Online Supplement

Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance

Supplementary Note

Associations at the 53 loci with changes in hip circumference in weight gainers

The association with lower levels of peripheral fat mass but higher cardiometabolic risk of the 53-SNP genetic score suggested that individuals with a greater number of alleles are unable to expand their peripheral fat compartment. To corroborate this finding, we used weight gain as a surrogate measure for a positive energy balance and change in hip circumference in weight-gainers as a surrogate measure for the changes in peripheral fat compartments. We tested the associations of the 53-SNP genetic score in longitudinal data from 9,150 participants of the EPIC-Norfolk cohort study who gained weight during a median follow-up of 3.7 years. In these individuals, the 53-SNP genetic score was not associated with the amount of weight gained during follow-up (beta coefficient [standard error] in kg of weight change per SD of genetic score, -0.026 [0.029]; p=0.37). However, in analyses adjusted for age, sex, hip circumference at baseline and weight at baseline and the amount of weight gained during follow-up, the 53-SNP genetic score was negatively associated with change in hip circumference (beta coefficient [standard error] in cm of hip circumference change per SD of genetic score, -0.069 [0.031]; p=0.027). In the same participants, in analyses adjusted for age, sex, waist circumference at baseline and weight at baseline and the amount of weight gained during follow-up, the 53-SNP genetic score was not associated with the change in waist circumference during follow-up (beta coefficient [standard error] in cm of waist circumference change per SD of genetic score, 0.055 [0.042]; p=0.20). These results support the notion that individuals with greater burden of the 53 alleles have a relative incapacity of expanding their peripheral fat compartment when challenged by a positive energy balance.

Selection of putative effector genes for experimental validation

In light of (a) the enrichment for loci overlapping adipose tissue active enhancer elements and affecting adipocyte gene expression and (b) the association of risk alleles with lower peripheral adiposity, but higher cardiometabolic risk, we hypothesised that some of the risk alleles may act via impaired adipogenesis. We further hypothesised that the effects on adipogenesis could be caused by the altered expression of an effector gene in peripheral adipose tissue (**Supplementary Figure 11A**). Therefore, to test this hypothesis, we selected five genes at four loci associated with (a) expression of a putative effector gene in subcutaneous adipocytes ($p<5 \times 10^{-08}$), (b) lower levels of peripheral fat ($p<5 \times 10^{-05}$ for hip circumference) and (c) higher risk of metabolic disease ($p<0.05$ for type 2 diabetes; see **Supplementary Tables 10 and 13 and Supplementary Figure 11** for details). For the *IRS1* (RTC=0.86) and *L3MBTL3* genes (r^2 between lead and best expression SNPs=0.83) there was evidence supporting co-localisation of phenotypic and expression signals. For the *CCDC92*, *DNAH10* and *FAM13A* genes, the lead expression SNPs (eSNPs) at the locus (rs825452 for *CCDC92*, rs78985577 for *DNAH10* and rs13149209 for *FAM13A*) were not captured by the HapMap-imputed FIadjBMI association data,[21, 22] meaning they could not be captured by our triangulation of fasting insulin and lipid data. However, the best HapMap proxy for each of those eSNPs was also associated with FIadjBMI in MAGIC,[1,2] further supporting our prioritisation of those genes (see below).

For *CCDC92*, the lead eSNP (rs825452, $p_{expression}=8.3 \times 10^{-31}$) was in very low linkage disequilibrium ($r^2=0.001$) with our lead SNP for association with FIadjBMI (rs7973683). However, rs7973683 was also strongly associated with *CCDC92* expression in adipocytes ($p_{expression}=2.1 \times 10^{-29}$), indicative of two distinct signals of association with *CCDC92* expression levels. Furthermore, while the lead eSNP was not available in FIadjBMI results, a strong proxy (rs825453; $r^2=1$) for the lead eSNP was also associated with FIadjBMI

(p=0.0053). In the same locus, we found that our lead SNP for association with FIadjBMI levels (rs7973683) was also associated with expression of *DNAH10* ($p_{expression}$=1.9 x 10^{-08}). This was in modest linkage disequilibrium (r^2=0.27) with the lead eSNP for *DNAH10* expression (rs78985577, $p_{expression}$=4.8 x 10^{-12}). While the lead eSNP was not available in FIadjBMI data, a strong proxy (rs1316952; r^2=0.83) was also associated with FIadjBMI levels (p=0.000086). At *FAM13A*, our lead SNP for association with FIadjBMI levels (rs3822072) was also associated with expression of *FAM13A* in subcutaneous adipocytes ($p_{expression}$=7.6 x 10^{-12}). Our lead SNP was in low linkage disequilibrium (r^2=0.038) with the lead eSNP (rs13149209, $p_{expression}$=4.5 x 10^{-21}), a modest proxy for which (rs2085600; r^2=0.72) was also associated with FIadjBMI levels (p=3.5 x 10^{-06}). These results suggest that multiple independent eQTLs of those genes in adipose tissue are also associated with insulin levels and therefore further support our prioritisation of these genes. Genes at all the loci showing the pre-specified pattern of association were studied experimentally, with the exception of *KLF14*. We did not seek to experimentally validate the *KLF14* gene, because it has been studied previously and previous studies suggest complex aetiologic mechanisms at this locus, including a potential parent-of-origin effect.[3] In dedicated figures and tables, we report association criteria (**Supplementary Figure 11B**), selection flow-chart (**Supplementary Figure 11C**), association estimates at loci with an eQTL signal in subcutaneous adipocytes (**Supplementary Table 10**) and at the prioritised loci (**Supplementary Table 13**). Loci that did not meet the criteria were not prioritised for experimental validation of putative effector genes (**Supplementary Figure 11 and Supplementary Table 10**). Finally, on the basis of our hypothesis, we expected that the siRNA knockdown of the candidate causal gene would have effects on adipogenesis in the direction predicted by the adipose tissue eQTL.

Whole and regional body composition analysis

Before scanning, the DEXA system was calibrated according to the manufacturer's guidelines using a spine phantom made of calcium hydroxyapatite, embedded in a lucite block. The enCORE software automatically demarcates the regional boundaries. A protocol was established to manually refine these demarcations and all the images were processed by one trained researcher, who corrected the demarcations according to a standardized procedure. The arm region was derived by positioning a line from the crease of the axilla and through the glenohumeral. The trunk region includes the neck, chest, abdominal and pelvic areas. The leg region includes all of the area below the lines that form the lower borders of the trunk. The android region was defined as the area between the ribs and the pelvis, and is enclosed by the trunk region. This region is outlined by iliac crest and with a superior height equivalent to 20% of the distance from the top of the iliac crest to the base of the skull. The gynoid region includes the hips and upper thighs, and overlaps both the leg and trunk regions. The upper demarcation is below the top of the iliac crest at a distance of 1.5 times the android height. The total height of the gynoid region is two times the height of the android region. Estimates of overall and regional body fat, lean and bone masses were derived using the DEXA software. The software also uses an inbuilt algorithm to determine visceral adipose tissue (in grams) within the android region. The subcutaneous abdominal adipose tissue (in grams) was calculated as android fat mass minus visceral abdominal adipose tissue.

List of sources for eQTL analyses

A general overview of a subset of eQTL datasets interrogated in this study has been published.[4] Specific citations for all >100 datasets included in the current query are provided below.

Tissues (PubMed ID): blood cell related eQTL studies included fresh lymphocytes (17873875), fresh leukocytes (19966804), leukocyte samples in individuals with Celiac disease (19128478), whole blood samples (18344981, 21829388, 22692066, 23818875, 23359819, 23880221, 24013639, 23157493, 23715323, 24092820, 24314549, 24956270, 24592274, 24728292, 24740359, 25609184, 22563384, 25474530, 25816334, 25578447), lymphoblastoid cell lines (LCL) derived from asthmatic children (17873877, 23345460), HapMap LCL from 3 populations (17873874), a separate study on HapMap CEU LCL (18193047), additional LCL population samples (19644074, 22286170, 22941192, 23755361, 23995691, 25010687, 25951796), neutrophils (26151758, 26259071), CD19+ B cells (22446964), primary PHA-stimulated T cells (19644074, 23755361), CD4+ T cells (20833654), peripheral blood monocytes (19222302,20502693,22446964, 23300628, 25951796, 26019233), long non-coding RNAs in monocytes (25025429) and CD14+ monocytes before and after stimulation with LPS or interferon-gamma (24604202), CD11+ dendritic cells before and after Mycobacterium tuberculosis infection (22233810) and a separate study of dendritic cells before or after stimulation with LPS, influenza or interferon-beta (24604203). Micro-RNA QTLs (21691150, 26020509), DNase-I QTLs (22307276), histone acetylation QTLs (25799442), and ribosomal occupancy QTLs (25657249) were also queried for LCL. Splicing QTLs (25685889) and micro-RNA QTLs (25791433) were queried in whole blood. Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose (18344981, 21602305, 22941192, 23715323, 25578447), visceral fat (25578447) stomach (21602305), endometrial carcinomas (21226949), ER+ and ER- breast cancer tumor

cells (23374354), liver (18462017,21602305,21637794, 22006096, 24665059, 25578447), osteoblasts (19654370), intestine (23474282) and normal and cancerous colon (25079323, 25766683), skeletal muscle (24306210, 25578447), breast tissue (normal and cancer)(24388359, 22522925), lung (23209423, 23715323, 24307700, 23936167, 26102239), skin (21129726, 22941192, 23715323, 25951796), primary fibroblasts (19644074, 23755361, 24555846), sputum (21949713), pancreatic islet cells (25201977), prostate (25983244), rectal mucosa (25569741), arterial wall (25578447) and heart tissue from left ventricles (23715323, 24846176) and left and right atria (24177373). Micro-RNA QTLs were also queried for gluteal and abdominal adipose (22102887) and liver (23758991). Methylation QTLs were queried in pancreatic islet cells (25375650). Further mRNA and micro-RNA QTLs were queried from ER+ invasive breast cancer samples, colon-, kidney renal clear-, lung- and prostate-adenocarcinoma samples (24907074). Brain eQTL studies included brain cortex (19222302, 19361613, 22685416, 25609184, 25290266), cerebellar cortex (25174004), cerebellum (20485568, 22685416, 22212596, 22832957, 23622250), frontal cortex (20485568, 22832957, 25174004), gliomas (24607568), hippocampus (22832957, 25174004), inferior olivary nucleus (from medulla) (25174004), intralobular white matter (25174004), occiptal cortex (25174004), parietal lobe (22212596), pons (20485568), pre-frontal cortex (22031444, 20351726, 22832957, 23622250), putamen (at the level of anterior commussure) (25174004), substantia nigra (25174004), temporal cortex (20485568, 22685416, 22832957, 25174004), thalamus (22832957) and visual cortex (23622250).

Additional eQTL data was integrated from online sources including ScanDB, the Broad Institute's GTEx Portal, and the Pritchard Lab (eqtl.uchicago.edu). Cerebellum, parietal lobe and liver eQTL data was downloaded from ScanDB. Results for GTEx Analysis V4 for 13 tissues were downloaded from the GTEx Portal and then additionally filtered as described below (www.gtexportal.org: thyroid, leg skin [sun exposed], tibial nerve, aortic artery, tibial

artery, skeletal muscle, esophagus mucosa, esophagus muscularis, lung, heart (left ventricle), stomach, whole blood, and subcutaneous adipose [23715323]). Splicing QTL (sQTL) results generated with sQTLseeker with false discovery rate $p \leq 0.05$ were retained.

Supplementary Tables

Supplementary Table 1. Phenotypes, participating studies and maximum sample size.

Analysis	Phenotype	Participating studies (N; PMID)	Maximum sample size, N
Identification of 53 loci	FIadjBMI	MAGIC (N=108,557; PMID: 22885924, 22581228)	108,557
	HDL cholesterol	GLGC (N=188,577; PMID: 24097068)	188,577
	Triglycerides	GLGC (N=188,577; PMID: 24097068)	188,577
Validation of genetic scores	FIadjBMI	Fenland (N=4,694; this study)	4,694
	HDL cholesterol	Fenland (N=6,101; this study)	6,101
	Triglycerides	Fenland (N=6,101; this study)	6,101
	Insulin sensitivity index	MAGIC (N=4,769; PMID: 24699409)	4,769
	Insulin sensitivity	GENESIS (N=2,764; PMID: 25798622)	2,764
Association with intermediate traits	DEXA	Fenland (N=9,747; this study); EPIC-Norfolk (N=3,101; this study)	12,848
	Body fat percentage	UK Biobank (N=110,358; this study); Fenland (N=9,747; this study); EPIC-Norfolk (N=3,101; this study)	123,206
	BMI	GIANT (N=339,198; 25673413); UK Biobank (N=111,995; this study)	451,193
	Waist circumference	GIANT (N=244,419; 25673412); UK Biobank (N=112,180; this study)	356,599
	Hip circumference	GIANT (N=227,412; 25673412); UK Biobank (N=112,172; this study)	339,584
	Waist-to-hip ratio	GIANT (N=226,586; 25673412); UK Biobank (N=112,158; this study)	338,744
	Fasting plasma glucose	MAGIC (N=133,010; PMID: 22885924, 22581228)	133,010
	2 hour glucose	MAGIC (N=42,854; PMID: 22885924, 20081857)	42,854
	HbA1c	MAGIC (N=46,368; PMID: 20858683)	46,368
	Alanine aminotransferase and gamma glutamyl transferase	Fenland (N=10,330; this study)	10,330
Association with disease	Type 2 diabetes	DIAGRAM (cases=34,840; controls=114,981; PMID: 22885922); InterAct (cases=6,410; controls=8,947; this study); UK Biobank (cases=4,586; controls=106,430; this study)	45,836 cases 230,358 controls
	Coronary heart disease	CARDIoGRAMplusC4D (cases=63,746; controls=130,681; PMID: 21378988, 23202125, 21378990);	63,746 cases 130,681 controls
	FPLD1	Cambridge FPLD1 consortium (cases=37; this study); UKHLS (controls=5,296)	37 cases 5,296 controls

Supplementary Table 2. List of the 53 genomic regions associated with insulin resistance phenotypes.

SNP	Genomic coordinate	Alleles (effect / other)	Beta FIadjBMI per allele[a]	FIadjBMI p-value	Beta triglycerides per allele[b]	Triglycerides p-value	Beta HDL cholesterol per allele[b]	HDL cholesterol p-value	Locus name	Putative effector genes[c]
Loci previously implicated in insulin resistance										
rs4846565	Chr1:219722104	G / A	0.022	1.76E-09	0.014	0.00019	-0.013	0.00078	*RNU5F-1/LYPLAL1*	*RNU5F-1*[N]
rs10195252*	Chr2:165513091	T / C	0.029	1.26E-16	0.028	6.99E-15	-0.025	3.49E-11	*COBLL1/GRB14*	*COBLL1*[N], *GRB14*[E]
rs2943645*	Chr2:227099180	T / C	0.032	2.26E-19	0.028	3.76E-15	-0.032	4.16E-17	*IRS1*	*IRS1*[E, EA]
rs308971	Chr3:12116620	G / A	0.036	2.97E-11	0.021	3.51E-05	-0.016	0.0033	*SYN2/PPARG*	*SYN2*[N, E], *PPARG*[MF]
rs3822072*	Chr4:89741269	A / G	0.020	1.80E-08	0.018	5.74E-07	-0.025	4.06E-12	*FAM13A*	*FAM13A*[N, E, EA, D]
rs6822892	Chr4:157734675	A / G	0.024	2.58E-10	0.012	0.00084	-0.019	1.93E-07	*PDGFC*	*PDGFC*[N, E, EA, D]
rs4865796*	Chr5:53272664	A / G	0.025	2.16E-12	0.010	0.0030	-0.013	0.00030	*ARL15/FST*	*ARL15*[N], *FST*[EA]
rs459193*	Chr5:55806751	G / A	0.025	1.15E-10	0.018	1.31E-05	-0.024	8.10E-09	*ANKRD55*	*ANKRD55*[N]
rs2745353*	Chr6:127452935	T / C	0.019	4.10E-07	0.017	1.18E-06	-0.020	7.42E-10	*RSPO3*	*RSPO3*[N, E, EA]
rs731839*	Chr19:33899065	G / A	0.025	5.13E-12	0.022	2.65E-09	-0.022	3.44E-09	*PEPD*	*PEPD*[N, E]
Additional loci										
rs683135*	Chr1:39895460	A / G	0.014	0.00024	0.017	6.18E-07	-0.027	7.09E-12	*MACF1*	*MACF1*[N, NS, E, EA]
rs17386142	Chr1:50815783	C / T	0.024	0.00092	0.022	0.0033	-0.022	0.00060	*DMRTA2*	*DMRTA2*[N], *CDKN2C*[D]
rs11577194	Chr1:110500175	T / C	0.011	0.0025	0.011	0.0011	-0.019	1.34E-07	*CSF1*	*CSF1*[N]
rs9425291	Chr1:172312769	A / G	0.015	2.71E-05	0.016	1.9E-05	-0.014	0.00046	*DNM3*	*DNM3*[N, E], *PIGC*[E, EA]
rs2249105	Chr2:65287896	A / G	0.016	1.04E-05	0.016	2.35E-06	-0.016	0.00016	*CEP68*	*CEP68*[N, E, EA]
rs492400	Chr2:219349752	T / C	0.010	0.0038	0.018	2.25E-06	-0.011	0.0049	*USP37*	*USP37*[N, E], *ZNF142*[NS, E, EA]
rs3864041	Chr3:15185634	T / C	0.011	0.0038	0.009	0.0038	-0.013	0.00028	*COL6A4P1*	*COL6A4P1*[N]
rs295449*	Chr3:47375955	A / G	0.011	0.0020	0.014	0.00093	-0.019	0.00011	*KLHL18*	*KLHL18*[N, E], *SCAP*[NS, E], *SETD2*[E, D]
rs11130329*	Chr3:52896855	A / C	0.024	0.00051	0.020	0.0018	-0.024	0.0010	*TMEM110-MUSTN1*	*TMEM110-MUSTN1*[N]
rs9881942	Chr3:123082416	A / G	0.013	0.00014	0.010	0.0036	-0.015	4.79E-06	*ADCY5*	*ADCY5*[N]
rs645040*	Chr3:135926622	T / G	0.014	0.0012	0.029	1.83E-12	-0.031	1.53E-12	*MSL2*	*MSL2*[N, D]
rs2699429*	Chr4:3480136	C / T	0.011	0.0037	0.025	1.15E-11	-0.013	0.0042	*DOK7*	*DOK7*[N, E]
rs4976033	Chr5:67714246	G / A	0.015	0.00013	0.014	0.00020	-0.022	6.42E-08	*PIK3R1*	*PIK3R1*[N, MF, D]
rs6887914	Chr5:112711486	C / T	0.013	0.0037	0.014	0.0024	-0.017	0.00039	*MCC*	*MCC*[N]
rs1045241	Chr5:118729286	C / T	0.012	0.0020	0.015	4.06E-05	-0.014	0.00040	*TNFAIP8*	*TNFAIP8*[N, E, EA]
rs2434612	Chr5:158022041	G / A	0.016	0.00034	0.015	0.00025	-0.020	0.000015	*EBF1*	*EBF1*[N, D]
rs966544	Chr5:173350405	G / A	0.012	0.0010	0.016	1.63E-06	-0.013	0.0018	*CPEB4*	*CPEB4*[N, E]
rs12525532	Chr6:35004819	T / C	0.019	8.95E-08	0.011	0.0026	-0.015	0.000040	*ANKS1A*	*ANKS1A*[N, EA]
rs6937438*	Chr6:43815364	A / G	0.013	0.0011	0.014	0.00034	-0.019	1.94E-06	*LOC100132354*	*LOC100132354*[N]
rs9492443	Chr6:130398731	C / T	0.014	0.0004	0.016	7.43E-05	-0.013	0.0042	*L3MBTL3*	*L3MBTL3*[N, E, EA]
rs3861397*	Chr6:139828916	G / A	0.014	0.00011	0.024	1.08E-10	-0.024	8.40E-11	*LOC645434*	*LOC645434*[N], *CITED2*[D]
rs17169104	Chr7:15883727	G / C	0.020	1.52E-06	0.017	7.62E-05	-0.017	0.00028	*MEOX2*	*MEOX2*[N]

rs972283*	Chr7:130466854	G / A	0.022	4.41E-06	0.017	2.34E-07	-0.029	4.60E-16	*KLF14*	*KLF14*[N, E, EA]
rs2126259*	Chr8:9185146	T / C	0.041	3.30E-13	0.017	0.0020	-0.075	1.53E-42	*PPP1R3B*	*LOC157273*[N], *PPP1R3B*[E]
rs1011685*	Chr8:19830769	C / T	0.019	0.00098	0.168	6.12E-197	-0.156	8.65E-150	*LPL*	*LPL*[N, NS, E, D]
rs4738141	Chr8:72469742	G / A	0.014	0.0014	0.020	2.45E-05	-0.019	0.00030	*EYA1*	*EYA1*[N, EA], *LOC105375892*[D]
rs7005992*	Chr8:126528955	C / G	0.016	0.0014	0.021	5.87E-06	-0.016	0.0011	*TRIB1*	*TRIB1*[N, D]
rs498313	Chr9:78034169	A / G	0.013	0.00073	0.011	0.0026	-0.014	0.00033	*MIR548H3*	*MIR548H3*[N]
rs10995441*	Chr10:64869239	G / T	0.014	0.00085	0.017	1.19E-06	-0.018	0.00011	*NRBF2*	*NRBF2*[N, E]
rs11231693	Chr11:63862612	A / G	0.036	7.19E-07	0.030	0.00012	-0.029	0.000069	*MACROD1*	*MACROD1*[N]
rs17402950	Chr12:14571671	G / A	0.027	0.0047	0.032	0.0049	-0.034	0.0028	*ATF7IP*	*ATF7IP*[N]
rs718314	Chr12:26453283	G / A	0.017	3.65E-05	0.012	0.0015	-0.020	5.88E-06	*ITPR2*	*ITPR2*[N, E, D]
rs7973683*	Chr12:124449223	C / A	0.019	6.99E-07	0.025	4.67E-12	-0.029	5.26E-14	*CCDC92/DNAH10*	*CCDC92*[N, NS, E, EA], *DNAH10*[E, EA]
rs7323406	Chr13:111628195	A / G	0.015	0.0027	0.014	0.0044	-0.016	0.0032	*ANKRD10*	*ANKRD10*[N, E, D]
rs7176058	Chr15:39464167	A / G	0.013	0.0036	0.016	0.00094	-0.015	0.00028	*C15orf54*	*C15orf54*[N], *THBS1*[EA]
rs8032586	Chr15:73081067	C / T	0.019	0.0046	0.025	0.0010	-0.021	0.0030	*LOC100287559*	*LOC100287559*[N]
rs754814	Chr17:4657034	T / C	0.011	0.0042	0.011	0.0022	-0.013	0.0014	*ZMYND15*	*ZMYND15*[N, E]
rs7227237*	Chr18:47174679	C / T	0.017	0.0013	0.017	0.00088	-0.020	0.00041	*LIPG*	*LIPG*[N, E]
rs8101064*	Chr19:7293119	T / C	0.042	0.00062	0.069	1.91E-06	-0.066	0.000022	*INSR*	*INSR*[N, MF, D]
rs4804833*	Chr19:7970635	A / G	0.016	7.11E-06	0.015	9.90E-06	-0.022	9.89E-08	*MAP2K7*	*MAP2K7*[N, E, D]
rs4804311*	Chr19:8615589	A / G	0.019	0.0026	0.039	1.49E-09	-0.051	3.74E-14	*MYO1F*	*MYO1F*[N, E, EA]
rs6066149	Chr20:45602638	G / A	0.013	0.0019	0.018	5.22E-06	-0.010	0.0037	*EYA2*	*EYA2*[N]
rs132985*	Chr22:38563471	C / T	0.016	4.69E-06	0.022	6.65E-11	-0.015	0.000017	*PLA2G6*	*PLA2G6*[N], *MAFF*[E, EA, D]

Genomic coordinates refer to human genome build 37 (hg19). Beta coefficients are in standardised units, fasting insulin beta coefficients were standardised using the standard deviation in 8,917 participants of the Fenland study. The gene column reports the nearest gene and/or additional candidate effector genes at the locus.

*polymorphism within 500 kb of a lead SNP for HDL cholesterol or triglyceride levels reported by the Global Lipids Genetics Consortium (PubMed ID: 24097068).

a From up to 108,557 participants of the MAGIC consortium (PubMed ID: 22885924, 22581228)

b From up to 188,577 participants of the Global Lipids Genetics Consortium (PubMed ID: 24097068)

c Assigned on the basis of the following criteria: N, nearest gene; NS, nonsynonymous variant in linkage disequilibrium with lead SNP (r^2 >0.8); E, evidence of association with gene expression in surveyed eQTL repositories; AE, evidence of association with gene expression in subcutaneous adipose tissue; MF, monogenic insulin resistance forms associated with mutations in this gene; D, gene prioritised by DEPICT software as likely causal (significant p-value after accounting for false discovery rate). Relevant criteria are reported as superscript near each gene. Further details about methodology for the adjudication of these criteria are reported in the Online Methods sections dedicated to prioritisation of putative effector genes.

Abbreviations: SNP, single nucleotide polymorphism; FIadjBMI, fasting insulin adjusted for body mass index; HDL, high-density lipoprotein cholesterol.

Supplementary Table 3. Association with type 2 diabetes of the 53-polymorphism genetic score in analyses stratified by sex or body mass index. Results are scaled per 4.5 alleles, i.e. a standard deviation of genetic risk score. Results are from the EPIC-InterAct and the UK Biobank studies.

Stratum	Participants, type 2 diabetes cases / non-cases	OR (95% CI)	p-value	p-interaction
Sex-stratified analysis				
Men	6,588 / 52,887	1.12 (1.09 – 1.16)	4.13E-14	0.90
Women	5,418 / 62,811	1.12 (1.08 – 1.16)	1.48E-11	
*BMI-stratified analysis**				
BMI < 25	1,298 / 39,930	1.16 (1.09 – 1.23)	3.71E-06	0.16
BMI ≥ 25 and BMI < 30	4,663 / 49,317	1.17 (1.13 – 1.22)	1.73E-16	
BMI ≥ 30	5,945 / 26,090	1.12 (1.08 – 1.16)	7.86E-10	

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index.
*Pairwise category heterogeneity tests: lean vs overweight: p=0.73; lean vs obese: p=0.31; overweight vs obese, p=0.061.

Supplementary Table 4. Associations of lead single nucleotide polymorphisms at the 53 loci with glycaemic, anthropometric traits and disease endpoints.
(see Supplementary Table Excel file)

Supplementary Table 5. Single nucleotide polymorphisms associated with higher risk of type 2 diabetes (45,836 cases 230,358 controls) and of coronary heart disease (63,746 cases 130,681 controls).

SNP	Locus name	Per allele OR type 2 diabetes (95% CI)	p-value	Per allele OR coronary heart disease (95% CI)	p-value
rs2943645	*IRS1*	1.09 (1.07-1.11)	1.1E-17	1.03 (1.01-1.05)	0.0010
rs6822892	*PDGFC*	1.04 (1.02-1.07)	2.1E-05	1.02 (1.00-1.04)	0.035
rs459193	*ANKRD55*	1.08 (1.06-1.11)	8.0E-13	1.02 (1.00-1.04)	0.025
rs4976033	*PIK3R1*	1.03 (1.01-1.05)	0.0022	1.07 (1.02-1.12)	0.0080
rs9492443	*L3MBTL3*	1.05 (1.03-1.07)	3.1E-05	1.02 (1.00-1.04)	0.028
rs3861397	*LOC645434*	1.03 (1.01-1.05)	0.0026	1.02 (1.00-1.04)	0.037
rs972283	*KLF14*	1.04 (1.02-1.06)	1.2E-05	1.03 (1.01-1.04)	0.0037
rs1011685	*LPL*	1.07 (1.04-1.10)	3.4E-05	1.09 (1.05-1.13)	8.7E-06
rs7973683	*CCDC92 / DNAH10*	1.03 (1.01-1.05)	0.0037	1.02 (1.00-1.04)	0.019
rs8101064	*INSR*	1.08 (1.01-1.16)	0.020	1.13 (1.02-1.25)	0.016
rs731839	*PEPD*	1.04 (1.02-1.06)	0.00021	1.03 (1.01-1.04)	0.0090

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Supplementary Table 6. Association of the genetic scores with alanine aminotransferase and gamma glutamyl transferase in 10,330 participants of the Fenland study.

Exposure	Outcome	Beta per SD of genetic score in SDs of biomarker	SE	P-Value
53-SNP score	Alanine aminotransferase	0.054	0.009	1.37E-09
43-SNP score		0.049	0.010	1.83E-06
53-SNP score	Gamma glutamyl transferase	0.054	0.009	1.04E-09
43-SNP score		0.045	0.010	6.39E-06

Abbreviations: SNP, single nucleotide polymorphism; SD, standard deviation; SE, standard error. Beta coefficients are in standardised units per SD of genetic score (4.5 alleles).

Supplementary Table 7. European Genome-Phenome Archive Study, Dataset and Sample IDs for the raw, whole exome sequence data for 9 FPLD1 individuals and their family members.

Family ID	Sample	EGA Study ID	EGA Dataset ID	EGA Sample ID
1	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015630
2	Proband	EGAS00001000025	EGAD00001000380	EGAN00001001252
2	Mother	EGAS00001000025	EGAD00001000380	EGAN00001001832
2	Father	EGAS00001000025	EGAD00001000380	EGAN00001001825
3	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015627
4	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015629
5	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015628
6	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015631
7	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015624
7	Father	EGAS00001000130	EGAD00001000419	EGAN00001015625
8	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015633
8	Father	EGAS00001000130	EGAD00001000419	EGAN00001015651
8	Sister 1	EGAS00001000130	EGAD00001000419	EGAN00001015652
8	Sister 2	EGAS00001000130	EGAD00001000419	EGAN00001015653
8	Sister 3	EGAS00001000130	EGAD00001000419	EGAN00001015654
8	Sister 4	EGAS00001000130	EGAD00001000419	EGAN00001015656
8	Brother	EGAS00001000130	EGAD00001000419	EGAN00001015655
9	Proband	EGAS00001000130	EGAD00001000419	EGAN00001015632

Supplementary Table 8. Characteristics of women with FPLD1 compared with obese women of the Fenland study. The *phenotype comparison* column summarises the results of comparisons between FPLD1 women and obese (BMI ≥30) Fenland study women for a given clinical variable (Student's t-test), whereas the *genetic score association pattern* column summarises the association of the 53-SNP genetic score with a given phenotype in our genetic association analyses (see Figure 1A and Supplementary Table 6).

	FPLD1 women			Fenland - obese women			Phenotype comparison, FPLD1 vs Fenland obese women, direction of association (p-value)[a]	Pattern of association of genetic score, direction of association (p-value)[a]
Variable, units	**N**	**Mean (SD)**	**Median (range)**	**N**	**Mean (SD)**	**Median (range)**		
Age, years	37	49 (12)	48 (22 - 75)	1171	49 (7)	50 (29 - 64)	N/A	N/A
Body mass index, kg/m^2	35	33 (4)	33 (26 - 47)	1171	35 (5)	33 (30 - 60)	N/A*	↓ (p=4.5E-08)
Waist circumference, cm	27	111 (12)	112 (78 - 143)	1170	103 (10)	102 (79 - 154)	↑ (p=4.6E-05)	↑ (p=0.0028)
Hip circumference, cm	27	108 (12)	108 (84 - 147)	1163	118 (10)	116 (96 - 178)	↓ (p=3.7E-07)	↓ (p=2.3E-34)
Waist-to-hip ratio	27	1.04 (0.09)	1.02 (0.91 - 1.22)	1163	0.87 (0.07)	0.87 (0.63 - 1.17)	↑ (p=3.1E-33)	↑ (p=3.3E-88)
Fasting plasma glucose, mmol/L	33	11 (5)	10.7 (4.9 - 21.9)	1163	5.0 (0.7)	4.9 (3.4 - 12.3)	↑ (p=8.5E-161)	↑ (p=2.9E-10)
HbA1c, %	35	9 (2)	8.4 (4.9 - 13.2)	789	5.6 (0.5)	5.6 (3.9 - 9.7)	↑ (p=6.9E-140)	↑ (p=2.3E-06)
Fasting insulin, pmol/L	29	208 (230)	151 (7.3 - 1210)	987	71.0 (49.4)	60.4 (2.6 - 702.0)	↑ (p=6.0E-30)	↑**
Triglycerides, mmol/L	34	2.8 (2.1)	2.6 (0.6 - 12.6)	1168	1.3 (0.7)	1.2 (0.2 - 7.4)	↑ (p=1.5E-27)	↑**
HDL cholesterol, mmol/L	34	1 (0.3)	1 (0.5- 2)	1168	1.5 (0.3)	1.4 (0.6 - 3.4)	↓ (p=5.4E-21)	↓**
Alanine aminotransferase, U/L	34	39 (25)	31 (13 - 126)	1168	29 (17)	25 (6 - 236)	↑ (p=0.00090)	↑ (p=1.4E-09)
Gamma glutamyl transferase, U/L	34	67 (51)	50 (12 - 212)	1168	35 (32)	27 (7 - 530)	↑ (p=2.2E-08)	↑ (p=1.0E-09)

a ↑ indicates associations (p<0.05) with higher levels of a given phenotype in FPLD1 (compared with obese women from the Fenland study) or for a greater number of risk alleles of the genetic score; ↓ indicates an association (p<0.05) with lower levels.

Abbreviations: N, number of participants; SD, standard deviation; FPLD1, familial partial lipodystrophy type 1; N/A not assessed. *matching variable **not reported, genetic score selection variable

Supplementary Table 9. Associations at the 53 loci with gene expression from eQTL repositories of multiple tissues.
(see Supplementary Table Excel file)

Supplementary Table 10. Associations of lead polymorphisms at the 53 loci in subcutaneous adipose tissue eQTL datasets.
(see Supplementary Table Excel file)

Supplementary Table 11. DEPICT annotation of putative effector genes.
(see Supplementary Table Excel file)

Supplementary Table 12. Associations at the *PIK3R1* locus. Comparison between phenotypic association patterns of the common single nucleotide polymorphism rs4976033 (effect allele: G; minor allele: G; minor allele frequency: 49.6%) at the *PIK3R1* locus (this study) and of rare loss-of-function mutations in *PIK3R1* (literature).

Phenotype	N of individuals or N of cases / N of controls	Beta in SDs or ln(OR) per G allele of rs4976033	P-Value	Association of rare loss of function mutations	Pubmed ID for rare loss-of-function mutation association
Height	358,297	-0.003 (0.0027)	0.32	Reduced	26497935; 23810378; 23810379; 23810382
Body mass index	447,441	-0.006 (0.0026)	0.02	Reduced*	26497935; 23810378; 23810379; 23810382
Body fat percentage	123,206	-0.020 (0.0033)	3.04E-09	Lipoatrophy or lipodistrophy*	26497935; 23810378; 23810379; 23810382
Waist-to-hip circumference	337,859	-0.003 (0.0027)	0.27	N/A	
LDL cholesterol	172,987	-0.001 (0.0040)	0.87	Normal*	23810379
HDL cholesterol	187,060	-0.021 (0.0037)	6.42E-08	Normal°	23810379
Triglycerides	177,755	0.0141 (0.0036)	0.00020	Normal°	26497935
Fasting glucose	133,010	0.002 (0.0023)	0.39	Raised°	23810379
2 hour glucose	42,854	0.008 (0.0120)	0.52	N/A	
Fasting insulin adjusted BMI	108,557	0.009 (0.0023)	0.00013	Insulin resistance*	26497935; 23810378
Type 2 diabetes	45,836 cases 230,358 controls	1.03 (1.01-1.05)	0.0022	High prevalence of early onset type 2 diabetes*	26497935; 23810378; 23810379
Coronary heart disease	8,660 cases 47,121 controls	1.07 (1.02-1.12)	0.0080	N/A	

Height data were from a meta-analysis of UK Biobank and GIANT data.
*Alignment between phenotypes associated with common and rare variants
°Lack of alignment between phenotypes associated with common and rare variants

Supplementary Table 13. Association estimates at loci selected for experimental validation of putative effector genes in cellular adipogenesis models.

SNP genomic coordinates	Insulin-raising / other allele	Putative effector gene	Direction of association with expression of the putative effector gene in subcutaneous adipocytes	p-value for expression of putative effector gene in subcutaneous adipocytes	Beta for hip circumference in standardised units (p-value)	OR of type 2 diabetes (p-value)
rs2943645 Chr2:227099180	T / C	*IRS1*	Lower expression	5.2E-09	-0.014 (9.4E-07)	1.09 (1.1E-17)
rs7973683 Chr12:124449223	C / A	*CCDC92*	Lower expression	2.1E-29	-0.014 (1.3E-06)	1.03 (3.7E-03)
rs7973683 Chr12:124449223	C / A	*DNAH10*	Lower expression	1.9E-08	-0.014 (1.3E-06)	1.03 (3.7E-03)
rs9492443 Chr6:130398731	C / T	*L3MBTL3*	Lower expression	9.1E-17	-0.021 (1.2E-11)	1.05 (3.1E-05)
rs3822072 Chr4:89741269	A / G	*FAM13A*	Higher expression	7.6E-12	-0.017 (5.5E-10)	1.04 (1.6E-05)

Genomic coordinates refer to build 37 (hg19). All association results are aligned to the insulin-raising (risk) allele. The co-localisation between association signals for gene expression in subcutaneous adipocytes and associations with fasting insulin are discussed in the Supplementary Note. Hip circumference association results are from a meta-analysis of the UK Biobank study and of the GIANT consortium. Type 2 diabetes association results are from a meta-analysis of DIAGRAM, InterAct and UK Biobank.

Supplementary Table 14. Characteristics of the participants with individual-level genotype data included in this study.

Study	Fenland	EPIC-Norfolk	InterAct	UK Biobank	UKHLS
Country	United Kingdom	United Kingdom	Multiple European countries	United Kingdom	United Kingdom
Participants	10,351	9150	15357	111016	5296
Cases / Controls	N/A	N/A	6410 / 8947	4586 / 106430	N/A
Age	48 (7)	58 (9)	53 (9)	57 (8)	53 (16)
Female sex, N (%)	5506 (53)	5015 (55)	9162 (60)	58390 (53)	5296 (100)
Genotyping chip	Affymetrix genome-Wide Human SNP Array 5.0 and Affymetrix UK Biobank Axiom Array	Affymetrix UK Biobank Axiom Array	Illumina 660w quad and Illumina CoreExome chip	Affymetrix UK Biobank Axiom Array	Illumina CoreExome Chip
Imputation panel	1000 Genomes Phase 1v3 and Phase 3	1000 Genomes Phase 3	1000 Genomes Phase 1v3	1000 Genomes Phase 3 plus UK10K	1000 Genomes Phase 3

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