Table S1: Differential enrichment of functional terms for low-CpG and high-CpG genes.

CpG class	GO BP term	Accession	Fold enrichment in class	Benjamini significance[1]
Low CpG	macromolecule metabolic process	GO:0043170	1.13	3.91E-14
Low CpG	cellular metabolic process	GO:0044237	1.09	1.04E-11
Low CpG	metabolic process	GO:0008152	1.08	1.20E-10
Low CpG	primary metabolic process	GO:0044238	1.08	8.05E-09
Low CpG	cellular process	GO:0009987	1.04	2.83E-08
Low CpG	nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	GO:0006139	1.17	2.85E-08
Low CpG	gene expression	GO:0010467	1.18	3.15E-08
Low CpG	RNA processing	GO:0006396	1.37	1.05E-07
Low CpG	biopolymer metabolic process	GO:0043283	1.12	1.42E-06
Low CpG	RNA metabolic process	GO:0016070	1.19	2.28E-06
Low CpG	macromolecule biosynthetic process	GO:0009059	1.28	2.88E-06
Low CpG	translation	GO:0006412	1.32	8.04E-06
Low CpG	mRNA metabolic process	GO:0016071	1.36	2.58E-05
Low CpG	cellular protein metabolic process	GO:0044267	1.13	4.50E-05
Low CpG	protein metabolic process	GO:0019538	1.12	4.55E-05
Low CpG	DNA metabolic process	GO:0006259	1.29	0.0001
Low CpG	mRNA processing	GO:0006397	1.34	0.0002
Low CpG	cellular macromolecule metabolic process	GO:0044260	1.11	0.0004

Low CpG	macromolecular complex assembly	GO:0065003	1.29	0.0005
Low CpG	biosynthetic process	GO:0009058	1.16	0.0010
Low CpG	cellular biosynthetic process	GO:0044249	1.18	0.0010
Low CpG	tRNA metabolic process	GO:0006399	1.56	0.0030
Low CpG	cellular component assembly	GO:0022607	1.22	0.0060
Low CpG	tRNA aminoacylation	GO:0043039	1.66	0.0062
Low CpG	tRNA aminoacylation for protein translation	GO:0006418	1.66	0.0062
Low CpG	transcription initiation from RNA polymerase II promoter	GO:0006367	1.50	0.0102
Low CpG	ribonucleoprotein complex biogenesis and assembly	GO:0022613	1.37	0.0139
Low CpG	protein catabolic process	GO:0030163	1.44	0.0154
Low CpG	transcription initiation	GO:0006352	1.47	0.0162
Low CpG	ribosome biogenesis and assembly	GO:0042254	1.53	0.0180
Low CpG	response to DNA damage stimulus	GO:0006974	1.43	0.0199
Low CpG	amino acid activation	GO:0043038	1.60	0.0200
Low CpG	protein-DNA complex assembly	GO:0065004	1.39	0.0242
Low CpG	macromolecule catabolic process	GO:0009057	1.28	0.0323
Low CpG	DNA repair	GO:0006281	1.44	0.0329
Low CpG	intracellular transport	GO:0046907	1.17	0.0330
Low CpG	protein transport	GO:0015031	1.19	0.0368
Low CpG	organelle organization and biogenesis	GO:0006996	1.12	0.0438

Low CpG	cofactor biosynthetic process	GO:0051188	1.40	0.0482
High CpG	multicellular organismal process	GO:0032501	1.32	1.20E-19
High CpG	cell communication	GO:0007154	1.37	4.10E-16
High CpG	organ development	GO:0048513	1.41	1.52E-11
High CpG	system development	GO:0048731	1.35	1.54E-11
High CpG	signal transduction	GO:0007165	1.35	1.71E-11
High CpG	multicellular organismal development	GO:0007275	1.28	2.92E-11
High CpG	biological adhesion	GO:0022610	1.77	7.40E-11
High CpG	cell adhesion	GO:0007155	1.77	7.40E-11
High CpG	anatomical structure development	GO:0048856	1.30	9.39E-11
High CpG	developmental process	GO:0032502	1.23	1.99E-09
High CpG	tissue development	GO:0009888	1.72	5.95E-09
High CpG	system process	GO:0003008	1.52	6.05E-09
High CpG	cell-cell adhesion	GO:0016337	2.04	6.16E-08
High CpG	behavior	GO:0007610	1.68	6.25E-08
High CpG	imaginal disc development	GO:0007444	1.49	1.04E-07
High CpG	cell surface receptor linked signal transduction	GO:0007166	1.44	2.39E-07
High CpG	anatomical structure morphogenesis	GO:0009653	1.30	3.28E-07
High CpG	cell-cell signaling	GO:0007267	1.53	3.32E-07
High CpG	neurological system process	GO:0050877	1.48	4.39E-07
High CpG	larval development	GO:0002164	1.46	9.93E-07
High CpG	mesoderm development	GO:0007498	1.93	1.10E-06
High CpG	ion transport	GO:0006811	1.57	2.30E-06
High CpG	transmission of nerve impulse	GO:0019226	1.53	4.83E-06

High CpG	cell migration	GO:0016477	1.59	5.99E-06
High CpG	appendage development	GO:0048736	1.62	6.62E-06
High CpG	organ morphogenesis	GO:0009887	1.41	7.84E-06
High CpG	metal ion transport	GO:0030001	1.85	7.86E-06
High CpG	imaginal disc-derived appendage development	GO:0048737	1.61	9.75E-06
High CpG	nervous system development	GO:0007399	1.37	9.90E-06
High CpG	larval development (sensu Amphibia)	GO:0002117	1.45	1.14E-05
High CpG	metamorphosis	GO:0007552	1.45	1.14E-05
High CpG	appendage morphogenesis	GO:0035107	1.61	1.40E-05
High CpG	imaginal disc morphogenesis	GO:0007560	1.45	1.55E-05
High CpG	imaginal disc-derived appendage morphogenesis	GO:0035114	1.60	2.15E-05
High CpG	G-protein coupled receptor protein signaling pathway	GO:0007186	1.73	2.24E-05
High CpG	pattern specification process	GO:0007389	1.47	4.56E-05
High CpG	central nervous system development	GO:0007417	1.69	7.22E-05
High CpG	localization of cell	GO:0051674	1.49	9.07E-05
High CpG	regionalization	GO:0003002	1.47	9.33E-05
High CpG	post-embryonic development	GO:0009791	1.34	0.0001
High CpG	locomotory behavior	GO:0007626	1.83	0.0001
High CpG	cell motility	GO:0006928	1.48	0.0001
High CpG	anatomical structure formation	GO:0048646	1.58	0.0002
High CpG	axon guidance	GO:0007411	1.72	0.0002

High CpG	cation transport	GO:0006812	1.55	0.0002
High CpG	axonogenesis	GO:0007409	1.61	0.0002
High CpG	ectoderm development	GO:0007398	1.69	0.0002
High CpG	homophilic cell adhesion	GO:0007156	2.28	0.0003
High CpG	imaginal disc-derived wing morphogenesis	GO:0007476	1.55	0.0004
High CpG	heart development	GO:0007507	1.93	0.0006
High CpG	wing disc development	GO:0035220	1.50	0.0007
High CpG	segmentation	GO:0035282	1.71	0.0007
High CpG	muscle system process	GO:0003012	2.05	0.0007
High CpG	muscle contraction	GO:0006936	2.05	0.0007
High CpG	wing disc morphogenesis	GO:0007472	1.52	0.0009
High CpG	instar larval or pupal development	GO:0002165	1.31	0.0012
High CpG	localization	GO:0051179	1.14	0.0014
High CpG	cellular developmental process	GO:0048869	1.21	0.0015
High CpG	cell differentiation	GO:0030154	1.21	0.0016
High CpG	synaptic transmission	GO:0007268	1.44	0.0021
High CpG	cellular morphogenesis during differentiation	GO:0000904	1.38	0.0024
High CpG	cell morphogenesis	GO:0000902	1.27	0.0024
High CpG	cellular structure morphogenesis	GO:0032989	1.27	0.0024
High CpG	neurogenesis	GO:0022008	1.36	0.0028
High CpG	cell fate commitment	GO:0045165	1.47	0.0028
High CpG	potassium ion transport	GO:0006813	2.08	0.0030
High CpG	sensory organ development	GO:0007423	1.38	0.0032
High CpG	leg disc development	GO:0035218	2.16	0.0037
High CpG	imaginal disc pattern formation	GO:0007447	1.85	0.0037
High CpG	calcium ion transport	GO:0006816	2.26	0.0041

High CpG	adult behavior	GO:0030534	1.92	0.0041
High CpG	open tracheal system development	GO:0007424	1.50	0.0051
High CpG	generation of neurons	GO:0048699	1.35	0.0053
High CpG	cuticle development	GO:0042335	1.90	0.0074
High CpG	rhythmic process	GO:0048511	1.90	0.0074
High CpG	circadian rhythm	GO:0007623	1.90	0.0074
High CpG	response to chemical stimulus	GO:0042221	1.44	0.0076
High CpG	striated muscle development	GO:0014706	1.68	0.0079
High CpG	calcium-dependent cell-cell adhesion	GO:0016339	2.40	0.0081
High CpG	cell fate determination	GO:0001709	1.64	0.0092
High CpG	limb development	GO:0060173	2.05	0.0099
High CpG	di-, tri-valent inorganic cation transport	GO:0015674	2.05	0.0099
High CpG	leg morphogenesis	GO:0035110	2.05	0.0099
High CpG	limb morphogenesis	GO:0035108	2.05	0.0099
High CpG	reproduction	GO:0000003	1.25	0.0099
High CpG	cell development	GO:0048468	1.20	0.0105
High CpG	muscle development	GO:0007517	1.47	0.0145
High CpG	aromatic amino acid family metabolic process	GO:0009072	2.40	0.0161
High CpG	dorsal/ventral pattern formation	GO:0009953	1.67	0.0176
High CpG	neuron differentiation	GO:0030182	1.34	0.0184
High CpG	neurite morphogenesis	GO:0048812	1.35	0.0205
High CpG	neurite development	GO:0031175	1.35	0.0205
High CpG	neuron morphogenesis during differentiation	GO:0048667	1.35	0.0205
High CpG	eye development	GO:0001654	1.36	0.0212
High CpG	regulation of developmental process	GO:0050793	1.37	0.0228

High CpG	reproductive process	GO:0022414	1.52	0.0263
High CpG	cell projection organization and biogenesis	GO:0030030	1.30	0.0280
High CpG	cell projection morphogenesis	GO:0048858	1.30	0.0280
High CpG	cell part morphogenesis	GO:0032990	1.30	0.0280
High CpG	skeletal muscle development	GO:0007519	1.63	0.0286
High CpG	blastoderm segmentation	GO:0007350	1.62	0.0292
High CpG	response to stimulus	GO:0050896	1.19	0.0317
High CpG	neuron development	GO:0048666	1.33	0.0321
High CpG	germarium-derived egg chamber formation	GO:0007293	1.84	0.0321
High CpG	response to external stimulus	GO:0009605	1.52	0.0359
High CpG	ventral cord development	GO:0007419	2.10	0.0400
High CpG	rhythmic behavior	GO:0007622	1.88	0.0466

Gene ontology biological process term enrichment is presented based on 1781 *D. melanogaster* orthologs of *A. mellifera* high CpG genes (1230 with GO annotation) and 2531 *D. melanogaster* orthologs of *A. mellifera* low CpG genes (1713 with GO annotation).

[1] Significance is denoted by a Benjamini correction for multiple testing.