

SUPPLEMENTAL MATERIAL

Supplemental Table S1. Genetic variants included in the T2D polygenic score.

SNP	Locus	CHR	POS	T2D raising allele	EAF	β	Reference
rs340879 ^a	<i>PROX1</i>	1	214156514	C	0.508	0.059	Morris et al. 2012
rs17106184	<i>FAFI</i>	1	50909985	G	0.921	0.063	Mahajan et al. 2014
rs340874	<i>PROX1</i>	1	214159256	C	0.376	0.068	Dupuis et al. 2010
rs10195252	<i>COBLL1</i>	2	165513091	T	0.603	0.06	Scott et al. 2012
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.067	Saxena et al. 2010
rs2943641	<i>IRS1</i>	2	227093745	C	0.751	0.094	Rung et al. 2009
rs3923113	<i>GRB14</i>	2	165501849	A	0.615	0.056	Kooner et al. 2011
rs7578326	<i>IRS1</i>	2	227020653	A	0.714	0.079	Voight et al. 2010
rs7578597	<i>THADA</i>	2	43732823	T	0.863	0.12	Zeggini et al. 2008
rs7607980	<i>COBLL1</i>	2	165551201	T	0.893	0.084	Manning et al. 2012
rs243021	<i>BCL11A</i>	2	60584819	A	0.496	0.058	Voight et al. 2010
rs11708067	<i>ADCY5</i>	3	123065778	A	0.850	0.089	Dupuis et al. 2010
rs2877716 ^b	<i>ADCY5</i>	3	123094451	C	0.811	0.086	Morris et al. 2012
rs13094957 ^c	<i>UBE2E2</i>	3	23457080	T	0.745	0.071	Morris et al. 2012
rs1801282	<i>PPARG</i>	3	12393125	C	0.930	0.1	Altshuler et al. 2000
rs4402960	<i>IGF2BP2</i>	3	185511687	T	0.389	0.11	Morris et al. 2012
rs4607103	<i>ADAMTS9</i>	3	64711904	C	0.646	0.052	Zeggini et al. 2008
rs6795735	<i>ADAMTS9</i>	3	64705365	C	0.287	0.048	Zeggini et al. 2008
rs16861329	<i>ST6GAL1</i>	3	186666461	C	0.835	0.057	Kooner et al. 2011
rs6446482	<i>WFS1</i>	4	6295693	G	0.721	0.085	Morris et al. 2012
rs6813195	<i>TMEM154</i>	4	153520475	C	0.592	0.055	Mahajan et al. 2014
rs4457053	<i>ZBED3</i>	5	76424949	G	0.203	0.059	Voight et al. 2010
rs459193	<i>ANKRD55</i>	5	55806751	G	0.606	0.073	Morris et al. 2012
rs4865796	<i>ARL15</i>	5	53272664	A	0.760	0.051	Scott et al. 2012
rs10946398	<i>CDKAL1</i>	6	20661034	C	0.405	0.12	Zeggini et al. 2008
rs9368222	<i>CDKAL1</i>	6	20686996	A	0.269	0.14	Scott et al. 2012
rs17168486	<i>DGKB</i>	7	14898282	T	0.272	0.069	Morris et al. 2012
rs2191349	<i>DGKB</i>	7	15064309	T	0.572	0.066	Dupuis et al. 2010
rs4607517	<i>GCK</i>	7	44235668	A	0.143	0.055	Dupuis et al. 2010
rs972283	<i>KLF14</i>	7	130466854	G	0.693	0.012	Voight et al. 2010
rs3802177 ^d	<i>SLC30A8</i>	8	118185025	G	0.744	0.11	Morris et al. 2012
rs516946	<i>ANK1</i>	8	41519248	C	0.804	0.08	Morris et al. 2012
rs896854	<i>TP53INP1</i>	8	95960511	T	0.484	0.05	Voight et al. 2010
rs10811661	<i>CDKN2A/B</i>	9	22134094	T	0.824	0.16	Morris et al. 2012
rs2796441	<i>TLE1</i>	9	84308948	G	0.603	0.066	Morris et al. 2012
rs13292136	<i>TLE4</i>	9	81952128	C	0.898	0.085	Voight et al. 2010

rs1111875	<i>HHEX</i>	10	94462882	C	0.544	0.11	Morris et al. 2012
rs11257655	<i>CDC123</i>	10	12307894	T	0.301	0.09	Zeggini et al. 2008
rs12571751	<i>ZMIZ1</i>	10	80942631	A	0.535	0.07	Morris et al. 2012
rs7903146	<i>TCF7L2</i>	10	114758349	T	0.228	0.31	Morris et al. 2012
rs10830963	<i>MTNR1B</i>	11	92708710	G	0.260	0.099	Dupuis et al. 2010
rs1552224	<i>ARAPI</i>	11	72433098	A	0.900	0.1	Voight et al. 2010
rs163184	<i>KCNQ1</i>	11	2847069	G	0.373	0.081	Morris et al. 2012
rs2237892	<i>KCNQ1</i>	11	2839751	C	0.851	0.11	Yasuda et al. 2008
rs8181588 ^e	<i>KCNQ1</i>	11	2831541	T	0.807	0.19	Wheeler et al. 2017
rs231362	<i>KCNQ1</i>	11	2691471	G	0.729	0.055	Voight et al. 2010
rs757110	<i>KCNJ11</i>	11	17418477	C	0.274	0.068	Gloyn et al. 2003
rs10842994	<i>KLHDC5</i>	12	27965150	C	0.862	0.074	Morris et al. 2012
rs2261181	<i>HMGA2</i>	12	66212318	T	0.156	0.11	Morris et al. 2012
rs7955901	<i>TSPAN8</i>	12	71433293	C	0.434	0.044	Morris et al. 2012
rs1531343	<i>HMGA2</i>	12	66174894	C	0.213	0.1	Voight et al. 2010
rs7957197	<i>HNF1A</i>	12	121460686	T	0.891	0.065	Voight et al. 2010
rs7961581	<i>TSPAN8</i>	12	71663102	C	0.238	0.038	Zeggini et al. 2008
rs1215451 ^f	<i>SPRY2</i>	13	80715893	G	0.771	0.083	Morris et al. 2012
rs12899811	<i>VPS33B</i>	15	91544076	G	0.636	0.042	Morris et al. 2012
rs2028299	<i>AP3S2</i>	15	90374257	C	0.270	0.063	Kooner et al. 2011
rs7178572	<i>HMG20A</i>	15	77747190	G	0.526	0.078	Kooner et al. 2011
rs8042680	<i>PRC1</i>	15	91521337	A	0.742	0.051	Voight et al. 2010
rs7202877	<i>CTRB2</i>	16	75247245	T	0.860	0.1	Morris et al. 2012
rs9939609	<i>FTO</i>	16	53820527	A	0.340	0.12	Frayling et al. 2007
rs11651052	<i>HNF1B</i>	17	36102381	A	0.424	0.072	Morris et al. 2012
rs12970134	<i>MC4R</i>	18	57884750	A	0.207	0.052	Morris et al. 2012
rs12454712	<i>BCL2</i>	18	60845884	T	0.624	0.049	Saxena et al. 2012
rs3794991	<i>SUGP1</i>	19	19610596	T	0.088	0.079	Saxena et al. 2012
rs481282	<i>HNF4A</i>	20	42989267	A	0.255	0.05	Kooner et al. 2011

T2D=type 2 diabetes, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes. ^aproxy for rs2075423, ^bproxy for rs11717195, ^cproxy for rs1496653, ^dproxy for rs13266634, ^eproxy for fs2237896, ^fproxy for rs1359790.

Supplemental Table S2. Genetic variants included in the FG polygenic score

SNP	Locus	CHR	POS	FG raising allele	EAF	β	Reference
rs340874	<i>PROX1</i>	1	214159256	C	0.376	0.014	Dupuis et al. 2010
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.029	Saxena et al. 2010
rs1371614	<i>DPYSL5</i>	2	27152874	T	0.268	0.016	Manning et al. 2012
rs552976	<i>G6PC2/ABCB11</i>	2	169791438	G	0.748	0.057	Soranzo et al. 2010
rs573225 ^a	<i>G6PC2</i>	2	169757541	A	0.855	0.063	Dupuis et al. 2010
rs11708067	<i>ADCY5</i>	3	123065778	A	0.850	0.023	Dupuis et al. 2010
rs10640 ^b	<i>AMT</i>	3	49454277	G	0.794	0.011	Scott et al. 2012
rs2877716 ^c	<i>ADCY5</i>	3	123094451	C	0.811	0.019	Morris et al. 2012
rs11920090	<i>SLC2A2</i>	3	170717521	T	0.816	0.027	Dupuis et al. 2010
rs4402960	<i>IGF2BP2</i>	3	185511687	T	0.389	0.012	Morris et al. 2012
rs8192675	<i>SLC2A2</i>	3	170724883	T	0.588	0.017	Wheeler et al. 2017
rs9368222	<i>CDKAL1</i>	6	20686996	A	0.269	0.014	Scott et al. 2012
rs10278336	<i>YKT6</i>	7	44245363	A	0.654	0.035	Morris et al. 2012
rs17168486	<i>DGKB</i>	7	14898282	T	0.272	0.031	Morris et al. 2012
rs2191349	<i>DGKB</i>	7	15064309	T	0.572	0.029	Dupuis et al. 2010
rs3824065	<i>YKT6</i>	7	44247258	C	0.655	0.034	Wheeler et al. 2017
rs4607517	<i>GCK</i>	7	44235668	A	0.143	0.064	Dupuis et al. 2012
rs6943153	<i>GRB10</i>	7	50791579	T	0.433	0.015	Scott et al. 2012
rs3802177 ^d	<i>SLC30A8</i>	8	118185025	G	0.744	0.028	Morris et al. 2012
rs4841132	<i>PPP1R3B</i>	8	9183596	A	0.093	0.03	Manning et al. 2012
rs983309	<i>PPP1R3B</i>	8	9177732	T	0.152	0.025	Scott et al. 2012
rs10758593	<i>GLIS3</i>	9	4292083	A	0.479	0.016	Morris et al. 2012
rs10811661	<i>CDKN2A/B</i>	9	22134094	T	0.824	0.024	Morris et al. 2012
rs16913693	<i>IKBKAP</i>	9	111680359	T	0.923	0.043	Scott et al. 2012
rs3829109	<i>DNLZ</i>	9	139256766	G	0.790	0.017	Scott et al. 2012
rs4918635 ^e	<i>ADRA2A</i>	10	113036224	C	0.718	0.031	Dupuis et al. 2010
rs7903146	<i>TCF7L2</i>	10	114758349	T	0.228	0.022	Morris et al. 2012
rs10501320	<i>MADD</i>	11	47293799	G	0.912	0.025	Strawbridge et al. 2011
rs10830963	<i>MTNR1B</i>	11	92708710	G	0.260	0.078	Dupuis et al. 2010
rs11605924	<i>CRY2</i>	11	45873091	A	0.674	0.022	Dupuis et al. 2010
rs1483121	<i>OR4S1</i>	11	48333360	G	0.959	0.029	Manning et al. 2012
rs1552224	<i>ARAPI</i>	11	72433098	A	0.900	0.02	Voight et al. 2010
rs174550	<i>FADS1</i>	11	61571478	T	0.702	0.02	Dupuis et al. 2010
rs174577	<i>FADS2</i>	11	61604814	C	0.608	0.02	Wheeler et al. 2017
rs7944584	<i>MADD</i>	11	47336320	A	0.878	0.025	Dupuis et al. 2010
rs10747083	<i>P2RX2</i>	12	133041618	A	0.760	0.014	Scott et al. 2012
rs2293941	<i>PDX1</i>	13	28491198	A	0.254	0.02	Manning et al. 2012
rs533873 ^f	<i>KL</i>	13	33555587	C	0.320	0.012	Scott et al. 2012

rs3783347	<i>WARS</i>	14	100839261	G	0.879	0.017	Scott et al. 2012
rs7163757 ^g	<i>C2CD4A</i>	15	62391608	C	0.505	0.02	Morris et al. 2012
rs2302593	<i>QPCTL</i>	19	46196634	C	0.576	0.014	Scott et al. 2012
rs6072275	<i>TOP1</i>	20	39743905	A	0.070	0.016	Scott et al. 2012
rs6113722	<i>FOXA2</i>	20	22557099	G	0.900	0.035	Scott et al. 2012

FG=fasting glucose, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes. ^aproxy for rs560887, ^bproxy for rs11715915, ^cproxy for rs11717195, ^dproxy for rs13266634, ^eproxy for rs10885122, ^fproxy for rs576674, ^gproxy for rs4502156.

Supplemental Table S3. Genetic variants included in the FI polygenic score

SNP	Locus	CHR	POS	FI raising allele	EAF	β	Reference
rs2820436	<i>LYPLAL1</i>	1	219640680	C	0.643	0.015	Scott et al. 2012
rs10195252	<i>COBLL1</i>	2	165513091	T	0.603	0.016	Scott et al. 2012
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.019	Saxena et al. 2010
rs7578326	<i>IRS1</i>	2	227020653	A	0.714	0.023	Voight et al. 2010
rs9884482	<i>TET2</i>	4	106081636	C	0.350	0.016	Scott et al. 2012
rs459193	<i>C5orf67</i>	5	55806751	G	0.606	0.014	Morris et al. 2012
rs4865796	<i>ARL15</i>	5	53272664	A	0.760	0.015	Mahajan et al. 2014
rs2745353	<i>RSPO3</i>	6	127452935	T	0.552	0.014	Scott et al. 2012
rs1167800	<i>HIP1</i>	7	75176196	A	0.686	0.016	Scott et al. 2012
rs4841132	<i>PPP1R3B</i>	8	9183596	A	0.093	0.03	Manning et al. 2012
rs983309	<i>PPP1R3B</i>	8	9177732	T	0.152	0.029	Scott et al. 2012
rs7903146	<i>TCF7L2</i>	10	114758349	C	0.772	0.018	Morris et al. 2012
rs731839	<i>PEPD</i>	19	33899065	G	0.460	0.014	Scott et al. 2012

FI=fasting insulin, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes.

Supplemental Table S4. Association of T2D polygenic score with glipizide and metformin endpoints in 639 white, non-Hispanic participants in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	436	-0.03 (-0.08, 0.01)	0.18
Glucose AOC (mmol/L*min)	435	12.20 (1.27, 23.13)	0.03
Time to glucose trough (min) [†]	436	-2.30 (-6.85, 2.25)	0.32
Slope to glucose trough (mmol/L/min) [†]	436	5.7e-4 (-2.1e-4, 1.4e-3)	0.15
Ln peak insulin (pmol/L) [‡]	427	0.04 (-0.02, 0.09)	0.19
Time to insulin peak (min) [‡]	427	-5.17 (-9.70, -0.65)	0.03
Slope to insulin peak (pmol/L/min) [‡]	423	-0.10 (-0.40, 0.19)	0.50
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	590	-0.004 (-0.04, 0.03)	0.56
Glucose AUC (mmol/L*min)	582	14.15 (1.07, 27.24)	0.03
Fasting insulin V2-V1 (pmol/L) [‡]	577	-1.64 (-5.17, 1.89)	0.36
Insulin AUC (pmol/L*min)	542	-204.97 (-2123.85, 1713.90)	0.83
Ln HOMA-IR V1 (mmol*pmol/L ²)	586	0.05 (-0.02, 0.12)	0.14
Ln HOMA-IR V2 (mmol*pmol/L ²)	586	0.02 (-0.05, 0.09)	0.54
HOMA-IR V2-V1 (mmol*pmol/L ²)	586	-0.75 (-1.70, 0.20)	0.12

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *191 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A p-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S5. Association of T2D polygenic score with glipizide and metformin endpoints in 209 black, non-Hispanic participants in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	115	0.003 (-0.10, 0.10)	0.96
Glucose AOC (mmol/L*min)	112	3.58 (-17.24, 24.40)	0.73
Time to glucose trough (min) [†]	115	-14.04 (-25.43, -2.65)	0.01
Slope to glucose trough (mmol/L/min) [†]	115	1.7e-3 (-8.3e-6, 0.003)	0.05
Ln peak insulin (pmol/L) [‡]	104	0.13 (-0.002, 0.25)	0.05
Time to insulin peak (min) [‡]	104	-14.60 (-27.34, -1.85)	0.02
Slope to insulin peak (pmol/L/min) [‡]	102	-0.05 (-0.88, -0.12)	0.01
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	192	-0.06 (-0.13, 0.02)	0.13
Glucose AUC (mmol/L*min)	183	-0.12 (-20.28, 20.04)	0.99
Fasting insulin V2-V1 (pmol/L) [‡]	180	-10.62 (-24.24, 2.99)	0.13
Insulin AUC (pmol/L*min)	169	-371.60 (-5059.66, 4316.37)	0.88
Ln HOMA-IR V1 (mmol*pmol/L ²)	190	0.008 (-0.13, 0.15)	0.91
Ln HOMA-IR V2 (mmol*pmol/L ²)	189	-0.07 (-0.23, 0.09)	0.41
HOMA-IR V2-V1 (mmol*pmol/L ²)	189	-2.21 (-5.31, 0.90)	0.16

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *96 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A p-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S6. Association of FG polygenic score with glipizide and metformin endpoints in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	639	0.01 (-0.03, 0.05)	0.53
Glucose AOC (mmol/L*min)	633	10.82 (1.42, 20.22)	0.02
Time to glucose trough (min) [†]	639	3.12 (-1.09, 7.33)	0.15
Slope to glucose trough (mmol/L/min) [†]	638	-2.3e-4 (-9.2e-4, 4.6e-4)	0.51
Ln peak insulin (pmol/L) [‡]	615	-5.1e-4 (-0.05, 0.05)	0.98
Time to insulin peak (min) [‡]	615	4.05 (-0.26, 8.35)	0.07
Slope to insulin peak (pmol/L/min) [‡]	609	0.005 (-0.23, 0.24)	0.96
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	924	0.02 (-0.01, 0.05)	0.24
Glucose AUC (mmol/L*min)	900	4.22 (-5.79, 14.22)	0.41
Fasting insulin V2-V1 (pmol/L) [‡]	891	-3.11 (-6.77, 0.55)	0.10
Insulin AUC (pmol/L*min)	831	371.72 (-1742.16, 2485.60)	0.73
Ln HOMA-IR V1 (mmol*pmol/L ²)	915	0.03 (-0.02, 0.09)	0.27
Ln HOMA-IR V2 (mmol*pmol/L ²)	914	-0.004 (-0.06, 0.06)	0.90
HOMA-IR V2-V1 (mmol*pmol/L ²)	914	-0.85 (-1.75, 0.05)	0.06

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *351 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A p-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S7. Association of FI polygenic score with glipizide and metformin endpoints in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	639	0.05 (0.007, 0.08)	0.02
Glucose AOC (mmol/L*min)	633	-0.78 (-9.93, 8.38)	0.87
Time to glucose trough (min) [†]	639	1.38 (-2.65, 5.40)	0.50
Slope to glucose trough (mmol/L/min) [†]	638	-3.8e-4 (-1.0e-3, 2.7e-4)	0.25
Ln peak insulin (pmol/L) [‡]	615	-0.004 (-0.05, 0.05)	0.87
Time to insulin peak (min) [‡]	615	1.63 (-2.62, 5.88)	0.45
Slope to insulin peak (pmol/L/min) [‡]	609	0.04 (-0.19, 0.27)	0.73
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	924	0.02 (-0.01, 0.05)	0.25
Glucose AUC (mmol/L*min)	900	-0.68 (-10.51, 9.14)	0.89
Fasting insulin V2-V1 (pmol/L) [‡]	891	-1.67 (-5.30, 1.96)	0.37
Insulin AUC (pmol/L*min)	831	968.00 (-1134.82, 3070.73)	0.37
Ln HOMA-IR V1 (mmol*pmol/L ²)	915	0.05 (-0.008, 0.10)	0.09
Ln HOMA-IR V2 (mmol*pmol/L ²)	914	0.01 (-0.05, 0.07)	0.68
HOMA-IR V2-V1 (mmol*pmol/L ²)	914	-0.59 (-1.47, 0.29)	0.19

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *351 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for Ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A p-value of <0.008 reflects statistical significance after adjustment for multiple testing.