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Supplemental information

**L2 Δ 13, a splicing isoform of lysyl
oxidase-like 2, causes adipose tissue loss
via the gut microbiota and lipid metabolism**

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1 **Supplementary Materials**

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4 **Methods.**

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6 **Methods.**

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9 **3.**

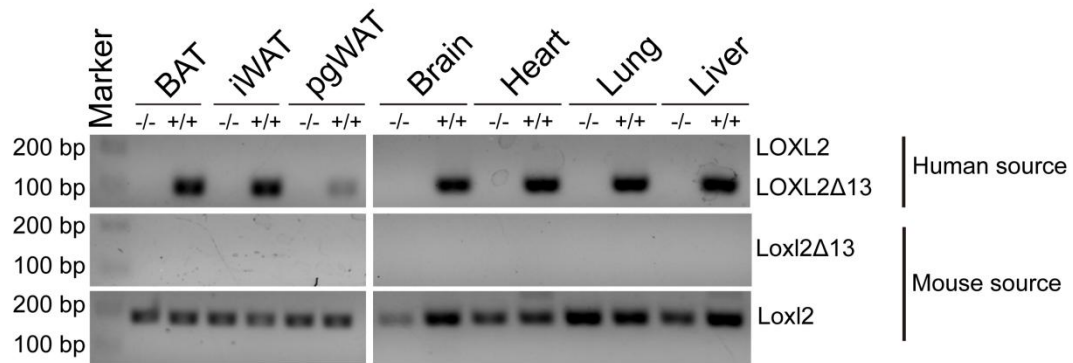
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1 **Supplementary figures**

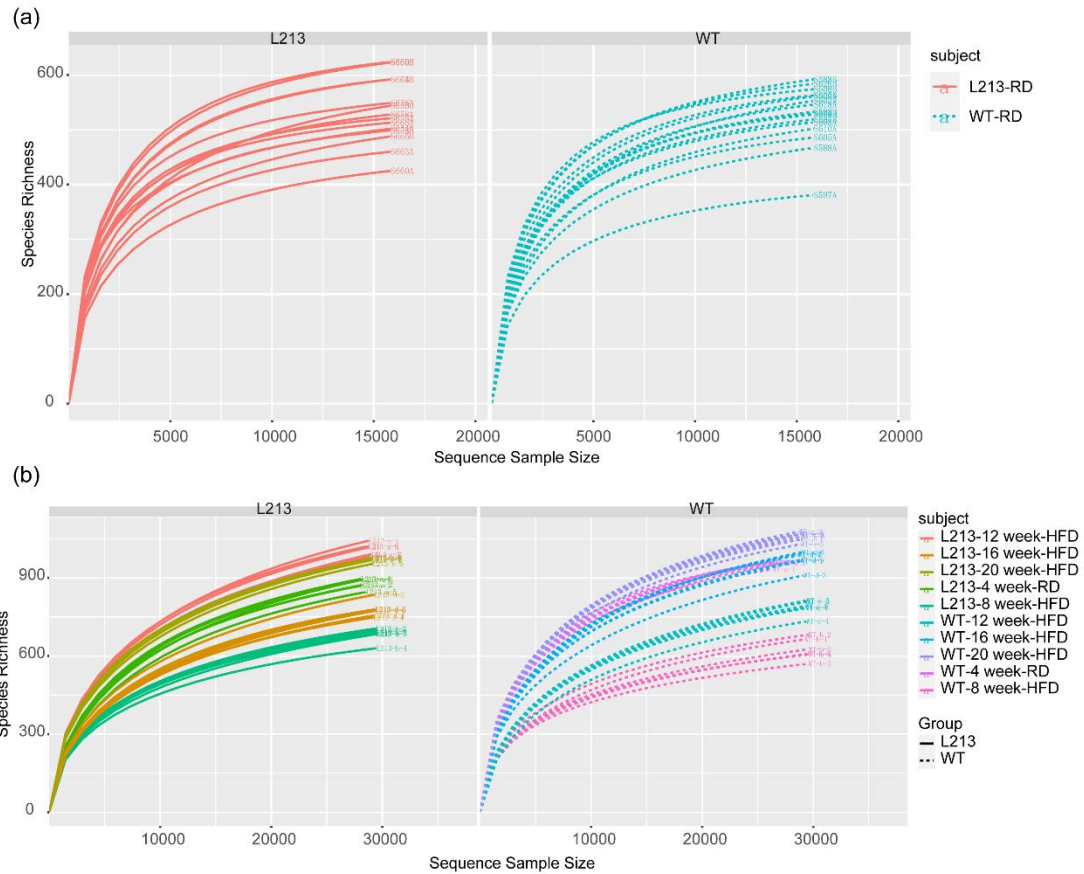


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3 **Figure S1. Expression of LOXL2Δ13 in various mouse tissues. Related to STAR**

4 **Methods.** RT-PCR was used to detect the expression of LOXL2Δ13 in various mouse tissues,
5 such as brain, heart, lung, liver, scapular (BAT), inguinal (iWAT) and perigonadal (pgWAT)
6 adipose tissue samples. -/-: control mice; +/+ : LOXL2Δ13 transgenic mice.

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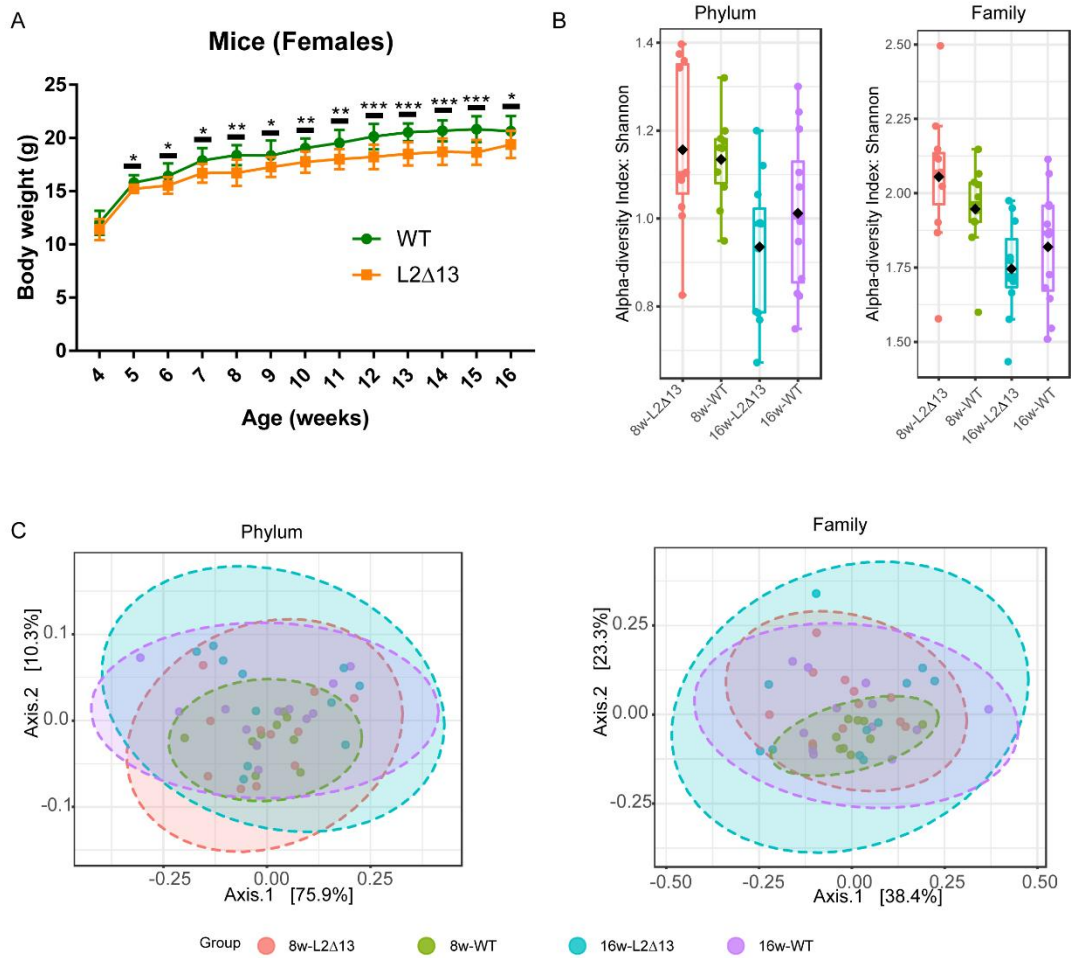
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2 **Figure S2. Rarefaction curve analysis of 16S rRNA sequencing. Related to STAR**

3 **Methods.** Rarefaction curves were used to evaluate the sequencing depth. The upper

4 part is the 16S rRNA analysis under a regular diet, while the bottom part represents

5 the high-fat diet.

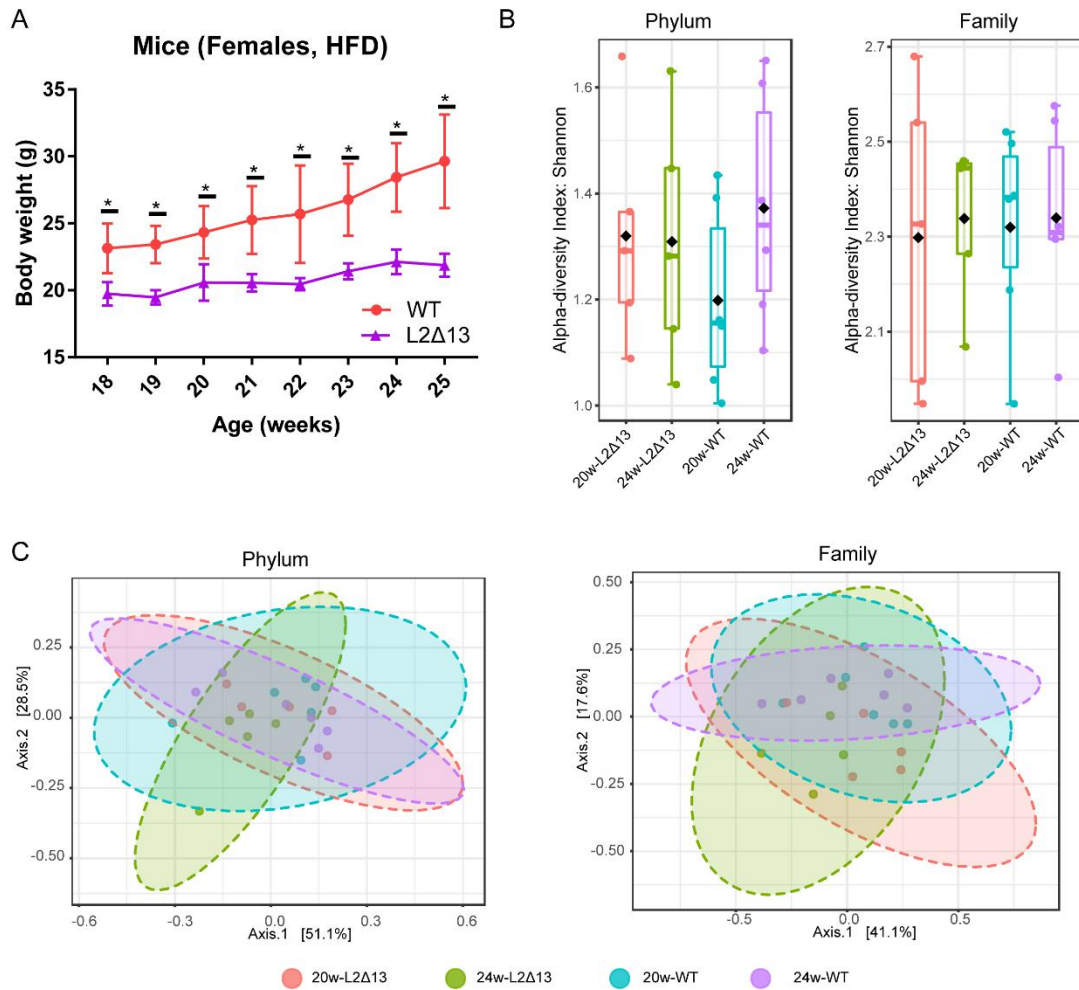


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2 **Figure S3. 16S rRNA sequencing for female mice under RD. Related to Figure 1.**

3 **A. Body weight of female mice. B. Alpha diversity of the microbiome in female mice.**

4 **C. Beta diversity of the microbiome in female mice.**

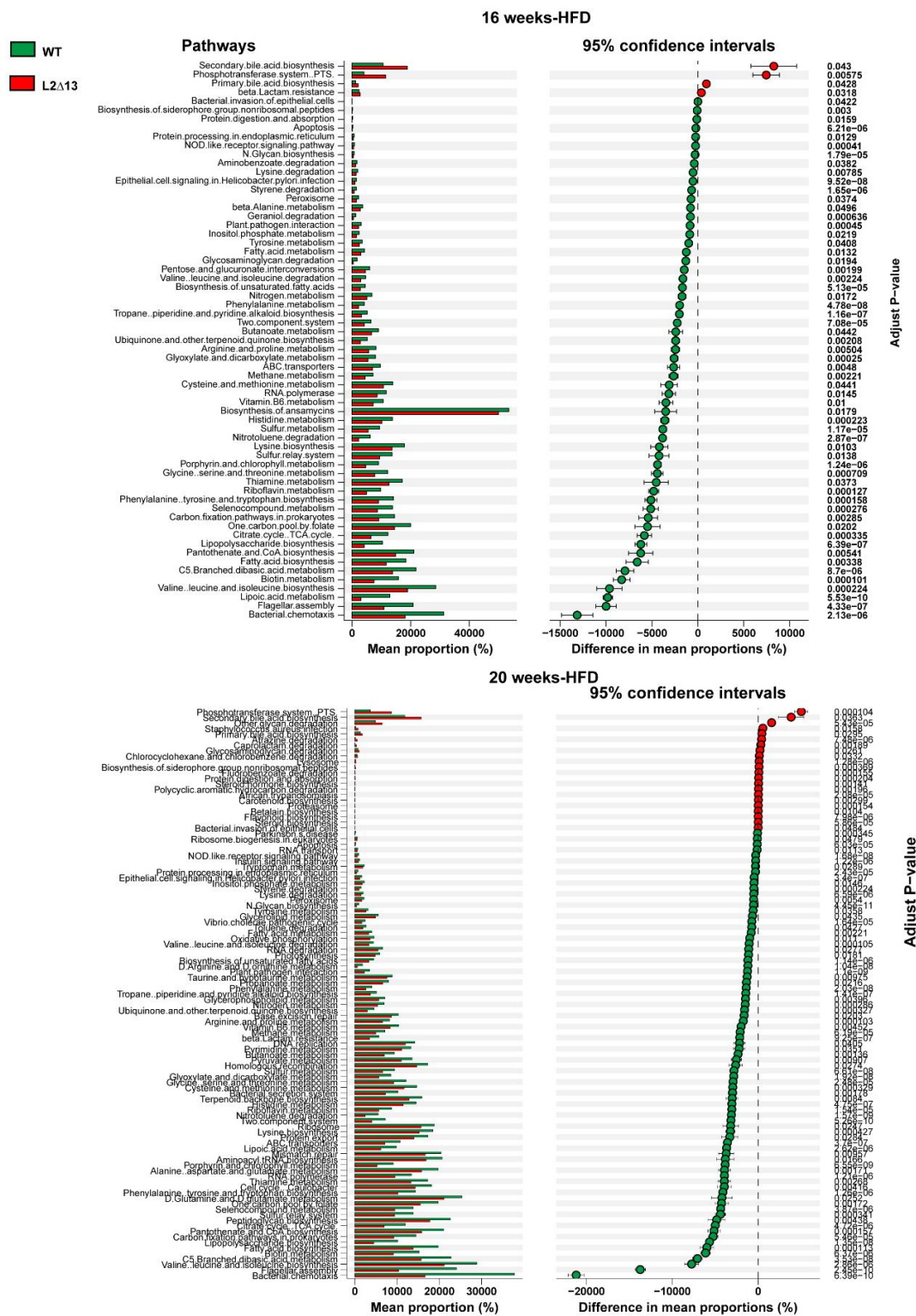


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2 **Figure S4. 16S rRNA sequencing for female mice under HFD. Related to Figure**
 3 **3. A.** Body weight of female mice under HFD. **B.** Alpha diversity of the microbiome
 4 in female mice under HFD. **C.** Beta diversity of the microbiome in female mice under
 5 HFD.

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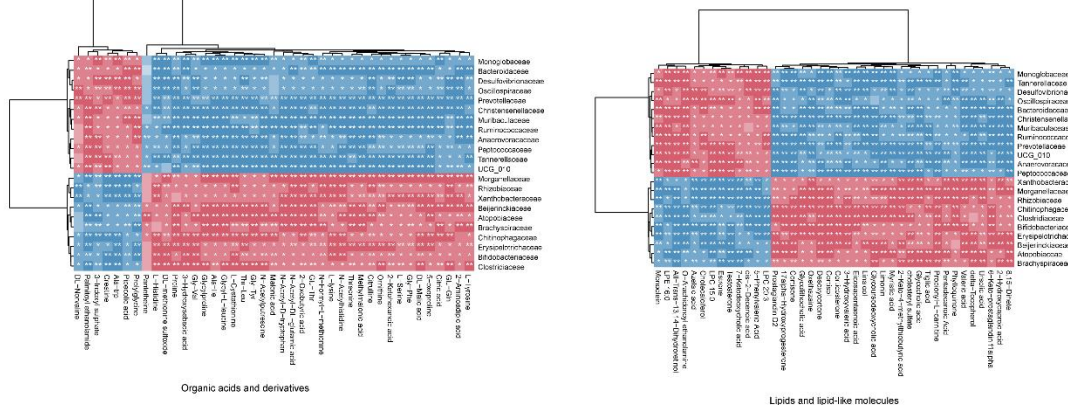
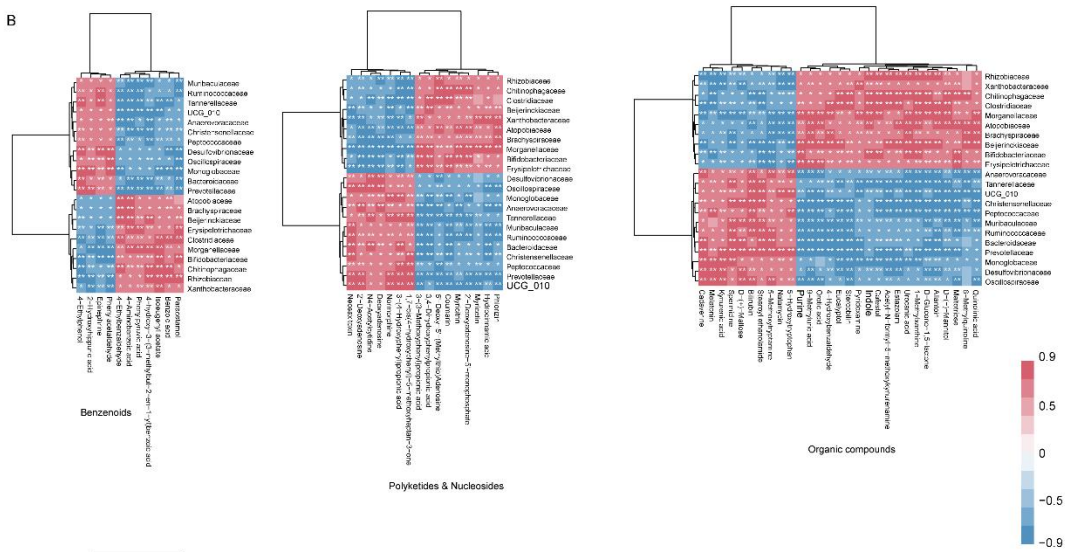
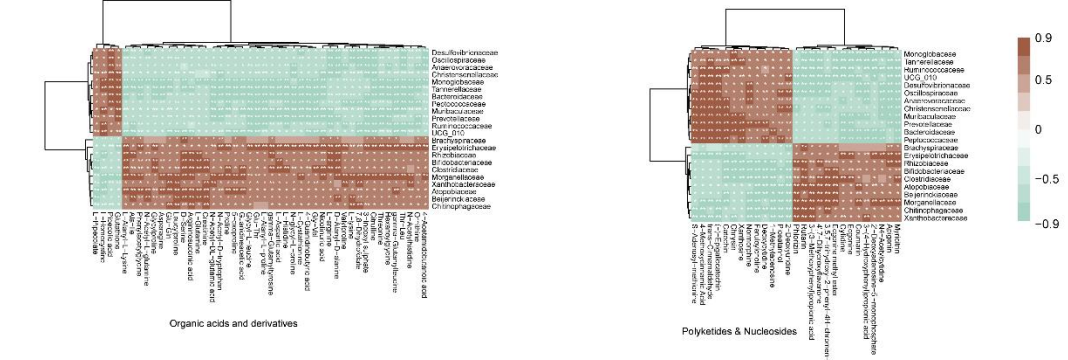
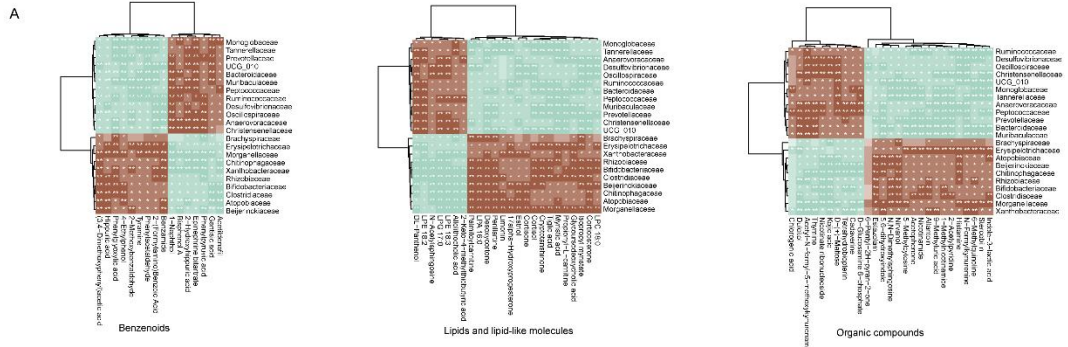


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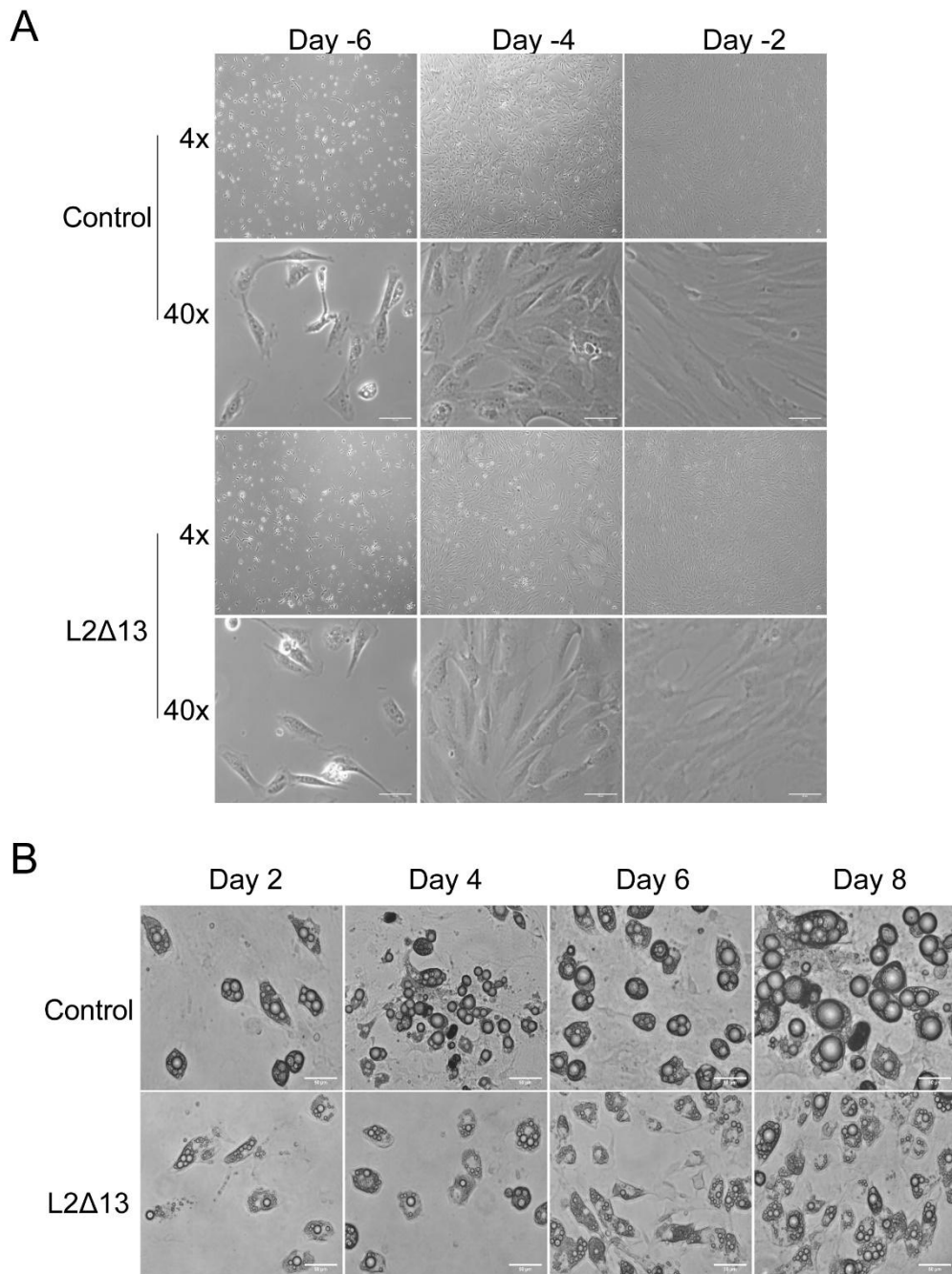
2 **Figure S5. PICRUSt2 analysis of the microbiotas under HFD. Related to Figure 4.**

3 The upper part is the PICRUSt2 results at 16 weeks, and the bottom part shows the

4 results at 20 weeks.



1 **Figure S6. Correlation analysis between DEMs and 22 crucial gut microbial**
2 **species. Related to Figure 5. (A)** DEMs were divided into five subclasses, and the
3 heatmap shows the Spearman correlation coefficient and p-value between DEMs and
4 microbiotas at 16 weeks. **(B)** Spearman correlation analysis between DEMs and 22
5 crucial gut microbial species at 20 weeks.
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2 **Figure S7. In vitro culture of primary adipose stem cell SVF. Related to STAR**

3 **Methods. (A)** After inoculation, cells in the P0 generation of SVFs began to grow

4 adhering to the wall. Continuous observation under the microscope showed that the

5 proliferation and growth of the cells were slow in the first 2 days (Day -6) and began

6 to grow exponentially on the 4th day (Day -4). On the 6th day, the cells reached the

1 contact inhibition state and appeared as fibroblasts (Day -2). **(B)** The cells grew to
2 more than 90% fusion (Day 0), at which time adipogenic differentiation could be
3 induced in vitro. After 2 days of adipogenic culture, a few cells became round and
4 lipid droplets appeared (Day 2). With the increase in time, the lipid droplets also
5 increased and gathered into larger droplets, and mature adipocytes were formed after
6 8 days. Scale bars represent 50 μ m.

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1 **Supplementary tables**

2 **Table S2. Primers for the qRT-PCR assays. Related to Figure 8 and Figure S1.**

3 **Table S4. Enrichment analysis of DEGs between L2Δ13 and WT mice under the**
4 **high-fat diet. Related to Figure 7.**

5 **Table S5. Enrichment analysis of DEGs between L2Δ13 and WT mice under the**
6 **regular diet. Related to Figure 8.**

7

Table S2. The primers for the qRT-PCR assay. Related to Figure 8 and Figure S1.

Primer	Sequence (5'-3')
Mogat2-F	TGGGAGCGCAGGTTACAGA
Mogat2-R	CAGGTGGCATAACAGGACAGA
Scd1-F	TTCTTGCATACACTCTGGTGC
Scd1-R	CGGGATTGAATGTTCTTGTCGT
Pck1-F	AGCATTCAACGCCAGGTTC
Pck1-R	CGAGTCTGTCAGTTCAATACCAA
Mttp-F	ATACAAGCTCACGTACTCCACT
Mttp-R	TCTCTGTTGACCCGCATTTTC
Angptl4-F	CCCCACGCACCTAGACAATG
Angptl4-R	GCCTCCATCTGAAGTCATCTCA
Nr1d1-F	TACATTGGCTCTAGTGGCTCC
Nr1d1-R	CAGTAGGTGATGGTGGGAAGTA
Mest-F	CTCCAGAACCGCAGAATCAAC
Mest-R	AGATACCTCCATTTCGACAGACAG
Ttpa-F	GGGCCATTGGTTGGGAAACA
Ttpa-R	AGCAGGAAAGCGTCTGTGAG
Oxtr-F	GATCACGCTCGCCGTCTAC
Oxtr-R	CCGTCTTGAGTCGCAGATTC
Npr3-F	GTCTACAGCGACGACAAACTC
Npr3-R	AGGTCCAAGTCTTTGGTCTCG
Pdk4-F	GACAGACGCTATCATCTACTT
Pdk4-R	CTTGGGATACACCAGTCAT
Adipoq-F	GTTCCCAATGTACCCATTCGC
Adipoq-R	TGTTGCAGTAGAACTTGCCAG
Plin4-F	TGTGACCAGCAGTGAAGATG
Plin4-R	TCCGACAAGGGCCGACT
Pparg-F	GTTGATTTCTCCAGCATTTTC
Pparg-R	TTGATCGCACTTTGGTATT
Pgc-1 α -F	ACAGGAACAGCAGCAGAG
Pgc-1 α -R	TAAGGTTTCGCTCAATAGTC
Foxo1-F	ATGCTCAATCCAGAGGGGAGG

Foxo1-R	ACTCGCAGGCCACTTAGAAAA
Apq7-F	AATATGGTGCGAGAGTTTCTGG
Apq7-R	AACCCAAGTTGACACCGAGAT
C/ebpd-F	CCTGCCATGTACGACGACGAG
C/ebpd-R	GCCGCTTTGTGGTTGCTGTTG
β -actin-F	GTGACGTTGACATCCGTAAGA
β -actin-R	GCCGGACTCATCGTACTCC

Primers for the RT-PCR assay to identify the alternative splicing L2 Δ 13 in mice

LOXL2&L2 Δ 13-qF	ACTGACGTGCCCCCTGGAGAC
LOXL2&L2 Δ 13-qR	CCCAAGCTTCCAGAGCCCGCTGAAGTG
Loxl2 Δ 13-qF	GGGAGACATTCAGAAGAGTT
Loxl2 Δ 13-qR	AAGGCTCCACCTGGAACAG
Loxl2-qF	GAGAACAAGGCATCACCA
Loxl2-qR	CATCATAGCGGCTCCTG

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1 **Table S4. The enrichment analysis of DEGs between L2A13 and WT mice under**
 2 **the high-fat diet. Related to Figure 7.**

Description	ID	Enrichment	LogP	count
HALLMARK	hallmark myogenesis	21.48485591	-54.60093701	53
HALLMARK	hallmark hypoxia	8.512867435	-13.07673682	21
HALLMARK	hallmark tnfa signaling via nfkb	6.080619597	-7.492884664	15
HALLMARK	hallmark epithelial mesenchymal transition	4.864495677	-5.102684911	12
HALLMARK	hallmark glycolysis	3.648371758	-3.048849647	9
HALLMARK	hallmark kras signaling up	3.648371758	-3.048849647	9
HALLMARK	hallmark il2 stat5 signaling	3.259293586	-2.465739178	8
HALLMARK	hallmark apical junction	3.242997118	-2.452570907	8
HALLMARK	hallmark kras signaling dn	3.242997118	-2.452570907	8
HALLMARK	hallmark complement	3.242997118	-2.452570907	8
HALLMARK	hallmark xenobiotic metabolism	3.242997118	-2.452570907	8
HALLMARK	hallmark fatty acid metabolism	3.591927188	-2.447822275	7
HALLMARK	hallmark apoptosis	3.524996868	-2.403037325	7
HALLMARK	hallmark cholesterol homeostasis	4.382428538	-1.875913284	4
HALLMARK	hallmark estrogen response early	2.837622478	-1.907040908	7
HALLMARK	hallmark mtorc1 signaling	2.432247839	-1.417319171	6
HALLMARK	hallmark uv response up	2.565662277	-1.331860972	5
HALLMARK	hallmark p53 pathway	2.432247839	-1.417319171	6
KEGG Pathway	Hypertrophic cardiomyopathy	7.61255771	-7.253208204	12
KEGG Pathway	Dilated cardiomyopathy	7.211896778	-6.987206734	12
KEGG Pathway	Oxytocin signaling pathway	5.489825272	-6.966679336	15
KEGG Pathway	Adrenergic signaling in cardiomyocytes	4.948162512	-5.60439587	13
KEGG Pathway	Arrhythmogenic right ventricular cardiomyopathy	6.761153229	-5.14758308	9
KEGG Pathway	Cardiac muscle contraction	5.885998229	-5.107386356	10
KEGG Pathway	p53 signaling pathway	5.55082333	-3.577532587	7
KEGG Pathway	Calcium signaling pathway	3.394789249	-3.359751863	11
KEGG Pathway	HIF-1 signaling pathway	4.114896059	-3.121666065	8
KEGG Pathway	MAPK signaling pathway	2.811455972	-3.085005962	13
KEGG Pathway	Glycolysis / Gluconeogenesis	4.567534626	-2.694775849	6
KEGG Pathway	Biosynthesis of amino acids	4.391860217	-2.608033952	6
KEGG Pathway	Glucagon signaling pathway	3.735133456	-2.555405189	7
KEGG Pathway	Carbon metabolism	3.386943049	-2.320188107	7
KEGG Pathway	Insulin signaling pathway	3.024857368	-2.282726103	8
KEGG Pathway	cGMP-PKG signaling pathway	2.718770611	-2.01360266	8
KEGG Pathway	Tight junction	2.702683211	-1.998994421	8
KEGG Pathway	Gastric acid secretion	3.806278855	-1.99243579	5
KEGG Pathway	Apoptosis	2.875246617	-1.944183877	7
KEGG Pathway	Apelin signaling pathway	2.81450197	-1.896911551	7
KEGG Pathway	Cholinergic synapse	3.031549531	-1.834944668	6
KEGG Pathway	Regulation of lipolysis in adipocytes	4.152304205	-1.80529018	4

KEGG Pathway	Insulin secretion	3.207538361	-1.696595768	5
KEGG Pathway	GnRH signaling pathway	3.102944719	-1.641152078	5
KEGG Pathway	Longevity regulating pathway	3.069579722	-1.623209279	5
KEGG Pathway	human papillomavirus infection	4.391860217	-1.514321113	3
KEGG Pathway	AMPK signaling pathway	2.556455947	-1.511879774	6
KEGG Pathway	Pentose phosphate pathway	4.177623134	-1.458481324	3
KEGG Pathway	Fructose and mannose metabolism	4.177623134	-1.458481324	3
KEGG Pathway	human immunodeficiency virus 1 infection	4.177623134	-1.458481324	3
KEGG Pathway	NF-kappa B signaling pathway	2.771562273	-1.457158253	5
KEGG Pathway	Proteoglycans in cancer	2.114599364	-1.431628761	8
KEGG Pathway	Mineral absorption	3.644309542	-1.309247644	3
KEGG Pathway	Salivary secretion	2.8908447	-1.301222342	4

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1 **Table S5. The enrichment analysis of DEGs between L2A13 and WT mice under**
2 **the regular diet. Related to Figure 8.**

Category	Description	Enrichment	LogP	Count
Hallmark	HALLMARK INTERFERON GAMMA RESPONSE	4.93919551	-32.3623578	75
Hallmark	HALLMARK ALLOGRAFT REJECTION	4.80748363	-30.62248392	73
Hallmark	HALLMARK IL2 STAT5 SIGNALING	3.97121247	-20.38286784	60
Hallmark	HALLMARK ADIPOGENESIS	3.819644528	-18.81841703	58
Hallmark	HALLMARK INTERFERON ALPHA RESPONSE	5.024061412	-16.59416339	37
Hallmark	HALLMARK EPITHELIAL MESENCHYMAL TRANSITION	3.490364827	-15.39977016	53
Hallmark	HALLMARK MYOGENESIS	3.424508887	-14.74903235	52
Hallmark	HALLMARK INFLAMMATORY RESPONSE	3.292797007	-13.48152311	50
Hallmark	HALLMARK TNFA SIGNALING VIA NFKB	3.095229186	-11.6672277	47
Hallmark	HALLMARK APICAL JUNCTION	3.029373246	-11.08624397	46
Hallmark	HALLMARK KRAS SIGNALING UP	3.029373246	-11.08624397	46
Hallmark	HALLMARK IL6 JAK STAT3 SIGNALING	3.784824145	-8.424015242	25
Hallmark	HALLMARK FATTY ACID METABOLISM	2.834306284	-7.604939401	34
Hallmark	HALLMARK ESTROGEN RESPONSE LATE	2.568381665	-7.369752571	39
Hallmark	HALLMARK ESTROGEN RESPONSE EARLY	2.502525725	-6.891206902	38
Hallmark	HALLMARK APOPTOSIS	2.617875881	-6.365660197	32
Hallmark	HALLMARK G2M CHECKPOINT	2.370813845	-5.975586868	36
Hallmark	HALLMARK E2F TARGETS	2.370813845	-5.975586868	36
Hallmark	HALLMARK COMPLEMENT	2.304957905	-5.539004196	35
Hallmark	HALLMARK XENOBIOTIC METABOLISM	2.304957905	-5.539004196	35
Hallmark	HALLMARK KRAS SIGNALING DN	2.239101964	-5.116918936	34
Hallmark	HALLMARK TGF BETA SIGNALING	3.658663341	-5.111827107	15
Hallmark	HALLMARK UV RESPONSE DN	2.469597755	-4.98321479	27
Hallmark	HALLMARK MITOTIC SPINDLE	2.117979984	-4.360772374	32
Hallmark	HALLMARK HYPOXIA	2.107390084	-4.317345454	32
Hallmark	HALLMARK P53 PATHWAY	2.041534144	-3.94043814	31
Hallmark	HALLMARK APICAL SURFACE	3.292797007	-3.460901635	11
Hallmark	HALLMARK UV RESPONSE UP	2.084048738	-3.436797578	25
Hallmark	HALLMARK WNT BETA CATENIN SIGNALING	2.822397434	-2.431099032	9
Hallmark	HALLMARK COAGULATION	1.90886783	-2.410553361	20
Hallmark	HALLMARK HEDGEHOG SIGNALING	2.926930672	-2.316574277	8
Hallmark	HALLMARK MTORC1 SIGNALING	1.712254443	-2.297291006	26
Hallmark	HALLMARK HEME METABOLISM	1.712254443	-2.297291006	26
Hallmark	HALLMARK NOTCH SIGNALING	2.881197381	-2.047101324	7
Hallmark	HALLMARK CHOLESTEROL HOMEOSTASIS	2.135868329	-2.021037727	12
Hallmark	HALLMARK PEROXISOME	1.899690581	-1.924620693	15
Hallmark	HALLMARK ANGIOGENESIS	2.561064338	-1.767473404	7
KEGG Pathway	Cytokine-cytokine receptor interaction	3.268405918	-17.64444471	67
KEGG Pathway	Rap1 signaling pathway	3.324156978	-14.43233417	53

KEGG Pathway	Primary immunodeficiency	7.47553915	-13.95921619	21
KEGG Pathway	Chemokine signaling pathway	3.473719919	-13.92766424	48
KEGG Pathway	Rap1 signaling pathway	3.119491901	-13.44756609	54
KEGG Pathway	T cell receptor signaling pathway	4.219895193	-12.35779793	33
KEGG Pathway	NF-kappa B signaling pathway	4.159322535	-11.11795244	30
KEGG Pathway	Pathways in cancer	2.367479367	-11.07505611	71
KEGG Pathway	PI3K-Akt signaling pathway	2.391610457	-10.98979199	69
KEGG Pathway	B cell receptor signaling pathway	4.637742263	-10.54291963	25
KEGG Pathway	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4.573329176	-10.39008588	25
KEGG Pathway	NF-kappa B signaling pathway	3.815951671	-10.37927308	31
KEGG Pathway	Leukocyte transendothelial migration	3.697175586	-10.2922253	32
KEGG Pathway	Hematopoietic cell lineage	3.937777864	-10.12042993	29
KEGG Pathway	Valine, leucine and isoleucine degradation	5.487995011	-10.1072038	20
KEGG Pathway	Cell adhesion molecules (CAMs)	3.292797007	-9.908637847	36
KEGG Pathway	PI3K-Akt signaling pathway	2.349246987	-9.47384343	61
KEGG Pathway	Focal adhesion	2.779848729	-8.95526586	42
KEGG Pathway	Regulation of actin cytoskeleton	2.671514552	-8.592246633	43
KEGG Pathway	ECM-receptor interaction	3.854981861	-8.289724408	24
KEGG Pathway	Adherens junction	4.024529675	-8.037799752	22
KEGG Pathway	Axon guidance	2.784765468	-7.995705928	37
KEGG Pathway	Th17 cell differentiation	3.292797007	-7.863537677	28
KEGG Pathway	Tight junction	2.789192758	-7.817739319	36
KEGG Pathway	Th17 cell differentiation	3.32357081	-7.699945117	27
KEGG Pathway	Regulation of lipolysis in adipocytes	4.314699526	-7.581326307	19
KEGG Pathway	Fc gamma R-mediated phagocytosis	3.473719919	-7.316980505	24
KEGG Pathway	Ras signaling pathway	2.33928436	-7.260296386	46
KEGG Pathway	Oxytocin signaling pathway	2.77288169	-6.964690408	32
KEGG Pathway	Oxytocin signaling pathway	2.699684502	-6.870449207	33
KEGG Pathway	Dilated cardiomyopathy	3.365970273	-6.767971349	23
KEGG Pathway	Small cell lung cancer	3.449596864	-6.705102181	22
KEGG Pathway	Th1 and Th2 cell differentiation	3.225597068	-6.656794929	24
KEGG Pathway	Measles	2.850480991	-6.644377674	29
KEGG Pathway	Th1 and Th2 cell differentiation	3.292797007	-6.580833779	23
KEGG Pathway	Calcium signaling pathway	2.532920774	-6.533307088	35
KEGG Pathway	Osteoclast differentiation	2.836871267	-6.393664196	28
KEGG Pathway	Measles	2.584220436	-6.060661646	31
KEGG Pathway	beta-Alanine metabolism	5.098524397	-5.892219947	12
KEGG Pathway	Osteoclast differentiation	2.672414962	-5.840973948	28
KEGG Pathway	NOD-like receptor signaling pathway	2.479282452	-5.820277265	32
KEGG Pathway	Epstein-Barr virus infection	2.070387415	-5.804156899	47
KEGG Pathway	Jak-STAT signaling pathway	2.532920774	-5.697951953	30
KEGG Pathway	Gastric acid secretion	3.336700967	-5.642948446	19
KEGG Pathway	cAMP signaling pathway	2.328240308	-5.641620867	35
KEGG Pathway	Gastric acid secretion	3.292797007	-5.549865141	19

KEGG Pathway	MAPK signaling pathway	2.117720428	-5.397942302	41
KEGG Pathway	HTLV-I infection	2.109448082	-5.35470175	41
KEGG Pathway	Platelet activation	2.634237605	-5.350811772	26
KEGG Pathway	Tryptophan metabolism	4.280636109	-5.337272159	13
KEGG Pathway	Cholinergic synapse	2.748769675	-5.323212344	24
KEGG Pathway	PPAR signaling pathway	3.292797007	-5.291141548	18
KEGG Pathway	Viral myocarditis	3.5718476	-5.263034423	16
KEGG Pathway	Tyrosine metabolism	4.515835895	-5.244734182	12
KEGG Pathway	aldosterone synthesis and secretion	2.840844476	-5.176498072	22
KEGG Pathway	Natural killer cell mediated cytotoxicity	2.574818712	-5.16156185	26
KEGG Pathway	Hippo signaling pathway	2.34659097	-5.145704165	31
KEGG Pathway	Salivary secretion	2.926930672	-4.968181113	20
KEGG Pathway	Hypertrophic cardiomyopathy (HCM)	3.015091235	-4.947604251	19
KEGG Pathway	Adipocytokine signaling pathway	3.245075311	-4.940705304	17
KEGG Pathway	Apoptosis	2.481528179	-4.861602632	26
KEGG Pathway	Phenylalanine metabolism	6.19820613	-4.847598402	8
KEGG Pathway	cGMP-PKG signaling pathway	2.343340201	-4.844787246	29
KEGG Pathway	Insulin secretion	2.863301745	-4.817646419	20
KEGG Pathway	TNF signaling pathway	2.683019783	-4.758767971	22
KEGG Pathway	cAMP signaling pathway	2.098065349	-4.731514994	36
KEGG Pathway	drug metabolism	2.589207903	-4.681961488	23
KEGG Pathway	Salivary secretion	2.802380431	-4.672259702	20
KEGG Pathway	Fluid shear stress and atherosclerosis	2.411625977	-4.634653978	26
KEGG Pathway	Amoebiasis	2.743997505	-4.531774464	20
KEGG Pathway	Aldosterone synthesis and secretion	2.891236396	-4.458237014	18
KEGG Pathway	Glutathione metabolism	3.414752451	-4.440518948	14