

Co-expression of synaptic genes in the sponge *Amphimedon queenslandica* uncovers ancient neural submodules

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Supplementary Files

Supplementary Table 1. Enriched pathways in *Amphimedon* developmental and cell type expression profiles. Expression modules with more than three interacting nodes are mapped to curated pathways in *Homo sapiens* documented by Reactome¹³⁷, KEGG⁵⁸ and Panther¹³⁸ (FDR < 0.05, p < 0.05).

Supplementary Fig. 1. Orthologues of synaptic genes in *Amphimedon queenslandica*.

Genome assembly Aqu2.1⁹⁶ is used for extraction of orthologues. Protein domain arrangements are shown in comparison to those of corresponding orthologues in *Homo sapiens* (grey-shaded).

Supplementary Fig. 2. Developmental expression profile of *Amphimedon* genes mapped to the KEGG⁵⁸ endocytosis and bacterial invasion of epithelial cells pathway.

Genes of the (A-B) KEGG endocytosis, (C-E) bacterial invasion of epithelial cells pathways. Genes of the A KEGG endocytosis pathway and the C KEGG bacterial invasion of epithelial cells pathway are enriched in co-expression modules of *Amphimedon* synaptic genes (Figs 3, 4). *Amphimedon* possess homologues of the majority of genes coding both pathways in *Homo sapiens*. Developmental expression profiles of the orthologues coding the B endocytosis pathway and the D bacterial invasion of epithelial cells pathway are largely developmentally

co-regulated (clades consisting the mapped synaptic genes are shaded grey), suggesting that both pathways are conserved in sponge. (E) Developmentally co-expressing genes of the bacterial invasion of epithelial cells pathway (grey clade in D) are expressed in all three cell types. Green, genes with *Amphimedon* orthologues; blue, genes without *Amphimedon* orthologues; orange, synaptic genes mapped to the corresponding pathway (see Figs 3, 4).

Supplementary Fig. 3. Validation of co-expressing gene sets via Monte Carlo sampling.

Boxplots indicate range of number of clades each gene set of interest (GOI) is observed in when sampled over 10,000 developmental / cell type specific expression dendrograms with randomly selected Aqu2.1 protein coding genes. This is contrasted against five sets of randomly selected control genes sampled in the same manner. Boxes show the interquartile range (IQR) and whiskers extend to 1.5 IQR; bold line and circles represent median and outliers respectively. Kruskal-Wallis test and Dunn's post-hoc test confirm all differences between GOI and controls are significant.

Supplementary Table 1.

Module (cell type)	Pathway	Ratio of protein in Gene Set	No. of proteins in geneset	Protein frm network (>3)	P-value (<0.05)	FDR (<0.05)	Nodes	
O1	Synaptic vesicle cycle(K)	0.0058	63	3	1.93E-06	8.50E-05	STX1B, CLTC, ATP6V1E1	
	Phagosome(K)	0.0142	154	3	2.79E-05	6.13E-04	STX12, ATP6V1E1, RAB7A	
	MHC class II antigen presentation(R)	0.0082	89	2	6.60E-04	9.24E-03	CLTC, RAB7A	
	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	1	2.76E-03	0.0303	STX1B	
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	1	4.13E-03	0.0309	STX1B	
	Endocytosis(K)	0.0239	260	2	5.46E-03	0.0309	CLTC, RAB7A	
	Synaptic vesicle trafficking(P)	0.0012	13	1	5.97E-03	0.0309	STX1B	
	LGI-ADAM interactions(R)	0.0013	14	1	6.42E-03	0.0309	STX1B	
	Collecting duct acid secretion(K)	0.0025	27	1	0.0124	0.0309	ATP6V1E1	
	ROS, RNS production in phagocytes(R)	0.0029	32	1	0.0146	0.0309	ATP6V1E1	
	FAS (CD95) signaling pathway(N)	0.0029	32	1	0.0146	0.0309	CLTC	
	IL8- and CXCR2-mediated signaling events(N)	0.0031	34	1	0.0155	0.0309	RAB7A	
	SNARE interactions in vesicular transport(K)	0.0031	34	1	0.0155	0.0309	STX1B	
	Arf6 trafficking events(N)	0.0031	34	1	0.0155	0.0309	CLTC	
	Iron uptake and transport(R)	0.0035	38	1	0.0174	0.0309	ATP6V1E1	
	TBC/RABGAPs(R)	0.0039	42	1	0.0192	0.0309	RAB7A	
	trans-Golgi Network Vesicle Budding(R)	0.0041	45	1	0.0205	0.0309	CLTC	
	Endocrine and other factor-regulated calcium reabsorption(K)	0.0043	47	1	0.0214	0.0309	CLTC	
	Posttranslational regulation of adherens junction stability and disassembly(N)	0.0044	48	1	0.0219	0.0309	RAB7A	
	Vibrio cholerae infection(K)	0.0047	51	1	0.0232	0.0309	ATP6V1E1	
	Parkinson disease(P)	0.0056	61	1	0.0278	0.0309	STX12	
	IL12-mediated signaling events(N)	0.0056	61	1	0.0278	0.0309	RAB7A	
	Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	1	0.0309	0.0309	ATP6V1E1	
	RAB GEFs exchange GTP for GDP on RABs(R)	0.0067	73	1	0.0331	0.0331	RAB7A	
	Bacterial invasion of epithelial cells(K)	0.0072	78	1	0.0354	0.0354	CLTC	
	L1CAM interactions(R)	0.0075	82	1	0.0372	0.0372	CLTC	
	Salmonella infection(K)	0.0079	86	1	0.0389	0.0389	RAB7A	
	Rheumatoid arthritis(K)	0.0083	90	1	0.0407	0.0407	ATP6V1E1	
	Lipid digestion, mobilization, and transport(R)	0.0084	91	1	0.0412	0.0412	CLTC	
	Amoebiasis(K)	0.009	98	1	0.0443	0.0443	RAB7A	
	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway(P)	0.0099	108	1	0.0487	0.0487	CLTC	
	Gr	Synaptic vesicle cycle(K)	0.0058	63	7	7.88E-15	2.84E-13	ATP6V0B, CLTB, AP2A2, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		ROS, RNS production in phagocytes(R)	0.0029	32	5	2.76E-11	4.97E-10	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		Iron uptake and transport(R)	0.0035	38	5	6.51E-11	7.81E-10	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		Vibrio cholerae infection(K)	0.0047	51	5	2.82E-10	2.54E-09	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	5	1.18E-09	8.29E-09	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		Collecting duct acid secretion(K)	0.0025	27	4	4.75E-09	2.39E-08	ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
		Rheumatoid arthritis(K)	0.0083	90	5	4.78E-09	2.39E-08	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1
Oxidative phosphorylation(K)		0.0122	133	5	3.32E-08	1.33E-07	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1	
Phagosome(K)		0.0142	154	5	6.87E-08	2.75E-07	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1	
Ion channel transport(R)		0.0156	169	5	1.09E-07	3.26E-07	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1	
Signaling by Insulin receptor(R)		0.0255	277	5	1.24E-06	3.73E-06	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1	
Lysosome(K)		0.0113	123	4	1.98E-06	5.93E-06	ATP6V0B, CLTB, ATP6V0C, ATP6V0A1	
Neutrophil degranulation(R)		0.0362	393	4	1.86E-04	3.72E-04	AP2A2, ATP6V0C, ATP6V1D, ATP6V0A1	
Tuberculosis(K)		0.0165	179	3	3.48E-04	6.97E-04	ATP6V0B, ATP6V0C, ATP6V0A1	
Endocrine and other factor-regulated calcium reabsorption(K)		0.0043	47	2	6.60E-04	1.32E-03	CLTB, AP2A2	
Interactions of neuroligins and neuroligins at synapses(R)		0.0046	50	2	7.46E-04	1.49E-03	DLG2, SHANK2	
Metabolic pathways(K)		0.1165	1266	5	1.80E-03	3.60E-03	ATP6V0B, ATP6V0C, ATP6V1D, ATP6V1C1, ATP6V0A1	
Clathrin-mediated endocytosis(R)		0.0108	117	2	3.97E-03	4.24E-03	CLTB, AP2A2	
Huntington disease(P)		0.0111	121	2	4.24E-03	4.24E-03	CLTB, AP2A2	
mTOR signaling pathway(K)		0.0142	154	2	6.77E-03	6.77E-03	ATP6V1D, ATP6V1C1	
Huntington's disease(K)		0.0178	193	2	0.0105	0.0105	CLTB, AP2A2	
Arf1 pathway(N)		0.0018	20	1	0.0164	0.0164	CLTB	
Endocytosis(K)	0.0239	260	2	0.0184	0.0184	CLTB, AP2A2		
adp-ribosylation factor(B)	0.0026	28	1	0.023	0.023	CLTB		
Li	Synaptic vesicle cycle(K)	0.0058	63	11	1.11E-16	1.99E-14	SNAP25, CACNA1A, AP2S1, ATP6V0E2, AP2M1, ATP6V1F, AP2B1, DNMI, DNMI2, STX1B, ATP6V0D1	
	Clathrin-mediated endocytosis(R)	0.0108	117	7	9.22E-09	8.20E-07	AP2S1, PACSIN2, AP2M1, AP2B1, EPN1, DNMI2, AMPH	
	Endocrine and other factor-regulated calcium reabsorption(K)	0.0043	47	5	9.23E-08	5.02E-06	AP2S1, AP2M1, AP2B1, DNMI, DNMI2	
	Endocytosis(K)	0.0239	260	8	1.14E-07	5.02E-06	RAB5C, AP2S1, AP2M1, AP2B1, DNMI, EPN1, DNMI2, AMPH	
	Bacterial invasion of epithelial cells(K)	0.0072	78	5	1.11E-06	3.87E-05	CDH1, CTNNA1, DNMI1, DNMI2, CTNNB1	
	Arf6 trafficking events(N)	0.0031	34	4	1.36E-06	3.93E-05	CDH1, CTNNA1, DNMI2, CTNNB1	
	Posttranslational regulation of adherens junction stability and disassembly(N)	0.0044	48	4	5.27E-06	1.32E-04	CDH1, CTNNA1, DNMI2, CTNNB1	
	E-cadherin signaling in keratinocytes(N)	0.0019	21	3	1.81E-05	3.99E-04	CDH1, CTNNA1, CTNNB1	
	Adherens junction(K)	0.0066	72	4	2.56E-05	4.87E-04	PTPRF, CDH1, CTNNA1, CTNNB1	
	Collecting duct acid secretion(K)	0.0025	27	3	3.82E-05	6.50E-04	ATP6V0E2, ATP6V1F, ATP6V0D1	
	Nectin adhesion pathway(N)	0.0028	30	3	5.22E-05	7.57E-04	CDH1, CTNNA1, CTNNB1	
	EPH-Ephrin signaling(R)	0.0082	89	4	5.82E-05	7.57E-04	AP2S1, AP2M1, AP2B1, DNMI	
	MHC class II antigen presentation(R)	0.0082	89	4	5.82E-05	7.57E-04	AP2S1, AP2M1, AP2B1, DNMI	
	ROS, RNS production in phagocytes(R)	0.0029	32	3	6.31E-05	7.57E-04	ATP6V0E2, ATP6V1F, ATP6V0D1	
	SNARE interactions in vesicular transport(K)	0.0031	34	3	7.54E-05	8.30E-04	STX16, VTI1A, STX1B	
	Internalization of ErbB1(N)	0.0032	35	3	8.22E-05	8.93E-04	DNMI1, EPN1, AMPH	
	E-cadherin signaling in the nascent adherens junction(N)	0.0033	36	3	8.93E-05	8.93E-04	CDH1, CTNNA1, CTNNB1	
	Iron uptake and transport(R)	0.0035	38	3	1.05E-04	9.42E-04	ATP6V0E2, ATP6V1F, ATP6V0D1	
	Stabilization and expansion of the E-cadherin adherens junction(N)	0.0039	42	3	1.40E-04	1.13E-03	CDH1, CTNNA1, CTNNB1	
	Beta-catenin independent WNT signaling(R)	0.0103	112	4	1.41E-04	1.13E-03	AP2S1, AP2M1, AP2B1, CTNNB1	
	Vibrio cholerae infection(K)	0.0047	51	3	2.48E-04	1.98E-03	ATP6V0E2, ATP6V1F, ATP6V0D1	
	Endometrial cancer(K)	0.0048	52	3	2.62E-04	2.05E-03	CDH1, CTNNA1, CTNNB1	
	RAC1 signaling pathway(N)	0.005	54	3	2.93E-04	2.05E-03	CDH1, CTNNA1, CTNNB1	
	endocytotic role of ndk phosphins and dynamin(B)	0.0012	13	2	4.56E-04	2.75E-03	AP2M1, EPN1	
	Synaptic vesicle trafficking(P)	0.0012	13	2	4.56E-04	2.75E-03	SNAP25, STX1B	
	Signaling events mediated by VEGFR1 and VEGFR2(N)	0.0058	63	3	4.58E-04	2.75E-03	CTNNA1, DNMI2, CTNNB1	
	Phagosome(K)	0.0142	154	4	4.70E-04	2.82E-03	RAB5C, ATP6V0E2, ATP6V1F, ATP6V0D1	
	Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	3	5.72E-04	3.32E-03	ATP6V0E2, ATP6V1F, ATP6V0D1	
	CDC42 signaling events(N)	0.0064	70	3	6.22E-04	3.32E-03	CDH1, CTNNA1, CTNNB1	
	Ion channel transport(R)	0.0156	169	4	6.65E-04	3.32E-03	ATP6V0E2, ATP6V1F, ATP2B2, ATP6V0D1	
Signaling events mediated by Hepatocyte Growth Factor Receptor (c-Met)(N)	0.0074	80	3	9.14E-04	4.57E-03	CDH1, CTNNA1, CTNNB1		
L1CAM interactions(R)	0.0075	82	3	9.81E-04	4.90E-03	AP2S1, AP2M1, AP2B1		
Rheumatoid arthritis(K)	0.0083	90	3	1.28E-03	6.14E-03	ATP6V0E2, ATP6V1F, ATP6V0D1		
Lipid digestion, mobilization, and transport(R)	0.0084	91	3	1.32E-03	6.14E-03	AP2S1, AP2M1, AP2B1		
Myogenesis(R)	0.0022	24	2	1.53E-03	6.14E-03	CTNNA1, CTNNB1		
Rap1 signaling pathway(K)	0.0195	212	4	1.54E-03	6.14E-03	CDH1, CTNNB1, PFN4, PFN2		

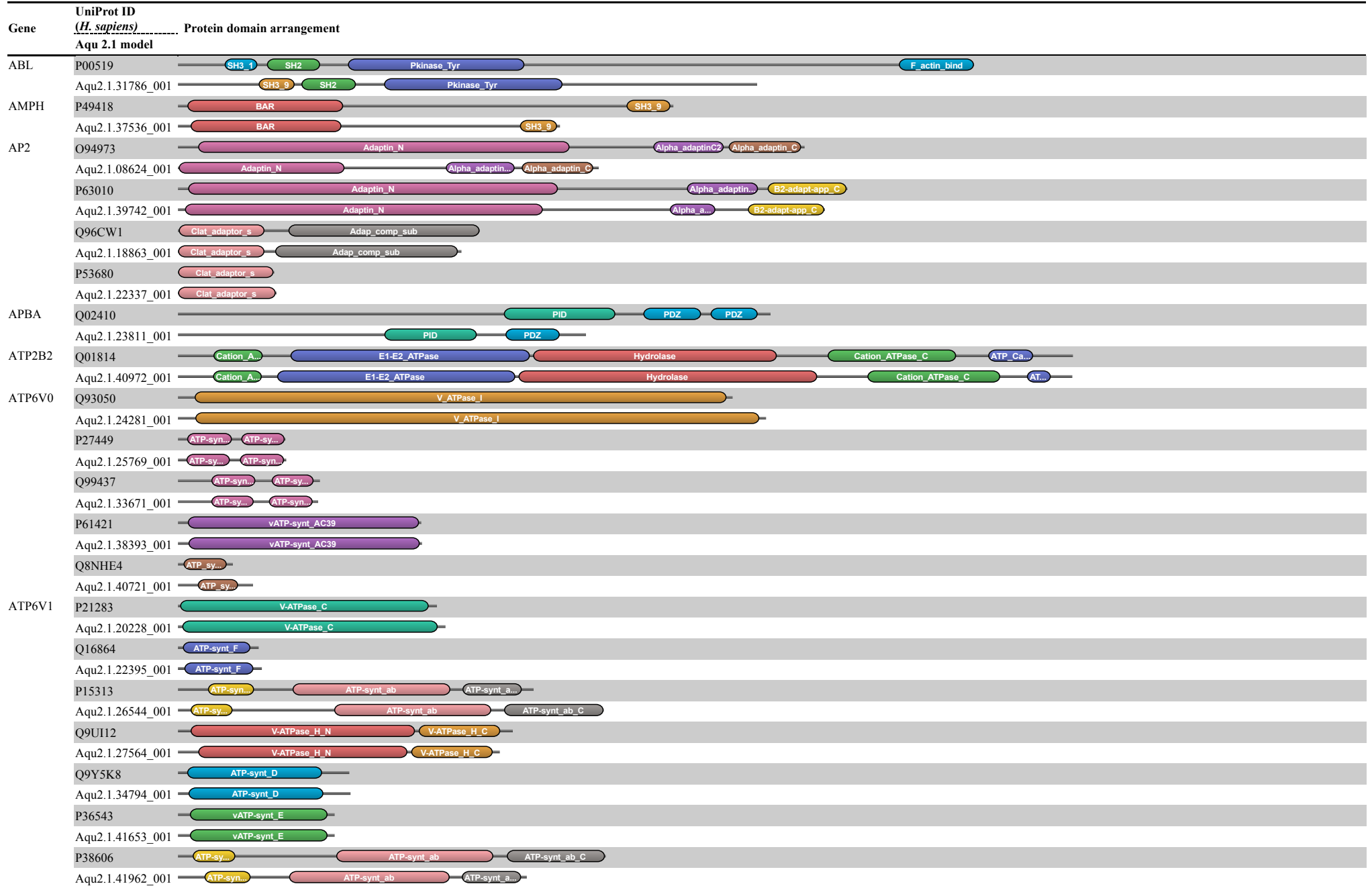
	Cadherin signaling pathway(P)	0.0092	100	3	1.73E-03	6.92E-03	CDH1,CTNNA1,CTNNB1
	Thyroid cancer(K)	0.0027	29	2	2.22E-03	8.87E-03	CDH1,CTNNB1
	Alzheimer disease-presenilin pathway(P)	0.0102	111	3	2.32E-03	9.30E-03	CDH1,CTNNA1,CTNNB1
	N-cadherin signaling events(N)	0.003	33	2	2.86E-03	0.0114	CTNNA1,CTNNB1
	Oxidative phosphorylation(K)	0.0122	133	3	3.86E-03	0.0154	ATP6V0E2,ATP6V1F,ATP6V0D1
	Neurotransmitter Receptor Binding And Downstream Transmission In The Postsynaptic Cell(R)	0.0123	134	3	3.94E-03	0.0158	AP2S1,AP2M1,AP2B1
	PAR1-mediated thrombin signaling events(N)	0.004	43	2	4.78E-03	0.0174	DNM1,DNM2
	Apoptotic execution phase(R)	0.0043	47	2	5.67E-03	0.0174	CDH1,CTNNB1
	Hippo signaling pathway(K)	0.0142	154	3	5.80E-03	0.0174	CDH1,CTNNA1,CTNNB1
	AlphaE beta7 integrin cell surface interactions(N)	0.0003	3	1	7.15E-03	0.0215	CDH1
	Pathogenic Escherichia coli infection(K)	0.0051	55	2	7.68E-03	0.023	CDH1,CTNNB1
	Metabotropic glutamate receptor group I pathway(P)	0.0004	4	1	9.53E-03	0.0286	HOMER1
	Shigellosis(K)	0.006	65	2	0.0106	0.0317	PFN4,PFN2
	Huntington's disease(K)	0.0178	193	3	0.0107	0.0322	AP2S1,AP2M1,AP2B1
	Cell junction organization(R)	0.0064	70	2	0.0122	0.0365	CDH1,CTNNA1
	Arrhythmogenic right ventricular cardiomyopathy (ARVC)(K)	0.0066	72	2	0.0128	0.0385	CTNNA1,CTNNB1
	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	1	0.0143	0.0426	STX1B
	Regulation of nuclear beta catenin signaling and target gene transcription(N)	0.0074	80	2	0.0157	0.0426	CDH1,CTNNB1
	Depolarization of the Presynaptic Terminal Triggers the Opening of Calcium Channels(R)	0.0006	7	1	0.0166	0.0426	CACNA1A
	sumoylation as a mechanism to modulate ctbp-dependent gene responses(B)	0.0006	7	1	0.0166	0.0426	CDH1
	Salmonella infection(K)	0.0079	86	2	0.0179	0.0426	PFN4,PFN2
	Integration of energy metabolism(R)	0.0085	92	2	0.0204	0.0426	SNAP25,CACNA1A
	Fc gamma R-mediated phagocytosis(K)	0.0086	93	2	0.0208	0.0426	DNM2,AMPH
	Effects of Botulinum toxin(N)	0.0008	9	1	0.0213	0.0426	SNAP25
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	1	0.0213	0.0426	STX1B
	Gap junction trafficking and regulation(R)	0.0008	9	1	0.0213	0.0426	AP2M1
	5HT3 type receptor mediated signaling pathway(P)	0.0009	10	1	0.0237	0.0473	SNAP25
Te	Synaptic vesicle cycle(K)	0.0058	63	2	2.00E-04	6.37E-03	STX1B,CLTC
	MHC class II antigen presentation(R)	0.0082	89	2	3.98E-04	6.37E-03	CLTC,RAB7A
	Phagosome(K)	0.0142	154	2	1.18E-03	0.013	STX12,RAB7A
	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	1	2.21E-03	0.0166	STX1B
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	1	3.31E-03	0.0166	STX1B
	Endocytosis(K)	0.0239	260	2	3.33E-03	0.0166	CLTC,RAB7A
	Synaptic_vesicle_trafficking(P)	0.0012	13	1	4.78E-03	0.0191	STX1B
	LGI-ADAM interactions(R)	0.0013	14	1	5.14E-03	0.0206	STX1B
	FAS (CD95) signaling pathway(N)	0.0029	32	1	0.0117	0.0223	CLTC
	IL8- and CXCR2-mediated signaling events(N)	0.0031	34	1	0.0125	0.0223	RAB7A
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	Arf6 trafficking events(N)	0.0031	34	1	0.0125	0.0223	CLTC
	TBC/RABGAPs(R)	0.0039	42	1	0.0154	0.0223	RAB7A
	trans-Golgi Network Vesicle Budding(R)	0.0041	45	1	0.0165	0.0223	CLTC
	Endocrine and other factor-regulated calcium reabsorption(K)	0.0043	47	1	0.0172	0.0223	CLTC
	Posttranslational regulation of adherens junction stability and disassembly(N)	0.0044	48	1	0.0176	0.0223	RAB7A
	Parkinson disease(P)	0.0056	61	1	0.0223	0.0223	STX12
	IL12-mediated signaling events(N)	0.0056	61	1	0.0223	0.0223	RAB7A
	RAB GEFs exchange GTP for GDP on RABs(R)	0.0067	73	1	0.0266	0.0266	RAB7A
	Bacterial invasion of epithelial cells(K)	0.0072	78	1	0.0284	0.0284	CLTC
	L1CAM interactions(R)	0.0075	82	1	0.0298	0.0298	CLTC
	Salmonella infection(K)	0.0079	86	1	0.0313	0.0313	RAB7A
	Lipid digestion, mobilization, and transport(R)	0.0084	91	1	0.0331	0.0331	CLTC
	Amoebiasis(K)	0.009	98	1	0.0356	0.0356	RAB7A
	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway(P)	0.0099	108	1	0.0392	0.0392	CLTC
	Beta-catenin independent WNT signaling(R)	0.0103	112	1	0.0406	0.0406	CLTC
	Clathrin-mediated endocytosis(R)	0.0108	117	1	0.0424	0.0424	CLTC
	Lysosome(K)	0.0113	123	1	0.0445	0.0445	CLTC
Na	Collecting duct acid secretion(K)	0.0025	27	2	1.85E-05	3.29E-04	ATP6V1A,ATP6V1B1
	ROS, RNS production in phagocytes(R)	0.0029	32	2	2.60E-05	3.29E-04	ATP6V1A,ATP6V1B1
	Iron uptake and transport(R)	0.0035	38	2	3.66E-05	3.29E-04	ATP6V1A,ATP6V1B1
	Vibrio cholerae infection(K)	0.0047	51	2	6.59E-05	3.95E-04	ATP6V1A,ATP6V1B1
	Synaptic vesicle cycle(K)	0.0058	63	2	1.00E-04	4.68E-04	ATP6V1A,ATP6V1B1
	Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	2	1.17E-04	4.68E-04	ATP6V1A,ATP6V1B1
	Rheumatoid arthritis(K)	0.0083	90	2	2.05E-04	6.14E-04	ATP6V1A,ATP6V1B1
	Oxidative phosphorylation(K)	0.0122	133	2	4.46E-04	1.19E-03	ATP6V1A,ATP6V1B1
	Phagosome(K)	0.0142	154	2	5.97E-04	1.19E-03	ATP6V1A,ATP6V1B1
	mTOR signaling pathway(K)	0.0142	154	2	5.97E-04	1.19E-03	ATP6V1A,ATP6V1B1
	Ion channel transport(R)	0.0156	169	2	7.18E-04	1.44E-03	ATP6V1A,ATP6V1B1
	Signaling by Insulin receptor(R)	0.0255	277	2	1.92E-03	3.83E-03	ATP6V1A,ATP6V1B1
	5HT3 type receptor mediated signaling pathway(P)	0.0009	10	1	2.76E-03	5.52E-03	VAMP8
	Beta3 adrenergic receptor signaling pathway(P)	0.0019	21	1	5.79E-03	5.79E-03	VAMP8
	Beta2 adrenergic receptor signaling pathway(P)	0.0019	21	1	5.79E-03	5.79E-03	VAMP8
	Oxytocin receptor mediated signaling pathway(P)	0.0019	21	1	5.79E-03	5.79E-03	VAMP8
	5HT4 type receptor mediated signaling pathway(P)	0.0021	23	1	6.34E-03	6.34E-03	VAMP8
	Corticotropin releasing factor receptor signaling pathway(P)	0.0023	25	1	6.89E-03	6.89E-03	VAMP8
	5HT2 type receptor mediated signaling pathway(P)	0.0024	26	1	7.16E-03	7.16E-03	VAMP8
	Beta1 adrenergic receptor signaling pathway(P)	0.0025	27	1	7.44E-03	7.44E-03	VAMP8
	SNARE interactions in vesicular transport(K)	0.0031	34	1	9.36E-03	9.36E-03	VAMP8
	trans-Golgi Network Vesicle Budding(R)	0.0041	45	1	0.0124	0.0124	VAMP8
	Clathrin-mediated endocytosis(R)	0.0108	117	1	0.032	0.032	VAMP8
	Platelet activation(K)	0.0112	122	1	0.0333	0.0333	VAMP8
	Metabolic pathways(K)	0.1165	1266	2	0.0376	0.0376	ATP6V1A,ATP6V1B1
Sk	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	2	1.83E-06	8.77E-05	STX1B,STX1A
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	2	4.11E-06	9.87E-05	STX1B,STX1A
	Synaptic_vesicle_trafficking(P)	0.0012	13	2	8.57E-06	1.19E-04	STX1B,STX1A
	LGI-ADAM interactions(R)	0.0013	14	2	9.94E-06	1.19E-04	STX1B,STX1A
	SNARE interactions in vesicular transport(K)	0.0031	34	2	5.85E-05	5.26E-04	STX1B,STX1A
	Synaptic vesicle cycle(K)	0.0058	63	2	2.00E-04	1.60E-03	STX1B,STX1A
	Effects of Botulinum toxin(N)	0.0008	9	1	3.31E-03	0.0199	STX1A
	RAB geranylgeranylation(R)	0.0014	15	1	5.51E-03	0.0219	RAB11B
	tumor suppressor arf inhibits ribosomal biogenesis(B)	0.0017	19	1	6.98E-03	0.0219	ABL1
	Insulin processing(R)	0.0018	20	1	7.34E-03	0.0219	STX1A
	Signaling by Robo receptor(R)	0.0021	23	1	8.44E-03	0.0219	ABL1
	Myogenesis(R)	0.0022	24	1	8.80E-03	0.0219	ABL1
	Lissencephaly gene (LIS1) in neuronal migration and development(N)	0.0026	28	1	0.0103	0.0219	ABL1
	ATM pathway(N)	0.0031	34	1	0.0125	0.0219	ABL1
	Neurotransmitter Release Cycle(R)	0.0037	40	1	0.0146	0.0219	STX1A
	TBC/RABGAPs(R)	0.0039	42	1	0.0154	0.0219	RAB11B

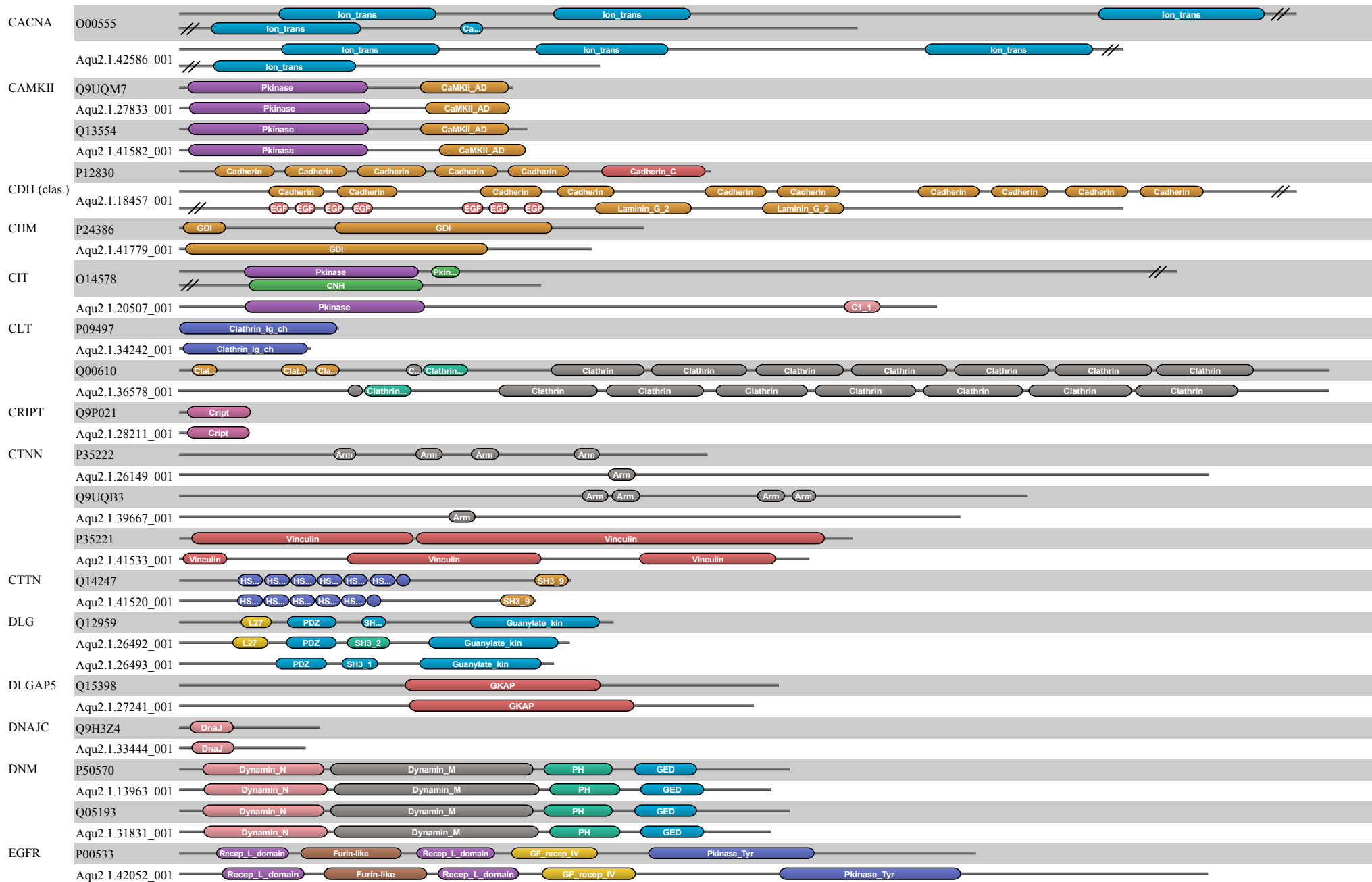
	Vasopressin-regulated water reabsorption(K)	0.004	44	1	0.0161	0.0219	RAB11B	
	DNA Double Strand Break Response(R)	0.0041	45	1	0.0165	0.0219	ABL1	
	Posttranslational regulation of adherens junction stability and disassembly(N)	0.0044	48	1	0.0176	0.0219	ABL1	
	Validated transcriptional targets of TAp63 isoforms(N)	0.0045	49	1	0.0179	0.0219	ABL1	
	Interactions of neuroligins and neuroligins at synapses(R)	0.0046	50	1	0.0183	0.0219	STX1A	
	Pathogenic Escherichia coli infection(K)	0.0051	55	1	0.0201	0.0219	ABL1	
	p53 pathway(N)	0.0052	57	1	0.0208	0.0219	ABL1	
	Viral myocarditis(K)	0.0054	59	1	0.0215	0.0219	ABL1	
	Neurotrophic factor-mediated Trk receptor signaling(N)	0.0055	60	1	0.0219	0.0219	ABL1	
	Regulation of retinoblastoma protein(N)	0.0059	64	1	0.0234	0.0234	ABL1	
	Shigellosis(K)	0.006	65	1	0.0237	0.0237	ABL1	
	Regulation of Telomerase(N)	0.0063	68	1	0.0248	0.0248	ABL1	
	Amphetamine addiction(K)	0.0063	68	1	0.0248	0.0248	STX1A	
	Chronic myeloid leukemia(K)	0.0067	73	1	0.0266	0.0266	ABL1	
	p73 transcription factor network(N)	0.0069	75	1	0.0273	0.0273	ABL1	
	Insulin secretion(K)	0.0078	85	1	0.0309	0.0309	STX1A	
	HDR through Homologous Recombination (HR) or Single Strand Annealing (SSA)(R)	0.0078	85	1	0.0309	0.0309	ABL1	
	ErbB signaling pathway(K)	0.0081	88	1	0.032	0.032	ABL1	
	Integration of energy metabolism(R)	0.0085	92	1	0.0334	0.0334	STX1A	
	Factors involved in megakaryocyte development and platelet production(R)	0.0101	110	1	0.0399	0.0399	ABL1	
	PDGFR-beta signaling pathway(N)	0.011	120	1	0.0434	0.0434	ABL1	
	Neurotrophin signaling pathway(K)	0.0111	121	1	0.0438	0.0438	ABL1	
	Cell cycle(K)	0.0114	124	1	0.0449	0.0449	ABL1	
	AMPK signaling pathway(K)	0.0114	124	1	0.0449	0.0449	RAB11B	
Pu	Neurotransmitter Receptor Binding And Downstream Transmission In The Postsynaptic Cell(R)	0.0123	134	6	1.60E-08	2.83E-06	CAMK2B, GABBR2, GABBR1, PRKCB, GRIP1, PICK1	
	Neurotransmitter Release Cycle(R)	0.0037	40	3	2.20E-05	1.93E-03	UNC13B, SYT1, PPF1A2	
	Effects of Botulinum toxin(N)	0.0008	9	2	7.15E-05	3.66E-03	UNC13B, SYT1	
	Axon guidance(K)	0.0163	177	4	8.32E-05	3.66E-03	CAMK2B, SEMA5B, EPHB1, PLXNA3	
	Synaptic vesicle trafficking(P)	0.0012	13	2	1.49E-04	5.21E-03	UNC13B, SYT1	
	GABAergic synapse(K)	0.0081	88	3	2.25E-04	5.50E-03	GABBR2, GABBR1, PRKCB	
	Morphine addiction(K)	0.0084	91	3	2.48E-04	5.50E-03	GABBR2, GABBR1, PRKCB	
	nitric oxide signaling pathway(B)	0.0016	17	2	2.54E-04	5.50E-03	PRKCB, NOS1	
	Circadian entrainment(K)	0.0088	96	3	2.90E-04	5.50E-03	CAMK2B, PRKCB, NOS1	
	vegf hypoxia and angiogenesis(B)	0.0026	28	2	6.82E-04	0.0116	PRKCB, NOS1	
	Calcium signaling pathway(K)	0.0167	182	3	1.84E-03	0.0294	CAMK2B, GABBR1, GRM3	
	cAMP signaling pathway(K)	0.0184	200	3	2.40E-03	0.0336	CAMK2B, GABBR2, GABBR1	
	Long-term depression(K)	0.0055	60	2	3.05E-03	0.0389	PRKCB, NOS1	
	Synaptic vesicle cycle(K)	0.0058	63	2	3.36E-03	0.0389	UNC13B, SYT1	
	Glioma(K)	0.0061	66	2	3.67E-03	0.0389	CAMK2B, PRKCB	
	Long-term potentiation(K)	0.0062	67	2	3.78E-03	0.0389	CAMK2B, PRKCB	
	Amphetamine addiction(K)	0.0063	68	2	3.89E-03	0.0389	CAMK2B, PRKCB	
	Gastric acid secretion(K)	0.0069	75	2	4.71E-03	0.042	CAMK2B, PRKCB	
	Aldosterone synthesis and secretion(K)	0.0075	82	2	5.60E-03	0.042	CAMK2B, PRKCB	
	Taste transduction(K)	0.0076	83	2	5.73E-03	0.042	GABBR2, GABBR1	
	Insulin secretion(K)	0.0078	85	2	6.00E-03	0.042	CAMK2B, PRKCB	
	Neuroactive ligand-receptor interaction(K)	0.0256	278	3	6.05E-03	0.042	GABBR2, GABBR1, GRM3	
	Potassium Channels(R)	0.008	87	2	6.28E-03	0.042	GABBR2, GABBR1	
	ErbB signaling pathway(K)	0.0081	88	2	6.42E-03	0.042	CAMK2B, PRKCB	
	Salivary secretion(K)	0.0083	90	2	6.70E-03	0.042	PRKCB, NOS1	
	GnRH signaling pathway(K)	0.0085	92	2	6.99E-03	0.042	CAMK2B, PRKCB	
	Inflammatory mediator regulation of TRP channels(K)	0.0091	99	2	8.05E-03	0.0435	CAMK2B, PRKCB	
	Estrogen signaling pathway(K)	0.0092	100	2	8.21E-03	0.0435	GABBR2, GABBR1	
	Melanogenesis(K)	0.0093	101	2	8.37E-03	0.0435	CAMK2B, PRKCB	
	HIF-1 signaling pathway(K)	0.0095	103	2	8.69E-03	0.0435	CAMK2B, PRKCB	
	Cardiac conduction(R)	0.0098	107	2	9.35E-03	0.0467	CAMK2B, NOS1	
	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway(P)	0.0099	108	2	9.52E-03	0.0476	PRKCB, GRM3	
	cbl mediated ligand-induced downregulation of egf receptors pathway(B)	0.0006	7	1	9.62E-03	0.0481	PRKCB	
	La	RAB GEFs exchange GTP for GDP on RABs(R)	0.0067	73	3	3.00E-06	2.10E-05	RAB3GAP2, CHM, RAB3GAP1
		RAB geranylgeranylation(R)	0.0014	15	2	1.90E-05	5.70E-05	CHM, RABGGTB
		Intra-Golgi and retrograde Golgi-to-ER traffic(R)	0.013	141	2	1.64E-03	3.28E-03	RAB3GAP2, RAB3GAP1
		Effects of Botulinum toxin(N)	0.0008	9	1	4.13E-03	4.13E-03	RAB3GAP2
		Signaling events mediated by PRL(N)	0.0021	23	1	0.0105	0.0105	RABGGTB
		Generic Transcription Pathway(R)	0.0455	494	2	0.0188	0.0188	CHM, RABGGTB
Sphingolipid metabolism(R)		0.0065	71	1	0.0322	0.0322	VAPB	
Gy	SNARE interactions in vesicular transport(K)	0.0031	34	2	9.73E-05	1.75E-03	STX5, STX2	
	Hippo signaling pathway(K)	0.0142	154	2	1.95E-03	0.0176	DLG1, SCRIB	
	Viral carcinogenesis(K)	0.0187	203	2	3.36E-03	0.0202	DLG1, SCRIB	
	SALM protein interactions at the synapses(R)	0.0018	20	1	9.17E-03	0.0318	DLG1	
	E-cadherin signaling in the nascent adherens junction(N)	0.0033	36	1	0.0165	0.0318	DLG1	
	Neurotransmitter Release Cycle(R)	0.0037	40	1	0.0183	0.0318	APBA1	
	Interactions of neuroligins and neuroligins at synapses(R)	0.0046	50	1	0.0228	0.0318	APBA1	
	Alzheimer disease-amyloid secretase pathway(P)	0.0054	59	1	0.0269	0.0318	APBA1	
	Synaptic vesicle cycle(K)	0.0058	63	1	0.0287	0.0318	STX2	
	CDC42 signaling events(N)	0.0064	70	1	0.0318	0.0318	DLG1	
	L1CAM interactions(R)	0.0075	82	1	0.0372	0.0372	DLG1	
	T cell receptor signaling pathway(K)	0.0097	105	1	0.0474	0.0474	DLG1	

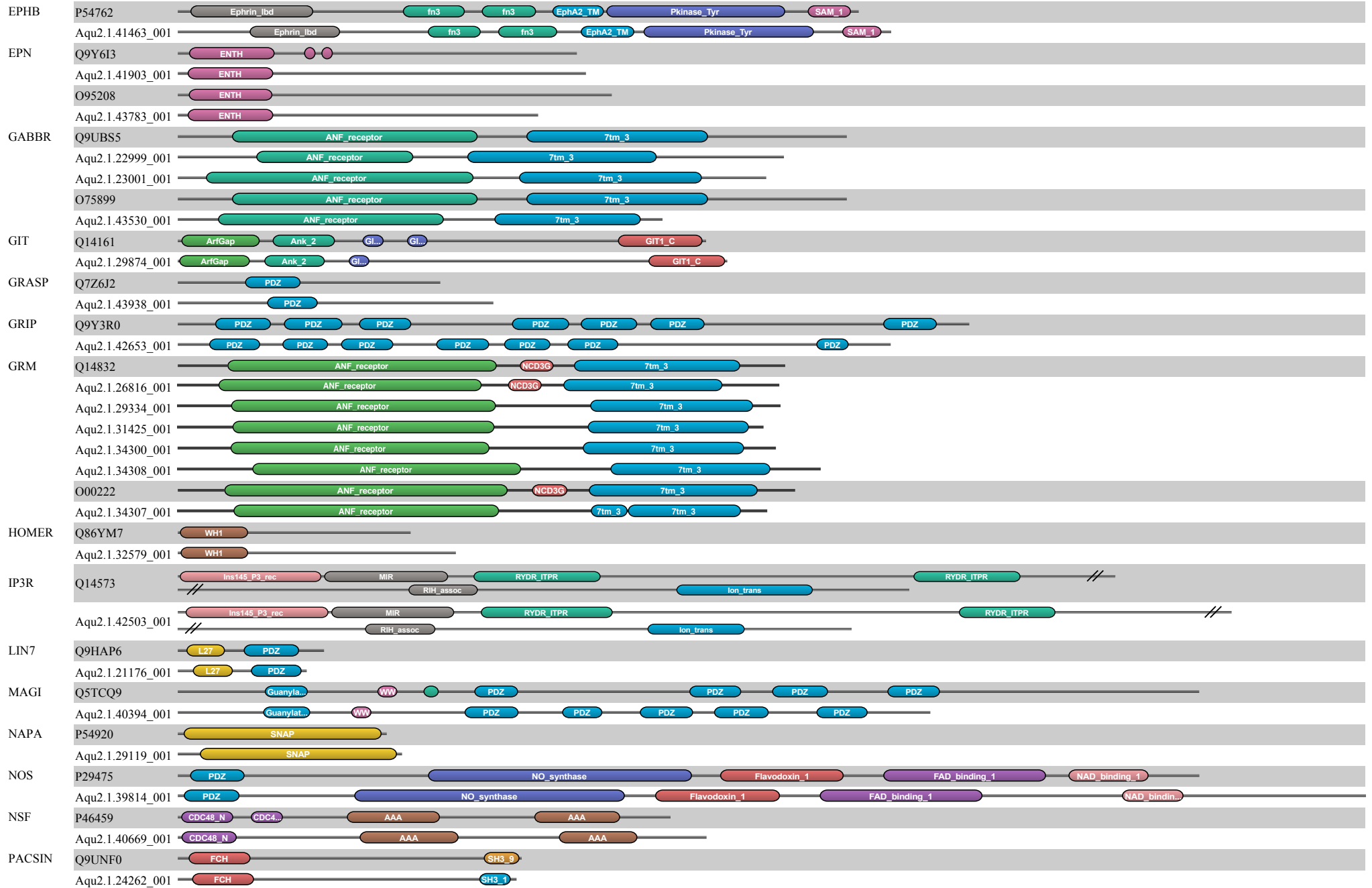
Module (dev'tal)	Pathway	Ratio of protein in Gene Set	No. of proteins in geneset	Protein frm (>3)	P-value (<0.05)	FDR (<0.05)	Nodes
Re	Synaptic vesicle cycle(K)	0.0058	63	8	1.55E-15	7.93E-14	ATP6V1A, ATP6V0B, STXBP1, STX1B, AP2S1, ATP6V1E1, ATP6V0C, ATP6V1D
	ROS, RNS production in phagocytes(R)	0.0029	32	5	2.79E-10	6.99E-09	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Iron uptake and transport(R)	0.0035	38	5	6.57E-10	1.12E-08	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Vibrio cholerae infection(K)	0.0047	51	5	2.84E-09	3.41E-08	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	5	1.18E-08	1.18E-07	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Rheumatoid arthritis(K)	0.0083	90	5	4.74E-08	3.32E-07	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Oxidative phosphorylation(K)	0.0122	133	5	3.26E-07	1.95E-06	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Phagosome(K)	0.0142	154	5	6.69E-07	3.34E-06	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Ion channel transport(R)	0.0156	169	5	1.05E-06	5.27E-06	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Signaling by Insulin receptor(R)	0.0255	277	5	1.17E-05	4.67E-05	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Metabolic pathways(K)	0.1165	1266	5	0.0123	0.0188	ATP6V1A, ATP6V0B, ATP6V1E1, ATP6V0C, ATP6V1D
	Collecting duct acid secretion(K)	0.0025	27	4	2.68E-08	2.14E-07	ATP6V1A, ATP6V1E1, ATP6V0C, ATP6V1D
	SNARE interactions in vesicular transport(K)	0.0031	34	3	8.56E-06	3.42E-05	STX16, VAMP8, STX1B
	Intra-Golgi and retrograde Golgi-to-ER traffic(R)	0.013	141	3	5.67E-04	1.70E-03	STX16, RAB3GAP2, RAB3GAP1
	mTOR signaling pathway(K)	0.0142	154	3	7.32E-04	2.20E-03	ATP6V1A, ATP6V1E1, ATP6V1D

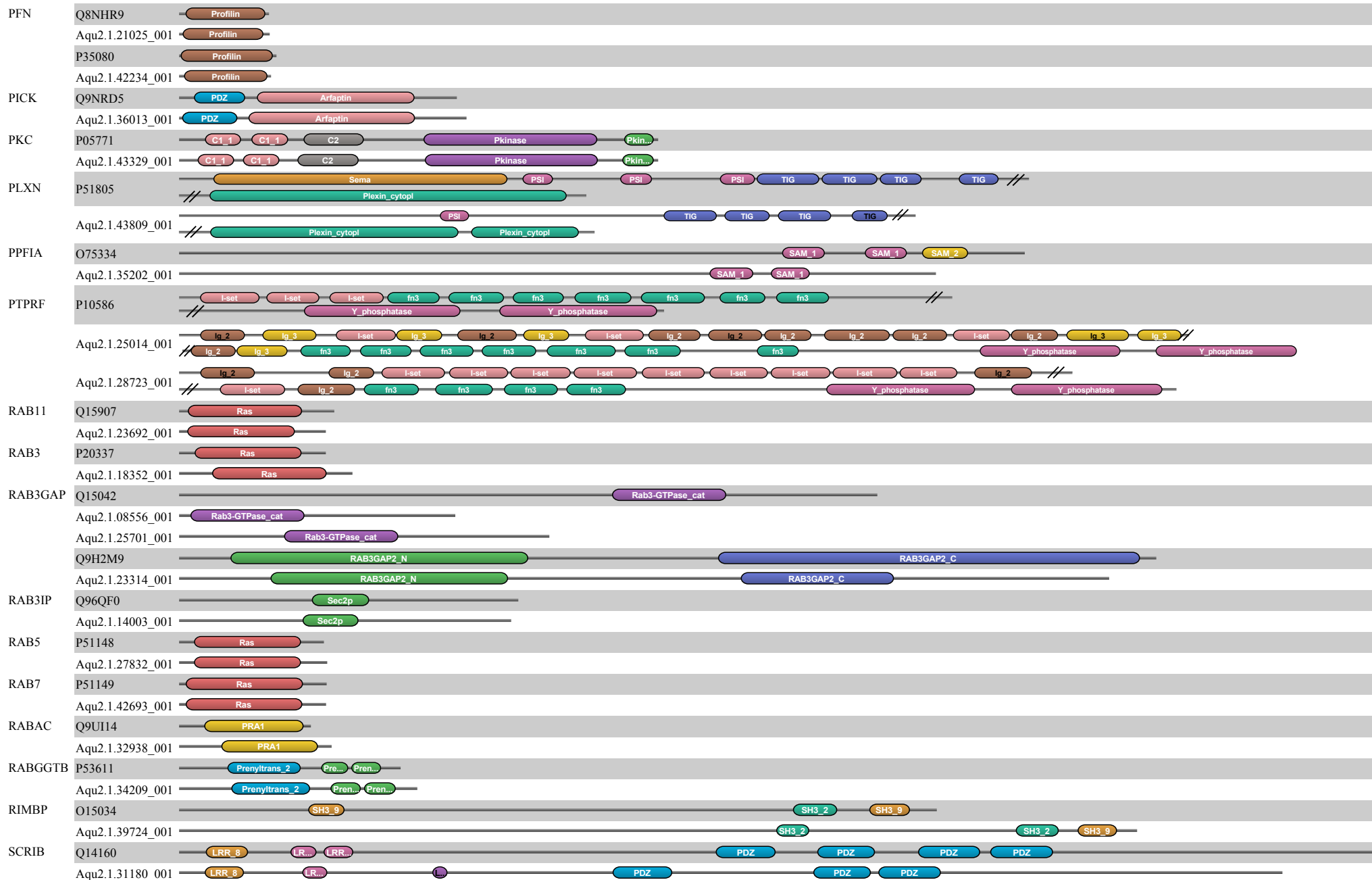
	Neutrophil degranulation(R)	0.0362	393	3	0.0103	0.0188	VAMP8,ATP6V0C,ATP6V1D
	Effects of Botulinum toxin(N)	0.0008	9	2	5.32E-05	1.60E-04	STXBP1,RAB3GAP2
	Synaptic vesicle trafficking(P)	0.0012	13	2	1.11E-04	3.32E-04	STXBP1,STX1B
	RAB GEFs exchange GTP for GDP on RABs(R)	0.0067	73	2	3.35E-03	0.0101	RAB3GAP2,RAB3GAP1
	Clathrin-mediated endocytosis(R)	0.0108	117	2	8.36E-03	0.0167	VAMP8,AP2S1
	Lysosome(K)	0.0113	123	2	9.20E-03	0.0184	ATP6V0B,ATP6V0C
	Tuberculosis(K)	0.0165	179	2	0.0188	0.0188	ATP6V0B,ATP6V0C
	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	1	7.15E-03	0.0143	STX1B
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	1	0.0107	0.0188	STX1B
	5HT3 type receptor mediated signaling pathway(P)	0.0009	10	1	0.0119	0.0188	VAMP8
	LGI-ADAM interactions(R)	0.0013	14	1	0.0166	0.0188	STX1B
	Beta2 adrenergic receptor signaling pathway(P)	0.0019	21	1	0.0248	0.0248	VAMP8
	Beta3 adrenergic receptor signaling pathway(P)	0.0019	21	1	0.0248	0.0248	VAMP8
	Oxytocin receptor mediated signaling pathway(P)	0.0019	21	1	0.0248	0.0248	VAMP8
	5HT4 type receptor mediated signaling pathway(P)	0.0021	23	1	0.0272	0.0272	VAMP8
	Corticotropin releasing factor receptor signaling pathway(P)	0.0023	25	1	0.0295	0.0295	VAMP8
	5HT2 type receptor mediated signaling pathway(P)	0.0024	26	1	0.0307	0.0307	VAMP8
	Beta1 adrenergic receptor signaling pathway(P)	0.0025	27	1	0.0318	0.0318	VAMP8
	Neurotransmitter Release Cycle(R)	0.0037	40	1	0.0468	0.0468	STXBP1
Go	Neurotransmitter Release Cycle(R)	0.0037	40	3	1.39E-05	1.71E-03	SYT1,DNAJC5,APBA1
Or	Synaptic vesicle cycle(K)	0.0058	63	20	1.11E-16	3.04E-14	NAPA,SNAP25,STXBP1,CLTC,CLTB,AP2A2,ATP6V1H,SLC17A6,SLC17A7,STX2,AP2M1,ATP6V1C1,NSF,UNC13B,AP2B1,DNM1,DNM2,STX1B,STX1A,ATP6V1B1
	Endocytosis(K)	0.0239	260	11	1.33E-09	7.36E-08	CLTC,CLTB,AP2A2,AP2M1,AP2B1,EPN1,DNM1,RAB11B,DNM2,EPN2,RAB7A
	Clathrin-mediated endocytosis(R)	0.0108	117	10	1.00E-11	9.11E-10	CLTC,CLTB,AP2A2,AP2M1,AP2B1,EPN1,DNM2,EPN2,CTTN,SYNJ1
	Endocrine and other factor-regulated calcium reabsorption(K)	0.0043	47	8	6.69E-12	9.11E-10	CLTC,CLTB,AP2A2,AP2M1,PRKCB,AP2B1,DNM1,DNM2
	Bacterial invasion of epithelial cells(K)	0.0072	78	7	1.23E-08	5.55E-07	CLTC,CLTB,CDH1,CTNNA1,DNM1,DNM2,CTTN
	Neurotransmitter Receptor Binding And Downstream Transmission In The Postsynaptic Cell(R)	0.0123	134	7	4.72E-07	1.41E-05	CAMK2B,AP2A2,AP2M1,NSF,GABBR1,PRKCB,AP2B1
	MHC class II antigen presentation(R)	0.0082	89	6	7.81E-07	2.11E-05	CLTC,AP2A2,AP2M1,AP2B1,DNM2,RAB7A
	Signalling by NGF(R)	0.0387	421	6	3.67E-03	0.0208	CAMK2B,CLTC,AP2A2,SYNGAP1,AP2M1,AP2B1
	Synaptic vesicle trafficking(P)	0.0012	13	5	1.36E-09	7.36E-08	SNAP25,STXBP1,UNC13B,STX1B,STX1A
	Neurotransmitter Release Cycle(R)	0.0037	40	5	3.51E-07	1.19E-05	SNAP25,STXBP1,SLC17A7,UNC13B,STX1A
	Phagosome(K)	0.0142	154	5	2.20E-04	3.34E-03	STX12,ATP6V1H,ATP6V1C1,RAB7A,ATP6V1B1
	Ion channel transport(R)	0.0156	169	5	3.37E-04	3.37E-03	CAMK2B,ATP6V1H,ATP6V1C1,ATP2B2,ATP6V1B1
	Huntington's disease(K)	0.0178	193	5	6.15E-04	4.92E-03	CLTC,CLTB,AP2A2,AP2M1,AP2B1
	Signaling by Insulin receptor(R)	0.0255	277	5	3.01E-03	0.0181	CAMK2B,SYNGAP1,ATP6V1H,ATP6V1C1,ATP6V1B1
	Effects of Botulinum toxin(N)	0.0008	9	4	3.78E-08	1.47E-06	SNAP25,STXBP1,UNC13B,STX1A
	Arf6 trafficking events(N)	0.0031	34	4	7.22E-06	1.59E-04	CLTC,CDH1,CTNNA1,DNM2
	SNARE interactions in vesicular transport(K)	0.0031	34	4	7.22E-06	1.59E-04	STX16,STX2,STX1B,STX1A
	Posttranslational regulation of adherens junction stability and disassembly(N)	0.0044	48	4	2.77E-05	5.26E-04	CDH1,CTNNA1,DNM2,RAB7A
	L1CAM interactions(R)	0.0075	82	4	2.16E-04	3.34E-03	CLTC,AP2A2,AP2M1,AP2B1
	Insulin secretion(K)	0.0078	85	4	2.47E-04	3.34E-03	CAMK2B,SNAP25,PRKCB,STX1A
	EPH-Ephrin signaling(R)	0.0082	89	4	2.94E-04	3.34E-03	AP2A2,AP2M1,AP2B1,DNM1
	Lipid digestion, mobilization, and transport(R)	0.0084	91	4	3.20E-04	3.37E-03	CLTC,AP2A2,AP2M1,AP2B1
	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway(P)	0.0099	108	4	6.08E-04	4.92E-03	CLTC,CLTB,GRM3,PRKCB
	Beta-catenin independent WNT signaling(R)	0.0103	112	4	6.96E-04	5.57E-03	CLTC,AP2A2,AP2M1,AP2B1
	Glutamatergic synapse(K)	0.0105	114	4	7.43E-04	5.94E-03	GRM3,SLC17A6,SLC17A7,PRKCB
	mTOR signaling pathway(K)	0.0142	154	4	2.23E-03	0.0134	ATP6V1H,ATP6V1C1,PRKCB,ATP6V1B1
	endocytotic role of ndk phosphins and dynamin(B)	0.0012	13	3	1.51E-05	3.18E-04	AP2M1,EPN1,SYNJ1
	ROS, RNS production in phagocytes(R)	0.0029	32	3	2.16E-04	3.34E-03	ATP6V1H,ATP6V1C1,ATP6V1B1
	IL8- and CXCR2-mediated signaling events(N)	0.0031	34	3	2.57E-04	3.34E-03	PRKCB,DNM1,RAB7A
	Internalization of ErbB1(N)	0.0032	35	3	2.80E-04	3.34E-03	EPN1,DNM1,SYNJ1
	E-cadherin signaling in the nascent adherens junction(N)	0.0033	36	3	3.04E-04	3.34E-03	CDH1,CTNNA1,CTTN
	Iron uptake and transport(R)	0.0035	38	3	3.56E-04	3.56E-03	ATP6V1H,ATP6V1C1,ATP6V1B1
	PAR1-mediated thrombin signaling events(N)	0.004	43	3	5.09E-04	4.58E-03	PRKCB,DNM1,DNM2
	trans-Golgi Network Vesicle Budding(R)	0.0041	45	3	5.80E-04	4.92E-03	NAPA,CLTC,DNM2
	Vibrio cholerae infection(K)	0.0047	51	3	8.32E-04	6.66E-03	ATP6V1H,ATP6V1C1,ATP6V1B1
	Signaling events mediated by VEGFR1 and VEGFR2(N)	0.0058	63	3	1.52E-03	0.0107	CTNNA1,PRKCB,DNM2
	Epithelial cell signaling in Helicobacter pylori infection(K)	0.0063	68	3	1.89E-03	0.0132	ATP6V1H,ATP6V1C1,ATP6V1B1
	Amphetamine addiction(K)	0.0063	68	3	1.89E-03	0.0132	CAMK2B,PRKCB,STX1A
	Adherens junction(K)	0.0066	72	3	2.22E-03	0.0134	PTPRF,CDH1,CTNNA1
	GABAergic synapse(K)	0.0081	88	3	3.90E-03	0.0208	NSF,GABBR1,PRKCB
	Rheumatoid arthritis(K)	0.0083	90	3	4.16E-03	0.0208	ATP6V1H,ATP6V1C1,ATP6V1B1
	Integration of energy metabolism(R)	0.0085	92	3	4.42E-03	0.0221	SNAP25,STXBP1,STX1A
	Retrograde endocannabinoid signaling(K)	0.0093	101	3	5.72E-03	0.0286	SLC17A6,SLC17A7,PRKCB
	Lysosome(K)	0.0113	123	3	9.78E-03	0.0403	CLTC,CLTB,ATP6V1H
	Oxidative phosphorylation(K)	0.0122	133	3	0.0121	0.0483	ATP6V1H,ATP6V1C1,ATP6V1B1
	Metabotropic glutamate receptor group III pathway(P)	0.0006	6	2	2.23E-04	3.34E-03	STX1B,STX1A
	Metabotropic glutamate receptor group II pathway(P)	0.0008	9	2	4.98E-04	4.58E-03	STX1B,STX1A
	LGI-ADAM interactions(R)	0.0013	14	2	1.19E-03	8.34E-03	STX1B,STX1A
	Arf1 pathway(N)	0.0018	20	2	2.40E-03	0.0144	CLTB,AP2M1
	E-cadherin signaling in keratinocytes(N)	0.0019	21	2	2.64E-03	0.0158	CDH1,CTNNA1
	Collecting duct acid secretion(K)	0.0025	27	2	4.30E-03	0.0215	ATP6V1C1,ATP6V1B1
	IL8- and CXCR1-mediated signaling events(N)	0.0026	28	2	4.62E-03	0.0231	PRKCB,DNM1
	Nectin adhesion pathway(N)	0.0028	30	2	5.28E-03	0.0264	CDH1,CTNNA1
	N-cadherin signaling events(N)	0.003	33	2	6.34E-03	0.0317	CTNNA1,CTTN
	Nicotine addiction(K)	0.0037	40	2	9.17E-03	0.0403	SLC17A6,SLC17A7
	TBC/RABGAPs(R)	0.0039	42	2	0.0101	0.0403	RAB11B,RAB7A
	Stabilization and expansion of the E-cadherin adherens junction(N)	0.0039	42	2	0.0101	0.0403	CDH1,CTNNA1
	Vasopressin-regulated water reabsorption(K)	0.004	44	2	0.011	0.044	NSF,RAB11B
	FGF signaling pathway(N)	0.0043	47	2	0.0125	0.0499	CDH1,CTTN
	AlphaE beta7 integrin cell surface interactions(N)	0.0003	3	1	0.0107	0.0428	CDH1

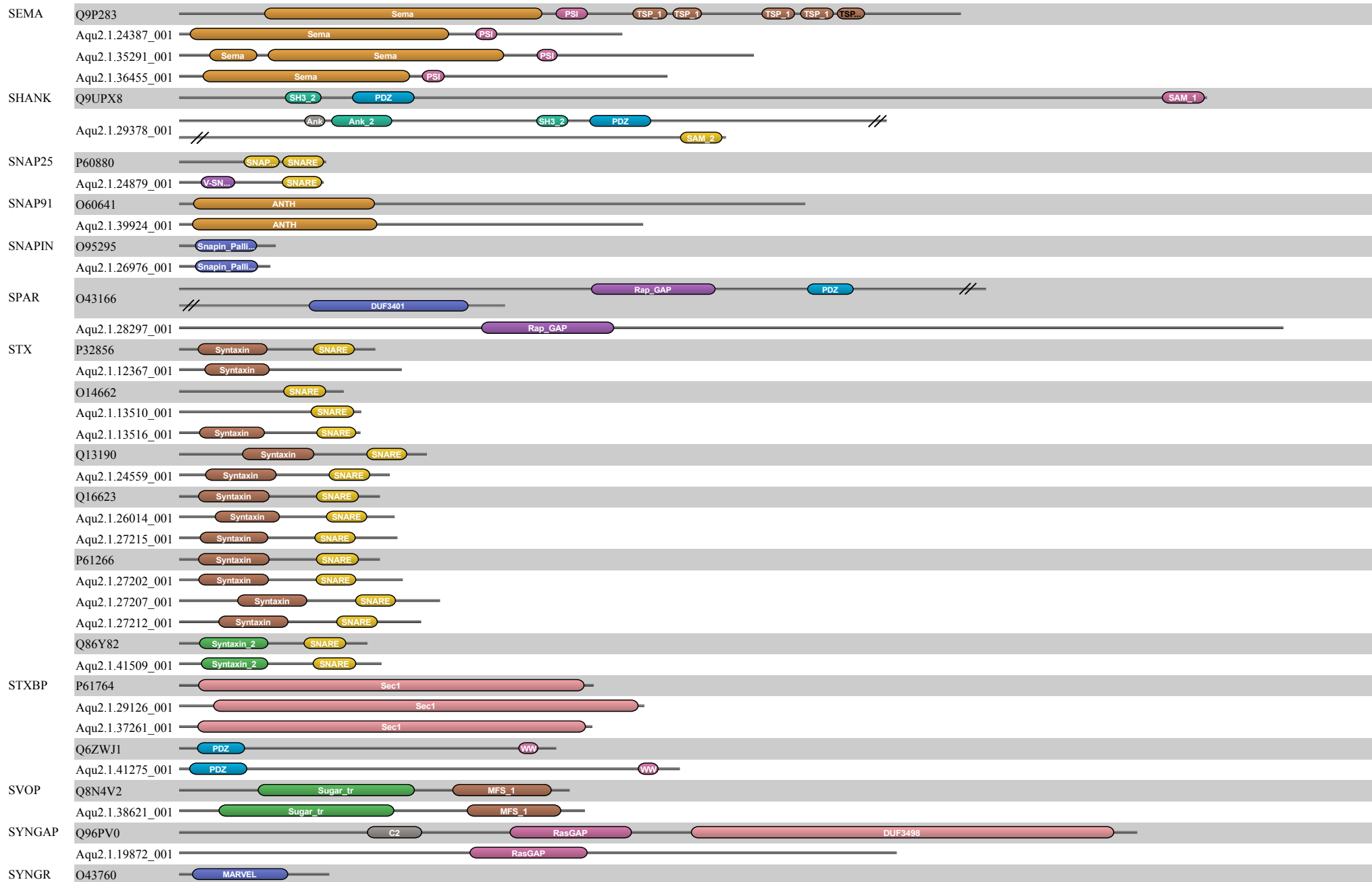
Supplementary Fig. 1.

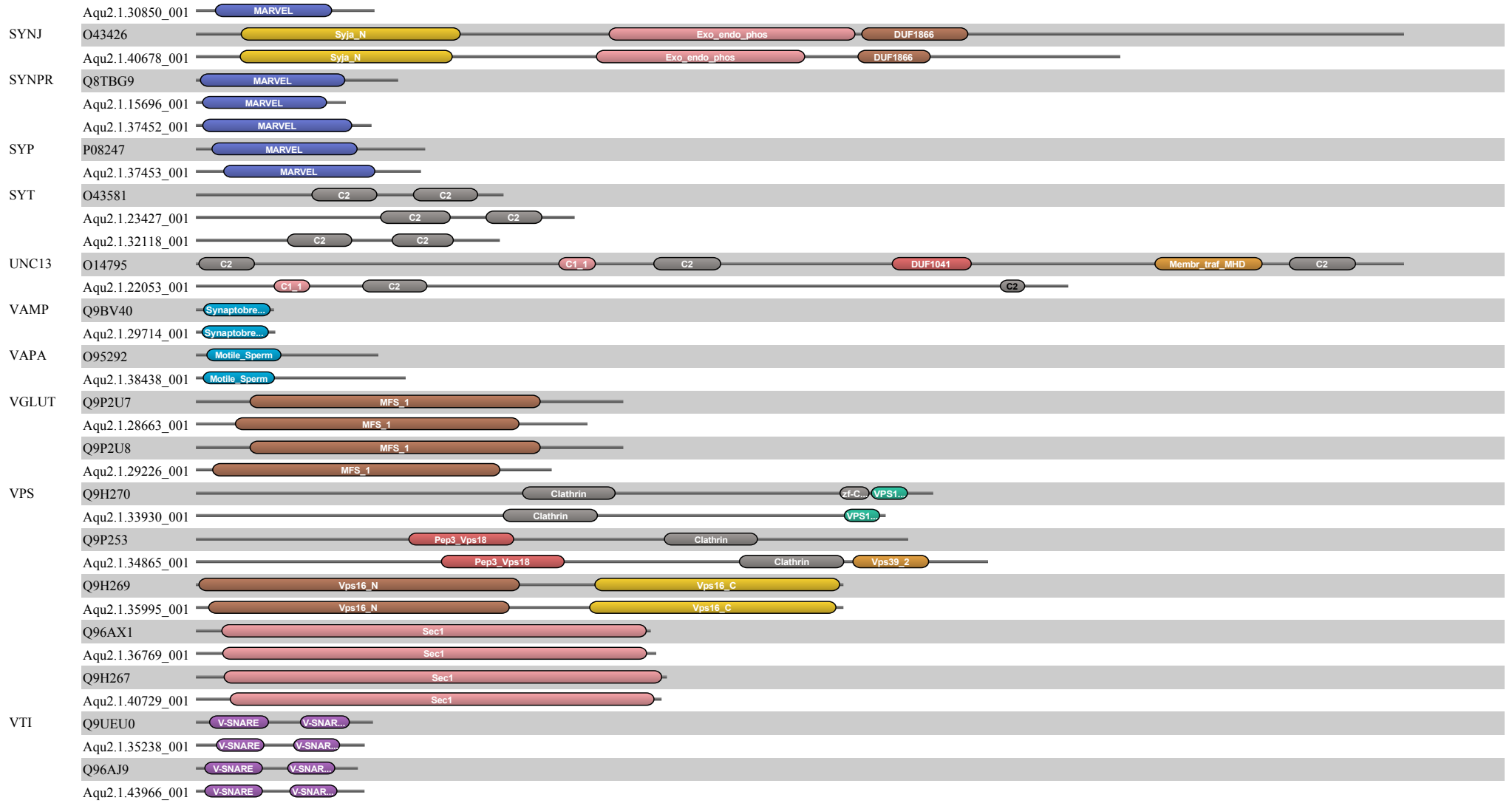




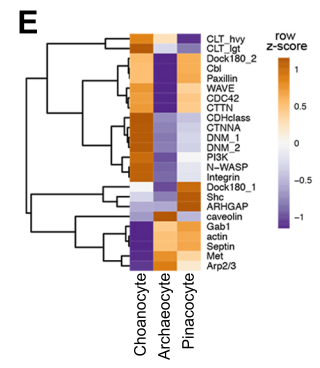
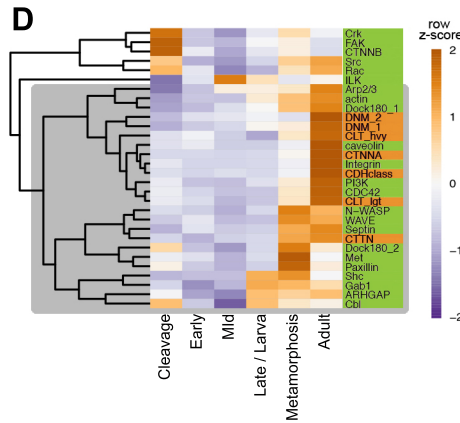
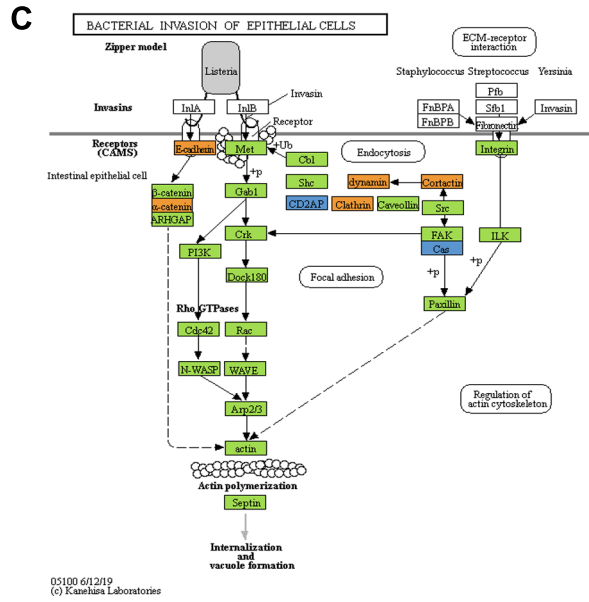
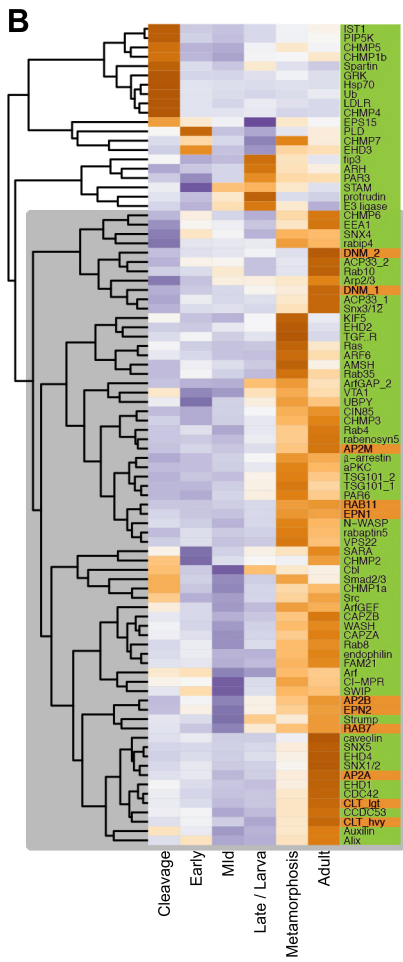
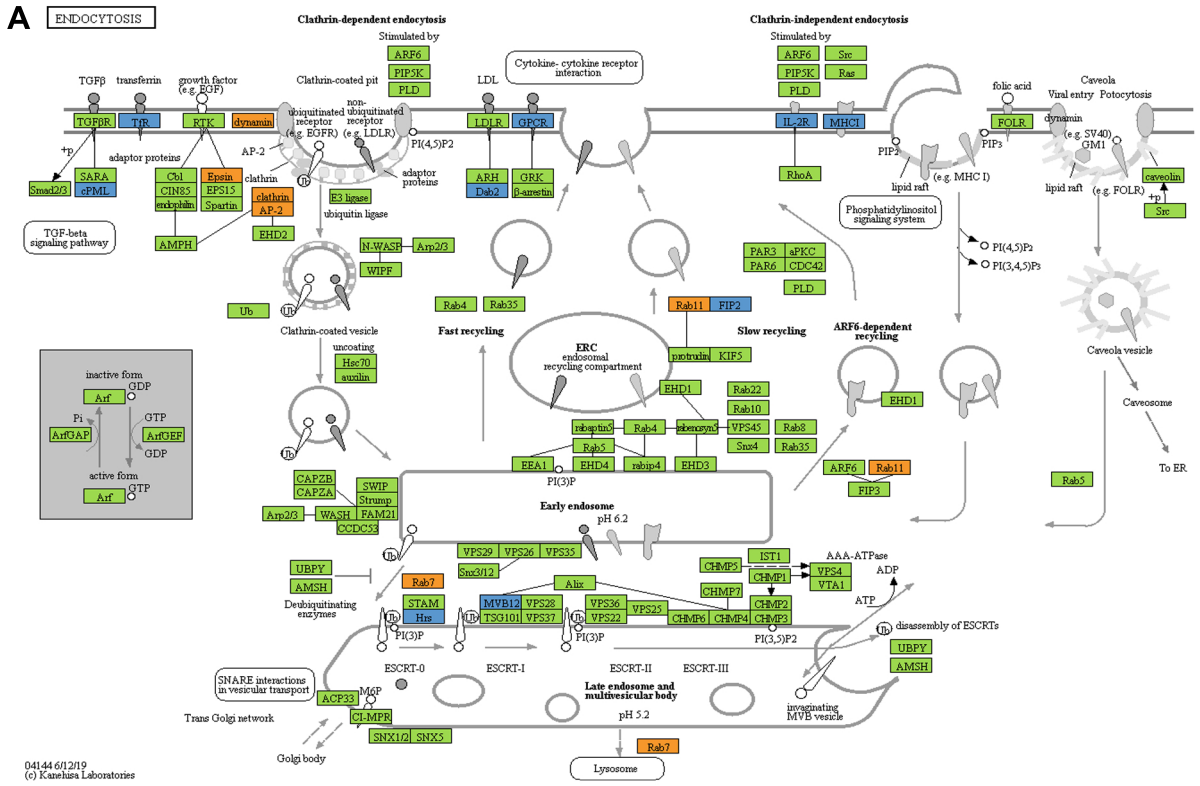








Supplementary Fig. 2.



Supplementary Fig. 3.

