

**Supplemental Figure 1. NR3E-paraestrol A interaction diagram.**

The interactions shown are those mediated by hydrogen bonds, hydrophobic contacts and  $\pi$ - $\pi$  interaction. Hydrogen bonds with the amino acids from the NR3E binding pocket are indicated by dashed lines between the atoms involved, while hydrophobic contacts are represented by an arc with spokes radiating towards the paraestrol A atoms they contact. The contacted atoms are shown with spokes radiating back. The figure was drafted using LIGPLOT v.4.5.3 and manually edited to add the paraestrol A carbon and ring numbering according to the IUPAC sterol nomenclature.

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NR3E Hydra magnipapillata -----
NR3F Trichoplax adhaerens ..... .MTSTF.... .....ASHS G...TPIEP V.....
NR3E Hydractinia symbiolongicarpus .....
NR3E Aurelia aurita .....
NR3E Rhopilema esculentum .....
NR3E Podocoryna carnea .....
NR3E Nanomia bijuga .....
NR3E Chironex fleckeri .....
NR3E Alatina alata .....
NR3E Morbakka virulenta .....
NR3E Tripedalia cystophora .....
NR3E Copula sivickisi .....
NR3E Chironex yamaguchi .....
ERRa Homo sapiens .....
ERRb Homo sapiens .....
ERRg Homo sapiens .....
ERR Drosophila melanogaster .....
ERR Crassostrea gigas .....
NR3D Crassostrea gigas .....
NR3D Aplysia californica .....
NR3D Platynereis dumerilii .....
ER Branchiostoma floridae .....
ERa Homo sapiens ..... .MTMTLHTKA SGMALLHQIQ G...NELEP L.....
ERb Homo sapiens ..... .MDIKNSP SSL.....NSPSS Y.....
SR Branchiostoma floridae ..... .MENQP NTVTNPMTT. ....QGLQP L.....
GR Homo sapiens PD..TKPKIK DNGDLVLSSP SNVTLPQVKT E.....K.....E
MR Homo sapiens PIQESTKHS CSGTSFKGNP TVNPFPMFDG S...YF.S F.MDDKDYYS LSGILGPPVP
AR Homo sapiens TKGLEGESLG CSGSAAAGSS GTLELPSTLS LYKSGALDEA AAYQSRDYNN FPLAL.....
PR Homo sapiens PR.....SSP CASSTPVAVG DFPDCAY.P DAEPKDDAYP LYSDFQPPAL

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NR3E Hydra magnipapillata -----
NR3F Trichoplax adhaerens ..... ..TSASDQL VFTSTAS... .SR..LDKGV DSGTTT.SDS KN.....
NR3E Hydractinia symbiolongicarpus .....
NR3E Aurelia aurita .....
NR3E Rhopilema esculentum .....
NR3E Podocoryna carnea .....
NR3E Nanomia bijuga ..... .M DSaelVVVpFK KR.....
NR3E Chironex fleckeri .....
NR3E Alatina alata .....
NR3E Morbakka virulenta .....
NR3E Tripedalia cystophora .....
NR3E Copula sivickisi .....
NR3E Chironex yamaguchi .....
ERRa Homo sapiens .....
ERRb Homo sapiens .....
ERRg Homo sapiens ..... .M DSVELCLPES FS...LHYE
ERR Drosophila melanogaster .....
ERR Crassostrea gigas .....
NR3D Crassostrea gigas ..... -MEAK YHDQ.QFEDA
NR3D Aplysia californica .....
NR3D Platynereis dumerilii .....
ER Branchiostoma floridae .....
ERa Homo sapiens ..... .NRPQLKI ..... .P..LERP..LGEVYL.SS KPA..VYNYP
ERb Homo sapiens ..... .NCSQSIL ..... .P..LE...HGSIIYIPSS YVDS.HHEYp
SR Branchiostoma floridae ..... .AYQQGYI VQQQQPS... .QPYRLPSPI QPEFVVISN. FP.....VG
GR Homo sapiens DFIELC.... ..... .TPGVIKQE KLGTVYCQAS FPGANII..G
MR Homo sapiens GFDGNCESG. .... .GFPVGIKQEP DDGSYYPEAS IPSSAIV..G
AR Homo sapiens ..... .AGPPPPP P..PPHPHAR IKLENPLDYG
PR Homo sapiens KIKEEEEGAE ASARSPRSYL VAGANPAAFP DFPLGPPPP. ..LPPRATPS .PGEAAV..T

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Supplemental Figure 2

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NR3E Hydra magnipapillata	-----	-----DSYVD	VECVH-----	-----QD	E-----INE	-----GDKN
NR3F Trichoplax adhaerens	.....	.DNIT.LHN	S--.DRIQPL	P...LAGLPI	Y.....TAP	.....TPAS
NR3E Hydractinia symbiolongicarpus	.....	-----	---MD.....	-----	-----SEA	.....SHTA
NR3E Aurelia aurita	.....	-----	-----	-----	-----	-----
NR3E Rhopilema esculentum	.....	-----	-----	-----	-----	-----
NR3E Podocoryna carnea	.....	-----	-----	-----	-----	-----
NR3E Nanomia bijuga	.....	.NNL.AVFN	SNKMETDEVV	P..PFSSKSN	K.....SES	.....ES.
NR3E Chironex fleckeri	.....	-----	-----	-----	-----	-----
NR3E Alatina alata	.....	-----	-----	-----	-----	-----
NR3E Morbakka virulenta	.....	-----	-----	-----	-----	-----
NR3E Tripedalia cystophora	.....	-----	-----	-----	-----	-----
NR3E Copula sivickisi	.....	-----	-----	-----	-----	-----
NR3E Chironex yamaguchi	.....	-----	-----	-----	-----	-----
ERRa Homo sapiens	.....	.MSSQ---.V	GIEPLYIKAE	PASPDSP.--	-----K	.....SSE
ERRb Homo sapiens	.....	.MSSD.RHLG	SS.GSFIKTE	PSSPSSGIDA	LSHHSP--S	.....SSD
ERRg Homo sapiens	E.....	ELLC RMSNK.RHI.	SS.SSFIKTE	PSSPASLTDS	VNHHSP--G	.....SSD
ERR Drosophila melanogaster	.....	-----MS.	GVSILHIKQE	VDTPSASCFS	PSSKSTATQS	.....TNG
ERR Crassostrea gigas	.....	-----	---MD.DIIKME	PGSPLGLSRC	GHS.....	-----LS
NR3D Crassostrea gigas	L.....	TVIQ GLSDPGG-TV	CRILRESSAA	ASATGDEA--	..E...SMS	.....ESI
NR3D Aplysia californica	.....	.MVSPS---P	CMP.LPL...	.SGAGGGG--	..E...GTA	.....SAH
NR3D Platynereis dumerilii	.....	-----	-----	-----	-----	-----
ER Branchiostoma floridae	.....	-----	---MAYPDIHII	P..PQGQTPR	M.....TTP	.....TKAA
Era Homo sapiens	E.....	GAAY EFNAAAA-AN	AQ-.YGQTGL	PYGPGEAAA	FGSN...GLG	.....FPP
ERb Homo sapiens	A.....	MTFY . . SPAV-MN	YSIPSNVTNL	EGGPGRQ.--	-----	-----
SR Branchiostoma floridae	N.....	MTQS QMSQ.-----	-----	PRGNDCAL.R	.....N.S	.....STA
GR Homo sapiens	NK.....	.MSAI.VHG	-----S	TSGGQMYHY.	MNTASL.--S	QQ..QDQKPI
MR Homo sapiens	V.....	-----	-----	NSGGQSFHYR	IGAQTISLS	RSARDQSFQH
AR Homo sapiens	SAWAAAAAQC	RYGDIA.LHG	A-----G	AAGP.....	-----	-----APPQ
PR Homo sapiens	AA.....	.PASA.VSS	A-----S	SSGSTLECLT	YKAEG.---	.....APPQ

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NR3E Hydra magnipapillata	L-----	-----	-----	-----	-----	-----
NR3F Trichoplax adhaerens	.....	-----	-----	-----	-----	-----
NR3E Hydractinia symbiolongicarpus	M.....	-----	-----	-----	-----	-----
NR3E Aurelia aurita	-.....	-----	-----	-----	-----	-----
NR3E Rhopilema esculentum	-.....	-----	-----	-----	-----	-----
NR3E Podocoryna carnea	-.....	-----	-----	-----	-----	-----
NR3E Nanomia bijuga	S.....	-----	-----	-----	-----	-----
NR3E Chironex fleckeri	-.....	-----	-----	-----	-----	-----
NR3E Alatina alata	-.....	-----	-----	-----	-----	-----
NR3E Morbakka virulenta	-.....	-----	-----	-----	-----	-----
NR3E Tripedalia cystophora	-.....	-----	-----	-----	-----	-----
NR3E Copula sivickisi	-.....	-----	-----	-----	-----	-----
NR3E Chironex yamaguchi	-.....	-----	-----	-----	-----	-----
ERRa Homo sapiens	-.....	T.ETE.....	-----	-----	-----	-----
ERRb Homo sapiens	-.....	A.SGGF...GL	A.....	-----	-----	LG.....
ERRg Homo sapiens	-.....	A.SGSY...SS	T.....	-----	-----	MN.....
ERR Drosophila melanogaster	-.....	KSSPSVSP.ERQLCSST	S.....	-----	-----	LS.....
ERR Crassostrea gigas	-.....	L.EESF...GR	D.....	-----	-----	VF.....
NR3D Crassostrea gigas	EKLV...PKE	E....SHGS	H.....	-----	-----	HS.....
NR3D Aplysia californica	.....	QAA T....STP	E.....	-----	-----	AG.....
NR3D Platynereis dumerilii	-.....	-----	-----	-----	-----	-----
ER Branchiostoma floridae	.KQSPMSPVM	SVHGMRQNGR	-----	-----	-----	IQ.....
Era Homo sapiens	.NSVSPSPML	L....LHPPP	Q.....	-----	-----	LS.....
ERb Homo sapiens	-...TTSPNV	L...WPTPG	H.....	-----	-----	LS.....
SR Branchiostoma floridae	.ISPOYFPFQ	VVRPYSPHR	P.....	-----	-----	-----
GR Homo sapiens	FNVIPPVPG	S..ENWNRC	-----	-----	Q	GSG...DDNL
MR Homo sapiens	.SSFPPVNTL	V..ESWKSH.	-----	-----	G	DLS...SRR.
AR Homo sapiens	-GSGSPSAAA	S..SSWHTLF	TAEQGQLYGP	CGGGGGGGGG	GGGGGGGGGG	GGGGGEAGAV
PR Homo sapiens	QGPFAPPPCK	A..PGASGCL	LPRDGLPSTS	ASAA.....	.....AA	GAA...PALY

Supplemental Figure 2 (continued)

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NR3E Hydra magnipapillata	--PINTSS--	-SNI-----	-----PRVIE-	--DTIN-I--	-----I----	-----
NR3F Trichoplax adhaerens	..CGMLRP..	.K.Q.....	.....Y----	..ASK....	....SIP..	...VVP....
NR3E Hydractinia symbiolongicarpus	...VLEKM..	----.....	.....EVK..	..EQVK.V.	....E....	....VVP....
NR3E Aurelia aurita	.....	.....	.....	..SALK.M.	....D....	....
NR3E Rhopilema esculentum	..-AFGRH..	..ESS.....	.....LILTK.	..SALK.M.	....D....	....
NR3E Podocoryna carnea	.....	.....	.....	.....	.....	.....
NR3E Nanomia bijuga	..ANV....	----.....	.....NNQFN.	..EDAQ.M.	....K....	....
NR3E Chironex fleckeri	..-MMD--..	.....	.....MQ..	..PT..Q..	....G....	....
NR3E Alatina alata	.....	.....	.....	.....	.....	.....
NR3E Morbakka virulenta	.....	.....	.....MQ..	..ST..Q..	....G....	....
NR3E Tripedalia cystophora	..-MD--..	.....	.....LP..	..HT..Q..	....G....	....
NR3E Copula sivickisi	.....	.....	.....MP..	..HT..Q..	....G....	....
NR3E Chironex yamaguchi	..-MD--..	.....	.....MQ..	..PT..Q..	....G....	....
ERRa Homo sapiens	.....	.....	.....	..-PP.VA.	....-	...LAPGP..
ERRb Homo sapiens	..T----HAN	GL--.....	.....	..SPP.MF.	....AGAG..	...L..GG..
ERRg Homo sapiens	..G----HQN	GL--.....	.....	..SPP.LY.	....PSAP..	...ILGGS..
ERR Drosophila melanogaster	..CDLHNVS	LNDG.....	.....-DS	L.KGSG.TS	....GGNG..	...GGGGG..
ERR Crassostrea gigas	..ADYNNDDY	G.DG.....	.....SYQNS	A..NSG.NI.	....SPCS..	...IDSS..
NR3D Crassostrea gigas	..GMVPOGS	FLSM.....	.....YMMHN	Q.VPSS.TTL	EFRDHGR..	...ILPLLDP
NR3D Aplysia californica	..SGTLPH..	---.....	.....NFLMDV	H.GPGT.LG	.....	...ASP
NR3D Platynereis dumerilii	..-MADD..	..QG.....	.....YT--	.....	.....	...PQR..
ER Branchiostoma floridae	..NGMMQQ..	..HHH.....	.....DILTL	H.NGGR..	....QVG..	...QVGD..
ERa Homo sapiens	..FLQPHGQ	QV--.....	.....YYL.N	E.PSGY.T.	..VREAGPP..	...AF.YRPN
ERb Homo sapiens	..LVVH-RQ	L--.....	.....HLYA.P	Q.KSPW.C.	..EARSLEH..	...TLPVNRE
SR Branchiostoma floridae	..-MADD..	..QP.....	.....QAAM..	.....YARNY	T..QNMEVRT	AVTDPQMGAW NRMQOPVYEE
GR Homo sapiens	TSL-----	GTLN.....	FPG---RTV	F.SNGY.SS	.....	.....
MR Homo sapiens	.....	.....	.....	..SDGY.PV	.....	.....
AR Homo sapiens	APYGY.RPPQ	GLAQESDFT	APDVWYPGGM	VSRVPY.PSP	TCVKSEMGPW	MDSYSGPY..
PR Homo sapiens	PAL-----	GL.G.....	LPQLGYQAAV	L.KEGL.PQ.	.....	...VYPPY..

**DBD**

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NR3E Hydra magnipapillata	-----	SSSPPSE-KG	LVQNKRPMTN	ARHAVPMLCL	VCTDKASGYH	YGVPS	CEGCK
NR3F Trichoplax adhaerens	.....	AVIV.....	---SVPNLEH	GTFSQNQA.	..G.R...L.	...L..	.....
NR3E Hydractinia symbiolongicarpus	.....	..ER..QP.R-	-ANLQSRLOS	NK.DQAF.V	..R....	...A..	.....
NR3E Aurelia aurita	.....	..K-----	---SCPGY	KDGEM.F.V	..G.S....	...A..	.....
NR3E Rhopilema esculentum	.....	..K-----	---SCPGF	KDGD.I.F.V	..G.S....	...A..	.....
NR3E Podocoryna carnea	.....	.....	.....	SKQDQ.F.V	..R....	...A..	.....
NR3E Nanomia bijuga	.....	..VKETNP.P-	-KAETP.TSE	.NTQRAF.V	..A.L....	...A..	.....
NR3E Chironex fleckeri	.....	..A-----	---CDTQES	RHGNS.F.V	..G.T....	...A..	.....
NR3E Alatina alata	.....	.....	.....	.....	.....	.....	.....
NR3E Morbakka virulenta	.....	..T-----	---CDSQNP	STGNS.F.V	..G.T....	...A..	.....
NR3E Tripedalia cystophora	.....	..T-----	---CDSQ.V	SHGSA.F.V	..G.T....	...A..	.....
NR3E Copula sivickisi	.....	..T-----	---CDSQ.V	SHGSA.F.V	..G.T....	...A..	.....
NR3E Chironex yamaguchi	.....	..A-----	---CDTQES	RHGNS.F.V	..G.T....	...A..	.....
ERRa Homo sapiens	APTRCLPGHK	EEEDGEG.A.	PGEQGGKLV	LSSLPKR..	..G.V....	...A..A.	.....
ERRb Homo sapiens	TPCRKS...	YEDCA.G.IM	EDSAIKCEYM	LNAIPKR..	..G.I....	...A..A.	.....
ERRg Homo sapiens	GPVRKL...	YDDCS.T.IV	EDPQTKCEYM	LNSMPKR..	..G.I....	...A..A.	.....
ERR Drosophila melanogaster	G...TSGG.	-----N.AT	NASAGAGSGS	V.DELRR..	..G.V...F.	...A..A.	.....
ERR Crassostrea gigas	SPIDTSKLD	INNI--A.TS	ITNSINCDQE	NIELPKR..	..G.V....	...S..A.	.....
NR3D Crassostrea gigas	S.....L	-----FA	DGRKCLKHGA	SA.GPNK.Q	..S.N...F.	...W..	.....
NR3D Aplysia californica	S.....S	H-----	MK.EVGGAVP	GSSIQAK.Q	..S.N...F.	...W..	.....
NR3D Platynereis dumerilii	SPEEEWGGQT	.EPS.IDLG.	HANADQLPSD	GDSKDVQK.Q	I.S.L...F.	...W..	.....
ER Branchiostoma floridae	CPDQFSKGR.	D.PAS.G.SS	IEN.QPQVKE	LDNKARAV.R	..G.H...F.	...W..	.....
ERa Homo sapiens	SDNRRQGGRE	R-----LA	STND.GS.AM	ESAKETRY.A	..N.Y....	...W..	.....
ERb Homo sapiens	TLKRKVSNGR	C-----	---ASPVTGP	GSKRDAHF.A	..S.Y....	...W..	.....
SR Branchiostoma floridae	SPQKGTGTEE	.APWTANQOV	KQAAVGTAS	PGSGHKPP.A	..HCPST.L.	...YA..	.....
GR Homo sapiens	.....	..P.MR.--DV	SSPPSSS.A	TTGPP.K.	..S.E...C.	...LT.GS.	.....
MR Homo sapiens	.....	..LEYI.E-.NV	SSSTL.SVST	GSSRPSKI.	..G.E...C.	...VT.GS.	.....
AR Homo sapiens	.....	..GDMRLE-.TA	RDH--VLPID	YFPPQKT.	..I.G.E...C.	...ALT.GS.	.....
PR Homo sapiens	.....	..LNYLRP-.DS	-EASQS.QYS	FESLPQKI.	..I.G.E...C.	...LT.GS.	.....

P-box

Supplemental Figure 2 (continued)

# DBD

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NR3E Hydra magnipapillata	AF	FKRSLQLK	QLNYKCPASN	N	TINKMSRK	CCQACRLGKC	HAVGMSKECK	KVKKRDIR--
NR3F Trichoplax adhaerens	.....I	S-SVA.T	.SGS	R	KVD.QR..	.....Q	FD...IR.GV	RKNRNPGRV
NR3E Hydractinia symbiolongicarpus	.....S	D.....S	.....S	.....DR	.....K	.....K	.D.....FL	GN.IKRPQE
NR3E Aurelia aurita	.....AT	D...R.G	.....S	.....K.D	.....R	.....R	NE.....FL	GN..IKKPSR
NR3E Rhopilema esculentum	.....AT	D...R.G	.....S	.....K.D	.....R	.....R	NE.....VI	D-----
NR3E Podocoryna carnea	.....S	E.....S	.....S	.....DR	.....Q	.....Q	.D.....FL	GN.IKRAQD
NR3E Nanomia bijuga	.....S	EM.....G	.....G	.....D	.....K	.....K	QD.....FL	GN.IKRPKP
NR3E Chironex fleckeri	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..TKNAK
NR3E Alatina alata	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..IKKSTK
NR3E Morbakka virulenta	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..IKKNAK
NR3E Tripedalia cystophora	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..IKKNAK
NR3E Copula sivickisi	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..IKKNAK
NR3E Chironex yamaguchi	.....AA	D...R.GN	.....GN	.....K.D	.....R	.....R	.E.....FL	GN..IKKNAK
ERRa Homo sapiens	.....TI	G-SIE.S	.....S	.....E	.....E.T	.....RR	A.....FT	LR...L.GV
ERRb Homo sapiens	.....TI	G-NIE.S	.....S	.....E	.....E.T	.....RR	S.....FM	LK...L.GV
ERRg Homo sapiens	.....TI	G-NIE.S	.....S	.....E	.....E.T	.....RR	S.....FM	LK...L.GV
ERR Drosophila melanogaster	.....TI	G-NIE.T	.....N	.....E	.....E	.....RR	A.....FQ	LLM.L.GV
ERR Crassostrea gigas	.....TI	G-NIE.S	.....NG	.....D	.....E.T	.....RR	A.....FQ	LR...L.GV
NR3D Crassostrea gigas	.....I	G-PVD.V	.....T	.....T	.....D	.....HR	S.....R	YE...N.GSQ
NR3D Aplysia californica	.....I	G-PVD.I	.....T	.....T	.....D	.....HR	S.....RR	YE...N.GSQ
NR3D Platynereis dumerilii	.....D	PVD.V	.....T	.....D	.....HR	S.....FR	LE...M.RRE	RRTTKVKSP
ER Branchiostoma floridae	.....I	QG.TD	.....I	.....GT	.....Q	.....DRNR	S.....YR	LM...T.DGR
ERa Homo sapiens	.....I	G-HND.M	.....T	.....Q	.....D	.....NR	S.....R	YE...M.GGI
ERb Homo sapiens	.....I	G-HND.I	.....T	.....Q	.....D	.....NR	S.....R	YE...V.CGS
SR Branchiostoma floridae	S	H.AHKR	AHP.V	.....N	.....V	.....DRRLK	N.P...K	L.M...F.EH
GR Homo sapiens	V	.....AVEG	.....H	.....L	.....AGR	.....D	.....I	.....D
MR Homo sapiens	V	.....AVEG	.....H	.....L	.....AGR	.....D	.....I	.....D
AR Homo sapiens	V	.....AAEG	.....KQK	.....L	.....ASR	.....D	.....D	.....FR
PR Homo sapiens	V	.....AMEG	.....H	.....L	.....AGR	.....D	.....I	.....D

P-box

D-box

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NR3E Hydra magnipapillata	-----D	----	TKSKNY	PRLNPDECI	ESVLT	-----	-----	-----
NR3F Trichoplax adhaerens	K...YEKPT	S...--VGQC	KSVTS	.SF	S.STASSFSQ	ADTDK	AEDN	SIQS..LKIN
NR3E Hydractinia symbiolongicarpus	K...QKQP	.....R--RK	SDKSS	EGFV	.STN	.....	.....	.....
NR3E Aurelia aurita	K...SK--	.....KQ	KFDDDE	RK	VEPTS	.....	.....	.....
NR3E Rhopilema esculentum	.....	.....	.....	.....	.....	.....	.....	.....
NR3E Podocoryna carnea	K...QKQP	.....R--RK	SDKSS	ENFV	.STN	.....	.....	.....
NR3E Nanomia bijuga	K...DAAK	.....QR	KT	E	ISES	NVV	.STN	.....
NR3E Chironex fleckeri	G...DGGKT	HKS	S.KLKQ	MSNDED	LKC	VEPTS	.....	.....
NR3E Alatina alata	.....	.....	MANDDD	LKC	VEPTS	.....	.....	.....
NR3E Morbakka virulenta	S...DSGKN	HKA	S.KLKQ	MAHDDD	LKC	VEPTS	.....	.....
NR3E Tripedalia cystophora	G...DSGKN	HKA	S.KLKQ	MSADDD	LKC	VEPTS	.....	.....
NR3E Copula sivickisi	G...DSAKN	HKA	S.KLKQ	MSADDD	LKC	VEPTS	.....	.....
NR3E Chironex yamaguchi	G...DGGKT	HKS	S.KLKQ	MSNDED	LKC	VEPTS	.....	.....
ERRa Homo sapiens	K...YKRRP	EVD	-----	-P	PF	GFPF	AGP	AVA..G
ERRb Homo sapiens	K...YKRRL	DSE	-----	-SSPYLSLQ	SPP	-----	.....	AKKPLT
ERRg Homo sapiens	K...YKRRR	DAE	-----	-NSPYLNPQL	VQP	-----	.....	AKKPYN
ERR Drosophila melanogaster	K...YRRNP	VSN	-----	-SYQTMQLLY	Q	N--	.....	TTSLCDV
ERR Crassostrea gigas	K...YKRTV	DSG	-----	-PIVQQIFPM	IKK	ACV..E	STKSD	FSSDN
NR3D Crassostrea gigas	SKPAATKRSR	ADSSDNTV	-----	-----	-----	-----	-----	-----
NR3D Aplysia californica	S.SLKGKRCR	ADSSDSAV	-----	-----	-----	-----	-----	-----
NR3D Platynereis dumerilii	G...S..PE	EKITK	VRT	-PNTK	NPKE	-----	.....	KGPPVENN
ER Branchiostoma floridae	K...RTHNQ	IDVSS	TADSC	KSSVS	LP--	--SSASAFDK	SRSASP	TENN
ERa Homo sapiens	K...HKRQR	DDGEGRG	-E	-----	-----	-----	-----	VGSA
ERb Homo sapiens	R...RQRSA	DEQLHCAGK	-----	-----	-----	-----	-----	AKRS
SR Branchiostoma floridae	P...KTKRSP	KRA	-----	-KTSH	PPA	E--	.....	TPPEQQ
GR Homo sapiens	I...QQA	TTG	---VS	QET	-----	SEN	-----	-----
MR Homo sapiens	I...HEE	QPQ	---QQ	QPPPP	PPPQ	SPEE	-----	-----
AR Homo sapiens	Q...EEG	EAS	---ST	TSP	-----	TEET	-----	-----
PR Homo sapiens	V...RAL	DAV	---A--	LPQPVGVPNE	SQA	-----	-----	-----

Supplemental Figure 2 (continued)

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NR3E Hydra magnipapillata -----
NR3F Trichoplax adhaerens EDK..... .YIDVNCT. .... .RL PSTPSPDKGY DIKILKEFIG
NR3E Hydractinia symbiolongicarpus .....
NR3E Aurelia aurita .....
NR3E Rhopilema esculentum .....
NR3E Podocoryna carnea .....
NR3E Nanomia bijuga .....
NR3E Chironex fleckeri .....
NR3E Alatina alata .....
NR3E Morbakka virulenta .....
NR3E Tripedalia cystophora .....
NR3E Copula sivickisi .....
NR3E Chironex yamaguchi .....
ERRa Homo sapiens .....EPEKL YAMPDPAG..
ERRb Homo sapiens .....EPDKL YAMPPPGM..
ERRg Homo sapiens .....EPEKI YAMPDPTV..
ERR Drosophila melanogaster .....EPDAL SVQTPPPQVH TTSITNDEAS
ERR Crassostrea gigas Q.....QLDKL YVNTESEI..
NR3D Crassostrea gigas .....T SGSPNPAKSA RK.....
NR3D Aplysia californica .....T NNGASSSKSS KR.....
NR3D Platynereis dumerilii ETVAVESVKT EAVSPQECSP SGHTSQEDLS VPMTSASQSF NLTPPPSTSS ST....SSPS
ER Branchiostoma floridae .....DS
ERa Homo sapiens .....MRAA NLWPSPLMIK RS.....
ERb Homo sapiens .....H... ..AP.....R.....
SR Branchiostoma floridae .....L YN.....
GR Homo sapiens .....GN.K TIVPAT....
MR Homo sapiens .....GT.T YIAPAKEPSV NT.....
AR Homo sapiens .....TQKL TVS.....
PR Homo sapiens .....SQRF TFSFG.....

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1021

H1

H3

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NR3E Hydra magnipapillata ----- --PIEIEHEN IIEQIRLTHS KL--YL---- ---GLDE-- -TV---NGTL
NR3F Trichoplax adhaerens SGKEYVIDQK RDGKQ.IVND V.KK.LEAEP PM..LP.... ...ACP.P.. .EAEDSGIRT
NR3E Hydractinia symbiolongicarpus .....AC...I.. A.QS.TSL.A E..... .KPED.. .CTIE.TR..
NR3E Aurelia aurita .....TQDA.L.K L.RT.TSL.D QE..KPS... ..LLPNV... .EED.LKPA
NR3E Rhopilema esculentum .....
NR3E Podocoryna carnea .....AC..M.I.. A.QS.TAL.. EF..... .KPED.. .SSVR.TR..
NR3E Nanomia bijuga .....AC..M.L.S M.QN.TTL.N EM..C..... .KS.D.. .RMEN.AE..
NR3E Chironex fleckeri .....TQDA.L.S VMKA.VSLEN ET..KEL... .RVSQP.. .DGVD.-VIT
NR3E Alatina alata .....TQDA.L.S VVKA.ITLEN ET..KEL... .RVSQS.. .EGAE.-VMT
NR3E Morbakka virulenta .....TQDA.L.S VVKA.VTLEN ET..KGL... .RVCQS.. .D.TE.-TMT
NR3E Tripedalia cystophora .....TQDA.L.S VVKA.VTLET ET..KEL... .RVSQP.. .DGSE.-VMT
NR3E Copula sivickisi .....TQDA.L.S VVKA.VTLET ET..KEL... .RVSQP.. .DGSD.-VMT
NR3E Chironex yamaguchi .....TQDA.L.S VMKA.VSLEN ET..KEL... .RVSQP.. .DGVD.-VIT
ERRa Homo sapiens .....PD..GHLPA
ERRb Homo sapiens .....PE..GDIKA
ERRg Homo sapiens .....PD..SDIKA
ERR Drosophila melanogaster SS......SGS.KL.S SV---VT--- ---PNGTCIFQ.. NNNNNDENEI
ERR Crassostrea gigas .....LEGGEVRF
NR3D Crassostrea gigas .....S...---QTVT .LQA.NKAAL PVLESHH... ---NH.. .GQPPTKVH.
NR3D Aplysia californica .....S...---RSAS .L.A.QKADL PVMDSYH... ---NH.. .NLPATRVH.
NR3D Platynereis dumerilii NGTSSLQ... IDASTFKIDP GL-P.DQP.P LVVILEENDL PPKICKEPLT AESEETEYS.
ER Branchiostoma floridae DGDSSGTREL RTASHORLKA L.DA.DVKEG EH..RGEENH PTGQQAGN... .WQEIS.PE.
ERa Homo sapiens .....KKN SLA.SLTADQ MVSA.LDAEP PLYSEY... ---.P.. .RPFSEASM
ERb Homo sapiens .....VRE LLLDALSP.Q LVLT.LEAEP PHVLI-S... ---RP.. .SAPFTEASM
SR Branchiostoma floridae .....PTVP L.SH.VNIEP NPILTGY... ---NP.. .QCTPTE.Y.
GR Homo sapiens .....PQLTPT LVSL.EVIEP EVLYAGY... ---S.. .S.PDSTWRI
MR Homo sapiens .....ALVPQL STISRALTPS PVMV.ENIEP EIVYAGY... ---S.. .SKPDTAEN.
AR Homo sapiens .....HIEGYEQPI FLNV.EAIEP GVVCAGH... ---N.. .NQPDSFAA.
PR Homo sapiens .....QTIQLIPP L.NL.MSIEP DVIIYAGH... ---N.. .KPDTSSS.

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Supplemental Figure 2 (continued)

	1081	H3	H4-5
NR3E Hydra magnipapillata	THKFGYGTGK	QLIHIDWAK	RIPGYSLLIL SDQAVLLOAT WVELMVANWL FLSITSTN-S
NR3F Trichoplax adhaerens	ITIIICEMVER	E.VMV.....	.....T.C.N.V.....S.L.VFMIDLA.R.MPYD..K
NR3E Hydractinia symbiolongicarpus	.Q..SW.VDQ	.V.....	QL...CN.VI...I...A..D.LAL..V.YH.LYVEE.A
NR3E Aurelia aurita	.SSLCDIV..	...AA.....	GL...ET.T.N...I...G.I.MLLL..I.Y.LPH...K
NR3E Rhopilema esculentum	--LTLDIV..	.VAA.....	GL...ET.T.N...I...G.I.MLLL..T.Y.LSHK..K
NR3E Podocoryna carnea	VQN.CW.VDQ	.V.....	QL...CN.VI...I...A..D.L.L..V.YH.LCIDD.A
NR3E Nanomia bijuga	IQ..CF.VDQ	.VR.....	QL...CN.SI...I...A..D.L.L..V.YH.LHVSE.K
NR3E Chironex fleckeri	.GYLCKQ.S.	.VAV.....	GL...DT.T.N...I...G.I...LLL..V...ERI..K
NR3E Alatina alata	.GYLCKQ...	.VAV.....	GL...DT.T.N...I...G.I...LLL..V...ERI..K
NR3E Morbakka virulenta	.GHLCKQ..R	.VAV.....	GL...DT.T.N...I...G.I...LLL..V...ERI..K
NR3E Tripedalia cystophora	.GYLCKQ..R	.VAV.....	GL...D.T.N...I...G.I...LLL..V...ERF..K
NR3E Copula sivickisi	.GYLCKQ..R	.VAV.....	GL...DT.T.N...I...G.I...LLL..V...ERI..K
NR3E Chironex yamaguchi	.GYLCKQ.S.	.VAV.....	GL...DT.T.N...I...G.I...LLL..V...ERI..K
ERRa Homo sapiens	VATLCDLDFDR	EIVVT.S...	S...F...S...MSV.SV.M.VL.LGVA.QR.LPLQD.E
ERRb Homo sapiens	LTTLCDLADR	E.VV..G...	H...F...S.G..MS...SA.M.IILIGIV.YR.LPYDD.K
ERRg Homo sapiens	LTTLCDLADR	E.VV..G...	H...F.T.S.A..MS...SA.M.IILIGVV.YR.LSPED.E
ERR Drosophila melanogaster	LSVLSDIYD.	E.VSV.G...	Q...FID.P.N..MK...VS.A.ILTQLT.R.LPFNG.K
ERR Crassostrea gigas	LATVSDLADR	E.VIT.S...	QV..FCT.S...MN...HS.L.ILCL.LV.R.CPYNG.Y
NR3D Crassostrea gigas	LNSLVKLAER	E.V.L.N...	NV...TD.S...VH.IECC.M...LLL.CA.R.EHGG.K
NR3D Aplysia californica	LNTLIKLADR	E.VYL.N...	HV...TC.T.G..VH.IECC.M...LLL.CA.R.MEHG.R
NR3D Platynereis dumerilii	L.RLI.LADM	E.VDVVN...	VL..F.G.E.R.RIAI.ESC.M..LCIGAA.WR.RLN.T.F
ER Branchiostoma floridae	IESVSSLVDR	E.TG..C.G.	K....K.S.N..VL.MES..LD.LILDIV.WC..RHKG.E
ERa Homo sapiens	MGLLTNLADR	E.V.M.N...	.V..FVD.T.H..VH..ECA.L.ILMIGLV.WR.MEHPG.K
ERb Homo sapiens	MMSLTKLADR	E.V.M.S...	K...FVE.S.F..VR.ESC.M.VLMMGLM.WR..DHFG.K
SR Branchiostoma floridae	MALVTDLANR	E.IEGLV...A	.L...GM.PM.D.VN.IRTV.LD.LMLGLV.WR.MEHRG.E
GR Homo sapiens	MTTLNMLG.R	.V.AAVK...	A...FRN.H.D.MT...YS.MF..AFALG.WR.YRQSSAN
MR Homo sapiens	LSTLNRLA..	.M.QVVK...	VL..FKN.P.E..IT.I.YS.MC.SSFALS.WR.YKH..SQ
AR Homo sapiens	LSLNLGER	.V.VVK...	AL..FRN.HV.D..MAVI.YS.MG..FAMG.WR.F.NV.SR
PR Homo sapiens	LTSLNQLGER	.LSVVK.S.	SL...FRN.HI.D..IT.I.YS.MS...FGLG.WR.YKHVSGQ

	1141	H6	H7	H8
NR3E Hydra magnipapillata	LK-LSHTFDI	SK-----	QDST-ELGF	-GLIYDQFLA LVHRTKGYKL DEEISCFA
NR3F Trichoplax adhaerens	.V.YACDMVM	GH.....	.KQ.R.AA.L	.DE.NRHAF.E..TKYRSISM.KO.FA.L.R
NR3E Hydractinia symbiolongicarpus	I..F.KF.S	TY.....	NEAR...C	.EN..C.IFS.AN.A.K.NM...A.L..
NR3E Aurelia aurita	IQ.F.SNLIV	CE.....	ALGS..F.L	.ETVHH.LSS.IT.VQ..CI...FV.L..
NR3E Rhopilema esculentum	TQ.F.ANLIV	CE.....	.TLA..AF.L	.ETVHT.LSS.IA.VQ..GI..V.FL.L..
NR3E Podocoryna carnea	I..F.RY.S	TY.....	DEAM....	.EN..C.V.S.AN.A.K.NM...L..
NR3E Nanomia bijuga	IR...MV.SL	.F.....	.EAK.NI..	.EE..SYLIS..N.A.K.NI.V...I..
NR3E Chironex fleckeri	VA.F.ADVVV	DD.....	.RM.H.T.L	.DSV.S.L.P..T.VRS.G...FV.L..
NR3E Alatina alata	VA.F.SDVVV	DD.....	.RT.R.T.L	.DSV.S.L.P..T.VRS.G...FV.L..
NR3E Morbakka virulenta	VA.F.SDVVV	DD.....	.MT.R.T.L	.DSV.S.L.P..T.V.S.E...FV.L..
NR3E Tripedalia cystophora	VA.F.SDVVV	DD.....	.RS.R.T.L	.DSV.S.L.P..T.VRN.E...FV.L..
NR3E Copula sivickisi	VA.F.SDVVV	DD.....	.RS.R.T.L	.DSV.S.L.P..T.VRN.E...FV.L..
NR3E Chironex yamaguchi	VA.F.ADVVV	DD.....	.RM.H.T.L	.DSV.S.L.P..T.VRS.G...FV.L..
ERRa Homo sapiens	.A.FAEDLVL	DE.....	.EGAR.AA.L	.ELGAAL.Q..R.LQALR.ER..YVLL..
ERRb Homo sapiens	.V.YAEDYIM	DE.....	.EH.R.LA.L	.LEL.RAI.Q..R.Y.KL.V.EK..FVTL..
ERRg Homo sapiens	.V.YADDYIM	DE.....	.DQ.K.LA.L	.LDLNNAI.Q..KKY.SM..EK..FVTL..
ERR Drosophila melanogaster	.C.FATDVWM	DE.....	.HLAK..C.Y	.TEF.YHCVO.IAQ.MERISP.RR..YVLL..
ERR Crassostrea gigas	..FAEDLQL	.V.....	.DECK.LCHC	.SPELDGISRK.AKKFTDMEV.TK..YLLL..
NR3D Crassostrea gigas	SLAFAPDLVL	DR.....	.SSWS.TVEM	.TE.FE.VA.VSEQMMONH.HKO.LLLLQ.
NR3D Aplysia californica	TLVFAPD.HL	ER.....	.QWA.LT.M	.DVLE.VS.VSEQMLLHG.NK..LLLQ.
NR3D Platynereis dumerilii	QVNFAENLHF	NE.....	.ETAK.KAKM	.SS.VGEIWO.ISQOFRYLE.SNH.FMLLRV
ER Branchiostoma floridae	KLL..GGVLV	NRNTISNRRN	NSSGD.DMEV	.LEMC..I.S.IATKFYEFD.QRR.YL.L..
ERa Homo sapiens	-LLFAPNLLL	DR.....	.NQCKCVE.M	.VE.F.ML..TSS.FRMN.OG..FV.L.S
ERb Homo sapiens	-LIFAPDLVL	DR.....	.DEGKCV.EI	.LE.F.ML..TTS.FREL..QHK.VL.V..
SR Branchiostoma floridae	WLVFAPDLLM	DR.....	.SLCR.LS.M	.EY.CTPM.E.FARQFADLQV.PQ.VYV.L..
GR Homo sapiens	.LCFAPDLI.	NE.....	.RM..LPCM	.YDQCKHM.Y.VSSELHRLQV.SY..YL.M.T
MR Homo sapiens	FLYFAPDLVF	NE.....	.EKM.H.QSAM	.YELCQGMHQ.ISLQFVRLQV.TF..YTIM.V
AR Homo sapiens	MLYFAPDLVF	NE.....	.YRM.H.KSRM	.YSQCVRMRH.SQEFGLWLOI.TPO.FL.M..
PR Homo sapiens	MLYFAPDLIL	NE.....	.RMK..SS.	.YSLCLTMWO.IPOEFVKLQV.SQ..FL.M.V

Supplemental Figure 2 (continued)

	H8		H9		H10-H11				
NR3E Hydra magnipapillata	1201	IILTNAAETTTQ	LSRP	---	AKVHALSN	QFCSSLQYYT	KNRH---	KE	NPLKFAKIVL
NR3F Trichoplax adhaerens		LR---	---	---	---	---	---	---	---
NR3E Hydractinia symbiolongicarpus		.S... .SSS	.AG	...	.E.ND.IT	T.S.T....	NS	R.	.Q...L..
NR3E Aurelia aurita		.G.L. .DSRG	.TGA	...	.S. .QD.V.	K.SLA.N.HI	SSQ	PD	Q.Q...I.
NR3E Rhopilema esculentum		.G.L. .DSRG	.TGS	...	.S. .QE.VK	K.S.A.N.HI	SSH	PD	Q.Q...I.
NR3E Podocoryna carnea		.G... .SSS	.V	...	.DN.NE.IT	T.S.T....	SS	RD	.Q...L..
NR3E Nanomia bijuga		.N... .SS	.TTS	...	.D. .NE.IQ	K.T.A...S	T. .S...	R.	S.Q...L..
NR3E Chironex fleckeri		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.A.HI	SSY	PD	K.Q.....
NR3E Alatina alata		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.M.HI	STY	PD	K.Q.....
NR3E Morbakka virulenta		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.T.HI	STY	PD	K.Q.....
NR3E Tripedalia cystophora		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.T.HI	NTY	PD	K.Q.....
NR3E Copula sivickisi		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.T.HI	NTY	PD	K.Q.....
NR3E Chironex yamaguchi		.G.M. .DSCG	.GS	...	.RG.QE.VR	KYSMA.A.HI	SSY	PD	K.Q.....
ERRa Homo sapiens		LA.A. .SDSVH	IEDA	...	.EA.EQ.RE	ALHEA.LE.E	AG. .AGPGG	GA	ERRRAGRLL.
ERRb Homo sapiens		LA.A. .SDSMY	IEDL	...	.EA.QK.QD	LLHEA. .D.E	LSQRH	---	.E.WRTG.LL.
ERRg Homo sapiens		.A.A. .ASDMH	IEDV	...	.EA.QK.QD	VLHEA. .D.E	AGQ.M.	---	.D.RRAG.MLM
ERR Drosophila melanogaster		LL.A. .CD-IL	.DDQ	...	.SSLR.FRD	TILN. .NDVV	YLLRH	SS	AVSHQQQLL.
ERR Crassostrea gigas		MT.C. .ID-VA	IENTS	...	.EA.RQ.QD	KLQD. .IE.V	.Y.YV.	-G	.LRRLGHLYM
NR3D Crassostrea gigas		MV.V. .VRR	.ASY	...	.NQIFNMQQ	SLLDAIVDTA	QK--Y.	HPD	.VRHVPAVL.
NR3D Aplysia californica		TV.V. .VRP	.DSF	...	.L.IQEMRQ	LILDVFMEVA	GRH-Q.	CFG	.WRHAPS.L.
NR3D Platynereis dumerilii		VTML. .SIR	.CL	...	.DAM.KIRQ	.YLEA.HFEC	GRFLGKIS	ES	SCVRM.Q.LC
ER Branchiostoma floridae		.T.VHGSLKG	.ESD	...	.TQ.RQ.QD	DLTDA.MDVC	SE	...	AL.GSRRP..ML.
ERa Homo sapiens		.L.L.SGVYT	FLSSTLKSLE	...	EKDHI.RVLD	KITDT.IHLM	AKA-GLTI	QQ	QHQL.QLL.
ERb Homo sapiens		M.L.L.SSMYP	.VTATQDA.D	...	SSR.LAH.L.	AVTDA.VWVI	AKS-GISS	QQ	QSMRL.NLLM
SR Branchiostoma floridae		LT.YTTAVSR	.QDY	...	.RQ.QR.QH	EINEA.AEAC	SSTFG	..F	S.GNI.RLMM
GR Homo sapiens		LL.LSSV--P	----	KGDLK	SQELFDEIRM	TYIKE.GKAI	VK.E.GNS	SO	.WQR.YQLTK
MR Homo sapiens		LL.LSTI--P	----	KGDLK	SQ.AFEEMRT	NYIKE.RKMV	TKCP.NNS	GO	SWQR.YQLTK
AR Homo sapiens		LL.LFSII--P	----	VDGLK	NQKFFDE.RM	NYIKE.DRTI	ACKR.KNH	TS	CSR.R.YQLTK
PR Homo sapiens		LL.L.LTI--P	----	LEGLR	SQTQFEEMRS	SYIRE.IKAI	GL.Q.KGV	VVS	SSQR.YQLTK

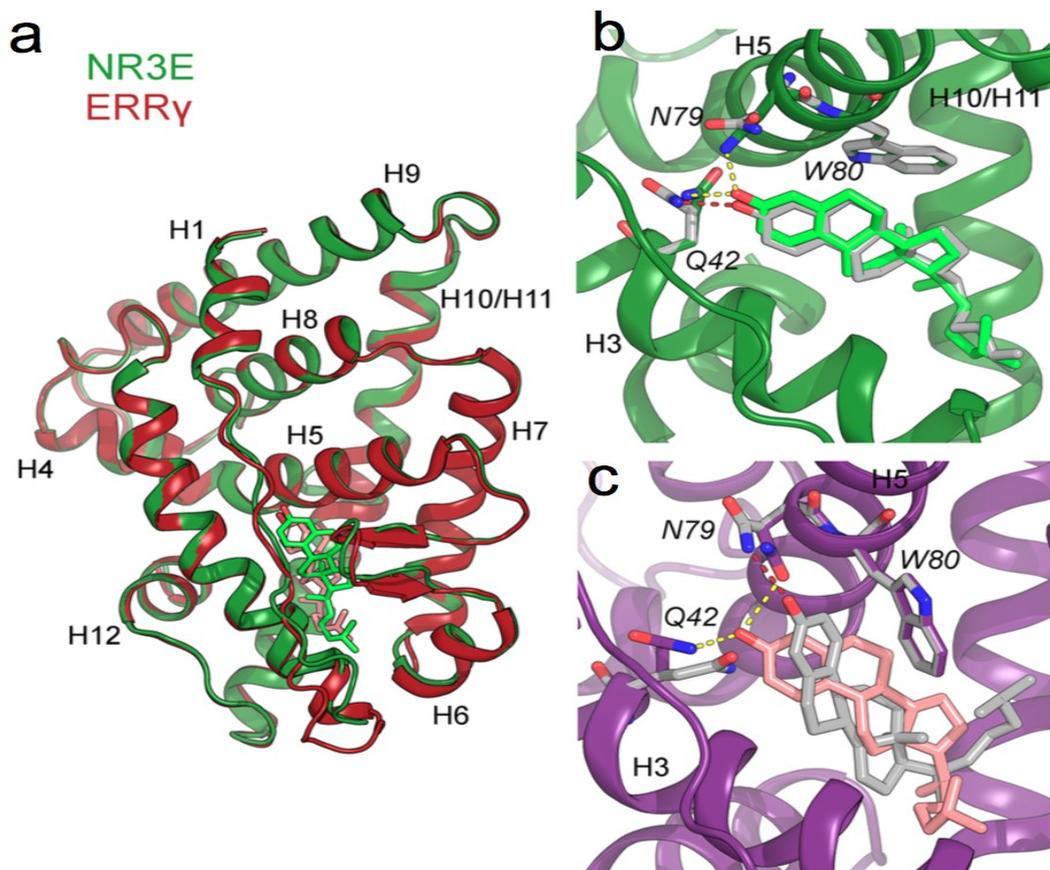
	H10-H11		H12				
NR3E Hydra magnipapillata	1261	ILPQLKYLVN	EVLKVLHALN	SM-SEK GAYL	SDLVVEMLDV	KNRQ-----	-----
NR3F Trichoplax adhaerens		.....M.	Q.IEY.YTMK	MN.NSSES	.....I.	.EA	.Q.L.....
NR3E Hydractinia symbiolongicarpus		.....V.	N.IEYFYRVK	IS.--SE.Q.	.....E.L.	.EA	.S.L.....
NR3E Aurelia aurita		.....CV.	N.IEYFYRVK	IS.--GE.Q.	.....E.L.	.EA	.S.L.....
NR3E Rhopilema esculentum		.....M.	Q.IEY.YKMK	MH.ES.ESN.	.....I.	.EA	.Q.L.....
NR3E Podocoryna carnea		.....V.	R.IEL.TKMK	MN.HQDKCA.	.....I.	.EA	.Q.L.....
NR3E Nanomia bijuga		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Chironex fleckeri		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Alatina alata		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Morbakka virulenta		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Tripedalia cystophora		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Copula sivickisi		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
NR3E Chironex yamaguchi		.....V.	H.IEF.YRVK	IS.--GE.Q.	.....L.	.EA	.S.L.....
ERRa Homo sapiens		T.L.RQTAG	K.AAHFYGVK	IE.--GKVP	HK.FL.	.EA	MMD.....
ERRb Homo sapiens		T.L.RQTAA	KAVQHIFYSVK	IQ.--GKVP	HK.FL.	.EA	.VG.EQLRGS
ERRg Homo sapiens		T.L.RQTST	KAVQHIFYSVK	IE.--GKVP	HK.FL.	.EA	V--.....
ERR Drosophila melanogaster		L.S.RQADD	ILRRFWRGIA	RD.--EVITM	KK.FL.	.EP	LA.....
ERR Crassostrea gigas		L.A.NHMKL	LAKQYWFVVK	KD.--GRIMM	HK.FL.	.EA	DS--.....
NR3D Crassostrea gigas		L.THIRQAGE	RGIAFFQR.K	IE.--GVVTF	C.LK.	.A	QDFLEKKSSN
NR3D Aplysia californica		L.THIRQAGE	RGITVFQK.K	ME.--GCVTF	C.LT.	.A	H.SSGERRRL
NR3D Platynereis dumerilii		..FARQVSL	KATTH.FNMH	NQ.--HAVPV	G..A.	.VA	QKELMTNEDS
ER Branchiostoma floridae		L.SH.RQVSA	RASSH.G.VR	NG.--LKVP.	Y.ILLDI.	TD	QVSEGQRDQQ
ERa Homo sapiens		.SHIRHMS	KGMEH.YSMK	CK.--NVVP.	Y.LL.	.A	HRHLHAPT SRG
ERb Homo sapiens		L.SHRVHAS	KGMEH.LNMK	CK.--NVVPV	Y.LL.	.NA	HVLRGCRSSI
SR Branchiostoma floridae		.VS.VRQ.SS	LGVDH.NR.R	GA.--ETVSV	EG.LR.	IV.E	PP.ITETIEDS
GR Homo sapiens		L.DSMHEV.E	NL.NYCFQTF	LDK-TMSIEF	PEMLA.	IITN	QIPK.....
MR Homo sapiens		L.DSMHD..S	DL.EFCFYTF	RESHALKVEF	PAML..	IISD	QLPK.....
AR Homo sapiens		L.DSVQPIAR	.LHFFTFD.L	IKSHMVSVDV	PEMMA.	IIS.	QVPK.....
PR Homo sapiens		L.DN.HD..K	QLHLYCLNFF	TQSRALSVEF	PEMMS.	VI.AA	QLPK.....

## Supplemental Figure 2. Full-length alignment of cnidarian NR3E with already known members of the NR3 family.

The DNA-binding domain (DBD) is highlighted with light grey. Within it, two interaction sites with DNA response elements (P-box and D-box) are boxed, and the nine conserved cysteine residues are highlighted in orange. The twelve helices of the ligand binding domain (LBD) are boxed based on the human ER $\alpha$  sequence. As in Figure 5, residues involved in estrogen binding in ER are highlighted in green. Homologous residues that are shared by the cnidarian NR3E and the vertebrate oxosteroid receptors (SRs) are highlighted in pink. The cnidarian-specific N79-W80 anchor is highlighted in brown.

	DBD	LBD
NR3E <i>Hydra magnipapillata</i>	--	--
NR3F <i>Trichoplax adhaerens</i>	66.7	28.8
NR3E <i>Hydractinia symbiolongicarpus</i>	85.1	51.2
NR3E <i>Aurelia aurita</i>	79.1	40.6
NR3E <i>Rhopilema esculentum</i>	79.1	41.7
NR3E <i>Podocoryna carnea</i>	85.1	52.1
NR3E <i>Nanomia bijuga</i>	83.6	49.3
NR3E <i>Chironex fleckeri</i>	79.1	42.2
NR3E <i>Alatina alata</i>	--	42.7
NR3E <i>Morbakka virulenta</i>	79.1	43.1
NR3E <i>Tripedalia cystophora</i>	79.1	42.2
NR3E <i>Copula sivickisi</i>	79.1	42.2
NR3E <i>Chironex yamaguchi</i>	79.1	42.2
ERRa <i>Homo sapiens</i>	68,2	24.4
ERRb <i>Homo sapiens</i>	66.7	26.8
ERRg <i>Homo sapiens</i>	66.7	26.3
ERR <i>Drosophila melanogaster</i>	65.2	21.2
ERR <i>Crassostrea gigas</i>	65.2	22.8
NR3D <i>Crassostrea gigas</i>	69.7	21.1
NR3D <i>Aplysia californica</i>	68,2	22.4
NR3D <i>Platynereis dumerilii</i>	69.7	19.7
ER <i>Branchiostoma floridae</i>	65.7	23.3
ERa <i>Homo sapiens</i>	71.2	22.8
ERb <i>Homo sapiens</i>	71.2	23.4
SR <i>Branchiostoma floridae</i>	53	18.2
GR <i>Homo sapiens</i>	56.1	19.4
MR <i>Homo sapiens</i>	57.6	17.5
AR <i>Homo sapiens</i>	51.5	16.6

**Supplemental Table 1. Identity percentages of DBDs and LBDs when compared to NR3E from *Hydra*.**



**Supplemental Figure 3. Paraestrol A docking into the ligand binding pocket of estrogen related receptor  $\gamma$  homology-based model of *Hydra* NR3E.** (a) Superposition of the NR3E structural model using ERR $\gamma$  structure (in dark green) where the paraestrol A is represented in light green, the ERR $\gamma$  structure used as template (PDB id: 3D24) is represented in red and for comparison the paraestrol A position found in the NR3E ER model in pink. (b) Detailed view of the ligand binding pocket of NR3E ERR $\gamma$ -based model, highlighting interactions (in yellow dashed lines) between the paraestrol and residues Q42 and N79. Results of the first round of docking experiments are represented in grey, showing one hydrogen bond (in red dashed line) between paraestrol and residue Q42. (c) Detailed view of the binding pocket of NR3E ER $\alpha$ -based model, highlighting interactions (in yellow dashed lines) between the paraestrol and residues Q42 and N79. Results of the first round of docking experiments are represented in grey, showing one hydrogen bond (in red dashed line) between paraestrol and residue N79.