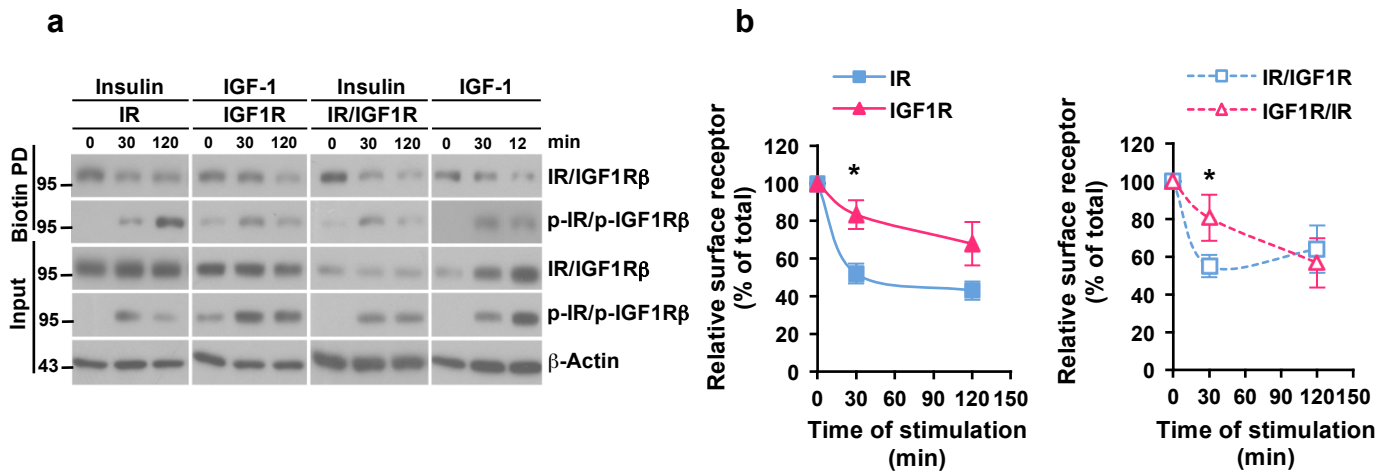


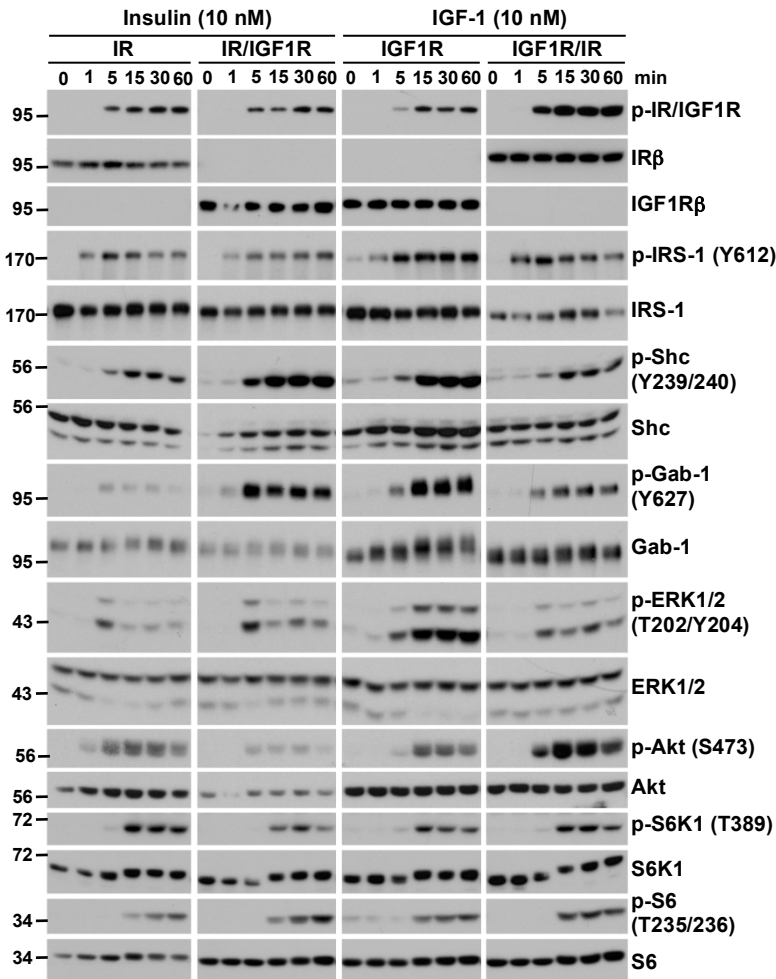
Supplementary Figure 1



Supplementary Figure 1. Receptor internalization following ligand binding. (a) Immunoblotting of total and phosphorylated IR and IGF1R beta-subunit in cell lysates and biotin-labeled cell surface fraction. Biotinylated fractions of the receptors pulled-down (PD) by Streptavidin Agarose beads are shown on the top. Receptor expression from the total lysates are shown at the bottom. (b) Quantification of relative surface receptor amount at different time point following initial administration of insulin or IGF-1. Data are presented as mean \pm SEM (*, $p < 0.05$; two-way ANOVA followed by Bonferroni *post hoc* tests, $n = 3$).

Supplementary Figure 2

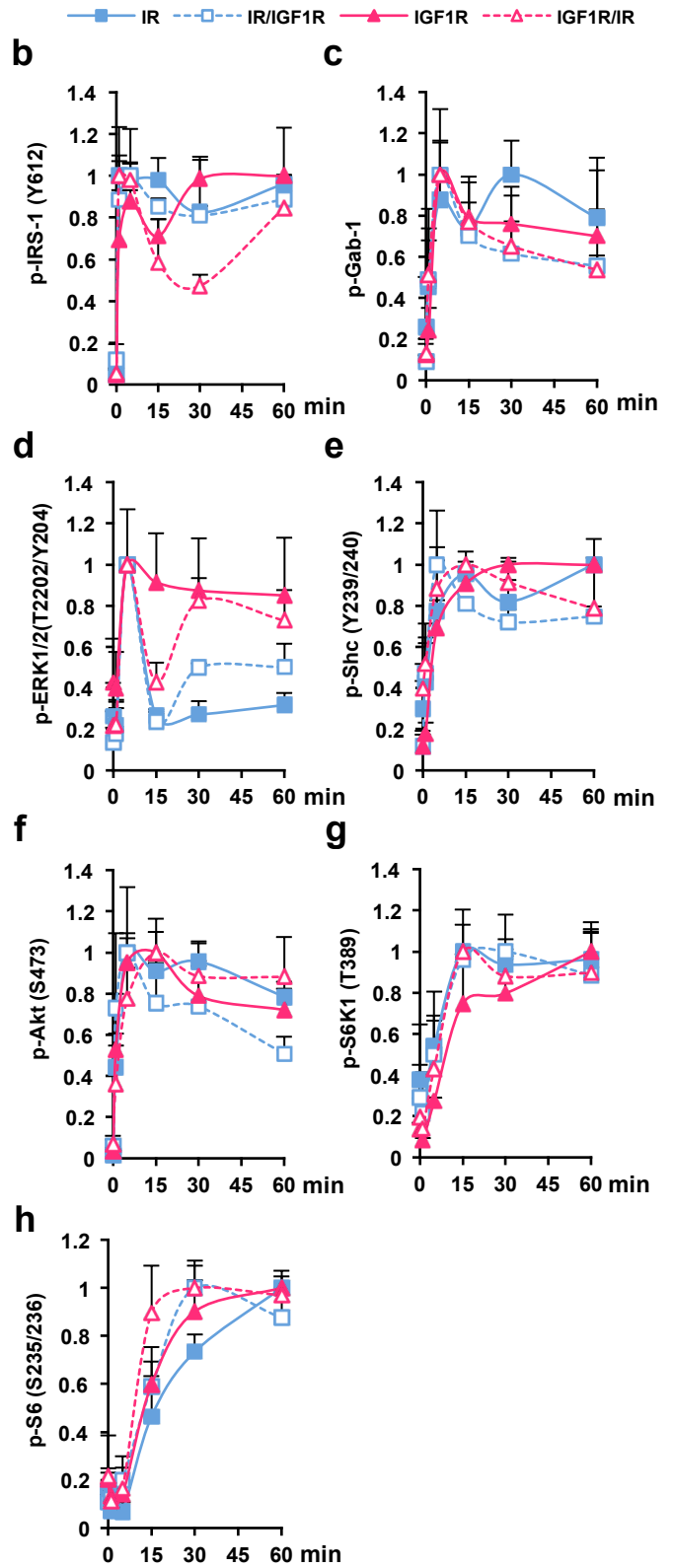
a



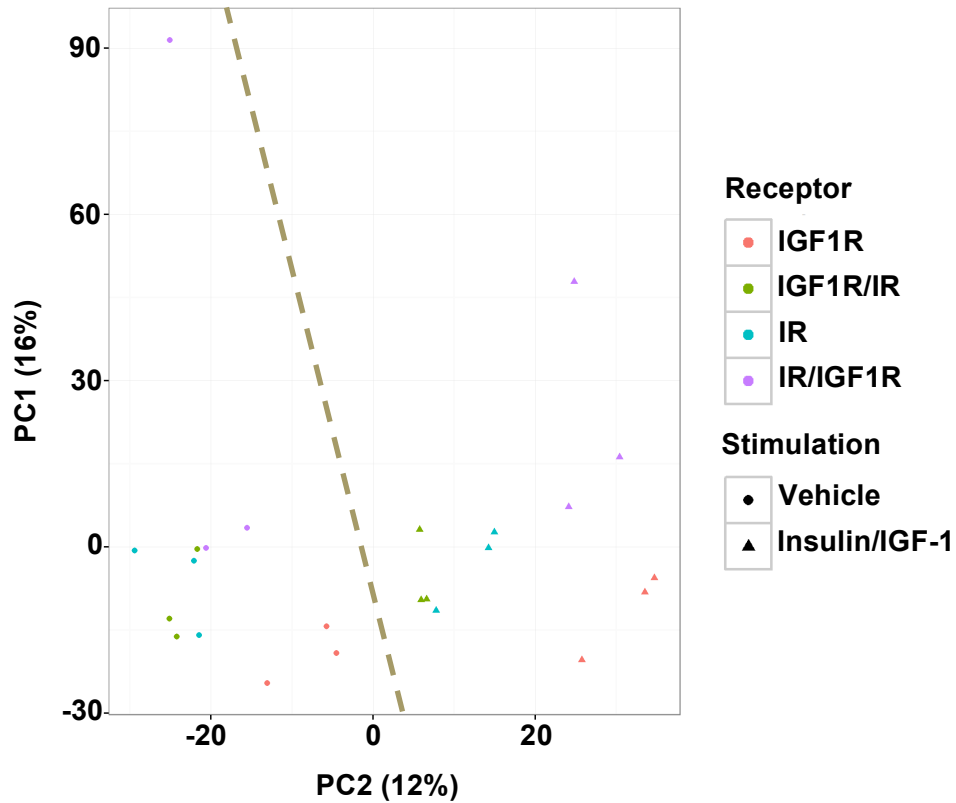
Supplementary Figure 2. Phosphorylation kinetics of common intracellular signaling targets of IR and IGF1R.

(a) Immunoblot analysis of protein phosphorylation following 10 nM insulin or IGF-1 stimulation for the indicated time duration. (b-h) Densitometry analysis of relative phosphorylation of each protein along the time-course.

Data was normalized to maximal phosphorylation. Data is presented as mean + SEM. n = 3.

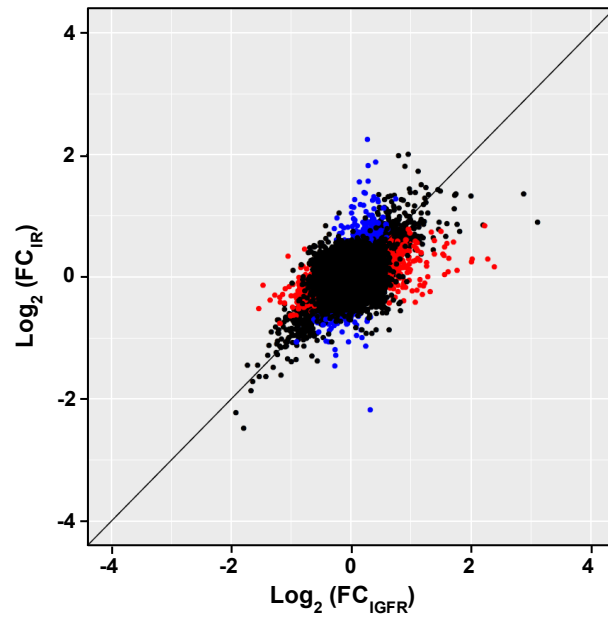


Supplementary Figure 3



Supplementary Figure 3. PCA plots of cells expressing 4 types of receptors in response to ligand stimulation. Each dot represents one cell line under one experimental condition (with or without ligand stimulation). At basal conditions (round dots), all four cell lines segregated on one principle component (PC1). Despite some degrees of clonal variation within each type of cell, the cells expressing receptors with intracellular domain of IR (IR and IGF1R/IR) tended to cluster together, whereas cells expressing normal IGF1R segregate further away from all other cell types. Upon ligand stimulation, all four types of cells showed a dramatic stimulation effect with segregations on the other principle component (PC2). Note, one clone of IR/IGF1R cells was an extreme outlier and excluded from the following bioinformatic analysis. See details in *Methods*.

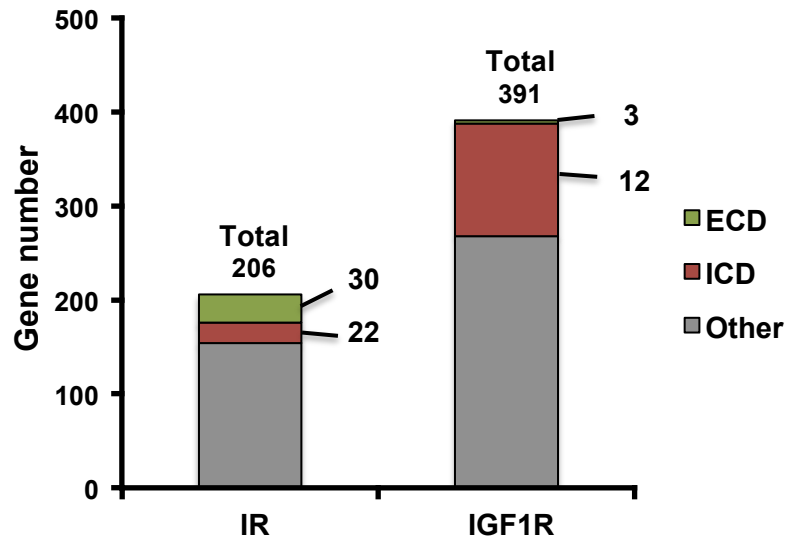
Supplementary Figure 4



Supplementary Figure 4. Similar overall gene expression regulation of insulin on IR and IGF-1 on IGF1R.

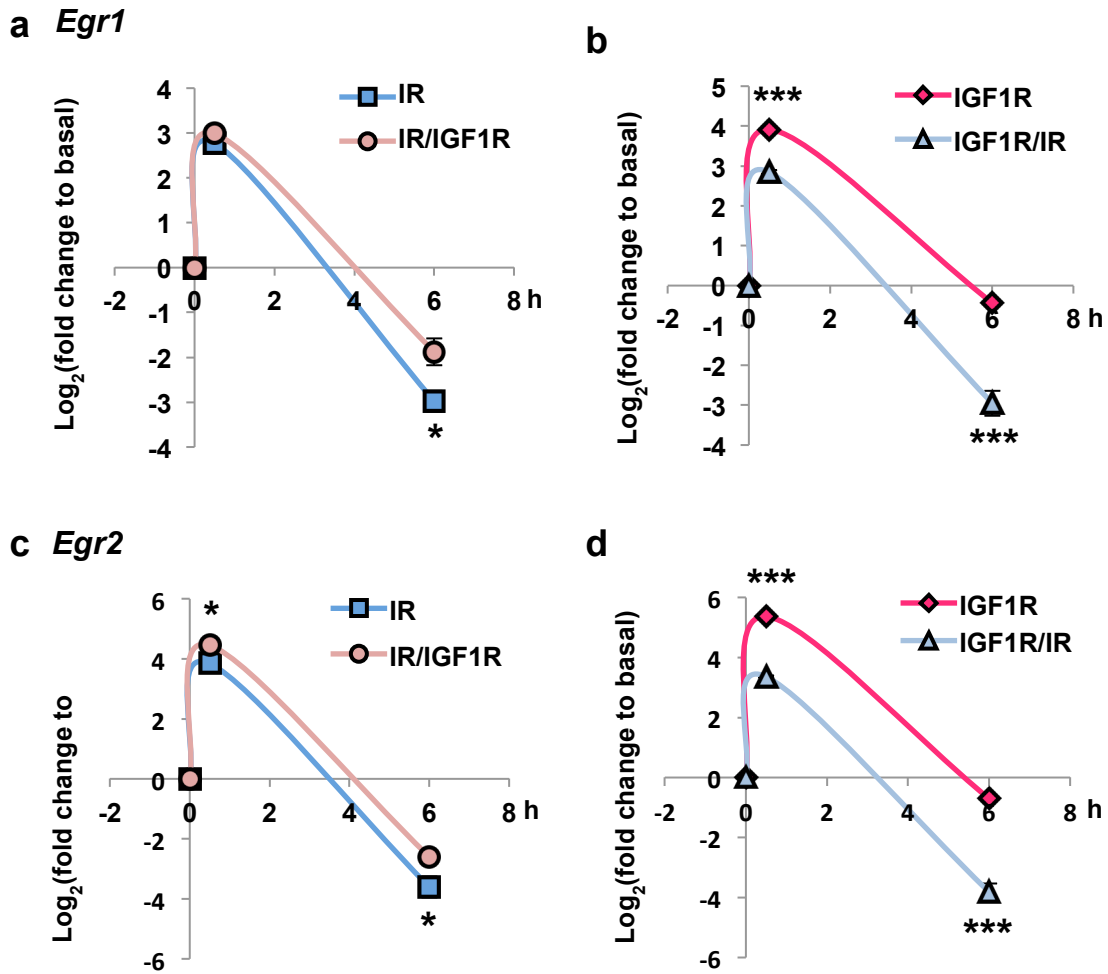
Dot plot showing distribution of fold change for gene expression after stimulation of cells expressing IR (*x*-axis) versus that in IGF1R (*y*-axis). Note the majority of the genes fall along the diagonal, indicating similar regulation by IR and IGF1R in response to insulin and IGF-1 stimulation, respectively. Blue dots represent the genes specifically regulated by IR by at least 50% (FDR < 0.05), but not IGF1R (FDR ≥ 0.05); red dots represent the genes specifically regulated by IGF1R by at least 50% (FDR < 0.05), but not IR (FDR ≥ 0.05).

Supplementary Figure 5



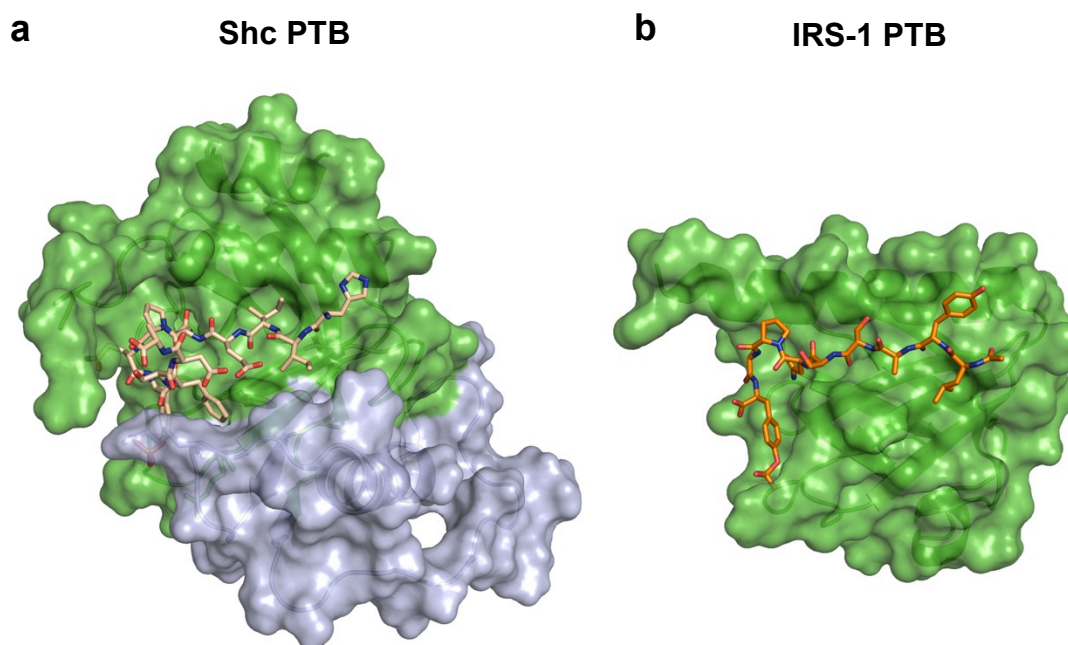
Supplementary Figure 5. Representation of genes uniquely regulated by IR and IGF1R corresponding to the intracellular and extracellular domains of the receptors. Among the 206 genes that were uniquely regulated by IR, 30 (15%) corresponded to the extracellular domain of the IR, whereas 22 (11%) corresponded to the intracellular domain of the IR. In contrast, of the 391 genes that were only regulated by IGF1R, only 3 (~1%) corresponded to the extracellular domain of the IGF1R, while 120 (31%) corresponded to the intracellular domain of the IGF1R.

Supplementary Figure 6



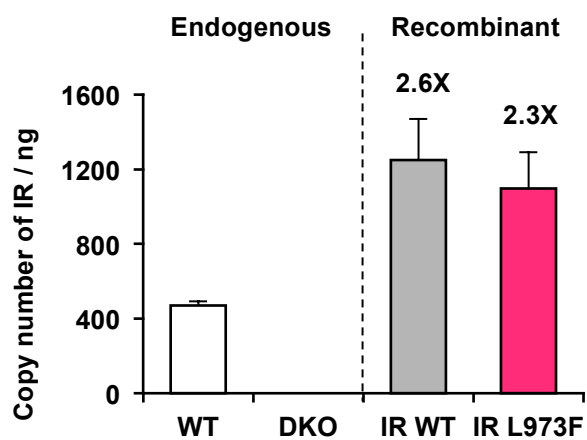
Supplementary Figure 6. Time course of *Egr1* and *Egr2* gene expression. Fold change of *Egr1* (a and b) and *Egr2* (c and d) on a log₂ scale in response to 100 nM insulin or 100 nM IGF-1 stimulation for 30 min and 6 hours were confirmed by qPCR, with TBP as the housekeeping gene. Data are presented as mean ± SEM (*, p < 0.05; *** p < 0.001. Student *t*-test. n = 6).

Supplementary Figure 7



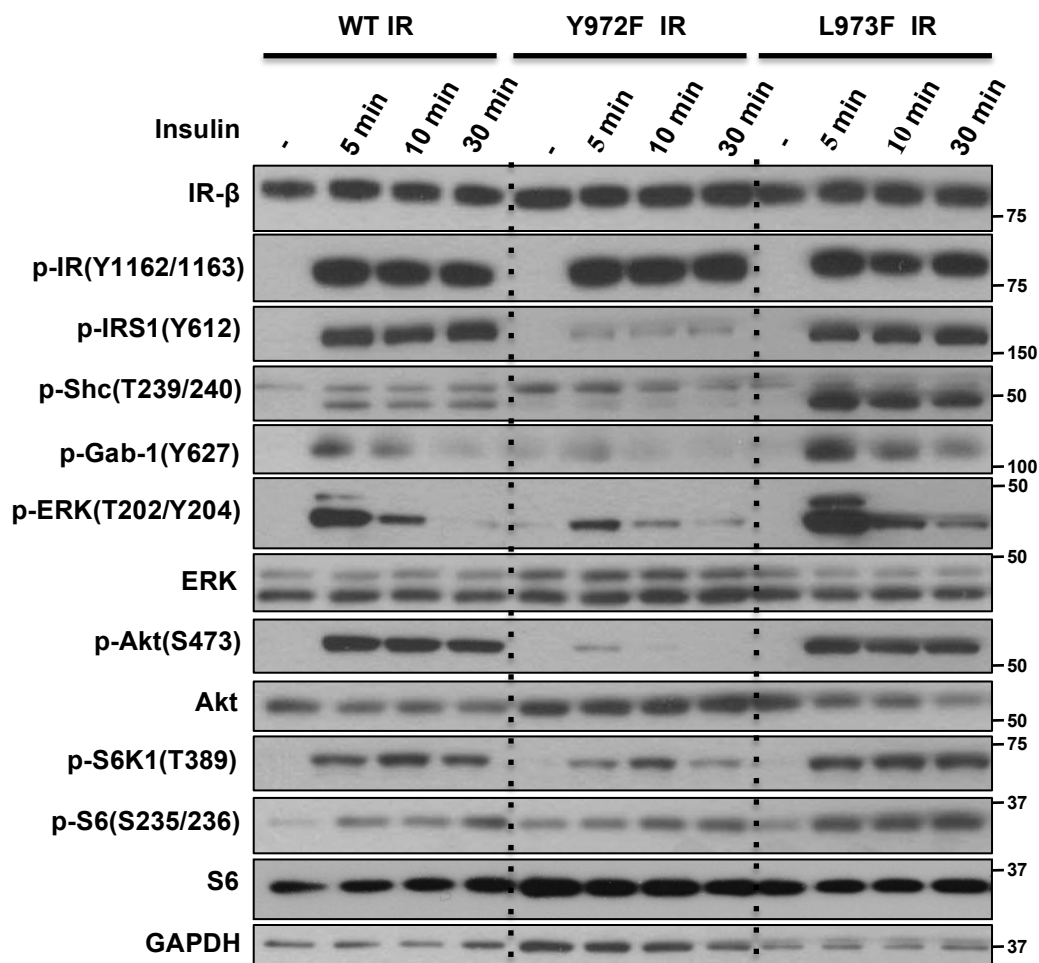
Supplementary Figure 7. Surface representations of the Shc PTB and IRS-1 PTB domains. (a) Surface representation of the solution NMR structure of the Shc PTB domain (green and grey) bound to a phosphorylated segment containing the NPxY motif from the TrkA receptor (ribbon). Structure modelled from Protein Data Bank deposition 1SHC. **(b)** Surface representation of the crystal structure of the IRS-1 PTB domain (green) bound to a phosphorylated segment of the juxtamembrane region of the insulin receptor (ribbon). Structure modelled from Protein Data Bank deposition 5U1M.

Supplementary Figure 8



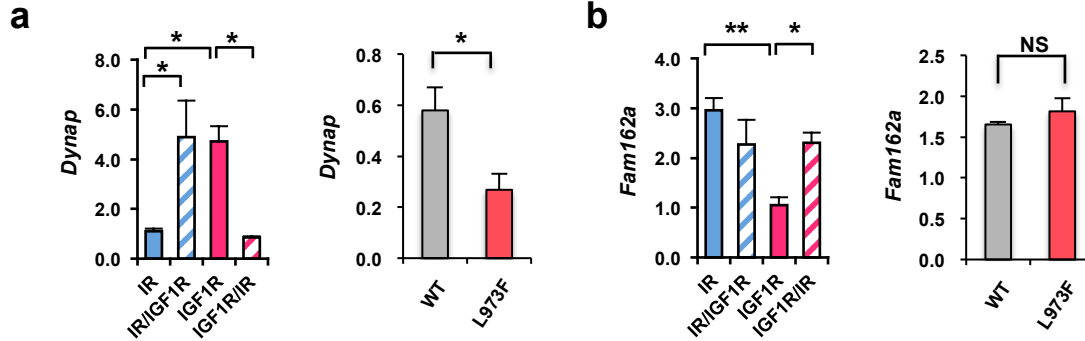
Supplementary Figure 8. Expression levels of receptors in cells expressing IR and IR^{L973F}. Relative mRNA levels of endogenous IR from wild-type and DKO cells, as well as over-expressed recombinant receptors, wild-type human IR and IR^{L973F}. Data are shown as mean \pm SEM copy number per ng total RNA. n = 3-5. Fold overexpression of each recombinant receptor to endogenous receptor is indicated.

Supplementary Figure 9



Supplementary Figure 9. Phosphorylation kinetics of common intracellular signaling targets of IR, IR Y972F and IR L973F. Immunoblot of protein phosphorylation following insulin stimulation for indicated time duration and antibodies.

Supplementary Figure 10



Supplementary Figure 10. Gene expression dependent on ICD of IR and IGF1R receptors but not

dependent on Leu⁹⁷³ in IR and Phe⁹⁵¹ in IGF1R. (a) Fold changes of expression in response to stimulation for *Dynap*, which is highly regulated by IGF1R-ICD, were confirmed in both chimeric receptor and point mutated IR receptor systems by qPCR, with TBP as the housekeeping gene. **(b)** Fold changes of expression in response to stimulation for *Fam162a*, which is highly regulated by IR-ICD were confirmed in both chimeric receptor and point mutated IR receptor systems by qPCR, with TBP as the housekeeping gene. Data are presented as the mean \pm SEM (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. One-way ANOVA followed by Newman-Keuls *post-hoc* analysis or Student *t*-test when appropriate, $n = 3-6$).

Supplementary Figure 11

Figure 1c

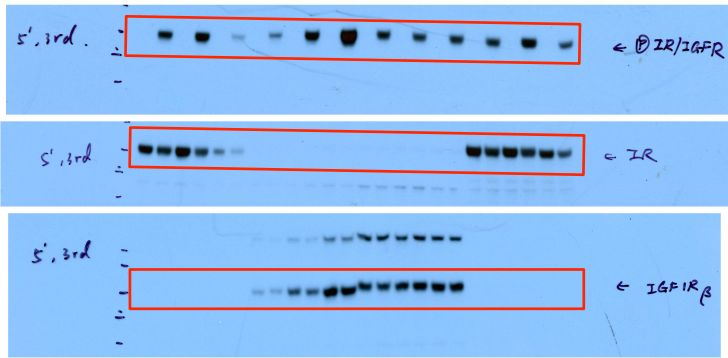
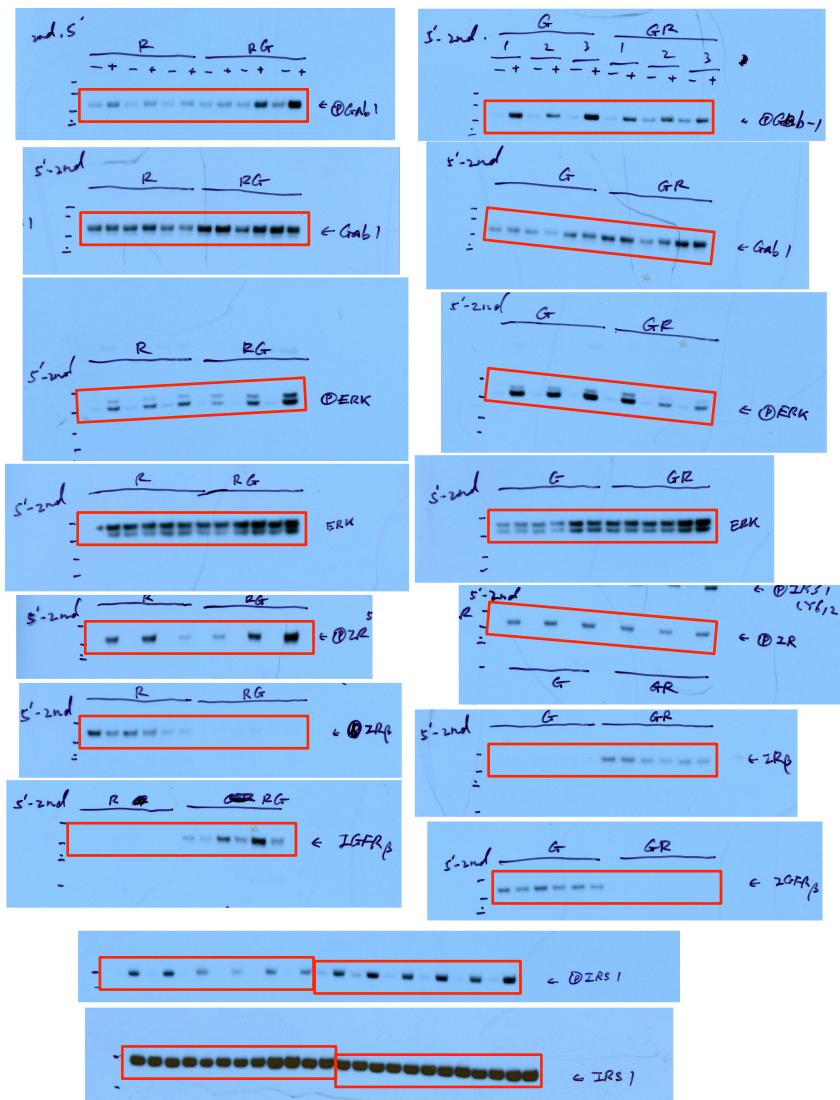
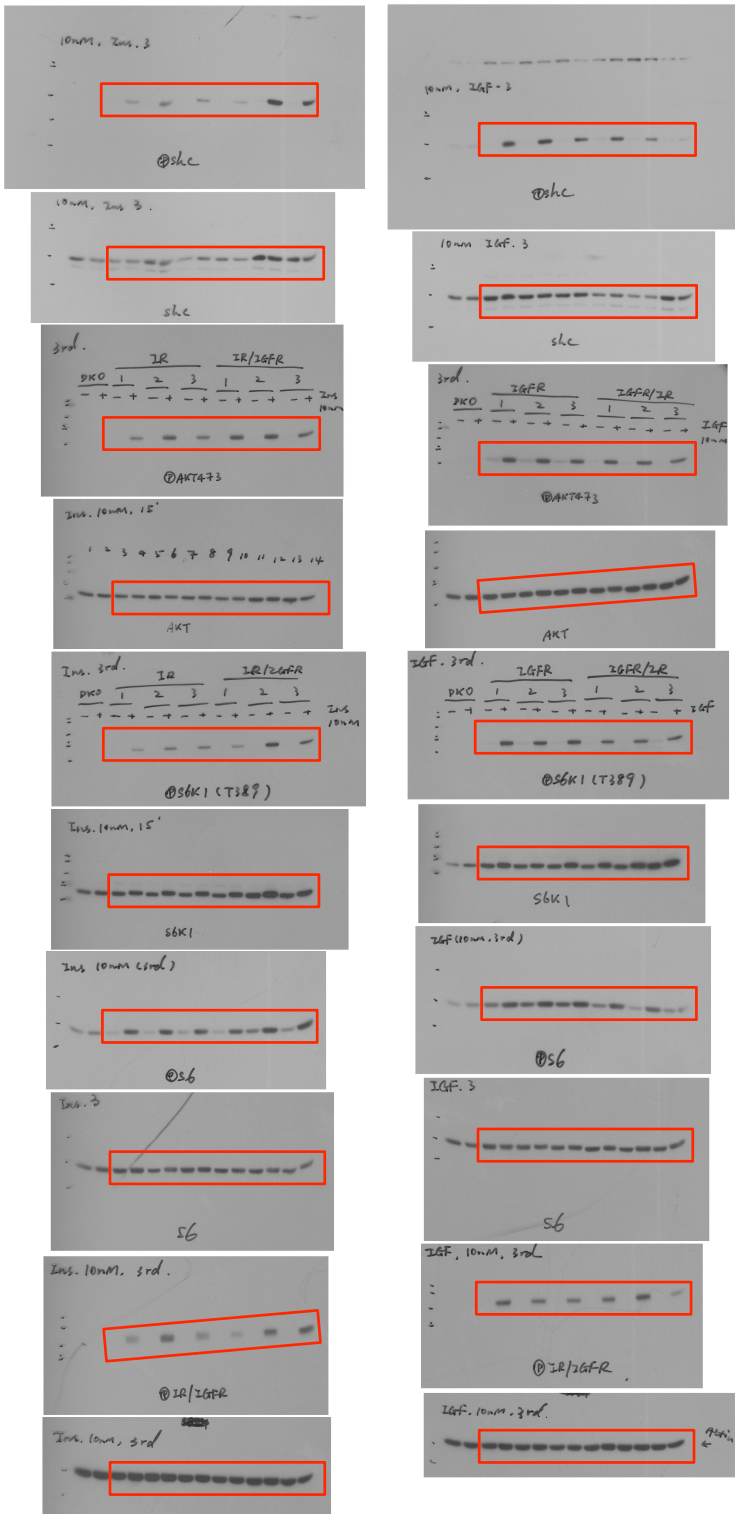


Figure 2a



Supplementary Figure 11. Uncut blots. The red sections indicate blot results shown in the indicated figures.

Supplementary Figure 12
Figure 2e



Supplementary Figure 12. Uncut blots. The red sections indicate blot results shown in the indicated figures.

Supplementary Figure 13

Figure 6b



Figure 6c

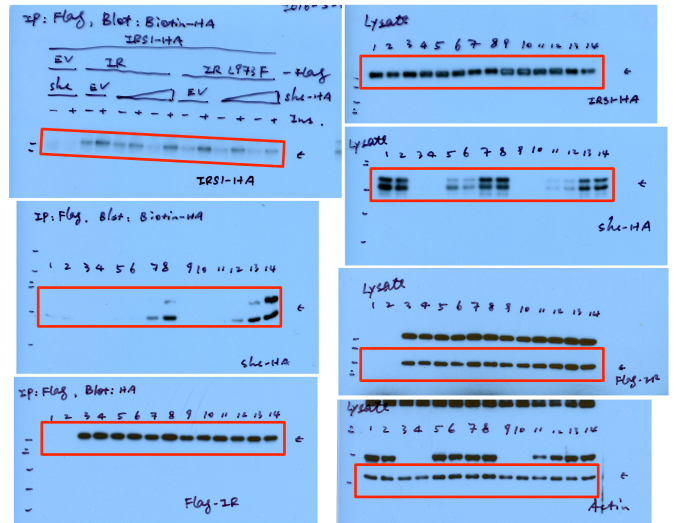
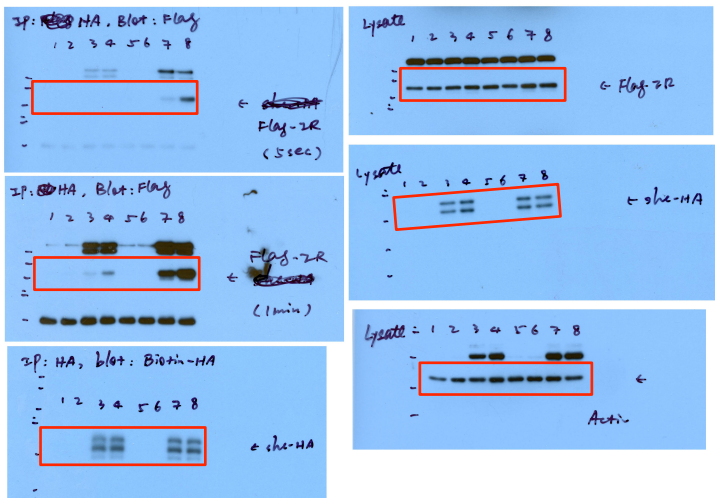


Figure 6d



Supplementary Figure 13. Uncut blots. The red sections indicate blot results shown in the indicated figures.

Supplementary Figure 14

Figure 7a

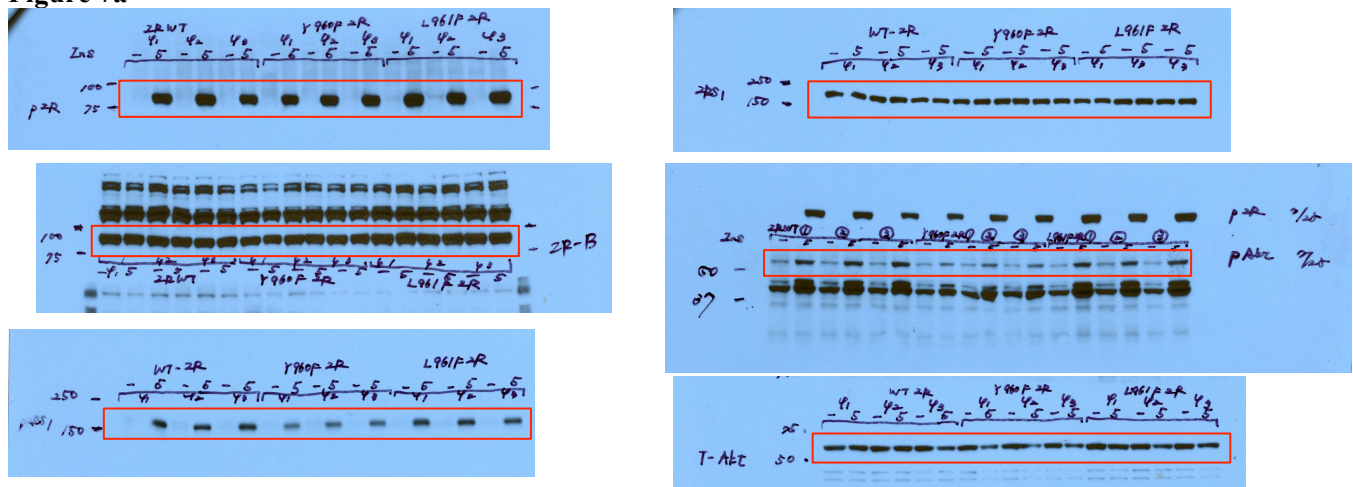
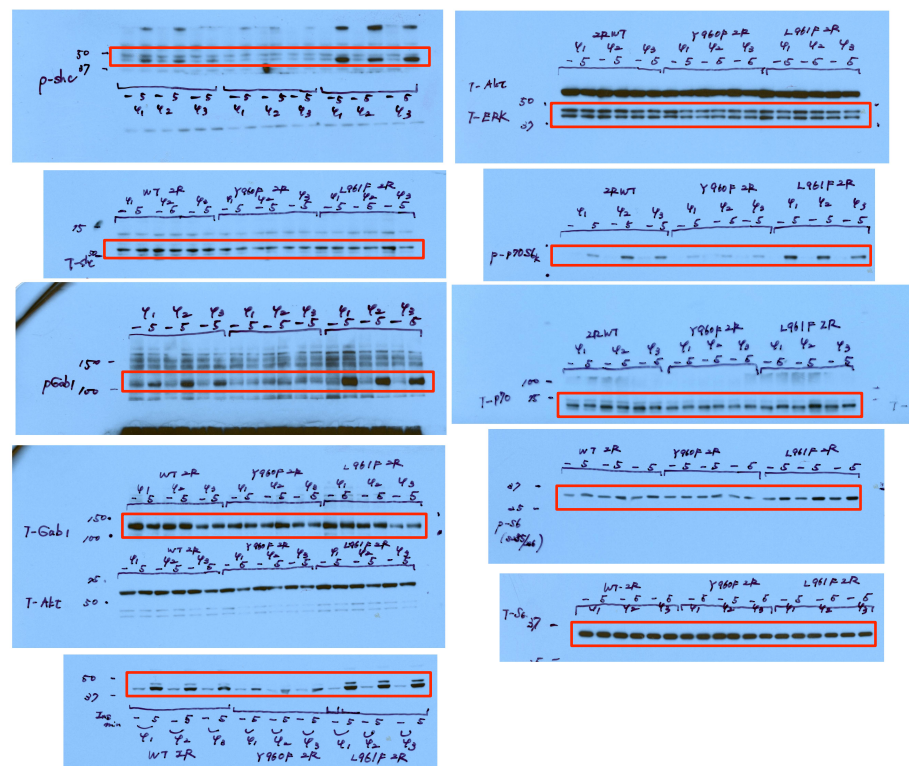


Figure 7c



Supplementary Figure 14. Uncut blots. The red sections indicate blot results shown in the indicated figures. Note, the labeling in these films used IR-A amino acid numbers. Thus, Y960F in IR-A is Y972F in IR-B, and L961F in IR-A is L973F in IR-B.

Supplementary Table 1

Top significant genes that were differentially regulated in IR and IGF1R in response to stimulation

Symbol	mRNA Accession	Name	Fold change to basal		Log ₂ (FC _{IR} /FC _{IGF1R})	p-value	FDR
			IR	IGF1R			
Group I							
<i>Mcpt8</i>	NM_008572	Mast cell protease 8	1.86	8.63	-2.22	1.71E-05	0.0591
<i>Sema7a</i>	NM_011352	Sema domain, immunoglobulin domain (ig), and GPI membrane anchor 7A	1.12	5.24	-2.22	7.79E-05	0.0976
<i>Dynap</i>	NM_029346	Dynalectin associated protein	1.22	4.86	-2.00	2.10E-06	0.0424
<i>Ndst3</i>	NM_031186	N-deacetylase/n-sulfotransferase (heparan glucosaminy) 3	1.22	4.06	-1.73	9.88E-05	0.112
<i>Hmga2</i>	NM_010441	High mobility group at-hook 2	1.08	3.41	-1.66	6.15E-06	0.0424
<i>Hbegf</i>	NM_010415	Heparin-binding EGF-like growth factor	0.85	2.50	-1.56	0.000217	0.155
<i>Erff1</i>	NM_133753	ERBB receptor feedback inhibitor 1	1.06	3.07	-1.54	0.000176	0.151
<i>Mir694</i>	NR_030467	microRNA 694	1.03	2.95	-1.52	4.56E-06	0.0424
<i>Tnc</i>	NM_011607	Tenascin C	2.57	7.36	-1.52	4.22E-05	0.0766
<i>Mir763</i>	NR_030434	microRNA 763	0.82	2.28	-1.48	5.56E-05	0.0766
<i>Gm12603</i>	NR_033533	Predicted gene 12603, long non-coding RNA.	1.80	4.59	-1.35	0.000262	0.159
<i>Havcr2</i>	NM_134250	Hepatitis A virus cellular receptor 2	1.23	3.10	-1.33	7.40E-06	0.0437
<i>Mmd</i>	NM_026178	Monocyte to macrophage differentiation-associated	0.93	2.35	-1.33	9.82E-06	0.0451
<i>Dusp4</i>	NM_176933	Dual specificity phosphatase 4	0.91	2.22	-1.29	5.50E-05	0.0766
<i>LOC100503338</i>	XR_106025	PREDICTED: uncharacterized LOC100503338, ncRNA	0.76	1.84	-1.27	2.14E-05	0.0591
<i>Tgfr1</i>	NM_009370	Transforming growth factor, beta receptor I	0.85	2.03	-1.25	0.000103	0.112
<i>Irs1</i>	NM_010570	Insulin receptor substrate 1	0.66	1.51	-1.18	5.13E-05	0.0766
<i>Arhgap6</i>	NM_001287530	Rho GTPase activating protein 6	0.89	1.88	-1.08	5.07E-06	0.0424
<i>Mgp</i>	NM_008597	Matrix gla protein	0.74	1.56	-1.07	0.000126	0.122
<i>Slc4a1</i>	NM_148933	Solute carrier organic anion transporter family, member 4a1	0.89	1.82	-1.03	0.000111	0.112
<i>D030025P21Rik</i>	NR_028577	RIKEN cDNA D030025P21 gene, long non-coding RNA.	0.66	1.34	-1.02	4.94E-05	0.0766
<i>Socs5</i>	NM_019654	Suppressor of cytokine signaling 5	0.92	1.84	-0.99	0.000196	0.153
<i>Olfir740</i>	NM_146667	Olfactory receptor 740	0.73	1.42	-0.97	0.000245	0.156
<i>Slit2</i>	NM_001291227	Slit homolog 2	0.95	1.85	-0.95	4.70E-05	0.0766
<i>Ccbe1</i>	NM_178793	Collagen and calcium binding EGF domains 1	1.36	2.58	-0.92	7.69E-05	0.0976
<i>Pde11a</i>	NM_001081033	Phosphodiesterase 11A	0.71	1.34	-0.91	0.000147	0.133
<i>Mir133a-2</i>	NR_029901	microRNA 133a-2	0.68	1.20	-0.83	0.000252	0.156
<i>Ngf</i>	NM_013609	Nerve growth factor	1.29	2.25	-0.81	0.000108	0.112
<i>Sestd1</i>	NM_175465	SEC14 and spectrin domains 1	0.84	1.43	-0.78	0.000216	0.155
<i>Mir31</i>	NR_029747	microRNA 31	0.97	1.61	-0.73	0.000253	0.156
<i>Cdc42ep3</i>	NM_026514	CDC42 effector protein (rho GTPase binding) 3	0.78	1.25	-0.69	0.000204	0.154
<i>Klf5</i>	NM_009769	Kruppel-like factor 5	0.81	1.30	-0.68	4.29E-05	0.0766
<i>Fam20c</i>	NM_030565	Family with sequence similarity 20, member C	0.77	1.21	-0.66	0.000281	0.161
<i>Fnip2</i>	NM_001162999	Folliculin interacting protein 2	0.96	1.47	-0.62	0.000228	0.155
<i>Mcl1</i>	NM_008562	Myeloid cell leukemia sequence 1	0.87	1.30	-0.57	0.00018	0.152
Group II							
<i>Fam43a</i>	NM_177632	Family with sequence similarity 43, member A	0.91	0.51	0.84	0.000137	0.128
<i>Rassf2</i>	NM_175445	Ras association (RalGDS/AF-6) domain family member 2	1.22	0.72	0.76	0.000127	0.122
<i>Snx29</i>	NM_028964	Sorting nexin 29	0.73	0.46	0.65	7.71E-05	0.0976
<i>Gm15716</i>	ENSMUST00000162457	Predicted gene 15716, non-coding RNA	1.15	0.73	0.65	0.000193	0.153
<i>Tapbp1</i>	NM_145391	TAP binding protein-like	0.94	0.60	0.64	0.000285	0.161
<i>Rdh12</i>	NM_030017	Retinol dehydrogenase 12	1.07	0.69	0.63	0.000245	0.156
<i>Cby1</i>	NM_028634	Chibby homolog 1	1.10	0.75	0.55	0.000224	0.155
Group III							
<i>Stc1</i>	NM_009285	Stanniocalcin 1	4.76	1.21	1.98	0.000205	0.154
<i>Bnip3</i>	NM_009760	BCL2/adenovirus E1B interacting protein 3	3.53	1.22	1.53	2.74E-05	0.0708
<i>Pdk1</i>	NM_172665	Pyruvate dehydrogenase kinase, isoenzyme 1	2.93	1.10	1.41	0.000107	0.112
<i>Fam162a</i>	NM_027342	Family with sequence similarity 162, member A	2.97	1.22	1.29	2.15E-05	0.0591
<i>Pfkf</i>	NM_008826	Phosphofructokinase, liver, b-type	2.60	1.16	1.17	2.08E-05	0.0591
<i>Gys1</i>	NM_030678	Muscle glycogen synthase 1	2.58	1.18	1.13	4.22E-05	0.0766
<i>S1pr1</i>	NM_007901	Sphingosine-1-phosphate receptor 1	1.79	0.89	1.01	0.000104	0.112
<i>Nek6</i>	NM_021606	NIMA (never in mitosis gene a)-related expressed kinase 6	1.74	0.92	0.92	2.12E-05	0.0591
<i>Mir467d</i>	NR_030572	microRNA 467d	1.63	0.87	0.90	0.000279	0.161
<i>Ddit4</i>	NM_029083	DNA-damage-inducible transcript 4	2.53	1.37	0.88	0.000245	0.156
<i>Nos2</i>	NM_010927	Inducible nitric oxide synthase 2	1.90	1.05	0.86	4.32E-05	0.0766
<i>Fbn1</i>	NM_007993	Fibrillin 1	1.52	0.84	0.86	0.000101	0.112
<i>Pgm2</i>	NM_028132	Phosphoglucomutase 2	2.10	1.19	0.83	0.000188	0.152
<i>B430319G15Rik</i>	NR_029474	RIKEN cDNA B430319G15 gene, long non-coding RNA.	1.83	1.04	0.81	0.000185	0.152
<i>Myd88</i>	NM_010851	Myeloid differentiation primary response gene 88	1.37	0.86	0.67	3.89E-05	0.0766
<i>Phospho1</i>	NM_153104	Phosphatase, orphan 1	1.89	1.27	0.58	0.000285	0.161
Group IV							
<i>Egr1</i>	NM_007913	Early growth response 1	0.22	1.25	-2.50	9.67E-06	0.0451
<i>Egr2</i>	NM_010118	Early growth response 2	0.45	1.18	-1.38	4.17E-05	0.0766

Supplementary Table 2

Selected top differentially regulated pathways by IR and IGF1R from gene set analysis (Reactome)

Highly regulated in IR			Highly regulated in IGF1R		
Pathway	p-value	FDR	Pathway	p-value	FDR
Regulation of Hypoxia inducible factor HIF by oxygen	6.89E-05	0.0214	Integrin cell surface interactions	0.000157	0.0214
Regulation of signaling by Cbl	4.00E-04	0.0253	Membrane binding and targeting of GAG proteins	0.00052	0.0263
Pyruvate metabolism	0.000838	0.0263	Keratan sulfate biosynthesis	0.000967	0.0263
Glycolysis	0.00124	0.0263	Mitochondrial fatty acid beta oxidation	0.00133	0.0263
Glucose metabolism	0.00175	0.0267	Grb2 events in ERBB2 signaling	0.00142	0.0264
TRAF3 dependent IRF activation pathway	0.00181	0.0267	Signaling by Rho GTPases	0.00158	0.0264
Autodegradation of the E3 ubiquitin ligase COP1	0.00187	0.0267	Branched chain amino acid catabolism	0.00163	0.0267
Gluconeogenesis	0.00214	0.0279	Mitotic prometaphase	0.00187	0.0267
Signaling by Wnt	0.00229	0.0279	Golgi associated vesicle biogenesis	0.00207	0.0279
Purine metabolism	0.00279	0.0301	Voltage gated potassium channels	0.00229	0.0279
ER phagosome pathway	0.00465	0.038	Keratan sulfate degradation	0.00544	0.0413
Cholesterol biosynthesis	0.00596	0.0429	Shc related events	0.016	0.0704
Pyrimidine metabolism	0.00736	0.0461	Glycosaminoglycan metabolism	0.0203	0.0802
Diabetes pathway	0.00854	0.0493	Semaphorin interactions	0.0209	0.0809
Bile acid and bile salt metabolism	0.0135	0.0642	Cell surface interactions at the vascular wall	0.0308	0.107

Supplementary Table 3

Top significant genes that were differentially regulated in IR-ECD and IGF1R-ECD in response to stimulation

Symbol	mRNA Accession	Name	Log ₂ (FC _{IR-ECD} /FC _{IGF1R-ECD})	p-value	FDR
Group I					
<i>Cck</i>	NM_001284508	Cholecystokinin	0.972	0.00066	0.23
<i>Mmp13</i>	NM_008607	Matrix metalloproteinase 13	0.785	0.000141	0.181
<i>Bnip3</i>	NM_009760	BCL2/adenovirus E1B interacting protein 3	0.774	0.000627	0.23
<i>Hp</i>	NM_017370	Haptoglobin	0.669	0.000523	0.225
<i>Gm25200</i>	ENSMUST00000083094	ncRNA:snoRNA	0.645	0.00028	0.205
<i>Pfkl</i>	ENSMUST00000061829	Unknown protein coding gene	0.587	0.000174	0.181
<i>Cd14</i>	NM_030678	Glycogen synthase 1	0.561	0.00105	0.294
<i>Olf11507</i>	NM_001170918	Olfactory receptor 1507	0.546	0.000558	0.225
<i>Mir1188</i>	NR_035419	microRNA 1188	0.536	0.00071	0.238
<i>Gm24151</i>	ENSMUST00000082758	ncRNA:snoRNA	0.534	0.000133	0.181
<i>Gm24527</i>	ENSMUST00000082920	ncRNA:snRNA	0.533	0.000802	0.254
<i>Il13ra1</i>	NM_133990	Interleukin 13 receptor, alpha 1	0.529	0.000184	0.181
<i>Ifitm6</i>	NM_001033632	Interferon induced transmembrane protein 6	0.522	0.000282	0.205
<i>Pdc</i>	NM_001159730	Phosducin	0.514	0.00031	0.205
<i>Gm24086</i>	ENSMUST00000175171	ncRNA:snRNA	0.508	0.000498	0.217
<i>Bri3</i>	NM_001163709	Brain protein 13	0.496	0.000242	0.205
<i>Myd88</i>	NM_010851	Myeloid differentiation primary response gene 88	0.487	4.99E-05	0.173
<i>Nek6</i>	NM_021606	NIMA (never in mitosis gene a)-related expressed kinase 6	0.487	0.000357	0.205
<i>Plac8</i>	ENSMUST00000031264	Unknown protein coding gene	0.487	0.000454	0.213
<i>Gp6</i>	NM_001163014	Glycoprotein 6	0.42	0.000223	0.196
Group II					
<i>Gm10722</i>	NR_028577	Predicted gene, 10722	-1.33	0.000154	0.181
<i>Gm21732</i>	ENSMUST00000179309	Predicted gene, 21732	-1.1	1.08E-06	0.0327
<i>Gm10721</i>	ENSMUST00000143083	Predicted gene, 10721	-1.08	0.000108	0.173
<i>Gm20854</i>	ENSMUST00000181549	Predicted gene, 20854	-0.983	1.70E-05	0.122
<i>Gm20213</i>	ENSMUST00000151376	Predicted gene, 20854, non-coding RNA	-0.958	0.000146	0.181
<i>Olf11463</i>	NM_001011840	Olfactory receptor 1463	-0.861	0.000214	0.192
<i>LOC102640642</i>	XM_006528646	PREDICTED: uncharacterized LOC102640642, transcript variant X2, mRNA.	-0.825	3.19E-05	0.173
<i>Olf1740</i>	NM_146667	Olfactory receptor 740	-0.814	9.76E-05	0.173
<i>Gm21788</i>	ENSMUST00000177878	Predicted gene, 21788	-0.808	0.000203	0.186
<i>Gm22956</i>	ENSMUST00000122520	Predicted gene, 22956, non-coding RNA	-0.794	0.000101	0.173
<i>Gm20736</i>	NM_001037748	Predicted gene, 20736	-0.786	0.000352	0.205
<i>Astx</i>	XM_006528435	PREDICTED: amplified spermatogenic transcripts X encoded	-0.775	8.74E-05	0.173
<i>Vmn1r114</i>	NM_001166837	Vomer nasal 1 receptor 114	-0.755	0.000107	0.173
<i>5031410106Rik</i>	NM_207657	RIKEN cDNA 5031410106 gene	-0.73	8.80E-05	0.173
<i>Gm20815</i>	NM_001017394	Predicted gene, 20815	-0.723	0.000389	0.205
<i>1700091H14Rik</i>	NR_073362	RIKEN cDNA 1700091H14 gene, long non-coding RNA.	-0.701	8.80E-05	0.173
<i>Gm15319</i>	NM_001177408	Predicted gene 15319	-0.699	5.45E-05	0.173
<i>Gm20738</i>	NM_207162	Predicted gene, 20738	-0.692	9.19E-05	0.173
<i>493043311Rik</i>	ENSMUST00000171664	RIKEN cDNA 493043311 gene	-0.668	0.000202	0.186
<i>D030025P21Rik</i>	XR_382991	RIKEN cDNA D030025P21 gene, long non-coding RNA.	-0.645	0.000194	0.186

Supplementary Table 4

Selected top differentially regulated pathways by IR-ECD and IGF1R-ECD from gene set analysis (Reactome)

Highly regulated in IR-ECD			Highly regulated in IGF1R-ECD		
Pathway	p-value	FDR	Pathway	p-value	FDR
Prolonged ERK activation events	9.87E-06	0.00331	Voltage gated potassium channels	0.00115	0.0215
Regulation of signaling by Cbl	0.000385	0.0215	Keratan sulfate degradation	0.00437	0.0215
Autodegradation of the E3 ubiquitin ligase Cop1	0.000779	0.0215	GPVI mediated activation cascade	0.00437	0.0215
Signaling by Wnt	0.000933	0.0215	ADP signaling through P2PY12	0.0173	0.0473
ER phagosome pathway	0.00108	0.0215	G protein activation	0.0214	0.0553
Triglyceride biosynthesis	0.00152	0.0215	Synthesis of PA	0.0349	0.0831
Metabolism of Vitamins and cofactors	0.00214	0.0215	Formation of fibrin clot clotting cascade	0.0394	0.0904
Pyruvate metabolism	0.00221	0.0215	Inhibition of insulin secretion by adrenaline noradrenaline	0.0394	0.0904
Metabolism of carbohydrates	0.00229	0.0215	Grb2 events in ERBB2 signaling	0.0434	0.0975
Cholesterol biosynthesis	0.00253	0.0215	Acyl chain remodeling of PC	0.0477	0.105

Supplementary Table 5

Top significant genes that were differentially regulated in IR-ICD and IGF1R-ICD in response to stimulation

Symbol	mRNA Accession	Name	Log ₂ (FC _{IR-ICD} /FC _{IGF1R-ICD})	p-value	FDR
Group I					
<i>Sema7a</i>	NM_011352	Sema domain, immunoglobulin domain (ig), and GPI membrane anchor 7A	-2.29	5.22E-06	0.0151
<i>Dynap</i>	NM_029346	Dynactin associated protein	-2.23	5.13E-08	0.00212
<i>Mcpt8</i>	NM_008572	Mast cell protease 8	-1.93	4.76E-06	0.0151
<i>Ndst3</i>	NM_031186	N-deacetylase/n-sulfotransferase (heparan glucosaminyl) 3	-1.83	5.26E-06	0.0151
<i>Hmga2</i>	NM_010441	High mobility group at-hook 2	-1.66	4.57E-07	0.00591
<i>Gm12603</i>	NR_033533	Predicted gene 12603, long non-coding RNA.	-1.56	7.29E-06	0.0151
<i>Mir763</i>	NR_030434	microRNA 763	-1.52	3.82E-06	0.0151
<i>Hbegf</i>	NM_010415	Heparin-binding EGF-like growth factor	-1.44	4.05E-05	0.0383
<i>Erff1</i>	ENSMUST00000073600	ERBB receptor feedback inhibitor 1	-1.43	2.93E-05	0.0319
<i>Tnc</i>	NM_011607	Tenascin C	-1.41	6.91E-06	0.0151
<i>Mir694</i>	NR_030467	microRNA 694	-1.39	7.90E-07	0.00591
<i>Mmd</i>	NM_026178	Monocyte to macrophage differentiation-associated	-1.32	7.87E-07	0.00591
<i>Dusp4</i>	NM_176933	Dual specificity phosphatase 4	-1.32	3.65E-06	0.0151
<i>Havcr2</i>	NM_134250	Hepatitis A virus cellular receptor 2	-1.27	8.58E-07	0.00591
<i>LOC100503338</i>	XR_106025	PREDICTED: uncharacterized LOC100503338, ncRNA	-1.21	2.73E-06	0.0151
<i>Arhgap6</i>	NM_001287530	Rho GTPase activating protein 6	-1.12	2.62E-07	0.00542
<i>Slc4a1</i>	NM_148933	Solute carrier organic anion transporter family, member 4a1	-1.10	5.80E-06	0.0151
<i>Ccnd1</i>	NM_007631	Cyclin D1	-1.08	0.000548	0.0934
<i>Thbd</i>	NM_009378	Thrombomodulin	-1.03	6.27E-06	0.0151
<i>Ccbe1</i>	NM_178793	Collagen and calcium binding EGF domains 1	-1.00	3.12E-06	0.0151
<i>Parvb</i>	NM_133167	Parvin, beta	-0.99	6.09E-06	0.0151
<i>Slc25a37</i>	NM_026331	Solute carrier family 25, member 37	-0.95	1.13E-05	0.0194
<i>Slit2</i>	NM_001291227	Slit homolog 2	-0.83	1.28E-05	0.0203
<i>Hmga1</i>	NM_001025427	High mobility group at-hook1	-0.82	7.07E-06	0.0151
<i>Ngf</i>	NM_013609	Nerve growth factor	-0.78	1.25E-05	0.0203
<i>Fnip2</i>	NM_001162999	Folliculin interacting protein 2	-0.65	1.41E-05	0.0216
<i>Fxyd5</i>	ENSMUST00000079996	FXYD domain-containing ion transport regulator 5	-0.63	2.90E-05	0.0319
<i>Klf5</i>	NM_009769	Kruppel-like factor 5	-0.63	7.85E-06	0.0154
Group II					
<i>Gm25987</i>	ENSMUST00000083234	Predicted gene 25987, snRNA	0.968	0.000115	0.0522
<i>Hist1h3c</i>	BC120800	Histone cluster 1, h3c	0.911	0.000109	0.0513
<i>3830403N18Rik</i>	NM_027510	RIKEN cDNA 3830403n18rik gene	0.884	0.000268	0.0686
<i>Zhx1</i>	NM_001042438	Zinc fingers and homeoboxes 1	0.76	5.71E-05	0.0421
<i>Acox2</i>	NM_001161667	Acyl-coenzyme A oxidase 2, branched chain	0.731	0.000345	0.0762
<i>Fcamr</i>	NM_0011170632	Fc receptor, iga, igm, high affinity	0.683	0.00033	0.0762
<i>Ipp</i>	NM_008389	IAP promoted placental gene	0.68	4.08E-05	0.0383
<i>Fig4</i>	NM_133999	FIG4 homolog	0.66	5.35E-05	0.0421
<i>Cdkn2d</i>	NM_009878	Cyclin-dependent kinase inhibitor 2D (p19, inhibits CDK4)	0.654	0.000155	0.0567
<i>H1f0</i>	NM_008197	H1 histone family, member 0	0.65	8.87E-05	0.0489
<i>Gm26425</i>	ENSMUST00000122529	Predicted gene 26425, snRNA	0.649	8.85E-05	0.0489
<i>Hist1h2bg</i>	BC060304	Histone cluster 1, h2bg	0.628	0.000118	0.0522
<i>Pcx</i>	NM_001162946	Pyruvate carboxylase	0.623	0.000267	0.0686
<i>Rassf2</i>	NM_175445	Ras association (ralgds/AF-6) domain family member 2	0.62	6.62E-05	0.0421
<i>Vmn1r129</i>	NM_001166725	Vomer nasal 1 receptor 129	0.588	0.000104	0.0507
Group III					
<i>Fam162a</i>	NM_027342	Family with sequence similarity 162, member A	0.784	0.000119	0.0522
<i>S1pr1</i>	NM_007901	Sphingosine-1-phosphate receptor 1	0.71	0.000167	0.0591
<i>Serpnb1a</i>	NM_025429	Serine (or cysteine) peptidase inhibitor, clade B, member 1a	0.692	0.000228	0.0647
<i>Ptch1</i>	NM_008957	Patched homolog 1	0.651	0.000233	0.0647
<i>Pfkf</i>	NM_008826	Phosphofruktokinase, liver, b-type	0.569	0.000641	0.0985
Group IV					
<i>Egr1</i>	NM_007913	Early growth response 1	-1.97	6.19E-06	0.0151
<i>Egr2</i>	NM_010118	Early growth response 2	-1.06	3.52E-05	0.0354

Supplementary Table 6

Selected top differentially regulated pathways by IR-ICD and IGF1R-ICD from gene set analysis (Reactome)

Highly regulated in IR-ICD			Highly regulated in IGF1R-ICD		
Pathway	p-value	FDR	Pathway	p-value	FDR
Pyrimidine metabolism	7.82E-06	0.000655	Signaling by Rho GTPases	3.32E-06	0.000445
Oxygen dependent Proline hydroxylation of hypoxia inducible factor alpha	0.000177	0.00439	PPARa activates gene expression	1.87E-05	0.00125
Gluconeogenesis	0.000233	0.00504	Grb2 events in ERBB2 signaling	0.000252	0.00512
Receptor ligand binding initiates the second proteolytic cleavage of Notch receptor	0.000752	0.00742	Branched chain amino acid catabolism	0.000295	0.00564
GPVI mediated activation cascade	0.00194	0.0118	Membrane binding and targetting of GAG proteins	0.000318	0.00592
TIE2 signaling	0.00229	0.0128	Sphingolipid metabolism	0.000331	0.00599
Synthesis secretion and deacylation of Ghrelin	0.0027	0.0138	Golgi associated vesicle biogenesis	0.000344	0.00606
Regulation of Insulin secretion by Glucagon like peptide 1	0.00308	0.0138	Trans Golgi network vesicle budding	0.000432	0.00672
Acyl chain remodeling of PE	0.00437	0.0138	Glycosaminoglycan metabolism	0.000465	0.007
Glycolysis	0.00495	0.0152	Semaphorin interaction	0.000752	0.00742
Synthesis of bile acids and bile salts via 24-Hydroxycholesterol	0.0131	0.0325	Keratan sulfate Keratin metabolism	0.000779	0.00742
Recycling of bile acids and salts	0.0131	0.0325	Mitochondrial fatty acid beta oxidation	0.000808	0.00742
PI3K Akt activation	0.0257	0.0569	Integrin cell surface interactions	0.00111	0.00848
Regulation of hypoxia inducible factor HIF by oxygen	0.0349	0.0739	Mitotic prometaphase	0.00115	0.00859
Phospholipase C mediated cascade	0.0477	0.0966	Cell cycle	0.002	0.0119

Supplementary Table 7

Primer list for quantitative PCR.

Gene Symbols	Primer sequences
Cck_F	GACCCCAGCCATAGAATAAGTG
Cck_R	TTGTTTCCTCATTCCACCTCC
Ccnd1_F	GCCCTCCGTATCTTACTTCAAG
Ccnd1_R	GCGGTCCAGGTAGTTCATG
CD14_F	TTTAACTCTGGCGTAGTCACC
CD14_R	GACCCTCAGAAACCAGGAG
Cdkn2d_F	CTTCATCGGGAGCTGGTG
Cdkn2d_R	AGGCATCTTGGACATTGGG
D030025P21Rik_F	TTCCACCCCAAACGTGCATAG
D030025P21Rik_R	AGTAGCCACCTTACCATTGC
Dynap_F	CTACCACCCTGCCACATTT
Dynap_R	GGCTTGAGGACCGAGAGTTC
Egr1_F	AGCGCCTTCAATCCTCAAG
Egr1_R	TTTGGCTGGGATAACTCGTC
Egr2_F	TTGACCAGATGAACGGAGTG
Egr2_R	TGCCCATGTAAGTGAAGGTC
Errfi1_F	CCTACAATCTGAACTCCCCTG
Errfi1_R	AAGCTTGACCTTGGAGATGG
Fam162a_F	AAATGCTTCCTCGTCTCTAAGG
Fam162a_R	CTCAAAATCTGTGGGCTTGTG
Fig4_F	ATGGAACGGTGAACCTTCTGG
Fig4_R	CTGGCTATTAGGGTCACATACAC
Gm10722_F	TGCCATATTCCATGCCTACAG
Gm10722_R	TGGCGAGAAAACAGAAAATCAC
Gm21732_F	CATCTGTGTTAGGGTCTCTGTG
Gm21732_R	TGGGCAGGTTGAGAAAGTTC
Hbegf_F	CCCCTATACACATATGACCACAC
Hbegf_R	CAACTTCACTTTCTCTTCACTTTCC
IR_F	AAATGCAGGAACCTCTCGGAAGCCT
IR_R	ACCTTCGAGGATTTGGCAGACCTT
IGF1R_F	ATCGCGATTTCTGCGCCAACA
IGF1R_R	TTCTTCTTTCATCGCCGCAGACT
Il13ra1_F	TGTGGAGTGATTGGAGTGAAG
Il13ra1_R	TGCGACAAAGACTGGAATGG
Mcpt8_F	AAACCTACAACGACTCCATCC
Mcpt8_R	CACAAGCGACAACCTGACAATG
Mmp13_F	TTGATGCCATTACCAGTCTCC
Mmp13_R	ACATGGTTGGGAAGTTCTGG
Pfkl_F	GGAAAGCCTATCTCATCCAGC
Pfkl_R	CCATACCCATCTTGCTACTCAG
Rassf2_F	AACCTGCCCTAATCCCATG
Rassf2_R	TAACCCCTCCACAATGAACTC
S1pr1_F	TGTAGACCCAGAGTCCTGC
S1pr1_R	TCAGTTACAGCAAAGCCAGG
Sema7a_F	GTCTACCACTTCAACTTCCCC
Sema7a_R	CCATTACCCCGCCTTTCTAG
Serpnb1a_F	CCCTGTGGATTTTCTGCATG
Serpnb1a_R	GCATTCACCAGCACAAAGTTTG
TBP_F	ACCCTTACCAATGACTCCTATG
TBP_R	TGACTGCAGCAAATCGCTTGG
Tnc_F	ATAGCCAACATCACAGACTCAG
Tnc_R	GCTCGTACTCCACTGTATTCC
Vmn1r114_F	CCAGTGCTCCATGGTACTTC
Vmn1r114_R	AGGATAGTTTGGGTTGCTCTG

