Brief Genetics Report

Single Nucleotide Polymorphisms of *PPARD* in Combination With the Gly482Ser Substitution of *PGC-1A* and the Pro12Ala Substitution of *PPARG2* Predict the Conversion From Impaired Glucose Tolerance to Type 2 Diabetes

The STOP-NIDDM Trial

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Peroxisome proliferator–activated receptor (PPAR)-δ regulates fatty acid oxidation and improves insulin sensitivity. We screened six single nucleotide polymorphisms (SNPs) of the PPAR-δ gene (*PPARD*) for an association with the conversion from impaired glucose tolerance (IGT) to type 2 diabetes in 769 subjects participating in the STOP-NIDDM trial. A 2.7-fold increase in the risk of diabetes was observed in female carriers of the C allele of rs6902123 (95% CI 1.44–5.30; adjusted *P* = 0.002). In the placebo group, subjects possessing both the 482Ser allele of the PPAR-γ coactivator-1α gene (*PGC-1A*) and the rare allele of two SNPs of *PPARD* (rs6902123 and rs3734254) had up to 2.5-fold increased risk for diabetes. Furthermore, women carrying the C allele of rs6902123 of *PPARD* and the Pro12Pro genotype of the PPAR-γ2 gene (*PPARG2*) had a 3.9-fold (95% CI 1.79–8.63; *P* = 0.001)-higher risk for diabetes than women with protective genotypes. Expression levels of PPAR-δ in subcutaneous adipose tissue of 87 offspring of Finnish patients with type 2 diabetes did not differ among the genotype groups of SNPs of *PPARD*. We conclude that SNPs in *PPARD* modify the conversion from IGT to type 2 diabetes, particularly in combination with the SNPs of *PGC-1A* and *PPARG2*. *Diabetes* 55:2148–2152, 2006

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FFA, free fatty acid; IGT, impaired glucose tolerance; LD, linkage disequilibrium; PGC-1α, PPAR-γ coactivator 1α; PPAR, peroxisome proliferator–activated receptor; SNP, single nucleotide polymorphism.

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Peroxisome proliferator–activated receptor (PPAR)-δ is a powerful regulator of lipid and glucose metabolism and energy homeostasis (1). Overexpression of PPAR-δ in adipose tissue leads to enhanced free fatty acid (FFA) oxidation, improved lipid profile, and protects from both genetically predisposed and high-fat diet–induced obesity (2). In skeletal muscle, the activation of PPAR-δ also induces fatty acid β-oxidation and energy expenditure (3). Treatment with synthetic PPAR-δ activators attenuates plasma glucose and insulin levels in obese mice (3), reduces fasting insulin in insulin-resistant monkeys (4), and can enhance insulin-stimulated glucose uptake in cultured human myotubes (5) but not in skeletal muscle (6).

The physiological function of PPAR-δ appears to be quite similar to that of PPAR-γ coactivator 1α (PGC-1α) (7). Indeed, many of the effects of PGC-1α on energy homeostasis may be mediated through PPAR-δ, as PGC-1α and PPAR-δ have a strong interaction (2). Moreover, PPAR-δ stimulates PGC-1α mRNA expression both in vitro and in vivo (3).

Cross-sectional studies have reported an association of single nucleotide polymorphisms (SNPs) of the PPAR-δ gene (*PPARD*) with lipid and glucose metabolism (8,9). Recently, we demonstrated that SNPs in *PPARD* were associated with skeletal muscle glucose uptake (10). One previous cross-sectional study (9) did not find association with diabetes. In the present study, we investigated the effect of the SNPs of *PPARD* and their interaction with common polymorphisms of the PGC-1α (*PGC-1A*) and PPAR-γ2 (*PPARG2*) genes on the risk of type 2 diabetes in the STOP-NIDDM trial.

RESEARCH DESIGN AND METHODS

The longitudinal, multicenter, double-blind, placebo-controlled STOP-NIDDM trial (mean follow-up 3.3 years) was carried out to evaluate the effect of acarbose on the conversion to type 2 diabetes in 1,429 subjects with impaired glucose tolerance (IGT) (11,12). DNA was available from 769 subjects. The informed consent form, approved by appropriate institutional review board, was signed by all participants of the study.

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		D'					
	SNPs	rs6902123	rs2267668	rs2016520	rs2076167	rs3734254	rs1053049
	rs6902123	-	0.668	0.093	0.934	0.591	0.947
	rs2267668	0.006	-	1.000	0.840	0.800	0.839
r^2	rs2016520	0.003	0.882	-	0.844	0.804	0.843
	rs2076167	0.250	0.506	0.578	-	0.982	1.000
	rs3734254	0.116	0.531	0.608	0.832	-	0.982
	rs1053049	0.253	0.497	0.568	0.985	0.819	-
	MAF	0.071	0.159	0.176	0.209	0.185	0.211

FIG. 1. Linkage disequilibrium statistics (D′, r^2) among the SNPs and the minor allele frequency (MAF) of SNPs of *PPARD*. SNPs are coded by National Center for Biotechnology Information's dbSNP accession numbers.

DNA analyses. Selection of the SNPs was based on the data available from HapMap project's website (13). Six SNPs were chosen from different haplotype blocks to cover the genomic region of *PPARD*. SNPs were genotyped using the TaqMan Allelic Discrimination Assays (Applied Biosystems, Foster City, CA) as previously described (10). Sequence information for oligonucleotide primers and probes is available from the authors.

Quantitative PCR. Total RNA from subcutaneous adipose tissue of 87 offspring of Finnish patients with type 2 diabetes was isolated using Trizol reagent (Invitrogen) and Qiagen RNeasy Mini kit (Qiagen, Hilden, Germany). Total RNA was DNase treated using a DNA-free kit (Ambion) and transcribed to cDNA using random primers and a high-capacity cDNA archive kit (Applied Biosystems). Quantitative RT-PCRs were performed in a 7500 Real-Time PCR System (Applied Biosystems) using 6 ng (RNA equivalents) of cDNA as template, gene-specific primers, and probes (sequence information is available upon request). PPAR-δ (Hs00602622_m1) expressions were normalized to large ribosomal protein P0 (RPLP0; Hs99999902_m1) using standard curve method.

Statistical analysis. We used the SPSS program (version 11.0 for Windows; SPSS, Chicago, IL) in data analysis and gave the results as either means ± SD or percentages. Non–normally distributed parameters were logarithmically transformed. Two-tailed Student's t test, nonparametric, χ^2, and Fisher's exact tests were used to compare variables between the groups, when appropriate. Logistic regression analysis was used to evaluate the effect of SNPs on the conversion to diabetes. Linkage disequilibrium (LD) statistics were calculated and haplotype blocks were visualized by using Haploview software (14) (available at http://www.broad.mit.edu/mpg/haploview/). Haplotype estimation from unrelated individuals was performed by using SNPHAP (available at http://www-gene.cimr.cam.ac.uk/clayton/software/).

RESULTS

The LD statistics (D′, r^2) and the minor allele frequencies of the SNPs of *PPARD* are shown in Fig. 1. As the number of homozygous subjects for the rare allele of each SNP was small, they were combined with heterozygous subjects in all statistical analyses. Frequencies of genotypes of four SNPs of *PPARD* followed the Hardy-Weinberg expectations. However, genotype distributions of rs2076167 and rs1053049 deviated from the Hardy-Weinberg equilibrium ($P < 0.025$ and <0.015, respectively). No genotyping errors were found. Despite that, SNPs rs2076167 and rs1053049 (both in tight LD with rs3734254; inter-SNP $D' > 0.98$, $r^2 > 0.8$; Fig. 1) were excluded from further statistical analyses.

The association of four SNPs of *PPARD* with the conversion to type 2 diabetes is presented in Table 1. Because rs6902123 had an interaction with sex in its effect on the conversion to diabetes (logistic regression analysis, $P = 0.008$), we show the results separately for men and women. The C allele of rs6902123 was more frequent among women who converted to diabetes compared with women who did not. In logistic regression analysis, the presence of the C allele in women increased the risk for the conversion to diabetes by 2.47-fold (95% CI 1.32–4.63;

TABLE 1
Conversion to type 2 diabetes (%) in all subjects and in men and women according to four SNPs of *PPARD*

	rs6902123*			rs2267668		
	TT	TC + CC	P†	AA	AG + GG	P†
n	667	95 + 7		544	205 + 20	
All subjects	39.5	46.1	0.207	40.0	41.5	0.690
Men	42.6	35.7	0.337	38.7	47.9	0.091
Women	36.5	58.7	0.004‡	41.2	34.3	0.220
	rs2016520			rs3734254		
	TT	TC + CC	P†	TT	TC + CC	P†
n	524	219 + 26		518	217 + 34	
All subjects	39.9	41.2	0.724	38.0	45.0	0.064
Men	39.6	45.0	0.305	39.1	45.7	0.211
Women	40.1	36.8	0.544	37.0	44.2	0.187

*P value for the interaction with sex = 0.008. †P value compares the conversion to diabetes between the two genotype groups (Fisher's exact test). ‡Statistically significant.

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TABLE 2
Four SNPs of *PPARD* in combination with the SNP rs8192687 G/A (Gly482Ser) of *PGC-1A* as predictors for the development of type 2 diabetes by treatment group (logistic regression analysis)

		Placebo group (n = 414)		Acarbose group (n = 355)		Genotype/ treatment interaction
		OR (95% CI)	*P*	OR (95% CI)	*P*	*P*
Model 1 (univariate)						
PPARD rs6902123	One risk (1)	1.49 (0.98–2.25)	0.061	0.80 (0.50–1.27)	0.339	0.015†
PGC-1A rs8192687	Both risk (2)	2.56 (1.13–5.80)†	0.024†	0.77 (0.32–1.81)	0.524	
		2.92 (1.26–6.75)†	0.012*†			
Model 2 (univariate)						
PPARD rs2267668	One risk (1)	1.51 (0.97–2.36)	0.067	0.70 (0.43–1.14)	0.153	0.027†
PGC-1A rs8192687	Both risk (2)	1.75 (0.97–2.36)	0.064	0.74 (0.39–1.40)	0.738	
Model 3 (univariate)						
PPARD rs2016520	One risk (1)	1.49 (0.95–2.33)	0.083	0.68 (0.14–1.12)	0.132	0.032†
PGC-1A rs8192687	Both risk (2)	1.74 (0.97–3.10)	0.061	0.76 (0.41–1.41)	0.377	
Model 4 (univariate)						
PPARD rs3734254	One risk (1)	1.63 (1.03–2.57)†	0.036†	0.81 (0.49–1.33)	0.397	0.031†
PGC-1A rs8192687	Both risk (2)	2.15 (1.21–3.80)†	0.009†	0.90 (0.48–1.69)	0.743	
		2.30 (1.27–4.15)†	0.006*†			

*Adjustment for age, sex, smoking, weight at baseline, and weight change. †Statistically significant. (rs6902123 T/**C**; rs2016520 T/**C**; rs3734254 T/**C**) + rs8192687 G/**A** genotypes were coded as (0) = TT + GG; (1) = TT + (GA + AA) and (TC + CC) + GG; (2) = (TC + CC) + (GA + AA). rs2267668 A/**G** + rs8192687 G/**A** genotypes were coded as (0) = AA + GG; (1) = AA + (GA + AA) and (AG + GG) + GG; (2) = (AG + GG) + (GA + AA).

P = 0.005), which remained statistically significant even after the adjustment for age, treatment group, smoking, weight at baseline, and weight change (odds ratio [OR] 2.76 [95% CI 1.44–5.30]; P = 0.002). In haplotype analysis based on different combinations of the four SNPs, none of the haplotypes increased the risk for the conversion to type 2 diabetes beyond that of individual SNPs (data not shown). The expression levels of PPAR-δ in subcutaneous adipose tissue of 87 offspring of Finnish patients with type 2 diabetes did not differ between the genotype groups of SNPs of *PPARD* (online appendix Table 1 [available at http://diabetes.diabetesjournals.org]).

Next, we investigated whether the SNPs of *PPARD* further increased the risk for the conversion to diabetes in carriers of the Gly482Ser (rs8192687) substitution of *PGC-1A*, which was previously shown to increase the risk of diabetes in participants of the STOP-NIDDM trial (15). To this aim, study participants were classified into three groups: subjects having both the nonrisk genotype of *PPARD* and the nonrisk genotype of *PGC-1A* (Gly482Gly) (the reference group), subjects with one risk allele of either *PPARD* or *PGC-1A*, and subjects possessing both the risk allele of *PPARD* and the 482Ser risk allele of *PGC-1A*. Subjects of the placebo group possessing both the 482Ser allele of *PGC-1A* and the C allele of two *PPARD* SNPs (rs6902123 and rs3734254) had a 2.56- and 2.15-fold higher risk for the conversion to type 2 diabetes compared with those having neither risk genotypes (Table 2). ORs varied from 2.30 to 2.92 after the adjustment for confounding factors. The presence of one risk allele (that of either *PGC-1A* or *PPARD*; Table 2) in subjects of the placebo group resulted in a 1.5 increase in the risk of diabetes, a finding similar to that observed earlier for the 482Ser allele of *PGC-1A* alone (15). The simultaneous presence of the *PPARD* risk allele and the 482Ser allele of *PGC-1A* increased the risk up to 2.2-fold, suggesting an additive effect. Furthermore, carriers of one or both risk alleles of *PPARD* and *PGC-1A* benefited more from the intervention (acarbose) than did noncarriers.

In women, the simultaneous presence of the two risk genotypes (the Pro12Pro genotype of *PPARG2* [rs1801282] and the C allele of rs6902123 of *PPARD*) increased the risk for the conversion from IGT to diabetes by 3.93-fold (95% CI 1.79–8.63; P = 0.001) compared with women having the protective genotypes (the 12Ala allele of *PPARG2* and the TT genotype of rs6902123 of *PPARD*) (P = 0.006 for the interaction between the combined genotypes and sex). Adjustment for confounding factors increased the risk to 5.06-fold (2.20–11.60; $P < 0.001$). Other SNPs of *PPARD*, together with the Pro12Pro genotype of *PPARG2*, had no additive effect on the conversion to type 2 diabetes.

DISCUSSION

This is the first study demonstrating that an SNP rs6902123 of *PPARD* alone and in combination with the Pro12Ala polymorphism of *PPARG2* and two SNPs (rs6902123 and rs3734254) of *PPARD* in combination with the Gly482Ser substitution of *PGC-1A* predicted the conversion from IGT to type 2 diabetes.

PPAR-δ plays a prominent role in energy homeostasis. Overexpression of PPAR-δ in skeletal muscle (3) and adipocytes (2) markedly increase fat catabolism in both tissues. Given the important role of FFAs in the development of type 2 diabetes (16), the upregulation of the oxidative phosphorylation pathway by PPAR-δ is beneficial in alleviation of insulin resistance and adiposity (1). PPAR-δ agonists increase glucose transport (5) and consequently decrease insulin and glucose levels (2,3). Therefore, variants in *PPARD* could potentially modify glucose metabolism. Indeed, we recently reported that SNPs of *PPARD* significantly modulated glucose uptake in skeletal muscle, measured by positron emission tomography (10). In the present study, the C allele of rs6902123 increased the risk of diabetes by 2.5-fold. The association was observed only in women but not in men. This sex difference remains unexplained.

SNPs of *PPARD* also increased the effect of the

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Gly482Ser substitution of *PGC-1A* on the risk of type 2 diabetes. This is not surprising since PPAR-δ appears to have a strong interaction with PGC-1α (2,7). Similarly to PGC-1α (7,17), PPAR-δ is also induced by fasting (18) and physical exercise (19), and it promotes the formation of highly oxidative skeletal muscle fibers (19). Moreover, PPAR-δ itself can increase expression of PGC-1α and lead to mitochondrial biogenesis and enhanced oxidative phosphorylation (3). The Gly482Ser substitution of *PGC-1A* has been linked to increased risk of diabetes (15,20), but no association of SNPs of *PPARD* with diabetes has been reported. The novel finding of our study was that SNPs of *PPARD* together with the Gly482Ser polymorphism of *PGC-1A* increased the risk of diabetes by 2.2-fold. Interestingly, acarbose prevented the progression from IGT to diabetes in subjects carrying one or both risk alleles of *PPARD* and *PGC-1A* (Table 2).

What could be the mechanisms via which acarbose modifies the effect of SNPs of *PPARD* and *PGC-1A* on the risk of diabetes? Postprandial hyperglycemia and high FFAs contribute to the production of reactive oxygen species (16,21), which increase mitochondrial mass, mainly by overexpression of nuclear respiratory factors and PGC-1α (22). Both acarbose and PGC-1α have a protective effect on reactive oxygen species formation, either by alleviating postprandial hyperglycemia and high FFAs or by transcriptionally regulating the mitochondrial antioxidant defense system (23). Thus, acarbose may interact with SNPs of *PPARD* and *PGC-1A* and reduce oxidative stress and the development of diabetes.

Whether the Gly482Ser substitution of *PGC-1A* is a functional variant remains unclear (24). As determined with the Genomatix Program (availabe at http://www.genomatix.de), the binding sites for known transcription factors are not altered by this polymorphism. Similarly, SNPs of *PPARD* included in the present study did not cause alterations in transcription factor binding sites and did not affect RNA expression levels of PPAR-δ in adipose tissue samples. It is possible, however, that above-mentioned polymorphisms of *PGC-1A* and *PPARD* are in strong LD with functional variants in these genes or in other genes nearby.

The simultaneous presence of the C allele of rs6902123 of *PPARD* and the Pro12Pro genotype of *PPARG2* increased the risk of diabetes by 3.9-fold in the present study, suggesting a gene-to-gene interaction. Both PPAR-δ and PPAR-γ2 are activated by PGC-1α (2,7) and seem to interfere with adipocyte differentiation (25). However, the mechanisms explaining the interaction of *PPARD* and *PPARG2* on the risk of diabetes remain to be determined.

The effects of the *PPARD*, *PGC-1A*, and *PPARG2* polymorphisms on the risk of diabetes in the present study might be overestimated because of multiple comparisons causing type I error. The threshold of statistical significance after the Bonferroni correction (one phenotype: conversion to diabetes and six polymorphisms analyzed) is $P = 0.008$. However, even after this adjustment, ORs for the conversion to diabetes were still mostly significant ($P = 0.006–0.024$, Table 2; $P = 0.001$ for the risk alleles of *PPARD* and *PPARG2*).

In summary, we have shown for the first time that SNPs of *PPARD* together with the Gly482Ser polymorphism of *PGC-1A* and the Pro12Ala genotype of *PPARG2* are associated with the risk of type 2 diabetes. Moreover, we have demonstrated that the treatment with acarbose was able to reduce the risk of diabetes in carriers of the risk genotypes in *PPARD* and *PGC-1A*.

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