Supplementary Table S1. Genes previously associated with T2D, DR and DN on IBC chip

Gene	Number of SNPs in Locus on IBC Chip	Previously Associated Phenotype
ACE	66	DN
ADAMTS9	2	T2D
ADIPOQ	23	DN
ADRB3	25	DR
AGER	30	DN
AKR1B1	24	DN, DR
APOE	21	DN
CCR5	1	DN
CDKAL1	373	T2D
CDKN2B	13	T2D
CNDP1	3	DN
CTGF	14	DN
EPO	14	DR, DN
FABP2	9	DN
FTO	325	T2D
HFE	9	DR
HHEX	9	T2D
ICAM1	35	DR
IGF2BP2	2	T2D
IGFBP1	2	DN
IL6R	46	DN
ITGA2	152	DR
KCNJ11	13	T2D
NFKBIA	41	DN
NOS3	55	DN
NPHS1	19	DN
PPARG	114	T2D
PRKCB1	141	DN
REN	59	DN
RENBP	10	DN
SELP	45	DN
SLC30A8	18	T2D
TCF2	1	T2D
TCF7L2	115	T2D, DN
TGFBR2	88	DN
TGFBR3	74	DN
TNF	9	DN
VEGFA	10	DR, DN
WFS1	39	T2D

IBC= ITMAT-Broad-CARe, T2D=Type 2 diabetes, DR=diabetic retinopathy, DN=diabetic nephropathy

Supplementary Table S2. Fundus Photography Protocols for Replication Cohorts.

Cohort	Number of Eyes Photographed per Participant	Number of Fields Photographed per Eye	Size of Each Field Photographed
AGES	Two	Two	45 degrees
BMES	Two	Five	30 degrees
Go-DARTS*	Two	Two	45 degrees
FIND-Eye	Two	Seven	30 degrees
FinnDiane†	Two	Two	45 degrees
Lublin	Two	Three	45 degrees
SiMES	Two	Two	45 degrees
SP2	Two	Two	45 degrees

*Go-DARTS determined DR phenotype for cases based on three data sources: a national retinal screening program, a regional retinal screening service and a validation database. They determined DR phenotype for controls from 19 different sources, including retinal screening services and diabetes clinics. Only the national and regional retinal screening patients had fundus photographs taken per this specified protocol.

†The FinnDiane sample includes some participants that were phenotyped by review of patient records.

Supplementary Table S3. Haplotype Association Results

(A) *SELP* (ETDRS grade ≥ 14 case definition)

Haplotype	Frequency in Cases	Frequency in Controls	Chi Square	p value
Haplotype 1:rs6663533|rs2227245|rs9332533|rs6019|rs6691048|rs2213873|rs16862377|rs12755775|rs6703462|rs6664922|rs3753305|rs3917854|rs6128|rs6136|rs6133|rs6127|rs3766122|rs3917793|rs760694|rs3917779|rs3917768				
TTCCTAAGGCGTCTCTTCGGG	0.18	0.17	0.43	0.51
TCTCCGAGGCCCCTCCTCTGT	0.36	0.33	0.75	0.39
TCTCCGAAGCCCCTCCTCTGT	0.12	0.11	0.08	0.78
TCTCCGCGTGGCCTCTTATGG	0.11	0.10	0.12	0.73
TTCCTAAGGCGTCGCTTCGGG	0.12	0.11	0.22	0.64
TTCCTAAGGCCTCTCCTCTGT	0.004	0.02	2.59	0.11
TCTCCGAGGCGCTTCTCCGGG	0.04	0.05	0.32	0.57
GCTGCGAGGCGCTTATTCGAT	0.02	0.05	4.58	0.03
TCTCCGAGGCGCCTCTTATGG	0.01	0.01	0.38	0.54
TCTCCGAGGCGCTTATTCGAT	0.04	0.06	1.67	0.20
Haplotype 2: rs2235302|rs3917731|rs6131|rs6125|rs3917707|rs2244526				
CTCCAC	0.09	0.09	0.02	0.89
TTTTCT	0.04	0.06	1.33	0.25
TTTCAT	0.11	0.15	3.38	0.07
TCCCAT	0.30	0.28	0.70	0.40
CTCCAT	0.46	0.42	1.31	0.25

(B) *FTO* (ETDRS grade ≥ 30 case definition)

Haplotype	Frequency in Cases	Frequency in Controls	Chi Square	p value
Haplotype 1: rs6499654|rs10521305|rs10521303|rs4784329				
TTTC	0.25	0.44	2.68	0.10
TTTA	0.05	0.07	0.12	0.73
TCGA	0.05	0.08	0.21	0.65
CTGA	0.05	0.03	0.28	0.60
TTGA	0.60	0.38	3.54	0.06
Haplotype 2: rs9931209|rs9934504|rs1558755				
TGC	0.45	0.42	0.51	0.48
GAT	0.02	0.03	0.83	0.36
TAT	0.18	0.13	2.13	0.14
TGT	0.35	0.41	2.01	0.16
Haplotype 3: rs12149433|rs9926180|rs7500562|rs12933928|rs13335343|rs1362570|rs16952634|rs17222465|rs2111112|rs10852525|rs9929152				
CAGGGTGCCGA	0.20	0.21	0.02	0.89
CTCAGTACTAG	0.01	0.02	1.58	0.21
CAGAGTGACGA	0.27	0.33	1.81	0.18
CAGAGTGCCGA	0.22	0.23	0.07	0.79
GTCAACGCTAG	0.13	0.09	2.80	0.09
CTCAGTACTGG	0.15	0.10	2.32	0.13
CTCAGTGCTGG	0.01	0.01	0.02	0.89
Haplotype 4: rs8056040|rs12935710				
AT	0.30	0.23	3.44	0.06
GC	0.10	0.11	0.08	0.78
AC	0.61	0.67	2.18	0.14
Haplotype 5: rs12708942|rs9806929|rs7197167|rs4783824				
AAGT	0.13	0.09	3.51	0.06
TGGC	0.17	0.14	1.40	0.24
TGTC	0.70	0.78	5.06	0.02
Haplotype 6: rs12232391|rs7193851|rs8053966|rs17821714				
GTTA	0.08	0.07	0.09	0.77
TCCG	0.18	0.16	0.49	0.48
TTCG	0.007	0.03	2.18	0.14
GTTG	0.27	0.26	0.05	0.81
TTTG	0.47	0.49	0.17	0.68

(C) *IDUA* (ETDRS grade ≥ 30 case definition). The variant associated to DR in CARe, rs6856425, is within Haplotype 1, which is significantly associated to DR as well.

Haplotype	Frequency in Cases	Frequency in Controls	Chi Square	p value
Haplotype 1: rs11248060|rs6829197				
TC	0.13	0.13	0.009	0.93
CC	0.14	0.05	19.06	1.3×10^{-5}
CG	0.74	0.82	6.58	0.01
Haplotype 2: rs3755955|rs6831280				
CG	0.48	0.43	0.57	0.45
TT	0.15	0.14	0.06	0.80
CT	0.37	0.44	0.87	0.35
Haplotype 3: rs4583705|rs3822030				
AA	0.16	0.15	0.07	0.80
GG	0.84	0.85	0.07	0.80

(D) *PDE4D* (ETDRS grade ≥ 14 case definition)

Haplotype	Frequency in Cases	Frequency in Controls	Chi Square	p value
Haplotype 1: rs153981|rs187645|rs889231|rs27168|rs13169097|rs1824159				
AGTCCT	0.14	0.09	7.69	0.006
CGCCTC	0.08	0.08	0.09	0.76
AGCTCC	0.05	0.08	3.06	0.08
AGTCCC	0.20	0.27	7.00	0.008
CACCCC	0.08	0.08	0.11	0.74
CGCCCC	0.45	0.40	2.56	0.11
Haplotype 2: rs27171|rs17780836				
GT	0.17	0.15	0.75	0.39
GC	0.13	0.12	0.31	0.58
AC	0.70	0.73	1.23	0.27
Haplotype 3: rs40122|rs35260|rs10472105|rs35259				
AAGT	0.36	0.49	16.44	5.0×10^{-5}
AGAC	0.11	0.07	4.59	0.03
TGGC	0.44	0.37	4.59	0.03
AGGC	0.10	0.07	2.38	0.12
Haplotype 4: rs35258|rs958851|rs17781354|rs13176940|rs13153653|rs6450517|rs17725522|rs6897015				
GGGTGGTG	0.19	0.28	9.52	0.002
TGGTGGTG	0.44	0.37	4.89	0.03
GGGCAATG	0.10	0.07	4.22	0.04
GTGCGATC	0.08	0.10	1.36	0.24
GGGCGACG	0.10	0.06	3.45	0.06
GTACGGTG	0.09	0.11	1.54	0.21

Supplementary Table S4. Mean values for the covariates included in the logistic regression model by cohort for European American cases and controls. Results are presented as mean ± standard deviation. P values are for the t test comparing cases to controls in each cohort. Cases are defined as having an ETDRS grade ≥ 14.

	Mean Age (years)			Mean Diabetes Duration (years)			Mean Fasting Glucose (mg/dL)			Mean Total Cholesterol (mg/dL)			Mean Systolic BP (mm Hg)			Mean Diastolic BP (mm Hg)		
	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
ARIC	62.1 ± 5.7	60.8 ± 5.5	0.01	14.7 ± 10.6	6.8 ± 7.9	2.2×10^{-18}	197 ± 72	164 ± 52	3.5×10^{-9}	203 ± 43	211 ± 44	0.03	140 ± 24	134 ± 21	0.002	74 ± 13	74 ± 12	0.22
CHS	79.2 ± 4.7	78.0 ± 4.2	0.12	16.1 ± 11.2	9.1 ± 8.9	0.0003	170 ± 51	148 ± 39	0.006	205 ± 46	189 ± 34	0.02	150 ± 23	143 ± 22	0.17	71 ± 10	73 ± 11	0.5
MESA	64.3 ± 10.6	66.4 ± 9.6	0.26	16.8 ± 10.3	7.7 ± 6.5	6.7×10^{-6}	155 ± 46	137 ± 33	0.009	183 ± 38	179 ± 37	0.53	137 ± 21	139 ± 21	0.67	73 ± 10	76 ± 12	0.08

ETDRS=Early Treatment Diabetic Retinopathy Study, BP= blood pressure

Supplementary Table S5. P values for comparison of European American cases and controls for the first three principal components of the IBC analyses

Principal component	p value, case definition ETDRS grade ≥ 14	p value, case definition ETDRS grade ≥ 30
1	0.78	0.66
2	0.17	0.11
3	0.34	0.36

IBC=ITMAT-Broad-CARe Chip, ETDRS=Early Treatment Diabetic Retinopathy Study,

Supplementary Table S6. Replication results in Europeans including only groups that used ETDRS grading consistently and included type 2 diabetes participants

		ARIC		CHS		MESA		AGES			BMES			FIND-Eye			Lublin			Meta-Analysis (Fixed Effects)		
	Number of controls	732		160		140		249			175			627			620					
	Number of cases ETDRS ≥ 14	153		33		36		92			67			105			576					
	Number of cases ETDRS ≥ 30	91		20		11		37			26			NA			138					
SNP	Minor Allele	Definition of Cases	OR	p value	OR	p value	OR	p value	MAF	OR	p value	MAF	OR	p value	MAF	OR	p value	MAF	OR	p value	Z score	OR	p value
rs9332570	G	ETDRS ≥ 14	0.43	0.0001	0.33	0.02	0.49	0.06	NA	0.75	0.26	0.21	1.24	0.42	0.19	0.79	0.26	NA	NA	NA	-2.71	0.75	0.007
rs35260	A	ETDRS ≥ 14	0.68	0.002	0.59	0.08	0.29	0.0001	NA	1.01	0.98	0.49	1.23	0.32	0.48	0.9	0.45	NA	NA	NA	-3.08	0.8	0.002
rs6128	T	ETDRS ≥ 14	0.48	0.0007	0.27	0.02	0.39	0.03	0.09	1.27	0.32	0.21	1.27	0.37	0.17	0.73	0.14	0.16	1.01	0.96	-1.84	0.87	0.07
rs7168655	A	ETDRS ≥ 14	1.59	0.0004	1.78	0.04	1.48	0.15	NA	0.91	0.57	0.34	0.96	0.83	0.36	1.08	0.63	NA	NA	NA	2.86	1.24	0.004
rs6133	A	ETDRS ≥ 14	0.39	0.0005	0.19	0.03	0.51	0.16	0.15	0.73	0.32	0.14	1.37	0.28	0.13	0.72	0.17	0.08	1.03	0.84	-2.23	0.8	0.03
rs3917779	A	ETDRS ≥ 14	0.40	0.0007	0.20	0.03	0.51	0.16	0.09	0.73	0.32	0.14	1.25	0.45	0.12	0.72	0.19	NA	NA	NA	-3.19	0.66	0.001
rs6856425	C	ETDRS ≥ 14	2.48	0.01	5.21	0.004	2.63	0.16	0.04	0.89	0.86	0.02	1.8	0.45	0.02	1.18	0.75	0.05	0.7	0.07	0.96	1.15	0.34
rs7105871	C	ETDRS ≥ 14	0.47	1.7×10^{-5}	0.97	0.91	0.86	0.62	NA	0.81	0.2	0.25	1.16	0.54	0.22	0.88	0.47	NA	NA	NA	-2.95	0.77	0.003
rs6856425	C	ETDRS ≥ 30	3.19	0.003	6.8	0.002	3.25	0.19	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.05	0.46	0.06	2.36	1.78	0.02

All results are adjusted for age and gender.

ETDRS=Early Treatment Diabetic Retinopathy Study, MAF=minor allele frequency, OR=odds ratio, NA=not available

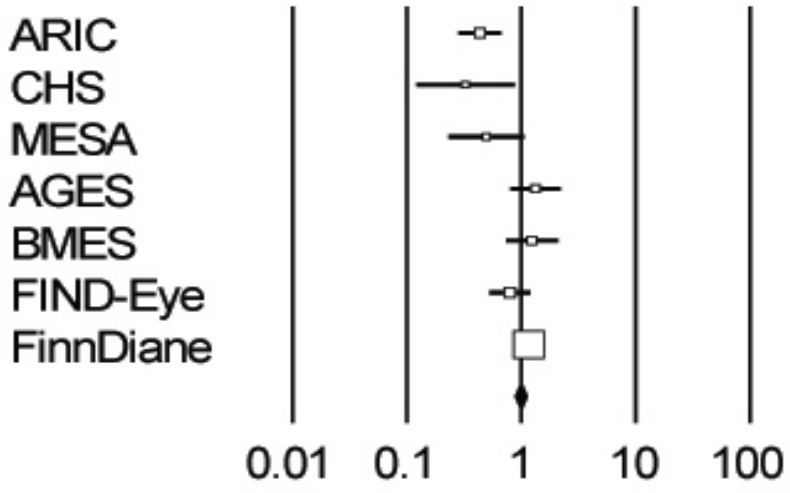
Supplementary Table S7. Percent power of the association study in discovery and replication cohorts for diabetic retinopathy defined as ETDRS grade ≥ 14 for different allele frequencies and genotype relative risks (GRR), assuming an additive model, a prevalence of diabetic retinopathy in the type 2 diabetes population of 0.3 and an alpha of 1×10^{-6}. The power calculations were obtained using the Genetic Power Calculator at http://pngu.mgh.harvard.edu/~purcell/gpc.

	Discovery Cohort CARe (221 cases, 1032 controls)			AGES (92 cases, 249 controls)			BMES (67 cases, 175 controls)			FIND-Eye (105 cases, 627 controls)			FinnDiane (2009 cases, 570 controls)			Go-DARTS (923 cases, 774 controls)			Lublin (576 cases, 630 controls)			Combined Replication Cohorts (3772 cases, 3025 controls)		
	GRR			GRR			GRR			GRR			GRR			GRR			GRR			GRR		
MAF	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5	1.25	1.4	1.5
0.1	0	5	20	0	0	1	0	0	0	0	0	2	2	33	70	3	37	75	1	16	46	83	100	100
0.2	1	22	58	0	1	3	0	0	1	0	2	10	15	84	99	15	85	99	5	57	90	100	100	100
0.3	2	36	74	0	1	6	0	0	2	0	5	16	30	96	100	29	96	100	11	78	98	100	100	100
0.4	3	40	76	0	2	7	0	1	2	0	5	17	40	98	100	37	98	100	15	84	99	100	100	100
0.5	3	37	71	0	2	6	0	1	2	0	5	15	42	99	100	38	98	100	16	83	98	100	100	100

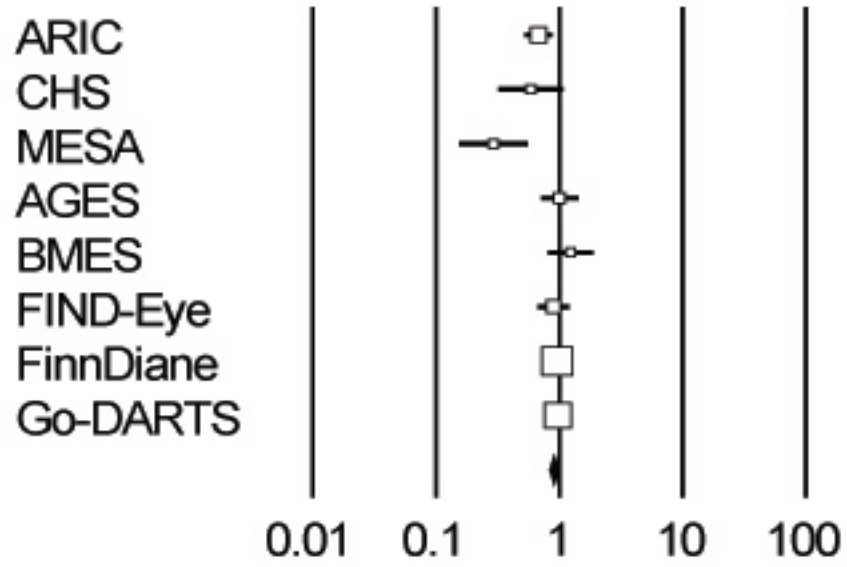
ETDRS=Early Treatment Diabetic Retinopathy Study, MAF=minor allele frequency

Supplementary Figure S1. Forest plots showing odds ratios and 95% confidence intervals for the association between each variant and DR (case definition ETDRS grade ≥14 unless otherwise noted) by cohort with the CMH replication meta-analysis result represented as a diamond.

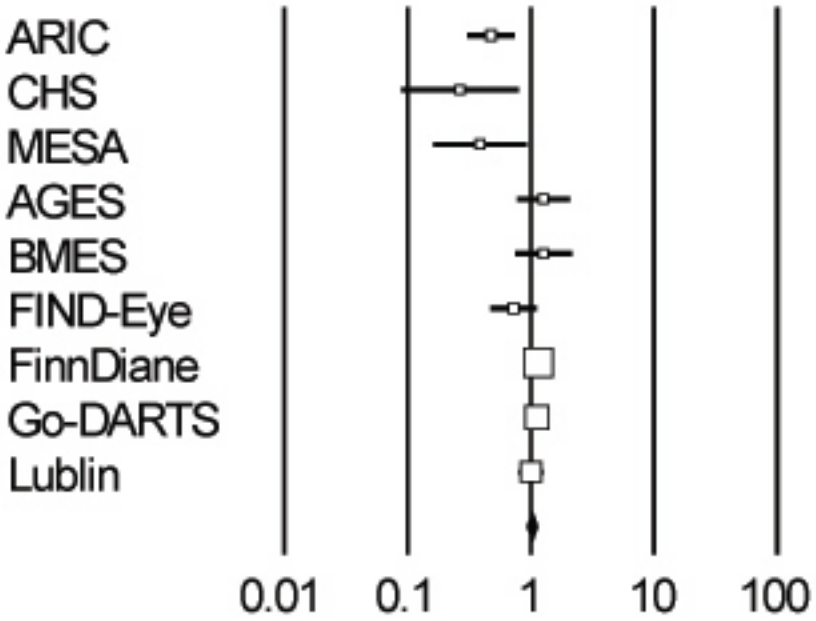
(A) rs9332570



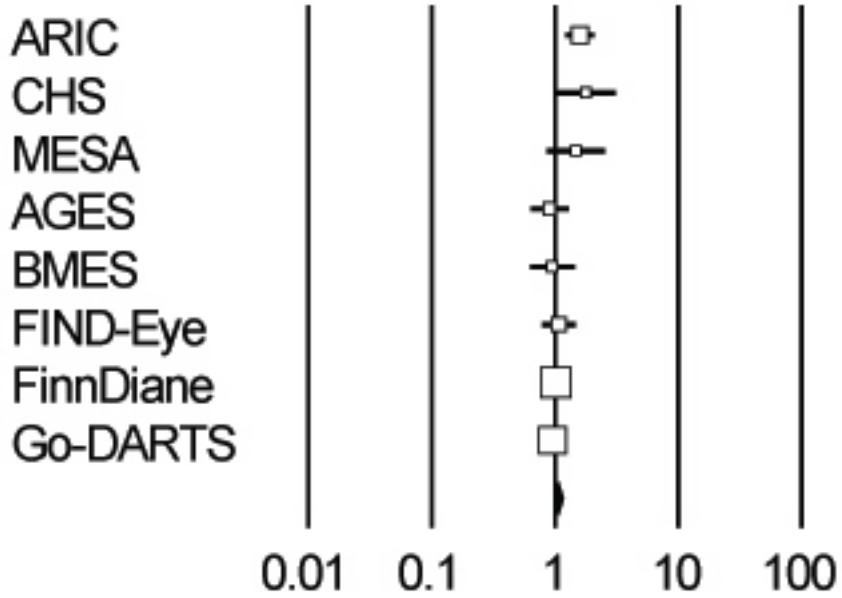
(B) rs35260



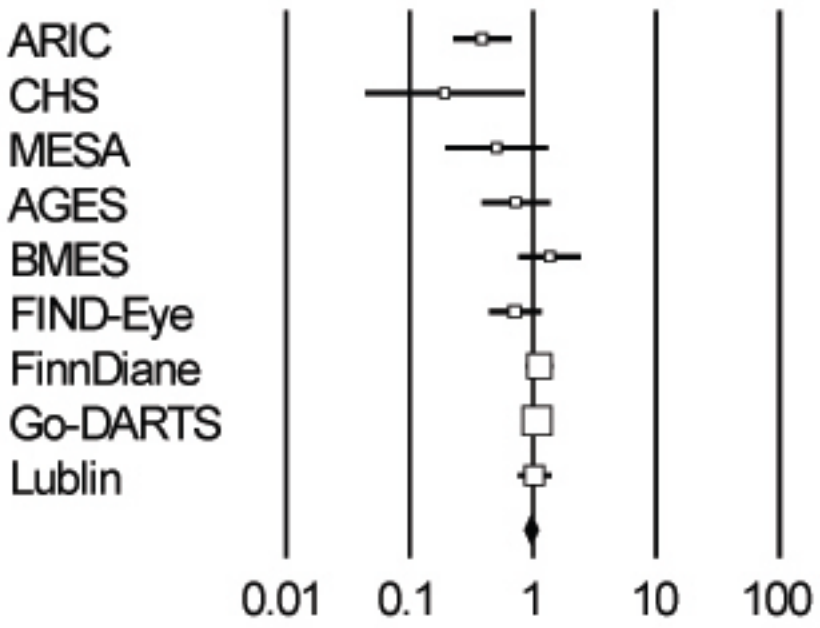
(C) rs6128



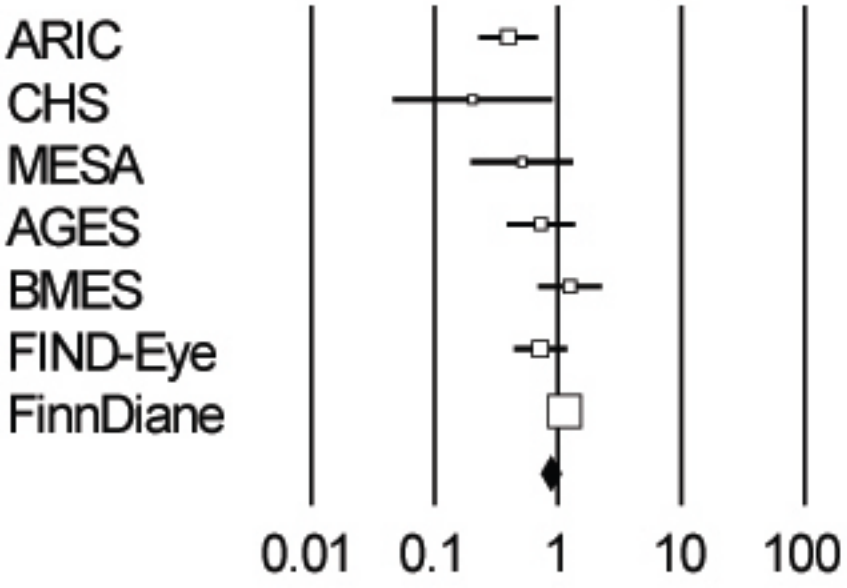
(D) rs7168655



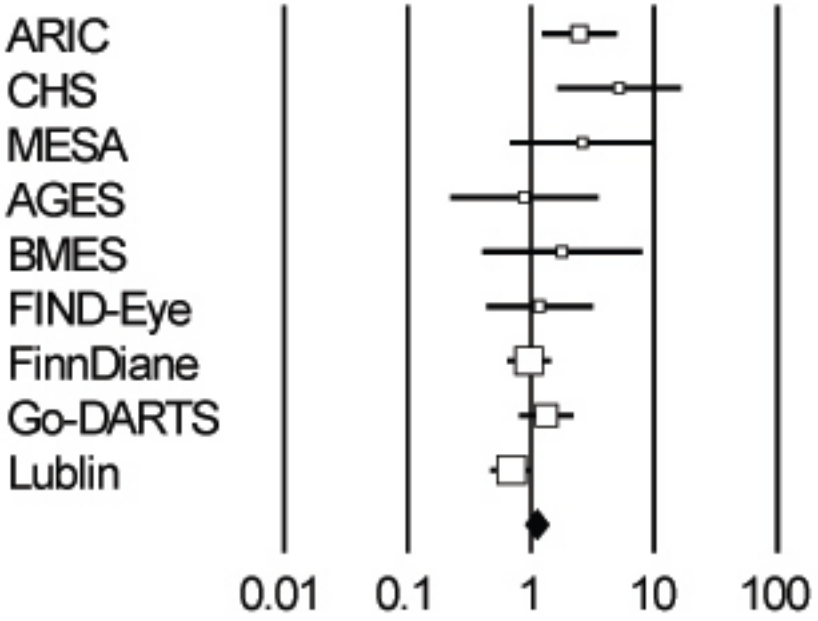
(E) rs6133



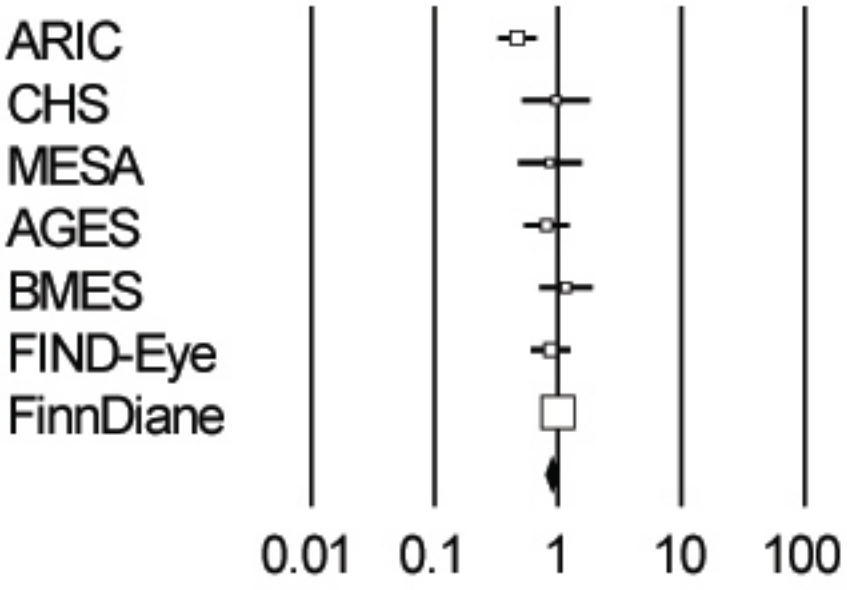
(F) rs3917779



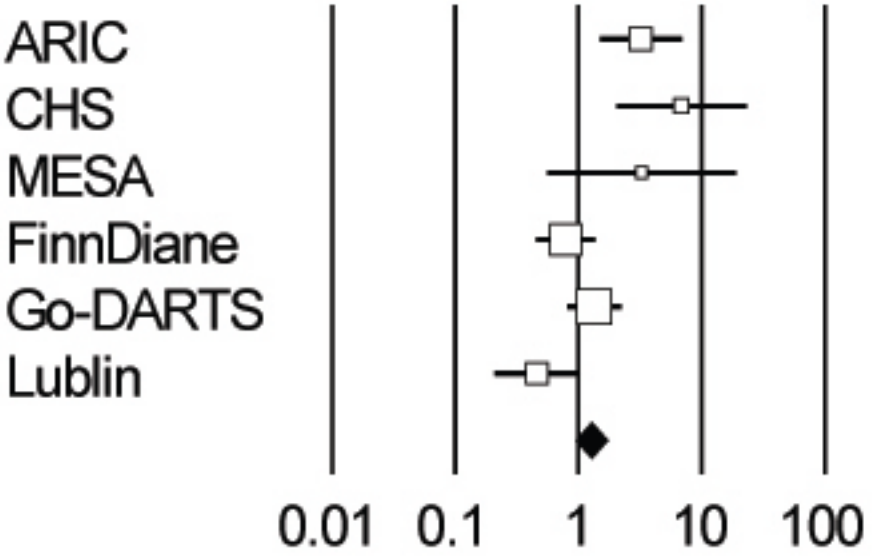
(G) rs6856425, for definition of DR cases as ETDRS grade ≥ 14



(H) rs7105871



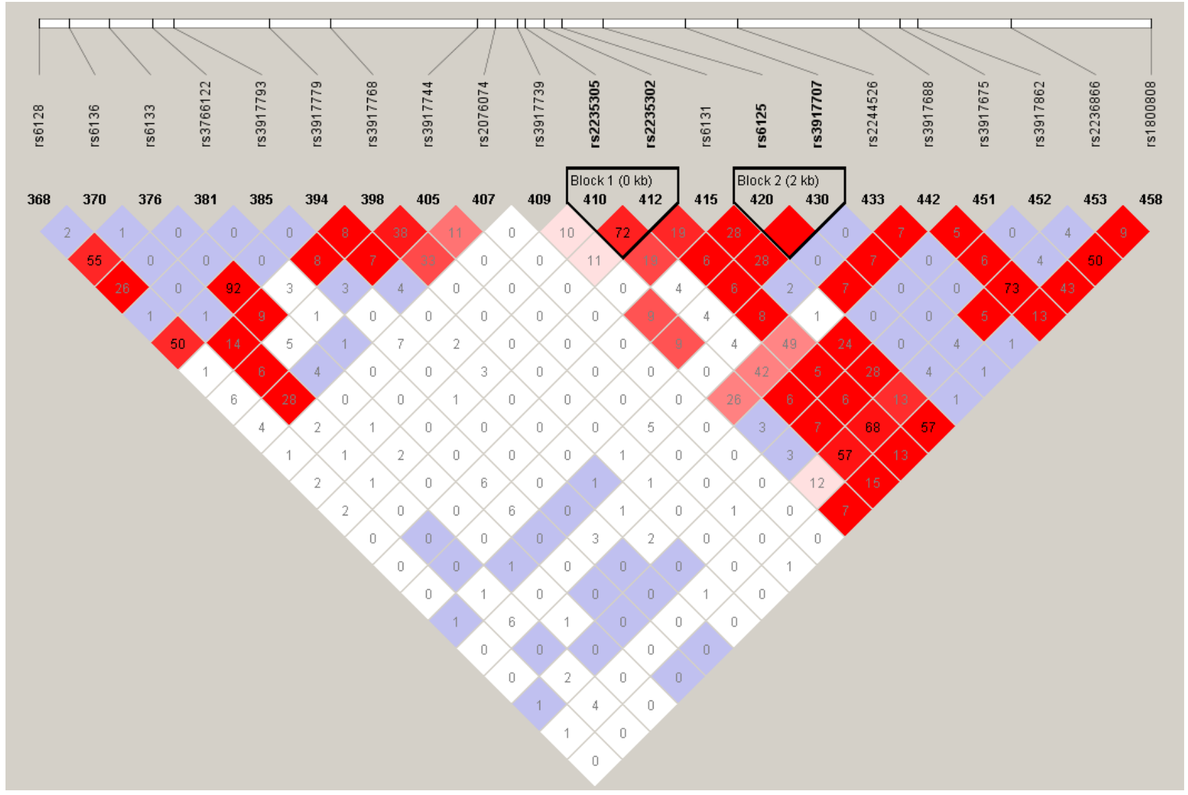
(I) rs6856425, for definition of DR cases as ETDRS grade ≥ 30



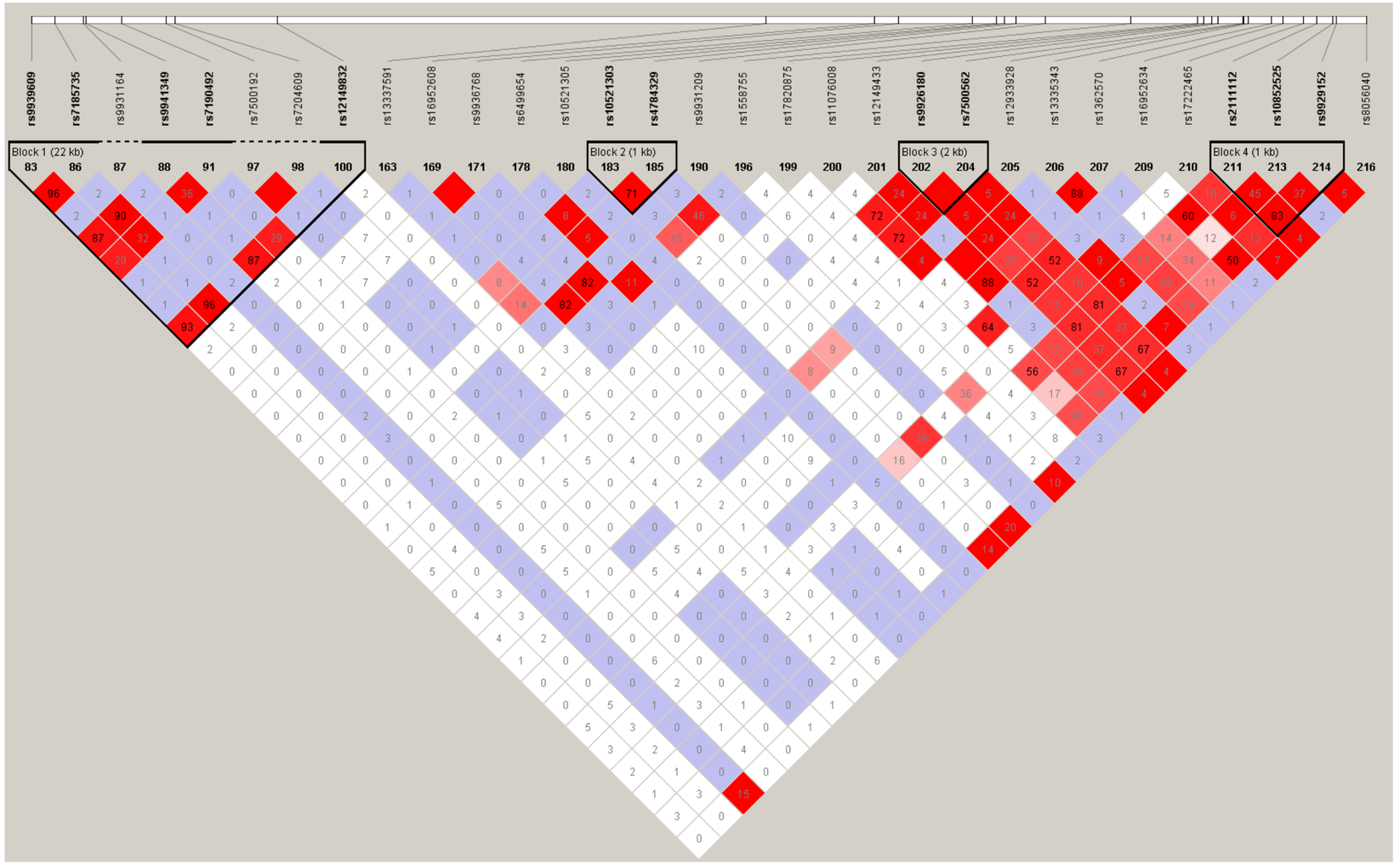
ETDRS=Early Treatment Diabetic Retinopathy Study, DR=diabetic retinopathy, CMH=Cochran-Mantel-Haenszel

Supplementary Figure S2. Linkage disequilibrium (LD) plots for genes associated with diabetic retinopathy in CARe, including the SNPs associated with diabetic nephropathy or type 2 diabetes in previous studies. Numbers within blocks represent r squared values. (A) LD plot of all *SELP* SNPs included on ITMAT-Broad-CARe (IBC) Chip and in HapMap, including rs6131, the SNP previously associated with diabetic microalbuminuria. (B) LD plot of *FTO* SNPs included on IBC Chip and in HapMap surrounding rs9926180, the most highly associated SNP in CARe, and rs9939609, the SNP associated previously to type 2 diabetes.

(A)



(B)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rs9936768
rs6499654
rs10521305
rs10521303
rs4784329
rs9931209
rs1558755
rs17820875
rs11076008
rs12149433
rs9926180
rs7500562
rs12933928
rs13335343
rs1362570
rs16952634
rs17222465
rs2111112
rs10852525
rs9929152
rs8056040
Block 1 (22 kb)
Block 2 (1 kb)
Block 3 (2 kb)
Block 4 (1 kb)

Supplementary Methods

CARe SNP Selection Criteria

Single nucleotide polymorphisms (SNPs) were chosen to densely map about 2,000 candidate genes relevant to phenotypes available in CARe. The density of the mapping varied as follows.[1] For 435 loci in genes and regions with a high likelihood of functional significance including established mediators of vascular disease and loci derived from genome-wide association studies (GWAS), tag SNPs were selected to capture known variation with MAF $\geq$ 0.02 and an $r^2 \geq 0.8$ in HapMap populations. For 1,349 loci that were deemed to be potentially involved in phenotypes of interest or established loci that required very large numbers of tagging SNPs, SNPs were selected for MAF $\geq$ 0.05 with an $r^2 \geq 0.5$ in HapMap populations. The last 232 loci were comprised mainly of the larger genes (> 100 kb) which were of lower interest *a priori* to the consortium investigators. Only non-synonymous SNPs and known functional variants of MAF $\geq$ 0.01 were captured for these loci.

CARe Genotyping Quality Control (QC)

DNA concentration was determined by the Picogreen assay (Invitrogen, Carlsbad, Calif) before storage in 2D bar-coded 0.75 mL Matrix tubes at −20°C in the SmaRTStore (RTS, Manchester, UK) automated sample handling system. As an initial quality check, seven SNPs that were selected because of previous strong associations to cardiovascular disease were genotyped using the Sequenom MassArray System platform (Sequenom, San Diego, Calif). All DNA samples passing initial quality checks were plated at a concentration of 5 ng/μL for processing on the platform.

Several QC procedures were performed on the genotype data separately for each cohort. Sample duplicates were identified and for each set of duplicates or monozygotic twins, data from the sample with the highest genotyping success rate were retained. Reported sex and genotype-inferred sex (two independent Sequenom assays for each sample) were compared for concordance. All discordant samples and samples for which no sex information was available were resolved in consultation with the relevant cohort or excluded. SNPs with a missing data rate >10% and samples with a genotyping success rate <90% were removed. Because several different ethnic groups were represented, with the expectation of differing genotype frequencies and admixture, no filters were applied for minor allele frequency (MAF) or Hardy-Weinberg probability values. All QC analyses were performed in PLINK.[2]

Replication Cohort Diabetic Retinopathy Definitions

AGES, BMES, SiMES, and SP2 fundus photographs were graded by the ETDRS scale used the same DR definitions as CARe. The fundus photographs for AGES were read by the University of Wisconsin Ocular Epidemiology Reading Center.

Go-DARTS: Go-DARTS defined DR cases as having either (1) severe retinopathy (four or more blot hemorrhages), venous beading or intraretinal microvascular abnormalities); or (2) proliferative retinopathy (new vessel formation or vitreous hemorrhage); or (3) evidence for diabetic-related laser photocoagulation treatment. The Go-DARTS controls were defined as having no record of any diabetic retinopathy. Genotyping of the Go-DARTS cohort was

performed with the Affymetrix 6.0 platform as part of the Wellcome Trust Case Control Consortium 2 and imputed to HapMap2 with IMPUTE2 as previously described.[3]

FIND-Eye: The fundus photographs for FIND-Eye were also read by the University of Wisconsin Ocular Epidemiology Reading Center. ETDRS grades were converted to a five-step scale: no DR (ETDRS = 10–12), mild NPDR (ETDRS = 14–20), moderate NPDR (ETDRS = 35–43), severe NPDR (ETDRS = 47–53), and proliferative DR (ETDRS $\geq$ 60). Accordingly, the following categories were created, based on the more severely involved eye: (1) no DR, (2) mild NPDR, (3) moderate NPDR, (4) severe NPDR, and (5) PDR. This five-step scale was used primarily in the case and control definitions. Specifically, cases were defined as grade of 4 or higher (mild nonproliferative DR or more severe, but not very mild NPDR) on a separate 24-step scale OR grade 2 or higher on this five-step scale. Controls were defined as grade of 3 or lower on the separate 24-step scale OR no fundus photograph AND less than grade 2 on the five-step scale.

FinnDiane: FinnDiane is a nationwide multicenter study of type 1 diabetes and its complications. All the patients in the proliferative retinopathy analysis (n=1632) had their classification based on fundus photographs (n=658) and/or fundus examinations performed by ophthalmologists. Those patients with images available had been photographed on a median of three separate occasions. All available ophthalmic data were used to score the severity of retinopathy according to the ETDRS scale by an ophthalmologist (KH) unaware of the demographic data and the presence or absence of other complications. The eye with the more severe retinopathy was used to represent the overall retinopathy severity for the particular patient. For patients who did not have ophthalmic records or fundus photographs available, DR

was classified as (1) laser-treated retinopathy, (2) background retinopathy, or (3) no retinopathy by their attending physician during their routine diabetes visits based on medical records. All controls were required to have a duration of type 1 diabetes of at least 10 years.

Medical University of Lublin: Patients were classified into three categories based on ETDRS grading of photographs or phenotype descriptions by referring ophthalmologists: (1) no retinopathy, (2) NPDR ranging from microaneurysms only to severe NPDR, and (3) PDR.

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References

1. Keating BJ, Tischfield S, Murray SS, et al. Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. PLoS One 2008;3:e3583.
2. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559-75.
3. Zhou K, Bellenguez C, Spencer CC, et al. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat Genet 2011;43:117-20.