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Physical activity modifies the effect of SNPs in the *SLC2A2* (GLUT2) and *ABCC8* (SUR1) genes on the risk of developing type 2 diabetes

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sulphonylurea receptor-1; glucose transporter-2; impaired glucose tolerance; exercise; single nucleotide polymorphism

GENETIC FACTORS AND LIFESTYLE interact in the development of type 2 diabetes. Physical activity, favorable dietary changes, and weight reduction were essential components of a success-

ful lifestyle intervention in two large randomized controlled trials on the prevention of type 2 diabetes in high-risk individuals with impaired glucose tolerance (IGT), including the Finnish Diabetes Prevention Study (DPS) (44) and the Diabetes Prevention Program (DPP) (22). In the DPS, increased physical activity was associated with a decreased risk of type 2 diabetes independently of changes in diet and body weight. The individuals who increased their physical activity most (i.e., were in the upper third of the change) were 66% less likely to develop type 2 diabetes than those in the lower third (24).

Two major pathogenetic factors leading to type 2 diabetes are insulin resistance and impaired insulin secretion (7). Thus the reduction in the risk of type 2 diabetes with physical activity may occur by an improvement in insulin sensitivity, β -cell function, or both. Numerous exercise-training studies have demonstrated that physical activity increases insulin sensitivity (18). The effect of physical activity on β -cell function is less clear, but some studies suggest that increased physical activity may improve early insulin secretion independently of insulin resistance (5, 11).

Glucose transporter-2 (GLUT2), encoded by the *SLC2A2* gene, is a facilitative glucose transporter that affects insulin secretion by regulating the entry of glucose into the pancreatic β -cell (6). The sulfonylurea-1 receptor (SUR1), encoded by the *ABCC8* gene, and K^+ inward rectifier (Kir6.2), encoded by the *KCNJ11* gene, are subunits of the pancreatic ATP-sensitive potassium (K_{ATP}) channels that regulate insulin secretion by coupling β -cell glucose metabolism to membrane potential. The activity of the K_{ATP} channels is inhibited by ATP, and, as the ATP concentration in the β -cells increases because of increased glucose metabolism, the β -cell membrane becomes depolarized, thereby triggering insulin exocytosis (41).

Single nucleotide polymorphisms (SNPs) in *SLC2A2* and *ABCC8*, but not the E23K polymorphism in *KCNJ11*, were associated with the conversion from IGT to type 2 diabetes in the DPS (28, 29). Recently, the association of the T110I polymorphism in *SLC2A2* with the risk of type 2 diabetes among Finnish subjects was replicated (50). The results of

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other case control studies with respect to SNPs in *SLC2A2* and *ABCC8* and risk of type 2 diabetes have, however, been inconsistent (1, 2, 13, 15, 32, 34, 36, 39, 40, 43, 47), whereas a meta-analysis confirmed the association of the K allele of the E23K polymorphism in *KCNJ11* with an increased risk of type 2 diabetes among Caucasians (47). The prospective DPP, however, unexpectedly found a lower risk of conversion from IGT to type 2 diabetes in the carriers of the K allele (14). The role of the E23K polymorphism of *KCNJ11* in the progression from IGT to type 2 diabetes thus remains unclear.

In the DPS, the lifestyle intervention decreased the risk of developing type 2 diabetes associated with the SNPs in *SLC2A2* and *ABCC8* independently of weight loss, indicating a strong gene-environment interaction (28, 29). In the present study, we report significant interactions of SNPs in *SLC2A2* and *ABCC8*, but not of the E23K polymorphism in *KCNJ11*, with moderate-to-vigorous physical activity on the conversion from IGT to type 2 diabetes in the DPS.

METHODS

Study design and population. The present study is a post hoc analysis of the Finnish DPS, a multicenter randomized controlled trial on the effects of lifestyle modification, including an increase in physical activity, favorable dietary changes, and weight reduction, on the prevention of type 2 diabetes in high-risk individuals. The design of the DPS has been described in detail elsewhere (12, 31).

In brief, altogether, 522 middle-aged (mean age 55 yr) overweight [mean body mass index (BMI) 31 kg/m²] Finnish individuals with IGT were randomly assigned to either an intervention group ($n = 265$) or a control group ($n = 257$). IGT was defined as a plasma glucose concentration of 7.8–11.0 mmol/l 2 h after the oral administration of 75 g of glucose in those whose plasma glucose concentration after an overnight fast was <7.8 mmol/l (49). The study protocol was approved by the ethics committee of the National Public Health Institute in Helsinki, Finland, and all participants gave written informed consent.

The intervention group received individualized counseling aimed at reducing body weight and the intake of total and saturated fat and increasing the intake of dietary fiber and physical activity. Endurance exercise, including walking, jogging, swimming, aerobic ball games, and skiing, was encouraged. Supervised, progressive, individually tailored circuit-type resistance training beginning 4–6 mo after the randomization was offered to the intervention group for free in three of five centers. Lifestyle physical activity was also promoted. The control group received general oral and written information about diet and exercise at baseline, but no specific individualized programs were offered to them (31).

Of the 522 participants, 507 had DNA available for genotyping of SNPs in *SLC2A2*, *ABCC8*, and *KCNJ11*. Of these 507 individuals, 482 completed a questionnaire quantifying the previous 12 mo of physical activity at baseline and at least once during the follow-up. Of these 482 subjects, 479 also gave sufficient information on changes in diet and body weight during the trial and are included in the present analyses.

Genotyping. The SNPs in *SLC2A2* [rs5393, rs5394, rs5400 (T110I), and rs5404 (T198T)], in *ABCC8* [rs3758947, rs2188966, rs3758953, and rs1799859 (R1273R)], and *KCNJ11* [rs5219 (E23K)] were genotyped using TaqMan Allelic Discrimination Assays (Applied Biosystems, Foster City, CA) as previously described (28, 29). Genotyping was repeated in 6.0% of samples, and it gave 100% identical results.

Assessment of physical activity and diet. At baseline and at each annual visit, all subjects completed a physical activity questionnaire. Physical activity was assessed using the validated Kuopio Ischemic

Heart Disease Risk Factor Study (KIHD) 12-mo Leisure Time Physical Activity Questionnaire (27). The questionnaire provides detailed quantitative information on the duration, frequency, and mean intensity of the most common lifestyle and structured physical activity as recalled over the previous 12 mo (37). Moderate-to-vigorous physical activity was defined as ≥ 3.5 METs and low-intensity physical activity as <3.5 METs (1 MET is defined as metabolic expenditure at rest, corresponding to an oxygen uptake of 3.5 ml O₂/kg). Common moderate-to-vigorous physical activities included moderate-to-high intensity walking, bicycling, swimming, resistance training, skiing, jogging, ball games, and lifestyle activities, such as chopping wood or clearing brush. Common low-intensity activities included low-intensity walking or bicycling, yard work and gardening, and picking berries and mushrooms (24). The assessment of diet by the 3-day food diary has been described elsewhere (31). The average intakes of energy, total fat, saturated fat, and dietary fiber were calculated at baseline and 1-, 2-, and 3-yr visits of the intervention period using a dietary analysis program developed at the National Public Health Institute, Helsinki, Finland (30).

Anthropometric measurements. Body weight and height were measured annually, and BMI was calculated as weight divided by height squared (kg/m²). Waist circumference was measured midway between the lowest rib and iliac crest.

Measurement of glucose homeostasis. All subjects underwent an oral glucose tolerance test (OGTT) at baseline and each annual visit, as described elsewhere (12, 44). Serum insulin concentration was measured by a radioimmunoassay (Pharmacia, Uppsala, Sweden).

Definition of type 2 diabetes. Diabetes was defined according to the 1985 criteria of the World Health Organization (49) as either a fasting plasma glucose concentration ≥ 7.8 mmol/l or a plasma glucose concentration ≥ 11.1 mmol/l 2 h after a 75-g oral glucose challenge. Participants were asked to fast and to refrain from strenuous exercise for 12 h before the OGTT. If the diagnosis of diabetes was not confirmed by a second OGTT, the subject continued in the study (12, 44).

A total of 86 cases of incident diabetes were diagnosed when the original trial ended after an average follow-up of 3.2 yr (44). To increase statistical power for detecting interactions between SNPs and physical activity, we extended the follow-up by 1 yr (average 4.1 yr, range 1–6 yr) (24, 30), during which time 116 participants, 104 of the 479 subjects whose DNA was available for genotyping and who provided sufficient information on physical activity, diet, and body weight, developed type 2 diabetes.

Statistical analyses. Because the number of subjects who were homozygous for the rare allele was low ($n < 20$) for many of the SNPs that were investigated (rs5393, rs5394, rs5400, rs5404, rs1799859), we preferred the dominant model in our analyses. Linkage disequilibria between the SNPs were estimated using Haploview, version 3.32 (available online at <http://www.broad.mit.edu/mpg/haploview/>). Haplotype frequencies were estimated using the expectation-maximization algorithm (8).

Differences among the genotypes at baseline were evaluated by the univariate ANOVA, general linear model, with adjustments for age, gender, and BMI (for glucose and insulin levels only). Appropriate transformations were used to normalize the distributions when required. When the variance and normality assumptions were not met, the Mann-Whitney U-test was used. The chi square test was applied to test differences in categorical variables.

The changes in total, moderate-to-vigorous, and low-intensity physical activity during the trial were calculated by subtracting the baseline physical activity values (in h/wk) from averaged annual physical activity values during the 4.1-yr follow-up (24). Changes in dietary, biochemical, and anthropometric measures during the trial were similarly calculated. However, the dietary intakes were available from the first 3 yr of the follow-up only (30). The intakes of total and saturated fat and fiber were adjusted by daily energy intake with linear regression analysis before further statistical analyses (25).

The association of the SNPs in *SLC2A2*, *ABCC8*, and *KCNJ11* with the conversion to type 2 diabetes according to changes in leisure time physical activity in the combined intervention and control groups was assessed using Cox proportional hazards models with adjustments for baseline values and changes in body weight and dietary intakes of energy and energy-adjusted saturated fat and fiber. Univariate ANOVA (general linear model) was used to assess the effect of the SNPs on the changes in insulin and glucose levels after stratification by the thirds of change in moderate-to-vigorous physical activity. Analyses were performed with SPSS 11.5 for Windows (Chicago, IL). Statistical significance was defined as $P < 0.05$.

RESULTS

The four SNPs in *SLC2A2* were located in the promoter (5393 and rs5394), in exon 3 [rs5400 (T110I)], and in exon 5 [rs5404 (T198T)] of *SLC2A2* (Fig. 1). The four SNPs in *ABCC8* were located in the promoter (rs3758947, rs2188966, and rs3758953) and in exon 31 [rs1799859 (R1273R)] of *ABCC8* (Fig. 1). The rs5219 (E23K) polymorphism was located in exon 1 of *KCNJ11*. The genotype frequencies of rs5393, rs5394, rs5400, rs5404, rs3758947, rs3758953, and rs1799859 were in Hardy-Weinberg equilibrium ($P > 0.05$). The allelic distribution of rs2188966 differed from that expected under Hardy-Weinberg equilibrium ($P < 0.001$). Therefore, we excluded this SNP from all further statistical analyses, although no genotyping errors were found when resequencing 6% of samples.

With an $r^2 \geq 0.8$ and a minor allele frequency (MAF) $\geq 5\%$, the rs5394, rs5400, and rs5404 polymorphisms tag 61% of the allelic variance of the *SLC2A2* gene in the HapMap CEU (Utah residents with ancestry from northern and western Europe, NCBI build 35). The linkage disequilibrium (LD) data for rs5393 were not available in the HapMap. However, rs5393 was in strong LD with rs5394, rs5400, and rs5404 ($r^2 > 0.8$ with each) (Table 1, top).

Of the four SNPs in *ABCC8*, three were located in the promoter region of the gene (rs3758947, rs2188966, and rs3758953), which was thus well covered. However, the four SNPs covered only 5% of the entire allelic variance of the *ABCC8* gene with an $r^2 \geq 0.8$ and MAF $\geq 5\%$ in the HapMap CEU. The SNPs rs3758947, rs2188966, and rs3758953 were in rather strong LD ($r^2 > 0.3$) (Table 1). The rs1799859 was not in LD with any of the other three SNPs ($r^2 < 0.02$) (Table 1).

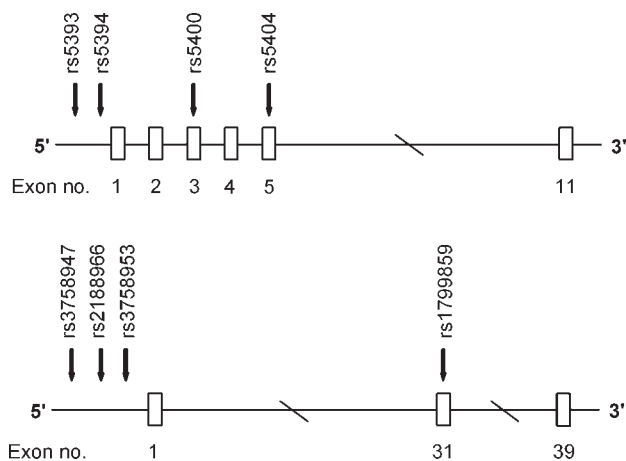


Fig. 1. Schematic positions of the single nucleotide polymorphisms in *SLC2A2* (top) and *ABCC8* (bottom). Exons are marked with white boxes.

Table 1. Pairwise linkage disequilibriums (r^2) between the SNPs in *SLC2A* and *ABCC8*

	SNP	rs5393	rs5394	rs5400
<i>SLC2A</i>	rs5394	0.816	—	—
	rs5400	0.825	0.673	—
	rs5404	0.815	0.955	0.689
	SNP	rs5393	rs2188966	rs3758953
<i>ABCC8</i>	rs2188966	0.484	—	—
	rs3758953	0.320	0.660	—
	rs1799859	0.013	0.005	0.005

Top: *SLC2A*. Bottom: *ABCC8*. Single nucleotide polymorphisms (SNPs) are in boldface.

The minor allele frequencies were 11% for the C allele of rs5393, 9% for the T allele of rs5394, 13% for the T (110I) allele of rs5400, 10% for the A allele of rs5404, 25% for the A allele of rs3758947, 40% for the A allele of rs2188966, 49% for the A allele of rs3758953, 17% for the A allele of rs1799859, and 49% for the C (23K) allele of rs5219. The four SNPs in *SLC2A2* formed seven haplotypes: ACCG, CTTA, ACTG, CCTG, CCTA, CTTG, and ACTA (28).

Baseline. The baseline characteristics of the subjects, categorized by the change in moderate-to-vigorous physical activity during the follow-up, are described in Table 2. In the 479 subjects with data on changes in physical activity, diet, and body weight, the carriers of the AA genotype of rs3758953 in *ABCC8* had a higher 2-h insulin level (624 ± 410 vs. 550 ± 386 pmol/l, $P = 0.002$) and a higher 2-h glucose level (9.1 ± 1.4 vs. 8.8 ± 1.5 mmol/l, $P = 0.024$) in an OGTT at baseline than the carriers of the G allele. The level of low-intensity physical activity was higher in the carriers of the CC genotype of rs5400 in *SLC2A2* at baseline than in the carriers of the T allele (4.7 ± 5.1 vs. 4.0 ± 5.0 h/wk, $P = 0.020$). No other differences in baseline characteristics (gender, age, weight, BMI, waist circumference, glucose or insulin levels, diet, or physical activity) were found among the genotypes.

Risk of type 2 diabetes and worsening glycemia. The interaction between rs5393, rs5394, or rs5404 of *SLC2A2* and the change in moderate-to-vigorous activity, categorized by the tertiles, was statistically significant, adjusting for the study group, age, gender, baseline moderate-to-vigorous physical activity, and baseline levels and changes in diet and weight ($P = 0.027$, $P = 0.022$, or $P = 0.022$, respectively) (Table 3). The carriers of the common homozygous genotypes of rs5393, rs5394, or rs5404 who were in the upper third of the change in moderate-to-vigorous physical activity were less likely to develop type 2 diabetes than those in the middle and lower thirds, whereas no statistical difference between the thirds was seen among the carriers of the rare allele (Table 3). The interaction of the CTTA haplotype formed of the rare alleles of rs5393, rs5394, rs5400, and rs5404 with the change in moderate-to-vigorous physical activity was also significant ($P = 0.021$). Those who did not carry the CTTA haplotype had a decreased risk of type 2 diabetes in the upper third of the change in moderate-to-vigorous physical activity compared with the middle and lower thirds, whereas no statistical difference between the thirds was seen among the carriers of the CTTA haplotype (Table 3). No interaction between the polymorphisms or haplotypes in *SLC2A2* and changes in total or low-intensity physical activity was found (data not shown).

Table 2. Baseline characteristics of participants according to thirds of the change in moderate-to-vigorous physical activity in the Finnish Diabetes Prevention Study

Median (Range) of Change in PA*	-1.5 h/wk (-13.5 to -0.1)	0.5 h/wk (-0.1 to 1.3)	2.6 h/wk (1.3 to 14.4)
Sex, male/female	53/105	50/110	56/105
Age, yr	56.1±7.0	53.9±7.1	56.5±6.6
Weight, kg	85.7±13.7	88.1±15.3	84.7±12.8
Body mass index, kg/m ²	31.2±4.1	31.8±5.1	30.7±3.9
Waist circumference, cm	100.8±10.7	102.2±11.7	100.5±10.1
Fasting plasma glucose, mmol/l	6.1±0.8	6.2±0.8	6.2±0.6
2-h plasma glucose, mmol/l	8.8±1.3	8.9±1.5	8.9±1.6
Fasting serum insulin, mU/l	13.8±6.5	15.5±7.6	14.7±7.4
2-h serum insulin, mU/l	86.9±62.6	99.0±56.8	98.6±75.7
Energy intake, kcal	1,753±506	1,794±551	1,766±528
Total fat intake, energy adjusted, g	72±13	73±13	72±13
Saturated fat intake, energy adjusted, g	32.9±8.5	32.8±8.0	32.7±8.3
Fiber intake, energy adjusted, g	20.6±7.2	19.6±6.7	19.6±5.7
Total physical activity, † h/wk	7.9 (4.7–11.1)	4.2 (2.1–7.6)	5.7 (3.5–9.1)
Moderate-to-vigorous physical activity, h/wk	4.4 (2.6–6.5)	0.8 (0.1–2.2)	1.2 (0.3–2.5)
Low-intensity physical activity, h/wk	2.7 (1.7–5.9)	2.7 (1.2–5.6)	3.5 (1.5–7.2)

Data are means ± SD or median (interquartile range). *PA denotes moderate-to-vigorous physical activity. †Total physical activity is the sum of moderate-to-vigorous and low-intensity physical activity.

The GG homozygotes for rs3758947 in *ABCC8* who were in the lower third of the change in moderate-to-vigorous physical activity had a significantly increased risk of developing type 2 diabetes compared with those in the upper third, whereas no

statistical difference between the thirds was seen among the carriers of the rare allele (Table 4). No interaction between the polymorphisms in *ABCC8* and changes in total or low-intensity physical activity was found (data not shown).

Table 3. Association of SNPs in *SLC2A2* with the risk of developing type 2 diabetes according to thirds of the change in moderate-to-vigorous physical activity

	Change in Moderate-to-Vigorous Physical Activity,* h/wk			P for Difference	P for Interaction†
	-1.5 (-13.5 to -0.1)	0.5 (-0.1 to 1.3)	2.6 (1.3 to 14.4)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>SLC2A2</i> rs5393 (A/C)					
AA (n = 374)	2.67 (1.25–5.70)	2.23 (1.13–4.37)	1	0.010	
C allele (n = 105)	0.26 (0.05–1.27)	0.43 (0.12–1.53)	1	0.082	0.027
Conversions (%), AA vs. C allele	36 (30) vs. 7 (19)	35 (29) vs. 8 (22)	12 (9) vs. 6 (19)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>SLC2A2</i> rs5394 (C/T)					
CC (n = 387)	2.67 (1.25–5.72)	2.25 (1.14–4.41)	1	0.010	
T allele (n = 92)	0.21 (0.04–1.19)	0.37 (0.10–1.42)	1	0.064	0.022
Conversions (%), CC vs. T allele	37 (29) vs. 6 (20)	36 (28) vs. 7 (21)	12 (9) vs. 6 (21)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>SLC2A2</i> rs5400 (C/T) (T110I)					
CC (n = 356)	2.42 (1.11–5.29)	2.37 (1.17–4.78)	1	0.023	
T allele (n = 123)	0.67 (0.18–2.58)	0.51 (0.17–1.53)	1	0.473	0.057
Conversions (%), CC vs. T allele	33 (29) vs. 10 (23)	34 (29) vs. 9 (21)	11 (9) vs. 7 (19)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>SLC2A2</i> rs5404 (G/A) (T198T)					
GG (n = 387)	2.62 (1.23–5.60)	2.27 (1.15–4.45)	1	0.011	
A allele (n = 92)	0.22 (0.04–1.23)	0.37 (0.10–1.40)	1	0.068	0.022
Conversions (%), GG vs. A allele	37 (29) vs. 6 (21)	36 (29) vs. 7 (21)	12 (9) vs. 6 (21)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>SLC2A2</i> CTTA haplotype‡					
Noncarriers (n = 388)	2.66 (1.25–5.68)	2.23 (1.14–4.38)	1	0.010	
CTTA carriers (n = 91)	0.21 (0.04–1.19)	0.37 (0.10–1.42)	1	0.062	0.021
Conversions (%), CTTA vs. Non	37(29) vs. 6(21)	36(28) vs. 7(21)	12(9) vs. 6(21)		

Model adjusted for age, gender, group, baseline value of moderate-to-vigorous physical activity, and baseline values and changes in body weight and in intakes of energy and energy-adjusted saturated fat and fiber. CI, confidence interval. *The median (range) of each tertile of change in moderate-to-vigorous physical activity is shown. †Adjusted interaction between moderate-to-vigorous physical activity (3 groups) and the polymorphism (2 groups) or the haplotype (2 groups) on the risk of developing type 2 diabetes. ‡Haplotype was constructed of the rare alleles of rs5393, rs5394, rs5400, and rs5404, respectively.

Although the interaction was not significant, the common homozygous (E/E) genotype carriers of the E23K polymorphism of the *KCNJ11* gene had a significantly higher risk of developing type 2 diabetes in the lower and middle thirds of change in moderate-to-vigorous physical activity, whereas no difference between the thirds was seen among the carriers of the rare allele (Table 4).

The SNPs of *SLC2A2* and the CTTA haplotype had a significant interaction with changes in moderate-to-vigorous physical activity on changes in 2-h glucose (Table 5). While there was a reduction in 2-h glucose levels in all thirds of the change in moderate-to-vigorous physical activity in the carriers of the common homozygous genotype of rs5393, rs5394, rs5400, or rs5404, or in the noncarriers of the CTTA haplotype, 2-h glucose decreased markedly only in the middle third of the carriers of the rare allele or the CTTA haplotype (Table 5).

Moreover, each SNP of *ABCC8* had a significant interaction with the changes in moderate-to-vigorous physical activity on the changes in fasting (data not shown) and 2-h plasma glucose concentrations (Table 6). Fasting and 2-h glucose levels increased in the lower third of the change in moderate-to-vigorous physical activity and decreased in the upper third in the carriers of the common genotypes of rs3758947 and rs3758953, and in the carriers of the rare allele of rs1799859 (R1273R), but such differences were not found across the thirds in the carriers of the other genotypes (Table 6).

The SNPs of *SLC2A2* and *ABCC8* were associated with the risk of type 2 diabetes during 3 yr of follow-up in the DPS (28, 29). For the present analyses, the follow-up time was increased until the end of the randomized trial period, i.e., to an average of 4.1 yr, which also increased statistical power to detect interactions between physical activity and SNPs in *SLC2A2*,

ABCC8, and *KCNJ11*. Nevertheless, our results were also statistically significant on the basis of the first 3 yr of follow-up (data not shown). Adjustment for the study group (intervention vs. control) did not attenuate the interaction between the *SLC2A2* and *ABCC8* genes and the change in moderate-to-vigorous physical activity during the follow-up.

DISCUSSION

Changes in moderate-to-vigorous physical activity modified the effect of SNPs of *SLC2A2* and *ABCC8* on glucose levels and the conversion from IGT to type 2 diabetes. Increased moderate-to-vigorous physical activity reduced the risk of type 2 diabetes associated with specific genotypes, independently of changes in diet and body weight.

The interaction of *SLC2A2* and *ABCC8* with physical activity on the risk of type 2 diabetes is a novel finding. *SLC2A2* and *ABCC8* have an essential role in glucose-induced insulin secretion (6, 41). Although there is still much debate over the relative contribution of insulin resistance and impaired β -cell function in the development of type 2 diabetes, reductions in both insulin sensitivity and β -cell function have occurred already by the time hyperglycemia develops (7). The transition from normal glucose tolerance through IGT to diabetes is characterized by a progressive decline of β -cell function (20). The interaction of SNPs of genes regulating insulin secretion with physical activity could thus be explained by a better preservation of β -cell function in the carriers of exercise-responsive genotypes.

Type 2 diabetes can be prevented or delayed by lifestyle modification, including increased physical activity, beneficial dietary changes, and weight reduction (22, 44). However, only

Table 4. Association of SNPs in *ABCC8* and *KCNJ11* with the risk of developing type 2 diabetes according to thirds of the change in moderate-to-vigorous physical activity

	Change in Moderate-to-Vigorous Physical Activity,* h/wk			P for Difference	P for Interaction†
	-1.5 (-13.5 to -0.1)	0.5 (-0.1 to 1.3)	2.6 (1.3 to 14.4)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>ABCC8</i> rs3758947 (G/A)					
GG (n = 272)	3.65 (1.60–8.33)	1.42 (0.71–2.84)	1	0.003	
A allele (n = 207)	1.04 (0.31–3.46)	2.25 (0.76–6.68)	1	0.972	0.007
Conversions (%), GG vs. A allele	32 (38) vs. 11 (15)	25 (27) vs. 18 (27)	13 (14) vs. 5 (8)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>ABCC8</i> rs3758953 (A/G)					
AA (n = 123)	5.16 (1.51–17.6)	1.80 (0.67–4.85)	1	0.012	
G allele (n = 356)	1.32 (0.59–2.99)	1.72 (0.83–3.57)	1	0.548	0.128
Conversions (%), AA vs. G allele	18 (47) vs. 25 (21)	13 (30) vs. 30 (26)	7 (17) vs. 11 (9)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>ABCC8</i> rs1799859 (A/G) (R1273R)					
GG (n = 332)	5.60 (1.72–18.2)	2.40 (0.84–6.91)	1	<0.001	
A allele (n = 147)	0.85 (0.39–1.87)	1.61 (0.80–3.25)	1	0.814	0.111
Conversions (%), GG vs. A allele	20 (48) vs. 23 (20)	18 (32) vs. 25 (24)	5 (10) vs. 13 (12)		
<i>Relative risk of conversion to type 2 diabetes (95% CI)</i>					
<i>KCNJ11</i> rs5219 (T/C) (E23K)					
TT (n = 127)	9.81 (1.53–63.1)	5.99 (1.46–24.7)	1	0.006	
C allele (n = 352)	1.28 (0.64–2.57)	1.26 (0.65–2.46)	1	0.498	0.203
Conversions (%), TT vs. C allele	11 (30) vs. 32 (26)	14 (30) vs. 29 (26)	3 (7) vs. 15 (13)		

Model adjusted for age, gender, group, baseline value of moderate-to-vigorous physical activity, and baseline values and changes in body weight and in intakes of energy and energy-adjusted saturated fat and fiber. *The median (range) of each tertile of change in moderate-to-vigorous physical activity is shown. †Adjusted interaction between moderate-to-vigorous physical activity (3 groups) and the polymorphism (2 groups) on the risk of developing type 2 diabetes.

Table 5. Association of SNPs in *SLC2A2* with changes in plasma 2-h glucose concentration according to thirds of the change in moderate-to-vigorous physical activity

	Change in Moderate-to-Vigorous Physical Activity,* h/wk			P for Trend	P for Interaction†
	-1.5 (-13.5 to -0.1)	0.5 (-0.1 to 1.3)	2.6 (1.3 to 14.4)		
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>SLC2A2</i> rs5393 (A/C)					
AA (n = 373)	-0.17±0.17	-0.22±0.15	-0.46±0.15	0.222	
C allele (n = 104)	-0.80±0.29	-1.24±0.23	-0.01±0.27	0.077	0.013
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>SLC2A2</i> rs5394 (C/T)					
CC (n = 385)	-0.18±0.17	-0.24±0.15	-0.46±0.15	0.233	
T allele (n = 92)	-0.87±0.31	-1.19±0.24	-0.03±0.28	0.070	0.023
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>SLC2A2</i> rs5400 (C/T) (T110I)					
CC (n = 355)	-0.26±0.17	-0.18±0.16	-0.46±0.15	0.414	
T allele (n = 122)	-0.42±0.27	-1.22±0.21	-0.05±0.25	0.375	0.016
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>SLC2A2</i> rs5404 (G/A) (T198T)					
GG (n = 385)	-0.18±0.17	-0.23±0.15	-0.46±0.14	0.231	
A allele (n = 92)	-0.93±0.31	-1.17±0.24	0.01±0.28	0.048	0.016
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>SLC2A2</i> CTTA haplotype‡					
Noncarriers (n = 386)	-0.15±0.17	-0.26±0.15	-0.45±0.15	0.207	
CTTA carriers (n = 91)	-0.95±0.31	-1.14±0.25	0.01±0.28	0.043	0.022

The values are adjusted for the baseline 2-h glucose concentration, age, gender, group, baseline value of moderate-to-vigorous physical activity, and baseline values and changes in body weight and in intakes of energy and energy-adjusted saturated fat and fiber. SE, standard error. *The median (range) of each tertile of change in moderate-to-vigorous physical activity is shown. †Adjusted interaction between moderate-to-vigorous physical activity (3 groups) and the polymorphism (2 groups) or the haplotype (2 groups) on the changes in plasma 2-h glucose concentration. ‡Haplotype was constructed of the rare alleles of rs5393, rs5394, rs5400, and rs5404, respectively.

a few studies have investigated the effects of such lifestyle interventions on insulin sensitivity and insulin secretion in persons with IGT (21, 46). On the basis of the 4-yr follow-up study of the DPS with repeated frequently sampled intravenous glucose tolerance test (FSIGT), insulin sensitivity improved along with lifestyle changes, while insulin secretion remained virtually unchanged (46). Most other data also indicate that physical activity, diet, and weight loss primarily increase insulin sensitivity. Insulin resistance and the associated glycemc stress may exhaust β -cells and impair their function. Regular physical activity may diminish glycemc stress by improving insulin sensitivity of target tissues (18). While the mechanisms of improved β -cell function in response to lifestyle interventions are still largely unknown, several studies suggest that physical activity (5, 11), diet (19, 26), weight loss (45), or their combination (21) may directly improve the first-phase insulin secretion that is an indicator of the β -cell function.

The effect of physical activity on insulin secretion may depend on the degree of glucose tolerance. In the normoglycemic population of the HERITAGE Study, insulin secretion was reduced in response to a 20-wk endurance training program among individuals who were in the highest quartile of baseline glucose tolerance, measured as the glucose disappearance index, whereas those in the lowest quartile of glucose tolerance showed an increase in insulin secretion (5). Similarly, exercise training increased insulin secretion in patients with type 2 diabetes (11), whereas in healthy individuals, exercise induced a decrease in early insulin secretion that was matched

with an accompanying increase in insulin action (10, 33). These diverging adaptations to physical activity may reflect the hyperbolic relationship between β -cell function and both insulin resistance (3) and prevailing plasma glucose concentration (9). A reduction in plasma glucose will increase insulin secretion if it is on the descending part of the curve, i.e., in persons with a failing β -cell function, such as those with IGT (20). In glucose-tolerant individuals, a compensatory decrease in insulin secretion follows the improvement in insulin sensitivity (3).

Because there is evidence that SNPs in *SLC2A2* and *ABCC8* modify insulin secretion (2, 16, 17, 35, 48), a change in insulin secretion is the most likely explanation for their interaction with physical activity on the risk of type 2 diabetes. However, we found no interaction between the changes in physical activity and SNPs in *SLC2A2* and *ABCC8* on changes in fasting or 2-h insulin levels. Insulin levels are strongly regulated by insulin resistance and are not reliable indicators of early insulin secretion. Therefore, changes in β -cell function among people carrying different genotypes cannot be excluded, because 30-min insulin, the insulinogenic index, or other more precise measures of early insulin secretion were not available in our study.

GLUT2 and SUR1 are also expressed in other tissues that regulate glucose homeostasis. Therefore, it is also possible that the interaction of physical activity with GLUT2 and SUR1 is mediated by effects in extrapancreatic tissues. GLUT2 is expressed in hepatocytes and participates in liver glucose uptake and release (6). It is also expressed in intestinal and renal cells, where it is involved in intestinal glucose absorption and renal

Table 6. Association of SNPs in *ABCC8* and *KCNJ11* with changes in 2-h glucose concentration according to thirds of the change in moderate-to-vigorous physical activity

	Change in Moderate-to-Vigorous Physical Activity,* h/wk			P for Trend	P for Interaction†
	-1.5 (-13.5 to -0.1)	0.5 (-0.1 to 1.3)	2.6 (1.3 to 14.4)		
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>ABCC8</i> rs3758947 (G-2886A)					
GG (n = 270)	0.15±0.23	-0.50±0.18	-0.58±0.18	0.020	
A allele (n = 207)	-0.64±0.20	-0.36±0.20	-0.28±0.19	0.224	0.015
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>ABCC8</i> rs3758953 (A-1273G)					
AA (n = 123)	0.20±0.38	-0.53±0.28	-0.98±0.26	0.021	
G allele (n = 354)	-0.42±0.16	-0.34±0.15	-0.21±0.15	0.369	0.001
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>ABCC8</i> rs1799859 (A/G) (R1273R)					
A allele (n = 146)	0.83±0.33	-0.18±0.23	-0.49±0.26	0.004	
GG (n = 331)	-0.74±0.17	-0.46±0.16	-0.41±0.15	0.158	0.002
<i>Change in plasma 2-h glucose, mean ± SE, mmol/l</i>					
<i>KCNJ11</i> rs5219 (T/C) (E23K)					
TT (n = 126)	-0.15±0.35	-0.10±0.25	-0.33±0.26	0.702	
C allele (n = 351)	-0.28±0.18	-0.61±0.16	-0.45±0.15	0.502	0.435

The values are adjusted for the baseline 2-h glucose concentration, age, gender, group, baseline value of moderate-to-vigorous physical activity, and baseline values and changes in body weight and in intakes of energy and energy-adjusted saturated fat and fiber. *The median (range) of each tertile of change in moderate-to-vigorous physical activity is shown. †Adjusted interaction between moderate-to-vigorous physical activity (3 groups) and the polymorphism (2 groups) on the changes in plasma 2-h glucose concentration.

glucose reabsorption. SUR1 is abundant in K_{ATP} channels in many regions in the brain, particularly in the hypothalamus (42). The activation of K_{ATP} channels in the mediobasal hypothalamus has been shown to inhibit hepatic gluconeogenesis, suggesting that the effects of SUR1 are partly centrally mediated (38). Nonetheless, the mechanisms that mediate the interaction of SNPs of *SLC2A2* and *ABCC8* with physical activity on the risk of type 2 diabetes are still unclear. It is interesting to note that a genome-wide scan, based on the HERITAGE Family Study, demonstrated that a marker within *ABCC8* exhibited one of the most significant linkages to maximal oxygen uptake in the sedentary state (4).

SNPs of *ABCC8*, but not the E23K of *KCNJ11*, were associated with the risk of type 2 diabetes in the DPS and interacted with physical activity in the present study. However, although the interaction between the E23K polymorphism and the change in moderate-to-vigorous physical activity was not significant, those who did not carry the lysine allele of the E23K polymorphism seemed to be more responsive to changes in moderate-to-vigorous physical activity. Our study may have been underpowered to detect an interaction between the E23K polymorphism and physical activity. SNPs of *ABCC8* and *KCNJ11* are also in significant linkage disequilibrium, which makes it difficult to distinguish their separate contribution to the development of type 2 diabetes (13). Nevertheless, the larger DPP also did not detect an interaction between the E23K polymorphism and the lifestyle intervention on the conversion to type 2 diabetes (14).

The sample size of the DPS is rather small for interaction analyses. However, the randomized controlled trial with repeated measurement of both exposures and outcomes during the follow-up increases the power to study interactions. Although accurate assessment of habitual physical activity is problematic in epidemiological studies, the correlation be-

tween vigorous physical activity measured with the KIHD questionnaire and maximal oxygen consumption is quite strong ($r = 0.40$) (23). Moreover, the questionnaire has been found to be quite repeatable (27). In addition, the annual administration of the questionnaire and the use of averaged physical activity levels reduce the measurement variability.

The primary limitation of our study is that the DPS was designed to assess the combined effect of increased physical activity, dietary modification, and weight reduction on the risk of developing type 2 diabetes, and it did not include a separate exercise group. Therefore, we cannot completely rule out the effects of dietary changes or weight loss on our results, although the findings remained statistically significant after the adjustment for changes in diet and weight. We also genotyped a limited number of SNPs that only partially cover the genes investigated. The observed associations may also represent false-positive results rather than true biological effects. The interaction of several SNPs in *SLC2A2* and *ABCC8* with physical activity, however, supports the plausibility of the observed associations.

The understanding of the contribution of genetic factors to the individual differences in response to physical activity is important from a public health and clinical perspective, because it may help to identify individuals who are likely to achieve greater benefits from regular physical activity, and those for whom other interventions, such as dietary changes or drug treatment, might be more effective. In the future, gene expression studies can be designed to determine whether physical activity affects the functioning of *SLC2A2* and *ABCC8*. Ultimately, a specific randomized clinical trial would be required to provide a definitive answer on whether polymorphisms in *SLC2A2* and *ABCC8* modify the effects of moderate-to-vigorous physical activity in the prevention of type 2 diabetes.

In summary, changes in moderate-to-vigorous physical activity during 4 years modified the effect of SNPs in *SLC2A2* and *ABCC8* on glucose levels and the conversion from IGT to type 2 diabetes among individuals with IGT. The interaction of physical activity with genes regulating insulin secretion indirectly suggests that physical activity not only improves insulin sensitivity but may also preserve β -cell function.

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During production, Table 1 was formatted incorrectly. The table is shown correctly here.

Table 1. Pairwise linkage disequilibriums (r^2) between the SNPs in *SLC2A2* and *ABCC8*

<i>SLC2A2</i>	rs5393	rs5394	rs5400
rs5394	0.816	—	—
rs5400	0.825	0.673	—
rs5404	0.815	0.955	0.689
<i>ABCC8</i>	rs3758947	rs2188966	rs3758953
rs2188966	0.484	—	—
rs3758953	0.320	0.660	—
rs1799859	0.013	0.005	0.005

Top: *SLC2A*. Bottom: *ABCC8*. Single nucleotide polymorphisms (SNPs) are in boldface.