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Genetic variants near the *IRS1* gene, physical activity and type 2 diabetes in US men and women

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To the Editor

Insulin receptor substrate 1 (IRS1) plays a key role in the insulin-stimulated signal transduction pathway [1]. Recently, a genome-wide association study showed that a variant (rs2943641) near the *IRS1* gene was associated with insulin resistance, hyperinsulinaemia and the risk of type 2 diabetes [2].

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In this study, we comprehensively examined the associations of the variants near the *IRS1* gene with type 2 diabetes risk in two nested case–control studies from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Because physical activity may modify the genetic effects on diabetes [3] and enhance insulin activation of IRS1-associated phosphatidylinositol 3-kinase activity [4], we further examined the gene–physical activity interactions in relation to the risk of diabetes.

Type 2 diabetes cases were identified by self-report methods that were confirmed with a validated supplementary questionnaire. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston. General information was derived from the baseline questionnaire. Physical activity was expressed as metabolic equivalent task (MET) h of moderate to vigorous exercise per week in men, and as h/week in women because MET was not measured at baseline.

We used genotyping data from a genome-wide scan. We examined associations with type 2 diabetes for the single-nucleotide polymorphisms (SNPs) near the reported SNP rs2943641 [2] (electronic supplementary material [ESM] Fig. 1). We used logistic regression to estimate ORs after adjustment for potential risk factors. An additive genetic model was applied in the first instance. Tests of interaction between SNPs and physical activity were assessed by including the cross-product of the tested variables and the main effects in the model. All SNPs fitted Hardy–Weinberg equilibrium. The SAS statistical package was used (SAS, version 9.0 for UNIX; SAS Institute, Cary, NC, USA). The meta-analysis was carried out by using Mix 1.7 software [5].

Patients with type 2 diabetes had a significantly higher BMI, engaged in less physical activity and were more likely to smoke and have a family history of diabetes than control participants, among both men (HPFS) and women (NHS) (ESM Table 1).

The nominally associated SNPs fell into two major linkage disequilibrium (LD) blocks. In one block, the reported SNP, rs2943641, was significantly associated with type 2 diabetes (per T allele, OR 0.88, 95% CI 0.80–0.97; p=0.008) in the combined analysis. Subjects with the T allele had 15% and 9% decreased risk for men (HPFS) and women (NHS), respectively (Table 1).

In another LD block, SNP rs1522813 showed the strongest association (ESM Figs. 1, 2), each A allele being associated with an 18% increased risk of diabetes (95% CI 1.06–1.30; p=0.002; Table 1). We further performed conditional analyses by simultaneously including SNPs from each LD block (the best-associated SNP rs1522813 and the reported SNP rs2943641); both SNPs remained significant in the conditional analyses (p=0.012 and 0.022, respectively). For the SNP rs1522813, each A allele was associated with an 11% increased risk of diabetes (95% CI 1.02–1.21); for the SNP rs2943641, each T allele was associated with a 9% decreased risk (95% CI 0.85–0.99). The population attributable risk of SNPs rs1522813 and rs2943641 was 9.28% and 6.58%, respectively. SNPs rs1522813 and rs2943641 showed weak LD in the study samples (r^2=0.02). The previously reported missense polymorphism Gly972Arg (rs1801278) in *IRS1* [6] was not associated with type 2 diabetes.

We further examined the associations of the two SNPs with diabetes risk stratified by physical activity. We observed a significant interaction (p=0.017; Fig. 1) between physical activity and rs1522813 in women (NHS). Among women with low levels of physical activity (low vs high levels, by median values), carriers of the A allele had a 39% increased risk of type 2 diabetes (p=0.007); among women with high levels of physical activity, carriers of the A allele had a 4% increased risk of diabetes (p=0.78). The test for interaction between rs1522813 and physical activity was not statistically significant in men (HPFS) (p=0.26). Physical activity did not interact with rs2943641 in either sex. In order to replicate our results, we also examined the associations between the two SNPs and the risk of type 2 diabetes in the Diabetes Genetics Replication and Meta-analysis Consortium (DIAGRAM). The ORs (95% CI) were 1.09 (1.04–1.13) for SNP rs2943641 and 1.01 (0.96–1.06) for rs1522813. In DIAGRAM, the associations for rs1522813 showed significant between-study heterogeneity. This may reflect the greater diversity in the DIAGRAM study samples, which were from a wide range of geographical regions (and therefore had more dissimilar LD structure). In the present study, with more homogeneous populations, SNP rs1522813 showed consistently significant associations with comparable effect size in two independent cohorts. The potential influence of environmental factors may also contribute to the difference.

We have demonstrated the associations of several previously reported genetic variants with the risk of type 2 diabetes in our cohorts [7]. In the present study, our data indicate that multiple variants near the *IRS1* gene may independently affect the risk of diabetes. SNP rs1522813 was associated with diabetes risk even after conditioning for the reported SNP, rs2943641. Our data support the notion that allelic heterogeneity may exist in the genetic architecture of type 2 diabetes, in line with the observations for other metabolic traits, such as the independent associations of multiple SNPs in the *MC4R* locus with obesity [8]. In addition, we found that SNP rs1522813 interacted with physical activity in relation to type 2 diabetes risk in women but not in men. This may be partly attributable to a higher level of physical activity in men than in women (mean physical activity in men and women in 1986 was 21.1 and 14.2 MET h/week, respectively; p<0.001). Because of the replication nature of the study, we did not control for multiple testing, but our data are consistent with a previous genome-wide association study [2] and in line with evidence from experimental studies [4].

In summary, we confirmed that polymorphisms near *IRS1* were significantly associated with the risk of type 2 diabetes, and we identified a new SNP independently associated with the disease. In addition, we report that physical activity might modify the association in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HPFS	Health Professionals Follow-up Study
IRS1	Insulin receptor substrate 1
LD	Linkage disequilibrium
MET	Metabolic equivalent task
NHS	Nurses' Health Study
SNP	Single nucleotide polymorphism

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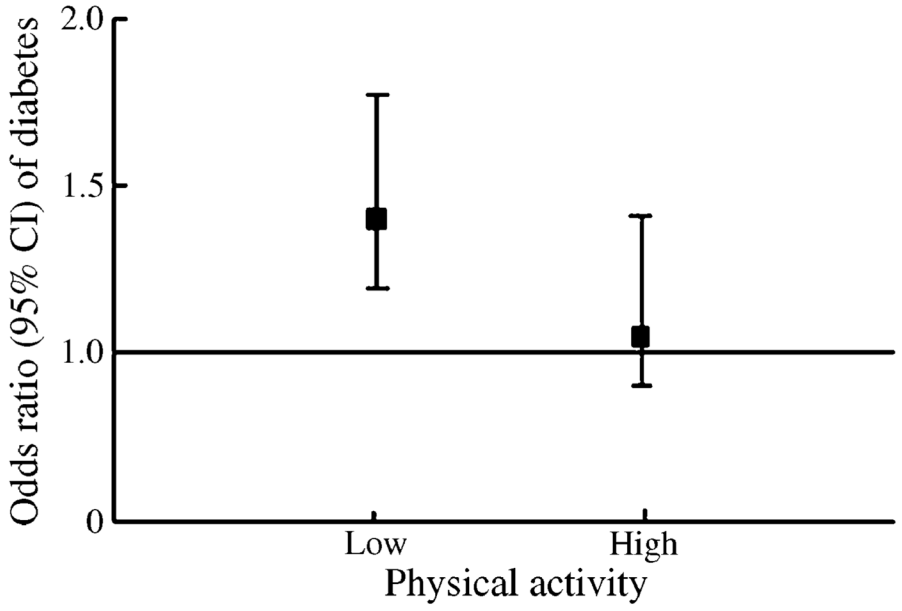

Fig. 1.

Interaction between physical activity and SNP rs1522813 on type 2 diabetes risk in women. Physical activity was classified into two groups according to the median value in controls (cutoff point 3.0 h/week). The stratified analyses of rs1522813 (carries of A allele comparison with GG genotypes) with type 2 diabetes risk according to physical activity were adjusted for age, BMI (five categories), family history of diabetes (yes, no), smoking (never, past, current), alcohol (five categories), menopausal status (pre- or post-menopausal [never, past or current hormone use]; women only), and quintiles of energy-adjusted polyunsaturated fatty acid:saturated fatty acid ratio, and intakes of *trans* fat and cereal fibre. *p* value for interaction=0.017

Table 1

SNPs rs1522813 and rs2943641 and type 2 diabetes in NHS and HPFS

e	NHS (women)						HPFS (men)						Meta-analysis	
	Cases (*n*=1,467)	Controls (*n*=1,754)	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value	Cases (*n*=1,124)	Controls (*n*=1,298)	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value	OR (95% CI)	*p* value
	784 (53.4)	1,003 (57.2)	1.00	–	1.00	–	550 (48.9)	691 (53.2)	1.00	–	1.00	–	–	–
	581 (39.6)	630 (35.9)	1.18 (1.02–1.37)	0.03	1.25 (1.03–1.51)	0.02	470 (41.8)	510 (39.3)	1.16 (0.98–1.37)	0.09	1.21 (1.00–1.46)	0.06	1.23 (1.07–1.41)	0.003
	102 (7.0)	121 (6.9)	1.08 (0.82–1.43)	0.60	1.21 (0.84–1.74)	0.30	104 (9.3)	97 (7.5)	1.35 (1.00–1.82)	0.05	1.38 (0.98–1.94)	0.07	1.29 (1.01–1.66)	0.042
	–		1.10 (0.99–1.23)	0.09	1.17 (1.01–1.35)	0.03	–	–	1.16 (1.02–1.31)	0.02	1.19 (1.03–1.37)	0.019	1.18 (1.06–1.30)	0.002
	641 (43.7)	722 (41.2)	1.00	–	1.00	–	510 (45.4)	539 (41.5)	1.00	–	1.00	–	–	–
	636 (43.4)	798 (45.5)	0.90 (0.77–1.04)	0.16	0.91 (0.75–1.11)	0.36	489 (43.5)	570 (43.9)	0.91 (0.76–1.08)	0.26	0.92 (0.76–1.12)	0.41	0.92 (0.80–1.05)	0.218
	190 (13.0)	234 (13.3)	0.91 (0.74–1.14)	0.42	0.83 (0.62–1.11)	0.21	125 (11.1)	189 (14.6)	0.70 (0.54–0.90)	0.006	0.67 (0.50–0.90)	0.008	0.75 (0.61–0.92)	0.006
	–		0.94 (0.85–1.04)	0.23	0.91 (0.80–1.04)	0.18	–	–	0.86 (0.76–0.96)	0.009	0.85 (0.74–0.97)	0.016	0.88 (0.80–0.97)	0.008

categories), family history of diabetes (yes, no), smoking (never, past or current), alcohol (five categories), menopausal status (pre- or post-menopausal [never, past or current quintiles of physical activity (MET h/week for men in HPFS, h/week for women in NHS) and quintiles of energy-adjusted polyunsaturated fatty acid:saturated fatty acid ratio, real fibre