	0.53 (0.25–1.16)	.11
rs822396	GG	13/16	1 [Reference]		1 [Reference]		6/9	1 [Reference]		1 [Reference]	
	GA	114/157	0.89 (0.41–1.93)	.77	0.56 (0.22–1.47)	.24	56/73	1.19 (0.40–3.56)	.76	1.42 (0.42–4.80)	.57
	AA	305/477	0.79 (0.37–1.66)	.53	0.48 (0.18–1.29)	.15	131/111	1.84 (0.63–5.36)	.26	2.48 (0.76–8.08)	.13
rs2241766	TT	279/435	1 [Reference]		1 [Reference]		151/164	1 [Reference]		1 [Reference]	
	TG	141/172	1.28 (0.98–1.67)	.07	1.20 (0.88–1.65)	.25	46/31	1.59 (0.95–2.64)	.08	1.32 (0.77–2.29)	.32
	GG	20/41	0.76 (0.44–1.33)	.33	0.76 (0.40–1.43)	.39	2/0	NA	NA	NA	NA
rs1501299	TT	45/58	1 [Reference]		1 [Reference]		15/17	1 [Reference]		1 [Reference]	
	TG	180/293	0.79 (0.51–1.22)	.29	0.77 (0.48–1.27)	.31	78/85	1.01 (0.47–2.18)	.98	1.29 (0.57–2.94)	.55
	GG	208/285	0.94 (0.61–1.44)	.78	0.91 (0.55–1.51)	.72	105/94	1.20 (0.57–2.56)	.63	1.56 (0.69–3.55)	.29
					ADIPOR1						
rs2232853	GG	261/393	1 [Reference]		1 [Reference]		107/107	1 [Reference]		1 [Reference]	
	GA	148/231	0.97 (0.74–1.25)	.79	1.02 (0.76–1.37)	.91	68/71	0.93 (0.60–1.43)	.73	1.00 (0.63–1.60)	.99
	AA	19/27	1.06 (0.58–1.95)	.85	0.80 (0.40–1.60)	.52	16/17	0.86 (0.41–1.80)	.69	0.69 (0.28–1.70)	.42
rs12733285	TT	69/105	1 [Reference]		1 [Reference]		19/14	1 [Reference]		1 [Reference]	
	TC	221/347	0.97 (0.69–1.37)	.86	0.75 (0.49–1.14)	.17	78/77	0.77 (0.36–1.64)	.49	0.65 (0.29–1.49)	.31
	CC	147/200	1.12 (0.77–1.62)	.55	1.09 (0.71–1.68)	.69	98/101	0.79 (0.37–1.67)	.53	0.79 (0.36–1.75)	.56
rs1342387	TT	99/179	1 [Reference]		1 [Reference]		32/32	1 [Reference]		1 [Reference]	
	TC	223/313	1.29 (0.96–1.74)	.10	1.43 (0.97–2.09)	.07	101/99	1.00 (0.57–1.78)	.99	1.10 (0.55–2.21)	.78

JAMA. Author manuscript; available in PMC 2009 April 1.

SNP	Genotype	Case-Control Study 1					Case-Control Study 2				
		No. of Cases/ No. of Controls	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value	No. of Cases/ No. of Controls	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
	CC	113/155	1.32 (0.93–1.86)	.12	1.44 (0.85–2.45)	.18	57/61	0.95 (0.51–1.77)	.87	0.94 (0.42–2.09)	.88
rs7539542	GG	44/63	1 [Reference]		1 [Reference]		26/24	1 [Reference]		1 [Reference]	
	GC	209/280	1.07 (0.70–1.63)	.76	1.09 (0.63–1.89)	.77	75/81	0.82 (0.43–1.56)	.55	1.12 (0.49–2.61)	.79
	CC	179/306	0.84 (0.55–1.28)	.42	0.97 (0.58–1.62)	.89	96/89	0.89 (0.47–1.70)	.73	1.20 (0.56–2.55)	.64
rs10920531	CC	153/236	1 [Reference]		1 [Reference]		79/73	1 [Reference]		1 [Reference]	
	CA	214/301	1.10 (0.84–1.43)	.50	0.78 (0.53–1.14)	.20	82/94	0.82 (0.53–1.78)	.38	0.94 (0.50–1.80)	.86
	AA	65/108	0.93 (0.64–1.34)	.69	0.75 (0.47–1.20)	.23	30/30	0.97 (0.53–1.78)	.92	1.03 (0.49–2.17)	.94

Abbreviations: CI, confidence interval; NA, data not available.

[a] Values adjusted for age, sex, race, and SNPs from the same gene.

Table 4

Combined Analysis Under Dominant Model

SNP	Genotype	No. of Cases/No. of Controls	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
			ADIPOQ			
rs266729	CC	321/443	1 [Reference]		1 [Reference]	
	GG/CG	308/412	0.64 (0.49–0.83)	.001	0.73 (0.53–0.99)	.04
rs822395	CC	230/287	1 [Reference]		1 [Reference]	
	AA/AC	394/563	0.90 (0.72–1.11)	.32	0.79 (0.61–1.02)	.07
rs822396	GG	120/166	1 [Reference]		1 [Reference]	
	AA/GA	505/677	1.04 (0.80–1.35)	.77	1.11 (0.81–1.52)	.51
rs2241766	TT	292/336	1 [Reference]		1 [Reference]	
	GG/TG	347/507	0.77 (0.62–0.94)	.01	0.83 (0.66–1.05)	.12
rs1501299	TT	195/310	1 [Reference]		1 [Reference]	
	GG/TG	436/522	1.29 (1.04–1.61)	.02	1.16 (0.91–1.48)	.24
			ADIPOR1			
rs2232853	GG	255/338	1 [Reference]		1 [Reference]	
	AA/GA	364/508	0.98 (0.80–1.21)	.86	0.94 (0.74–1.17)	.56
rs12733285	TT	240/361	1 [Reference]		1 [Reference]	
	CC/TC	392/483	1.21 (0.98–1.49)	.07	1.16 (0.91–1.48)	.23
rs1342387	TT	131/211	1 [Reference]		1 [Reference]	
	CC/TC	494/628	1.02 (0.82–1.25)	.89	0.88 (0.67–1.15)	.35
rs7539542	GG	235/304	1 [Reference]		1 [Reference]	
	CC/GC	394/539	0.95 (0.76–1.17)	.61	0.94 (0.73–1.20)	.61
rs10920531	CC	293/374	1 [Reference]		1 [Reference]	
	AA/CA	330/468	0.92 (0.75–1.12)	.40	0.93 (0.73–1.18)	.54

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nuclotide polymorphism.

[a]Values adjusted for age, sex, race, and SNPs from the same gene.