

**Table S1.** List of up- and down-regulated *cyp* genes by caffeine treatment\*

<b>Coding sequence</b>	<b>Gene name</b>	<b>Chromosome</b>	<b>Fold increased</b>	<b>p-value</b>	<b>GO ID</b>	<b>GO term name</b>
C49G7.8	<i>cyp-35A4</i>	5	33.2	0.0113	0055114	oxidation-reduction process
K09D9.2	<i>cyp-35A3</i>	5	32.5	0.0211	0055114	oxidation-reduction process
K07C6.5	<i>cyp-35A5</i>	5	28.9	0.0071	0055114	oxidation-reduction process
C03G6.15	<i>cyp-35A2</i>	5	28.5	0.0084	0055114	oxidation-reduction process
B0213.15	<i>cyp-34A9</i>	5	10.0	0.0056	0055114	oxidation-reduction process
F08F3.7	<i>cyp-14A5</i>	5	8.3	0.0054	0055114	oxidation-reduction process
R04D3.1	<i>cyp-14A4</i>	X	7.9	0.0181	0055114	oxidation-reduction process
K07C6.3	<i>cyp-35B2</i>	5	6.5	0.0233	0055114	oxidation-reduction process
C50H11.15	<i>cyp-33C9</i>	5	3.4	0.0027	0055114	oxidation-reduction process
C26F1.2	<i>cyp-32A1</i>	5	3.3	0.0125	0055114	oxidation-reduction process
F42A9.5	<i>cyp-33E2</i>	4	2.9	0.0146	0055114	oxidation-reduction process
F41B5.2	<i>cyp-33C7</i>	5	2.8	0.0517	0055114	oxidation-reduction process
F14F7.3	<i>cyp-13A12</i>	3	2.7	0.0348	0055114	oxidation-reduction process
K07C6.4	<i>cyp-35B1</i>	3	2.4	0.0062	0055114	oxidation-reduction process
K09A11.2	<i>cyp-14A1</i>	X	2.4	0.0383	0055114	oxidation-reduction process
F44C8.1	<i>cyp-33C4</i>	5	2.4	0.0400	0055114	oxidation-reduction process
B0213.12	<i>cyp-34A7</i>	5	2.4	0.0510	0055114	oxidation-reduction process
C49C8.4	<i>cyp-33E1</i>	4	2.2	0.0246	0055114	oxidation-reduction process
F41B5.7	<i>cyp-33C6</i>	5	2.2	0.0495	0055114	oxidation-reduction process
F42A9.4	<i>cyp-33E3</i>	4	2.1	0.0161	0055114	oxidation-reduction process
K09A11.3	<i>cyp-14A2</i>	X	2.0	0.0185	0055114	oxidation-reduction process
F41B5.4	<i>cyp-33C3</i>	5	2.0	0.0337	0055114	oxidation-reduction process
T10B9.4	<i>cyp-13A8</i>	2	2.0	0.0128	0055114	oxidation-reduction process
E03E2.1	<i>cyp-43A1</i>	X	2.0	0.0147	0055114	oxidation-reduction process
F41B5.3	<i>cyp-33C5</i>	5	1.8	0.0500	0055114	oxidation-reduction process
C36A4.2	<i>cyp-25A2</i>	3	1.8	0.0401	0055114	oxidation-reduction process
C34B7.3	<i>cyp-36A1</i>	1	1.7	0.0172	0055114	oxidation-reduction process

ZK177.5	<i>cyp-44A1</i>	2	0.9	0.0386	0055114	oxidation-reduction process
C01G6.6	<i>mtrr-1</i>	2	0.5	0.0246	0055114	oxidation-reduction process

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\*Only *cyp* genes that showed  $p < 0.05$  are listed as described in Materials and Methods.

**Table S2.** Transition of % distribution of worms in each developmental stage in 24 h intervals for 96 h at different caffeine concentration

<b>0 mM</b>	<b>24 h</b>	<b>48 h</b>	<b>72 h</b>	<b>96 h</b>
<b>L1</b>	0.0	0.0	0.0	0.0
<b>L2</b>	2.3 ± 3.1	0.0	0.0	0.0
<b>L3</b>	97.4 ± 0.6	0.0	0.0	0.0
<b>L4</b>	0.3 ± 1.0	41.5 ± 5.1	0.0	0.0
<b>YA</b>	0.0	58.4 ± 3.2	1.3 ± 1.2	0.0
<b>A</b>	0.0	0.1 ± 0.5	98.7 ± 0.5	100.0
<b>10 mM</b>	<b>24 h</b>	<b>48 h</b>	<b>72 h</b>	<b>96 h</b>
<b>L1</b>	3.0 ± 3.5	0.0	0.0	0.0
<b>L2</b>	91.7 ± 1.9	23.4 ± 2.8	1.4 ± 2.3	0.0
<b>L3</b>	5.3 ± 1.7	71.1 ± 8.0	1.8 ± 2.4	0.0
<b>L4</b>	0.0	5.5 ± 6.6	20.4 ± 2.8	0.0
<b>YA</b>	0.0	0.0	24.5 ± 8.5	1.1 ± 1.3
<b>A</b>	0.0	0.0	51.9 ± 12.1	98.9 ± 0.4
<b>30 mM</b>	<b>24 h</b>	<b>48 h</b>	<b>72 h</b>	<b>96 h</b>
<b>L1</b>	100.0	90.6 ± 1.4	86.7 ± 3.7	86.1 ± 3.4
<b>L2</b>	0.0	9.2 ± 2.1	13.1 ± 2.2	13.4 ± 1.2
<b>L3</b>	0.0	0.2 ± 0.1	0.2 ± 0.4	0.5 ± 0.2
<b>L4</b>	0.0	0.0	0.0	0.0
<b>YA</b>	0.0	0.0	0.0	0.0
<b>A</b>	0.0	0.0	0.0	0.0

Average percent distributions of worms in each developmental stage after caffeine treatment are summarized. Data are presented as a line graph in Fig. 2. About 2,700 individuals (triplicates of 900 individuals per plate) were scored for each concentration of caffeine treatment. L1 to L4, L1 to L4 larval stages; YA, young adult stage; A, adult stage



72 h						
0 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L2	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L3	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L4	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
YA	0.0 ± 0.00	1.5 ± 0.01	1.7 ± 0.02	0.0 ± 0.00	0.4 ± 0.01	0.7 ± 0.01
A	100.0 ± 0.00	98.5 ± 0.23	98.3 ± 0.19	100.0 ± 0.00	99.6 ± 0.17	99.3 ± 0.79
10 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	0.2 ± 0.01	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L2	10.6 ± 0.15	9.4 ± 0.22	0.0 ± 0.00	0.0 ± 0.00	13.4 ± 0.05	0.0 ± 0.00
L3	27.7 ± 0.10	16.5 ± 0.06	12.7 ± 0.10	21.1 ± 0.03	21.1 ± 0.10	16.0 ± 0.07
L4	47.1 ± 0.14	18.9 ± 0.07	16.0 ± 0.14	14.4 ± 0.05	14.2 ± 0.16	15.7 ± 0.05
YA	13.7 ± 0.16	14.1 ± 0.10	21.8 ± 0.09	15.1 ± 0.02	21.3 ± 0.09	22.9 ± 0.05
A	0.7 ± 0.01	41.0 ± 0.17	49.5 ± 0.21	49.3 ± 0.04	30.0 ± 0.04	45.4 ± 0.35
30 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	94.2 ± 0.02	52.1 ± 0.23	54.0 ± 0.11	52.8 ± 0.10	52.9 ± 0.06	31.2 ± 0.06
L2	5.5 ± 0.02	41.8 ± 0.07	44.8 ± 0.02	42.8 ± 0.03	44.9 ± 0.02	62.8 ± 0.03
L3	0.3 ± 0.01	5.4 ± 0.04	1.2 ± 0.01	4.4 ± 0.01	2.2 ± 0.01	6.0 ± 0.04
L4	0.0 ± 0.00	0.7 ± 0.01	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
YA	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
A	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
96 h						
0 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L2	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L3	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L4	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
YA	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
A	100.0 ± 0.00	100.0 ± 0.00	100.0 ± 0.00	100.0 ± 0.00	100.0 ± 0.00	100.0 ± 0.00
10 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L2	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L3	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
L4	9.6 ± 0.04	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
YA	1.9 ± 0.01	7.1 ± 0.02	3.5 ± 0.01	2.6 ± 0.02	6.9 ± 0.02	2.5 ± 0.03
A	88.5 ± 0.04	92.9 ± 0.06	96.5 ± 0.13	97.4 ± 0.15	93.1 ± 0.11	97.5 ± 0.65
30 mM	mock	<i>cyp-35A2</i>	<i>cyp-35A3</i>	<i>cyp-35A4</i>	<i>cyp-35A5</i>	quadruple*
L1	94.0 ± 0.02	50.8 ± 0.23	52.5 ± 0.11	50.5 ± 0.10	52.5 ± 0.06	30.5 ± 0.06
L2	5.7 ± 0.02	44.0 ± 0.02	46.0 ± 0.02	45.0 ± 0.02	45.0 ± 0.02	63.0 ± 0.17
L3	0.3 ± 0.01	4.5 ± 0.01	1.5 ± 0.03	4.5 ± 0.01	2.5 ± 0.01	6.5 ± 0.04
L4	0.0 ± 0.00	0.7 ± 0.02	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
YA	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
A	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00

\*RNAi depletion was treated in quadruple combination of *cyp-35A2*, *cyp-35A3*, *cyp-35A4*, and *cyp-35A5*.

N2 worms synchronized at the L1 larval stage were treated with soaking RNAi (single or quadruple RNAi) to deplete *cyp-35A* family gene activity. Worms were then transferred to 0 mM, 10 mM or 30 mM caffeine-containing NGM plates and cultured at 20°C. 250 worms were examined for each RNAi of *cyp* genes at each concentration of caffeine. After culturing, their larval development was scored in 24 h intervals for 96 h, and average values of percent distribution of worms in each developmental stage after respective RNAi are summarized.