

Soy isoflavones induce feminization of Japanese eel (*Anguilla japonica*)

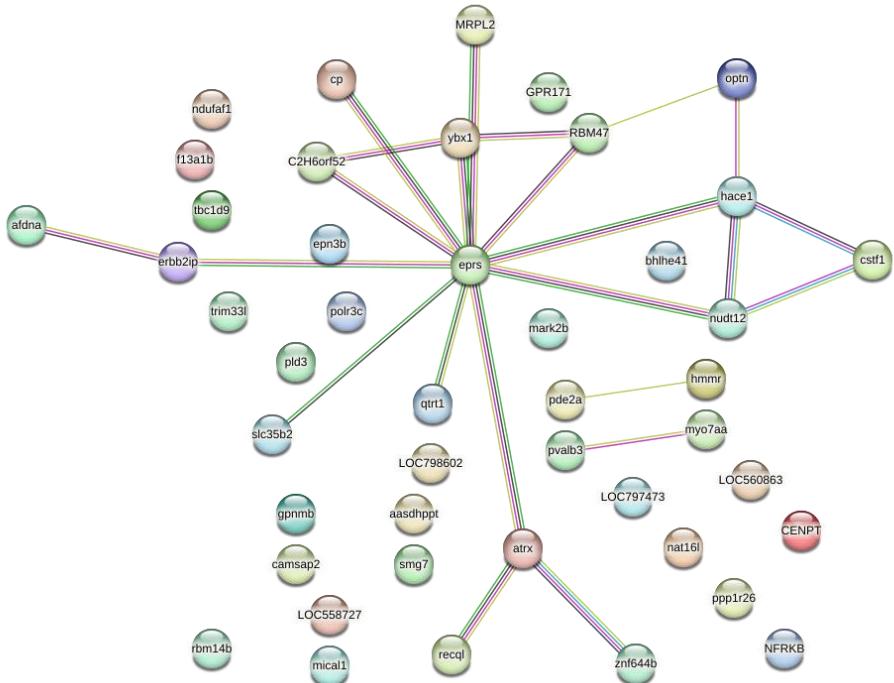
Supplementary Materials

Hiroyuki Inaba^{1,2,3}, Yuzo Iwata^{1,4}, Takashi Suzuki^{1,5}, Moemi Horiuchi⁶, Ryohei Surugaya⁶, Shigeho Ijiri⁶, Ai Uchiyama⁷, Ryoko Takano⁷, Seiji Hara^{2,8}, Takashi Yazawa⁹ & Takeshi Kitano^{2*}

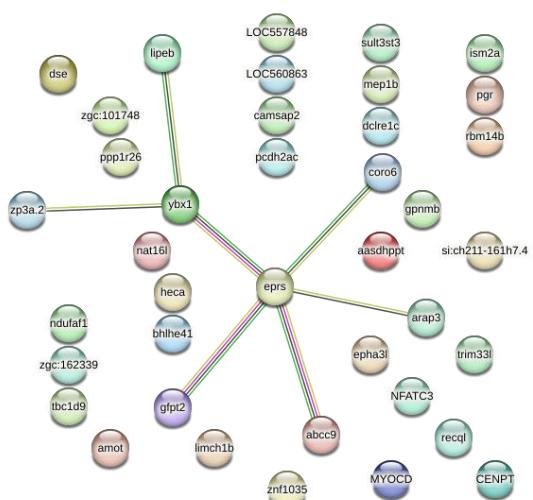
Supplementary Table S1. Differentially expressed genes with FPKM values that changed by >10-fold in E2- and genistein-treated eels compared with the genes of control eels.

	No.	Tracking_id	Gene name	STRING protein	GO Term
E2 up-regulated genes	1	MSTRG.1006.3	transcription elongation regulator 1-like isoform X4	LOC797473	P-DNA-dependent transcription; F-transcription copolymer activity; F-RNA polymerase binding
	2	MSTRG.1087.2	RNA-binding 14-b isoform X3	rhn14b	F-RNA binding
	3	MSTRG.1086.2	b7c1 domain family member 9b isoform X2	hmc1	Cytoskeleton
	4	MSTRG.1097.2	BCI domain family member 9b isoform X2	thcl4b	Fusilli ion binding
	5	MSTRG.1107.2	apoptotic chromatin condensation inducer in the nucleus-like	ybs1	F-protein dehydrogenase activity
	6	MSTRG.1194.7	Y-box binding 2 isoform X2	nat16	Fatty-acid binding
	7	MSTRG.1197.1	histidine N-acetyltransferase-like	RBM47	F-RNA binding; C-motifs
	8	MSTRG.1263.4	RNA-binding 4-like isoform X2	rcsf1	P-DNA replication; P-DNA repair; P-DNA recombination; F-hydrolyase activity; F-catalytic activity, acting on DNA; F-ATP-dependent activity; C-motifs
	9	MSTRG.1304.2	ATP-dependent DNA helicase Q1 isoform X2	otp6	Cytoplasmic vesicle
	10	MSTRG.1344.2	hydrolase of proteins	MRLP2	P-mitochondrial gene expression; F-RNA binding; F-mitochondrial activity; C-mitochondria; Cytoplasm
	11	MSTRG.1397.2	39kDa ribosomal protein L2, mitochondrial	pdc2a	cGMP-dependent 3'-5'-cyclic phosphodiesterase isoform X4
	12	MSTRG.1409.2	cGMP-dependent 3'-5'-cyclic phosphodiesterase isoform X4	asdhp1	P-manno acid metabolic process; P-protein modification process; F-transfase activity; C-yrosine
	13	MSTRG.1493.2	L-aminoacyl-tRNA-synthetase-like dehydrogenase-phosphoamino-1 transferase isoform X3	myt7aa	P-mitochondrial transport; F-cell differentiation; P-antennular structure development; P-lysosome process; F-cytoskeletal motor activity; F-cytoskeletal protein binding; C-cytoskeleton
	14	MSTRG.1500.2	uncharacterized protein 14 isoform X3	GPR171	G-protein coupled receptor 171
	15	MSTRG.1504.2	product of cnc-like protein 1	p45	P-mitigation of DNA-damaged transcription; P-mitochondrial structure development; F-DNA binding; F-catalytic activity; F-transcription regulator activity; C-motifs
	16	MSTRG.1552.2	5'-T-monoester PLD3	cst1	P-mitochondrial gene expression; F-RNA binding; F-transcription regulator activity; C-motifs
	17	MSTRG.1617.3	cleavage stimulation factor subunit 1		P-mitochondrial gene expression; F-RNA binding; F-transcription regulator activity; C-motifs
	18	MSTRG.1670.2	--NA--		
	19	MSTRG.1713.2	--NA--		
	20	MSTRG.1923.2	transcriptional regulator ZDTRX-like	NPRK8	C-mitochondria
	21	MSTRG.2090.5	queuine tRNA(ribosyl)transferase catalytic subunit 1 isoform X1	atrx	Compartments
	22	MSTRG.2095.1	class I basic helix-loop-helix 41 isoform X1	qtr1	P-DNA metabolic process; F-transfase activity; F-catalytic activity, acting on RNA; C-mitochondria
	23	MSTRG.2075.8	queuine tRNA(ribosyl)transferase catalytic subunit 1 isoform X1	blhh3	P-mitigation of DNA-damaged transcription; F-cell differentiation; P-antennular structure development; F-DNA binding; F-transcription regulator activity
	24	MSTRG.2149.1	parvalbumin alpha	pvab3	Fusilli ion binding
	25	MSTRG.2204.2	quantum sensor 3-like	qv3b	Flipid binding
	26	MSTRG.2248.2	transmembrane T-kinase	CDNP7	F-cell differentiation; P-glycan binding; P-mitochondrial structure development; F-DNA binding; F-transcription regulator activity
	27	MSTRG.2266.8	LOW-QUALITY-PROTEIN_afadin-like	zfif6	P-cell adhesion; P-glycan binding; P-mitochondrial structure development
	28	MSTRG.2331.7	protein SMG7 isoform X8	sing7	F-hydrolyase activity; C-peptides
	29	MSTRG.2342.2	zinc finger 644	ztf64b	P-mitigation of DNA-damaged transcription; F-DNA binding; F-transcription regulator activity; C-motifs
	30	MSTRG.2366.2	spindlin-W-like	LOC797662	P-mitochondrial gene expression
	31	MSTRG.2402.2	quantum sensor 1 isoform X1		
	32	MSTRG.2465.1	phosphatase 1 regulatory subunit 26 isoform X1	ppp1r26	P-mitigation of phosphate activity; F-protein phosphatase inhibitor activity
	33	MSTRG.2560.2	peroxiredoxin NAD(P)H:prostaglandin reductase NUDT1 isoform X1	nudt12	F-hydrolyase activity; C-peptides
	34	MSTRG.2695.1	serine/threonine-protein kinase MARK2-like isoform X9	mar2b	P-cell differentiation; P-mitochondrial matrix organization; P-antennular structure development; P-transmembrane transport; P-carbohydrate derivative metabolic process; F-transpose activity
	35	MSTRG.2767.0	dehydrogenase/epoxidase -phospholipase 5'-phosphate transporter 1 isoform X2	slc5b2	P-cell differentiation; P-GTP-binding
	36	MSTRG.2908.2	GTPase-IMAP family member 8-like	LOC506863	F-GTP-binding
	37	MSTRG.2947.2	uncharacterized protein 14 isoform X1	gtpc1	F-transfase activity; C-mitochondria
	38	MSTRG.3373.2	quaternary ammonium protein 1 isoform X1	gtpc2	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity
	39	MSTRG.3383.4	DNA-directed RNA polymerase III subunit RPC1 isoform X1	ppp1r27	P-mitigation of DNA-damaged transcription; F-DNA binding; C-motifs
	40	MSTRG.3469.2	LOW-QUALITY-PROTEIN_afelin	erbb2ip	P-mitigation of DNA-damaged transcription; P-signaling
	41	MSTRG.4812.6	tRNA selencytome 1-associated 1-like	C2H6orf2	F-acidic acid binding; C-intermediary anatomical structure
	42	MSTRG.4813.6	transmembrane ion channel factor 1-alpha-like isoform X2	trans3f1	F-transfase activity; C-enzymes and co-factors
	43	MSTRG.4770.2	transmembrane ion channel factor 1-beta-like isoform X1	cp	F-oxidoreductase activity; C-cytoskeletal region
	44	MSTRG.674.4	coagulation factor XIIa isoform X1	11ab1b	F-cell differentiation; P-antennular structure development
	45	MSTRG.650.1	cholinesterase-regulated spectrin-associated isoform X3	cansap2	F-cell differentiation; P-antennular structure development; F-cytoskeletal protein binding; C-cytoskeleton
	46	MSTRG.7318.2	F-actin-monomer gene 1-like isoform X4	micall	P-mitochondrial structure development; F-cytoskeletal protein binding; F-oxidoreductase activity
	47	MSTRG.7352.2	glutamyl tRNA synthetase	epn1	P-mRNA metabolic process; F-amino acid metabolic process; F-ligase activity; F-catalytic activity, acting on RNA
	48	MSTRG.7570.2	ATP-dependent DNA helicase 1-like isoform X1	nduf1	P-mitochondrial membrane and energy; P-mitochondrial regulation; P-protein-containing complex assembly; C-mitochondria
	49	MSTRG.7765.2	EF-hand protein HACB isoform X1	efhac1	P-mitochondrial gene expression; F-DNA activity; F-catalytic activity, acting on a protein
E2 down-regulated genes	1	MSTRG.1122.7	finger CCHC domain-containing 7 isoform X2	zcch7	F-protein binding; F-protein binding; C-yrosine
	2	MSTRG.1278.2	palmitoyl transferase ZDHHC5a	zhdh5a	P-protein modification process; F-protein activity; F-catalytic activity, acting on a protein; C-plasma membrane
	3	MSTRG.1370.3	inactive carboxy-peptidase-like	cpn3a	P-protein maturation; F-protein activity; F-catalytic activity, acting on a protein; C-cytoskeletal space
	4	MSTRG.1404.2	BCL2-associated athanogene 1-like isoform X1	gloc1	P-mitigation of DNA-damaged transcription; C-WISN complex
	5	MSTRG.1555.2	basic helix-loop-helix protease precursor-like isoform X2	maprb1	F-protein binding; C-intermediary anatomical structure
	6	MSTRG.1592.0	microtubule-associated protein 1B family member 1-like	maglb	F-protein binding; C-cytoskeleton
	7	MSTRG.1610.0	microtubule-associated protein 1B, WW and POZ domain-containing 1B isoform X8	shb472	F-protein binding; P-GTP-binding; C-yrosine
	8	MSTRG.1684.6	weak autotin with coiled-coil domains and kyrin repeat -like isoform X1	dmp62	P-mitochondrial process; F-ligase activity; C-ideophenonic acid
	9	MSTRG.1760.2	dual headdog subunit B member 2 isoform X5	dhdb2	P-mitochondrial process; F-ligase activity; C-ideophenonic acid
	10	MSTRG.1773.2	beta-1,4-endoglucanase 1-like isoform X1	ptp1b	P-mitochondrial process; F-ligase activity; C-ideophenonic acid
	11	MSTRG.1877.2	the GTPase-activating-like	ATBH-GAP16	P-mitochondrial regulation
	12	MSTRG.1918.2	synapsin-5-like	svx5d	P-mitochondrial protein; P-mitochondrial transport; P-mitochondrial organization; F-molecular adaptor activity; C-Golgi apparatus
	13	MSTRG.2094.2	transcriptional regulator ATRX-like	atrx	Compartides
	14	MSTRG.2104.2	serine/threonine kinase MARK1 isoform X2	zg-153725	P-mitochondrial organization; P-protein modification process; F-transfase activity; F-catalytic activity, acting on a protein
	15	MSTRG.2114.2	serine/threonine kinase MARK1 isoform X2	LOC506982	F-mitochondrial gene expression
	16	MSTRG.2116.2	transmembrane acid 1-like	LOC506106	P-mitochondrial gene expression; F-DNA binding; F-hydrolyase activity; F-catalytic activity, acting on RNA; C-organelle
	17	MSTRG.2121.2	transmembrane acid 1-like	LOC506106	P-mitochondrial gene expression; F-DNA binding; F-hydrolyase activity; F-catalytic activity, acting on RNA; C-organelle
	18	MSTRG.2307.2	activated CICD2 kinase 1-like isoform X5	LOC505919	P-quinol: P-protein modification process; F-transfase activity; F-catalytic activity, acting on a protein; C-plasma membrane
	19	MSTRG.2314.3	activated CICD2 kinase 1-like isoform X1	zg-162946	C-mitochondria; C-nucleus
	20	MSTRG.2342.4	beta-1,4-endoglucanase 1-like isoform X1	gnt3	P-mitochondrial activity; F-catalytic activity, acting on a protein; C-Golgi apparatus
	21	MSTRG.2404.2	beta-1,4-endoglucanase 1-like isoform X1	cdthb1	P-mitochondrial activity; F-catalytic activity, acting on a protein; C-Golgi apparatus
	22	MSTRG.2469.2	beta-1,4-endoglucanase 1-like isoform X1	dhdb1	P-mitochondrial activity; F-catalytic activity, acting on a protein; C-Golgi apparatus
	23	MSTRG.2562.2	DNA damage-binding 2 isoform X3	ddb2	P-DNA damage; F-DNA binding; C-motifs; C-Cdk4-RNK1 E2 ubiquitin ligase complex
	24	MSTRG.2562.2	oxytocin receptor LXR-alpha-like	arh3	P-mitigation of DNA-damaged transcription; P-mitochondrial process; P-signaling; F-DNA binding; F-molecular transducer activity; F-transcription regulator activity; C-motifs
	25	MSTRG.2767.2	BRO1 domain-containing protein BROX	bror1	C-mitochondria
	26	MSTRG.2993.1	NLR family CARD-domain-containing 3-like isoform X2	szh21-19h16.4	P-mitochondrial gene silencing; F-DNA binding; F-molecular transducer activity; F-transcription regulator activity
	27	MSTRG.3256.2	two pore cation channel 1-like isoform X2	ndrg2	P-mitochondrial gene expression; P-mitochondrial structure development
	28	MSTRG.3302.2	two pore cation channel 1-like isoform X3	tpn1	P-mitochondrial transport; F-molecular adaptor activity; C-yrosine
	29	MSTRG.3312.2	electrostatic sodium bicarbonate transporter 1 isoform X3	sk4d4	P-mitochondrial transport; F-molecular adaptor activity
	30	MSTRG.3372.2	chloroblast protein homolog 6-like	cbt6a	P-mitigation of DNA-damaged transcription; P-protein modification process; F-mitochondrial activity; F-catalytic activity, acting on a protein; C-motifs
	31	MSTRG.3471.2	ubiquitin-conjugating enzyme E2-like	UBED6L1	P-mitochondrial process; F-mitochondrial gene expression; F-mitochondrial transport; P-mitochondrial structure development
	32	MSTRG.3514.2	calmodulin-binding protein 2 isoform X2	cambp2	P-mitochondrial process; F-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial structure development
	33	MSTRG.3518.2	calmodulin-binding protein 2 isoform X3	CNP7	P-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial structure development
	34	MSTRG.3524.2	calmodulin-binding protein 2 isoform X3	dhb1	P-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial structure development
	35	MSTRG.3541.2	calmodulin-binding protein 2 isoform X3	heca	F-protein activity
	36	MSTRG.3542.2	calmodulin-binding protein 2 isoform X3	nat16	F-protein activity; F-protein modification process; F-transfase activity
	37	MSTRG.3705.2	lipid	lipb	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	38	MSTRG.3714.2	islet1-like homeobox 1	isnt1a	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	39	MSTRG.3767.2	uncharacterized protein 14 isoform X3	isnt1b	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	40	MSTRG.3804.2	uncharacterized protein 14 isoform X3	isnt1b	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	41	MSTRG.3824.2	uncharacterized protein 21-1616-74 isoform X1	trans3f1	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	42	MSTRG.2634.1	uncharacterized protein szh21-1616-74 isoform X1	szh21-16h17.4	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	43	MSTRG.1194.7	Y-box-binding 2 isoform X2	ybx1	F-fatty-acid binding
	44	MSTRG.2075.7	zinc finger 501-like	zfp105	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
	45	MSTRG.1914.2	uncharacterized protein 14 isoform X3	zfp3a2	P-mitochondrial gene expression; F-mitochondrial transport; F-catalytic activity, acting on a protein; C-motifs
Genistein up-regulated genes	1	MSTRG.1177.0	ATP-binding cassette subfamily A member 1-like isoform X2	NFATC3	P-mitigation of DNA-damaged transcription; F-signaling; F-DNA binding; F-transcription regulator activity
	2	MSTRG.1207.0	phosphoglycerate 3-kinase regulatory subunit 26 isoform X1	pp162339	P-mitigation of phosphate activity; P-protein phosphatase inhibitor activity
	3	MSTRG.1506.1	PREDICTED_ uncharacterized protein C11orf16 isoform X2	pp162339	P-mitigation of phosphate activity; P-protein phosphatase inhibitor activity
	4	MSTRG.1259.6	PREDICTED_ uncharacterized protein LOC100964325 isoform X4	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	5	MSTRG.1440.1	prostaglandin receptor type 2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	6	MSTRG.1441.1	prostaglandin receptor type 2-like	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	7	MSTRG.1177.9	proteoglycan alpha-3-like isoform X13	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	8	MSTRG.1087.2	QRN-71 isoform X1	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	9	MSTRG.1094.2	TBC1 domain family member 9B isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	10	MSTRG.1104.2	transmembrane ion channel factor 1-alpha-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	11	MSTRG.1105.2	transmembrane ion channel factor 1-beta-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	12	MSTRG.1106.2	transmembrane ion channel factor 1-gamma-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	13	MSTRG.1107.2	transmembrane ion channel factor 1-epsilon-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	14	MSTRG.1108.2	transmembrane ion channel factor 1-eta-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	15	MSTRG.1109.2	transmembrane ion channel factor 1-omega-like isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	16	MSTRG.3039.1	--NA--	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	17	MSTRG.3040.1	carboxylic acid-rich C-terminal domain-containing protein 1-like	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	18	MSTRG.1095.2	Werner syndrome ATP-dependent helicase isoform X1	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	19	MSTRG.4665.2	UFO189P protein C5e22 homolog	MTFR1	P-mitigation of DNA-damaged transcription; P-mitochondrial gene expression; F-DNA binding; C-mitochondria
	20	MSTRG.5577.2	transcript termination factor 1, mitochondrial	crb3f3	P-mitigation of DNA-damaged transcription; F-DNA binding; C-mitochondria
	21	MSTRG.2074.1	ATP-binding cassette subfamily C member 9 isoform X1	std1	P-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial organization; F-molecular adaptor activity; C-Golgi apparatus
	22	MSTRG.1908.2	ribosome biogenesis protein BMS1 homolog isoform X2	std1	P-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial organization; F-molecular adaptor activity; C-Golgi apparatus
	23	MSTRG.1914.2	ribosome biogenesis protein BMS1 homolog isoform X2	std1	P-mitochondrial gene expression; P-mitochondrial transport; P-mitochondrial organization; F-molecular adaptor activity; C-Golgi apparatus
	24	MSTRG.2082.9	ATP-binding cassette subfamily C member 9 isoform X2	arh13	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	25	MSTRG.1809.5	ATP-binding cassette subfamily C member 9 isoform X2	bbg3	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	26	MSTRG.1809.5	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	27	MSTRG.1809.5	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
Genistein down-regulated genes	1	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	2	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	3	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	4	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	5	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	6	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	7	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2	pp162378	P-mitochondrial gene expression; F-DNA binding; F-transcription regulator activity; C-motifs
	8	MSTRG.1177.0	ATP-binding cassette subfamily C member 9 isoform X2</		

(A)



(B)



- : From curated databases
- : Experimentally determined
- : Gene neighborhood
- : Gene fusions
- : Gene co-occurrence
- : Textmining
- : Co-expression
- : Protein homology

Supplementary Figure S1. Functional and physiological networks visualized by STRING.

(A) Functional and physiological networks within the 49 genes up-regulated by E2

(B) Functional and physiological networks within the 45 genes up-regulated by Genistein