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Common variation at *PPARGC1A/B* and change in body composition and metabolic traits following preventive interventions: the Diabetes Prevention Program

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Disclosure: A previous version of this paper (doi 10.1007/s00125-013-2911-3) was retracted because of an inadvertent overlap with an earlier, broader study (Jablonski et al, Diabetes, 2010; doi: 10.2337/db10-0543). In the retracted article, one of the key findings had been reported in the supplementary materials of Jablonski et al. The article was retracted at the request of the authors before it was published in print form. The retracted paper has now been completely replaced by this version.

Duality of interest

KAJ (the DPP Genetics Program) has a research grant from the National Institutes of Health. JCF has received consulting honoraria from Novartis, Lilly and Pfizer, and has National Institutes of Health grants. PWF has received speaking honoraria from Novo Nordisk and other academic/non-profit organisations, and has research grants from the National Institutes of Health, European Union and Novo Nordisk and other academic/non-profit organisations.

LMD has a financial interest in Omada Health, a company that develops online behaviour-change programmes, with a focus on diabetes. LD's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict-of-interest policies.

CAC, LKB, ESH and WCK declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement

ESH, LMD, WCK and the full DPP Research Group planned and carried out the clinical trial. PWF, CAC, KAJ and JCF conceived the analysis. CAC and KAJ conducted the statistical analysis. JCF supervised the genotyping. LKB conducted in silico functional analyses. PWF drafted the initial version of the manuscript, upon which all co-authors commented. All co-authors helped interpret the data and reviewed and edited the manuscript before approving the final version of the manuscript for submission.

Abstract

Aims/hypothesis—*PPARGC1A* and *PPARGCB* encode transcriptional coactivators that regulate numerous metabolic processes. We tested associations and treatment (i.e. metformin or lifestyle modification) interactions with metabolic traits in the Diabetes Prevention Program, a randomised controlled trial in persons at high risk of type 2 diabetes.

Methods—We used Tagger software to select 75 *PPARGCA1* and 94 *PPARGC1B* tag single-nucleotide polymorphisms (SNPs) for analysis. These SNPs were tested for associations with relevant cardiometabolic quantitative traits using generalised linear models. Aggregate genetic effects were tested using the sequence kernel association test.

Results—In aggregate, *PPARGC1A* variation was strongly associated with baseline triacylglycerol concentrations ($p=2.9\times10^{-30}$), BMI ($p=2.0\times10^{-5}$) and visceral adiposity ($p=1.9\times10^{-4}$), as well as with changes in triacylglycerol concentrations ($p=1.7\times10^{-5}$) and BMI ($p=9.9\times10^{-5}$) from baseline to 1 year. *PPARGC1B* variation was only 3 associated with baseline subcutaneous adiposity ($p=0.01$). In individual SNP analyses, Gly482Ser (rs8192678, *PPARGC1A*) was associated with accumulation of subcutaneous adiposity and worsening insulin resistance at 1 year (both $p<0.05$), while rs2970852 (*PPARGC1A*) modified the effects of metformin on triacylglycerol levels ($p_{interaction}=0.04$).

Conclusions/interpretation—These findings provide several novel and other confirmatory insights into the role of *PPARGC1A* variation with respect to diabetesrelated metabolic traits.

Trial registration—ClinicalTrials.gov NCT00004992

Keywords

Cholesterol; Dyslipidaemia; Gene × environment interaction; Gene × lifestyle interaction; Genetics; Lifestyle intervention; Metformin; Pharmacogenetics; *PPARGC1A*; *PPARGC1B*; Randomised controlled trial; Triacylglycerol

Introduction

PPARGC1A and *PPARGC1B* encode homologous proteins (peroxisome proliferator-activated receptor coactivator-1α and -1β, respectively) that, through nuclear transcription factor coactivation, regulate adipogenesis, insulin signalling, lipolysis, mitochondrial biogenesis, angiogenesis and hepatic gluconeogenesis. Metabolic stress 4 and lipid abundance affect PPARGC1A/B expression [1–3]. PPARGC1A is expressed predominantly in mitochondria-rich tissues [4], such as high-oxidative capacity skeletal muscle, heart, brown fat, liver and brain. These and other data support the hypothesis that *PPARGC1A* variation interacts with lifestyle factors to modulate the expression of cardiometabolic phenotypes.

Associations of *PPARGC1A* single-nucleotide polymorphisms (SNPs) with a range of cardiovascular and metabolic traits, including type 2 diabetes [5–8], insulin resistance [9, 10], glucose concentrations [7, 11], dyslipidaemia [12], obesity [7, 13] and aerobic fitness [7, 14–16], have been reported, as have interactions between *PPARGC1A* variants and lifestyle factors [7, 8, 13, 14, 17]. Most existing studies on *PPARGC1A* variation, however,

have been cross-sectional epidemiological investigations, from which causal inference is difficult, and none except one prior report from the Diabetes Prevention Program (DPP) [8] has systematically examined variations across the *PPARGC1A* and *PPARGC1B* loci. Nonetheless, experimental studies in animals and humans have illustrated that *PPARGC1A* transcription increases with exercise [18], cold exposure [1, 19], fasting [20] and fatty acid infusion [1, 20]. In prior DPP analyses focused on the associations and treatment interactions of 1,590 variants across 40 genes [8], we highlighted that the rs3736265 variant (*PPARGC1A*) was significantly associated with diabetes in the DPP and Diabetes Genetics Replication and Meta-analysis Consortium (DIAGRAM) datasets [8]. Here, we extend those findings by examining associations and treatment interactions for *PPARGC1A* and *PPARGC1B* variants with relevant cardiometabolic quantitative traits (i.e. BMI, waist circumference, subcutaneous and visceral adipose tissue, fasting and 2 h glucose, and triacylglycerols).

Methods

DPP

The DPP study [21, 22] was a multicentre randomised controlled trial in which the effects of metformin and lifestyle modification on the incidence of diabetes were assessed. Non-diabetic persons (n=3,234) with elevated fasting glucose and impaired glucose tolerance were randomised to placebo, metformin (850 mg twice daily) or lifestyle modification (~7% weight loss and ~150 min physical activity/week). The principal endpoint was diabetes development, confirmed by OGTT. Quantitative metabolic traits, adipose tissue accumulation and weight change were assessed. Participants provided written informed consent. The 27 DPP centres (listed in the 5 electronic supplementary material [ESM]) obtained institutional review board approval and the study was performed according to the Declaration of Helsinki.

Participants

Consent for genetic analysis was obtained from 93.3% of DPP participants with 1 year outcome data available. Of these participants, 56.1% were white, 20.4% were African-American, 16.7% were Hispanic, 4.4% were Asian-American and 2.5% were American Indian. The mean ± SD age (51±11 years) and BMI (34.1±6.7 kg/m^2) of participants at enrolment were similar to those of the entire DPP population.

Quantitative traits

Body composition measurements included anthropometrics and, in a subgroup (n=725), abdominal computed tomography, as described elsewhere [23]. Triacylglycerols were measured in fasting samples and glucose and insulin were measured in fasting and post-glucose challenge samples from which HOMA-IR was computed, as previously described [8].

Genotyping

As described elsewhere [8], Tagger software [24] was used to capture variants in *PPARGC1A/B* (20 kb upstream and 10 kb downstream) with minor allele frequencies of

more than 5% at $r^2 \geq 0.8$ in the European (Centre d'Etude du Polymorphisme Humain: Utah residents with northern and western Europe ancestry [CEU]) and African (Yoruba in Ibadabn, Nigeria [YRI]) HapMap populations. After successful genotyping, we captured 98% of common CEU variants in both genes at $r^2 \geq 0.8$ (100% at $r^2 \geq 0.5$), and 98% (*PPARGC1A*) and 88% (*PPARGC1B*) of common YRI variants at $r^2 \geq 0.8$ (99% and 98%, respectively, at $r^2 \geq 0.5$). Genotyping was performed on an oligonucleotide pool array (BeadArray; Illumina, San Diego, CA, USA) and supplemented with rescue genotyping on a Sequenom platform. Allele frequencies in each ethnic group for each *PPARGC1A/B* SNP were in Hardy– Weinberg equilibrium.

Statistical analysis

Outcomes with right-skewed distributions were logarithmically transformed. For individual SNP analyses, associations and treatment interactions were tested in generalised linear models, with genotype, intervention and genotype by intervention interactions as the independent variables. When an interaction was evident, analyses were performed by treatment arm, and if no interaction was evident then analyses included the full cohort adjusted for treatment group, included in the model as a three-level class variable. Differences between means were tested using 6 pairwise contrasts. A two-sided exact binomial test was used to determine whether an apparent excess of statistically significant associations within either gene differed variation at each locus using the sequence kernel association test (SKAT) [25], a region-specific, score-based, variance-components test that uses multiple regression and makes no a priori assumptions about each variant's effect magnitude or directionality [25]. All analyses were adjusted for age at randomisation, sex and ethnicity; models assessing genetic associations with 1 year change in outcomes were further adjusted for the respective baseline trait. Two-sided *p* values per gene and per trait are reported. Bonferroni adjustment for multiple comparisons was used to determine if nominally significant results observed remained significant in the presence of the many statistical tests that had been performed. $p<0.05$ was considered nominally statistically significant. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Genotype associations with baseline traits

Overall, 7.5% of all association tests were nominally statistically significant (139 of the 1,859 tests performed, of which 93 nominally significant associations would be expected by chance: binomial test $p<0.0001$). In SKAT analyses, *PPARGC1A* variation was strongly associated with baseline triacylglycerol concentrations ($p=2.9\times10^{-30}$), BMI ($p=2.0\times10^{-5}$) and visceral adiposity ($p=1.9\times10^{-4}$). *PPARGC1B* variation was associated with baseline subcutaneous adiposity ($p=0.01$). In individual SNP analyses, the extensively researched non-synonymous variant Gly482Ser (rs8192678) was nominally associated with baseline HOMA-IR in a direction consistent with earlier reports (β=0.25 [SE 0.12]/Ser482 allele/year; $p=0.04$) [5], which appeared to be driven by baseline BMI (β=0.37 [SE 0.18] kg/m^2/Ser482 allele/year; $p=0.04$) and baseline subcutaneous adipose area (β=13.8 [SE 6.1] cm^2/Ser482 allele/year; $p=0.02$). The Gly482Ser association with HOMA-IR was smaller and no longer statistically significant when also adjusted for BMI (β=0.15, SE 0.11 per Ser482

allele/year, p=0.17). Individually, no other *PPARGC1A/B* SNPs showed evidence of association.

Genotype associations with change in traits from baseline to 1 year

In SKAT analyses, *PPARGC1A* variation was strongly associated with changes in triacylglycerol concentrations ($p=1.7\times10^{-5}$) and BMI ($p=9.9\times10^{-5}$) from baseline to 1 year. No aggregate effects of *PPARGC1B* were observed. For all SNPs that did not show evidence of gene × treatment interactions, we tested associations with metabolic traits in the pooled DPP sample after adjusting for treatment, but there was no evidence of association (data not shown).

Genotype × treatment interactions

Of the SNP × treatment interaction tests, 6.1% (113 of 1,859 tests, of which 93 nominally significant associations would be expected by chance: binomial test p=0.04) yielded statistically significant results ($p<0.05$). We performed stratified analyses by treatment arm for each of these 113 SNPs (Table 1). The most statistically significant association was between the rs2970852 SNP and change in triacylglycerol concentrations in metformin-treated participants, with the minor (T) allele associating with a mean increase in triacylglycerol concentrations in the metformin group ($p_{nominal}=0.0001$) that was of significantly greater magnitude than the changes seen in the lifestyle and placebo groups (Table 1). None of the individual SNP tests exceeded the Bonferroni p value threshold of $p=2.7\times10^{-4}$.

Discussion

To our knowledge, this is the first comprehensive assessment of the effects of *PPARGC1A/B* variation on cardiometabolic traits within the context of a prospective study. In aggregate, variation at *PPARGC1A* was robustly associated with triacylglycerol concentrations, BMI and visceral adiposity at baseline, and with 1 year change in BMI and triacylglycerol concentrations. Variation at *PPARGC1B* was nominally associated with baseline subcutaneous adiposity, but not with other traits. Nominally significant associations with baseline HOMA-IR, BMI and fat mass for Gly482Ser (rs8192678, *PPARGC1A*) were observed, which are directionally consistent with previous reports [5–7]. The attenuation of the Gly482Ser association with HOMA-IR when adjusted for BMI indicates that BMI mediates this effect. The *PPARGC1A* rs2970852 SNP conveyed a strong (Bonferroni-corrected) effect on change in triacylglycerol concentrations following metformin treatment. As previously reported [8], the rs3736265 *PPARGC1A* variant was associated with diabetes incidence in the DPP and diabetes prevalence in the DIAGRAM dataset; however, this variant was not associated with the quantitative metabolic traits studied here. The Gly482Ser, rs2970852 and rs3736265 variants were in weak linkage disequilibrium ($r^2<0.16$ for pairwise SNP comparisons in the European [CEU], African [YRI] and Asian [Han Chinese in Beijing, China, and Japanese in Tokyo, Japan] HapMap panels). A number of other *PPARGC1A/B* variants showed nominal evidence of association and interaction for cardiometabolic traits in the DPP, suggesting that *PPARGC1A* may be a pleiotropic locus.

The Gly482Ser (rs8192678) variant encodes a missense change in amino acid sequence [26]. We used the publicly available assessment tools SIFT (http://sift.jcvi.org) [27] and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2) [28] to determine if amino acid changes could be detrimental to the protein function (conducted 12 September 2013). SNPs were consistent for both bioinformatics tools. PolyPhen-2 predictions were based on the HumDiv testing model. This model was compiled from all damaging alleles with known effects on the molecular function causing human Mendelian diseases present in the UniProtKB database, together with differences between human proteins and their closely related mammalian homologues, assumed to be non-damaging. Gly482Ser, rs2970852 and rs3736265 were not found to be deleterious in any of these analyses. Moreover, analyses of sequence conservation and putative effects on protein structure failed to show any significant effects of the amino acid changes on protein function. This contrasts with the findings of Choi et al [29], where the Gly482Ser change reportedly affected coactivator activity on mitochondrial transcription factor A promoter-mediated luciferase.

The proportion of nominally statistically significant tests of association and treatment interactions exceeded the 5% expected by chance. Assessments of aggregate effects using SKAT showed robust associations between *PPARGC1A* variation and baseline BMI and visceral adiposity, and with triacylglycerol concentrations at baseline and follow-up. These findings withstood Bonferroni correction. Existing experimental evidence from humans and animals illustrating that these genes are responsive to lifestyle factors and control transcriptional networks involved in energy metabolism further strengthen our results [30]. Thus, it is possible that some of the nominally statistically significant individual SNP tests of association and interaction identified here that did not withstand Bonferroni correction may be true positives. Indeed, the significant excess of nominally significant association signals for most of the hypothesis tests supports this notion.

In summary, there is a significant excess of individual SNP associations and interactions for *PPARGC1A* variants and cardiometabolic traits, and aggregated variation at this locus was strongly associated with triacylglycerol concentrations, body composition and adiposity in the DPP cohort; however, there is little evidence that *PPARGC1B* variation conveys strong cardiometabolic effects in this cohort. Our current findings build on our prior observation that a variant (rs3736265) in *PPARGC1A* is significantly associated with diabetes in both the DPP and DIAGRAM datasets [8], although this variant was not associated with any of the quantitative traits studied here. These detailed analyses of biologically sound candidate genes for type 2 diabetes elucidate their roles in metabolic traits and treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CEU	Centre d'Etude du Polymorphisme Humain: Utah residents with northern and western Europe ancestry
DIAGRAM	Diabetes Genetics Replication and Meta-analysis Consortium
DPP	Diabetes Prevention Program
SKAT	Sequence kernel association test
SNP	Single-nucleotide polymorphism
YRI	Yoruba in Ibadabn, Nigeria

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Table 1

SNP × treatment interactions that were nominally statistically significant ($p<0.05$)

Gene	SNP	Major(minor) allele	Outcome	Placebo		Metformin		Lifestyle	
				β (SE)	*p*	β (SE)	*p*	β (SE)	*p*
PPARGC1A	rs1878950	C(T)	Δ Fasting plasma glucose (mmol/l)	11.7 (3.4)	0.0006	2.26 (2.75)	0.41	1.12 (2.98)	0.71
PPARGC1A	rs2970868	C(G)	Δ Fasting plasma glucose (mmol/l)	6.07 (1.73)	0.0005	−0.38 (1.29)	0.77	1.00 (1.48)	0.50
PPARGC1B	rs6650970	T(C)	Δ Fasting plasma glucose (mmol/l)	−2.46 (1.11)	0.03	2.78 (0.86)	0.001	1.19 (0.86)	0.17
PPARGC1B	rs11746690	G(A)	Δ Fasting plasma glucose (mmol/l)	−2.88 (1.18)	0.02	2.75 (0.92)	0.003	0.96 (0.91)	0.29
PPARGC1B	rs12110130	A(G)	Δ Fasting plasma glucose (mmol/l)	0.89 (2.42)	0.71	−3.55 (1.81)	0.05	5.51 (1.74)	0.002
PPARGC1A	rs741579	A(G)	Δ 2 h glucose (mmol/l)	32.5 (12.1)	0.007	−6.12 (8.27)	0.46	−9.90 (8.16)	0.22
PPARGC1A	rs957615	G(A)	Δ 2 h glucose (mmol/l)	−9.42 (2.65)	0.0004	3.09 (2.36)	0.19	−2.56 (2.33)	0.27
PPARGC1A	rs2932974	A(G)	Δ Triacylglycerol (mmol/l)	−3.13 (4.24)	0.46	−13.7 (4.03)	0.0007	5.30 (3.98)	0.18
PPARGC1A	rs2970852	C(T)	Δ Triacylglycerol (mmol/l)	3.91 (3.93)	0.32	13.9 (3.6)	0.0001	−2.22 (3.50)	0.53
PPARGC1A	rs2970855	T(A)	Δ Triacylglycerol (mmol/l)	−1.49 (3.50)	0.67	−11.6 (3.3)	0.0004	2.52 (3.30)	0.45
PPARGC1A	rs4619879	A(C)	Δ Triacylglycerol (mmol/l)	−2.00 (3.50)	0.57	−9.72 (3.25)	0.003	2.87 (3.25)	0.38
PPARGC1A	rs4697046	C(T)	Δ Triacylglycerol (mmol/l)	−1.43 (3.54)	0.69	−11.3 (3.3)	0.0007	3.86 (3.31)	0.24
PPARGC1A	rs16874290	A(G)	Δ Waist circumference (cm)	−0.31 (0.93)	0.74	−3.15 (1.06)	0.003	0.21 (1.12)	0.85
PPARGC1A	rs1878949	A(C)	Δ BMI (kg/m^2)	−0.36 (0.11)	0.0007	0.06 (0.10)	0.55	0.07 (0.15)	0.61
PPARGC1A	rs10938972	G(A)	Δ BMI (kg/m^2)	−0.46 (0.11)	0.00004	0.06 (0.11)	0.55	0.18 (0.16)	0.25
PPARGC1B	rs10071329	A(G)	Δ SAT L2/L3 (cm^2)	−8.40 (18.65)	0.65	5.00 (17.03)	0.77	148.0 (43.4)	0.0008
PPARGC1A	rs17576576	A(G)	Δ VAT L2/L3 (cm^2)	12.5 (3.0)	0.00004	−4.48 (3.53)	0.21	1.95 (4.83)	0.69

Data are SNP variants and change from baseline to year 1 in glucose, insulin or triacylglycerol concentrations, or adiposity in the DPP β coefficients are shown per copy of the minor allele under an additive model. Alleles are coded on the + strand. Since treatment interactions were evident, the associations were tested within each treatment group directly, after adjusting for age at randomisation, sex and ethnicity SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue