Supporting Information

Kumaki et al. 10.1073/pnas.0802636105



Fig. S1. Construction of the mammalian promoter/enhancer database. Mammalian full-length cDNA and EST sequences were mapped onto mammalian genome sequences to identify 24,749 human genes with 50,373 TSSs and 26,047 mouse genes with 43,863 TSSs. These mammalian genes were then compared to identify 16,268 human-mouse orthologs (65.7% of human genes and 62.5% of mouse genes). The positional information of adjacent orthologs was used to determine 434 human-mouse syntenic regions, which contained 750,043 human-mouse conserved genomic regions. The 862 consensus TFBSs from TRANSFAC were then mapped on these conserved genomic regions to identify the 7,804,559 sites conserved between human and mouse in non-coding regions. Human-rat comparisons were performed using the same procedure. Finally, visualization of putative promoter/enhancer and TFBSs data, and curation of current genes were integrated into a free and publicly accessible website (Mammalian Promoter/Enhancer Database; http://promoter.cdb.riken.jp/).



Fig. 52. Functional clock-controlled elements used to train HMMs. (*A*) Bioluminescence from functional clock-controlled elements fused to the SV40 basic promoter driving a dLuc reporter (SV40-dLuc) in NIH 3T3 fibroblasts. Known clock-controlled promoter (*Per2* promoter), known clock-controlled element fused to the SV40 basic promoter (*Nfi/3* RRE), or the SV40 basic promoter alone (SV40 promoter) driving luciferase were used as controls. The colors in descending order from magenta to black to green represent the detrended bioluminescence. Columns represent time points, and rows represent the predicted elements on the designated genes. (*B* and *C*) Raw bioluminescence data of positive and negative controls (*B*), or functional clock-controlled elements inserted into SV40-dLuc reporters (*C*). Error bars indicate the standard error of mean (SEM) determined from independent experimental duplicates for each condition.



Fig. S3. Detailed information on experimental validation of HMM-based predictions at the cellular level. Raw bioluminescence data from positive and negative controls (*A*), and predicted clock-controlled elements inserted into the SV40-dLuc reporter that generate strong circadian transcriptional activity with high amplitude of the (*B*) E-box, (*C*) D-box, and (*D*) RRE, and weak circadian transcriptional activity with low amplitude or arrhythmic transcriptional activity of the (*E*) E-box, (*F*) D-box, and (*G*) RRE. Raw bioluminescence data from 14 low-score E-boxes inserted into the SV40-dLuc reporter (*H*). Only the low-score E-box No. 8 generated strong circadian transcriptional activity with high amplitude. The low-score E-box No. 14 was not measured due to the difficulty of reporter construction. Error bars indicate the standard error of mean (SEM) determined from independent experimental replicates (*n* = 2 or 3) for each element tested.

Pattern1	
Per1 E-box2	TAGAGCCACGTGAGGGCG
Per1 E-box3	TTTAGCCACGTGACAGTG
Per1 E-box5	CAAGTCCACGTGCAGGGA
Nr1d1 E-box1	CGGGCCCACGTGCTGCAT
Nr1d1 E-box2	GGGTGCCACGTGCGAGGG
Nr1d2 E-box1	ACTGGCCACGTGCACGGT
Dbp E-box	CCTCGCCACGTGAGTCCG
Bhlhb2 E-box	CCGGGCCACGTGAAGCGT
Rorc E-box	AGGTGCCACGTGCACCAG
High-scoring E-box	CGGGGCCACGTGCAGGCG

Pattern2	
Per1 E-box1	AGGGAACACGTGCAGGCT
Per1 E-box4	TAACGACACGTGGGCCCT
Nr1d2 E-box2	CGGAGACACGTGAGGCCG
MGI:1926224 E-box	AAGAGACACGTGCTGGGG
Lrrc35 E-box	ACGTGACACGTGCGGCGG
1300001101Rik E-box	CGGGGACACGTGCGCGCA
Cpne7 E-box	CCGAGACACGTGTGCCCG

Fig. S4. Two patterns revealed in the adjacent sequence of high-amplitude E-boxes. High-amplitude E-box sequences classified into two patterns were shown. Information contents of the relative frequency of each nucleic acid at the position of the pattern were shown by sequence logos.



Fig. 55. Analysis of affinity to amplitude mechanism. (*A*) Affinity analysis of competitive binding data. The relative affinities of regulators for known clock controlled elements vs. synthetic elements were determined from competitive binding assay data shown in Fig. 4. A series of signal of binding between labeled oligonucleotide of positive control element and regulators, which were challenged with unlabeled oligonucleotides of positive control element (blue), high-scoring element (red), low-scoring element (green), or negative control element (black) in competition assays. This data were fitted by the model data (purple) using the least-squares method and the affinities relative to that of positive control were determined from fitting data. The value of relative affinities (positive control is 1.0) are indicated. See also *SI Appendix* for more detail. (*B*) *In silico* analysis of affinity to amplitude mechanism when affinity of an activator and repressor are balanced. The relative amplitudes of oscillation of output plotted against strength of regulators binding affinity when the affinity of an activator and repressor are the same; *n* indicates the Hill coefficient at competitive regulation. Amplitude was normalized so that the maximum value at *n* = 1 is 100%.

Other Supporting Information Files

SI Appendix

Gene	GeneID	Element	Organism	chr	Start	End	Sequence	Evidence	Affymetrix Probe ID			
FI 15	(0001	DDE	Mouse	9	78317303	78317325	Mouse TCTTGTAAATTGGGTCATGGCGT		02406			
Elov15	68801	KKE	Human	6	53273932	53273910		ref. 1, ref. 2	93496_at			
DC004004 0074		DDE	Mouse	17	27851244	27851266	Mouse AGTCTGAATATAGGTCAATGTGA		05517 i et			
BC004004	80748	KKE	Human	6	36927126	36927148	Human TTTGGG <mark>AATCTAGGTCA</mark> TTCTGA	rel. 1, rel. 2	95517_1_at			
M = -61	11426	DDE	Mouse	4	121994185	121994207	Mouse CCCTGAAAAGTAGGTCAGTGCCT	and O	08402			
Macf1	11426	KKE	Human	1	39277738	39277716	Human CCCTGA <mark>AAAGTAGGTCA</mark> GCGCCT	ref. 2	98402_at			
A 405	107502	DDE	Mouse	7	32213618	32213640	Mouse CAAGTAAAACTGGGTCACGAAGG	rof 1 rof 2	102006 at			
АIJЭ	107505		Human	19	55118372	55118350	Human GGAGGG <mark>TAACTGGGTCA</mark> CGCAGG	rel. 1, rel. 2	103000_at			
Caldal	12926		Mouse	8	11309356	11309378	Mouse GGCAGGAAAATGGGTCAGTGCTG	mof 1 mof 2	101002 of			
<i>C014a</i> 1	12820	KKEI	Human	13	109748860	109748882	Human AGCAGG <mark>AAAATGGGTCA</mark> GTGATG	fel. 1, fel. 2	101093_at			
C - 14 - 1	12926	DDE2	Mouse	8	11337102	11337124	Mouse TCAGCCAAACTAGGTCAAAACCT		101002 at			
Col4a1	12826	KKE2	Human	13	109781193	109781215	Human TCAGCC <mark>AAAATAGGTCA</mark> AAACAG	ref. 1, ref. 2	101093_at			
D10E (1721	225906	DDE	Mouse	19	7972840	7972862	Mouse AGGAAGAAAATAGGTCAGACATG		07240			
DI9Erta/21e	225896	KKE	Human	11	62201916	62201894	Human AAGAAG <mark>AAATTAGGTCA</mark> GACATC	ref. 1, ref. 2	97240_g_at, 97241_at			
References 1. Ueda HR, <i>et</i> 2. Panda S, <i>et a</i>	References 1. Ueda HR, <i>et al.</i> (2002) A transcription factor response element for gene expression during circadian night. <i>Nature</i> 418:534-539. 2. Panda S, <i>et al.</i> (2002) Coordinated transcription of key pathways in the mouse by the circadian clock. <i>Cell</i> 109:307-320.											

Table S1. Functional RREs from known clock-controlled genes used in this study

Element information on the gene symbol ('Gene'), NCBI GeneID ('GeneID'), element type ('Element'), the position ('Start' and 'End') on a chromosome ('chr') of mouse and human ('Organism') and the sequence alignment of human-mouse RREs ('Sequence') are indicated. Experimental evidence on clock-controlled genes ('Evidence') and Affymetrix probe ID detecting circadian expression of the genes ('Affymetrix Probe ID') are also indicated. The canonical consensus sequences for the RRE ([A/T]A[A/T]NT[A/G]GGTCA) is indicated in red. The function of these mouse RREs sequences in the context of a luciferase reporter was experimentally determined in **Fig. S2**.

Gene	GeneID	Element	Organism	chr	Start	End	Score of HMMER	Sequence	Evidence
Per1	18626	E-box 1	Mouse	11	68707450	68707433	15.39	AGGGAA <mark>CACGTG</mark> CAGGCT	ref. 1
Per1	18626	E-box 2	Mouse	11	68707634	68707617	17.87	TAGAGCCACGTGAGGGCG	ref. 1
Per1	18626	E-box 3	Mouse	11	68710224	68710241	11.48	TTTAGCCACGTGACAGTG	ref. 1
Per1	18626	E-box 4	Mouse	11	68710970	68710987	12.10	TAACGACACGTGGGCCCT	ref. 1
Per1	18626	E-box 5	Mouse	11	68711333	68711350	13.45	CAAGTC <mark>CACGTG</mark> CAGGGA	ref. 2
Nr1d1	217166	E-box 1	Mouse	11	98445288	98445271	14.71	CGGGCCCACGTGCTGCAT	ref. 2
Nr1d1	217166	E-box 2	Mouse	11	98445008	98444991	15.77	GGGTGC <mark>CACGTG</mark> CGAGGG	ref. 2
Nr1d2	353187	E-box 1	Mouse	14	14904545	14904528	16.38	ACTGGC <mark>CACGTG</mark> CACGGT	ref. 2
Nr1d2	353187	E-box 2	Mouse	14	14904442	14904425	17.71	CGGAGACACGTGAGGCCG	ref. 2
Dbp	13170	E-box	Mouse	7	33110149	33110166	15.23	CCTCGC <mark>CACGTG</mark> AGTCCG	ref. 2
Bhlhb2	20893	E-box	Mouse	6	109049680	109049697	18.55	CCGGGC <mark>CACGTG</mark> AAGCGT	ref. 2
Rorc	19885	E-box	Mouse	3	94357502	94357519	16.45	AGGTGC <mark>CACGTG</mark> CACCAG	ref. 2
			2 3						
Per1	18626	D-box	Mouse	11	68711473	68711496	17.30	GCCTGGCATTATGCAACCCGCCTC	ref. 2
Per2	18627	D-box	Mouse	1	91377818	91377795	16.48	TGTGCGTCTTATGTAAAGAGAGCG	ref. 2
Per3	18628	D-box 1	Mouse	4	148930820	148930797	18.62	CCCGCGCGTTATGTAAGGTACTCG	ref. 2
Per3	18628	D-box 2	Mouse	4	148930773	148930750) 16.10 GCCCGCGGTTATGTAACCCCCGCC		ref. 2
Nr1d1	217166	D-box	Mouse	11	98445195	98445218	19.41	GGAGCTCATTATGTAACGAGGCCG	ref. 2

Table S2. Functional clock-controlled elements used as train HMMs

Nr1d2	353187	D-box	Mouse	14	14904456	14904479	17.41	AGCTCGCATTATGTAATGCTGCGT	ref. 2
Rora	19883	D-box 1	Mouse	9	69195245	69195222	11.78	AAGCTGTTTTATGTAATAGCTTTG	ref. 2
Rora	19883	D-box 2	Mouse	9	68926158	68926135	16.84	CACTGCTGTTATGTAACCAAACGT	ref. 2
Rora	19883	D-box 3	Mouse	9	68894279	68894302	17.42	CGAGCGGGTTATGTAACAGGGTTA	ref. 2
Rorb	225998	D-box	Mouse	19	18304970	18304993	14.84	TCCAGTTCTTATGTAATGAATATA	ref. 2
		17 19 23 23 23 53	ấ 3'						
Arntl	11865	RRE	Mouse	7	100478066	100478088	19.72	AGGCAGAAAGTAGGTCAGGGACG	ref. 2
Npas2	18143	RRE	Mouse	1	39516271	39516293	14.66	GAAAAATATGTAGGTCAGTGGAA	ref. 2
Nfil3	114519	RRE 1	Rat	17	18094293	18094271	15.64	AGTGTGTTAGTAGGTCAGTTCCG	ref. 2
Nfil3	18030	RRE 2	Mouse	13	52011542	52011520	21.79	ACAGAAAAGTGGGTCAGTTTGT	ref. 2
Clock	12753	RRE	Mouse	5	75037420	75037442	15.91	AGGAAT <mark>AAAGTGGGTCA</mark> CAAGGC	ref. 2
Cry1	12952	RRE 1	Mouse	10	84829678	84829656	20.81	GACTAG <mark>AAAGTAGGTCA</mark> TTGTGA	ref. 2
Cry1	12952	RRE 2	Mouse	10	84829601	84829623	16.47	GTTTCTAAAGTAGGTCATCGCTA	ref. 2
Rorc	19885	RRE	Mouse	3	94352279	94352301	19.40	GGAATA <mark>AAAGTGGGTCA</mark> TCTTGT	ref. 2
Elov15	68801	RRE	Mouse	9	78317303	78317325	17.19	TCTTGT <mark>AAATTGGGTCA</mark> TGGCGT	This study
BC004004	80748	RRE	Mouse	17	27851266	27851244	17.53	AGTCTG <mark>AATATAGGTCA</mark> ATGTGA	This study
Macf1	11426	RRE 2	Mouse	4	121994185	121994207	20.05	CCCTGAAAAGTAGGTCAGTGCCT	This study
Atf5	107503	RRE	Mouse	7	32213618	32213640	14.65	CAAGTAAAACTGGGTCACGAAGG	This study
Col4a1	12826	RRE 1	Mouse	8	11309378	11309356	19.92	GGCAGG <mark>AAAATGGGTCA</mark> GTGCTG	This study
Col4a1	12826	RRE 2	Mouse	8	11337124	11337102	14.10	TCAGCCAAACTAGGTCAAAACCT	This study
D19Ertd721e	225896	RRE	Mouse	19	7972862	7972840	18.30	AGGAAGAAAATAGGTCAGACATG	This study

2 12 5' - N N T N D							
References							
1. Hida A, e	et al. (2000) The human and mouse	Period1	genes: five w	ell-conserved	E-boxes add	litively contribute to the enhancement of mF	er1
transcript and unpab	ion. <i>Genomics</i> 65:224-233. sihed data of Ueda, H.R. <i>et al.</i>						

2. Ueda HR, et al. (2005) System-level identification of transcriptional circuits underlying mammalian circadian clocks. Nat Genet 37:187-192.

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Element information on the gene symbol ('Gene'), NCBI GeneID ('GeneID'), element type ('Element'), the position ('Start' and 'End') on a chromosome ('chr') of mouse and rat ('Organism') and the sequence ('Sequence') are indicated. Experimental evidence on functional clock-controlled elements ('Evidence') and match score of HMMER search performed using the constructed HMMs ('Score of HMMER') is also indicated. Canonical consensus sequences for the E-box (CACGTG), D-box (TTATG[T/C]AA) and RRE ([A/T]A[A/T]NT[A/G]GGTCA) are indicated in red. Information contents of the relative frequency of each nucleic acid at the position of the pattern for each element were shown by sequence logos.

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No.	Gene	GeneID	Element	FDR	Organism	chr	Start	End	Score of HMMER	Sequence
	Doul	19676	Eboy	0.042	Mouse	11	68711333	68711350	13.45	Mouse CAAGTCCACGTGCAGGGA
-	Feri	18020	E-DOX	0.045	Human	17	7996626	7996609	16.13	
1	Eama	26270	Ebor	0.002	Mouse	19	6635826	6635809	18.03	Mouse CGGACGCACGTGGCCCCG
1	Esrra	20379	E-DOX	0.002	Human	11	63828852	63828869	18.03	Human CGGACG <mark>CACGTG</mark> GCCCCG
2	Foud2	15221	Ebor	0.014	Mouse	4	97986368	97986351	17.23	Mouse CGCGGTCACGTGGCCCCG
2	FOXUS	13221	E-DOX	0.014	Human	1	63500197	64500214	15.64	
3	MCI:1026224	268850	E box	0.017	Mouse	16	6032279	6032296	14.92	Mouse AAGAGACACGTGCTGGGG
5	MOI.1920224	208839	E-00X	0.017	Human	16	6473013	6473030	17.35	Human AAGGGA <mark>CACGTG</mark> CGGGCG
4	A V 122525	221622	Eboy	0.021	Mouse	10	43388228	43388211	17.00	Mouse CCCCCGCACGTGGCGCCC
4	ARIZZJZJ	331023	E-00X	0.021	Human	6	107543034	107543051	15.19	Human CCCCCC <mark>CACGTG</mark> GCGCCC
5	I rro35	272580	E box	0.021	Mouse	9	42544300	42544317	16.09	Mouse ACGTGACACGTGCGGCGG
5	LITCSS	212389	L-UUX	0.021	Human	11	120399989	120399972	16.09	Human ACGTGA <mark>CACGTG</mark> CGGCGG
6	1300001101 B ik	74148	E boy	0.021	Mouse	11	74262482	74262499	15.91	Mouse CGGGGACACGTGCGCGCA
0	13000011011.01	74140	E-00X	0.021	Human	17	2561349	2561332	15.91	Human CGGGGA <mark>CACGTG</mark> CGCGCA
7	Crue7	102278	Eboy	0.023	Mouse	8	122590893	122590910	13.74	Mouse CCGAGACACGTGTGCCCG
	Cpne/	102278	E-00X	0.025	Human	16	88169660	88169677	17.87	Human CCGAGC <mark>CACGTG</mark> CGCCCG
0	Dpra 1	226160	Eboy	0.024	Mouse	19	45397616	45397633	15.71	Mouse CGGGTCCACGTGGGGGGCG
0	r prc1	220109	E-DOX	0.024	Human	10	103883430	103883447	15.71	Human CGGGTC <mark>CACGTG</mark> GGGGCG

		1 - 1 - 2		0.024	Mouse	12	107682267	107682284	15.64	Mouse CCTGGCCACGTGGGCGCG
9	Jag2	16450	E-box	0.024	Human	14	104704954	104704971	15.64	
10	$B_{\rm mg}10$	20085	Eboy	0.024	Mouse	7	13623927	13623944	15.62	Mouse CGCGGCCACGTGCGAGCG
10	Kps19	20083	E-DOX	0.024	Human	19	47056319	47056336	15.62	Human CGCGGC <mark>CACGTG</mark> CGAGCG
	Dar?	19629	Dhoy	0	Mouse	4	148930797	148930820	18.62	Mouse CCCGCGCGTTATGTAAGGTACTCG
-	rers	18028	D-00x	0	Human	1	7778455	7778432	21.11	Human CCCGCGCGTTATGTAACGCGCCCC
1	Gria?	14800	D hoy	0.051	Mouse	3	81194005	81193982	17.31	Mouse CGGGGCTGTTACATAATGCCCACC
1	Onaz	14800	D-00X	0.031	Human	4	158501155	158501178	17.63	Human CGGGGCTGTTACATAACGCCCACC
2	Snrv4	24066	D-box	0 122	Mouse	18	39043332	39043309	16.38	Mouse AGGTGCGTTTACATAACGCCGGGC
2	Зргуч	24000	D-00X	0.122	Human	5	141683774	141683751	16.80	Human AGGTGCGTTTACATAACACCAGGC
3	FtvA	18612	D-box	0 181	Mouse	11	101455967	101455990	17.09	Mouse CACACGTCTTATGTAACCCAGTTC
5	Livt	10012		0.101	Human	17	38978809	38978832	15.20	Human ACACGTTCTTATGTAACCGAGCCC
4	Pogz	229584	D-box	0 181	Mouse	3	94832639	94832662	16.89	Mouse CCCCTGTGTTATGTAATCCCGCTC
	1082	229304		0.101	Human	1	148244037	148244014	15.15	Human CCCTTGTGTTATGTAATCTCTGCT
5	Fmn?	54418	D-box	0.209	Mouse	1	174628879	174628902	14.89	Mouse ACCGCGCATTATGCAAAGCGGCAG
5	1 mm2	54410	D-00X	0.207	Human	1	236581260	236581283	16.89	Human GCCGCGCATTATGCAAAGCGGCGG
6	Plch1	18795	D-box	0 325	Mouse	2	134535724	134535747	15.25	Mouse GGGGCGCGTTATGCAATGGGGCGC
0	1 101	10775		0.525	Human	20	8061473	8061496	15.25	Human GGGGCGCGTTATGCAATGGGCGCA
7	Irf?hn1	272359	D-box	0 363	Mouse	7	10526613	10526636	16.21	Mouse CCCGCGCGTTATGTAACTTTCCCT
/	11520171	272337	DUUX	0.505	Human	19	51081280	51081257	13.67	Human CAGGCGTGTTATGTAACTTTCCCT
8	Slc22a20	381203	D-box	0 363	Mouse	19	5775101	5775078	14.95	Mouse CTGCCTTTTTACATAAGGCCTGGG
0	51022020	501205		0.505	Human	11	64737873	64737896	14.81	Human CGGCCTCTCTACATAAAGCCGGGG
9	Trim8	93679	D-box	0.387	Mouse	19	45844359	45844336	14.62	Mouse GACACTCATTACATAAACAGCAGC

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Human GACACTCATTACATAAACAGCAGC

					Human	10	104395331	104395308	14.62		
10	— — —	01010	51	0.000	Mouse	X	8817583	8817560	13.68	Mouse	AGAGGGTCTTACATAAGCCAGGGG
10	Tspan/	21912	D-box	0.388	Human	X	38177725	38177702	15.27	Human	AGAGGGTCTTACATAAGCCGGGGG
					Mouse	7	100478066	100478088	20.38	Mouse	AGGCAGAAAGTAGGTCAGGGACG
-	Arntl	11865	RRE	0.066	Human	11	13255933	13255955	20.38	Human	AGGCAG <mark>AAAGTAGGTCA</mark> GGGACG
					Mouse	11	69217609	69217631	20.61	Mouse	GCGGAGAAAGTAGGTCACTGCCG
	Atp1b2	11932	RRE	0.066	Human	17	7495878	7495856	19.61	Human	GCGGAGAAAGTAGGTCACAGCCG
	a ta	700.42	DDD	0.000	Mouse	17	23484948	23484970	18.81	Mouse	GAACGGAAAGTGGGTCAGCGCCG
2	Spsb3	79043	RRE	0.083	Human	16	1772556	1772534	19.64	Human	GGGCGGAAAGTGGGTCAGGGCCG
	74.010			0.404	Mouse	17	44564473	44564495	19.35	Mouse	GAGAGAAAAGTGGGTCATTGAGA
3	Zfp318	57908	RRE	0.104	Human	6	43417992	43417970	18.25	Human	AAGAGAAAAGTGGGTCATTGAGC
			DDD	0.110	Mouse	19	45123691	45123713	17.41	Mouse	ATCTCCAAAGTAGGTCAGTGTCT
4	Mgea5	76055	RRE	0.112	Human	10	103568543	103568565	20.12	Human	CCATAGAAAGTAGGTCAGTTCTT
-	T 1	16706	DDE	0.120	Mouse	11	97476169	97476191	16.54	Mouse	TTCGTGAAAGTGGGTCATGGTCT
5	Lasp1	16/96	RRE	0.139	Human	17	34284865	34284887	19.34	Human	
	D I	20100	DDD	0.140	Mouse	7	18096374	18096352	17.94	Mouse	AGGCTCTGACCTATTTAAATTCT
6	Ryr1	20190	RRE	0.148	Human	19	43616749	43616771	17.45	Human	AGACTCTGACCTATTTAAATTCT
		11400	DDE	0.140	Mouse	7	121856769	121856791	15.44	Mouse	TACTTAAAAGTAGGTCAGAAAAA
/	Adam12	11489	RRE	0.148	Human	10	128077170	128077148	19.88	Human	
	17200001005	100707	DDD	0.1.00	Mouse	16	84900535	84900513	16.17	Mouse	TCTTAATGACCCAATTTCTAAAT
8	A/30009L09Rik	402727	RRE	0.168 —	Human	21	25632353	25632331	18.49	Human	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
9	Myo1b	17912	RRE	0.179	Mouse	1	52270010	52269988	18.02	Mouse	TGGTGCTGACCCACTTTCCTCTT

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 Human GGATATTGACCTACTTTCCCCTT

					Human	2	191953461	191953483	16.47	
10	D12E / 1150	52549	DDE	0.000	Mouse	13	37218548	37218570	16.99	Mouse GATGCGAAAGTGGGTCAGGAATG
10	D13Ertd150e	52548	RRE	0.203	Human	6	6997855	6997877	16.67	
1	ci o	20.420	low-score		Mouse	3	67055808	67055791	0.64	Mouse GATAAACACGTGTGTATC
1	Shox2	20429	E-box	-	Human	3	159121615	159121598	0.64	
	170005711150:1	79460	low-score		Mouse	4	122900755	122900738	1.39	Mouse TATTCTCACGTGATAAAC
2	1/0003/H13Kik	/8460	E-box	-	Human	1	38322547	38322564	1.39	
2		425252	low-score		Mouse	11	35821433	35821450	1.83	Mouse GACAAGCACGTGCCAGAC
3	-	435255	E-box	-	Human	5	167485618	167485601	1.83	
4	TL 15	21294	low-score		Mouse	3	99126851	99126834	1.83	Mouse GTTTTTCACGTGCTTGAC
4	10x15	21384	E-box	-	Human	1	119301655	119301672	2.39	
5	S41-4	59021	low-score		Mouse	2	164147516	164147533	2.12	Mouse GAAGAGCACGTGATCTGC
3	51K4	38231	E-box	-	Human	20	43041498	43041515	2.28	 Human GAAAAC <mark>CACGTG</mark> GTTTGC
6	Uhala	22201	low-score		Mouse	Х	19009993	19009976	2.61	Mouse GTTACTCACGTGAGGTAC
0	Ubelx	22201	E-box	-	Human	Х	46825349	46825332	2.61	
7		211022	low-score		Mouse	3	129597003	129596986	2.80	Mouse TGCAAACACGTGATTTCC
/	-	211823	E-box	-	Human	4	112078186	112078203	2.80	
0	Dref44	105220	low-score		Mouse	13	53770222	53770239	2.80	Mouse GTAAAACACGTGGATTTT
0	KNJ44	105259	E-box	-	Human	5	175887078	175887095	2.80	
0	Dahasl	10450	low-score	-	Mouse	15	36663158	36663141	2.93	Mouse AAATACCACGTGTTGAAC
9	Γάδρει	18438	E-box	-	Human	8	101802352	101802335	2.93	
10			low-score		Mouse	16	74421611	74421628	3.03	Mouse GCTAAGCACGTGGAAGTC
10	-	-	E-box	-	Human	3	77581572	77581555	3.03	

11	C220011E02	220027	low-score		Mouse	17	49541248	49541231	3.08	Mouse GTTTCCCACGTGTTTGGC
11	C330011F03	520057	E-box		Human	3	17954468	17954451	3.08	Human GTTTCC <mark>CACGTG</mark> TTTGGC
10	Dukaa	19754	low-score		Mouse	17	85008129	85008146	3.20	Mouse ATATAACACGTGCTAAAA
12	ГТКСе	18734	E-box	-	Human	2	46068028	46068045	3.20	Human ATATAA <mark>CACGTG</mark> CTAAAA
12	Man2k0	228272	low-score		Mouse	12	77032273	77032290	2.44	Mouse GACAAACACGTGTGCGTC
15	тарэку	336372	E-box	-	Human	14	70276648	70276665	4.03	Human GACAAA <mark>CACGTG</mark> TATGCA
14	7fby 1b	24126	low-score		Mouse	2	45057246	45057229	3.29	Mouse GTATTACACGTGAAAAGC
14	Zjnx10	24130	E-box	-	Human	2	145095987	145095970	3.29	
15	Duffha 2	10024	low-score		Mouse	7	94860226	94860243	4.93	Mouse GTTTCCCACGTGTGTCCC
13	г руюр2	19024	E-box	-	Human	11	7489362	7489379	1.76	Human GTTTCC <mark>CACGTG</mark> TTTGTC

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The element information including the gene symbol ('Gene'), NCBI GeneID ('GeneID'), element type ('Element'), the position ('Start' and 'End') on a chromosome ('chr') of mouse and human ('Organism'), the sequence alignments of human and mouse ('Sequence') and the match score of HMMER search ('Score of HMMER') are indicated. The estimated accuracy of the HMM-based prediction is indicated as false discovery rate ('FDR'). The mouse elements were used for experimental validation. The element type 'low-score E-box' indicate evolutionary conserved 15 most low-score E-boxes with the core consensus sequence 'CACGTG' in non-coding regions. The function of these element sequences in the context of a luciferase reporter was experimentally determined in **SI Fig. S3**.

Elei	ment	Gene	Alignment	Accession	Domain position	Domain name	Туре	Homology
E-box		Arntl	-KNAREAHSQIEKRRRDKMNSFIDELASLVPTCNAMSRKLDKLTVLRMAVQHMKTLR	NP_031515.1	71-126	HLH	Activator	Identity 30%, Similarity 57% to Bhlhb2
		Clock	DKAKRVSRNKSEKKRRDQFNVLIKELGSMLPGNARKMDKSTVLQKSIDFLRKHKE	NP_031741.1	32-86		Activator	Identity 22%, Similarity 55% to Bhlhb2
	JX	Bhlhb2	KETYKLPHRLIEKKRRDRINECIAQLKDLLPEHLKLTTLGHLEKAVVLELTLKHVKALTNLID	NP_035628.1	50-112		Repressor	-
			: : : **:***::* * ::* ::* ::* ::: * :::					
D-box		Dbp	KDEKYWSRRYKNNEAAKRSRDARRLKENQISVRAAFLEKENALLRQEVVAVRQE	NP_058670.1	254-307	h7IP 2	Activator	Identity 44%, Similarity 69% to Nfil3
	ox	Nfil3	KDAMYWEKRRKNNEAAKRSREKRRLNDLVLENKLIALGEENATLKAELLSLK	NP_059069.1	72-123		Repressor	-
			** **.:* ********* ****: :. : * :*** *: *:::::					
RRE		Rora	IPCKICGDKSSGIHYGVITCEGCKGFFRRSQQSNATYS-CPRQKNCLIDRTSRNRCQHCRLQKCLAVGMSRDAVKFG	NP_038674.1	71-146	zf-C4	Activator	Identity 65%, Similarity 81% to Nr1d1
	Ξ	Nr1d1	-LCKVCGDVASGFHYGVHACEGCKGFFRRSIQQNIQYKRCLKNENCSIVRINRNRCQQCRFKKCLSVGMSRDAVRFG	NP_663409.2	132-207		Repressor	
			:* :**:**** :*********** * * * * :::** * * ****:** ::***:***:**					

The gene symbol ('Gene') of DNA binding activators and repressors, target element ('Element'), alignment ('Alignment') of DNA binding domain, accession No. ('Accession') of

protein sequence, position of DNA binding domain ('Domain position') at the protein sequence and name of the DNA binding domain ('Domain name') are indicated. Homology

('Homology') between DNA binding domains of DNA binding activators and repressors is also indicated.

Table S4. Similarity between DNA binding domains of DNA binding activators and repressors

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