Electronic Supplementary Material (ESI) for Molecular Omics.

Supporting information

A drug discovery approach based on comparative transcriptomics between two potentially toxin-secreting marine annelids: *Glycera alba* and *Hediste diversicolor*

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Table S.1. Sampling.

	Sample Name	Species	Organ	Number of Individuals	Number of Raw Reads
1	GaPR1	*Glycera alba*	Proboscis	1	39 749 500
2	GaPR2	*Glycera alba*	Proboscis	2 (pool)	43 177 154
3	GaPR3l	*Glycera alba*	Proboscis	3 (pool)	45 489 590
4	GaBW1	*Glycera alba*	Skin	1	43 073 170
5	GaBW2	*Glycera alba*	Skin	3 (pool)	46 741 642
6	GaBW3	*Glycera alba*	Skin	3 (pool)	38 915 178
7	Hd1G	*Hediste diversicolor*	Glands	15 (pool)	31 099 868
8	Hd2G	*Hediste diversicolor*	Glands	10 (pool)	123 202 926
9	Hd3G	*Hediste diversicolor*	Glands	10 (pool)	49 858 858
10	Hd1PR	*Hediste diversicolor*	Proboscis	15 (pool)	42 056 540
11	Hd2PR	*Hediste diversicolor*	Proboscis	10 (pool)	94 650 066
12	Hd3PR	*Hediste diversicolor*	Proboscis	10 (pool)	42 195 514

Table S.2. The primers sequences used for PCR and RT-qPCR. The genes of interest amplified encoded for an ovoinhibitor (Ov), a cysteine-rich venom protein (TX31), a pathogenesis-related protein (a CRISP) (Pat) and thyrostimulin beta-5 subunit (Thy), whereas housekeeping calibrators were 18S and beta-actin (BAct). The primer forward of the Thyrostimulin beta-5 subunit was used for PCR and RT-qPCR.

Target	Primers	PCR or RT-qPCR	Primer Sequences	Amplicon Size
18S	Foward	PCR/RT-qPCR	CGATGGTACGTGATATGCC	176
	Reverse	PCR/RT-qPCR	CGAATGAGTCCCGTATTGT	
BAct	Foward	PCR/RT-qPCR	CGGTATCGTGCTGGATTC	163
	Reverse	PCR/RT-qPCR	CGTGGTGGTGAAGCTGTA	
Ov	Foward_1	PCR	GCTTACATCTTATCATGCTC	639
	Reverse_1	PCR	CTGTATTGCACTCAGGTTC	
	Foward_2	PCR	CTACAAGTCGTGTCATGC	789
	Reverse_2	PCR	CTGCTTCTATTGGTTGGC	
TX31	Foward	PCR	GAATCCTGAACCTGTCTGTG	954
	Reverse	PCR	CAACCTGTTCTTAACATACTCC	
Pat	Foward	PCR	GTGGTCAAGATCAGAACTGC	667
	Reverse	PCR	GGAAACCATTTACAGGAGAGG	
Thy	Foward	PCR/RT-qPCR	GGACAGGCATGAAGGACA	465
	Reverse	PCR	CTCACAACGATTCGCAACT	
Ov	Foward	RT-qPCR	GTGTACCTACGAATACAACC	150
	Reverse	RT-qPCR	CCATCAGATCCGCAAACT	
TX31	Foward	RT-qPCR	AGGCTTCTTGAATGATGCT	172
	Reverse	RT-qPCR	TGTGTTGGACAGTGGTT	
Pat	Foward	RT-qPCR	ACCTCATCATCCTCTTTGC	140
	Reverse	RT-qPCR	TCTGCTGCTCAGTCTTGC	
Thy	Reverse	RT-qPCR	AGGATACAGACGGCAGTG	167

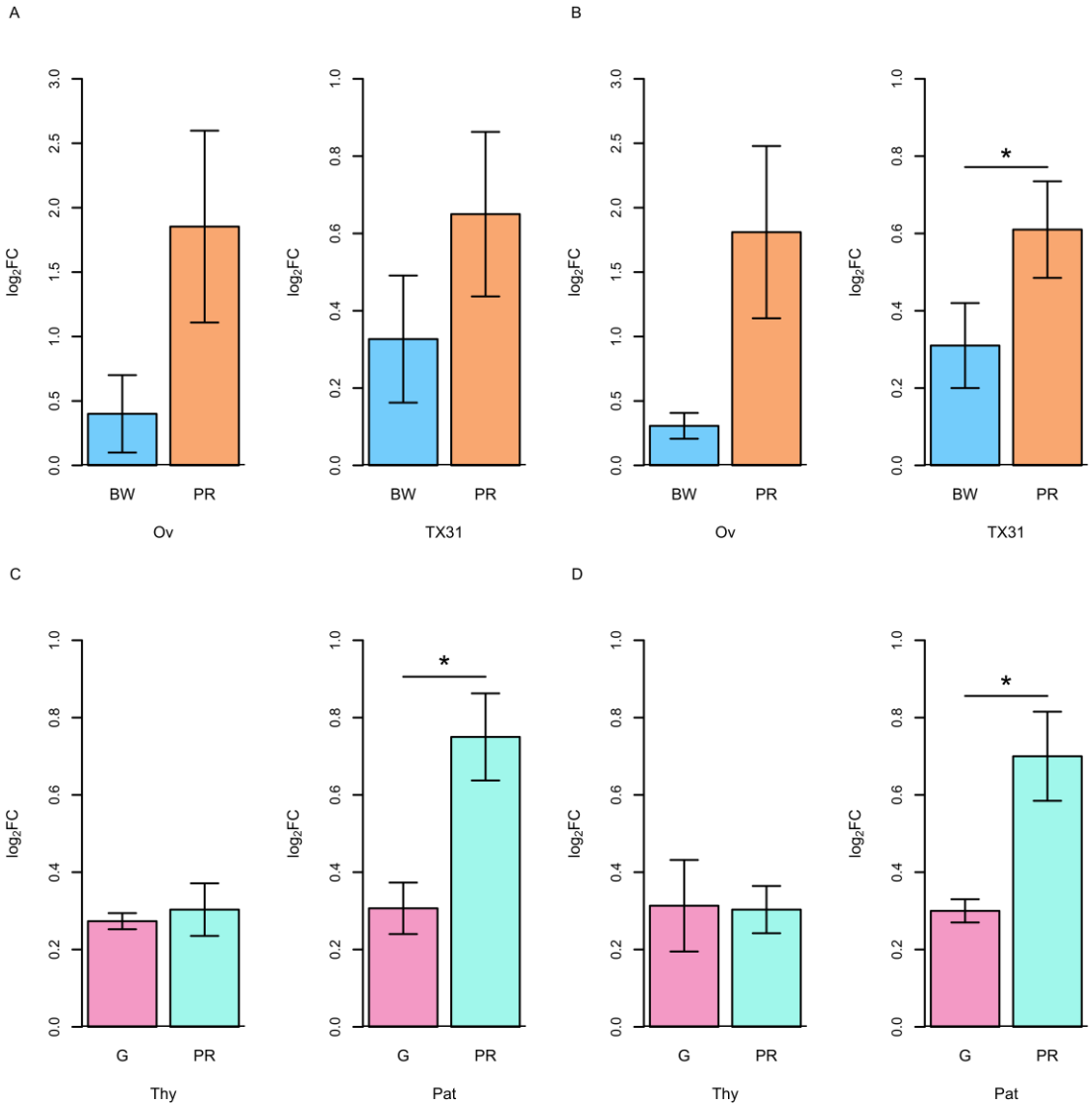

Figure S.1. Relative expression of selected genes in *Glycera alba* and *Hediste diversicolor*. The expressed sequence tags (EST) detected by RT-qPCR were in mRNAs that encoded for an ovoinhibitor-like protein (Ov), a cysteine-rich venom protein (TX31), a pathogenesis-related protein (a CRISP) (Pat) and thyrostimulin beta-5 subunit (Thy). Relative levels of expression of Ov and TX31 were compared between *Glycera alba*'s proboscis (PR) and skin (BW) (A and B), while, for Thy and Pat, the comparison was between *Hediste diversicolor*'s glands (G) and proboscis (PR) (C and D). In A) and C), the levels of expression were normalized with the house-keeping gene 18S, while in B) and D) were with beta-actin. *indicates significant differences between organs (Student's

t-test, $p < 0.05$). Although the relative expression of gene that encoded the ovoinhibitor-like protein was not found to be significantly different, likely due to relatively high error and low *n*, the trend is similar to RNA-Seq-based quantification, i.e., a higher expression in the proboscis relative to the skin. The relative expression of the gene that encodes thyrostimulin beta-5 subunit was not either found to be significantly different between *H. diversicolor*'s organs. This might be due to the $\log_2$FC value, which was 2.33.

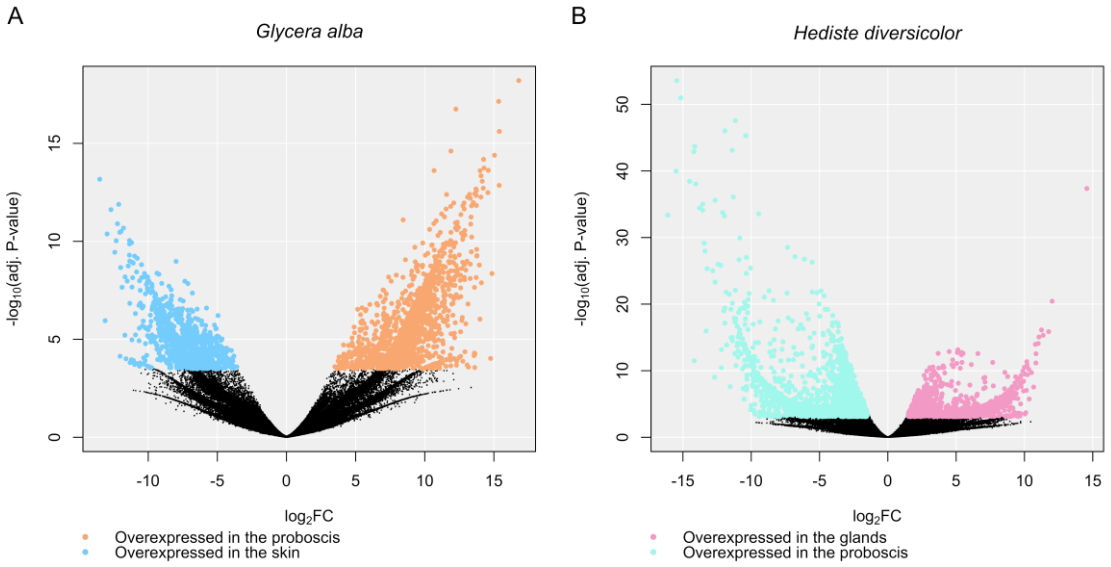

Figure S.2. Volcano plot of differentially-expressed genes. A) between *Glycera alba*'s proboscis and skin. B) between *Hediste diversicolor*'s glands and proboscis. Black dots represent genes that are not differentially-expressed between organs. The cut-off for differential expression was set at $| \log_2FC | > 1.5$ and FDR-adjusted $p < 0.05$.

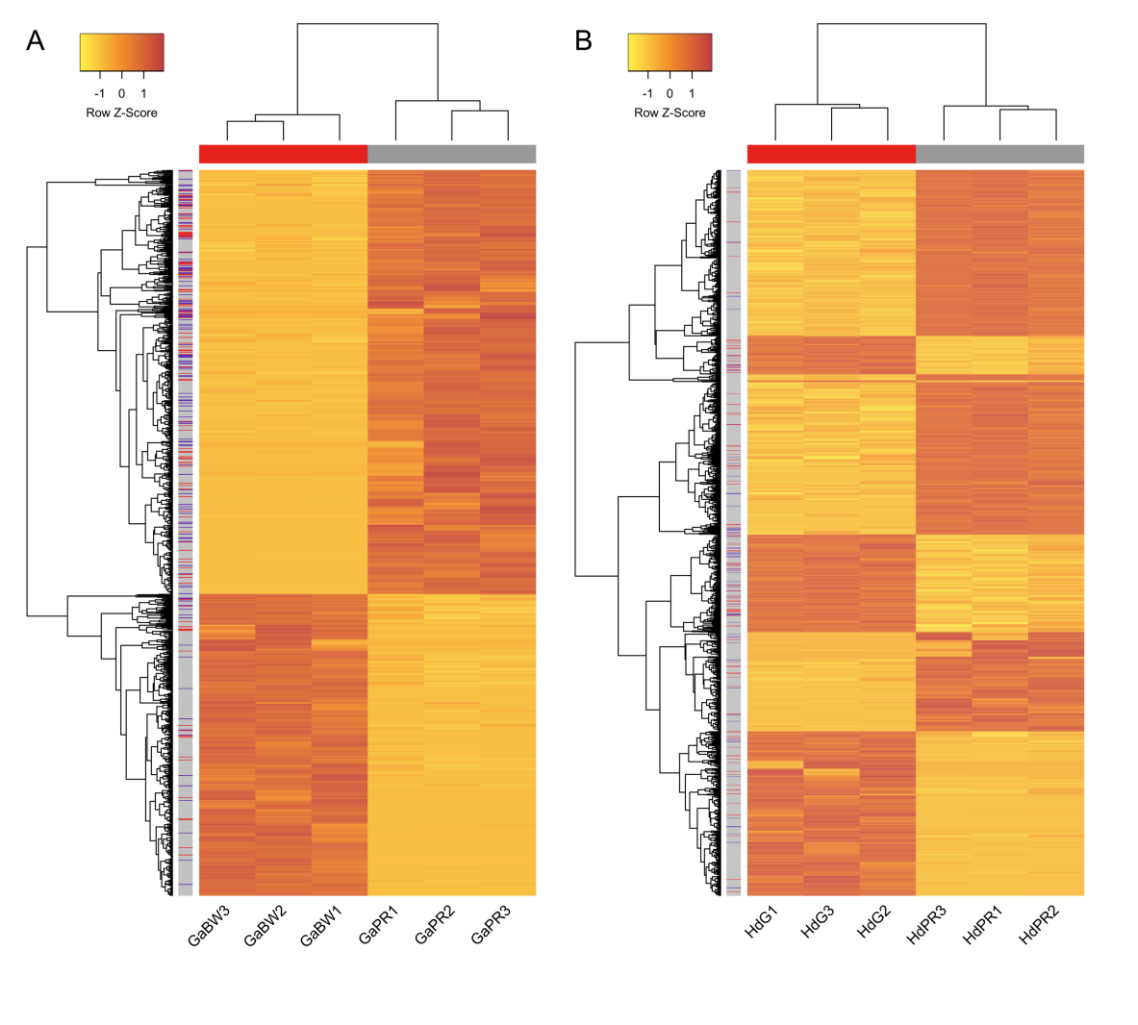

Figure S.3. Heatmaps illustrating differential gene expression profiling. A) between *Glycera alba*'s proboscis (PR) and skin (BW). B) between *Hediste diversicolor*'s glands (G) and proboscis (PR). A $|\log_2 FC| > 1.5$ and an FDR adjusted $p < 0.05$ were the cut-offs set for differential expression. The horizontal dendrogram illustrates the association between the three independent replicates, whereas the vertical dendrogram represents the association between the expression profiling of different genes. The metric and function of the cluster analysis are Euclidian distances and complete linkage, respectively. Side bars indicate coding regions with homology-matching with potential toxins (blue) and permeabilizing or diffusing agents (red).

Table S.3. Top10 overexpressed genes in *Glycera alba*'s proboscis relative to the skin. The cut-offs established were $log_2FC > 1.5$ and an FDR-adjusted $p < 0.05$.

log_2FC	log_2CPM	FDR*p*	Protein	Accession	%ID	*e*-value	Organism
14.595	6.903	2.37E-14	Cysteine-rich venom protein (CRVP) (Substrate-specific endoprotease Tex31)	Q7YT83	35.567	1.59E-22	*Conus textile*
14.566	6.875	3.27E-13	Pancreatic triacylglycerol lipase (Fragment)	Q64425	34.921	1.75E-47	*Myocastor coypus*
14.093	6.402	1.31E-08	Plasma kallikrein (Plasma prekallikrein) (PKK) [Cleaved into: Plasma kallikrein heavy chain; Plasma kallikrein light chain]	P03952	39.382	3.43E-45	*Homo sapiens*
14.061	6.369	5.51E-13	Tenascin-R (Neural recognition molecule J1-160/180)	Q8BYI9	35.859	8.64E-26	*Mus musculus*
13.950	6.259	1.62E-09	Cysteine-rich venom protein (CRVP) (Substrate-specific endoprotease Tex31)	Q7YT83	37.008	6.51E-39	*Conus textile*
13.759	6.068	5.63E-10	Tenascin-R (Restrictin)	Q05546	36.869	2.78E-26	*Rattus norvegicus*
13.756	6.065	2.58E-10	Prolow-density lipoprotein receptor-related protein 1 [Cleaved into: Low-density lipoprotein receptor-related protein 1 85 kDa subunit (LRP-85); Low-density lipoprotein receptor-related protein 1 515 kDa subunit (LRP-515); Low-density lipoprotein receptor-related protein 1 intracellular domain (LRPICD)]	G3V928	34.848	2.02E-46	*Rattus norvegicus*
13.717	6.027	7.02E-09	Glycerotoxin (Fragment)	A0A1U9VX95	31.017	2.37E-172	*Glycera tridactyla*
13.613	5.923	2.73E-04	Ovoinhibitor (Serine protease inhibitor Kazal-type 5) (allergen Gal d OIH)	P10184	29.216	1.34E-30	*Gallus gallus*

log_2FC	**log_2CPM**	**FDR*p***	**Protein**	**Accession**	**%ID**	***e*-value**	**Organism**
13.595	5.905	2.24E-08	A disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAM-TS 7)	Q1EHB3	30.000	1.50E-19	*Rattus norvegicus*

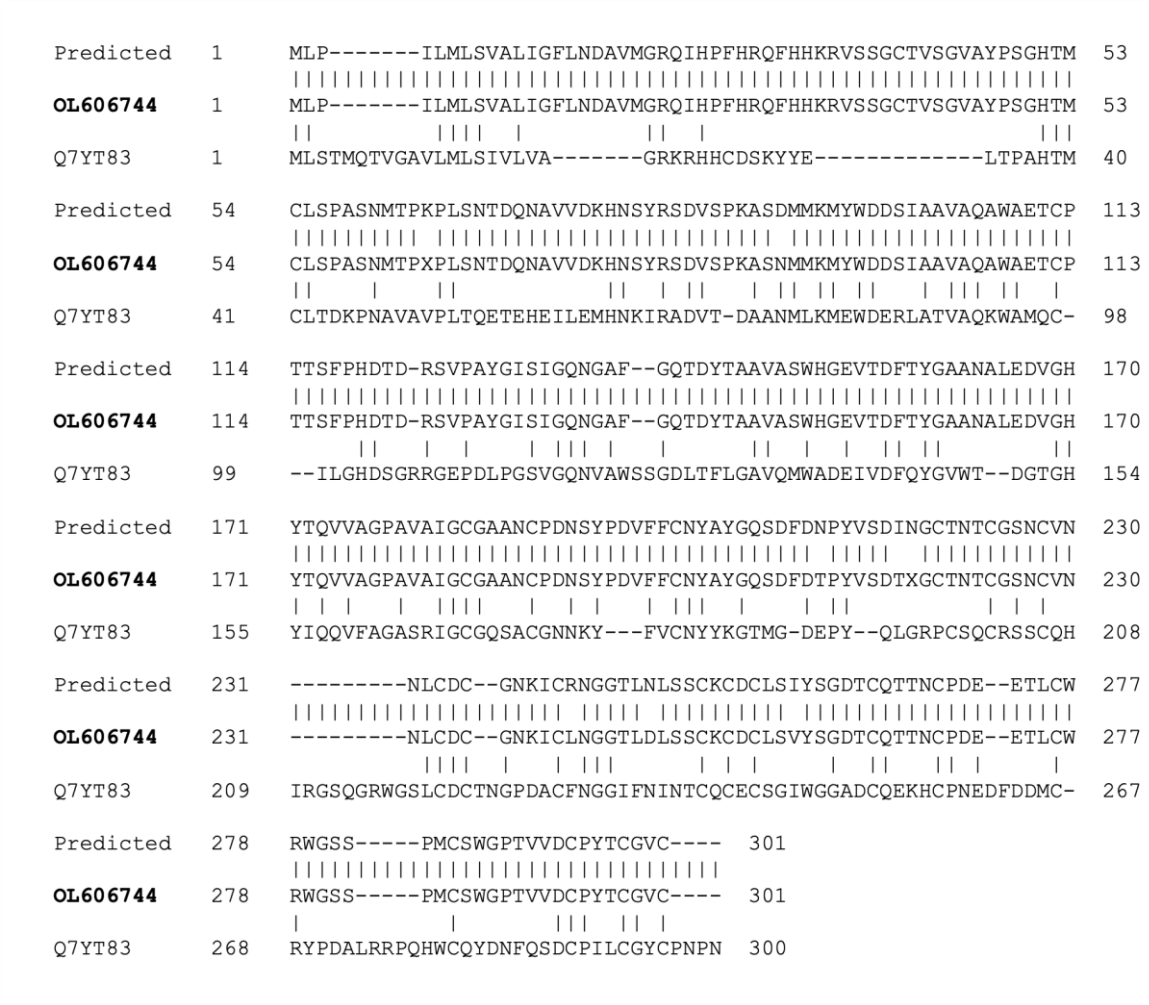

Figure S.4. Aminoacid sequence of a cysteine-rich venom protein isolated from *Glycera alba*. The validated sequence (GenBank accession OL606744) was aligned with the original translated transcript as reconstructed by Trinity (predicted) along with the best hit produced by homology-matching against Swiss-Prot (cysteine-rich venom protein from *Conus textile*, Q7YT83).

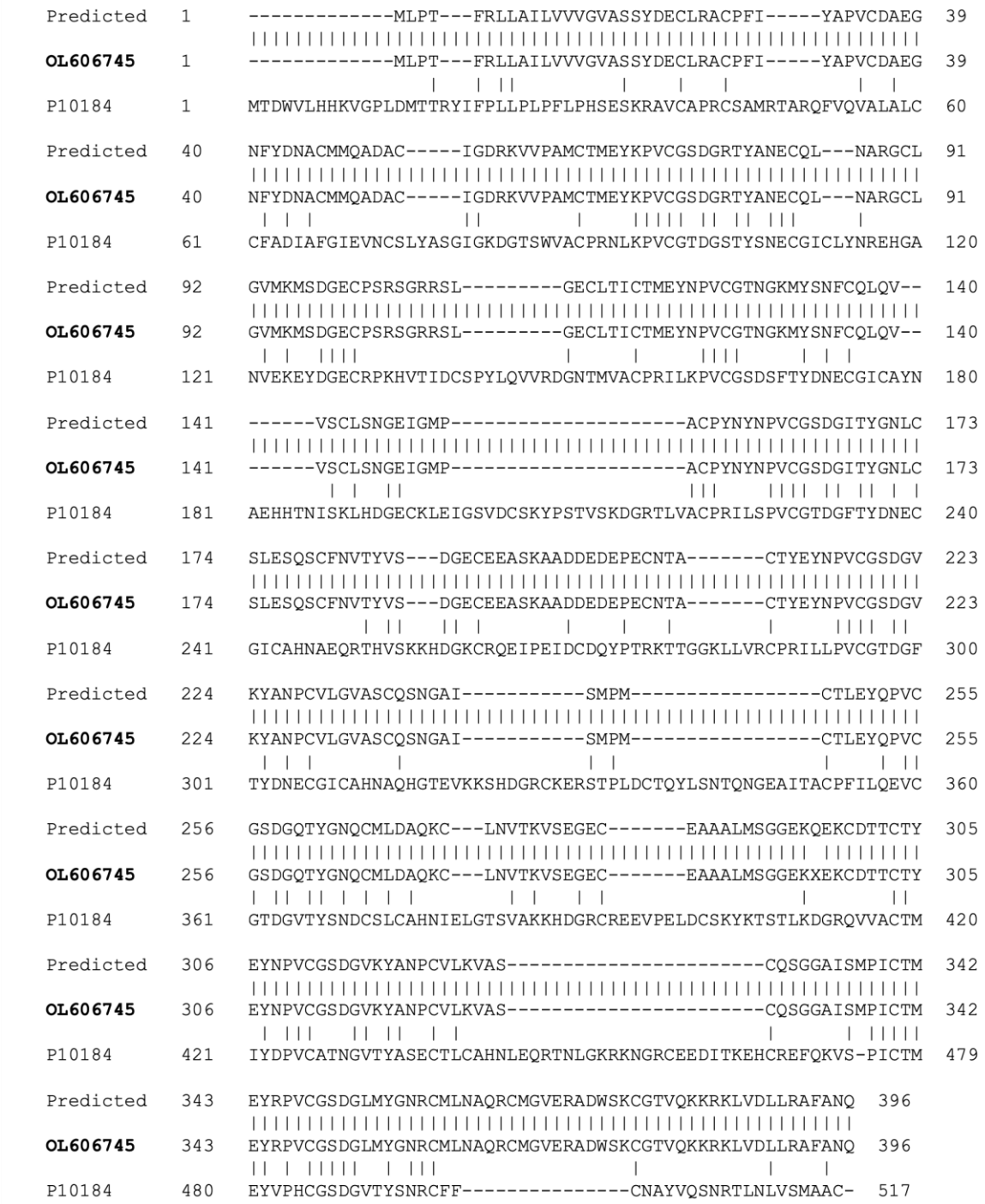

Figure S.5. Aminoacid sequence of an ovoinhibitor-like protein isolated from *Glycera alba*. The validated sequence (GenBank accession OL606745) was aligned with the original

translated transcript as reconstructed by Trinity (predicted) along with the best hit produced by homology-matching against Swiss-Prot (ovoinhibitor from *Gallus gallus*, P10184).

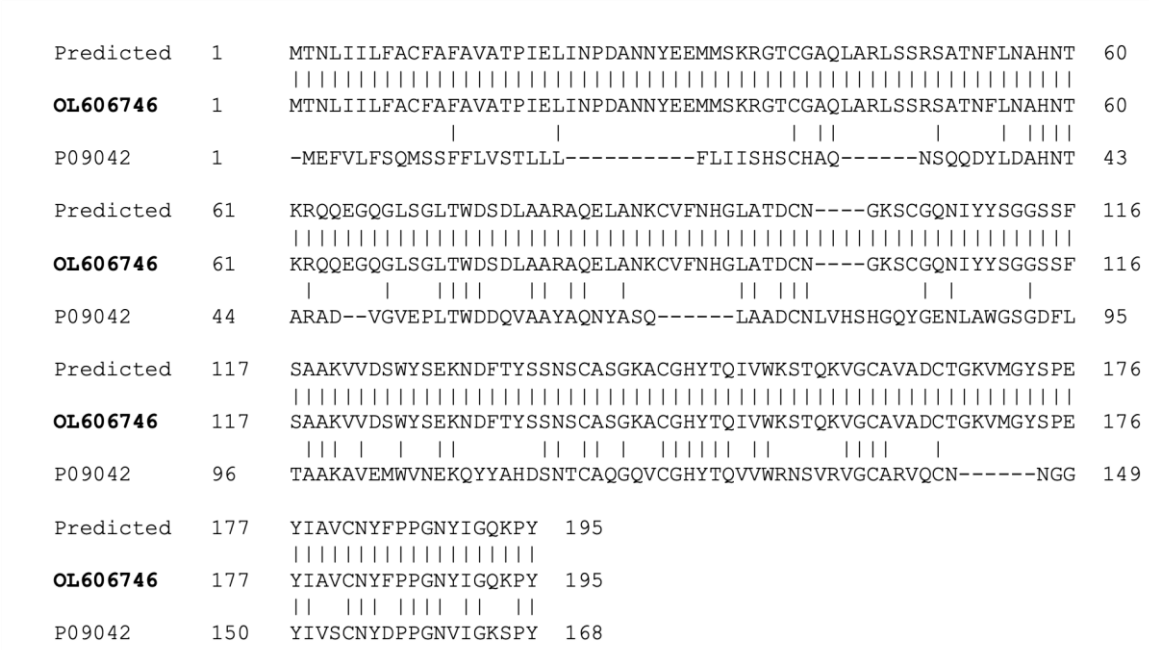

Figure S.6. Aminoacid sequence of a pathogenesis-related protein (a CRISP) isolated from *Hediste diversicolor*. The validated sequence (GenBank accession OL606746) was aligned with the original translated transcript as reconstructed by Trinity (predicted) along with the best hit produced by homology-matching against Swiss-Prot (pathogenesis-related protein 1C from *Nicotiana tabacum*, P09042).

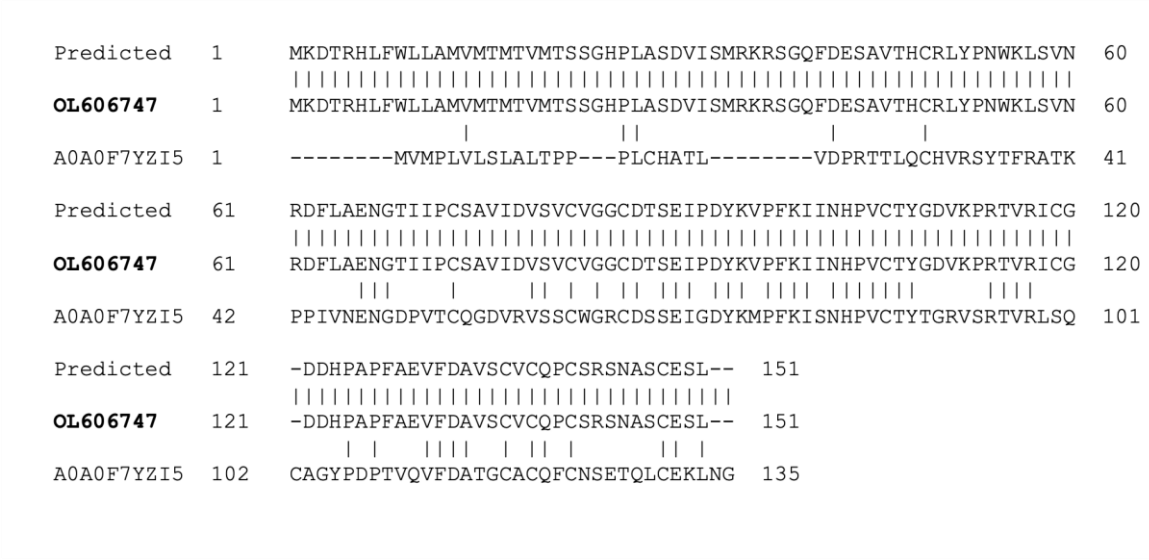

Figure S.7. Aminoacid sequence of thyrostimulin beta-5 subunit isolated from *Hediste diversicolor*. The validated sequence (GenBank accession OL606747) was aligned with the original translated transcript as reconstructed by Trinity (predicted) along with the best hit produced by homology-matching against Swiss-Prot (thyrostimulin beta-5 subunit from *Conus victoriae*, A0A0F7YZI5).

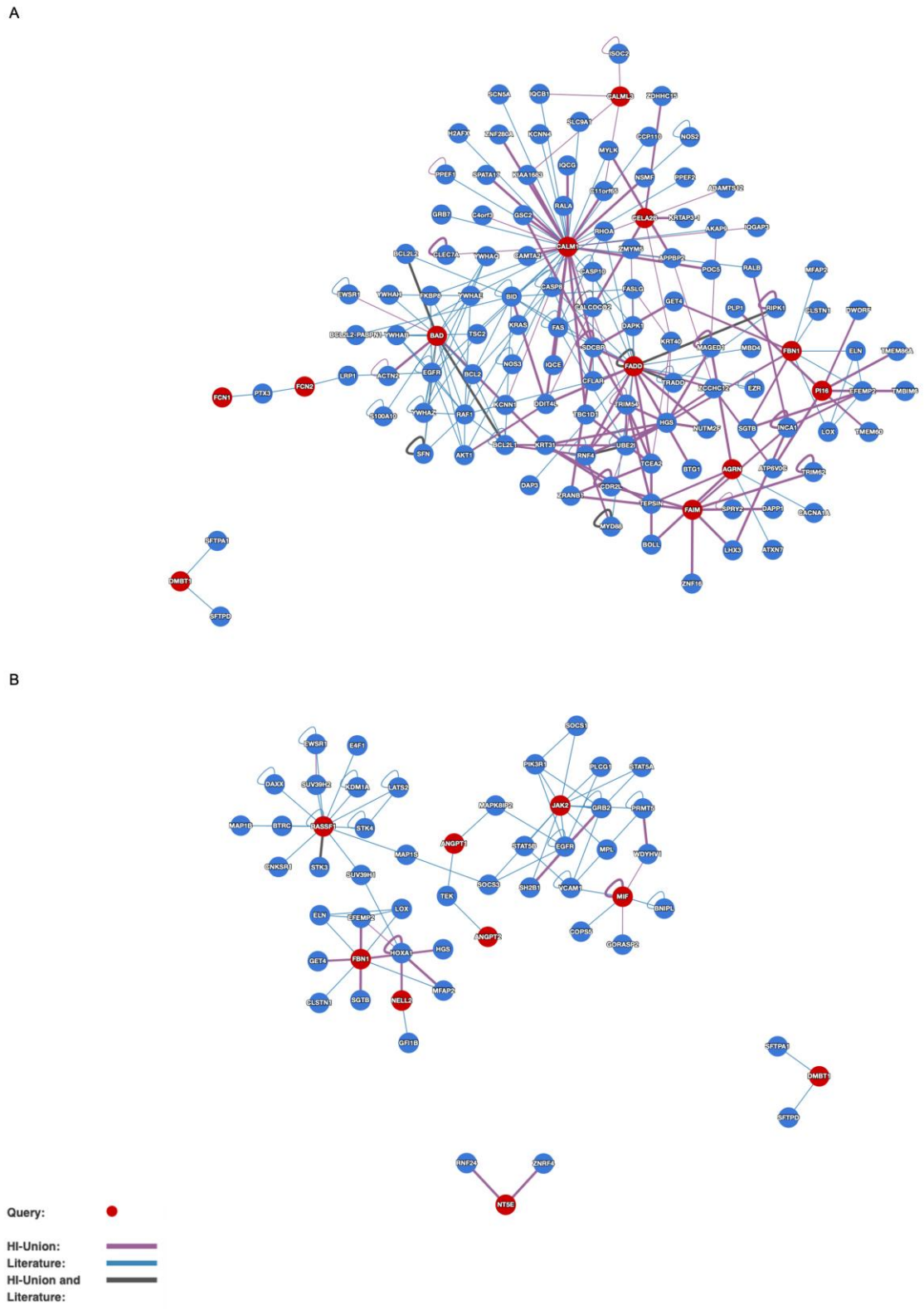

Figure S.8. Protein-protein interactions between the potential interactors from the proboscis and skin of *Glycera alba* and the human proteome retrieved from the HuRI platform. Interactors

were the human homologs of putative proteins up-regulated in the proboscis (A) and in the skin (B).

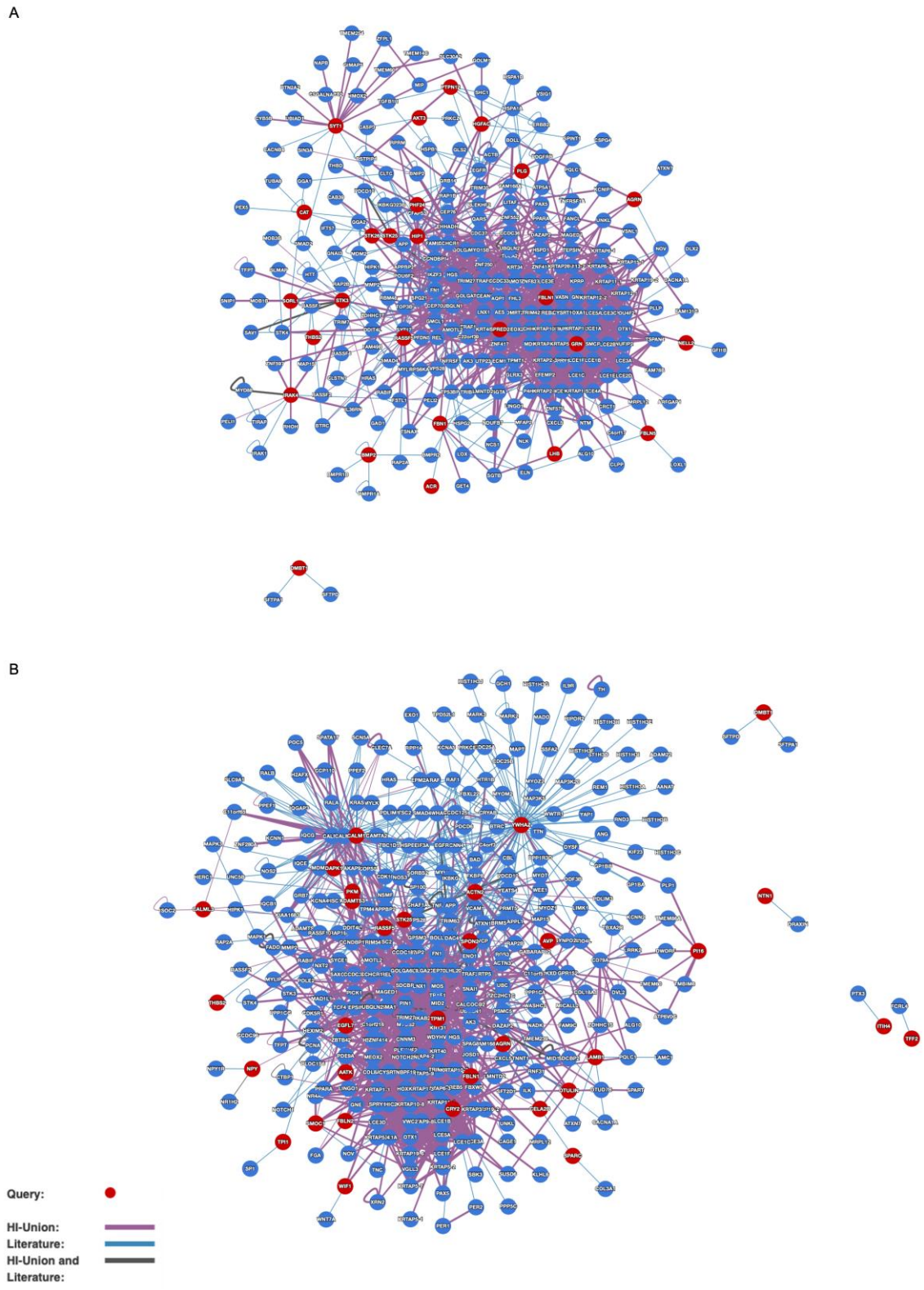

Figure S.9. Protein-protein interactions between the potential interactors from the glands and proboscis of *Hediste diversicolor* and the human proteome retrieved from the HuRI platform.

Interactors were the human homologs of putative proteins up-regulated in the glands (A) and in the proboscis (B).

Table S.4. Enriched biological processes affected by the potential interactors from the proboscis of *Glycera alba* and their human targets. The interactors were the human homologs of the proteins up-regulated in the proboscis. The FDR-adjusted $p < 0.05$ was set as the cut-off. The GO enrichment analysis was performed in the Database for Annotation, Visualization and Integrated Discovery (DAVID).

	GO Terms	%	FDR*p*	Human targets	Interactor
1	positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway [GO:1900740]	8.065	1.60E-10	BCL2, BID, CASP8, SFN, YWHAB, YWHAE, YWHAH, YWHAZ, YWHAQ	BAD
2	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors [GO:1902042]	8.065	2.12E-10	FAS, FASLG, CASP8, DAPK1, NOS3, RAF1, TRADD, RIPK1, CFLAR	FADD
3	extrinsic apoptotic signaling pathway via death domain receptors [GO:0008625]	7.258	2.98E-08	FAS, FASLG, BCL2, BID, CASP10, DAPK1, TRADD	BAD, FADD
4	regulation of extrinsic apoptotic signaling pathway via death domain receptors [GO:1902041]	5.645	1.78E-07	FAS, FASLG, CASP8, TRADD, RIPK1, CFLAR	FADD
5	membrane organization [GO:0061024]	6.452	2.14E-07	SFN, RALA, YWHAB, YWHAE, YWHAH, YWHAZ, YWHAQ, TBC1D1	
6	activation of cysteine-type endopeptidase activity involved in apoptotic signaling pathway [GO:0097296]	4.839	2.08E-06	FAS, FASLG, CASP8, TRADD, RIPK1	FADD
7	negative regulation of apoptotic process [GO:0043066]	13.710	4.05E-06	AKT1, FAS, BCL2, BCL2L1, BCL2L2, EGFR, MYD88, RAF1, SLC9A1, TMBIM6, YWHAZ, ZNF16, LHX3, CFLAR, SPRY2, FKBP8	FAIM

	GO Terms	%	FDR*p*	Human targets	Interactor
8	positive regulation of I-kappaB kinase/NF-kappaB signaling [GO:0043123]	8.871	9.95E-06	FASLG, RHOA, CASP8, CASP10, MYD88, UBE2I, TRADD, RIPK1, CFLAR, TRIM62	FADD
9	regulation of apoptotic process [GO:0042981]	9.677	1.14E-05	ACTN2, FAS, BCL2L1, BCL2L2, BID, CASP8, CASP10, DAPK1, RAF1, CFLAR, MAGED1	FADD
10	death-inducing signaling complex assembly [GO:0071550]	4.032	1.14E-05	CASP8, RAF1, TRADD, RIPK1	FADD
11	extrinsic apoptotic signaling pathway [GO:0097191]	5.645	2.41E-05	FAS, FASLG, CASP8, TRADD, RIPK1	BAD, FADD
12	cellular response to mechanical stimulus [GO:0071260]	6.452	2.66E-05	AKT1, FAS, CASP8, EGFR, MYD88, SLC9A1	BAD, FADD
13	apoptotic signaling pathway [GO:0097190]	6.452	2.66E-05	FAS, FASLG, CASP8, CASP10, DAPK1, DAP3, RIPK1	FADD
14	apoptotic process [GO:0006915]	13.710	4.06E-05	FAS, FASLG, BCL2, CASP8, CASP10, DAPK1, MYD88, RAF1, RALB, DAP3, TRADD, RIPK1, CFLAR, FKBP8	BAD, FADD, FAIM
15	activation of cysteine-type endopeptidase activity involved in apoptotic process [GO:0006919]	6.452	6.78E-05	FAS, FASLG, BID, CASP8, TRADD, RIPK1	BAD, FADD
16	extrinsic apoptotic signaling pathway in absence of ligand [GO:0097192]	4.839	1.52E-04	FAS, BCL2, BCL2L1, BCL2L2	BAD, FADD
17	necroptotic signaling pathway [GO:0097527]	3.226	3.15E-04	FAS, FASLG, RIPK1	FADD
18	release of cytochrome c from mitochondria [GO:0001836]	4.032	7.47E-04	BCL2, BCL2L1, BID, SFN	BAD
19	substantia nigra development [GO:0021762]	4.839	8.14E-04	RHOA, PLP1, YWHAE, YWHAH, YWHAQ	CALM1

	GO Terms	%	FDR*p*	Human targets	Interactor
20	viral process [GO:0016032]	8.871	1.08E-03	RHOA, ATP6V0C, H2AFX, RALA, TSC2, UBE2I, YWHAB, YWHAE, CFLAR, CALCOCO2, FKBP8	
21	signal transduction [GO:0007165]	16.129	5.74E-03	AKT1, FAS, FASLG, DAPK1, EGFR, SFN, GRB7, MYD88, RAF1, RALA, RALB, YWHAZ, TRADD, HGS, AKAP9, DAPP1, TRIM54, IQGAP3	FADD, AGRN, AGRN
22	positive regulation of apoptotic process [GO:0043065]	8.065	5.98E-03	AKT1, FAS, FASLG, BCL2L1, BID, SLC9A1, TRADD, RIPK1	BAD, FADD
23	positive regulation of cell growth [GO:0030307]	4.839	9.14E-03	AKT1, BCL2, EGFR, SFN, SDCBP, SLC9A1	
24	intrinsic apoptotic signaling pathway in response to DNA damage [GO:0008630]	4.032	1.00E-02	BCL2, BCL2L1, BCL2L2, SFN	BAD
25	regulation of nitric-oxide synthase activity [GO:0050999]	3.226	2.54E-02	AKT1, EGFR, NOS3	CALM1
26	protein heterooligomerization [GO:0051291]	4.032	3.62E-02	CASP8, YWHAB, TRADD, RIPK1	FADD
27	positive regulation of peptidyl-serine phosphorylation [GO:0033138]	4.032	3.96E-02	AKT1, BCL2, RAF1, AKAP9, SPRY2	
28	Ras protein signal transduction [GO:0007265]	4.032	3.96E-02	KRAS, RALA, RALB, SDCBP, IQGAP3	
29	positive regulation of intrinsic apoptotic signaling pathway [GO:2001244]	3.226	4.45E-02	BCL2, BCL2L1, BID	BAD

FDRp – False discovery rate adjusted p-value; % – Percentage of proteins

Table S.5. Enriched biological processes affected by the potential interactors from the skin of *Glycera alba* and their human targets. The interactors were the human homologs of the proteins up-regulated in the skin. The FDR-adjusted $p < 0.05$ was set as the cut-off. The GO enrichment analysis was performed in the Database for Annotation, Visualization and Integrated Discovery (DAVID).

	GO Terms	%	FDR*p*	Human targets	Interactor
1	leukocyte migration [GO:0050900]	12.963	7.88E-04	GRB2, PIK3R1, PLCG1, TEK	ANGPT1, ANGPT2, MIF, MIF
2	JAK-STAT cascade [GO:0007259]	9.259	7.88E-04	STAT5A, STAT5B, SOCS1, SOCS3	JAK2
3	Tie signaling pathway [GO:0048014]	5.556	4.84E-03	TEK	ANGPT1, ANGPT2
4	viral process [GO:0016032]	14.815	4.84E-03	DAXX, E4F1, GRB2, PIK3R1, PLCG1, SUV39H1, VCAM1, BTRC	
5	glomerulus vasculature development [GO:0072012]	5.556	6.68E-03	TEK	ANGPT1, ANGPT2
6	cell proliferation [GO:0008283]	14.815	1.15E-02	E4F1, EGFR, ELN, MPL, GFI1B, PRMT5, KDM1A	MIF, MIF

FDRp – False discovery rate adjusted p-value; % – Percentage of proteins

Table S.6. Enriched biological processes affected by the potential interactors from the glands of *Hediste diversicolor* and their human targets. The interactors were the human homologs of the proteins up-regulated in the glands. The FDR-adjusted $p < 0.05$ was set as the cut-off. The GO enrichment analysis was performed in the Database for Annotation, Visualization and Integrated Discovery (DAVID).

	GO Terms	**%**	**FDR*p***	**Target**	**Interactor**
1	peptide cross-linking [GO:0018149]	5.495	3.80E-12	FN1, LCE2B, CRCT1, LCE4A, LCE5A, LCE1A, LCE1B, LCE1C, LCE1D, LCE1E, LCE1F, LCE2D, LCE3A, LCE3C, LCE3E	
2	keratinocyte differentiation [GO:0030216]	6.227	3.80E-12	CASP3, STK4, LCE2B, CRCT1, SAV1, LCE4A, LCE5A, LCE1A, LCE1B, LCE1C, LCE1D, LCE1E, LCE1F, LCE2D, LCE3A, LCE3C, LCE3E	
3	keratinization [GO:0031424]	4.762	7.75E-10	LCE2B, LCE4A, LCE5A, LCE1A, LCE1B, LCE1C, LCE1D, LCE1E, LCE1F, LCE2D, LCE3A, LCE3C, LCE3E	
4	hippo signaling [GO:0035329]	2.564	5.52E-04	CASP3, STK4, AMOTL2, SAV1, MOB1B, AMOT	STK3, STK3
5	signal transduction by protein phosphorylation [GO:0023014]	2.930	6.33E-04	BMPR1A, BMPR1B, BMPR2, STK4, CAB39	STK3, STK3, STK25, STK26, STK26
6	protein stabilization [GO:0050821]	4.396	7.07E-04	HSPA1A, HSPA1B, HSPD1, STK4, RASSF2, CDC37, RASSF1, PDCD10, NLK, SAV1	HIP1, STK3, STK3
7	positive regulation of I-kappaB kinase/NF-kappaB signaling [GO:0043123]	4.396	3.07E-03	ECM1, IRAK1, MYD88, REL, TNFRSF1A, IKBKG, LITAF, ZDHHC17, PELI2, PELI1, TIRAP	IRAK4

	GO Terms	%	FDR*p*	Target	Interactor
8	signal transduction [GO:0007165]	12.821	4.36E-03	ECM1, EGFR, ERBB2, GRB14, HRAS, IRAK1, MYD88, PDGFRB, PRKCZ, RAP2B, CXCL5, SHC1, STK4, THBD, TNFRSF1A, TRAF1, TRAF2, BTRC, PSTPIP1, HGS, LITAF, ZDHHC17, RPS6KA6, SAV1, RASSF4, LINGO1, TIRAP	GRN, GRN, LHB, SORL1, STK3, STK3, AKT3, STK25, IRAK4, AGRN, AGRN, AGRN, AGRN
9	cellular response to BMP stimulus [GO:0071773]	2.198	8.45E-03	BMPR1A, BMPR1B, BMPR2, SMAD4, SPINT1	BMP2
10	response to hydrogen peroxide [GO:0042542]	2.564	1.02E-02	CASP3, HSPD1, PDGFRB, PDCD10	CAT, STK25, STK26, STK26
11	extracellular matrix organization [GO:0030198]	4.396	1.17E-02	APP, ELN, FN1, HSPG2, LOX, LOXL1, MFAP2, SPINT1	FBLN1, FBN1, FBN1, FBLN5, AGRN, AGRN, AGRN, AGRN
12	positive regulation of NF-kappaB transcription factor activity [GO:0051092]	3.663	1.17E-02	HSPA1A, HSPA1B, IRAK1, MYD88, PRKCZ, TRAF1, TRAF2, IKBKG, TIRAP	CAT
13	positive regulation of MAP kinase activity [GO:0043406]	2.564	1.79E-02	EGFR, ERBB2, HRAS, IRAK1, PDGFRB, MAGED1, PDCD10	
14	protein phosphorylation [GO:0006468]	6.593	2.13E-02	APP, BMPR1A, BMPR1B, ERBB2, IRAK1, SMAD2, PRKCZ, STK4, RASSF2, RPS6KA6, NLK, TRIB3, HIPK1	BMP2, STK3, STK3, AKT3, STK25, STK26, STK26

	GO Terms	%	FDR*p*	Target	Interactor
15	cellular protein metabolic process [GO:0044267]	3.297	2.26E-02	APP, HSPG2, MMP2, SFTPD, GGA2, GGA1, SFTPA1	DMBT1, DMBT1, DMBT1, DMBT1, DMBT1, PLG, PLG

FDRp – False discovery rate adjusted p-value; % – Percentage of proteins

Table S.7. Enriched biological processes affected by potential interactors from the proboscis of *Hediste diversicolor* and their human targets. The interactors were the human homologs of the proteins up-regulated in the proboscis. The FDR-adjusted $p < 0.05$ was set as the cut-off. The GO enrichment analysis was performed in the Database for Annotation, Visualization and Integrated Discovery (DAVID).

	GO Terms	**%**	**FDR*p***	**Target**	**Interactor**
1	regulation of gene silencing [GO:0060968]	2.8169	2.58E-11	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
2	DNA replication-dependent nucleosome assembly [GO:0006335]	3.0986	1.97E-07	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F, CHAF1A	
3	cellular protein metabolic process [GO:0044267]	4.7887	4.00E-07	APP, FGA, MMP2, SFTPD, UBC, HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F, SFTPA1	DMBT1, DMBT1
4	telomere organization [GO:0032200]	2.8169	4.25E-07	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
5	chromatin silencing at rDNA [GO:0000183]	2.8169	7.66E-06	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
6	negative regulation of gene expression, epigenetic [GO:0045814]	3.0986	7.79E-06	TRIM27, HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	

	GO Terms	%	FDR*p*	Target	Interactor
7	regulation of tumor necrosis factor-mediated signaling pathway [GO:0010803]	2.5352	1.57E-05	TNFAIP3, TRAF1, TRAF2, UBC, IKBKG, MADD, RNF31, HIPK1	OTULIN, OTULIN, OTULIN, OTULIN
8	protein heterotetramerization [GO:0051290]	2.8169	1.58E-05	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
9	MAPK cascade [GO:0000165]	5.6338	1.10E-04	ARAF, CALM2, CALM3, EGFR, HRAS, KRAS, MARK3, MAP3K5, MOS, PPP5C, MAPK1, MAPK3, PSMA1, PSMC5, RAF1, UBC, AKAP9, LRRK2	ACTN2, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
10	muscle contraction [GO:0006936]	3.6620	1.45E-04	ACTN3, CALM2, CALM3, CRYAB, MYLK, TPM4, TTN, DYSF, MYOM2, MYOT, TRIM63	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, TPM1
11	response to calcium ion [GO:0051592]	2.8169	2.12E-04	AANAT, BAD, CALM2, CALM3, EGFR, FGA, TTN, PDCD6	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, SPARC, SPARC

	GO Terms	%	FDR*p*	Target	Interactor
12	positive regulation of gene expression, epigenetic [GO:0045815]	2.8169	3.46E-04	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
13	positive regulation of protein serine/threonine kinase activity [GO:0071902]	2.2535	4.88E-04	CALM2, CALM3, RALB, STK3, STK4, CDK5R1, PDCD10	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
14	cell-cell adhesion [GO:0098609]	5.3521	4.88E-04	CBL, MARK2, ENO1, GOLGA2, SDCBP, YWHAE, HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F, PDLIM1	PKM, PKM, YWHAZ
15	peptide cross-linking [GO:0018149]	2.5352	4.88E-04	COL3A1, FN1, LCE3D, LCE5A, LCE1A, LCE1B, LCE1C, LCE1F, LCE3A	
16	protein phosphorylation [GO:0006468]	7.0423	6.33E-04	APP, CDC25B, CTBP1, MARK2, ILK, LIMK1, MAP3K5, MYLK, CDK16, PRKAB2, PRKCE, MAPK1, MAPK3, RAF1, STK3, STK4, PICK1, RASSF2, MAP3K20, LRRK2, HIPK1, SBK3	DAPK1, AATK, AATK, STK25
17	hippo signaling [GO:0035329]	1.9718	1.01E-03	DVL2, STK3, STK4, YWHAE, YAP1, WWTR1, AMOTL2	

	GO Terms	%	FDR*p*	Target	Interactor
18	blood coagulation [GO:0007596]	4.2254	1.01E-03	FGA, GP1BA, GP1BB, HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F, BLOC1S6, AK3	
19	G2/M transition of mitotic cell cycle [GO:0000086]	3.6620	1.01E-03	CALM2, CALM3, CDC25A, CDC25B, TPD52L1, UBC, WEE1, YWHAE, BTRC, CCP110, AKAP9, CEP70	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
20	circadian regulation of gene expression [GO:0032922]	2.5352	1.01E-03	PER1, PPARA, PPP1CA, PPP1CC, PER2, USP2, MAGED1, PRMT5	CRY2
21	keratinocyte differentiation [GO:0030216]	2.8169	1.11E-03	NOTCH1, STK4, YAP1, LCE3D, LCE5A, LCE1A, LCE1B, LCE1C, LCE1F, LCE3A	
22	wound healing [GO:0042060]	2.8169	1.61E-03	COL3A1, EGFR, FN1, TNC, MAP3K5, PPARA, RAF1	SPARC, SPARC, TFF2, TPM1
23	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors [GO:1902042]	1.9718	2.56E-03	FGA, NOS3, RAF1, TNFAIP3, TRAF2, FADD	DAPK1
24	regulation of circadian rhythm [GO:0042752]	2.2535	2.71E-03	PER1, PPARA, PPP1CA, PPP1CC, PER2, BTRC, MAGED1	CRY2
25	positive regulation of protein autophosphorylation [GO:0031954]	1.6901	2.83E-03	CALM2, CALM3, RAP2A, RAP2B, RASSF2	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1,

	GO Terms	%	FDR*p*	Target	Interactor
					CALM1, CALM1, CALM1
26	nucleosome assembly [GO:0006334]	3.0986	6.01E-03	H2AFX, HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
27	response to hypoxia [GO:0001666]	3.6620	7.02E-03	ANG, BAD, CRYAB, KCNA5, SMAD4, MMP2, NOS2, PPARA, RAF1, TH, VCAM1, PDLIM1	PKM, PKM
28	regulation of nitric-oxide synthase activity [GO:0050999]	1.6901	7.56E-03	CALM2, CALM3, EGFR, GCH1, NOS3	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
29	positive regulation of MAP kinase activity [GO:0043406]	2.2535	7.60E-03	EGFR, HRAS, ILK, KRAS, TPD52L1, MAGED1, PDCD10, LRRK2	
30	positive regulation of epithelial cell proliferation [GO:0050679]	2.2535	8.18E-03	BAD, EGFR, HRAS, LAMC1, NOTCH1, SCN5A, NR4A3	LAMB1, LAMB1, LAMB1, LAMB1

	GO Terms	%	FDR*p*	Target	Interactor
31	platelet degranulation [GO:0002576]	2.8169	8.53E-03	APP, CALM2, CALM3, FGA, FN1, TTN	ACTN2, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, ITIH4, SPARC, SPARC
32	positive regulation of cell migration [GO:0030335]	3.6620	1.12E-02	EGFR, GRB7, HRAS, ILK, MYLK, NOTCH1, MAPK1, SDCBP, SNAI1, PDCD10, COL18A1, WASHC1	LAMB1, LAMB1, LAMB1, LAMB1
33	positive regulation of axon extension [GO:0045773]	1.6901	1.31E-02	FN1, ILK, LIMK1, MAPT, DISC1	NTN1, NTN1
34	gene silencing by RNA [GO:0031047]	2.8169	1.38E-02	HIST1H3A, HIST1H3D, HIST1H3C, HIST1H3E, HIST1H3I, HIST1H3G, HIST1H3J, HIST1H3H, HIST1H3B, HIST1H3F	
35	keratinization [GO:0031424]	1.9718	1.47E-02	LCE3D, LCE5A, LCE1A, LCE1B, LCE1C, LCE1F, LCE3A	
36	angiogenesis [GO:0001525]	3.9437	1.61E-02	ANG, COL8A1, FN1, MEOX2, MMP2, MYH9, NOS3, NOV, WNT7A, PDCD6, PDCD10, COL18A1, UNC5B	EGFL7
37	response to corticosterone [GO:0051412]	1.4085	1.61E-02	AANAT, CALM2, CALM3, TH	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1

	GO Terms	%	FDR*p*	Target	Interactor
38	platelet activation [GO:0030168]	2.8169	1.61E-02	COL3A1, FGA, GP1BA, GP1BB, PRKCE, MAPK1, MAPK3, RAF1, RAP2B	YWHAZ
39	extracellular matrix organization [GO:0030198]	3.6620	1.65E-02	APP, COL3A1, COL8A1, FGA, FN1, TNC, LAMC1, VCAM1, COL18A1	FBLN1, LAMB1, LAMB1, LAMB1, LAMB1, SPARC, SPARC, AGRN, AGRN, AGRN, AGRN
40	microtubule cytoskeleton organization [GO:0000226]	2.2535	1.78E-02	MARK2, MAPT, MARK3, MID1, ATXN7, WEE1, DISC1, MAP1S	
41	entrainment of circadian clock by photoperiod [GO:0043153]	1.4085	2.26E-02	PER1, PPP1CA, PPP1CC, USP2	CRY2
42	viral process [GO:0016032]	4.5070	2.42E-02	ATP6V0C, H2AFX, MDM2, MAP3K5, MAPK1, MAPK3, RALA, SP1, SP100, TSC2, VCAM1, YWHAE, BTRC, CALCOCO2, FKBP8	FBLN1
43	Fc-epsilon receptor signaling pathway [GO:0038095]	3.3803	2.42E-02	CALM2, CALM3, HRAS, KRAS, MAPK1, MAPK3, PSMA1, PSMC5, UBC, IKBKG, BTRC	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1

	GO Terms	%	FDR*p*	Target	Interactor
44	regulation of cell cycle [GO:0051726]	2.8169	2.42E-02	CDC25A, CTBP1, CDK16, TSC2, WEE1, MADD, PER2, BTRC, COPS5, CCNDBP1	
45	positive regulation of protein dephosphorylation [GO:0035307]	1.4085	2.50E-02	CALM2, CALM3, PIN1, NSMF	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
46	cerebral cortex development [GO:0021987]	1.9718	2.62E-02	BAD, COL3A1, H2AFX, PAX5, TH, YWHAE	NPY
47	positive regulation of protein phosphorylation [GO:0001934]	2.8169	2.66E-02	DVL2, EGFR, HRAS, KRAS, PIN1, MAPK3, RALB, RAP2A, STK4, LRRK2	
48	negative regulation of protein binding [GO:0032091]	1.9718	2.66E-02	GOLGA2, PIN1, PPARA, PPP1CA, RALB, TMBIM6, LRRK2	
49	muscle filament sliding [GO:0030049]	1.6901	2.66E-02	ACTN3, TNNT1, TPM4, TTN	ACTN2, TPM1
50	positive regulation of nitric-oxide synthase activity [GO:0051000]	1.4085	2.66E-02	CALM2, CALM3, GCH1, KRAS	CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1, CALM1
51	regulation of cytokinesis [GO:0032465]	1.4085	2.66E-02	CALM2, CALM3, PIN1, CCP110	CALM1, CALM1, CALM1, CALM1,

	GO Terms	%	FDR*p*	Target	Interactor
					CALM1, CALM1, CALM1, CALM1, CALM1
52	stimulatory C-type lectin receptor signaling pathway [GO:0002223]	2.5352	2.97E-02	HRAS, KRAS, PSMA1, PSMC5, RAF1, UBC, IKBKG, BTRC, CLEC7A	
53	response to ethanol [GO:0045471]	2.5352	2.97E-02	BAD, CBL, HTR1B, TNC, TBXA2R, TH, VCAM1	AVP, SPARC, SPARC
54	axon guidance [GO:0007411]	3.0986	3.03E-02	HRAS, KRAS, SMAD4, MAPK1, MAPK3, NR4A3, CDK5R1, ZNF280A, DRAXIN	NTN1, NTN1, SPON2
55	negative regulation of neuron death [GO:1901215]	1.6901	3.11E-02	PPARA, PPP5C, REL, TRAF2, IKBKG, LRRK2	
56	platelet aggregation [GO:0070527]	1.6901	3.35E-02	FGA, GP1BA, HSPB1, ILK, MYH9, RAP2B	
57	signal transduction [GO:0007165]	10.7042	3.35E-02	EGFR, FGA, GRB7, HRAS, IL9R, LIMK1, PDE9A, PRKAB2, PRKCE, MAPK1, RAF1, RALA, RALB, RAP2B, CXCL5, STK3, STK4, TRAF1, TRAF2, FADD, BTRC, HGS, AKAP9, APPL1, TRIM54, TRIM63, LINGO1, IQGAP3, UNC5B, RASSF10	AVP, DAPK1, SPARC, SPARC, YWHAZ, STK25, WIF1, SMOC1, SMOC1, SMOC1, AGRN, AGRN, AGRN, AGRN
58	neuron death [GO:0070997]	1.1268	3.35E-02	CBL, MEOX2, SLC9A1, LRRK2	
59	endocardium development [GO:0003157]	0.8451	3.51E-02	NOTCH1, STK3, STK4	
60	positive regulation of cyclic nucleotide metabolic process [GO:0030801]	0.8451	3.51E-02	CALM2, CALM3	CALM1, CALM1, CALM1, CALM1,

	GO Terms	%	FDR*p*	Target	Interactor
					CALM1, CALM1, CALM1, CALM1, CALM1
61	positive regulation of cell proliferation [GO:0008284]	5.6338	4.06E-02	CDC25B, EGFR, FN1, HRAS, TNC, ILK, KRAS, MDM2, NOTCH1, MAPK1, CXCL5, SDCBP, HDAC4, YAP1, PDCD10, WWTR1, COL18A1, HIPK1	AVP, NTN1, NTN1
62	positive regulation of JNK cascade [GO:0046330]	1.9718	4.30E-02	HRAS, MAP3K5, SDCBP, STK3, TPD52L1, WNT7A, RASSF2	

FDRp – False discovery rate adjusted p-value; % – Percentage of proteins