

孤儿受体GPR88的可能内源性配体的预测

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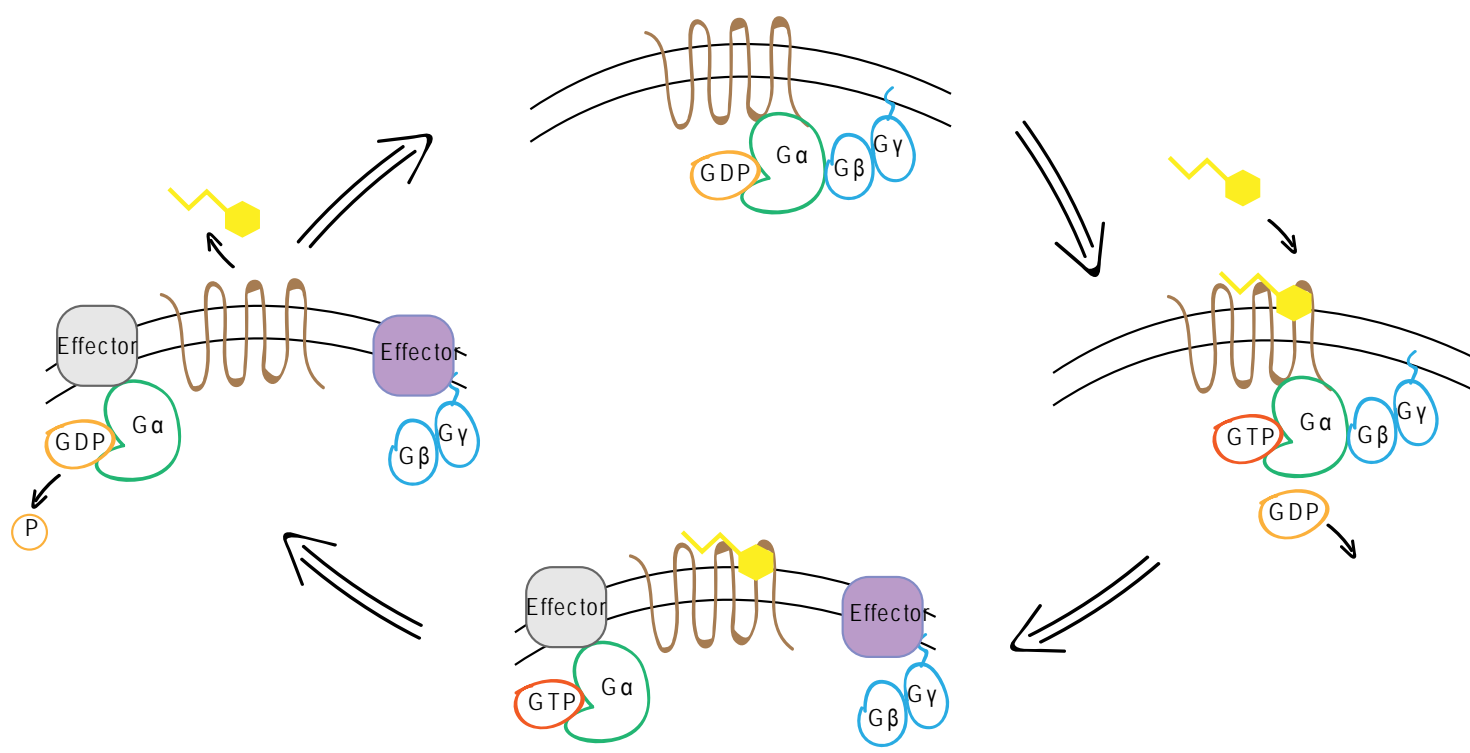
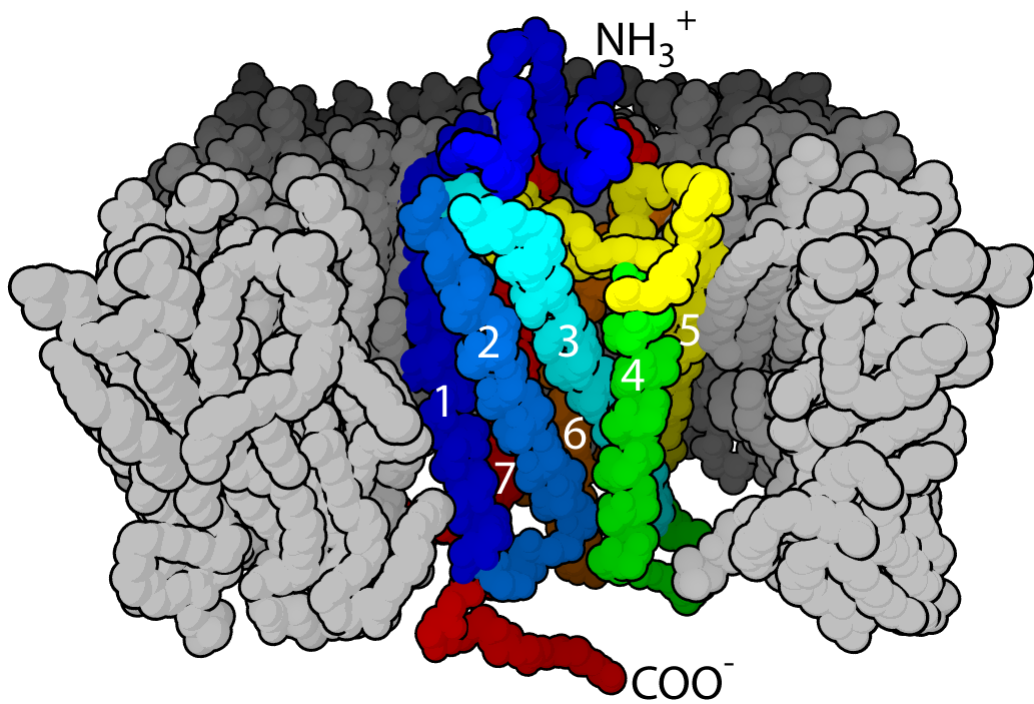
- 背景
 - G-protein coupled receptor (GPCR) 家族介绍
 - 我们为什么会对GPR88感兴趣?
- GPR88的基本信息
 - 进化保守性
 - 基因表达水平
- 可能内源性配体的性质
 - GPR88结构及可能结合位点预测
 - 从已知外源性配体可获得的信息
- 未来可做工作

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G 蛋白偶联受体

- G 蛋白偶联受体 (G Protein-Coupled Receptors, GPCRs)



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GPCRs 分类

- 基于序列结构的 GPCRs 分类
 - GRAFS 系统 – Fredriksson *et al.*
 - 谷氨酸, Glutamate
 - 视紫红质, Rhodopsin
 - 黏附分子, Adhesion
 - 卷曲受体, Frizzled
 - 分泌素, Secretin

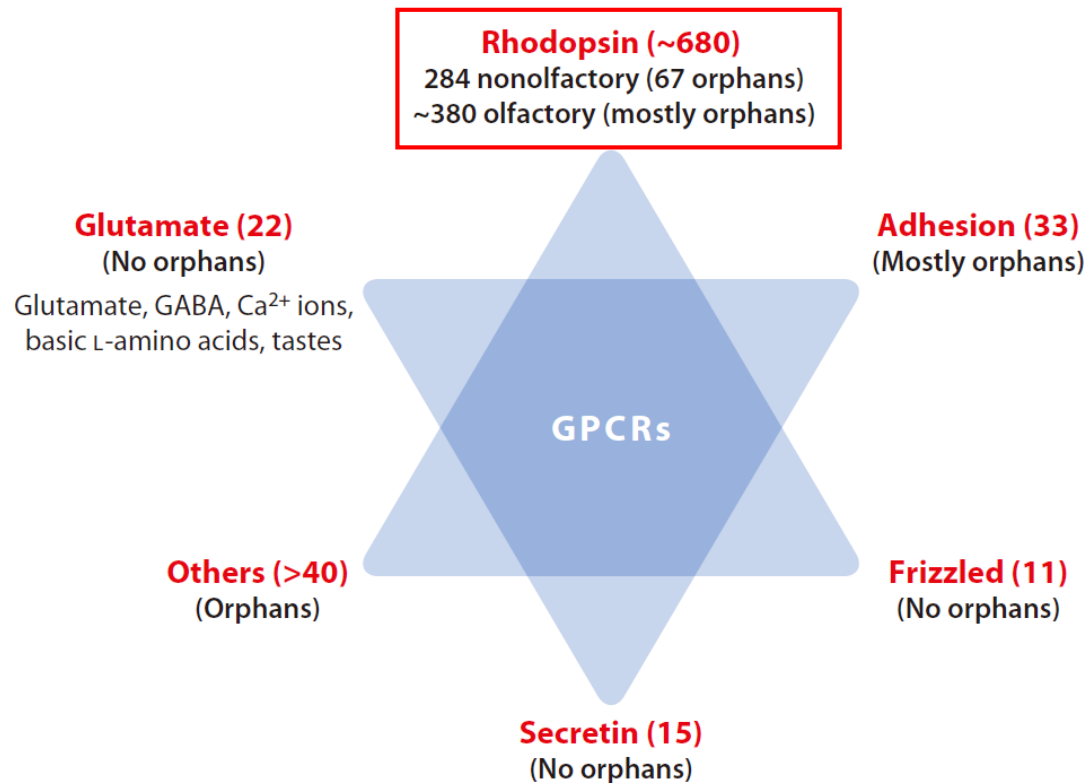
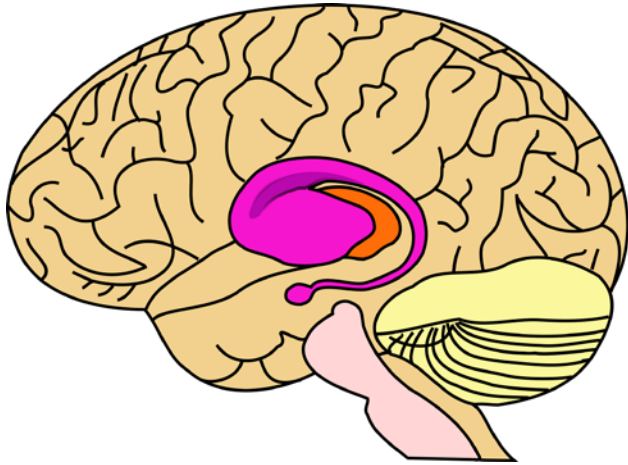


Table 2 The GPCRs of the *Rhodopsin* family and their transmitters

Ligand type	Phylogenetic cluster	Ligands	Number of paired receptors	Number of orphan receptors	Names of orphan receptors
Light	Opsin	Photon	9	3	GPR21, GPR45, GPR52
Amine	Biogenic amine	Acetylcholine, serotonin, adrenaline, noradrenaline, dopamine, histamine, tyramine	37	12	GPR88, GPR152, GPR153, GPR160, GPR162, and seven TAARs
	Melatonin	Melatonin	2	4	GPR50, GPR61, GPR62, GPR135

Civelli *et al.*, 2012, *Annual Reviews*

GPR88高表达在大脑纹状体中



Wikimedia Commons, the free media repository.

- 纹状体具有调节认知、肌肉张力、协调复杂运动的功能
- 临床症状:
 - 自闭症
 - 帕金森
 - 成瘾
 - ...
- 在药物治疗中，GPR88表达量改变
 - 稳定情绪药物（Ogden *et al.*, 2004, Mol. Psychiatry）
 - 抗抑郁药（Conti *et al.*, 2007, Mol. Psychiatry）
 - 治疗成瘾药（Befort *et al.*, 2008, Eur. J. Neurosci.）

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进化保守性

- 物种间

- UniProt

Highlight

Annotation

- Chain
- Natural variant
- Glycosylation
- Topological domain
- Transmembrane**

Amino acid properties

- Similarity
- Hydrophobic
- Negative
- Positive
- Aliphatic
- Tiny
- Aromatic
- Charged
- Small
- Polar
- Big
- Serine Threonine

Q9EPB7	GPR88_MOUSE	1	MTNSSSTSTSTTTGGSLLLLCEEEESWAGRRI PVS	LLYSGLAIGGTLANGMVIYLV	SSFR	
Q9ESP4	GPR88_RAT	1	MTNSSSTSTSTTTGGSLLLLCEEEESWAGRRI PVS	LLYSGLAIGGTLANGMVIYLV	SSFR	
Q9GZNO	GPR88_HUMAN	1	MTNSSSTSTSTTTGGSLLLLCEEEESWAGRRI PVS	LLYSGLAIGGTLANGMVIYLV	SSFR	
*****:*****						
Q9EPB7	GPR88_MOUSE	61	KLQTTSNAFIVNG	CAADLSVCALWMPQEAVLGLL	PSGSAEPPGDWDGGGGSYRLLR	GGLL
Q9ESP4	GPR88_RAT	61	KLQTTSNAFIVNG	CAADLSVCALWMPQEAVLGLL	PAGSAEPPGDWDSGGGGSYRLLR	GGLL
Q9GZNO	GPR88_HUMAN	61	KLQTTSNAFIVNG	CAADLSVCALWMPQEAVLGLL	PTGSAEPPADWDGAGGSYRLLR	GGLL
*****:*****						
Q9EPB7	GPR88_MOUSE	121	GLGLTVSLLSHCLVAL	NRYLLITRAPATYQVLYQRRHT	VGMLALSWALALGLVLLLPWA	
Q9ESP4	GPR88_RAT	121	GLGLTVSLLSHCLVAL	NRYLLITRAPATYQVLYQRRHT	AGMLALSWALALGLVLLLPWA	
Q9GZNO	GPR88_HUMAN	121	GLGLTVSLLSHCLVAL	NRYLLITRAPATYQALYQRRHT	AGMLALSWALALGLVLLLPWA	
*****:*****						
Q9EPB7	GPR88_MOUSE	181	PKPGAEPQVHYPAL	LAAGALLAQTALLLHCYLGIV	RRVRVSVKRVSVLNFHLLHQ	LPGC
Q9ESP4	GPR88_RAT	181	PKPGAEPQVHYPAL	LAAGALLAQTALLLHCYLGIV	RRVRVSVKRVSVLNFHLLHQ	LPGC
Q9GZNO	GPR88_HUMAN	181	PRPGAAPRVHYPAL	LAAAALLAQTALLLHCYLGIV	RRVRVSVKRVSVLNFHLLHQ	LPGC
*:*** **:******:*****						
Q9EPB7	GPR88_MOUSE	241	AAAAAFPAPHPAGPGGAHHPAQ	QPLPAALQPRRAQRRLSGLS	VLLLCVFLLATQPL	
Q9ESP4	GPR88_RAT	241	AAAAAFPAPHPAGGGAHHPAQ	QPLPAALQPRRAQRRLSGLS	VLLLCVFLLATQPL	
Q9GZNO	GPR88_HUMAN	241	AAAAAFPQAHPAGPGGAHHPAQ	QPLPALHPRAQRRLSGLS	VLLLCVFLLATQPL	
*****.* **** ***** **:******						
Q9EPB7	GPR88_MOUSE	301	VWVSLASGFS	LPVPWGVQAASWLLCCALSAL	NPLLYTWRNEEFRRSVRSVLP	PGVDAAAA
Q9ESP4	GPR88_RAT	301	VWVSLASGFS	LPVPWGVQAASWLLCCALSAL	NPLLYTWRNEEFRRSVRSVLP	PGVDAAAA
Q9GZNO	GPR88_HUMAN	301	VWVSLASGFS	LPVPWGVQAASWLLCCALSAL	NPLLYTWRNEEFRRSVRSVLP	PGVDAAAA
*****:*****						
Q9EPB7	GPR88_MOUSE	361	AAAATAVPAMSQAQLGTRAAGQHW			
Q9ESP4	GPR88_RAT	361	AAAATAVPAMSQAQLGTRAAGQHW			
Q9GZNO	GPR88_HUMAN	361	AVAATAVPAVSQAQLGTRAAGQHW			
*.*****:*****						

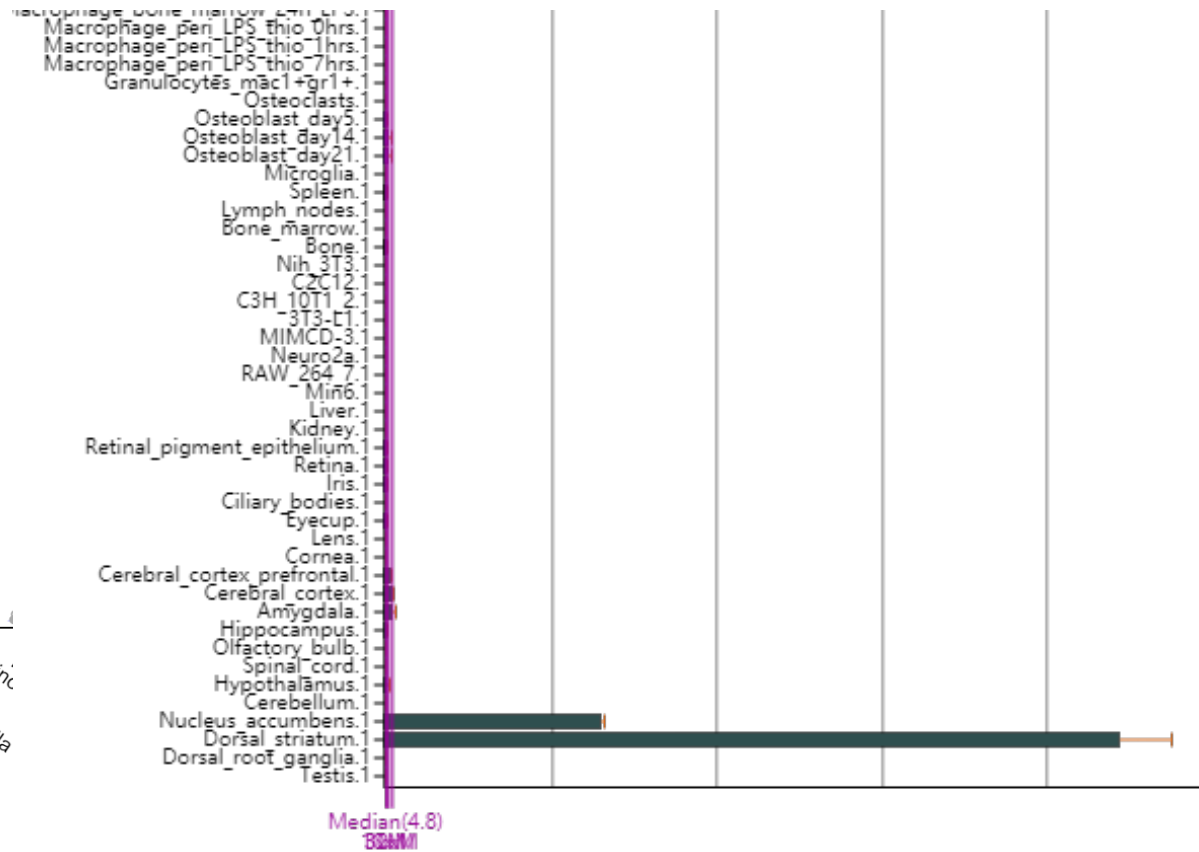
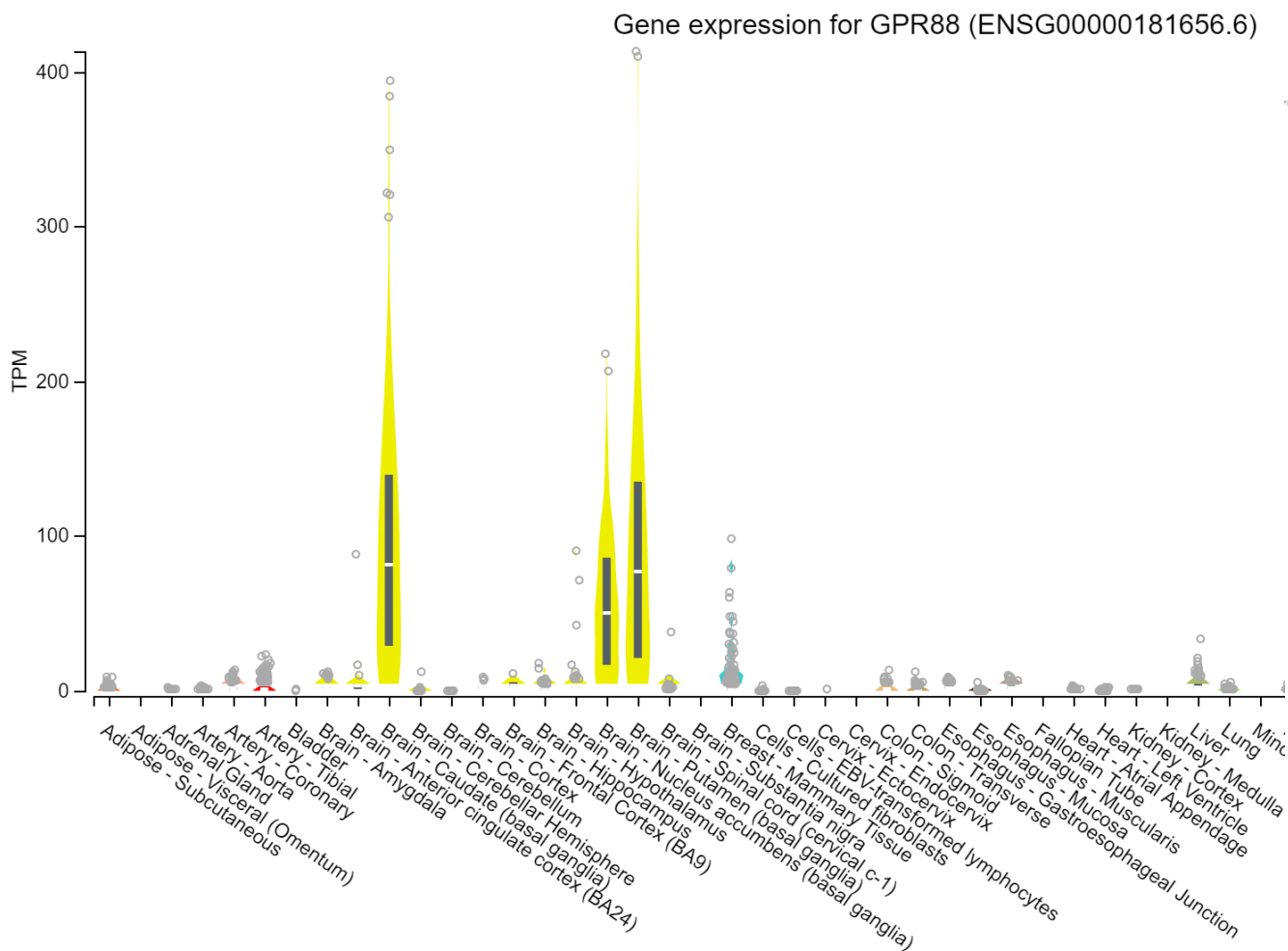
相似度: 95.052%

基因表达水平

- 物种内

• GTEx (人体内基因表达水平)

BioGPS (小鼠体内基因表达水平)



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GPR88结构及可能结合位点的预测

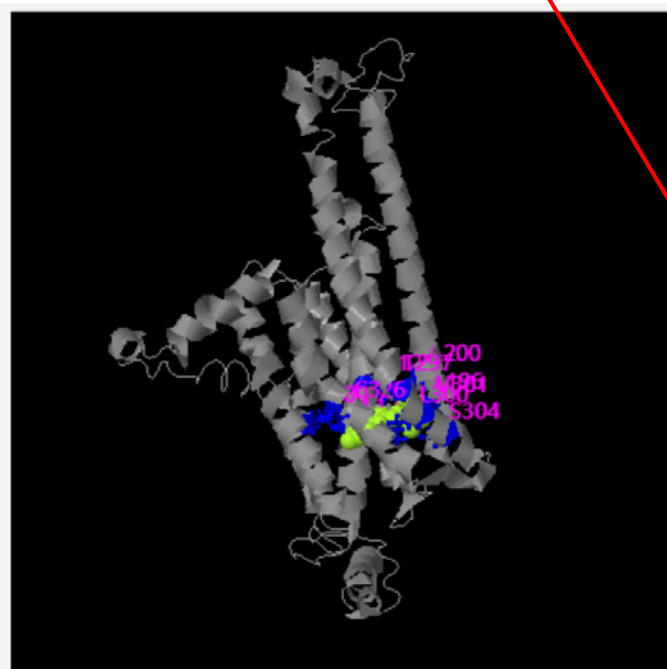
- I-TASSER

Predicted function using [COFACTOR](#) and [COACH](#)

(This section reports biological annotations of the target protein by COFACTOR and COACH based on the I-TASSER structure prediction. While COFACTOR deduces protein functions (ligand-binding sites, EC and GO) using structure comparison and protein-protein networks, COACH is a meta-server approach that combines multiple function annotation results (on ligand-binding sites) from the COFACTOR, TM-SITE and S-SITE programs.)

Ligand binding sites

[Download](#) the residue-specific ligand binding probability, which is estimated by SVM.



Click to view	Rank	C-score	Cluster size	PDB Hit	Lig Name	Download Complex	Ligand Binding Site Residues
<input checked="" type="radio"/>	1	0.15	69	3pxoA	RET	Rep. , Mult	80,120,125,196,200,297,300,301,304,326
<input type="radio"/>	2	0.06	28	2y04A	Y01	Rep. , Mult	68,72,75,122,155,159,162,166
<input type="radio"/>	3	0.05	19	4mbsA	MRV	Rep. , Mult	38,88,91,120,121,124,188,192,193,196,297,300,304,308,318,322,323
<input type="radio"/>	4	0.03	9	2y01A	Y01	Rep. , Mult	57,68,75,119,122,166
<input type="radio"/>	5	0.03	10	2rh1A	CLR	Rep. , Mult	43,47,50,51,82,350

[Download](#) the residue-specific ligand binding probability, which is estimated by SVM.

[Download](#) the all possible binding ligands and detailed prediction summary.

[Download](#) the templates clustering results.

- (a) **C-score** is the confidence score of the prediction. C-score ranges [0-1], where a higher score indicates a more reliable prediction.
 (b) **Cluster size** is the total number of templates in a cluster.
 (c) **Lig Name** is name of possible binding ligand. Click the name to view its information in [the BioLiP database](#).
 (d) **Rep** is a single complex structure with the most representative ligand in the cluster, i.e., the one listed in the **Lig Name** column.
Mult is the complex structures with all potential binding ligands in the cluster.

r=GLY;n=117 :prob=0.132
r=LEU;n=120 :prob=0.839
r=GLY;n=121 :prob=0.822
r=LEU;n=124 :prob=0.764
 r=TYR;n=192 :prob=0.133
 r=PRO;n=193 :prob=0.169
 r=LEU;n=196 :prob=0.306
 r=THR;n=297 :prob=0.220
r=LEU;n=300 :prob=0.825
 r=VAL;n=301 :prob=0.116
r=SER;n=304 :prob=0.749
 r=GLN;n=318 :prob=0.100
 r=TRP;n=322 :prob=0.352
 r=CYS;n=326 :prob=0.139

Reset to initial orientation Spin On/Off

Yang and Zhang, 2015, *Nucleic Acids Research*
 Zhang *et al.*, 2017, *Nucleic Acids Research*

亮氨酸被预测具有较高的结合可能性

- NCBI (blastp) & UniProt

Q9EPB7	GPR88_MOUSE	30	RRIPVSLLYSGLAIGGTLANGMVIYLVSSFRKLQT-TSNAFIVNGCAADLSVCALWMPQE	88
P97718	ADA1A_MOUSE	25	KAILLGVILGGLIIFGVLGNILVILSVACHRHLHS-VTHYYIVNLAVADLLLTSTVLPFS	83
P28334	5HT1B_MOUSE	44	WKVLLVALLALITLATTLSTNAFVIATVYRTRKLHT-PANYLIASLAVTDLLVSILVMPIS	102
P18762	ADRB2_MOUSE	32	WVVGMAILMSVIVLAIIVFGNVLVITAIKFERLQT-VTNYFIIISLACADLVMGLAVVPFG	90
P97288	5HT4R_MOUSE	18	EKVLLTFLAVVILMAILGNLLVMVAVCRDRQLRKIKTNYFIVSLAFADLLVSVLVMPFG	77
Q9R1C8	5HT6R_MOUSE	28	WV---AAALCVVIVLTAANSLLIALICTQPALRN-TSNFFLVSLFTSDLMVGLVVMPPA	83
P97717	ADA1B_MOUSE	44	RAISVG-CLGAFILFAIVGNILVILSVACNRHLRT-PTNYFIVNLAIADLLLSFTDLPFS	101
P34971	ADRB1_MOUSE	57	WTAGMGLLLALIVLLIVVGNVLVIVAIAKTPRLQT-LTNLFIMSLASADLVMGLLVVPFG	115
Q5QD10	TAA7D_MOUSE	46	PRLILYAVFGFGAVLAVCGNLLVMTSILHFRQLHS-PANFLVASLACADFLVGVMVMPFS	104
Q60614	AA2BR_MOUSE	7	-DALYVALELVIAALAVAGNVLVCAAVGASSALQT-PTNYFLVSLATADVAVGLFAIPFA	64
			.* :: : *:. :: : . :*. : :*	
Q9EPB7	GPR88_MOUSE	89	AVLGLLPSGSAEPPGDWDGGGGSYRLLRGGILGLGTVSLLSHCLVALNRYLLITRAPAT	148
P97718	ADA1A_MOUSE	84	AIFEI-----LGYWAFGR-VFCNIWAAVDVLCCTASIMGLCIISIDRYIGVS-YPLR	133
P28334	5HT1B_MOUSE	103	TMYTV-----TGRWTLGQ-VVCDFWLSSDITCCTASIMHLCVIALDRYWAIT-DAVE	152
P18762	ADRB2_MOUSE	91	ASHIL-----MKMWNFGN-FWCFWTSIDVLCVIASIETLCVIAVDRYVAIT-SPFK	140
P97288	5HT4R_MOUSE	78	AIELV-----QDIWAYGE-MFCLVRTSLDVLLTTASIFHLCCISLDRYYAICCQPLV	128
Q9R1C8	5HT6R_MOUSE	84	MLNAL-----YGRWVLAR-GLCLLWTAFDVMCCSASILNLCLISLDRYLLIL-SPLR	133
P97717	ADA1B_MOUSE	102	ATLEV-----LGYWVLGR-IFCDIWAAVDVLCCTASILSLCAISIDRYIGVR-YSLQ	151
P34971	ADRB1_MOUSE	116	ATIVV-----WGRWEYGS-FFCELWTSVDVLCVIASIETLCVIALDRYLAIT-SPFR	165
Q5QD10	TAA7D_MOUSE	105	MVRSV-----EGCWYFGE-SYCKFHSCFEGSFCYSSLFHLCFISVDRYIAVS-DPLT	154
Q60614	AA2BR_MOUSE	65	ITISL-----GFCTDF---HGCFLFACFVLVLTQSSIFSL LAVAVDRYLAIR-VPLR	112
			: . *: :*:** :	

Binding-site probability: □ 0.1 ~ 0.5

□ > 0.5

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可能遇到的困难

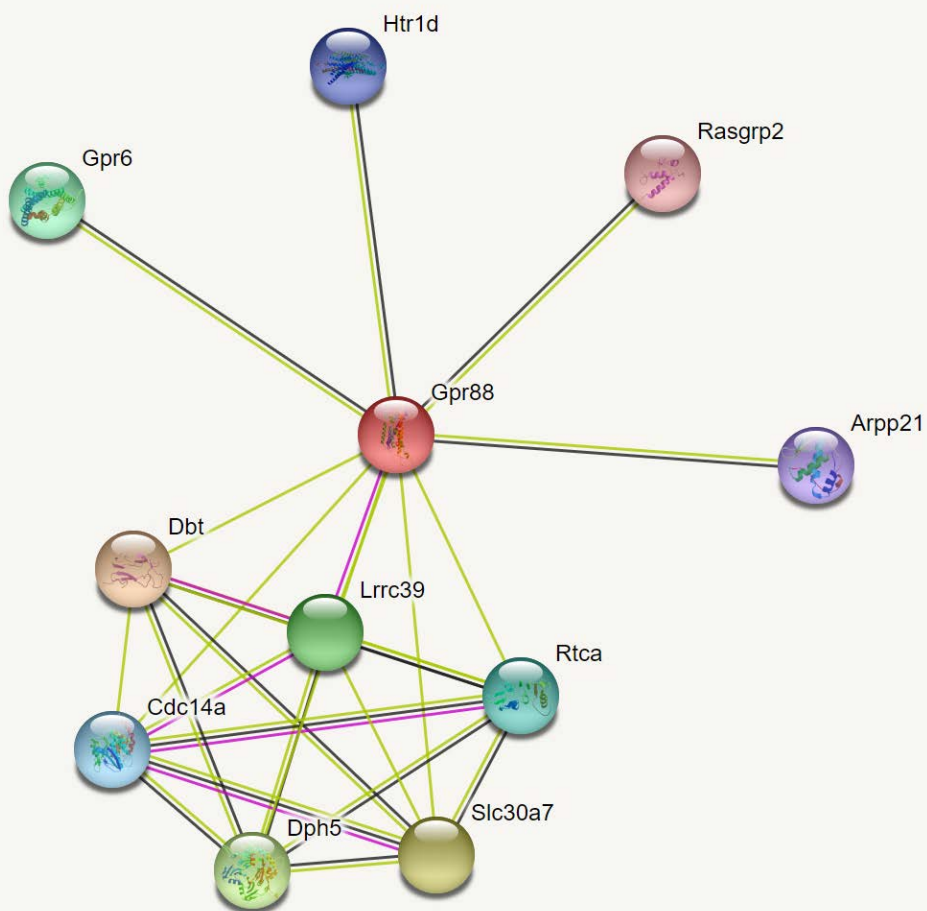
- 内源性配体未知；
- 孤儿受体的激活需要多种配体同时结合；
- 孤儿受体的功能行使，不同于经典模型；
-

Civelli *et al.*, 2012, *Annual Review*

如果我们找不到内源性配体的话... ..

蛋白质互作

- STRING



Known Interactions

- from curated databases
- experimentally determined

Predicted Interactions

- gene neighborhood
- gene fusions
- gene co-occurrence

Others

- textmining
- co-expression
- protein homology

Your Input:

Gpr88






Probable G-protein coupled receptor 88; Probable G-protein coupled receptor implicated in a large repertoire of behavioral responses that engage motor activities, spatial learning, and emotional processing. May play a role in the regulation of cognitive and motor function (384 aa)

Predicted Functional Partners:

- Dbt Dihydrolipoamide branched chain transacylase E2; The branched-chain alpha-keto dehydrogenase complex catalyzes the over...
- Slc30a7 Zinc transporter 7; Seems to facilitate zinc transport from the cytoplasm into the Golgi apparatus. Partly regulates cellular zinc...
- Dph5 Diphthine methyl ester synthase; S-adenosyl-L-methionine-dependent methyltransferase that catalyzes four methylations of th...
- Lrrc39 Leucine-rich repeat-containing protein 39; Component of the sarcomeric M-band which plays a role in myocyte response to bio...
- Gpr6 G-protein coupled receptor 6; Orphan receptor with constitutive G(s) signaling activity that activate cyclic AMP. Promotes neuro...
- Rtca RNA 3'-terminal phosphate cyclase; Catalyzes the conversion of 3'-phosphate to a 2',3'- cyclic phosphodiester at the end of RN...
- Cdc14a Dual specificity protein phosphatase CDC14A; Dual-specificity phosphatase. Required for centrosome separation and producti...
- Htr1d 5-hydroxytryptamine receptor 1D; G-protein coupled receptor for 5-hydroxytryptamine (serotonin). Also functions as a receptor...
- Arpp21 Cyclic AMP-regulated phosphoprotein, 21 (789 aa)
- Rasgrp2 RAS guanyl-releasing protein 2; Functions as a calcium- and DAG-regulated nucleotide exchange factor specifically activating ...

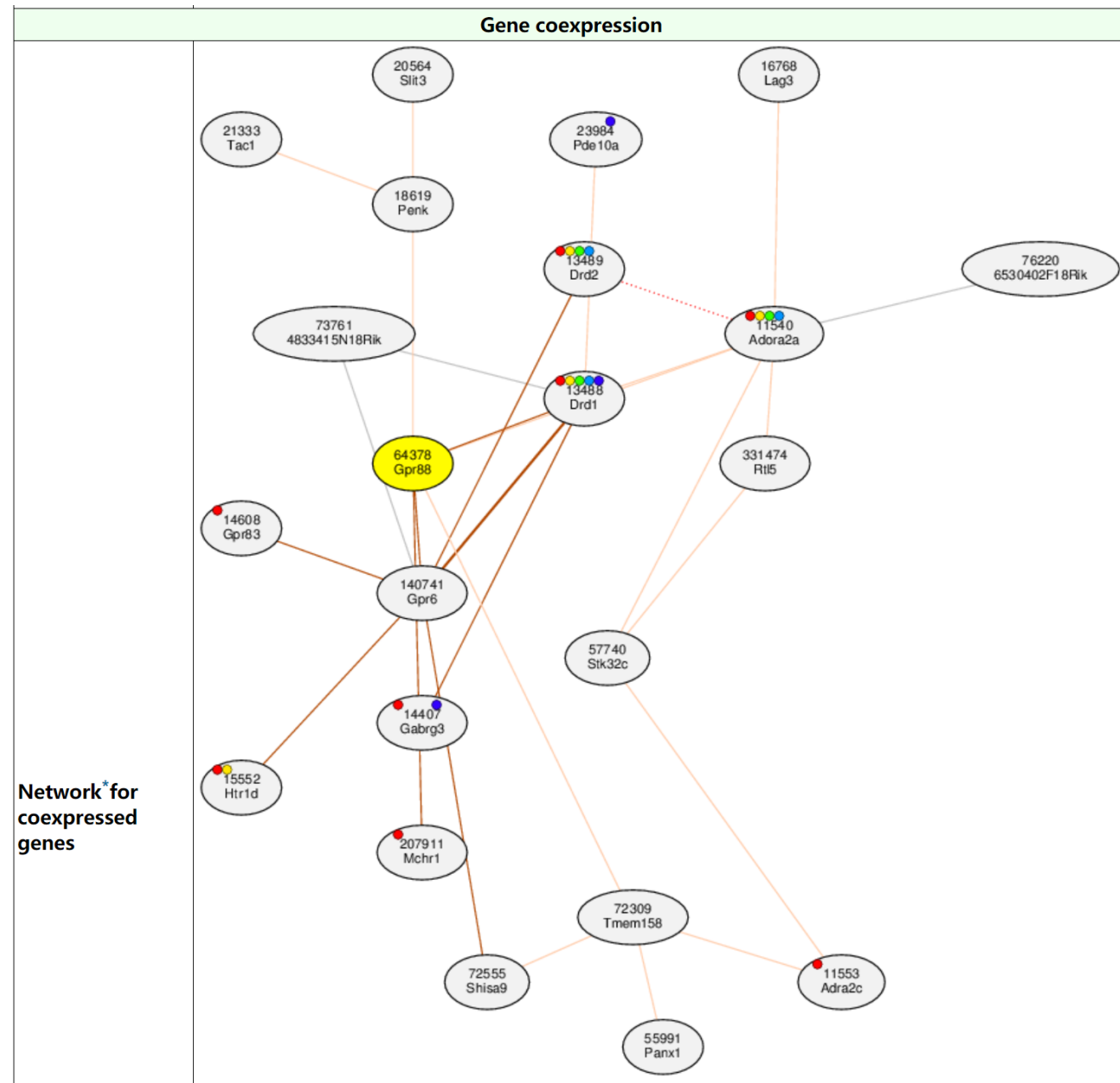
基因共表达

- COPRESdb

KEGG* ID	Title	#genes	Link to the KEGG* map (Multiple genes)
mmu04080	Neuroactive ligand-receptor interaction	8	
mmu04024	cAMP signaling pathway	4	
mmu05012	Parkinson's disease	3	
mmu05034	Alcoholism	3	
mmu05032	Morphine addiction	3	

Genes directly connected with Gpr88 on the network

MR*	Locus	Fuction*	Coexpression detail	Entrez Gene ID*
457.8	Gpr6	G protein-coupled receptor 6	[detail]	140741
524.1	Drd1	dopamine receptor D1	[detail]	13488
1323.2	Mchr1	melanin-concentrating hormone receptor 1	[detail]	207911
1801.9	Adora2a	adenosine A2a receptor	[detail]	11540
2455.4	Penk	preproenkephalin	[detail]	18619
2484.4	Tmem158	transmembrane protein 158	[detail]	72309



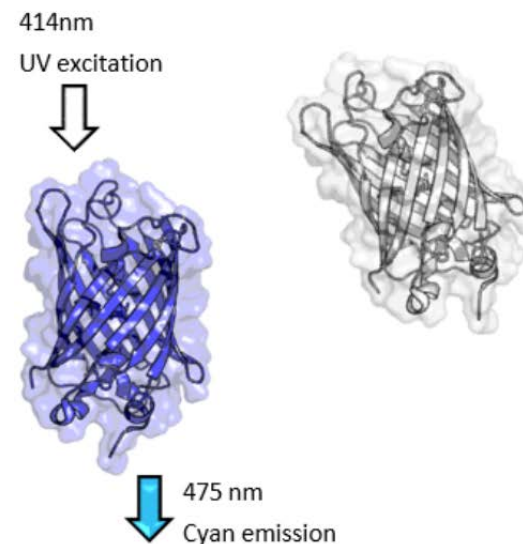
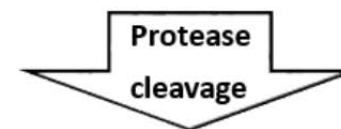
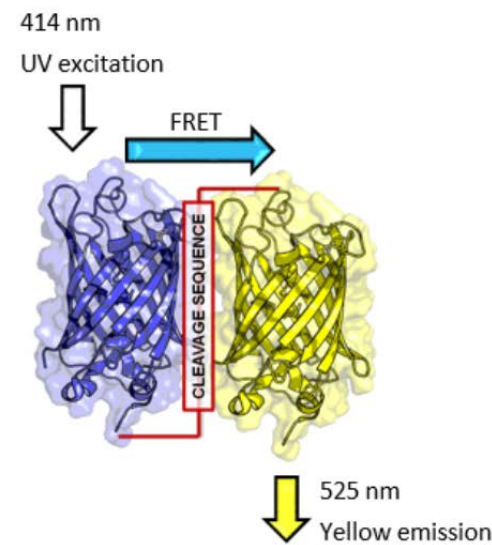
未来实验工作

- 蛋白互作

- FRET (Fluorescence Resonance Energy Transfer)
- ...

- 基因共表达

- 免疫荧光 (Immunofluorescence)
- ...



致谢

感谢罗静初老师的指导
感谢小组成员的努力
感谢听取报告的同学

Thanks!
Q & A