New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk

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Supplementary Table 1a: Study characteristics and details of analysis metrics and methods for all Stage 1 discovery cohorts [attached in Excel]

Supplementary Table 1b: Study characteristics and details of analysis metrics and methods for all Stage 2 replication cohorts [attached in Excel]

Supplementary Table 2: Association statistics for single nucleotide polymorphisms that did not reach genome-wide significance ($P<5 \times 10^{-8}$)

Glucose/HOMA-B selected SNPs					**Fasting glucose**					**HOMA-B**				
SNP	Nearest gene	Effect allele	Non-effect allele	Freq	Discovery *P* value	Replication *P* value	Replication beta ± SE	Global *P* value	Joint Analysis N	Discovery *P* value	Replication *P* value	Replication beta ± SE	Global *P* value	Joint Analysis N
rs457420	*CRSP8/BRD3*	T	C	0.43	1.6×10^{-5}	0.305	0.003 ± 0.003	8.8×10^{-4}	108,256	0.571	0.250	-0.004 ± 0.003	0.738	85,508
rs4243291	*FLJ44881*	A	G	0.21	3.5×10^{-6}	0.228	0.006 ± 0.005	0.026	108,565	0.163	0.366	-0.005 ± 0.005	0.397	84,557
rs10493846	*HFM1*	T	G	0.26	0.195	0.606	-0.002 ± 0.004	0.277	102,196	3.4×10^{-6}	0.810	-0.001 ± 0.004	0.003	78,974
Insulin/HOMA-IR selected SNPs					**Fasting insulin**					**HOMA-IR**				
rs4912494	*CHRD/EPHB3*	T	G	0.34	1.7×10^{-6}	0.173	-0.006 ± 0.005	1.1×10^{-5}	77,011	2.6×10^{-6}	0.207	-0.006 ± 0.005	2.2×10^{-5}	77,837
rs11167682	*BC042059*	T	G	0.24	2.4×10^{-5}	0.130	0.007 ± 0.004	5.6×10^{-5}	82,878	6.5×10^{-6}	0.117	0.006 ± 0.005	3.9×10^{-5}	81,256
rs6479526	*PTPDC1*	T	C	0.21	2.5×10^{-5}	0.564	0.003 ± 0.004	5.0×10^{-4}	90,670	4.5×10^{-6}	0.493	0.003 ± 0.005	1.8×10^{-4}	89,183
rs4675095	*IRS1*	A	T	0.94	8.5×10^{-4}	0.432	-0.006 ± 0.008	3.9×10^{-3}	91,210	1.1×10^{-4}	0.851	-0.002 ± 0.008	4.6×10^{-3}	89,831
rs588262	*RBM26*	T	C	0.96	6.5×10^{-6}	0.904	-0.001 ± 0.010	0.018	85,387	1.5×10^{-6}	0.984	0.0002 ± 0.010	0.010	83,936
rs1416802	*PLXDC2/NEBL*	A	G	0.77	0.007	0.947	0.0003 ± 0.004	0.063	91,231	0.004	0.688	0.002 ± 0.004	0.027	89,742
rs6947696	*CDK6/SAMD9*	A	G	0.13	7.3×10^{-6}	0.733	-0.002 ± 0.007	0.087	78,775	4.7×10^{-5}	0.504	-0.005 ± 0.007	0.183	77,333

Directly genotyped and imputed single nucleotide polymorphisms (SNPs) were assessed for association with fasting glucose, fasting insulin, and homeostasis model assessment of β-cell function (HOMA-B) and insulin resistance (HOMA-IR). Twenty one discovery cohorts with genome-wide data were meta-analyzed (discovery) and 25 SNPs were promoted for replication of the same trait in an additional set of 33 cohorts with *in silico* or *de novo* genotype data (replication). A joint analysis was then performed (global). The beta coefficients are obtained from the replication cohorts so as to avoid an overestimate of the effect size caused by the "winner's curse". Freq denotes the allele frequency of the effect allele. N=sample size. Global *P* values adjusted for body mass index did not significantly change the results.

Supplementary Table 3: Effects of known type 2 diabetes-associated loci on fasting glucose-related and insulin-related traits in MAGIC

						DIAGRAM T2D		Fasting glucose		Fasting insulin		HOMA-B		HOMA-IR	
Marker	chr	position (NCBI 35)	gene	risk allele	other allele	OR (95% CI)	*P*-value	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value
rs10923931	1	120,230,001	*NOTCH2*	T	G	1.23 (1.12-1.35)	6.9×10^{-6}	0.011 (-0.001 - 0.022)	0.068	-0.001 (-0.012 - 0.011)	0.935	-0.005 (-0.015 - 0.006)	0.382	0.001 (-0.011 - 0.014)	0.869
rs7578597	2	43,644,474	*THADA*	T	C	1.23 (1.11-1.37)	1.1×10^{-4}	0.026 (0.014 - 0.037)	2.4×10^{-5}	-0.013 (-0.026 – 0.000)	0.056	-0.023 (-0.035 – -0.012)	7.0×10^{-5}	-0.009 (-0.023 - 0.004)	0.189
rs1801282	3	12,368,125	*PPARG*	C	G	1.19 (1.09-1.30)	2.0×10^{-4}	0.013 (0.003 - 0.024)	0.014	0.016 (0.005 - 0.026)	5.5×10^{-3}	0.006 (-0.003 - 0.015)	0.181	0.016 (0.005 - 0.027)	5.6×10^{-3}
rs4607103	3	64,686,944	*ADAMTS9*	C	T	1.15 (1.06-1.23)	3.1×10^{-4}	0.01 (0.001 - 0.018)	0.026	0.006 (-0.002 - 0.015)	0.152	0.001 (-0.007 - 0.009)	0.827	0.006 (-0.004 - 0.015)	0.235
rs1470579	3	187,011,782	*IGF2BP2*	C	A	1.17 (1.10-1.25)	3.1×10^{-7}	0.009 (0.001 - 0.017)	0.019	-0.007 (-0.015 - 0.001)	0.099	-0.011 (-0.018 – -0.004)	1.4×10^{-3}	-0.008 (-0.017 – 0.000)	0.047
rs10010131	4	6,410,987	*WFS1*	G	A	1.10 (1.03-1.16)	4.0×10^{-3}	0.018 (0.011 - 0.025)	9.4×10^{-7}	0.006 (-0.001 - 0.014)	0.097	-0.003 (-0.010 - 0.003)	0.318	0.008 (0.001 - 0.016)	0.035
rs7756992	6	20,787,688	*CDKAL1*	G	A	1.26 (1.18-1.34)	2.0×10^{-11}	0.010 (0.001 - 0.018)	0.020	-0.011 (-0.019 - -0.002)	0.011	-0.010 (-0.017 – -0.002)	7.5×10^{-3}	-0.010 (-0.018 - -0.001)	0.029
rs864745	7	27,953,796	*JAZF1*	T	C	1.15 (1.08-1.22)	4.6×10^{-5}	0.006 (-0.001 - 0.013)	0.117	-0.002 (-0.01 - 0.005)	0.583	-0.004 (-0.010 - 0.003)	0.283	-0.001 (-0.009 - 0.007)	0.771
rs13266634	8	118,253,964	*SLC30A8*	C	T	1.10 (1.02-1.19)	0.033	0.027 (0.018 - 0.036)	5.5×10^{-10}	-0.004 (-0.013 - 0.005)	0.441	-0.016 (-0.023 – -0.009)	2.4×10^{-5}	0.000 (-0.010 - 0.009)	0.969
rs10811661	9	22,124,094	*CDKN2A/B*	T	C	1.26 (1.16-1.37)	2.0×10^{-7}	0.019 (0.009 - 0.028)	1.0×10^{-4}	0.003 (-0.007 - 0.012)	0.612	-0.009 (-0.017 – 0.000)	0.051	0.005 (-0.005 - 0.016)	0.301
rs12779790	10	12,368,016	*CDC123*	G	A	1.17 (1.09-1.27)	4.7×10^{-5}	0.016 (0.006 - 0.025)	1.2×10^{-3}	0.000 (-0.011 - 0.010)	0.940	-0.011 (-0.019 – -0.002)	0.015	-0.001 (-0.012 - 0.010)	0.851
rs1111875	10	94,452,862	*HHEX*	C	T	1.18 (1.11-1.25)	4.0×10^{-7}	0.009 (0.002 - 0.016)	0.014	0.002 (-0.006 - 0.009)	0.669	-0.004 (-0.011 - 0.002)	0.203	0.003 (-0.005 - 0.011)	0.487
rs7903146	10	114,748,339	*TCF7L2*	T	C	1.40 (1.31-1.50)	3.1×10^{-23}	0.023 (0.015 - 0.031)	2.8×10^{-8}	-0.012 (-0.021 - -0.004)	4.6×10^{-3}	-0.020 (-0.027 - -0.013)	1.4×10^{-7}	-0.010 (-0.018 – -0.001)	0.034

rs2237892	11	2,796,327	*KCNQ1*	C	T	1.18 (1.03-1.34)	0.014	0.011 (-0.005 - 0.334)	0.165	-0.019 (-0.035 - 0.041)	0.031	-0.020 (-0.034 - -0.006)	0.006	-0.019 (-0.036 – -0.001)	0.036
rs5215	11	17,365,206	*KCNJ11*	C	T	1.17 (1.10-1.24)	4.1×10^{-7}	-0.003 (-0.011 - 0.004)	0.401	-0.002 (-0.01 - 0.006)	0.587	0.001 (-0.006 - 0.007)	0.780	-0.002 (-0.010 - 0.006)	0.655
rs7961581	12	69,949,369	*TSPAN8*	C	T	1.17 (1.10-1.25)	3.7×10^{-5}	0.006 (-0.002 - 0.015)	0.122	-0.002 (-0.011 - 0.006)	0.603	-0.001 (-0.009 - 0.006)	0.711	0.001 (-0.008 - 0.010)	0.845
rs9939609	16	52,378,028	*FTO*	A	T	1.14 (1.07-1.21)	1.7×10^{-5}	0.006 (-0.001 - 0.013)	0.095	0.014 (0.007 - 0.022)	1.9×10^{-4}	0.008 (0.001 - 0.014)	0.023	0.014 (0.007 - 0.022)	3.2×10^{-4}
rs757210	17	33,170,628	*TCF2*	T	C	na	na	0.003 (-0.008 - 0.013)	0.614	-0.006 (-0.018 - 0.005)	0.264	-0.009 (-0.018 – 0.000)	0.043	-0.011 (-0.023 – 0.000)	0.058
Sample size for each trait								27,858 – 46,186		21,140 – 38,244		19,680 – 36,466		19,812 – 36,946	

Supplementary Table 4: Known effects of human mutations and null mouse phenotypes for selected genes around novel fasting glucose and insulin-associated loci

				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
rs2191349	***DGKB***	121,475	Diacylglycerol (DAG) kinase, regulator of second messenger DAG Brain								7689223 17021016
rs2191349	***TMEM195***	175,634	Encodes transmembrane protein 195, an integral membrane phosphoprotein Highly expressed in liver								
rs11708067	***ADCY5***	Intronic	Adenylate cyclase 5, synthesis of cAMP Highly expressed in heart			**Other systems**: Targeted inactivation of this gene has been shown to result in motor dysfunction					12503609 12665504 12223546
rs11708067	*SEC22A*	74,425	Encodes interacting proteins that may play a role in endoplasmic reticulum (ER)-Golgi transport								8621431
rs11708067	*PDIA5*	184,828	Protein disulfide isomerase family A, member 5								14627699
rs7944584	***MADD***	Intronic	Death domain-containing adaptor protein, interacts with the death domain of TNF-alpha receptor 1, propagates apoptotic signal Brain, white blood cells			**Other systems**: Neonatal lethality; nervous system phenotype; respiratory system phenotype; hyporesponsive to tactile stimuli					11359932
rs7944584	*MYBPC3*	16,637	Encodes the cardiac isoform of myosin-binding protein C. Expressed exclusively in heart muscle	115197	CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC	**Cardiovascular**: Numerous cardiovascular problems					15737656
rs7944584	*SPI1*	40,089	Encodes an ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development			**Growth/Size**: Postnatal growth retardation **Other systems**: Abnormal blood development; abnormal erythrocyte count; decreased B lymphocyte count; spleen abnormalities; premature death; enlarged liver; abnormal bone marrow morphology; increased tumor incidence; abnormal eye development; B & T cell abnormalities					16432184 15328162 8896458

				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
			Myeloid and B cells								
rs7944584	*NR1H3*	45,924	Liver X receptor alpha. Liver X receptors (LXRs) are established mediators of lipid-inducible gene expression Expressed in metabolically active tissues, such as liver, kidney, intestines, and the adrenal glands			**Metabolism/homeostasis**: Abnormal cellular cholesterol metabolism; increased circulating alanine transaminase level; abnormal lipid homeostasis; increased cholesterol level; increased circulating LDL cholesterol level **Cardiovascular**: Abnormal blood circulation **Other systems**: Increased circulating LDL cholesterol level; enlarged liver; pale liver; abnormal brain morphology					10809236 9630215 17657314 15372105
rs7944584	*ACP2*	65,957	This gene encodes the beta subunit of lysosomal acid phosphatase (LAP) Lysosomal compartment			**Growth/Size**: Growth retarded with missense mutation (Gly244Glu) **Other systems**: Generalized lysosomal storage phenomena in the kidney and central nervous system; progressive skeletal disorder; increased disposition toward generalized seizures; abnormal hair shaft, and skin malformations with missense mutation (Gly244Glu)					15503243 9228031
rs7944584	*DDB2*	75,557	Encodes a protein that is necessary for the repair of ultraviolet light-damaged DNA Ubiquitously expressed; with highest levels in corneal endothelium and lowest levels in brain. Isoform D1 is highly expressed in brain and heart. Isoform D2, isoform D3 and isoform D4 are weakly expressed			**Other systems**: Mutant mice are prone to both spontaneous and UV-induced skin cancer					10713455 17967871 18936169
rs7944584	*SLC39A13*	93,862	SLC39A13 belongs to a subfamily of proteins that show structural characteristics of zinc transporters	612350	SPONDYLOCHEIRODYSPLASIA, EHLERS-DANLOS SYNDROME-LIKE	**Other systems**: Mice homozygous for disruption of this gene display skeletal abnormalities and dental abnormalities					12659941 18513683
rs7944584	*PSMC3*	104,000	Involved in the ATP-dependent degradation of ubiquitinated proteins			**Other systems**: Mice homozygous for disruptions in this gene die as embryos					8419915
rs7944584	*RAPSN*	122,988	Receptor-associated protein of the synapse; contains a conserved cAMP-dependent protein kinase phosphorylation site	608931	MYASTHENIC SYNDROME, CONGENITAL, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY	**Other systems**: Homozygotes for a targeted null mutation exhibit absence of acetylcholine receptor clusters at end plate band of neuromuscular synapses, muscle weakness, and respiratory distress leading to lethality within hours of birth					3170600 17119023 12832540

				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
				208150	FETAL AKINESIA DEFORMATION SEQUENCE; FADS						
rs7944584	*PACSIN3*	128,362	PACSINs are a family of cytoplasmic phosphoproteins that play a role in vesicle formation and transport								11082044 11179684
rs7944584	*ARFGAP2*	137,901	GTPase-activating protein (GAP) for ADP ribosylation factor 1 (ARF1)								19015319 17760859
rs7944584	C11orf49	150,393									
rs7944584	*CUGBP1*	153,626	RNA-binding protein implicated in the regulation of several post-transcriptional events Ubiquitous expression			**Growth/Size**: Decreased body size; fetal growth retardation **Cardiovascular**: Dilated cardiomyopathy, arrhythmias, and systolic and diastolic dysfunction **Other systems**: Postnatal lethality; reproductive system abnormalities					17823658 17130239
rs7944584	*PTPMT1*	250,855	Mediates dephosphorylation of mitochondrial proteins, thereby playing an essential role in ATP production			**Metabolism/homeostasis**: Knockdown of Ptpmt1 expression in a rat pancreatic insulinoma cell line altered the mitochondrial phosphoprotein profile and enhanced both ATP production and insulin secretion.					16039589
rs7944584	*KBTBD4*	257,430									
rs7944584	*NDUFS3*	264,312	First enzyme complex in the electron transport chain of mitochondria								19034380
rs7944584	*C1QTNF4*	274,896	Complement C1q tumor necrosis factor-related protein 4 precursor								
rs7944584	*MTCH2*	302,548									15899861
rs11605924	***CRY2***	Intronic	Cryptochrome 2, circadian regulator of calcium ion oscillation Brain, prostate, heart, uterus			**Metabolism/homeostasis**: Abnormal body temperature regulation; increased oxygen consumption; impaired glucose tolerance; increased insulin sensitivity **Adipose tissue**: Decreased adipose tissue amount ; decreased abdominal adipose tissue amount; decreased subcutaneous adipose tissue amount; abnormal brown adipose tissue morphology **Growth/Size**: Decreased body weight **Cardiovascular**: Abnormal vasoconstriction; increased heart rate **Other systems**: Abnormal circadian rhythm, period and phase; hypoactivity; nervous system phenotype; vision/eye phenotype					9822380 10217146 15860530
rs11605924	*MAPK8IP1*	34,111	The protein encoded by this gene is a regulator of the pancreatic beta-cell function	12583	DIABETES MELLITUS, NONINSULIN-DEPENDENT	**Metabolism/ homeostasis**: Jip1 mutant mice were resistant to diet-induced obesity and showed reduced diet-induced insulin resistance. **Other systems**: Decreased susceptibility to ischemic brain injury; ataxia					11390367 1531402

				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
rs11605924	*SLC35C1*	38,525	Encodes a GDP-fucose transmembrane transporter (FucT1) located in the Golgi apparatus	266265	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIc; CDG2C	**Growth/Size**: Growth retardation **Other systems**: Partial perinatal and postnatal lethality; reduced fertility; leukocytosis; defective lung and primary lymph node development and altered lymphocyte rolling and adhesion					18541720
rs11605924	LOC143678	54,995									
rs11605924	*PEX16*	58,130	Integral peroxisomal membrane protein								9837814
rs11605924	*GYLTL1B*	70,105	Glycosyltransferase which participates in glycosylation of alpha-dystroglycan Placenta, pancreas, mammary gland, and kidney								15661757 15752776
rs11605924	*PHF21A*	77,780	Component of the BHC complex, a corepressor complex that represses transcription of neuron-specific genes in non-neuronal cells			**Other systems**: Abnormal suckling behavior; neonatal lethality					16684532
rs10885122	***ADRA2A***	201,523	α_{2A} adrenergic receptor, neurotransmitter and potassium channel regulator Pancreas			**Metabolism/homeostasis**: Abnormal glucose homeostasis; hypoglycemia **Cardiovascular**: Abnormal blood pressure; cardiac hypertrophy; abnormal heart rate **Other systems**: Embryogenesis phenotype; nervous system phenotype					8670421 10385696 10334470
rs10885122	*SHOC2*	268,671	Leucine-rich repeat protein SHOC-2, a positive modulator of the RAS pathway								16301319
rs174550	***FADS1***	Intronic	Member of the fatty acid desaturase (FADS) gene family; regulate unsaturation of fatty acids through the introduction of double bonds between defined carbons of the fatty acyl chain Encodes fatty acid desaturase (FADS) enzyme Expressed in many tissues, it is most abundant in the liver, brain, adrenal gland and heart								18936223 18320251
rs174550	*FEN1*	6,770	Flap endonuclease 1 (FEN-1) is			**Other systems**: Prenatal lethality; absence of the cells of the blastocyst that develop					12119409

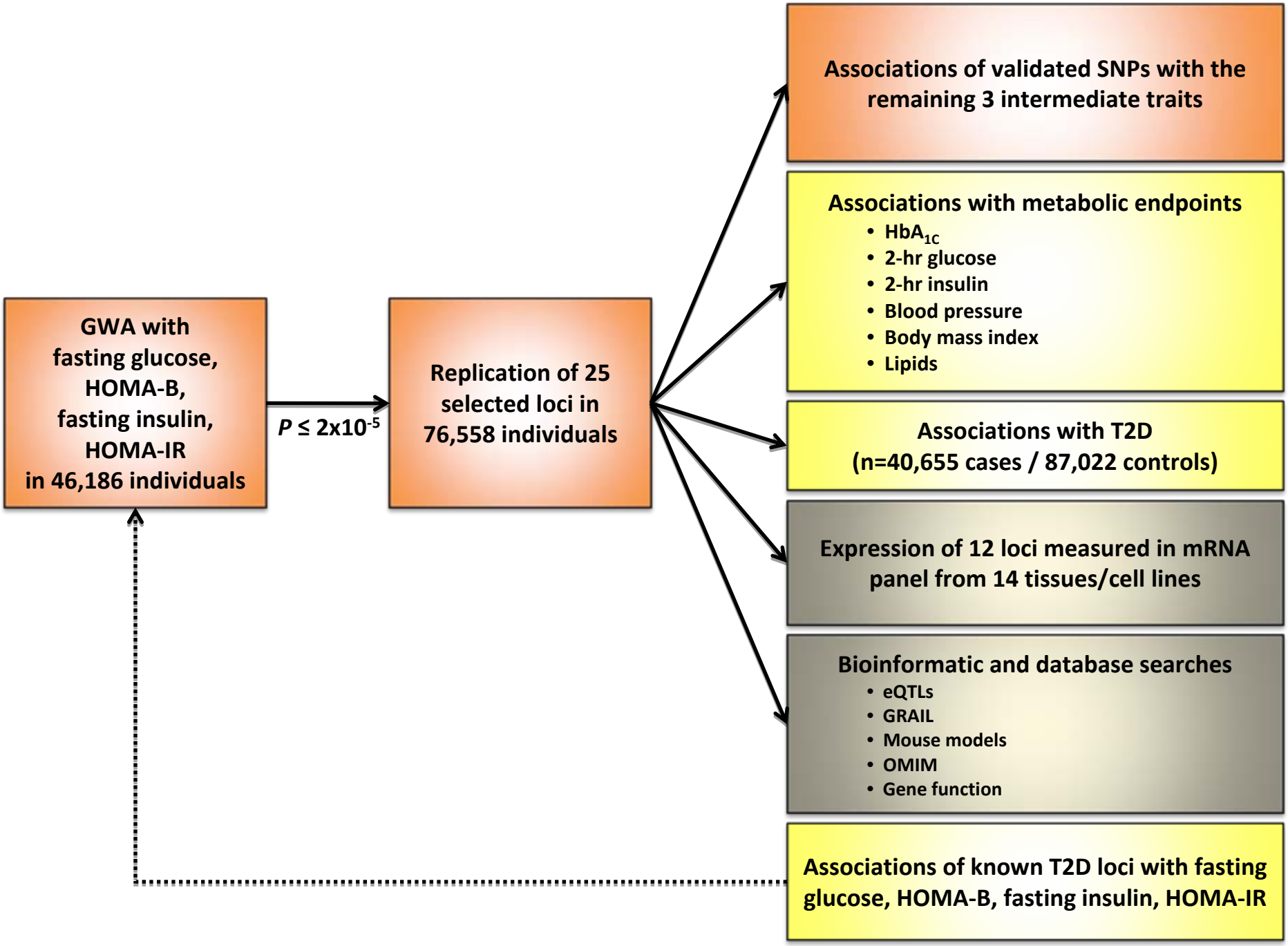
				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
			a nuclear enzyme involved in DNA metabolism, such as replication, repair, and recombination Ubiquitously expressed in all tissues			into the body of the embryo; abnormal DNA repair; rapid progression of cancer					17589521 15189154
rs174550	C11orf10	11,396	Function unknown Expressed in bone marrow, brain, heart, kidney, liver, lung, muscle, placenta, pancreas, spleen, prostate, stomach, testis, thymus, uterus								12427278
rs174550	*FADS2*	12,271	Member of the fatty acid desaturase (FADS) gene family; regulate unsaturation of fatty acids through the introduction of double bonds between defined carbons of the fatty acyl chain Encodes fatty acid desaturase (FADS) enzyme			**Cardiovascular**: Abnormal PGE2 physiology **Other systems**: Mice homozygous for a null allele display absence of long-chain polyunsaturated fatty acids; infertility; arrest of spermiogenesis and folliculogenesis; impaired platelet function					19172737
rs174550	C11orf9	15,489	Transcription regulation								10828591
rs174550	*FADS3*	69,521	Member of the fatty acid desaturase (FADS) gene family; regulate unsaturation of fatty acids through the introduction of double bonds between defined carbons of the fatty acyl chain								10860662
rs174550	*RAB3IL1*	93,296	Guanine nucleotide exchange factor for Rab3A, a GTPase that regulates synaptic vesicle exocytosis								16189514 11516400
rs174550	*BEST1*	146,349	Encodes a member of the bestrophin gene family; may form chloride ion channels or may regulate voltage-gated L-type calcium-ion channels Predominantly expressed in the	153700 608161	MACULAR DYSTROPHY, VITELLIFORM; VMD MACULAR DYSTROPHY, VITELLIFORM,	**Other systems**: Mice homozygous for a null mutation exhibit altered eye electrophysiology					15556645 10453731 10394929

				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
			basolateral membrane of the retinal pigment epithelium	611809 193220	ADULT-ONSET; AVMD BESTROPHINOPATHY ; ARB VITREORETINOCHOROIDOPATHY; VRCP						
rs174550	*FTH1*	160,281	Stores iron in a soluble, non-toxic, readily available form. Important for iron homeostasis.			**Metabolism/homeostasis**: Abnormal protein level; abnormal iron homeostasis					3020541
rs340874	***PROX1***	2,604	Prospero homeobox protein, transcription regulator, co-repressor of hepatocyte nuclear factor 4α			**Metabolism/homeostasis**: Edema; increased circulating glucagon level; increased circulating insulin level; increased circulating leptin level; abnormal circulating enzyme level; cyanosis; increased triglyceride level **Adipose tissue**: Increased adipose tissue amount ; increased fat cell size; abnormal fat pad morphology **Growth/Size**: Increased susceptibility to age related obesity **Cardiovascular**: Cardiovascular system phenotype; abnormal lymph circulation; abnormal lymph circulation; chylothorax **Other systems**: Abnormal suckling behavior; hypoactivity					16488887
rs11920090	***SLC2A2***	Intronic	GLUT2, mediates facilitated bidirectional glucose transport, "glucose sensor" Pancreas, kidney, liver, intestine	227810	FANCONI-BICKEL SYNDROME	**Metabolism/homeostasis**: Hyperglycaemia; Abnormal glucose homeostasis; Increased circulating glucagon; decreased circulating insulin; abnormal glucose tolerance; abnormal lipid homeostasis; increased fatty acid level; Abnormal pancreatic islet morphology,; decreased pancreas weight **Growth/Size**: Decreased body weight					9354799 11044475
rs7034200	***GLIS3***	Intronic	GLI-similar zinc finger protein, repressor/ activator of transcription, involved in the development of pancreatic beta cells, the thyroid, eye, liver and kidney	610199	DIABETES MELLITUS, NEONATAL, WITH CONGENITAL HYPOTHYROIDISM						14500813
rs35767	***IGF1***	1,153	Insulin-like growth factor, growth factor and hormone activity	608747	INSULIN-LIKE GROWTH FACTOR I DEFICIENCY IGF1	**Metabolism/homeostasis**: Increased circulating growth hormone level; abnormal glucose Homeostasis; decreased circulating glucose level; increased circulating insulin level; insensitivity to growth hormone **Growth/Size**: Growth retarded; abnormal body size; Decreased length; postnatal slow weight gain **Other systems**: Perinatal death with many immature organ systems; respiratory, nervous, skeleton and muscle phentoypes depending on background of partial knockouts.					8402901 9731712 8276243
rs4675095	***IRS1***	Intronic	Major insulin receptor substrate which may play an important	125853	DIABETES MELLITUS, NONINSULIN-	**Metabolism/homeostasis**: Impaired glucose tolerance, and mild insulin and IGF-1 resistance					1385403

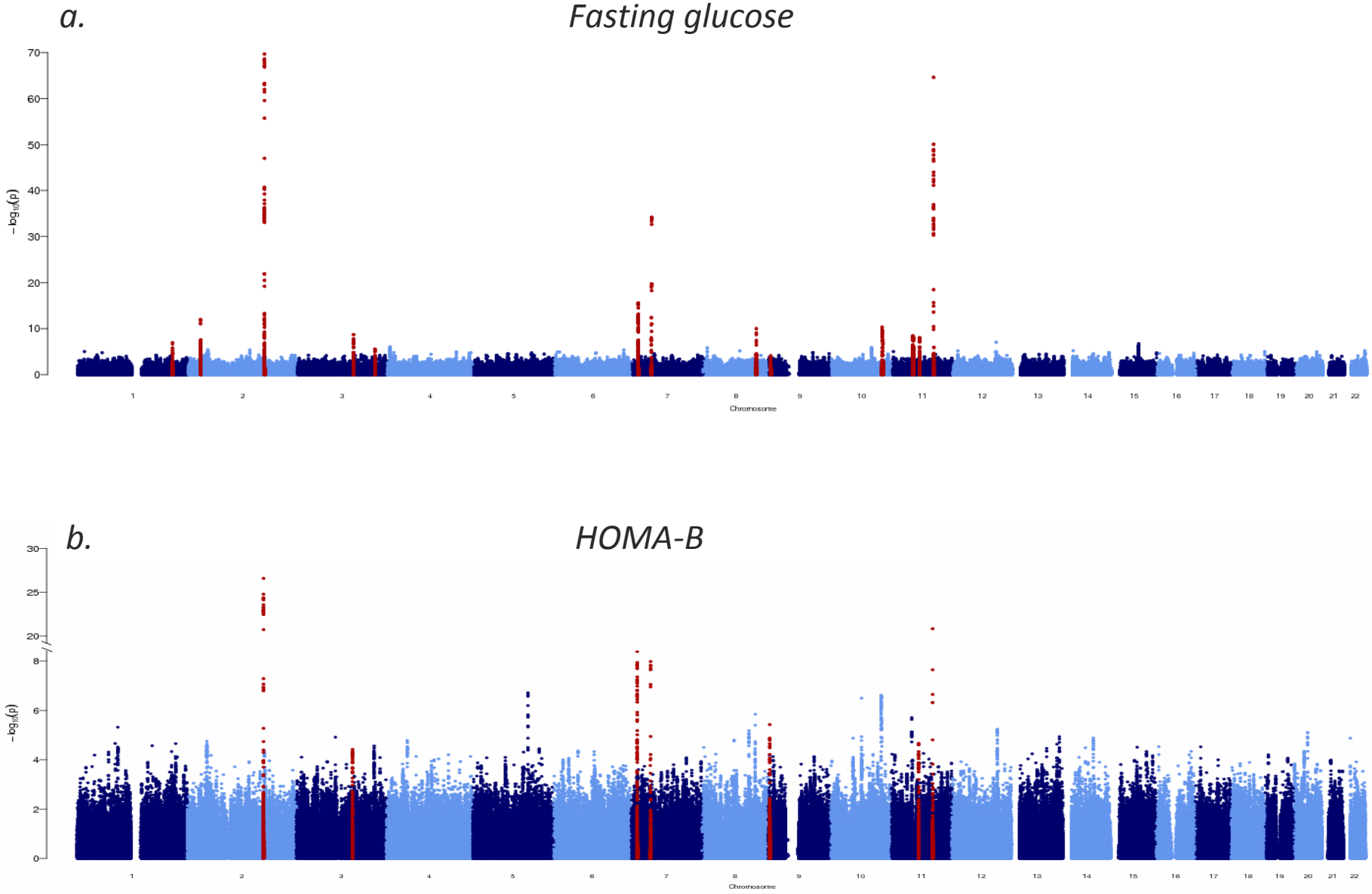
				Human Disease		Mouse Knockout					
Lead SNP	**Genes in region**	**Distance to gene (bp)**	**Function/Expression**	**OMIM**	**Phenotype**	**Metabolism/ homeostasis**	**Adipose tissue**	**Growth/ Size**	**Cardiovascular**	**Other systems**	**PubMed**
			role in insulin signal transmission Overexpressed in skeletal muscle,and adipocytes	147545	DEPENDENT CORONARY ARTERY DISEASE, SUSCEPTIBILITY TO	**Growth/Size**: 50 percent reductions in body weights at birth and at 4 months of age					
rs11071657	***FAM148B***	21,775	May play a role in regulating genes which control cellular architecture								15527968
rs11071657	*FAM148A*	70,853	May play a role in regulating genes which control cellular architecture								15527968
rs11071657	*VPS13C*	81,315	Encodes chorein, a protein similar to yeast Vps13p Ubiquitous expression								15498460
rs6479526	***PTPDC1***	Intronic	Function not yet determined. Protein contains a characteristic motif of protein tyrosine phosphatases								17971504
rs6479526	*BARX1*	112,982	Encodes a member of the Bar subclass of homeobox transcription factors			**Other systems**: Mice homozygous for a null mutation die around E13 embryonic stage. Prior to death, embryo shows shrunken and malformed stomach but normal intestine					15809042

SUPPLEMENTARY FIGURE LEGENDS:

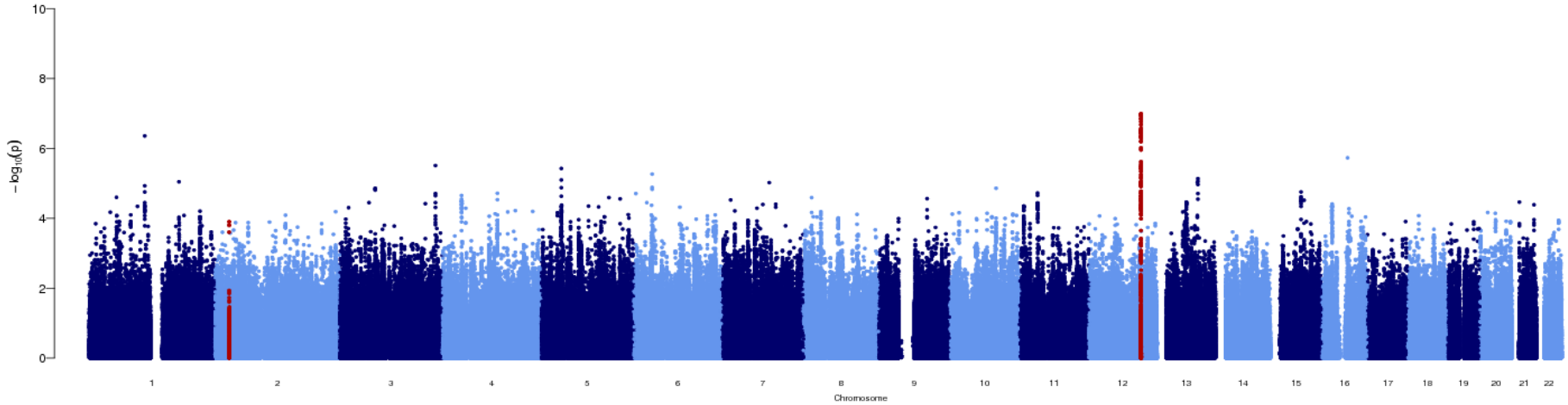
Supplementary Figure 1: Flow chart detailing the study design.


GWA with fasting glucose, HOMA-B, fasting insulin, HOMA-IR in 46,186 individuals
P ≤ 2x10-5
Replication of 25 selected loci in 76,558 individuals
Associations of validated SNPs with the remaining 3 intermediate traits
Associations with metabolic endpoints
• HbA1C
• 2-hr glucose
• 2-hr insulin
• Blood pressure
• Body mass index
• Lipids
Associations with T2D (n=40,655 cases / 87,022 controls)
Expression of 12 loci measured in mRNA panel from 14 tissues/cell lines
Bioinformatic and database searches
• eQTLs
• GRAIL
• Mouse models
• OMIM
• Gene function
Associations of known T2D loci with fasting glucose, HOMA-B, fasting insulin, HOMA-IR

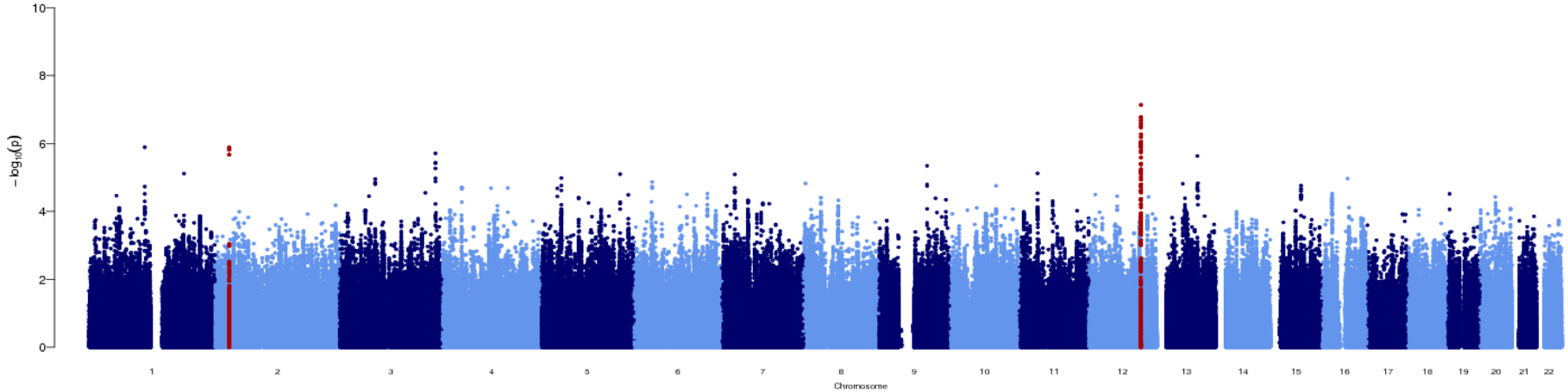
Supplementary Figure 2: Manhattan plots of the association *P* values for fasting glucose (a), β-cell function by homeostasis model assessment (HOMA-B) (b), fasting insulin (c) and insulin resistance by homeostasis model assessment (HOMA-IR) (d). Directly genotyped and imputed single nucleotide polymorphisms (SNPs) are plotted with their meta-analysis *P* values (as –log10 values) as a function of genomic position (NCBI Build 35). The SNPs that achieved genome-wide significance ($P<5\times10^{-8}$) on replication are shown in red.


a.
Fasting glucose
−log10(p)
Chromosome
b.
HOMA-B
−log10(p)
Chromosome

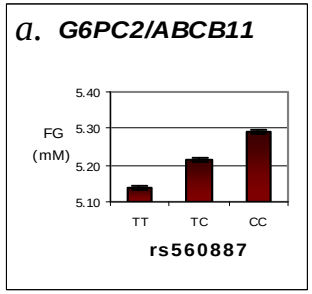
c. *Fasting insulin*

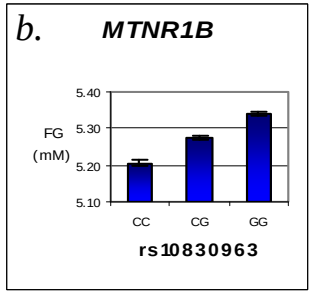


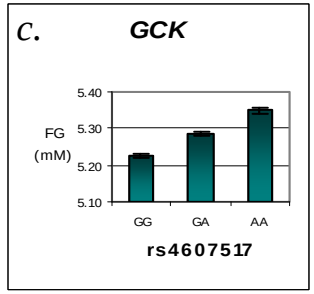
d. *HOMA-IR*

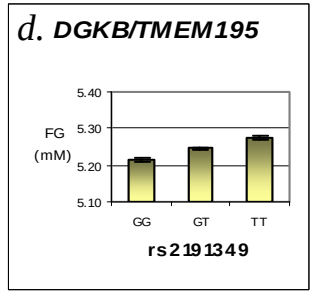


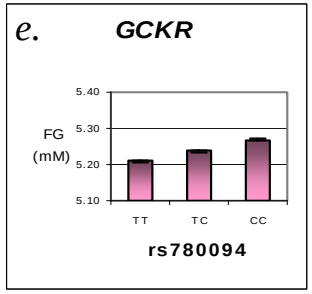
Supplementary Figure 3: Variation in levels of fasting glucose (FG, mmol/L) at novel loci by genotype at each individual locus estimated in 48 cohorts.

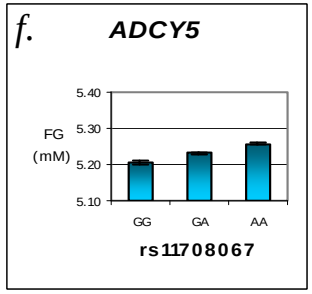

a. G6PC2/ABCB11
FG (mM)
5.40
5.30
5.20
5.10
TT
TC
CC
rs560887

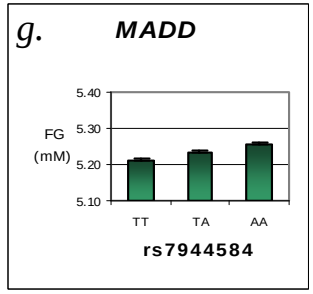

b. MTNR1B
FG (mM)
5.40
5.30
5.20
5.10
CC
CG
GG
rs10830963

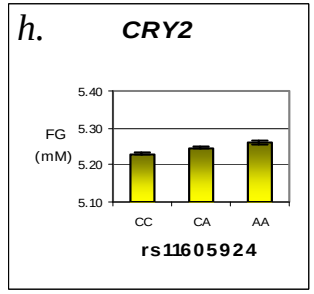

c. GCK
FG (mM)
5.40
5.30
5.20
5.10
GG
GA
AA
rs4607517

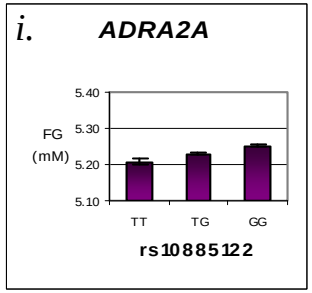

d. DGKB/TMEM195
FG (mM)
5.40
5.30
5.20
5.10
GG
GT
TT
rs2191349

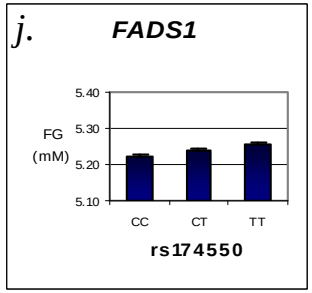

e. GCKR
FG (mM)
5.40
5.30
5.20
5.10
TT
TC
CC
rs780094

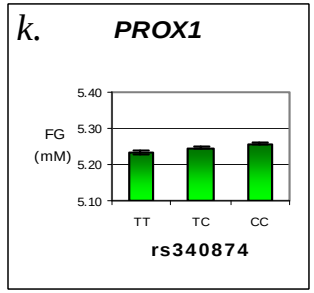

f. ADCY5
FG (mM)
5.40
5.30
5.20
5.10
GG
GA
AA
rs11708067

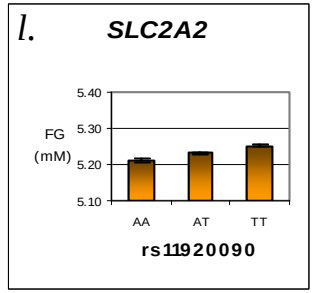

g. MADD
FG (mM)
5.40
5.30
5.20
5.10
TT
TA
AA
rs7944584

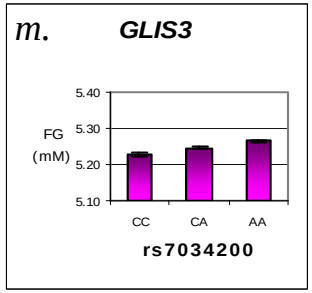

h. CRY2
FG (mM)
5.40
5.30
5.20
5.10
CC
CA
AA
rs11605924

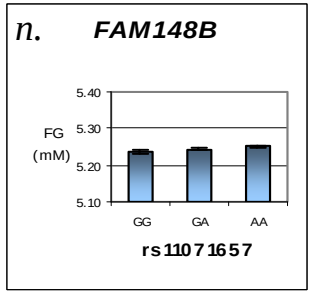

i. ADRA2A
FG (mM)
5.40
5.30
5.20
5.10
TT
TG
GG
rs10885122

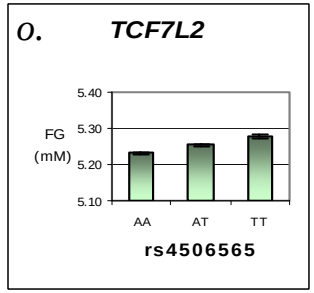

j. FADS1
FG (mM)
5.40
5.30
5.20
5.10
CC
CT
TT
rs174550

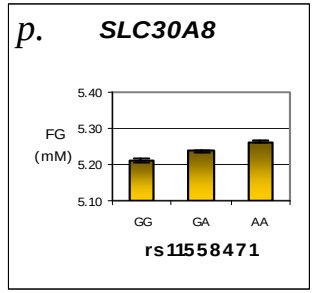

k. PROX1
FG (mM)
5.40
5.30
5.20
5.10
TT
TC
CC
rs340874


l. SLC2A2
FG (mM)
5.40
5.30
5.20
5.10
AA
AT
TT
rs11920090


m. GLIS3
FG (mM)
5.40
5.30
5.20
5.10
CC
CA
AA
rs7034200

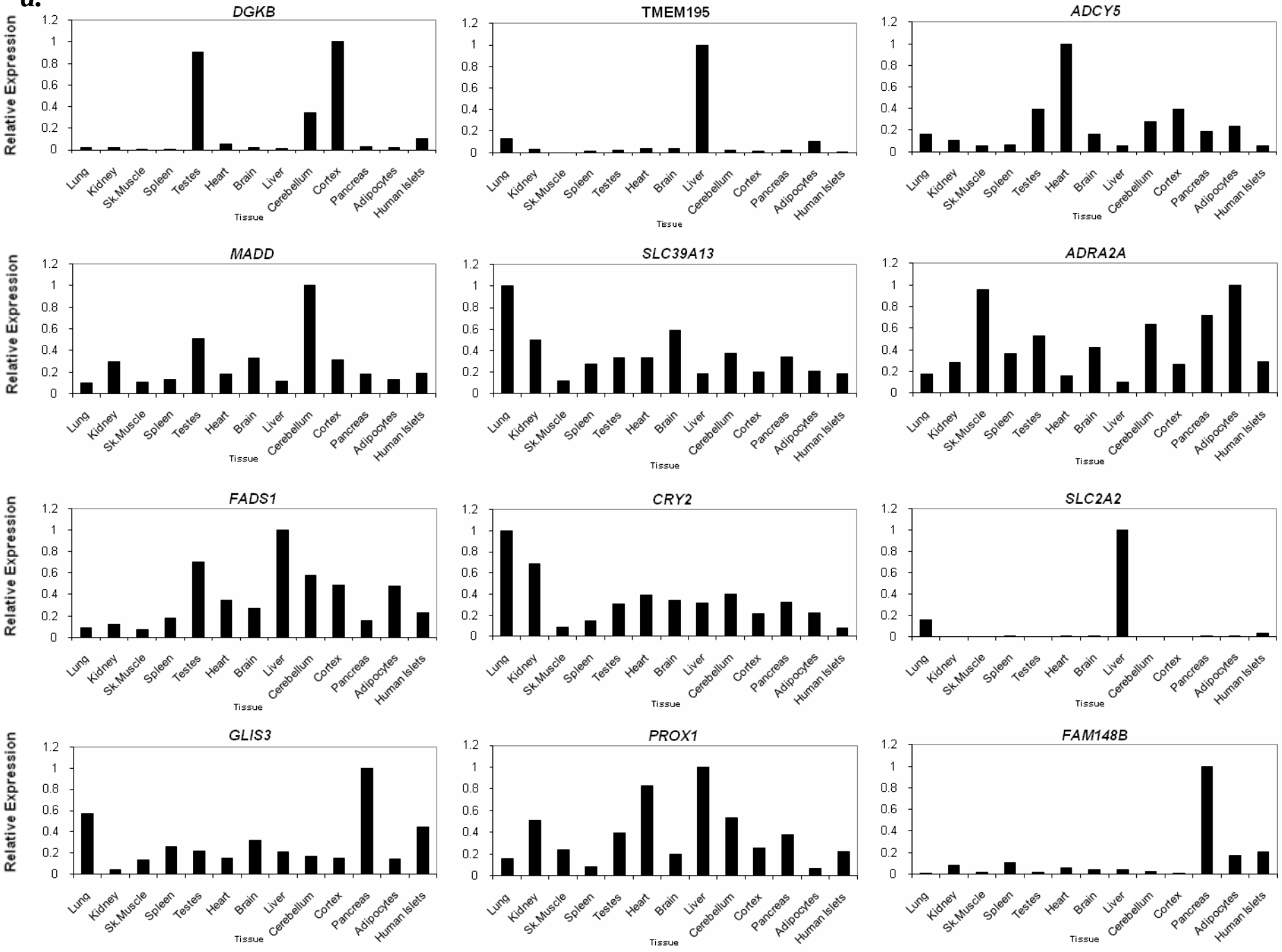

n. FAM148B
FG (mM)
5.40
5.30
5.20
5.10
GG
GA
AA
rs11071657

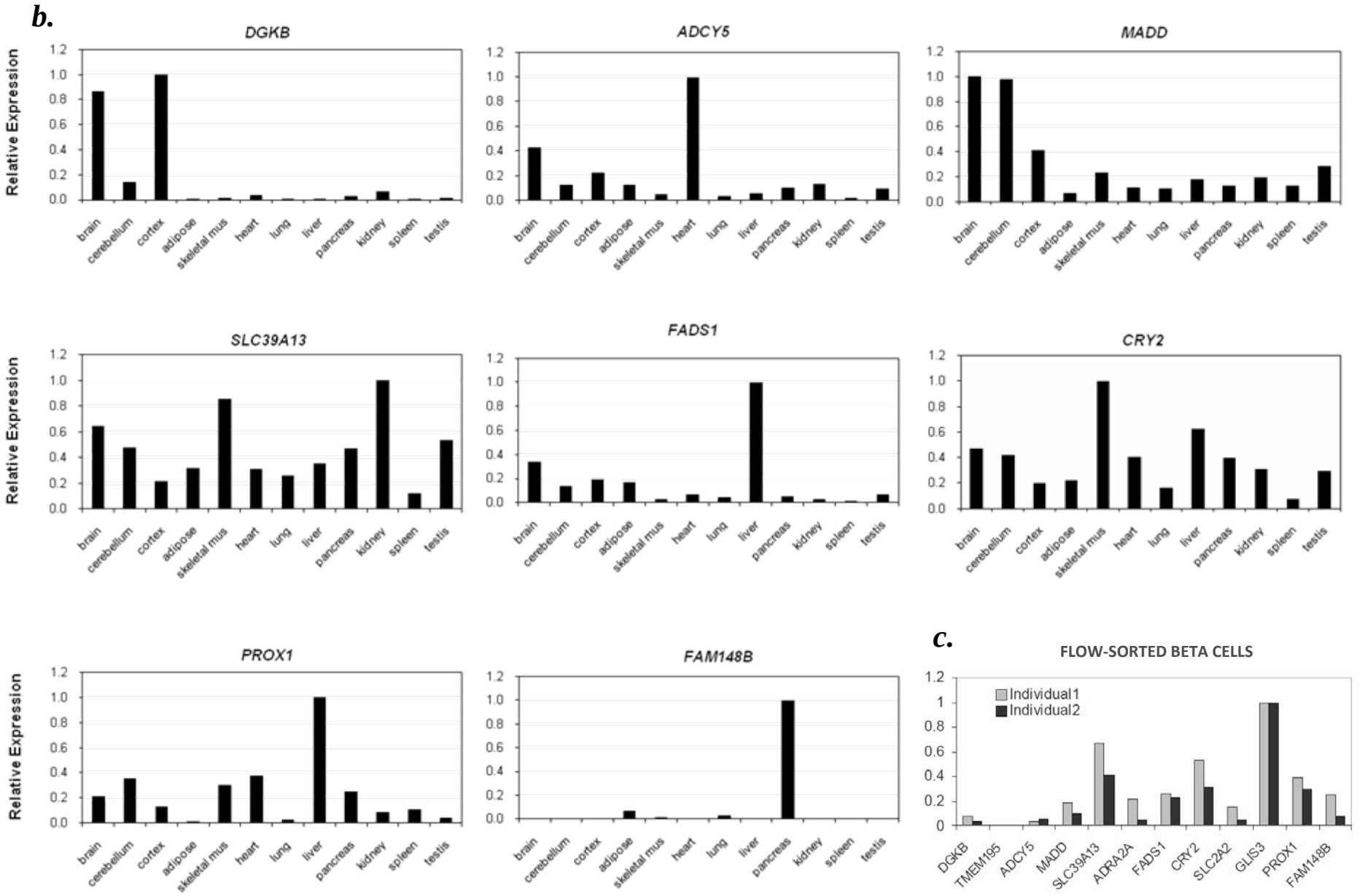

o. TCF7L2
FG (mM)
5.40
5.30
5.20
5.10
AA
AT
TT
rs4506565


p. SLC30A8
FG (mM)
5.40
5.30
5.20
5.10
GG
GA
AA
rs11558471

Supplementary Figure 4: (a) Expression of novel fasting glucose and insulin-associated transcripts in various human tissues. The data have been normalized to the tissue showing the highest expression for each novel locus. (b) Duplicate experiment in a separate laboratory. (c) Expression pattern of fasting glucose-associated loci in human flow-sorted β cells. cDNAs from two human donors were reverse transcribed and relative expression measured by quantitative PCR. All samples were run in triplicate and normalized to the β actin relative expression level.

a.


DGKB
TMEM195
ADCY5
MADD
SLC39A13
ADRA2A
FADS1
CRY2
SLC2A2
GLIS3
PROX1
FAM148B
Relative Expression
Tissue
Lung
Kidney
Sk.Muscle
Spleen
Testes
Heart
Brain
Liver
Cerebellum
Cortex
Pancreas
Adipocytes
Human Islets


b.
DGKB
ADCY5
MADD
SLC39A13
FADS1
CRY2
PROX1
FAM148B
Relative Expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
brain
cerebellum
cortex
adipose
skeletal mus
heart
lung
liver
pancreas
kidney
spleen
testis
c.
FLOW-SORTED BETA CELLS
Individual1
Individual2
DGKB
TMEM195
ADCY5
MADD
SLC39A13
ADRA2A
FADS1
CRY2
SLC2A2
GLIS3
PROX1
FAM148B