

Electronic supplementary information (ESI)

The coordinated expression, interaction and evolution of the neuroendocrine genes.

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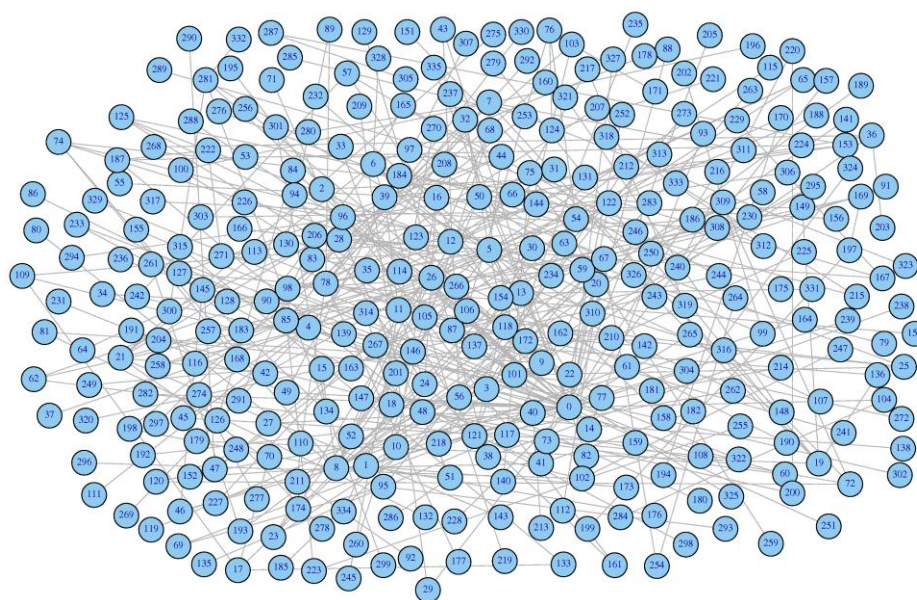


Fig. S1: The Barabasi-Albert (BA) network generated randomly for comparison with the real network.

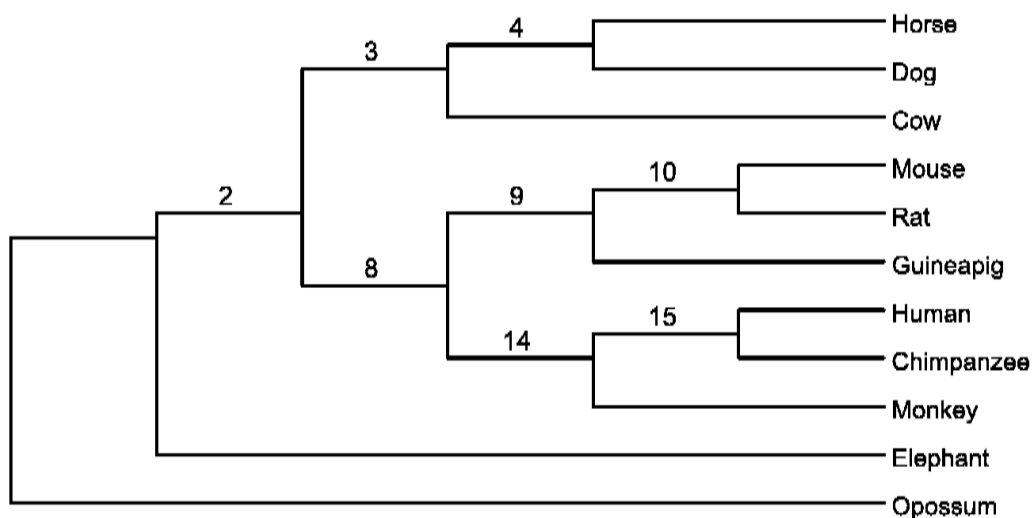


Fig. S2: The phylogenetic tree showing relationship among species used for evolutionary studies. Numbers indicate the number of respective internal node.

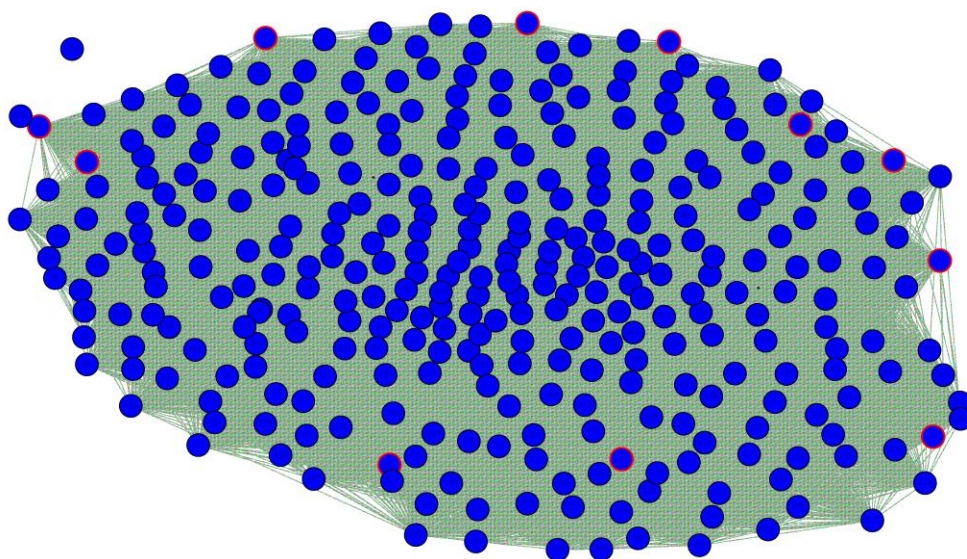


Fig. S3: Gene coexpression network of the neuroendocrine genes. Neuroendocrine genes are circled in red color.

Table S1: Spearman rank correlation between neuroendocrine genes.

Gene pair	Spearman correlation coefficient (ρ)	P- value
<i>GnRH-GnIH</i>	0.49	4.36×10^{-11}
<i>PDYN-TAC3</i>	0.72	2.2×10^{-16}
<i>GnRH-KISS1</i>	0.40	1.58×10^{-7}
<i>GnRH-PDYN</i>	0.38	7.17×10^{-7}
<i>GnIH-PDYN</i>	0.42	3.72×10^{-8}
<i>GnRH-TAC3</i>	0.36	4.01×10^{-6}
<i>GnIH-TAC3</i>	0.52	3.52×10^{-12}
<i>GnIH-KISS1</i>	0.49	5.70×10^{-11}
<i>PDYN-KISS1</i>	0.58	8.92×10^{-16}
<i>TAC3-KISS1</i>	0.78	2.20×10^{-16}
<i>GHRH-SST</i>	0.54	2.70×10^{-13}
<i>GHRH-GnRH</i>	0.38	7.16×10^{-7}
<i>GHRH-GnIH</i>	0.35	6.20×10^{-6}
<i>SST-GnRH</i>	0.33	2.44×10^{-5}
<i>SST-GnIH</i>	0.36	3.55×10^{-6}
<i>GHRH-TAC3</i>	0.64	2.20×10^{-16}
<i>GHRH-PDYN</i>	0.51	5.86×10^{-16}
<i>SST-INS</i>	0.74	2.20×10^{-16}
<i>SST-TAC3</i>	0.78	2.20×10^{-16}
<i>SST-PDYN</i>	0.71	2.20×10^{-16}
<i>CALCA-PTH</i>	0.44	8.34×10^{-9}
<i>INS-GCG</i>	0.77	2.20×10^{-16}
<i>CALCA-INS</i>	0.74	2.20×10^{-16}
<i>CALCA-GCG</i>	0.61	2.20×10^{-16}

<i>PTH-INS</i>	0.43	1.30×10^{-8}
<i>PTH-GCG</i>	0.43	1.56×10^{-8}

Table S2: Genomic locations of neuroendocrine genes in human

Gene	Accession number	Genomic location	Strand
Gonadotropin- releasing hormone (<i>GNRH1</i>)	ENSG00000147437	8: 25276776-25282170	Reverse
Gonadotropin- releasing hormone (<i>GNIH/NPVF</i>)	ENSG00000105954	7: 25264189-25268105	Reverse
Kisspeptin (<i>KISS1</i>)	ENSG00000170498	1: 204159469-204165614	Reverse
Tachykinin3 (<i>TAC3</i>)	ENSG00000166863	12: 57403784-57422667	Reverse
Prodynorphin (<i>PDYN</i>)	ENSG00000101327	20: 1959403-1974732	Reverse
Growth hormone releasing hormone (<i>GHRH</i>)	ENSG00000118702	20: 35879489-35890238	Reverse
Somatostatin (<i>SST</i>)	ENSG00000157005	3: 187386694-187388187	Reverse
Parathormone (<i>PTH</i>)	ENSG00000152266	11: 13513602-13517728	Reverse
Calcitonin (<i>CALCA</i>)	ENSG00000110680	11: 14988214-14993900	Reverse
Insulin (<i>INS</i>)	ENSG00000254647	11: 2181009-2182571	Reverse
Glucagon (<i>GCG</i>)	ENSG00000115263	2: 162999392-163008914	Reverse

Table S3: A comparative account of the degree between neuroendocrine genes. The degree of nodes in a randomly generated scale-free Barabasi-Albert (BA) network is given for comparison. Numbers in parentheses indicate the number of node for the gene in the neuroendocrine network.

Gene pair	Degree of nodes in real network		Difference	Degree of nodes in BA network		Difference
	Node1	Node 2		Node 1	Node 2	
<i>GnRH(0)-GnIH(1)</i>	173	161	1.07	38	7	5.43
<i>PDYN(3)-TAC3(4)</i>	201	190	1.06	2	4	2.00
<i>GnRH(0)-KISS1(5)</i>	173	176	1.02	38	11	3.45
<i>GnRH(0)-PDYN(3)</i>	173	201	1.16	38	2	19.00
<i>GnIH(1)-PDYN(3)</i>	161	201	1.24	7	2	3.50
<i>GnRH(0)-TAC3(4)</i>	173	190	1.09	38	4	9.50
<i>GnIH(1)-TAC3(4)</i>	161	190	1.18	7	4	1.75
<i>GnIH(1)-KISS1(5)</i>	161	176	1.09	7	11	1.57
<i>PDYN(3)-KISS1(5)</i>	201	176	1.14	2	11	5.50
<i>TAC3(3)-KISS1(5)</i>	190	176	1.08	4	11	2.75
<i>GHRH(6)-SST(7)</i>	190	170	1.12	22	10	2.20
<i>GHRH(6)-GnRH(0)</i>	190	173	1.10	22	38	1.73
<i>GHRH(6)-GnIH(1)</i>	190	161	1.18	22	7	3.14
<i>SST(7)-GnRH(0)</i>	170	173	1.02	10	38	3.80
<i>SST(7)-GnIH(1)</i>	170	161	1.05	10	7	1.43
<i>GHRH(6)-TAC3(4)</i>	190	190	1.00	22	4	5.50
<i>GHRH(6)-PDYN(3)</i>	190	201	1.06	22	2	11
<i>SST(7)-INS(10)</i>	170	189	1.11	10	7	1.43
<i>SST(7)-TAC3(4)</i>	170	190	1.12	10	4	2.5
<i>SST(7)-PDYN(3)</i>	170	201	1.18	10	2	5

<i>CALCA(8)-PTH(9)</i>	180	174	1.03	6	16	2.66
<i>INS(10)-GCG(11)</i>	189	188	1.01	7	2	3.50
<i>CALCA(8)-INS(10)</i>	180	189	1.05	6	7	1.17
<i>CALCA(8)-GCG(11)</i>	180	188	1.04	6	2	3.00
<i>PTH(9)-INS(10)</i>	174	189	1.09	16	7	2.29
<i>PTH(9)-GCG(11)</i>	174	188	1.08	16	2	8.00

Table S4: A comparison of clustering coefficients between the neuroendocrine genes.

Gene pair	Clustering Coefficient of gene1	Clustering Coefficient of gene 2	Difference
<i>GnRH-GnIH</i>	0.85	0.87	1.02
<i>PDYN-TAC3</i>	0.87	0.87	1.00
<i>GnRH-KISS1</i>	0.85	0.91	1.07
<i>GnRH-PDYN</i>	0.85	0.87	1.02
<i>GnIH-PDYN</i>	0.87	0.87	1.00
<i>GnRH-TAC3</i>	0.85	0.87	1.02
<i>GnIH-TAC3</i>	0.87	0.87	1.00
<i>GnIH-KISS1</i>	0.87	0.91	1.04
<i>PDYN-KISS1</i>	0.87	0.91	1.04
<i>TAC3-KISS1</i>	0.87	0.91	1.04
<i>GHRH-SST</i>	0.87	0.89	1.02
<i>GHRH-GnRH</i>	0.87	0.85	1.02
<i>GHRH-GnIH</i>	0.87	0.87	1.00
<i>SST-GnRH</i>	0.89	0.85	1.05
<i>SST-GnIH</i>	0.89	0.87	1.02
<i>GHRH-TAC3</i>	0.87	0.87	1.00
<i>GHRH-PDYN</i>	0.87	0.87	1.00
<i>SST-INS</i>	0.89	0.87	1.02
<i>SST-TAC3</i>	0.89	0.87	1.02
<i>SST-PDYN</i>	0.89	0.87	1.02
<i>CALCA-PTH</i>	0.89	0.85	1.04
<i>INS-GCG</i>	0.87	0.88	1.01
<i>CALCA-INS</i>	0.89	0.87	1.02
<i>CALCA-GCG</i>	0.89	0.88	1.01

<i>PTH-INS</i>	0.85	0.87	1.02
<i>PTH-GCG</i>	0.85	0.88	1.04

Table S5: A comparison of geodesic distance and Jaccard similarity index between the neuroendocrine genes.

Gene pair	Geodesic distance	Jaccard similarity
<i>GnRH-GnIH</i>	0.00140	0.53
<i>PDYN-TAC3</i>	0.00229	0.66
<i>GnRH-KISS1</i>	0.00290	0.49
<i>GnRH-PDYN</i>	0.00153	0.41
<i>GnIH-PDYN</i>	0.00171	0.38
<i>GnRH-TAC3</i>	0.00267	0.35
<i>GnIH-TAC3</i>	0.00253	0.32
<i>GnIH-KISS1</i>	0.00274	0.50
<i>PDYN-KISS1</i>	0.00327	0.50
<i>TAC3-KISS1</i>	0.00347	0.50
<i>GHRH-SST</i>	0.00089	0.49
<i>CALCA-PTH</i>	0.00095	0.59
<i>INS-GCG</i>	0.00133	0.65
<i>CALCA-INS</i>	0.00088	0.50
<i>CALCA-GCG</i>	0.00082	0.57
<i>PTH-INS</i>	0.00136	0.50
<i>PTH-GCG</i>	0.00089	0.52

Table S6: A comparison of closeness and Burt's constraint between the neuroendocrine genes.

Gene pair	Closeness (a measure of Centrality) of a node		Difference	Burt's constraint		Difference
	Node 1	Node 2		Node 1	Node 2	
	<i>GnRH-GnIH</i>	0.67		0.66	1.01	
<i>PDYN-TAC3</i>	0.72	0.70	1.02	0.023	0.025	1.08
<i>GnRH-KISS1</i>	0.67	0.68	1.01	0.024	0.026	1.08
<i>GnRH-PDYN</i>	0.67	0.72	1.07	0.024	0.023	1.04
<i>GnIH-PDYN</i>	0.66	0.72	1.09	0.027	0.023	1.17
<i>GnRH-TAC3</i>	0.67	0.70	1.04	0.024	0.025	1.04
<i>GnIH-TAC3</i>	0.66	0.70	1.06	0.027	0.025	1.08
<i>GnIH-KISS1</i>	0.66	0.68	1.03	0.027	0.026	1.03
<i>PDYN-KISS1</i>	0.72	0.68	1.05	0.023	0.026	1.13
<i>TAC3-KISS1</i>	0.70	0.68	1.02	0.025	0.026	1.04
<i>GHRH-SST</i>	0.70	0.67	1.04	0.026	0.036	1.38
<i>CALCA-PTH</i>	0.68	0.68	1.00	0.027	0.026	1.03
<i>INS-GCG</i>	0.70	0.70	1.00	0.026	0.026	1.00
<i>CALCA-INS</i>	0.68	0.70	1.02	0.027	0.026	1.03
<i>CALCA-GCG</i>	0.68	0.70	1.02	0.027	0.026	1.03
<i>PTH-INS</i>	0.68	0.70	1.02	0.026	0.026	1.00
<i>PTH-GCG</i>	0.68	0.70	1.02	0.026	0.026	1.00

Table S7: Accession numbers of the gene sequences used in the study. All sequences are collected from the Ensembl database except three highlighted sequences which are collected from the NCBI Reference sequence.

Species	<i>GnRH</i>	<i>GnIH</i>	<i>TAC3</i>	<i>PDYN</i>	<i>GHRH</i>	<i>SST</i>	<i>PTH</i>
Human	ENSG 00000147437	ENSG 00000105954	ENSG 00000166863	ENSG 00000101327	ENSG 00000118702	ENSG 00000157005	ENSG 00000152266
Chimpanzee	ENSPTRG 00000020091	ENSPTRG 00000018998	ENSPTRG 00000005117	ENSPTRG 00000013172	ENSPTRG 00000013472	ENSPTRG 00000015727	ENSPTRG 00000003379
Monkey	ENSMMUG 00000029018	ENSMMUG 00000008369	ENSMMUG 00000003203	ENSMMUG 00000009984	ENSMMUG 00000031295	ENSMMUG 00000000850	ENSMMUG 00000007017
Cow	ENSBTAG 00000000164	ENSBTAG 00000019447	ENSBTAG 00000021807	ENSBTAG 00000034258	ENSBTAG 00000012710	ENSBTAG 00000017312	ENSBTAG 00000019080
Elephant	ENSLAFG 00000003526	ENSLAFG 00000008838	ENSLAFG 00000017982	ENSLAFG 00000012785	ENSLAFG 00000016485	ENSLAFG 00000012303	ENSLAFG 00000028790
Horse	ENSECAG 00000010664	ENSECAG 00000021063	XM_0014884 15.2	ENSECAG 00000007241	ENSECAG 00000011318	ENSECAG 00000023368	ENSECAG 00000019608
Dog	ENSCAFG 00000008985	ENSCAFG 00000002863	ENSCAFG 00000000155	ENSCAFG 00000006748	ENSCAFG 00000008743	ENSCAFG 00000013891	ENSCAFG 00000008177
Guinea Pig	ENSCPOG 00000015538	ENSCPOG 00000013784	ENSCPOG 00000012924	ENSCPOG 00000024291	ENSCPOG 00000020252	ENSCPOG 00000009662	ENSCPOG 00000003894
Mouse	ENSMUSG 00000015812	ENSMUSG 00000029831	ENSMUSG 00000025400	ENSMUSG 00000027400	ENSMUSG 00000027643	ENSMUSG 00000004366	ENSMUSG 00000059077
Rat	ENSRNOG 00000013441	ENSRNOG 00000010806	ENSRNOG 00000004229	ENSRNOG 00000026036	ENSRNOG 00000007782	ENSRNOG 00000001837	ENSRNOG 00000014318
Opossum	ENSMODG 00000016713	ENSMODG 00000000610	ENSMODG 00000019398	ENSMODG 00000013953	XM_001381707.1	ENSMODG 00000008503	ENSMODG 00000008738

Table S7 continued.

Species	CALCA	INS	GCG				
Human	ENSG 00000110680	ENSG 00000254647	ENSG 00000115263				
Chimpanzee	ENSPTRG 00000033390	ENSPTRG 00000003172	ENSPTRG 00000012580				
Monkey	ENSMMUG 00000020245	ENSMMUG 00000031267	ENSMMUG 00000003198				
Cow	ENSBTAG 00000027735	ENSBTAG 00000013003	ENSBTAG 00000000730				
Elephant	ENSLAFG 00000003276	ENSLAFG 00000020914	ENSLAFG 00000005647				
Horse	ENSECAG 00000008818	ENSECAG 00000024609	ENSECAG 00000005660				
Dog	ENSCAFG 00000008546	ENSCAFG 00000010092	ENSCAFG 00000010414				
Guinea Pig	ENSCPOG 00000009939	ENSCPOG 00000008198	ENSCPOG 00000024193				
Mouse	ENSMUSG 00000030666	ENSMUSG 00000035804	ENSMUSG 00000000394				
Rat	ENSRNOG 00000011074	ENSRNOG 00000012052	ENSRNOG 00000005498				
Opossum	ENSMODG 00000007251	P18109.1	ENSMODG 00000005566				