

**Supplementary Table 1:** Distribution of plesiomorphic bilaterian neuropeptides and neuropeptide receptors in xenacoelomorphs.

	Xboc	Xpro	Asc	Nwe s	Msti	Ste	Dgy m	Dlon	Hmia	Ipul	Ema c	Csub	Cma c
Bursicon/GlyHo*										( P )			
Bursicon B*	P												
GlyHo A*	P	P		2xP									
GlyHo B*	P	P											
ILP*	P	2xP	23xP	3xP	P		P						
Prokineticin	2xP			R P	P								
Achatin	P	P		R P	R P			R					
Vasotocin	R P	R P	R P										
GnRH	R P	R P	P	4xP	P	P							
NpY/F				R1,2 3xP	R1								
t-FMRFa	R			R	3xR		R						
Tachykinin	R			R2			R1,2	R1,2	2x R2	R1		R2	R1,2
Luqin	R			R					R				
Allatotropin	R			R	R		3xR	2xR	R				
Leucokinin	R			R									
Sulfakinin	2xR			3xR				R					
TRH				R1,2	R1,2								
ETH				R	R								
CCHa					R								
NpS										R		R	R
e-FMRFa/MIP							R						
Asta-A	R			R					2xR			R	R
MCH			R	2xR	R		R		3xR				R
Calcitonin	2xR P	3xR	P	2xR P	R 2xP	2xP							
CRF	R	2xR		2xR	R								
PDF	R			4xR	R								
PTH	R												

R = receptor, P = Peptide. A number before “R/P” indicates number of similar sequences, while a number behind “R” indicates separated groups of xenacoelomorph sequences in this bilaterian receptor group. Brackets indicate that this sequence shows great divergence. The asterisks indicates that we only tested for the presence of peptides, but not receptors (as these receptors are also known from non-bilaterian).

**Supplementary Table 2:** Distribution of novel neuropeptides in xenacoelomorphs and number of detected precursors.

	Xboc	Xpro	Asc	Nwe s	Msti	Ste	Dgy m	Dlon	Hmia	Ipul	Ema c	Csub	Cma c
SFNa	1	1	1	3			1					1	
LxFa	1			1			3	1	1	2		1	
PxFVa	1			2									
AWDF				1			1	1	1*	1		1	1*
LWDY				1				1		2		1	1*
FxxxFa			1				1	1		1*		1	1
FNMa							1	1				1	
MRF										1	1	1	
SSxxxF										1*	1		3*
MxGFG							1	1	2*	1*	1		1*
LRIGa			1	3		1							
ELa			1	2		1							
WDLa			1	1	1	1							
LRFDIa	1	1											

The asterisks indicates that at least one of the processed peptides from this precursors was detected by mass spectrometry.

**Supplementary Table 3:** Affinity of xenacoelomorph GPCRs to protostome and deuterostome sequences of the corresponding receptor types in the RAxML and FastTree sequence analysis.

Receptors	RAxML	FastTree
<i>Prokineticin</i>	Deuterostome	Deuterostome
<i>Np-F/Np-Y/PRP 1</i>	Protostome (Np-F)	Protostome (Np-F)
<i>Np-F/Np-Y/PRP 2</i>	Deuterostome (PRP)	Deuterostome (PRP)
<i>Leucokinin</i>	Both	Both
<i>Lugin</i>	Deuterostome	Deuterostome
<i>Tachykinin 1</i>	Both	Both
<i>Tachykinin 2</i>	Deuterostome	Deuterostome
<i>Tachykinin 3</i>	Deuterostome	Both
<i>t-FMRFamide 1</i>	Both	Both
<i>t-FMRFamide 2</i>	Deuterostome	Deuterostome
<i>t-FMRFamide 3</i>	Protostome	Protostome
<i>Asta-A/Galanin</i>	Protostome	Both
<i>Asta-C/MCH 1</i>	Both	Deuterostome
<i>Asta-C/MCH 2</i>	Deuterostome	Deuterostome
<i>GGN-EP/GRP</i>	Deuterostome	Deuterostome
<i>ETH</i>	Both	Both
<i>TRH 1</i>	Both	Both
<i>TRH 2</i>	Protostome	Protostome
<i>Sulfakinin/CCK 1</i>	Both	Both
<i>Sulfakinin/CCK 2</i>	Deuterostome	Deuterostome
<i>GnRH</i>	Both	Both
<i>Achatin 1</i>	Both	Both
<i>Achatin 2</i>	Deuterostome	Deuterostome
<i>CCAP/Np-S</i>	Deuterostome	Deuterostome
<i>Vasotocin 1</i>	Both	Deuterostome
<i>Vasotocin 2</i>	Both	Both to vasotocin/CCAP/Achatin/GnRH
<i>Allatotropin/Orexin</i>	Deuterostome	Deuterostome
<i>DH31/Calcitonin</i>	Both	Deuterostome
<i>PDF 1</i>	Deuterostome	Deuterostome
<i>PDF 2</i>	Deuterostome	Deuterostome
<i>DH44/CRF</i>	Deuterostome	Deuterostome
<i>PTH</i>	Deuterostome	Both

The sequence affinities reflect the previous controversies of the phylogenetic placement of Xenacoelomorpha. However, these affinities are based on our gene trees (Figure 1a and 1b and Supplementary Figure 3a and 3b) and not on species trees. Therefore, they are not appropriate to determine any phylogenetic relationships. The evaluation is simply based on whether the most closely related sequence is a deuterostome or protostome sequences and do not reflect any support by bootstrap values or SH-like support values. "Both" indicates a similar affinity to protostome and deuterostome sequences. If the xenacoelomorph sequences group in more than one cluster within the same receptor type, these clusters are indicated by numbers.

**Supplementary Table 4:** Species and accession numbers of sequencing data and tissues/stages of original RNA source.

Species	Accession No.	RNA source	Animal clade
<i>Childia submaculatum</i>	SRX1534054	Several complete adults	Acoela
<i>Convolutriloba macropyga</i>	SRX1343815	Several complete embryos and hatchlings	Acoela
<i>Diopisthoporus gymnopharyngeus</i>	SRX1534055	Several complete adults	Acoela
<i>Diopisthoporus longitubus</i>	SRX1534056	Several complete adults	Acoela
<i>Eumecynostomum macrobursalium</i>	SRX1534057	Several complete adults	Acoela
<i>Hofstenia miamia</i>	PRJNA241459	Several regenerating and developmental stages	Acoela
<i>Isodiametra pulchra</i>	SRX1343817	Several complete embryos and adults	Acoela
<i>Ascoparia</i> sp.	SRX1343822	Several complete adults	Nemertodermatida
<i>Meara stichopi</i>	SRX1343814	Several complete embryos and adults	Nemertodermatida
<i>Nemertoderma westbladi</i>	SRX1343819	Several complete adults	Nemertodermatida
<i>Sterreria</i> sp.	SRX1343821	Several complete adults	Nemertodermatida
<i>Xenoturbella bocki</i>	SRX1343818	Single complete adult	Xenoturbella
<i>Xenoturbella profunda</i>	SRP064117	Body wall of a single specimen	Xenoturbella

**Supplementary Table 5:** Species and accession number of sequencing data or origin of genomes.

Species	Accession No. / link	Animal clade
<i>Astrotoma agssizii</i>	SRR1695485	Echinodermata
<i>Labidiaster annulatus</i>	SRR1695480, SRR1695481	Echinodermata
<i>Leptosynapta clarki</i>	SRR1695478	Echinodermata
<i>Acanthaster planci</i>	OIST Marine Genomics Unit, Great Barrier Reef COTS Assembly; <a href="http://marinegenomics.oist.jp/cots/viewer/download?project_id=46">http://marinegenomics.oist.jp/cots/viewer/download?project_id=46</a>	Echinodermata
<i>Saccoglossus mereschkowskii</i>	SRR1695461	Hemichordata
<i>Ptychodera flava</i>	OIST Molecular Genetics Unit; <a href="https://groups.oist.jp/molgenu/hemichordate-genomes">https://groups.oist.jp/molgenu/hemichordate-genomes</a>	Hemichordata