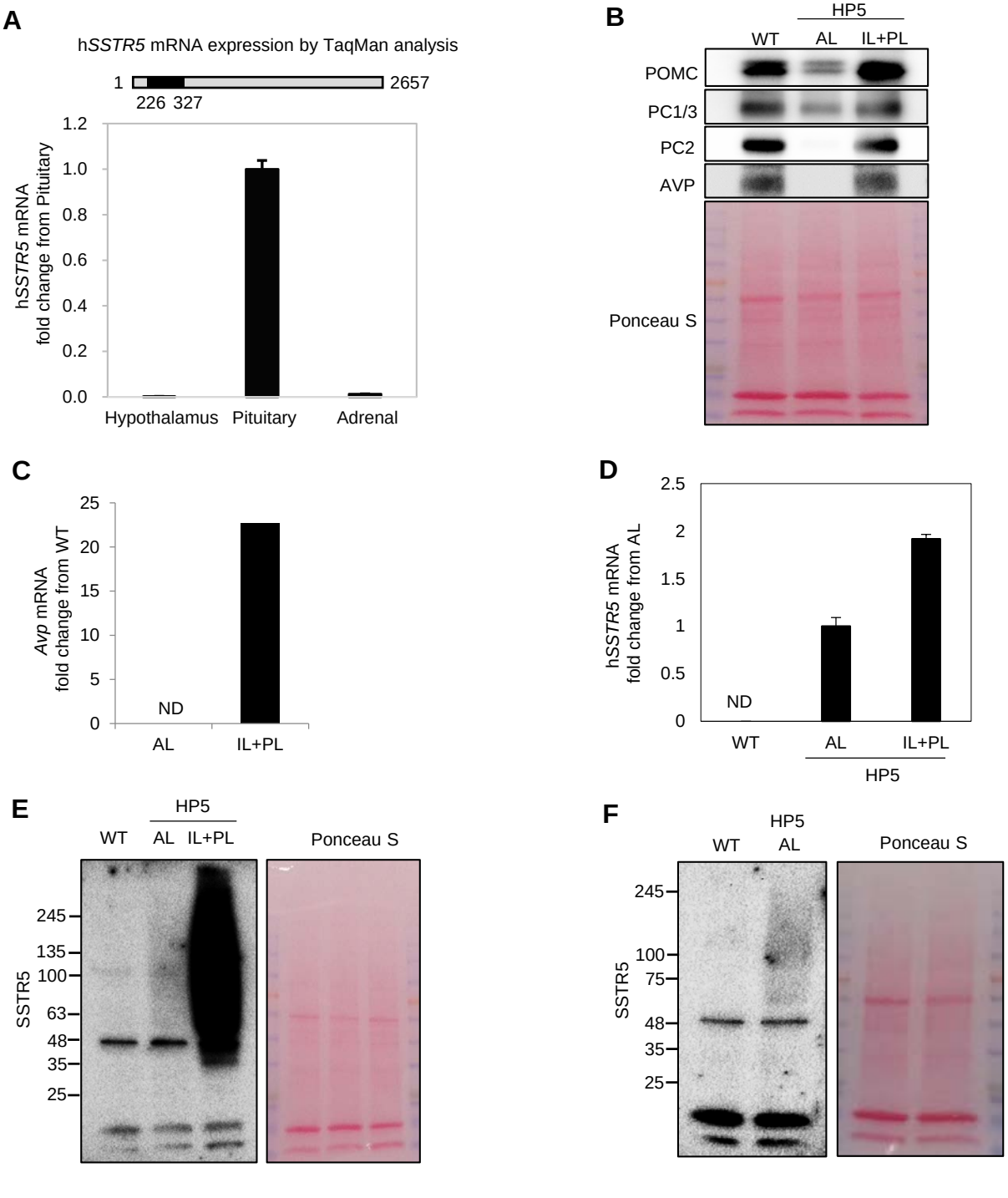
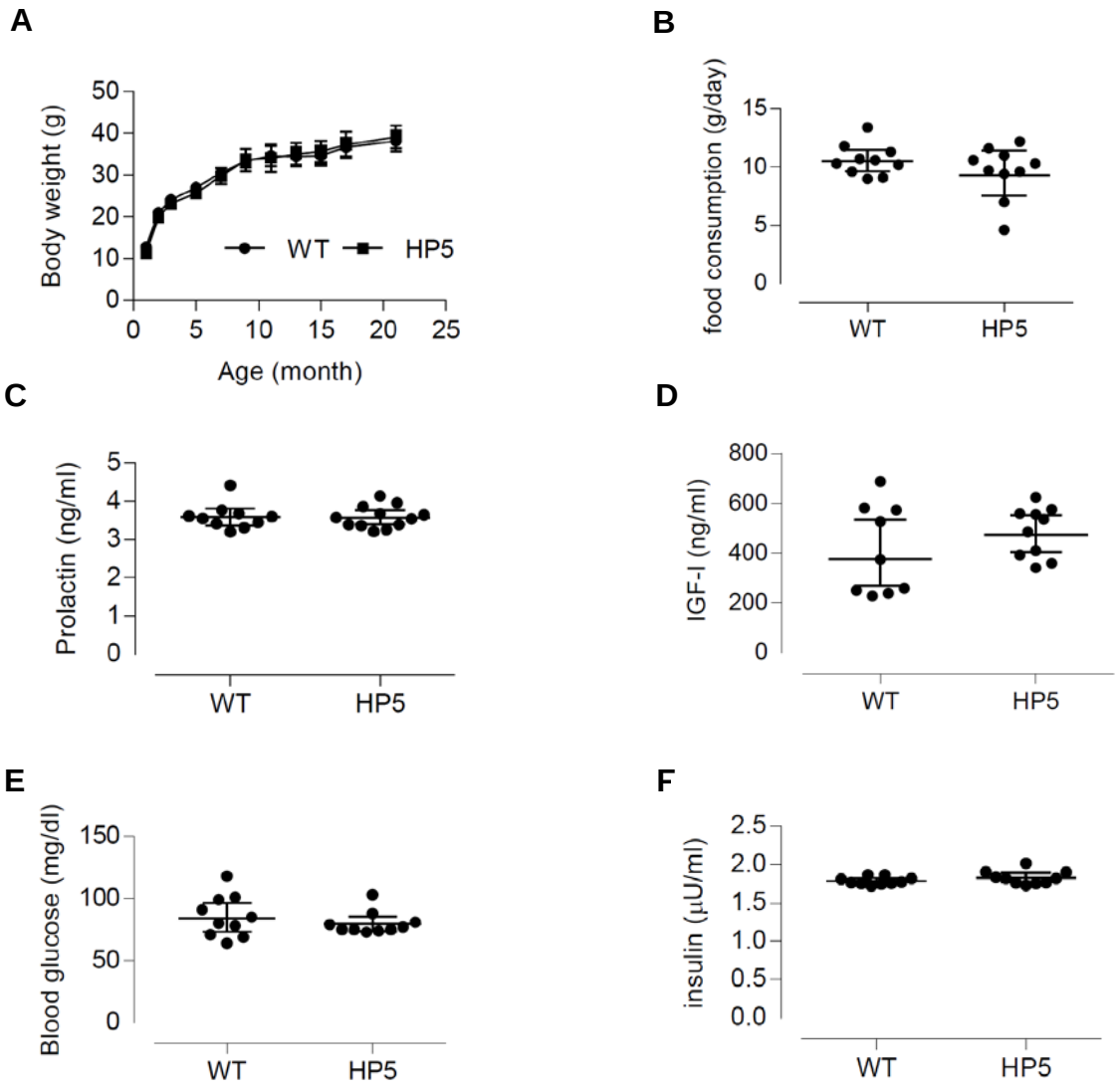
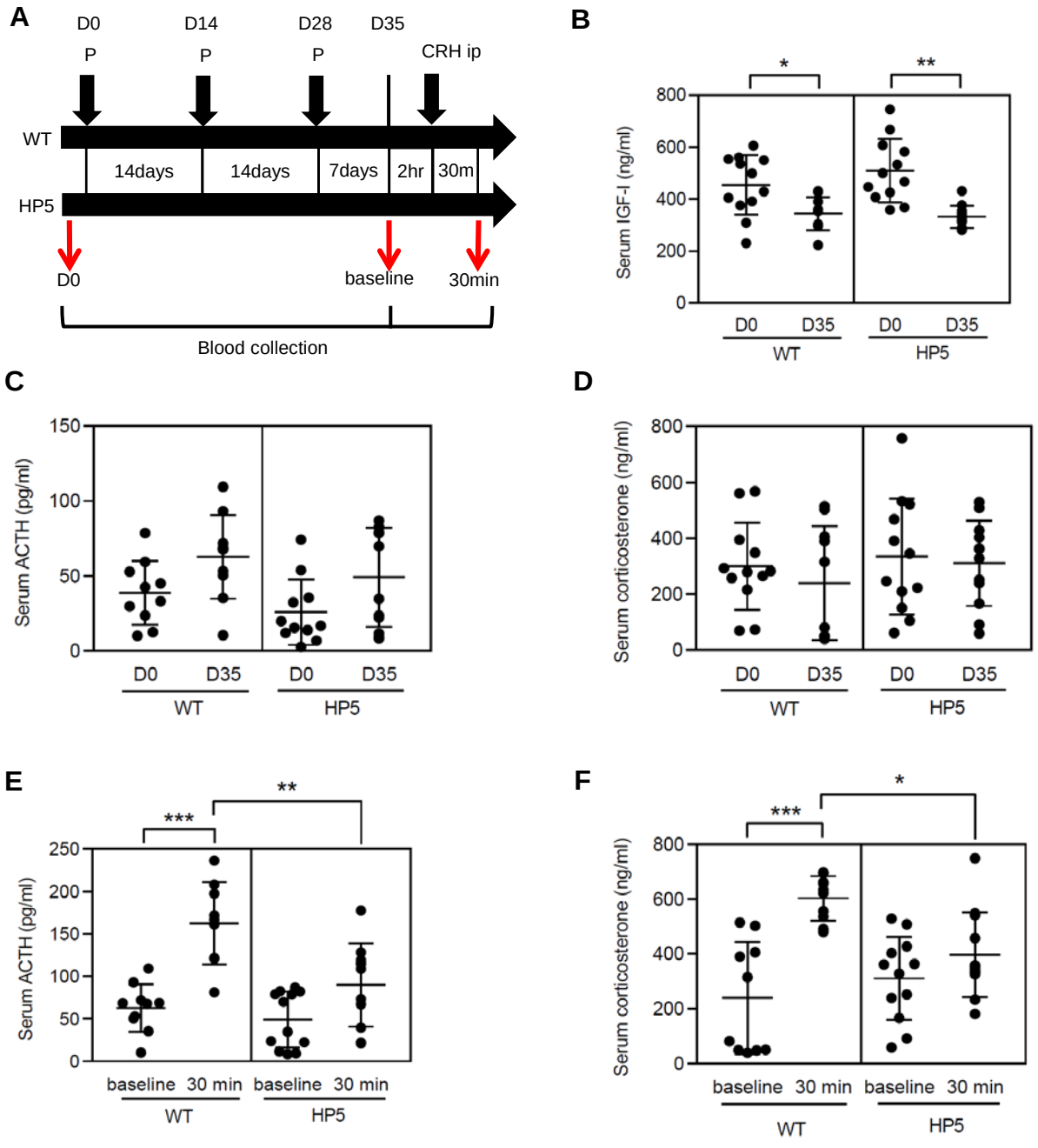


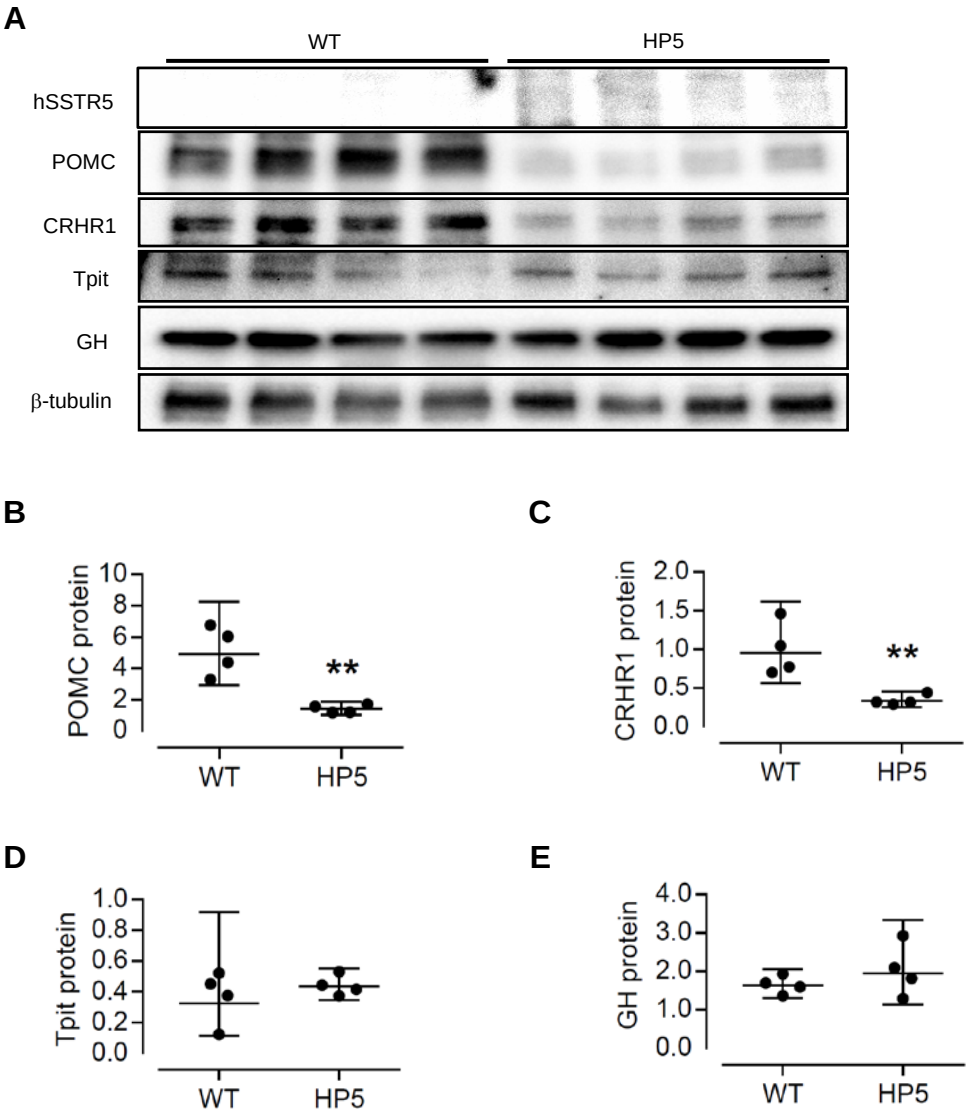
Supplemental Figure S1. (**A**) Upper, hybridization sequence of the TaqMan primer used for selective identification of h*SSTR5* in qRTPCR. Lower, h*SSTR5* mRNA expression in pituitary, hypothalamus, and adrenal gland in HP5, normalized to *Gapdh*. (**B**) Expression of POMC, PC1/3, PC2, and AVP in WT mouse whole pituitary, as well as in HP5 mouse anterior (AL) and intermediate and posterior (IL+PL) lobes of pituitary. (**C**) Mouse *Avp* mRNA expression in AL vs IL+PL in HP5, normalized to *Gapdh* mRNA expression. ND, not detected. (**D**) h*SSTR5* mRNA expression in AL vs IL+PL HP5 pituitary, normalized to *Gapdh*. ND, not detected. (**E-F**) Western blot showing hSSTR5 expression in WT and HP5 pituitary. Anti-HA antibody was used to detect hSSTR5 and Ponceau S staining served as loading control. (**E**) Pituitary extracts from WT mice, and AL and IL+PL from HP5 mice; (**F**) Whole WT pituitary and AL only from HP5 mice loaded separately.



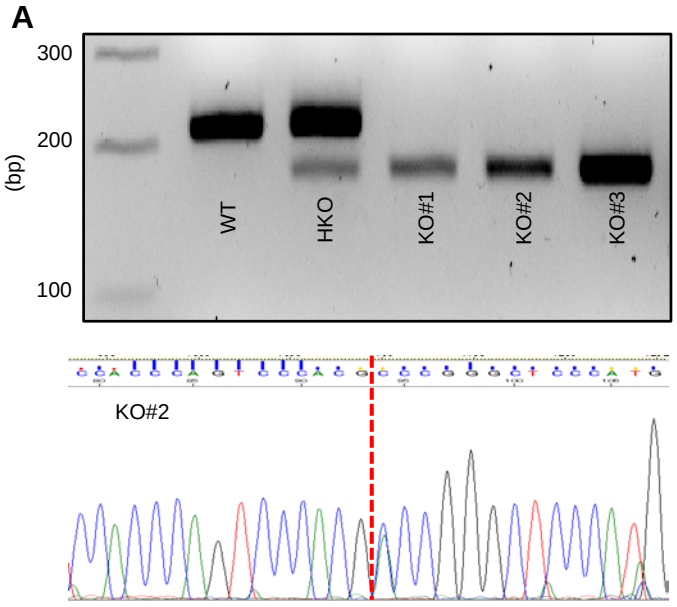
Supplemental Figure S2. (**A**) Growth curve in WT (n=10) and HP5 (n=10) mice up to 23 months of age. (**B**) Average daily food consumption for 2 days for WT (n=10) and HP5 (n=10) mice measured in metabolic cages. Baseline (**C**) prolactin and (**D**) IGF-I levels in WT (n=9) and HP5 (n=10) mice. Fasting (**E**) serum glucose and (**F**) insulin levels in WT (n=10) and HP5 (n=10) mice. Results are presented as mean ± SEM.

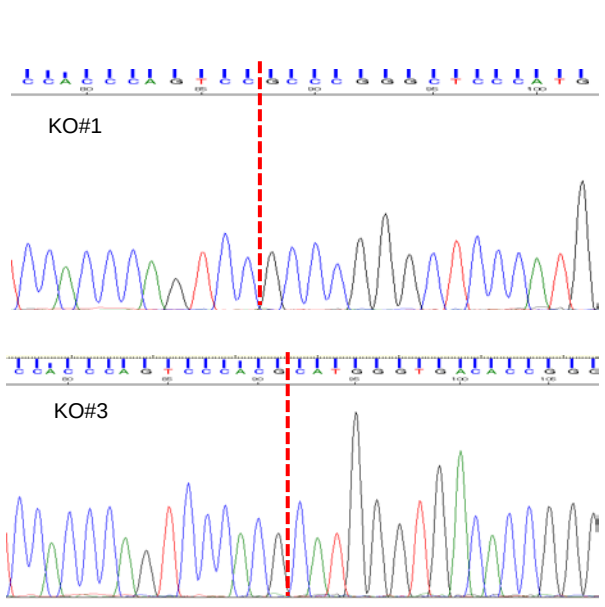


Supplemental Figure S3. Pasireotide LAR treatment of WT (n=12) and HP5 (n=12) mice. (**A**) Experimental design. P, pasireotide LAR injection. (**B-D**) Levels before the first injection (D0) and at study end on day 35 (D35) of (**B**) IGF-I, (**C**) morning ACTH, and (**D**) corticosterone. Two WT mice were excluded because of unexplained death during the protocol. (**E,F**) Levels of (**E**) ACTH and (**F**) corticosterone measured 2 hours before (baseline) and 30 minutes after (30 min) intraperitoneal injection of CRH (40 mg/kg) in WT (n=10) and HP5 (n=12) mice. Results are presented as mean ± SEM. *p≤0.05; **p≤0.01; ***p≤0.0001; 2-tailed unpaired t-test.



Supplemental Figure S4. (**A**) Western blot analysis of WT (n=4) and HP5 (n=4) dissected anterior pituitary lobes for hSSTR5, POMC, CRHR1, Tpit, and GH protein and compared with β-tubulin. (**B-E**) Quantitative analysis of Western blot results in (A) performed by scanning densitometry. Protein levels were normalized to β-tubulin. Results are presented as mean ± SEM. **p≤0.01; 2-tailed unpaired t-test.





C

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WT: GTGTCACCCATGGGAGCCCGGGCGGTATTAGTGCCTGTGCTCTACTTGTTGGTATGCACCGTGGGACTGGGTGGAAACACA   0bp del
KO#1: GTGTCACCCATGGGAGCCCGGGC**************************************************************GGACTGGGTGGAAACACA   40bp del
KO#2: GTGTCACCCATGGGAGCCCGGG**************************************************************CGTGGGACTGGGTGGAAACACA   37bp del
KO#3: GTGTCACCCATG**************************************************************************CGTGGGACTGGGTGGAAACACA   47bp del

WT: MEPLSLTSTPSWNASAASSSSHNWSLVDPVSPMGARAVLVPVLYLLVCTVGLGGNTLVIYVVLRYAKMKTVTNVYILNLAVADVLFMLGLPFLA
    TQNAVSYWPFGSFLCRLVMTLDGINQFTSIFCLMVMSVDRYLAVVHPLRSARWRRPRVAKLASAAVWVFSLLMSLPLLVFADVQEGWGTCNL
    SWPEPVGLWGAAFITYTSVLGFFGPLLVICLCYLLIVVKVKAAGMRVGSSRRRRSERKVTRMVVVVVLVFVGCWLPFFIVNIVNLAFTLPEEPT
    SAGLYFFVVVLSYANSCANPLLYGFLSDNFRQSFRKALCLRRGYGVEDADAIEPRPDKSGRPQTTLPTRSCEANGLMQTSRL
KO#1: MEPLSLTSTPSWNASAASSSSHNWSLVDPVSPMGARADWVETHWSSMWCCGTPR*
KO#2: MEPLSLTSTPSWNASAASSSSHNWSLVDPVSPMGARAWDWVETHWSSMWCCGTPR*
KO#3: MEPLSLTSTPSWNASAASSSSHNWSLVDPVSPMRGTGWKHTGHLCGVAVRQDEDSY*
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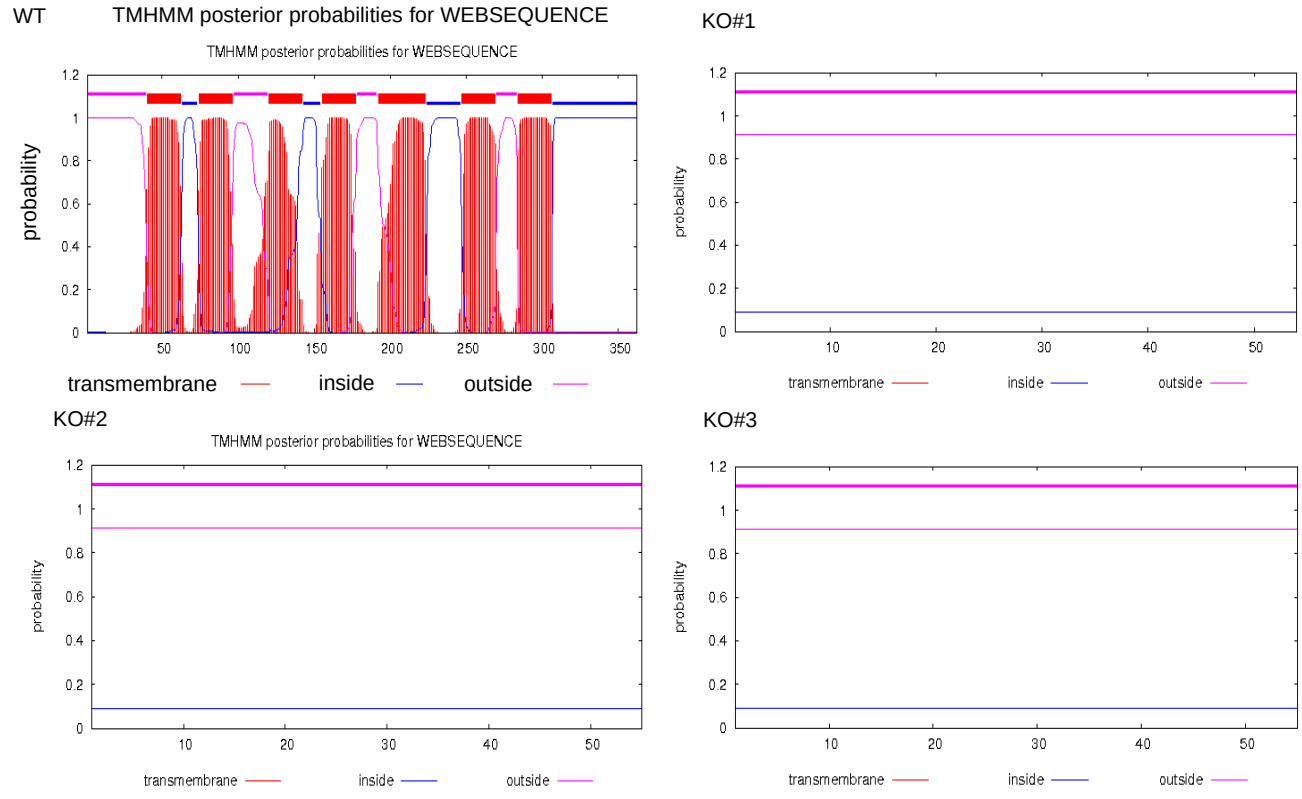
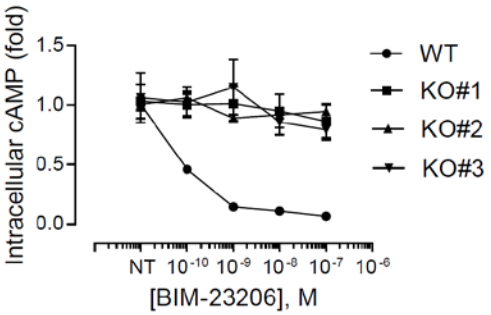
D

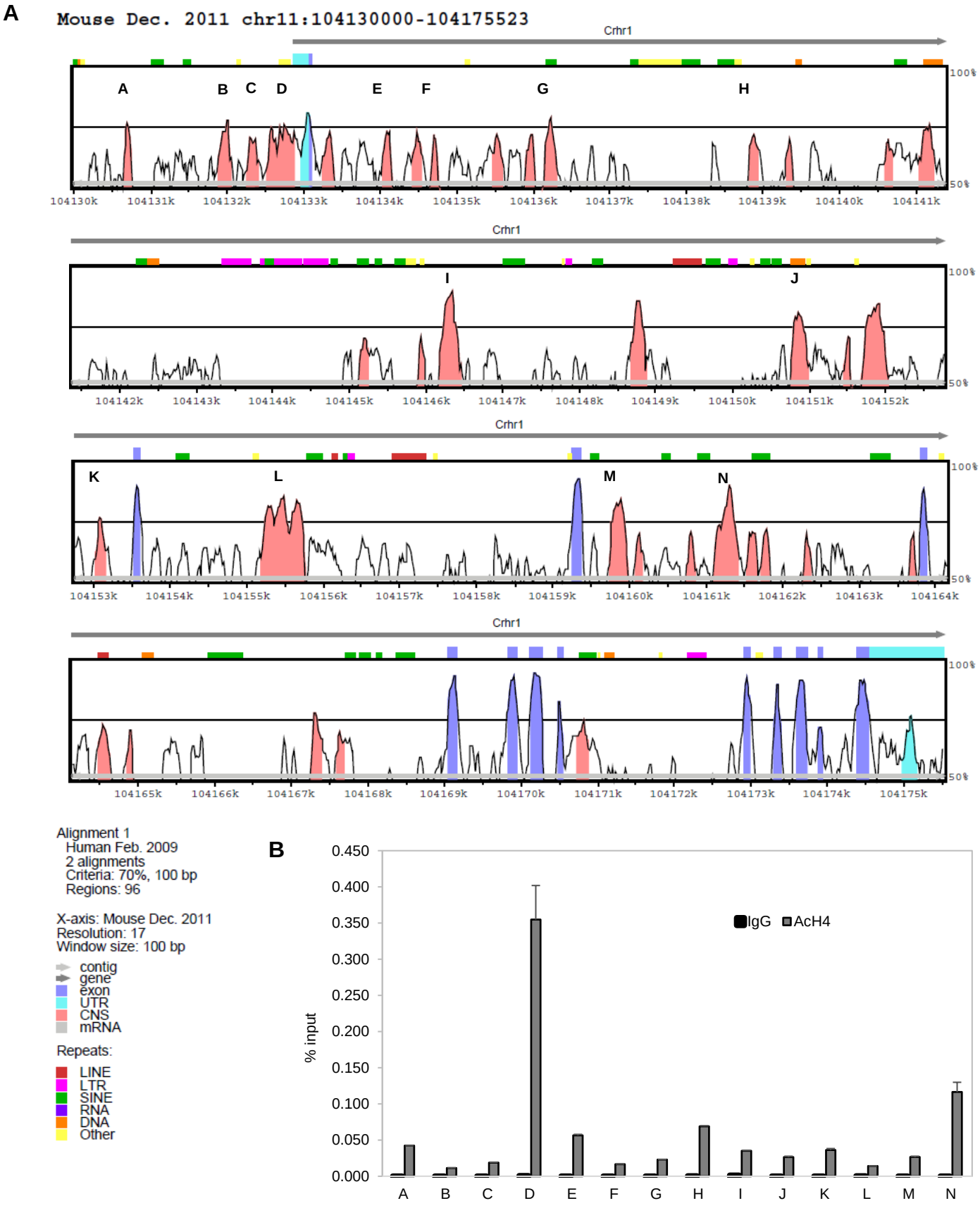


Supplemental Figure S5

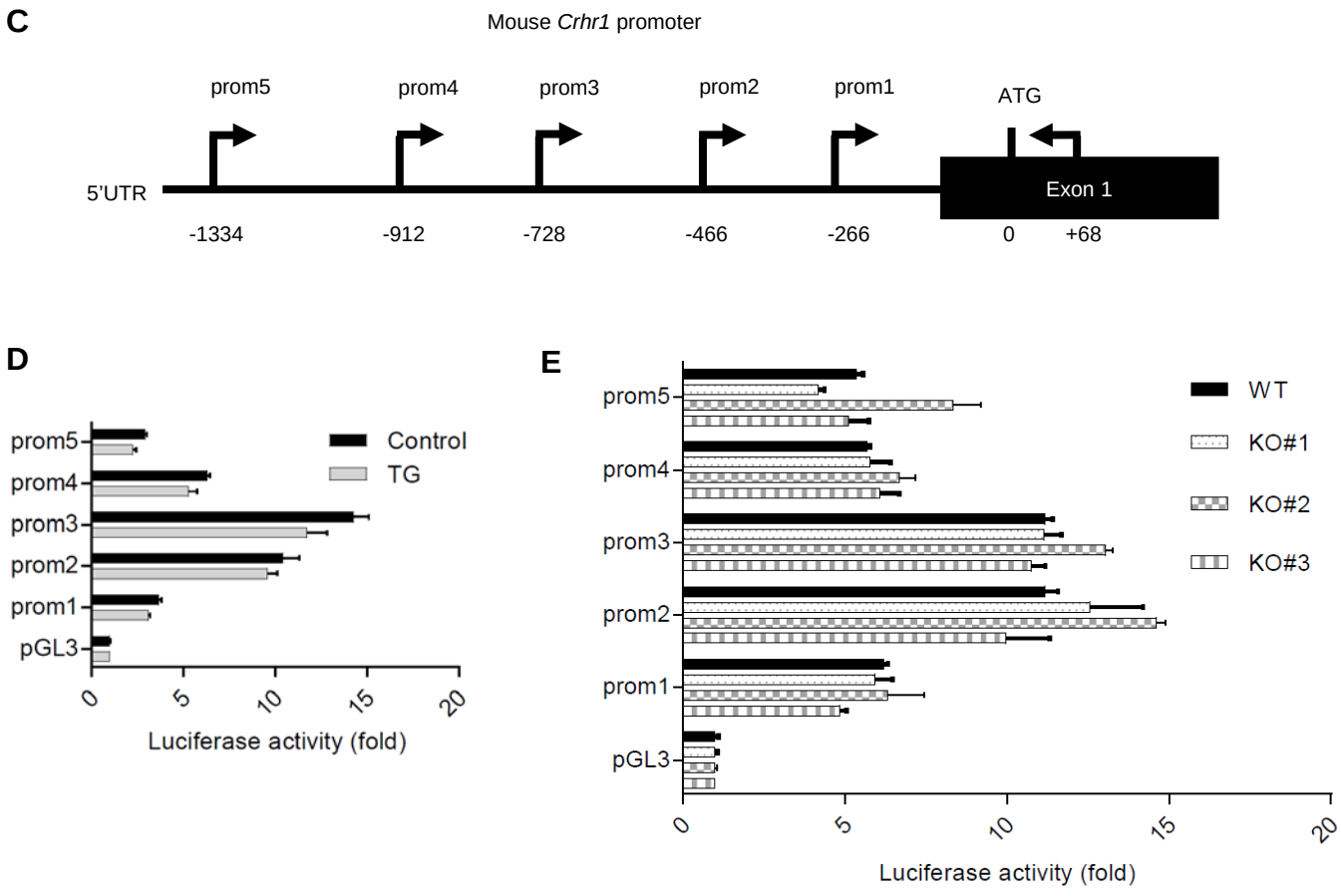
E



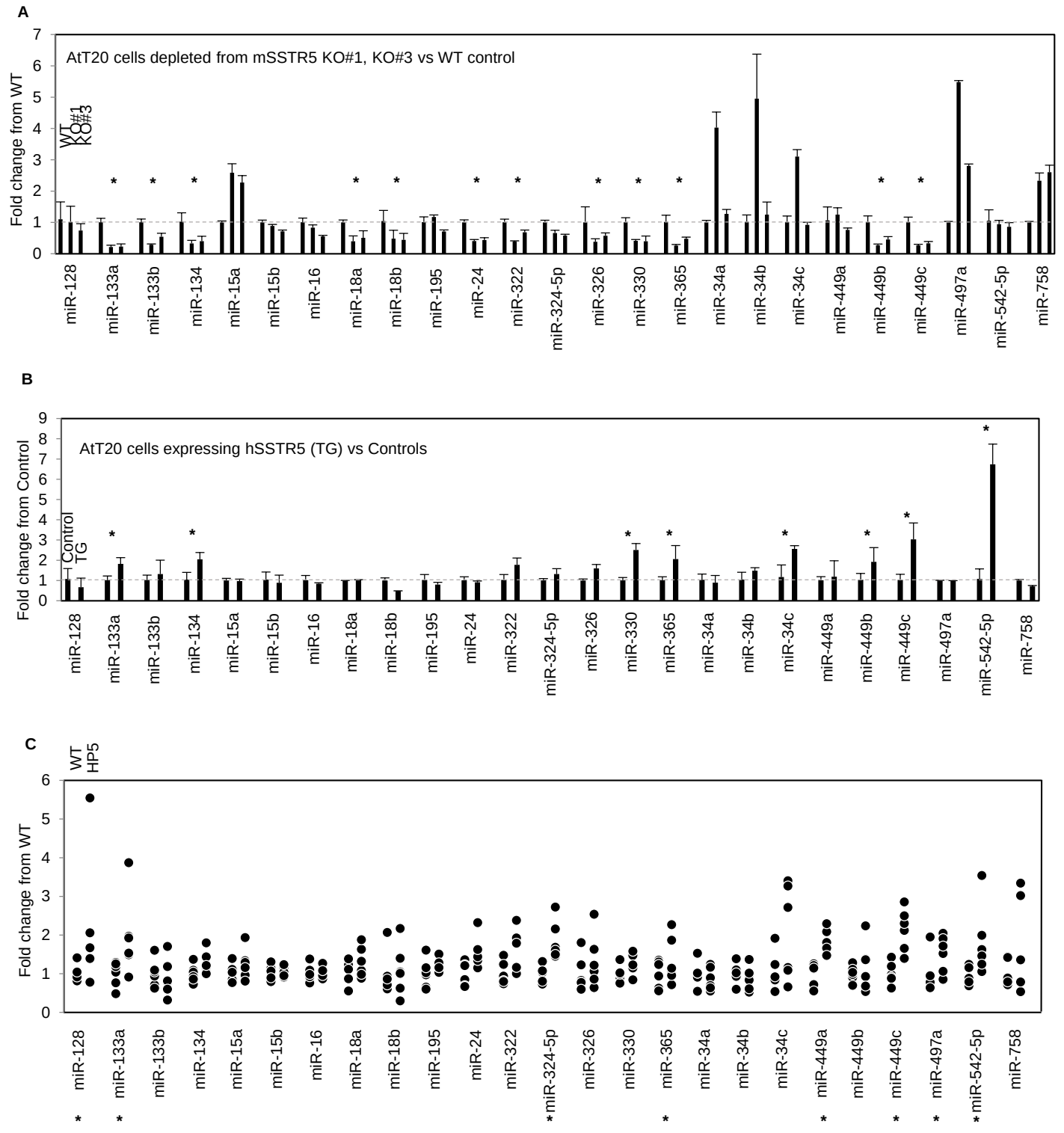
Supplemental Figure S5. Endogenous mouse *Sstr5* deleted in AtT20 cells using CRIPSR/Cas9. (**A**) PCR analysis of clone DNA confirming SSTR5 deletion in three KO clones (KO#1, KO#2, KO#3). A heterozygous clone (HKO) and cells that maintained SSTR5 (WT) served as controls. (**B**) DNA sequences in WT and KO clones. Deletions are indicated by asterisks and their lengths are given in the numbers on the right. (**C**) Amino acid sequences in KO clones derived from (B). (**D**) Prediction of transmembrane helices in proteins using TMHMM Server v. 2.0 (http://www.cbs.dtu.dk/services/TMHMM/). Depicted are posterior probabilities of inside (blue), outside (pink), and transmembrane (red) helices and predicted structure of mouse SSTR5 in WT and KO#1-3. KO#1-3 clones lost all transmembrane helices of mouse SSTR5 while WT conserved 7 transmembrane helices. (**E**) SSTR5 WT and KO clones (n=4/group) were treated with 10 µM forskolin alone (NT) or with increasing doses of the SSTR5-specific agonist BIM-23206 for 30 minutes and intracellular cAMP levels were measured using LANCE cAMP kit. Y-axis represents percent cAMP level fold change from forskolin-only control. Experiments were performed in duplicate. Results are presented as mean ± SEM.



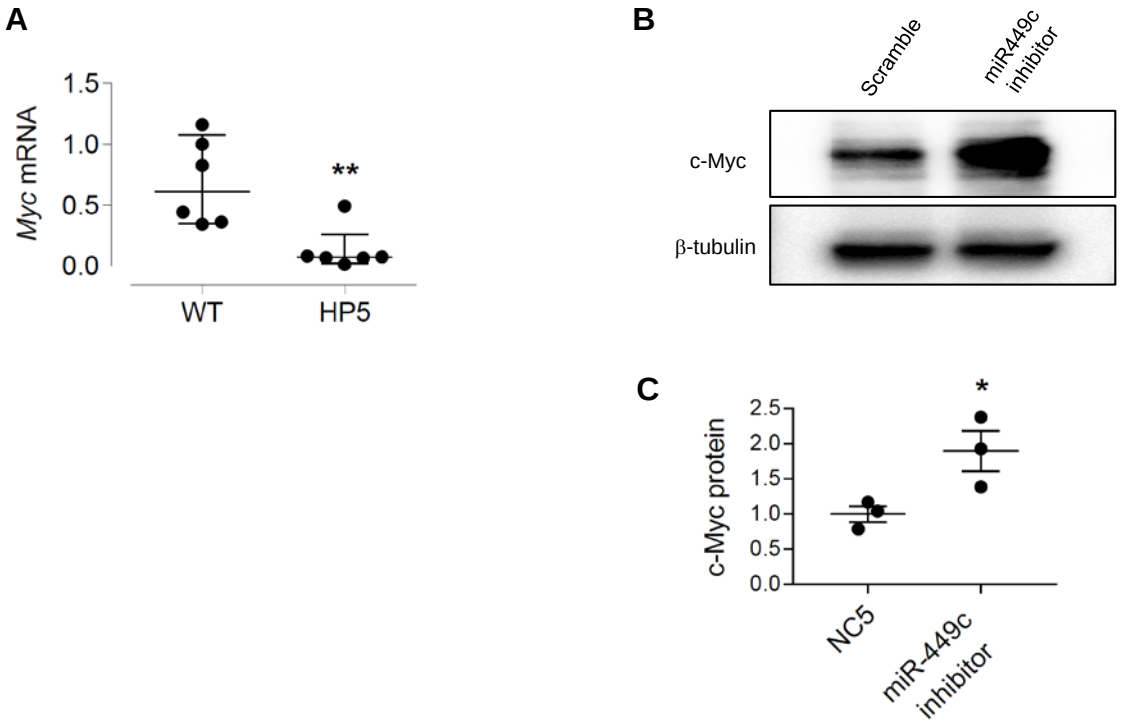
Supplemental Figure 6



Supplemental Figure S6. (**A**) Map of sequence conservation in the *Crhr1* genomic region between human and mouse. Results of analysis were performed by the web-based alignment program Vista Genome Browser (http://pipeline.lbl.gov/index.html) in a genomic region encompassing DNA sequence from –2.4 kb to +42.5 kb. Peaks corresponding to the exons are depicted in blue. Conserved 100 bp noncoding sequences (CNS) with 75% identity are depicted in pink and labeled A through N. (**B**) Quantification of histone acetylation after ChIP analysis from AtT20 cells. Y-axis represents percentage of input DNA for acetylated histone 4 antibody (AcH4, grey) or IgG antibody (IgG; black) at the conserved sequences (A-N), analyzed by qRTPCR and depicted as mean ± SEM. (**C**) Map of luciferase reporter plasmids to measure mouse *Crhr1* promoter activity. Five promoter fragments were generated up to 1334 bp upstream of ATG (prom1 to 5). (**D**) AtT20 cells stably expressing hSSTR5 (**E**) and AtT20 cells in which mouse SSTR5 was knocked out (KO#1-3) and their respective controls were transfected with luciferase reporter plasmids at –1334/+68 (prom5), –912/+68 (prom4), –728/+68 (prom3), –466/+68 (prom2), and –266/+68 (prom1), or pGL3 control. Transcriptional activities of mouse *Crhr1* were normalized to pGL3 controls and 10ng pRL-CMV plasmid cotransfected to normalize transfection efficiency. Experiments were performed in triplicate and cells transfected in quadruplicate wells. Representative results are presented.



Supplemental Figure S7. Original data showing relative expression of 25 miRNAs used for the heat map depicted in Figure 6A. (**A**) miRNA expression in AtT20 cells depleted from mSSTR5 by CRISPR/Cas9 KO clones (KO#1 and KO#3) compared with their respective WT controls. Asterisks indicate genes in which SSTR5 KO clones exhibited ≤0.5-fold change in at least one of two clones compared with WT. (**B**) miRNA expression in AtT20 cells stably overexpressing hSSTR5 compared with control. Asterisks indicates genes in which hSSTR5-overexpressing transfectants exhibited ≥1.8-fold expression compared with control. (**C**) miRNA expression in pituitary glands derived from WT (n=5, the first dot column for each miR) and HP5 (n=5, the second dot column for each miR) mice normalized to U6 small nuclear RNA. Asterisks indicate genes exhibiting ≥1.8-fold increase in miRNA expression level in HP5 pituitary compared with WT. Results were analyzed by qRTPCR and are presented as mean ± SEM.



Supplemental Figure S8. (**A**) *Myc* mRNA levels in pituitary tissue derived from WT (n=6) and HP5 (n=6) mice. mRNA expression levels were normalized to *Gapdh.* (**B**) Western blot analysis of c-Myc levels in AtT20 cells transfected with 200 nM miRNA-449c inhibitor or scramble as a negative control and collected after 48 hours. (**C**) Quantitation densitometry of 3 Western blots described in (B) with protein levels normalized to β-tubulin. NC5, negative control of miRNA inhibitor. Experiments were performed in triplicate. Results are presented as mean ± SEM. *p≤0.05; **p≤0.01; 2-tailed unpaired t-test.

Baseline

WT HP5

After treatment

WT HP5

Supplemental Movie S1. Activity and well-being of WT and HP5 mice after LPS injection. WT (n=2, left side) and HP5 (n=2, right side) mice 72 hours after receiving 5 mg/kg LPS intraperitoneal injection. Mobility and activity and condition of fur were evaluated by video observation. While WT mice are mobile and active with normal fur, HP5 mice appear wasted, are less mobile, and have lost their fur.

Supplemental Table S1. Primer sequence for ChIP assay.

A	Forward	CTGGCTGGAGACACTTCAGG
	Reverse	TTTTGGCTCTGAGCTCACCC
B	Forward	GCCAACCTAGACGAAGACCC
	Reverse	GGACTGGGCACCTAGTCTGT
C	Forward	GTGTGTTTAGGCCAAAGGCG
	Reverse	GCTGGGGAATAGGGCGATTT
D	Forward	GGATCCCCGGTTTTTCCCTA
	Reverse	GCTTGCGGCAGTGCG
E	Forward	GGAAAGGCGATTGCGTTCAA
	Reverse	GGGACATTTTAAACGCGTGGT
F	Forward	AATGGGGAGTGAGAGTCGGT
	Reverse	GGTGCCGCTTTCTGAACAAG
G	Forward	CAAATGTGCCCTTTGGAGCC
	Reverse	CCACACTGATGACCTACCCG
H	Forward	ACTGGCGGGTGGAAACATTT
	Reverse	TTCTGACGTGTCCTCTGCAC
I	Forward	AGCTTAGGACCCAGGGAGAC
	Reverse	GACGGGAAAATCTCCTGCCT
J	Forward	CAGCCCAGGTCCTCTGTGAG
	Reverse	TCTGTCTGTCTGTCTGTCTTGG
K	Forward	CCTTCCAGTCATAGGGCCAC
	Reverse	CCATTGAGGGCTCTGTGTCA
L	Forward	AAGGCCCCATCATGTGACAG
	Reverse	AACAACAGGAAGAGGAGCCG
M	Forward	GCATCTGCCACCCTCAGAAT
	Reverse	TTTGGAGCTTGGGGATGACC
N	Forward	GGGGCAGAACTGCTCCTAAT
	Reverse	CGCAGGAGGGAGAACGGTAA

Supplemental Table S2. qRTPCR primer sequence.

Pitx1	Forward	GAGAACTCCGCCAGCGAATC
	Reverse	CTCTGGCCCCTTGGCTTC
Tpit	Forward	CCTTTCGCCAAGGCCTTCTT
	Reverse	AGTAGGTCACATGCTGGCTC
NeuroD1	Forward	GGCTCCAGGGTTATGAGATCG
	Reverse	CGCTCTCGCTGTATGATTTGG
Gapdh	Forward	TTCACCACCATGGAGAAGGC
	Reverse	GAAGGGGCGGAGATGATGAC
Crhr1	Forward	GGGCAGCCCGTGTGAATTAT
	Reverse	GAAGAGGACAAAGGCCACCA
Gh1	Forward	GCTTCTCAGAGACCATCCCG
	Reverse	ATCCTGCTGAGGAACTGCAC
Avp	Forward	GCTACTTCCAGAACTGCCCAAG
	Reverse	GAAGCAGCGTCCTTTGCCG
Pomc	Forward	TGTACCCCAACGTTGCTGAG
	Reverse	AGGACCTGCTCCAAGCCTAA
Avpr1b	Forward	ACGAGAATGCCCCTAATGAAG
	Reverse	GTTGAAGCCCATATAGATCCAGG

Supplemental Table S3. miRNA primer sequence.

mmu-miR-128	CGGGGCCGTAGCACTGTCTGA
mmu-miR-133a	GCTGGTAAAATGGAACCAAAT
mmu-miR-133b	GCTGGTCAAACGGAACCAAGTC
mmu-miR-134	TGTGACTGGTTGACCAGAGGGG
mmu-miR-15a	TAGCAGCACATAATGGTTTGTG
mmu-miR-15b	TAGCAGCACATCATGGTTTACA
mmu-miR-16	TAGCAGCACGTAAATATTGGCG
mmu-miR-18a	TAAGGTGCATCTAGTGCAGATAG
mmu-miR-18b	TAAGGTGCATCTAGTGCTGTTAG
mmu-miR-195	TAGCAGCACAGAAATATTGGC
mmu-miR-24-1	GTGCCTACTGAGCTGATATCAGT
mmu-miR-322	CAGCAGCAATTCATGTTTTGGA
mmu-miR-324-5p	CGCATCCCCTAGGGCATTGGTGT
mmu-miR-326	GGGGGCAGGGCCTTTGTGAAGGCG
mmu-miR-330	TCTCTGGGCCTGTGTCTTAGGC
mmu-miR-365	AGGGACTTTTGGGGGCAGATGTG
mmu-miR-34a-5p	TGGCAGTGTCTTAGCTGGTTGT
mmu-miR-34b-5p	AGGCAGTGTAATTAGCTGATTGT
mmu-miR-34c-5p	AGGCAGTGTAGTTAGCTGATTGC
mmu-miR-449a	TGGCAGTGTATTGTTAGCTGGT
mmu-miR-449b	AGGCAGTGTTGTTAGCTGGC
mmu-miR-449c	AGGCAGTGCATTGCTAGCTGG
mmu-miR-497a	CAGCAGCACACTGTGGTTTGTA
mmu-miR-542-3p	TGTGACAGATTGATAACTGAAA
mmu-miR-758	TGGTTGACCAGAGAGCACACG

Supplemental Table S4. miRNA inhibitor sequence.

mmu-miR-365-1	agggacuuuuggggcagaugug
mmu-miR-330	ucucugggccugugucuuaggc
mmu-miR-133a	gcugguaaaauggaaccaaau
mmu-miR-322-5p	cagcagcaauucauguuuugga
mmu-miR-449b	aggcaguguuguuagcuggc
mmu-miR-449c-5p	aggcagugcauugcuagcugg
mmu-miR-18b-5p	uaaggugcaucuagugcuguuag
mmu-miR-542-3p	ugugacagauugauaacugaaa
mmu-miR-134	ugugacugguugaccagagggg
NC5 negative control	accauauugcgcguauagucgc