Diabetes Genetic Predisposition Score and Cardiovascular Complications Among Patients With Type 2 Diabetes

QIBIN QI, PHD[1]
JAMES B. MEIGS, MD, MPH[2]
KATHRYN M. REXRODE, MD, MPH[3]
FRANK B. HU, MD, PHD[1,4,5]
LU QI, MD, PHD[1,5]

OBJECTIVE—To examine the association between genetic predisposition to type 2 diabetes (T2D) and risk of cardiovascular disease (CVD) among patients with T2D.

RESEARCH DESIGN AND METHODS—The current study included 1,012 men and 1,310 women with T2D from the Health Professionals Follow-up Study and Nurses' Health Study, including 677 patients with CVD and 1,645 non-CVD control subjects. A genetic predisposition score (GPS) was calculated on the basis of 36 established independent diabetes-predisposing variants.

RESULTS—Each additional diabetes-risk allele in the GPS was associated with a 3% increased risk of CVD (odds ratio [OR] 1.03 [95% CI 1.00–1.06]). The OR was 1.47 (1.11–1.95) for CVD risk by comparing extreme quartiles of the GPS (P for trend = 0.01). We also found that the GPS was positively associated with hemoglobin A_{1c} levels (P = 0.009).

CONCLUSIONS—Genetic predisposition to T2D is associated with an increased risk of cardiovascular complications in patients with T2D.

Diabetes Care 36:737–739, 2013

It has been postulated that type 2 diabetes (T2D) and cardiovascular disease (CVD) might spring from a "common soil" where both conditions share common genetic and environmental antecedents (1). Identification of the shared genetic risk factors may improve our understanding of the etiological link of these two diseases. A recent study reported a significant association between a genetic score based on multiple diabetes-predisposing variants and increased risk of coronary heart disease (CHD) in a general population (2). In this study, we constructed a genetic predisposition score (GPS) on the basis of 36 established T2D-predisposing variants, and examined its association with cardiovascular complications among people with T2D.

RESEARCH DESIGN AND METHODS

Study population

The Nurses' Health Study (NHS) is a prospective cohort study of 121,700 female registered nurses who were 30–55 years old starting in 1976 (3). The Health Professionals Follow-up Study (HPFS) is a prospective cohort study of 51,529 male health professionals who were 40–75 years old starting in 1986 (4). For the current analysis, NHS and HPFS participants were T2D cases who had genotype data from the T2D genome-wide association scans (5). T2D cases were diagnosed during follow-up through 2006. CVD cases were defined as CHD (fatal or nonfatal myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty) or stroke (fatal or nonfatal) (6). Only CVD events that occurred after the diagnosis of diabetes through 2006 are included in the current study. Controls were defined as those free of CVD after the diagnosis of diabetes through 2006. Finally, after excluding participants with unknown CVD status or CVD events occurring before the diagnosis of diabetes, a total of 1,012 men and 1,310 women with T2D of European ancestry were included: 347 men (317 CHD and 30 stroke) and 330 women (270 CHD and 60 stroke) with CVD, and 1,645 (665 men and 980 women) non-CVD control subjects. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, and all participants provided written informed consent.

Assessment of covariates and biochemical markers

Information about anthropometric data and lifestyle has been collected biennially by questionnaires since inception (3,4). BMI was calculated as weight (kg)/height^2 (m^2). Blood samples were collected in 1990 and 1994 for women and men, respectively. Measurements of hemoglobin A_{1c} (HbA_{1c}), triglycerides, total and HDL cholesterols, adiponectin, and C-reactive protein have been described elsewhere (7).

Genotyping and GPS calculation

We selected 36 single nucleotide polymorphisms (SNPs) associated with T2D at a genome-wide significance level in Caucasians (8,9). SNP genotyping and imputation have been described elsewhere (5). For each individual, we summed the number of risk alleles of the SNPs to produce a GPS (10). Most of the SNPs included in the GPS were genotyped or had a high imputation quality score (Supplementary Table 1).

From the [1]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the [2]General Medicine Division and the Center for Human Genetic Research and Diabetes Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; the [3]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the [4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and the [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.
Corresponding author: Lu Qi, nhlqi@channing.harvard.edu.
Received 3 May 2012 and accepted 14 August 2012.
DOI: 10.2337/dc12-0852
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0852/-/DC1.

Statistical analyses

We used logistic regression to estimate odds ratios (ORs) and 95% CI for CVD risk. General linear regression models were applied to test associations between the GPS and biochemical markers. The results in men and women were combined by inverse variance–weighted, fixed-effects meta-analysis. Statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC).

RESULTS—Characteristics of participants are shown in Supplementary Table 2. The GPS showed consistent associations with CVD in men and women, with a combined OR per diabetes risk allele of 1.03 (95% CI 1.00–1.05). The OR for CVD was 1.40 (1.06–1.84) by comparing extreme quartiles of the GPS (*P* for trend = 0.03) (Table 1). There was a linear relationship between the GPS and CVD risk (Supplementary Fig. 1). Results were similar when the outcome was restricted to CHD (excluding stroke cases).

We further examined the associations between the GPS and biochemical risk factors in a subgroup of diabetic patients (Supplementary Table 3). The GPS was significantly associated with elevated HbA_{1c} levels ($P = 0.009$). To test the potential mediators underlying the association for CVD risk, we further included several Framingham risk factors (total cholesterol, HDL cholesterol, and systolic blood pressure) in the multivariate adjusted model, and the association did not change. Further adjustment for HbA_{1c} attenuated the association (OR 1.35 [95% CI 1.03–1.78] by comparing extreme quartiles of the GPS; *P* for trend = 0.049).

CONCLUSIONS—Our data indicate that the genetic predisposition to T2D may increase CVD risk among people with T2D. This suggests that CVD may partly share the genetic predisposition with T2D, supporting the "common soil" hypothesis at a genetic level (1). Several studies have examined the associations between the individual diabetes-predisposing genetic variants and CVD risk and yield inconsistent results (11–14). In the current study, most individual SNPs were not significantly associated with CVD risk (Supplementary Table 4). This was not surprising because these SNPs individually only explain a very small proportion of the variation in T2D risk. Thus, we estimated the overall genetic susceptibility to T2D by computing a GPS on the basis of 36 well-established diabetes-predisposing variants. Consistently, Pfister et al. (2) also found that a diabetes genetic score was significantly associated with increased CHD risk in a general population.

We observed that the GPS was positively associated with HbA_{1c}, a marker reflecting severity of hyperglycemia. The association for CVD risk was attenuated after adjustment for HbA_{1c}. These findings suggest that the GPS might reflect the severity of hyperglycemia, which may partly account for the observed genetic association for CVD risk. Consistently, epidemiological studies have shown that poor glycemic control was associated with increased CVD risk among diabetic patients (15). Because HbA_{1c} levels were not measured at baseline and only a subgroup of the participants had data on this marker, we were limited to perform more analysis to test potential mechanisms underlying the observed associations. In addition, the covariates were assessed in participants either before or after the diagnosis of T2D. However, the observed genetic associations were less likely to be affected since genetic variants are randomly assigned and generally uncorrelated with the covariates.

In conclusion, we found that the genetic predisposition to T2D was significantly associated with an increased risk of CVD in patients with T2D. Further studies are needed to examine the relationship among the genetic predisposition to T2D, glycemic control, and CVD.

Acknowledgments—This study was supported by grants DK-091718, HL-071981, HL-073168, CA-87969, CA-49449, HL-34594, HL-088521, U01-HG-004399, DK-080140, DK-58845, and DK-46200 from the National Institutes of Health. L.Q. is a

Table 1—*Association between the GPS and risk of CVD in patients with T2D*

		Quartile of GPS				
	Continuous GPS	Q1	Q2	Q3	Q4	*P* for trend
Men						
n (cases/controls)		85/189	114/218	66/127	82/131	
GPS median (range)		35 (24–36)	38 (37–39)	41 (40–41)	43 (42–50)	
OR (95% CI)						
Age and BMI adjusted	1.04 (1.00–1.07)	1.00	1.23 (0.86–1.76)	1.21 (0.80–1.82)	1.45 (0.98–2.15)	0.09
Multivariate adjusted*	1.04 (1.00–1.08)	1.00	1.24 (0.86–1.78)	1.23 (0.81–1.87)	1.47 (0.98–2.20)	0.08
Women						
n (cases/controls)		99/315	75/217	90/268	66/180	
GPS median (range)		35 (25–36)	38 (37–38)	40 (39–41)	43 (42–50)	
OR (95% CI)						
Age and BMI adjusted	1.02 (0.98–1.06)	1.00	1.07 (0.74–1.55)	1.04 (0.73–1.47)	1.35 (0.92–1.99)	0.18
Multivariate adjusted*	1.03 (0.99–1.06)	1.00	1.07 (0.73–1.55)	1.11 (0.78–1.58)	1.47 (0.99–2.18)	0.08
Combined†						
Age and BMI adjusted	1.03 (1.00–1.05)	1.00	1.15 (0.89–1.49)	1.10 (0.85–1.44)	1.40 (1.06–1.84)	0.03
Multivariate adjusted*	1.03 (1.00–1.06)	1.00	1.15 (0.89–1.49)	1.16 (0.88–1.52)	1.47 (1.11–1.95)	0.01

*Adjusted for age, BMI, family history of myocardial infarction (yes or no), smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), physical activity (quintiles), and menopausal status (pre- or postmenopausal [never, past, or current hormone use], women only). †Results were combined between women and men using inverse variance weights under fixed model, as there was no detectable heterogeneity between women and men (all *P* for heterogeneity >0.57).

recipient of the American Heart Association Scientist Development Award (0730094N).

No potential conflicts of interest relevant to this article were reported.

Q.Q. designed the study, researched data, and wrote the manuscript. J.B.M., K.M.R., and F.B.H. contributed to discussion and edited and reviewed the manuscript. L.Q. designed the study, reviewed data, contributed to discussion, and edited and reviewed the manuscript. L.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank all the participants of the NHS and the HPFS for their continued cooperation.

References

1. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes 1995;44:369–374
2. Pfister R, Barnes D, Luben RN, Khaw KT, Wareham NJ, Langenberg C. Individual and cumulative effect of type 2 diabetes genetic susceptibility variants on risk of coronary heart disease. Diabetologia 2011; 54:2283–2287
3. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62
4. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991;338:464–468
5. Qi L, Cornelis MC, Kraft P, et al.; Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC); Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. Hum Mol Genet 2010;19: 2706–2715
6. Qi Q, Workalemahu T, Zhang C, Hu FB, Qi L. Genetic variants, plasma lipoprotein (a) levels, and risk of cardiovascular morbidity and mortality among two prospective cohorts of type 2 diabetes. Eur Heart J 2012; 33:325–334
7. He M, Cornelis MC, Franks PW, Zhang C, Hu FB, Qi L. Obesity genotype score and cardiovascular risk in women with type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 2010;30:327–332
8. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med 2010;363: 2339–2350
9. Grarup N, Sparsø T, Hansen T. Physiologic characterization of type 2 diabetes-related loci. Curr Diab Rep 2010;10:485–497
10. Qi Q, Li H, Wu Y, et al. Combined effects of 17 common genetic variants on type 2 diabetes risk in a Han Chinese population. Diabetologia 2010;53:2163–2166
11. AshokKumar M, Veera Subhashini NG, Kanthimathi S, et al. Associations for lipoprotein lipase and peroxisome proliferator-activated receptor-γ gene and coronary artery disease in an Indian population. Arch Med Res 2010;41:19–25.e1
12. Bielinski SJ, Pankow JS, Folsom AR, North KE, Boerwinkle E. TCF7L2 single nucleotide polymorphisms, cardiovascular disease and all-cause mortality: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia 2008;51:968–970
13. Dallongeville J, Iribarren C, Ferrières J, et al. Peroxisome proliferator-activated receptor gamma polymorphisms and coronary heart disease. PPAR Res 2009;2009: 543746
14. Ridker PM, Cook NR, Cheng S, et al. Alanine for proline substitution in the peroxisome proliferator-activated receptor gamma-2 (PPARG2) gene and the risk of incident myocardial infarction. Arterioscler Thromb Vasc Biol 2003;23:859–863
15. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287:2570–2581