

1 **Genome-wide association study of a lipedema phenotype among women in the UK Biobank**
2 **identifies multiple genetic risk factors**

3 **Short Title:** Genome-wide association study of lipedema

4 Yann C. Klimentidis ^{1,2*}, Zhao Chen ¹, Manuel L. Gonzalez-Garay ³, Dionysios Grigoriadis ⁴,
5 Ege Sackey ⁴, Alan Pittman ⁴, Pia Ostergaard ⁴, Karen L. Herbst ^{5,6}

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7 ¹ Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public
8 Health, University of Arizona, Tucson, AZ, USA

9 ² BIO5 Institute, University of Arizona, AZ, USA

10 ³ College of Medicine, University of Arizona, Tucson, AZ, USA

11 ⁴ Genetics Research Centre, Molecular and Clinical Sciences Institute, St George's University of
12 London, London, UK.

13 ⁵ TREAT Program, College of Medicine, University of Arizona, Tucson, AZ, USA

14 ⁶ Total Lipedema Care, 240 South La Cienega Blvd, Beverly Hills, CA, USA

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16 * **Corresponding Author:** Department of Epidemiology and Biostatistics, Mel and Enid
17 Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, USA, 85724, 520-
18 621-0147, yann@email.arizona.edu

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20

21 **ABSTRACT**

22 Lipedema is a common disorder characterized by excessive deposition of subcutaneous adipose
23 tissue (SAT) in the legs, hips, and buttocks, mainly occurring in adult women. Although it
24 appears to be heritable, no specific genes have yet been identified. To identify potential genetic
25 risk factors for lipedema, we used bioelectrical impedance analysis and anthropometric data from
26 the UK Biobank to identify women with and without a lipedema phenotype. Specifically, we
27 identified women with both a high percentage of fat in the lower limbs and a relatively small
28 waist, adjusting for hip circumference. We performed a genome-wide association study (GWAS)
29 for this phenotype, and performed multiple sensitivity GWAS. In an independent case/control
30 lipedema study, we attempted to replicate our top hits. We identified 18 significant loci ($p < 5 \times$
31 10^{-9}), several of which have previously been identified in GWAS of waist-to-hip ratio with larger
32 effects in women. Two loci (*VEGFA* and *GRB14-COBL1*) were significantly associated with
33 lipedema in the independent replication study. Follow-up analyses suggest an enrichment of
34 genes expressed in blood vessels and adipose tissue, among other tissues. Our findings provide a
35 starting point towards better understanding the genetic and physiological basis for lipedema.

36

37 **Keywords:** lipedema, lipoedema, genetic, genome-wide association study, body fat distribution

38 **INTRODUCTION**

39 Lipedema has been recognized since the 1940s as a condition occurring mainly in women
40 and is characterized by the bilateral enlargement of the lower limbs which in many instances
41 exaggerate the female form [1]. It can be debilitating with respect to resulting pain and impaired
42 mobility [2].

43 There are very few prevalence estimates for lipedema. A prevalence of 11% was
44 observed in a sample of women from a lymphedema clinic in Germany [3], and a prevalence of
45 9.7% was observed in a small sample of professional German women [4]. Family history has
46 been reported, suggesting that lipedema is heritable [1,5,6]. Further evidence supporting a
47 genetic contribution is that lipedema subcutaneous adipose tissue (SAT) is highly resistant to
48 lifestyle changes such as diet and exercise, occurs after menarche, and occurs nearly exclusively
49 in women. These lines of evidence suggest that environmental (non-genetic) factors may not play
50 a predominant role.

51 Although lipedema does appear to be heritable, individual genetic loci associated with it
52 have yet to be found. Identifying such loci will provide much-needed insight into the
53 pathophysiology of lipedema, and potentially enable the development of therapeutics, and the
54 identification of individuals at high risk. However, since lipedema is rarely diagnosed, and is not
55 widely recognized, there are currently no large collections of diagnosed lipedema cases with
56 whom genetic risk factors could be identified.

57 Here, we used body fat percentage and anthropometric measurements from the UK
58 Biobank to classify women into those that appear to have a lipedema phenotype, and those
59 without, in an effort to identify genetic risk factors for lipedema. Given the lack of evidence thus

60 far for a single highly penetrant gene for lipedema [5], we hypothesized that multiple individual
61 genetic variants across the genome are associated with the lipedema phenotype among adult
62 women.

63

64 **METHODS**

65 *UK Biobank*

66 The UK Biobank is a prospective cohort study of approximately 500,000 adults living in
67 the UK, aged 39 to 70 [7,8]. Participants were measured for a variety of traits and diseases from
68 2006 to 2010 at 22 centers across the UK. Only women were included in this study, and to
69 minimize the potential confounding effects of ancestry, only women self-identifying European
70 ancestry were included. All participants gave written informed consent, and ethical approval was
71 obtained from the North West Multicentre Research Ethics Committee, the National Information
72 Governance Board for Health & Social Care, and the Community Health Index Advisory Group.

73

74 *Phenotypic measurements*

75 We used bioelectrical impedance analysis (BIA) data obtained using a Tanita BC418MA
76 segmental body composition analyzer. Women who were pregnant, an amputee, wheelchair
77 bound, unable to stand, or using a pacemaker were not measured (i.e. excluded). We excluded
78 women whose left leg fat % was 30% greater or lesser than their right leg fat %, to exclude those
79 with obvious uni-lateral enlargement of the legs, based on a scatterplot visualization. We
80 averaged the left and right leg fat percentages and used this average in all subsequent analyses.
81 The UK Biobank specify that hip and waist circumferences measurements were obtained in

82 centimeters (cm) with a Seca 200 cm tape. The tape was first passed around the smallest part of
83 the trunk (natural indent). If no natural indent could be found, the waist measurement was taken
84 at the level of the umbilicus. The hip circumference was measured at the widest part of the hips.

85

86 *Lipedema definition*

87 We defined lipedema first as having a relatively high leg fat % along with a relatively
88 small waist circumference. We first obtained the residuals from a linear regression in which the
89 average of the left and right leg fat percentages was the outcome, and the independent variables
90 were height, hip circumference, age, and recruitment center. These covariates were included as
91 most leg fat is likely to be located on the upper end of the leg (by the hip), and it is therefore
92 important to take into account the anthropometric characteristics of hip size and overall body size
93 in order to minimize confounding from these characteristics. Furthermore, since lipedema
94 usually involves high levels of fat deposition throughout the leg, and not only at the hip, these
95 adjustments helps us to identify women with a high fat percentage throughout the leg, and not
96 just at the hip level. We then obtained the residuals from a linear regression in which waist
97 circumference was the outcome, and the independent variables were the same as those listed
98 above for leg fat percentage. Women were deemed to be lipedema cases if they were in the >65th
99 percentile of the leg fat percentage residual and in the <51.3rd percentile of the waist
100 circumference residual (these cutoffs were chosen to achieve a prevalence of 10%). Controls
101 were individuals with <=45th leg fat residual percentile residual or those in the >=71.3rd waist
102 circumference residual percentile. The resulting “buffer zone” of individuals was to exclude
103 potential false positives or false negatives. We also considered as a sensitivity analysis a
104 lipedema phenotype at an assumed 5% prevalence. In this case, women were deemed to be

105 lipedema cases if they were in the $>75^{\text{th}}$ percentile of the leg fat percentage residual and in the
106 $<46.7^{\text{th}}$ percentile of the waist circumference residual, and controls were individuals with $\leq 65^{\text{th}}$
107 leg fat residual percentile residual or those in the $\geq 56.7^{\text{th}}$ waist circumference residual
108 percentile.

109

110 *Leg pain*

111 Since leg pain is an associated feature of lipedema, we used responses to the following
112 question asked at the baseline exam at each UK Biobank recruitment center: “Do you get a pain
113 in either leg on walking?” This question was administered to a subset (~40%) of UK Biobank
114 participants, as it was introduced by the UK Biobank towards the end of recruitment. A lack of
115 an affirmative response to this question was required to define a patient as a control.

116

117 *Genetic data*

118 The vast majority of UK Biobank participants were genotyped with the Affymetrix UK
119 Biobank Axiom Array (Santa Clara, USA). Approximately 10% of participants were genotyped
120 with the Affymetrix UK BiLEVE Axiom Array. Tens of millions of additional SNP genotypes
121 were obtained through imputation using the Haplotype Reference Consortium [9] and UK10K
122 [10] haplotype data as references. Principal component analysis was performed by the UK
123 Biobank team, using fastPCA software on a set of 147,604 high-quality directly genotyped
124 markers. Individuals with an unusually high heterozygosity rate, a $>5\%$ missing rate, or a
125 mismatch between self-reported and genetically-inferred sex were excluded. These and other
126 details regarding the genotyping, imputation, and QC procedures are available elsewhere [8].

127 SNPs not in Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$), with a high missingness ($> 1.5\%$), a low
128 minor allele frequency ($< 0.1\%$), or low imputation quality ($\text{info} < 0.4$) were excluded. A total of
129 16.8 million SNPs were available for analysis, including those on the X chromosome.

130

131 *Statistical analyses*

132 We tested the association between each SNP with case-control status using linear
133 regression implemented in the BOLT-LMM software [11,12], which implements a linear mixed
134 model regression, including SNPs other than the one tested as random effects, and thereby
135 correcting for population stratification and relatedness. Since BOLT-LMM implements a linear
136 regression model, the effect size estimates for case-control outcomes are unreliable. As
137 previously done in other studies [13,14], we therefore estimated the effect sizes of the genome-
138 wide significant ($p < 5 \times 10^{-9}$) SNPs with logistic regression in R [15]. We included age, hip
139 circumference, recruitment center, genotyping platform, and the first 10 principal components
140 (PCs) as covariates in both the BOLT-LMM and the logistic regression SNP association models.
141 Hip circumference was included to account for overall body size and for proportion of fat in
142 thighs. We performed multiple sensitivity analyses. First, we considered a model without any
143 adjustment for hip circumference. Since there is considerable uncertainty regarding the actual
144 prevalence of lipedema, we also considered a prevalence of 5% instead of 10%. We also
145 performed an analysis only in women with BMI < 30 to avoid obesity complicating the analyses.
146 Finally, we considered analyses in which we added into our case definition an affirmative
147 response regarding self-reported leg pain. SNPs were considered genome-wide significant if $p <$
148 5×10^{-9} . This threshold was chosen instead of the more typical threshold because we performed
149 multiple GWAS analyses, and to optimize our ability to replicate findings in our much smaller

150 replication dataset. To estimate SNP-based heritability, and to estimate genetic correlations of
151 our lipedema phenotype with a wide range of other human traits and diseases, including other
152 body composition and cardiometabolic traits and diseases, we used the online implementation
153 (<http://ldsc.broadinstitute.org/>) of the LD score regression method [16–18]. Details of each
154 phenotype and GWAS used in these genetic correlations can be found on the aforementioned
155 website. We examined the LD-score regression intercept, as well as the Q-Q plot, to assess
156 genomic inflation. We tested the association of each of the significant SNPs identified with
157 potentially relevant anthropometric measures among all UK Biobank women of European
158 ancestry, using linear regression, including age, chip, 10 PCs, and center as covariates.

159 Gene expression enrichment patterns across different tissues were examined through the
160 web-based platform, Functional Mapping and Annotation of Genome-Wide Association Studies
161 (FUMA GWAS) [19], that uses data from GTEx v7 [20], and the MAGMA gene-based analysis
162 for identification of associated genes [21]. Briefly, the MAGMA gene-based analysis uses all the
163 SNPs in a gene as the unit of analysis to test the association of each gene across the genome with
164 the phenotype. A genome-wide significance threshold of $p < 2.6 \times 10^{-6}$ was used. We also used
165 the FUMA GWAS platform to identify eQTL from GTEx v7 and from a large blood eQTL study
166 [22], by interrogating all top SNPs, and all SNPs in LD ($r^2 > 0.6$) of top SNPs.

167 Pathway over-representation analysis was performed for the unique genes identified by
168 the aforementioned eQTL analysis, using the SOAP/WSDL interface of the
169 ConsensusPathwayDB-human. ConsensusPathwayDB is a project of the Max Planck Institute for
170 Molecular Genetics that integrates multiple interaction networks [23,24].

171

172 *Replication study*

173 We sought to replicate our top findings in a case/control study of clinically diagnosed
174 lipedema cases, as previously described [25]. Briefly, 130 lipedema cases recruited from two
175 specialist UK clinics at St George’s University Hospital NHS Trust and the University Hospitals
176 of Derby and Burton NHS Trust were genotyped with Illumina Infinium microarrays. Unaffected
177 females (N=5,848) enrolled in the Understanding Society UK study [26] genotyped with
178 Illumina HumanCoreExome-12 (v1.0) were selected as the control group to the replication
179 cohort controls (European Genome-phenome Archive ID: EGAD00010000890). Assuming a
180 SNP with 50% allele frequency and OR of 1.07 (in line with our findings in UK Biobank), for a
181 case-control study to have 80% power to detect an association with a nominally significant p-
182 value ($p < 0.05$), would require a sample size of $>12,000$ cases and controls. Therefore, based on
183 the study design, sample size, phenotype definitions, and effect sizes found in the discovery
184 sample, we are highly underpowered to detect a statistically significant effect in the UK
185 Lipoedema study, given the much smaller sample size. However, given the limitations of the
186 phenotype definition, as well as other factors in the UK Biobank study, those effect sizes are
187 likely attenuated compared to the effect sizes we may observe in a study with a more accurate
188 case-control definition. Details of the ‘UK Lipoedema’ cohort genotyping can be found
189 elsewhere [25]. Imputation was performed by aligning variants to the 1,000 Genomes [27]
190 reference and the normalized variants were imputed using the Michigan Imputation server [28].
191 Post imputation quality controls were used to remove low-quality ($r^2 \leq 0.8$) imputed variants
192 before further analyses. The association analysis was performed using a univariate linear mixed
193 model, implemented in GEMMA software (version 0.98.1) [29]. The p-value distribution was
194 assessed using a Quantile-Quantile (Q-Q) plot, and there was no inflation effect observed on the

195 association analysis. Given the 14 statistically significant top hits that we were able to test in the
196 replication study, a significant replication was determined based on a p -value <0.0036 , according
197 to a Bonferroni correction.

198

199 **RESULTS**

200 *GWAS*

201 In this study, we defined lipedema cases and controls based on leg fat mass and waist
202 circumference. The characteristics of the different case ($n=24,450$) and control ($n=165,227$)
203 groups are shown in Table 1. The inferred lipedema cases tend to have a higher leg fat % and a
204 lower waist-to-hip ratio (WHR).

205 Cases are shown in green in Figure 1 with respect to unadjusted waist circumference and
206 unadjusted leg fat %, and in Supplementary Figure 1 with respect to the residualized values of
207 these variables that were used to determine cases and controls. The LD-score regression intercept
208 (<1.02) and Q-Q plot (Supplementary Figure 2) from the genome-wide association study suggest
209 little evidence of systematic inflation of effect sizes, beyond the polygenic signal associated with
210 the lipedema phenotype. SNP-based heritability for our main model was 5.13% (see
211 Supplementary Table 1).

212 We find 18 loci significantly associated with the primary lipedema phenotype as defined
213 in this study (see Figure 2 and Table 2). Associations of these 18 significant SNPs with relevant
214 anthropometric traits among all UK Biobank European-ancestry women are shown in
215 Supplementary Table 2. In analyses not adjusting for hip circumference, the results are relatively
216 similar, with generally smaller magnitudes of association (see Supplementary Table 3 and

217 Supplementary Figure 3). The same is observed for the other sensitivity analyses (see
218 Supplementary Figures 4-5). The addition of leg pain as a criterion for cases (n=1,724 cases;
219 165,227 controls) resulted in no genome-wide significant loci (Supplementary Figure 6). Only
220 the *LYPLALI* locus exhibited a ‘suggestive level’ of significance ($p=4.5 \times 10^{-6}$, see
221 Supplementary Table 4). The gene-based analysis, in which the collection of SNPs in each gene
222 is taken as the unit of analysis instead of each SNP individually, identified 72 genes associated
223 with lipedema (Supplementary Figure 7 and Supplementary Table 5).

224

225 *Genetic correlations with other traits and diseases*

226 We observed significant positive genetic correlations of the lipedema phenotype with
227 body fat and leptin levels (Supplementary Figure 8). We also find nominally significant positive
228 genetic correlations with hip circumference, primary biliary cirrhosis and BMI. We find
229 nominally significant negative genetic correlations with WHR, age at first birth, forced vital
230 capacity, birth weight, and age at menopause (Supplementary Figure 8)

231

232 *Associations of loci with tissue-specific gene expression levels*

233 Genes implicated by eQTL analysis, and which may provide insight into the genetic
234 regulation of the lipedema phenotype, vary by locus and by tissue. For example, the *RSPO3* top
235 SNP, rs72959041, is associated with the expression level of the *RSPO3* gene in subcutaneous
236 adipose tissue, as are *ZNF664* with the rs11057418 SNP, and *TIPARP* with the rs4680338 SNP
237 (Supplementary Table 6). The top SNP at the *GRB14-COBLL1* locus is associated with
238 expression of several genes in various tissues. A list of these gene expression patterns for the

239 significant (FDR<0.05) eQTLs of the top SNPs can be found in Supplementary Table 6. Upon
240 expanding this analysis to all SNPs in LD ($r^2>0.6$) with the top SNPs, a more extensive list of
241 genes and tissues was identified (Supplementary Table 7). A list of genes sorted by relevant and
242 highly represented tissues is shown in Supplementary Table 8. Tissue enrichment analyses based
243 on the gene-based (MAGMA) analysis identify arterial blood vessels as the main tissues where
244 these genes may exert their actions (Supplementary Figure 9).

245

246 *Pathway analysis*

247 Our pathway analysis results show significant enrichment for multiple pathways and
248 Gene Ontology Terms (Supplementary Table 9). Noteworthy are: a) the EGFR1 signaling
249 pathway, a pathway that induces growth, differentiation, migration, adhesion and cell survival
250 through multiple hormone interactions [30]; and b) GO:0003785 actin monomer binding, a
251 regulator of actin cytoskeleton dynamics in cells [31].

252

253 *Replication*

254 In a replication cohort of phenotyped lipedema patients from the ‘UK Lipoedema’ study,
255 we were able to obtain results for 14 out of 18 locus lead variants (see Table 2). We identified
256 two statistically significant associations also showing the same direction of effect as in UK
257 Biobank: near *VEGFA* ($p=5.0 \times 10^{-4}$) and near *GRB14-COBL1* ($p=2.3 \times 10^{-3}$). Two nominally
258 significant loci ($p<0.05$; *ADAMTS9* and *LYPLAL1*) were also directionally consistent.

259

260 **DISCUSSION**

261 Using an inferred lipedema phenotype based on high leg fat % and small waist in the UK
262 Biobank, we performed the first GWAS of a lipedema phenotype and identified 18 loci across
263 the genome. Two of these loci (*VEGFA* and *GRB14-COBLL1*) were significantly associated with
264 lipedema in an independent case-control study including clinically diagnosed lipedema cases.

265 Loci in/near *RSPO3*, *GRB14-COBLL1*, *ZNF664-FAM101A* (near *CCDC92*), *VEGFA*,
266 *ADAMTS9*, *LYPLALI*, *ANKRD55-MAP3K1* have previously been found to be associated with
267 WHR, and importantly, to exhibit stronger effects in women than in men [32–34]. Importantly,
268 we show that these loci are associated with leg fat % independently of hip circumference,
269 indicating that these associations are not predominately driven by hip circumference or fat
270 around the hip, but rather fat throughout the lower limbs.

271 Pain in the lower limbs is a common complaint among lipedema patients [2] and when
272 including pain as a criterion in the GWAS, only one of the loci, rs749853052 near *LYPLALI*,
273 exhibited a ‘suggestive level’ of significance. We strongly suspect that the reduced sample size
274 when incorporating leg pain information resulted in reduced statistical power to detect
275 significantly associated loci. The *LYPLALI* variant is over 250 kb downstream of the *LYPLALI*
276 (lysophospholipase-like 1) gene. The function of this locus is still unknown, although it may act
277 as a triglyceride lipase or lysophospholipase [35,36]. This locus has been associated with WHR,
278 with a stronger effect in women than in men [32,37,38]. It has also been associated with a
279 “favorable adiposity” or gynoid phenotype [39], and with non-alcoholic fatty liver disease [40].
280 It has also been found to be more abundantly expressed in the subcutaneous adipose tissue of
281 obese compared to lean individuals [41], potentially making it an interesting association to
282 explore in the context of lipedema.

283 One of the novel loci identified on chromosome 5 is located in the *LINC01184* non-
284 coding gene, and just upstream of the *SLC12A2* gene. Our eQTL analysis revealed that the top
285 SNP at this locus is associated with increased expression of the fibrillin 2 (*FBN2*) gene in the
286 thyroid. The *FBN2* gene is located downstream of the *SLC12A2* gene. This locus was also
287 identified in a GWAS of varicose veins of the lower extremities [42]. The allele associated with
288 decreased risk of varicose veins is in strong LD ($r^2 > 0.93$) with the allele associated with
289 increased odds for the lipedema phenotype, suggesting a potential connection between lipedema
290 and varicose veins.

291 We identified an intronic variant in the *ADAMTSL3* gene which codes for a glycoprotein.
292 *ADAMTSL3* localizes to the extra-cellular matrix (ECM) [43] where it may modulate the
293 *ADAMTS* proteinases [44]. *ADAMTS* proteins are involved in ECM or cell-matrix interactions
294 [44]. As the ECM is important for the regulation of adipocyte expansion and proliferation [45],
295 *ADAMTS* and *ADAMTS*-like protein could be important in that process. Interestingly,
296 *ADAMTSL3* has been associated with overall body fat [46] and lean body mass [47].

297 Finally, another locus worth highlighting is at the *DNAH10-CCDC92-ZNF664* locus.
298 Knockdown of both *DNAH10* and *CCDC92* has previously been shown to result in lowered
299 mRNA levels of the respective gene, and in reduced lipid accumulation in mouse adipocytes,
300 consistent with an impairment of lipid accumulation in peripheral adipose tissues in humans [48].
301 This locus was also implicated in abnormally high HDL-C levels [49], and in large HDL
302 particles [50], further suggesting the involvement of this locus in adipose tissue growth and its
303 consequences.

304 Of course, for any of the above, the question remains if the inferred lipedema phenotype
305 has any resemblance to a clinically defined lipedema cohort. When validating 14 SNPs in the

306 ‘UK Lipoedema’ cohort [25], the *VEGFA* and *GRB14-COBL1* loci were significantly
307 associated with lipoedema. In addition to the well-established association of these loci with WHR
308 [34], they have also been associated with other cardiometabolic traits and diseases [51,52], as
309 well as with a favorable pattern of adiposity [39,53]. Interestingly, other loci identified with
310 favorable adiposity overlap with some of those identified here, such as *ANKRD55/MAP3KI*,
311 *DNAH10/CCDC92*, and *FAM101A* [39,53]. It has been suggested previously that despite higher
312 BMI, lipoedema patients have relatively lower risk of type 2 diabetes [54] and the gynoid SAT
313 may protect against cardiovascular risk [55].

314 Among the strengths of our study are the large sample size that enabled our genetic
315 investigation and identification of associated loci. Although there are other studies of lipoedema,
316 they have much smaller samples, and thereby do not have sufficient power to detect the tiny
317 effect sizes that characterize the genetic architecture of most traits that do not have a single-gene
318 cause. Another strength is the availability of relatively detailed body composition measures.
319 Given the small effect sizes typically observed for the genetics of complex traits and diseases, a
320 large sample size increased our probability of detecting loci associated with the lipoedema
321 phenotype, at the cost of the quality of the phenotype (i.e. absence of a lipoedema diagnosis, see
322 next paragraph). A major limitation of this study is that we could not rely on an actual diagnosis
323 or on a validated classifier of lipoedema. Since the recognition and diagnosis of lipoedema is in its
324 infancy, and is still very limited, it is currently difficult to obtain large collections of genotyped
325 women with diagnosed lipoedema. The binary classifier that we used likely mis-classified a
326 number of lipoedema cases and controls. However, the larger sample size and the availability of a
327 replication cohort consisting of diagnosed lipoedema cases likely counter-balanced some of the
328 resulting loss in power from the discovery cohort. It is possible that the 16 loci identified in the

329 UK Biobank discovery cohort that were not replicated in the replication cohort are loci that are
330 not associated with lipedema, but rather with other associated aspects of body shape that are
331 similar to, but not related, to lipedema. However, it is possible that some of the other discovered
332 loci are implicated in lipedema, but we were underpowered to detect their association, and that
333 only through the study of further cohorts could we confirm the potential role of these loci in
334 lipedema. Another limitation of our study is that it is limited to people of European (mainly
335 British) ancestry, and to individuals between the ages of 40 and 70, many years after lipedema
336 typically initiates, and when the lipedema phenotype is more likely to be confounded by frank
337 obesity.

338 In conclusion, we have identified 18 loci associated with an inferential lipedema
339 phenotype in adult women of European descent, among which, 2 successfully replicate in a study
340 of clinically diagnosed lipedema cases. Some have previously been identified as female-specific
341 loci for WHR, while others have not previously been linked to body composition phenotypes. In
342 a replication study with clinically diagnosed lipedema cases, we successfully replicate the
343 *VEGFA* and *GRB14-COBLI1* loci, which have previously been associated with fat distribution
344 patterns. We hope that these loci and the genes and tissues that they implicate will provide
345 starting points towards a better understanding of the pathophysiology of lipedema, and
346 eventually to treatment and prevention approaches.

347

348

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354

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359 and Meta-analysis), CKDGen (Chronic Kidney Disease Genetics consortium), dbGAP (database
360 of Genotypes and Phenotypes), DIAGRAM (DIAbetes Genetics Replication And Meta-analysis),
361 ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis), EAGLE (EARly
362 Genetics & Lifecourse Epidemiology Eczema Consortium, excluding 23andMe), EGG (Early
363 Growth Genetics Consortium), GABRIEL (A Multidisciplinary Study to Identify the Genetic and
364 Environmental Causes of Asthma in the European Community), GCAN (Genetic Consortium for
365 Anorexia Nervosa), GEFOS (GEnetic Factors for OSteoporosis Consortium), GIANT (Genetic
366 Investigation of ANthropometric Traits), GIS (Genetics of Iron Status consortium), GLGC
367 (Global Lipids Genetics Consortium), GPC (Genetics of Personality Consortium), GUGC
368 (Global Urate and Gout consortium), HaemGen (haematological and platelet traits genetics
369 consortium), HRgene (Heart Rate consortium), IIBDGC (International Inflammatory Bowel
370 Disease Genetics Consortium), ILCCO (International Lung Cancer Consortium), IMSGC
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379

380 **ETHICAL APPROVAL**

381 All participants gave written informed consent, and ethical approval was obtained from the North
382 West Multicentre Research Ethics Committee, the National Information Governance Board for
383 Health & Social Care, and the Community Health Index Advisory Group.

384

385 **DATA AVAILABILITY**

386 The data that supports the findings of this study are available from the UK Biobank, but
387 restrictions apply to the availability of these data, which were used under an agreement for the
388 current study. Summary statistics from the main UK Biobank GWAS conducted in this study
389 will be made available in the GWAS Catalog upon publication. The data from the UK
390 Lipoedema study used here as a replication dataset are not currently publically available, but will
391 be made publically available as part of an imminent publication in PLoS One [reference
392 forthcoming].

393

394

395 **CONFLICT OF INTEREST**

396 The authors declare no conflict of interest.

397

398 **AUTHOR CONTRIBUTIONS**

399 YCK, PO, KLH, and ZC designed the studies. YCK and PO provided access to data. YCK, DG,
400 MLGG, ES, and AP performed data analyses. YCK drafted manuscript. All authors contributed
401 to manuscript revision, read and approved the submitted version.

402

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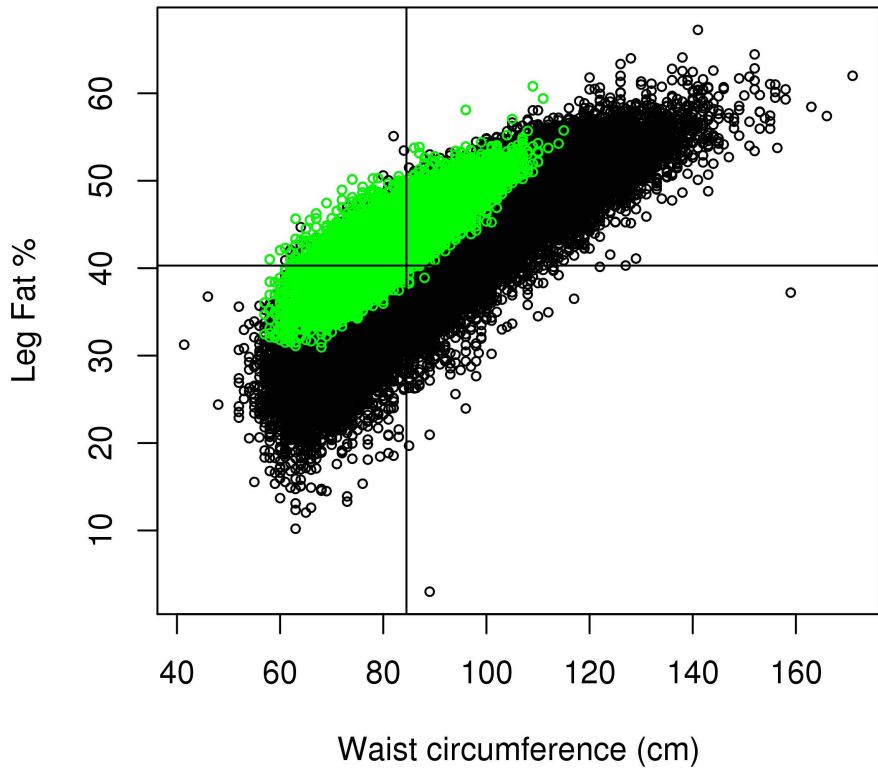
565

566 **FIGURE LEGENDS**

567 **Figure 1:** Scatter plot of raw, unadjusted waist circumference and leg fat % measurements of
568 females in the UK Biobank, indicating in green the lipedema phenotype cases. The horizontal
569 and vertical lines indicate the mean of leg fat % and waist circumference of entire female
570 sample, respectively.

571

572 **Figure 2:** Manhattan plot of GWAS of the inferred lipedema phenotype from the UK Biobank,
573 at an assumed 10% prevalence. Loci that were successfully replicated in the ‘UK Lipoedema’
574 cohort are shown in red. The red horizontal line represents the genome-wide significance p-value
575 threshold of 5×10^{-9} .



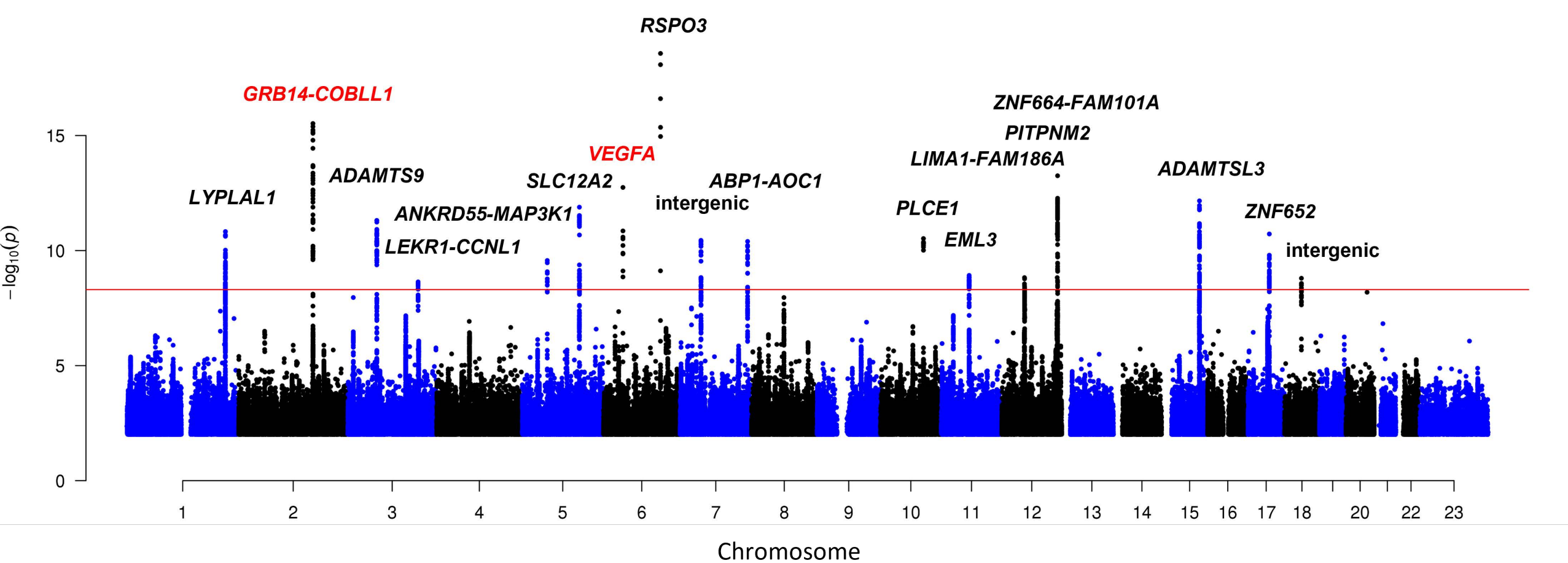


Table 1: Inferred lipedema case and control characteristics in the UK Biobank. Means and standard deviations are shown for each trait in cases and controls in analyses adjusting and not adjusting for hip circumference (HC).

	HC-Adjusted		Not HC-Adjusted	
	Cases (n=24,450)	Controls (n=165,227)	Cases (n=24,450)	Controls (n=134,347)
Age (yrs)	56.7 (7.71)	56.6 (7.98)	56.7 (7.8)	56.3 (8.03) **
BMI (kg/m ²)	26.9 (3.85)	27 (5.55) **	28.5 (2.31)	25.7 (5.99) ***
Waist Circumference (cm)	80.1 (7.83)	85.6 (13.7) ***	84.7 (4.07)	81.7 (14.9) ***
Hip Circumference (cm)	103 (7.68)	103 (11.1) ***	106 (5.55)	101 (11.9) ***
WHR	0.78 (0.032)	0.83 (0.078) ***	0.80 (0.049)	0.81 (0.075) ***
Mean Leg Fat %	42.5 (3.53)	39.6 (6.1) ***	43.9 (2.03)	38.0 (6.17) ***

*p<0.05, **p<0.0001, *** p<2x10⁻¹⁶, comparing controls to cases

HC: hip circumference; WHR: waist-to-hip ratio

Table 2: List of lead variants showing significant association with the lipedema phenotype (hip circumference (HC) adjusted) from the UK Biobank GWAS, including associations of the corresponding SNPs with lipedema in the UK Lipoedema replication study. The SNPs have been annotated to their nearest gene(s). Effect size (OR) and p-values are shown for both analyses. The SNPs have been sorted in ascending order of p-value from UK Biobank GWAS. The rows with bold font indicates the successfully replicated loci.

SNP	Chr	BP	Nearest gene	UK Biobank					UK Lipoedema study				
				A1	A0	A1 Freq	OR	p-value	SNP	A1	A1 Freq	OR	p-value
rs72959041	6	127,454,893	<i>RSPO3</i>	G	A	0.95	1.24	2.70E-19	rs72959041	A	0.052	0.9920	0.24
rs1128249	2	165,528,624	<i>GRB14-COBL1</i>	G	T	0.61	0.92	3.00E-16	rs1128249	T	0.385	1.0086	2.26E-03
rs11057418	12	124,508,976	<i>ZNF664-FAM101A</i>	G	C	0.798	1.1	5.60E-14	rs11057418	C	0.204	0.9998	0.95
rs6905288	6	43,758,873	<i>VEGFA</i>	G	A	0.429	1.07	1.80E-13	rs6905288	A	0.550	0.9029	4.96E-04
rs6602994	15	84,490,757	<i>ADAMTSL3</i>	T	C	0.276	0.92	6.90E-13	rs7164141 ^a	G	0.730	1.0033	0.27
rs10649697	5	127,432,908	<i>SLC12A2</i>	T	TAGA	0.246	0.92	1.30E-12	no proxy found				
rs4616635	3	64,702,275	<i>ADAMTS9</i>	C	G	0.723	0.93	4.90E-12	rs4616635	G	0.269	1.0064	3.60E-03
rs749853052	1	219,747,226	<i>LYPLAL1</i>	TG	T	0.702	0.93	1.50E-11	rs2820443 ^b	C	0.291	1.0070	0.02
rs536569640	12	123,553,002	<i>PITPNM2</i>	TAATA	T	0.726	1.08	1.90E-11	no proxy found				
rs28394864	17	47,450,775	<i>ZNF652</i>	G	A	0.538	1.07	1.90E-11	rs28394864	A	0.441	0.9986	0.62
rs543302184	10	96,009,182	<i>PLCE1</i>	T	TA	0.58	1.07	3.00E-11	no proxy found				
rs11772918	7	46,609,344	intergenic	A	G	0.46	0.93	3.60E-11	rs11772918	G	0.531	0.9986	0.62
rs62492368	7	150,537,635	<i>ABP1/AOC1</i>	G	A	0.694	1.07	4.00E-11	rs62492368	A	0.309	0.9973	0.36
rs5868014	5	55,860,907	<i>ANKRD55-MAP3K1</i>	GC	G	0.814	1.08	2.70E-10	rs28650790 ^c	T	0.190	0.9933	0.05
rs71490394	11	62,370,155	<i>EML3</i>	G	A	0.629	1.07	1.20E-09	rs71490394	A	0.351	0.9956	0.13
rs28849840	12	50,703,384	<i>LIMAI-FAM186A</i>	G	A	0.65	0.94	1.50E-09	rs28849840	A	0.349	0.9969	0.29
rs565113908	18	37,904,550	intergenic	T	G	0.999	0.52	1.60E-09	no proxy found				
rs4680338	3	156,794,425	<i>LEKRI-CCNLI</i>	C	G	0.595	0.94	2.30E-09	rs4680338	G	0.403	1.0044	0.12

A1 refers to effect allele that OR (odds ratio) corresponds to; A1 Freq: effect allele frequency

^a A allele at rs7164141 in LD ($r^2=1.0$) with T allele of rs6602994

^b C allele at rs2820443 in LD ($r^2=1.0$) with no G nucleotide at rs749853052

^c C allele at rs28650790 in LD ($r^2=1.0$) with C allele at rs5868014

Supplementary Table 1: Mean χ^2 , LD-score regression intercept and SNP-based heritability (h^2) from lipedema phenotype GWAS with adjustment for hip circumference.

	Mean χ^2	Intercept	h^2
Hip Circ. adjusted	1.210	1.0164 (0.0072)	0.0513 (0.0038)

Supplementary Table 2: Associations of 18 significant SNPs for lipedema phenotype with each relevant phenotype among all UK Biobank women (European ancestry). Linear regression models included age, center, chip, and 10 genetic principal components as covariates.

SNP	Effect allele	Nearest gene(s)	Height			BMI			WC			HC			WHR			Leg Fat %		
			beta	se	p	beta	se	p	beta	se	p	beta	se	p	beta	se	p	beta	se	p
rs72959041	G	<i>RSPO3</i>	-0.26	0.04	6.5E-11	0.15	0.03	1.2E-05	-0.61	0.08	2.4E-13	0.76	0.07	2.2E-28	-0.0119	0.0005	2.7E-148	0.15	0.04	4.7E-05
rs1128249	G	<i>GRB14-COBL1</i>	-0.01	0.02	0.46	-0.08	0.01	1.8E-08	0.08	0.04	0.03	-0.34	0.03	6.5E-30	0.0035	0.0002	2.0E-68	-0.10	0.02	8.6E-10
rs11057418	G	<i>ZNF664-FAM101A</i>	0.01	0.02	0.55	0.07	0.02	3.6E-04	-0.12	0.05	0.01	0.24	0.04	1.4E-10	-0.0031	0.0003	4.5E-35	0.08	0.02	1.4E-04
rs6905288	G	<i>VEGFA</i>	0.00	0.02	0.92	0.05	0.01	8.0E-04	-0.25	0.04	2.5E-12	0.17	0.03	1.9E-08	-0.0037	0.0002	1.8E-79	0.002	0.02	0.88
rs6602994	T	<i>ADAMTSL3</i>	-0.30	0.02	3.1E-53	-0.02	0.02	0.25	-0.24	0.04	9.2E-10	-0.25	0.03	1.9E-14	-0.0003	0.0002	0.15	-0.14	0.02	9.9E-17
rs10649697	T	<i>SLC12A2</i>	0.07	0.02	1.8E-04	0.00	0.02	0.94	-0.08	0.04	0.04	0.00	0.03	0.90	-0.0008	0.0002	2.9E-04	-0.17	0.02	8.6E-22
rs4616635	C	<i>ADAMTS9</i>	-0.03	0.02	0.09	-0.04	0.02	8.2E-03	0.20	0.04	5.5E-07	-0.22	0.03	7.4E-12	0.0036	0.0002	1.4E-61	-0.05	0.02	8.2E-03
rs749853052	TG	<i>LYPLAL1</i>	-0.09	0.02	4.0E-06	-0.06	0.02	9.0E-05	0.04	0.04	0.28	-0.38	0.03	5.2E-33	0.0034	0.0002	2.6E-58	-0.08	0.02	2.1E-06
rs536569640	TAATA	<i>PITPNM2</i>	0.05	0.02	0.01	0.06	0.02	9.0E-04	-0.03	0.04	0.53	0.20	0.04	2.6E-08	-0.0019	0.0002	3.1E-15	0.07	0.02	1.1E-04
rs28394864	G	<i>ZNF652</i>	0.11	0.02	9.6E-10	-0.03	0.01	0.03	-0.08	0.04	0.03	0.01	0.03	0.72	-0.0008	0.0002	1.8E-05	0.03	0.02	0.06
rs543302184	T	<i>PLCE1</i>	0.00	0.02	0.89	-0.01	0.02	0.39	0.04	0.04	0.27	0.06	0.03	0.05	-0.0001	0.0002	0.68	0.08	0.02	2.9E-07
rs11772918	A	intergenic	0.03	0.02	0.13	0.01	0.01	0.42	0.01	0.04	0.89	0.00	0.03	0.97	0.0000	0.0002	0.81	-0.06	0.02	1.4E-04
rs62492368	G	<i>ABPI/AOC1</i>	-0.13	0.02	1.6E-12	-0.01	0.02	0.54	-0.12	0.04	0.00	-0.04	0.03	0.19	-0.0008	0.0002	1.8E-04	0.05	0.02	2.5E-03
rs5868014	GC	<i>ANKRD55-MAP3K1</i>	0.02	0.02	0.31	0.02	0.02	0.36	-0.29	0.05	1.7E-10	0.03	0.04	0.41	-0.0030	0.0002	1.8E-32	-0.004	0.02	0.84
rs71490394	G	<i>EML3</i>	0.02	0.02	0.23	0.01	0.02	0.53	-0.14	0.04	1.6E-04	0.07	0.03	0.02	-0.0019	0.0002	2.2E-21	0.02	0.02	0.18
rs28849840	G	<i>LIM1-FAM186A</i>	-0.11	0.02	2.4E-10	0.03	0.02	0.08	0.03	0.04	0.36	-0.05	0.03	0.08	0.0007	0.0002	2.6E-04	-0.04	0.02	0.01
rs565113908	T	intergenic	-0.46	0.26	0.08	-0.35	0.22	0.12	-0.32	0.54	0.56	-1.08	0.45	0.02	0.0051	0.0030	0.09	-0.44	0.24	0.06
rs4680338	C	<i>LEKRI-CCNL1</i>	-0.01	0.02	0.69	0.01	0.01	0.63	0.26	0.04	1.1E-12	0.05	0.03	0.07	0.0020	0.0002	7.4E-24	0.01	0.02	0.61

Supplementary Table 3: Loci showing significant association with lipedema phenotype (hip circumference (HC) adjusted and not adjusted), ordered by ascending p-value.

SNP	Chr	BP	Nearest gene	A1	A0	A1 Freq	OR	p-value	Not HC adjusted	
									OR	p-value
rs72959041	6	127,454,893	<i>RSPO3</i>	G	A	0.950	1.24	2.7E-19	1.13	1.5E-08
rs1128249	2	165,528,624	<i>GRB14-COBL1</i>	G	T	0.610	0.92	3.0E-16	0.93	2.0E-12
rs11057418	12	124,508,976	<i>ZNF664-FAM101A</i>	G	C	0.798	1.10	5.6E-14	1.08	3.0E-09
rs6905288	6	43,758,873	<i>VEGFA</i>	G	A	0.429	1.07	1.8E-13	1.06	5.7E-09
rs6602994	15	84,490,757	<i>ADAMTSL3</i>	T	C	0.276	0.92	6.9E-13	0.94	7.3E-07
rs10649697	5	127,432,908	<i>SLC12A2</i>	T	TAGA	0.246	0.92	1.3E-12	0.92	9.1E-12
rs4616635	3	64,702,275	<i>ADAMTS9</i>	C	G	0.723	0.93	4.9E-12	0.92	4.1E-13
rs749853052	1	219,747,226	<i>LYPLAL1</i>	TG	T	0.702	0.93	1.5E-11	0.95	1.5E-06
rs536569640	12	123,553,002	<i>PITPNM2</i>	TAATA	T	0.726	1.08	1.9E-11	1.05	4.1E-06
rs28394864	17	47,450,775	<i>ZNF652</i>	G	A	0.538	1.07	1.9E-11	1.04	1.2E-05
rs543302184	10	96,009,182	<i>PLCE1</i>	T	TA	0.580	1.07	3.0E-11	1.04	2.7E-05
rs11772918	7	46,609,344	intergenic	A	G	0.460	0.93	3.6E-11	0.96	5.7E-04
rs62492368	7	150,537,635	<i>ABP1/AOC1</i>	G	A	0.694	1.07	4.0E-11	1.05	2.2E-05
rs5868014	5	55,860,907	<i>ANKRD55-MAP3K1</i>	GC	G	0.814	1.08	2.7E-10	1.06	5.6E-07
rs71490394	11	62,370,155	<i>EML3</i>	G	A	0.629	1.07	1.2E-09	1.04	5.2E-04
rs28849840	12	50,703,384	<i>LIM1-FAM186A</i>	G	A	0.650	0.94	1.5E-09	0.96	5.6E-05
rs565113908	18	37,904,550	intergenic	T	G	0.999	0.52	1.6E-09	0.57	4.2E-06
rs4680338	3	156,794,425	<i>LEKRI-CCNLI</i>	C	G	0.595	0.94	2.3E-09	0.96	2.1E-04

A1 refers to effect allele that OR (adds ratio) corresponds to; A1 Freq: effect allele frequency

Supplementary Table 4: Association of top SNPs identified in main model with lipedema phenotype incorporating leg pain in case definition (n=1,724 cases; 165,227 controls).

SNP	Chr	BP	Nearest gene	A1	A0	A1 Freq	Beta	SE	p-value
rs749853052	1	219,747,226	<i>LYPLAL1</i>	TG	T	0.70	-0.0017	0.0004	4.5E-06
rs11772918	7	46,609,344	<i>intergenic</i>	A	G	0.46	-0.0014	0.0004	9.3E-05
rs62492368	7	150,537,635	<i>ABP1/AOC1</i>	G	A	0.69	0.0011	0.0004	2.9E-03
rs11057418	12	124,508,976	<i>ZNF664-FAM101A</i>	G	C	0.80	0.0013	0.0004	4.4E-03
rs6905288	6	43,758,873	<i>VEGFA</i>	G	A	0.43	0.0009	0.0004	8.1E-03
rs72959041	6	127,454,893	<i>RSPO3</i>	G	A	0.95	0.0020	0.0008	1.5E-02
rs28849840	12	50,703,384	<i>LIM1-FAM186A</i>	G	A	0.65	-0.0009	0.0004	1.8E-02
rs5868014	5	55,860,907	<i>ANKRD55-MAP3K1</i>	GC	G	0.81	0.0010	0.0004	2.0E-02
rs71490394	11	62,370,155	<i>EML3</i>	G	A	0.63	0.0007	0.0004	6.3E-02
rs536569640	12	123,553,002	<i>PITPNM2</i>	TAATA	T	0.72	0.0007	0.0004	1.0E-01
rs1128249	2	165,528,624	<i>GRB14-COBL1</i>	G	T	0.61	-0.0006	0.0004	1.1E-01
rs4616635	3	64,702,275	<i>ADAMTS9</i>	C	G	0.72	-0.0005	0.0004	1.7E-01
rs10649697	5	127,432,908	<i>SLC12A2</i>	T	TAGA	0.25	-0.0006	0.0004	1.7E-01
rs543302184	10	96,009,182	<i>PLCE1</i>	T	TA	0.58	0.0005	0.0004	1.7E-01
rs6602994	15	84,490,757	<i>ADAMTSL3</i>	T	C	0.28	-0.0003	0.0004	3.7E-01
rs28394864	17	47,450,775	<i>ZNF652</i>	G	A	0.54	0.0003	0.0003	4.0E-01
rs4680338	3	156,794,425	<i>LEKRI-CCNL1</i>	C	G	0.60	0.0000	0.0004	9.4E-01

A1 refers to effect allele that OR (adds ratio) corresponds to; A1 Freq: effect allele frequency

Supplementary Table 5: List of statistically significant genes identified by MAGMA gene-based analysis.

SYMBOL	GENE	CHR	START	STOP	NSNPS	ZSTAT	P
<i>ADAMTSL3</i>	ENSG00000156218	15	84312838	84718594	1182	8.1051	2.64E-16
<i>FAM101A</i>	ENSG00000178882	12	124447788	124810570	1182	7.5703	1.86E-14
<i>ZNF664</i>	ENSG00000179195	12	124446392	124509986	152	7.5307	2.52E-14
<i>COBLL1</i>	ENSG00000082438	2	165500134	165710189	722	7.2338	2.35E-13
<i>CCDC92</i>	ENSG00000119242	12	124393207	124467378	211	6.9978	1.30E-12
<i>EML3</i>	ENSG00000149499	11	62359690	62390237	49	6.4505	5.58E-11
<i>MIR3654</i>	ENSG00000255508	11	62317075	62369003	90	6.4354	6.16E-11
<i>EEF1G</i>	ENSG00000254772	11	62317073	62352401	67	6.4096	7.29E-11
<i>TUTI</i>	ENSG00000149016	11	62332517	62369649	61	6.3347	1.19E-10
<i>DNAH10</i>	ENSG00000197653	12	124237042	124430753	671	6.2883	1.60E-10
<i>MTA2</i>	ENSG00000149480	11	62350686	62379312	50	6.2354	2.25E-10
<i>DNAH10OS</i>	ENSG00000250091	12	124400971	124429531	96	6.2321	2.30E-10
<i>HCAR1</i>	ENSG00000196917	12	123094824	123225390	341	6.2095	2.66E-10
<i>RP11-81K2.1</i>	ENSG00000262039	17	47438102	47564350	387	6.1863	3.08E-10
<i>B3GAT3</i>	ENSG00000149541	11	62372768	62399647	42	6.1822	3.16E-10
<i>ROM1</i>	ENSG00000149489	11	62369194	62392592	36	6.1605	3.63E-10
<i>ZNF652</i>	ENSG00000198740	17	47356568	47449835	231	6.1296	4.40E-10
<i>HOXA10</i>	ENSG00000253293	7	27200210	27229880	62	5.9142	1.67E-09
<i>RP11-1102P16.1</i>	ENSG00000253379	8	72305675	72514260	555	5.9107	1.70E-09
<i>GANAB</i>	ENSG00000089597	11	62382298	62424104	66	5.8639	2.26E-09
<i>INTS5</i>	ENSG00000185085	11	62404320	62430774	53	5.8271	2.82E-09
<i>PLXND1</i>	ENSG00000004399	3	129264018	129335661	264	5.769	3.99E-09
<i>RP1-170O19.20</i>	ENSG00000257184	7	27193154	27229632	80	5.7509	4.44E-09
<i>TMEM176A</i>	ENSG00000002933	7	150487491	150512208	118	5.6638	7.40E-09
<i>AOC1</i>	ENSG00000002726	7	150511715	150568592	301	5.5426	1.49E-08
<i>RHO</i>	ENSG00000163914	3	129237483	129264012	75	5.5378	1.53E-08
<i>HOXA9</i>	ENSG00000078399	7	27192054	27220117	63	5.4871	2.04E-08
<i>SHOX2</i>	ENSG00000168779	3	157804948	157834292	70	5.4604	2.38E-08
<i>PTCH1</i>	ENSG00000185920	9	98195262	98289339	290	5.4283	2.85E-08
<i>RP11-831H9.11</i>	ENSG00000255432	11	62407166	62442650	69	5.3922	3.48E-08
<i>PHOSPHO1</i>	ENSG00000173868	17	47290724	47318128	79	5.3621	4.11E-08
<i>C11orf83</i>	ENSG00000204922	11	62427745	62451159	50	5.3619	4.12E-08
<i>HIFOO</i>	ENSG00000178804	3	129252057	129280310	79	5.3404	4.64E-08
<i>VEGFA</i>	ENSG00000112715	6	43727921	43764224	89	5.2946	5.97E-08
<i>C11orf48</i>	ENSG00000162194	11	62420287	62449727	66	5.288	6.18E-08
<i>SMARCD1</i>	ENSG00000066117	12	50468755	50504495	46	5.282	6.39E-08
<i>IFT122</i>	ENSG00000163913	3	129148968	129249198	331	5.1602	1.23E-07
<i>UBXN1</i>	ENSG00000162191	11	62433970	62456567	41	5.1549	1.27E-07
<i>MBD4</i>	ENSG00000129071	3	129139787	129168878	121	5.1508	1.30E-07
<i>TMCC1</i>	ENSG00000172765	3	129356635	129622419	399	5.1126	1.59E-07
<i>ATF1</i>	ENSG00000123268	12	51147493	51224905	137	5.1124	1.59E-07

<i>STH</i>	ENSG00000256762	17	44066616	44087060	118	5.1041	1.66E-07
<i>METTL12</i>	ENSG00000214756	11	62422781	62445968	54	5.0879	1.81E-07
<i>SOSTDC1</i>	ENSG00000171243	7	16491106	16580205	404	5.0718	1.97E-07
<i>NSMCE2</i>	ENSG00000156831	8	126093921	126389362	750	5.0617	2.08E-07
<i>GPD1</i>	ENSG00000167588	12	50487602	50515102	39	5.0608	2.09E-07
<i>WNT3</i>	ENSG00000108379	17	44829872	44920520	148	5.0357	2.38E-07
<i>MAPT</i>	ENSG00000186868	17	43961748	44115700	789	5.0201	2.58E-07
<i>HCAR2</i>	ENSG00000182782	12	123175840	123197890	60	5.0169	2.63E-07
<i>SPPL2C</i>	ENSG00000185294	17	43912256	43934438	138	5.005	2.79E-07
<i>LRRC37A</i>	ENSG00000176681	17	44360099	44425160	11	4.9343	4.02E-07
<i>KANSL1</i>	ENSG00000120071	17	44097282	44312733	751	4.922	4.28E-07
<i>COL5A2</i>	ENSG00000204262	2	189886622	190054605	484	4.9212	4.30E-07
<i>ABI3</i>	ENSG00000108798	17	47277589	47310587	102	4.9182	4.37E-07
<i>CRHR1</i>	ENSG00000120088	17	43689267	43923194	1024	4.8865	5.13E-07
<i>SH3GL3</i>	ENSG00000140600	15	84105980	84297495	510	4.8503	6.16E-07
<i>HOXA11</i>	ENSG00000005073	7	27211129	27234842	45	4.8215	7.12E-07
<i>NUAK2</i>	ENSG00000163545	1	205261187	205300883	145	4.7535	1.00E-06
<i>FAM118A</i>	ENSG00000100376	22	45694849	45747836	181	4.7373	1.08E-06
<i>DFNB31</i>	ENSG00000095397	9	117154360	117277730	448	4.7363	1.09E-06
<i>LIMA1</i>	ENSG00000050405	12	50559571	50687329	165	4.7244	1.15E-06
<i>SLC12A2</i>	ENSG00000064651	5	127409458	127535380	276	4.7092	1.24E-06
<i>GOLGA6L4</i>	ENSG00000184206	15	84894525	84924120	56	4.666	1.54E-06
<i>EFCAB12</i>	ENSG00000172771	3	129110164	129157494	205	4.665	1.54E-06
<i>PHB</i>	ENSG00000167085	17	47471414	47502246	87	4.6499	1.66E-06
<i>ARL17B</i>	ENSG00000228696	17	44342150	44449130	78	4.6242	1.88E-06
<i>PXDNL</i>	ENSG00000147485	8	52222138	52732005	1931	4.6082	2.03E-06
<i>COX14</i>	ENSG00000178449	12	50495762	50524240	45	4.5988	2.12E-06
<i>MANEA</i>	ENSG00000172469	6	96015419	96067333	177	4.5984	2.13E-06
<i>SIRT4</i>	ENSG00000089163	12	120730119	120761052	101	4.5875	2.24E-06
<i>DIP2B</i>	ENSG00000066084	12	50888768	51152450	442	4.5818	2.31E-06
<i>CCDC71L</i>	ENSG00000253276	7	106287211	106311442	76	4.5619	2.53E-06

NSNPs: the number of SNPs annotated to that gene that were found in the data and were not excluded based on internal SNP QC

Supplementary Table 6: All significant (FDR<0.05) eQTL of top SNPs in GTEx data

SNP	Chr	BP	Nearest gene	Association with gene expression							
				Tissue	Gene	testedAllele	p	signed_stats	FDR	RiskIncAllele	alignedDirection
rs72959041	6	127454893	<i>RSPO3</i>	Adipose_Subcutaneous	RSPO3	A	4.03E-07	0.577513	0.00087	G	-
rs1128249	2	165528624	<i>GRB14-COBLL1</i>	Muscle_Skeletal	SLC38A11	T	1.15E-09	0.357779	2.03E-65	T	+
				Thyroid	SLC38A11	T	3.32E-06	0.288704	6.14E-53	T	+
				Esophagus_Muscularis	GRB14	T	1.15E-05	-0.214349	4.56E-13	T	-
				Nerve_Tibial	SCN2A	T	1.74E-08	-0.22464	7.21E-06	T	-
rs11057418	12	124508976	<i>ZNF664-FAM101A</i>	Esophagus_Muscularis	DNAH100S	C	3.70E-05	-0.262404	2.38E-29	G	+
				Artery_Tibial	DNAH100S	C	1.53E-07	-0.275824	4.85E-27	G	+
				Heart_Left_Ventricle	CCDC92	C	8.02E-07	-0.334128	1.20E-15	G	+
				Adipose_Visceral_Omentum	CCDC92	C	2.87E-06	-0.257291	9.25E-14	G	+
				Nerve_Tibial	DNAH100S	C	2.62E-07	-0.29144	9.54E-12	G	+
				Nerve_Tibial	CCDC92	C	1.99E-06	-0.2958249	5.12E-09	G	+
				Breast_Mammary_Tissue	CCDC92	C	7.88E-06	-0.175046	1.27E-07	G	+
rs28394864	17	47450775	<i>ZNF652</i>	Adipose_Subcutaneous	ZNF664	C	5.20E-06	-0.161064	5.93E-05	G	+
				Cells_Transformed_fibroblasts	ZNF652	A	1.71E-06	-0.206487	2.18E-06	G	+
				Muscle_Skeletal	ZNF652	A	1.01E-05	-0.110076	8.44E-06	G	+
rs62492368	7	150537635	<i>ABP1/AOC1</i>	Artery_Tibial	ZNF652	A	4.17E-08	-0.194245	2.23E-05	G	+
				Heart_Left_Ventricle	AOC1	A	3.40E-08	-0.45069	3.37E-28	G	+
				Heart_Atrial_Appendage	AOC1	A	8.79E-09	-0.502597	3.21E-27	G	+
				Liver	AOC1	A	2.07E-09	-0.658249	8.70E-26	G	+
				Heart_Atrial_Appendage	TMEM176B	A	7.95E-07	-0.363111	4.25E-16	G	+
				Esophagus_Muscularis	AOC1	A	9.90E-08	0.385626	3.83E-09	G	-
				Thyroid	AOC1	A	1.57E-09	0.359027	1.00E-05	G	-
				Adrenal_Gland	KCNH2	A	1.47E-05	-0.281308	6.86E-05	G	+
				Esophagus_Gastroesophageal_Junction	AOC1	A	5.63E-06	0.422531	0.00721	G	-
				Thyroid	CHPF2	A	1.25E-05	-0.090761	0.02358	G	+
rs28849840	12	50703384	<i>LIMA1-FAM186A</i>	Cells_Transformed_fibroblasts	LARP4	A	1.12E-05	-0.121571	4.37E-26	A	-
				Nerve_Tibial	CERS5	A	2.94E-09	0.291341	1.47E-18	A	+
				Artery_Aorta	ATF1	A	3.46E-08	-0.260824	2.33E-15	A	-
				Cells_Transformed_fibroblasts	LETMD1	A	1.43E-05	0.0970487	9.98E-11	A	+
				Whole_Blood	ATF1	A	2.20E-08	0.215199	2.34E-09	A	+
				Colon_Sigmoid	ATF1	A	2.94E-05	-0.260598	4.41E-09	A	-
				Cells_Transformed_fibroblasts	DIP2B	A	5.01E-05	-0.16402	5.34E-08	A	-
				Lung	ATF1	A	4.35E-07	0.177455	8.62E-06	A	+
				Thyroid	LIMA1	A	7.11E-05	0.130247	7.53E-05	A	+
				Adrenal_Gland	COX14	A	7.29E-07	-0.313171	0.00049	A	-
				Muscle_Skeletal	COX14	A	6.16E-06	-0.119708	0.00065	A	-
				Spleen	CERS5	A	1.73E-05	0.346744	0.00073	A	+
				Brain_Putamen_basal_ganglia	DIP2B	A	9.31E-06	0.263417	0.00444	A	+
rs4680338	3	156794425	<i>LEKR1-CCNL1</i>	Artery_Tibial	TIPARP	G	5.88E-10	0.244865	4.47E-06	G	+
				Adipose_Subcutaneous	TIPARP	G	5.39E-07	0.212427	0.00128	G	+

Supplementary Table 7: eQTL of all SNPs in LD ($r^2 > 0.6$) with top SNPs, using data from GTEx v7. Only results with $FDR < 0.05$ are shown. Chromosome and position are shown to indicate loci in general, but do not imply that the eQTL is for this particular variant.

Chr	Region (bp)	Gene	Tissue(s)
6	127454893	<i>RSPO3</i>	Adipose_Subcutaneous
2	165528624	<i>GRB14</i>	Esophagus_Muscularis
2	165528624	<i>SLC38A11</i>	Muscle_Skeletal, Thyroid
2	165528624	<i>SCN2A</i>	Nerve_Tibial
2	165528624	<i>FIGN</i>	Skin_Sun_Exposed_Lower_leg
2	165528624	<i>COBLL1</i>	Thyroid
12	124508976	<i>CCDC92</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Adrenal_Gland, Artery_Tibial, Breast_Mammary_Tissue, Esophagus_Mucosa, Heart_Atrial_Appendage, Heart_Left_Ventricle, Lung, Muscle_Skeletal, Nerve_Tibial, Prostate, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Spleen, Thyroid, Whole_Blood
12	124508976	<i>DNAH10OS</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Artery_Aorta, Artery_Tibial, Brain_Anterior_cingulate_cortex_BA24, Brain_Cortex, Brain_Frontal_Cortex_BA9, Breast_Mammary_Tissue, Colon_Sigmoid, Colon_Transverse, Esophagus_Gastroesophageal_Junction, Esophagus_Mucosa, Esophagus_Muscularis, Heart_Atrial_Appendage, Heart_Left_Ventricle, Lung, Muscle_Skeletal, Nerve_Tibial, Prostate, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Testis, Thyroid
12	124508976	<i>DNAH10</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Artery_Tibial, Cells_Transformed_fibroblasts, Colon_Sigmoid, Esophagus_Gastroesophageal_Junction, Esophagus_Muscularis, Nerve_Tibial, Testis, Thyroid, Whole_Blood
12	124508976	<i>TCTN2</i>	Adipose_Subcutaneous, Muscle_Skeletal
12	124508976	<i>ZNF664</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Cells_Transformed_fibroblasts, Heart_Atrial_Appendage, Heart_Left_Ventricle, Nerve_Tibial, Thyroid, Whole_Blood
12	124508976	<i>FAM101A</i>	Adrenal_Gland, Nerve_Tibial
12	124508976	<i>ATP6V0A2</i>	Nerve_Tibial
12	124508976	<i>TMED2</i>	Skin_Not_Sun_Exposed_Suprapubic
15	84490757	<i>GOLGA6L4</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Brain_Cortex, Breast_Mammary_Tissue, Colon_Sigmoid, Esophagus_Mucosa, Esophagus_Muscularis, Nerve_Tibial, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Thyroid
15	84490757	<i>UBE2Q2L</i>	Adipose_Subcutaneous, Artery_Aorta, Artery_Tibial, Cells_Transformed_fibroblasts, Colon_Transverse, Esophagus_Mucosa, Esophagus_Muscularis, Heart_Atrial_Appendage, Lung, Muscle_Skeletal, Nerve_Tibial, Skin_Sun_Exposed_Lower_leg, Thyroid
15	84490757	<i>WDR73</i>	Adipose_Visceral_Omentum, Artery_Aorta, Artery_Tibial, Breast_Mammary_Tissue, Esophagus_Muscularis, Muscle_Skeletal, Nerve_Tibial, Pancreas, Thyroid
15	84490757	<i>ZSCAN2</i>	Adrenal_Gland, Lung, Whole_Blood
15	84490757	<i>ADAMTSL3</i>	Artery_Aorta, Artery_Tibial, Brain_Cerebellar_Hemisphere, Brain_Cerebellum, Cells_EBV-transformed_lymphocytes, Esophagus_Muscularis, Ovary, Thyroid
15	84490757	<i>NMB</i>	Artery_Tibial, Cells_Transformed_fibroblasts, Colon_Sigmoid, Colon_Transverse, Esophagus_Mucosa, Esophagus_Muscularis, Nerve_Tibial, Pancreas, Skin_Not_Sun_Exposed_Suprapubic, Spleen, Stomach, Testis
15	84490757	<i>ALPK3</i>	Heart_Atrial_Appendage, Skin_Sun_Exposed_Lower_leg
15	84490757	<i>SH3GL3</i>	Small_Intestine_Terminal_Ileum
5	127432908	<i>SLC12A2</i>	Brain_Cerebellum
5	127432908	<i>FBN2</i>	Spleen, Thyroid
3	64702275	<i>ADAMT59</i>	Artery_Aorta
1	219747226	<i>EPRS</i>	Artery_Tibial
1	219747226	<i>SLC30A10</i>	Skin_Sun_Exposed_Lower_leg
17	47450775	<i>ZNF652</i>	Adipose_Subcutaneous, Artery_Tibial, Cells_Transformed_fibroblasts, Muscle_Skeletal
17	47450775	<i>GNGT2</i>	Thyroid, Whole_Blood
10	96009182	<i>C10orf129</i>	Adipose_Visceral_Omentum
10	96009182	<i>NOC3L</i>	Adrenal_Gland, Artery_Aorta, Brain_Frontal_Cortex_BA9, Esophagus_Muscularis, Heart_Atrial_Appendage, Heart_Left_Ventricle, Lung, Muscle_Skeletal, Nerve_Tibial, Pancreas, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Spleen, Thyroid
10	96009182	<i>PLCE1</i>	Lung, Skin_Sun_Exposed_Lower_leg
7	150537635	<i>TMEM176B</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Brain_Cerebellum, Heart_Atrial_Appendage, Heart_Left_Ventricle, Pancreas, Pituitary, Thyroid
7	150537635	<i>AOC1</i>	Adipose_Visceral_Omentum, Esophagus_Gastroesophageal_Junction, Esophagus_Muscularis, Heart_Atrial_Appendage, Heart_Left_Ventricle, Liver, Skin_Sun_Exposed_Lower_leg, Thyroid
7	150537635	<i>KCNH2</i>	Adrenal_Gland, Artery_Tibial, Nerve_Tibial
7	150537635	<i>TMEM176A</i>	Brain_Hypothalamus, Heart_Atrial_Appendage, Heart_Left_Ventricle, Lung, Nerve_Tibial
7	150537635	<i>CHPF2</i>	Thyroid

7	150537635	<i>ASIC3</i>	Thyroid
11	62370155	<i>ROM1</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Artery_Aorta, Artery_Coronary, Artery_Tibial, Breast_Mammary_Tissue, Cells_Transformed_fibroblasts, Colon_Sigmoid, Esophagus_Muscularis, Heart_Left_Ventricle, Lung, Nerve_Tibial, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Thyroid
11	62370155	<i>EML3</i>	Adipose_Subcutaneous, Adipose_Visceral_Omentum, Adrenal_Gland, Artery_Aorta, Artery_Tibial, Brain_Caudate_basal_ganglia, Brain_Nucleus_accumbens_basal_ganglia, Brain_Putamen_basal_ganglia, Breast_Mammary_Tissue, Cells_EBV-transformed_lymphocytes, Cells_Transformed_fibroblasts, Colon_Sigmoid, Colon_Transverse, Esophagus_Gastroesophageal_Junction, Esophagus_Mucosa, Esophagus_Muscularis, Heart_Atrial_Appendage, Heart_Left_Ventricle, Lung, Minor_Salivary_Gland, Muscle_Skeletal, Nerve_Tibial, Pancreas, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Small_Intestine_Terminal_Ileum, Spleen, Stomach, Testis, Thyroid, Vagina, Whole_Blood
11	62370155	<i>EEF1G</i>	Adipose_Subcutaneous, Artery_Aorta, Artery_Tibial, Esophagus_Mucosa, Esophagus_Muscularis, Lung, Nerve_Tibial, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Thyroid
11	62370155	<i>C11orf83</i>	Adipose_Visceral_Omentum, Artery_Tibial, Breast_Mammary_Tissue, Esophagus_Muscularis, Heart_Atrial_Appendage, Heart_Left_Ventricle, Muscle_Skeletal, Nerve_Tibial, Pituitary, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Thyroid
11	62370155	<i>B3GAT3</i>	Adrenal_Gland, Artery_Tibial, Brain_Amygdala, Brain_Caudate_basal_ganglia, Brain_Cerebellum, Brain_Frontal_Cortex_BA9, Brain_Hippocampus, Brain_Nucleus_accumbens_basal_ganglia, Brain_Spinal_cord_cervical_c-1, Brain_Substantia_nigra, Colon_Transverse, Esophagus_Gastroesophageal_Junction, Esophagus_Mucosa, Esophagus_Muscularis, Heart_Atrial_Appendage, Nerve_Tibial, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Testis, Thyroid
11	62370155	<i>MTA2</i>	Artery_Tibial, Brain_Cerebellar_Hemisphere, Cells_Transformed_fibroblasts, Colon_Transverse, Esophagus_Mucosa, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Spleen, Testis, Vagina
11	62370155	<i>C11orf48</i>	Brain_Cerebellar_Hemisphere, Brain_Cerebellum, Breast_Mammary_Tissue, Lung, Nerve_Tibial, Skin_Sun_Exposed_Lower_leg, Spleen, Thyroid, Whole_Blood
11	62370155	<i>TTC9C</i>	Cells_Transformed_fibroblasts, Nerve_Tibial, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg
11	62370155	<i>METTL12</i>	Esophagus_Muscularis, Nerve_Tibial, Thyroid
11	62370155	<i>INTS5</i>	Lung, Skin_Not_Sun_Exposed_Suprapubic, Skin_Sun_Exposed_Lower_leg, Whole_Blood
11	62370155	<i>UBXN1</i>	Muscle_Skeletal
12	50703384	<i>RACGAP1</i>	Adipose_Subcutaneous
12	50703384	<i>COX14</i>	Adrenal_Gland, Cells_Transformed_fibroblasts, Lung, Muscle_Skeletal, Nerve_Tibial
12	50703384	<i>ATF1</i>	Artery_Aorta, Artery_Tibial, Colon_Sigmoid, Esophagus_Muscularis, Lung, Muscle_Skeletal, Whole_Blood
12	50703384	<i>CERS5</i>	Brain_Cerebellar_Hemisphere, Brain_Cerebellum, Lung, Nerve_Tibial, Spleen, Testis, Thyroid
12	50703384	<i>DIP2B</i>	Brain_Putamen_basal_ganglia, Cells_Transformed_fibroblasts
12	50703384	<i>SMARCD1</i>	Cells_Transformed_fibroblasts, Skin_Sun_Exposed_Lower_leg
12	50703384	<i>LARP4</i>	Cells_Transformed_fibroblasts
12	50703384	<i>LETMD1</i>	Cells_Transformed_fibroblasts, Muscle_Skeletal
12	50703384	<i>LIMA1</i>	Esophagus_Gastroesophageal_Junction, Esophagus_Muscularis, Thyroid, Whole_Blood
3	156794425	<i>TIPARP</i>	Adipose_Subcutaneous, Artery_Tibial

Supplementary Table 8: Lists of genes that are differentially expressed in relevant and highly represented tissues of interest, according to eQTL analysis.

Adipose Subcutaneous	Adipose Visceral Omentum	Thyroid	Artery Tibial	Artery Aorta	Nerve tibial
<i>CCDC92</i>	<i>CCDC92</i>	<i>WDR73</i>	<i>DNAH10OS</i>	<i>ATF1</i>	<i>CCDC92</i>
<i>DNAH10OS</i>	<i>DNAH10OS</i>	<i>ZNF664</i>	<i>WDR73</i>	<i>DNAH10OS</i>	<i>WDR73</i>
<i>DNAH10</i>	<i>EML3</i>	<i>DNAH10OS</i>	<i>ATF1</i>	<i>ROM1</i>	<i>DNAH10OS</i>
<i>EEF1G</i>	<i>ROM1</i>	<i>CCDC92</i>	<i>CCDC92</i>	<i>EML3</i>	<i>CERS5</i>
<i>EML3</i>	<i>DNAH10</i>	<i>B3GAT3</i>	<i>DNAH10</i>	<i>UBE2Q2L</i>	<i>NMB</i>
<i>ROM1</i>	<i>WDR73</i>	<i>EML3</i>	<i>ZNF652</i>	<i>WDR73</i>	<i>EML3</i>
<i>UBE2Q2L</i>	<i>C11orf83</i>	<i>ROM1</i>	<i>EEF1G</i>	<i>ADAMTSL3</i>	<i>ROM1</i>
<i>EYA1</i>	<i>GOLGA6L4</i>	<i>METTL12</i>	<i>ROM1</i>	<i>ADAMTS9</i>	<i>B3GAT3</i>
<i>WDR73</i>	<i>TMEM176B</i>	<i>UBE2Q2L</i>	<i>NMB</i>	<i>EEF1G</i>	<i>C11orf83</i>
<i>HCAR3</i>	<i>ZNF664</i>	<i>LIMA1</i>	<i>UBE2Q2L</i>	<i>NMB</i>	<i>GOLGA6L4</i>
<i>ZNF664</i>	<i>AOC1</i>	<i>GOLGA6L4</i>	<i>EYA1</i>	<i>NOC3L</i>	<i>UBE2Q2L</i>
<i>TIPARP</i>	<i>C10orf129</i>	<i>C11orf48</i>	<i>MTA2</i>		<i>EEF1G</i>
<i>TMEM176B</i>		<i>EEF1G</i>	<i>ADAMTSL3</i>		<i>EYA1</i>
<i>ZNF652</i>		<i>NMB</i>	<i>EML3</i>		<i>METTL12</i>
<i>RACGAP1</i>		<i>DNAH10</i>	<i>TIPARP</i>		<i>DNAH10</i>
<i>RSPO3</i>		<i>C11orf83</i>	<i>C11orf83</i>		<i>ZNF664</i>
<i>GOLGA6L4</i>		<i>SLC38A11</i>	<i>B3GAT3</i>		<i>FAM101A</i>
<i>TCTN2</i>		<i>AOC1</i>	<i>EPRS</i>		<i>SCN2A</i>
		<i>FBN2</i>	<i>KCNH2</i>		<i>TTC9C</i>
		<i>CERS5</i>			<i>COX14</i>
		<i>TMEM176B</i>			<i>ATP6V0A2</i>
		<i>NOC3L</i>			<i>TMEM176A</i>
		<i>GNGT2</i>			<i>C11orf48</i>
		<i>CHPF2</i>			<i>HCAR2</i>
		<i>COBLL1</i>			<i>KCNH2</i>
		<i>ADAMTSL3</i>			<i>NOC3L</i>
		<i>ASIC3</i>			
		<i>ZSCAN2</i>			

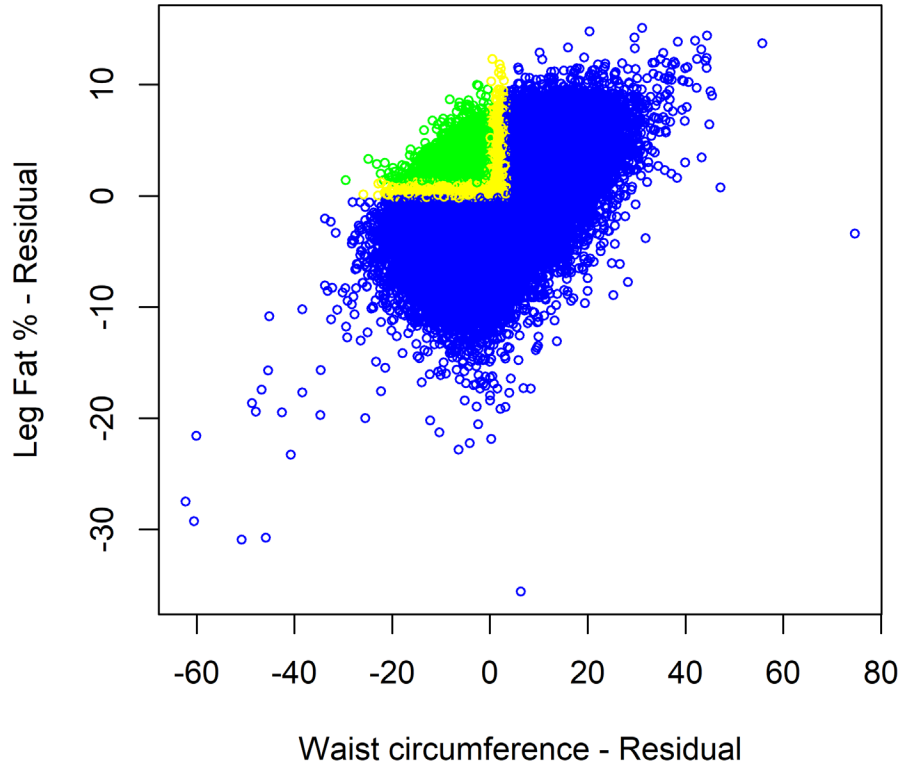
Supplementary Table 9: Pathway over-representation analysis using all genes obtained from eQTL analysis listed in Supplementary Table 5.

Pathway name/Gene ontology term	Set size	Candidates contained	p-value	q-value	Pathway source	Genes Contained
Dermatan sulfate biosynthesis	17	2(11.8%)	0.000898	0.0193	HumanCyc	<i>CHPF2, B3GAT3</i>
EGFR1	455	6(1.3%)	0.00107	0.0193	NetPath	<i>GRB14, SH3GL3, PLCE1, MTA2, RACGAP1, ATF1</i>
Glycosaminoglycan biosynthesis – chondroitin sulfate / dermatan sulfate	20	2(10.0%)	0.00125	0.0193	KEGG	<i>CHPF2, B3GAT3</i>
Proteoglycan biosynthesis	30	2(6.7%)	0.00281	0.0315	EHMN	<i>CHPF2, B3GAT3</i>
GO:0032154 cleavage furrow	55	3(5.5%)	0.000444	0.0164	GO CC 3	<i>WDR73, RACGAP1, LIM1</i>
GO:0032155 cell division site part	65	3 (4.6%)	0.000726	0.0271	GO CC 2	<i>WDR73, RACGAP1, LIM1</i>
GO:0032153 cell division site	82	3 (3.7%)	0.00142	0.0271	GO CC 2	<i>WDR73, RACGAP1, LIM1</i>
GO:0003785 actin monomer binding	27	2 (7.4%)	0.00241	0.0275	GO MF 5	<i>COBLL1, LIM1</i>
GO:0015020 glucuronosyltransferase activity	35	2 (5.7%)	0.00404	0.0275	GO MF 5	<i>CHPF2, B3GAT3</i>

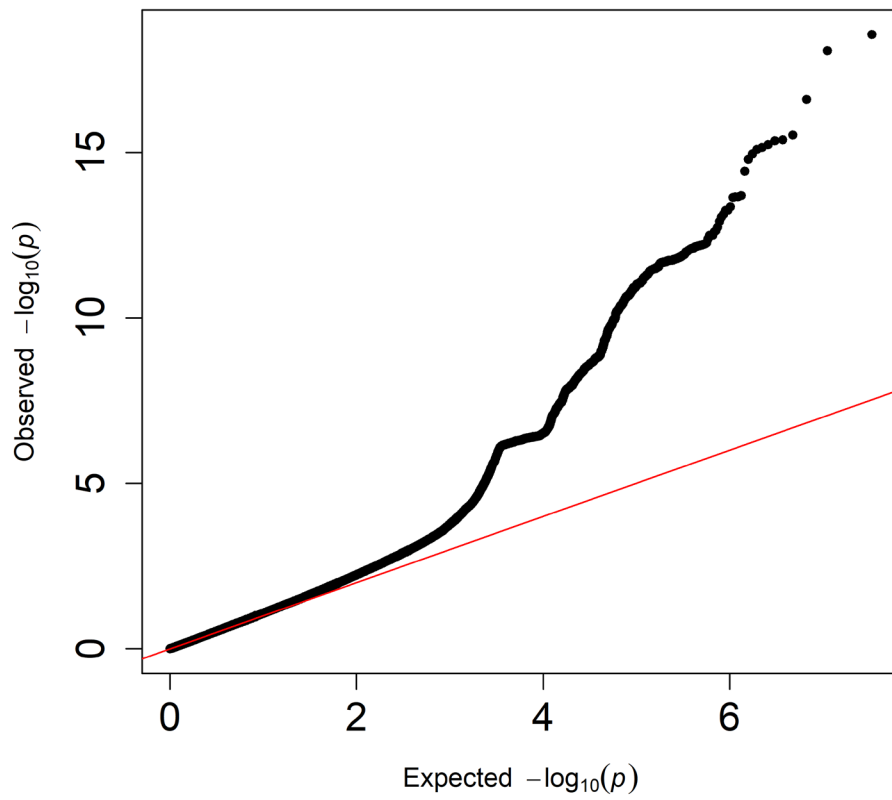
<http://cpdb.molgen.mpg.de/download/CPDB.wsd1>

Kamburov, A. et al. (2013) The ConsensusPathDB interaction database: 2013 update. Nucleic Acids Res.

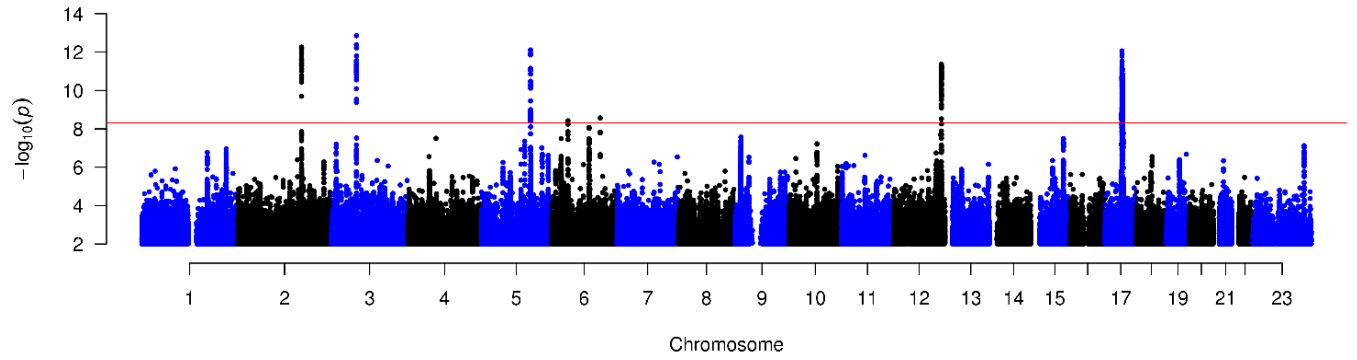
Supplementary Figure 1: Scatter plot of residualized waist circumference and leg fat % measurements of females in the UK Biobank, indicating in green the lipedema phenotype cases, in yellow the ‘buffer’ individuals, and in blue, the controls. Independent variables used to generate residuals were height, hip circumference, age, and recruitment center.



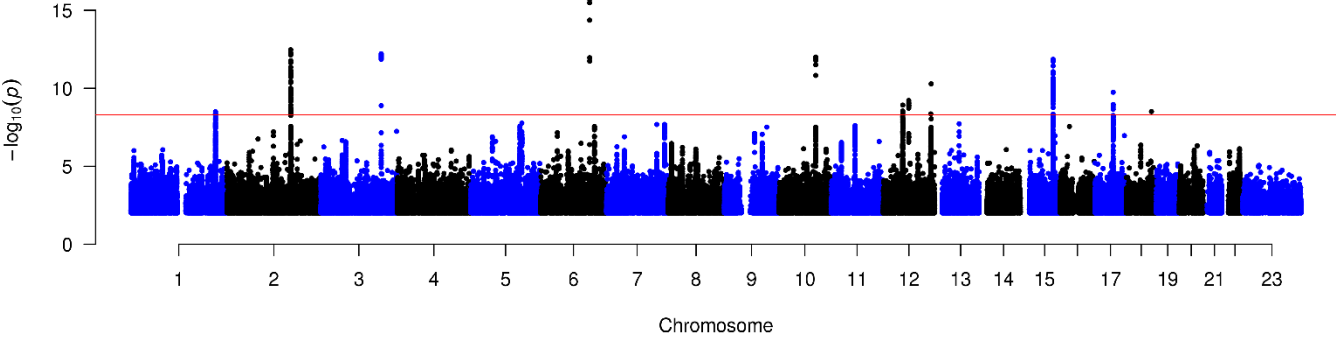
Supplementary Figure 2: Q-Q plot of GWAS of lipedema phenotype at 10% prevalence, with adjustment for hip circumference.



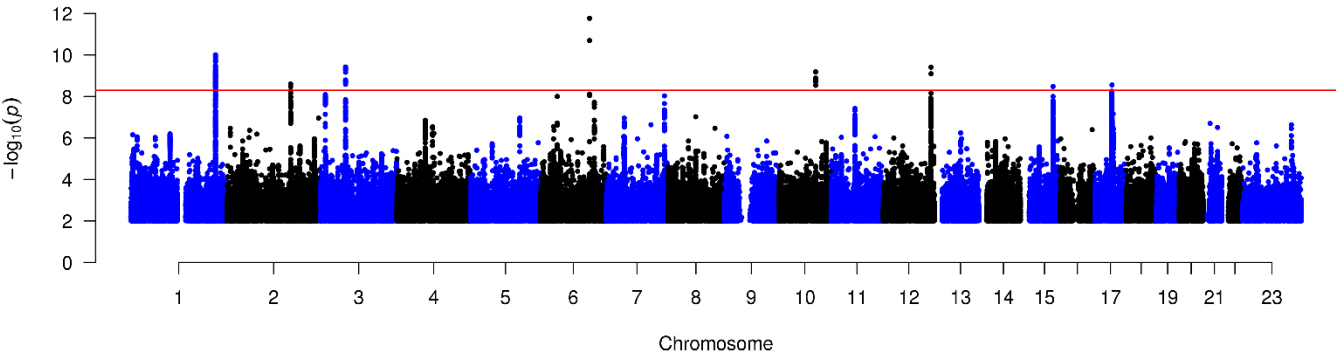
Supplementary Figure 3: Manhattan plot of lipedema phenotype at 10% prevalence with no adjustment for hip circumference.



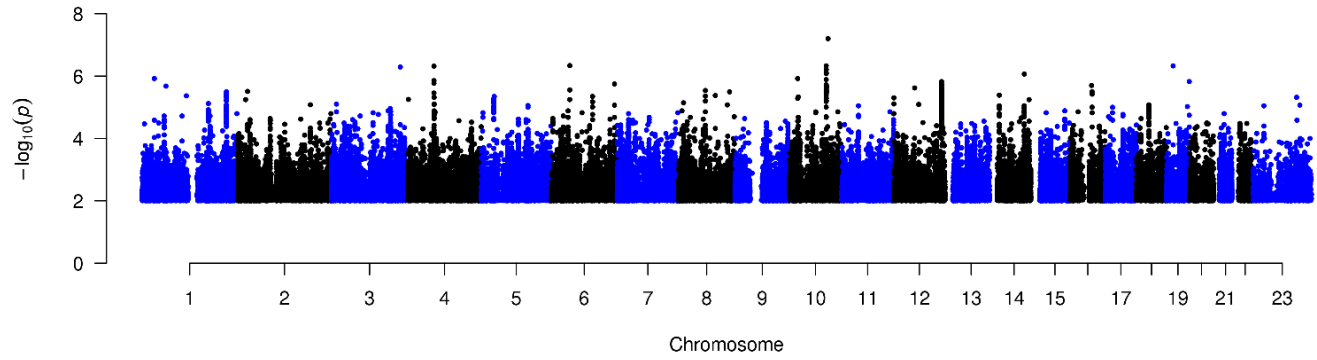
Supplementary Figure 4: Manhattan plots of lipedema phenotype at 10% prevalence among women with BMI <30



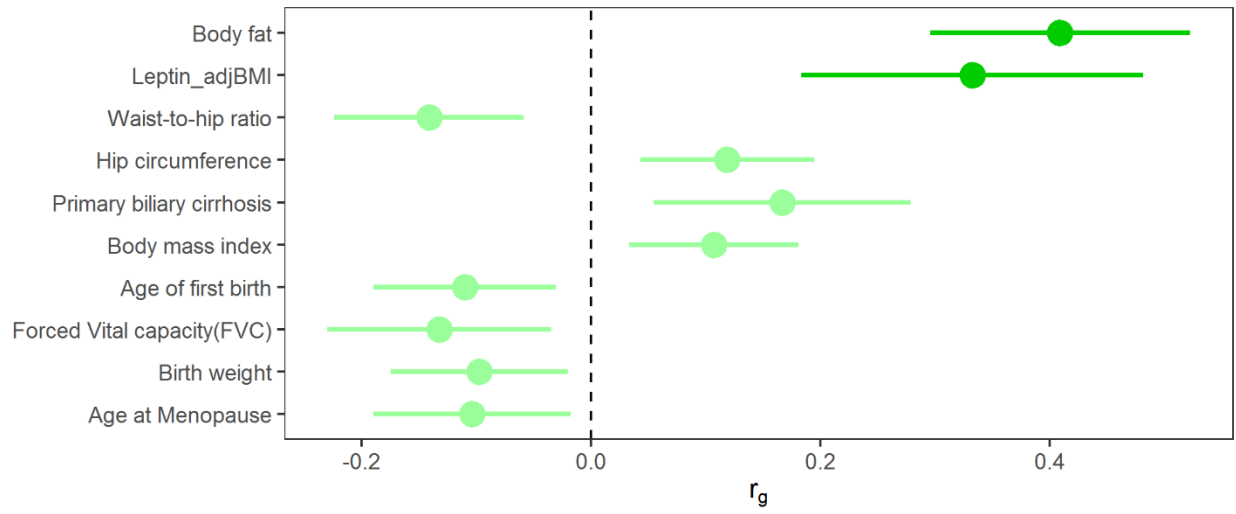
Supplementary Figure 5: Manhattan plots of lipedema phenotypes at 5% prevalence



Supplementary Figure 6: Manhattan plot of lipedema phenotype at 10% prevalence including leg pain as criteria for cases, hip adjusted, excluding SNPs with MAF<0.01.



Supplementary Figure 8: Genetic correlation of lipedema phenotype with other traits. Dark green color indicates $p < 2.5 \times 10^{-4}$, and light green color indicates $p < 0.05$.



Supplementary Figure 9: Results of gene-based enrichment analysis for 53 tissue types, based on GTEx v7 integrated in FUMA-GWAS. Dashed line represents the Bonferroni-corrected significance threshold.

