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Common variants in genes encoding adiponectin (*ADIPOQ*) and its receptors (*ADIPOR1/2*), adiponectin concentrations, and diabetes incidence in the Diabetes Prevention Program

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Competing interests

Nothing to declare.

Lists of Diabetes Prevention Program Research Group investigators are provided in the Supporting Information (Appendix S1).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Lists of DPP Research Group investigators.

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Abstract

Aims—Baseline adiponectin concentrations predict incident Type 2 diabetes mellitus in the Diabetes Prevention Program. We tested the hypothesis that common variants in the genes encoding adiponectin (*ADIPOQ*) and its receptors (*ADIPOR1*, *ADIPOR2*) would associate with circulating adiponectin concentrations and/or with diabetes incidence in the Diabetes Prevention Program population.

Methods—Seventy-seven tagging single-nucleotide polymorphisms (SNPs) in *ADIPOQ* (24), *ADIPOR1* (22) and *ADIPOR2* (31) were genotyped. Associations of SNPs with baseline adiponectin concentrations were evaluated using linear modelling. Associations of SNPs with diabetes incidence were evaluated using Cox proportional hazards modelling.

Results—Thirteen of 24 *ADIPOQ* SNPs were significantly associated with baseline adiponectin concentrations. Multivariable analysis including these 13 SNPs revealed strong independent contributions from rs17366568, rs1648707, rs17373414 and rs1403696 with adiponectin concentrations. However, no *ADIPOQ* SNPs were directly associated with diabetes incidence. Two *ADIPOR1* SNPs (rs1342387 and rs12733285) were associated with ~18% increased diabetes incidence for carriers of the minor allele without differences across treatment groups, and without any relationship with adiponectin concentrations.

Conclusions—*ADIPOQ* SNPs are significantly associated with adiponectin concentrations in the Diabetes Prevention Program cohort. This observation extends prior observations from unselected populations of European descent into a broader multi-ethnic population, and confirms the relevance of these variants in an obese/dysglycaemic population. Despite the robust relationship between adiponectin concentrations and diabetes risk in this cohort, variants in *ADIPOQ* that relate to adiponectin concentrations do not relate to diabetes risk in this population. *ADIPOR1* variants exerted significant effects on diabetes risk distinct from any effect of adiponectin concentrations.

[Clinical Trials Registry Nos; NCT 00004992 (Diabetes Prevention Program) and NCT 00038727 (Diabetes Prevention Program Outcomes Study)]

Keywords

adiponectin; diabetes; genetics; polymorphism

Introduction

In the Diabetes Prevention Program (DPP), a randomized clinical trial involving a multi-ethnic cohort of people who were overweight and dysglycaemic, lower adiponectin concentrations at baseline were associated with increased diabetes risk [1]. Differences in adiponectin concentrations by sex and by race/ethnicity did not in turn affect the association between adiponectin concentrations and Type 2 diabetes mellitus risk. Therefore, not all factors that affect adiponectin concentrations in turn affect adiponectin-associated diabetes risk.

It is unclear if genetic determinants of adiponectin concentrations or actions contribute importantly to diabetes risk. Upstream, intronic and 3' untranslated region variants in *ADIPOQ* (the gene encoding the adiponectin protein) are recognized that are significantly related to adiponectin concentrations [2–6]. Although individual study results vary, in meta-analyses these common upstream variants exert modest overall effects on adiponectin

concentrations [6–8]. Exonic variants with clear functional effects on the adiponectin transcript have also been recognized [3,9]. Concordant effects of common variants in *ADIPOQ* on both adiponectin concentrations and diabetes prevalence have been reported in many case–control studies [3,5,10–12]. Many reports of equal quality find associations with adiponectin concentrations, but not with prevalent diabetes [3,4,6,13–15]. A similar mix of positive [11,16,17] and negative [14] results have been found in studies evaluating prospective diabetes risk.

Genetic associations of the known adiponectin receptors with adiponectin concentrations or with diabetes have been less extensively studied. The literature includes positive and negative reports of associations of *ADIPOR1* and *ADIPOR2* variants with adiponectin concentrations [18,19], and/or with diabetes [20–23].

We have evaluated the genetic determinants of adiponectin concentrations and the association of these variants with prospectively ascertained diabetes outcomes in the Diabetes Prevention Program. We have investigated the associations of 77 tagging polymorphisms, localizing to the *ADIPOQ*, *ADIPOR1* and *ADIPOR2* regions, with adiponectin concentrations and with the subsequent development of diabetes in the DPP.

Patients and methods

The DPP was a multi-centre, placebo-controlled, randomized, clinical trial designed to assess the impact of metformin or lifestyle modification on diabetes incidence. The characteristics of the DPP cohort, details of the study design and outcome have been reported in detail previously [24]. Briefly, individuals from five race/ethnic groups (white, African American, Hispanic, Asian/Pacific Islanders and American Indian ancestry) qualified for the study by virtue of being overweight or obese and having impaired fasting and 2-h glucose concentrations. Data for the current report was contributed by subjects from the three main treatment arms who gave permission to analyse DNA (2890 of 3234 total subjects). Written informed consent was obtained from each participant, and each of the 27 study centres obtained approval from their respective institutional review boards prior to initiation of the study protocol.

Total circulating adiponectin was measured using a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical, Tokyo, Japan) [1]. Measurements from baseline samples were included in the current analyses.

We used the multi-marker tagging option in Tagger [25] to select common variants ($> 5\%$ minor allele frequency, at $r^2 \geq 0.8$) within the *ADIPOQ*, *ADIPOR1* or *ADIPOR2* regions (+20 kb upstream and 10 kb downstream) represented within the European and African ancestry HapMap populations. Genotyping was performed on the Illumina BeadArray platform (Illumina, San Diego, CA, USA). The mean genotyping success rate was 99.5%. We genotyped 24, 22 and 31 tagging single-nucleotide polymorphisms (SNPs) in *ADIPOQ*, *ADIPOR1* and *ADIPOR2*, respectively. These SNPs provided coverage of 85, 96 and 98% of known variants in *ADIPOQ*, *ADIPOR1* and *ADIPOR2*, respectively, in Europeans in HapMap. Coverage was slightly lower but comparable in the African population in HapMap.

Statistical analysis

Analyses were performed using SAS v9.2 (SAS Institute, Cary, NC, USA) or Stata 9.2 (StataCorp., College Station, TX, USA). The analytic endpoints were adiponectin concentrations at baseline and diabetes incidence at 3.2 years (study end). Two-sided *P*-values were reported for all results.

We used generalized linear models to test additive genotype associations with natural log-transformed baseline adiponectin levels (adjusting for age, baseline weight, sex and race/ethnicity). In view of the large number of *ADIPOQ* SNPs that contributed individually to adiponectin concentrations, we performed multivariable and backward stepwise regression analysis (adjusting for age, baseline weight, sex and race/ethnicity) to identify the strongest independent signals.

Genotype main effects and treatment interactions on diabetes incidence were tested using Cox proportional hazards models under an additive genetic model (adjusted for sex, baseline age and self-reported race/ethnicity). If there was no evidence of genotype by treatment interactions, the statistical models were further adjusted for treatment group and this full model was taken as the primary comparison. Where such interactions were seen, we analysed separate models for each treatment group. Differences between means were tested using pairwise contrasts and the *P*-values were adjusted for multiple comparisons using Holm's procedure [26] within each set of tests pertaining to the same general hypothesis (i.e. genotype associations with adiponectin levels). A genetic risk score was calculated by assigning scores to each individual's combination of alleles for the four SNPs, with alleles associated with lower adiponectin concentrations assigned a value of one [27].

Comparisons of variants associated with adiponectin concentrations were made against summary data from three genome-wide association studies participating in the AdipoGen consortium [4]. Comparisons of variants associated with Type 2 diabetes were made using the DIAGRAM consortium database [28].

Results

Population characteristics

The DPP cohort was multi-ethnic, with 1624 (56.2%) participants self-identifying as being of European descent, 582 (20.1%) of African descent, 479 (16.6%) of Hispanic descent, 124 (4.3%) of Asian/Pacific Islander descent and 81 (2.8%) of American Indian descent. The subgroup with data available for genetic analyses was not materially different in demographics or anthropometrics from the complete study population (not shown). Also, the main study results in the genetic studies cohort are essentially the same as for the complete study cohort: event rate 10.7% per 100 person-years in placebo subjects, 7.7% per 100 person-years in metformin subjects and 5.0% per 100 person-years in lifestyle subjects; *P* = 0.0002 for each pairwise comparison. The relationships of adiponectin concentrations with diabetes incidence within the DPP have been reported in detail previously [1]. Allele frequencies for SNPs that were significantly associated with serum adiponectin concentrations or diabetes incidence are presented stratified by ethnic group in Table 1.

Adiponectin concentrations

We found significant associations of 13 *ADIPOQ* SNPs with adiponectin concentrations (Table 2). The most strongly associated variants were: rs17366568 (not in linkage disequilibrium with any other variants analysed); rs1648707, rs182052 and rs6810075 (in linkage disequilibrium at $r^2 = 0.8$ with each other, except among African Americans, see also Supporting Information, Fig. S1); rs10937273 (not in linkage disequilibrium); and rs16861210 (in linkage disequilibrium $r^2 = 0.79$ with rs822387 in white populations only, not in linkage disequilibrium for the population as a whole). None of the evaluated SNPs from the *ADIPOR1* or *ADIPOR2* regions was significantly associated with adiponectin concentrations. These associations were unaffected by substitution of waist circumference or BMI for weight in the models (data not shown).

In a multivariable analysis of determinants of adiponectin concentration simultaneously including all 13 individually significant *ADIPOQ* SNPs (adjusting for weight, age at randomization, sex and race/ethnicity), only four remained significantly associated with log adiponectin concentrations [rs17366658 (β -0.12, $P < 0.001$), rs1648707 (β -0.08, $P = 0.02$), rs17373414 (β 0.05, $P = 0.01$) and rs1403696 (β -0.06, $P = 0.03$)]. Collinearity diagnostics indicated that rs1648707 and rs182052 were modestly collinear (condition index 10.8), consistent with their known linkage disequilibrium. A backward stepwise regression analysis produced similar results (not shown), except that a fifth SNP also survived the elimination procedure (rs822387; β 0.04, $P = 0.03$).

Differences in adiponectin concentrations between homozygote major allele carriers and homozygote minor allele carriers (Table 2) ranged from 10 to 40%. In the multivariable analyses, approximately 7% of variability in adiponectin concentrations could be attributed to *ADIPOQ* SNPs. By comparison, sex and age each accounted for ~25% of total variability.

Our cohort includes subjects from the main minority populations in the USA. All results presented are adjusted for age, sex and race/ethnicity (each of which contributes significantly to circulating adiponectin concentrations in our data). To further address the possibility that ethnic variations in genotype frequencies and phenotypes might be influencing the observed genotype–phenotype relationships, modelling was repeated using only subjects from the largest single ethnic group (namely those of European descent). Previous analyses using ancestry informative markers have shown that this subset of the DPP is largely free of significant admixture (average proportion of European ancestry = 98.9%). In this analysis, essentially the same results were obtained as in the complete cohort ($n = 1624$; rs17366568 $P = 10^{-15}$; rs1648707 $P = 10^{-11}$; rs10937273 $P = 10^{-5}$; rs16861210 $P = 10^{-8}$). These parallel results suggest that the observations in the complete cohort are not affected by confounding by population stratification.

In Table 3 we present a comparison of the currently reported *ADIPOQ* SNPs that associate with adiponectin concentrations, against the *ADIPOQ* SNPs in the data sets contributing to the AdipoGen cohort. In that aggregate cohort, a highly significant association of SNP rs17366568 with circulating adiponectin concentrations was reported. We observed a similarly strong association of this particular SNP with adiponectin concentrations (Table 3), and each of our other main associations was also shown in at least one of the cohorts comprising this earlier study group. Previous work extensively evaluated associations of rs17300539 (G-11391A), rs266729 (C-11377G), rs2241766 (T+45G) and rs1501299 (T +276G) with adiponectin concentrations. Two of these SNPs were confirmed in our data set indirectly via linkage disequilibrium (rs17300539:our rs822387, linkage disequilibrium = 0.78, and rs266729:our rs182052, linkage disequilibrium = 0.73). Our data overall confirm these previously reported associations of upstream *ADIPOQ* variants with adiponectin concentrations, and extend the generalizability of these associations into a population with mixed ethnicity more advanced metabolic risk.

A novel association of SNP rs4311394 in a distant gene (*ARL15*) with adiponectin concentrations was recently reported (4). In the DPP data set this variant was not directly assessed; however other variants in *ARL15* (rs12654393, rs6876198, and 1445887) were available for analysis. Of these, rs12654393 and rs6876198 were in strong linkage disequilibrium with rs4311394 ($r^2 > 0.95$ in both HapMap CEU and YRI populations). None of these variants was associated with adiponectin concentrations in our data set.

Diabetes incidence

None of the *ADIPOQ* variants we evaluated was directly associated with diabetes incidence in this cohort. Combining the four SNPs that were independently associated with

adiponectin concentrations (rs17366568, rs1648707, rs17373414 and rs1403696) into a single genetic risk score underscored this finding: the associated diabetes hazard ratio was 1.02 (95% CI 0.94–1.10, $P = 0.62$), with no difference in this effect across treatment groups.

Two SNPs from the *ADIPOR1* gene (rs1342387 and rs12733285) were significantly associated with diabetes incidence (Table 4). These SNPs were in modest linkage disequilibrium ($r^2 = 0.54$ in white populations, weaker in other subgroups). Two *ADIPOR2* SNPs with nominally significant associations with diabetes incidence were in linkage disequilibrium (rs7134070 and rs11836547). Two SNPs interacted with treatment to influence diabetes incidence (*ADIPOQ* rs17373414 and *ADIPOR2* rs758027), with borderline statistical significance (Table 4).

In Table 5 we present a comparison of the SNPs associated with prevalent Type 2 diabetes in the DPP and in the DIAGRAM data sets. No *ADIPOR1* polymorphisms were associated with prevalence of Type 2 diabetes in the DIAGRAM cohort, including those associated with Type 2 diabetes in the DPP. Three of the Type 2 diabetes-associated SNPs from the DIAGRAM data set (rs822391, rs7649121 and rs822396) were associated with adiponectin concentrations in our population, but despite this association these SNPs were not associated with Type 2 diabetes incidence in the DPP.

Discussion

In the DPP cohort we identified associations of adiponectin concentrations with 13 of 24 evaluated SNPs in the *ADIPOQ* region, and with no SNPs in *ADIPOR1* (22 SNPs evaluated) or *ADIPOR2* (31 SNPs evaluated). The strongest individual signals were observed at rs17366568 and rs1648707/rs182052/rs6810075 (these three in linkage disequilibrium). Multivariable analyses revealed that this data set presents at least four potent independent associations of *ADIPOQ* with adiponectin concentrations (rs17366568, rs1648707, rs17373414 and rs1403696). Despite these associations with adiponectin concentrations, none of the *ADIPOQ* variants evaluated was associated with diabetes incidence in the DPP cohort. We found treatment interactions of one *ADIPOR2* and one *ADIPOQ* variant with incidence of Type 2 diabetes, with borderline statistical significance. Two *ADIPOR1* variants were significantly associated with diabetes incidence.

Gene variants and adiponectin concentrations

The DPP cohort differs in important ways from cohorts in which associations of *ADIPOQ* SNPs with adiponectin concentrations have been previously reported. Our cohort was specifically selected to be overweight and have impaired glucose tolerance. Also, only 56% of our cohort is of European descent, with the remainder made up from a mixture of other race/ethnicity groups. Despite these differences, the variants in *ADIPOQ* that were associated with adiponectin concentrations in the DPP were the same as those previously reported in other European-descent populations not enriched in obesity and diabetes risk ([2,4,6] and Table 3). The magnitude of the effect of these variants on adiponectin concentrations was consistent between our report and these prior observations (i.e. between-genotype differences of 10–40% in adiponectin concentrations). The magnitudes of these effects, together with the strength of the statistical associations, suggest that these polymorphisms are robust genetic determinants of circulating adiponectin concentrations in humans. Nevertheless, the proportion of total variation in adiponectin concentrations accounted for by these genetic determinants is low, while non-genetic factors related to sex, race/ethnicity, age and obesity are more potent determinants of the overall concentration of adiponectin.

Our results confirm adiponectin-associated variants reported from the AdipoGen cohorts [4], and thereby extend these observations into a multi-ethnic population and into an obese dysglycaemic population. Among the SNPs evaluated in the Framingham Offspring Study cohort [3], we confirmed association of adiponectin concentrations with one variant (rs822387, association $P = 10^{-2}$) but we found significant associations with SNPs that were not associated with adiponectin concentrations in that cohort (rs10937273, rs16861194, rs182052 and rs17373414). Because we selected variants for genotyping that were represented in at least 5% of the population, our measurements did not include the rare exonic variant (rs17300539, Y111H) that those authors found most strongly associated with adiponectin concentrations.

Gene variants and diabetes incidence

In the DPP cohort we found no evidence for direct effects of *ADIPOQ* variants on diabetes risk. *ADIPOR2* rs758027 and *ADIPOQ* rs17373414 interacted with treatment intervention to modify diabetes risk with borderline significance (Table 4). We found significant univariate associations of two *ADIPOR1* variants with diabetes risk, namely rs1342387 and rs12733285.

Early evaluations suggested that the *ADIPOQ* region in 3q27 harboured a diabetes risk gene (e.g. [9,29]). A meta-analysis of the initial literature showing diabetes associations with rs17360539 and rs266729 (the most widely investigated upstream variants) suggests an ~8% increase in diabetes risk among carriers of these variants in European populations [7,8]. The linked variants that we evaluated (rs822387 and rs182052) were associated with adiponectin concentrations but not diabetes incidence in our data set. *ADIPOQ* variants have been associated with diabetes prevalence in other populations, including variants that were associated with adiponectin concentrations but not diabetes in our cohort (e.g. rs1648707, [4] and rs16861194 [30]). A recent publication from the Finnish Diabetes Prevention Study found associations of three *ADIPOQ* variants (rs266729, rs2241766 and rs2082940, the latter two in linkage disequilibrium) with prospective diabetes risk in a study design similar to ours, although focused on a European population [17]. Combining these variants in a single model left only rs266729 associated with diabetes risk. In that population only one of five adiponectin-associated variants was associated with diabetes [17]. Our data replicate some of these observed associations with adiponectin concentrations (rs16861210, rs17366568) with similar effect sizes, but we did not evaluate the variants found to be associated with diabetes in that population.

The contribution of *ADIPOQ* variants to adiponectin variability is low in our cohort (~7%). In turn, adiponectin explains only a portion of diabetes risk (hazard ratio ~0.8 per 3 µg/ml (i.e. ~1 SD) increase [1]). This means that the net effect being conveyed from the gene through the concentrations onto diabetes risk is proportionally small. However, even very large studies have failed to find the expected associations between genetic determinants of adiponectin concentrations and genetic determinants of diabetes risk [3,4]. An alternative interpretation is that the combined effects of other determinants of adiponectin-associated diabetes risk (e.g. age, sex) are masking a complex combined effect of *ADIPOQ* SNPs in a population. Overall, the positive association of adiponectin concentrations with diabetes risk in the DPP and other populations is not simply explained by genetic variants in *ADIPOQ* that contribute to adiponectin concentrations.

The two *ADIPOR1* variants that were associated with diabetes incidence in our population showed no evidence of association with adiponectin concentrations. *ADIPOR1* and *ADIPOR2* variants have previously been associated with diabetes prevalence, and with diabetes risk factors [23] (although others have failed to find such associations [21]). However, we found no evidence that this relationship is mediated by effects on adiponectin

concentrations in the DPP. The variants associated with diabetes incidence in the DPP are in non-coding regions of the *ADIPOR1* gene, possibly reflecting a modulation of transcription rather than a direct effect on gene product function. These observations require confirmation and further mechanistic exploration.

Limitations

The DPP population is enriched in obesity and dysglycaemia, resulting in an altered signal range for related phenotypic features, including diabetes risk, compared with samples from the general population. This is advantageous in the current context of confirming and extending previously reported associations into populations not previously analysed. However, the generalizability of our findings is accordingly reduced. The DPP sample size was derived using the primary study goals of examining effects on diabetes outcome, and not optimized a priori for questions relating to the current genetic analyses. And although we have a mixture of race/ethnicity groups in our study population, the absolute numbers of participants in each of the non-European subgroups is too small to allow meaningful evaluations within each group.

Conclusions

Common variants in the upstream coding region of the *ADIPOQ* gene are associated with adiponectin concentrations in the obese, dysglycaemic population recruited into the US Diabetes Prevention Program, with independent signals localizing to four upstream variants (rs17366568, rs1648707, rs17373414 and rs1403696). None of the *ADIPOQ* variants evaluated associated directly with diabetes risk. Variants in the genes for adiponectin receptors (*ADIPOR1* and *ADIPOR2*) did not associate with adiponectin concentrations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Minor allele frequencies by race/ethnicity group for variants significantly associated with adiponectin or diabetes in the Diabetes Prevention Program (DPP)

Gene	Location *	SNP	Association	Major/minor	Whole population (n = 2890)	White (n = 1624)	African American (n = 582)	Hispanic (n = 479)	Asian American (n = 124)	American Indian (n = 81)
<i>ADIPOQ</i>	3:184984816	rs6810075	Adiponectin	A/G	0.38	0.363	0.335	0.438	0.419	0.488
<i>ADIPOQ</i>	3:184985946	rs10937273	Adiponectin	G/A	0.35	0.419	0.180	0.332	0.411	0.235
<i>ADIPOQ</i>	3:184987944	rs1648707	Adiponectin	T/G	0.41	0.353	0.527	0.455	0.435	0.494
<i>ADIPOQ</i>	3:184992255	rs822387	Adiponectin	A/G	0.13	0.081	0.317	0.100	0.020	0.025
<i>ADIPOQ</i>	3:184995644	rs16861194	Adiponectin	A/G	0.13	0.079	0.236	0.163	0.157	0.123
<i>ADIPOQ</i>	3:184997001	rs182052	Adiponectin	C/T	0.38	0.353	0.365	0.444	0.419	0.494
<i>ADIPOQ</i>	3:185002720	rs16861210	Adiponectin	C/T	0.10	0.092	0.185	0.088	0.008	0.012
<i>ADIPOQ</i>	3:185005007	rs7649121	Adiponectin	A/T	0.18	0.187	0.112	0.208	0.165	0.309
<i>ADIPOQ</i>	3:185006675	rs17366568	Adiponectin	C/T	0.09	0.126	0.025	0.058	0.093	0.025
<i>ADIPOQ</i>	3:185007781	rs3774261	Adiponectin	C/T	0.45	0.403	0.572	0.481	0.508	0.333
<i>ADIPOQ</i>	3:185011704	rs9842733	Adiponectin	A/T	0.02	0.001	0.086	0.011	0	0
<i>ADIPOQ</i>	3:185016088	rs1403696	Adiponectin	G/A	0.05	0.005	0.178	0.042	0.016	0.049
<i>ADIPOQ</i>	3:185017480	rs17373414	Adiponectin, Type 2 diabetes	C/T	0.08	0.120	0.026	0.059	0.020	0.031
<i>ADIPOI</i>	1:176043603	rs1342387	Type 2 diabetes	G/A	0.47	0.455	0.491	0.511	0.399	0.630
<i>ADIPOI</i>	1:176051286	rs12733285	Type 2 diabetes	G/A	0.26	0.318	0.201	0.211	0.133	0.099
<i>ADIPOI</i>	12:3399697	rs758027	Type 2 diabetes	T/C	0.02	0.001	0.097	0.012	0	0
<i>ADIPOI</i>	12:3475269	rs7134070	Type 2 diabetes	T/C	0.03	0.004	0.131	0.023	0.036	0.012

* Physical locations for each single-nucleotide polymorphism (SNP) are presented as **chromosome:location**, using genome build 37.3 from the SNP database (dbSNP). Minor allele frequencies presented in bold were not in Hardy–Weinberg equilibrium within that subgroup. Minor allele frequencies for the whole population reflect unweighted means adding all subgroups.

Table 2
ADIPOQ and *ADIPOI* variants found to be associated with adiponectin concentrations in the Diabetes Prevention Program (DPP)

Gene	SNP (location)*	Allele [†]	Genotype counts [‡]			Adiponectin concentrations (95% CI); mg/dl			Coefficient (95% CI) [§]	P-value [¶]
			M	m	MM	Mm	mm	mm		
ADIPOQ	rs6810075 ^A (3:184984816)	A	G	1126	1356	407	7.014 (6.820–7.213)	6.457 (5.984–6.455)	0.936 (0.919–0.954)	6.9E-12
ADIPOQ	rs10937273 (3:184985946)	G	A	1257	1233	395	6.423 (6.255–6.595)	6.690 (6.510–6.875)	1.053 (1.033–1.074)	1.3E-07
ADIPOQ	rs1648707 ^A (3:184987944)	T	G	1009	1375	504	7.117 (6.912–7.327)	6.484 (6.317–6.654)	0.929 (0.911–0.946)	4.9E-15
ADIPOQ	rs822387 ^B (3:184992255)	A	C	2213	592	71	6.535 (6.384–6.690)	6.886 (6.643–7.138)	1.05 (1.020–1.080)	9.2E-04
ADIPOQ	rs16861194 (3:184995644)	A	G	2209	612	68	6.698 (6.539–6.862)	6.398 (6.190–6.613)	0.958 (0.932–0.984)	1.9E-03
ADIPOQ	rs182052 ^A (3:184997001)	C	T	1124	1346	415	7.015 (6.820–7.215)	6.497 (6.329–6.669)	0.934 (0.917–0.951)	8.9E-13
ADIPOQ	rs16861210 ^B (3:185002720)	C	T	2328	520	42	6.525 (6.376–6.676)	7.051 (6.795–7.317)	1.081 (1.049–1.114)	2.7E-07
ADIPOQ	rs7649121 (3:185005007)	A	T	1956	830	98	6.731 (6.568–6.898)	6.428 (6.239–6.623)	0.952 (0.929–0.974)	5.0E-05
ADIPOQ	rs17366568 (3:185006675)	C	T	2402	455	32	6.714 (6.563–6.869)	5.969 (5.744–6.203)	0.882 (0.855–0.910)	9.8E-15
ADIPOQ	rs3774261 (3:185007781)	C	T	893	1378	618	6.425 (6.234–6.623)	6.584 (6.415–6.757)	1.036 (1.017–1.054)	1.8E-04
ADIPOQ	rs9842733 (3:185011704)	A	T	2774	113	1	6.640 (6.491–6.792)	5.870 (5.467–6.304)	0.882 (0.823–0.945)	3.7E-04
ADIPOQ	rs1403696 (3:185016088)	G	A	2633	236	21	6.672 (6.519–6.828)	6.118 (5.813–6.440)	0.922 (0.882–0.964)	3.5E-04
ADIPOQ	rs17373414 (3:185017480)	C	T	2430	435	26	6.561 (6.414–6.713)	6.989 (6.714–7.274)	1.069 (1.034–1.105)	7.7E-05
SNPs below were nominally associated but did not meet significance after adjustment for multiple comparisons:										
ADIPOQ	rs12758184 (3:176066880)	A	G	1443	1162	286	6.529 (6.357–6.706)	6.593 (6.413–6.778)	1.023 (1.003–1.044)	2.6E-02
ADIPOQ	rs16861205 (3:184997853)	G	A	2257	585	48	6.687 (6.528–6.849)	6.395 (6.184–6.614)	0.961 (0.933–0.988)	5.7E-03
ADIPOQ	rs822391 (3:185000021)	T	C	2072	719	96	6.524 (6.370–6.683)	6.787 (6.571–7.009)	1.035 (1.010–1.061)	6.7E-03
ADIPOQ	rs822396 (3:185003099)	T	C	1947	836	101	6.534 (6.377–6.695)	6.737 (6.536–6.945)	1.033 (1.008–1.057)	8.4E-03
ADIPOQ	rs12495941 (3:185004402)	G	T	1209	1290	388	6.521 (6.347–6.701)	6.611 (6.437–6.790)	1.023 (1.004–1.043)	1.6E-02
ADIPOQ	rs1403697 (3:185012915)	T	C	2738	144	8	6.641 (6.491–6.794)	6.038 (5.657–6.444)	0.924 (0.872–0.979)	7.7E-03
ADIPOI	rs10800890 (1:176075770)	G	C	2222	532	132	6.633 (6.464–6.807)	6.720 (6.487–6.960)	0.967 (0.939–0.998)	3.6E-02

* Single-nucleotide polymorphisms (SNPs) with shared superscripts ^A ^B are in linkage disequilibrium. SNPs are presented in order of physical location, listed separately for those above and below the multiple-comparison adjusted significance cut point (per Holm procedure = 0.05/14 = 3.6E-3). Physical locations of each SNP are presented as **chromosome:location**, using genome build 37.3 from the SNP database (dbSNP).

[†] The major allele for each SNP is represented as 'M' and the minor allele as 'm'.

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[‡] Age, sex and race-adjusted least-square means and confidence intervals of adiponectin concentrations are presented for each genotype.

[§] The coefficient is an estimate of the effect of one additional minor allele on adiponectin concentration derived from a linear model of natural log adiponectin concentration as a function of the number of minor alleles (0, 1 or 2). The anti-log of the regression coefficient is listed for each SNP, and represents this effect as a multiplier per minor allele. For example, for rs1648707, the estimated mean adiponectin concentration is multiplied by 0.929 for each additional minor allele. All variants with nominal significance ($P < 0.05$) are listed.

[¶] The notation for P -values indicates the coefficient and its exponent, with E indicating the power of the base-10 exponent (i.e. $9.8E-15 = 9.8 \times 10^{-15}$).

Table 3

Comparison of single-nucleotide polymorphisms (SNPs) in *ADIPOQ* associated with adiponectin in Diabetes Prevention Program (DPP) and in AdipoGen cohorts*

Adiponectin concentrations		TWINS UK*		GEMS* controls		GEMS* cases		CoLaus*	
SNP (effect allele)	DPP	β -coefficient [‡]	P-value [‡]	β -coefficient [‡]	P-value [‡]	β -coefficient [‡]	P-value [‡]	β -coefficient [‡]	P-value [‡]
rs1648707 ^A (G)	-0.074	4.9E-15	0.03	+0.066	0.18	+0.043	0.38	+0.127	5.4E-09
rs17366568 (T)	-0.126	9.8E-15	0.08	-0.245	6.9E-4	-0.210	3.0E-3	-0.220	1.9E-13
rs182052 ^A (T)	-0.068	8.9E-13	3.8E-3	-0.061	0.21	-0.038	0.43	-0.128	1.3E-09
rs6810075 ^A (G)	-0.066	6.8E-12	3.7E-3	-0.082	0.11	-0.064	0.20	-0.13	4.9E-9
rs10937273 (A)	+0.052	1.3E-07	0.73	+0.084	0.10	+0.058	0.25	+0.084	6.6E-05
rs16861210 ^B (T)	0.078	2.7E-07	0.62	+0.149	0.23	+0.289	9.3E-3	+0.295	1.1E-11
rs7649121 (T)	-0.049	5.0E-05	0.62	+0.094	0.22	-0.025	0.74	-0.081	0.012
rs17373414 (T)	+0.067	7.7E-05	0.027	+0.368	0.008	+0.417	0.002	+0.284	6.1E-09
rs3774261 (T)	+0.035	1.8E-04	6.1E-4	+0.134	6.4E-3	+0.207	2.6E-05	+0.123	5.0E-10
Rs822387 ^B (C)	+0.049	9.2E-04	7.3E-05	+0.123	+0.29	+0.274	0.009	+0.277	4.2E-11
rs16861194 (G)	-0.043	1.9E-03	0.19	-0.056	0.48	0.026	0.74	-0.118	0.002

[‡]The notation for P-values indicates the coefficient and its exponent, with E indicating the power of the base-10 exponent (i.e. 9.8E-15 = 9.8×10^{-15}).

*In all instances, the β -coefficients represent the change in ln(adiponectin) per allele; on the natural scale this therefore represents a power increase or decrease in concentration per allele (i.e. β -0.074 = $e^{(-0.074)}$ -fold change in adiponectin mg/dl per allele).

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Table 5

Comparison of single-nucleotide polymorphisms (SNPs) in *ADIPOQ*, *ADIPOR1* and *ADIPOR2* associated with diabetes in the Diabetes Prevention Program (DPP) and in DIAGRAM

DPP adiponectin association		DPP coefficient (logAPN per effect allele)	DPP diabetes incidence		DIAGRAM Type 2 diabetes Case/control (prevalence)	
SNP (effect allele) (gene)	P		Hazard ratio (95% CI)	P	Odds ratio (95% CI)	P
SNPs associated with Type 2 diabetes in the DPP						
rs1342387 (A) (<i>ADIPOR1</i>)	0.95	—	1.17 (1.05–1.32)	0.005	1.007 (0.945–1.073)	0.84
rs12733285 (A) (<i>ADIPOR1</i>)	0.27	—	1.18 (1.04–1.34)	0.009	1.007 (0.932–1.088)	0.86
rs2232847 (T) (<i>ADIPOR1</i>)	0.67	—	0.85 (0.75–0.97)	0.018	1.019 (0.956–1.086)	0.57
rs12826079* (T) (<i>ADIPOR2</i>)	0.72	—	1.60 (1.06–2.42)	0.026	1.032 (0.906–1.176)	0.63
SNPs associated with Type 2 diabetes in DIAGRAM						
rs822391 (C) (<i>ADIPOQ</i>)	0.007	0.0296	0.89 (0.76–1.05)	0.159	1.183 (1.082–1.294)	0.000232
rs7649121 (T) (<i>ADIPOQ</i>)	0.00005	–0.048	0.89 (0.76–1.04)	0.154	1.126 (1.024–1.240)	0.0147
rs822396 (C) (<i>ADIPOQ</i>)	0.008	0.0296	0.95 (0.81–1.10)	0.498	1.201 (1.098–1.314)	0.000064

rs7134070 in *ADIPOR2* was not directly genotyped in DIAGRAM; an SNP in linkage disequilibrium with this SNP was evaluated in DIAGRAM (denoted by *), and is presented instead.