

Supplementary Online Material

Predicting genetic modifier loci using functional gene networks

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Summary of changes between WormNet v. 1 and WormNet v. 2

The calculation of WormNet v. 2 involved a number of substantial differences from WormNet v. 1 (summarized in **Table S1**), resulting in omission of many WormNet v. 1 linkages from WormNet v. 2 (as diagrammed in **Figure 1B**). The large majority of removed links result from a decision to omit co-expression linkages between homologous genes with extremely similar DNA sequences. While these linkages may reflect true functional associations, this cannot be distinguished from the possibility that these very high scoring linkages arise not from co-expression but rather from cross-hybridization artifacts on the DNA microarrays, e.g., as measured in (Ramani et al. 2008). We therefore opted for a more conservative strategy of omitting these linkages.

Specifically, 42.6% (163,964/384,700) of version 1 linkages were omitted from version 2, with the omitted linkages characterized as follows: 87.6% (143,594/163,964) of the removed links derived from co-expression patterns between genes with cDNA probes with a high likelihood for cross-hybridization. 5.7% (9,307/163,964) were removed as a consequence of increasing the genome set from 149 genomes to 424 genomes in version 2—more genomes allows for more accurate phylogenetic profile and gene neighbor linkages, and consequently removal of spurious links. 3.2% (5,215/163,964) of linkages derived from yeast datasets and 3% (4,970/163,964) from human datasets; these were removed due to a switch from species-based scoring of transferred linkages to species and data-type-based scoring of transferred linkages, which gave finer-grained scores capable of better filtering out low quality associations. In total, these 3 changes account for >99% of the omitted links and contribute to the enhanced predictive ability of version 2.

Roughly 42% (68,997/163,964) of the removed links were classified as “core” links of the version 1. A “core” network is not defined for version 2, as the edge weights of WormNet v.2 are informative about the likelihoods of functional association between genes, and in general, using the complete network provides substantially better predictive ability. Nonetheless, applying an accuracy threshold similar to WormNet v.1 results in 95,000 links exceeding this threshold. Comparing the network of 95,000 links with the v.1-core shows 39% (44,832/113,829) of the v.1 core set are retained, with the remaining 61% of links removed almost entirely (99.3%) due the changes detailed above (*i.e.*, removal of co-expression links at risk of cross-hybridization, of gene neighbor links that failed to score well with the expanded genome set, or of links scoring poorly following the more fine-grained dataset-based rather than species-based orthologous transfer of linkages, all of which produced high confidence linkages in v. 1 but that are not supported under the stricter analysis of v. 2.

Figure S1. Comparison of the predictive power of WormNet version 2 (full version, covering 15,139 genes) to various genome-wide *C. elegans* gene networks, testing cross-validated recovery of genes affiliated with each of 43 RNAi phenotypes (**Table S3**). STRING version 8.2 (Jensen et al. 2009) and FunCoup version 1 (Alexeyenko and Sonnhammer 2009) were downloaded and linkages between *C. elegans* genes extracted for analysis. The STRING network includes 150,462 linkages among 8,570 genes; FunCoup includes 1,868,676 linkages among 13,415 genes. **(A)** In general, WormNet v. 2 shows a comparable or higher combination of predictive ability (measured as area under a ROC curve (AUC)) and gene coverage than the other networks, including WormNet v. 1. **(B)** AUC scores by the four networks for each of 43 RNAi phenotypes. More than 50% of all tested 43 RNAi phenotypes (22 phenotypes) are predicted best by WormNet v.2.

Figure S1A

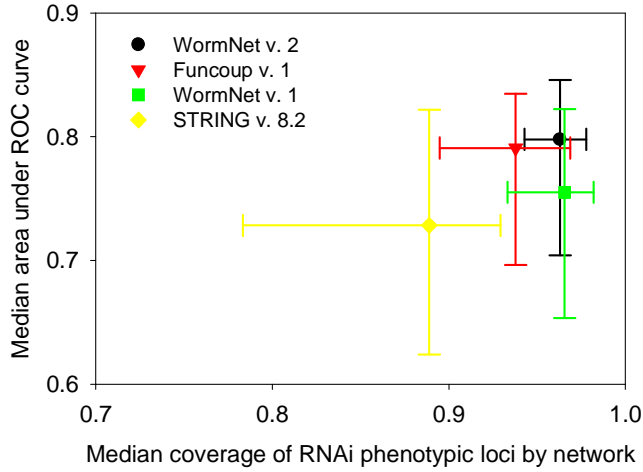


Figure S1B

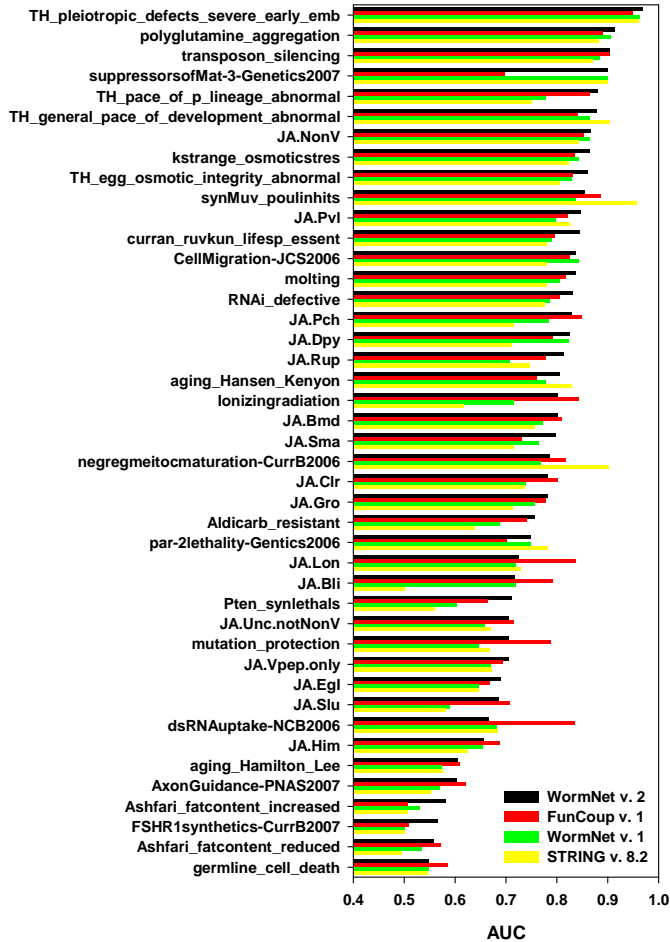


Table S1. Comparison between WormNet version 1 and version 2

WormNet version 1	WormNet version 2
Based on 19,735 genes annotated by WormBase140	Based on 20,081 genes annotated by WormBase170
Trained using Gene Ontology biological process annotation on March 2005	Trained using Gene Ontology biological process annotation on January 2007
384,700 links among 16,113 genes (82 % of annotated genes by WormBase140)	999,367 links among 15,139 genes (75.5% of annotated genes by WormBase170)
May include many false co-expression links by cross-hybridization during microarray analysis	Conservative analysis of co-expression links, filtering gene pairs with the potential to cross-hybridize based on high nucleotide sequence similarity
Phylogenetic profile and gene neighbor analysis using 133 bacterial genomes	Phylogenetic profile and gene neighbor analysis using 424 bacterial genomes
Linkage transfer from orthologs scored by species (yeast, fly, and human)	Linkage transfer from orthologs scored by data set and species (total 14 data sets for fly, human, and yeast)
	Links from domain co-occurrence for yeast and human proteins
	Links from co-expression, affinity purification/mass spectrometry of protein complexes (AP-MS), and yeast two hybrid (Y2H) for human transcripts/proteins

Table S2. Twenty-one different lines of evidences supporting *C. elegans* gene functional associations in WormNet version 2.

Data set	Description	# genes	# gene pairs
CE-CC	Co-citation of worm genes (Lee et al. 2008)	1,298	6,192
CE-CX	Co-expression among worm genes (Lee et al. 2008; Shapira et al. 2006)	12,179	602,569
CE-GN	Gene neighbourhoods of bacterial and archaeal orthologs of worm genes (Lee et al. 2008)	2,813	21,642
CE-GT	Worm genetic interactions (Uren et al. 2008)	1,009	2,224
CE-LC	Literature curated worm protein physical interactions	2,014	2,531
CE-PG	Co-inheritance of bacterial and archaeal orthologs of worm genes (Lee et al. 2008)	3,003	102,985
CE-YH	High-throughput yeast 2-hybrid assays among worm genes (Li et al. 2004)	2,444	3,807
DM-PI	Fly protein physical interactions (Lee et al. 2008)	2,978	9,254
HS-CC	Co-citation of human genes	971	1,693
HS-CX	Co-expression among human genes	3,716	50,634
HS-DC	Co-occurrence of domains among human proteins	2,341	5,871
HS-LC	Literature curated linkages from protein-protein interaction DBs (HPRD, BIND, BioGRID, IntAct, MINT) and pathway DB (Reactome), and Rual <i>et al.</i> (Rual et al. 2005)	2,815	24,906
HS-MS	Human protein complexes from affinity purification/mass spectrometry (Ewing et al. 2007)	790	1,599
HS-YH	High-throughput yeast 2-hybrid assays among human genes (Rual et al. 2005; Stelzl et al. 2005)	464	458
SC-CC	Co-citation of yeast genes (Lee et al. 2007)	2,102	17,906
SC-CX	Co-expression among yeast genes (Lee et al. 2007)	2,191	93,774
SC-DC	Co-occurrence of domains among yeast proteins	1,609	10,660
SC-GT	Yeast genetic interactions (Lee et al. 2007)	1,929	12,304
SC-LC	Literature curated yeast protein physical interactions (Lee et al. 2007)	1,749	9,084
SC-MS	Yeast protein complexes from affinity purification/mass spectrometry (Lee et al. 2007)	2,170	92,381
SC-TS	Yeast protein interactions inferred from tertiary (Lee et al. 2007) structures of complexes	668	4,153

Table S3. 43 RNAi phenotypes used for network evaluation

Phenotype	Predictability	Library screened	Reference
Nonviable	strong	Ahringer	(Kamath et al. 2003)
Growth defective (not Nonviable)	strong		
Visible post-embryonic phenotypes (not nonviable/growth defective)	weak		
Dumpy	strong		
Body morphology defect	strong		
Small	strong		
Long	strong		
Clear	strong		
Blistered	strong		
Protruding vulva	strong		
Egg laying abnormal	weak		
Patchy coloration	strong		
High incidence of males	weak		
Ruptured	strong		
Sluggish	weak		
Uncoordinated (not Nonviable)	weak		
Fat content reduced	random	Ahringer	(Ashrafi et al. 2003)
Fat content increased	random		
Transposon silencing defective	strong	Ahringer	(Vastenhouw et al. 2003)
Mutator	weak	Ahringer	(Pothof et al. 2003)
Polyglutamine toxicity enhanced	strong	Ahringer	(Nollen et al. 2004)
Germ line apoptosis increased	random	Ahringer	(Lettre et al. 2004)
Synthetic multivulva	strong	Ahringer	(Poulin et al. 2005)
Egg osmotic integrity abnormal	strong	Cenix	(Sonnichsen et al. 2005)
Egg size abnormal	n/a		
Pace of development abnormal	strong		
Pace of p-lineage development abnormal	strong		
Severe pleiotropic defects	strong		
Aldicarb resistant/synapse function defective	weak	2,072 genes from Ahringer	(Sieburth et al. 2005)
Lifespan increased (Hamilton)	weak	Ahringer	(Hamilton et al. 2005)
Lifespan increased (Hansen)	strong	Ahringer	(Hansen et al. 2005)
Molting defect	strong	Ahringer	(Frand et al. 2005)
RNA interference defective	strong	Ahringer + Vidal	(Kim et al. 2005)
PTEN(<i>daf-18</i>) synthetic lethality	weak	Ahringer	(Suzuki and Han 2006)
Radiation sensitive	strong	Ahringer	(van Haaften et al. 2006)
FSHR1 synthetic interactions	random		(Cho et al. 2007)
Axon guidance	weak	4,577 genes from Ahringer	(Schmitz et al. 2007)
Osmotic stress response	strong	Ahringer	(Lamitina et al. 2006)
Distal tip cell migration	strong	Ahringer	(Cram et al. 2006)
dsRNA uptake	strong	Ahringer	(Saleh et al. 2006)
Meiotic maturation	strong	Ahringer	(Govindan et al. 2006)
Suppressors of <i>par-2</i> lethality	strong	Ahringer	(Labbe et al. 2006)
MAT-3 suppressors	strong	Ahringer	(Stein et al. 2007)
Lifespan increased (Curran)	strong	2,700 genes from Ahringer	(Curran and Ruvkun 2007)

Table S4. Protein-protein interactions for the consolidated yeast interactome.

Description	# interactions	# proteins
DIP (small scale only) (Xenarios et al. 2002)	2,822	1,515
MIPS (Mewes et al. 2008)	2,353	1,788
BIOGRID (Breitkreutz et al. 2008)	11,942	3,360
Genome-wide yeast two hybrid screen by Uetz <i>et al.</i> (Uetz et al. 2000)	851	930
Genome-wide yeast two hybrid screen by Ito <i>et al.</i> (Ito et al. 2001)	3,996	2,911
AP-MS by Gavin <i>et al.</i> (Gavin et al. 2006)	18,200	2,569
AP-MS by Krogan <i>et al.</i> (LCMS) (Krogan et al. 2006)	22,787	3,528
AP-MS by Krogan <i>et al.</i> (MALDI) (Krogan et al. 2006)	18,193	2,836
The consolidated yeast interactome	65,033	5,275

Table S5

C. elegans DNA microarray mRNA expression data sets analyzed for co-expression, downloaded from the Stanford Microarray Database (SMD) (Gollub et al. 2003), Gene Expression Omnibus (GEO) (Barrett et al. 2005), and Stuart *et al.* (Stuart et al. 2003). Five subsets of SMD, one subset of GEO, and the non-redundant Stuart *et al.* set showed significant correlation between mRNA co-expression and log likelihood scores and were therefore incorporated into the network.

Array group	Literature sources	# experiments
SMD Aging	Lund J, <i>et al.</i> (Lund et al. 2002)	26
SMD Dauer	Wang, J. and Kim, SK (Wang and Kim 2003)	50
SMD L1	Wang, J. and Kim, SK (Wang and Kim 2003)	44
SMD Developmental stages	Jiang M. <i>et al.</i> (Jiang et al. 2001)	26
SMD Ras	Romagnolo B. <i>et al.</i> (Romagnolo et al. 2002)	40
GEO aeruginosa	Shapira M. <i>et al.</i> (Shapira et al. 2006)	18
Stuart nonredundant	Stuart <i>et al.</i> (Stuart et al. 2003)	635

Table S6. RNAi clones tested as modifiers of *vab-1(e699)*.

Ranked coupling to previously known modifiers	Gene	Gene public_name	Gene sequence name	RNAi clone identifier	Validated genetic interaction
3	WBGene00001904	<i>his-30</i>	F35H10.1	T23D8.6	
18	WBGene00001946	<i>his-72</i>	Y49E10.6	ZK131.2	
20	WBGene00001928	<i>his-54</i>	F07B7.11	F45F2.2	
33	WBGene00001892	<i>his-18</i>	K06C4.10	ZK131.1	
35	WBGene00001884	<i>his-10</i>	ZK131.4	F17E9.12	
67	WBGene00001585	<i>gfl-1</i>	M04B2.3	M04B2.3	
68	WBGene00021636	<i>pcaf-1</i>	Y47G6A.6	Y47G6A_241.b	
72	WBGene00006542	<i>tbp-1</i>	T20B12.2	T20B12.2	Yes
74	WBGene00013676	<i>ekl-4</i>	Y105E8A.17	Y105E8C.d	Yes
75	WBGene00001974	<i>hmg-4</i>	T20B12.8	C32F10.5	
81	WBGene00005015	<i>spt-5</i>	K08E4.1	K08E4.1	
83	WBGene00000376	<i>ccr-4</i>	ZC518.3	ZC518.3	
84	WBGene00006396	<i>taf-12</i>	Y56A3A.4	Y56A3A.4	
87	WBGene00000506	<i>cic-1</i>	H14E04.5	H14E04.5	
88	WBGene00016583	<i>tag-335</i>	C42C1.5	C42C1.5	
91	WBGene00004109	<i>pqn-19</i>	C34G6.7	C34G6.7	
93	WBGene00012203	<i>rga-1</i>	W02B12.8	W02B12.8	
94	WBGene00020687	<i>ruvb-2</i>	T22D1.10	T22D1.10	
95	WBGene00010333	<i>F59E10.3</i>	F59E10.3	F59E10.3	
98	WBGene00007784	<i>ruvb-1</i>	C27H6.2	C27H6.2	
102	WBGene00017967	<i>ada-2</i>	F32A5.1	F32A5.7	Yes
103	WBGene00001834	<i>hda-1</i>	C53A5.3	C53A5.3	
104	WBGene00001064	<i>dpy-2</i>	T14B4.6	T14B4.6	
106	WBGene00012000	<i>T24H10.1</i>	T24H10.1	T24H10.1	
112	WBGene00006414	<i>tag-29</i>	T24F1.1	T24F1.1	
113	WBGene00001065	<i>dpy-3</i>	EGAP7.1	EGAP7.1	Yes
114	WBGene00000161	<i>apa-2</i>	T20B5.1	T20B5.1	Yes
115	WBGene00004356	<i>rhi-1</i>	F46H6.1	F46H6.1	
116	WBGene00004269	<i>rab-6.1</i>	F59B2.7	F59B2.7	
117	WBGene00004033	<i>pkc-2</i>	E01H11.1	E01H11.2	
119	WBGene00021292	<i>Y25C1A.5</i>	Y25C1A.5	Y25C1A.5	
120	WBGene00003795	<i>npp-9</i>	F59A2.1	F59A2.1	

124	WBGene00004305	<i>ran-4</i>	R05D11.3	R05D11.3	
125	WBGene00004270	<i>rab-6.2</i>	T25G12.4	T25G12.4	
126	WBGene00000868	<i>cyb-3</i>	T06E6.2	T06E6.2	
127	WBGene00016408	<i>tag-251</i>	C34E10.5	C34E10.5	
128	WBGene00000123	<i>ama-1</i>	F36A4.7	F36A4.7	
132	WBGene00007333	<i>ufd-3</i>	C05C10.6	C05C10.6	
137	WBGene00002994	<i>lin-5</i>	T09A5.10	T09A5.10	
138	WBGene00001092	<i>dro-1</i>	F53A2.5	F53A2.5	
141	WBGene00006387	<i>taf-6.1</i>	W09B6.2	W09B6.2	
143	WBGene00019799	<i>M151.7</i>	M151.7	M151.2	
149	WBGene00001329	<i>epr-1</i>	T04C10.2	T04C10.2	
153	WBGene00006386	<i>taf-5</i>	F30F8.8	F30F8.8	
154	WBGene00021754	<i>Y50D7A.4</i>	Y50D7A.4	Y50D7_162.b	
155	WBGene00001086	<i>dpy-27</i>	R13G10.1	R13G10.1	Yes
156	WBGene00008117	<i>C46F11.2</i>	C46F11.2	C46F11.2	
157	WBGene00010924	<i>M153.1</i>	M153.1	M153.1	
160	WBGene00008346	<i>C56A3.8</i>	C56A3.8	C56A3.8	
161	WBGene00002189	<i>kin-1</i>	ZK909.2	ZK909.1	
165	WBGene00010556	<i>rack-1</i>	K04D7.1	K04D7.1	Yes
168	WBGene00004415	<i>rpl-4</i>	B0041.4	B0041.4	
171	WBGene00010778	<i>gpdh-2</i>	K11H3.1	K11H3.1	
178	WBGene00007277	<i>C03D6.5</i>	C03D6.5	F10G7.3	
180	WBGene00003172	<i>mec-8</i>	F46A9.6	C17E4.11	
181	WBGene00002299	<i>let-23</i>	ZK1067.1	ZK1067.1	
182	WBGene00006745	<i>unc-5</i>	B0273.4	B0273.4	
183	WBGene00003965	<i>pdk-1</i>	H42K12.1	H42K12.2	
184	WBGene00005014	<i>spt-4</i>	F54C4.2	F54C4.2	Yes
186	WBGene00004274	<i>rab-11.1</i>	F53G12.1	W04G5.2	
187	WBGene00000766	<i>coq-6</i>	K07B1.2	K07B1.2	
189	WBGene00000380	<i>cct-5</i>	C07G2.3	C07G2.3	
190	WBGene00003902	<i>pab-1</i>	Y106G6H.2	Y106G6H.2	
191	WBGene00009103	<i>F25B3.6</i>	F25B3.6	F25B3.6	Yes
192	WBGene00004682	<i>rsd-3</i>	C34E11.1	C34E11.1	
194	WBGene00004408	<i>rpa-0</i>	F25H2.10	F25H2.10	
195	WBGene00004340	<i>rfc-4</i>	F31E3.3	F31E3.3	
196	WBGene00001259	<i>emb-5</i>	T04A8.14	T04A8.14	
198	WBGene00000271	<i>brf-1</i>	F45E12.2	F45E12.2	Yes
199	WBGene00016250	<i>C30C11.4</i>	C30C11.4	C30C11.4	Yes
201	WBGene00015916	<i>C17G10.2</i>	C17G10.2	C17G10.2	

203	WBGene00004747	<i>sdc-3</i>	C25D7.3	C25D7.3	Yes
204	WBGene00001037	<i>dnj-19</i>	T05C3.5	C24G6.5	
205	WBGene00015658	<i>C09G12.9</i>	C09G12.9	C09G12.9	
206	WBGene00019983	<i>R09E12.3</i>	R09E12.3	R09E12.3	
207	WBGene00000159	<i>aps-1</i>	F29G9.3	F29G9.3	
208	WBGene00004418	<i>rpl-7</i>	F53G12.10	F53G12.10	
209	WBGene00011867	<i>chc-1</i>	T20G5.1	T20G5.1	
211	WBGene00003825	<i>ntl-2</i>	B0286.4	B0286.4	Yes
215	WBGene00006388	<i>taf-7.1</i>	F54F7.1	F54F7.1	
216	WBGene00017268	<i>F08F8.2</i>	F08F8.2	F08F8.2	Yes
218	WBGene00004416	<i>rpl-5</i>	F54C9.5	F54C9.5	
221	WBGene00001115	<i>dyp-1</i>	F47G6.1	F47G6.1	
222	WBGene00015814	<i>C16A3.10</i>	C16A3.10	C16A3.10	
225	WBGene00009827	<i>F47G4.6</i>	F47G4.6	F47G4.6	
226	WBGene00004336	<i>ret-1</i>	W06A7.3	W06A7.3	
232	WBGene00001716	<i>grl-7</i>	T02E9.2	T02E9.2	
233	WBGene00020658	<i>T21F4.1</i>	T21F4.1	T21F4.1	
237	WBGene00010272	<i>F58G6.1</i>	F58G6.1	F58G6.1	
238	WBGene00001070	<i>dpy-8</i>	C31H2.2	C31H2.2	
241	WBGene00019272	<i>H42K12.3</i>	H42K12.3	H42K12.3	
244	WBGene00016769	<i>C49C8.5</i>	C49C8.5	C49C8.5	

Table S7. RNAi clones tested as modifiers of *sos-1(cs41)*.

Ranked coupling to previously known modifiers	Gene	Gene public_name	Gene sequence name	RNAi clone identifier	Validated genetic interaction
3	WBGene00001904	<i>his-30</i>	F35H10.1	T23D8.6	
18	WBGene00001892	<i>his-18</i>	K06C4.10	ZK131.1	Yes
20	WBGene00001884	<i>his-10</i>	ZK131.4	F17E9.12	
35	WBGene00021636	<i>pcaf-1</i>	Y47G6A.6	Y47G6A_241.b	
36	WBGene00001928	<i>his-54</i>	F07B7.11	F45F2.2	Yes
42	WBGene00002299	<i>let-23</i>	ZK1067.1	ZK1067.1	
48	WBGene00001585	<i>gfl-1</i>	M04B2.3	M04B2.3	
55	WBGene00001946	<i>his-72</i>	Y49E10.6	ZK131.2	
56	WBGene00013676	<i>ekl-4</i>	Y105E8A.17	Y105E8C.d	Yes
62	WBGene00002280	<i>let-2</i>	F01G12.5	F01G12.5a	
76	WBGene00003186	<i>mek-2</i>	Y54E10BL.6	Y54E10B_152.b	Yes
84	WBGene00004266	<i>rab-1</i>	C39F7.4	C39F7.4	
88	WBGene00017967	<i>ada-2</i>	F32A5.1	F32A5.7	
91	WBGene00001834	<i>hda-1</i>	C53A5.3	C53A5.3	
92	WBGene00019799	<i>M151.7</i>	M151.7	M151.2	
96	WBGene00001974	<i>hmg-4</i>	T20B12.8	C32F10.5	
100	WBGene00004269	<i>rab-6.1</i>	F59B2.7	F59B2.7	
103	WBGene00008346	<i>C56A3.8</i>	C56A3.8	C56A3.8	
104	WBGene00004271	<i>rab-7</i>	W03C9.3	W03C9.3	
106	WBGene00004305	<i>ran-4</i>	R05D11.3	R05D11.3	
107	WBGene00005015	<i>spt-5</i>	K08E4.1	K08E4.1	
110	WBGene00006396	<i>taf-12</i>	Y56A3A.4	Y56A3A.4	
111	WBGene00006414	<i>tag-29</i>	T24F1.1	T24F1.1	
112	WBGene00006745	<i>unc-5</i>	B0273.4	B0273.4	
113	WBGene00004272	<i>rab-8</i>	D1037.4	D1037.4	
117	WBGene00006619	<i>try-1</i>	ZK546.15	ZK546.15	Yes
122	WBGene00004270	<i>rab-6.2</i>	T25G12.4	T25G12.4	
123	WBGene00010778	<i>gpdh-2</i>	K11H3.1	K11H3.1	
124	WBGene00000766	<i>coq-6</i>	K07B1.2	K07B1.2	
125	WBGene00004268	<i>rab-5</i>	F26H9.6	F26H9.6	
126	WBGene00008117	<i>C46F11.2</i>	C46F11.2	C46F11.2	
127	WBGene00004356	<i>rhi-1</i>	F46H6.1	F46H6.1	

128	WBGene00010924	<i>M153.1</i>	M153.1	M153.1	
132	WBGene00006788	<i>unc-53</i>	F45E10.1	F45E10.1	Yes
133	WBGene00020658	<i>T21F4.1</i>	T21F4.1	T21F4.1	
138	WBGene00006386	<i>taf-5</i>	F30F8.8	F30F8.8	
139	WBGene00010556	<i>rack-1</i>	K04D7.1	K04D7.1	Yes
141	WBGene00017268	<i>F08F8.2</i>	F08F8.2	F08F8.2	
142	WBGene00003172	<i>mec-8</i>	F46A9.6	C17E4.11	
144	WBGene00006387	<i>taf-6.1</i>	W09B6.2	W09B6.2	
149	WBGene00010160	<i>F56G4.5</i>	F56G4.5	Y53H1C.a	
150	WBGene00006542	<i>tbp-1</i>	T20B12.2	T20B12.2	Yes
154	WBGene00004888	<i>smo-1</i>	K12C11.2	K12C11.2	
157	WBGene00002074	<i>ima-3</i>	F32E10.4	F32E10.4	
158	WBGene00004979	<i>sph-1</i>	F42G8.11	F42G8.11	
159	WBGene00015372	<i>C03B1.1</i>	C03B1.1	C03B1.1	
161	WBGene00006836	<i>unc-112</i>	C47E8.7	C47E8.7	
162	WBGene00004273	<i>rab-10</i>	T23H2.5	T23H2.5	
165	WBGene00006388	<i>taf-7.1</i>	F54F7.1	F54F7.1	
168	WBGene00004928	<i>soc-1</i>	F41F3.2	F41F3.2	
173	WBGene00003011	<i>lin-25</i>	F56H9.5	F56H9.5	
174	WBGene00019259	<i>H34C03.2</i>	H34C03.2	H34C03.2	
178	WBGene00001115	<i>dyb-1</i>	F47G6.1	F47G6.1	
179	WBGene00013202	<i>Y54E5A.7</i>	Y54E5A.7	Y54E5A.7	
183	WBGene00000271	<i>brf-1</i>	F45E12.2	F45E12.2	Yes
184	WBGene00001064	<i>dpy-2</i>	T14B4.6	T14B4.6	
185	WBGene00015814	<i>C16A3.10</i>	C16A3.10	C16A3.10	
186	WBGene00004274	<i>rab-11.1</i>	F53G12.1	W04G5.2	
190	WBGene00004895	<i>smu-1</i>	CC4.3	CC4.3	
191	WBGene00001082	<i>dpy-23</i>	R160.1	R160.1	Yes
199	WBGene00000188	<i>arl-3</i>	F19H8.3	F19H8.3	
203	WBGene00001259	<i>emb-5</i>	T04A8.14	T04A8.14	
205	WBGene00001131	<i>dys-1</i>	F15D3.1	F15D3.1	
208	WBGene00008458	<i>E02H1.6</i>	E02H1.6	E02H1.6	
209	WBGene00003904	<i>pab-3</i>	C17E4.5	C17E4.5	
212	WBGene00005014	<i>spt-4</i>	F54C4.2	F54C4.2	
213	WBGene00001087	<i>dpy-28</i>	Y39A1B.3	Y39A1B.3	Yes
215	WBGene00004896	<i>smu-2</i>	Y49F6B.4	Y49F6B.n	
225	WBGene00006765	<i>unc-29</i>	T08G11.5	T08G11.5	
231	WBGene00004386	<i>rnp-3</i>	K08D10.3	K08D10.3	
232	WBGene00004385	<i>rnp-2</i>	K08D10.4	K08D10.4	

233	WBGene00006588	<i>tnt-3</i>	C14F5.3	C14F5.3	
237	WBGene00002152	<i>irs-1</i>	R11A8.6	R11A8.6	
242	WBGene00000895	<i>dac-1</i>	B0412.1	B0412.1	
244	WBGene00012930	<i>obr-1</i>	Y47D3A.17	Y47D3A.s	
246	WBGene00019030	<i>inft-1</i>	F58B6.2	F58B6.2	
247	WBGene00014234	<i>vps-29</i>	ZK1128.8	ZK1128.8	
248	WBGene00006391	<i>taf-9</i>	T12D8.7	T12D8.7	Yes
250	WBGene00014106	<i>ZK856.5</i>	ZK856.5	ZK856.5	
251	WBGene00018339	<i>F42A10.1</i>	F42A10.1	F42A10.1	
253	WBGene00013687	<i>exoc-8</i>	Y105E8B.2	Y105E8A.b	Yes
256	WBGene00018976	<i>fhod-2</i>	F56E10.2	F56E10.2	
259	WBGene00004206	<i>pst-1</i>	M03F8.2	M03F8.2	
260	WBGene00009132	<i>F25H8.2</i>	F25H8.2	F25H8.2	
263	WBGene00000242	<i>bbs-2</i>	F20D12.3	F20D12.3	
268	WBGene00003157	<i>mcm-5</i>	R10E4.4	R10E4.4	
269	WBGene00003845	<i>odd-1</i>	B0280.4	B0280.4	
273	WBGene00006751	<i>unc-11</i>	C32E8.10	C32E8.10	
274	WBGene00006746	<i>unc-6</i>	F41C6.1	F41C6.1	
275	WBGene00003930	<i>pat-3</i>	ZK1058.2	ZK1058.2	
281	WBGene00011605	<i>T08A11.2</i>	T08A11.2	T08A11.2	
283	WBGene00004736	<i>sca-1</i>	K11D9.2	K11D9.2	
284	WBGene00004504	<i>rpt-4</i>	F23F1.8	F23F1.8	

Table S8. RNAi clones tested as modifiers of *ark-1(sy247)*.

Ranked coupling to previously known modifiers	Gene	Gene public_name	Gene sequence name	RNAi clone identifier	Validated genetic interaction
1	WBGene00001585	<i>gfl-1</i>	M04B2.3	M04B2.3	
2	WBGene00013676	<i>ekl-4</i>	Y105E8A.17	Y105E8C.d	Yes
3	WBGene00021636	<i>pcaf-1</i>	Y47G6A.6	Y47G6A_241.b	
5	WBGene00005015	<i>spt-5</i>	K08E4.1	K08E4.1	
8	WBGene00001974	<i>hmg-4</i>	T20B12.8	C32F10.5	
15	WBGene00019799	<i>M151.7</i>	M151.7	M151.2	
19	WBGene00016188	<i>C28G1.3</i>	C28G1.3	C28G1.3	
22	WBGene00000868	<i>cyb-3</i>	T06E6.2	T06E6.2	
23	WBGene00008346	<i>C56A3.8</i>	C56A3.8	C56A3.8	
24	WBGene00019305	<i>K02D10.5</i>	K02D10.5	K02D10.5	
25	WBGene00001834	<i>hda-1</i>	C53A5.3	C53A5.3	
26	WBGene00002299	<i>let-23</i>	ZK1067.1	ZK1067.1	
27	WBGene00006373	<i>syn-3</i>	F55A11.2	F55A11.2	
28	WBGene00017268	<i>F08F8.2</i>	F08F8.2	F08F8.2	
29	WBGene00017967	<i>ada-2</i>	F32A5.1	F32A5.7	
30	WBGene00022534	<i>syn-16</i>	ZC155.7	ZC155.7	
31	WBGene00001172	<i>egl-3</i>	C51E3.7	C51E3.7	
43	WBGene00016376	<i>sec-10</i>	C33H5.9	C33H5.9	
44	WBGene00006742	<i>unc-2</i>	T02C5.5	T02C5.5	
45	WBGene00006386	<i>taf-5</i>	F30F8.8	F30F8.8	
47	WBGene00006396	<i>taf-12</i>	Y56A3A.4	Y56A3A.4	
48	WBGene00012386	<i>Y6B3A.1</i>	Y6B3A.1	Y6B3A.1	
49	WBGene00007703	<i>gbf-1</i>	C24H11.7	C24H11.7	
51	WBGene00009827	<i>F47G4.6</i>	F47G4.6	F47G4.6	
56	WBGene00001904	<i>his-30</i>	F35H10.1	T23D8.6	
73	WBGene00002074	<i>ima-3</i>	F32E10.4	F32E10.4	
74	WBGene00004033	<i>pkc-2</i>	E01H11.1	E01H11.2	
75	WBGene00010160	<i>F56G4.5</i>	F56G4.5	Y53H1C.a	
76	WBGene00006542	<i>tbp-1</i>	T20B12.2	T20B12.2	
		<i>brf-1</i>			
80	WBGene00000271		F45E12.2	F45E12.2	Yes
85	WBGene00003186	<i>mek-2</i>	Y54E10BL.6	Y54E10B_152.b	

87	WBGene00004897	<i>snb-1</i>	T10H9.4	T10H9.4	
89	WBGene00009103	<i>F25B3.6</i>	F25B3.6	F25B3.6	
90	WBGene00012936	<i>Y47D3A.29</i>	Y47D3A.29	Y47D3A.d	
92	WBGene00006388	<i>taf-7.1</i>	F54F7.1	F54F7.1	
93	WBGene00006387	<i>taf-6.1</i>	W09B6.2	W09B6.2	
96	WBGene00001920	<i>his-46</i>	B0035.9	ZK131.1	
103	WBGene00001884	<i>his-10</i>	ZK131.4	F17E9.12	
113	WBGene00012000	<i>T24H10.1</i>	T24H10.1	T24H10.1	
116	WBGene00000536	<i>clk-1</i>	ZC395.2	ZC395.2	
119	WBGene00004888	<i>smo-1</i>	K12C11.2	K12C11.2	
121	WBGene00000187	<i>arl-1</i>	F54C9.10	F54C9.10	
123	WBGene00005014	<i>spt-4</i>	F54C4.2	F54C4.2	
124	WBGene00000123	<i>ama-1</i>	F36A4.7	F36A4.7	
125	WBGene00001064	<i>dpy-2</i>	T14B4.6	T14B4.6	
127	WBGene00001946	<i>his-72</i>	Y49E10.6	ZK131.2	
132	WBGene00016960	<i>C56C10.1</i>	C56C10.1	C56C10.1	
133	WBGene00004723	<i>sap-49</i>	C08B11.5	C08B11.5	
134	WBGene00002280	<i>let-2</i>	F01G12.5	F01G12.5a	
139	WBGene00000376	<i>ccr-4</i>	ZC518.3	ZC518.3	
144	WBGene00006595	<i>top-1</i>	M01E5.5	M01E5.5	
145	WBGene00010618	<i>K07A1.14</i>	K07A1.14	R11E3.1	
150	WBGene00001087	<i>dpy-28</i>	Y39A1B.3	Y39A1B.3	Yes
151	WBGene00016140	<i>rpb-2</i>	C26E6.4	C26E6.4	
153	WBGene00003157	<i>mcm-5</i>	R10E4.4	R10E4.4	
154	WBGene00006746	<i>unc-6</i>	F41C6.1	F41C6.1	
158	WBGene00011605	<i>T08A11.2</i>	T08A11.2	T08A11.2	
161	WBGene00001926	<i>his-52</i>	F07B7.4	F45F2.2	
168	WBGene00016583	<i>tag-335</i>	C42C1.5	C42C1.5	
169	WBGene00000229	<i>atp-2</i>	C34E10.6	C34E10.6	
171	WBGene00004874	<i>smc-4</i>	F35G12.8	F35G12.8	
172	WBGene00004386	<i>rnp-3</i>	K08D10.3	K08D10.3	
173	WBGene00004385	<i>rnp-2</i>	K08D10.4	K08D10.4	
174	WBGene00006588	<i>tnt-3</i>	C14F5.3	C14F5.3	
180	WBGene00001086	<i>dpy-27</i>	R13G10.1	R13G10.1	
181	WBGene00000479	<i>cgh-1</i>	C07H6.5	C07H6.5	
182	WBGene00007877	<i>C33A11.1</i>	C33A11.1	Y15E3B.g	
185	WBGene00008748	<i>F13E6.4</i>	F13E6.4	F13E6.4	
187	WBGene00000895	<i>dac-1</i>	B0412.1	B0412.1	
188	WBGene00007019	<i>mdt-19</i>	Y71H2B.6	Y71H2_389.c	

194	WBGene00004206	<i>pst-1</i>	M03F8.2	M03F8.2	
197	WBGene00000149	<i>apl-1</i>	C42D8.8	C42D8.8	
200	WBGene00001082	<i>dpy-23</i>	R160.1	R160.1	
209	WBGene00010565	<i>K04G2.6</i>	K04G2.6	K04G2.6	
210	WBGene00010364	<i>H04D03.3</i>	H04D03.3	H04D03.3	
212	WBGene00010062	<i>F54F3.3</i>	F54F3.3	F54F3.3	
213	WBGene00021515	<i>Y41D4B.12</i>	Y41D4B.12	Y41D4A_3457.b	
217	WBGene00020391	<i>T10B5.5</i>	T10B5.5	T10B5.5	
225	WBGene00020742	<i>T23H2.3</i>	T23H2.3	F59A7.8	
226	WBGene00001840	<i>hel-1</i>	C26D10.2	C26D10.2	
228	WBGene00006940	<i>wee-1.3</i>	Y53C12A.1	Y53C12A.1	
230	WBGene00011938	<i>T22H6.2</i>	T22H6.2	T22H6.2	
231	WBGene00013151	<i>Y53F4B.4</i>	Y53F4B.4	Y53F4B.f	
234	WBGene00004408	<i>rpa-0</i>	F25H2.10	F25H2.10	
251	WBGene00007110	<i>B0035.11</i>	B0035.11	B0035.11	Yes
252	WBGene00001352	<i>evl-14</i>	H38K22.1	H38K22.1	
253	WBGene00000084	<i>aex-1</i>	D2030.10	D2030.10	
254	WBGene00001684	<i>gpd-2</i>	K10B3.8	K10B3.8	
257	WBGene00001187	<i>egl-19</i>	C48A7.1	C48A7.1	
258	WBGene00003003	<i>lin-14</i>	T25C12.1	T25C12.1	
260	WBGene00000106	<i>alg-2</i>	T07D3.7	F48F7.1	

Table S9. Validated novel genetic modifiers for three tested genes, and their supporting evidences. Note that diverse data types support these predicted and validated genetic modifiers, suggesting benefit from data integration.

A. *ark-1* novel genetic interaction partners

sequence name	public name	supporting evidence: fraction of contribution
Y105E8A.17	ekl-4	SC-LC:0.51 SC-MS:0.27 SC-CC:0.22
F45E12.2	brf-1	SC-CC:0.48 SC-GT:0.36 CE-CX:0.16
Y39A1B.3	dpy-28	CE-CC:0.51 SC-DC:0.49
B0035.11	na	CE-CX:0.52 SC-GT:0.48

B. *sos-1* novel genetic interaction partners

sequence name	public name	supporting evidence: fraction of contribution
K06C4.10	his-18	SC-MS:0.21 SC-GT:0.18 HS-LC:0.17 SC-TS:0.11 SC-DC:0.09 SC-LC:0.08 SC-CX:0.08 SC-CC:0.07
F07B7.11	his-54	SC-MS:0.21 SC-CC:0.18 SC-TS:0.14 SC-DC:0.12 SC-LC:0.10 SC-CX:0.09 HS-CX:0.09 HS-LC:0.07
Y105E8A.17	ekl-4	SC-LC:0.51 SC-MS:0.27 SC-CC:0.22
Y54E10BL.6	mek-2	DM-PI:0.25 HS-CC:0.20 CE-CC:0.19 CE-GT:0.15 HS-LC:0.13 SC-GT:0.08
ZK546.15	try-1	HS-CC:0.56 HS-LC:0.32 HS-CX:0.11
F45E10.1	unc-53	CE-GT:0.39 CE-CC:0.32 CE-LC:0.21 CE-CX:0.08
K04D7.1	rack-1	SC-CC:0.55 SC-CX:0.29 SC-MS:0.16
T20B12.2	tbp-1	SC-LC:0.25 SC-GT:0.20 SC-CC:0.20 HS-LC:0.18 CE-CX:0.11 SC-MS:0.07
F45E12.2	brf-1	SC-CC:0.57 SC-GT:0.43
R160.1	dpy-23	CE-CC:0.46 HS-LC:0.36 CE-CX:0.18
Y39A1B.3	dpy-28	CE-CC:0.51 SC-DC:0.49
T12D8.7	taf-9	HS-DC:1.00
Y105E8B.2	exoc-8	HS-DC:1.00

C. *vab-1* novel genetic interaction partners

sequence name	public name	supporting evidence: fraction of contribution
T20B12.2	tbp-1	SC-CC:0.27 SC-LC:0.24 SC-MS:0.16 CE-CX:0.09 SC-GT:0.08 HS-LC:0.08 DM-PI:0.07
Y105E8A.17	ekl-4	SC-LC:0.51 SC-CC:0.30 SC-MS:0.19
F32A5.1	ada-2	SC-CC:0.26 SC-MS:0.26 SC-LC:0.15 CE-CX:0.11 SC-GT:0.10 DM-PI:0.07 SC-CX:0.06
EGAP7.1	dpy-3	CE-CC:0.58 CE-CX:0.33 SC-GT:0.09

T20B5.1	apa-2	SC-TS:0.48 CE-CX:0.32 SC-MS:0.20
R13G10.1	dpy-27	CE-CC:0.89 CE-GN:0.11
K04D7.1	rack-1	SC-CC:0.29 SC-MS:0.29 SC-CX:0.26 CE-CX:0.16
F54C4.2	spt-4	SC-GT:0.58 SC-CC:0.27 CE-CX:0.11 SC-MS:0.04
F25B3.6	na	SC-CC:0.44 CE-CX:0.29 SC-GT:0.27
F45E12.2	brf-1	CE-CX:0.38 SC-CC:0.35 SC-GT:0.27
C30C11.4	na	SC-CC:0.54 SC-MS:0.46
C25D7.3	sdc-3	CE-CC:0.54 CE-GT:0.26 CE-CX:0.21
B0286.4	ntl-2	SC-LC:1.00
F08F8.2	na	SC-CC:1.00

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