

Supplementary Table 9A. TF binding sites that correspond to *ab initio*-predicted motifs derived from the Penk family promoter regions.

Motif no.	Motif Occurrence	Motif	TF binding sites
1	3	CCAGTAACCTGCG	FXR:RXR-alpha, LXR-alpha:RXR-alpha, LXR-beta:RXR-alpha, ERRalpha1
2	3	TATAAAGTGGCTGT	<u>TFIID</u> , <u>TBP</u>
3	3	GATCTAAAGAAGAAA	AR, GR
4	3	CCAAGTCCGTC	SF-1, GR
5	3	TTAAGATCCCCA	<u>NF-kappaB1</u> , <u>NF-kappaB2</u> , <u>NF-kappaB2 precursor</u> , <u>AP-2alpha</u> , <u>AP-2alphaA</u>
6	3	GTGATDCAGGA	<u>AP-1</u> , c-Fos, c-Jun, JunD
7	3	TCCAGVAAGDH	c-Ets-1, Elk-1, SAP-1a, SAP-1b, SRF, PEA3, ELF-1
8	3	CAGGCGTCGGCGCG	DREB1A, ZF5, E2F
9	3	CGATTGGGGCGCGC	<u>NFI/CTF</u> , <u>CTF</u> , <u>NF-Y</u>
10	3	CCAGAVAGGCAG	UBP-1, GATA-1, GATA-3, Meis-1a, Meis-1b, GATA-4, RXR-beta, VDR, MOT3
11	3	CCGGTCTCTA	Unknown
12	3	AGCCCGTGBC	USF-1, USF1, USF2, USF2b, USF, HMBP, EmBP-1a
13	3	GTGACTTTGCCCA	DSF, GCN4, COUP-TF1, RAR-beta, RXR-alpha, RAR-alpha1, TLX, Pax-2.1, Pax-2.2, IRF-4, IRF-8, AP-2alpha, AP-2alphaA, C/EBPgamma, PPAR-gamma:RXR-alpha, VDR, LXR-alpha:RXR-alpha
14	3	GATCTGTBTT	Sox2, Meis-1a, Meis-1b, GR
15	3	TGAAATTTGG	Unknown
16	3	GCTGTGGGGACGTCC	AML1, AML1a, AML1c, <u>MZF1</u> , MIG1, <u>MZF-1</u> , <u>AP-2alpha</u> , <u>AP-2alphaA</u> , MBP-1, <u>NF-kappaB1</u> , <u>NF-kappaB2</u> , <u>NF-kappaB2 precursor</u>
17	3	BHHCAAGAGGA	Unknown
18	3	GGAAGGGGCAG	VDR, LXR-alpha:RXR-alpha, CAC-binding protein, NF-E2, PPAR-gamma:RXR-alpha, Sp1
19	3	AHGCCCCAACC	Sp1, PPAR-gamma:RXR-alpha, VDR, LXR-alpha:RXR-alpha, AP-2alphaA, ADR1 C/EBPalpha, C/EBPbeta
20	3	GGACAGGATG	Meis-1a, Meis-1b, Elk-1, SAP-1a, SAP-1b, SRF, E47, Fli-1, Net, TCF

All motifs were detected in mouse, rat and human sequences. The underlined TF binding sites are known to bind TFs in the proenkephalin promoter region [24][25][26][27]. The species abbreviations are Hs: *Homo sapiens*; Mm: *Mus musculus*; Rn: *Rattus norvegicus*. Unknown: motif does not match any of the TRANSFAC-listed TF binding sites.

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25. Kobierski LA, Wong AE, Srivastava S, Borsook D, Hyman SE. **Cyclic AMP-dependent activation of the proenkephalin gene requires phosphorylation of CREB at serine-133 and a Src-related kinase.** *J Neurochem* 1999, **73**: 129-138.
26. Fu W, Shah SR, Jiang H, Hilt DC, Dave HP, et al. **Transactivation of proenkephalin gene by HTLV-1 tax1 protein in glial cells: involvement of Fos/Jun complex at an AP-1 element in the proenkephalin gene promoter.** *J Neurovirol* 1997, **3**: 16-27.
27. Le Y, Gagneten S, Larson T, Santha E, Dobi A, et al. **Far-upstream elements are dispensable for tissue-specific proenkephalin expression using a Cre-mediated knock-in strategy.** *J Neurochem* 2003, **84**: 689-697.

Supplementary Table 9B. Motif arrangements in promoter region in mouse (4922504O09), human (HIX0007519.2) and rat (NM_017139) of Penk family members. The species abbreviations are Hs: *Homo sapiens*; Mm: *Mus musculus*; Rn: *Rattus norvegicus*.

Species	Motif arrangement
Hs,Rn	3-5-15-18-4-16-8-9-2-10-1-13
Mm, Hs	7-12-3-5-1-13
Hs, Rn	3-5-1-13-20
Mm, Hs, Rn	3-5-1-13