Supplementary Information for:

The frequent evolutionary birth and death of functional promoters in mouse and human

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Containing:

Supplementary Materials and Methods

Promoter definition

Promoters were annotated as coding (found within 500 bp of the 5' end of an annotated protein-coding transcript), noncoding (found within 500 bp of the 5' end of an annotated noncoding transcript), or anonymous (more than 500 bp from the 5' end of any annotated genes) as in Forrest et al.

Expression data

Promoters with a median TPM across all 52 tissue types greater than 0 were defined as 'broadly-expressed' and those with a median TPM equal to 0 were defined as 'tissue-restricted'. Those broadly-expressed promoters with a median:maximum TPM ratio greater than 0.2 where also labelled as 'housekeeping'. Promoters with biased expression in one or more samples were also recorded.

The most pronounced effect on promoter width is breadth of expression (Supp. Fig. 17): consistent with previous findings (e.g. Carninci et al. 2006) tissue-restricted promoters exhibit smaller spans than more broadly utilised promoters regardless of evolutionary outcome. Amongst the broadly expressed promoters there is a modest tendency for inserted promoters to have a greater span than matched promoters of similar expression breadth (1.2-fold in human, Mann-Whitney *U* test, $p = 1.45 \times 10^{-8}$; in mouse, Mann-Whitney *U* test, $p = 8.9 \times 10^{-2}$). For promoters whose sequence aligns between species, but where promoter activity is diminished or ablated in the other species there is also a tendency towards narrower span, however, such promoters also tend towards lower expression levels (Supp. Fig. 14) which may bias the detected extent of the cluster span.

Multi-species alignments

Where promoters could be projected by Ensembl into multiple abutting alignment blocks we recorded the maximum and minimum position of these locations requiring that all projections were on the same chromosome and strand. Promoters that were projected into multiple chromosomes or strands were recorded as being aligned in the projected species, but it was not possible to unambiguously define the orthologous projected sequence in this species. Promoter projections that were found within gapped or unaligned sequence were called as missing sequence in the projected species.

Promoters were projected through the UCSC genome alignments using the liftOver tool (Hinrichs et al. 2006). Chain files detailing the same genome assemblies used in the Ensembl alignments (hg19, mm9, canFam2, equCab2, bosTau6, susScr3) were downloaded directly from the UCSC Genome Browser. All liftOver parameters were left at their default settings. Unmapped promoters were called as missing sequence in the projected species.

When considering projections of promoter sequence between human and mouse, a promoter was annotated as conserved if its projected location was within 50 bp of a CAGE tag cluster in the opposite species. Due to the high false positive rate within pairwise genome alignments (Jordan and Goldman 2012) we only consider the projected location of promoters and the length of sequence gaps across promoters that were supported by the 12-way mammalian genome alignments. We annotated these projected promoters based on the status of the projected clusters as below:

1. Matched. The projected cluster shows the same robust expression bias in the source and target genomes.

2. Divergent. The projected cluster shows a different expression bias in the target genome, but is still expressed above the “robust” threshold (supported by at least 11 CAGE tags and 1TPM in a single experiment, as in Forrest et al. 2014) in the target species.

3. Diminished. The projected cluster shows diminished expression relative to the source promoter, i.e. it passes the “permissive” (at least 3 CAGE tags in a single experiment, as in Forrest et al. 2014), but not the “robust”, threshold in the target species.

4. Aligned. The projected position contains no identified CAGE tag clusters in the target genome.

When promoters were projected near to more than one CAGE tag cluster we considered only the first annotation as described above, e.g. a promoter which was projected near to a matched and a permissive CAGE cluster would be described as matched. Unlike the initial set of source promoters and the matched promoters, neither the robust nor permissive cluster sets being projected into were filtered on their sequence features. This allowed us to generously detect transcription in the projected species and gave us the greatest confidence possible from this data that there was genuinely no transcription arising from projected locations marked as ‘aligned’.

Recently inserted and deleted promoters were identified in both human and mouse using both the Ensembl and UCSC alignments. We combined both sets of alignments to increase our power to detect an aligned position and thereby increase our confidence that alignment gaps genuinely arise from unaligned sequence. Although the multiple-species alignments have a greater accuracy than the pairwise genome alignments produced by UCSC (Jordan and

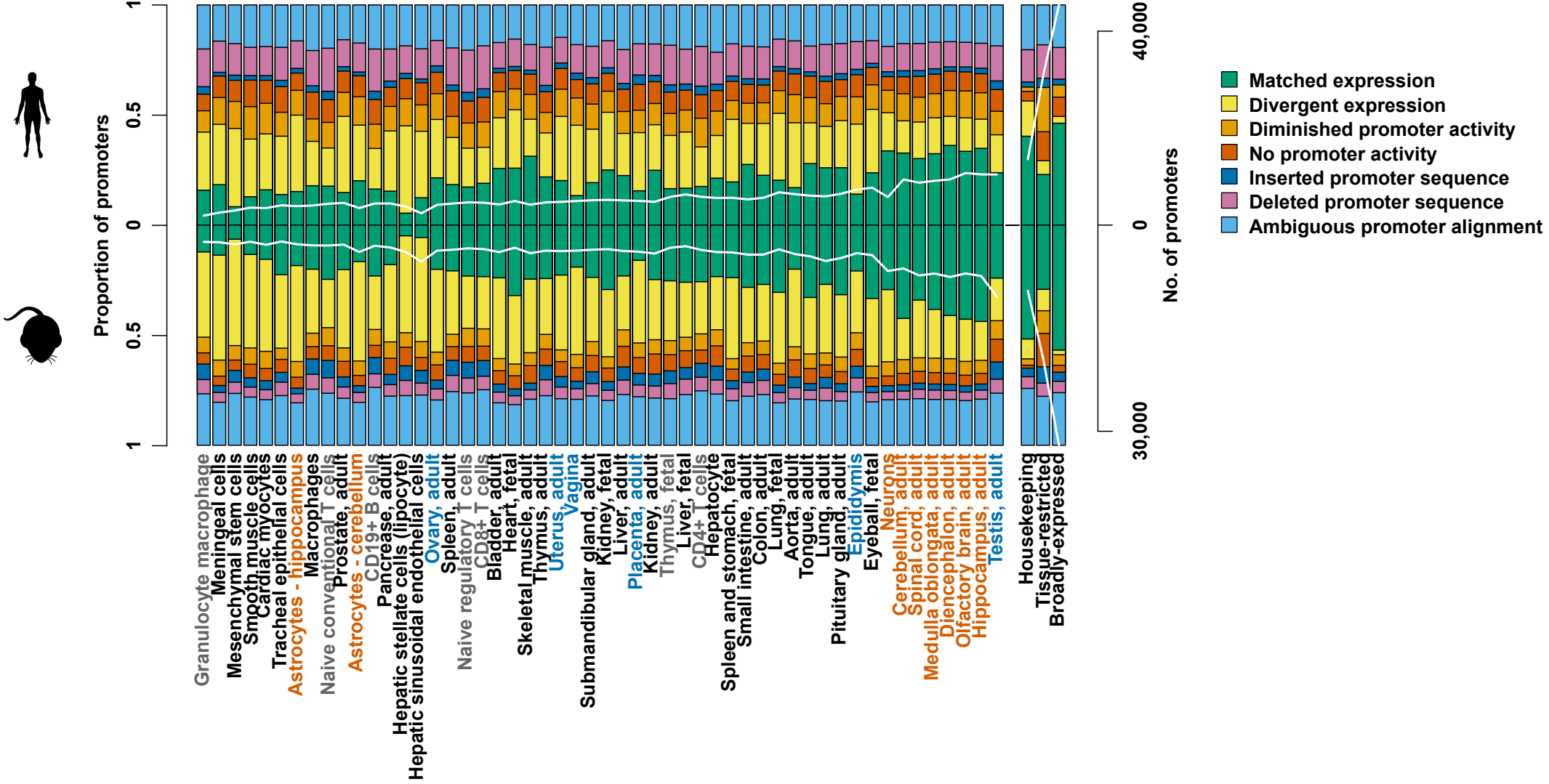
Goldman 2012), pairwise alignments still assign over 50% of aligned sequence near to the correct orthologous gene loci, even when there is no aligning sequence in the multiple species alignment.

In contrast to the tissue differences in expression bias and conservation, there was no correlation (Spearman's correlation, $p > 0.8$ for both species) in the proportion of tissue-biased promoters with unresolved sequence, arguing against systematic biases in the ambiguous alignments that we have conservatively excluded.

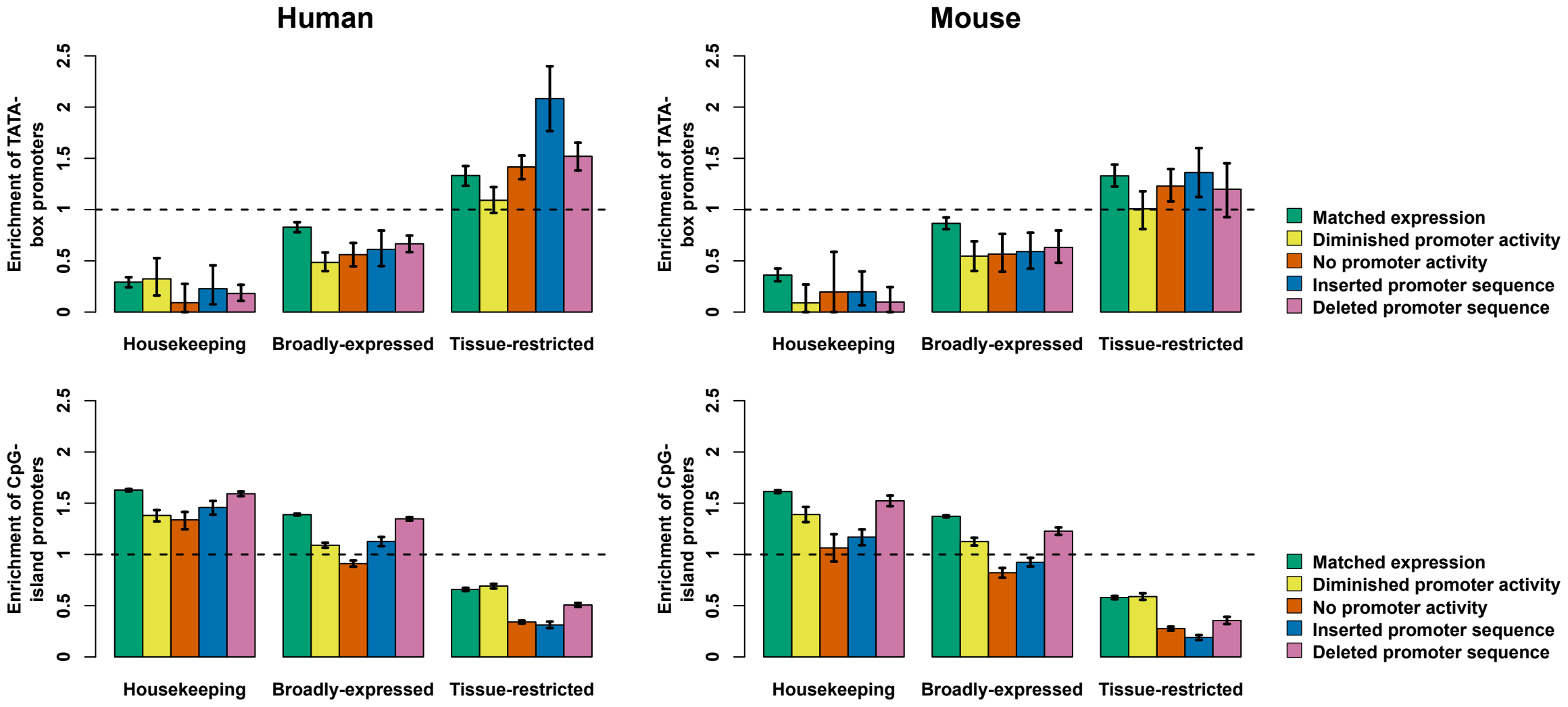
Evolutionary conservation was assessed for each base position in aligning sequence using the GERP++ program (Davydov et al. 2010). All parameters were left at their default positions.

Repetitive elements

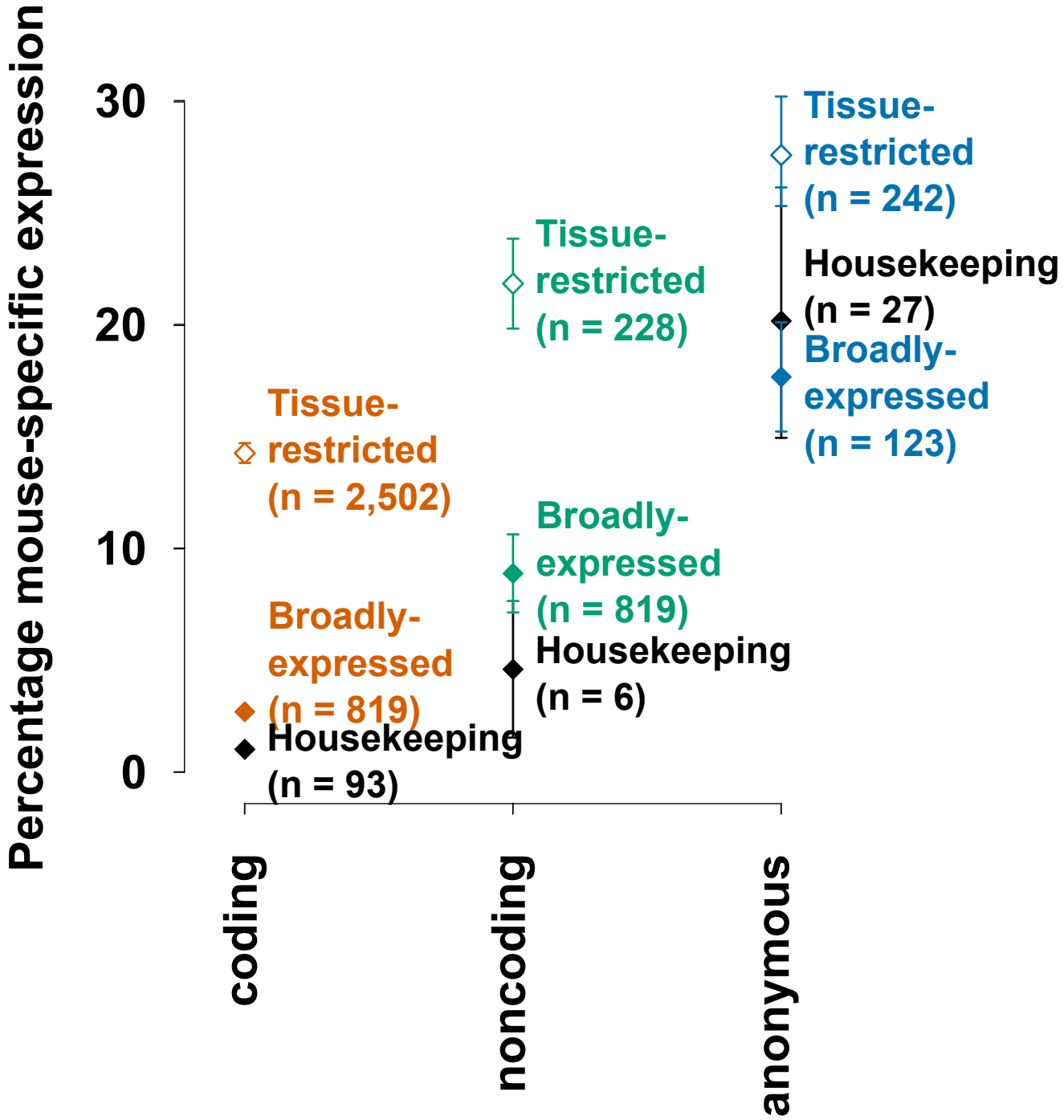
Repetitive element positions were collected from the RepeatMasker tracks available from the UCSC Genome Browser (Kent et al. 2002) for the hg19 and mm9 genome assemblies. The enrichment of repetitive elements at various 250 bp windows around the promoter was calculated by comparing the proportion of promoters with a particular evolutionary outcome and that overlapped a repetitive element to the proportion of promoters whose shuffled position had the same evolutionary outcome and which also overlapped a repetitive element. The significance of this enrichment was judged by plotting the 95% confidence interval for 100 samplings (with replacement) using the shuffled promoter positions as both the



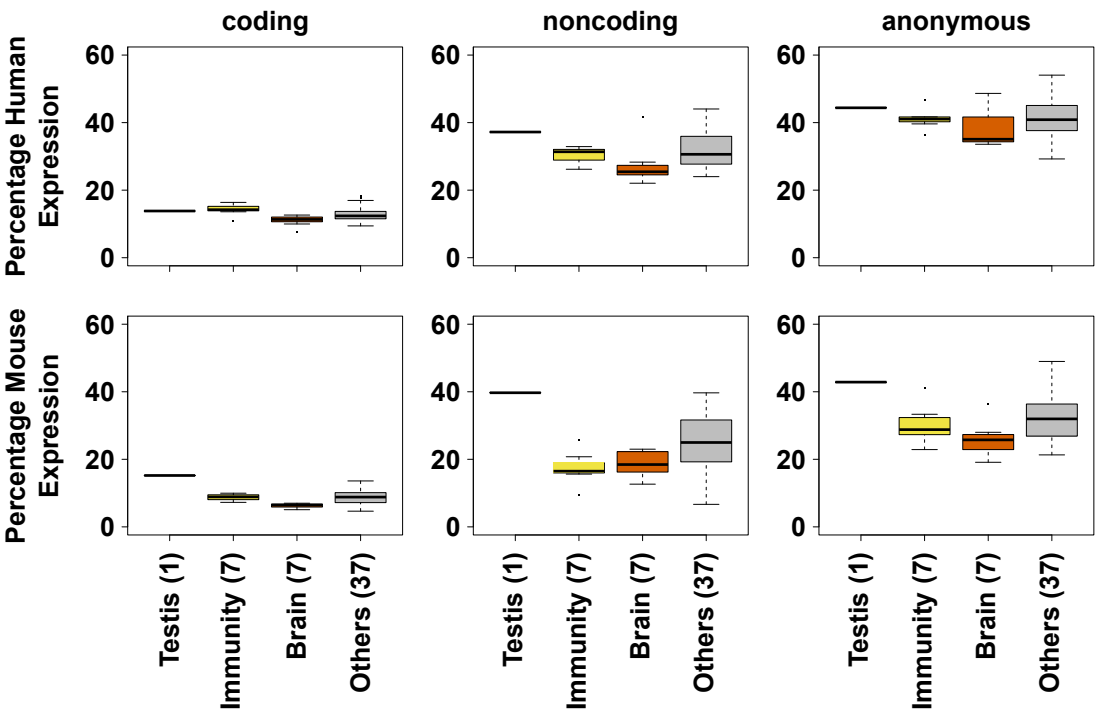
Supplementary Figure 1: Proportion of promoters displaying each evolutionary outcome in human and mouse. Samples are ordered by rank of human:mouse average promoter count per sample. The white line denotes the number of promoters with that tissue bias or expression profile (right axis).



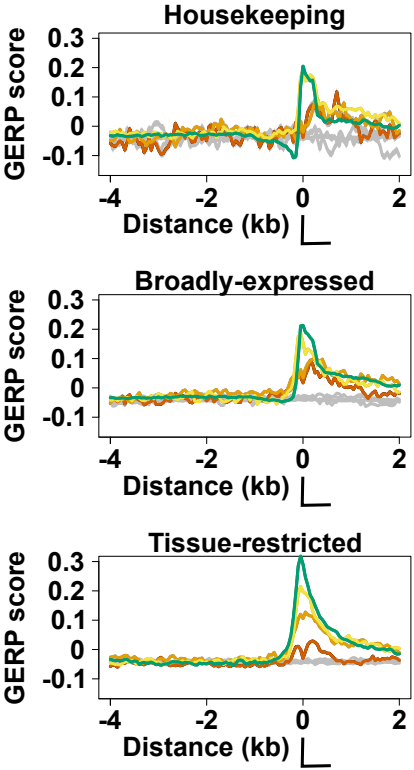
Supplementary Figure 2: Enrichment of TATA box motifs around tissue-restricted promoters (top row) and CpG islands around housekeeping and broadly-expressed promoters (bottom row) relative to the complete promoter set. The error bars represent the 95% confidence interval from 1,000 samplings of the data with replacement.



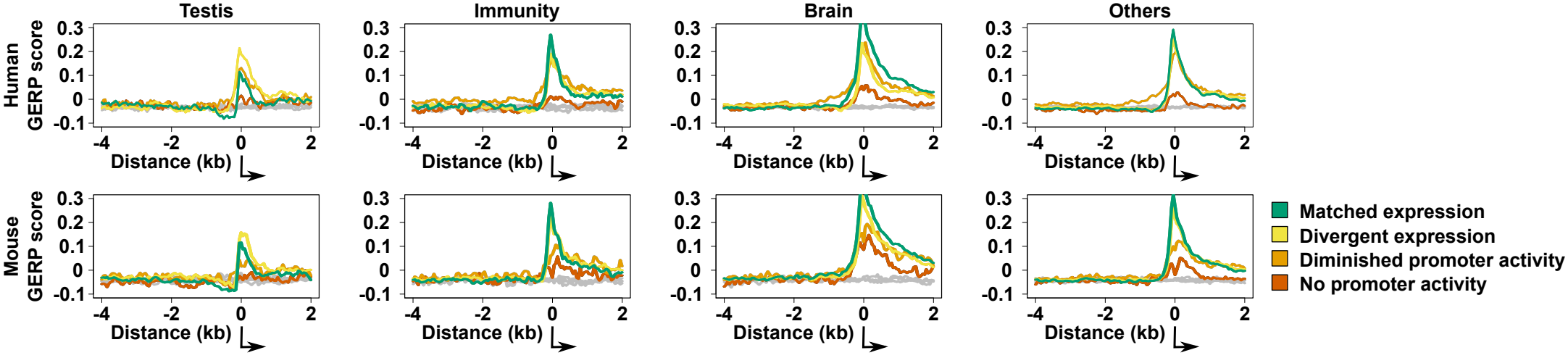
Supplementary Figure 3: The percentage of mouse promoters of a particular class and expression profile which can be aligned to human but show no transcriptional activity at the aligned position. The error bars represent the 95% confidence interval from 1,000 samplings of the data with replacement.



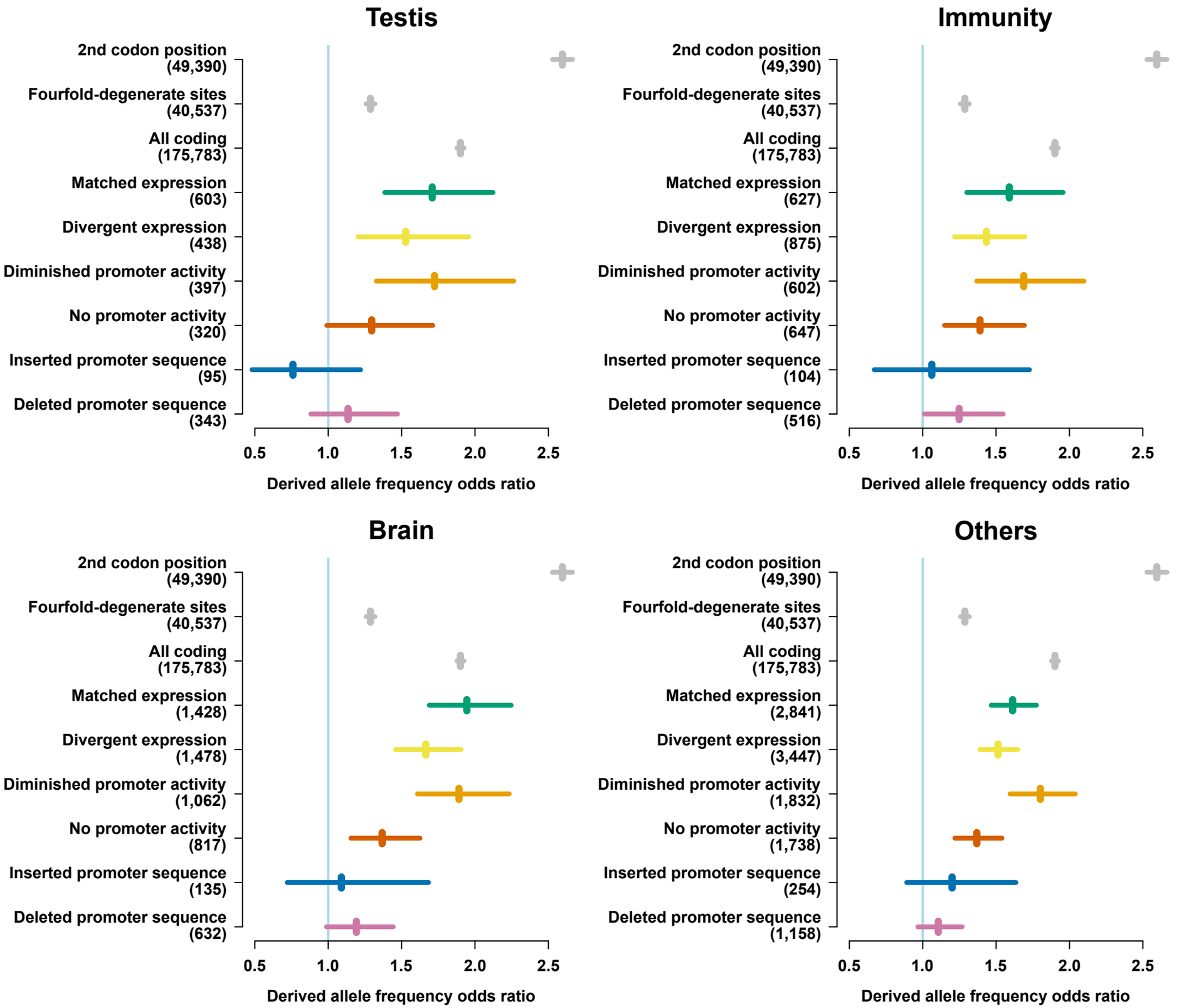
Supplementary Figure 4: Expression turnover at tissue-biased promoters in human (top row) and mouse (bottom row) shown as the percentage of tissue-biased promoters which can be aligned to the opposite species but show no evidence for transcription at the aligned position. The number of sample types for each tissue (described in Fig. 1F) are shown in brackets.



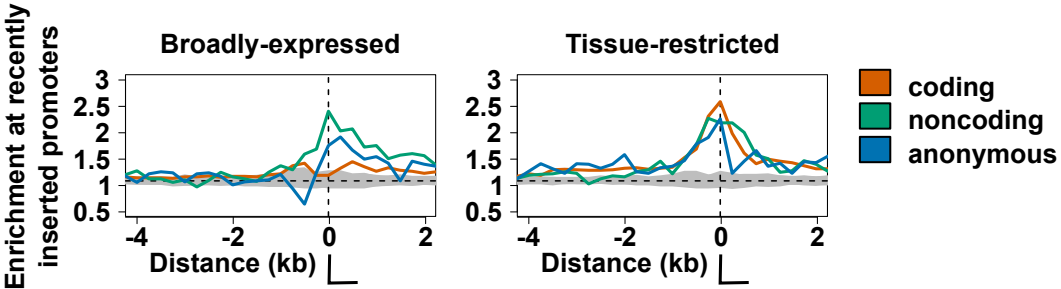
Supplementary Figure 5: Mean GERP conservation scores in 50 bp windows around mouse protein-coding promoters with different evolutionary outcomes. Grey lines indicate the GERP scores for genome permuted intervals. The standard error of the mean scores is shown in grey behind each line. The direction of transcription is shown by the black arrows. The sample sizes of promoters contributing to each line are detailed in Supp. Table 3.



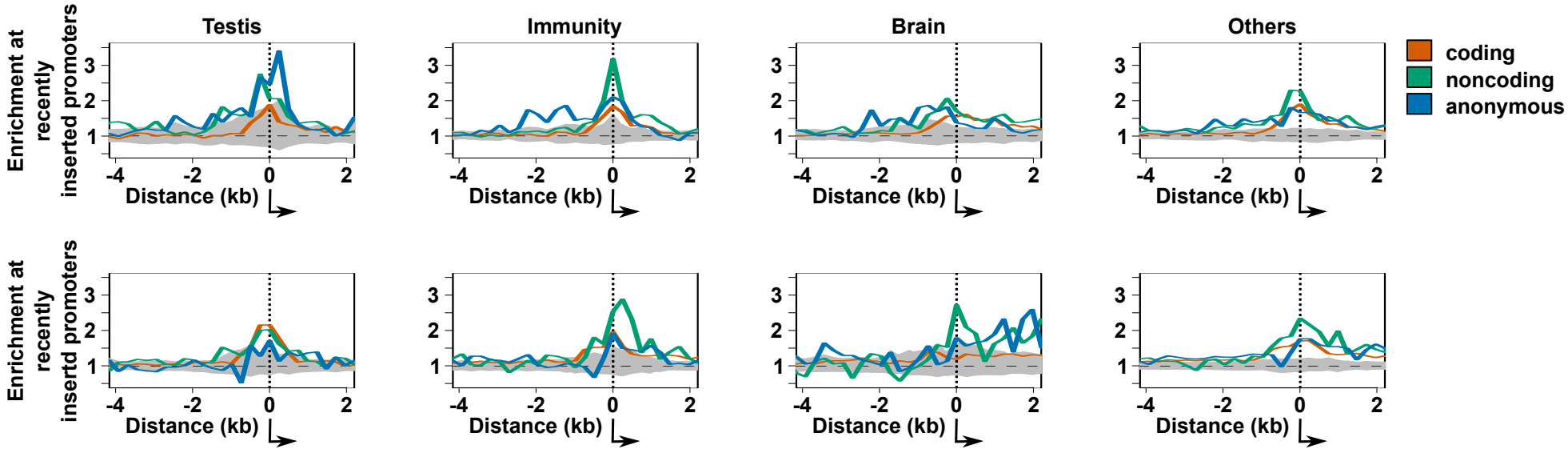
Supplementary Figure 6: Mean GERP conservation scores in 50 bp windows around human (top row) and mouse (bottom row) protein-coding promoters with different evolutionary outcomes. Grey lines indicate the GERP scores for genome permuted intervals. The standard error of the mean scores is shown in grey behind each line. The direction of transcription is shown by the black arrows. The sample sizes of promoters contributing to each line are detailed in Supp. Table 3.
Note, the human 'Testis' and 'Others' plots are also in Figure 2.



Supplementary Figure 7: Derived allele frequencies in promoters of different tissue biases and evolutionary outcomes. Odds ratios of derived allele frequencies for rare (< 1.5%) and non-rare (> 5%) derived allele compared between the genome wide distribution and the tested sequence category as labelled. Odds ratios of 1.0 indicate equality with the genome wide distribution, higher values indicate relative selective constraint and values < 1 are indicative of net positive selection. Odds ratio for SNPs at the 2nd codon position, fourfold-degenerate sites and within all protein-coding sequence are shown in grey as points of reference for comparison. The number of informative SNPs overlapping each category are shown in brackets next to the axis labels.

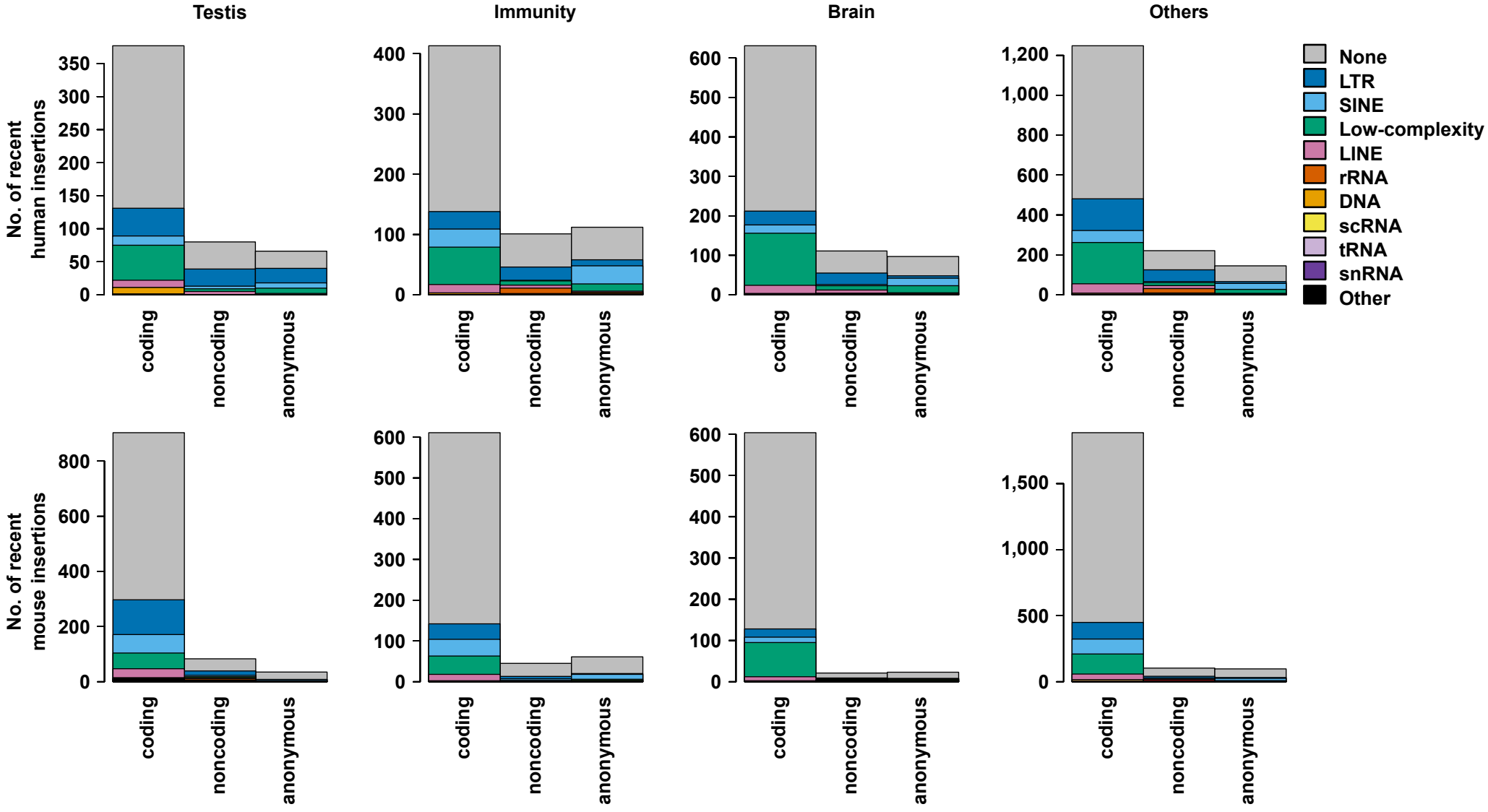


Supplementary Figure 8: Enrichment of repetitive elements across recently inserted mouse promoters relative to the genome-wide expectation for such insertions across promoter classes and expression profiles. The 95% confidence interval for genome permuted intervals is shown in grey and the direction of transcription is shown by the arrows. The number of promoters which contribute to each enrichment are shown in the corresponding histograms in Supp. Fig. 10.

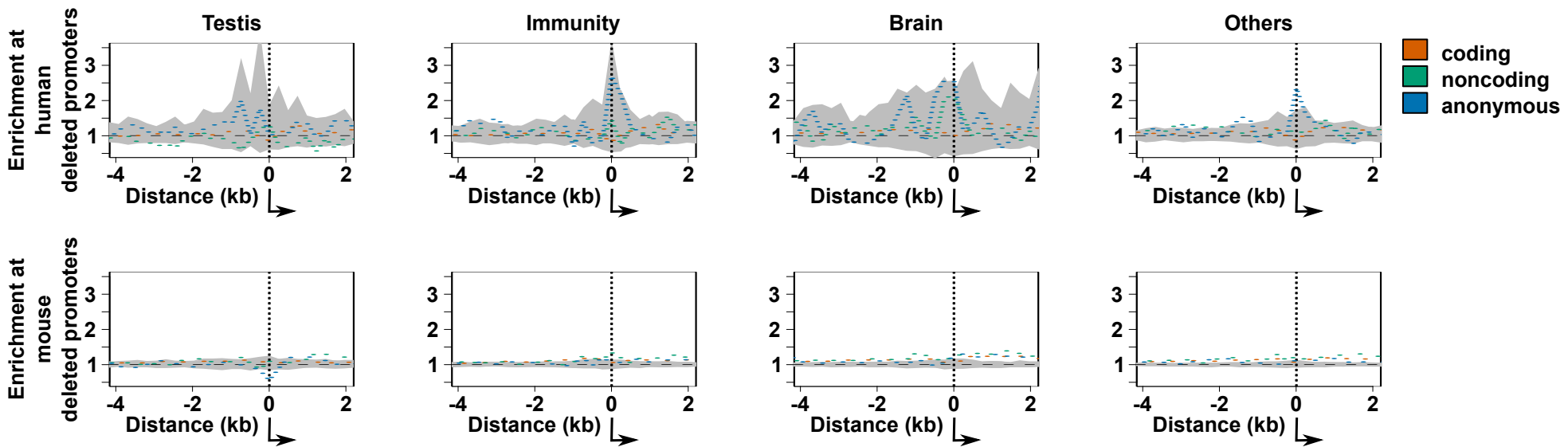


Supplementary Figure 9: Enrichment of repetitive elements across recently inserted human (top row) and mouse (bottom row) promoters relative to genome-wide expectation for such insertions across promoter classes and expression profiles. The 95% confidence interval for genome permuted intervals is shown in grey and the direction of transcription is shown by the arrows. The number of promoters which contribute to each enrichment are shown in the corresponding histograms in Supp. Fig. 11.
Note, human 'Testis' and 'Others' results are in the main text.

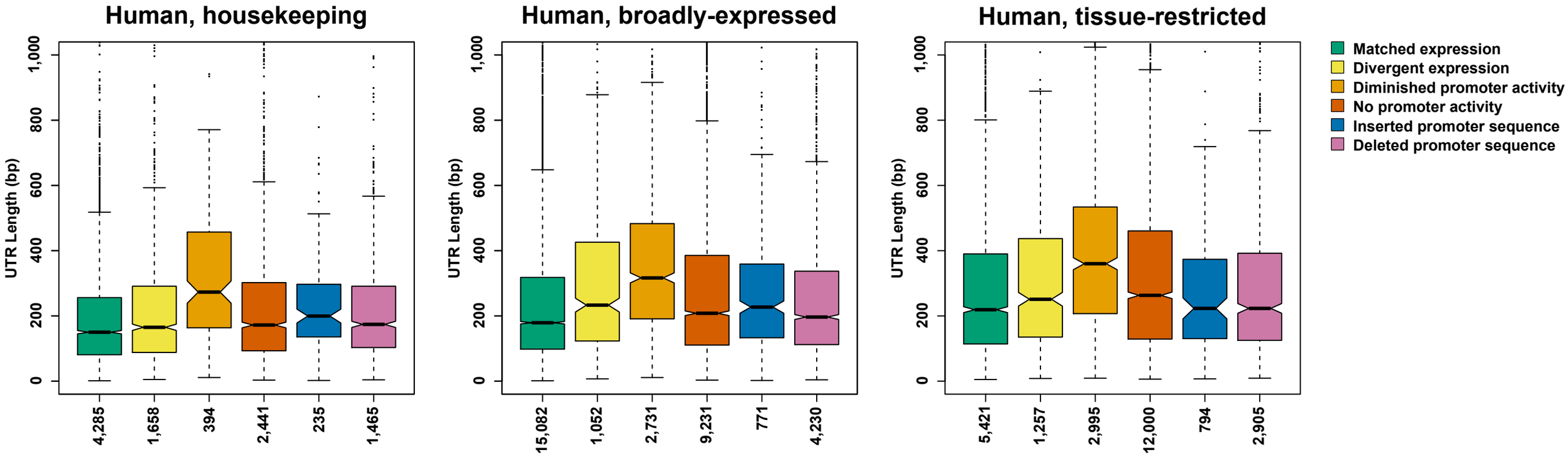
Supplementary Figure 10: Frequency of repetitive element families across recently inserted mouse promoters.



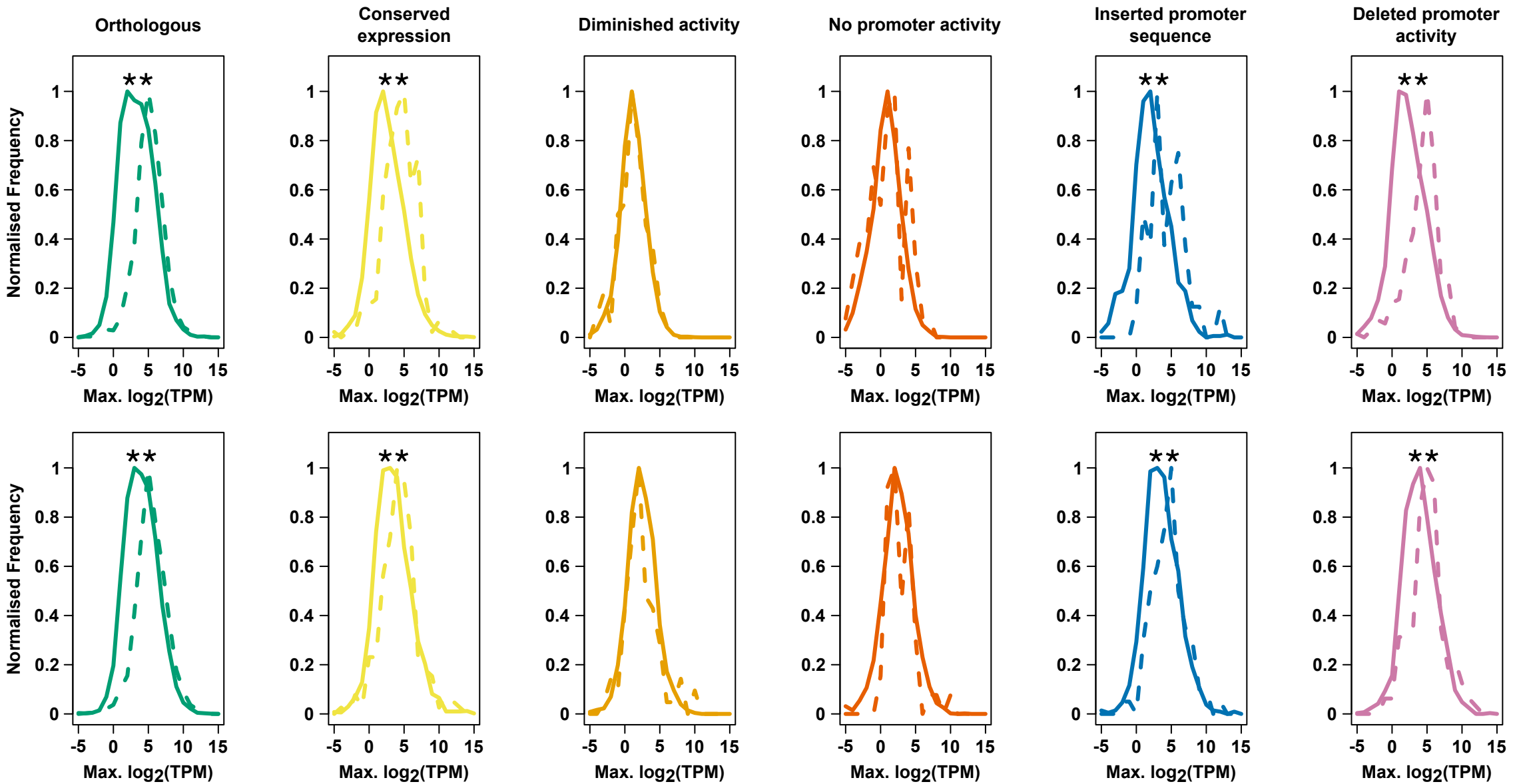
Supplementary Figure 11: Frequency of repetitive elements across recently inserted human (top row) and mouse (bottom row) promoters. Note, the human 'Testis' and 'Others' plots are in the main text.



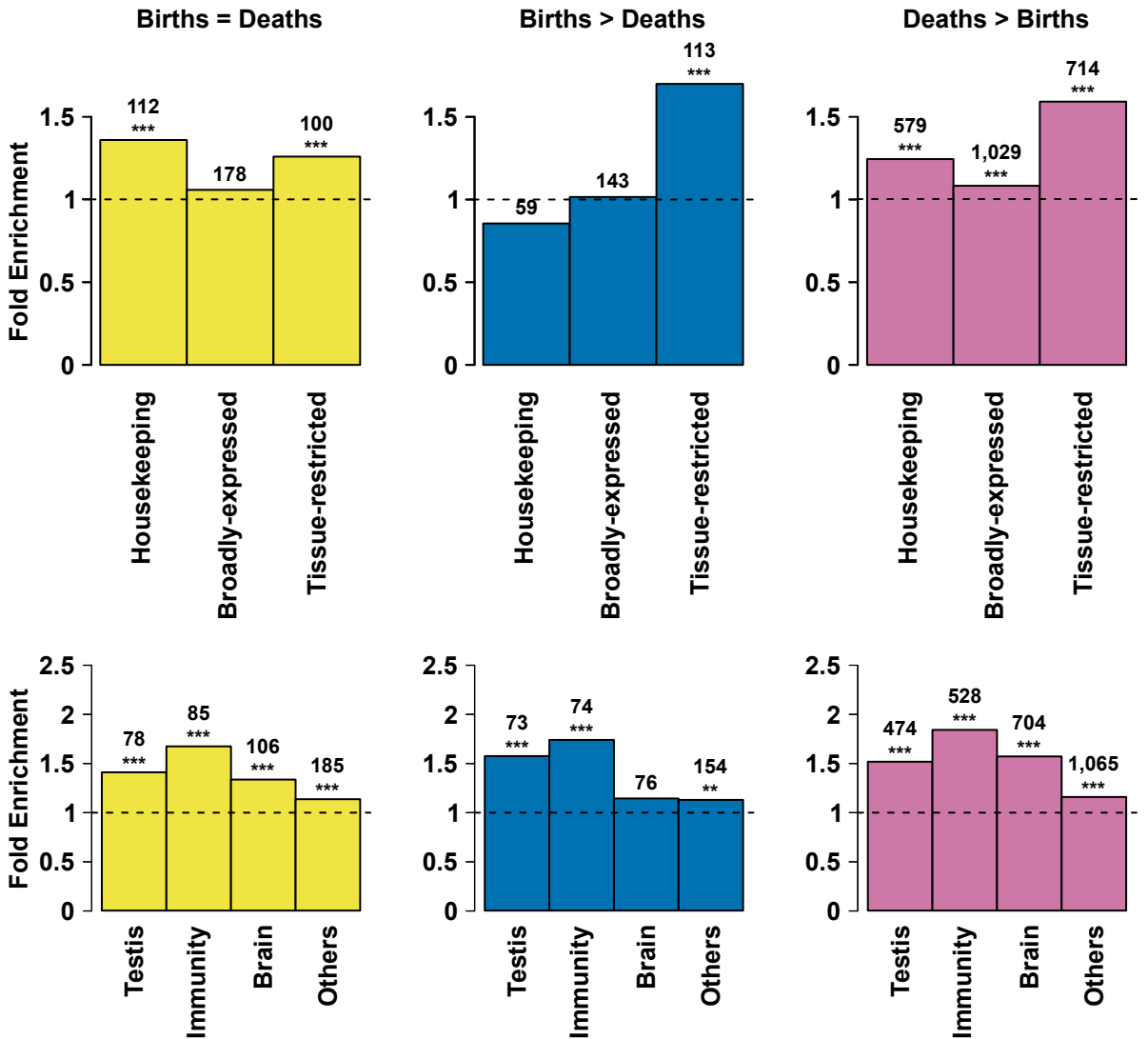
Supplementary Figure 12: Enrichment of repetitive elements across deleted human (top row) and mouse (bottom row) promoters relative to genome-wide expectation for such insertions across promoter classes and expression profiles. The 95% confidence interval for genome permuted intervals is shown in grey and the direction of transcription is shown by the arrows.



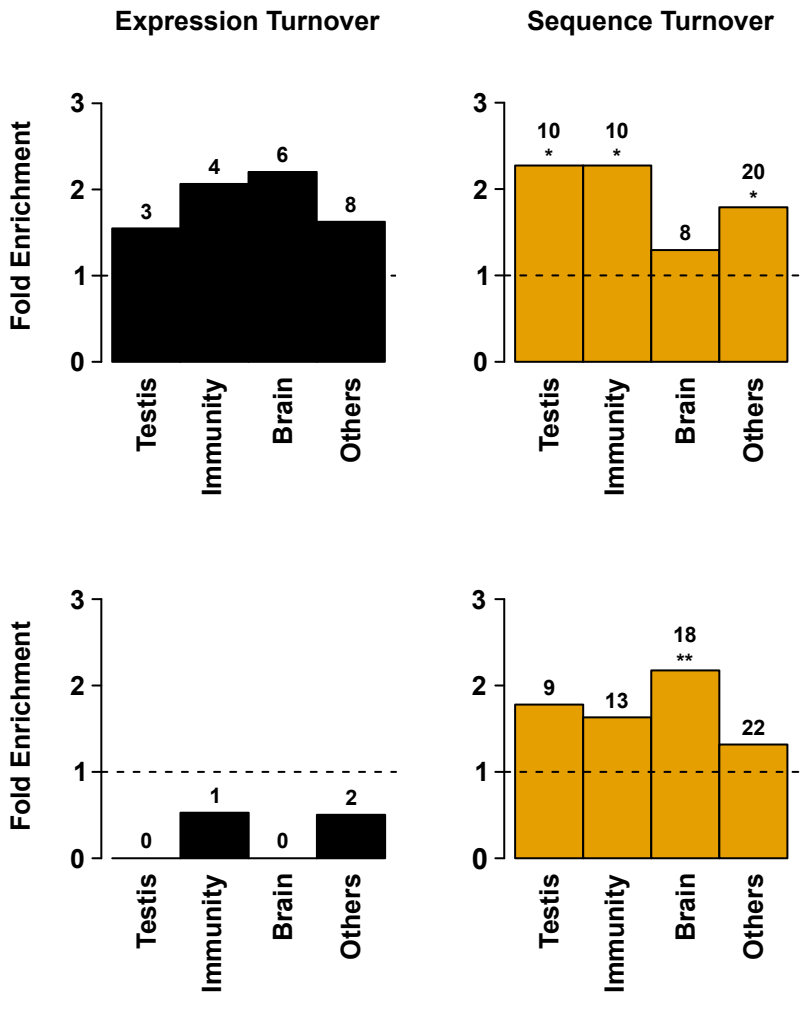
Supplementary Figure 13: UTR lengths for promoters of different expression profiles and expression outcomes in human (top row) and mouse (bottom row). The numbers below each bar represent the number of promoters in each category.



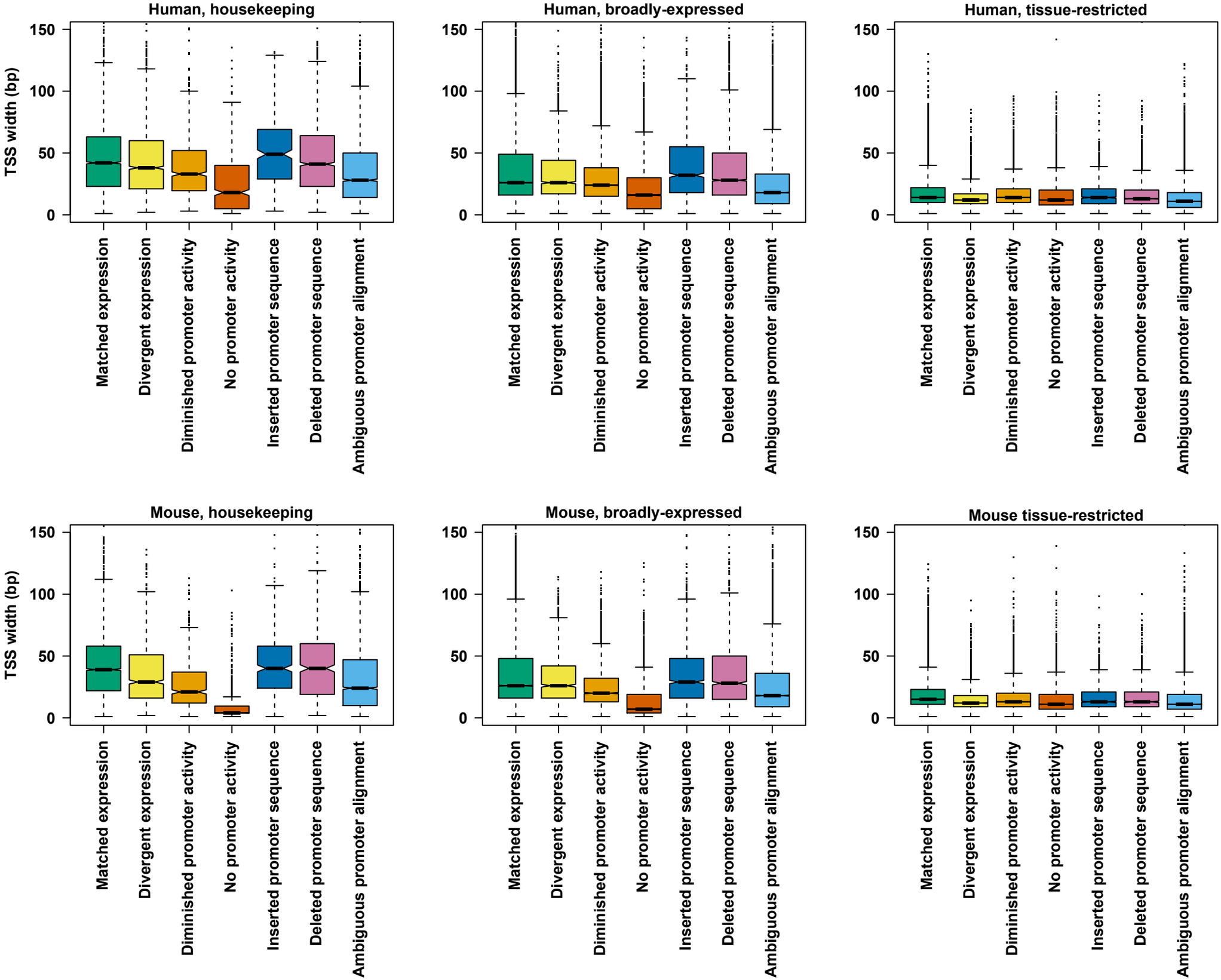
Supplementary Figure 14: Maximum expresion levels for promoters at genes with only one promoter (dashed line) or multiple promoters (solid line) in human (top row) and mouse (bottom row), split by their evolutionary outcome (Student's t-test, ** indicates $p < 0.01$).



Supplementary Figure 15: Enrichments and depletions of mouse orthologous genes with different turnover events and expression profiles relative to genes with a conserved promoter architecture (chi-squared test, ** indicates $p < 0.01$ and * indicates $p < 0.001$).**



Supplementary Figure 16: Enrichments and depletions of human (top row) and mouse (bottom row) orthologous genes with coding sequence positive selection when classified by promoter expression turnover, and biased promoter expression relative to genes with the same biased expression and a conserved promoter architecture (chi-squared test, * indicates $p < 0.05$ and ** indicates $p < 0.01$).



Supplementary Figure 17: TSS widths for human (top row) and mouse (bottom row) promoters of different expression profiles and evolutionary ouctomes as determined by CAGE tag cluster genomic span.

Supplementary Table 1: Description of CAGE libraries from 52 matched tissue and cell type samples.

Sample	Tissue	No. of human libraries	Total no. of human reads	Mean no. of human reads per library	No. of mouse libraries	Total no. of mouse reads	Mean no. of mouse reads per library
1. Macrophages	Others	3	46,639,368	15,546,456	2	9,889,780	4,944,890
2. Smooth muscle cells	Others	8	73,323,647	9,165,456	1	15,429,422	15,429,422
3. Astrocytes – cerebellum	Others	3	44,677,041	14,892,347	2	18,752,092	9,376,046
4. Astrocytes – hippocampus	Others	3	49,630,829	16,543,610	5	45,080,335	9,016,067
5. Cardiac myocytes	Others	3	31,040,877	10,346,959	3	34,370,048	11,456,683
6. CD19+ B cells	Immune	11	31,321,661	2,847,424	1	19,666,309	19,666,309
7. CD4+ T cells	Immune	3	64,853,572	21,617,857	1	7,950,052	7,950,052
8. CD8+ T cells	Immune	11	61,068,513	5,551,683	1	13,206,663	13,206,663
10. Tracheal epithelial cells	Others	3	44,495,261	14,831,754	3	33,521,735	11,173,912
11. Neurons	Brain	3	45,616,125	15,205,375	23	381,909,293	16,604,752
13. Mesenchymal stem cells	Others	3	29,911,725	9,970,575	3	40,730,304	13,576,768
14. Meningeal cells	Brain	3	61,439,084	20,479,695	2	12,588,081	6,294,041
15. Hepatocyte	Others	3	43,574,444	14,524,815	4	75,845,747	18,961,464
16. Hepatic stellate cells (lipocyte)	Others	2	12,748,122	6,374,061	1	8,034,548	8,034,548
17. Hepatic sinusoidal endothelial cells	Others	3	28,758,426	9,586,142	1	14,698,558	14,698,558
18. Granulocyte macrophage	Immune	3	14,306,445	4,768,815	3	10,824,161	3,608,054
19. Naïve conventional T cells	Immune	3	62,655,181	20,885,060	2	51,120,874	25,560,437
20. Regulatory T cells	Immune	3	6,767,976	2,255,992	1	32,842,390	32,842,390
22. Aorta, adult	Others	1	15,522,500	15,522,500	1	26,818,869	26,818,869
23. Cerebellum, adult	Brain	3	49,213,875	16,404,625	1	13,705,951	13,705,951
24. Colon, adult	Others	2	30,564,796	15,282,398	1	24,327,359	24,327,359
25. Diencephalon, adult	Brain	1	14,322,973	14,322,973	1	18,220,629	18,220,629
26. Epididymis, adult	Others	1	23,060,107	23,060,107	1	17,171,276	17,171,276
27. Eyeball, fetal	Others	1	12,893,052	12,893,052	4	77,726,825	19,431,706
28. Heart, fetal	Others	1	38,500,121	38,500,121	8	135,731,237	16,966,405
29. Hippocampus, adult	Brain	2	41,754,400	20,877,200	1	18,391,994	18,391,994

30. Kidney, adult	Others	1	35,257,500	35,257,500	1	24,314,299	24,314,299
31. Kidney, fetal	Others	1	37,272,614	37,272,614	5	79,599,593	15,919,919
32. Liver, adult	Others	1	33,987,955	33,987,955	1	21,909,352	21,909,352
33. Liver, fetal	Others	1	3,991,557	3,991,557	7	137,626,766	19,660,967
34. Lung, adult	Others	1	29,135,546	29,135,546	1	23,899,646	23,899,646
35. Lung, fetal	Others	1	26,713,019	26,713,019	6	104,243,748	17,373,958
36. Medulla oblongata, adult	Brain	3	80,112,408	26,704,136	1	25,631,785	25,631,785
37. Olfactory brain, adult	Brain	1	25,660,257	25,660,257	1	11,932,450	11,932,450
38. Ovary, adult	Others	1	28,941,480	28,941,480	1	22,083,329	22,083,329
39. Pancreas, adult	Others	1	14,419,361	14,419,361	1	20,323,168	20,323,168
40. Pituitary gland, adult	Others	2	25,791,611	12,895,806	1	14,688,460	14,688,460
41. Placenta, adult	Others	1	32,296,567	32,296,567	2	39,887,596	39,887,596
42. Prostate, adult	Others	1	26,745,658	26,745,658	1	19,826,260	19,826,260
44. Small intestine, adult	Others	1	33,551,529	33,551,529	1	15,209,132	15,209,132
45. Spinal cord, adult	Brain	2	35,888,205	17,944,103	1	22,013,688	22,013,688
46. Spleen, adult	Others	1	27,799,723	27,799,723	1	23,742,740	23,742,740
47. Spleen and stomach, fetal	Others	2	40,424,089	20,212,045	7	128,858,772	18,408,396
48. Submandibular gland, adult	Others	1	21,643,640	21,643,640	1	23,692,755	23,692,755
49. Testis, adult	Testis	2	54,573,885	27,286,943	1	22,371,259	22,371,259
50. Thymus, adult	Others	1	34,668,350	34,668,350	1	15,628,443	15,628,443
51. Thymus, fetal	Immune	1	31,479,670	31,479,670	5	96,954,665	19,390,933
52. Tongue, adult	Others	1	22,309,531	22,309,531	1	19,050,243	19,050,243
53. Bladder, adult	Others	1	30,568,213	30,568,213	1	17,695,462	17,695,462
54. Uterus, adult	Others	1	21,399,131	21,399,131	1	21,587,635	21,587,635
55. Vagina, adult	Others	1	8,483,079	8,483,079	1	18,789,307	18,789,307
56. Skeletal muscle, adult	Others	1	32,749,470	32,749,470	1	20,227,576	20,227,576

Supplementary Table 2: Number of promoters of each expression profile displaying each evolutionary outcome in human and mouse.

		Human							Mouse						
Counterpart	Description	Matched expression	Divergent expression	Diminished promoter activity	No promoter activity	Inserted promoter sequence	Deleted promoter sequence	Ambiguous promoter alignment	Matched expression	Divergent expression	Diminished promoter activity	No promoter activity	Inserted promoter sequence	Deleted promoter sequence	Ambiguous promoter alignment
Housekeeping	Housekeeping	5477	2172	594	262	317	1989	2760	4948	863	276	126	374	506	2468
Tissue-restricted	Tissue-restricted	7131	1947	4079	6250	1293	4714	5622	5713	1906	2011	2973	1451	1174	4351
Broadly-expressed	Broadly-expressed	21012	1401	3972	2532	1179	6535	8778	18200	662	1538	1004	1339	1644	7645
1	Macrophage (monocyte)	721	814	411	491	117	646	836	592	858	181	165	206	199	752
2	Smooth Muscle Cells - Aortic	463	943	531	432	76	461	693	323	1027	179	149	103	109	529
3	Astrocytes - cerebellum	707	887	453	333	61	462	608	649	1765	256	183	121	174	762
4	Astrocytes - hippocampus	595	1356	440	306	83	488	638	514	1216	199	139	72	114	538
5	Cardiac Myocyte	561	890	487	366	75	461	663	446	1201	224	159	117	130	594

6	CD19+ B Cells	730	822	491	499	169	855	893	697	732	218	167	223	185	792
7	CD4+ T Cells	1024	1047	762	620	231	1051	1100	931	857	266	218	229	222	894
8	CD8+ T Cells	879	756	532	517	181	902	860	819	829	274	229	249	214	881
10	Tracheal Epithelial Cells	567	1081	443	476	117	611	787	538	798	122	141	107	145	539
11	Neurons	1943	1001	586	358	127	663	1088	1959	2190	435	291	183	247	1379
13	Mesenchymal Stem Cells	251	1068	369	289	70	430	529	180	1357	185	131	152	142	661
14	Meningeal Cells	471	702	312	250	44	364	421	341	1190	182	106	79	111	487
15	Hepatocyte	1192	1081	618	522	160	812	1200	920	949	288	362	249	249	914
16	Hepatic Stellate Cells	206	1508	468	347	90	476	706	192	1724	259	330	261	269	883
17	Hepatic Sinusoidal Endothelial	302	733	291	244	42	333	484	302	2514	384	311	309	287	1213
18	granulocyte macrophage	309	514	189	147	66	334	390	298	945	174	124	172	158	570
19	naive conventional T cells	779	762	512	454	168	861	865	734	653	244	200	235	208	703
20	naive regulatory T cells	811	826	536	466	187	897	963	784	803	279	243	243	228	804
22	aorta, adult	1086	1882	815	603	151	806	1043	843	1484	251	328	203	216	884
23	cerebellum, adult	3079	1378	1159	723	258	1161	1653	2674	1178	396	327	180	238	1313
24	colon, adult	1275	1329	528	454	156	821	1075	1158	1105	265	283	220	277	988
25	diencephalon, adult	3409	1245	1107	824	189	1076	1574	3103	1483	499	388	206	305	1573
26	epididymis	1032	2332	908	735	181	923	1222	852	1148	308	313	216	261	989
27	eye, fetal	1831	2221	859	610	142	795	1252	1460	1348	235	167	124	184	863
28	heart, fetal	1286	1319	470	414	92	619	771	1055	1025	175	197	103	132	608
29	hippocampus, adult	3644	1385	1256	903	261	1185	1820	3241	1309	441	356	206	303	1549
30	kidney, adult	1195	993	463	475	138	684	851	1026	1132	269	378	225	227	887
31	kidney, fetal	1304	1364	499	424	130	641	846	1028	1071	181	216	139	161	714
32	liver, adult	1144	974	506	513	135	781	1032	871	922	282	353	226	246	868

33	liver, fetal	1060	1614	632	570	177	1001	1272	799	768	188	236	162	215	708
34	lung, adult	1542	1115	610	601	138	854	1065	1409	1629	284	296	253	300	1058
35	lung, fetal	1379	2054	698	599	139	843	1051	1077	1135	178	173	120	163	679
36	medulla oblongata, adult	2960	1489	1002	807	224	1100	1546	2701	1563	462	368	194	299	1466
37	olfactory brain, adult	3593	1632	1313	925	242	1201	1820	3013	1347	442	342	199	273	1427
38	ovary, adult	895	1107	488	405	122	481	673	749	1400	216	258	149	187	765
39	pancreas, adult	687	1220	496	386	128	649	893	585	1143	242	239	151	170	726
40	pituitary gland, adult	1686	1386	709	493	176	885	1135	1514	1355	316	264	172	204	961
41	placenta, adult	777	1320	508	583	215	707	882	621	1454	258	278	205	205	854
42	prostate, adult	677	1582	498	441	94	559	723	574	1010	173	202	130	145	605
44	small intestine, adult	1460	991	483	453	136	784	994	1218	1082	262	312	205	268	958
45	spinal cord, adult	2644	1452	987	827	228	1078	1534	2498	1921	452	393	203	314	1549
46	spleen, adult	818	949	425	516	118	748	868	746	1032	202	223	245	264	873
47	spleen, fetal	1102	1597	482	489	136	822	994	950	1464	190	209	147	215	805
48	submaxillary gland	989	1246	584	471	146	730	963	850	1044	226	264	193	200	801
49	testis, adult	2484	1797	1115	1030	410	1662	1940	2504	2010	877	1071	812	660	2457
50	thymus, adult	1025	938	437	440	135	814	900	902	943	249	275	243	268	836
51	thymus, fetal	962	1406	579	563	194	1045	1065	834	894	210	242	191	225	696
52	tongue	1696	1123	695	593	118	710	1134	1495	1166	303	310	138	191	944
53	bladder, adult	1091	976	502	368	83	496	724	943	1441	217	239	144	191	757
54	uterus, adult	968	1395	594	450	119	558	705	859	1286	201	258	180	200	799
55	vagina	666	1588	615	416	146	643	896	709	1473	224	229	127	178	775
56	skeletal muscle, adult	1316	707	476	384	78	489	758	1004	1368	238	327	126	172	855

Supplementary Table 3: Sample sizes for GERP plots across various figures.

Figure	Species	Expression Profile	Evolutionary outcome	Sample size
Figure 2b	Human	Broadly-expressed	Diminished promoter activity	3372
Figure 2b	Human	Broadly-expressed	Divergent expression	1279
Figure 2b	Human	Broadly-expressed	Matched expression	20,205
Figure 2b	Human	Broadly-expressed	No promoter activity	2,054
Figure 2b	Human	Housekeeping	Diminished promoter activity	529
Figure 2b	Human	Housekeeping	Divergent expression	2,110
Figure 2b	Human	Housekeeping	Matched expression	5,383
Figure 2b	Human	Housekeeping	No promoter activity	226
Figure 2b	Human	Tissue-restricted	Diminished promoter activity	3,307
Figure 2b	Human	Tissue-restricted	Divergent expression	1,770
Figure 2b	Human	Tissue-restricted	Matched expression	6,592
Figure 2b	Human	Tissue-restricted	No promoter activity	4,628
Supplementary Figure 5	Mouse	Broadly-expressed	Diminished promoter activity	1,332
Supplementary Figure 5	Mouse	Broadly-expressed	Divergent expression	618
Supplementary Figure 5	Mouse	Broadly-expressed	Matched expression	17,738
Supplementary Figure 5	Mouse	Broadly-expressed	No promoter activity	819
Supplementary Figure 5	Mouse	Housekeeping	Diminished promoter activity	239
Supplementary Figure 5	Mouse	Housekeeping	Divergent expression	835
Supplementary Figure 5	Mouse	Housekeeping	Matched expression	4,885
Supplementary Figure 5	Mouse	Housekeeping	No promoter activity	93
Supplementary Figure 5	Mouse	Tissue-restricted	Diminished promoter activity	1,690

Supplementary Figure 5	Mouse	Tissue-restricted	Divergent expression	1,805
Supplementary Figure 5	Mouse	Tissue-restricted	Matched expression	5,395
Supplementary Figure 5	Mouse	Tissue-restricted	No promoter activity	2,502
Figure 2c/Supplementary Figure 6	Human	Others	Diminished promoter activity	3,998
Figure 2c/Supplementary Figure 6	Human	Others	Divergent expression	13,844
Figure 2c/Supplementary Figure 6	Human	Others	Matched expression	11,525
Figure 2c/Supplementary Figure 6	Human	Others	No promoter activity	3,560
Figure 2c/Supplementary Figure 6	Human	Testis	Diminished promoter activity	931
Figure 2c/Supplementary Figure 6	Human	Testis	Divergent expression	1,696
Figure 2c/Supplementary Figure 6	Human	Testis	Matched expression	2,377
Figure 2c/Supplementary Figure 6	Human	Testis	No promoter activity	803
Supplementary Figure 6	Human	Brain	Diminished promoter activity	2,445
Supplementary Figure 6	Human	Brain	Divergent expression	5,010
Supplementary Figure 6	Human	Brain	Matched expression	6,216
Supplementary Figure 6	Human	Brain	No promoter activity	1,718
Supplementary Figure 6	Human	Immunity	Diminished promoter activity	1,118
Supplementary Figure 6	Human	Immunity	Divergent expression	3,115
Supplementary Figure 6	Human	Immunity	Matched expression	2,002
Supplementary Figure 6	Human	Immunity	No promoter activity	959
Supplementary Figure 6	Mouse	Brain	Diminished promoter activity	924
Supplementary Figure 6	Mouse	Brain	Divergent expression	5,601
Supplementary Figure 6	Mouse	Brain	Matched expression	5,297
Supplementary Figure 6	Mouse	Brain	No promoter activity	672
Supplementary Figure 6	Mouse	Immunity	Diminished promoter activity	509
Supplementary Figure 6	Mouse	Immunity	Divergent expression	3,000
Supplementary Figure 6	Mouse	Immunity	Matched expression	1,826

Supplementary Figure 6	Mouse	Immunity	No promoter activity	507
Supplementary Figure 6	Mouse	Others	Diminished promoter activity	1,783
Supplementary Figure 6	Mouse	Others	Divergent expression	12,970
Supplementary Figure 6	Mouse	Others	Matched expression	9,715
Supplementary Figure 6	Mouse	Others	No promoter activity	1,929
Supplementary Figure 6	Mouse	Testis	Diminished promoter activity	768
Supplementary Figure 6	Mouse	Testis	Divergent expression	1,926
Supplementary Figure 6	Mouse	Testis	Matched expression	2,423
Supplementary Figure 6	Mouse	Testis	No promoter activity	918

Supplementary Table 4: Enrichment and depletion of RepeatMasker annotation overlaps at promoters of different types, expression profiles and evolutionary outcomes relative to their evolutionarily conserved counterparts.

Species	Expression Profile	Promoter Type	Evolutionary Outcome	Percentage overlapped by RepeatMasker annotation	Enrichment relative to matched promoters	p-value
human	all	all	aligned	9.09	1.18	0.000026401
human	all	anonymous	aligned	6.66	0.82	0.42742
human	all	coding	aligned	8.26	1.06	0.1657
human	all	noncoding	aligned	15.78	2.71	2.4883E-13
human	broadly-expressed	all	aligned	7.66	0.82	0.0044916
human	broadly-expressed	anonymous	aligned	9.32	0.82	0.53742
human	broadly-expressed	coding	aligned	7.4	0.78	0.0024403
human	broadly-expressed	noncoding	aligned	8.33	1.19	0.51906
human	housekeeping	all	aligned	9.54	1.08	0.69496
human	housekeeping	anonymous	aligned	7.14	NA	NA
human	housekeeping	coding	aligned	9.29	1.05	0.80057
human	housekeeping	noncoding	aligned	14.29	1.49	0.56309
human	tissue-restricted	all	aligned	9.66	2.47	9.0204E-41
human	tissue-restricted	anonymous	aligned	5.76	0.86	0.74925
human	tissue-restricted	coding	aligned	8.64	2.28	2.5699E-27
human	tissue-restricted	noncoding	aligned	17.71	4.22	3.89E-10
mouse	all	all	aligned	5.36	1.02	0.76328
mouse	all	anonymous	aligned	4.11	0.92	0.83528

mouse	all	coding	aligned	5.45	1.03	0.65701
mouse	all	noncoding	aligned	5.88	1.41	0.27632
mouse	broadly-expressed	all	aligned	6.27	1.03	0.83181
mouse	broadly-expressed	anonymous	aligned	4.88	0.69	0.50726
mouse	broadly-expressed	coding	aligned	6.23	1.02	0.89232
mouse	broadly-expressed	noncoding	aligned	9.84	1.76	0.22326
mouse	housekeeping	all	aligned	7.14	1.2	0.58127
mouse	housekeeping	anonymous	aligned	3.7	NA	NA
mouse	housekeeping	coding	aligned	6.45	1.09	0.82173
mouse	housekeeping	noncoding	aligned	33.33	2.5	0.20574
mouse	tissue-restricted	all	aligned	5.05	1.78	1.5127E-07
mouse	tissue-restricted	anonymous	aligned	3.72	2.42	0.37926
mouse	tissue-restricted	coding	aligned	5.2	1.82	2.0063E-07
mouse	tissue-restricted	noncoding	aligned	4.82	1.91	0.21315
human	all	all	matched	7.71	NA	NA
human	all	anonymous	matched	8.08	NA	NA
human	all	coding	matched	7.76	NA	NA
human	all	noncoding	matched	5.82	NA	NA
human	broadly-expressed	all	matched	9.39	NA	NA
human	broadly-expressed	anonymous	matched	11.38	NA	NA
human	broadly-expressed	coding	matched	9.43	NA	NA
human	broadly-expressed	noncoding	matched	6.99	NA	NA
human	housekeeping	all	matched	8.84	NA	NA
human	housekeeping	anonymous	matched	0	NA	NA
human	housekeeping	coding	matched	8.81	NA	NA
human	housekeeping	noncoding	matched	9.62	NA	NA

human	tissue-restricted	all	matched	3.91	NA	NA
human	tissue-restricted	anonymous	matched	6.67	NA	NA
human	tissue-restricted	coding	matched	3.79	NA	NA
human	tissue-restricted	noncoding	matched	4.2	NA	NA
mouse	all	all	matched	5.24	NA	NA
mouse	all	anonymous	matched	4.48	NA	NA
mouse	all	coding	matched	5.27	NA	NA
mouse	all	noncoding	matched	4.17	NA	NA
mouse	broadly-expressed	all	matched	6.11	NA	NA
mouse	broadly-expressed	anonymous	matched	7.06	NA	NA
mouse	broadly-expressed	coding	matched	6.11	NA	NA
mouse	broadly-expressed	noncoding	matched	5.58	NA	NA
mouse	housekeeping	all	matched	5.96	NA	NA
mouse	housekeeping	anonymous	matched	0	NA	NA
mouse	housekeeping	coding	matched	5.9	NA	NA
mouse	housekeeping	noncoding	matched	13.33	NA	NA
mouse	tissue-restricted	all	matched	2.84	NA	NA
mouse	tissue-restricted	anonymous	matched	1.54	NA	NA
mouse	tissue-restricted	coding	matched	2.85	NA	NA
mouse	tissue-restricted	noncoding	matched	2.53	NA	NA
human	all	all	permissive	5.54	0.72	2.1657E-11
human	all	anonymous	permissive	8.06	1	0.99501
human	all	coding	permissive	5.39	0.69	1.9404E-11
human	all	noncoding	permissive	4.52	0.78	0.24026
human	broadly-expressed	all	permissive	6.9	0.73	4.8141E-07
human	broadly-expressed	anonymous	permissive	10.07	0.88	0.69277

human	broadly-expressed	coding	permissive	6.91	0.73	0.000002324
human	broadly-expressed	noncoding	permissive	4.08	0.58	0.085577
human	housekeeping	all	permissive	9.6	1.09	0.53743
human	housekeeping	anonymous	permissive	13.79	NA	NA
human	housekeeping	coding	permissive	9.64	1.09	0.51926
human	housekeeping	noncoding	permissive	5.56	0.58	0.48893
human	tissue-restricted	all	permissive	4.22	1.08	0.43033
human	tissue-restricted	anonymous	permissive	6.68	1	0.99581
human	tissue-restricted	coding	permissive	3.84	1.01	0.90658
human	tissue-restricted	noncoding	permissive	4.9	1.17	0.65027
mouse	all	all	permissive	4.23	0.81	0.010002
mouse	all	anonymous	permissive	3.77	0.84	0.6843
mouse	all	coding	permissive	4.17	0.79	0.0098487
mouse	all	noncoding	permissive	6.11	1.47	0.28896
mouse	broadly-expressed	all	permissive	6.31	1.03	0.75703
mouse	broadly-expressed	anonymous	permissive	5.97	0.85	0.74825
mouse	broadly-expressed	coding	permissive	6.46	1.06	0.61254
mouse	broadly-expressed	noncoding	permissive	4.23	0.76	0.65279
mouse	housekeeping	all	permissive	5.8	0.97	0.91028
mouse	housekeeping	anonymous	permissive	5.26	NA	NA
mouse	housekeeping	coding	permissive	5.86	0.99	0.98064
mouse	housekeeping	noncoding	permissive	5.88	0.44	0.40823
mouse	tissue-restricted	all	permissive	2.64	0.93	0.63892
mouse	tissue-restricted	anonymous	permissive	2.37	1.54	0.68784
mouse	tissue-restricted	coding	permissive	2.37	0.83	0.28376
mouse	tissue-restricted	noncoding	permissive	7.34	2.9	0.045023

human	all	all	species-lost	10.4	1.35	1.1188E-18
human	all	anonymous	species-lost	12.11	1.5	0.074764
human	all	coding	species-lost	9.51	1.23	5.6448E-08
human	all	noncoding	species-lost	17.39	2.99	5.371E-16
human	broadly-expressed	all	species-lost	9.76	1.04	0.3687
human	broadly-expressed	anonymous	species-lost	15.96	1.4	0.22498
human	broadly-expressed	coding	species-lost	9.33	0.99	0.8042
human	broadly-expressed	noncoding	species-lost	11.55	1.65	0.020947
human	housekeeping	all	species-lost	10.31	1.17	0.052412
human	housekeeping	anonymous	species-lost	10	NA	NA
human	housekeeping	coding	species-lost	10.34	1.17	0.046641
human	housekeeping	noncoding	species-lost	9.46	0.98	0.97658
human	tissue-restricted	all	species-lost	11.29	2.89	1.5243E-54
human	tissue-restricted	anonymous	species-lost	9.35	1.4	0.45333
human	tissue-restricted	coding	species-lost	9.81	2.59	6.5077E-35
human	tissue-restricted	noncoding	species-lost	20.8	4.95	1.4997E-12
mouse	all	all	species-lost	5.57	1.06	0.4564
mouse	all	anonymous	species-lost	10.43	2.33	0.040801
mouse	all	coding	species-lost	5.26	1	0.98299
mouse	all	noncoding	species-lost	7.41	1.78	0.11959
mouse	broadly-expressed	all	species-lost	6.63	1.09	0.4005
mouse	broadly-expressed	anonymous	species-lost	12.07	1.71	0.30617
mouse	broadly-expressed	coding	species-lost	6.26	1.02	0.81219
mouse	broadly-expressed	noncoding	species-lost	13.51	2.42	0.069462
mouse	housekeeping	all	species-lost	8.5	1.43	0.024221
mouse	housekeeping	anonymous	species-lost	12.5	NA	NA

mouse	housekeeping	coding	species-lost	8.07	1.37	0.056138
mouse	housekeeping	noncoding	species-lost	28.57	2.14	0.29858
mouse	tissue-restricted	all	species-lost	4.09	1.44	0.022959
mouse	tissue-restricted	anonymous	species-lost	8.77	5.69	0.065273
mouse	tissue-restricted	coding	species-lost	3.73	1.31	0.13292
mouse	tissue-restricted	noncoding	species-lost	5.1	2.02	0.24819
human	all	all	species-inserted	37.54	4.87	0
human	all	anonymous	species-inserted	44.05	5.45	1.3739E-20
human	all	coding	species-inserted	31.29	4.03	0
human	all	noncoding	species-inserted	58.63	10.07	0
human	broadly-expressed	all	species-inserted	23.66	2.52	3.4133E-56
human	broadly-expressed	anonymous	species-inserted	38.24	3.36	2.2968E-06
human	broadly-expressed	coding	species-inserted	18.47	1.96	1.737E-19
human	broadly-expressed	noncoding	species-inserted	46.62	6.67	7.7285E-30
human	housekeeping	all	species-inserted	12.3	1.39	0.03629
human	housekeeping	anonymous	species-inserted	25	NA	NA
human	housekeeping	coding	species-inserted	11.9	1.35	0.070099
human	housekeeping	noncoding	species-inserted	13.33	1.39	0.67834
human	tissue-restricted	all	species-inserted	50.19	12.84	0
human	tissue-restricted	anonymous	species-inserted	48	7.2	7.2673E-10
human	tissue-restricted	coding	species-inserted	45.47	12	0
human	tissue-restricted	noncoding	species-inserted	64.47	15.35	1.2101E-61
mouse	all	all	species-inserted	19.46	3.71	0
mouse	all	anonymous	species-inserted	28.46	6.35	9.717E-10
mouse	all	coding	species-inserted	17.57	3.33	0
mouse	all	noncoding	species-inserted	38.92	9.33	2.6924E-32

mouse	broadly-expressed	all	species-inserted	12.17	1.99	4.3066E-18
mouse	broadly-expressed	anonymous	species-inserted	25.76	3.65	0.0015147
mouse	broadly-expressed	coding	species-inserted	9.85	1.61	2.5012E-07
mouse	broadly-expressed	noncoding	species-inserted	41.54	7.44	1.4751E-14
mouse	housekeeping	all	species-inserted	7.22	1.21	0.32545
mouse	housekeeping	anonymous	species-inserted	27.27	NA	NA
mouse	housekeeping	coding	species-inserted	6.57	1.11	0.60538
mouse	housekeeping	noncoding	species-inserted	7.69	0.58	0.58236
mouse	tissue-restricted	all	species-inserted	26.19	9.22	0
mouse	tissue-restricted	anonymous	species-inserted	31.58	20.51	4.9837E-06
mouse	tissue-restricted	coding	species-inserted	24.9	8.74	0
mouse	tissue-restricted	noncoding	species-inserted	37.5	14.82	9.983E-17
human	all	all	unaligned	6.8	0.88	0.00054767
human	all	anonymous	unaligned	9.76	1.21	0.42626
human	all	coding	unaligned	6.65	0.86	0.00007002
human	all	noncoding	unaligned	6.54	1.12	0.49831
human	broadly-expressed	all	unaligned	7.85	0.84	0.000021392
human	broadly-expressed	anonymous	unaligned	12.19	1.07	0.81874
human	broadly-expressed	coding	unaligned	7.71	0.82	4.5505E-06
human	broadly-expressed	noncoding	unaligned	7.64	1.09	0.70861
human	housekeeping	all	unaligned	8.84	1	0.99563
human	housekeeping	anonymous	unaligned	10.81	NA	NA
human	housekeeping	coding	unaligned	8.83	1	0.97072
human	housekeeping	noncoding	unaligned	8.22	0.85	0.78593
human	tissue-restricted	all	unaligned	5.16	1.32	0.00071645
human	tissue-restricted	anonymous	unaligned	8.13	1.22	0.66464

human	tissue-restricted	coding	unaligned	4.78	1.26	0.010878
human	tissue-restricted	noncoding	unaligned	5.8	1.38	0.27741
mouse	all	all	unaligned	5.3	1.01	0.80621
mouse	all	anonymous	unaligned	5.63	1.26	0.54512
mouse	all	coding	unaligned	5.29	1	0.92112
mouse	all	noncoding	unaligned	5.23	1.25	0.44062
mouse	broadly-expressed	all	unaligned	6.75	1.1	0.053393
mouse	broadly-expressed	anonymous	unaligned	7.66	1.08	0.86007
mouse	broadly-expressed	coding	unaligned	6.78	1.11	0.048795
mouse	broadly-expressed	noncoding	unaligned	4.66	0.84	0.66647
mouse	housekeeping	all	unaligned	6.65	1.12	0.25002
mouse	housekeeping	anonymous	unaligned	2.08	NA	NA
mouse	housekeeping	coding	unaligned	6.74	1.14	0.15768
mouse	housekeeping	noncoding	unaligned	6.06	0.45	0.29558
mouse	tissue-restricted	all	unaligned	2.76	0.97	0.81511
mouse	tissue-restricted	anonymous	unaligned	3.69	2.4	0.38741
mouse	tissue-restricted	coding	unaligned	2.52	0.88	0.3297
mouse	tissue-restricted	noncoding	unaligned	5.67	2.24	0.10318

Supplementary Table 5: GO term analysis

GO analyses were performed using GORILLA (http://cbl-gorilla.cs.technion.ac.il/)

GO annotation was based on http://www.geneontology.org/ human and mouse gene annotation, updated on December 13th 2014.

P-value reported is the raw (uncorrected) enrichment p-value calculated by GORILLA
FDR q-value is the Benjamini and Hochberg multiple testing correction.

Enrichment (N, B, n, b) is defined as:
N – number of genes in background set (background set contains target set)
B – number of genes in background set associated with GO term
n – number of genes in target set
b – number of genes in target set associated with GO term

Only GO term enrichments with a raw p-value < 0.001 are reported and only those with an FDR of < 1% are considered in the manuscript main text.

Evolutionary Outcome	GO Term	Description	P-value	FDR q-value	Enrichment	N	B	n	b
Expression Turnover	GO:0065008	regulation of biological quality	2.08E-07	0.00257	1.09	12771	2010	7261	1246
Expression Turnover	GO:0048519	negative regulation of biological process	0.00000266	0.0165	1.06	12771	3119	7261	1883
Expression Turnover	GO:0050878	regulation of body fluid levels	0.00000269	0.0111	1.18	12771	444	7261	299
Expression	GO:0007599	hemostasis	0.00000321	0.00993	1.2	12771	361	7261	247

Turnover									
Expression Turnover	GO:0050817	coagulation	0.00000343	0.00848	1.2	12771	358	7261	245
Expression Turnover	GO:0007596	blood coagulation	0.00000343	0.00707	1.2	12771	358	7261	245
Expression Turnover	GO:0009605	response to external stimulus	0.00000345	0.0061	1.12	12771	963	7261	614
Expression Turnover	GO:0034330	cell junction organization	0.00000489	0.00756	1.3	12771	158	7261	117
Expression Turnover	GO:0030100	regulation of endocytosis	0.00000789	0.0108	1.33	12771	127	7261	96
Expression Turnover	GO:0030155	regulation of cell adhesion	0.00000932	0.0115	1.22	12771	286	7261	198
Expression Turnover	GO:0010646	regulation of cell communication	0.00000943	0.0106	1.08	12771	2037	7261	1246
Expression Turnover	GO:0034329	cell junction assembly	0.0000135	0.0139	1.31	12771	134	7261	100
Expression Turnover	GO:0042221	response to chemical	0.0000219	0.0208	1.07	12771	2124	7261	1293
Expression Turnover	GO:0051128	regulation of cellular component organization	0.0000237	0.021	1.09	12771	1408	7261	872
Expression Turnover	GO:0001775	cell activation	0.0000319	0.0263	1.17	12771	409	7261	272
Expression Turnover	GO:0023051	regulation of signaling	0.0000402	0.0311	1.07	12771	2023	7261	1231
Expression Turnover	GO:0048523	negative regulation of	0.0000477	0.0347	1.06	12771	2880	7261	1729

		cellular process							
Expression Turnover	GO:0051056	regulation of small GTPase mediated signal transduction	0.0000484	0.0333	1.24	12771	205	7261	144
Expression Turnover	GO:0090287	regulation of cellular response to growth factor stimulus	0.0000558	0.0363	1.28	12771	146	7261	106
Expression Turnover	GO:0050900	leukocyte migration	0.0000571	0.0353	1.26	12771	160	7261	115
Expression Turnover	GO:0045765	regulation of angiogenesis	0.0000582	0.0343	1.28	12771	143	7261	104
Expression Turnover	GO:0050896	response to stimulus	0.0000848	0.0476	1.04	12771	4808	7261	2836
Expression Turnover	GO:0071495	cellular response to endogenous stimulus	0.0000868	0.0466	1.12	12771	735	7261	467
Expression Turnover	GO:1901342	regulation of vasculature development	0.0000932	0.048	1.26	12771	158	7261	113
Expression Turnover	GO:0044763	single-organism cellular process	0.0000932	0.0461	1.03	12771	7075	7261	4127
Expression Turnover	GO:0032879	regulation of localization	0.000122	0.058	1.08	12771	1515	7261	928
Expression Turnover	GO:0002376	immune system process	0.000127	0.0581	1.09	12771	1110	7261	689
Expression Turnover	GO:0065009	regulation of molecular	0.000145	0.0642	1.07	12771	1969	7261	1193

		function							
Expression Turnover	GO:0071417	cellular response to organonitrogen compound	0.000151	0.0645	1.17	12771	353	7261	234
Expression Turnover	GO:0008360	regulation of cell shape	0.000152	0.0627	1.31	12771	105	7261	78
Expression Turnover	GO:0016477	cell migration	0.000157	0.0625	1.13	12771	542	7261	349
Expression Turnover	GO:0045216	cell-cell junction organization	0.000169	0.0651	1.27	12771	136	7261	98
Expression Turnover	GO:0050906	detection of stimulus involved in sensory perception	0.00017	0.0635	1.43	12771	53	7261	43
Expression Turnover	GO:1903729	regulation of plasma membrane organization	0.00017	0.0617	1.43	12771	53	7261	43
Expression Turnover	GO:0045766	positive regulation of angiogenesis	0.00017	0.0601	1.35	12771	81	7261	62
Expression Turnover	GO:1902531	regulation of intracellular signal transduction	0.000175	0.06	1.09	12771	1048	7261	651
Expression Turnover	GO:0040012	regulation of locomotion	0.000189	0.063	1.14	12771	490	7261	317
Expression Turnover	GO:0010033	response to organic	0.000192	0.0625	1.07	12771	1749	7261	1063

		substance							
Expression Turnover	GO:0007162	negative regulation of cell adhesion	0.000207	0.0656	1.31	12771	101	7261	75
Expression Turnover	GO:0060759	regulation of response to cytokine stimulus	0.000216	0.0667	1.38	12771	65	7261	51
Expression Turnover	GO:0048870	cell motility	0.000217	0.0654	1.12	12771	595	7261	380
Expression Turnover	GO:0009966	regulation of signal transduction	0.000229	0.0673	1.07	12771	1783	7261	1082
Expression Turnover	GO:0070887	cellular response to chemical stimulus	0.000261	0.075	1.07	12771	1487	7261	908
Expression Turnover	GO:0048583	regulation of response to stimulus	0.000303	0.0852	1.06	12771	2254	7261	1355
Expression Turnover	GO:0048518	positive regulation of biological process	0.000307	0.0843	1.04	12771	3733	7261	2210
Expression Turnover	GO:0033124	regulation of GTP catabolic process	0.000317	0.0851	1.14	12771	433	7261	281
Expression Turnover	GO:0030168	platelet activation	0.00032	0.0841	1.23	12771	161	7261	113
Expression Turnover	GO:0002682	regulation of immune system process	0.00036	0.0927	1.1	12771	790	7261	495
Expression	GO:0009719	response to	0.000364	0.0919	1.09	12771	1026	7261	635

Turnover		endogenous stimulus							
Expression Turnover	GO:0043087	regulation of GTPase activity	0.000366	0.0905	1.14	12771	432	7261	280
Expression Turnover	GO:1903078	positive regulation of protein localization to plasma membrane	0.000372	0.0902	1.61	12771	23	7261	21
Expression Turnover	GO:0006952	defense response	0.000377	0.0895	1.1	12771	750	7261	471
Expression Turnover	GO:1901699	cellular response to nitrogen compound	0.000381	0.089	1.15	12771	373	7261	244
Expression Turnover	GO:0006641	triglyceride metabolic process	0.000426	0.0975	1.36	12771	66	7261	51
Expression Turnover	GO:0007015	actin filament organization	0.000454	0.102	1.27	12771	118	7261	85
Expression Turnover	GO:1903076	regulation of protein localization to plasma membrane	0.000467	0.103	1.42	12771	47	7261	38
Expression Turnover	GO:0051050	positive regulation of transport	0.000485	0.105	1.12	12771	531	7261	339
Expression	GO:0060627	regulation of	0.000494	0.105	1.17	12771	268	7261	179

Turnover		vesicle-mediated transport							
Expression Turnover	GO:0010595	positive regulation of endothelial cell migration	0.000502	0.105	1.41	12771	50	7261	40
Expression Turnover	GO:0065007	biological regulation	0.000518	0.107	1.02	12771	7461	7261	4333
Expression Turnover	GO:0051270	regulation of cellular component movement	0.000565	0.114	1.13	12771	477	7261	306
Expression Turnover	GO:0001959	regulation of cytokine-mediated signaling pathway	0.000569	0.113	1.37	12771	59	7261	46
Expression Turnover	GO:0006814	sodium ion transport	0.000595	0.117	1.28	12771	100	7261	73
Expression Turnover	GO:0001525	angiogenesis	0.000603	0.116	1.19	12771	217	7261	147
Expression Turnover	GO:0044699	single-organism process	0.000618	0.118	1.02	12771	8350	7261	4834
Expression Turnover	GO:1901700	response to oxygen-containing compound	0.000642	0.12	1.09	12771	937	7261	580
Expression Turnover	GO:0060326	cell chemotaxis	0.000667	0.123	1.29	12771	91	7261	67
Expression	GO:0040011	locomotion	0.000669	0.122	1.11	12771	678	7261	426

Turnover									
Expression Turnover	GO:0030029	actin filament-based process	0.000674	0.121	1.17	12771	261	7261	174
Expression Turnover	GO:0048522	positive regulation of cellular process	0.000702	0.124	1.04	12771	3420	7261	2024
Expression Turnover	GO:0043207	response to external biotic stimulus	0.000727	0.127	1.14	12771	384	7261	249
Expression Turnover	GO:0051272	positive regulation of cellular component movement	0.000744	0.128	1.17	12771	250	7261	167
Expression Turnover	GO:0030032	lamellipodium assembly	0.000744	0.126	1.52	12771	29	7261	25
Expression Turnover	GO:0048521	negative regulation of behavior	0.000744	0.124	1.52	12771	29	7261	25
Expression Turnover	GO:0048585	negative regulation of response to stimulus	0.000768	0.127	1.09	12771	896	7261	555
Expression Turnover	GO:0060341	regulation of cellular localization	0.000774	0.126	1.1	12771	741	7261	463
Expression Turnover	GO:0009628	response to abiotic stimulus	0.000818	0.131	1.1	12771	775	7261	483
Expression	GO:0051336	regulation of	0.00089	0.141	1.09	12771	941	7261	581

Turnover		hydrolase activity							
Expression Turnover	GO:0051239	regulation of multicellular organismal process	0.000936	0.146	1.06	12771	1664	7261	1005
Expression Turnover	GO:0006953	acute-phase response	0.000937	0.145	1.66	12771	17	7261	16
Expression Turnover	GO:0071310	cellular response to organic substance	0.000954	0.146	1.07	12771	1283	7261	782
Expression Turnover	GO:0010810	regulation of cell-substrate adhesion	0.000964	0.145	1.24	12771	126	7261	89
Expression Turnover	GO:0090004	positive regulation of establishment of protein localization to plasma membrane	0.000969	0.144	1.59	12771	21	7261	19
Expression Turnover	GO:0010594	regulation of endothelial cell migration	0.000972	0.143	1.3	12771	81	7261	60
Expression Turnover	GO:0042127	regulation of cell proliferation	0.000987	0.144	1.08	12771	1074	7261	659
Human insertion	GO:0015909	long-chain fatty acid transport	0.000175	1	4.78	12487	30	696	8
Human insertion	GO:0015908	fatty acid transport	0.000283	1	4.04	12487	40	696	9

Human insertion	GO:0015711	organic anion transport	0.000313	1	2.02	12487	249	696	28
Human insertion	GO:0070098	chemokine-mediated signaling pathway	0.000322	0.992	5.02	12487	25	696	7
Human insertion	GO:0080184	response to phenylpropanoid	0.000559	1	8.97	12487	8	696	4
Human insertion	GO:0015718	monocarboxylic acid transport	0.000566	1	2.84	12487	82	696	13
Human insertion	GO:0035814	negative regulation of renal sodium excretion	0.000661	1	13.46	12487	4	696	3
Human insertion	GO:0006766	vitamin metabolic process	0.000675	1	2.67	12487	94	696	14
Human insertion	GO:0009225	nucleotide-sugar metabolic process	0.000861	1	4.33	12487	29	696	7
Human insertion	GO:0019752	carboxylic acid metabolic process	0.000951	1	1.53	12487	643	696	55
Human deletion	GO:0000737	DNA catabolic process endonucleolytic	0.000256	1	2.82	12550	50	1246	14
Human deletion	GO:0006309	apoptotic DNA fragmentation	0.000294	1	4.7	12550	15	1246	7
Human deletion	GO:0031503	protein complex localization	0.000477	1	4.41	12550	16	1246	7
Human	GO:0009066	aspartate family	0.000663	1	2.99	12550	37	1246	11

deletion		amino acid metabolic process							
Human deletion	GO:0007159	leukocyte cell-cell adhesion	0.000751	1	3.15	12550	32	1246	10
Human deletion	GO:2001199	negative regulation of dendritic cell differentiation	0.000977	1	10.07	12550	3	1246	3
Human deletion	GO:2001198	regulation of dendritic cell differentiation	0.000977	1	10.07	12550	3	1246	3
Human deletion	GO:2000392	regulation of lamellipodium morphogenesis	0.000977	1	10.07	12550	3	1246	3
Mouse insertion	GO:0098542	defense response to other organism	4.13E-07	0.00497	2.77	12858	142	949	29
Mouse insertion	GO:0051707	response to other organism	0.0000055	0.0331	2.33	12858	186	949	32
Mouse insertion	GO:0045010	actin nucleation	0.0000443	0.178	6.32	12858	15	949	7
Mouse insertion	GO:0006575	cellular modified amino acid metabolic process	0.0000532	0.16	2.56	12858	111	949	21
Mouse insertion	GO:0006952	defense response	0.000116	0.28	1.69	12858	426	949	53
Mouse insertion	GO:0043207	response to external biotic	0.000129	0.259	1.85	12858	285	949	39

		stimulus							
Mouse insertion	GO:0006520	cellular amino acid metabolic process	0.000152	0.261	1.98	12858	219	949	32
Mouse insertion	GO:0051607	defense response to virus	0.000171	0.258	2.86	12858	71	949	15
Mouse insertion	GO:0010216	maintenance of DNA methylation	0.000392	0.524	9.03	12858	6	949	4
Mouse insertion	GO:0006656	phosphatidylcholine biosynthetic process	0.000399	0.48	6.77	12858	10	949	5
Mouse insertion	GO:0002826	negative regulation of T-helper 1 type immune response	0.000401	0.439	13.55	12858	3	949	3
Mouse insertion	GO:0009607	response to biotic stimulus	0.000636	0.638	1.72	12858	308	949	39
Mouse insertion	GO:0034314	Arp2/3 complex-mediated actin nucleation	0.000687	0.636	6.16	12858	11	949	5
Mouse insertion	GO:0006304	DNA modification	0.00072	0.62	3.04	12858	49	949	11
Mouse insertion	GO:1901605	alpha-amino acid metabolic process	0.000722	0.58	2.19	12858	124	949	20
Mouse insertion	GO:0002218	activation of innate immune response	0.000764	0.575	3.23	12858	42	949	10
Mouse	GO:0009615	response to virus	0.000929	0.658	2.38	12858	91	949	16

insertion									
Mouse insertion	GO:0009069	serine family amino acid metabolic process	0.00097	0.649	4.78	12858	17	949	6
Mouse deletion	GO:0043436	oxoacid metabolic process	0.00000223	0.0271	1.32	13215	558	3557	199
Mouse deletion	GO:0006082	organic acid metabolic process	0.00000225	0.0136	1.32	13215	571	3557	203
Mouse deletion	GO:0019752	carboxylic acid metabolic process	0.00000412	0.0166	1.33	13215	514	3557	184
Mouse deletion	GO:0044283	small molecule biosynthetic process	0.00000612	0.0185	1.48	13215	243	3557	97
Mouse deletion	GO:0008610	lipid biosynthetic process	0.00000989	0.024	1.42	13215	307	3557	117
Mouse deletion	GO:0006629	lipid metabolic process	0.0000126	0.0254	1.27	13215	660	3557	226
Mouse deletion	GO:0016053	organic acid biosynthetic process	0.0000228	0.0395	1.54	13215	174	3557	72
Mouse deletion	GO:0046394	carboxylic acid biosynthetic process	0.0000228	0.0346	1.54	13215	174	3557	72
Mouse deletion	GO:0044711	single-organism biosynthetic	0.0000288	0.0388	1.25	13215	684	3557	231

		process							
Mouse deletion	GO:0044281	small molecule metabolic process	0.0000584	0.0709	1.17	13215	1346	3557	423
Mouse deletion	GO:0044255	cellular lipid metabolic process	0.0000984	0.108	1.28	13215	493	3557	170
Mouse deletion	GO:0006520	cellular amino acid metabolic process	0.000119	0.12	1.41	13215	234	3557	89
Mouse deletion	GO:0050830	defense response to Gram-positive bacterium	0.00027	0.252	2.32	13215	24	3557	15
Mouse deletion	GO:0072330	monocarboxylic acid biosynthetic process	0.000382	0.331	1.57	13215	109	3557	46
Mouse deletion	GO:1901879	regulation of protein depolymerization	0.000619	0.5	1.74	13215	62	3557	29
Mouse deletion	GO:0050667	homocysteine metabolic process	0.000624	0.472	3.25	13215	8	3557	7
Mouse deletion	GO:0008207	C21-steroid hormone metabolic process	0.000715	0.51	2.97	13215	10	3557	8
Mouse deletion	GO:0006631	fatty acid metabolic process	0.000864	0.582	1.4	13215	183	3557	69

Mouse deletion	GO:0006694	steroid biosynthetic process	0.000907	0.579	1.69	13215	66	3557	30
Mouse deletion	GO:0030032	lamellipodium assembly	0.000913	0.554	2.04	13215	31	3557	17
Mouse deletion	GO:0043244	regulation of protein complex disassembly	0.000955	0.551	1.67	13215	69	3557	31