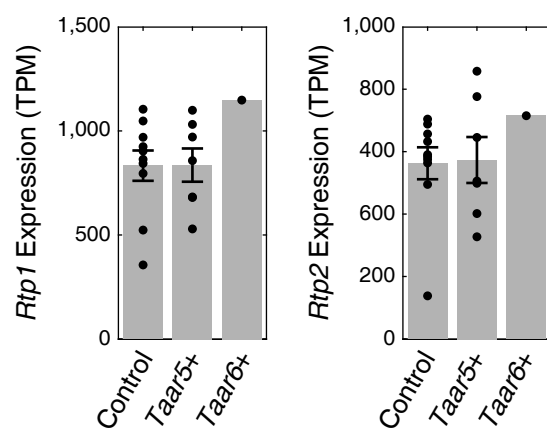
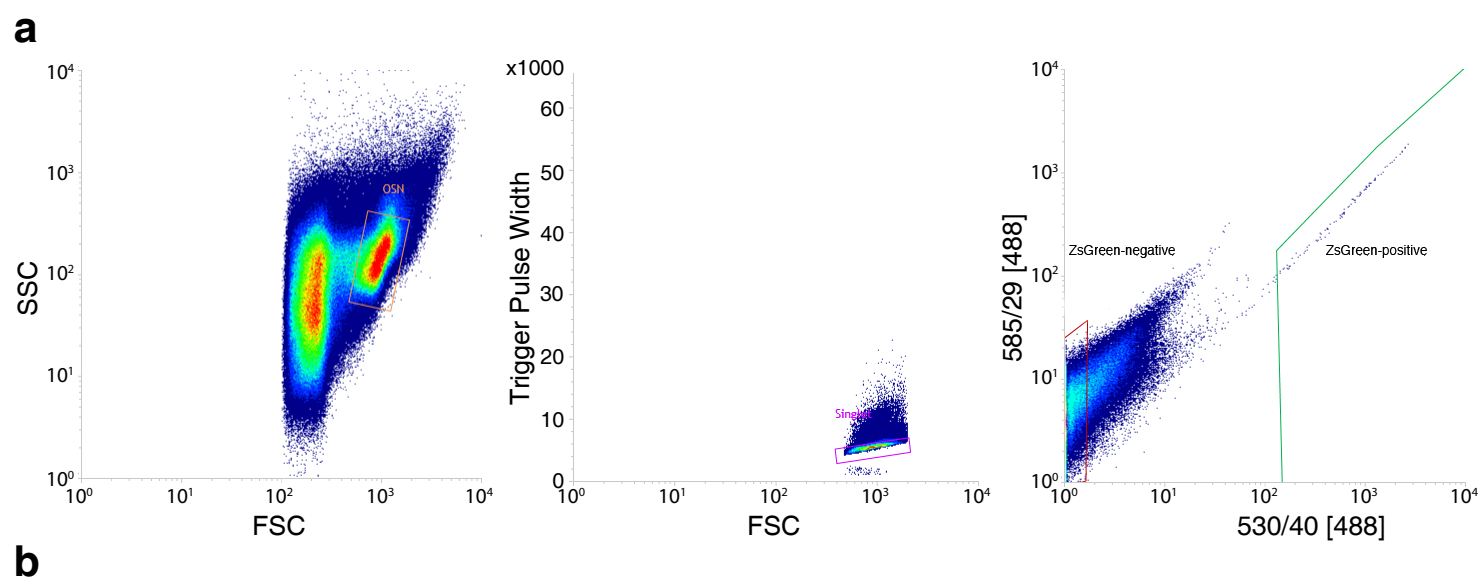
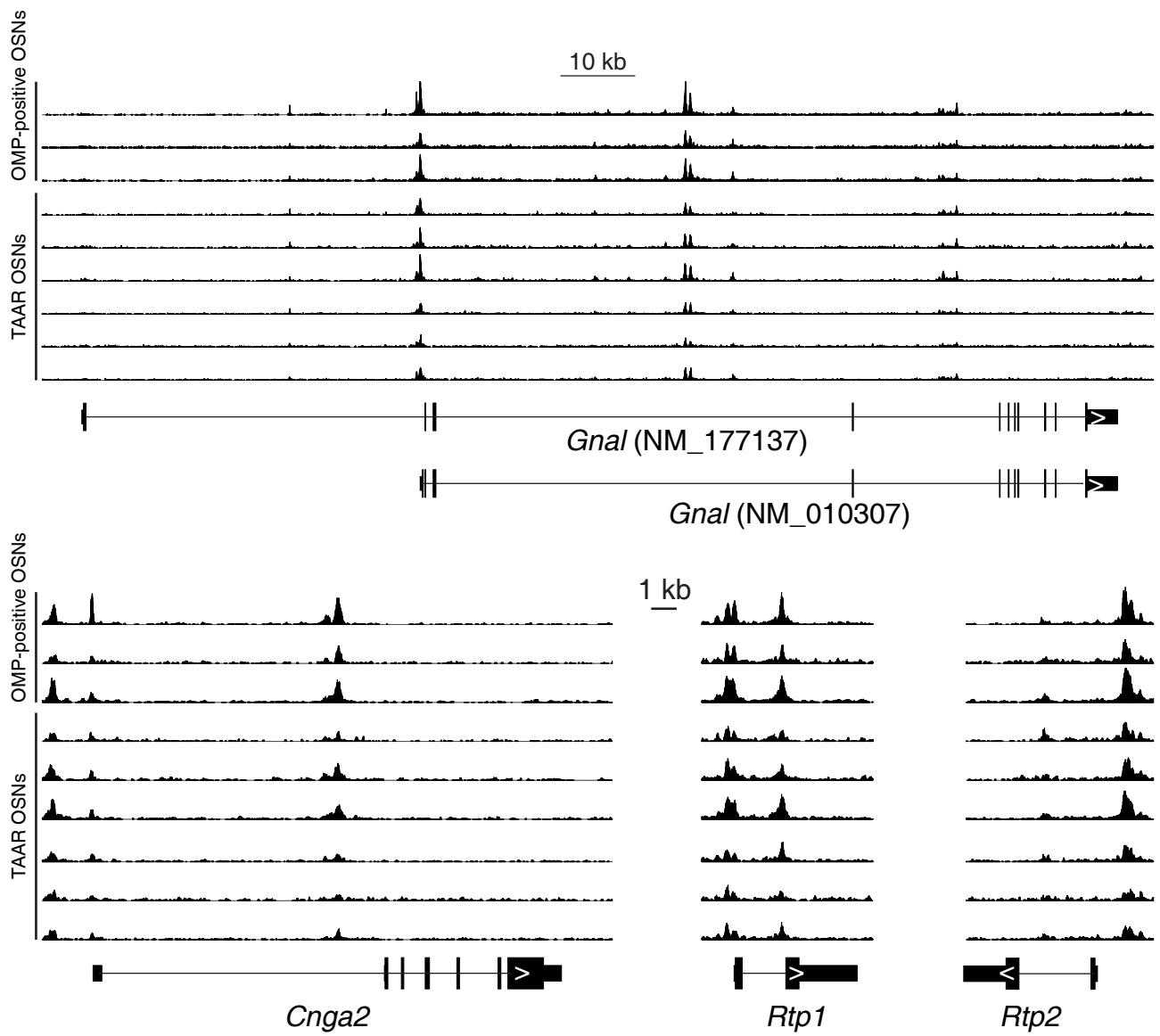
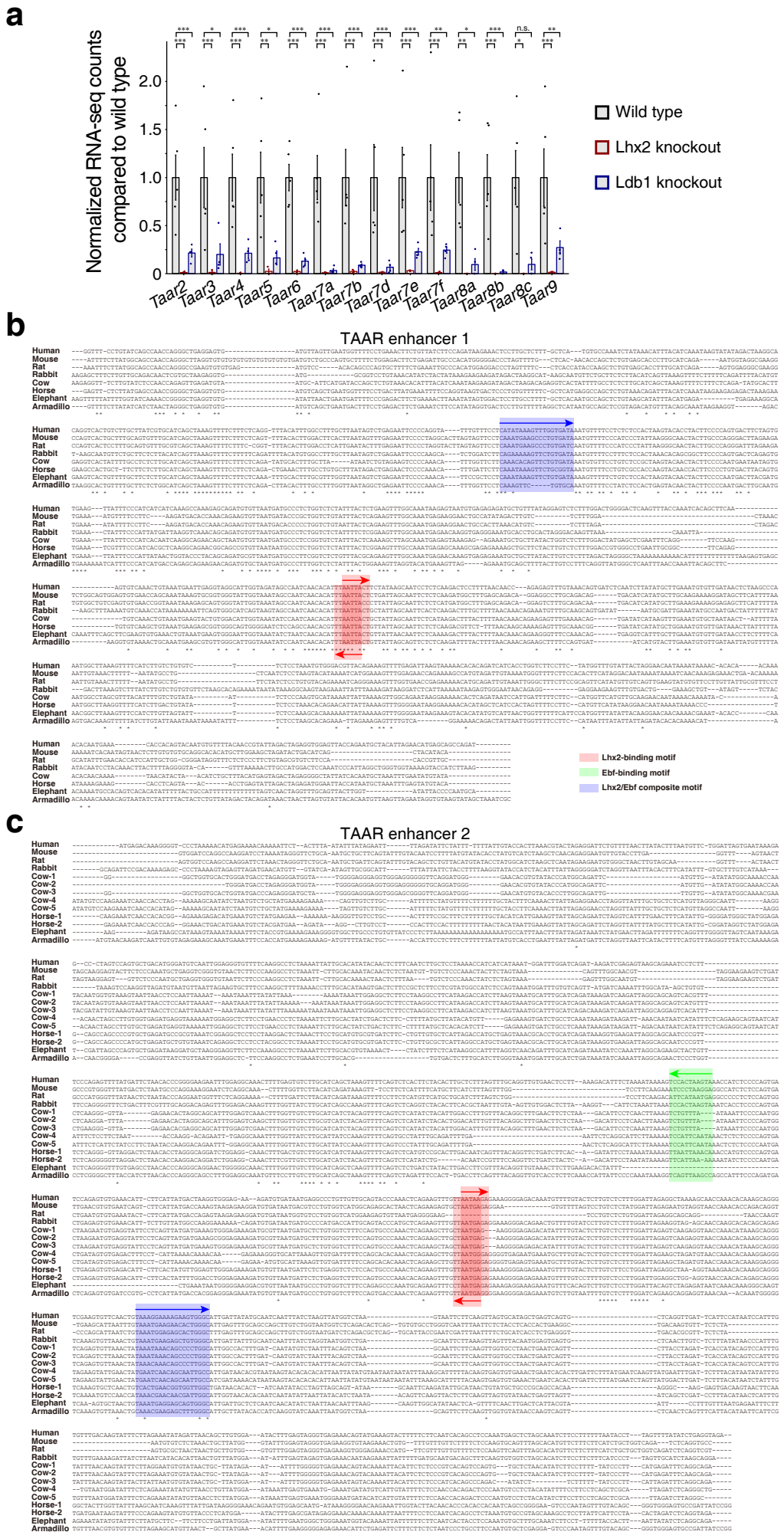




Supplementary figure 1

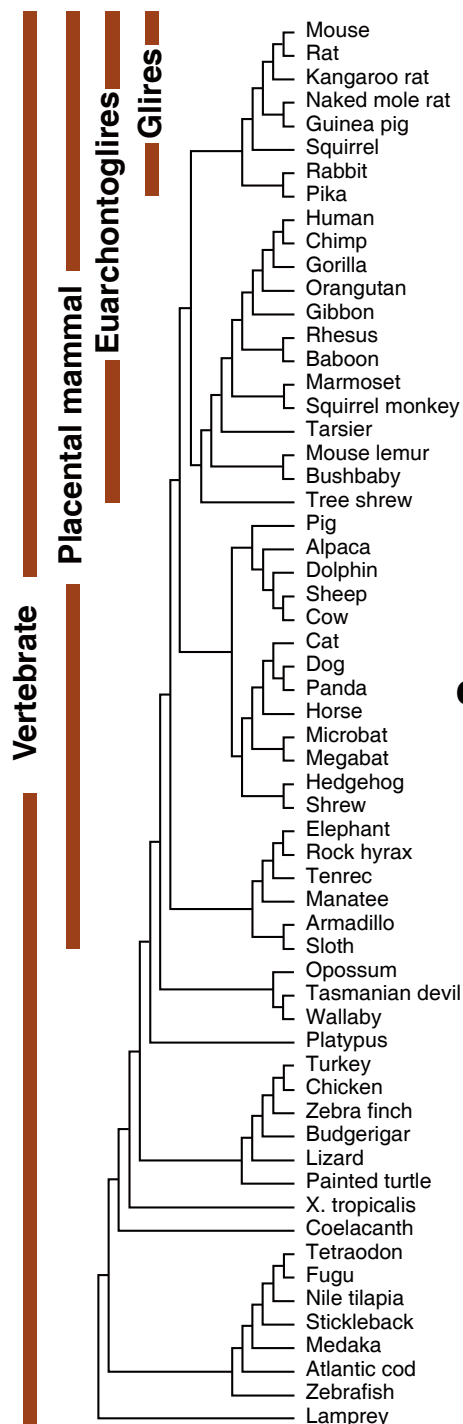


Supplementary figure 2

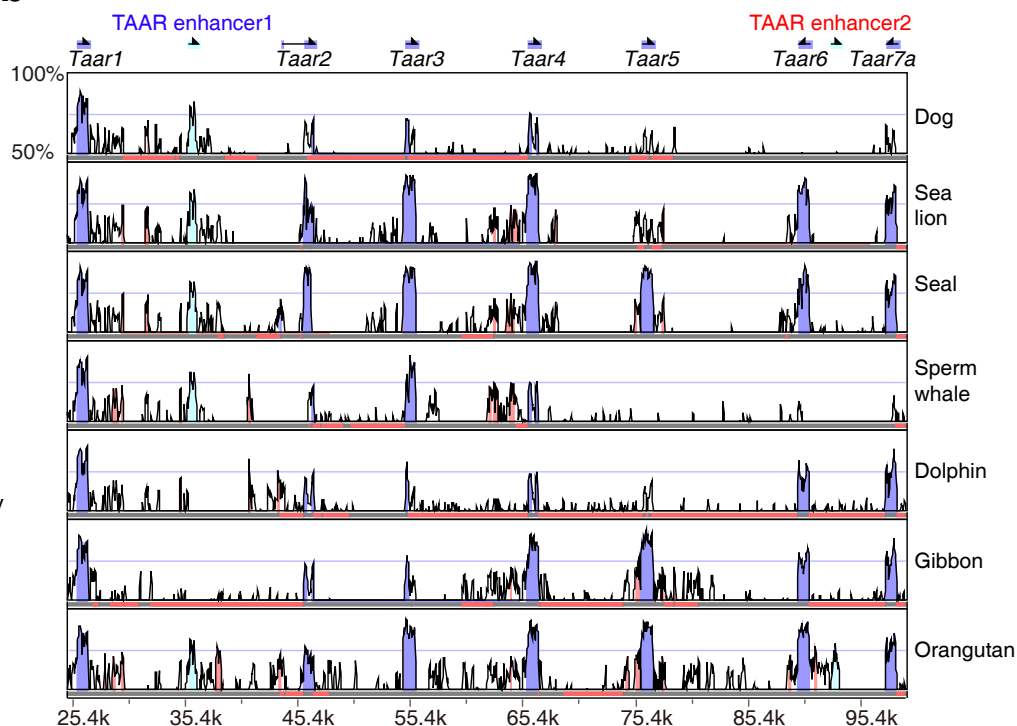


Supplementary figure 3

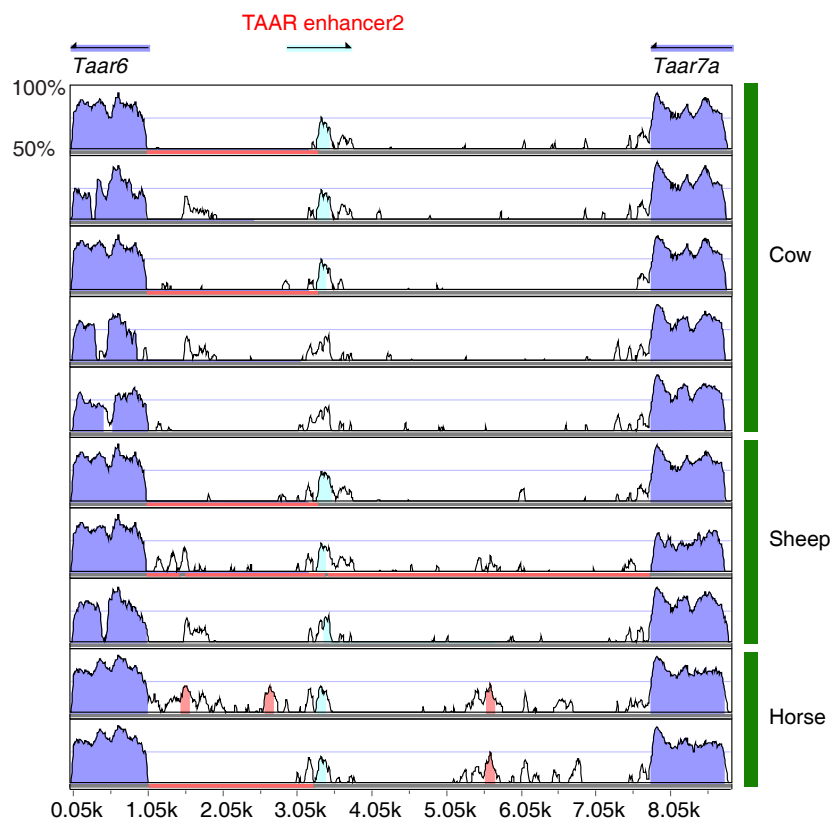
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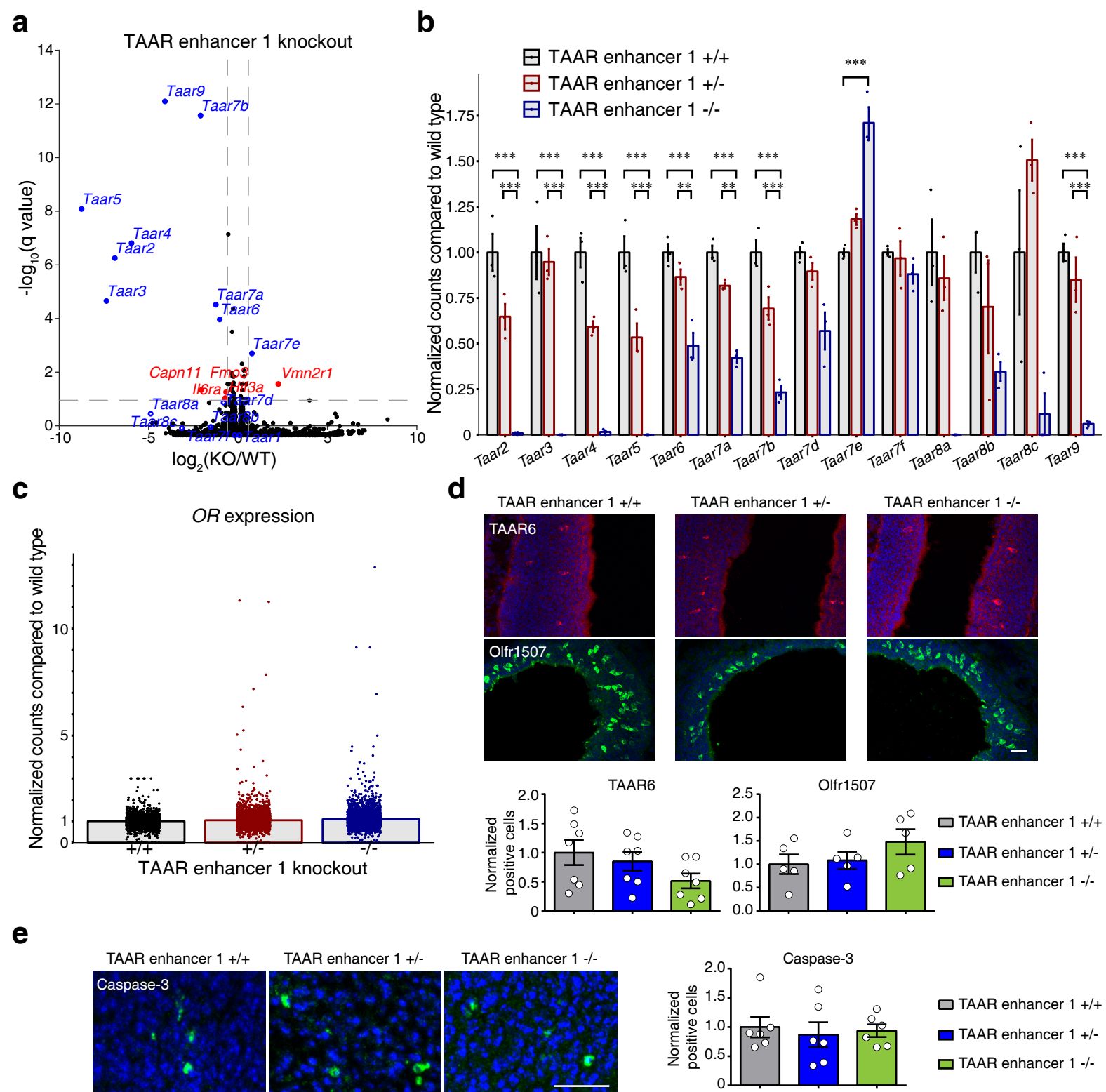
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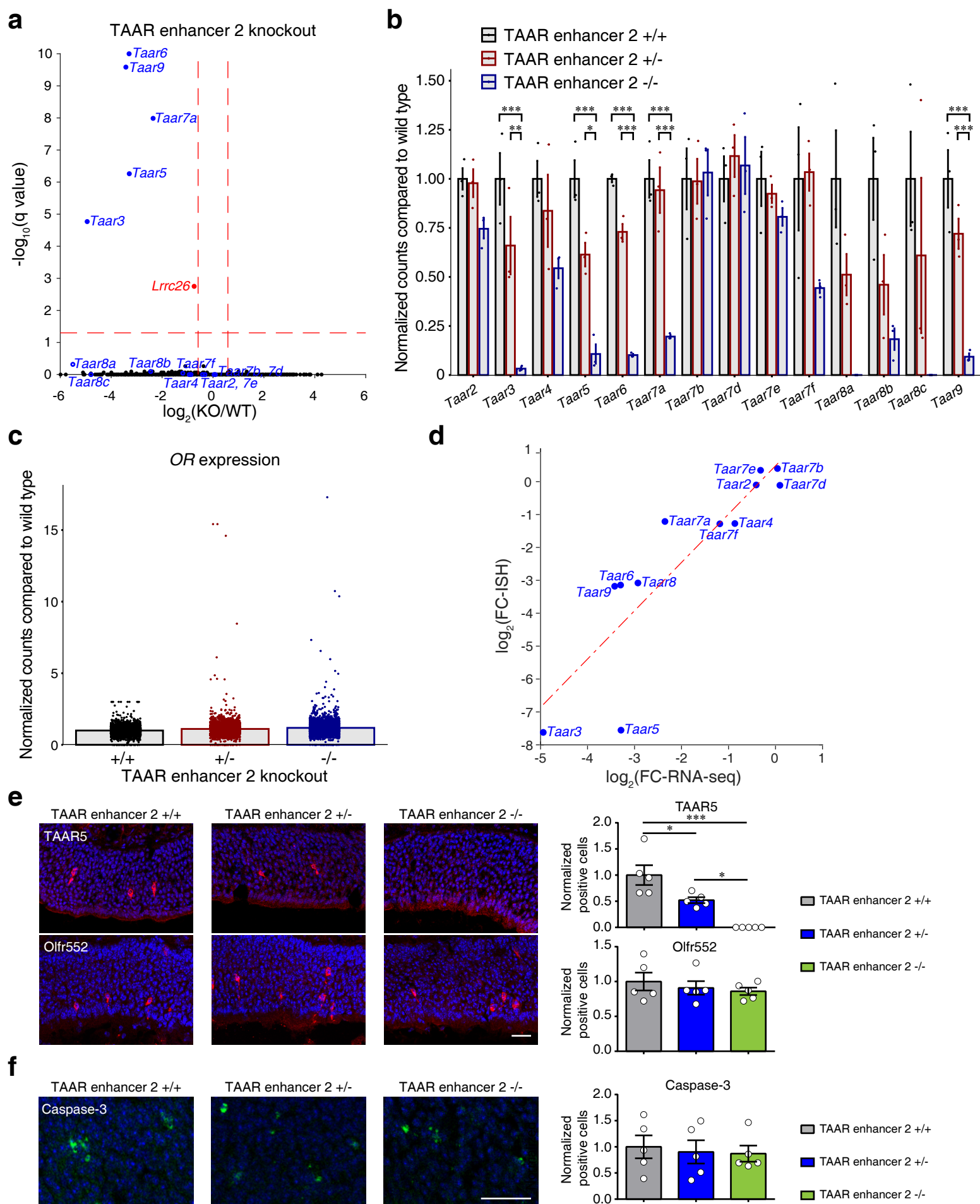
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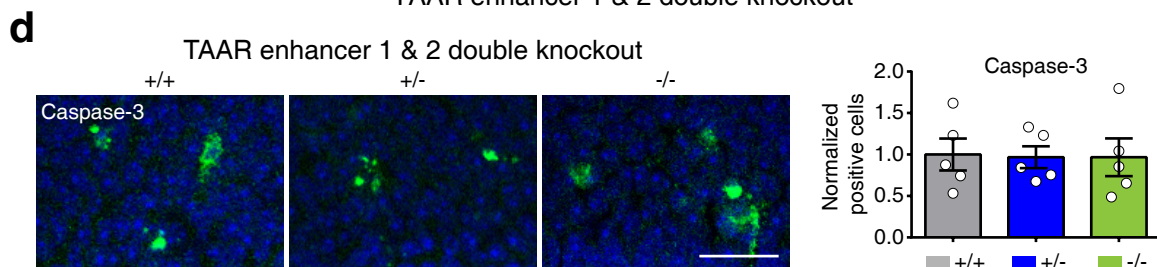
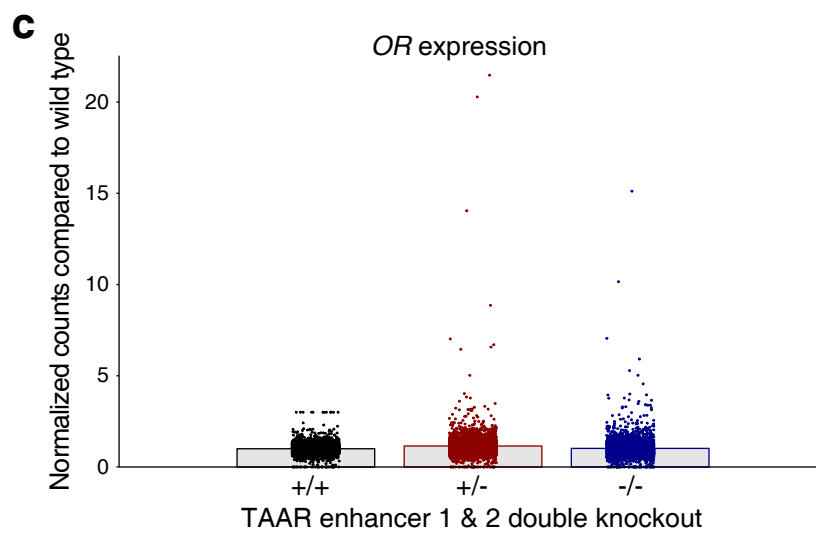
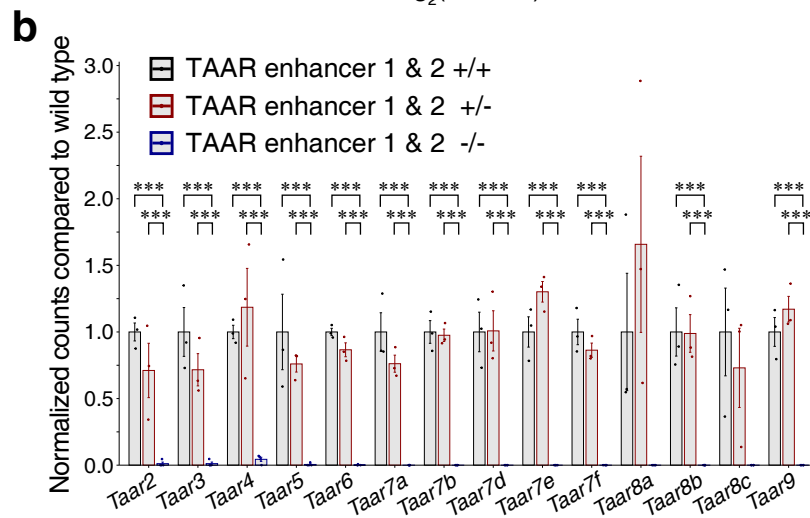
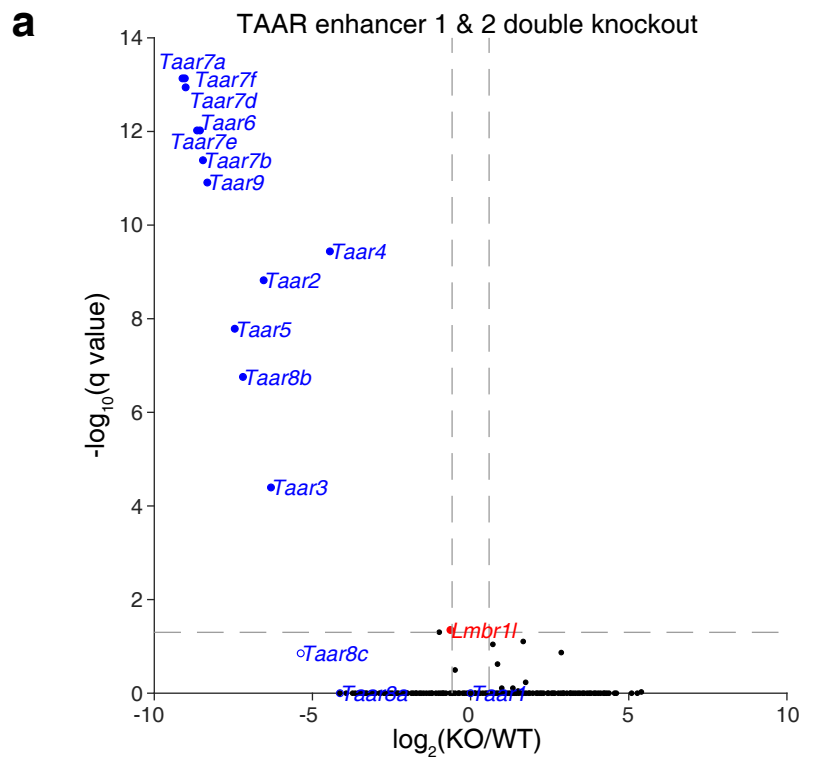
Supplementary figure 4



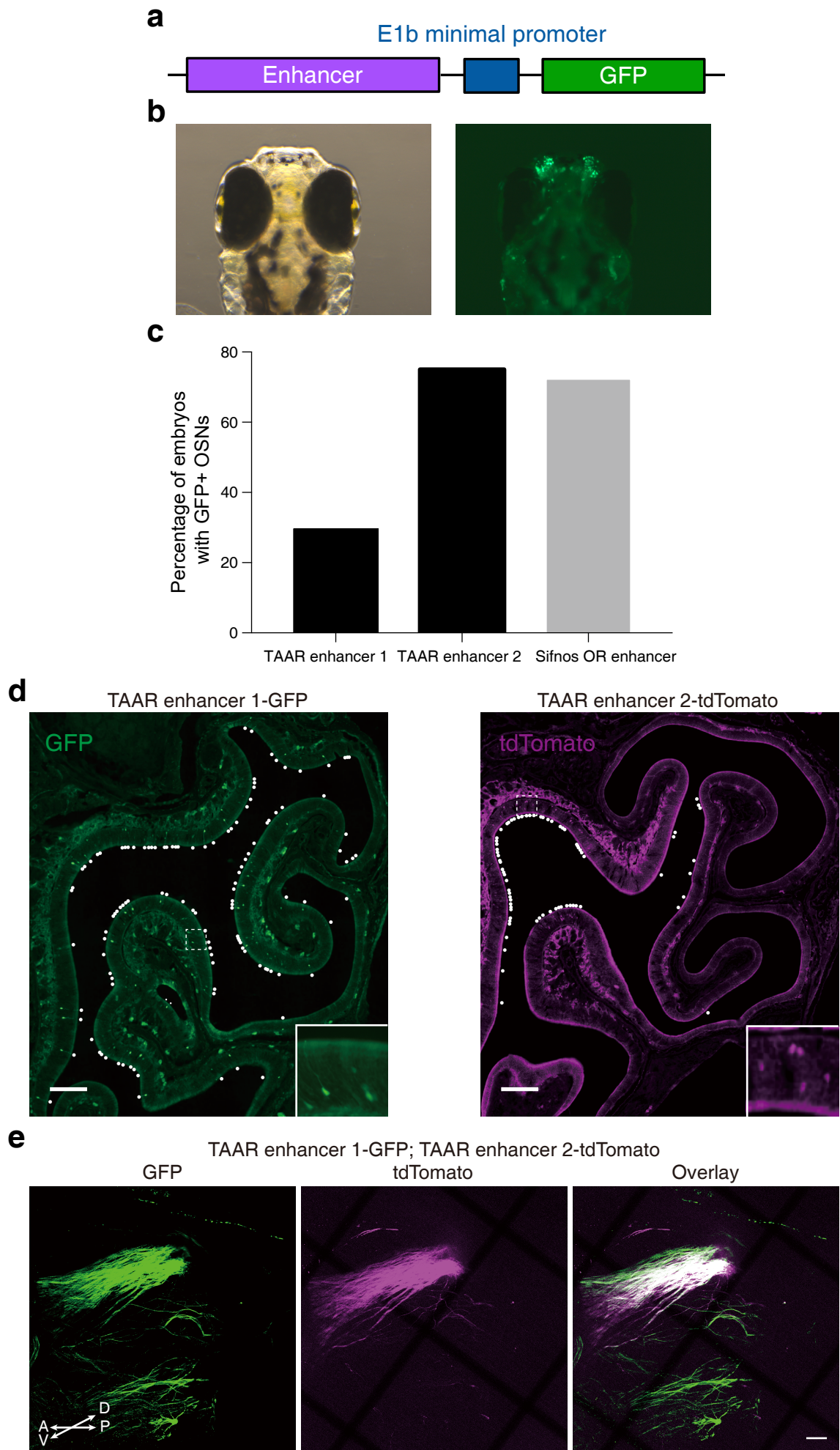
Supplementary figure 5



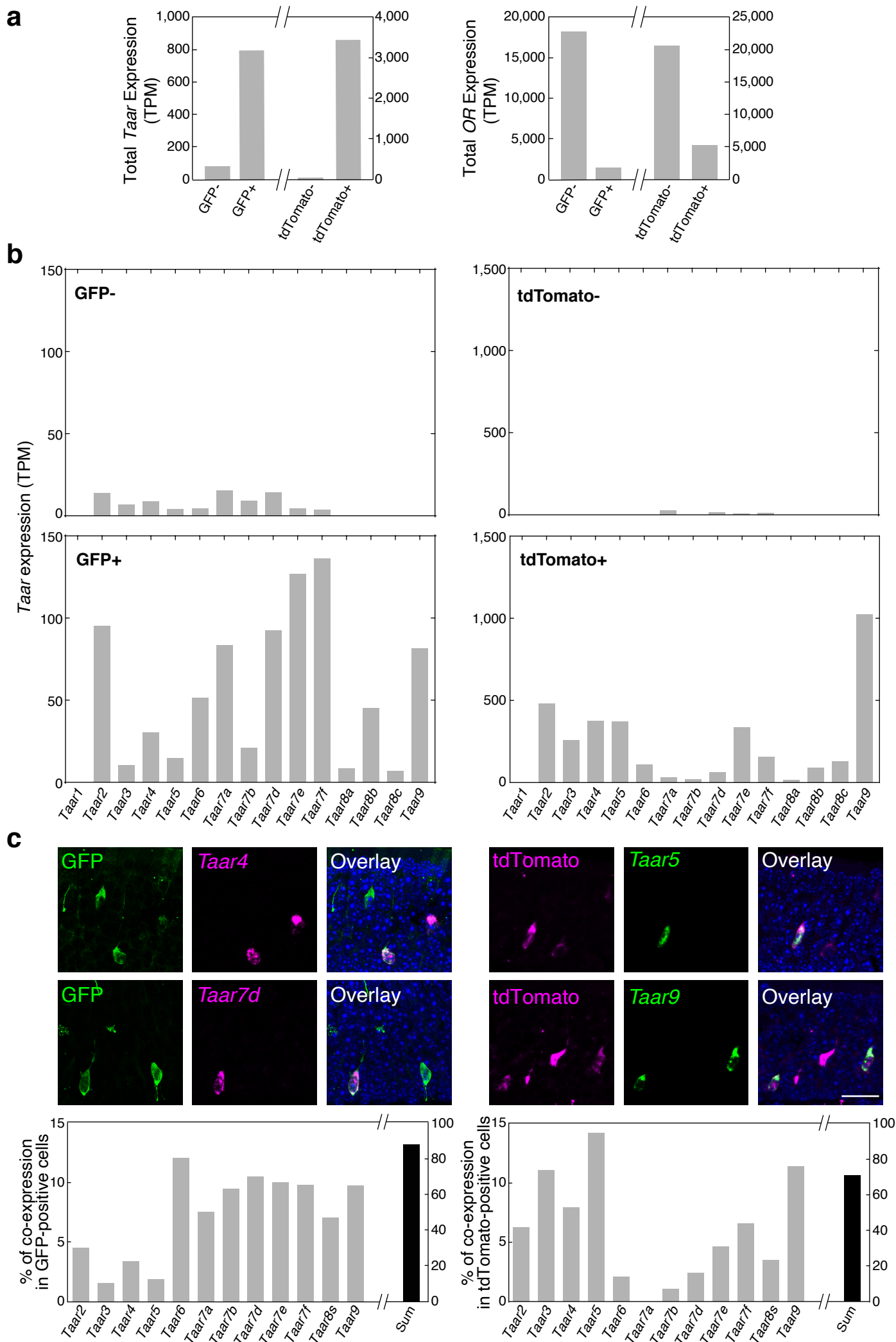
Supplementary figure 6



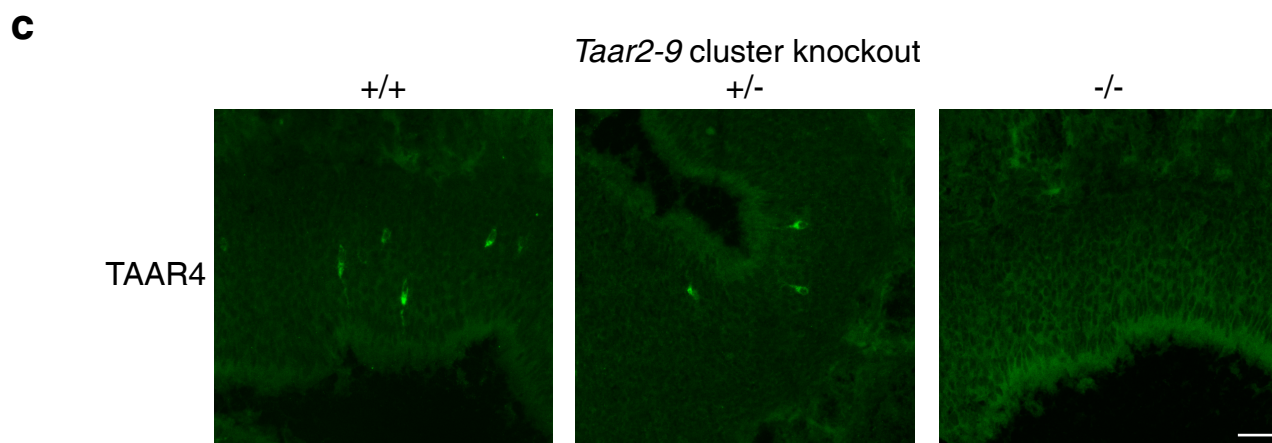
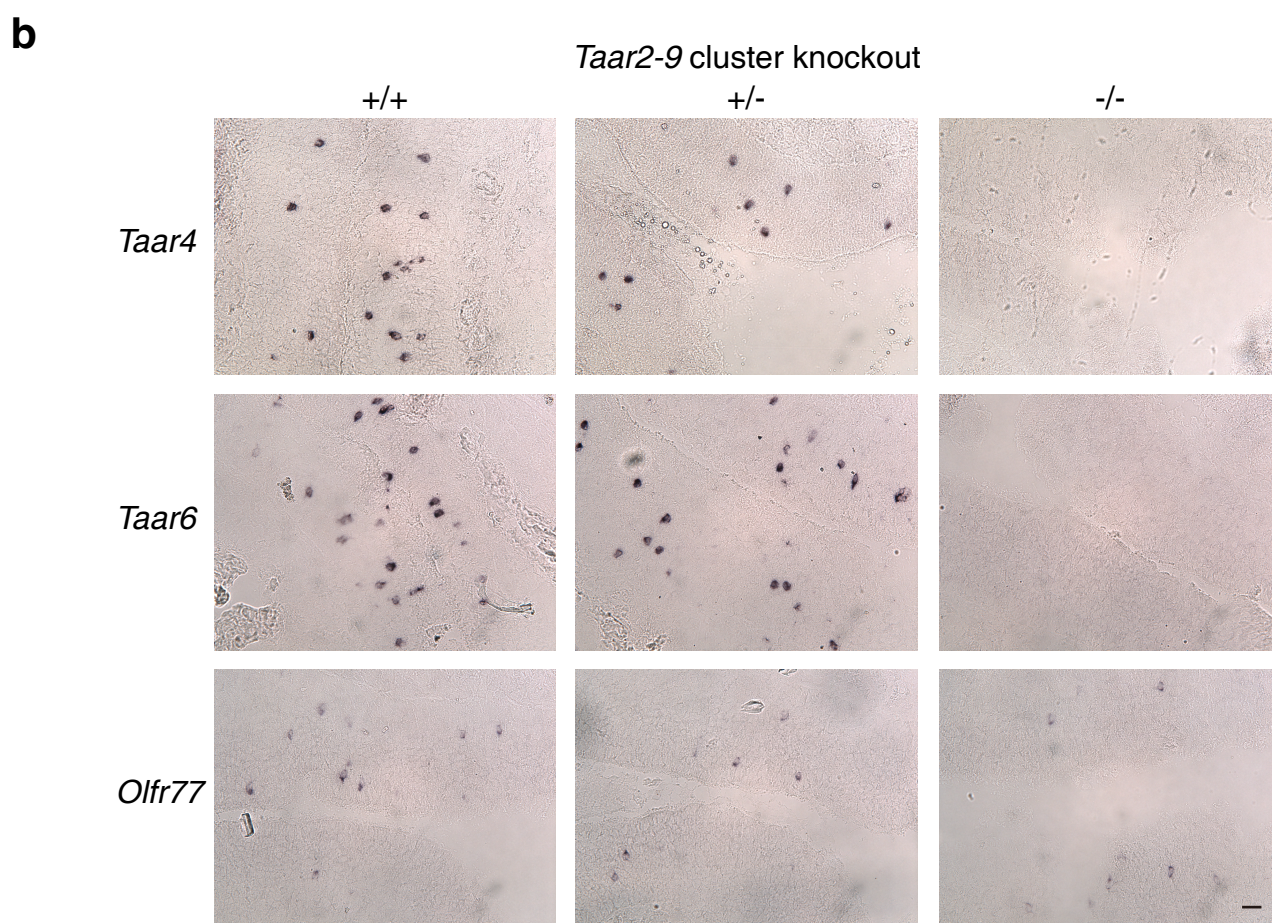
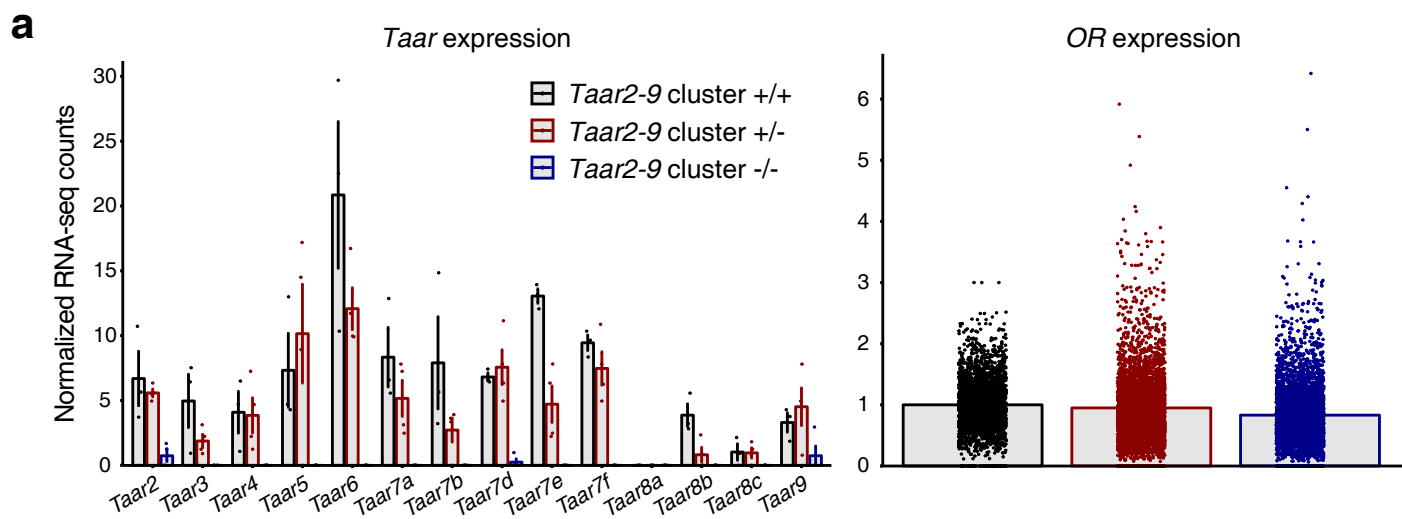
Supplementary figure 7



Supplementary figure 8



Supplementary figure 9



Supplementary figure 10

Supplementary Table 1. The information of extracted genome sequences from various mammalian species				
Species	Species	Genome assembly version	Genome coordinates	Genome regions
Mouse	Mus musculus	GRCm38.p4	chr10:23894688-24188961	Vnn1-Taar cluster-Stx7
			chr10:23920406-23941583	Taar1-Taar2
			chr10:23984609-23993481	Taar6-Taar7a
Human	Homo sapiens	GRCh38.p12	chr6:c132646026-132617150	Taar1-Taar2
			chr6:c132571359-132559024	Taar6-Taar7P
Chimpanzee	Pan troglodytes	Clint_PTRv2	chr6:c130003330-129974149	Taar1-Taar2P
			chr6:c129928126-129909449	Taar6-Taar8P
Orangutan	Pongo abelii	Susie_PABv2	chr6:c131193663-130936926	Vnn1-Taar cluster-Stx7
Gibbon	Nomascus leucogenys	Nleu_3.0	chr3:c119980447-119808147	Vnn1-Taar cluster-Stx7
Tarsier	Carlito syrichta	Tarsius_syrichta-2.0.1	NW_007247600.1:c380786-349157	Taar1-Taar2
			NW_007247600.1:c287550-257458	Taar6-Taar8
Rat	Rattus norvegicus	Rnor_6.0	chr1:c22596475-22578025	Taar1-Taar2
			chr1:c22537236-22528659	Taar6-Taar7a
Rabbit	Oryctolagus cuniculus	OryCun2.0	chr12:c122918612-122891431	Taar1-Taar2
			chr12:c122850827-122831128	Taar6-Taar6
Hedgehog	Erinaceus europaeus	EriEur2.0	NW_006804730.1:c662714-641243	Taar1-Taar2
			NW_006804730.1:c550178-516925	Taar6-Taar6
Pig	Sus scrofa	Sscrofa11.1	chr1:31037826-31074574	Taar1-Taar2
			chr1:31124661-31135694	Taar6-Taar7a
Cow	Bos taurus	ARS-UCD1.2	chr9:c70827654-70784406	Taar1-Taar2
			chr9:70591888-70609286	Taar6-Taar7aP
			chr9:c70554482-70533382	Taar8P-Taar7a
			chr9:c70711073-70693872	Taar6-Taar7a
			chr9:70618129-70633589	Taar8P-Taar7a
			chr9:c70534425-70518751	Taar7a-Taar7aP
Sheep	Ovis aries	Oar_rambouillet_v1.0	chr8:c64047965-64031195	Taar6-Taar7a
			chr8:c66398793-66380107	Taar6-Taar6P
			chr8:c64021497-64002370	Taar8P-Taar7a
Dolphin (Yangtze River dolphin)	Lipotes vexillifer	Lipotes_vexillifer_v1	NW_006784126.1:187583-324150	Vnn1-Taar cluster-Stx7
Sperm whale	Physeter catodon	ASM283717v2	chr10:30946785-31107969	Vnn1-Taar cluster-Stx7
			chr10:31012694-31027703	Taar1-Taar3P
Horse	Equus caballus	EquCab3.0	chr10:c80023263-80001724	Taar1-Taar2

			chr10:c79907708-79891692	Taar6-Taar7a
			chr10:79906594-79921740	Taar6-Taar7a
Cat	Felis catus	Felis_catus_9.0	chrB2:c122585612-122538799	Taar1-Taar2
			chrB2:122466294-122482960	Taar6-Taar7a
Dog	Canis lupus familiaris	CanFam3.1	chr1:c25544283-25704579	Vnn1-Taar cluster-Stx7
Sea lion (California sea lion)	Zalophus californianus	mZalCal1.pri.v2	chr7:31727731-31962268	Vnn3-Taar cluster-Stx7
Seal (Hawaiian monk seal)	Neomonachus schauinslandi	ASM220157v1	NW_018734349.1:31564931-31783478	Vnn1-Taar cluster-Stx7
Big brown bat	Eptesicus fuscus	EptFus1.0	NW_007370651.1:55488823-55512018	Taar1-Taar2
			NW_007370651.1:55537933-55555994	Taar5-Taar9
Elephant	Loxodonta africana	Loxafr3.0	NW_003573420.1:27517488-27557889	Taar1-Taar2
			NW_003573420.1:27626820-27662685	Taar4-Taar7a
Armadillo	Dasypus novemcinctus	Dasnov3.0	NW_004498224.1:c223592-203709	begin-Taar2
			NW_004498224.1:c125945-91587	Taar6P-Taar7aP
Koala	Phascolarctos cinereus	phaCin_unsw_v4.1	NW_018343979.1:c15437684-15405259	Taar1-Taar2
			NW_018343979.1:c15183169-15157886	Taar6-Taar7a
Opossum	Monodelphis domestica	MonDom5	chr2:c407125000-407094705	Taar1-Taar2
			chr2:c406934871-406909558	Taar6-Taar7a
Platypus	Ornithorhynchus anatinus	Ornithorhynchus_anatinus	NW_001794460.1:c1524776-1501778	Taar1-Taar2

Supplementary Table 2. *In situ* analysis in TAAR enhancer 1 knockout mice.

Receptor probe	n	WT (mean $\pm$ s.e.)		Heterozygous (mean $\pm$ s.e.)		Homozygous (mean $\pm$ s.e.)		One-way ANOVA p value
		Cell number	% of WT	Cell number	% of WT	Cell number	% of WT	
<i>Taar2</i>	5	21.0 $\pm$ 2.5	100.0 $\pm$ 12.1	13.4 $\pm$ 2.8	63.8 $\pm$ 13.4	0	0	< 0.0001
<i>Taar3</i>	15	22.5 $\pm$ 1.7	100.0 $\pm$ 7.6	15.1 $\pm$ 1.2	66.9 $\pm$ 5.2	0	0	< 0.0001
<i>Taar4</i>	7	24.4 $\pm$ 1.5	100.0 $\pm$ 6.2	20.4 $\pm$ 1.5	83.6 $\pm$ 6.3	1.6 $\pm$ 0.6	6.4 $\pm$ 2.3	< 0.0001
<i>Taar5</i>	7	13.3 $\pm$ 1.4	100.0 $\pm$ 10.9	9.1 $\pm$ 1.2	68.8 $\pm$ 8.8	0	0	< 0.0001
<i>Taar6</i>	10	98.6 $\pm$ 16.2	100.0 $\pm$ 16.4	82.5 $\pm$ 11.7	83.7 $\pm$ 11.9	32.0 $\pm$ 5.6	32.5 $\pm$ 5.6	0.0015
<i>Taar7a</i>	8	57.5 $\pm$ 10.7	100.0 $\pm$ 18.6	36.5 $\pm$ 3.6	63.5 $\pm$ 6.3	17.3 $\pm$ 2.2	30.0 $\pm$ 3.7	0.0013
<i>Taar7b</i>	8	66.1 $\pm$ 11.5	100.0 $\pm$ 17.3	45.0 $\pm$ 6.6	68.1 $\pm$ 10	13.9 $\pm$ 4.4	21.0 $\pm$ 6.7	0.0006
<i>Taar7d</i>	6	35.2 $\pm$ 6.3	100.0 $\pm$ 17.8	27.2 $\pm$ 2.8	77.3 $\pm$ 7.8	14.3 $\pm$ 2.8	40.8 $\pm$ 8.0	0.0117
<i>Taar7e</i>	5	30.0 $\pm$ 7.2	100.0 $\pm$ 23.9	30.6 $\pm$ 6.3	102.0 $\pm$ 20.9	45.4 $\pm$ 4.5	151.3 $\pm$ 14.9	0.1700
<i>Taar7f</i>	9	34.1 $\pm$ 4.0	100.0 $\pm$ 11.8	29.9 $\pm$ 4.4	87.6 $\pm$ 12.8	22.2 $\pm$ 2.1	65.1 $\pm$ 6.3	0.0846
<i>Taar8s</i>	5	45.8 $\pm$ 14.8	100.0 $\pm$ 32.3	47.2 $\pm$ 5.9	103.1 $\pm$ 12.9	9.8 $\pm$ 2.7	21.4 $\pm$ 6.0	0.0242
<i>Taar9</i>	9	29.0 $\pm$ 2.7	100.0 $\pm$ 9.2	23.6 $\pm$ 3.1	81.2 $\pm$ 10.8	2.2 $\pm$ 0.5	7.7 $\pm$ 1.6	< 0.0001
<i>Olfir1507</i>	4	181.0 $\pm$ 22.6	100.0 $\pm$ 12.5	174.0 $\pm$ 10.5	96.1 $\pm$ 5.8	218.3 $\pm$ 27.2	120.6 $\pm$ 15.0	0.3320
<i>Olfir578</i>	5	52.6 $\pm$ 7.4	100.0 $\pm$ 14.2	49.2 $\pm$ 5.2	93.5 $\pm$ 9.9	54.0 $\pm$ 5.9	102.7 $\pm$ 11.1	0.8575

Supplementary Table 3. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 1 knockout mice.

Receptor probe	Expression [% of WT, <i>in situ</i>] (mean $\pm$ s.e.)	n	p value	Expression [% of WT, RNA-seq]	n	p value
<i>Taar2</i>	0	5	1.5×10^{-6}	0.8	3	2.5×10^{-7}
<i>Taar3</i>	0	15	1.7×10^{-13}	0.6	3	1.0×10^{-7}
<i>Taar4</i>	6.4 ± 2.3	7	4.5×10^{-9}	1.6	3	7.0×10^{-8}
<i>Taar5</i>	0	7	8.7×10^{-7}	0.2	3	3.7×10^{-9}
<i>Taar6</i>	32.5 ± 5.6	10	1.1×10^{-3}	49.2	3	4.9×10^{-5}
<i>Taar7a</i>	30.0 ± 3.7	8	2.4×10^{-3}	42.3	3	1.4×10^{-5}
<i>Taar7b</i>	21.0 ± 6.7	8	8.0×10^{-4}	23.4	3	1.2×10^{-12}
<i>Taar7d</i>	40.8 ± 8.0	6	1.2×10^{-2}	57.0	3	6.1×10^{-2}
<i>Taar7e</i>	151.3 ± 14.9	5	0.106174	171.4	3	9.0×10^{-4}
<i>Taar7f</i>	65.1 ± 6.3	9	1.9×10^{-2}	88.0	3	0.999160
<i>Taar8a</i>				3.4	3	0.158900
<i>Taar8b</i>	21.4 ± 6.0	5	0.401288	34.8	3	0.495081
<i>Taar8c</i>				11.4	3	0.546081
<i>Taar9</i>	7.7 ± 1.6	9	3.2×10^{-8}	5.9	3	3.6×10^{-13}
<i>Olfir1507</i>	120.6 ± 15.0	4	0.332264	120.7	3	0.941256
<i>Olfir578</i>	102.7 ± 11.1	5	0.886369	118.2	3	0.9098223

Supplementary Table 4. *In situ* analysis in TAAR enhancer 2 knockout mice.

Receptor probe	n	WT (mean $\pm$ s.e.)		Heterozygous (mean $\pm$ s.e.)		Homozygous (mean $\pm$ s.e.)		One-way ANOVA p value
		Cell number	% of WT	Cell number	% of WT	Cell number	% of WT	
<i>Taar2</i>	7	18.7 $\pm$ 2.3	100.0 $\pm$ 12.2	18.4 $\pm$ 2.3	98.5 $\pm$ 12.6	17.4 $\pm$ 2.1	93.1 $\pm$ 11.1	0.9137
<i>Taar3</i>	4	24.3 $\pm$ 3.0	100.0 $\pm$ 12.3	13.3 $\pm$ 1.4	54.6 $\pm$ 5.7	0	0	< 0.0001
<i>Taar4</i>	8	34.6 $\pm$ 3.7	100.0 $\pm$ 10.8	29.4 $\pm$ 3.2	84.8 $\pm$ 9.2	14.3 $\pm$ 1.3	41.2 $\pm$ 3.6	0.0002
<i>Taar5</i>	4	13.3 $\pm$ 1.1	100.0 $\pm$ 8.4	6.8 $\pm$ 0.9	50.9 $\pm$ 6.4	0	0	< 0.0001
<i>Taar6</i>	5	98.8 $\pm$ 17.4	100.0 $\pm$ 17.6	69.8 $\pm$ 19.0	70.6 $\pm$ 19.3	11.0 $\pm$ 2.3	11.1 $\pm$ 2.4	0.0042
<i>Taar7a</i>	6	50.0 $\pm$ 4.4	100.0 $\pm$ 8.8	27.8 $\pm$ 4.7	55.7 $\pm$ 9.4	21.5 $\pm$ 4.8	43.0 $\pm$ 9.6	0.0014
<i>Taar7b</i>	8	57.6 $\pm$ 11.3	100.0 $\pm$ 19.5	63.0 $\pm$ 10.0	109.3 $\pm$ 17.3	76.0 $\pm$ 7.3	131.9 $\pm$ 12.7	0.4005
<i>Taar7d</i>	3	46.0 $\pm$ 13.2	100.0 $\pm$ 28.8	32.0 $\pm$ 4.0	69.6 $\pm$ 8.8	42.0 $\pm$ 13.8	91.3 $\pm$ 30.0	0.6817
<i>Taar7e</i>	5	30.2 $\pm$ 1.8	100.0 $\pm$ 5.9	28.4 $\pm$ 3.0	94.0 $\pm$ 9.9	38.4 $\pm$ 4.1	127.2 $\pm$ 13.6	0.0906
<i>Taar7f</i>	4	39.3 $\pm$ 0.8	100.0 $\pm$ 1.9	34.0 $\pm$ 3.6	86.6 $\pm$ 9.1	16.3 $\pm$ 2.5	41.4 $\pm$ 6.4	0.0003
<i>Taar8s</i>	4	42.8 $\pm$ 3.1	100.0 $\pm$ 7.3	38.0 $\pm$ 5.8	88.9 $\pm$ 13.7	5.0 $\pm$ 1.6	11.7 $\pm$ 3.7	0.0002
<i>Taar9</i>	10	28.0 $\pm$ 3.9	100.0 $\pm$ 14.1	22.1 $\pm$ 2.7	78.9 $\pm$ 9.8	3.0 $\pm$ 0.5	10.7 $\pm$ 1.9	< 0.0001
<i>Olfir1507</i>	4	117.8 $\pm$ 36.1	100.0 $\pm$ 30.7	157.8 $\pm$ 33.5	134.0 $\pm$ 28.4	91.0 $\pm$ 18.5	77.3 $\pm$ 15.7	0.3387
<i>Olfir578</i>	5	57.4 $\pm$ 7.6	100.0 $\pm$ 13.3	69.8 $\pm$ 4.1	121.6 $\pm$ 7.1	59.4 $\pm$ 4.9	103.5 $\pm$ 8.6	0.2981

Supplementary Table 5. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 2 knockout mice.

Receptor probe	Expression [% of WT, <i>in situ</i>] (mean $\pm$ s.e.)	n	p value	Expression [% of WT, RNA-seq]	n	p value
<i>Taar2</i>	93.1 $\pm$ 11.1	7	0.659573	75.2	3	0.999913
<i>Taar3</i>	0	4	1.8×10^{-4}	3.3	3	1.7×10^{-5}
<i>Taar4</i>	41.2 $\pm$ 3.6	8	1.4×10^{-4}	54.9	3	0.999913
<i>Taar5</i>	0	4	2.1×10^{-5}	10.2	3	5.5×10^{-7}
<i>Taar6</i>	11.1 $\pm$ 2.4	5	1.1×10^{-3}	10.2	3	3.0×10^{-30}
<i>Taar7a</i>	43.0 $\pm$ 9.6	6	1.4×10^{-3}	19.6	3	1.0×10^{-8}
<i>Taar7b</i>	131.9 $\pm$ 12.7	8	0.193209	102.9	3	0.999913
<i>Taar7d</i>	91.3 $\pm$ 30.0	3	0.844460	106.7	3	0.999913
<i>Taar7e</i>	127.2 $\pm$ 13.6	5	0.104065	80.2	3	0.999913
<i>Taar7f</i>	41.4 $\pm$ 6.4	4	1.2×10^{-4}	44.0	3	0.909372
<i>Taar8a</i>				2.2	3	0.481418
<i>Taar8b</i>	11.7 $\pm$ 3.7	4	3.7×10^{-5}	18.3	3	0.803564
<i>Taar8c</i>				3.6	3	0.999913
<i>Taar9</i>	10.7 $\pm$ 1.9	10	6.4×10^{-6}	9.3	3	2.6×10^{-10}
<i>Olfir1507</i>	77 $\pm$ 15.7	4	0.533878	128.7	3	0.999913
<i>Olfir578</i>	103 $\pm$ 8.6	5	0.831055	100.6	3	0.999913

Supplementary Table 6. *In situ* analysis in TAAR enhancer 1 & 2 knockout mice.

Receptor probe	n	WT (mean $\pm$ s.e.)		Heterozygous (mean $\pm$ s.e.)		Homozygous (mean $\pm$ s.e.)		One-way ANOVA p value
		Cell number	% of WT	Cell number	% of WT	Cell number	% of WT	
<i>Taar2</i>	5	23.2 $\pm$ 4.6	100 $\pm$ 19.9	14.2 $\pm$ 2.3	61.2 $\pm$ 10.0	0	0	0.0005
<i>Taar3</i>	10	24.3 $\pm$ 5.1	100 $\pm$ 21.1	15.3 $\pm$ 1.9	63.0 $\pm$ 7.8	0	0	< 0.0001
<i>Taar4</i>	5	38.6 $\pm$ 4.9	100 $\pm$ 12.8	25.6 $\pm$ 2.8	66.3 $\pm$ 7.4	0	0	< 0.0001
<i>Taar5</i>	5	26.8 $\pm$ 6.5	100 $\pm$ 24	20.8 $\pm$ 4.9	77.6 $\pm$ 18.0	0	0	0.0040
<i>Taar6</i>	10	113.1 $\pm$ 14.1	100 $\pm$ 12.5	74.6 $\pm$ 11.0	66.0 $\pm$ 9.7	0	0	< 0.0001
<i>Taar7s</i>	5	276.6 $\pm$ 48.8	100 $\pm$ 17.6	224.0 $\pm$ 39.6	81.0 $\pm$ 14.3	0	0	0.0004
<i>Taar8s</i>	10	113.4 $\pm$ 13.8	100 $\pm$ 12.2	87.2 $\pm$ 8.3	76.9 $\pm$ 7.3	0	0	< 0.0001
<i>Taar9</i>	10	34.2 $\pm$ 4.0	100 $\pm$ 11.7	32.6 $\pm$ 3.4	95.3 $\pm$ 10.0	0	0	< 0.0001
<i>Olfir1507</i>	8	195.0 $\pm$ 30.8	100 $\pm$ 15.8	215.3 $\pm$ 35.3	110.4 $\pm$ 18.1	228.9 $\pm$ 28.0	117.4 $\pm$ 14.4	0.7496
<i>Olfir578</i>	10	49.0 $\pm$ 4.7	100 $\pm$ 9.6	60.4 $\pm$ 5.7	123.3 $\pm$ 11.7	38.9 $\pm$ 5.8	79.4 $\pm$ 11.8	0.0318

Supplementary Table 7. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 1 & 2 double knockout mice.

Receptor probe	Expression [% of			Expression [% of		
	WT, <i>in situ</i>] (mean $\pm$ s.e.)	n	p value	WT, RNA-seq]	n	p value
<i>Taar2</i>	0	5	1.0×10^{-3}	1.1	≥ 3	1.5×10^{-9}
<i>Taar3</i>	0	10	1.7×10^{-4}	1.3	≥ 3	4.0×10^{-5}
<i>Taar4</i>	0	5	1.6×10^{-5}	4.6	≥ 3	3.6×10^{-10}
<i>Taar5</i>	0	5	3.3×10^{-3}	0.6	≥ 3	1.6×10^{-8}
<i>Taar6</i>	0	10	2.3×10^{-7}	0.3	≥ 3	9.5×10^{-13}
<i>Taar7a</i>				0.2	≥ 3	7.3×10^{-14}
<i>Taar7b</i>				0.3	≥ 3	4.1×10^{-12}
<i>Taar7d</i>	0	5	4.7×10^{-4}	0.2	≥ 3	1.1×10^{-13}
<i>Taar7e</i>				0.2	≥ 3	9.5×10^{-13}
<i>Taar7f</i>				0.2	≥ 3	7.3×10^{-14}
<i>Taar8a</i>				5.7	≥ 3	1
<i>Taar8b</i>	0	10	1.7×10^{-7}	0.7	≥ 3	1.8×10^{-7}
<i>Taar8c</i>				2.4	≥ 3	0.140657
<i>Taar9</i>	0	10	9.3×10^{-8}	0.3	≥ 3	1.2×10^{-11}
<i>Olfir1507</i>	117.4 ± 14.4	8	0.429866	117.6	≥ 3	1
<i>Olfir578</i>	79.4 ± 11.8	10	0.192455	116.4	≥ 3	1

Supplementary Table 8. List of *in situ* probes.

OR genes							
Gene	Synonym	OR class	Zone	Accession #	Nucleotide position	Cross-hybridized genes	Reference
Mixed OR probes							
<i>Olfir644</i>	MOR13-1	I	1.0	AY317765.1	1-942	<i>Olfir643</i>	
<i>Olfir578</i>	MOR7-1	I	1.0	NM_147115	4-790	-	
<i>Olfir1019</i>	MOR180-1	II	1.0	AY318214.1	315-864	-	
<i>Olfir1034</i>	MOR227-8P, MOR245-14P, Olfir1533-ps1	II	1.0	NM_001011872.2	1-1013	<i>Olfir1036</i>	
<i>Olfir145</i>	MOR161-6, K21	II	1.0	NM_146313.1	1-930	<i>Olfir874</i> , <i>Olfir876</i>	<i>Olfir875</i> ,
<i>Olfir1395</i>	MOR277-1	II	2.0	NM_146877.1	420-900	-	
<i>Olfir2</i>	MOR103-15, 17	II	4.0	AY317835.1	163-665	-	
<i>Olfir1507</i>	MOR28, MOR244-1	II	5.0	AY318726.1	1-899	<i>Olfir1508</i>	
Mixed class I OR probes							
<i>Olfir543</i>	MOR42-2	I	1.0	NM_001011782	38-987	-	
<i>Olfir547</i>	MOR31-4	I	1.0	NM_147079	31-910	-	
<i>Olfir552</i>	MOR28-1	I	1.0	NM_147102	15-927	-	
<i>Olfir639</i>	MOR12-1	I	1.0	NM_147084	1-922	-	Tetsuo Iwata,
<i>Olfir653</i>	MOR33-1	I	1.0	NM_147074	32-960	-	et al., (2017).
<i>Olfir672</i>	MOR32-4	I	1.0	NM_146760	9-919	-	
<i>Olfir692</i>	MOR36-1	I	1.0	NM_146355	23-952	-	
<i>Olfir690</i>	MOR31-2, Ors18	I	1.0	NM_020290	8-1002	-	
Taar genes (mixed Taar probes are composed of Taar2, Taar3, Taar4, Taar5, Taar6, Taar7s, Taar8s, and Taar9)							
Gene	Zone (dorsal or ventral)		Accession #		Nucleotide position		
Taar2	Dorsal		NM_001007266.1		29-996		
Taar3	Dorsal		NM_001008429.1		21-1009		
Taar4	Dorsal		NM_001008499.1		47-1041		
Taar5	Dorsal		NM_001009574.1		25-988		
Taar6	Both dorsal and ventral		NM_001010828.1		33-1027		
Taar7a	Ventral		NM_001010829.1		3' UTR		
Taar7b	Ventral		NM_001010827.1		3' UTR		
Taar7d	Both dorsal and ventral		NM_001010838.1		3' UTR		
Taar7e	Dorsal		NM_001010835.1		3' UTR		
Taar7f	Dorsal		NM_001010839.1		3' UTR		
Taar7s	Both dorsal and ventral		NM_001010829.1		78-934		
Taar8s	Dorsal		NM_001010830.1		34-925		
Taar9	Dorsal		NM_001010831.1		91-1004		
Other genes							
GFP			-	U55762		679-1398	

Supplementary Table 9. List of primers for mouse genotyping and *in situ* probe production.

Target	Forward primer sequence	Reverse primer sequence	Product size [bp]
Mouse genotyping			
<i>Taar5-ires-cre</i> mouse	GCTAGAAGAGATGCCTTGTGTG	GCAAACCTTAGACTTCTCCGAC	761 (WT)
	CGTAACCTGGATAGTGAAACAGG	GCAAACCTTAGACTTCTCCGAC	427 (Cre)
<i>Taar6-ires-cre</i> mouse	GGAATTATCCAGTGCCCTCAAC	GTATCTGTGGTGCTTCAGGAGAC	846 (WT)
	CGTAACCTGGATAGTGAAACAGG	GTATCTGTGGTGCTTCAGGAGAC	486 (Cre)
TAAR enhancer 1 knockout mouse	AGCTGGGGATACAATGGTTG	GTTGTGAGCAAACTAGGGTC	591 (WT)
TAAR enhancer 2 knockout mouse	AGCTGGGGATACAATGGTTG	GTTGACCACATGCTATGAACC	355 (KO)
TAAR enhancer 2 knockout mouse	AGCAGACAAACTTACCCCTTC	GATCCACCTGTCCTTATGCTC	353 (WT)
TAAR enhancer 1 & 2 double knockout mouse	AGCAGACAAACTTACCCCTTC	GTGAGTTTGAGACCACCTTAGC	439 (KO)
TAAR enhancer 1	AGCTGGGGATACAATGGTTG	GTTGTGAGCAAACTAGGGTC	591 (WT)
	AGCTGGGGATACAATGGTTG	GCAGTGTTTCATTTACAGGTGG	312 (KO)
TAAR enhancer 2	AGCAGACAAACTTACCCCTTC	GATCCACCTGTCCTTATGCTC	353 (WT)
	AGCAGACAAACTTACCCCTTC	GTGAGTTTGAGACCACCTTAGC	439 (KO)
TAAR enhancer 1-GFP transgenic mouse	GTGAGTCAAAATGACGCATG	GTTGTGAGCAAACTAGGGTC	379
TAAR enhancer 2-tdTomato transgenic mouse	GTGAGTCAAAATGACGCATG	GTCATAAACCCACGGGCATC	432
<i>Taar2-9</i> cluster	CAGCTAAGCACCCTACCAC	GAATGAGGATGTTGGTCAATG	508 (WT)
knockout mouse	CAGCTAAGCACCCTACCAC	GGAGTTATCACAGAGCTTCAGTCGAG	702 (KO)
<i>lox-ZsGreen</i> mouse	AAGGGAGCTGCAGTGGAAGTA	CCGAAAATCTGTGGGAAGTC	297 (WT)
	GGCATTAAGCAGCGTATCC	AACCAGAAGTGGCACCTGAC	199 (KI)
<i>In situ</i> probe production			
<i>Taar2</i>	CCTTTGATTGTTTCAGAGTACGG	CCTTTGATTGTTTCAGAGTACGG	968
<i>Taar3</i>	CGAAGACTTATCCAGCTGTC	TTGCAGTGTCTGAATTAGAGC	989
<i>Taar4</i>	TTGCTGCTGCAACAGTTCT	AGGATGTGCAGGATGCAG	995
<i>Taar5</i>	TCTGGAGAGCAGCCTACA	GTGTCCTTGGTGAGAAGATC	964
<i>Taar6</i>	GCAGCTCTGCTATGAGAATGT	CAGAGAACAAGTTCATAGTGGCT	995
<i>Taar7a</i>	GATTCTTGTTTAGTTGGGG	TGTAAATCTTGAATGGGTC	656
<i>Taar7b</i>	GATTCTTGTTTAGTTGGGGA	GCACACCTTTGAAAACCTTC	1049
<i>Taar7d</i>	GATTCTTGTTTAGTCGGGG	CTACTGAGCTACCTCTTCAG	1044
<i>Taar7e</i>	TTTCTCTTGCTCCCAGTTCTC	GTGCATATCTTTGAACACTTC	704
<i>Taar7f</i>	ACTCTGTCAACTGAGGCTCAG	CAAGAGCAAATTATACAGGG	500
<i>Taar7s</i>	AGAGCTGTGCTATGAGAACC	CTAGGATTTCATACACATACGTGG	857
<i>Taar8s</i>	CTCTGCTATGAGAACACGAATG	GGTTCATGGCTGAGTTATAATAGG	892
<i>Taar9</i>	CCTCGAGCCATCCTCTATG	GAATCAGCCCTGAAGACTTTGC	914
<i>Olfir644</i>	ATGGGAGGTGAAGCCCACAA	AAATTTGTTCCCCAGCAGGA	942
<i>Olfir578</i>	GCCATCCTTTACAACAGCAGC	GGTTCATGGCTGAGTTATAATAGG	785
<i>Olfir1019</i>	AGGCTTTGTGGATGCTGAGT	CAAGGGGTTTCAGCATAGGAA	550

<i>Olf1034</i>	CGTTTTTCCTTGCAGAAAAC	ACACATTTGGATAAACACGC	1013
<i>Olf145</i>	ATGGCCACTGAAAATGCCTC	GGAAAATGAACTTCTGCTCA	930
<i>Olf1395</i>	TGTCTGCTGGCTCATGGTAG	TCCGGTCACTTCTTTGTTCC	481
<i>Olf12</i>	ACCCTCCACAAACCCATGTA	GAAGCCCCAGTGACAGAGAG	503
<i>Olf1507</i>	ATGGAAAAGGCTGTCCTCA	GCACTCTTCATGTCCTCATTC	899
<i>Olf1543</i>	GGTGAGGATGGAAATACCAGTATC	GGTGACTGCATTCCACAGAG	950
<i>Olf1547</i>	CACACAGTCTTCCATTGTTGG	GCTCCTGGATTGCTTGGT	880
<i>Olf1552</i>	TATCACCTCAACCCACCCAG	GAATAGCCCTAAGACTCGCTCT	913
<i>Olf1639</i>	ATGGGAGCAGAGAACAATGAAAGTC	AGTTGGCAATCCCTGTTGG	922
<i>Olf1653</i>	TCTCTGCTGCTATCCCAATG	GTGGAGATTATTGTCACCTTCTCTTAC	929
<i>Olf1672</i>	AGGCAACAGCTCATGGATTCA	TATCACCACACGATCTCGAATCTG	911
<i>Olf1692</i>	ACAGAATGGCAGAAAGTTCGCA	ATCGGTCCCTAATCTGCTTGG	930
<i>Olf1690</i>	TTTGACCAGACCTCACAGCTG	ATGCTGTCCCTAATTGCTTGG	995
<i>GFP</i>	ATGGTGAGCAAGGGCGA	TTACTTGTACAGCTCGTCCATGC	720
<i>Degenerate OR</i>	GCITA(C/T)GA(C/T)CGITA(C/T)GTIGCIA TITG	ACIACIGAIAG(G/A)TGIGAI(G/C)C(G/A) CAIGT	327

Supplementary Table10. List of plasmid information.

plasmid	Addgene #	Usage
PBCAG-eGFP	40973	Modified this plasmid for PiggyBac transposon system
pX330-U6-Chimeric_BB-CBh-hSpCas9	42230	sgRNA template
pX260-U6-DR-BB-DR-Cbh-NLS-hSpCas9-NLS-H1-shorttracr-PGK-puro	42229	SpCas9 template

Supplementary Figure 1. Representative FACS density plots. (a) Representative plots with gates showing sorted ZsGreen-positive and ZsGreen-negative cells in *Taar5-ires-Cre; lox-ZsGreen* mice. (b) The classical olfactory chaperon molecules (*Rtp1* and *Rtp2*) were expressed at similar level in reporter-positive (*Taar5+* or *Taar6+*) and reporter-negative (control) cells (n = 10 for control cells, n = 7 for *Taar5+* reporter-positive cells, n = 1 for *Taar6+* reporter-positive cells). Data are presented as mean values $\pm$ SEM.

Supplementary Figure 2. Similar chromatin accessibility of canonical signaling molecules between TAAR OSNs and OMP-positive OSNs. ATAC-seq signals plotted across different genomic regions containing various olfactory signaling molecules. ATAC-seq signals were normalized to median peak values of each sample. Below the signal tracks, exons of genes were depicted. Arrows inside exons indicate direction of sense strand. The NM_010307 isoform of *Gnal* gene is possibly the major variant expressed in the MOE based on the fact that ATAC-seq peaks are found in its promoter region but not the NM_177137 isoform. This is consistent with our RNA-seq data.

Supplementary Figure 3. The *Taar* genes were downregulated in mature OSNs when *Lhx2* or *Ldb1* is deleted. (a) Published RNA-seq data of 5 mature OSN samples from control mice, 3 mature OSN samples from *Lhx2* knockout mice, and 4 mature OSN samples from *Ldb1* knockout mice were retrieved from the GEO (GSE112153) ¹⁷ and analyzed to examine changes of the *Taar* gene expression. Normalized counts of the 14 olfactory *Taar* genes were depicted in control mice, *Lhx2* knockout mice, and *Ldb1* knockout mice. Data are presented as mean values $\pm$ SEM. (b, c) Multiple alignment of TAAR enhancer 1 (b) and TAAR enhancer 2 (c) obtained from 8 placental mammals. Motif analyses in the mouse sequences revealed 2 *Lhx2*-binding motifs (pink box) and 1 *Lhx2*/*Ebf* composite motif (light purple box) in TAAR enhancer 1 (b), and 2 *Lhx2*-binding motifs, 1 *Ebf*-binding motif (light green box), and 1 *Lhx2*/*Ebf* composite motif in TAAR enhancer 2 (c). The orientation of the motifs is represented by arrows pointing in different directions. Note that there are duplications of TAAR enhancer

2 in cow and horse. In a, n.s. not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, by the Wald test (two-sided) in DESeq2 package.

Supplementary Figure 4. Conservation analysis of the two TAAR enhancers. (a) Summary of 8 Glires, 21 Euarchontoglires, 40 placental mammals, and 60 vertebrates included in the conservation analysis in Figure 3a. The subset information and evolutionary relationships were obtained from UCSC. (b) VISTA nucleotide percent identity plots of the mouse *Taar* cluster ranging from *Taar1* to *Taar7a* compared with that in orangutan, gibbon, dolphin, sperm whale, seal, sea lion, and dog. (c) VISTA nucleotide percent identity plots of mouse TAAR enhancer 2 and two adjacent *Taar* genes compared with that in cow, sheep, and horse. The arrows indicate the transcriptional orientations of *Taar* genes in mouse genome. Conservation between 50% and 100% are shown as peaks. Highly conserved regions (> 100 bp width and > 70% identity) in exons, intergenic regions, and TAAR enhancers are shown in blue, red, and cyan, respectively.

Supplementary Figure 5. Downregulation of specific *Taar* genes by TAAR enhancer 1 deletion. (a) The 14 DEGs were identified using the criteria of $q < 0.05$ and fold change > 1.5-fold in RNA-seq data of homozygous TAAR enhancer 1 knockout mice and wild type mice. The 9 *Taar* genes that showed significant changes are indicated by blue dots. The 5 other DEGs are indicated by red dots. And other *Taar* genes are indicated by blue circles. (b) Normalized counts of the 14 olfactory *Taar* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 knockout mice ($n = 3$). Data are presented as mean values $\pm$ SEM. (c) Normalized counts of the *OR* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 knockout mice. (d) Top, representative confocal images of immunohistochemistry staining for TAAR6 and Olfr1507 in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 knockout mice. Blue fluorescence represented DAPI counterstaining. Scale bar = 25 μ m. Bottom, percentage of positive cell numbers in

heterozygous (+/-) or homozygous (-/-) mice compared to wild type (+/+) was plotted. Data are presented as mean values $\pm$ SEM (n = 7 for TAAR6 staining, n = 5 for Olfr1507 staining). (e) Left, representative confocal images of immunohistochemistry staining for Caspase-3 in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 knockout mice. Blue fluorescence represented DAPI counterstaining. Scale bar = 25 μ m. Right, percentage of positive cell numbers in heterozygous (+/-) or homozygous (-/-) mice compared to wild type (+/+) was plotted. Data are presented as mean values $\pm$ SEM (n = 6). In b, ** p < 0.01, *** p < 0.001, by the LRT and Wald test (two-sided) in DESeq2 package.

Supplementary Figure 6. Downregulation of specific *Taar* genes by TAAR enhancer 2

deletion. (a) The 6 DEGs were identified using the criteria of q < 0.05 and fold change > 1.5-fold in RNA-seq data of homozygous TAAR enhancer 2 knockout mice and wild type mice. The 5 *Taar* genes that showed significant changes are indicated by blue dots. Another DEG is indicated by red dots. All of the other *Taar* genes are indicated by blue circles. (b) Normalized counts of the 14 olfactory *Taar* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 2 knockout mice (n = 3). Data are presented as mean values $\pm$ SEM. (c) Normalized counts of the *OR* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 2 knockout mice (n = 3). (d) Correlation between log2-fold change values of positive cell numbers by *in situ* hybridization (Y-axis, n $\geq$ 3) and gene expression by RNA-seq (X-axis, n = 3) for the *Taar* genes. Pearson correlation coefficient r = 0.88 (two-sided, no adjustments were made), p = 0.0001. (e) Left, representative images of immunohistochemistry staining for TAAR5 and Olfr552 in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 2 knockout mice. Blue fluorescence represented DAPI counterstaining. Scale bar = 25 μ m. Right, percentage of positive cell numbers in heterozygous (+/-) or homozygous (-/-) mice compared to wild type (+/+) was plotted. Data are presented as mean values $\pm$ SEM (n = 5). (f) Left, representative images of immunohistochemistry staining for Caspase-3 in wild

type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 2 knockout mice. Blue fluorescence represented DAPI counterstaining. Scale bar = 25 μ m. Right, percentage of positive cell numbers in heterozygous (+/-) or homozygous (-/-) mice compared to wild type (+/+) was plotted. Data are presented as mean values $\pm$ SEM (n = 5). In b, * p < 0.05, ** p < 0.01, *** p < 0.001, by the LRT and Wald test (two-sided) in DESeq2 package. In e, * p < 0.05, *** p < 0.001, by one-way ANOVA and post-hoc Tukey's test.

Supplementary Figure 7. Loss of *Taar* gene expression by deletion of the two TAAR enhancers. (a) The 13 DEGs were identified using the criteria of q < 0.05 and fold change > 1.5-fold in RNA-seq data of homozygous TAAR enhancer 1 & 2 double knockout mice and wild type mice. The 12 *Taar* genes that showed significant changes are indicated by blue dots. Another DEG is indicated by red dots. All of the other *Taar* genes are indicated by blue circles. (b) Normalized counts of the 14 olfactory *Taar* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 & 2 double knockout mice (n $\geq$ 3). Data are presented as mean values $\pm$ SEM. (c) Normalized counts of the *OR* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 & 2 double knockout mice. (d) Left, representative images of immunohistochemistry staining for Caspase-3 in wild type (+/+), heterozygous (+/-), and homozygous (-/-) TAAR enhancer 1 & 2 double knockout mice. Blue fluorescence represented DAPI counterstaining. Scale bar = 25 μ m. Right, percentage of positive cell numbers in heterozygous (+/-) or homozygous (-/-) mice compared to wild type (+/+) was plotted. Data are presented as mean values $\pm$ SEM (n = 5). In b, *** p < 0.001, by the LRT and Wald test (two-sided) in DESeq2 package.

Supplementary Figure 8. Functional analysis of TAAR enhancers in zebrafish and mouse. (a) Schematic depiction of the E1b reporter expression construct used in zebrafish embryo injection. Various enhancer candidates were amplified from mouse genomic DNA and

fused to the E1b minimal promoter followed by the GFP sequence. (b) Representative bright field (left) and fluorescent images of injected zebrafish larvae head at 4 dpf (days post-fertilization). (c) Percentage of injected zebrafish embryos with GFP-positive OSNs at 24-48 hpf (hours post-fertilization) for the TAAR enhancers or the Sifnos OR enhancer that served as a positive control. (d) Images of the MOE sections from TAAR enhancer 1-GFP (left) or TAAR enhancer 2-tdTomato mice (right). To better show the reporter-positive cells, the positions of reporter-positive OSNs are highlighted with white dots. Insets show higher magnification of reporter-positive OSNs ($n \geq 3$). Scale bar = 200 μm . (e) Whole-mount fluorescent images of the medial view of olfactory bulb in TAAR enhancer 1-GFP; TAAR enhancer 2-tdTomato transgenic mice. A, anterior; P, posterior; D, dorsal; V, ventral ($n \geq 3$). Scale bar = 200 μm .

Supplementary Figure 9. The TAAR OSN-specific enhancer activity of the two TAAR enhancers. (a) FACS-sorted reporter-positive (GFP⁺ in TAAR enhancer 1-GFP mice or tdTomato⁺ in TAAR enhancer 2-tdTomato mice) and reporter-negative (GFP⁻ in TAAR enhancer 1-GFP mice or tdTomato⁻ in TAAR enhancer 2-tdTomato mice) cells were collected for RNA-seq experiments. The TPM values extracted for the total *Taar* and *OR* genes were plotted. (b) The TPM values of all the 15 *Taar* genes were plotted in reporter-positive (GFP⁺ or tdTomato⁺) and reporter-negative (GFP⁻ or tdTomato⁻) cells, showing that reporter-positive cells had higher *Taar* gene expression than reporter-negative cells. (c) Top left, confocal images of *in situ* hybridization of individual probes of *Taar* genes (magenta) and the following immunohistochemistry by the GFP antibody (green) in a TAAR enhancer 1-GFP transgenic mouse. Top right, confocal images of *in situ* hybridization of individual probes of *Taar* genes (green) and the following immunohistochemistry by the tdTomato antibody (magenta) in a TAAR enhancer 2-tdTomato transgenic mouse. Scale bar = 25 μm . Bottom, bar plots showing the percentages of GFP-positive cells (left) or tdTomato-positive cells (right) that were co-labeled with individual *Taar* probes ($n \geq 3$).

Supplementary Figure 10. Validation of *Taar2-9* cluster knockout mice. (a) Normalized counts of the 14 olfactory *Taar* genes and the *OR* genes from RNA-seq data were depicted in wild type (+/+), heterozygous (+/-), and homozygous (-/-) *Taar2-9* cluster knockout mice. Expression of the olfactory *Taar* genes was abolished, while expression of the *OR* genes was not significantly changed ($n \geq 3$). Data are presented as mean values $\pm$ SEM. (b) Representative images of *Taar4*, *Taar6*, and *Olf77* expression in wild type (+/+), heterozygous (+/-), and homozygous (-/-) *Taar2-9* cluster knockout mice using single color *in situ* hybridization. Scale bar = 25 μ m ($n \geq 3$). (c) Representative confocal images of immunohistochemistry staining for TAAR4 in wild type (+/+), heterozygous (+/-), and homozygous (-/-) *Taar2-9* cluster knockout mice. Scale bar = 25 μ m ($n \geq 3$).

Supplementary Table 1. List of genome sequences used for VISTA plots. The information of extracted genome sequences from various mammalian species was listed.

Supplementary Table 2. *In situ* analysis in TAAR enhancer 1 knockout mice. Summary of quantification results (the number of sections analyzed, the average number of positive cells per section, percentage of expression, and statistics) for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization experiments. Percentage of expression was calculated by dividing the average number per section of heterozygous or homozygous TAAR enhancer 1 knockout mice by that of wild type littermates. p values were calculated by one-way ANOVA.

Supplementary Table 3. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 1 knockout mice. Summary of quantification results for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization and RNA-seq experiments. Percentage of expression for *in situ* was calculated by dividing the average number per section of

homozygous TAAR enhancer 1 knockout mice by that of wild type littermates. Percentage of expression for RNA-seq (Supplementary Data 1) was displayed on the right column (ratio of homozygous and wild type TAAR enhancer 1 knockout mice). p values were calculated by one-way ANOVA and post-hoc Tukey's test for *in situ*, and by the LRT and Wald test (two-sided) for RNA-seq.

Supplementary Table 4. *In situ* analysis in TAAR enhancer 2 knockout mice. Summary of quantification results (the number of sections analyzed, the average number of positive cells per section, percentage of expression, and statistics) for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization experiments. Percentage of expression was calculated by dividing the average number per section of heterozygous or homozygous TAAR enhancer 2 knockout mice by that of wild type littermates. p values were calculated by one-way ANOVA.

Supplementary Table 5. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 2 knockout mice. Summary of quantification results for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization and RNA-seq experiments. Percentage of expression for *in situ* was calculated by dividing the average number per section of homozygous TAAR enhancer 2 knockout mice by that of wild type littermates. Percentage of expression for RNA-seq (Supplementary Data 1) was displayed on the right column (ratio of homozygous and wild type TAAR enhancer 2 knockout mice). p values were calculated by one-way ANOVA and post-hoc Tukey's test for *in situ*, and by the LRT and Wald test (two-sided) for RNA-seq.

Supplementary Table 6. *In situ* analysis in TAAR enhancer 1 & 2 double knockout mice. Summary of quantification results (the number of sections analyzed, the average number of positive cells per section, percentage of expression, and statistics) for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization experiments. Percentage of

expression was calculated by dividing the average number per section of heterozygous or homozygous TAAR enhancer 1 & 2 double knockout mice by that of wild type littermates. p values were calculated by one-way ANOVA.

Supplementary Table 7. Comparison of *in situ* and RNA-seq analyses in TAAR enhancer 1 & 2 double knockout mice. Summary of quantification results for all of the functional *Taar* genes and 2 representative *OR* genes by *in situ* hybridization and RNA-seq experiments. Percentage of expression for *in situ* was calculated by dividing the average number per section of homozygous TAAR enhancer 1 & 2 double knockout mice by that of wild type littermates. Percentage of expression for RNA-seq (Supplementary Data 1) was displayed on the right column (ratio of homozygous and wild type TAAR enhancer 1 & 2 double knockout mice). p values were calculated by one-way ANOVA and post-hoc Tukey's test for *in situ*, and by the LRT and Wald test (two-sided) for RNA-seq.

Supplementary Table 8. List of *in situ* probes. Summary of probes used for *in situ* analyses of *OR*, *Taar*, and *GFP* mRNA expression. The cross-hybridized genes were listed if the percentage coverage and nucleotide identity were both above 80%.

Supplementary Table 9. List of primers for mouse genotyping and *in situ* probe production. Summary of primers used for mouse genotyping and *in situ* probe production. WT, wild type; KO, knockout; KI, knockin.

Supplementary Table 10. List of plasmid information. Summary of plasmids used for generating sgRNA, spCas9 mRNA, and PiggyBac transposon system.