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Time-to-Event Genome-Wide Association Study for Incident Cardiovascular Disease in People With Type 2 Diabetes

Soo Heon Kwak, Ryan B. Hernandez-Cancela, Daniel A. DiCorpo, David E. Condon, Jordi Merino, Peitao Wu, Jennifer A. Brody, Jie Yao, Xiuqing Guo, Fariba Ahmadizar, Mariah Meyer, Murat Sincan, Josep M. Mercader, Sujin Lee, Jeffrey Haessler, Ha My T. Vy, Zhaotong Lin, Nicole D. Armstrong, Shaopeng Gu, Noah L. Tsao, Leslie A. Lange, Ningyuan Wang, Kerri L. Wiggins, Stella Trompet, Simin Liu, Ruth J.F. Loos, Renae Judy, Philip H. Schroeder, Natalie R. Hasbani, Maxime M. Bos, Alanna C. Morrison, Rebecca D. Jackson, Alexander P. Reiner, JoAnn E. Manson, Ninad S. Chaudhary, Lynn K. Carmichael, Yii-Der Ida Chen, Kent D. Taylor, Mohsen Ghanbari, Joyce van Meurs, Achilleas N. Pitsillides, Bruce M. Psaty, Raymond Noordam, Ron Do, Kyong Soo Park, J. Wouter Jukema, Maryam Kavousi, Adolfo Correa, Stephen S. Rich, Scott M. Damrauer, Catherine Hajek, Nam H. Cho, Marguerite R. Irvin, James S. Pankow, Girish N. Nadkarni, Robert Sladek, Mark O. Goodarzi, Jose C. Florez, Daniel I. Chasman, Susan R. Heckbert, Charles Kooperberg, Josée Dupuis, Rajeev Malhotra, Paul S. de Vries, Ching-Ti Liu, Jerome I. Rotter, and James B. Meigs, on behalf of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium

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Time-to-Event Genome-Wide Association Study for Incident Cardiovascular Disease in People With Type 2 Diabetes

Aim

- To identify genetic risk factors for incident cardiovascular disease (CVD) among people with type 2 diabetes (T2D)

Methods

- We conducted a multi-ancestry time-to-event genome-wide association study for incident CVD among people with T2D
- We also tested 204 known coronary artery disease (CAD) variants for association with incident CVD

❖ Sample size and event rate according to ancestry

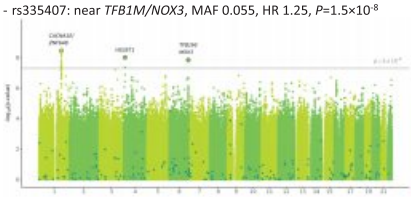
Ancestry	Total (N)	Event (N)	Event Rate (%)
European/European American	31,118 (63.2%)	4,918 (54.9%)	15.8
African American	11,124 (22.6%)	2,844 (31.8%)	25.6
Hispanic/Latino	4,325 (8.8%)	934 (10.4%)	21.6
East Asian	2,663 (5.4%)	260 (2.9%)	9.8
Total	**49,230**	**8,956**	**18.2**

Conclusions

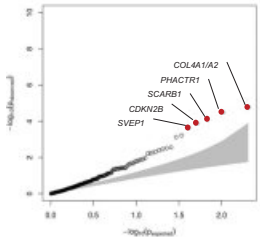
- The data point to novel and known genomic regions associated with incident CVD among individuals with T2D

Results

- We identified three novel genetic loci for incident CVD
  - rs147138607: near *CACNA1E/ZNF648*, MAF 0.107, HR 1.23, $P=3.6\times10^{-9}$
  - rs77142250: near *HS3ST1*, MAF 0.013, HR 1.89, $P=9.9\times10^{-9}$
  - rs335407: near *TFB1M/NOX3*, MAF 0.055, HR 1.25, $P=1.5\times10^{-8}$



- Among 204 known CAD loci, 35 were associated with incident CVD in people with T2D ($P<0.05$), and 5 were significant after Bonferroni correction ($P<0.00024$, 0.05/204)



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  People with type 2 diabetes (T2D) are at increased risk of cardiovascular disease (CVD).
- **What is the specific question(s) we wanted to answer?**
  What are the genetic risk factors for CVD that are specific in T2D?
- **What did we find?**
  We identified three novel genetic loci for incident CVD in 49,230 participants with T2D: rs147138607 (near *CACNA1E/ZNF648*), rs77142250 (near *HS3ST1*), and rs335407 (near *TFB1M/NOX3*). Among the 204 known coronary artery disease loci that were identified in the general population, 5 were significantly associated with incident CVD in T2D, and a higher polygenic score was associated with an increased risk of incident CVD.
- **What are the implications?**
  These genetic findings may partially explain the excess risk of CVD among people with T2D and point to potential targets for intervention.

BRIEF REPORT

Time-to-Event Genome-Wide Association Study for Incident Cardiovascular Disease in People With Type 2 Diabetes

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Soo Heon Kwak,[1,2,3] Ryan B. Hernandez-Cancela,[4] Daniel A. DiCorpo,[4] David E. Condon,[5] Jordi Merino,[2,3,6,7] Peitao Wu,[4] Jennifer A. Brody,[8] Jie Yao,[9] Xiuqing Guo,[9] Fariba Ahmadizar,[10,11] Mariah Meyer,[12] Murat Sincan,[4] Josep M. Mercader,[2,3,6] Sujin Lee,[13] Jeffrey Haessler,[14] Ha My T. Vy,[15] Zhaotong Lin,[16] Nicole D. Armstrong,[17] Shaopeng Gu,[18] Noah L. Tsao,[19] Leslie A. Lange,[12] Ningyuan Wang,[4] Kerri L. Wiggins,[8] Stella Trompet,[20,21] Simin Liu,[22] Ruth J.F. Loos,[15] Renae Judy,[19] Philip H. Schroeder,[2,3,6] Natalie R. Hasbani,[23] Maxime M. Bos,[10] Alanna C. Morrison,[23] Rebecca D. Jackson,[24] Alexander P. Reiner,[14,25] JoAnn E. Manson,[26] Ninad S. Chaudhary,[17] Lynn K. Carmichael,[18] Yii-Der Ida Chen,[9] Kent D. Taylor,[9] Mohsen Ghanbari,[10] Joyce van Meurs,[10] Achilleas N. Pitsillides,[4] Bruce M. Psaty,[8,25,27] Raymond Noordam,[20] Ron Do,[15] Kyong Soo Park,[1] J. Wouter Jukema,[21,28] Maryam Kavousi,[10] Adolfo Correa,[29] Stephen S. Rich,[30] Scott M. Damrauer,[19,31] Catherine Hajek,[18] Nam H. Cho,[32] Marguerite R. Irvin,[17] James S. Pankow,[33] Girish N. Nadkarni,[15] Robert Sladek,[34] Mark O. Goodarzi,[35] Jose C. Florez,[2,3,6] Daniel I. Chasman,[26] Susan R. Heckbert,[8,25] Charles Kooperberg,[14] Josée Dupuis,[4,36] Rajeev Malhotra,[37] Paul S. de Vries,[23] Ching-Ti Liu,[4] Jerome I. Rotter,[9] and James B. Meigs,[2,6,38] on behalf of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium

[1]*Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea*
[2]*Broad Metabolism Program and Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA*
[3]*Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA*
[4]*Department of Biostatistics, Boston University School of Public Health, Boston, MA*
[5]*Sanford Imagenetics, Sanford Health, Sioux Falls, SD*
[6]*Department of Medicine, Harvard Medical School, Boston, MA*
[7]*Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark*
[8]*Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA*

OBJECTIVE

To identify genetic risk factors for incident cardiovascular disease (CVD) among people with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

We conducted a multiancestry time-to-event genome-wide association study for incident CVD among people with T2D. We also tested 204 known coronary artery disease (CAD) variants for association with incident CVD.

RESULTS

Among 49,230 participants with T2D, 8,956 had incident CVD events (event rate 18.2%). We identified three novel genetic loci for incident CVD: rs147138607 (near *CACNA1E/ZNF648*, hazard ratio [HR] 1.23, $P = 3.6 \times 10^{-9}$), rs77142250 (near *HS3ST1*, HR 1.89, $P = 9.9 \times 10^{-9}$), and rs335407 (near *TFB1M/NOX3*, HR 1.25, $P = 1.5 \times 10^{-8}$). Among 204 known CAD loci, 5 were associated with incident CVD in T2D (multiple comparison–adjusted $P < 0.00024$, 0.05/204). A standardized polygenic score of these 204 variants was associated with incident CVD with HR 1.14 ($P = 1.0 \times 10^{-16}$).

CONCLUSIONS

The data point to novel and known genomic regions associated with incident CVD among individuals with T2D.

Type 2 diabetes (T2D) is a significant risk factor for cardiovascular disease (CVD), leading to a two- to threefold higher likelihood of developing CVD. CVD is the leading cause of morbidity and mortality in people with diabetes (1,2), and previous studies suggest that life expectancy is reduced by up to 8 years in people with T2D (3). Although CVD mortality rates have declined substantially in the general population in recent decades, this improvement has been less substantial in people with T2D (4).

Beyond conventional risk factors, recent genome-wide association studies (GWAS) have identified at least 204 genetic loci associated with CVD in the general population. These studies have been mostly conducted among people with European ancestry (5), which calls for ancestry-diverse studies. Genetic risk factors of CVD in the general population are mostly thought to be relevant to people with T2D (6). Still, genetic variants of CVD in people with T2D have not been thoroughly investigated. Most studies have

been underpowered and were cross-sectional (7–9). In this study, we performed a time-to-event GWAS of incident CVD in a large, multiancestry sample of people with T2D, ensuring that the occurrence of T2D preceded any CVD event.

RESEARCH DESIGN AND METHODS

Study Design and Participating Cohorts

This is a meta-analysis of ancestry-specific, cohort-level, time-to-event GWAS for incident CVD in people with T2D, the majority of whom were from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium (10). Details of the methods and study participants can be found in Supplementary Methods. In brief, we studied 49,230 participants with T2D from 16 cohorts and of multiple ancestries. In the case of multiancestry cohorts, participants were grouped into major continental ancestries, resulting in 28 ancestry-specific subgroups (Supplementary Table 1).

Definition of T2D and CVD

T2D was defined for each cohort according to a participant having one or more of the American Diabetes Association criteria (11) (Supplementary Table 2). Participants with known type 1 diabetes or other specific types of diabetes were excluded. To minimize contamination with type 1 diabetes, we excluded people with age at diabetes diagnosis <40 years. CVD was defined as a composite of *1*) coronary artery disease (CAD), *2*) cerebrovascular disease, and *3*) death from a cardiovascular cause (Supplementary Table 3 and Supplementary Methods). An incident CVD event was defined as the first CVD event occurring at least 1 year after T2D diagnosis.

Statistical Analyses

We applied Cox proportional hazards modeling for the time-to-event GWAS (Supplementary Methods). Each single nucleotide variation (SNV) was tested for its association with incident CVD with consideration of observation time and adjustment for covariates. Observation time was defined as years between age at diagnosis of T2D and age at incident CVD for cases or years between age at diagnosis of T2D and age at last follow-up. A time-to-event GWAS was performed for each ancestry-specific cohort subgroup with either the GWASTools R package (12) or the gwasurvivr R package (13) (Supplementary Table 4). The primary analysis included age at diagnosis of T2D and sex as covariates, and significant principal components were used to adjust for population stratification.

Cohort-Level Analysis and Meta-analysis

For each cohort there were specific preimputation genotype quality control criteria (Supplementary Table 5). Genotype imputation was performed with use of a population-specific reference panel. Within each cohort, analysis was performed separately for four major ancestry groups: Admixed African American (AFR), East Asian (EAS), European (EUR), and Admixed Hispanic (HIS). Meta-analysis of cohort-level summary statistics was conducted with an inverse variance–weighted fixed-effects method as implemented in METAL (14). A conventional genome-wide significance threshold was set as $P < 5.0 \times 10^{-8}$ (15,16). The methods for conducting downstream analysis on the significant variants can be found in Supplementary Methods.

Association of Known 204 CAD Variants

We tested 204 previously reported CAD variants identified in the general population for association with incident CVD in people with T2D (5,6). With adjustment for multiple comparisons, the

[9]*Department of Pediatrics, Institute for Translational Genomics and Population Sciences, The Lundquist Institute for Biomedical Innovation, Harbor-UCLA Medical Center, Torrance, CA*
[10]*Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[11]*Department of Data Science and Biostatistics, Julius Global Health, University Medical Center Utrecht, Utrecht, the Netherlands*
[12]*Department of Biomedical Informatics, University of Colorado Anschutz Medical Campus, Aurora, CO*
[13]*Division of Vascular Surgery and Endovascular Therapy, Massachusetts General Hospital, Boston, MA*
[14]*Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA*
[15]*Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*
[16]*Department of Biostatistics, University of Minnesota, Minneapolis, MN*
[17]*Department of Epidemiology, The University of Alabama at Birmingham, Birmingham, AL*
[18]*Department of Internal Medicine, Sanford Health, Sioux Falls, SD*
[19]*Corporal Michael J. Crescenz VA Medical Center and Department of Surgery, Perelman School of Medicine, Philadelphia, PA*
[20]*Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands*
[21]*Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands*
[22]*Department of Epidemiology, Brown University, Providence, RI*
[23]*Human Genetics Center, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX*
[24]*Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Ohio State University, Columbus, OH*
[25]*Department of Epidemiology, University of Washington, Seattle, WA*
[26]*Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[27]*Department of Health Systems and Population Health, University of Washington, Seattle, WA*
[28]*Netherlands Heart Institute, Utrecht, the Netherlands*
[29]*Department of Medicine, University of Mississippi Medical Center, Jackson, MS*
[30]*Center for Public Health Genomics, University of Virginia, Charlottesville, VA*
[31]*Department of Genetics, Perelman School of Medicine, Philadelphia, PA*
[32]*Department of Preventive Medicine, Ajou University School of Medicine, Suwon, Korea*
[33]*Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN*
[34]*Department of Medicine and Department of Human Genetics, McGill University, Montreal, Quebec, Canada*
[35]*Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA*
[36]*Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada*
[37]*Cardiovascular Research Center, Cardiology Division, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA*
[38]*Department of General Internal Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, MA*

Corresponding author: James B. Meigs, jmeigs@mgh.harvard.edu

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association's significance threshold was set as $P < 0.00024$ (0.05/204). In addition, a weighted polygenic score based on these 204 known CAD variants was constructed as previously described (6) and tested for association with incident CVD in people with T2D.

RESULTS

Study Overview

A total of 49,230 people with T2D, who had not developed CVD either at the time of T2D diagnosis or within 1 year thereafter, were included in the analysis (Supplementary Table 6). Individuals with European ancestry comprised ∼63.2% (N = 31,118) of the participants, while the remaining 36.8% (N = 18,112) were of non-European ancestry (AFR 22.6%, n = 11,124; HIS 8.8%, 4,325; EAS 5.4%, 2,663). Among 49,230 participants with T2D, 8,956 developed incident CVD (event rate 18.2%) over a mean follow-up duration ranging from 3.2 to 33.7 years. Detailed clinical characteristics of the participants can be found in Supplementary Table 7.

Loci for Incident CVD in People With T2D

We tested 15,471,776 SNVs with overall minor allele frequency (MAF) ≥1% for association with incident CVD. A plot of expected-by-observed association statistics showed minimal inflation (λ_{GC} = 1.09 for variants with MAF ≥1%) (Supplementary Fig. 1*A*). We identified three SNVs associated with incident CVD in people with T2D at genome-wide significance (Supplementary Fig. 1*B* and Table 1). The variant rs147138607 (chromosome 1 [chr1]: 181855562:G>C, MAF 10.7%) had a hazard ratio (HR) for incident CVD in T2D of 1.23 (95% CI 1.15–1.32, $P = 3.6 \times 10^{-9}$) and resides in an intergenic region between the genes *CACNA1E* and *ZNF648* (Fig. 1*A*). The second most significant variant, rs77142250 (chr4:11444867:T>C, MAF 1.3%), was present at low frequency (1.3%) only in those of African ancestry, had an HR 1.89 (95% CI 1.52–2.35, $P = 9.9 \times 10^{-9}$), and resides near the gene *HS3ST1* (Fig. 1*B*). The third variant, rs335407 (chr6:155665441:C>T, MAF 5.5%), had an HR of 1.25 (95% CI 1.16–1.35, $P = 1.58 \times 10^{-8}$) and resides in an intergenic region between the genes *TFB1M* and *NOX3* (Fig. 1*C*). Results from the downstream analysis of these three variants can be found in Supplementary Results.

Role of Known CAD Variants in People With T2D

Among the 204 CAD variants identified in the general population (Supplementary Table 8), we observed nominally significant associations with consistent direction of effect for CAD in people with T2D for 35 SNVs, which included 5 that were significant after Bonferroni correction ($P < 0.00024$, 0.05/204) (Fig. 2*A*). For the 204 variants, we further observed consistency in the direction of association for risk of CVD between the general population and people with T2D (Fig. 2*B*). The CAD polygenic score consisting of these 204 variants was associated with increased CVD in people with T2D, with an estimated HR of 1.14 (95% CI 1.12–1.16) per 1-SD increase (Table 2). We showed that the association between the CAD polygenic score and CVD differed by ancestry groups (nonsignificant in East Asians with use of European-derived summary statistics).

CONCLUSIONS

In this study, we sought to identify novel genetic loci associated with incident CVD in people with T2D by performing a time-to-event GWAS. We discovered three distinct SNVs that reached genome-wide significance: rs147138607, between *CACNA1E* and *ZNF648*; rs77142250, near *HS3ST1*; and rs335407, between *TFB1M* and *NOX3*. We found that most CAD variants already known from cross-sectional GWAS in the general population were also associated with incident CVD events in people with T2D. Furthermore, a polygenic score composed of 204 CAD variants was associated with incident CVD. To the best of our knowledge, this is the first large-scale genetic association study with investigation of genetic risk factors of incident CVD specifically in people with T2D.

The main objective of this study was to identify genetic variants that could explain the excess risk of CVD in people with T2D. We show that for people with T2D there is enrichment of genetic risk factors of CAD observed in the general population: *1*) there was an excess number of common single variants known to be associated with CAD in people with T2D and *2*) polygenic score composed of these variants was significantly associated with incident CVD in people with T2D. Furthermore, we identified genetic

Table 1—Genetic variants significantly associated with incident CVD in people with T2D in basic model

chr	POS (rsID)	Effect allele	Ancestry	Frequency	HR (95% CI)	*P*	Het *P*	Sample size
1	181855562 (rs147138607)	G>C	European/European American	0.018	1.20 (1.00–1.44)	0.047	0.756	24,457
			African American	0.127	1.22 (1.12–1.33)	2.3×10^{-6}	0.381	8,929
			Hispanic/Latinx	0.065	1.26 (1.03–1.55)	0.027	0.198	3,163
			East Asian	0.050	1.55 (1.07–2.25)	0.021	0.469	2,511
			Combined	0.107	1.23 (1.15–1.32)	3.6×10^{-9}	0.713	39,060
4	11444867 (rs77142250)	T>C	African American	0.013	1.89 (1.52–2.35)	9.9×10^{-9}	0.363	9,748
6	155665441 (rs335407)	C>T	European/European American	0.027	1.33 (1.19–1.50)	1.4×10^{-3}	0.664	29,910
			African American	0.084	1.18 (1.05–1.31)	3.8×10^{-3}	0.891	7,765
			Hispanic/Latinx	0.033	1.34 (0.99–1.81)	0.055	0.596	3,163
			East Asian	0.026	0.92 (0.45–1.88)	0.810	0.541	2,511
			Combined	0.055	1.25 (1.16–1.35)	1.5×10^{-8}	0.859	43,349

Three distinct genetic loci increased risk of incident CVD among individuals with T2D with genome-wide significance in time-to-event analysis ($P < 5.0 \times 10^{-8}$). Het *P*, significance of heterogeneity; POS, position in GRCh37/hg19; rsID, reference single nucleotide polymorphism identifier.

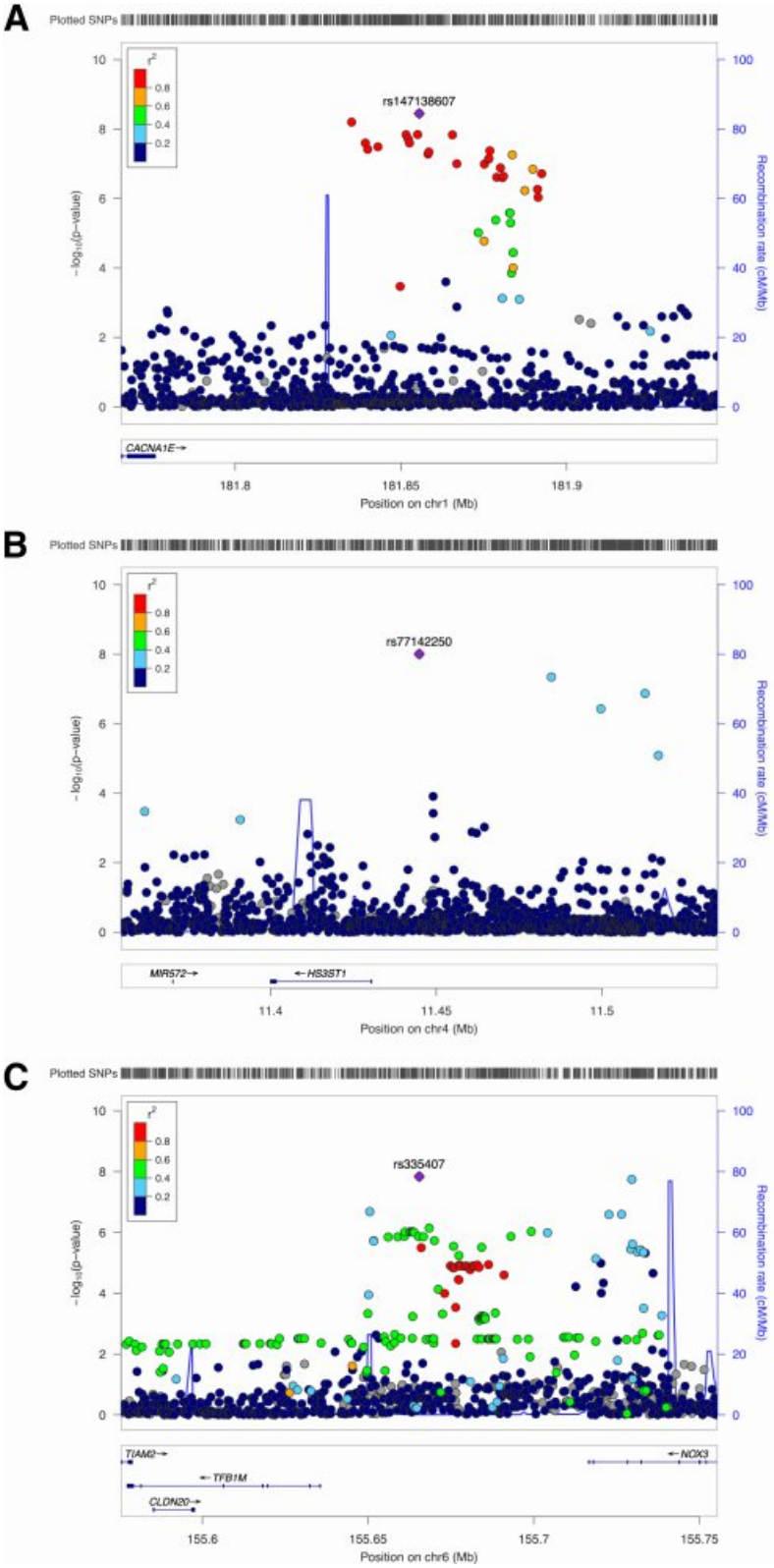

Figure 1—Regional association plots for the three genome-wide significant variants. *A*: rs147138607, near *CACNA1E* and *ZNF648*. *B*: rs77142250, near *HS3ST1*. *C*: rs335407, near *TFB1M* and *NOX3*. The hash marks above the panels represent the position of each SNP that was genotyped or imputed. The negative $\log_{10}$ of *P* values from the Cox regression is shown on the *y*-axis. Estimated recombination rates are plotted to reflect recombination hot spots. The single nucleotide polymorphisms (SNPs) in linkage disequilibrium with the most significant single nucleotide polymorphism are color coded to represent their strength of linkage disequilibrium based on European ancestry for *A* and *C* and African ancestry for *B*.

loci associated with incident CVD, specifically in people with T2D. These variants were not identified as genetic risk factors of CVD in the general population. Taken together, we show that the excess CVD risk for people with T2D is conferred at least in part by the excess of known CAD variants and variants with effects specifically in the context of T2D. However, further research is required to quantify the excess risk conferred by these genetic risk factors.

The strengths of this study include the use of time-to-event GWAS for incident CVD rather than performance of a conventional case-control analysis. This study also benefits from the fact that we included samples from different ancestries and performed a multiancestry meta-analysis (36.8% non-European). Multiancestry meta-analysis is known to increase power where association signal is shared across ancestry groups and improves fine-mapping resolution. Interestingly, all three variants showed significance for African ancestry, while rs147138607 and rs335407 were also nominally significant for European ancestry. It should be noted that the rs77142250 variant was exclusively present in individuals with African ancestry, with a low MAF of 1.3%. Moreover, investigators of recent multiancestry GWAS advocate a more stringent level of statistical significance, set at $P < 5.0 \times 10^{-9}$ (17). Therefore, our findings require further replication.

In conclusion, we discovered three loci that are associated with incident CVD and show that known CAD variants identified in the general population are also enriched in people with T2D. While these findings necessitate validation, they offer insight into the increased risk of CVD observed in individuals with T2D.

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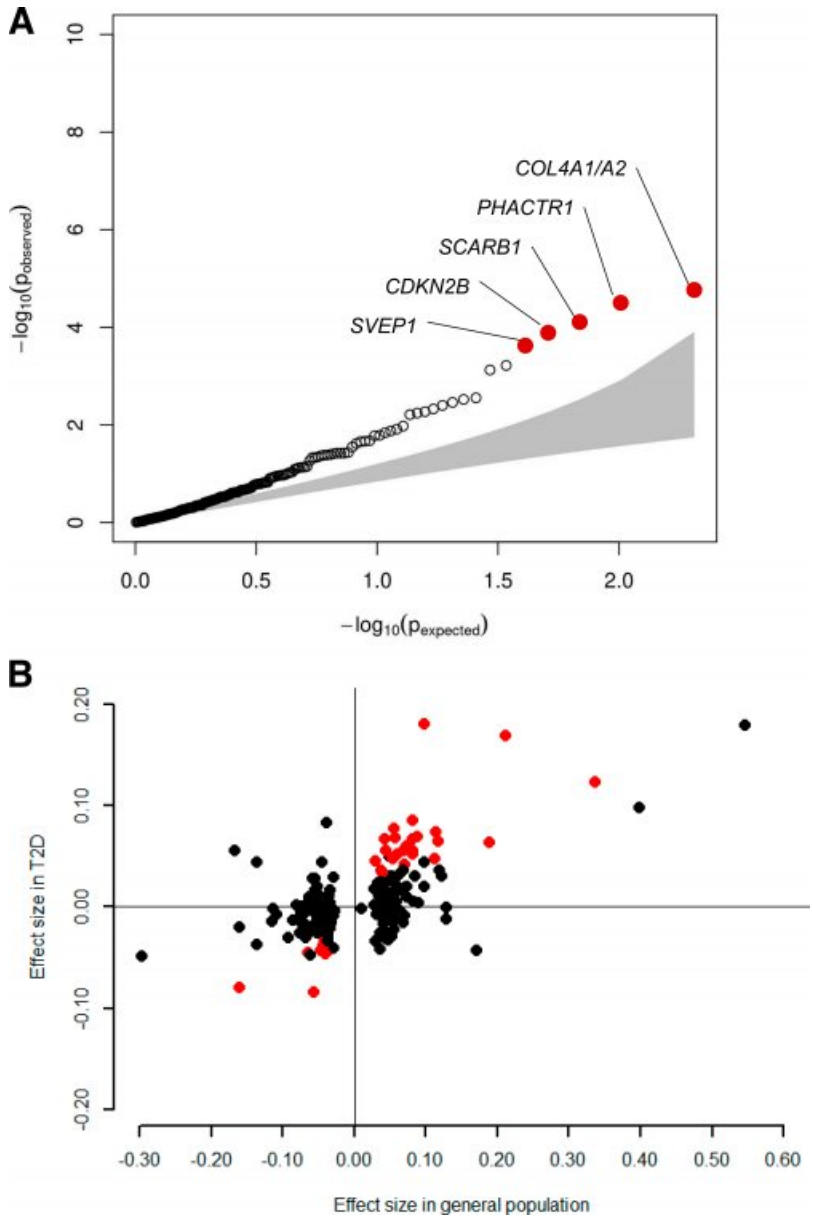

Figure 2—Association of 204 previously identified CAD variants with incident CVD in people with T2D. *A*: Quantile-quantile plot showing the distribution of the observed *P* values for the 204 CAD variants with risk of incident CVD in people with T2D against the expected distribution under the null hypothesis. Red dots highlight five variants that were significantly associated with incident CVD after Bonferroni correction. *B*: Comparison of the effect size of 204 known CAD variants in the general population and incident CVD in people with T2D. Effect size of the known 204 CAD variants for prevalent CAD in the general population (*x*-axis, β-coefficient from logistic regression analysis) and incident CVD in people with T2D (*y*-axis, β-coefficient from Cox regression analysis) is plotted. Red dots highlight 35 variants that were nominally ($P < 0.05$) associated with incident CVD and had same direction of association in the general population.

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Table 2—Association of polygenic score of 204 known CAD variants and incident CVD in people with T2D

Ancestry	HR	95% CI	Het *P*	*P*
European/European American	1.18	1.14–1.21	0.010	$<1.0 \times 10^{-16}$
African American	1.10	1.05–1.15	0.255	8.3×10^{-5}
Hispanic/Latinx	1.10	1.03–1.18	0.474	0.0031
East Asian	0.99	0.88–1.13	0.586	0.982
Overall	1.14	1.12–1.16	0.002	$<1.0 \times 10^{-16}$

Polygenic score of 204 CAD variants discovered from the general population was associated with increased risk of incident CVD in people with T2D. HR for 1-SD increase in PRS. Het *P*, significance of heterogeneity.

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