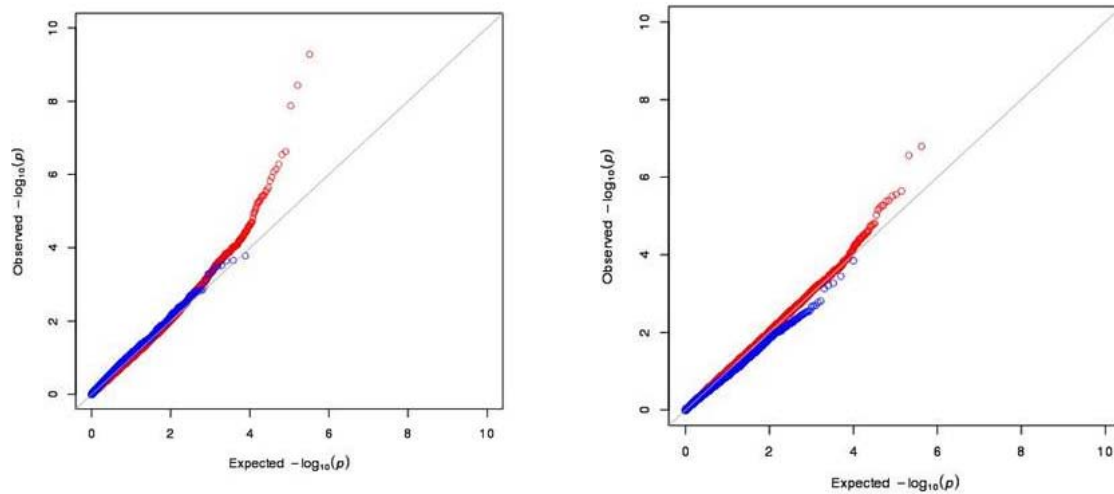


Supplemental Data

Genetic Risk Factors for Type 2 Diabetes:

A *Trans*-Regulatory Genetic Architecture?

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**Figure S1. Top SNP associations with T2D are enriched for *trans* regulatory variations for differentially expressed transcripts (FDR<0.05) between insulin sensitive and insulin resistant individuals.** For each tissue (adipose on the left, muscle on the right), shown here are the Q-Q plots for the distributions of p values for the *trans* and *cis* associations with transcripts differentially expressed between insulin sensitive and insulin resistant individuals (FDR<0.05)

among the top SNP associations with T2D ( $n = 1,000$ ) in the Wellcome Trust Case Control study. Red (blue) indicates the distribution of p values for all *trans* (*cis*, respectively) associations (with differentially expressed transcripts) among the top associations with T2D. The x-axis is the expected  $-\log_{10}(\text{p value})$  while the y-axis is the observed  $-\log_{10}(\text{p value})$ .

ABCB11	169487694	169596078	2
ABCC8	17371007	17455024	11
ACP2	47217428	47226938	11
ADAM30	120237678	120240635	1
ADAMTS9	64476369	64648404	3
ADCY5	124486088	124650081	3
ARAP1	72073761	72115820	11
ARFGAP2	47142427	47154994	11
ART2P	71909642	71910331	11
ATG16L2	72203098	72218327	11
C11orf10	61313180	61316660	11
C11orf9	61279436	61312564	11
C12orf27	119893409	119894477	12
C12orf43	119925230	119938682	12
C2orf16	27652892	27659092	2
C3orf65	186913773	186918648	3
C8orf38	96106396	96140113	8
CAMK2B	44225415	44331748	7
CCDC121	27702009	27705382	2
CCNE2	95961627	95976659	8
CDC123	12277970	12332592	10
CDKN1C	2861440	2863550	11
CHCHD9	81196013	81196774	9
CRY2	45825604	45861371	11
CUGBP1	47446520	47531263	11
DAGLA	61204485	61271048	11
DDB2	47193088	47217338	11
DKFZp686O24166	17328795	17355463	11
DKFZp779M0652	45749558	45750484	11
DNAJC5G	27351792	27357799	2
DPY19L4	95801326	95873244	8
EIF2B4	27440722	27446827	2
EIF5A2	172088897	172109119	3
EML2	50804497	50834508	19
FADS1	61323678	61340885	11
FADS2	61352288	61391400	11
FADS3	61397573	61415581	11
FAH	78232395	78265736	15
FAM148A	60146467	60150407	15
FAM148B	60243028	60244773	15

FBXO46	50905726	50925990	19
FEN1	61316725	61321285	11
FES	89228712	89240009	15
FLJ38723	60322241	60337310	15
FNDC4	27568253	27571589	2
FTHL3P	27468993	27469946	2
FURIN	89212888	89227690	15
G6PC2	169465995	169474755	2
GCK	44150394	44195562	7
GCKR	27573209	27600054	2
GIPR	50863341	50877556	19
GPN1	27705406	27727216	2
GSTM1L	12274295	12274951	3
GTF3C2	27402224	27433371	2
GYLTL1B	45899771	45907222	11
hCG_1776259	114820979	114821705	10
hCG_1992539	17206273	17207420	11
HDDC3	89275158	89276777	15
HHEX	94439660	94445387	10
HMGA2	64504506	64646337	12
HMGCS2	120092524	120113040	1
HNF1A	119900931	119924697	12
HNF1B	33120546	33179208	17
IDE	94203579	94323831	10
IFT172	27520743	27566074	2
IGF1	101313805	101398453	12
IGF2BP2	186844220	187025520	3
INTS8	95904709	95961896	8
KCNJ11	17363370	17366781	11
KCNQ1	2422796	2826915	11
KCNQ1DN	2848502	2849688	11
KCNQ1OT1	2674976	2675567	11
KIF11	94342970	94405129	10
KLF14	130068017	130069399	7
KRTCAP3	27518766	27520667	2
LOC100127949	72329190	72329804	11
LOC100128036	172153341	172195364	3
LOC100128081	28186471	28248398	7
LOC100128150	130158497	130158809	7
LOC100128217	14991339	15178594	7
LOC100128354	92310256	92310483	11

LOC100128548	95971840	95973547	8
LOC100128609	43313004	43314100	2
LOC100128970	17413794	17414303	11
LOC100129287	76478148	76478746	5
LOC100129473	61290975	61291562	11
LOC100129623	6354314	6355893	4
LOC100129726	43307509	43309436	2
LOC100129940	64535926	64562087	12
LOC100129972	60161935	60162797	15
LOC100129995	27783665	27784535	2
LOC100130098	96154017	96155024	8
LOC100130191	89246451	89247656	15
LOC100130981	27642441	27644312	2
LOC100131061	89377085	89377462	15
LOC100131297	89374360	89376774	15
LOC100131326	61340577	61350557	11
LOC100132702	89274413	89279354	15
LOC100132907	120370655	120371066	1
LOC143678	45884660	45885408	11
LOC204010	64438300	64439043	12
LOC283014	94418083	94419684	10
LOC285484	6253074	6285983	4
LOC347674	130157647	130158595	7
LOC388553	50934793	50967601	19
LOC390363	119826638	119837311	12
LOC390638	89377463	89379247	15
LOC642791	92287416	92293615	11
LOC643550	119838829	119839424	12
LOC643897	12086724	12087862	3
LOC646736	226715694	226753594	2
LOC728723	76418381	76470883	5
LOC729983	22144357	22145867	9
LOC730057	64651913	64704316	3
LOC732199	17169270	17172540	11
LOC767850	120197246	120198237	1
MADD	47247534	47308157	11
MAN2A2	89248423	89266818	15
MAPK8IP1	45863777	45884591	11
MGC40574	43307848	43309497	2
MPV17	27385863	27399472	2
MTNR1B	92342436	92355595	11

MYBPC3	47309532	47330828	11
MYL7	44144987	44147440	7
NBPF7	120178910	120189301	1
NOSTRIN	169367352	169429810	2
NOTCH2	120255698	120413798	1
NR1H3	47237308	47246971	11
NRBP1	27504976	27518629	2
NUCB2	17254861	17309645	11
NUDT5	12249578	12278148	10
OASL	119942477	119961162	12
P2RX7	120055060	120108258	12
PACSIN3	47155653	47164533	11
PDE2A	71964832	72063059	11
PEX16	45887795	45896181	11
PLEKHF2	96215207	96238088	8
PPARG	12304348	12450854	3
PPM1G	27457564	27485999	2
PPP2R2C	6373205	6525226	4
PRC1	89310271	89338807	15
PROX1	212228482	212276388	1
PSMC3	47396895	47404599	11
QPCTL	50887771	50899049	19
RAB3IL1	61421348	61441572	11
RAPSN	47415890	47427305	11
RCCD1	89299109	89307358	15
REG4	120138230	120155725	1
RP11-145E5.4	21984789	22111093	9
RPL22L1	172065357	172070738	3
SEC22A	124403464	124474049	3
SEC61A2	12211703	12246831	10
SLC22A18AS	2864749	2877506	11
SLC2A2	172196830	172227461	3
SLC30A8	118216517	118258133	8
SLC35C1	45783911	45791142	11
SLC39A13	47386757	47394622	11
SLC4A1AP	27739841	27771350	2
SNORA47	76412014	76412151	5
SNRPD2	50882557	50887281	19
SNX17	27446892	27453497	2
SPC25	169435646	169455189	2
SPI1	47332984	47356702	11

STARD10	72143421	72182397	11
SUPT7L	27727182	27739952	2
SYN2	12020861	12208531	3
TCF7L2	114700200	114916062	10
THADA	43311478	43676688	2
TIMP4	12169567	12175646	3
TP53INP1	96007376	96030766	8
TRIM54	27359103	27383810	2
TSPAN8	69805143	69838045	12
UCN	27383768	27384633	2
UNC45A	89274413	89298326	15
VPS13C	59931879	60139938	15
VPS33B	89342777	89366836	15
WFS1	6322477	6355892	4
YKT6	44207102	44220417	7
ZBED3	76408287	76418785	5
ZFAND6	78139075	78217766	15
ZFP36L2	43304209	43307248	2
ZNF512	27659396	27699466	2
ZNF513	27453605	27457096	2

**Table S1. Transcripts (n=183) near the SNPs (n=68) reproducibly associated with Type 2 diabetes and glucose homeostasis traits.** Genes are annotated by their start position, end position, and chromosome.

<b>Gene</b>	<b>SNP</b>	<b>P-value</b>
<i>MAPK8IP1</i>	rs2696490	7.18x10 <sup>-24</sup>
<i>TCF7L2</i>	rs11198893	2.19x10 <sup>-11</sup>
<i>SEC61A2</i>	rs12935562	2.12x10 <sup>-10</sup>
<i>PPP2R2C</i>	rs3765618	4.78x10 <sup>-10</sup>
<i>KRTCAP3</i>	rs1647266	1.71x10 <sup>-7</sup>
<i>SUPT7L</i>	rs2178197	7.10x10 <sup>-10</sup>
<i>VPS33B</i>	rs7403304	9.86x10 <sup>-7</sup>
<i>SYN2</i>	rs13089415	3.8x10 <sup>-8</sup>
<i>OASL</i>	rs959398	1.94x10 <sup>-8</sup>
<i>KRTCAP3</i>	rs35980734	2.9x10 <sup>-10</sup>

**Table S2. eQTLs for adipose transcripts near T2D/GT SNPs.**



<b>Gene</b>	<b>SNP</b>	<b>P-value</b>
<i>MAPK8IP1</i>	rs2696490	$3.5 \times 10^{-17}$
<i>C11orf9</i>	rs2278210	$5.4 \times 10^{-12}$
<i>GTF3C2</i>	rs7733988	$1.12 \times 10^{-10}$

**Table S3. eQTLs for muscle transcripts near T2D/GT SNPs.**

<b>T2D/GT SNP</b>	<b>P-value</b>	<b>Transcript</b>	<b>P-value (IR vs IS)</b>
rs2881654	0.0001079	PRO0478	0.000069
rs2881654	0.0008118	GGT6	0.000153
rs7041847	8.03E-05	MRPS6	0.00094
rs7041847	0.0008064	MRPS6	0.00094
rs2881654	0.000574	HDAC10	0.00101
rs7041847	3.71E-05	CHMP1A	0.00183

**Table S4. Muscle transcripts associated with established T2D/GT SNPs and differentially expressed between insulin sensitive and insulin resistant individuals.** Differentially expressed transcripts are defined as FDF<0.05. SNP-transcript p-values are also shown.

<b>T2D/GT SNP</b>	<b>P-value</b>	<b>Transcript</b>	<b>P-value (IR vs IS)</b>
rs4712523	0.0005294	SMG1	4.04E-08
rs4712523	0.0001706	EAF1	5.15E-08
rs4712523	0.0004362	DSCR3	6.09E-08
rs4712523	0.0005059	MRPS30	0.000000896
rs2881654	0.0007216	CRTAP	0.00000305
rs4244883	0.0001909	VPS26B	0.00000497
rs4712523	0.0003233	HK2	0.00000945
rs13089415	0.000478	TTC7B	0.0000107
rs243083	0.0006411	TTC7B	0.0000107
rs6931514	0.0003618	HNRPA3	0.0000171
rs6931514	0.0005643	HNRPA3	0.0000171
rs2881654	0.000184	REEP3	0.0000633
rs8034335	0.0008804	SETD2	0.000172
rs4411878	0.0002174	KIF1B	0.000243
rs174576	0.000596	FXD5	0.000384
rs11138147	0.0002779	CFHR1	0.000389
rs7845219	0.0004327	MMP9	0.00332
rs4411878	0.000878	GPAM	0.00452
rs4712523	0.0009177	GPAM	0.00452
rs8034335	0.0001591	ADIPOR2	0.00485
rs2881654	0.0001606	PHF20L1	0.00818
rs11603334	0.000284	PHF20L1	0.00818
rs4731702	0.0004683	PDK4	0.0184
rs2881654	7.58E-05	C13orf1	0.0551

**Table S5. Adipose transcripts associated with established T2D/GT SNPs and differentially expressed between insulin sensitive and insulin resistant individuals.** Differentially expressed transcripts are defined as FDF<0.05. SNP-transcript p-values are also shown. We found that transcripts nominally associated with T2D/GT ( $p<10^{-3}$ ) are more likely to be differentially expressed between IR and IS individuals than transcripts associated, at the same nominal level of significance, with a random set of allele frequency matched SNPs.