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Supplementary Information for

Lack of Adipocyte Purinergic $P2Y_6$ Receptor Greatly Improves Whole Body Glucose Homeostasis

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Supplementary Figures and Tables

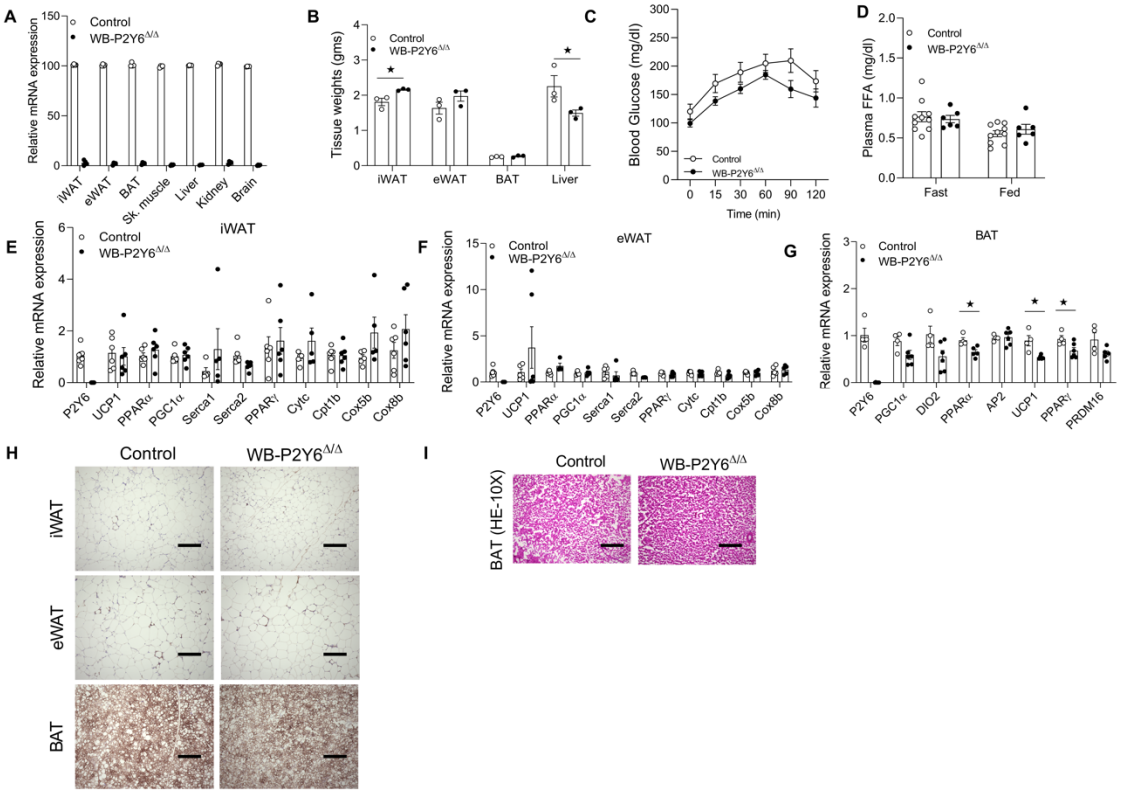

Fig. S1. Metabolic and expression profiling of WB-P2Y6$^{\Delta/\Delta}$ and control mice on HFD.

(A) mRNA levels of P2Y$_6$R in different tissues of WB-P2Y6$^{\Delta/\Delta}$ and control mice (n=3-4/group).

(B) Tissue weights (iWAT, eWAT and BAT) of WB-P2Y6$^{\Delta/\Delta}$ and control mice (n=3/group).

(C) Pyruvate tolerance test (PTT, 2 g/kg sodium pyruvate, i.p.) (n=5-9/group).

(D) Fasting and fed plasma free fatty acid (FFA) levels (n=6-9/group).

(E) – (G) Gene expression analysis in (E) iWAT, (F) eWAT and (G) BAT of WB-P2Y6$^{\Delta/\Delta}$ and control mice (n=5-6/group).

(H) Representative UCP1 stained sections of iWAT, eWAT and BAT of WB-P2Y6$^{\Delta/\Delta}$ and control mice.

(I) Representative H&E-stained sections of BAT from WB-P2Y6$^{\Delta/\Delta}$ and control mice on HFD. 18sRNA was taken as normalization control for RT-PCR analysis. (A-B, D-G: two-tailed Student's t-test; C: two-way ANOVA followed by Bonferroni's post hoc test).

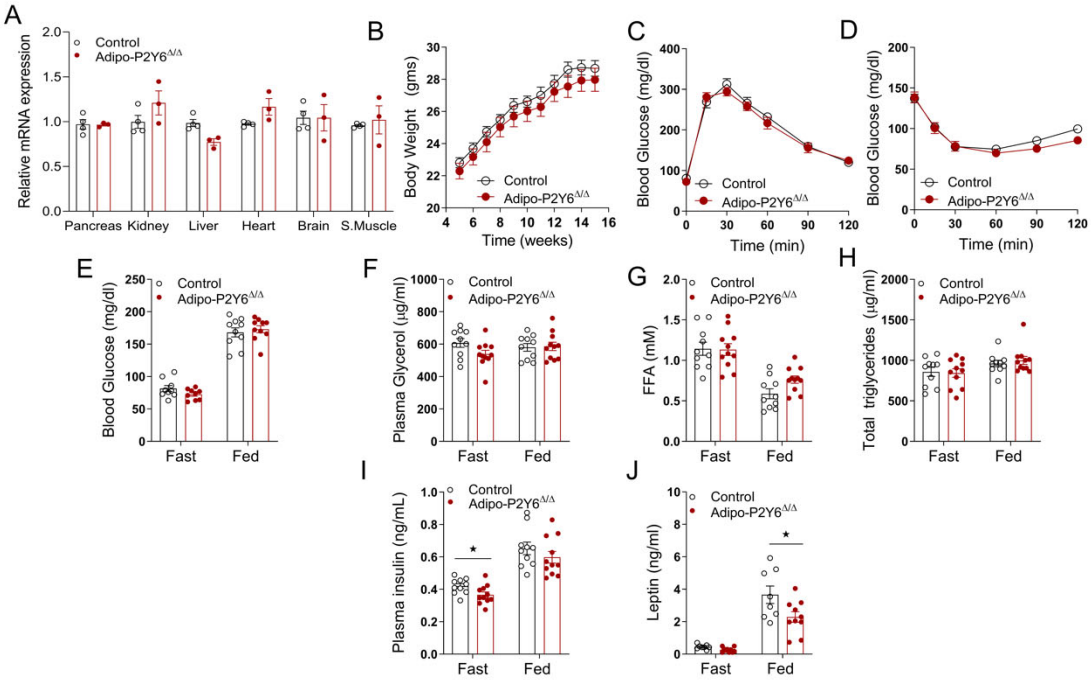

Fig. S2. Metabolic analysis of adipo-P2Y6$^{\Delta/\Delta}$ and control mice maintained on chow diet (CD).

(A) mRNA levels of $P2Y_6R$ in pancreas, kidney, liver, heart, brain and skeletal muscle of adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=3/group).
(B) Body weight measurements on CD (n=10-11/group).
(C) Glucose tolerance test (IGTT, 2g /kg glucose i.p.) (n=9-10/group).
(D) Insulin tolerance test (ITT, 0.75 U/kg insulin i.p.) (n=9-10/group).
(E) Fasting and fed blood glucose levels (n=9-10/group).
(F) Fasting and fed plasma glycerol levels (n=9-10/group).
(G) Fasting plasma free fatty acid (FFA) levels (n=10-11/group).
(H) Fasting and fed total triglyceride levels (n= 10-11/group).
(I) Fasting and fed plasma insulin levels (n=10-11/group).
(J) Fasting and fed plasma leptin levels (n=8-10/group).

All data are expressed as means ± SEM. *p< 0.05 (A-B, E-J: two-tailed Student's t-test; C-D: two-way ANOVA followed by Bonferroni's post hoc test).

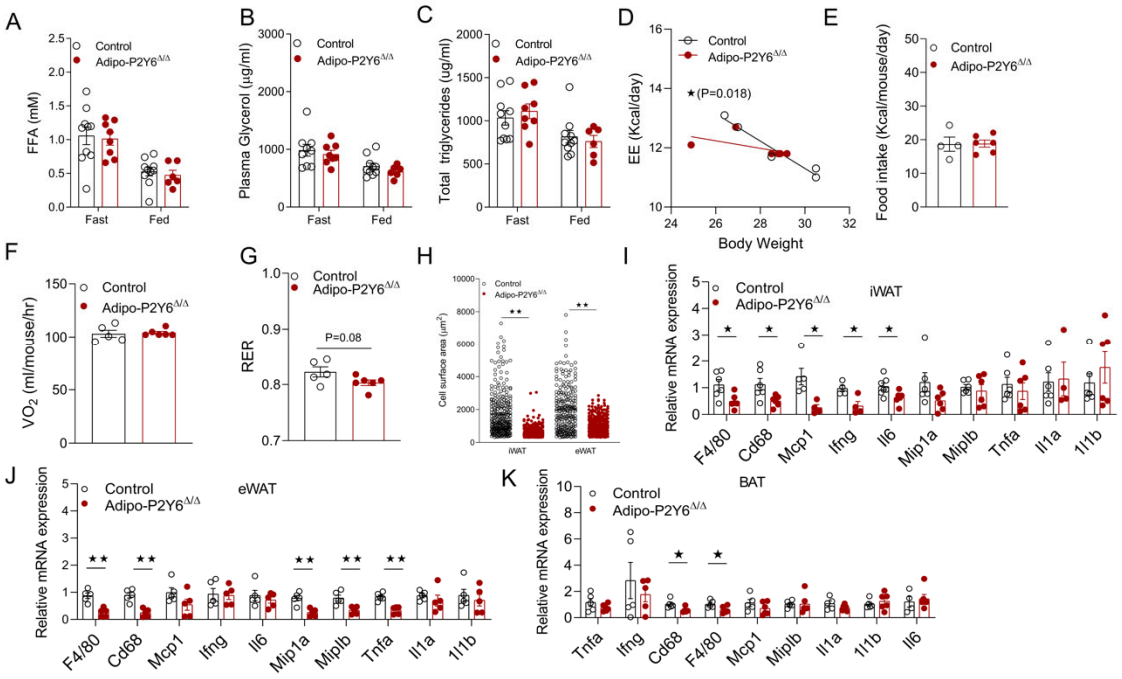

Fig. S3. Metabolic analysis of adipo-P2Y6$^{\Delta/\Delta}$ and control mice on high fat diet (HFD).

(A) Fasting plasma free fatty acid (FFA) levels (n=6-10/group).
(B) Fasting and fed plasma glycerol levels (n=6-10/group).
(C) Fasting and fed total triglyceride levels (n=6-10/group).
(D) Total energy expenditure vs total body mass (n=5-6/group).
(E) Food intake (n=4-6/group).
(F) Oxygen consumption rate ($V0_2$) (n=5-6/group).
(G) Respiratory exchange ratio (RER) (n=5-6/group).
(H) Cell surface area quantified using Adiposoft software in iWAT and eWAT sections. (n=5 sections/group).

(I-K) mRNA expression levels of inflammatory markers in (I) iWAT, (J) eWAT, and (K) BAT of HFD fed adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=4-6/group).

18sRNA was taken as normalization control for RT-PCR analysis. Data (A-C, E-K) are expressed as means ± SEM. Analysis of covariance (ANCOVA) was performed for data (D). *p< 0.05 (two-tailed Student's t-test). Indirect calorimetry studies (D-G) were done with mice during first week of HFD feeding.

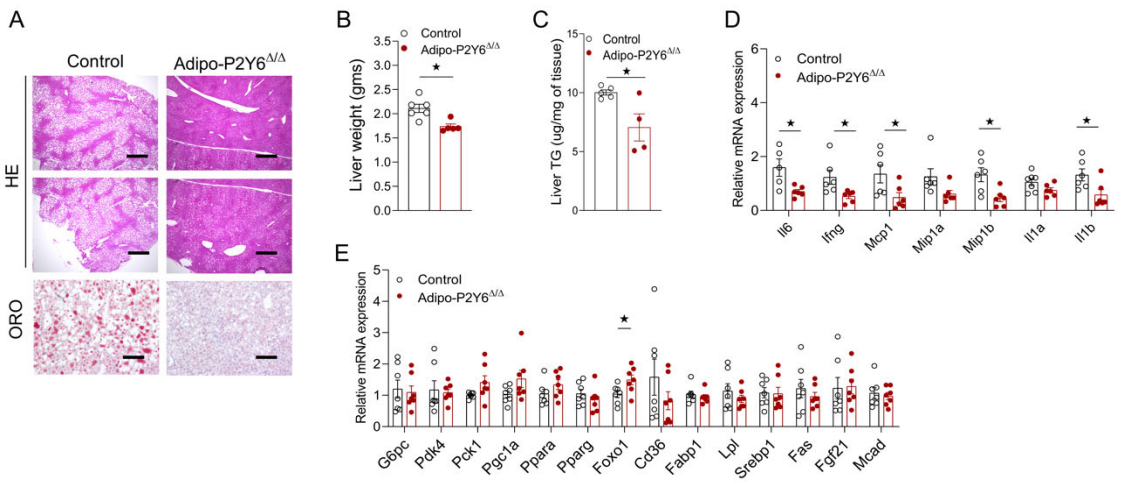

Fig. S4. Reduced hepatic steatosis and hepatic inflammation in adipo-P2Y6$^{\Delta/\Delta}$ mice maintained on high fat diet (HFD).

(A) Representative H&E and Oil Red O (ORO) stained sections of liver from adipo-P2Y6$^{\Delta/\Delta}$ and control mice on HFD.
(B) Liver weight (grams) from adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=5-6/group).
(C) Liver triglyceride (TG) levels from adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=4/group).
(D) mRNA expression levels of inflammatory markers in the liver of adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=5-6/group).
(E) Expression analysis of genes involved in hepatic glucose and lipid metabolism (n=7/group).

18sRNA was taken as normalization control for RT-PCR analysis. All data are expressed as means ± SEM. *p< 0.05 (two-tailed Student's t-test).

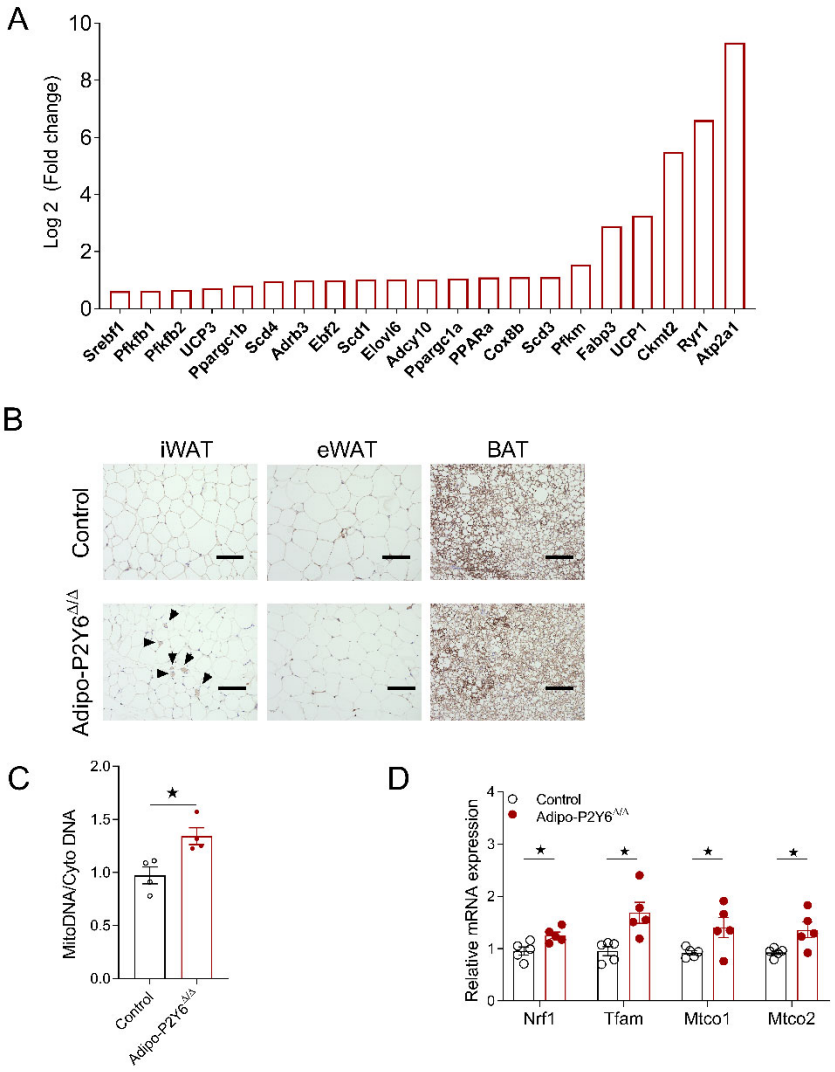

Fig. S5. Expression profiling and UCP1 staining in adipose tissues of adipo-P2Y6$^{\Delta/\Delta}$ mice maintained on HFD.

(A) Log2 (Fold change) of genes involved in imparting beige-like phenotype to iWAT of adipo-P2Y6$^{\Delta/\Delta}$ mice ($p<0.05$) (n=6 libraries/group).
(B) Representative UCP1 stained sections of iWAT, eWAT and BAT of adipo-P2Y6$^{\Delta/\Delta}$ and control mice.
(C) MitoDNA (mitochondrial DNA)/CytoDNA (cytoplasmic DNA) in iWAT of adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=4/group).
(D) mRNA expression levels of mitochondrial biogenesis markers in the iWAT of adipo-P2Y6$^{\Delta/\Delta}$ and control mice (n=4-6/group).

The expression of 18sRNA was used to normalize qRT-PCR data. All data are expressed as means ± SEM. *p< 0.05, **p< 0.01, ***p< 0.001 (two-tailed Student's t-test).

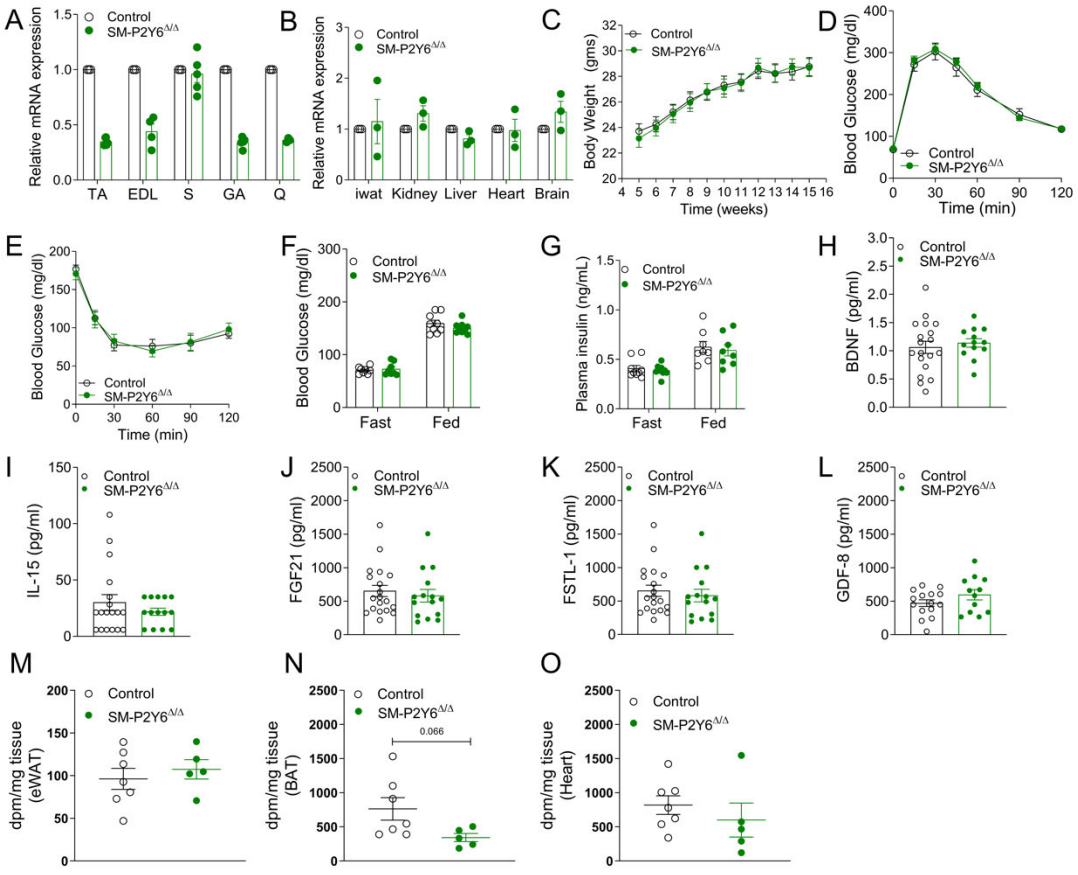

Fig. S6. Metabolic analysis of SM-P2Y6$^{\Delta/\Delta}$ and control mice maintained on CD or HFD.

(A) mRNA levels of P2Y$_6$R in tibialis anterior (TA), gastrocnemius (G), quadriceps (Q), soleus (S) muscle of SM-P2Y6$^{\Delta/\Delta}$ and control mice (n=3-4/group).

(B) mRNA levels of P2Y$_6$R in IWAT, kidney, liver, heart and brain of SM-P2Y6$^{\Delta/\Delta}$ and control mice (n=3/group).

(C) Body weight measurements on CD (n=9/group).

(D) Glucose tolerance test (IGTT, 2g /kg glucose i.p.) (n=9/group).

(E) Insulin tolerance test (ITT, 0.75 U/kg insulin i.p.) (n=9/group).

(F) Fasting and fed blood glucose levels (n=8-9/group).

(G) Fasting and fed plasma insulin levels (n=8-9/group).

(H-L) Multiplex quantification of myokines in the plasma of SM-P2Y6$^{\Delta/\Delta}$ and control mice (n=13-16/group).

(M-O) In vivo glucose uptake in eWAT, BAT and heart tissues of SM-P2Y6$^{\Delta/\Delta}$ and control mice (n=5-7/group).

18sRNA was taken as normalization control for RT-PCR analysis. All data are expressed as means ± SEM. (A-C, F-O: two-tailed Student's t-test; D-E: two-way ANOVA followed by Bonferroni's post hoc test).

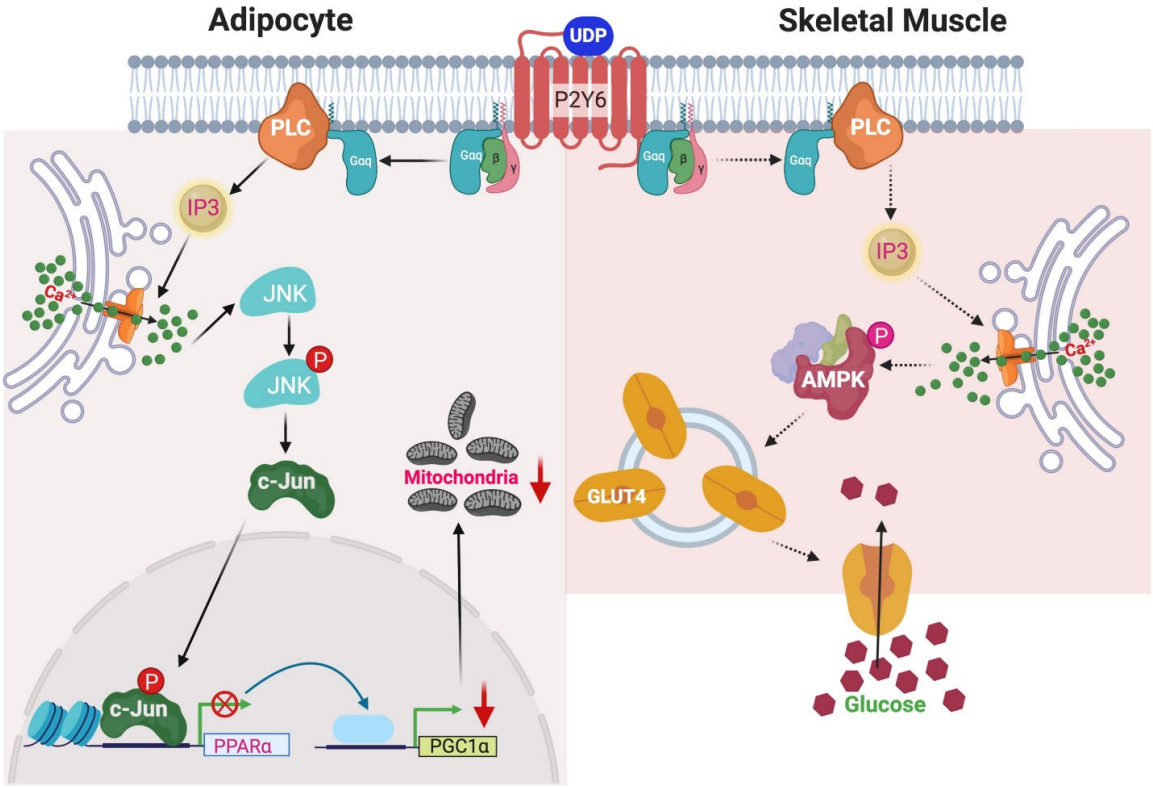

Fig. S7. Molecular mechanism for the action of $P2Y_6R$ in white adipocytes and skeletal muscle.

Table S1. Differentially regulated (up- and down-regulated) genes in iWAT of adipo-P2Y6 $^{\Delta/\Delta}$ mice.

Log 2 (Fold change)	Gene symbol		Log 2 (Fold change)	Gene symbol	Log 2 (Fold change)	Gene symbol
12.878	Myh4		-3.645	Siglece	-0.646	App
9.759	Ckm		-3.252	Arg1	-0.646	Itga5
9.429	Mylk4		-3.244	Spp1	-0.644	Slco3a1
9.327	Atp2a1		-2.956	Cck	-0.642	Plekho1
9.264	Tnnt3		-2.907	Slit2	-0.641	Ephb3
8.79	LOC100503495		-2.753	Nptx1	-0.639	Nes
8.683	Tcap		-2.715	Gpr50	-0.639	Il17d
8.666	Myoz1		-2.65	Gdf3	-0.639	Cdh5
8.519	A930016O22Rik		-2.285	Rpph1	-0.638	Tead2
8.466	Actn3		-2.228	Aadac	-0.638	Cmtm3
8.435	Myom2		-2.165	Hpgds	-0.637	Notch4
7.96	Ano5		-2.153	Acoxl	-0.636	Mxra8
7.632	Trim54		-2.133	Tmem132b	-0.635	Aspn
7.46	Mybpc2		-2.106	Rmrp	-0.631	Arhgap18
7.401	Trim63		-2.092	Itgad	-0.63	Sox17
7.261	Tnni2		-2.088	Hpx	-0.628	Vat1
7.186	Myf6		-2.062	Xkr5	-0.628	Sparcl1
7.16	Art1		-2.044	Hist1h2ap	-0.622	Lipa
7.096	Gm8210		-2.044	Hist1h2ao	-0.619	Col6a3
7.087	2310002L09Rik		-2.025	Egfem1	-0.618	Lmo1
6.987	LOC637171		-1.992	D2Ertd640e	-0.618	Hist2h3c2-ps
6.898	Myh2		-1.991	D330022K07Rik	-0.616	2010001K21Rik
6.822	Tnnc2		-1.982	Dpep3	-0.615	Cyp4b1
6.778	Ppp1r3a		-1.938	1600015I10Rik	-0.611	Adamts2
6.754	2310045N14Rik		-1.912	Gm949	-0.61	Plxnb2
6.679	Ky		-1.9	Il1rn	-0.609	Gpc1
6.606	Ryr1		-1.898	Atp6v0d2	-0.608	Notch3
6.59	Myot		-1.895	Tm4sf19	-0.608	Fam189a2
6.309	Igfn1		-1.892	Aspm	-0.608	Tmem165
6.306	Mypn		-1.878	Vipr2	-0.608	Gnao1
6.291	Klhl31		-1.869	Clec4d	-0.607	Hist1h2bh
6.288	Odf3l2		-1.861	BC030867	-0.607	Ctla2b
6.278	Xirp2		-1.852	Rnu3b2	-0.605	Ctla2a
6.275	Cacna1s		-1.852	Rnu3b1	-0.605	Mtap7
6.262	Nrap		-1.852	Rnu3b3	-0.604	Ppap2a
6.205	Myh3		-1.836	Them5	-0.604	Spats2
6.026	Ttn		-1.836	Myh7b	-0.603	Col15a1
6.001	Mylpf		-1.83	Rnu3b4	-0.603	Pea15a
5.996	Smpx		-1.793	Ptprz1	-0.603	Smc2

5.984	Mylk2		-1.791	Gm5150	-0.602	Nrp2
5.969	2310065F04Rik		-1.79	Wisp1	-0.601	Myl9
5.89	LOC100503752		-1.778	LOC790964	-0.6	2810405K02Rik
5.878	Lmod2		-1.778	Oit3	-0.6	Gpr56
5.82	Nctc1		-1.773	4931431B13Rik	-0.6	Lhfp
5.81	Eef1a2		-1.771	Rnf128	-0.599	Sdsl
5.799	Tmem233		-1.764	Chrm4	-0.598	Col6a1
5.754	2310015B20Rik		-1.762	Trem2	-0.598	Tinagl1
5.621	Kbtbd10		-1.76	Gtse1	-0.597	Sparc
5.601	Pvalb		-1.754	LOC434410	-0.597	Slc25a24
5.563	Asb11		-1.753	Rn18s	-0.597	Fstl1
5.525	Lrrc38		-1.74	Mrgprg	-0.595	Col5a1
5.514	Myoz3		-1.738	Masp1	-0.595	4-Sep
5.498	Hhatl		-1.728	Lars2	-0.595	Pxn
5.497	Ckmt2		-1.699	Vsig8	-0.594	Cela1
5.492	Myo18b		-1.694	Dnahc12	-0.593	1300015D01Rik
5.461	Myh1		-1.667	Lipf	-0.593	Ptgfrn
5.388	Rpl3l		-1.654	Gpnmb	-0.592	Lrrc1
5.337	Ampd1		-1.646	Scn8a	-0.59	LOC100503009
5.276	1110002E22Rik		-1.643	Adam8	-0.59	Neurl1b
5.268	Smtnl1		-1.64	Tm7sf4	-0.588	Morf4l1
5.246	Hfe2		-1.635	8030451A03Rik	-0.585	Prkcdbp
5.229	Dhrs7c		-1.623	Tlr13	-0.585	Adamts12
5.139	Abra		-1.614	Bub1b	-0.585	Me1
5.137	Rbfox1		-1.611	Mmp12	-0.583	Col4a1
5.099	LOC100503103		-1.599	Dhrs9		
5.094	Hrc		-1.585	Kif2c		
5.063	Jsrp1		-1.567	Gm9696		
5.026	Clcn1		-1.558	Dusp5		
4.995	Kbtbd5		-1.543	Olr1		
4.959	Sh3bgr		-1.54	Slc9a4		
4.868	2310010M20Rik		-1.531	Emid2		
4.834	Kcnj12		-1.529	Hk3		
4.785	Mybpc1		-1.519	AA914427		
4.68	Mb		-1.516	Mis18bp1		
4.612	Cacng1		-1.515	LOC640053		
4.612	Kcnj11		-1.506	Oxtr		
4.575	Asb5		-1.504	Tnip3		
4.517	Pygm		-1.499	Cacng5		
4.453	Kcna7		-1.493	Cenpi		
4.385	Lmod3		-1.484	Kif23		
4.365	Neb		-1.484	Shcbp1		
4.32	Ube2c		-1.484	Syt4		

4.277	Sgcg		-1.475	Tmem144
4.153	Plcd4		-1.466	C130079G13Rik
4.107	Lrrc2		-1.464	Hmmr
3.965	Apobec2		-1.463	Ctgf
3.899	Trdn		-1.463	Tph2
3.836	1810041L15Rik		-1.453	F10
3.704	Txlnb		-1.446	Ccnb1
3.652	Pgam2		-1.446	Btbd17
3.646	Ddit4l		-1.443	Slc25a13
3.611	Sypl2		-1.438	Ubd
3.547	Acta1		-1.434	2010317E24Rik
3.543	Tmod4		-1.424	Spag5
3.506	Dusp13		-1.402	Fam64a
3.422	A530098C11Rik		-1.4	Cthrc1
3.32	Trim72		-1.395	4833422F24Rik
3.288	Dusp27		-1.395	Gpr176
3.26	Ucp1		-1.392	Clspn
3.235	Slc9a2		-1.391	Ccdc107
3.227	Sec14l5		-1.391	2210406H18Rik
3.195	Rabep2		-1.382	C3ar1
3.152	Ncam2		-1.373	Melk
3.124	Unc13c		-1.371	Slc37a2
3.054	Scn4a		-1.352	Kif22
2.993	Wnk2		-1.349	Shroom2
2.969	Ank1		-1.347	Gm16499
2.967	Ppp1r14c		-1.331	Zfp367
2.882	Fabp3		-1.329	Diap3
2.844	Fbxo40		-1.323	Thbs1
2.826	Accsl		-1.323	Nuf2
2.801	A630019I02Rik		-1.323	Ina
2.731	Pld5		-1.321	2010300C02Rik
2.604	Dok7		-1.319	Cdc20
2.581	Hepacam		-1.305	Arl11
2.572	Mup11		-1.298	Dlgap5
2.524	Mup10		-1.296	Adamts4
2.51	Eno3		-1.292	Fgf9
2.481	Ldb3		-1.291	Ccnb2
2.478	Sema3d		-1.282	Top2a
2.454	Gm10032		-1.28	Neil3
2.453	LOC100503313		-1.275	Nceh1
2.393	Cmya5		-1.272	Mxd3
2.379	Agt		-1.259	Gm15270
2.369	LOC100048884		-1.257	Atf3

2.36	Asb14		-1.255	Ccna2
2.354	Tpm2		-1.255	Cenpe
2.339	Asb16		-1.254	Chsy3
2.334	Tpm1		-1.249	Foxm1
2.333	Casq1		-1.248	Iqgap3
2.316	Mup7		-1.231	Prr11
2.296	Asb2		-1.229	Mki67
2.294	Mup17		-1.226	Cd68
2.294	Mup19		-1.226	Spna1
2.292	Mup15		-1.225	Emr1
2.272	Mup2		-1.224	1700023B13Rik
2.262	Stac3		-1.224	Dpep2
2.242	Mtap4		-1.22	Tpx2
2.225	Synpo2l		-1.219	Cd300a
2.195	Ppl		-1.219	Cd300lb
2.194	Pde4dip		-1.217	Nck1
2.181	LOC100039029		-1.216	Gsg1l
2.165	Smyd1		-1.214	Fam65c
2.159	Gpr165		-1.213	Itgax
2.138	LOC671917		-1.209	Prc1
2.123	Prtn3		-1.205	Depdc1a
2.105	Tmem38a		-1.205	Dbf4
2.103	Cldn19		-1.201	Cenpm
2.094	C030030A07Rik		-1.2	Sgol2
2.083	Fa2h		-1.198	Pbk
2.012	Myoc		-1.197	Mtl5
2.01	Tmem56		-1.193	Birc5
1.987	Tuba8		-1.189	Lgals3
1.973	A330074K22Rik		-1.18	S100a8
1.955	Rbm20		-1.177	Cenpf
1.944	Scn4b		-1.168	Casc5
1.904	C7		-1.166	Stil
1.904	Gldn		-1.162	Mpeg1
1.895	Myl1		-1.159	Fam83d
1.883	Pcdh20		-1.159	Cd200r1
1.843	Gsta4		-1.159	Ccnf
1.836	Baiap2l2		-1.159	Bub1
1.814	Vstm2b		-1.159	Zwilch
1.799	D430041D05Rik		-1.157	Rab15
1.779	Il1r2		-1.151	E030010A14Rik
1.757	Dhcr7		-1.151	Kirrel3
1.745	Gjc3		-1.151	Kif4
1.744	Ehbp1		-1.151	AI605517

1.741	Lrrtm1		-1.145	Trfr2
1.702	Phkg1		-1.145	Clec4a2
1.696	Murc		-1.142	Ncaph
1.682	Zfp949		-1.142	Ckap2l
1.671	Aspg		-1.138	D2Ertd750e
1.668	Cyp2f2		-1.137	Igsf6
1.655	Drp2		-1.137	Mastl
1.624	Rassf6		-1.135	Cd84
1.609	Ugt8a		-1.131	Esco2
1.576	Acacb		-1.128	Mrc2
1.544	Vnn1		-1.124	Postn
1.54	Pfkm		-1.117	Scg3
1.522	Sbk2		-1.113	Dfna5
1.508	Mal		-1.112	F630043A04Rik
1.5	Lrrn4		-1.109	Tbxas1
1.499	Gm7582		-1.103	Slc13a3
1.491	Des		-1.101	E130306D19Rik
1.49	Pon1		-1.1	C77080
1.487	Nfe2l3		-1.096	Hmox1
1.468	Dkk2		-1.091	Kif11
1.462	Chl1		-1.081	Spc25
1.46	Gm5567		-1.062	Gpsm2
1.453	LOC100503433		-1.059	Gas2l3
1.453	Mpz		-1.053	Ccdc99
1.452	Aatk		-1.052	Casq2
1.448	LOC100503923		-1.049	Clec12a
1.419	D930003E18Rik		-1.043	Rin3
1.414	Slc1a3		-1.042	Fcer1g
1.376	Gpx3		-1.042	Brca1
1.375	Gm129		-1.034	Cdca2
1.36	Sult1e1		-1.032	Unc79
1.357	B230303O12Rik		-1.032	Plk1
1.352	LOC100041903		-1.028	Rnd2
1.348	St6galnac5		-1.028	Lilrb4
1.337	Cfd		-1.027	Kcnj14
1.333	Acsm3		-1.024	5430435G22Rik
1.319	Slc43a1		-1.02	Kcnq1
1.293	Zfp563		-1.02	Ckap2
1.291	LOC100503767		-1.019	Cdca8
1.272	LOC552874		-1.018	Ccl9
1.25	Fn3k		-1.017	Gp49a
1.248	A330049M08Rik		-1.017	Atp1a3
1.248	2310046A06Rik		-1.016	Ryr2

1.243	LOC100503206		-1.012	Ect2
1.239	Mpzl2		-1.008	Plxna4
1.233	Acaca		-0.998	Fhl2
1.228	Ccdc37		-0.997	Sh3bgrl2
1.222	Fam83g		-0.997	Disc1
1.207	Orm3		-0.995	Rgs2
1.198	4930573O21Rik		-0.994	Rccd1
1.193	Sctr		-0.99	Ephb1
1.189	Slc2a3		-0.988	Dhcr24
1.187	Celsr2		-0.986	Ret
1.185	Ank3		-0.983	Cdk1
1.172	4931408A02Rik		-0.981	Cd276
1.163	Plp1		-0.981	Gm4952
1.153	BC005764		-0.966	Rad51ap1
1.152	Cdh9		-0.965	Tnfrsf11a
1.15	Kcna1		-0.962	Aplnr
1.142	Ism1		-0.96	LOC100503416
1.134	Angpt1		-0.957	Tbx18
1.134	Lgi2		-0.954	Myo1f
1.116	Clip4		-0.95	Lgmn
1.101	Scd3		-0.95	Mfap4
1.1	Cox8b		-0.948	Nek2
1.096	Ppara		-0.948	Diras2
1.095	Rorc		-0.947	Olfm2
1.093	Morn1		-0.944	Fstl3
1.084	Inmt		-0.943	Slc11a1
1.067	Thrsp		-0.942	F2r
1.06	Ppargc1a		-0.941	Sncaip
1.056	Eif4a2		-0.936	Trp53i11
1.05	C2		-0.929	Adamts7
1.046	Reln		-0.927	Stmn1
1.032	Myo5c		-0.925	Dpysl3
1.032	Adcy10		-0.923	Slc15a3
1.026	Elovl6		-0.922	Gucy1a2
1.023	LOC100503180		-0.916	Tnc
1.021	Plekhb1		-0.915	Clec7a
1.019	Mbp		-0.913	Cdkn1a
1.018	Pcsk4		-0.913	Lair1
1.017	Pck1		-0.91	Sdc1
1.016	Scd1		-0.909	P2ry6
1.008	Gulp1		-0.907	Cep70
1.005	Cd209b		-0.907	Upp1
1	4921509J17Rik		-0.904	2610524H06Rik

0.987	Adrb3		-0.904	Sh2d3c
0.987	Ebf2		-0.903	Cd93
0.987	B230218P12Rik		-0.903	Fam70a
0.987	Lima1		-0.9	Pik3ap1
0.979	2010016I18Rik		-0.9	Ccdc64
0.979	Hmgcs2		-0.898	Pawr
0.978	Gli2		-0.898	Rell1
0.972	Six4		-0.897	Tril
0.97	Itgb8		-0.895	Mgp
0.967	Chrna5		-0.892	Clec4a3
0.967	Cetn4		-0.888	Ppfia3
0.959	Thbd		-0.888	Galntl4
0.958	Scd4		-0.885	Gm11223
0.957	Ift81		-0.883	C1qtnf5
0.955	Plac8		-0.88	Col28a1
0.954	Ccl8		-0.877	Mfrp
0.954	LOC100503254		-0.874	Tmem200b
0.952	Dennd2d		-0.871	Espl1
0.945	Slc5a6		-0.868	Ube2c
0.944	Kcna2		-0.868	Calr4
0.942	5930403L14Rik		-0.862	Cldn5
0.94	A930009E05Rik		-0.861	Cks2
0.934	Gm10673		-0.86	4930506M07Rik
0.929	Peli3		-0.858	Bmx
0.927	1520402A15Rik		-0.857	Kcna5
0.925	Esr1		-0.847	Sdc3
0.919	Gm13111		-0.847	Fam129b
0.912	9530015I06Rik		-0.845	Pbx3
0.911	Lrrc4		-0.844	Pla2g7
0.91	6330439K17Rik		-0.839	Capg
0.909	Ankrd5		-0.827	Cdca3
0.901	9330132A10Rik		-0.825	Lamb3
0.901	Usp2		-0.824	C1qtnf6
0.895	Dbp		-0.824	Fblim1
0.894	Slc1a5		-0.823	Ucp2
0.888	Vmn2r29		-0.823	Olfr558
0.882	Nap1l3		-0.823	Myof
0.877	Col20a1		-0.823	Fbn1
0.877	Parm1		-0.815	S100b
0.869	Abcg4		-0.815	Eln
0.868	Aacs		-0.813	Kcnj15
0.855	Cp		-0.813	Unc119
0.855	LOC100503148		-0.813	Glyctk

0.851	Bivm		-0.813	Ccdc144b
0.845	Sfxn1		-0.812	Cacna1d
0.84	Cdh19		-0.808	2600006K01Rik
0.84	2900064B18Rik		-0.807	Plekhg1
0.836	Prx		-0.805	Kcnc2
0.835	Steap4		-0.804	Pla2g2e
0.833	Bhlhe41		-0.803	Alox5ap
0.825	Vat1l		-0.801	Plekhh2
0.821	Gpr64		-0.799	Anpep
0.819	Pard6g		-0.798	4930414N08Rik
0.814	Tef		-0.797	Fam124a
0.814	Ppargc1b		-0.795	Sorbs2
0.806	Zfp961		-0.793	Mbd1
0.805	Hlf		-0.785	Arhgap11a
0.797	Phka2		-0.784	LOC100504290
0.796	Prodh		-0.783	Tnfrsf23
0.794	A830018L16Rik		-0.783	Copg2as2
0.79	Met		-0.782	Emilin1
0.79	Bhlhb9		-0.78	6330405D24Rik
0.789	LOC100504738		-0.777	Thsd1
0.788	Gpd2		-0.776	Angpt2
0.78	St3gal4		-0.775	Mark1
0.776	Pla2g5		-0.772	Pde3a
0.776	Mettl7a1		-0.771	Nusap1
0.773	S100a1		-0.77	Specc1
0.772	LOC100504139		-0.768	Vash1
0.772	LOC100036513		-0.768	D030055H07Rik
0.771	Cenpv		-0.763	Fcgr3
0.767	Podn		-0.761	Ndufa4l2
0.767	Pdp2		-0.758	Fam20c
0.765	Gstm7		-0.756	Slc16a12
0.765	Chrdl1		-0.756	Poln
0.761	Mlxipl		-0.756	Prssl1
0.753	9330161A08Rik		-0.75	Tns3
0.752	ND5		-0.747	Ptprk
0.752	Acss3		-0.747	Pvrl3
0.744	Lgals12		-0.745	Sema6b
0.741	Tcf7l2		-0.744	Hfe
0.739	Hsd11b1		-0.744	LOC100504890
0.736	LOC100505258		-0.744	LOC100504490
0.733	Rgs7		-0.744	Col5a2
0.731	Prr5l		-0.74	Pld3
0.729	Mtus1		-0.74	LOC100045292

0.726	Zfp467		-0.739	Mamdc2
0.725	Sema3b		-0.738	Fgf13
0.715	Il15ra		-0.737	Pam
0.713	Nrn1		-0.735	Tubb2a
0.709	Ucp3		-0.732	Hydin
0.705	Fign		-0.731	Oip5
0.704	1700008J07Rik		-0.731	Kcne1l
0.702	Popdc2		-0.73	Tmem44
0.702	E330009J07Rik		-0.728	Sema7a
0.701	Gm3289		-0.727	Slc9a5
0.698	Clcn2		-0.726	Loxl2
0.698	Pde3b		-0.722	Slc13a4
0.697	A530020G20Rik		-0.722	Rtn2
0.697	C3		-0.714	Spry1
0.697	Gbe1		-0.712	Fam110c
0.696	2010011I20Rik		-0.711	D14Ertd449e
0.696	Gstm6		-0.71	Gm10395
0.681	Irs2		-0.71	Gm9746
0.68	Oscp1		-0.702	Ltbp4
0.675	Pnldc1		-0.701	P2ry1
0.67	Aspa		-0.698	Rian
0.669	Ppm1k		-0.695	Pdlim7
0.668	Klhl2		-0.693	Gm3601
0.668	LOC100502725		-0.692	Vldlr
0.667	Nnat		-0.692	E130203B14Rik
0.664	1700029J07Rik		-0.691	Tagln2
0.662	Pfkfb2		-0.69	Myl4
0.659	Thrb		-0.69	Mical2
0.657	Bckdhb		-0.688	Bgn
0.654	Hyal1		-0.686	Col4a2
0.653	Sec24b		-0.681	Ppic
0.652	Pygo1		-0.681	Fkbp10
0.651	Per3		-0.681	Tmem37
0.649	Dhtkd1		-0.68	Tanc1
0.649	D3Ertd254e		-0.677	Ldb2
0.647	Adhfe1		-0.676	9030425E11Rik
0.644	St3gal6		-0.676	Copg2
0.642	2810055G20Rik		-0.673	Tmem132a
0.641	N4bp2l1		-0.672	Fbln2
0.64	A130038J17Rik		-0.67	Pde2a
0.634	Maob		-0.67	Fabp5
0.634	Pde1a		-0.67	Col3a1
0.633	Nr1d1		-0.67	Kif20a

0.633	Aldh5a1		-0.669	Hspg2
0.632	Ppp1r9a		-0.667	Dbn1
0.626	Vegfa		-0.667	Hsd17b7
0.625	Apoe		-0.665	Esam
0.625	Dkc1		-0.665	Csf2ra
0.622	Pfkfb1		-0.665	Afap1l2
0.617	Trpv1		-0.664	Lbp
0.614	Srebf1		-0.663	S100a6
0.613	Zfp809		-0.662	Mcf2l
0.609	Akap1		-0.661	Smtn
0.607	Gpr146		-0.659	Tpd52
0.607	Pxmp2		-0.658	Tm6sf1
0.605	Nudt6		-0.658	Mpzl1
0.604	Sqrdl		-0.657	S1pr1
0.604	Dnajc28		-0.656	Ctsl
0.601	Dbt		-0.656	Tie1
0.596	Aldh6a1		-0.655	Fam122b
0.595	Cept1		-0.654	Sh3pxd2b
0.592	Nfia		-0.652	Ablim3
0.586	Blcap		-0.652	Ccdc88a
0.585	LOC100048759		-0.651	C1qtnf9
0.584	B230208H17Rik		-0.65	Prnp
0.581	Lman2l		-0.649	Col6a2

Table S2. Differentially regulated (up- and down-regulated) genes in BAT of adipo-P2Y6 $^{\Delta/\Delta}$ mice.

Log 2 (Fold change)	Gene symbol		Log 2 (Fold change)	Gene symbol	Log 2 (Fold change)	Gene symbol	Log 2 (Fold change)	Gene symbol
8.853	Myh7		-5.552	Itgad	-1.185	Bcl6b	-0.804	Fcgr2b
6.613	Gm8210		-3.846	2610307P16Rik	-1.184	Ret	-0.801	Phactr2
6.126	Myl2		-3.758	Saa3	-1.178	Trim59	-0.787	Stmn1
5.916	Myh6		-3.668	Tph2	-1.143	Foxm1	-0.761	Cybb
5.665	Kng1		-3.135	Rtkn2	-1.139	Sgms2	-0.761	Tpm4
4.36	Tnnt1		-3.126	Mrgprg	-1.129	Vash1	-0.759	4632428N05Rik
2.786	Tbx15		-3.047	Nr5a2	-1.116	Dnahc11	-0.755	Klf6
2.45	Ddit4l		-2.94	Slc5a7	-1.106	Dbf4	-0.749	Emilin1
1.982	Smyd1		-2.899	Mmp12	-1.106	Gpr65	-0.748	Epha4
1.937	A030001D16Rik		-2.814	Gdf15	-1.091	Zfyve28	-0.739	Gm11223
1.923	Unc13d		-2.733	Oxtr	-1.086	Cachd1	-0.738	Prkcdbp
1.762	Cfd		-2.691	Unc79	-1.066	Cxcr4	-0.736	Cotl1
1.751	Spnb1		-2.538	Pbk	-1.064	Synpo2	-0.735	Rgl1
1.73	Phkg1		-2.435	Atp8b4	-1.053	Arhgap28	-0.73	Vcam1
1.545	1500002F19Rik		-2.379	Tubb2b	-1.041	Col28a1	-0.727	Tmem71
1.445	Fhl3		-2.18	F10	-1.04	Emb	-0.725	Robo4
1.329	Vat1l		-2.166	Ubd	-1.038	Adm	-0.706	Mcc
1.296	Nt5e		-2.155	Ifltd1	-1.037	Pion	-0.705	2900026A02Rik
1.252	LOC100504738		-2.15	Uchl1	-1.012	Slc6a13	-0.705	Cdc42ep3
1.204	Car3		-2.131	Mis18bp1	-1.01	Itga9	-0.704	Plscr4
1.203	Esr1		-2.082	Iqgap3	-1.008	Fmod	-0.694	Dapk1
1.116	Mmd2		-2.06	Itgax	-1.007	Prrx1	-0.689	Sirpa
1.085	Zmym3		-2.004	Shcbp1	-0.999	Pla2g2e	-0.686	Zfp366
0.984	Zfp949		-1.997	Kcnj14	-0.999	2310028H24Rik	-0.684	Cd93
0.974	6330408M09Rik		-1.958	Fgf13	-0.995	Mtap1b	-0.684	Adam19
0.956	Pde4dip		-1.93	Dlgap5	-0.99	Npr3	-0.682	Fam111a
0.927	Osbp2		-1.863	Atp6v0d2	-0.979	Ctss	-0.674	Klhl13
0.905	Rasd1		-1.853	Prnd	-0.977	Pla2g2d	-0.67	Kalrn
0.873	Gprc5c		-1.722	6820408C15Rik	-0.968	Cd44	-0.669	Tgfb1i1
0.844	Slc1a3		-1.673	1700047G03Rik	-0.96	Copg2as2	-0.667	Fam49a
0.837	Gpx3		-1.649	Ncf4	-0.949	Me1	-0.665	St8sia4
0.824	Itpka		-1.637	Pde1c	-0.938	Myo1d	-0.662	9430037G07Rik
0.818	LOC100048759		-1.623	E2f8	-0.93	Pik3c2b	-0.645	Stard9
0.805	C3		-1.622	Cenpf	-0.927	Tanc2	-0.642	Oas2
0.803	Col23a1		-1.614	Tnc	-0.921	Zmynd15	-0.64	2610305D13Rik
0.785	Radil		-1.54	Gpnmb	-0.916	Mpeg1	-0.638	Parp14

0.772	Gm6658		-1.517	Ctgf	-0.909	Cdh23	-0.637	Shroom4
0.743	Luc7l2		-1.507	Cd200r1	-0.903	Arhgef26	-0.618	Smtn
0.739	Ankrd9		-1.495	Dyrk4	-0.897	Pawr	-0.618	Anxa3
0.729	Slc2a12		-1.486	Mest	-0.895	Tbx18	-0.617	Pea15a
0.712	Ampd2		-1.477	Tpx2	-0.88	Tuba1a	-0.617	9330159M 07Rik
0.709	Atp5k		-1.47	C81189	-0.862	Sncg	-0.617	Ifit2
0.706	Srl		-1.446	C3ar1	-0.86	Arhgap25	-0.616	Tshz2
0.7	Prkag2		-1.444	Lbp	-0.854	Colec12	-0.61	Kirrel
0.681	Eif4a2		-1.373	Gm15428	-0.853	Fam92a	-0.608	11-Sep
0.681	Ankrd5		-1.362	Top2a	-0.852	Chrnb1	-0.604	Lrrfip1
0.671	5930403L1 4Rik		-1.342	Fcgr4	-0.85	Plekhg1	-0.593	Phldb2
0.667	Des		-1.34	Lgals3	-0.843	Ctsc	-0.592	Ifi203
0.652	Tst		-1.338	Mki67	-0.838	Fscn1	-0.592	Nid2
0.643	Acsm3		-1.327	2810417H 13Rik	-0.829	Ppp1r16b	-0.592	Prcp
0.631	Rps28		-1.29	Brca1	-0.825	Chic1	-0.592	Ugp2
0.62	Rfc4		-1.285	Msr1	-0.82	Arhgap11a	-0.588	Gm10791
0.613	Hyal1		-1.278	Prnp	-0.819	Slc1a1	-0.587	Serpinb9
0.582	LOC10050 2825		-1.268	Nup210	-0.818	Edn1	-0.584	Tanc1
			-1.267	Cd84	-0.818	Shroom2	-0.584	Cntln
			-1.21	Clec7a	-0.805	Tspan6	-0.583	Nid1
							-0.583	Ednrb

Table S3. List of primers used for RT-PCR studies.

Gene name	Forward (5'-3')	Reverse (5'-3')
P2ry6	GACCTGATGTATGCCTGTTCAC	CAGGATGCTGCCATGTAGATTG
18S rRNA	CGGCTACCACATCCAAGGAA	GCTGGAATTACCGCGGCT
Leptin	CAAGCAGTGCCTATCCAGA	AAGCCCAGGAATGAAGTCCA
Adiponectin	GCACTGGCAAGTTCTACTGCAA	GTAGGTGAAGAGAACGGCCTTGT
F4/80	TCCTGCTGTGTCGTGCTGTTC	GCCGTCTGGTTGTCAGTCTTGTC
Cd68	TGTCTGATCTTGCTAGGACCG	GAGAGTAACGGCCTTTTTGTGA
Mcp1	GCTCAGCCAGATGCAGTTAA	TCTTGAGCTTGGTGACAAAAACT
Il6	TAGTCCTTCCTACCCCAATTTCC	TTGGTCCTTAGCCACTCCTTC
Tnfa	CCCTCACACTCAGATCATCTTCT	GCTACGACGTGGGCTACAG
Ifng	CGGCACAGTCATTGAAAGCCTA	GTTGCTGATGGCCTGATTGTC
Mip1a	TGAGAGTCTTGGAGGCAGCGA	TGTGGGTACTTGGCAGCAAACA
Mip1b	AACAACATGAAGCTCTGCGT	AGAAACAGCAGGAAGTGGGA
IL1a	ACGTCAAGCAACGGGAAGAT	AAGGTGCTGATCTGGGTTGG
IL1b	CTCCACCTCAATGGACAGAA	GCCGTCTTTCATTACACAGG
Ucp1	ACTGCCACACCTCCAGTCATT	CTTTGCCTCACTCAGG ATTGG
Cidea	TGCTCTTCTGTATCGCCCAGT	GCCGTGTTAAGGAATCTG CTG
Pgc1a	AGCCGTGACCACTGACAAC GAG	GCTGCATGGTTCTGAGTGCTAAG
Ppara	GCGTACGGCAATGGCTTTAT	GAACGGCTTCCTCAGGTTCTT
Pparg	GTGCCAGTTTCGATCCGTAGA	GGCCAGCATCGTGTAGATGA
Cytc	AAATCTCCACGGTCTGTTCGG	GGGTATCCTCTCCCCAGGTG
Cpt1	TTGCCCTACAGCTCTGGCATTTCC	GCACCCAGATGATTGGGATACTGT
Mcad	ATGACGGAGCAGCCAATGAT	TCGTCACCCTTCTTCTCTGCTT
Ap2	CGCAGACGACAGGAAGGT	TTCCATCCCACTTCTGCAC
Epsti1	ACCCTGATAGCACCAAACGA	AGGTCTGCCAGTTCTTGCTC
Eva1	CCACTTCTCCTGAGTTTACAGC	GCATTTTAACCGAACATCTGTCC
Tbx1	GGCAGGCAGACGAATGTTC	TTGTCATCTACGGGCACAAAG
Glut4	GTGACTGGAACACTG GTCCTA	CCAGCCAGTTGCATTGTAG
Srebp1	AGTGGCAAAGGAGGCACTAC	CACCCTCTGGAAGACCACA
Fas	GGAGGTGGTGATAGCCGGTAT	TGGGTAATCCATAGAGCCCAG
Tmem26	ACCCTGTCATCC CACAGAG	TGTTTGGTGGAGTCCT AAGGTC
Glut1	CAGTTCGGCTATAACACTGGTG	GCCCCCGACAGAGAAGATG
Nrf1	GGAGCACTTACTGGAGTCC	CTGTCCGATATCCTGGTGGT
Tfam	GCAAAGGATGATTCGGCTCAGGGAA	CCGGATCGTTTCACACTTCGACGG
MtCo1	ACTATACTACTAACAGACCG	GGTTCTTTTTTTCCGGAGTA
MtCo2	AACCATAGGGCACCAATGATAC	GGATGGCATCAGTTTTAAGTCC
Esrrg	GCAAGGCATTCTTCAAGAGG	GGCTGGGCAGCTGTACTCTA
Ppard	GACCAGAACACACGCTTCCT	CCGACATTCCATGTTGAGG

Prdm16	CAGCACGGTGAAGCCATTC	GCGTGCATCCGCTT GTG
Lpl	CCCTACAAAGTGTTCCATTA	CTCGCTCTCGGCCACTGT
Ndufs1	AGGATATGTTCGCACAACTGG	TCATGGTAACAGAATCGAGGGA
Ndufv2	GCAAGGAATTTGCATAAGACAGC	TAGCCATCCATTCTGCCTTTG
Atp50	TCTCGACAGGTTCGGAGCTT	AGAGTACAGGGCGGTTGCATA
Cox5b	TTCAAGGTTACTTCGCGGAGT	CGGGACTAGATTAGGGTCTTCC
Cd36	AGATGACGTGGCAAAGAACAG	CCTTGGCTAGATAACGAACTCTG
Fabp1	ATGAACTTCTCCGGCAAGTACC	CTGACACCCCCTTGATGTCC
Foxo1	TTCAATTCGCCACAATCTGTCC	GGGTGATTTTCCGCTCTTGC
Myh2	TCACATCCAACAAGAAGCCAGAGC	CCCTGGCTGACAAATGGGTAATCA
Myh4	AGTCCCAGGTCAACAAGCTG	TTTCTCCTGTCACCTCTCAACA
Myh7	ACCAGGCCCTTTGACCTCAAGAAA	TCTTGTCGAACTTGGGTGGGTTCT
Cox8b	GAACCATGAAGCCAACGACT	GCGAAGTTCACAGTGGTTCC
Dio2	CATTGATGAGGCTCACCCTTC	GGTTCCGGTGCTTCTTAACCT
Fgf21	CTGCTGGGGGTCTACCAAG	CTGCGCCTACCACTGTTCC
G6pc	CGACTCGCTATCTCCAAGTGA	GTTGAACCAGTCTCCGACCA
Pdk4	CCGCTTAGTGAACACTCCTTC	TGACCAGCGTGTCTACAAACT
Pck1	CTGCATAACGGTCTGGACTTC	CAGCAACTGCCCGTACTCC
Serca1	TGTTTGTCCTATTTCGGGGTG	AATCCGCACAAGCAGGTCTTC
Serca2	GAGAACGCTCACACAAAGACC	CAATTCGTTGGAGCCCCAT
Universal-Cre	ACCTGAAGATGTTCGCGATTATCT	ACCGTCAGTACGTGAGATATCTT
Mitochondrial DNA primers		
CoxII	GCCGACTAAATCAAGCAACA	CAATGGGCATAAAGCTATGG
Globin	GAAGCGATTCTAGGGAGCAG	GGAGCAGCGATTCTGAGTAGA
Chip primers		
Ppara-promoter	TGGCATAGCACACATTTCGT	GCTTTGCTTGTGTCGTCCTT