Neuroproteomic Profiling of the Anxiolytic Potential of *Stypopodium zonale* in *Drosophila*

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Figure S1. Short-run SDS-PAGE of control (C1-C5) and experimental (E1-E5) *Drosophila* head protein samples prior to in-gel digestion.

Table S1. TMT10plex labelling design.

Table S2. List of 66 differentially abundant proteins with their accession numbers and descriptions that met the significance criteria of $p \leq 0.05$ and a fold change (FC) $\geq |1.5|$.

Table S3. Annotation of 66 *Drosophila melanogaster* proteins identified by quantitative proteomics using the UniProt database.

Table S4. Canonical pathways with their corresponding -log(p-value), z-score and molecules associated to each pathway.

Table S5. IPA Pathway interaction table.

Figure S1. Short-run SDS-PAGE of control (C1-C5) and experimental (E1-E5) *Drosophila* head protein samples prior to in-gel digestion.



Comparable band intensity across lanes reflects normalization to equal total protein input (100 µg per sample) prior to in-gel digestion and LC-MS/MS analysis. This uniform Coomassie staining supports the use of these samples for quantitative proteomic comparison.

Table S1. TMT10plex labelling design.

TMT Label	Sample ID
126	C1
127N	C2
127C	C3
128N	C4
128C	C5
129N	E1
129C	E2
130N	E3
130C	E4
131N	E5
131C	N/A

A TMT 10-plex labeling strategy was used to analyze *Drosophila* head proteins, with five control samples (C) and five experimental samples (E) assigned across the multiplex. Only four biological replicates per group are presented in the manuscript, as statistical filtering indicated that protein abundance measurements were most robust and reproducible across these four samples.

Table S2. List of 66 differentially abundant proteins with their accession numbers and descriptions that met the significance criteria of $p \leq 0.05$ and a fold change (FC) $\geq |1.5|$.

Accesion	Description	FC	log2(FC)	p value	-LOG10(p)
Q960T2	Synapse-associated protein of 47 kDa [OS=Drosophila melanogaster]	-2.8322	-1.5019	2.25E-07	6.6475
Q23970	Pheromone-binding protein-related protein 6 [OS=Drosophila melanogaster]	-2.6168	-1.3878	5.72E-08	7.243
P06002	Opsin Rh1 [OS=Drosophila melanogaster]	-2.5137	-1.3298	3.92E-09	8.4062
P29746	Protein bangles and beads [OS=Drosophila melanogaster]	-2.4291	-1.2804	5.26E-08	7.2793
P54195	General odorant-binding protein 28a [OS=Drosophila melanogaster]	-2.2982	-1.2005	9.53E-06	5.0208
P54192	General odorant-binding protein 19d [OS=Drosophila melanogaster]	-2.2099	-1.144	3.36E-06	5.4743
Q06943	High mobility group protein Z [OS=Drosophila melanogaster]	-2.0177	-1.0127	4.09E-06	5.3884
Q9NFZ3	Guanine nucleotide-binding protein subunit gamma-e [OS=Drosophila melanogaster]	-1.9425	-0.95794	1.28E-05	4.8918
Q9W369	Beta-alanyl-dopamine/carcinine hydrolase [OS=Drosophila melanogaster]	-1.9352	-0.95248	1.48E-06	5.8285
P54193	General odorant-binding protein 83a [OS=Drosophila melanogaster]	-1.9145	-0.937	3.59E-05	4.4453
Q05783	High mobility group protein D [OS=Drosophila melanogaster]	-1.8663	-0.9002	2.05E-07	6.6879
P29829	Guanine nucleotide-binding protein subunit beta-2 [OS=Drosophila melanogaster]	-1.8448	-0.88345	2.41E-08	7.6171
Q9TVP3	J domain-containing protein [OS=Drosophila melanogaster]	-1.839	-0.87892	8.07E-06	5.0933
Q27377	Putative odorant-binding protein A10 [OS=Drosophila melanogaster]	-1.8154	-0.8603	7.58E-05	4.1205
P04950	Opsin Rh3 [OS=Drosophila melanogaster]	-1.7997	-0.84773	7.92E-06	5.1011

Q9W1C9	Ejaculatory bulb-specific protein 3 [OS=Drosophila melanogaster]	-1.7547	-0.81124	8.71E-07	6.06
P16914	Protein elav [OS=Drosophila melanogaster]	-1.7463	-0.80434	8.08E-06	5.0926
P62152	Calmodulin [OS=Drosophila melanogaster]	-1.7311	-0.79171	9.30E-07	6.0313
Q9VV36	Retinin [OS=Drosophila melanogaster]	-1.7302	-0.79097	6.61E-07	6.18
P25157	Guanine nucleotide-binding protein subunit alpha homolog [OS=Drosophila melanogaster]	-1.6983	-0.76408	1.90E-06	5.7218
P41044	Calbindin-32 [OS=Drosophila melanogaster]	-1.6952	-0.76142	9.13E-06	5.0396
Q03751	DnaJ homolog subfamily C member 5 homolog [OS=Drosophila melanogaster]	-1.6888	-0.75599	0.0028	2.5528
Q9VSL3	Pyrimidodiazepine synthase [OS=Drosophila melanogaster]	-1.6728	-0.74223	2.07E-05	4.6842
P20228	Glutamate decarboxylase [OS=Drosophila melanogaster]	-1.6658	-0.73622	5.00E-06	5.3012
Q9VV43	Tubulin polymerization-promoting protein homolog [OS=Drosophila melanogaster]	-1.6539	-0.72587	3.02E-08	7.5194
Q9W0C1	Neuronal synaptobrevin [OS=Drosophila melanogaster]	-1.6516	-0.72384	0.00038602	3.4134
Q9VYY3	Ubiquitin-like modifier-activating enzyme 5 [OS=Drosophila melanogaster]	-1.6381	-0.71201	0.0010336	2.9856
A1Z9A8	Small ribosomal subunit protein mS39 [OS=Drosophila melanogaster]	-1.628	-0.70311	0.00079041	3.1021
P22465	Annexin B10 [OS=Drosophila melanogaster]	-1.6268	-0.70202	1.84E-06	5.7361
Q8T390	Endophilin-A [OS=Drosophila melanogaster]	-1.6198	-0.69581	1.59E-08	7.7975
P13368	Protein sevenless [OS=Drosophila melanogaster]	-1.6097	-0.68678	1.40E-05	4.8551
P23625	G protein alpha q subunit [OS=Drosophila melanogaster]	-1.6075	-0.68484	1.02E-07	6.9918
Q9VQF7	Bacchus [OS=Drosophila melanogaster]	-1.6057	-0.68322	6.66E-07	6.1765
P43332	U1 small nuclear ribonucleoprotein A [OS=Drosophila melanogaster]	-1.5996	-0.67768	1.17E-06	5.9307
P26308	Guanine nucleotide-binding protein subunit beta-1 [OS=Drosophila melanogaster]	-1.5898	-0.66887	4.09E-05	4.3878
Q9VVA0	Cold shock domain-containing protein CG9705 [OS=Drosophila melanogaster]	-1.5798	-0.65976	8.43E-05	4.0743

Q9VI75	Phosphatidylinositol-binding clathrin assembly protein LAP [OS=Drosophila melanogaster]	-1.5727	-0.65327	1.27E-06	5.8945
P48451	Calcineurin subunit B type 1 [OS=Drosophila melanogaster]	-1.5429	-0.62564	8.34E-05	4.0786
P38040	Guanine nucleotide-binding protein subunit gamma-1 [OS=Drosophila melanogaster]	-1.5411	-0.62397	0.00017549	3.7558
P92177	14-3-3 protein epsilon [OS=Drosophila melanogaster]	-1.5332	-0.61658	0.000157	3.8041
Q9VLR5	RNA polymerase II transcriptional coactivator [OS=Drosophila melanogaster]	-1.5327	-0.6161	0.00096068	3.0174
O18404	3-hydroxyacyl-CoA dehydrogenase type-2 [OS=Drosophila melanogaster]	-1.523	-0.60689	5.10E-06	5.2928
Q9VHV5	ADP-ribosylation factor-like protein 8 [OS=Drosophila melanogaster]	-1.5129	-0.59727	1.98E-05	4.7025
Q9V427	Innexin inx2 [OS=Drosophila melanogaster]	-1.5117	-0.59621	1.07E-08	7.971
P19107	Phosrestin-1 [OS=Drosophila melanogaster]	-1.5074	-0.59203	1.59E-09	8.7978
P36975	Synaptosomal-associated protein 25 [OS=Drosophila melanogaster]	-1.5061	-0.59084	2.96E-06	5.5287
Q7K4Q5	Probable protein phosphatase CG10417 [OS=Drosophila melanogaster]	-1.5051	-0.58988	0.00053208	3.274
P61209	ADP-ribosylation factor 1 [OS=Drosophila melanogaster]	-1.5051	-0.58983	2.89E-06	5.5392
P11996	Larval serum protein 1 beta chain [OS=Drosophila melanogaster]	1.5275	0.6112	3.29E-07	6.483
P07486	Glyceraldehyde-3-phosphate dehydrogenase 1 [OS=Drosophila melanogaster]	1.5277	0.61131	2.40E-07	6.6194
Q9W401	Probable citrate synthase, mitochondrial [OS=Drosophila melanogaster]	1.5771	0.65725	3.69E-06	5.4327
Q9I7U4	Titin [OS=Drosophila melanogaster]	1.5905	0.66949	3.30E-08	7.481
P02844	Vitellogenin-2 [OS=Drosophila melanogaster]	1.5973	0.67565	1.78E-07	6.7496
Q9VVW1	Accessory gland protein Acp76A [OS=Drosophila melanogaster]	1.6465	0.71942	4.26E-06	5.3707
Q9VAI6	General odorant-binding protein 99b [OS=Drosophila melanogaster]	1.6546	0.7265	2.13E-05	4.6719

Q9NJH0	Elongation factor 1-gamma [OS=Drosophila melanogaster]	1.6731	0.74253	1.20E-08	7.9215
O46202	Accessory gland protein Acp62F [OS=Drosophila melanogaster]	1.7042	0.76906	0.00039858	3.3995
Q9VUY9	Phosphoglucomutase [OS=Drosophila melanogaster]	1.7137	0.77713	2.46E-10	9.6083
Q9XTL9	Glycogen phosphorylase [OS=Drosophila melanogaster]	1.7182	0.78091	1.70E-07	6.7698
P41043	Glutathione S-transferase S1 [OS=Drosophila melanogaster]	1.7537	0.81039	9.17E-08	7.0377
P11997	Larval serum protein 1 gamma chain [OS=Drosophila melanogaster]	1.8127	0.85816	2.22E-07	6.6545
Q9V770	Probable cytochrome P450 6a17 [OS=Drosophila melanogaster]	1.8392	0.8791	0.00017837	3.7487
P42281	Acyl-CoA-binding protein homolog [OS=Drosophila melanogaster]	1.8587	0.89433	0.0022496	2.6479
O46199	Accessory gland protein Acp53Ea [OS=Drosophila melanogaster]	1.9095	0.9332	1.70E-05	4.7684
P35554	Flightin [OS=Drosophila melanogaster]	2.1192	1.0835	2.78E-06	5.5566
Q24388	Larval serum protein 2 [OS=Drosophila melanogaster]	2.1403	1.0978	3.68E-08	7.4346

Differentially less abundant proteins (n=48) are indicated in blue, corresponding to negative fold change (FC) and $\log_2$ fold change ($\log_2$FC) values. Differentially more abundant proteins (n=18) are indicated in red, corresponding to positive FC and $\log_2$FC values.

Table S3. Annotation of 66 *Drosophila melanogaster* proteins identified by quantitative proteomics using the UniProt database.

Accession	Protein names	Gene Names
P29746	Protein bangles and beads	bnb CG7088
P42281	Acyl-CoA-binding protein homolog (ACBP) (Diazepam-binding inhibitor homolog) (DBI)	Acbp2 Dbi CG8627
P35554	Flightin (Muscle protein 27)	fln FTN mp27 CG7445
P61209	ADP-ribosylation factor 1 (EC 3.6.5.2)	Arf1 Arf79F CG8385
Q9V427	Innexin inx2 (Innexin-2) (Gap junction protein prp33) (Pas-related protein 33)	Inx2 prp33 CG4590
Q9VHV5	ADP-ribosylation factor-like protein 8 (Novel small G protein indispensable for equal chromosome segregation) (dGie)	Arl8 Gie CG7891

Q9VV43	Tubulin polymerization-promoting protein homolog (TPPP) (Protein ringmaker)	ringer CG45057
Q9W369	Beta-alanyl-dopamine/carcinine hydrolase (EC 3.5.1.-) (NBAD/carcinine hydrolase) (Protein tan) [Cleaved into: Beta-alanyl-dopamine/carcinine hydrolase alpha subunit; Beta-alanyl-dopamine/carcinine hydrolase beta subunit]	t CG12120
P23625	G protein alpha q subunit (Guanine nucleotide-binding protein G(q) subunit alpha) (Guanine nucleotide-binding protein alpha-q) (dGQalpha)	Galphaq dgq dGqalpha Galpha Galpha49b Gq Gqalpha CG17759
Q9NFZ3	Guanine nucleotide-binding protein subunit gamma-e (Ggamma(e))	Ggamma30A Ggammae CG3694
P29829	Guanine nucleotide-binding protein subunit beta-2	Gbeta76C Gb76C Gbe Gbetae CG8770
P25157	Guanine nucleotide-binding protein subunit alpha homolog (Protein concertina)	cta CTR CG17678
P16914	Protein elav (Embryonic lethal abnormal visual protein)	elav CG4262
P48451	Calcineurin subunit B type 1 (Protein phosphatase 2B regulatory subunit 1)	CanB CANB1 CNB CNB1 CG4209
P43332	U1 small nuclear ribonucleoprotein A (U1 snRNP A) (U1-A) (U1A) (Sex determination protein snf)	snf D25 fs(1)1621 liz CG4528
P62152	Calmodulin (CaM)	Cam CG8472
P92177	14-3-3 protein epsilon (Suppressor of Ras1 3-9)	14-3-3epsilon 14-3-3e SR3-9 CG31196
Q05783	High mobility group protein D (HMG-D)	HmgD CG17950
Q06943	High mobility group protein Z (HMG-Z)	HmgZ CG17921
Q9VI75	Phosphatidylinositol-binding clathrin assembly protein LAP (Like-AP180)	lap CG2520
Q9I7U4	Titin (D-Titin) (Kettin)	sls titin CG1915
P41043	Glutathione S-transferase S1 (EC 2.5.1.18) (GST class-sigma 1) (Glutathione S-transferase 2)	GstS1 GST2 GSTS1-1 CG8938
Q7K4Q5	Probable protein phosphatase CG10417 (EC 3.1.3.16)	CG10417
Q9VSL3	Pyrimidodiazepine synthase (EC 1.5.4.1) (Protein sepia)	se CG6781
Q9VVA0	Cold shock domain-containing protein CG9705	CG9705
Q9NJH0	Elongation factor 1-gamma (EF1gamma) (eEF-1B gamma)	eEF1gamma Ef1g CG11901
P20228	Glutamate decarboxylase (GAD) (EC 4.1.1.15)	Gad1 Gad Glb CG14994
Q9TVP3	J domain-containing protein (dJDP)	jdp CG2239
Q9XTL9	Glycogen phosphorylase (EC 2.4.1.1)	Glyp Glp1 CG7254
Q9VYY3	Ubiquitin-like modifier-activating enzyme 5 (Ubiquitin-activating enzyme 5) (UFM1-activating enzyme)	Uba5 CG1749
Q960T2	Synapse-associated protein of 47 kDa	Sap47 CG8884
P26308	Guanine nucleotide-binding protein subunit beta-1	Gbeta13F Gb13F CG10545
P22465	Annexin B10 (Annexin X) (Annexin-10)	AnxB10 AnnX CG9579
P36975	Synaptosomal-associated protein 25 (SNAP-25) (Synaptosomal-associated 25 kDa protein)	Snap25 CG40452

P19107	Phosrestin-1 (49 kDa arrestin-like protein) (Arrestin-2) (Arrestin-B) (Phosrestin I)	Arr2 ArrB CG5962
P06002	Opsin Rh1 (Neither inactivation nor afterpotential E protein) (Outer R1-R6 photoreceptor cells opsin)	ninaE Rh1 CG4550
Q9VUY9	Phosphoglucomutase 1 (PGM) (EC 5.4.2.2) (Glucose phosphomutase)	Pgm1 CG5165
P41044	Calbindin-32	Cbp53E cbn CG6702
Q8T390	Endophilin-A (SH3 domain-containing GRB2-like protein)	EndoA endo CG14296
P07486	Glyceraldehyde-3-phosphate dehydrogenase 1 (EC 1.2.1.12) (Glyceraldehyde-3-phosphate dehydrogenase I) (GAPDH I)	Gapdh1 Gadph-1 CG12055
Q9W0C1	Neuronal synaptobrevin (n-syb)	nSyb CG17248
Q9V770	Probable cytochrome P450 6a17 (EC 1.14.-.-) (CYPVIA17)	Cyp6a17 CG10241
Q27377	Putative odorant-binding protein A10 (Antennal protein 10) (OS-D protein)	a10 OS-D CG6642
Q9W1C9	Ejaculatory bulb-specific protein 3 (Ejaculatory bulb-specific protein III) (PEB-meIII) (PEBmelIII)	EbpIII PebIII CG11390
Q9VAI6	General odorant-binding protein 99b	Obp99b CG7592
P54192	General odorant-binding protein 19d (Odorant-binding protein 19d) (Pheromone-binding protein-related protein 2) (PBPRP-2)	Obp19d Pbprp2 CG1668
P54193	General odorant-binding protein 83a (Odorant-binding protein 83a) (Odorant-binding protein OS-F) (Pheromone-binding protein-related protein 3) (PBPRP-3)	Obp83a OS-F Pbprp3 CG11421
P54195	General odorant-binding protein 28a (Odorant-binding protein 28a) (Pheromone-binding protein-related protein 5) (PBPRP-5)	Obp28a Pbprp5 CG6641
Q23970	Pheromone-binding protein-related protein 6 (PBPRP-6) (Odorant-binding protein OS-E)	Obp83b Os-E PBPRP6 CG11422
P02844	Vitellogenin-2 (Vitellogenin II) (Yolk protein 2)	Yp2 CG2979
Q9VV36	Retinin	retinin CG13057
O46199	Accessory gland protein Acp53Ea	Acp53Ea CG8622
O46202	Accessory gland protein Acp62F	Acp62F CG1262
Q9VVW1	Accessory gland protein Acp76A	Acp76A CG3801
P11997	Larval serum protein 1 gamma chain (Hexamerin-1-gamma)	Lsp1gamma Lsp1-g CG6821
P11996	Larval serum protein 1 beta chain (Hexamerin-1-beta)	Lsp1beta Lsp1-b CG4178
Q24388	Larval serum protein 2 (LSP-2) (Hexamerin-2)	Lsp2 CG6806
P38040	Guanine nucleotide-binding protein subunit gamma-1	Ggamma1 G1 CG8261
P04950	Opsin Rh3 (Inner R7 photoreceptor cells opsin)	Rh3 RH92CD CG10888
Q9W401	Probable citrate synthase, mitochondrial (EC 2.3.3.16) (Protein knockdown)	Cs1 kdn l(1)G0030 CG3861
O18404	3-hydroxyacyl-CoA dehydrogenase type-2 (EC 1.1.1.35) (17-beta-hydroxysteroid dehydrogenase 10) (17-beta-HSD 10) (EC 1.1.1.51, EC 1.1.1.62) (3-hydroxyacyl-CoA dehydrogenase type II) (Hydroxysteroid dehydrogenase) (EC 1.1.1.-, EC 1.1.1.53) (Mitochondrial ribonuclease P protein 2) (Mitochondrial RNase P protein 2) (Scully protein) (Type II HADH)	scu MRPP2 CG7113
A1Z9A8	Small ribosomal subunit protein mS39 (Pentatricopeptide repeat domain-containing protein 3 homolog, mitochondrial)	Ptcd3 CG4679

Q9VQF7	Bacchus	Bacc CG9894
Q9VLR5	RNA polymerase II transcriptional coactivator (p11)	Ssb-c31a CG8396
P13368	Protein sevenless (EC 2.7.10.1)	sev HD-265 CG18085
Q03751	DnaJ homolog subfamily C member 5 homolog (Cysteine string protein)	Csp CG6395

The table lists the accession numbers, protein names, and corresponding gene identifiers for each differentially abundant protein included in the analysis, based on UniProt annotations.

Table S4. Canonical pathways with their corresponding -log(p-value), z-score and molecules associated to each pathway.

Ingenuity Canonical Pathways	-log(p-value)	z-score	Molecules
GABA synthesis, release, reuptake and degradation	5.12	NA	DNAJC5,GAD1,VAMP2
trans-Golgi Network Vesicle Budding	3.93	NA	ARF1,PICALM,VAMP2
Protein Kinase A Signaling	3.86	-1.342	GNA13,GNB1,PPP3R1,PYGM, YWHAE
Prostanoid Biosynthesis	3.78	NA	HPGDS,TBXAS1
Glycogen Degradation II	3.73	NA	PGM1,PYGM
Glycogen Degradation III	3.63	NA	PGM1,PYGM
Cargo recognition for clathrin-mediated endocytosis	3.43	NA	PICALM,SH3GL3,VAMP2
Oxytocin Signaling Pathway	3.41	-2	GAD1,GNA13,GNB1,PPP3R1
Huntington's Disease Signaling	3.41	NA	DNAJC5,GNB1,SH3GL3,VAMP2
α-Adrenergic Signaling	3.41	NA	GNA13,GNB1,PYGM
Glutaryl-CoA Degradation	3.32	NA	HSD17B10,TBXAS1
fMLP Signaling in Neutrophils	3.22	NA	GNA13,GNB1,PPP3R1
GABA Receptor Signaling	3.22	NA	GAD1,GNA13,GNB1
Clathrin-mediated endocytosis	3.16	NA	PICALM,SH3GL3,VAMP2
Thrombin signalling through proteinase activated receptors (PARs)	3.09	NA	GNA13,GNB1
Gene and protein expression by JAK-STAT signaling after IL-12 stimulation	3.04	NA	ARF1,GSTO1
Signal amplification	3.02	NA	GNA13,GNB1
Relaxin Signaling	2.99	NA	GAD1,GNA13,GNB1
Gαq Signaling	2.9	NA	GNA13,GNB1,PPP3R1
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	2.85	NA	HPGDS,TBXAS1
Tryptophan Degradation III (Eukaryotic)	2.82	NA	HSD17B10,TBXAS1
Glutathione-mediated Detoxification	2.76	NA	GSTO1,HPGDS
Apelin Muscle Signaling Pathway	2.76	NA	GNA13,GNB1
Clathrin-mediated Endocytosis Signaling	2.69	NA	PICALM,PPP3R1,SH3GL3
Intrinsic Pathway for Apoptosis	2.64	NA	PPP3R1,YWHAE
Phototransduction Pathway	2.6	NA	GNB1,OPN4
NRF2-mediated Oxidative Stress Response	2.54	NA	DNAJC12,DNAJC5,GSTO1
Ephrin B Signaling	2.45	NA	GNA13,GNB1
AMPK Signaling	2.44	NA	GNA13,GNB1,PPM1G

Sensory processing of sound by inner hair cells of the cochlea	2.43	NA	DNAJC5,VAMP2
ERK5 Signaling	2.43	NA	GNA13,YWHAE
Translocation of SLC2A4 (GLUT4) to the plasma membrane	2.4	NA	VAMP2,YWHAE
Cardiac Hypertrophy Signaling	2.39	NA	GNA13,GNB1,PPP3R1
Sperm Motility	2.38	NA	GNA13,GNB1,ROS1
Antiproliferative Role of Somatostatin Receptor 2	2.37	NA	GAD1,GNB1
Circadian Rhythm Signaling	2.34	NA	GAD1,GNB1,OPN4
G alpha (12/13) signalling events	2.33	NA	GNA13,GNB1
Glutamate Dependent Acid Resistance	2.32	NA	GAD1
Opioid Signaling Pathway	2.3	NA	GNA13,GNB1,PPP3R1
Unfolded protein response	2.28	NA	DNAJC12,DNAJC5
Eicosanoid Signaling	2.22	NA	GNB1,HPGDS,TBXAS1
IL-1 Signaling	2.2	NA	GNA13,GNB1
p75 NTR receptor-mediated signalling	2.12	NA	GNA13,YWHAE
Opioid Signalling	2.1	NA	GNB1,PPP3R1
Beta-catenin independent WNT signaling	2.06	NA	GNB1,PPP3R1
NADH Repair	2.02	NA	GAPDH
Gαs Signaling	1.97	NA	GNA13,GNB1
Integration of energy metabolism	1.93	NA	GNB1,VAMP2
CCR3 Signaling in Eosinophils	1.92	NA	GNA13,GNB1
G Beta Gamma Signaling	1.92	NA	GNA13,GNB1
SNARE Signaling Pathway	1.91	NA	DNAJC5,VAMP2
Gαi Signaling	1.89	NA	GNA13,GNB1
Ascorbate Recycling (Cytosolic)	1.88	NA	GSTO1
GABAergic Receptor Signaling Pathway (Enhanced)	1.86	NA	GAD1,GNB1
Apelin Endothelial Signaling Pathway	1.86	NA	GNA13,GNB1
Glutamate Degradation III (via 4-aminobutyrate)	1.84	NA	GAD1
Endocannabinoid Neuronal Synapse Pathway	1.79	NA	GNB1,PPP3R1
Androgen Signaling	1.74	NA	GNA13,GNB1
CXCR4 Signaling	1.72	NA	GNA13,GNB1
Netrin Signaling	1.7	NA	PPP3R1,VAMP2
Aldosterone Signaling in Epithelial Cells	1.7	NA	DNAJC12,DNAJC5
Arsenate Detoxification I (Glutaredoxin)	1.69	NA	GSTO1
Cardiac β-adrenergic Signaling	1.67	NA	GNA13,GNB1
Axonal Guidance Signaling	1.63	NA	GNA13,GNB1,PPP3R1
GDP-glucose Biosynthesis	1.62	NA	PGM1
Ephrin Receptor Signaling	1.6	NA	GNA13,GNB1
Synaptic Long Term Depression	1.59	NA	GAD1,GNA13
Signaling by Hippo	1.58	NA	YWHAE
IL-8 Signaling	1.57	NA	GNA13,GNB1
Cardiac Hypertrophy Signaling (Enhanced)	1.55	NA	GNA13,GNB1,PPP3R1
Other interleukin signaling	1.55	NA	VAMP2
Glucose and Glucose-1-phosphate Degradation	1.55	NA	PGM1
Insertion of tail-anchored proteins into the endoplasmic reticulum membrane	1.53	NA	VAMP2
G alpha (q) signalling events	1.53	NA	GNB1,OPN4
RHOGDI Signaling	1.52	NA	GNA13,GNB1

Thrombin Signaling	1.5	NA	GNA13,GNB1
Role of NFAT in Cardiac Hypertrophy	1.5	NA	GNB1,PPP3R1
Insulin processing	1.45	NA	VAMP2
rRNA processing	1.42	NA	HSD17B10
Isoleucine Degradation I	1.42	NA	HSD17B10
RHO GTPases activate PKNs	1.41	NA	YWHAE
Vitamin-C Transport	1.41	NA	GSTO1
Pancreatic Secretion Signaling Pathway	1.4	NA	GNA13,VAMP2
Activation of kainate receptors upon glutamate binding	1.4	NA	GNB1
Signaling by Rho Family GTPases	1.38	NA	GNA13,GNB1
Colorectal Cancer Metastasis Signaling	1.36	NA	GNA13,GNB1
Protein Ubiquitination Pathway	1.36	NA	DNAJC12,DNAJC5
Oxytocin in Spinal Neurons Signaling Pathway	1.35	NA	GAD1
Glycogen metabolism	1.35	NA	PYGM
G-protein beta:gamma signalling	1.34	NA	GNB1
CLEAR Signaling Pathway	1.33	NA	PPP3R1,YWHAE
NGF-stimulated transcription	1.32	NA	SH3GL3
Mechanisms of Viral Exit from Host Cells	1.32	NA	SH3GL3
TCA Cycle II (Eukaryotic)	1.32	NA	CS
Incretin synthesis, secretion, and inactivation	1.3	NA	GNB1
Glycolysis I	1.3	NA	GAPDH
G-Protein Coupled Receptor Signaling	1.27	NA	GNA13,GNB1,PPP3R1
Fatty Acid β-oxidation I	1.26	NA	HSD17B10
Gluconeogenesis I	1.25	NA	GAPDH
Synaptogenesis Signaling Pathway	1.24	NA	DNAJC5,VAMP2
Vasopressin regulates renal water homeostasis via Aquaporins	1.23	NA	GNB1
Branched-chain amino acid catabolism	1.23	NA	HSD17B10
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	1.23	NA	YWHAE
Neuroinflammation Signaling Pathway	1.22	NA	GAD1,PPP3R1
GPER1 signaling	1.22	NA	GNB1
nNOS Signaling in Neurons	1.22	NA	PPP3R1
Smooth Muscle Contraction	1.21	NA	ANXA6
Glutaminergic Receptor Signaling Pathway (Enhanced)	1.2	NA	PPP3R1,VAMP2
Estrogen Biosynthesis	1.18	NA	HSD17B10
Signaling by EGFR	1.17	NA	SH3GL3
G alpha (z) signalling events	1.14	NA	GNB1
Mitochondrial Dysfunction	1.13	NA	HSD17B10,PPP3R1
Transcriptional Regulation by MECP2	1.12	NA	GAD1
Gap Junction Signaling	1.12	NA	GAD1,PPP3R1
Mitochondrial protein import	1.11	NA	CS
GABA receptor activation	1.11	NA	GNB1
UFMylation Signaling Pathway	1.1	NA	UBA5
GM-CSF Signaling	1.09	NA	PPP3R1
Glutamate Receptor Signaling	1.08	NA	GNB1
Sensory perception of taste	1.07	NA	GNB1

Neurotransmitter release cycle	1.06	NA	VAMP2
Estrogen Receptor Signaling	1.05	NA	GNA13,GNB1
IL-3 Signaling	1.04	NA	PPP3R1
Maturity Onset Diabetes of Young (MODY) Signaling	1.03	NA	GAPDH
Stearate Biosynthesis I (Animals)	1.01	NA	TBXAS1
Signaling by MET	1.01	NA	SH3GL3
Estrogen-Dependent Breast Cancer Signaling	1.01	NA	HSD17B10
HIPPO signaling	0.998	NA	YWHAE
Xenobiotic Metabolism AHR Signaling Pathway	0.998	NA	GSTO1
RHO GTPase cycle	0.983	NA	GNA13,PICALM
ABRA Signaling Pathway	0.979	NA	PPP3R1
RANK Signaling in Osteoclasts	0.979	NA	PPP3R1
RAB GEFs exchange GTP for GDP on RABs	0.975	NA	YWHAE
Extra-nuclear estrogen signaling	0.97	NA	GNB1
G Protein Signaling Mediated by Tubby	0.959	NA	GNA13,GNB1
Olfactory Signaling Pathway	0.958	NA	GNB1
Eukaryotic Translation Elongation	0.953	NA	EEF1G
Class B/2 (Secretin family receptors)	0.953	NA	GNB1
Neutrophil degranulation	0.953	NA	DNAJC5,PGM1
PI Metabolism	0.949	NA	ARF1
Visual phototransduction	0.949	NA	GNB1
Mitochondrial translation	0.949	NA	PTCD3
Protein folding	0.937	NA	GNB1
Cellular response to heat stress	0.925	NA	YWHAE
VEGF Signaling	0.925	NA	YWHAE
Serotonin Receptor Signaling	0.922	NA	GNA13,GNB1
Potassium Channels	0.917	NA	GNB1
COPI-mediated anterograde transport	0.917	NA	ARF1
Paxillin Signaling	0.917	NA	ARF1
IGF-1 Signaling	0.917	NA	YWHAE
SAPK/JNK Signaling	0.914	NA	GNA13,GNB1
CCR5 Signaling in Macrophages	0.912	NA	GNA13,GNB1
TP53 Regulates Metabolic Genes	0.902	NA	YWHAE
Platelet homeostasis	0.895	NA	GNB1
Role of NFAT in Regulation of the Immune Response	0.893	NA	GNA13,GNB1,PPP3R1
Metabolism of water-soluble vitamins and cofactors	0.881	NA	GSTO1
Antioxidant Action of Vitamin C	0.871	NA	GSTO1
Sleep NREM Signaling Pathway	0.867	NA	YWHAE
IL-15 Production	0.861	NA	ROS1
Cholecystokinin/Gastrin-mediated Signaling	0.858	NA	GNA13
Sphingosine-1-phosphate Signaling	0.858	NA	GNA13
RHOA Signaling	0.851	NA	GNA13
ROBO SLIT Signaling Pathway	0.845	NA	ARF1
Neuroprotective Role of THOP1 in Alzheimer's Disease	0.845	NA	YWHAE
Endocannabinoid Developing Neuron Pathway	0.845	NA	GNB1
14-3-3-mediated Signaling	0.842	NA	YWHAE

MHC class II antigen presentation	0.835	NA	ARF1
Gα12/13 Signaling	0.826	NA	GNA13
Phospholipase C Signaling	0.817	NA	GNA13,GNB1,PPP3R1
TEC Kinase Signaling	0.813	NA	GNA13,GNB1
Synaptic Long Term Potentiation	0.809	NA	PPP3R1
MSP-RON Signaling in Cancer Cells Pathway	0.809	NA	YWHAE
P2Y Purinergic Receptor Signaling Pathway	0.8	NA	GNB1
Role of Chondrocytes in Rheumatoid Arthritis Signaling Pathway	0.798	NA	PPP3R1
Breast Cancer Regulation by Stathmin1	0.794	NA	GNA13,GNB1
Insulin Receptor Signaling	0.792	NA	VAMP2
Xenobiotic Metabolism General Signaling Pathway	0.792	NA	GSTO1
WNT/SHH Axonal Guidance Signaling Pathway	0.779	NA	YWHAE
CREB Signaling in Neurons	0.774	NA	GNA13,GNB1
Endocannabinoid Cancer Inhibition Pathway	0.771	NA	GNA13
Necroptosis Signaling Pathway	0.756	NA	PPP3R1
Epithelial Adherens Junction Signaling	0.753	NA	YWHAE
Ferroptosis Signaling Pathway	0.753	NA	ARF1
Corticotropin Releasing Hormone Signaling	0.751	NA	GAD1
Inhibition of ARE-Mediated mRNA Degradation Pathway	0.748	NA	YWHAE
Aryl Hydrocarbon Receptor Signaling	0.746	NA	GSTO1
C-type lectin receptors (CLRs)	0.744	NA	PPP3R1
G alpha (s) signalling events	0.741	NA	GNB1
Systemic Lupus Erythematosus in T Cell Signaling Pathway	0.737	NA	GNA13,PPP3R1
Phagosome Maturation	0.73	NA	VAMP2
Tight Junction Signaling	0.71	NA	VAMP2
Signaling by the B Cell Receptor (BCR)	0.703	NA	PPP3R1
Protein Sorting Signaling Pathway	0.699	NA	ARF1
Cellular Effects of Sildenafil (Viagra)	0.689	NA	GNB1,PPP3R1
D-myo-inositol (3,4,5,6)-tetrakisphosphate Biosynthesis	0.689	NA	PPP3R1
Xenobiotic Metabolism CAR Signaling Pathway	0.68	NA	GSTO1
Xenobiotic Metabolism PXR Signaling Pathway	0.676	NA	GSTO1
FXR/RXR Activation	0.675	NA	GSTO1
GNRH Signaling	0.675	NA	GNB1
Dopamine-DARPP32 Feedback in cAMP Signaling	0.669	NA	PPP3R1
3-phosphoinositide Degradation	0.667	NA	PPP3R1
Oxytocin in Brain Signaling Pathway	0.661	NA	GNB1
PI3K/AKT Signaling	0.659	NA	YWHAE
D-myo-inositol-5-phosphate Metabolism	0.657	NA	PPP3R1
Mitotic G2-G2/M phases	0.655	NA	YWHAE
Role of Tissue Factor in Cancer	0.655	NA	GNA13
Adrenomedullin signaling pathway	0.655	NA	GAD1
Cilium Assembly	0.652	NA	YWHAE
Endothelin-1 Signaling	0.652	NA	GNA13
Mitotic Prometaphase	0.65	NA	YWHAE
Phase I - Functionalization of compounds	0.646	NA	TBXAS1

Intra-Golgi and retrograde Golgi-to-ER traffic	0.644	NA	ARF1
Integrin Signaling	0.644	NA	ARF1
HIF1α Signaling	0.641	NA	PPP3R1
3-phosphoinositide Biosynthesis	0.629	NA	PPP3R1
Fc epsilon receptor (FCERI) signaling	0.627	NA	PPP3R1
HER-2 Signaling in Breast Cancer	0.619	NA	ARF1
Autophagy	0.619	NA	PPP3R1
Calcium Signaling	0.619	NA	PPP3R1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	0.609	NA	PPP3R1
Hepatic Cholestasis	0.599	NA	PPP3R1
cAMP-mediated signaling	0.599	NA	PPP3R1
Actin Cytoskeleton Signaling	0.587	NA	GNA13
Orexin Signaling Pathway	0.585	NA	GNB1
Neurovascular Coupling Signaling Pathway	0.572	NA	GAD1
LPS/IL-1 Mediated Inhibition of RXR Function	0.568	NA	GSTO1
Superpathway of Inositol Phosphate Compounds	0.566	NA	PPP3R1
Molecular Mechanisms of Cancer	0.553	NA	GNA13,GNB1
Cell Cycle Checkpoints	0.549	NA	YWHAE
Chronic Myeloid Leukemia Signaling	0.542	NA	PPP3R1
Processing of Capped Intron-Containing Pre-mRNA	0.528	NA	SNRPA
Histone Modification Signaling Pathway	0.523	NA	YWHAE
Xenobiotic Metabolism Signaling	0.52	NA	GSTO1
Insulin Secretion Signaling Pathway	0.519	NA	VAMP2
G alpha (i) signalling events	0.514	NA	GNB1
Senescence Pathway	0.512	NA	PPP3R1
Role of Osteoclasts in Rheumatoid Arthritis Signaling Pathway	0.504	NA	PPP3R1
Pulmonary Fibrosis Idiopathic Signaling Pathway	0.486	NA	GNA13
Myelination Signaling Pathway	0.476	NA	PPP3R1
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	0.473	NA	PPP3R1
Class I MHC mediated antigen processing and presentation	0.426	NA	UBA5
Neutrophil Extracellular Trap Signaling Pathway	0.403	NA	PPP3R1
RAR Activation	0.383	NA	GNB1
Calcium-induced T Lymphocyte Apoptosis	0.366	NA	PPP3R1
Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes	0.366	NA	PPP3R1
Type I Diabetes Mellitus Signaling	0.336	NA	GAD1
ICOS-ICOSL Signaling in T Helper Cells	0.335	NA	PPP3R1
NUR77 Signaling in T Lymphocytes	0.333	NA	PPP3R1
CD28 Signaling in T Helper Cells	0.328	NA	PPP3R1
PKCθ Signaling in T Lymphocytes	0.306	NA	PPP3R1
p70S6K Signaling	0.293	NA	YWHAE
Glucocorticoid Receptor Signaling	0.29	NA	PPP3R1
PI3K Signaling in B Lymphocytes	0.289	NA	PPP3R1
CTLA4 Signaling in Cytotoxic T Lymphocytes	0.279	NA	ARF1
T Cell Receptor Signaling	0.276	NA	PPP3R1

B Cell Receptor Signaling	0.267	NA	PPP3R1
Chaperone Mediated Autophagy Signaling Pathway	0.265	NA	PPP3R1
Systemic Lupus Erythematosus in B Cell Signaling Pathway	0.23	NA	PPP3R1
Systemic Lupus Erythematosus Signaling	0	NA	SNRPA

Of the 66 differentially abundant *Drosophila* head proteins, 33 were successfully mapped to human orthologs in the IPA database and assigned to canonical pathways in which they have established functional roles. The z-score predicts whether a pathway is activated or inhibited by comparing the observed direction of protein changes in the data to the expected direction of change curated in the IPA knowledge base. The two pathways predicted to be inhibited, based on a negative z-score, were protein kinase A (PKA) signaling pathway and oxytocin signaling pathway. Both are highlighted in orange. Gene identifiers are used for each protein.

Table S5. IPA Pathway interaction table.

From Molecule(s)	Relationship Type	To Molecule(s)
ANXA6	causation	Mobilization of Ca2+
ANXA6	causation	Quantity of Ca2+
ANXA6	causation	Transmembrane transport of ion
ANXA6	correlation	Severe psychological disorder
ARF1	causation	Dendritic growth/branching
ARF1	causation	Development of neural cells
ARF1	causation	Development of neurons
ARF1	causation	Migration of neurons
ARF1	causation	Synaptic depression
ARF1	causation	Transmembrane transport of ion
ATP6V0C	causation	Release of catecholamine
CARHSP1	causation	Signal transduction
DBI	causation	Long-term potentiation
DNAJC12	correlation	Severe psychological disorder
DNAJC5	causation	Apoptosis of neurons
DNAJC5	causation	Exocytosis
DNAJC5	causation	Neurodegeneration
DNAJC5	causation	Neurotransmission
DNAJC5	causation	Release of catecholamine
DNAJC5	causation	Synaptic transmission
DNAJC5	causation	Transport of synaptic vesicles
GAD1	causation	Migration of neurons
GAD1	causation	Neurotransmission
GAD1	causation	Oxytocin Signaling Pathway
GAD1	causation	Quantity of neurons

GAD1	causation	Severe psychological disorder
GAD1	causation	Synaptic transmission
GAD1	correlation	Severe psychological disorder
GAPDH	causation	Apoptosis of neurons
GAPDH	causation	Neurodegeneration
GNA13	causation	Dendritic growth/branching
GNA13	causation	Development of neural cells
GNA13	causation	Development of neurons
GNA13	causation	Migration of neurons
GNA13	causation	Mobilization of Ca2+
GNA13	causation	Oxytocin Signaling Pathway
GNA13	causation	Protein Kinase A Signaling
GNA13	causation	Quantity of Ca2+
GNA13	causation	Signal transduction
GNB1	causation	Mobilization of Ca2+
GNB1	causation	Neurodegeneration
GNB1	causation	Oxytocin Signaling Pathway
GNB1	causation	Protein Kinase A Signaling
GNB1	causation	Quantity of Ca2+
GNB1	causation	Signal transduction
GSTO1	correlation	Severe psychological disorder
HSD17B10	causation	Apoptosis of neurons
HSD17B10	causation	Long-term potentiation
OPN4	causation	Quantity of Ca2+
PICALM	causation	Dendritic growth/branching
PICALM	causation	Development of neural cells
PICALM	causation	Development of neurons
PICALM	causation	Transport of synaptic vesicles
PPP3R1	causation	Development of neural cells
PPP3R1	causation	Long-term potentiation
PPP3R1	causation	Neurotransmission
PPP3R1	causation	Oxytocin Signaling Pathway
PPP3R1	causation	Protein Kinase A Signaling
PPP3R1	causation	Quantity of neurons
PPP3R1	causation	Synaptic depression
PPP3R1	causation	Synaptic transmission
PPP3R1	correlation	Severe psychological disorder
PYGM	causation	Protein Kinase A Signaling
ROS1	causation	Signal transduction
SCGN	causation	Exocytosis
SH3GL3	causation	Neurotransmission
SH3GL3	causation	Quantity of neurons
SH3GL3	causation	Recycling of synaptic vesicles

SH3GL3	causation	Signal transduction
SH3GL3	causation	Synaptic depression
SH3GL3	causation	Synaptic transmission
SH3GL3	correlation	Severe psychological disorder
TBXAS1	correlation	Severe psychological disorder
TPPP	causation	Development of neural cells
VAMP2	causation	Development of neural cells
VAMP2	causation	Development of neurons
VAMP2	causation	Exocytosis
VAMP2	causation	Long-term potentiation
VAMP2	causation	Neurotransmission
VAMP2	causation	Quantity of neurons
VAMP2	causation	Recycling of synaptic vesicles
VAMP2	causation	Release of catecholamine
VAMP2	causation	Transport of synaptic vesicles
YWHAE	causation	Migration of neurons
YWHAE	causation	Protein Kinase A Signaling
YWHAE	causation	Quantity of Ca2+
YWHAE	causation	Signal transduction
YWHAE	causation	Transmembrane transport of ion
YWHAE	correlation	Severe psychological disorder

Summary of the neurobiological functions associated with the 33 human ortholog proteins and whether the supporting evidence for each protein-function relationship is causative or correlative. Gene identifiers are used for each protein.