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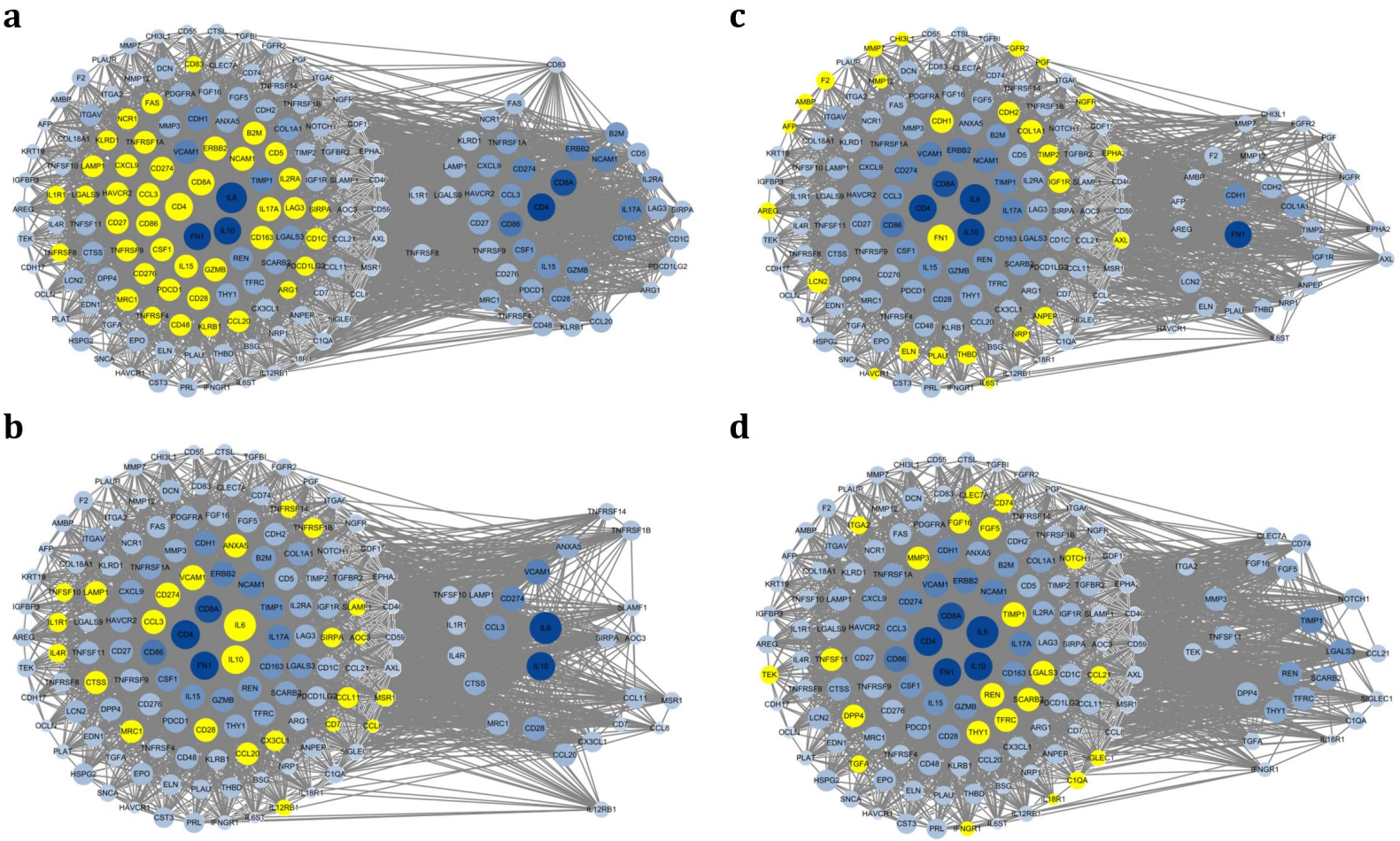
SUPPLEMENTARY FIGURES

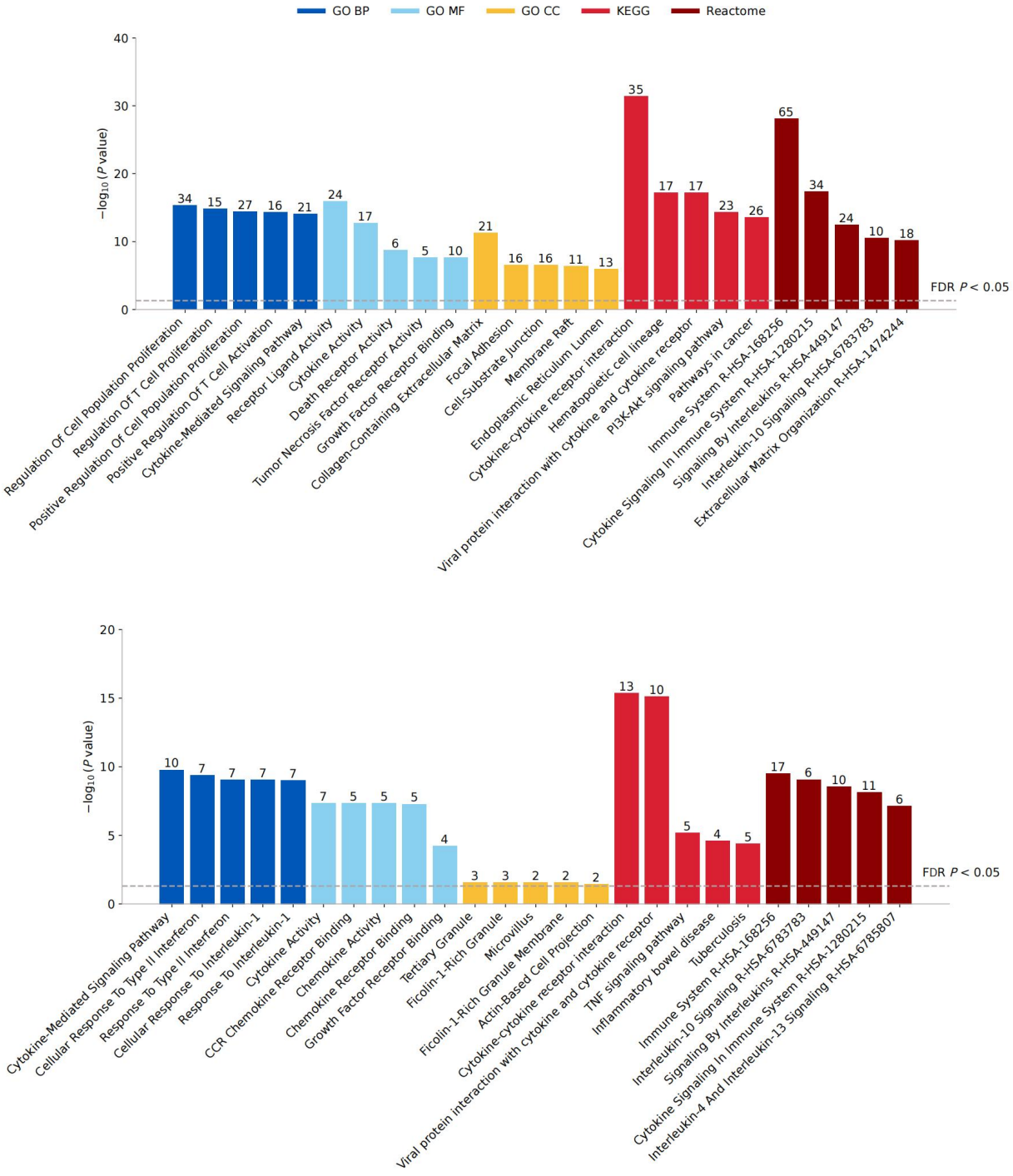
Supplementary Fig. S1

The MCODE subnetworks 1 (**a**), 2 (**b**), 3 (**c**), and 4 (**d**) underlying DR pathogenesis.



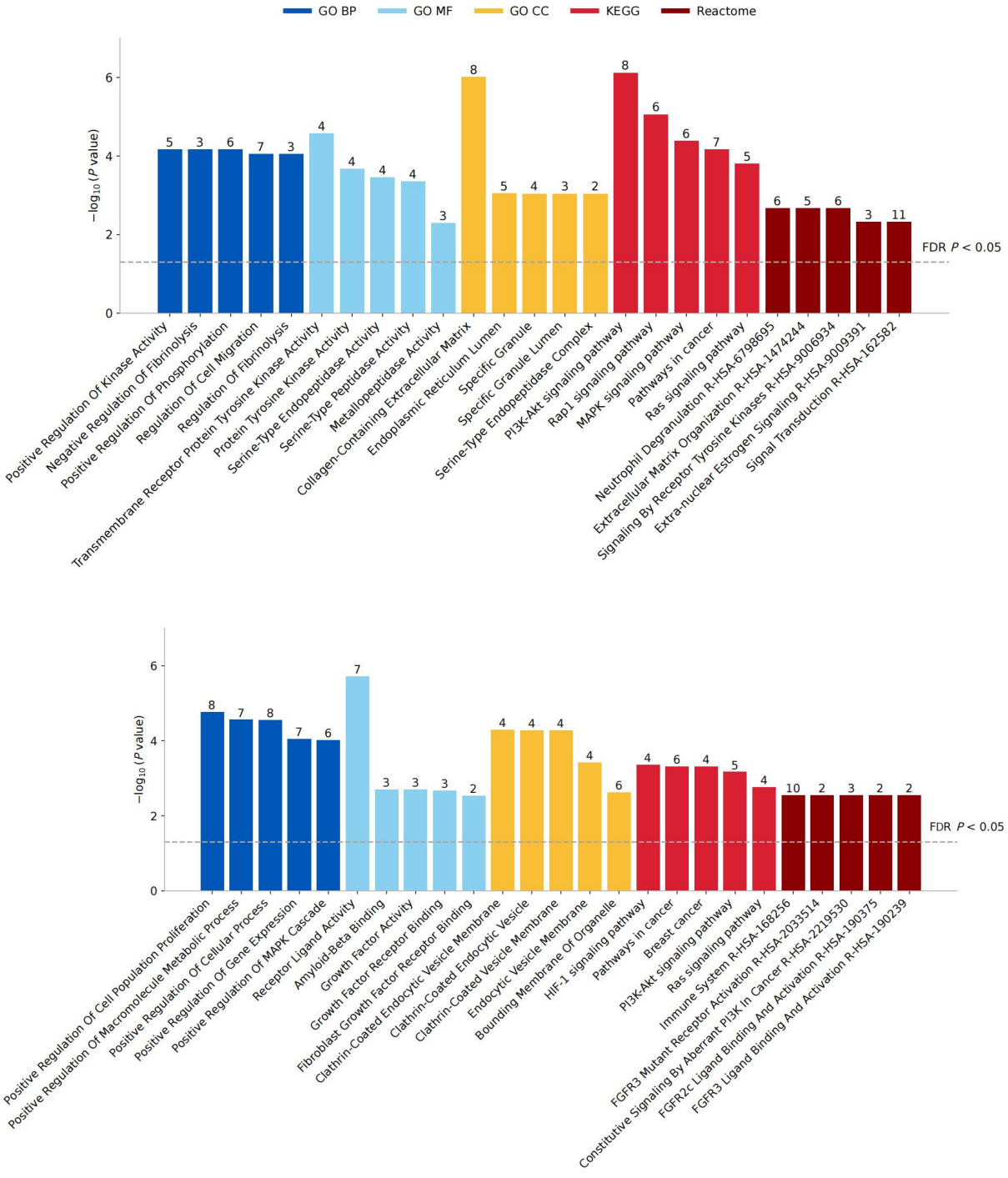
Supplementary Fig. S2

Functional enrichment for MCODE subnetworks 1 and 2.

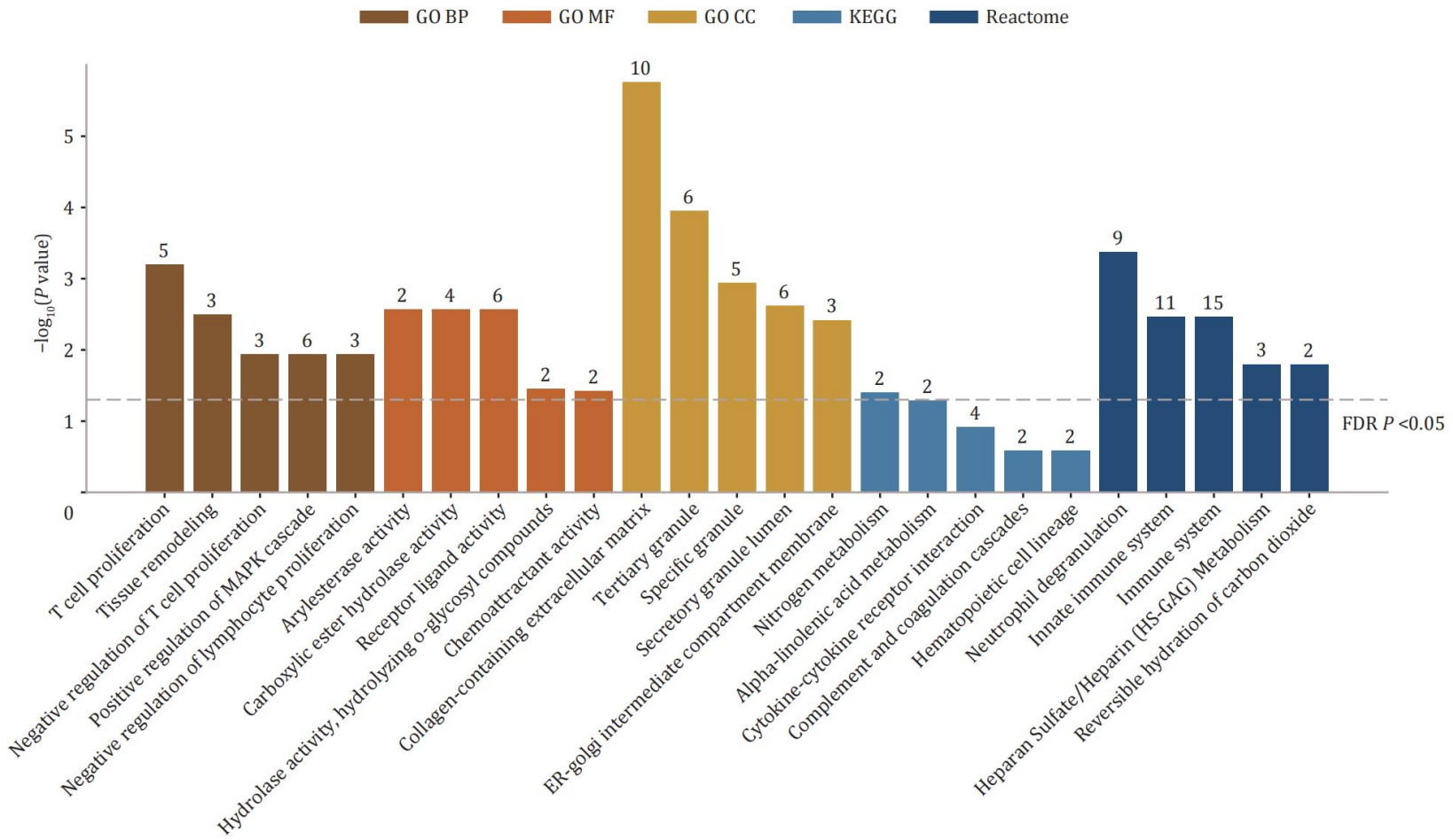


Supplementary Fig. S3

Functional enrichment for MCODE subnetworks 3 and 4.



Supplementary Fig. S4
Functional enrichment for pathways underlying DR progression.



SUPPLEMENTARY TABLES

Supplementary Table S1

Baseline characteristics of the UKB participants included in the study.

Characteristics *	**UKB population**			***P*** **†**
	Overall	**Non-DR**	**Incident-DR**	
No. of subjects	10,521	10,096	425	–
Age, years	59.63±7.30	59.61±7.30	60.11±7.31	0.167
Sex				
Female	5,254 (49.9%)	5,092 (50.4%)	162 (38.1%)	6.52×10^{-7}
Male	5,267 (50.1%)	5,004 (49.6%)	263 (61.9%)	
Ethnicity				
Caucasian	9,243 (87.9%)	8,889 (88.0%)	354 (83.3%)	0.003
East Asian	425 (4.0%)	396 (3.9%)	29 (6.8%)	
South Asian	50 (0.5%)	50 (0.5%)	0 (0.0%)	
Black	470 (4.5%)	445 (4.4%)	25 (5.9%)	
Other/mixed	264 (2.5%)	248 (2.5%)	16 (3.8%)	
Unknown	69 (0.7%)	68 (0.7%)	1 (0.2%)	
Educational attainment				
Level O	4,415 (42.0%)	4,218 (41.8%)	197 (46.4%)	0.290
Level A	480 (4.6%)	463 (4.6%)	17 (4.0%)	
University	5,406 (51.4%)	5,202 (51.5%)	204 (48.0%)	
Missing	220 (2.1%)	213 (2.1%)	7 (1.6%)	
Smoking				
Never	5,074 (48.2%)	4,875 (48.3%)	199 (46.8%)	0.062
Ever/current	3,958 (37.6%)	3,779 (37.4%)	179 (42.1%)	

Missing	1,489 (14.2%)	1,442 (14.3%)	47 (11.1%)	
Body mass index, kg/m^2	29.62±5.56	29.55±5.54	31.38±5.68	2.47×10^{-10}
Duration of diabetes, days †	123.04±542.70	120.10±530.06	192.70±782.89	0.007
Systolic blood pressure, mmHg	137.10±18.32	137.09±18.37	137.40±17.25	0.732
Hemoglobin A1c, mmol/mol	44.68±10.41	44.16±9.67	57.40±17.39	6.98×10^{-42}

* Continuous data are presented as mean ± standard deviation and categorical variables as number (percentage). Differences in population groups were compared using two-sided Student's t-test for continuous variables and Pearson's χ^2-test for discrete variables.
† Adjustment for multiple comparisons was not applied.
‡ Duration of diabetes was considered zero for participants with pre-diabetes.

Supplementary Table S2

Baseline characteristics of the UKB participants stratified by dataset.

Characteristics *	**UKB population**			***P*** **†**
	Overall population	**Discovery set**	**Test set**	
No. of subjects	10,521	8,451	2,070	–
Age, years	59.63±7.30	59.57±7.32	59.88±7.18	0.089
Sex				
Female	5,254 (49.9%)	4,186 (49.5%)	1,068 (51.6%)	0.098
Male	5,267 (50.1%)	4,265 (50.5%)	1,002 (48.4%)	
Ethnicity				
Caucasian	9,243 (87.9%)	7,399 (87.6%)	1,844 (89.1%)	0.507
East Asian	425 (4.0%)	347 (4.1%)	78 (3.8%)	
South Asian	50 (0.5%)	43 (0.5%)	7 (0.3%)	
Black	470 (4.5%)	389 (4.6%)	81 (3.9%)	
Other/mixed	264 (2.5%)	216 (2.6%)	48 (2.3%)	
Unknown	69 (0.7%)	57 (0.7%)	12 (0.6%)	
Educational attainment				
Level O	4,415 (42.0%)	3,562 (42.1%)	853 (41.2%)	0.644
Level A	480 (4.6%)	376 (4.4%)	104 (5.0%)	
University	5,406 (51.4%)	4,335 (51.3%)	1,071 (51.7%)	
Missing	220 (2.1%)	178 (2.1%)	42 (2.0%)	
Smoking				
Never	5,074 (48.2%)	4,091 (48.4%)	983 (47.5%)	0.675
Ever/current	3,958 (37.6%)	3,162 (37.4%)	796 (38.5%)	
Missing	1,489 (14.2%)	1,198 (14.2%)	291 (14.1%)	

Body mass index, kg/m^2	29.62 (5.56)	29.64 (5.52)	29.54 (5.70)	0.489
Duration of diabetes, days ‡	123.04±542.70	123.88±550.15	119.58±511.27	0.747
Systolic blood pressure, mmHg	137.10±18.32	137.16±18.26	136.87±18.55	0.525
Hemoglobin A1c, mmol/mol	44.68±10.41	44.70±10.48	44.60±10.12	0.692

* Continuous data are presented as mean ± standard deviation and categorical variables as number (percentage). Differences in population groups were compared using two-sided Student's t-test for continuous variables and Pearson's χ^2-test for discrete variables.
† Adjustment for multiple comparisons was not applied.
‡ Duration of diabetes was considered zero for participants with pre-diabetes.

Supplementary Table S3

Identifying DR-associated proteins in model 1 (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
GDF15	Cardiometabolic	1.770 (1.666–1.881)	2.74×10^{-72}
PLXNB2	Cardiometabolic	1.668 (1.562–1.780)	6.34×10^{-50}
CA12	Oncology	1.497 (1.418–1.581)	2.34×10^{-45}
IL1R1	Neurology	1.701 (1.579–1.831)	3.45×10^{-42}
CD276	Inflammation	1.816 (1.670–1.975)	1.93×10^{-41}
DSC2	Neurology	1.459 (1.383–1.539)	1.79×10^{-40}
HAVCR1	Oncology	1.640 (1.527–1.762)	2.12×10^{-39}
PLA2G7	Neurology	0.666 (0.628–0.706)	2.79×10^{-39}
EFNA4	Neurology	1.462 (1.382–1.545)	6.63×10^{-38}
SPINK4	Inflammation	1.648 (1.528–1.778)	8.79×10^{-36}
LIFR	Inflammation	1.541 (1.443–1.646)	1.48×10^{-35}
REN	Cardiometabolic	1.538 (1.440–1.643)	5.27×10^{-35}
NEFL	Neurology	1.563 (1.458–1.676)	5.82×10^{-34}
VSIG4	Neurology	1.611 (1.493–1.738)	1.23×10^{-32}
TNFRSF1A	Neurology	1.551 (1.445–1.665)	1.04×10^{-31}
CHAD	Inflammation II	0.567 (0.517–0.621)	1.11×10^{-31}
SCARA5	Neurology	1.635 (1.510–1.770)	1.57×10^{-31}
DLL1	Oncology	1.625 (1.502–1.759)	2.72×10^{-31}
SPINK1	Neurology	1.484 (1.391–1.582)	4.62×10^{-31}
ADA2	Cardiometabolic	1.571 (1.459–1.691)	4.82×10^{-31}
LGALS4	Inflammation	1.613 (1.492–1.744)	5.05×10^{-31}
CD27	Oncology	1.540 (1.434–1.653)	9.35×10^{-31}
KLRB1	Inflammation	1.638 (1.510–1.776)	1.06×10^{-30}
AREG	Oncology	1.525 (1.422–1.635)	2.09×10^{-30}
MUC13	Neurology	1.504 (1.405–1.609)	3.57×10^{-30}
CDH1	Cardiometabolic	1.405 (1.327–1.488)	2.03×10^{-29}
REG4	Inflammation	1.568 (1.454–1.691)	2.03×10^{-29}
TNFRSF11A	Inflammation	1.547 (1.437–1.665)	4.51×10^{-29}
GFRA1	Oncology	1.587 (1.467–1.717)	1.26×10^{-28}
KLK4	Oncology	1.530 (1.421–1.646)	7.29×10^{-28}

* CPH models were adjusted for age, sex, and ethnicity.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S4

Replicating DR-associated proteins in model 2 (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
GDF15	Cardiometabolic	1.734 (1.620–1.856)	2.06×10^{-53}
CA12	Oncology	1.503 (1.417–1.595)	1.13×10^{-38}
PLA2G7	Neurology	0.667 (0.626–0.710)	2.64×10^{-33}
SPINK4	Inflammation	1.632 (1.507–1.768)	2.27×10^{-30}
CD276	Inflammation	1.691 (1.548–1.848)	1.69×10^{-28}
SPINK1	Neurology	1.500 (1.400–1.607)	4.79×10^{-28}
NEFL	Neurology	1.559 (1.444–1.682)	1.59×10^{-27}
VSIG4	Neurology	1.611 (1.484–1.749)	1.59×10^{-27}
KLK4	Oncology	1.574 (1.453–1.706)	4.30×10^{-26}
DLL1	Oncology	1.608 (1.478–1.750)	9.66×10^{-26}
AREG	Oncology	1.508 (1.399–1.625)	1.40×10^{-24}
EFNA4	Neurology	1.420 (1.331–1.514)	3.64×10^{-24}
DSC2	Neurology	1.412 (1.324–1.506)	1.65×10^{-23}
IL1R1	Neurology	1.528 (1.411–1.654)	1.95×10^{-23}
CD27	Oncology	1.510 (1.396–1.632)	8.47×10^{-23}
REG1A	Cardiometabolic	1.468 (1.365–1.578)	9.14×10^{-23}
REG4	Inflammation	1.531 (1.411–1.660)	2.21×10^{-22}
TFF3	Cardiometabolic	1.404 (1.316–1.499)	3.49×10^{-22}
EPHA2	Oncology	1.489 (1.379–1.607)	4.09×10^{-22}
TNFRSF1A	Neurology	1.496 (1.383–1.619)	1.32×10^{-21}
PIK3IP1	Neurology	1.474 (1.366–1.590)	1.68×10^{-21}
HAVCR1	Oncology	1.507 (1.390–1.634)	4.50×10^{-21}
LGALS4	Inflammation	1.525 (1.403–1.658)	5.76×10^{-21}
DCBLD2	Oncology	1.608 (1.463–1.767)	9.44×10^{-21}
REN	Cardiometabolic	1.460 (1.354–1.574)	1.17×10^{-20}
EDA2R	Oncology	1.614 (1.467–1.776)	1.26×10^{-20}
KLRB1	Inflammation	1.541 (1.413–1.681)	1.89×10^{-20}
LAYN	Neurology	1.473 (1.363–1.592)	2.15×10^{-20}
TNFRSF11A	Inflammation	1.481 (1.367–1.605)	7.12×10^{-20}
SCARA5	Neurology	1.533 (1.402–1.676)	5.51×10^{-19}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S5
Sensitivity analyses additionally adjusting for hypoglycaemic medications (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
CA12	Oncology	1.415 (1.321–1.517)	2.13×10^{-19}
NEFL	Neurology	1.459 (1.349–1.578)	5.03×10^{-18}
KLK4	Oncology	1.460 (1.343–1.586)	4.14×10^{-16}
CD276	Inflammation	1.473 (1.351–1.606)	1.05×10^{-15}
VSIG4	Neurology	1.456 (1.336–1.588)	9.70×10^{-15}
EDA2R	Oncology	1.480 (1.351–1.622)	2.10×10^{-14}
LAYN	Neurology	1.375 (1.273–1.485)	1.74×10^{-13}
PIK3IP1	Neurology	1.372 (1.271–1.482)	2.13×10^{-13}
GDF15	Cardiometabolic	1.380 (1.276–1.492)	2.13×10^{-13}
SCARA5	Neurology	1.429 (1.310–1.560)	3.38×10^{-13}
DLL1	Oncology	1.412 (1.298–1.537)	3.59×10^{-13}
IGFBP2	Cardiometabolic	1.479 (1.344–1.629)	3.59×10^{-13}
TFF3	Cardiometabolic	1.353 (1.255–1.458)	6.61×10^{-13}
EPHA2	Oncology	1.365 (1.262–1.476)	1.32×10^{-12}
TNFRSF1A	Neurology	1.365 (1.261–1.478)	2.86×10^{-12}
EFNA4	Neurology	1.334 (1.239–1.435)	3.13×10^{-12}
GFRA1	Oncology	1.378 (1.268–1.497)	6.08×10^{-12}
CD27	Oncology	1.377 (1.267–1.497)	1.06×10^{-11}
CKB	Cardiometabolic II	1.485 (1.338–1.648)	1.39×10^{-11}
SPINK1	Neurology	1.321 (1.227–1.422)	1.72×10^{-11}
CKAP4	Inflammation	1.338 (1.239–1.446)	2.07×10^{-11}
SPINK4	Inflammation	1.355 (1.249–1.471)	4.81×10^{-11}
REG1A	Cardiometabolic	1.331 (1.231–1.438)	7.60×10^{-11}
EFNA1	Neurology	1.324 (1.226–1.430)	1.31×10^{-10}
TGFBR2	Oncology	1.300 (1.208–1.398)	1.97×10^{-10}
OGN	Neurology	1.346 (1.234–1.468)	2.08×10^{-9}
TNFRSF14	Inflammation	1.305 (1.207–1.411)	2.53×10^{-9}
EPHB4	Cardiometabolic	1.300 (1.203–1.404)	2.67×10^{-9}
FAM3C	Cardiometabolic	1.332 (1.224–1.448)	2.67×10^{-9}
IGFBP4	Neurology	1.293 (1.198–1.396)	3.61×10^{-9}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and hypoglycaemic medications.
† Data are presented as per-SD change of protein values.
‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S6

Sensitivity analyses excluding participants who experienced DR within the initial 2 years of follow-up (top 30 shown).

Proteins *	Panels	HR (95% CI) †	P_{FDR} ‡
GDF15	Cardiometabolic	1.695 (1.572–1.827)	9.56×10^{-40}
PLA2G7	Neurology	0.652 (0.609–0.697)	2.06×10^{-32}
CA12	Oncology	1.482 (1.388–1.582)	5.65×10^{-29}
SPINK4	Inflammation	1.602 (1.469–1.748)	1.29×10^{-23}
NEFL	Neurology	1.549 (1.425–1.683)	3.35×10^{-22}
CD276	Inflammation	1.657 (1.504–1.826)	7.69×10^{-22}
SPINK1	Neurology	1.482 (1.375–1.599)	7.69×10^{-22}
IL1R1	Neurology	1.554 (1.427–1.692)	1.34×10^{-21}
VSIG4	Neurology	1.586 (1.450–1.736)	2.89×10^{-21}
DLL1	Oncology	1.570 (1.432–1.721)	2.07×10^{-19}
KLK4	Oncology	1.546 (1.415–1.690)	2.07×10^{-19}
REG1A	Cardiometabolic	1.465 (1.354–1.584)	4.95×10^{-19}
AREG	Oncology	1.488 (1.370–1.615)	6.39×10^{-19}
DCBLD2	Oncology	1.630 (1.473–1.804)	6.39×10^{-19}
LGALS4	Inflammation	1.537 (1.404–1.681)	1.56×10^{-18}
EFNA4	Neurology	1.402 (1.306–1.506)	2.51×10^{-18}
CD27	Oncology	1.488 (1.366–1.620)	1.41×10^{-17}
REG4	Inflammation	1.503 (1.376–1.642)	2.33×10^{-17}
HAVCR1	Oncology	1.498 (1.371–1.637)	5.89×10^{-17}
TFF3	Cardiometabolic	1.388 (1.292–1.492)	6.99×10^{-17}
DSC2	Neurology	1.397 (1.298–1.504)	7.98×10^{-17}
KLRB1	Inflammation	1.531 (1.393–1.682)	9.10×10^{-17}
FGFBP1	Oncology	0.705 (0.652–0.763)	4.40×10^{-16}
EPHA2	Oncology	1.453 (1.336–1.581)	4.98×10^{-16}
PLXNB2	Cardiometabolic	1.424 (1.314–1.543)	7.99×10^{-16}
IGFBP3	Cardiometabolic	0.724 (0.673–0.779)	8.01×10^{-16}
SPOCK1	Neurology	0.645 (0.583–0.714)	2.21×10^{-15}
TNFRSF1A	Neurology	1.458 (1.337–1.591)	2.25×10^{-15}
REN	Cardiometabolic	1.423 (1.310–1.545)	5.31×10^{-15}
TNFRSF11A	Inflammation	1.452 (1.330–1.585)	9.25×10^{-15}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S7

The marginal increase in variance of DR-associated proteins explained attributable to hypoglycaemic medication use (top 30 shown).

Proteins	**Panels**	**Base r^2 (95% CI) ***	**Integrated r^2 (95% CI) †**	**Marginal gap ‡**	**P_{FDR} §**
CD276	Inflammation	0.091 (0.080–0.102)	0.121 (0.108–0.133)	0.030 (0.013–0.046)	3.79×10^{-4}
CA12	Oncology	0.068 (0.058–0.078)	0.093 (0.081–0.104)	0.025 (0.010–0.039)	0.001
IGFBP2	Cardiometabolic	0.261 (0.246–0.276)	0.285 (0.270–0.300)	0.024 (0.003–0.046)	0.027
CKB	Cardiometabolic II	0.245 (0.229–0.262)	0.267 (0.251–0.284)	0.022 (−0.001–0.045)	0.060
CTRB1	Neurology	0.024 (0.018–0.030)	0.045 (0.037–0.053)	0.021 (0.011–0.031)	4.30×10^{-5}
GHR	Inflammation II	0.162 (0.148–0.177)	0.183 (0.168–0.198)	0.021 (−0.001–0.042)	0.056
AFM	Inflammation II	0.128 (0.115–0.142)	0.148 (0.134–0.162)	0.020 (0.000–0.039)	0.049
CELA3A	Cardiometabolic	0.020 (0.014–0.025)	0.039 (0.031–0.046)	0.019 (0.010–0.028)	7.37×10^{-5}
CPA1	Cardiometabolic	0.026 (0.019–0.032)	0.044 (0.036–0.052)	0.019 (0.008–0.029)	3.36×10^{-4}
CTRC	Inflammation	0.044 (0.036–0.052)	0.062 (0.052–0.071)	0.018 (0.006–0.030)	0.004
GFRA1	Oncology	0.161 (0.147–0.174)	0.178 (0.164–0.192)	0.018 (−0.002–0.037)	0.075
SCARA5	Neurology	0.110 (0.098–0.121)	0.127 (0.114–0.139)	0.017 (0.000–0.034)	0.052
LAYN	Neurology	0.154 (0.140–0.167)	0.170 (0.156–0.183)	0.016 (−0.003–0.035)	0.108
GUCA2A	Neurology	0.066 (0.056–0.075)	0.081 (0.071–0.092)	0.016 (0.001–0.030)	0.033
COL6A3	Cardiometabolic	0.193 (0.179–0.207)	0.207 (0.193–0.222)	0.015 (−0.006–0.035)	0.158
WNT9A	Inflammation	0.194 (0.179–0.208)	0.208 (0.193–0.223)	0.014 (−0.006–0.035)	0.172
KLK4	Oncology	0.135 (0.122–0.147)	0.148 (0.135–0.161)	0.014 (−0.005–0.032)	0.143
CCN3	Cardiometabolic	0.130 (0.118–0.143)	0.144 (0.131–0.157)	0.014 (−0.004–0.032)	0.140
NBL1	Oncology	0.101 (0.089–0.112)	0.114 (0.102–0.126)	0.013 (−0.003–0.030)	0.113
CELA2A	Cardiometabolic II	0.016 (0.010–0.021)	0.029 (0.022–0.036)	0.013 (0.004–0.022)	0.003
TNFRSF19	Oncology	0.103 (0.091–0.114)	0.116 (0.104–0.128)	0.013 (−0.004–0.030)	0.122

EPHB4	Cardiometabolic	0.090 (0.079–0.101)	0.103 (0.092–0.115)	0.013 (−0.003–0.029)	0.104
SLITRK2	Oncology	0.116 (0.104–0.128)	0.129 (0.116–0.141)	0.013 (−0.004–0.030)	0.146
JAM2	Neurology	0.084 (0.073–0.094)	0.097 (0.085–0.108)	0.013 (−0.003–0.028)	0.106
TGFBR2	Oncology	0.183 (0.169–0.197)	0.195 (0.181–0.209)	0.013 (−0.007–0.033)	0.217
NECTIN4	Oncology	0.056 (0.047–0.065)	0.068 (0.059–0.078)	0.012 (−0.001–0.025)	0.074
EPHA2	Oncology	0.124 (0.111–0.136)	0.136 (0.123–0.149)	0.012 (−0.006–0.030)	0.196
CTRL	Neurology II	0.084 (0.072–0.095)	0.096 (0.084–0.108)	0.012 (−0.005–0.029)	0.159
DCBLD2	Oncology	0.139 (0.127–0.152)	0.151 (0.138–0.164)	0.012 (−0.007–0.030)	0.210
OGN	Neurology	0.165 (0.152–0.179)	0.177 (0.163–0.191)	0.012 (−0.008–0.031)	0.243

* Adjusted r^2 for the base model. Base model included age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Adjusted r^2 for the model integrating hypoglycaemic medications.

‡ The marginal proportion of variance in protein abundance attributable to hypoglycaemic medication was quantified as the difference in adjusted R^2 between the two models.

§ *P* values were calculated through two-sided non-parametric bootstrap tests with 1,000 iterations followed by controlling FDR for multiple testing.

Supplementary Table S8

Subgroup analyses performed in high-genetic-risk participants (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
GDF15	Cardiometabolic	1.741 (1.608–1.884)	3.14×10^{-39}
CA12	Oncology	1.548 (1.432–1.673)	3.68×10^{-25}
SPINK1	Neurology	1.544 (1.427–1.670)	3.09×10^{-24}
SPINK4	Inflammation	1.678 (1.516–1.856)	9.04×10^{-21}
DSC2	Neurology	1.400 (1.309–1.499)	1.49×10^{-19}
TFF3	Cardiometabolic	1.511 (1.389–1.644)	3.98×10^{-19}
DLL1	Oncology	1.644 (1.480–1.826)	7.72×10^{-18}
REG4	Inflammation	1.626 (1.466–1.803)	1.34×10^{-17}
EFNA4	Neurology	1.477 (1.358–1.606)	2.79×10^{-17}
VSIG4	Neurology	1.625 (1.463–1.805)	3.86×10^{-17}
CD276	Inflammation	1.665 (1.491–1.861)	5.22×10^{-17}
HAVCR1	Oncology	1.601 (1.445–1.774)	5.60×10^{-17}
LGALS4	Inflammation	1.619 (1.457–1.798)	6.93×10^{-17}
KLK4	Oncology	1.600 (1.443–1.774)	9.45×10^{-17}
REG1A	Cardiometabolic	1.472 (1.349–1.606)	7.68×10^{-16}
PIK3IP1	Neurology	1.518 (1.379–1.670)	2.59×10^{-15}
NEFL	Neurology	1.548 (1.400–1.712)	3.54×10^{-15}
TNFRSF1A	Neurology	1.528 (1.385–1.686)	3.93×10^{-15}
EFNA1	Neurology	1.517 (1.377–1.672)	5.12×10^{-15}
IL1R1	Neurology	1.519 (1.378–1.674)	5.57×10^{-15}
EPHA2	Oncology	1.540 (1.392–1.703)	6.41×10^{-15}
LAYN	Neurology	1.518 (1.376–1.674)	1.16×10^{-14}
AREG	Oncology	1.484 (1.351–1.631)	2.68×10^{-14}
CD27	Oncology	1.542 (1.390–1.710)	3.22×10^{-14}
EDA2R	Oncology	1.634 (1.452–1.837)	3.25×10^{-14}
DCBLD2	Oncology	1.647 (1.458–1.859)	1.03×10^{-13}
TNFRSF11A	Inflammation	1.498 (1.355–1.655)	2.28×10^{-13}
IGFBP4	Neurology	1.470 (1.335–1.617)	3.60×10^{-13}
KLRB1	Inflammation	1.538 (1.379–1.714)	7.97×10^{-13}
PLA2G7	Neurology	0.685 (0.623–0.754)	8.84×10^{-13}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S9

Subgroup analyses performed in low-genetic-risk participants (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
PLA2G7	Neurology	0.642 (0.586–0.702)	1.60×10^{-18}
GDF15	Cardiometabolic	1.570 (1.378–1.789)	1.79×10^{-8}
CD276	Inflammation	1.569 (1.359–1.810)	7.06×10^{-7}
VSIG4	Neurology	1.529 (1.334–1.753)	8.07×10^{-7}
AREG	Oncology	1.489 (1.308–1.694)	1.01×10^{-6}
CA12	Oncology	1.427 (1.270–1.603)	1.13×10^{-6}
NEFL	Neurology	1.480 (1.293–1.694)	5.19×10^{-6}
CD27	Oncology	1.443 (1.271–1.639)	5.58×10^{-6}
REN	Cardiometabolic	1.423 (1.259–1.608)	5.58×10^{-6}
GFRA1	Oncology	1.455 (1.276–1.659)	6.56×10^{-6}
SEL1L	Cardiometabolic II	1.257 (1.159–1.364)	9.58×10^{-6}
LAYN	Neurology	1.414 (1.247–1.602)	1.52×10^{-5}
PIK3IP1	Neurology	1.406 (1.240–1.594)	2.48×10^{-5}
EFNA4	Neurology	1.341 (1.201–1.496)	3.42×10^{-5}
EDA2R	Oncology	1.524 (1.297–1.791)	5.55×10^{-5}
EPHA2	Oncology	1.410 (1.235–1.608)	5.55×10^{-5}
KLK4	Oncology	1.431 (1.247–1.642)	5.55×10^{-5}
REG1A	Cardiometabolic	1.409 (1.236–1.606)	5.55×10^{-5}
SCARA5	Neurology	1.442 (1.252–1.660)	5.55×10^{-5}
TNFRSF1A	Neurology	1.411 (1.235–1.613)	6.20×10^{-5}
SPINK4	Inflammation	1.417 (1.238–1.623)	6.50×10^{-5}
CKAP4	Inflammation	1.382 (1.216–1.570)	8.98×10^{-5}
CD74	Neurology	1.452 (1.252–1.684)	1.04×10^{-4}
TGFBR2	Oncology	1.365 (1.204–1.547)	1.38×10^{-4}
DLL1	Oncology	1.422 (1.228–1.646)	2.87×10^{-4}
KRT19	Inflammation	1.407 (1.218–1.625)	3.93×10^{-4}
EPHB4	Cardiometabolic	1.343 (1.183–1.526)	5.91×10^{-4}
IGFBP3	Cardiometabolic	0.770 (0.687–0.862)	5.91×10^{-4}
OGN	Neurology	1.396 (1.208–1.613)	6.06×10^{-4}
SPON2	Cardiometabolic	1.397 (1.207–1.616)	6.55×10^{-4}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S10

Interaction effects of protein levels and genetic susceptibility on DR risk (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
TNFSF8	Cardiometabolic II	0.694 (0.567–0.849)	3.82×10^{-4}
CHIT1	Cardiometabolic	1.492 (1.194–1.864)	4.24×10^{-4}
NAAA	Neurology	0.679 (0.547–0.844)	4.69×10^{-4}
CD109	Neurology	0.718 (0.592–0.870)	7.14×10^{-4}
PPP1R12B	Oncology II	0.711 (0.582–0.868)	8.34×10^{-4}
MTPN	Cardiometabolic	0.710 (0.580–0.869)	8.90×10^{-4}
SWAP70	Oncology II	0.708 (0.576–0.869)	9.63×10^{-4}
CD70	Inflammation	0.725 (0.599–0.878)	9.93×10^{-4}
ITGAM	Neurology	0.742 (0.614–0.897)	0.002
PRKD2	Cardiometabolic II	0.686 (0.537–0.876)	0.002
AOC1	Inflammation	0.720 (0.580–0.892)	0.003
MCAM	Cardiometabolic	0.761 (0.637–0.911)	0.003
CLGN	Neurology II	1.437 (1.132–1.826)	0.003
IGHMBP2	Cardiometabolic II	0.728 (0.591–0.898)	0.003
L1CAM	Oncology	0.744 (0.613–0.905)	0.003
CHRM1	Neurology II	0.754 (0.625–0.909)	0.003
DDX58	Oncology	0.713 (0.570–0.893)	0.003
VEGFD	Inflammation	1.343 (1.104–1.634)	0.003
ANGPTL7	Oncology	0.766 (0.638–0.920)	0.004
GFAP	Oncology	0.733 (0.592–0.908)	0.004
FRZB	Neurology	0.740 (0.601–0.912)	0.005
ERBB2	Oncology	0.742 (0.603–0.913)	0.005
CTSF	Oncology	0.738 (0.598–0.911)	0.005
SLAMF6	Oncology	0.751 (0.616–0.917)	0.005
ZNF174	Inflammation II	0.711 (0.560–0.903)	0.005
FCRL1	Cardiometabolic	0.760 (0.627–0.922)	0.005
IL3	Oncology II	0.696 (0.539–0.900)	0.006
ZBP1	Inflammation II	0.720 (0.569–0.909)	0.006
RSPO1	Neurology	0.745 (0.605–0.919)	0.006
SMARCA2	Neurology	0.748 (0.609–0.921)	0.006

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components. Protein levels, polygenic risk categories (top 50% and bottom 50%), and an interaction term of protein × polygenic risk was included in the models.

† Data are presented as the effects of per-SD change of protein values on DR risk differing by polygenic risk categories.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S11

Subgroup analyses performed in male participants (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
GDF15	Cardiometabolic	1.679 (1.533–1.839)	2.22×10^{-25}
PIK3IP1	Neurology	1.554 (1.413–1.709)	1.18×10^{-16}
SPINK1	Neurology	1.575 (1.428–1.737)	1.18×10^{-16}
LAYN	Neurology	1.528 (1.387–1.683)	4.74×10^{-15}
SPINK4	Inflammation	1.577 (1.422–1.750)	4.74×10^{-15}
CD276	Inflammation	1.649 (1.469–1.851)	1.08×10^{-14}
PLA2G7	Neurology	0.646 (0.584–0.715)	1.08×10^{-14}
EDA2R	Oncology	1.696 (1.500–1.917)	1.23×10^{-14}
CD27	Oncology	1.532 (1.384–1.696)	7.51×10^{-14}
AREG	Oncology	1.550 (1.395–1.722)	8.81×10^{-14}
CA12	Oncology	1.541 (1.389–1.710)	9.25×10^{-14}
VSIG4	Neurology	1.599 (1.428–1.790)	9.25×10^{-14}
EFNA4	Neurology	1.446 (1.323–1.581)	1.11×10^{-13}
TNFRSF1A	Neurology	1.495 (1.353–1.653)	6.36×10^{-13}
NEFL	Neurology	1.478 (1.341–1.628)	6.46×10^{-13}
DLL1	Oncology	1.571 (1.403–1.758)	6.57×10^{-13}
KLK4	Oncology	1.516 (1.367–1.682)	6.57×10^{-13}
EPHA2	Oncology	1.473 (1.336–1.624)	1.31×10^{-12}
GFRA1	Oncology	1.498 (1.352–1.660)	1.89×10^{-12}
EFNA1	Neurology	1.473 (1.334–1.627)	2.75×10^{-12}
TGFBR2	Oncology	1.455 (1.321–1.603)	3.68×10^{-12}
TFF3	Cardiometabolic	1.450 (1.317–1.597)	6.06×10^{-12}
FAM3C	Cardiometabolic	1.538 (1.373–1.723)	1.49×10^{-11}
CLMP	Oncology	1.517 (1.357–1.696)	2.60×10^{-11}
JAM2	Neurology	1.465 (1.322–1.623)	3.38×10^{-11}
REN	Cardiometabolic	1.429 (1.297–1.574)	5.27×10^{-11}
IGFBP4	Neurology	1.438 (1.303–1.587)	5.57×10^{-11}
EPHB4	Cardiometabolic	1.423 (1.292–1.567)	8.94×10^{-11}
REG1A	Cardiometabolic	1.446 (1.307–1.600)	8.94×10^{-11}
SCARF2	Neurology	1.527 (1.358–1.719)	1.87×10^{-10}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S12

Subgroup analyses performed in female participants (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
GDF15	Cardiometabolic	1.743 (1.560–1.949)	3.85×10^{-19}
CA12	Oncology	1.473 (1.355–1.602)	1.78×10^{-16}
PLA2G7	Neurology	0.675 (0.617–0.739)	1.51×10^{-14}
CD276	Inflammation	1.696 (1.479–1.945)	2.26×10^{-11}
KLK4	Oncology	1.657 (1.454–1.889)	2.26×10^{-11}
DCBLD2	Oncology	1.767 (1.517–2.057)	1.09×10^{-10}
VSIG4	Neurology	1.564 (1.386–1.764)	1.53×10^{-10}
SPINK4	Inflammation	1.596 (1.404–1.815)	3.40×10^{-10}
SPINK1	Neurology	1.426 (1.289–1.579)	2.37×10^{-9}
EFNA4	Neurology	1.395 (1.267–1.537)	3.44×10^{-9}
REG1A	Cardiometabolic	1.462 (1.310–1.632)	3.44×10^{-9}
TFF3	Cardiometabolic	1.382 (1.257–1.519)	4.81×10^{-9}
MUC13	Neurology	1.500 (1.330–1.691)	7.82×10^{-9}
FGFBP1	Oncology	0.589 (0.504–0.689)	8.06×10^{-9}
HAVCR1	Oncology	1.564 (1.368–1.787)	1.10×10^{-8}
REG4	Inflammation	1.531 (1.344–1.744)	2.62×10^{-8}
DLL1	Oncology	1.541 (1.346–1.765)	6.41×10^{-8}
IGFBP3	Cardiometabolic	0.697 (0.623–0.781)	6.41×10^{-8}
IL17C	Inflammation	1.411 (1.267–1.572)	6.41×10^{-8}
DSC2	Neurology	1.350 (1.228–1.484)	6.87×10^{-8}
EPHA2	Oncology	1.484 (1.311–1.681)	7.01×10^{-8}
REN	Cardiometabolic	1.461 (1.295–1.647)	9.02×10^{-8}
CD27	Oncology	1.488 (1.311–1.688)	9.19×10^{-8}
SCARA5	Neurology	1.516 (1.327–1.732)	1.17×10^{-7}
LGALS4	Inflammation	1.543 (1.342–1.774)	1.25×10^{-7}
CTRC	Inflammation	0.680 (0.601–0.770)	1.26×10^{-7}
SPOCK1	Neurology	0.613 (0.524–0.718)	1.44×10^{-7}
GFRA1	Oncology	1.531 (1.334–1.757)	1.45×10^{-7}
NEFL	Neurology	1.627 (1.390–1.906)	1.47×10^{-7}
PON3	Inflammation	0.830 (0.780–0.882)	2.64×10^{-7}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S13

Interaction effects of protein levels and sex on DR risk (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
CHIT1	Cardiometabolic	0.521 (0.404–0.671)	4.50×10^{-7}
NPTX1	Neurology	1.651 (1.335–2.042)	3.66×10^{-6}
FCRL2	Inflammation	1.503 (1.240–1.823)	3.45×10^{-5}
CBLN4	Oncology	1.477 (1.226–1.780)	3.96×10^{-5}
CNTN4	Neurology	1.491 (1.222–1.819)	8.13×10^{-5}
CDH6	Cardiometabolic	1.446 (1.196–1.748)	1.40×10^{-4}
ADAMTS8	Oncology	1.442 (1.190–1.746)	1.83×10^{-4}
CGA	Neurology	1.784 (1.306–2.436)	2.73×10^{-4}
BGN	Oncology	1.487 (1.200–1.843)	2.86×10^{-4}
FCRL1	Cardiometabolic	1.421 (1.175–1.718)	2.88×10^{-4}
COX5B	Oncology	1.458 (1.188–1.790)	3.05×10^{-4}
ROBO2	Neurology	1.459 (1.185–1.797)	3.67×10^{-4}
CNTN5	Neurology	1.465 (1.186–1.809)	4.01×10^{-4}
LGALS3	Cardiometabolic	0.725 (0.604–0.869)	5.00×10^{-4}
CNTN1	Cardiometabolic	1.414 (1.155–1.732)	8.14×10^{-4}
FAP	Cardiometabolic	1.379 (1.142–1.664)	8.21×10^{-4}
PNLIPRP2	Inflammation	0.686 (0.550–0.857)	8.91×10^{-4}
IL2	Inflammation	1.408 (1.150–1.724)	9.38×10^{-4}
FRZB	Neurology	1.388 (1.142–1.688)	9.91×10^{-4}
PRSS2	Cardiometabolic	1.361 (1.132–1.636)	0.001
ENG	Cardiometabolic	1.376 (1.137–1.666)	0.001
FLRT2	Neurology	1.391 (1.140–1.698)	0.001
PEAR1	Cardiometabolic	1.374 (1.130–1.670)	0.001
CEACAM3	Oncology	1.443 (1.150–1.810)	0.002
SLAMF6	Oncology	1.394 (1.135–1.714)	0.002
CST5	Neurology	1.395 (1.134–1.716)	0.002
SCARF2	Neurology	1.355 (1.121–1.639)	0.002
ZBTB17	Cardiometabolic	0.748 (0.624–0.898)	0.002
AOC3	Cardiometabolic	1.345 (1.115–1.622)	0.002
PVR	Neurology	1.358 (1.119–1.648)	0.002

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components. Protein levels, polygenic risk categories (top 50% and bottom 50%), and an interaction term of protein × polygenic risk was included in the models.

† Data are presented as the effects of per-SD change of protein values on DR risk differing by polygenic risk categories.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S14
Associations between blood proteins and overall retinal thickness (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
PON3	Inflammation	0.131 (0.092–0.170)	6.02×10^{-8}
IGFBP2	Cardiometabolic	0.107 (0.069–0.144)	1.04×10^{-5}
ITGAV	Oncology	0.097 (0.060–0.134)	7.14×10^{-5}
CCL3	Inflammation	−0.079 (−0.110–−0.048)	1.03×10^{-4}
CKB	Cardiometabolic II	0.101 (0.061–0.140)	1.10×10^{-4}
OGN	Neurology	−0.093 (−0.133–−0.053)	5.63×10^{-4}
CCL7	Inflammation	−0.080 (−0.115–−0.045)	6.81×10^{-4}
LILRA5	Cardiometabolic	−0.079 (−0.115–−0.043)	0.001
SLITRK1	Inflammation II	0.089 (0.049–0.128)	0.001
TNFRSF10A	Neurology	−0.085 (−0.125–−0.045)	0.002
BCAN	Neurology	0.077 (0.040–0.115)	0.003
CD300E	Oncology	−0.078 (−0.116–−0.040)	0.003
FGFBP1	Oncology	0.077 (0.040–0.114)	0.003
OMG	Oncology	0.077 (0.040–0.115)	0.003
SIGLEC1	Inflammation	−0.075 (−0.112–−0.039)	0.003
ADGRG2	Cardiometabolic	0.076 (0.038–0.114)	0.003
CD4	Inflammation	−0.070 (−0.106–−0.035)	0.003
RTN4R	Oncology	−0.076 (−0.114–−0.038)	0.003
APOC1	Inflammation II	0.077 (0.038–0.115)	0.004
GDF15	Cardiometabolic	−0.086 (−0.131–−0.042)	0.004
LRTM2	Neurology II	0.073 (0.036–0.111)	0.004
TFRC	Cardiometabolic	−0.067 (−0.101–−0.032)	0.004
TPP1	Inflammation	−0.070 (−0.106–−0.034)	0.004
SCARB2	Neurology	−0.079 (−0.120–−0.038)	0.005
IL6	Cardiometabolic	−0.069 (−0.105–−0.032)	0.006
NPTXR	Cardiometabolic	0.069 (0.032–0.105)	0.006
CRH	Oncology	0.066 (0.031–0.101)	0.006
VSIG4	Neurology	−0.074 (−0.114–−0.034)	0.006
LEPR	Cardiometabolic	0.067 (0.031–0.103)	0.007
RNASE1	Inflammation II	−0.075 (−0.116–−0.035)	0.007

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.
† Data are presented as per-SD change of protein values.
‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S15

Associations between blood proteins and photoreceptor layer (top 30 shown).

Proteins *	Panels	β (95% CI) †	P_{FDR} ‡
TNFRSF10A	Neurology	−0.119 (−0.161–−0.078)	1.32×10^{-5}
PON3	Inflammation	0.115 (0.073–0.156)	2.32×10^{-5}
SEL1L	Cardiometabolic II	−0.109 (−0.150–−0.069)	3.70×10^{-5}
SIGLEC1	Inflammation	−0.101 (−0.139–−0.062)	5.20×10^{-5}
NPC2	Cardiometabolic II	−0.109 (−0.152–−0.067)	7.45×10^{-5}
LILRA5	Cardiometabolic	−0.094 (−0.132–−0.057)	1.06×10^{-4}
CSF1	Inflammation	−0.097 (−0.137–−0.058)	1.39×10^{-4}
TPP1	Inflammation	−0.093 (−0.131–−0.055)	1.39×10^{-4}
RELT	Neurology	−0.104 (−0.147–−0.061)	1.55×10^{-4}
CKAP4	Inflammation	−0.092 (−0.130–−0.053)	1.98×10^{-4}
AGRN	Inflammation	−0.094 (−0.134–−0.054)	2.07×10^{-4}
CEACAM21	Inflammation	−0.087 (−0.124–−0.050)	2.07×10^{-4}
PSAP	Cardiometabolic II	−0.098 (−0.140–−0.057)	2.07×10^{-4}
CFD	Inflammation II	−0.099 (−0.142–−0.056)	2.76×10^{-4}
PRAP1	Cardiometabolic II	−0.095 (−0.136–−0.054)	2.85×10^{-4}
LAIR1	Inflammation	−0.084 (−0.122–−0.047)	4.90×10^{-4}
CD79B	Inflammation	−0.086 (−0.124–−0.047)	4.94×10^{-4}
PALM2	Neurology II	−0.095 (−0.138–−0.052)	5.08×10^{-4}
FABP4	Cardiometabolic	−0.090 (−0.131–−0.049)	6.41×10^{-4}
ATRAID	Oncology II	−0.090 (−0.133–−0.048)	9.40×10^{-4}
FSTL3	Inflammation	−0.090 (−0.133–−0.048)	9.70×10^{-4}
CCL3	Inflammation	−0.068 (−0.101–−0.036)	9.75×10^{-4}
CTHRC1	Cardiometabolic II	−0.091 (−0.134–−0.048)	9.75×10^{-4}
TFF1	Neurology	−0.085 (−0.125–−0.045)	9.75×10^{-4}
FSTL1	Cardiometabolic II	−0.083 (−0.123–−0.044)	0.001
CD300E	Oncology	−0.083 (−0.122–−0.043)	0.001
SERPINF1	Inflammation II	−0.087 (−0.130–−0.044)	0.002
VSIG4	Neurology	−0.084 (−0.125–−0.042)	0.002
CST3	Cardiometabolic	−0.085 (−0.128–−0.043)	0.002
HAVCR2	Neurology	−0.079 (−0.118–−0.040)	0.002

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S16

Associations between blood proteins and RNFL and GC-IPL thickness.

Proteins *	Panels	β (95% CI) †	P_{FDR} ‡
RNFL			
CCL21	Inflammation	−0.080 (−0.116–−0.044)	0.008
HYAL1	Cardiometabolic	−0.074 (−0.111–−0.037)	0.028
MSR1	Neurology	−0.076 (−0.115–−0.037)	0.030
SPON1	Inflammation	−0.074 (−0.113–−0.035)	0.035
CTSL	Cardiometabolic	−0.067 (−0.104–−0.030)	0.050
GC-IPL			
ADGRG1	Oncology	−0.079 (−0.121–−0.038)	0.044
FGFBP1	Oncology	0.072 (0.035–0.109)	0.044
OMD	Inflammation	0.072 (0.036–0.109)	0.044

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S17

Associations between blood proteins and RPE thickness.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
APOL1	Inflammation II	0.070 (0.033–0.108)	0.017
CD160	Inflammation	−0.069 (−0.105–−0.033)	0.015
CD300C	Neurology	−0.083 (−0.120–−0.046)	0.002
CD300LF	Oncology	−0.086 (−0.122–−0.049)	0.001
CES1	Cardiometabolic	−0.066 (−0.105–−0.027)	0.034
CHIT1	Cardiometabolic	0.062 (0.029–0.096)	0.017
CLEC4D	Inflammation	−0.067 (−0.102–−0.031)	0.017
CPM	Neurology	−0.072 (−0.110–−0.035)	0.015
CTSS	Neurology	−0.067 (−0.107–−0.026)	0.045
CTSZ	Cardiometabolic	−0.061 (−0.098–−0.024)	0.045
DSC2	Neurology	−0.082 (−0.122–−0.043)	0.007
EFNA1	Neurology	−0.070 (−0.108–−0.032)	0.018
EPHB6	Neurology	−0.064 (−0.102–−0.026)	0.034
FUT3_FUT5	Neurology	−0.071 (−0.109–−0.034)	0.015
IL12B	Inflammation	−0.061 (−0.098–−0.024)	0.045
KLRB1	Inflammation	−0.100 (−0.136–−0.063)	7.61×10^{-5}
NCR1	Inflammation	−0.061 (−0.098–−0.023)	0.045
OMD	Inflammation	0.066 (0.029–0.104)	0.023
PLA2G10	Neurology	0.061 (0.025–0.096)	0.034
PRRT3	Cardiometabolic II	−0.071 (−0.109–−0.032)	0.018
TNFRSF1A	Neurology	−0.074 (−0.115–−0.033)	0.018
ULBP2	Neurology	−0.076 (−0.113–−0.039)	0.009

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S18

Subgroup analyses of blood proteins and photoreceptor layer thickness in high-genetic-risk participants (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
TNFRSF10A	Neurology	−0.133 (−0.190–−0.077)	0.003
AGRN	Inflammation	−0.122 (−0.178–−0.066)	0.005
FSTL3	Inflammation	−0.127 (−0.186–−0.068)	0.005
SIGLEC1	Inflammation	−0.117 (−0.171–−0.062)	0.005
FOLR2	Neurology	−0.110 (−0.165–−0.056)	0.006
GOLM2	Neurology	−0.104 (−0.155–−0.054)	0.006
PSAP	Cardiometabolic II	−0.121 (−0.180–−0.062)	0.006
RNASE6	Inflammation II	−0.126 (−0.188–−0.064)	0.006
TPP1	Inflammation	−0.115 (−0.171–−0.059)	0.006
CD74	Neurology	−0.110 (−0.166–−0.054)	0.008
LAIR1	Inflammation	−0.105 (−0.159–−0.051)	0.008
CSF1	Inflammation	−0.107 (−0.162–−0.051)	0.008
HAVCR2	Neurology	−0.108 (−0.165–−0.052)	0.008
LILRA5	Cardiometabolic	−0.103 (−0.157–−0.050)	0.008
CCL3	Inflammation	−0.082 (−0.125–−0.038)	0.010
MSR1	Neurology	−0.110 (−0.169–−0.052)	0.010
ATRAID	Oncology II	−0.100 (−0.154–−0.046)	0.011
BPIFB2	Cardiometabolic II	−0.104 (−0.161–−0.048)	0.011
CD79B	Inflammation	−0.100 (−0.154–−0.046)	0.011
TNFRSF10B	Neurology	−0.139 (−0.215–−0.064)	0.011
CD300E	Oncology	−0.103 (−0.160–−0.047)	0.011
ASGR1	Neurology	−0.102 (−0.157–−0.046)	0.012
APOC1	Inflammation II	0.099 (0.044–0.154)	0.013
COL6A3	Cardiometabolic	−0.104 (−0.162–−0.046)	0.013
NPC2	Cardiometabolic II	−0.110 (−0.171–−0.048)	0.013
PRSS53	Neurology II	0.098 (0.042–0.153)	0.015
FABP4	Cardiometabolic	−0.096 (−0.151–−0.041)	0.016
REN	Cardiometabolic	−0.100 (−0.157–−0.042)	0.016
CEACAM21	Inflammation	−0.091 (−0.144–−0.038)	0.017
ACVRL1	Neurology	−0.096 (−0.153–−0.040)	0.019

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S19

Subgroup analyses of blood proteins and photoreceptor layer thickness in low-genetic-risk participants (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
MMP3	Neurology	0.126 (0.077–0.175)	3.90×10^{-4}
CD300C	Neurology	−0.128 (−0.180–−0.075)	6.71×10^{-4}
CD300LF	Oncology	−0.115 (−0.166–−0.063)	0.001
CTHRC1	Cardiometabolic II	0.130 (0.074–0.187)	0.001
EFNA1	Neurology	−0.121 (−0.174–−0.067)	0.001
IL12B	Inflammation	−0.117 (−0.169–−0.066)	0.001
KIRREL2	Neurology	−0.115 (−0.167–−0.063)	0.002
TNFRSF8	Neurology	−0.111 (−0.163–−0.059)	0.002
CD5	Oncology	−0.108 (−0.161–−0.056)	0.003
EPHB6	Neurology	−0.109 (−0.161–−0.057)	0.003
CD28	Oncology	−0.108 (−0.163–−0.054)	0.005
FOLR2	Neurology	−0.101 (−0.152–−0.050)	0.006
DSC2	Neurology	−0.105 (−0.159–−0.050)	0.009
ULBP2	Neurology	−0.101 (−0.153–−0.048)	0.009
FABP4	Cardiometabolic	−0.102 (−0.156–−0.048)	0.009
IL12A_IL12B	Oncology	−0.097 (−0.149–−0.046)	0.010
TNFRSF4	Inflammation	−0.101 (−0.154–−0.047)	0.010
TNFRSF9	Neurology	−0.101 (−0.158–−0.044)	0.018
CGA	Neurology	−0.091 (−0.143–−0.040)	0.019
ADGRG2	Cardiometabolic	−0.086 (−0.135–−0.037)	0.020
CTSS	Neurology	−0.098 (−0.154–−0.042)	0.020
PRG2	Cardiometabolic II	−0.089 (−0.141–−0.038)	0.022
CD7	Inflammation II	−0.092 (−0.146–−0.038)	0.026
CLMP	Oncology	−0.089 (−0.142–−0.036)	0.026
FCER2	Neurology	−0.085 (−0.136–−0.034)	0.026
LRRN1	Inflammation	0.087 (0.036–0.139)	0.026
XG	Cardiometabolic	−0.092 (−0.146–−0.037)	0.026
SMOC2	Inflammation	0.090 (0.036–0.144)	0.026
IGFBP3	Cardiometabolic	−0.090 (−0.144–−0.036)	0.026
PDCD1	Oncology	−0.086 (−0.139–−0.034)	0.026

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S20

Subgroup analyses of blood proteins and photoreceptor layer thickness in male participants.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
SEL1L	Cardiometabolic II	−0.170 (−0.244–−0.096)	0.005
CEACAM21	Inflammation	−0.121 (−0.179–−0.063)	0.010
CXCL16	Cardiometabolic	−0.131 (−0.193–−0.069)	0.010
ATRAID	Oncology II	−0.125 (−0.188–−0.062)	0.012
CCL3	Inflammation	−0.100 (−0.152–−0.049)	0.012
MRC1	Inflammation II	−0.140 (−0.211–−0.069)	0.012
PLA2G10	Neurology	−0.112 (−0.171–−0.054)	0.012
PRAP1	Cardiometabolic II	−0.138 (−0.209–−0.067)	0.012
SIGLEC1	Inflammation	−0.127 (−0.190–−0.064)	0.012
GSTA1	Cardiometabolic	−0.116 (−0.177–−0.055)	0.014
PSAP	Cardiometabolic II	−0.126 (−0.193–−0.059)	0.015
PON3	Inflammation	0.117 (0.054–0.181)	0.018
CCL7	Inflammation	−0.115 (−0.178–−0.052)	0.018
CKAP4	Inflammation	−0.102 (−0.159–−0.045)	0.018
CTHRC1	Cardiometabolic II	−0.129 (−0.201–−0.057)	0.018
SETMAR	Neurology	−0.114 (−0.177–−0.050)	0.018
VSIG4	Neurology	−0.114 (−0.178–−0.050)	0.018
TCL1A	Neurology	−0.094 (−0.149–−0.040)	0.026
NPC2	Cardiometabolic II	−0.113 (−0.179–−0.047)	0.027
PALM2	Neurology II	−0.118 (−0.186–−0.049)	0.027
CSF1	Inflammation	−0.110 (−0.176–−0.044)	0.036
LMNB2	Neurology II	−0.111 (−0.177–−0.044)	0.036
KYNU	Inflammation	−0.104 (−0.168–−0.041)	0.038
AGRN	Inflammation	−0.104 (−0.168–−0.040)	0.039
FOLR2	Neurology	−0.099 (−0.161–−0.038)	0.040
LILRA5	Cardiometabolic	−0.098 (−0.158–−0.037)	0.040
FSTL1	Cardiometabolic II	−0.099 (−0.161–−0.038)	0.041
TNFRSF10C	Cardiometabolic	−0.091 (−0.148–−0.034)	0.043

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S21

Subgroup analyses of blood proteins and photoreceptor layer thickness in female participants (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
TNFRSF10A	Neurology	−0.162 (−0.215–−0.109)	1.58×10^{-6}
ASGR1	Neurology	−0.108 (−0.157–−0.058)	0.006
FSTL3	Inflammation	−0.111 (−0.163–−0.058)	0.006
PON3	Inflammation	0.117 (0.062–0.172)	0.006
SNCG	Neurology	−0.101 (−0.149–−0.053)	0.006
TPP1	Inflammation	−0.097 (−0.145–−0.049)	0.009
RELT	Neurology	−0.112 (−0.168–−0.056)	0.009
BPIFB2	Cardiometabolic II	−0.095 (−0.144–−0.047)	0.010
LILRA5	Cardiometabolic	−0.092 (−0.140–−0.045)	0.010
C1QTNF1	Cardiometabolic	−0.099 (−0.151–−0.047)	0.010
LAIR1	Inflammation	−0.089 (−0.136–−0.043)	0.010
NPC2	Cardiometabolic II	−0.105 (−0.160–−0.050)	0.010
TFF1	Neurology	−0.102 (−0.155–−0.048)	0.010
CFD	Inflammation II	−0.101 (−0.154–−0.047)	0.012
ADM	Oncology	−0.088 (−0.136–−0.039)	0.013
CCL15	Cardiometabolic	−0.086 (−0.133–−0.039)	0.013
CHRDL1	Inflammation	−0.105 (−0.162–−0.048)	0.013
CSF1	Inflammation	−0.088 (−0.137–−0.040)	0.013
DPY30	Oncology	−0.088 (−0.137–−0.040)	0.013
RETN	Cardiometabolic	−0.086 (−0.133–−0.039)	0.013
CST3	Cardiometabolic	−0.095 (−0.149–−0.040)	0.023
SIGLEC1	Inflammation	−0.082 (−0.130–−0.034)	0.026
AGRN	Inflammation	−0.085 (−0.136–−0.034)	0.027
B2M	Inflammation II	−0.091 (−0.144–−0.037)	0.027
CD79B	Inflammation	−0.081 (−0.129–−0.033)	0.027
COL18A1	Cardiometabolic	−0.088 (−0.141–−0.036)	0.027
PRRT3	Cardiometabolic II	0.087 (0.035–0.139)	0.027
CD300E	Oncology	−0.082 (−0.132–−0.032)	0.028
FABP4	Cardiometabolic	−0.086 (−0.138–−0.034)	0.028
PILRB	Cardiometabolic	−0.081 (−0.131–−0.032)	0.028

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S22

Subgroup analyses of blood proteins and overall retinal thickness in high-genetic-risk participants.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} **‡**
CXCL16	Cardiometabolic	−0.116 (−0.167–−0.064)	0.004
IGFBP2	Cardiometabolic	0.120 (0.066–0.173)	0.004
CKB	Cardiometabolic II	0.120 (0.064–0.177)	0.006
OGN	Neurology	−0.117 (−0.172–−0.063)	0.006
ITGAV	Oncology	0.103 (0.050–0.157)	0.022
RTN4R	Oncology	−0.099 (−0.152–−0.047)	0.022
CCL3	Inflammation	−0.076 (−0.118–−0.035)	0.028
TNFRSF13B	Inflammation	−0.091 (−0.141–−0.041)	0.031
CCL7	Inflammation	−0.085 (−0.132–−0.038)	0.033
BCAN	Neurology	0.094 (0.041–0.148)	0.035
CCL27	Cardiometabolic	0.087 (0.035–0.138)	0.040
CD4	Inflammation	−0.084 (−0.133–−0.034)	0.040
IL19	Cardiometabolic	−0.091 (−0.145–−0.037)	0.040
IL5RA	Inflammation	−0.088 (−0.139–−0.037)	0.040
MMP7	Cardiometabolic	−0.095 (−0.151–−0.039)	0.040
SIGLEC1	Inflammation	−0.089 (−0.141–−0.037)	0.040
FOLR2	Neurology	−0.086 (−0.138–−0.035)	0.041
CD163	Cardiometabolic	−0.087 (−0.139–−0.034)	0.047

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S23

Subgroup analyses of blood proteins and RNFL, GC-IPL, and RPE thickness in high-genetic-risk participants.

Proteins *	**Panels**	**β (95% CI) †**	***P* ‡**
RNFL			
CALCA	Neurology	−0.109 (−0.159–−0.059)	0.016
GC-IPL			
–	–	–	–
RPE			
–	–	–	–

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests.

Supplementary Table S24

Subgroup analyses of blood proteins and overall retinal, RNFL, GC-IPL, RPE thickness in low-genetic-risk participants (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
Overall			
PON3	Inflammation	0.127 (0.072–0.182)	0.005
RNFL			
–	–	–	–
GC-IPL			
–	–	–	–
RPE			
MMP3	Neurology	0.126 (0.077–0.175)	3.90×10^{-4}
CD300C	Neurology	−0.128 (−0.180–−0.075)	6.71×10^{-4}
CD300LF	Oncology	−0.115 (−0.166–−0.063)	0.001
CTHRC1	Cardiometabolic II	0.130 (0.074–0.187)	0.001
EFNA1	Neurology	−0.121 (−0.174–−0.067)	0.001
IL12B	Inflammation	−0.117 (−0.169–−0.066)	0.001
KIRREL2	Neurology	−0.115 (−0.167–−0.063)	0.002
TNFRSF8	Neurology	−0.111 (−0.163–−0.059)	0.002
CD5	Oncology	−0.108 (−0.161–−0.056)	0.003
EPHB6	Neurology	−0.109 (−0.161–−0.057)	0.003
CD28	Oncology	−0.108 (−0.163–−0.054)	0.005
FOLR2	Neurology	−0.101 (−0.152–−0.050)	0.006
DSC2	Neurology	−0.105 (−0.159–−0.050)	0.009
ULBP2	Neurology	−0.101 (−0.153–−0.048)	0.009
FABP4	Cardiometabolic	−0.102 (−0.156–−0.048)	0.009
IL12A_IL12B	Oncology	−0.097 (−0.149–−0.046)	0.010
TNFRSF4	Inflammation	−0.101 (−0.154–−0.047)	0.010
TNFRSF9	Neurology	−0.101 (−0.158–−0.044)	0.018
CGA	Neurology	−0.091 (−0.143–−0.040)	0.019
ADGRG2	Cardiometabolic	−0.086 (−0.135–−0.037)	0.020
CTSS	Neurology	−0.098 (−0.154–−0.042)	0.020
PRG2	Cardiometabolic II	−0.089 (−0.141–−0.038)	0.022
CD7	Inflammation II	−0.092 (−0.146–−0.038)	0.026
CLMP	Oncology	−0.089 (−0.142–−0.036)	0.026
FCER2	Neurology	−0.085 (−0.136–−0.034)	0.026
LRRN1	Inflammation	0.087 (0.036–0.139)	0.026
XG	Cardiometabolic	−0.092 (−0.146–−0.037)	0.026
SMOC2	Inflammation	0.090 (0.036–0.144)	0.026
IGFBP3	Cardiometabolic	−0.090 (−0.144–−0.036)	0.026
PDCD1	Oncology	−0.086 (−0.139–−0.034)	0.026

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.
† Data are presented as per-SD change of protein values.
‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S25

Subgroup analyses of blood proteins and overall retinal thickness in male participants (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
PON3	Inflammation	0.158 (0.100–0.216)	7.15×10^{-5}
GSTA1	Cardiometabolic	−0.120 (−0.176–−0.063)	0.006
IGFBP2	Cardiometabolic	0.123 (0.065–0.180)	0.006
VSIG2	Oncology II	−0.129 (−0.188–−0.070)	0.006
CKB	Cardiometabolic II	0.124 (0.062–0.186)	0.008
COL6A3	Cardiometabolic	−0.120 (−0.179–−0.061)	0.008
GDF15	Cardiometabolic	−0.135 (−0.203–−0.068)	0.008
IMMT	Oncology II	−0.119 (−0.180–−0.058)	0.010
TNFRSF10A	Neurology	−0.119 (−0.179–−0.058)	0.010
DCXR	Oncology	−0.114 (−0.174–−0.055)	0.012
FABP1	Inflammation	−0.108 (−0.166–−0.050)	0.013
OCLN	Neurology II	−0.113 (−0.173–−0.053)	0.013
SLAMF7	Inflammation	−0.095 (−0.146–−0.044)	0.013
APOC1	Inflammation II	0.108 (0.049–0.167)	0.016
EPS8L2	Oncology	−0.109 (−0.169–−0.050)	0.016
OGN	Neurology	−0.109 (−0.170–−0.049)	0.016
SPINK4	Inflammation	−0.104 (−0.161–−0.047)	0.016
CCN5	Neurology	−0.116 (−0.180–−0.051)	0.016
CD300E	Oncology	−0.107 (−0.166–−0.047)	0.016
CCL20	Inflammation	−0.103 (−0.163–−0.043)	0.021
CCL3	Inflammation	−0.082 (−0.129–−0.035)	0.021
CCL7	Inflammation	−0.101 (−0.159–−0.043)	0.021
IL17RB	Inflammation	0.099 (0.042–0.156)	0.021
PRSS8	Inflammation	−0.102 (−0.161–−0.043)	0.021
AREG	Oncology	−0.113 (−0.180–−0.046)	0.023
IGFBP7	Cardiometabolic	−0.105 (−0.167–−0.043)	0.023
PRAP1	Cardiometabolic II	−0.110 (−0.175–−0.046)	0.023
ADGRG1	Oncology	−0.090 (−0.144–−0.036)	0.025
SEL1L	Cardiometabolic II	−0.114 (−0.182–−0.046)	0.025
CCN4	Oncology	−0.093 (−0.149–−0.036)	0.027

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S26

Subgroup analyses of blood proteins and RNFL, GC-IPL, and RPE thickness in male participants.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} **‡**
RNFL			
–	–	–	–
GC-IPL			
ADGRG1	Oncology	−0.121 (−0.175–−0.066)	0.009
RPE			
ANGPTL4	Inflammation	−0.114 (−0.170–−0.058)	0.022
KLRB1	Inflammation	−0.115 (−0.171–−0.058)	0.022
UMOD	Cardiometabolic	0.118 (0.059–0.177)	0.022
CD8A	Neurology	−0.098 (−0.150–−0.046)	0.031
FUT3_FUT5	Neurology	−0.108 (−0.166–−0.051)	0.031
CD160	Inflammation	−0.098 (−0.152–−0.045)	0.033
CXCL16	Cardiometabolic	0.107 (0.048–0.165)	0.033
EFNA1	Neurology	−0.106 (−0.164–−0.047)	0.033
CD300LF	Oncology	−0.099 (−0.154–−0.043)	0.037
INHBB	Inflammation II	−0.116 (−0.182–−0.050)	0.037
CEACAM21	Inflammation	0.095 (0.041–0.150)	0.041
DSC2	Neurology	−0.105 (−0.167–−0.043)	0.049

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S27

Subgroup analyses of blood proteins and overall retinal thickness in female participants.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} **‡**
ADGRG2	Cardiometabolic	0.090 (0.040–0.140)	0.044
CCL3	Inflammation	−0.077 (−0.118–−0.037)	0.026
CHAD	Inflammation II	0.083 (0.035–0.132)	0.050
FAM3D	Oncology II	0.089 (0.039–0.138)	0.044
IGFBP2	Cardiometabolic	0.097 (0.047–0.147)	0.026
ITGA11	Inflammation	0.084 (0.036–0.131)	0.048
ITGAV	Oncology	0.128 (0.079–0.178)	2.83×10^{-4}
NPTXR	Cardiometabolic	0.098 (0.050–0.145)	0.022
PON3	Inflammation	0.107 (0.053–0.162)	0.024
SLITRK1	Inflammation II	0.090 (0.038–0.142)	0.050
VSIG4	Neurology	−0.094 (−0.148–−0.041)	0.048

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S28

Subgroup analyses of blood proteins and RNFL, GC-IPL, and RPE thickness in female participants.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} **‡**
RNFL			
CCL21	Inflammation	−0.089 (−0.135–−0.044)	0.040
CCL8	Oncology	−0.102 (−0.152–−0.053)	0.036
GC-IPL			
CHAD	Inflammation II	0.099 (0.049–0.149)	0.034
OMD	Inflammation	0.105 (0.058–0.152)	0.008
RPE			
–	–	–	–

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, and status of diabetes.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S29

Associations between blood proteins and diabetic polygenic susceptibility, with aligning associated directionality to incident DR (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
RTN4R	Oncology	0.199 (0.153–0.244)	2.80×10^{-15}
HSD11B1	Inflammation	−0.166 (−0.205–−0.127)	2.25×10^{-14}
ADGRG2	Cardiometabolic	−0.235 (−0.292–−0.177)	1.61×10^{-13}
OMD	Inflammation	−0.137 (−0.173–−0.101)	6.73×10^{-12}
ADGRG1	Oncology	0.067 (0.049–0.085)	1.74×10^{-11}
PRAP1	Cardiometabolic II	0.166 (0.121–0.210)	2.84×10^{-11}
WIF1	Oncology	−0.167 (−0.213–−0.121)	1.06×10^{-10}
PON3	Inflammation	−0.161 (−0.207–−0.114)	6.18×10^{-10}
FGFBP1	Oncology	−0.164 (−0.212–−0.116)	9.89×10^{-10}
GDF15	Cardiometabolic	0.106 (0.075–0.137)	1.08×10^{-9}
NPY	Oncology	0.085 (0.060–0.110)	1.67×10^{-9}
PRCP	Cardiometabolic	0.162 (0.112–0.213)	1.22×10^{-8}
APOM	Cardiometabolic	−0.171 (−0.225–−0.116)	3.05×10^{-8}
MATN3	Neurology	−0.157 (−0.207–−0.107)	3.05×10^{-8}
DMP1	Cardiometabolic II	−0.097 (−0.129–−0.065)	1.20×10^{-7}
APOD	Inflammation II	−0.135 (−0.182–−0.089)	2.82×10^{-7}
EPHA1	Inflammation	0.133 (0.087–0.179)	4.41×10^{-7}
PTPRZ1	Cardiometabolic II	−0.167 (−0.225–−0.108)	6.05×10^{-7}
UMOD	Cardiometabolic	−0.083 (−0.112–−0.054)	6.05×10^{-7}
CRHBP	Inflammation	0.154 (0.099–0.209)	1.10×10^{-6}
KLRB1	Inflammation	0.111 (0.071–0.151)	1.73×10^{-6}
DNER	Inflammation	−0.163 (−0.222–−0.103)	1.82×10^{-6}
PTPRH	Oncology II	0.108 (0.068–0.148)	2.30×10^{-6}
CPM	Neurology	0.116 (0.073–0.159)	2.99×10^{-6}
IL18R1	Inflammation	0.127 (0.079–0.176)	5.50×10^{-6}
AFP	Neurology	−0.066 (−0.092–−0.040)	9.13×10^{-6}
TNXB	Neurology	−0.159 (−0.221–−0.097)	9.62×10^{-6}
B4GAT1	Neurology	−0.174 (−0.243–−0.106)	1.04×10^{-5}
GCG	Oncology	0.033 (0.020–0.047)	1.33×10^{-5}
FABP1	Inflammation	0.041 (0.025–0.058)	1.34×10^{-5}

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S30

Associations between blood proteins and diabetic polygenic susceptibility, with opposite associated directionality to incident DR (top 30 shown).

Proteins *	Panels	β (95% CI) †	P_{FDR} ‡
CKB	Cardiometabolic II	−0.141 (−0.169–−0.112)	1.27×10^{-18}
IGFBP2	Cardiometabolic	−0.106 (−0.129–−0.083)	3.68×10^{-17}
GSTA1	Cardiometabolic	0.062 (0.044–0.080)	1.45×10^{-9}
AFM	Inflammation II	0.294 (0.205–0.382)	3.77×10^{-9}
TIMP4	Neurology	−0.127 (−0.167–−0.087)	1.92×10^{-8}
LEPR	Cardiometabolic	−0.156 (−0.206–−0.105)	6.20×10^{-8}
GHR	Inflammation II	0.194 (0.129–0.258)	1.41×10^{-7}
LDLR	Cardiometabolic	0.084 (0.053–0.114)	2.30×10^{-6}
CDHR5	Cardiometabolic	0.115 (0.072–0.158)	4.00×10^{-6}
TACSTD2	Oncology	−0.152 (−0.212–−0.093)	1.01×10^{-5}
LTBP2	Cardiometabolic	−0.111 (−0.159–−0.063)	7.75×10^{-5}
CFP	Inflammation II	0.198 (0.111–0.285)	1.05×10^{-4}
BPIFB2	Cardiometabolic II	0.057 (0.032–0.083)	1.09×10^{-4}
DCXR	Oncology	0.064 (0.034–0.093)	2.58×10^{-4}
CHGB	Neurology	−0.078 (−0.114–−0.042)	2.60×10^{-4}
WNT9A	Inflammation	−0.113 (−0.168–−0.057)	5.82×10^{-4}
MEP1B	Cardiometabolic	0.029 (0.015–0.043)	5.83×10^{-4}
IL17RB	Inflammation	−0.062 (−0.093–−0.031)	6.48×10^{-4}
ADAMTS13	Cardiometabolic	0.135 (0.067–0.203)	8.25×10^{-4}
MCAM	Cardiometabolic	−0.095 (−0.143–−0.047)	8.41×10^{-4}
FCN2	Cardiometabolic	0.077 (0.037–0.117)	0.001
CES1	Cardiometabolic	0.033 (0.016–0.050)	0.001
FGL1	Inflammation II	−0.055 (−0.084–−0.026)	0.002
GH1	Cardiometabolic	−0.018 (−0.027–−0.008)	0.002
SLC39A14	Neurology	−0.095 (−0.147–−0.043)	0.002
HRC	Cardiometabolic II	−0.101 (−0.156–−0.045)	0.003
FBLN2	Cardiometabolic II	−0.098 (−0.153–−0.044)	0.003
WFIKKN1	Neurology	0.072 (0.032–0.112)	0.003
ITIH3	Cardiometabolic	−0.074 (−0.117–−0.031)	0.004
NEFL	Neurology	−0.061 (−0.098–−0.025)	0.005

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S31

SNP–protein associations of 58 known DR risk variants (top 30 shown).

Proteins *	**rs ID**	**β (95% CI) †**	P_{FDR} ‡
ITGA2	rs2910964	−0.155 (−0.166–−0.144)	2.56×10^{-161}
TNXB	rs184003	−0.157 (−0.171–−0.142)	1.15×10^{-93}
CPM	rs4470583	−0.373 (−0.429–−0.318)	1.48×10^{-36}
BTN3A2	rs1800629	0.103 (0.087–0.118)	2.08×10^{-34}
KLRB1	rs4470583	−0.364 (−0.422–−0.306)	3.08×10^{-31}
BTN3A2	rs1800625	0.093 (0.078–0.109)	6.65×10^{-29}
SIGLEC8	rs4470583	−0.394 (−0.463–−0.326)	3.40×10^{-26}
CPM	rs899036	−0.094 (−0.110–−0.078)	6.24×10^{-26}
TIMP4	rs1801282	0.121 (0.100–0.143)	7.71×10^{-26}
RNASET2	rs1800625	−0.060 (−0.072–−0.049)	1.10×10^{-22}
TFRC	rs4470583	0.317 (0.257–0.377)	2.21×10^{-22}
ESAM	rs4470583	−0.259 (−0.308–−0.210)	2.56×10^{-22}
RNASET2	rs1800629	−0.060 (−0.072–−0.049)	2.56×10^{-22}
DNER	rs4470583	0.204 (0.164–0.244)	1.81×10^{-20}
KLRB1	rs899036	−0.088 (−0.105–−0.070)	5.93×10^{-20}
CPM	rs11101355	−0.063 (−0.076–−0.050)	1.80×10^{-19}
CPM	rs11101357	−0.063 (−0.076–−0.050)	1.80×10^{-19}
GHRL	rs4470583	−0.628 (−0.755–−0.502)	1.90×10^{-19}
CPM	rs1399634	−0.071 (−0.085–−0.056)	2.61×10^{-19}
ELN	rs4470583	−0.260 (−0.314–−0.206)	1.56×10^{-18}
DNER	rs899036	0.054 (0.042–0.066)	3.65×10^{-16}
SIGLEC8	rs11101355	−0.072 (−0.088–−0.056)	3.65×10^{-16}
SIGLEC8	rs11101357	−0.072 (−0.088–−0.056)	3.65×10^{-16}
AGRP	rs4470583	−0.341 (−0.418–−0.265)	9.65×10^{-16}
PRSS8	rs4470583	−0.289 (−0.354–−0.225)	1.25×10^{-15}
PRRT3	rs899036	−0.077 (−0.095–−0.059)	1.22×10^{-14}
CES1	rs4470583	−0.601 (−0.741–−0.461)	1.71×10^{-14}
TFRC	rs11101357	0.059 (0.045–0.073)	2.66×10^{-14}
TFRC	rs11101355	0.059 (0.045–0.073)	2.67×10^{-14}
CDH2	rs899036	−0.071 (−0.087–−0.054)	2.75×10^{-14}

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S32

Sensitivity analysis excluding SNPs in strong linkage disequilibrium ($r^2 > 0.8$ within ±1 Mb) with cis-pQTLs of DR-associated proteins (top 30 shown).

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
CKB	Cardiometabolic II	−0.146 (−0.175–−0.117)	2.14×10^{-20}
IGFBP2	Cardiometabolic	−0.114 (−0.136–−0.091)	4.43×10^{-20}
HSD11B1	Inflammation	−0.147 (−0.186–−0.108)	5.30×10^{-11}
RTN4R	Oncology	0.168 (0.123–0.214)	8.76×10^{-11}
AFM	Inflammation II	0.318 (0.229–0.406)	2.37×10^{-10}
GHR	Inflammation II	0.222 (0.157–0.287)	1.95×10^{-9}
GSTA1	Cardiometabolic	0.061 (0.043–0.079)	2.84×10^{-9}
LDLR	Cardiometabolic	0.103 (0.072–0.134)	4.11×10^{-9}
PON3	Inflammation	−0.148 (−0.194–−0.102)	2.23×10^{-8}
ADGRG2	Cardiometabolic	−0.183 (−0.241–−0.125)	4.54×10^{-8}
TIMP4	Neurology	−0.123 (−0.163–−0.083)	7.98×10^{-8}
PRCP	Cardiometabolic	0.155 (0.105–0.205)	8.70×10^{-8}
PRAP1	Cardiometabolic II	0.137 (0.092–0.182)	1.11×10^{-7}
OMD	Inflammation	−0.110 (−0.145–−0.074)	1.18×10^{-7}
LEPR	Cardiometabolic	−0.152 (−0.202–−0.102)	1.60×10^{-7}
ADGRG1	Oncology	0.052 (0.034–0.070)	7.07×10^{-7}
CDHR5	Cardiometabolic	0.123 (0.080–0.166)	9.10×10^{-7}
EPHA1	Inflammation	0.126 (0.080–0.172)	2.54×10^{-6}
WIF1	Oncology	−0.128 (−0.174–−0.081)	2.78×10^{-6}
MATN3	Neurology	−0.135 (−0.185–−0.085)	4.10×10^{-6}
IL18R1	Inflammation	0.126 (0.077–0.174)	1.11×10^{-5}
CFP	Inflammation II	0.224 (0.137–0.310)	1.30×10^{-5}
NPY	Oncology	0.065 (0.039–0.090)	1.49×10^{-5}
TACSTD2	Oncology	−0.146 (−0.205–−0.087)	3.75×10^{-5}
CRHBP	Inflammation	0.135 (0.080–0.190)	3.80×10^{-5}
BPIFB2	Cardiometabolic II	0.060 (0.035–0.086)	6.93×10^{-5}
CPM	Neurology	0.102 (0.059–0.145)	8.06×10^{-5}
PTPRH	Oncology II	0.094 (0.055–0.134)	8.06×10^{-5}
CHGB	Neurology	−0.085 (−0.121–−0.049)	9.91×10^{-5}
ITIH3	Cardiometabolic	−0.100 (−0.143–−0.057)	1.01×10^{-4}

* Linear models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, SBP, status of diabetes, and the first ten genetic principal components. Protein quantitative trait loci (pQTLs) for the top-ranked proteins were derived from a GWAS conducted by the UKB.[1]

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S33

Component and topology of MCODE subnetwork 1 (top 20 shown).

Proteins	Degree	Radiality	Average path length	Clustering coefficient	Closeness centrality	Betweenness centrality	Neighbourhood connectivity
IL15	85	0.994	2.278	0.397	0.439	0.003	56.729
GZMB	83	0.995	2.203	0.405	0.454	0.006	60.133
CSF1	83	0.995	2.203	0.365	0.454	0.004	60.398
HAVCR2	69	0.994	2.282	0.435	0.438	0.005	59.986
CD48	56	0.994	2.333	0.445	0.429	0.005	60.357
B2M	79	0.995	2.146	0.267	0.466	0.018	56.772
CD163	86	0.995	2.179	0.332	0.459	0.010	56.233
PDCD1LG2	47	0.994	2.379	0.590	0.420	0.001	69.915
CD5	57	0.994	2.317	0.463	0.432	0.002	63.228
PDCD1	65	0.994	2.280	0.507	0.439	0.003	65.415
CD83	40	0.994	2.429	0.608	0.412	0.000	75.200
TNFRSF9	54	0.994	2.386	0.571	0.419	0.001	66.222
CD8A	139	0.996	1.992	0.253	0.502	0.022	50.302
CD86	109	0.995	2.117	0.319	0.472	0.013	53.330
CD276	52	0.994	2.350	0.560	0.425	0.001	68.462
LGALS9	45	0.994	2.382	0.560	0.420	0.001	69.622
TNFRSF4	45	0.994	2.413	0.606	0.414	0.001	69.733
FAS	51	0.994	2.374	0.507	0.421	0.001	66.431
IL2RA	63	0.994	2.355	0.472	0.425	0.001	62.810
CD4	170	0.996	1.875	0.200	0.533	0.050	46.335

Supplementary Table S34

Component and topology of MCODE subnetwork 2 (top 20 shown).

Proteins	Degree	Radiality	Average path length	Clustering coefficient	Closeness centrality	Betweenness centrality	Neighbourhood connectivity
CX3CL1	48	0.994	2.357	0.467	0.424	0.008	66.854
SLAMF1	40	0.994	2.411	0.467	0.415	0.002	67.375
MRC1	58	0.994	2.315	0.436	0.432	0.002	62.948
CD28	74	0.994	2.259	0.470	0.443	0.002	62.122
TNFRSF1B	47	0.994	2.408	0.439	0.415	0.004	62.723
CCL8	30	0.993	2.483	0.667	0.403	0.000	78.067
LAMP1	56	0.994	2.270	0.397	0.440	0.008	63.107
IL1R1	45	0.994	2.432	0.516	0.411	0.001	66.467
CD7	34	0.994	2.394	0.538	0.418	0.001	66.412
CTSS	65	0.995	2.195	0.295	0.456	0.011	56.923
ANXA5	66	0.995	2.170	0.347	0.461	0.010	63.773
CCL11	49	0.994	2.389	0.429	0.419	0.002	61.980
VCAM1	101	0.995	2.096	0.311	0.477	0.010	58.347
CD274	94	0.995	2.131	0.355	0.469	0.008	58.511
AOC3	31	0.994	2.402	0.735	0.416	0.000	86.581
IL10	162	0.996	1.925	0.213	0.520	0.030	48.006
IL12RB1	38	0.993	2.472	0.508	0.405	0.001	64.211
CCL20	56	0.994	2.339	0.421	0.427	0.002	60.768
MSR1	40	0.994	2.366	0.405	0.423	0.004	65.150
IL4R	44	0.994	2.440	0.463	0.410	0.001	63.614

Supplementary Table S35

Component and topology of MCODE subnetwork 3 (top 20 shown).

Proteins	Degree	Radiality	Average path length	Clustering coefficient	Closeness centrality	Betweenness centrality	Neighbourhood connectivity
FGFR2	40	0.994	2.376	0.291	0.421	0.006	45.500
AXL	39	0.994	2.307	0.391	0.433	0.006	68.615
IGF1R	58	0.994	2.258	0.288	0.443	0.006	53.655
PGF	28	0.994	2.408	0.542	0.415	0.001	69.357
ANPEP	46	0.995	2.230	0.305	0.448	0.017	57.739
AFP	33	0.994	2.286	0.360	0.437	0.005	68.545
MMP7	41	0.994	2.291	0.370	0.436	0.005	58.000
MMP12	35	0.994	2.382	0.516	0.420	0.001	72.914
PLAU	45	0.994	2.298	0.348	0.435	0.006	55.200
NGFR	41	0.994	2.338	0.280	0.428	0.010	54.293
AREG	43	0.994	2.299	0.290	0.435	0.006	58.349
CDH2	56	0.995	2.237	0.310	0.447	0.009	51.161
HAVCR1	29	0.994	2.330	0.416	0.429	0.001	70.069
TIMP2	50	0.994	2.256	0.342	0.443	0.003	55.660
ELN	48	0.994	2.256	0.343	0.443	0.005	58.125
COL1A1	75	0.995	2.171	0.226	0.461	0.014	44.640
EPHA2	41	0.994	2.387	0.278	0.419	0.005	40.024
CDH1	91	0.995	2.102	0.199	0.476	0.038	45.593
CHI3L1	35	0.994	2.331	0.383	0.429	0.004	65.457
LCN2	56	0.995	2.208	0.260	0.453	0.019	54.161

Supplementary Table S36

Component and topology of MCODE subnetwork 4 (top 20 shown).

Proteins	Degree	Radiality	Average path length	Clustering coefficient	Closeness centrality	Betweenness centrality	Neighbourhood connectivity
FGF5	55	0.994	2.267	0.397	0.441	0.003	64.309
SCARB2	72	0.995	2.166	0.261	0.462	0.020	54.333
TGFA	41	0.994	2.304	0.411	0.434	0.005	65.902
ITGA2	42	0.994	2.280	0.364	0.439	0.004	67.976
FGF16	50	0.994	2.288	0.425	0.437	0.002	67.040
C1QA	42	0.994	2.312	0.318	0.433	0.005	54.262
DPP4	57	0.995	2.205	0.306	0.454	0.010	60.509
TEK	43	0.994	2.325	0.328	0.430	0.004	59.349
LGALS3	82	0.995	2.086	0.276	0.479	0.013	55.220
IL18R1	27	0.993	2.510	0.658	0.398	0.000	76.074
THY1	67	0.995	2.154	0.313	0.464	0.014	59.687
CCL21	42	0.994	2.390	0.454	0.418	0.004	65.595
CLEC7A	42	0.994	2.368	0.443	0.422	0.002	63.786
NOTCH1	50	0.994	2.256	0.301	0.443	0.009	58.220
MMP3	61	0.995	2.219	0.326	0.451	0.005	57.803
IFNGR1	35	0.994	2.443	0.583	0.409	0.000	71.971
TIMP1	92	0.995	2.078	0.270	0.481	0.012	53.424
TFRC	67	0.995	2.154	0.290	0.464	0.018	58.612
TNFSF11	57	0.994	2.277	0.326	0.439	0.007	59.018
SIGLEC1	38	0.994	2.402	0.514	0.416	0.002	65.895

Supplementary Table S37
Summary of top 30 proteins of Shapley additive explanations and C-statistics for predicting DR.

Proteins	Panels	SHAP	C-statistics
PLXNB2	Cardiometabolic	0.164	0.722 (0.657–0.788)
GDF15	Cardiometabolic	0.134	0.712 (0.644–0.780)
REN	Cardiometabolic	0.134	0.669 (0.600–0.739)
CHAD	Inflammation II	0.096	0.652 (0.584–0.720)
NEFL	Neurology	0.082	0.621 (0.557–0.685)
FGFBP1	Oncology	0.080	0.644 (0.594–0.694)
CD276	Inflammation	0.065	0.636 (0.564–0.707)
CREG1	Oncology	0.052	0.566 (0.491–0.641)
CPA1	Cardiometabolic	0.049	0.593 (0.517–0.669)
CDH1	Cardiometabolic	0.049	0.615 (0.542–0.688)
WIF1	Oncology	0.048	0.612 (0.555–0.670)
IL1R1	Neurology	0.043	0.625 (0.563–0.687)
CHRDL2	Cardiometabolic	0.034	0.544 (0.477–0.612)
TGFBI	Cardiometabolic	0.033	0.576 (0.505–0.646)
DCBLD2	Oncology	0.031	0.620 (0.559–0.682)
BCAN	Neurology	0.030	0.617 (0.553–0.680)
MIA	Oncology	0.030	0.595 (0.525–0.666)
PLA2G7	Neurology	0.028	0.608 (0.543–0.672)
BGLAP	Cardiometabolic II	0.028	0.607 (0.534–0.680)
DDX4	Inflammation II	0.026	0.536 (0.454–0.618)
NCAM2	Neurology	0.025	0.533 (0.466–0.600)
MUC13	Neurology	0.023	0.574 (0.503–0.646)
COL15A1	Cardiometabolic II	0.023	0.519 (0.438–0.601)
RTBDN	Oncology	0.022	0.511 (0.440–0.582)
SPOCK1	Neurology	0.021	0.569 (0.497–0.642)
ANGPTL4	Inflammation	0.021	0.594 (0.532–0.655)
DPP6	Oncology	0.020	0.574 (0.505–0.643)
LTA4H	Oncology	0.019	0.592 (0.524–0.659)
AOC3	Cardiometabolic	0.018	0.614 (0.542–0.687)
CD8A	Neurology	0.017	0.540 (0.458–0.623)

Supplementary Table S38

Subgroup analyses stratified by polygenic risk and sex for the performance of three top-ranked proteins (PLXNB2, GDF15, and REN) in predicting DR.

Subgroups *	**PLXNB2**	**GDF15**	**REN**
Polygenic risk			
High	0.726 (0.639–0.814)	0.686 (0.595–0.778)	0.615 (0.522–0.709)
Low	0.711 (0.607–0.814)	0.743 (0.640–0.845)	0.753 (0.659–0.848)
Sex			
Men	0.717 (0.628–0.805)	0.708 (0.621–0.796)	0.671 (0.579–0.763)
Women	0.729 (0.630–0.827)	0.702 (0.591–0.813)	0.655 (0.550–0.761)

* Performance for proteins predicting incident DR was assessed by Cox model. Data were presented as C-statistics (95% CI).

Supplementary Table S39

Baseline characteristics of the GDES participants included in the study.

Characteristics *	**GDES population**			***P*** **†**
	Overall	**Non-DR**	**Incident-DR**	
No. of subjects	352	316	36	–
Age, years	63.17±6.98	63.14±6.84	63.39±8.21	0.839
Sex				
Female	151 (42.9%)	138 (43.7%)	13 (36.1%)	0.490
Male	201 (57.1%)	178 (56.3%)	23 (63.9%)	
Educational attainment				
Junior High School and below	168 (47.7%)	152 (48.1%)	16 (44.4%)	0.823
High School	111 (31.5%)	98 (31.0%)	13 (36.1%)	
University and above	73 (20.7%)	66 (20.9%)	7 (19.4%)	
Smoking				
Never	305 (86.6%)	274 (86.7%)	31 (86.1%)	0.990
Ever/current	47 (13.4%)	42 (13.3%)	5 (13.9%)	
Body mass index, kg/m^2	24.10±3.11	24.02±3.05	24.81±3.59	0.147
Duration of diabetes, years	6.53±5.47	6.22±4.96	9.22±8.57	0.002
Systolic blood pressure, mmHg	134.69±17.48	134.34±17.25	137.81±19.31	0.260
Hemoglobin A1c, mmol/mol	51.73±13.53	50.43±11.81	63.18±20.76	8.71×10^{-4}

* Continuous data are presented as mean ± standard deviation and categorical variables as number (percentage). Differences in population groups were compared using two-sided Student's t-test for continuous variables and Pearson's χ^2-test for discrete variables.

† Adjustment for multiple comparisons was not applied.

Supplementary Table S40

Replicated proteins associated with incident DR in the GDES (top 30 shown).

Proteins *	Panels	HR (95% CI) †	P_{FDR} ‡
CLEC1A	Cardiometabolic	3.035 (2.184–4.217)	6.82×10^{-9}
NOTCH1	Cardiometabolic	2.504 (1.909–3.285)	6.82×10^{-9}
PLXNB2	Cardiometabolic	2.321 (1.805–2.986)	6.82×10^{-9}
MCAM	Cardiometabolic	2.650 (1.975–3.556)	7.68×10^{-9}
ADAM15	Cardiometabolic	2.416 (1.841–3.171)	1.19×10^{-8}
GAS6	Cardiometabolic	2.484 (1.879–3.285)	1.19×10^{-8}
CD55	Cardiometabolic	2.691 (1.982–3.655)	1.19×10^{-8}
CST3	Cardiometabolic	2.697 (1.969–3.695)	2.67×10^{-8}
AOC3	Cardiometabolic	2.522 (1.876–3.389)	3.19×10^{-8}
HSPG2	Cardiometabolic	2.912 (2.058–4.119)	4.46×10^{-8}
LTBP2	Cardiometabolic	2.591 (1.894–3.544)	6.20×10^{-8}
BOC	Cardiometabolic	2.279 (1.732–2.997)	9.06×10^{-8}
COL6A3	Cardiometabolic	2.523 (1.851–3.438)	1.01×10^{-7}
IL6ST	Cardiometabolic	2.222 (1.697–2.909)	1.19×10^{-7}
GDF15	Cardiometabolic	2.248 (1.710–2.954)	1.19×10^{-7}
LRP11	Cardiometabolic	2.325 (1.742–3.103)	1.65×10^{-7}
CD46	Cardiometabolic	2.325 (1.743–3.102)	1.65×10^{-7}
NRP1	Cardiometabolic	2.091 (1.622–2.695)	1.96×10^{-7}
PTGDS	Cardiometabolic	2.362 (1.749–3.189)	3.00×10^{-7}
TCN2	Cardiometabolic	2.059 (1.597–2.655)	3.50×10^{-7}
CDH1	Cardiometabolic	2.003 (1.568–2.558)	3.50×10^{-7}
CD59	Cardiometabolic	2.574 (1.843–3.595)	3.68×10^{-7}
ADGRE5	Cardiometabolic	2.265 (1.695–3.026)	3.89×10^{-7}
CCN3	Cardiometabolic	2.454 (1.785–3.374)	3.89×10^{-7}
XG	Cardiometabolic	2.750 (1.907–3.966)	7.00×10^{-7}
COL4A1	Cardiometabolic	2.041 (1.571–2.651)	9.39×10^{-7}
PDGFRA	Cardiometabolic	2.042 (1.569–2.657)	1.13×10^{-6}
DCN	Cardiometabolic	2.186 (1.636–2.921)	1.16×10^{-6}
ADA2	Cardiometabolic	1.989 (1.542–2.566)	1.16×10^{-6}
IL18BP	Cardiometabolic	1.983 (1.536–2.560)	1.37×10^{-6}

* CPH models were adjusted for age, sex, HbA1c, duration of diabetes, BMI, and SBP.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S41

Proteins replicated associations with photoreceptor layer thickness in the GDES.

Proteins *	**Panels**	**β (95% CI) †**	P_{FDR} ‡
C1QTNF1	Cardiometabolic	−0.240 (−0.399–−0.082)	0.013
CD59	Cardiometabolic	−0.335 (−0.513–−0.157)	0.003
COL18A1	Cardiometabolic	−0.222 (−0.386–−0.058)	0.028
EFEMP1	Cardiometabolic	−0.313 (−0.493–−0.134)	0.005
FABP4	Cardiometabolic	−0.267 (−0.434–−0.101)	0.009
GSTA1	Cardiometabolic	−0.280 (−0.437–−0.123)	0.004
GUSB	Cardiometabolic	−0.345 (−0.505–−0.185)	6.13×10^{-4}
IGFBP6	Cardiometabolic	−0.289 (−0.475–−0.102)	0.012
NPTXR	Cardiometabolic	0.232 (0.069–0.394)	0.020
PLAT	Cardiometabolic	−0.283 (−0.441–−0.126)	0.004
REN	Cardiometabolic	−0.362 (−0.533–−0.190)	7.08×10^{-4}
SEMA3F	Cardiometabolic	−0.284 (−0.447–−0.120)	0.005
SPON2	Cardiometabolic	−0.329 (−0.496–−0.161)	0.002
TIMP1	Cardiometabolic	−0.231 (−0.411–−0.051)	0.036
TNFRSF10C	Cardiometabolic	−0.206 (−0.372–−0.041)	0.043

* Linear models were adjusted for age, sex, HbA1c, duration of diabetes, BMI, and SBP.

† Data are presented as per-SD change of protein values.

‡ *P* values were calculated through two-sided Student's t-tests followed by controlling FDR for multiple testing.

Supplementary Table S42
Protein biomarker associated with DR progression in the GDES cohort (top 30 shown).

Proteins *	**Panels**	**HR (95% CI) †**	P_{FDR} ‡
SIGLEC7	Cardiometabolic	4.286 (2.765–6.644)	2.82×10^{-8}
GPNMB	Cardiometabolic	3.297 (2.245–4.840)	2.09×10^{-7}
BOC	Cardiometabolic	2.827 (1.991–4.015)	7.69×10^{-7}
CLEC1A	Cardiometabolic	2.853 (1.983–4.104)	1.28×10^{-6}
ADAM15	Cardiometabolic	2.643 (1.885–3.706)	1.28×10^{-6}
CLC	Cardiometabolic	2.655 (1.866–3.778)	3.53×10^{-6}
PLXNB2	Cardiometabolic	2.246 (1.674–3.015)	3.60×10^{-6}
ACOX1	Cardiometabolic	2.398 (1.723–3.338)	8.80×10^{-6}
CHIT1	Cardiometabolic	2.898 (1.939–4.330)	8.80×10^{-6}
QPCT	Cardiometabolic	2.662 (1.835–3.861)	9.23×10^{-6}
PLA2G2A	Cardiometabolic	2.646 (1.825–3.836)	9.50×10^{-6}
EDIL3	Cardiometabolic	2.287 (1.666–3.141)	9.74×10^{-6}
GUSB	Cardiometabolic	2.330 (1.658–3.275)	3.15×10^{-5}
MCFD2	Cardiometabolic	2.012 (1.517–2.670)	3.30×10^{-5}
REN	Cardiometabolic	2.324 (1.648–3.277)	3.72×10^{-5}
OSMR	Cardiometabolic	2.976 (1.901–4.659)	4.24×10^{-5}
XG	Cardiometabolic	2.749 (1.812–4.171)	4.25×10^{-5}
ACTA2	Cardiometabolic	2.023 (1.512–2.706)	4.27×10^{-5}
CLUL1	Cardiometabolic	2.151 (1.561–2.964)	5.37×10^{-5}
LRP11	Cardiometabolic	2.101 (1.535–2.875)	6.51×10^{-5}
VSTM2L	Cardiometabolic	2.295 (1.611–3.270)	7.31×10^{-5}
RETN	Cardiometabolic	1.992 (1.478–2.684)	1.00×10^{-4}
LEP	Cardiometabolic	2.204 (1.556–3.122)	1.38×10^{-4}
CGREF1	Cardiometabolic	1.896 (1.425–2.522)	1.69×10^{-4}
HSPG2	Cardiometabolic	2.058 (1.491–2.841)	1.69×10^{-4}
CA5A	Cardiometabolic	2.064 (1.490–2.858)	1.74×10^{-4}
SFTPD	Cardiometabolic	2.179 (1.536–3.092)	1.74×10^{-4}
FCRL1	Cardiometabolic	2.271 (1.559–3.307)	2.25×10^{-4}
GDF15	Cardiometabolic	1.805 (1.377–2.365)	2.25×10^{-4}
PI3	Cardiometabolic	1.954 (1.438–2.654)	2.25×10^{-4}

* CPH models were adjusted for age, sex, ethnicity, HbA1c, duration of diabetes, BMI, and SBP.
† Data are presented as per-SD change of protein values.
‡ *P* values were calculated through two-sided Wald tests followed by controlling FDR for multiple testing.

Supplementary Table S43
Druggability profile of REN.

Drug	Group	Indication	Trial phase
ALISKIREN	Approved	Type 2 Diabetes Mellitus	4
		Hypertension	4
		Coronary Artery Disease (CAD) / Type 2 Diabetes Mellitus	4
		Chronic Kidney Disease (CKD) / Hypertension / Proteinuria	4
		Blood Pressures / Chronic Kidney Disease (CKD) / Proteinuria	4
		Chronic Kidney Disease (CKD) / Hypertension	4
		Chronic Kidney Disease (CKD) / Proteinuria	4
		Diabetes Mellitus / Hypertension	4
		Essential Hypertension (Mild to Moderate)	4
		Heart Failure	4
		Hypertension	4
		Hypertension, Essential Hypertension	4
		Hypertension / Left Ventricle Hypertrophy	4
		Hypertension / Obesity, Abdominal / Syndrome, Metabolic	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Immunoglobulin A Nephropathy	4
		Kidney Diseases	4
		Stage II Hypertension	4
		Diabetes / Hypertension / Prehypertension	4
		Albuminuria / Diabetes / Macroalbuminuric Diabetic Nephropathy / Microalbuminuria / Proteinuria	4

		Cardiac Transplant / Hypertension	4
		Deficiency, Vitamin D / Hypertension	4
		Diabetes / Hypertension / Stage II Hypertension	4
		Diabetic Nephropathy / Focal Segmental Glomerulosclerosis (FSGS) / Glomerulopathy (Obesity-associated) / Hypertensive Nephrosclerosis / Immunoglobulin A Nephropathy / Membranous Nephropathy / Proteinuric Kidney Disease	4
		Hypertension	4
		Hypertension With Metabolic Syndrome	4
		Kidney Diseases / Renal Failure, Chronic Renal Failure	4
		Chronic Kidney Disease (CKD) / Hypertension / Muscle Sympathetic Nerve Activity	4
		Congestive Heart Failure (CHF)	4
		Diabetes Mellitus	4
		Dialysis therapy / Hypertension	4
		End Stage Renal Disease (ESRD) / Hypertension	4
		Glomerulonephritis, IGA / Hypertension	4
		Heart Failure	4
		Hypertension	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Hypertensive Left Ventricular Hypertrophy	4
		Peritoneal Membrane Failure	4
		Type 2 Diabetes with Nephropathy	4
		Diabetes Mellitus / Hypertension	4
		Hypertension	4

		Hypertension / Type 2 Diabetes Mellitus	4
		Hypertension	3
		Hypertension	3
		Heart Failure	3
		Acute Decompensated Heart Failure (ADHF) / Congestive Heart Failure (CHF)	3
		Chronic Heart Failure (CHF)	3
		Coronary Artery Atherosclerosis / Coronary Artery Disease (CAD)	3
		Diabetes / Hypertension	3
		Hypertension	3
		Hypertension Arterial	3
		Hypertension, Diabetes Mellitus	3
		Hypertension, Essential Hypertension	3
		Hypertension / Left Ventricular Hypertrophy / Overweight	3
		Immunoglobulin A Nephropathy	3
		Marfan Syndrome	3
		Moderate to Severe Hypertension	3
		Myocardial Infarction	3
		Cardiovascular Disease (CVD) / Type 2 Diabetes Mellitus	3
		Cardiovascular Events	3
		Endothelial Dysfunction	3
		Atrial Fibrillation	3
		Hypertension	2
		Diabetic Nephropathy	2

		Endothelial Dysfunction / Hypertension / Resistance, Insulin / Syndrome, Metabolic	2
		Heart Failure	2
		Hypertension	2
		Myocardial Ischemia / Post Acute Coronary Syndrome	2
		C3 Glomerulonephritis / Complement 3 Glomerulopathy (C3G) / Complement Abnormality / Membranoproliferative Glomerulonephritis (MPGN) / Membranoproliferative Glomerulonephritis, Type II	2
		Ankle Edema / Hypertension	2
		Diabetic Macular Edema (DME)	2
		Heart Failure / Kidney Failure	2
		Hypertension / Obesity, Abdominal	2
		Non-diabetic Nephropathy	2
		Diabetes / Hypertension	2
		Atherosclerosis	2, 3
		End Stage Renal Disease (ESRD)	1
		Hypertension	1
		Renal Function	1
		Diabetes Mellitus / Endocrine System Diseases / Metabolic Diseases / Metabolism Disorder, Glucose	1
		Healthy Volunteers (HV)	1
		Hypertension	1
		Hypertension / Syndrome, Metabolic	1
		Hypertension	1, 2

		Type 2 Diabetes Mellitus	1, 2
		Coronavirus Disease 2019 (COVID- 19) / COVID / Hypertension	Not Available
		Hypertension	Not Available
		Hypertension Arterial	Not Available
		Type 2 Diabetes Mellitus	Not Available
		Albuminuria	Not Available
		Diabetes	Not Available
		Abdominal Aortic Aneurysm (AAA) / Hypertension	Not Available
		Aortic Compliance / Diastolic Function / Insulin Sensitivity	Not Available
		Hypertension	Not Available
		Atherosclerosis / Diabetes Mellitus	Not Available
		Heart Failure	Not Available
		Heart Failure, Diastolic	Not Available
		Idiopathic Membranous Nephropathy	Not Available
Minoxidil	Approved	Androgenetic Alopecia (AGA)	4
		Alopecia Areata (AA)	4
		Beard Enhancement	4
		Eyebrow Hypotrichosis / Thinning Eyebrows	4
		Female Pattern Hair Loss	4
		Hypotrichosis of Eyebrows / Thinning Eyebrows	4
		Central Centrifugal Cicatricial Alopecia (CCCA)	4
		Androgenetic Alopecia (AGA)	4
		Chest Hair Enhancement	4
		Female Androgenetic Alopecia	4

		Alopecia	3
		Alopecia	3
		Androgenetic Alopecia (AGA)	3
		Androgenetic Alopecia (AGA) / Female Pattern Hair Loss	3
		Androgenetic Alopecia (AGA) / Hair Loss	3
		Androgenetic Alopecia (AGA) / Female Pattern Baldness	3
		Androgenetic Alopecia (AGA)	3
		Female Pattern Alopecia	3
		Androgenetic Alopecia (AGA) / Female Pattern Baldness	3
		Androgenetic Alopecia (AGA)	2, 3
		Androgenetic Alopecia (AGA)	2, 3
		Alopecia / Androgenetic Alopecia (AGA) / Hair Loss	2
		Alopecia / Female Pattern Baldness / Hair Loss	2
		Alopecia / Hair Loss	2
		Androgenetic Alopecia (AGA)	2
		Androgenetic Alopecia (AGA) / Female Pattern Hair Loss / Ludwig Type 1 / Ludwig Type 2	2
		Female Pattern Hair Loss	2
		Williams Beuren Syndrome	2
		Alopecia / Survivors of Childhood Cancer	2
		Ovarian Cancer	2
		Androgenetic Alopecia (AGA) / Male Pattern Hair Loss	2
		Alopecia	1, 2
		Androgenetic Alopecia (AGA)	1, 2
		Acne Vulgaris	1, 2

		Dermatology / Female Pattern Baldness	1, 2
		Anaesthetics Adverse Reaction / Assessment, Self / Objective (Goal)	1, 2
		Healthy Volunteers (HV)	1
		Androgenetic Alopecia (AGA)	1
		Pharmacokinetics	1
		Permanent Chemotherapy-induced Alopecia	0
		Alopecia Areata (AA)	0
		Anatomic Stage 1 Breast Cancer AJCC v8 / Anatomic Stage IA Breast Cancer AJCC v8 / Anatomic Stage IB Breast Cancer AJCC v8 / Anatomic Stage II Breast Cancer AJCC v8 / Anatomic Stage IIA Breast Cancer AJCC v8 / Anatomic Stage IIB Breast Cancer AJCC v8 / Anatomic Stage III Breast Cancer AJCC v8 / Anatomic Stage IIIA Breast Cancer AJCC v8 / Anatomic Stage IIIB Breast Cancer AJCC v8 / Anatomic Stage IIIC Breast Cancer AJCC v8 / Anatomic Stage IV Breast Cancer AJCC v8 / Endocrine Therapy-Induced Alopecia / Prognostic Stage 2 Breast Cancer AJCC v8 / Prognostic Stage I Breast Cancer AJCC v8 / Prognostic Stage IA Breast Cancer AJCC v8 / Prognostic Stage IB Breast Cancer AJCC v8 / Prognostic Stage IIA Breast Cancer AJCC v8 / Prognostic Stage IIB Breast Cancer AJCC v8 / Prognostic Stage III Breast Cancer AJCC v8 / Prognostic Stage IIIA Breast Cancer AJCC v8 / Prognostic Stage IIIB Breast Cancer AJCC v8 / Prognostic Stage IIIC Breast Cancer AJCC v8 / Prognostic Stage IV Breast Cancer AJCC v8	0
		Hypotrichosis	0

		Androgenetic Alopecia (AGA)	Not Available
		Alopecia / Female Pattern Hair Loss	Not Available
		Androgenetic Alopecia (AGA)	Not Available
		Coronavirus Disease 2019 (COVID-19) / COVID / Hypertension	Not Available
		Female Pattern Hair Loss, Androgenic Alopecia	Not Available
		Fissure; Anal	Not Available
		Male Pattern of Hair Loss, Androgenic Alopecia	Not Available
		Alopecia Areata (AA)	Not Available
		Androgenetic Alopecia (AGA)	Not Available
		Treatment Induced Hypertension	Not Available
		Androgenetic Alopecia (AGA)	Not Available
		Androgenetic Alopecia (AGA) / Female Pattern Hair Loss	Not Available
Lisinopril	Approved	Coronary Artery Disease (CAD)	4
		Atherosclerosis / Cardiovascular Disease (CVD) / Cerebral Arteriosclerosis / Coronary Heart Disease (CHD) / Diabetes Mellitus / Hypertension	4
		Perioperative Hypertension	4
		Cardiovascular Disease (CVD) / Chronic Kidney Disease (CKD) / Hypertension, Essential Hypertension / Stroke	4
		Diabetic Nephropathy	4
		Diabetic Nephropathy / Hypertension	4
		Heart Failure / Left Ventricular Dysfunction	4
		Human Immunodeficiency Virus (HIV) Infections	4
		Hypertension	4
		Hypertension, Essential Hypertension / Secondary	4

		Hypertension	
		Induction of Intraoperative Hypotension	4
		Paediatric Hypertension	4
		Stage 2 Diastolic Hypertension	4
		Cardiovascular Disease (CVD) / Type 2 Diabetes Mellitus	4
		Coronavirus Disease 2019 (COVID- 19) / Glomerulonephritis / Immunoglobulin A Nephropathy	4
		Hypertension	4
		Renal Insufficiency, Chronic / Type 2 Diabetic Nephropathy	4
		Coronavirus Disease 2019 (COVID- 19) / Hypertension	4
		Cardiovascular Disease (CVD) / Osteoarthritis (OA)	4
		Neurological Dysphagia / Pneumonia	4
		Early Diabetic Nephropathy / Hypertension	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Hypertension	4
		Proteinuria / Renal Insufficiency, Chronic	4
		Drug-Induced Cardiomyopathy / Hearth Failure with Reduced Ejection Fraction (HFrEF)	4
		Atherosclerosis / Cardiovascular Disease (CVD) / coronary heart disease (CHD) / Diabetes Mellitus / High Cholesterol / Hypertension / Type 2 Diabetes Mellitus	3
		Cardiovascular Disease (CVD) / Coronary Heart Disease (CHD) / Diabetes Mellitus / Heart Failure / High Cholesterol / Hypertension / Myocardial Infarction / Myocardial Ischemia	3
		Diabetic Nephropathy	3

		Heart Failure	3
		Hypertension	3
		Hypertension / Obesity, Abdominal	3
		Kidney, Polycystic	3
		Left Ventricular Hypertrophy	3
		Community-acquired Pneumonia, Influenza, COVID-19 / Coronavirus Disease 2019 (COVID- 19)	3
		Glomerulonephritis / Kidney Diseases / Type 2 Diabetes Mellitus	3
		Heart Failure, Congestive and Microalbuminuria	3
		Haemodialysis Treatment / Hypertension / Left Ventricular Hypertrophy	3
		Hyperkalaemia / Renal Insufficiency, Chronic	3
		Hyperoxaluria	3
		Cardiovascular Disease (CVD)	3
		Becker's Muscular Dystrophy (BMD) / Duchenne Muscular Dystrophy (DMD) / Limb Girdle Muscular Dystrophy	2, 3
		Hypertension / Mild Cognitive Impairment (MCI)	2
		Breast Cancer / Cardiac Toxicities	2
		Dyspnea / Non-Small Cell Lung Cancer (NSCLC) / Small Cell Lung Cancer (SCLC)	2
		Aging / Cognitive Impairment (CI) / Hypertension	2
		Cardiovascular Disease (CVD) / Chronic Kidney Disease (CKD)	2
		Focal Segmental Glomerulosclerosis (FSGS)	2
		Hypertension, Essential Hypertension	2

		Oligospermia	2
		Pacemakers, Heart Failure	2
		Hepatocellular Carcinoma / Steatohepatitis, Non-alcoholic	2
		Systemic Lupus Erythematosus	2
		Albuminuria / Human Immunodeficiency Virus Infection (HIV) / Acquired Immunodeficiency Syndrome (AIDS) / Kidney Diseases / Predisposition, Genetic	2
		Hypertension / Unspecified Adult Solid Tumour, Protocol Specific	2
		Acute Coronary Syndrome (ACS) / Hypertension Arterial	2
		Extracapillary Glomerulonephritis	2
		Breast Carcinoma / Hematopoietic and Lymphoid System Neoplasm / Lymphoma / Sarcomas	2
		Diabetes Complications / Diabetic Retinopathy (DR) / Eye Diseases / Type 1 Diabetes Mellitus	2
		Prehypertension	1, 2
		Healthy Volunteers (HV)	1
		To Determine Bioequivalence Under Fed Conditions	1
		Type 2 Diabetes Mellitus	1
		Gastroparesis	1
		Bioequivalence	1
		Healthy Volunteers (HV)	1
		Therapeutic Equivalency	1
		Hypertension	1
		Diabetes / Healthy Volunteers (HV)	1

		Fasting	1
		Fed	1
		Hypertension	1
		Stroke	1
		Type 2 Diabetes Mellitus	1
		Healthy Volunteers (HV)	1
		Hypertension Resistant to Conventional Therapy	1
		Prostate Cancer / Radiation Toxicity / Urinary Complications	0
		Anaesthetics Adverse Reaction / Delirium	Not Available
		Cardiovascular Disease (CVD) / Coronary Heart Disease (CHD) / Hypertension / Myocardial Infarction	Not Available
		Coronavirus Disease 2019 (COVID-19) / COVID / Hypertension	Not Available
		Hypertension	Not Available
		Hypertension Arterial	Not Available
		Hyperparathyroidism	Not Available
		Cardiovascular Risk / Human Immunodeficiency Virus (HIV) Infections	Not Available
		Diabetic Nephropathy / Type 1 Diabetes Mellitus	Not Available
		Atrial Fibrillation / Chronic Heart Failure (CHF)	Not Available
		Cardiomyopathy / Duchenne Muscular Dystrophy (DMD)	Not Available
		Cardiovascular Disease (CVD) / Cerebrovascular Diseases / Peripheral Arterial Disease (PAD)	Not Available
		Healthy Volunteers (HV)	Not Available
		Hypertension	Not Available

		Hypertension, Essential Hypertension	Not Available
		Hypertension / Hypertension Treatment / Hypertension, Grade 1 / N of 1 Study Design	Not Available
		Hypertension / Plasma Renin Activity	Not Available
		Diabetic Kidney Disease (DKD)	Not Available
		Chest Pain	Not Available
		Type 2 Diabetes Mellitus	Not Available
		Dementia	Not Available
		Heart Failure, Diastolic	Not Available
		Hypertension	Not Available
		Microalbuminuria / Pre-Eclampsia	Not Available
SPH-3217	Approved	Hypertension, Essential Hypertension	3
		Hypertension, Essential Hypertension	2
		Mild to Moderate Ulcerative Colitis	2
		Ulcerative Colitis	2
		Hypertension	1
		Primary Mild and Moderate Hypertension	1, 2
		Drug-Drug Interaction (DDI)	1, 2
IMARIKIREN	Approved	Renal / Hepatic Impairment	1
		Type 2 Diabetes Mellitus / Microalbuminuria	2
HYDROCHLOROTHIAZIDE	Approved	Hypertension, Essential Hypertension	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Angina Pectoris / Diabetes Mellitus / Myocardial Infarction / Stroke	4
		Atrial Fibrillation	4

		Diabetic Nephropathy	4
		Hypertension	4
		Hypertension / Prehypertension / Syndrome, Metabolic	4
		Albuminuria / Hypertension / Type 2 Diabetes Mellitus	4
		Blood Pressures	4
		Chronic Kidney Disease (CKD)	4
		Coronary Artery Disease (CAD) / Hypertension	4
		Diabetes Mellitus	4
		Diabetes Mellitus / Hypertension	4
		Edema / Nephrotic Syndrome	4
		Erectile Dysfunction / Hypertension / Ventricular Remodelling	4
		Essential Hypertension (Mild to Moderate)	4
		Hypertension	4
		Hypertension, Dyslipidaemia	4
		Hypertension, Essential Hypertension	4
		Hypertension / Hyperuricemia / Menopause	4
		Hypertension / Impaired Renal Function	4
		Hypertension / Left Ventricle Hypertrophy	4
		Hypertension / Left Ventricular Hypertrophy	4
		Hypertension / Obesity	4
		Hypertension / Obesity, Abdominal / Syndrome, Metabolic	4
		Hypertension / Pharmacogenetics	4
		Hypertension / Syndrome, Metabolic	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Hypokalaemia	4

		Obstructive Sleep Apnoea (OSA)	4
		Paediatric Hypertension	4
		Stage 2 Systolic Hypertension	4
		Stage II Hypertension	4
		Type 2 Diabetes Mellitus	4
		Hyperoxaluria / Urolithiasis	4
		Hypertension, Essential Hypertension	4
		Chronic Kidney Disease (CKD) / Hypertension	4
		Hypertension	4
		Hypertension, Essential Hypertension	4
		Coronavirus Disease 2019 (COVID- 19) / Hypertension	4
		End Stage Renal Disease (ESRD) / Hypertension / Proteinuria	4
		Anxiety / Hypertension	4
		Metabolism Disorder, Glucose / Renal Function Disorder	4
		Acute Heart Failure (AHF) / Chronic Heart Failure (CHF) / Heart Failure	4
		Blood Pressures	4
		Cerebral Small Vessels Disease	4
		Chronic Kidney Disease (CKD)	4
		Chronic Kidney Insufficiencies / Diuresis Preserved / Haemodialysis Treatment	4
		Hyperhomocysteinaemia / Hypertension	4
		Hypertension	4
		Hypertension Resistant to Conventional Therapy / Hypertension, Essential Hypertension	4

		Hypertension, Essential Hypertension	4
		Diabetes Mellitus / Hypertension	4
		Hypertension	4
		Hypertension / Type 2 Diabetes Mellitus	4
		Lipotoxicity / Syndrome, Metabolic	4
		Type 2 Diabetes Mellitus	4
		Cardiac Arrest / Cardiovascular Disease (CVD) / Hypertension / Sudden Cardiac Death	3
		Hypertension	3
		Atherosclerosis / Cardiovascular Disease (CVD) / Coronary Heart Disease (CHD) / Diabetes Mellitus / High Cholesterol / Hypertension / Type 2 Diabetes Mellitus	3
		Kidney Stones	3
		Atherosclerotic Cardiovascular Diseases / Hypertension, Essential Hypertension	3
		Chronic Kidney Disease (CKD) / Hypertension	3
		Essential Arterial Hypertension	3
		Heart Failure	3
		Hypertension	3
		Hypertension, Essential Hypertension	3
		Hypertension; Hypertrophy, Left Ventricular	3
		Hypertension / Metabolic Disorders	3
		Hypertension / Obesity, Abdominal	3
		Hypertension / Type 2 Diabetes Mellitus	3
		Isolated Systolic Hypertension (ISH)	3

		Mild to Severe Hypertension	3
		Safety	3
		The Elderly (≥ 70 Years) With Essential Hypertension	3
		Autosomal Dominant Polycystic Kidney Disease （ADPKD)	3
		Essential Arterial Hypertension	3
		Hypertension Arterial	3
		Gestational Hypertension / Postpartum Pre-Eclampsia / Postpartum Pregnancy-Induced Hypertension / Pre-Eclampsia / Superimposed Preeclampsia	3
		Hypertension	3
		Hypertension	3
		Cardiovascular Events	3
		Hypertension	3
		Acute Heart Failure (AHF) / Acute Kidney Injury (AKI)	3
		Hypertension	3
		Resistant Hypertension	3
		Essential Arterial Hypertension	3
		Grade I or II Essential Hypertension	2, 3
		Dent's Disease / Kidney Stones	2, 3
		Type 2 Diabetes Mellitus	2
		Hyperlipidaemias / Hypertension	2
		Aging / Cognitive Impairment (CI) / Hypertension	2
		Autosomal Dominant Hypocalcaemia or Primary Hypoparathyroidism Related to Other Cause but Complicated by Hypercalciuria Under Treatment	2

		Hypertension	2
		Hypertension, Essential Hypertension	2
		Hypertension / Obesity	2
		Hypertension / Type 2 Diabetes Mellitus	2
		Mild Hypertension	2
		Kidney Stones	2
		Hypertension / Obesity / Prehypertension	2
		Hypertension / Type 2 Diabetes Mellitus	2
		Impaired Glucose Tolerance / Prehypertension	2
		Non-diabetic Nephropathy	2
		Critically Ill Patients / Hypernatremia	2
		Optic; Neuritis, With Demyelination	2
		Diabetes / Hypertension	2
		Hypertension, Essential Hypertension	1, 2
		Healthy Volunteers (HV)	1
		Hypertension, Essential Hypertension	1
		Kidney Diseases	1
		Healthy Volunteers (HV)	1
		Bioequivalence	1
		Healthy Volunteers (HV)	1
		Photosensitivity	1
		Diabetes Mellitus / Endocrine System Diseases / Metabolic Diseases / Metabolism Disorder, Glucose	1
		Diabetes in Adults	1
		Drug-Drug Interaction (DDI)	1

		Fasting	1
		Fed	1
		Healthy Volunteers (HV)	1
		Hypertension	1
		Type 2 Diabetes Mellitus	1
		Blood Pressures / Diabetes / Diuretics Drug Reactions / Obesity / Resistance, Insulin / Sympathetic Nerve Activity	1
		Bioequivalence	1
		Healthy Volunteers (HV)	1
		Chronic Pain / Diuretics Drug Reactions / Hypertension / Spinal Cord Stimulation (SCS)	0
		Healthy Volunteers (HV)	0
		Hypertension	0
		Stiffness, Aortic / Systolic Hypertension	0
		Hypertension / Proteinuria / Type 2 Diabetes Mellitus	0
		Syndrome, Metabolic	0
		Blood Pressures / Hypertension	0
		Hypertension	Not Available
		Aging / Hypertension	Not Available
		Cardiovascular Disease (CVD) / Coronary Heart Disease (CHD) / Hypertension / Myocardial Infarction	Not Available
		Cardiovascular Disease (CVD) / Hypertension	Not Available
		Coronavirus Disease 2019 (COVID 鈥?9) / COVID / Hypertension	Not Available
		Healthy Normotensive Participants	Not Available

		Healthy Volunteers (HV)	Not Available
		Hypertension	Not Available
		Hypertension, Essential Hypertension	Not Available
		Hypertension / Melanoma / Non-Melanoma Skin Cancer	Not Available
		Gitelman's syndrome	Not Available
		Hypertension	Not Available
		Hypertension Arterial	Not Available
		Idiopathic Hypercalciuria / Kidney Stones	Not Available
		Kidney Stones	Not Available
		Albuminuria / Diabetes Mellitus / Endothelial Dysfunction	Not Available
		Cardiovascular Disease (CVD) / Cerebrovascular Diseases / Peripheral Arterial Disease (PAD)	Not Available
		Congestive Heart Failure (CHF)	Not Available
		Critical Care / Fluid Shifts	Not Available
		Hypertension	Not Available
		Hypertension, Essential Hypertension	Not Available
		Hypertension / Hypertension Treatment / Hypertension, Grade 1 / N of 1 Study Design	Not Available
		Hypertension / Plasma Renin Activity	Not Available
		Hypertension / Type 2 Diabetes Mellitus	Not Available
		Nephrogenic Diabetes Insipidus	Not Available
		Nocturia	Not Available
		Type 2 Diabetes Mellitus / Vascular Disorders	Not Available
		Proteinuria	Not Available
		Breastfed Infants of Mothers on Select DOI / Lactating Women	Not Available

		on Select DOI	
		Obesity, Morbid	Not Available
		Acute Decompensated Heart Failure (ADHF)	Not Available
		Angina, Microvascular / Hypertension	Not Available
		Diabetes Mellitus / Hypertension Arterial	Not Available
		Chronic Kidney Disease (CKD) / Secondary Hyperparathyroidism (SHPT)	Not Available
		Idiopathic Hypercalciuria / Kidney Stones	Not Available
		Diuretic Abuse	Not Available
		Hypertension	Not Available
ALISKIREN FUMARATE	Approved	Stroke	4
		Hypertension	4
Remikiren	Development		
N-{2-[6-(2,4-DIAMINO-6-ETHYLPYRIMIDIN-5-YL)-2,2-DIMETHYL-3-OXO-2,3-DIHYDRO-4H-1,4-BENZOXAZIN-4-YL]ETHYL}ACETAMIDE	Development		
N-{2-[6-(2,4-DIAMINO-6-ETHYLPYRIMIDIN-5-YL)-2,2-DIMETHYL-3-OXO-2,3-DIHYDRO-4H-1,4-BENZOTHIAZIN-4-YL]ETHYL}ACETAMIDE	Development		
N-Methyl-N-(Methylbenzyl)Formamide	Development		
N,N-dimethylformamide	Development		
Isoamyl alcohol	Development		
Enalkiren	Development		
6-ETHYL-5-[9-(3-METHOXYPROPYL)-9H-CARBAZOL-2-YL]PYRIMIDINE-2,4-DIAMINE	Development		

6-ethyl-5-[(2S)-1-(3-methoxypropyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-7-yl]pyrimidine-2,4-diamine	Development		
6-(2,4-DIAMINO-6-ETHYLPYRIMIDIN-5-YL)-4-(3-METHOXYPROPYL)-2,2-DIMETHYL-2H-1,4-BENZOXAZIN-3(4H)-ONE	Development		
5-{4-[(3,5-DIFLUOROBENZYL)AMINO]PHENYL}-6-ETHYLPYRIMIDINE-2,4-DIAMINE	Development		
3-Phenyl-1,2-Propandiol	Development		
2-Methyl-3-(2-Aminothiazolo)Propanal	Development		
2-Cyclopropylmethylenepropanal	Development		
1-Methyl-2-Oxy-5,5-Dimethyl Pyrrolidine	Development		
1-Hydroxy-2-Amino-3-Cyclohexylpropane	Development		
(2S)-6-(2,4-DIAMINO-6-ETHYLPYRIMIDIN-5-YL)-2-(3,5-DIFLUOROPHENYL)-4-(3-METHOXYPROPYL)-2H-1,4-BENZOXAZIN-3(4H)-ONE	Development		
VTP-27999	Druggable		
SPP1148	Druggable		
1alpha-Hydroxyvitamin D5	Druggable		
TERLAKIREN	Druggable		
MURAGLITAZAR	Druggable		
IMARIKIREN HYDROCHLORIDE	Druggable		

SUPPLEMENTARY METHODS

NPX transformation

The NPX (Normalized Protein Expression) method is a data processing approach used in Olink proteomics assays to produce relative protein expression values that are comparable across samples and experimental conditions.[1,3,4] The first step involved normalizing the raw counts for each sample and assay by dividing them by the counts of the extension control specific to each sample. This step helps adjust for technical variation across samples by establishing a common baseline:

$$\boldsymbol{ExtNPX_{i,j} = log_2\left(\frac{counts(sample_j Assay_i)}{Counts(ExtCtrl_j)}\right)}$$

where $\boldsymbol{i}$ denotes specific assay or detected protein, j denotes sample identifier, and the log2-transformation reduces the impact of extreme values and approximates a normal distribution. This formula was applied to all assays and samples, including negative controls, plate controls and sample controls. To correct for variability within an assay plate, the log2-transformed extension control-normalized values ($\boldsymbol{ExtNPX_{i,j}}$) were adjusted by subtracting the median NPX value of the plate controls:

$$NPX_{i,j} = ExtNPX_{i,j} - median\big(ExtNPX(PlateCtrl_i)\big)$$

This standardization step ensured consistency within each plate by reducing intra-plate variation. The final normalization step was applied to ensure comparability across plates. This involved adjusting the NPX values by the median NPX of each plate:

$$NPX_{Intnorm_{i,j}} = NPX_{i,i} - plate\ median(NPX_i)$$

This adjustment helps to standardize NPX values across different plates, minimizing technical variation and allowing cross-plate comparisons.

Colour fundus acquisition and DR grading

Stereoscopic colour fundus photographs of seven standard fields were obtained for each eye using a digital fundus camera (Canon CX-1, Tokyo, Japan) after pupil dilation during each follow-up visit. Field 1 is centred at the optic disc, field 2 at the macula, and field 3 is temporal to the macula. Fields 4 to 7 are tangential to horizontal lines passing through the upper and lower poles of the disc and to a vertical line passing through its center.[5]

DR was graded from baseline and follow-up fundus photographs using the modified Airlie House classification system, which was adopted for use in the ETDRS and became the gold standard for DR grading.[5-10] “Cannot grade” is recorded when inadequate photographic quality or obscuration from vitreous

hemorrhages (VH) or other abnormality makes it impossible to determine whether the characteristic being graded is present.[8] The participant's DR level was derived by concatenating the levels for both eyes, giving the eye with higher level greater weight. This scheme provided a 15-step scale (10/10, 15/<15, 15/15, 20/<20, 20/20, 35/<35, 35/35, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of PDR are grouped as one level.[6-9] The diabetic macular oedema (DME) was graded according to the DRCR.net criteria based on OCT imaging. For classification purposes, if the DR severity could not be graded in one eye, it was considered to have a score equivalent to that in the other eye. DR progression was defined as an increase in DR severity over two or more steps.[6-9]

Quality control for OCT measurement

Quality control measures for OCT scanning were implemented to ensure accurate data, as previously described.[11-13] These measures included the image quality score (IQS), internal limiting membrane (ILM) indicator, validity count, and motion indicators. The IQS measures the signal strength, while the ILM indicator identifies blinks and segmentation errors. The validity count detects significant clipping in the OCT scan's z-axis dimension. The motion indicators utilize Pearson correlations and absolute differences of the nerve fiber layer and full retinal thicknesses from each set of consecutive B-scans to identify blinks, eye-motion artifacts, and segmentation errors. Participants with low signal strength (Q < 45) were excluded from the analysis. Additionally, participants representing the poorest 20% of the population in each of these measures were also excluded.

Centring and standardization of raw PRSs

After computing the raw PRS value for an individual using the derived PRS weights, a centring and standardization step was further applied. This generated a corrected PRS value, allowing for interpretation as having a mean of 0 and a standard deviation of 1 among individuals with similar ancestry. The methodology for centring and standardization was discussed elsewhere.[14] In brief, the centred PRS was obtained by subtracting the PRS value predicted from a linear regression of the PRS against the first four principal component scores[15], fitted in 1000 Genomes Project individuals[16]. Next, genetic ancestry for each individual was inferred. This process involved estimating the proportion of an individual's genome associated with distinct high-level ancestry groups. The inference was achieved through principal component (PC) analysis applied to common single nucleotide polymorphism genotypes in the 1000 Genomes reference dataset using standard methods.[17] The genotypes were projected onto the PC axes, yielding individual PC scores. These scores were subsequently transformed using a SoftMax transformation (base=exp(3)) based on cosine

similarity, which enabled estimation of ancestry proportions. The centred PRS was then divided by the standard deviation of the PRS in the 1000 Genomes ancestry group closest to the individual, resulting in a centred and variance standardized PRS.

OCT-A image acquisition, segmentation, and quality control

Following pupil dilation with 0.5% tropicamide plus 0.5% phenylephrine eye drops, all GDES participants underwent OCT-A imaging with the Angio Macula 6×6 mm scan mode centred on the fovea and the Angio Disc 6×6 mm scan mode centred on the optic nerve head during each follow-up visit, using a swept-source OCT-A (Triton DRI-OCT; Topcon, Tokyo, Japan), as we previously described.[9,18-24] Automatic image segmentation was executed using built-in software (IMAGEnet 6, version 1.22) to segment the macular and the optic disc region into the SCP and DCP.[6,9,21,24] Specifically, for the macular region, the SCP slab was segmented from 2.6 μm below the internal limiting membrane to 15.6 μm below the junction between the inner plexiform and the inner nuclear layers, and the DCP slab was segmented from 15.6 μm to 70.2 μm below the inner plexiform and inner nuclear layers. For the optic disc region, the SCP was segmented from the posterior border of the retinal nerve fibre layer to the posterior border of the inner plexiform layer, and the DCP from the posterior border of the inner plexiform layer to the retinal pigment epithelium. The segmentation of retinal layers was manually reviewed and corrected by the same ophthalmologist (WW). Motion artifacts were minimized by the instrument's built-in eye movement tracker system, and projection artifacts were eliminated using the artifact elimination algorithm during OCT-A imaging, followed by manual verification.[25] Poor-quality images were excluded based on predefined criteria[26] including: (1) image quality score (IQS) <60; (2) poor clarity; (3) residual motion artifacts; (4) poor local signal or occlusion artifacts; (5) incorrect segmentation; (6) signal loss; (7) decentring; and (8) uncompensated projection artifacts on DCP. Magnification effects were corrected using Littman and Bennett's methods prior to all quantitative analysis.[27]

SUPPLEMENTARY NOTES

STROBE statement

Checklist of items that should be included in reports of cohort studies.[28]

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	24
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	24
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	25
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	26
Bias	9	Describe any efforts to address potential sources of bias	30
Study size	10	Explain how the study size was arrived at	30

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	26
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	30
		(*b*) Describe any methods used to examine subgroups and interactions	30
		(*c*) Explain how missing data were addressed	30
		(*d*) If applicable, explain how loss to follow-up was addressed	24
		(*e*) Describe any sensitivity analyses	30
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarize follow-up time (e.g., average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating	NA

		estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	18	Summarize key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalizability	21	Discuss the generalizability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	32

*Give information separately for exposed and unexposed groups.
An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. Information on the STROBE Initiative is available at http://www.strobe-statement.org.

SUPPLEMENTARY REFERENCES

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2. Kurki, M. I. et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. **613**, 508-518 (2023).
3. Eldjarn, G. H. et al. Large-scale plasma proteomics comparisons through genetics and disease associations. *Nature*. **622**, 348-358 (2023).
4. Dhindsa, R. S. et al. Rare variant associations with plasma protein levels in the UK Biobank. *Nature*. **622**, 339-347 (2023).
5. Grading Diabetic Retinopathy from Stereoscopic Color Fundus Photographs - An Extension of the Modified Airlie House Classification: ETDRS Report Number 10. *Ophthalmology*. **127**, S99-S119 (2020).
6. Sun, Z. et al. OCT Angiography Metrics Predict Progression of Diabetic Retinopathy and Development of Diabetic Macular Edema: A Prospective Study. *Ophthalmology*. **126**, 1675-1684 (2019).
7. Cheung, C. Y. et al. Retinal vascular geometry and 6 year incidence and progression of diabetic retinopathy. *Diabetologia*. **60**, 1770-1781 (2017).
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