Supporting Information

Liao and Weng 10.1073/pnas.1415046112

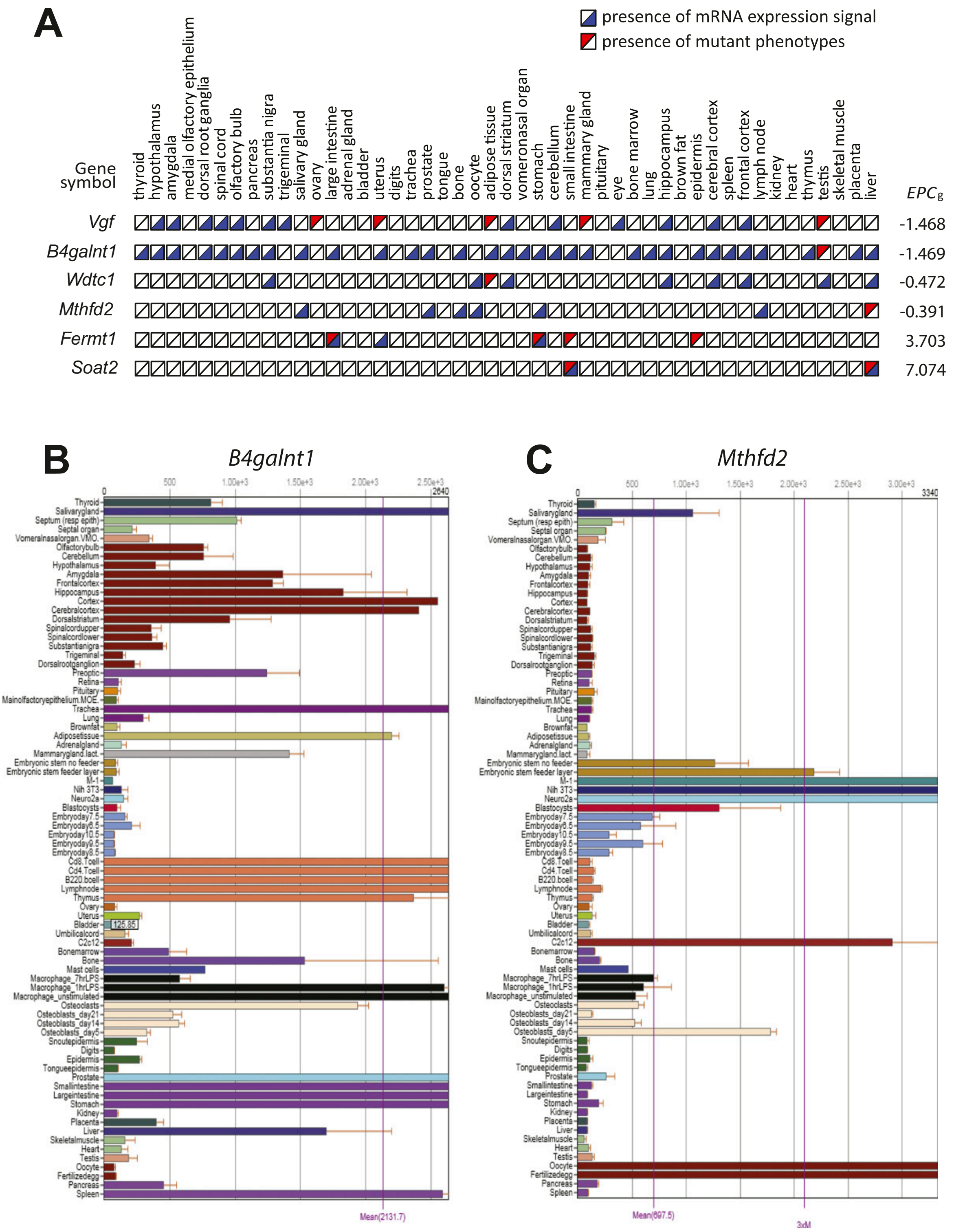

Fig. S1. (*A*) Expression profiles, phenotypic profiles, and EPC_t of VGF nerve growth factor inducible (*Vgf*), beta-1,4-N-acetyl-galactosaminyl transferase 1 gene (*B4galnt1*), WD and tetratricopeptide repeats 1 (*Wdtc1*), NAD-dependent methylenetetrahydrofolate dehydrogenase-methenyltetrahydrofolate cyclohydrolase gene (*Mthfd2*), fermitin family member 1 (*Fermt1*), and sterol O-acyltransferase 2 (*Soat2*) genes. The complete tissue expression profiles of *B4galnt1* (*B*) and *Mthfd2* (*C*) genes, obtained from dataset "GeneAtlas GNF1M, gcrma" of BioGPS (biogps.org/) are shown.

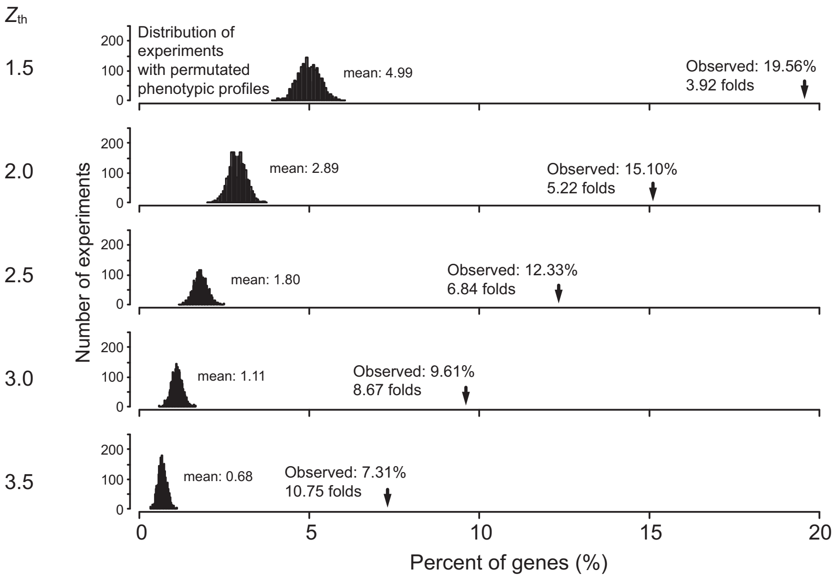

Fig. S2. Ratios of the percentage of mouse genes with $EPC_g \geq Z_{th}$ (Z_{th} = 1.5, 2.0, 2.5, 3.0, or 3.5) to the percentage estimated from 2,500 experiments with permutated phenotypic profiles increases as the Z_{th} used increased. Z_{th}, the cutoff value used to define statistically significant expression-phenotype connection.

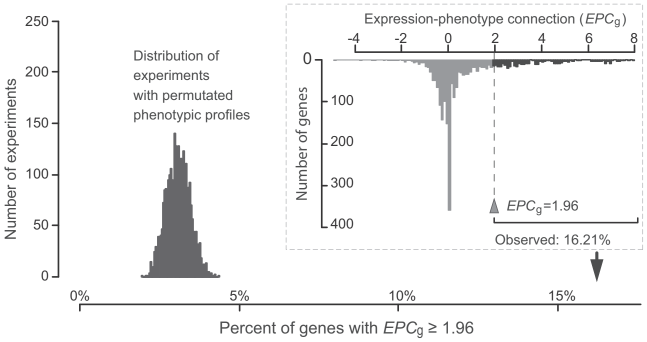

Fig. S3. Regenerated Fig. 1*A* using phenotypic entries of 2,532 genes obtained before the publication date of GeneAtlas v2.

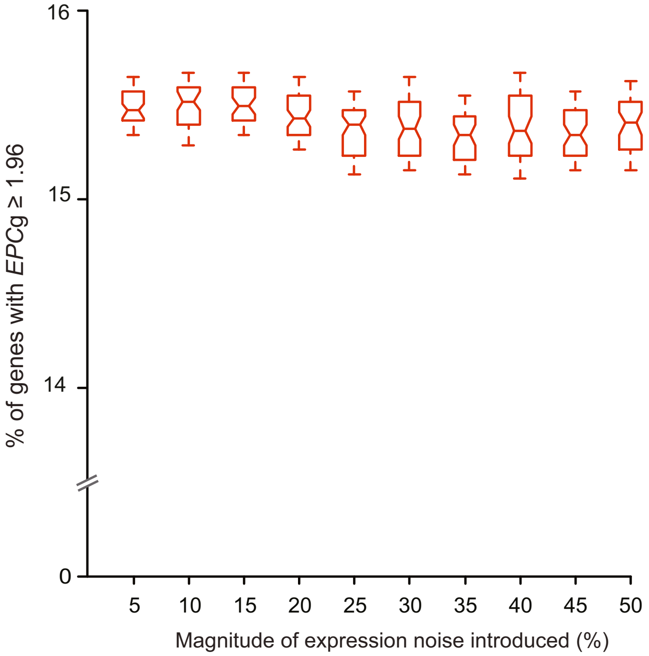

Fig. S4. Box plots for the percentage of mouse genes with *EPC*$_g$ ≥1.96 when expression noises within a range of magnitude (5–50% of the original values) were added. Each box presents the distribution of estimations calculated based on 50 replicates. The values of the upper quartile, median, and lower quartile are indicated in each box, whereas the bars outside the box indicate semiquartile ranges.

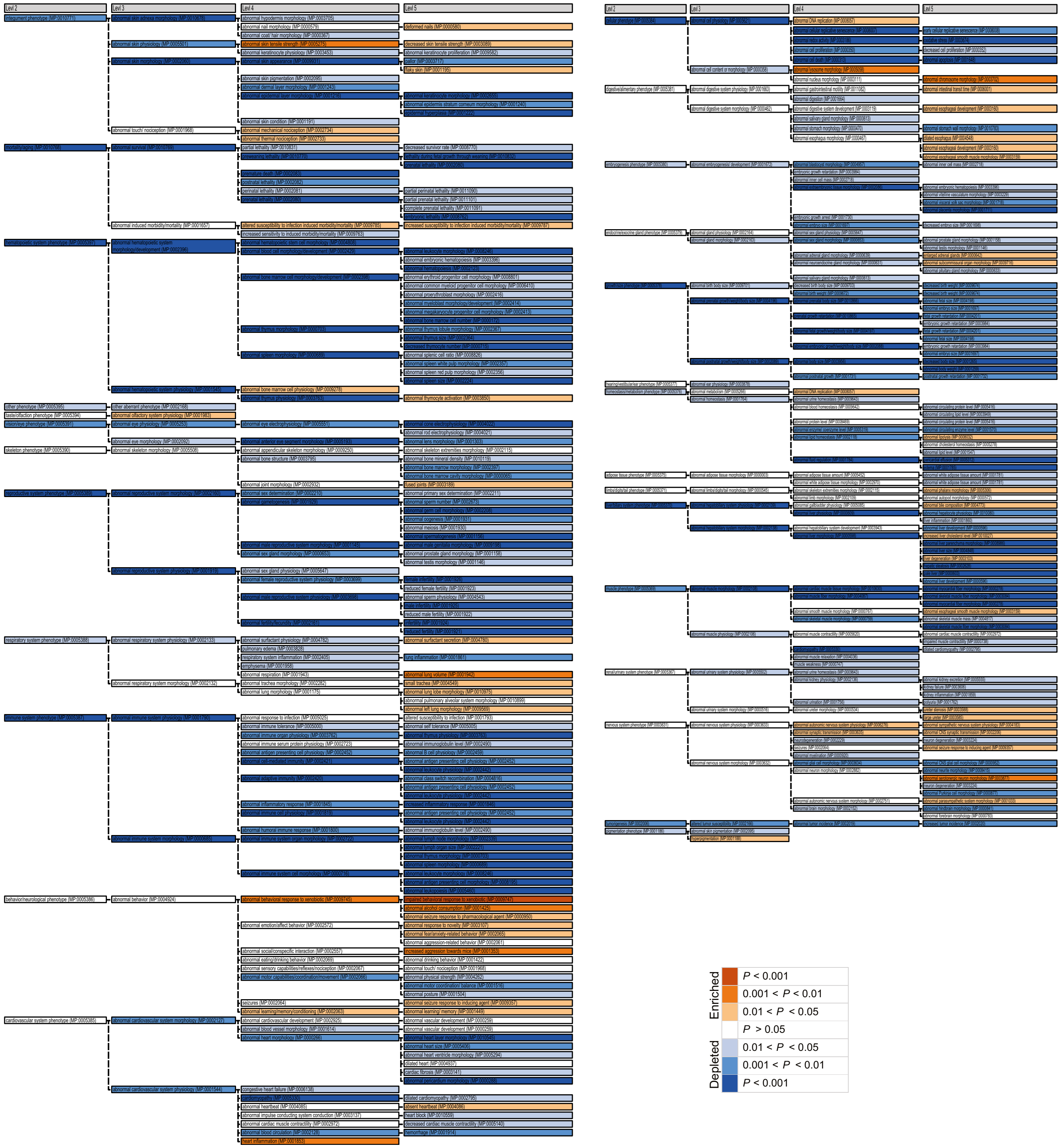

Fig. S5. Enriched/depleted phenotypes of mouse genes showing mutant phenotypes without a corresponding expression-expressed tissue (i.e., genes with $N_{EP} = 0$, $N_E > 0$, $N_P > 0$) vs. genes with $N_{EP} > 0$. Analysis was conducted by Mammalian Phenotype Enrichment Analysis (MamPhEA, evol.nhri.org.tw/MamPhEA) using default parameters.

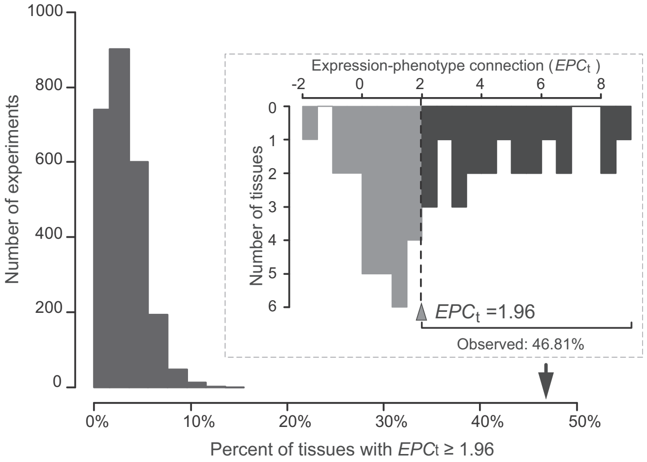

Fig. S6. Percentage of mouse tissues with $EPC_t \geq 1.96$ was 46.81% (arrowhead from the distribution in the *Inset*) and was significantly greater than the percentage of mouse tissues with $EPC_t \geq 1.96$ estimated from 2,500 experiments with permutated phenotypic profiles.

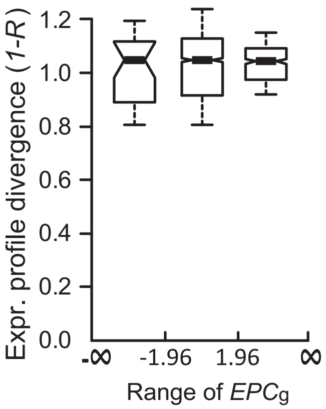

Fig. S7. Under the neutral model of transcriptome evolution, genes with higher EPC_g do not have more conserved gene expression (Expr.) profiles following the rodent-primate divergence. The $1 - R$ values of human-mouse orthologs under the neutral model were calculated after randomizing the tissue expression profile of the human gene of each ortholog. The box plots show the distributions of $1 - R$ for mouse genes with three different ranges of EPC_g. The values of the upper quartile, median, and lower quartile are indicated in each box, and the bars outside the box indicate semiquartile ranges. *P* values are from the Mann–Whitney *U* test.

Table S1. Forty-seven mouse tissues profiled by Gene Altas v2 oligonucleotide microarray experiments and their corresponding tissue names, presented as MA codes, in MGI for the records of mutant strain phenotyping

No.	Gene Atlas v2 tissues*	Corresponding tissues with MGI phenotypic code (MA code)
1	Adipose tissue	Adipose tissue (MA:0000009)
2	Adrenal gland	Adrenal gland (MA:0000116)
3	Amygdala	Amygdala (MA:0000887)
4	Bladder	Urinary bladder (MA:0000380)
5	Bone	Bone (MA:0001459)
6	Bone marrow	Bone marrow (MA:0000134)
7	Brown fat	Brown adipose tissue (MA:0000057)
8	Cerebellum	Cerebellum (MA:0000198)
9	Cerebral cortex	Cerebral cortex (MA:0000185)
10	Digits	Limb digit (MA:0000690)
11	Dorsal root ganglia	Dorsal root ganglion (MA:0000232)
12	Dorsal striatum	Dorsal striatum (MA:0002971)
13	Epidermis	Epidermis (MA:0000153)
14	Eye	Eye (MA:0000261)
15	Frontal cortex	Frontal cortex (MA:0000905)
16	Heart	Heart (MA:0000072)
17	Hippocampus	Hippocampus (MA:0000191)
18	Hypothalamus	Hypothalamus (MA:0000173)
19	Kidney	Kidney (MA:0000368)
20	Large intestine	Large intestine (MA:0000333)
21	Liver	Liver (MA:0000358)
22	Lung	Lung (MA:0000415)
23	Lymph node	Lymph node (MA:0000139)
24	Mammary gland	Mammary gland (MA:0000145)
25	Medial olfactory epithelium	Nasal cavity olfactory epithelium (MA:0001325)
26	Olfactory bulb	Main olfactory bulb (MA:0000194)
27	Oocyte	Oocyte (MA:0000388)
28	Ovary	Ovary (MA:0000384)
29	Pancreas	Pancreas (MA:0000120)
30	Pituitary	Pituitary gland (MA:0000176)
31	Placenta	Placenta (MA:0000386)
32	Prostate	Prostate gland (MA:0000404)
33	Salivary gland	Salivary gland (MA:0000346)
34	Skeletal muscle	Skeletal muscle tissue (MA:0002439)
35	Small intestine	Small intestine (MA:0000337)
36	Spinal cord lower and spinal cord upper	Spinal cord (MA:0000216)
37	Spleen	Spleen (MA:0000141)
38	Stomach	Stomach (MA:0000353)
39	Substantia nigra	Substantia nigra (MA:0000210)
40	Testis	Testis (MA:0000411)
41	Thymus	Thymus (MA:0000142)
42	Thyroid	Thyroid gland (MA:0000129)
43	Tongue	Tongue (MA:0000347)
44	Trachea	Trachea (MA:0000441)
45	Trigeminal	Trigeminal V nerve (MA:0001100)
46	Uterus	Uterus (MA:0000389)
47	Vomeronasal organ	Vomeronasal organ (MA:0000289)

The substructures of each tissue (in MA codes) and the associated phenotypic codes (in MP IDs) are available as Dataset S1. MA, Mouse Anatomy.

*Tissues profiled by Gene Altas v2 but not included in the present study due to the lack of a corresponding MGI MA code are "B220$^+$ B cells," "blastocysts," "CD4$^+$ T cells," "CD8$^+$ T cells," "embryo day 6.5," "embryo day 7.5," "embryo day 8.5," "embryo day 9.5," "embryo day 10.5," "fertilized egg," "preoptic," "snout epidermis," and "umbilical cord."

Table S2. Results of hypergeometric tests in searching for tissues with enriched mutant phenotypes for a given gene set, defined as genes expressed in the tissue indicated

Expressed tissue of the gene set (EPC_t)*	Tissue with enriched mutant phenotypes	P value after Bonferroni correction for multiple testing
Placenta (8.73)	**Placenta**	**3.36E-14**
Placenta (8.73)	Heart	1.75E-08
Placenta (8.73)	Liver	2.45E-05
Liver (8.47)	**Liver**	**1.60E-14**
Liver (8.47)	Heart	9.10E-04
Liver (8.47)	Placenta	5.39E-03
Heart (8.17)	**Heart**	**3.53E-13**
Heart (8.17)	Liver	1.33E-04
Thymus (6.91)	**Thymus**	**1.75E-08**
Thymus (6.91)	Thyroid	2.42E-06
Thymus (6.91)	Bone marrow	2.50E-06
Thymus (6.91)	Spleen	5.38E-04
Thymus (6.91)	Liver	9.18E-04
Thymus (6.91)	Placenta	1.49E-03
Bone marrow (6.74)	**Bone marrow**	**2.04E-08**
Bone marrow (6.74)	Heart	3.14E-05
Bone marrow (6.74)	Liver	1.99E-03
Testis (6.47)	**Testis**	**3.69E-07**
Testis (6.47)	Placenta	1.75E-03
Skeletal muscle (5.61)	Heart	6.08E-06
Skeletal muscle (5.61)	**Skeletal muscle**	**3.93E-05**
Skeletal muscle (5.61)	Liver	1.64E-03
Cerebellum (5.55)	**Cerebellum**	**4.64E-05**
Epidermis (5.44)	Heart	7.93E-07
Epidermis (5.44)	**Epidermis**	**1.26E-04**
Epidermis (5.44)	Liver	5.39E-03
Eye (5.4)	**Eye**	**7.50E-05**
Eye (5.4)	Heart	1.05E-03
Spleen (4.86)	Bone marrow	6.24E-04
Spleen (4.86)	**Spleen**	**2.94E-03**
Spleen (4.86)	Liver	2.38E-02
Lymph node (4.41)	Spleen	5.09E-11
Lymph node (4.41)	Bone marrow	1.34E-07
Lymph node (4.41)	Thymus	1.51E-05
Lymph node (4.41)	Liver	5.32E-05
Lymph node (4.41)	Thyroid	1.71E-04
Lymph node (4.41)	Heart	5.02E-03
Lymph node (4.41)	**Lymph node**	**1.31E-02**
Brown fat (4.2)	Heart	2.45E-08
Brown fat (4.2)	Liver	6.48E-06
Brown fat (4.2)	Skeletal muscle	4.19E-02
Kidney (3.95)	Liver	3.46E-06
Kidney (3.95)	Heart	2.51E-03
Kidney (3.95)	Placenta	1.07E-02
Hippocampus (3.78)	Cerebellum	6.77E-03
Small intestine (3.29)	Liver	1.53E-05
Small intestine (3.29)	Placenta	8.76E-03
Lung (3.21)	Heart	3.41E-12
Lung (3.21)	Liver	1.37E-05
Lung (3.21)	Placenta	4.74E-05
Lung (3.21)	Bone marrow	2.89E-02
Pituitary (3.03)	Liver	5.68E-03
Pituitary (3.03)	Heart	3.85E-02
Bladder (2.32)	Heart	1.41E-07
Bladder (2.32)	Placenta	4.94E-04
Bladder (2.32)	Liver	1.43E-02
Oocyte (2.29)	Heart	2.53E-03
Oocyte (2.29)	Placenta	2.63E-03
Stomach (2.21)	Heart	6.48E-06
Stomach (2.21)	Liver	4.20E-04
Stomach (2.21)	Placenta	3.83E-03

Table S2. Cont.

Expressed tissue of the gene set (*EPC_t*)*	Tissue with enriched mutant phenotypes	*P* value after Bonferroni correction for multiple testing
Medial olfactory epithelium (1.95)	Liver	2.04E-02
Bone (1.94)	Bone marrow	7.09E-11
Bone (1.94)	Liver	1.00E-04
Bone (1.94)	Heart	3.34E-04
Bone (1.94)	Spleen	5.35E-03
Bone (1.94)	Epidermis	1.35E-02
Mammary gland (1.86)	Placenta	3.68E-04
Mammary gland (1.86)	Liver	4.47E-04
Mammary gland (1.86)	Heart	2.18E-03
Trachea (1.64)	Heart	6.35E-04
Trachea (1.64)	Epidermis	7.17E-04
Trachea (1.64)	Liver	7.96E-04
Trachea (1.64)	Bone marrow	2.30E-03
Trachea (1.64)	Placenta	3.48E-03
Trachea (1.64)	Spleen	3.73E-03
Digits (1.46)	Epidermis	4.59E-10
Digits (1.46)	Heart	1.54E-03
Digits (1.46)	Placenta	5.01E-03
Adipose tissue (1.42)	Liver	9.01E-07
Adipose tissue (1.42)	Bone marrow	8.48E-05
Adipose tissue (1.42)	Placenta	1.23E-03
Adipose tissue (1.42)	Spleen	3.52E-03
Adipose tissue (1.42)	Heart	3.54E-03
Adipose tissue (1.42)	Thymus	1.66E-02
Uterus (1.39)	Heart	9.96E-06
Uterus (1.39)	Placenta	1.37E-04
Uterus (1.39)	Liver	2.53E-04
Vomeronasal organ (1.28)	Heart	4.83E-05
Vomeronasal organ (1.28)	Placenta	3.23E-02
Adrenal gland (1.05)	Heart	2.01E-08
Adrenal gland (1.05)	Liver	8.88E-08
Adrenal gland (1.05)	Placenta	1.09E-03
Tongue (1.01)	Heart	5.11E-08
Tongue (1.01)	Epidermis	4.92E-05
Tongue (1.01)	Liver	9.83E-03
Tongue (1.01)	Placenta	1.35E-02
Tongue (1.01)	Skeletal muscle	3.16E-02
Pancreas (0.92)	Heart	6.00E-03
Olfactory bulb (0.85)	Cerebellum	6.22E-03
Olfactory bulb (0.85)	Hippocampus	3.75E-02
Thyroid (0.79)	Heart	7.58E-03
Prostate (0.77)	Heart	8.42E-06
Prostate (0.77)	Liver	2.21E-04
Large intestine (0.3)	Placenta	8.92E-03
Large intestine (0.3)	Heart	2.23E-02
Large intestine (0.3)	Liver	3.80E-02
Spinal cord (0.29)	Heart	1.11E-02
Spinal cord (0.29)	Cerebellum	1.80E-02
Hypothalamus (0.24)	Cerebellum	5.71E-03
Salivary gland (0.15)	Liver	7.57E-04
Salivary gland (0.15)	Heart	5.86E-03
Salivary gland (0.15)	Placenta	9.70E-03
Dorsal root ganglia (0.04)	Heart	2.44E-02
Frontal cortex (–0.01)	Cerebellum	1.49E-03
Ovary (–0.33)	Heart	4.27E-07
Ovary (–0.33)	Liver	9.26E-06
Ovary (–0.33)	Placenta	2.37E-05
Substantia nigra (–0.59)	Cerebellum	8.76E-05
Dorsal striatum (–0.76)	Cerebellum	7.37E-03
Amygdala (–1.75)	Cerebellum	3.79E-03

Only the results with a Bonferroni-corrected *P* value <0.05 are shown. The tests supporting a gene set expressed in a tissue with enrichment of abnormal phenotypes in the same tissue are highlighted in bold font.

*Sorted by *EPC_t*.

Table S3. Information on genes with mRNA in situ hybridization data used to produce Fig. 4

	Corresponding EMAP IDs (no. of genes* used to generate Fig. 4)	
Theiler stage	Eye	Heart
TS12	**EMAP:304 (3)**	EMAP:315 (18)
TS13	**EMAP:540 (0)**	**EMAP:560 (3)**
TS14	**EMAP:873 (8)**	EMAP:897 (21)
TS15	EMAP:1285 (42)	EMAP:1317 (67)
TS16	EMAP:1786 (32)	EMAP:1827 (26)
TS17	EMAP:2364 (31)	EMAP:2411 (41)
TS18	EMAP:3003 (11)	EMAP:3056 (10)
TS19	**EMAP:3605 (9)**	**EMAP:3666 (3)**
TS20	EMAP:4327 (13)	**EMAP:4396 (1)**
TS21	**EMAP:5201 (1)**	**EMAP:5285 (0)**
TS23	EMAP:7786 (438)	EMAP:7907 (137)

Developmental stages with insufficient sample sizes (<10 genes) are marked with bold font and were not computed for stage-specific EPC_t.

*Genes with mRNA in situ hybridization data in the EMAGE database.

Other Supporting Information Files

Dataset S1 (TXT)