Supplementary Tables and Figures for “Genome-Wide Prediction of cis-Regulatory Regions Using Supervised Deep Learning Methods”

Yifeng Li*[1,2], Wenqiang Shi†[1], and Wyeth W. Wasserman‡[1]

[1]Centre for Molecular Medicine and Therapeutics, BC Children’s Hospital Research Institute, Department of Medical Genetics, University of British Columbia
[2]Digital Technologies Research Centre, National Research Council Canada

Table S1: Numbers of labelled regions in our data.

Cell	A-E	I-E	A-P	I-P	A-X	I-X	UK	Total
A549	387	40,387	10,907	128,998	8,998	14,712	81,217	285,606
GM12878	2,878	28,156	10,816	73,891	8,226	19,078	80,004	223,049
HelaS3	1847	32,179	10,759	79,009	9,123	22,071	81,502	236,485
HepG2	1465	34,556	11,467	96,184	9,931	19,071	79,417	252,091
HUVEC	1226	35,143	11,254	101,861	9,739	18,249	80,333	257,805
K562	894	34,392	10,076	82,829	9,033	20,261	78,081	235,566
MCF7	249	36,873	10,733	81,510	10,829	13,653	82,663	236,510

Table S2: Number of features used for each cell type and number of common features between any two cell types in our labelled data.

Cell	A549	GM12878	HelaS3	HepG2	HMEC	HUVEC	K562	MCF7
A549	45	38	26	38	15	19	38	25
GM12878	-	101	50	54	16	21	69	26
HelaS3	-	-	74	43	16	22	56	23
HepG2	-	-	-	72	16	21	57	28
HMEC	-	-	-	-	16	16	16	9
HUVEC	-	-	-	-	-	24	24	13
K562	-	-	-	-	-	-	135	29
MCF7	-	-	-	-	-	-	-	38

*E-mail address: yifeng@cmmt.ubc.ca, and yifeng.li@nrc-cnrc.gc.ca.
†E-mail address: shi@cmmt.ubc.ca.
‡Corresponding author, E-mail address: wyeth@cmmt.ubc.ca.

Table S3: Confusion matrices of classifying CRE-seq and MPRA validated regions using DECRES.

Original Class\DECRES Class	A-E	A-P	BG	Total
CRE-seq Positive Combined Predicted Enhancer in K562	254	0	132	386
CRE-seq Negative Combined Predicted Enhancer in K562	433	1	378	812
Combined Predicted Repressed Region in K562	0	0	298	298
Total	687	1	808	1496
MPRA Positive Enhancer in K562	120	0	2	122
MPRA Negative Enhancer in K562	179	0	15	194
Total	299	0	17	316
MPRA Positive Enhancer in HepG2	182	1	3	186
MPRA Negative Enhancer in HepG2	217	5	45	267
Total	399	6	48	453

Table S4: Numbers of predicted and cell-specific *cis*-regulatory regions in the whole human genome. Columns 2-3: results of two-class prediction. Columns 4-7: results of three class prediction.

Cell	A-E+A-P	Specific	A-E	Specific	A-P	Specific
GM12878	90,192	27,904	70,905	27,185	19,287	6,090
HelaS3	100,102	22,268	92,509	22,866	7,593	979
HepG2	114,873	35,986	105,007	41,109	9,866	2,135
HMEC	104,621	28,774	88,803	26,262	15,818	3,043
HUVEC	110,347	16,415	97,069	35,073	13,278	582
K562	133,940	30,835	122,321	56,374	11,619	371

Table S5: Numbers of predicted A-Es and A-Ps on the 102,021 BDT loci. AiA: Active in the FANTOM Enhancer Atlas. IiA: Inactive in the FANTOM Enhancer Atlas. NiA: Not included in the FANTOM Enhancer Atlas. Specific: Predicted cell-specific A-Es.

Cell	A-E	A-P	BG
GM12878	11,910	1,975	88,136
HelaS3	12,743	226	89,052
HepG2	10,761	488	90,772
HMEC	13,356	1,267	87,398
HUVEC	17,192	758	84,071
K562	13,936	288	87,797

Table S6: Overlap between our predicted A-Es and the FANTOM enhancer atlas.

Cell\Element	AiA	IiA	NiA	Specific
GM12878	2,088	5,144	4,678	4,199
HelaS3	1,459	6,435	4,849	1,073
HepG2	1,178	4,888	4,695	1,495
HMEC	1,250	6,644	5,462	1,916
HUVEC	879	8,716	7,597	3,560
K562	750	7,383	5,803	2,965

Table S7: Transcription factors whose binding motifs are enriched in specific cells.

Cell	Transcription Factor	Functionality
GM12878	RUNX1	RUNX1 and other Runt-related factors play crucial roles in haematopoiesis. Translocation of RUNX1 leads to severe acute myeloid leukemia [11].
GM12878	REL/NF-κB Factors	Play a critical role in immune response to infection [4].
HelaS3	C/EBP-Related Factors	C/EBP-related factors, a subfamily of the basic leucine zipper factors (bZIP), regulating genes involved in immune and inflammatory responses, are expressed in cervix [1].
HelaS3	CREB-Related Factors (Another bZIP Subfamily)	Possibly up-regulate Bcl-2 expression in apoptotic HeLa cells induced by trichosanthin [15].
HelaS3	TEAD1	Plays a role of apoptotic resistance in Hela cells [9].
HelaS3	AP-2 Factors	Can act as tumor suppressor, and malfunction of AP-2 was found in cervical cancer cells [2].
HelaS3	HOX Factors	a subgroup of HOX genes involve in cervical carcinoma [8].
HepG2	HNF1A, HNF1B, FOXA1, FOXA2, HNF4A, and HNF4G	These factors are hepatocyte nuclear factors that regulate liver-specific genes [3, 16].
HepG2	C/EBPs	Have a pivotal role in liver development and function [13].
HMEC	TEAD Family	Members of this family regulate epithelial-mesenchymal transition [17].
HUVEC	GATA Factors	Involve in networks of key determinants of vascular endothelial cell identity [7].
HUVEC	SOX Factors	Regulate vascular cell development and growth (vasculogenesis) [12].
HUVEC	CREB-Related Factors	Involve in several specific pathways in HUVEC cell [14].
K562	GATA-Type, NFYA, and NFYB USF1	The NFY factors cooperate with GATA1 to mediate erythroid-specific transcription, and coassociate with FOS binding to both promoters and enhancers in K562 [5]. The NFY factors are also found cooperate with USF1 and USF2 to active HOXB4 for hematopoiesis [18].
K562	STAT5	Maintains the high-level cell proliferation of K562 [10].

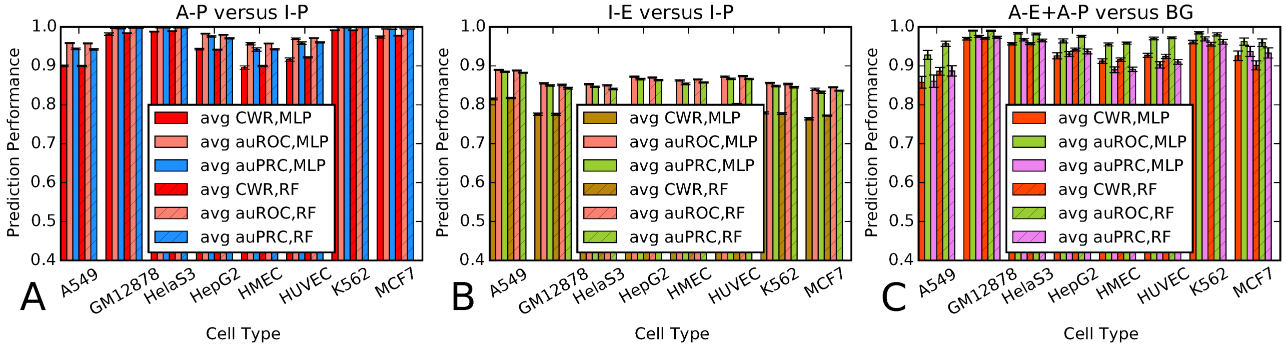


Figure S1: Mean performance and standard deviation of 10-fold cross-validations using the MLP model on our labelled data of eight cell types. A-E: Active Enhancer, A-P: Active Promoter, A-X: Active Exon, I-E: Inactive Enhancer, I-P: Inactive Promoter, I-X: Inactive Exon, UK: Unknown or Uncharacterized, BG: I-E+I-P+A-X+I-X+UK.

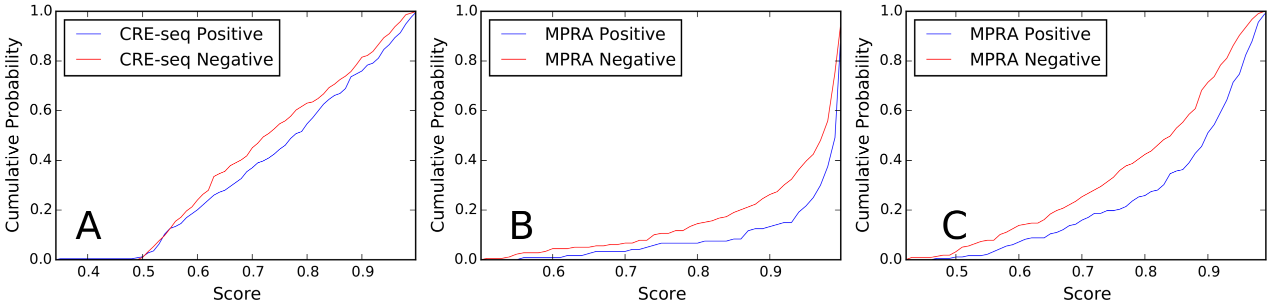


Figure S2: Cumulative DECRES membership probabilities (scores) of enhancers that were tested as positives and negatives by CRE-seq or MPRA. These enhancers were predicted as A-Es by DECRES (See Table S3).

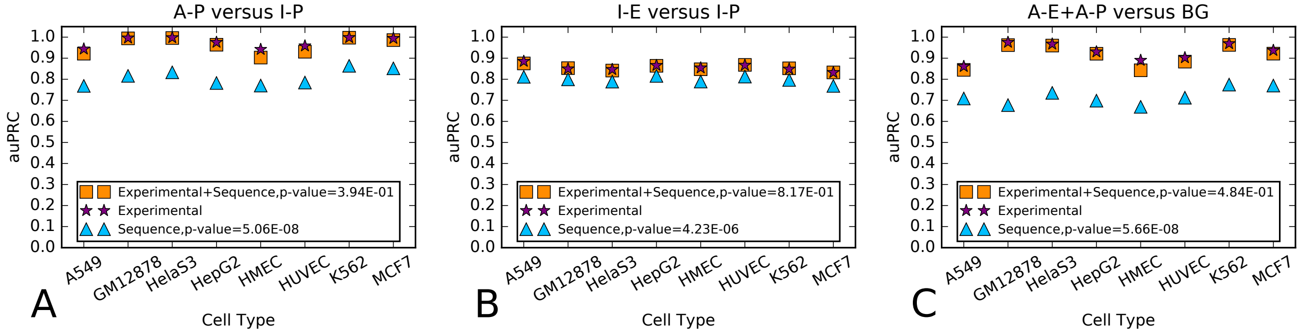


Figure S3: Comparing the mean auPRCs over 100 resampling and retraining on our labelled regions using different feature sets. "Experimental" means our experimentally derived next generation sequencing feature set. "Sequence" means the set of 351 sequence properties used in [6]. "Experimental+Sequence" means the combination of these two sets. The p-values in each legend were obtained using two-tailed Student's t-test to compare "Experimental"-based results with "Experimental+Sequence"-based and "Sequence"-based results, respectively.

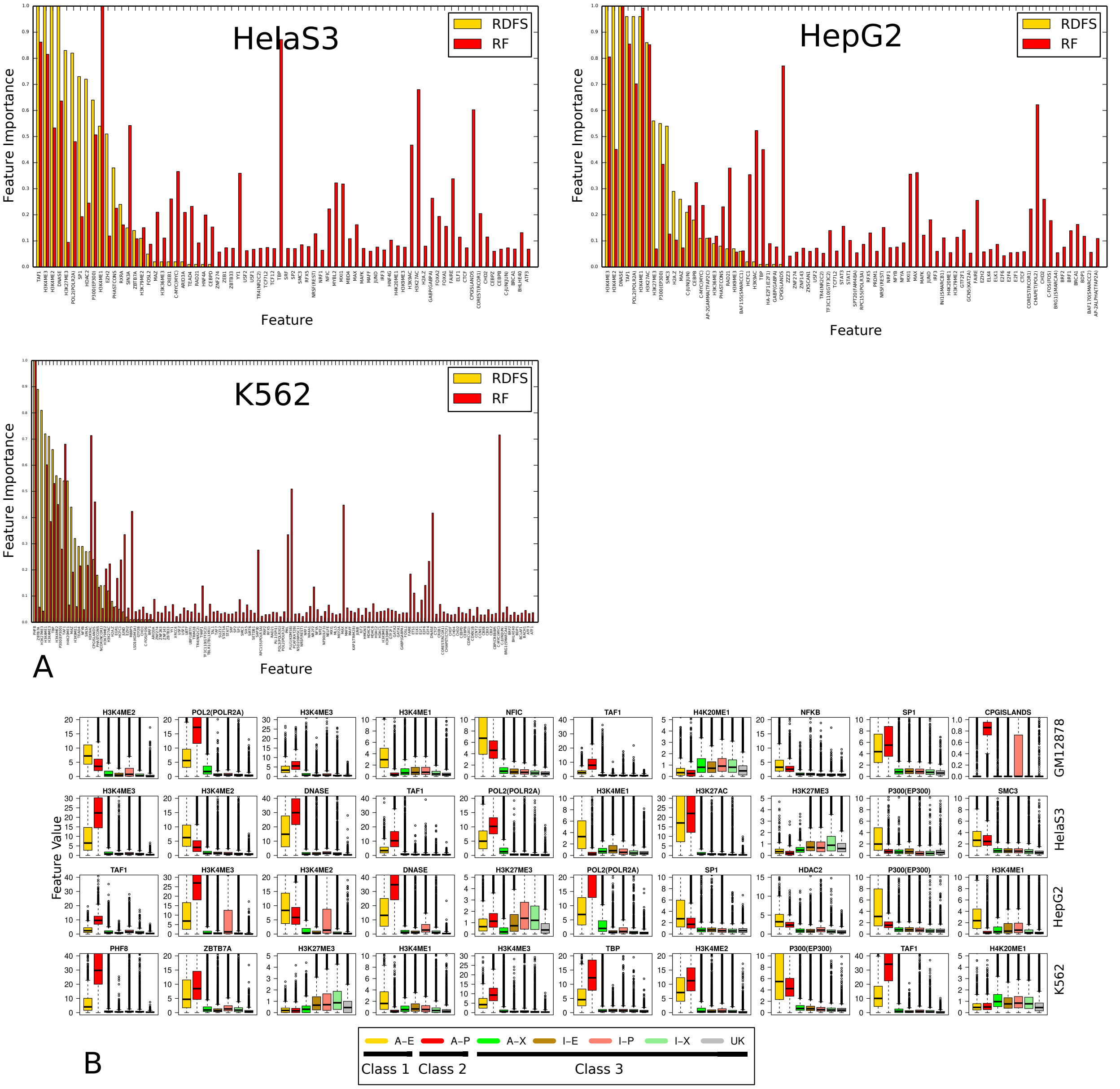


Figure S4: Feature importance and box plots of top features in the 3-class (A-E versus A-P versus BG) scenario. A: Feature importance discovered by randomized DFS (RDFS) and random forest (RF) on HelaS3, HepG2 and K562 cells. RF's feature importance scores were normalized to [0,1] for better comparison with RDFS. B: For the top 10 features of the 3-class models generated for four well-characterized cell lines, box plots depict the range of observed feature values (log2 scale) for 7 sequence classes.

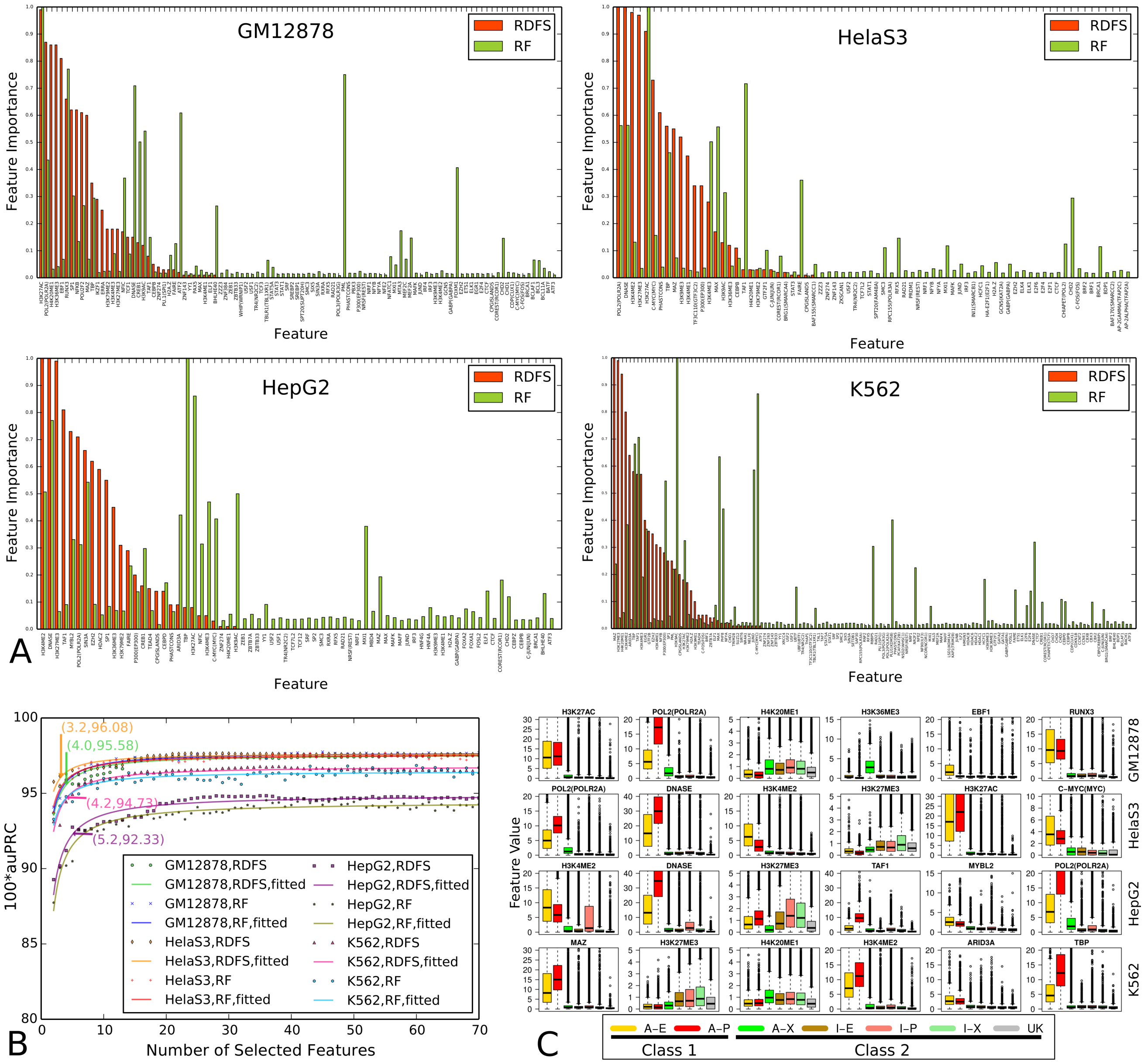


Figure S5: Feature importance, classification performance, and top features in the 2-class (A-E+A-P versus BG) scenario. A: Feature importance discovered by randomized DFS (RDFS) and random forest (RF). The random forest's feature importance scores were normalized to [0,1] for better comparison with randomized DFS. B: auPRC versus the number of features incorporated into the RDFS and RF. The annotated points indicate where a line with slope 0.5 intersects a fitted curve). C: For the top 6 features of the 2-class models generated for four well-characterized cell lines, box plots depict the range of observed feature values (log2 scale) for 7 sequence classes.

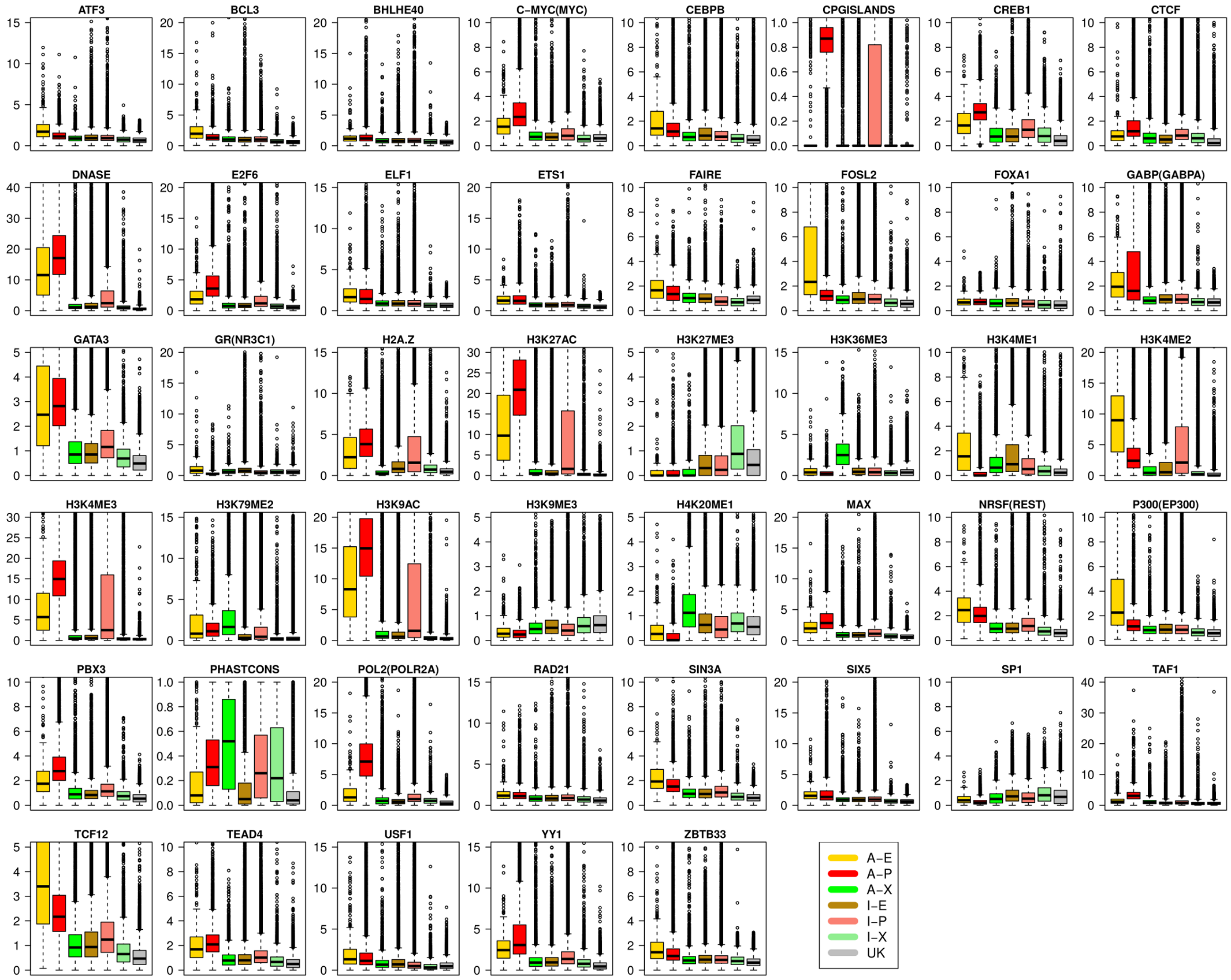


Figure S6: Box plots of all features for A549.

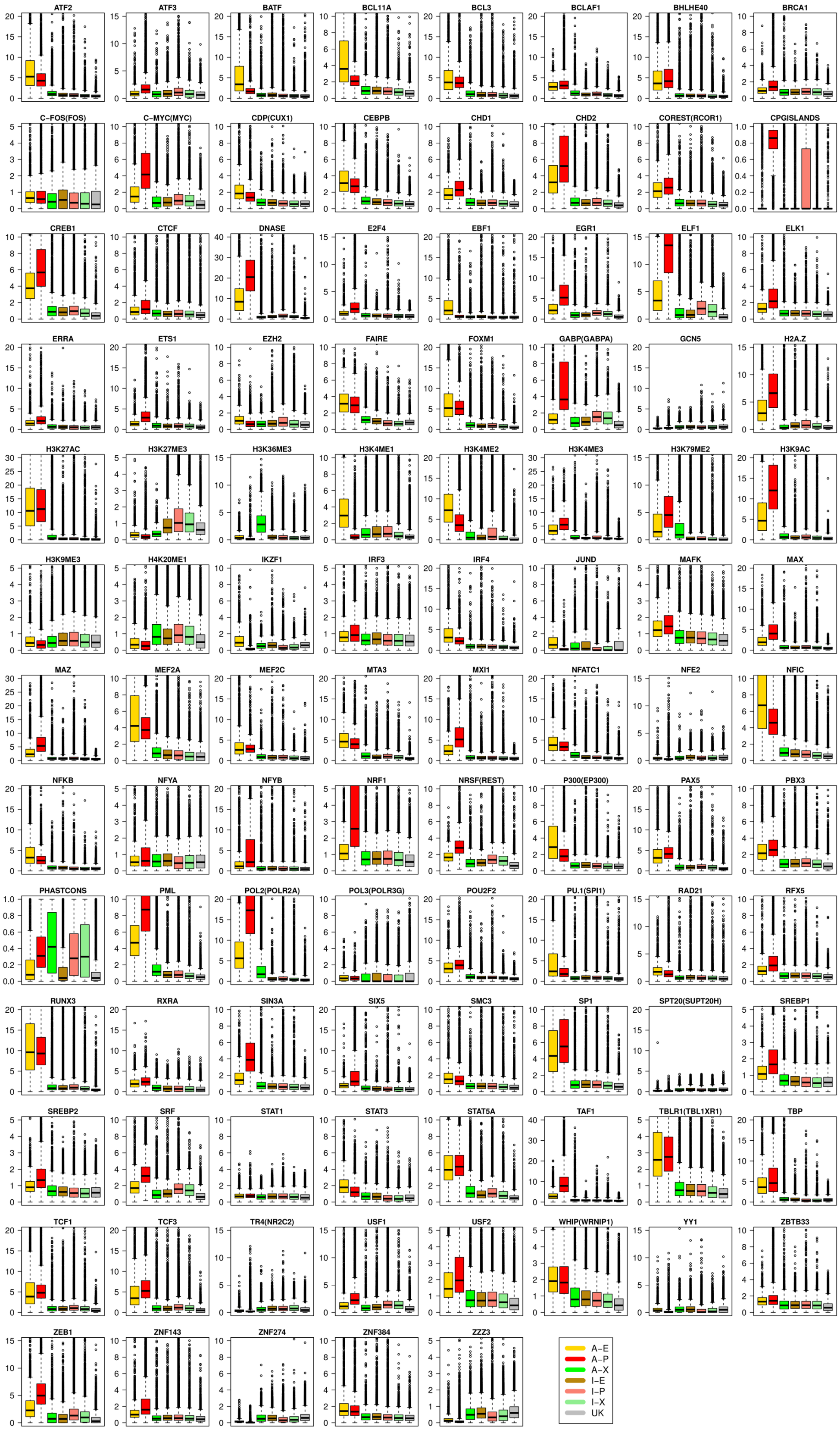


Figure S7: Box plots of all features for GM12878.

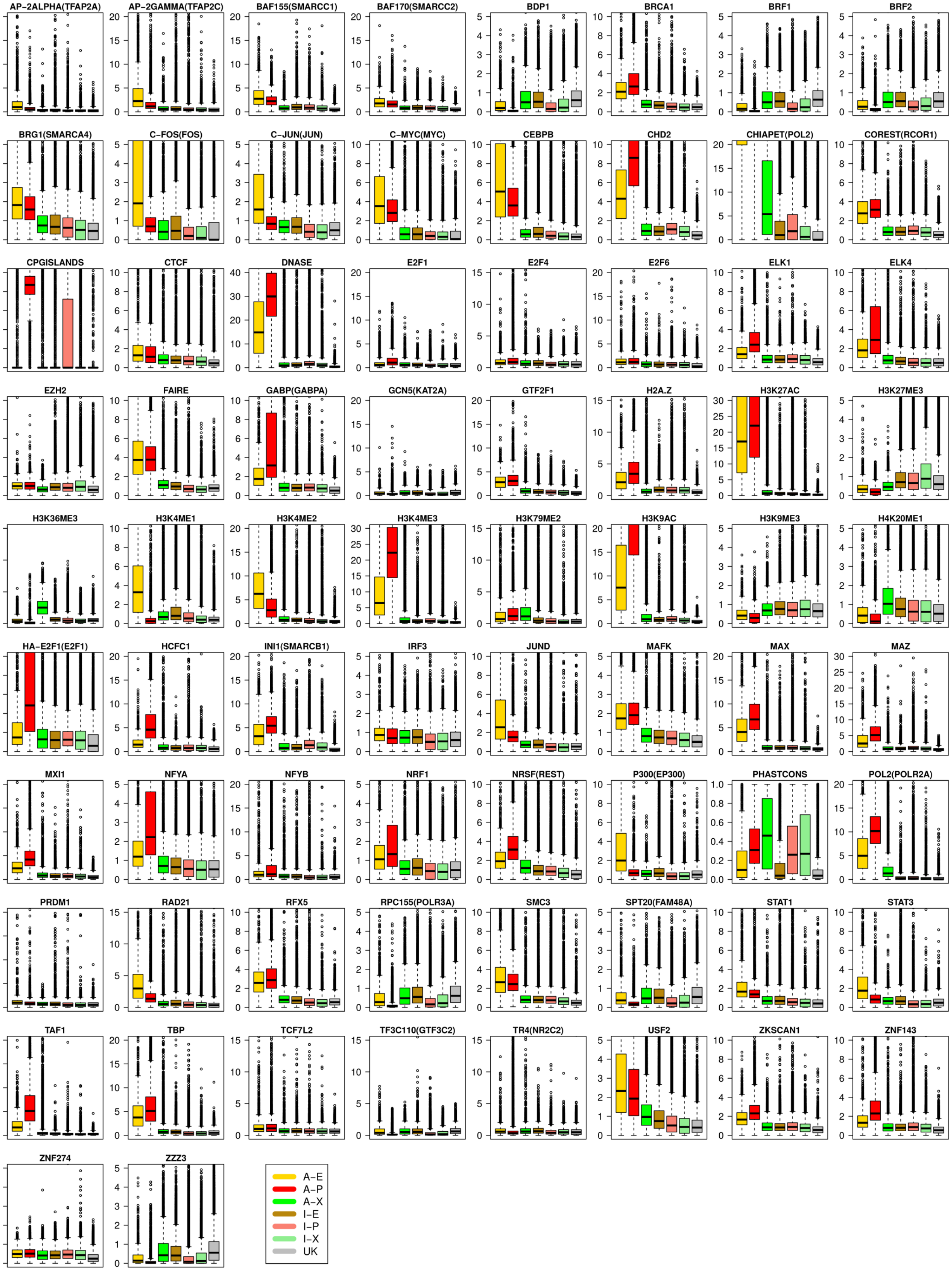


Figure S8: Box plots of all features for HelaS3.

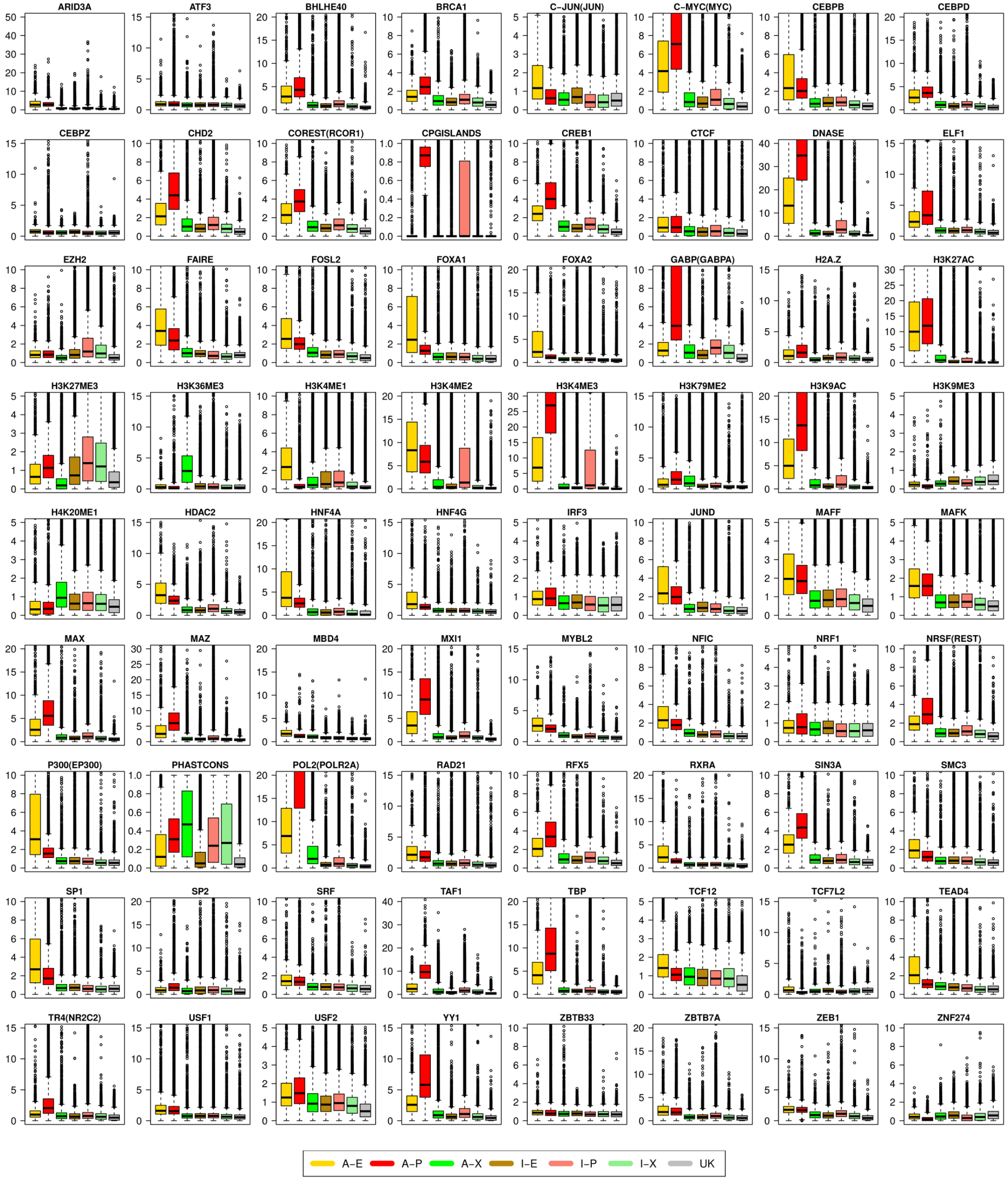


Figure S9: Box plots of all features for HepG2.

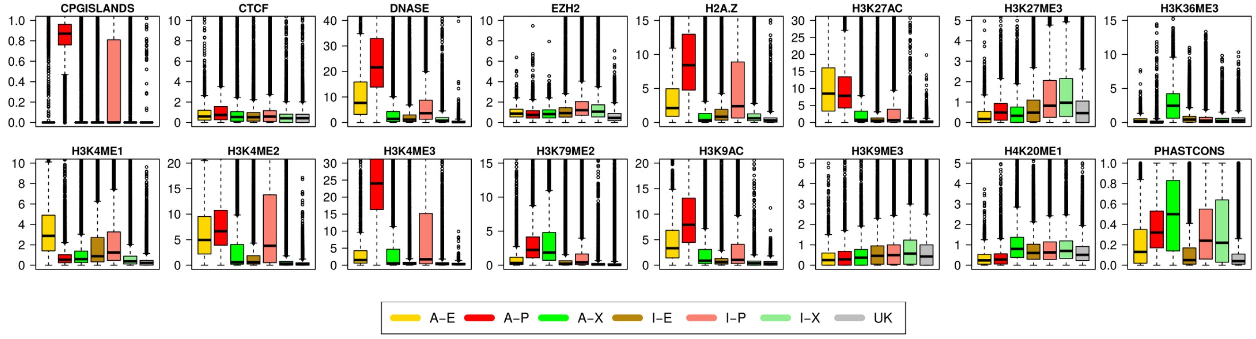


Figure S10: Box plots of all features for HMEC.

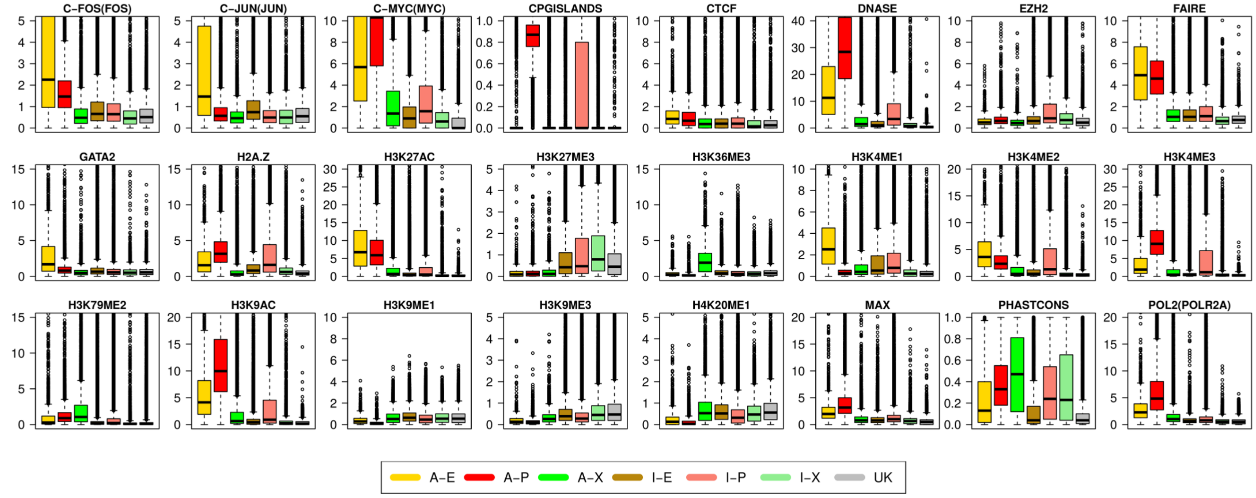


Figure S11: Box plots of all features for HUVEC.

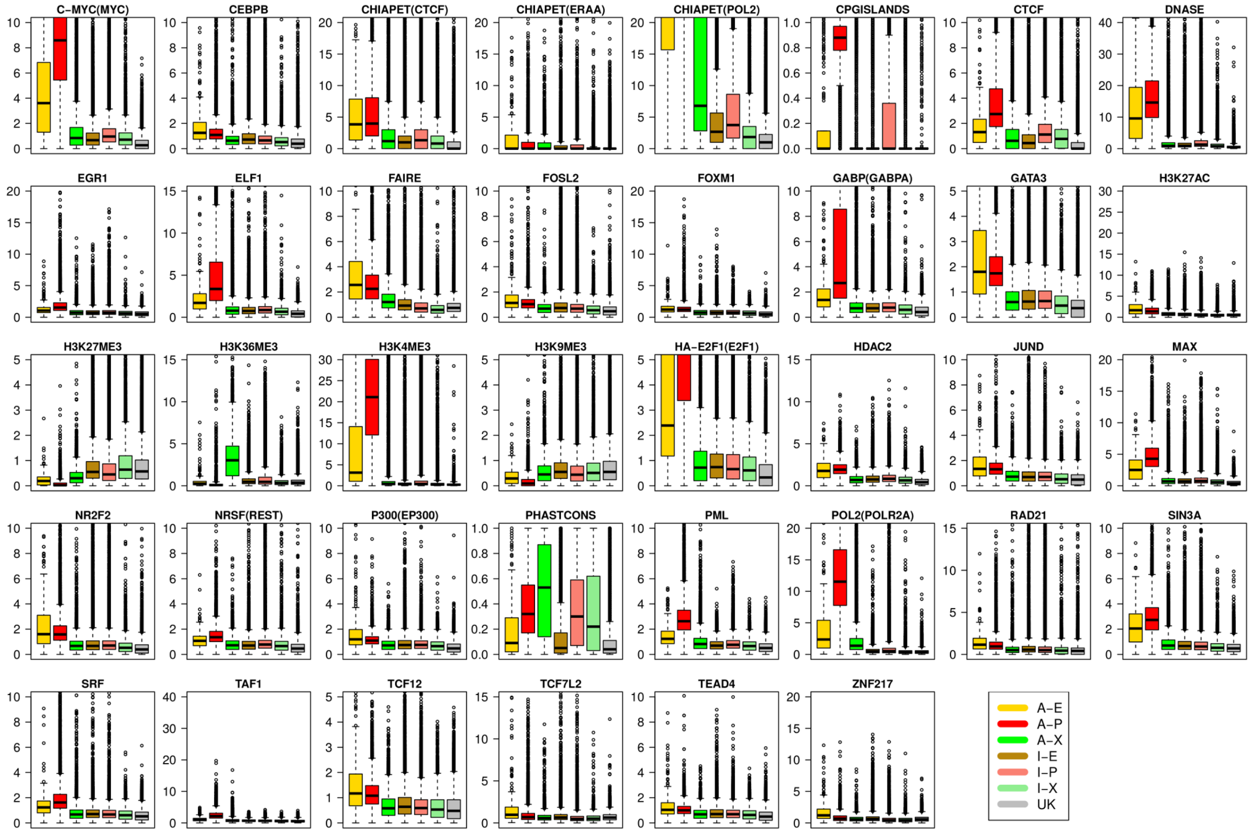


Figure S12: Box plots of all features for MCF7.

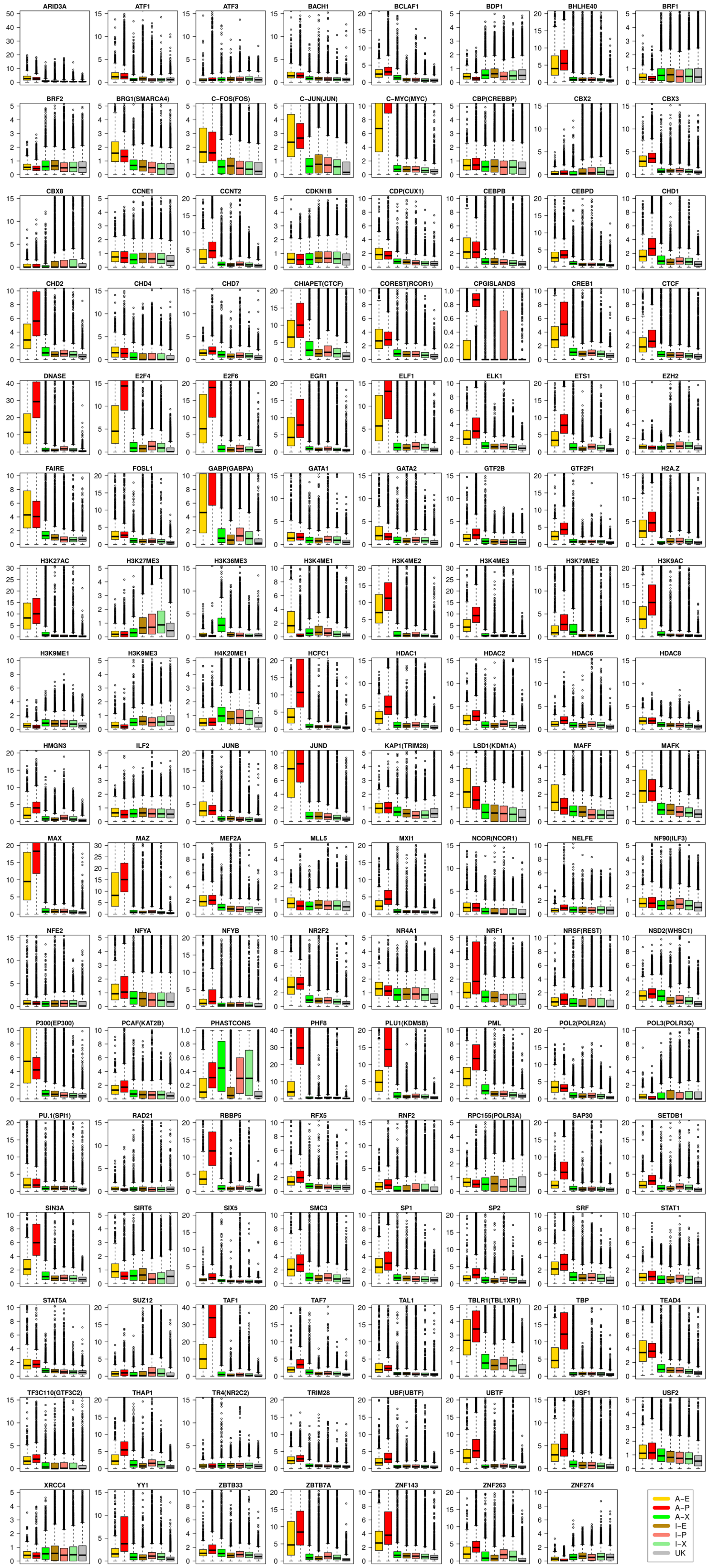
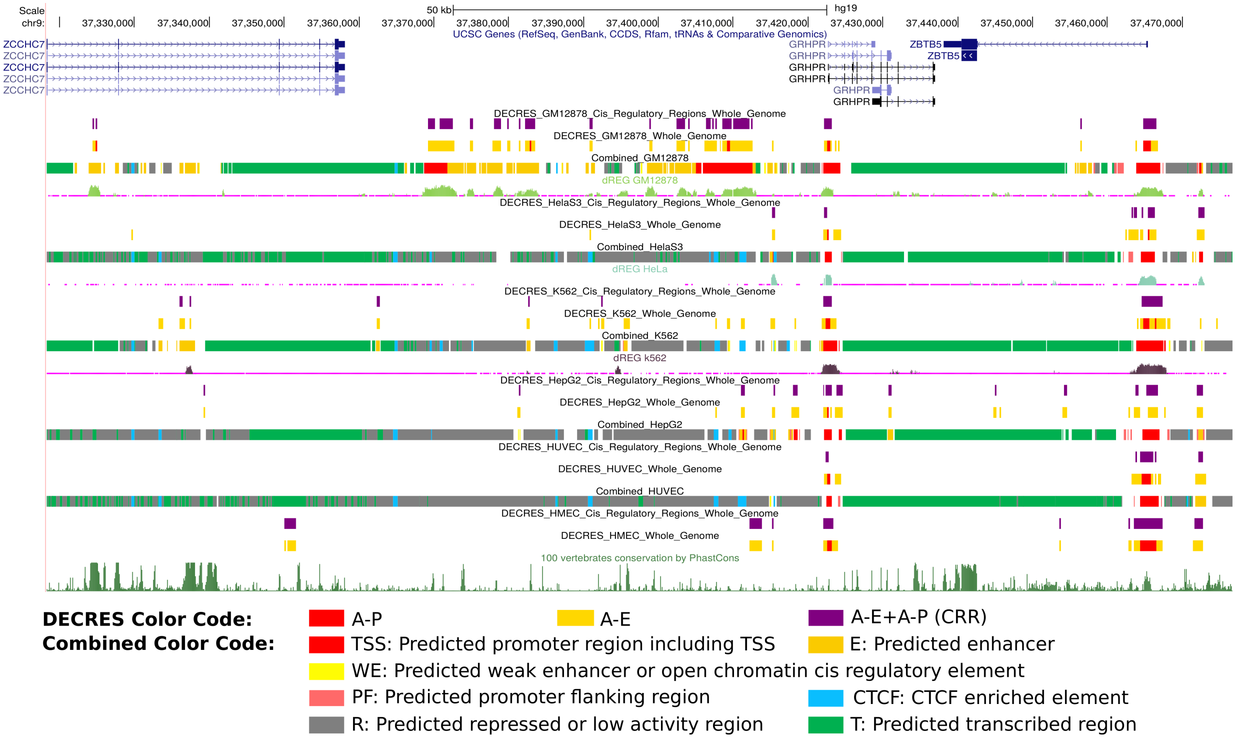


Figure S13: Box plots of all features for K562.


Scale
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UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
ZCCHC7
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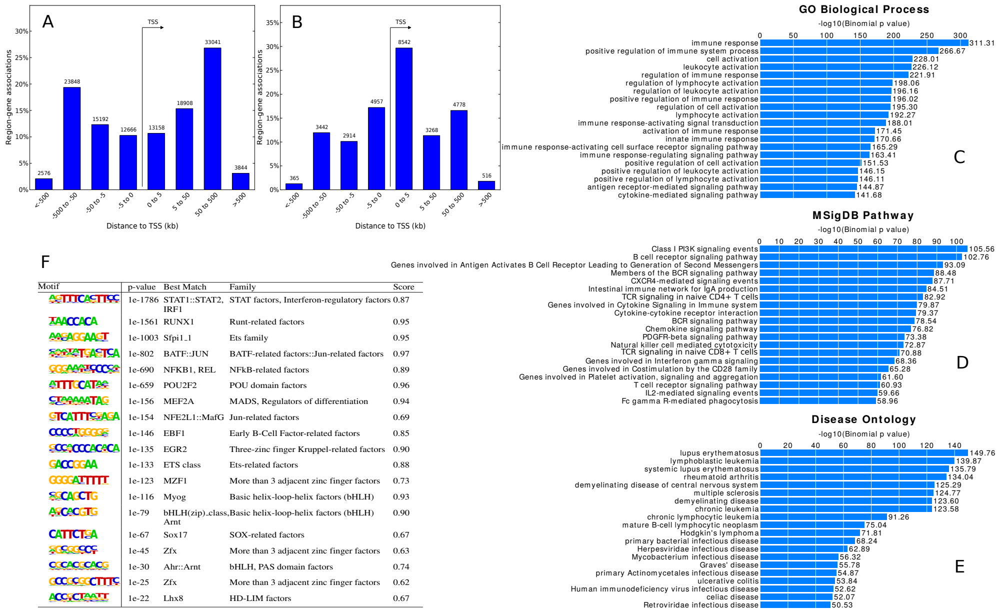
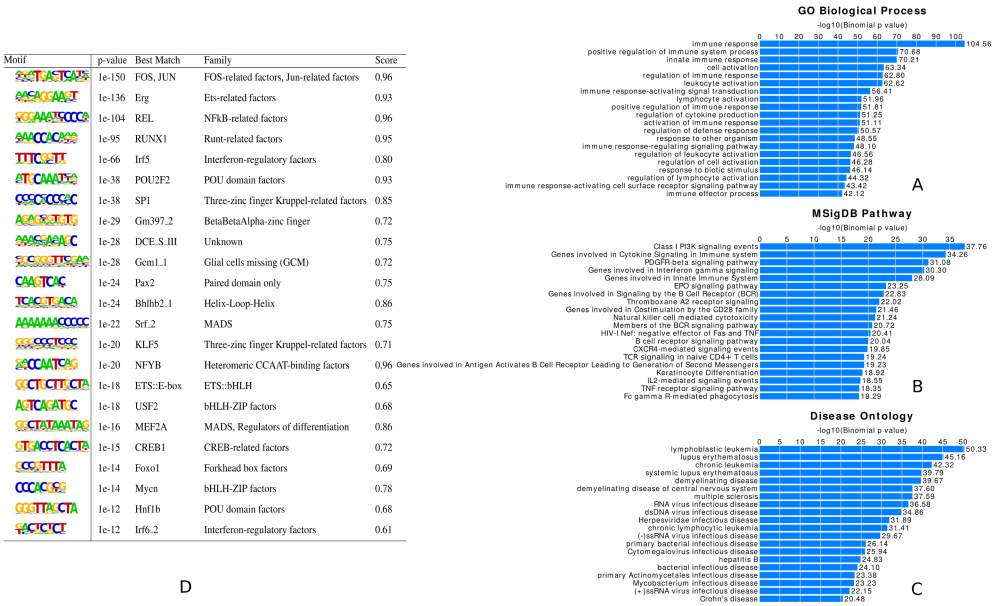
GRHPR
ZBTB5
ZBTB5
DECRES_GM12878_Cis_Regulatory_Regions_Whole_Genome
DECRES_GM12878_Whole_Genome
Combined_GM12878
dREG GM12878
DECRES_HelaS3_Cis_Regulatory_Regions_Whole_Genome
DECRES_HelaS3_Whole_Genome
Combined_HelaS3
dREG HeLa
DECRES_K562_Cis_Regulatory_Regions_Whole_Genome
DECRES_K562_Whole_Genome
Combined_K562
dREG k562
DECRES_HepG2_Cis_Regulatory_Regions_Whole_Genome
DECRES_HepG2_Whole_Genome
Combined_HepG2
DECRES_HUVEC_Cis_Regulatory_Regions_Whole_Genome
DECRES_HUVEC_Whole_Genome
Combined_HUVEC
DECRES_HMEC_Cis_Regulatory_Regions_Whole_Genome
DECRES_HMEC_Whole_Genome
100 vertebrates conservation by PhastCons
DECRES Color Code:
Combined Color Code:
🟥 A-P
🟨 A-E
🟪 A-E+A-P (CRR)
🟥 TSS: Predicted promoter region including TSS
🟧 E: Predicted enhancer
🟨 WE: Predicted weak enhancer or open chromatin cis regulatory element
🟥 PF: Predicted promoter flanking region
🟦 CTCF: CTCF enriched element
⬛ R: Predicted repressed or low activity region
🟩 T: Predicted transcribed region

Figure S14: An example of predicted regulatory regions in the UCSC Genome Browser.



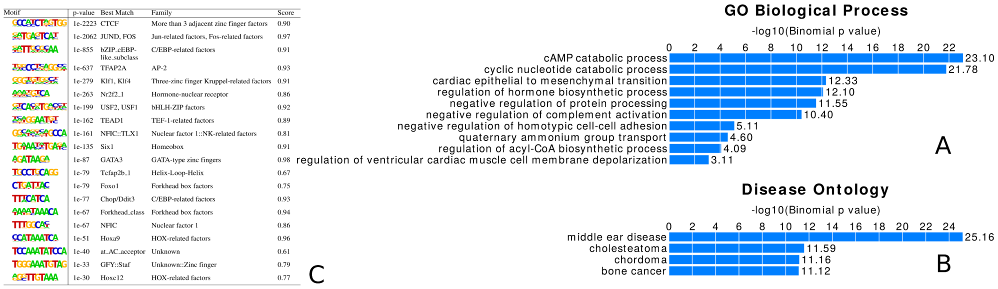
Motif	p-value	Best Match	Family	Score
AGTTTCACTTCC	1e-1786	STAT1::STAT2, IRF1	STAT factors, Interferon-regulatory factors	0.87
TAACCACA	1e-1561	RUNX1	Runt-related factors	0.95
AAGAGGAAGT	1e-1003	Sfpi1_1	Ets family	0.95
GAATATGAGTCA	1e-802	BATF::JUN	BATF-related factors::Jun-related factors	0.97
GGGAAATCCCCA	1e-690	NFKB1, REL	NFkB-related factors	0.89
ATTTGCATAA	1e-659	POU2F2	POU domain factors	0.96
CTAAAAATAG	1e-156	MEF2A	MADS, Regulators of differentiation	0.94
GTCATTTGAAGA	1e-154	NFE2L1::MafG	Jun-related factors	0.69
CCCCTGGGGG	1e-146	EBF1	Early B-Cell Factor-related factors	0.85
GCCACCCACACA	1e-135	EGR2	Three-zinc finger Kruppel-related factors	0.90
GACCGGAA	1e-133	ETS class	Ets-related factors	0.88
GGGGATTTTT	1e-123	MZF1	More than 3 adjacent zinc finger factors	0.73
GGCAGCTG	1e-116	Myog	Basic helix-loop-helix factors (bHLH)	0.93
AGCACGTG	1e-79	bHLH(zip)_class, Arnt	Basic helix-loop-helix factors (bHLH)	0.90
CATTCTGA	1e-67	Sox17	SOX-related factors	0.67
GGCGGCCC	1e-45	Zfx	More than 3 adjacent zinc finger factors	0.63
CGCACGCACG	1e-30	Ahr::Arnt	bHLH, PAS domain factors	0.74
GCCGCGGCTTTC	1e-25	Zfx	More than 3 adjacent zinc finger factors	0.62
ACCGCTAATT	1e-22	Lhx8	HD-LIM factors	0.67

Figure S15: Functional and motif analysis of the DECRES genome-wide predictions on cell line GM12878. A: Distance from the predicted A-Es to gene TSSs. B: Distance from the predicted A-Ps to gene TSSs. C,D,E: Top 20 enriched biological processes, pathways, and diseases, respectively, in the predicted cell-specific CRRs. F: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.



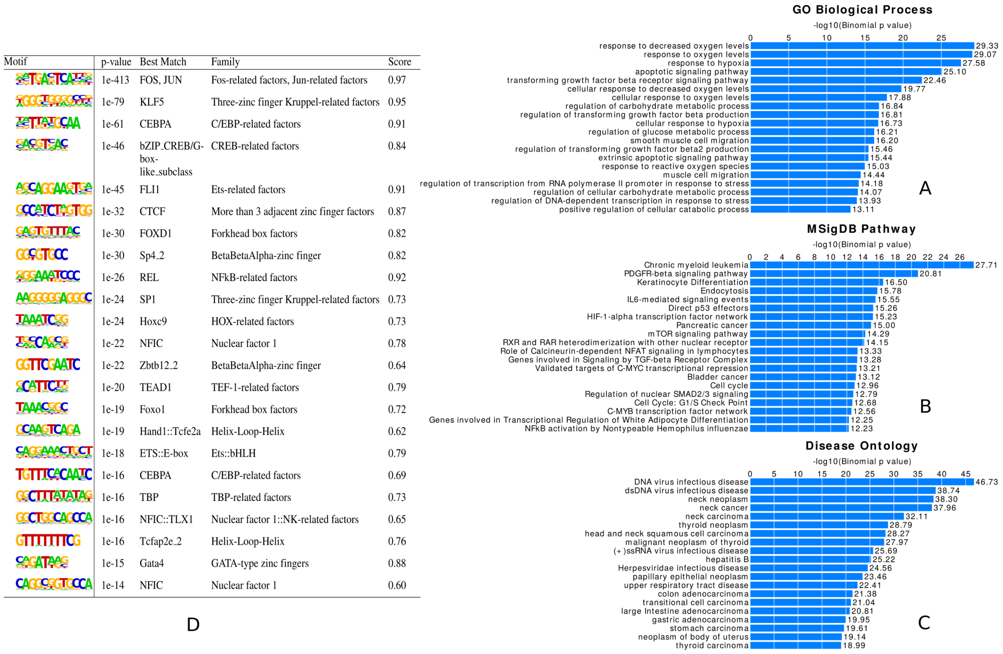
Motif	p-value	Best Match	Family	Score
ATGACTCAT	1e-150	FOS, JUN	FOS-related factors, Jun-related factors	0.96
AACAGGAAGT	1e-136	Erg	Ets-related factors	0.93
GGGAAATCCCCA	1e-104	REL	NFkB-related factors	0.96
AAACCACAAA	1e-95	RUNX1	Runt-related factors	0.95
TTTCGGTT	1e-66	Irf5	Interferon-regulatory factors	0.80
ATGCAAATCA	1e-38	POU2F2	POU domain factors	0.93
CCCCACCCCAC	1e-38	SP1	Three-zinc finger Kruppel-related factors	0.85
AGAGCGTGTG	1e-29	Gm397_2	BetaBetaAlpha-zinc finger	0.72
AAACGAAAGC	1e-28	DCE_S_III	Unknown	0.75
GGCGGGTTCGAA	1e-28	Gcm1_1	Glial cells missing (GCM)	0.72
CAAGTCAC	1e-24	Pax2	Paired domain only	0.75
TCACGTGACA	1e-24	Bhlhb2_1	Helix-Loop-Helix	0.86
AAAAAAACCCCC	1e-22	Srf_2	MADS	0.75
GGGCCCTCCC	1e-20	KLF5	Three-zinc finger Kruppel-related factors	0.71
GACCAATCAG	1e-20	NFYB	Heteromeric CCAAT-binding factors	0.96
GGCTGCTTGCTA	1e-18	ETS::E-box	ETS::bHLH	0.65
AGTCAGATGC	1e-18	USF2	bHLH-ZIP factors	0.68
GGCTATAAATAG	1e-16	MEF2A	MADS, Regulators of differentiation	0.86
GTGACCTCACTA	1e-15	CREB1	CREB-related factors	0.72
GCCGTTTA	1e-14	Foxo1	Forkhead box factors	0.69
CCCACGCG	1e-14	Mycn	bHLH-ZIP factors	0.78
GGGTTAGCTA	1e-12	Hnf1b	POU domain factors	0.68
GACTCTCT	1e-12	Irf6_2	Interferon-regulatory factors	0.61

Figure S16: Functional and motif analysis of the DECRES NiA enhancers on cell line GM12878. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: the families of best-matched TFs. Column 5: best match scores.



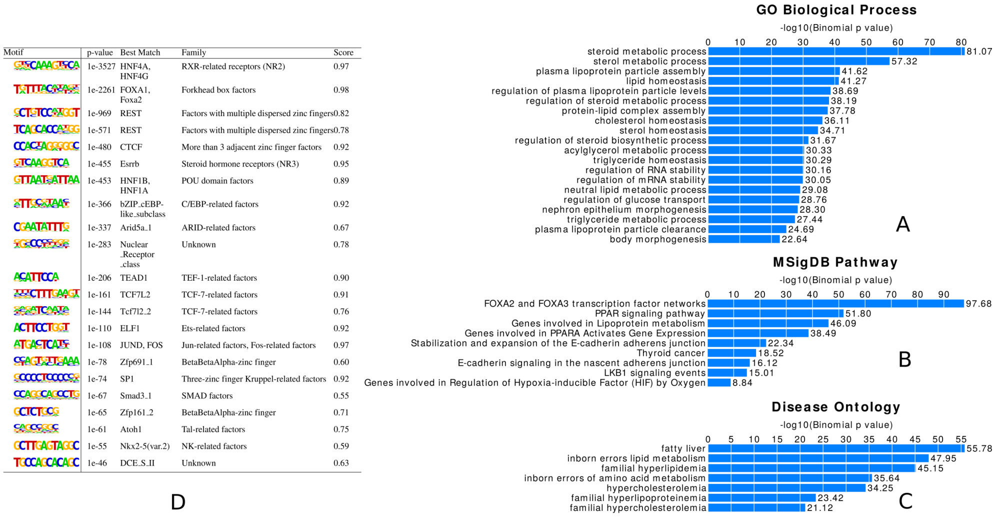
Motif	p-value	Best Match	Family	Score
GCCATCTAGTGG	1e-2223	CTCF	More than 3 adjacent zinc finger factors	0.90
ATGACTCAT	1e-2062	JUND, FOS	Jun-related factors, Fos-related factors	0.97
GATTGCGCAA	1e-855	bZIP_cEBP-like_subclass	C/EBP-related factors	0.91
TGGCCTCAGGCC	1e-637	TFAP2A	AP-2	0.93
GGGTGTGGCT	1e-279	Klf1, Klf4	Three-zinc finger Kruppel-related factors	0.91
AAATGTCA	1e-263	Nr2f2_1	Hormone-nuclear receptor	0.86
GTCACGTGACGT	1e-199	USF2, USF1	bHLH-ZIP factors	0.92
TCAGGAATGT	1e-162	TEAD1	TEF-1-related factors	0.89
GGCAACACAGCCA	1e-161	NFIC::TLX1	Nuclear factor 1::NK-related factors	0.81
TGAAATATGATA	1e-135	Six1	Homeobox	0.91
AGATAAGA	1e-87	GATA3	GATA-type zinc fingers	0.98
TGCCTGCAGG	1e-79	Tcfap2b_1	Helix-Loop-Helix	0.67
CTGATTAC	1e-79	Foxo1	Forkhead box factors	0.75
TTTCATCA	1e-77	Chop/Ddit3	C/EBP-related factors	0.93
AAAATAAACA	1e-67	Forkhead_class	Forkhead box factors	0.94
TTTGGCAC	1e-67	NFIC	Nuclear factor 1	0.86
CCATAAATCA	1e-51	Hoxa9	HOX-related factors	0.96
TCCAAATATCCA	1e-40	at_AC_acceptor	Unknown	0.61
TGGGAAATGTAG	1e-33	GFY::Staf	Unknown::Zinc finger	0.79
AGGTTGTAAA	1e-30	Hoxc12	HOX-related factors	0.77

Figure S17: Functional and motif analysis of the DECRES genome-wide predictions on cell line HelaS3. A,B: Top enriched biological processes and diseases (no pathways enriched for HelaS3), respectively, in the predicted cell-specific CRRs. C: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.



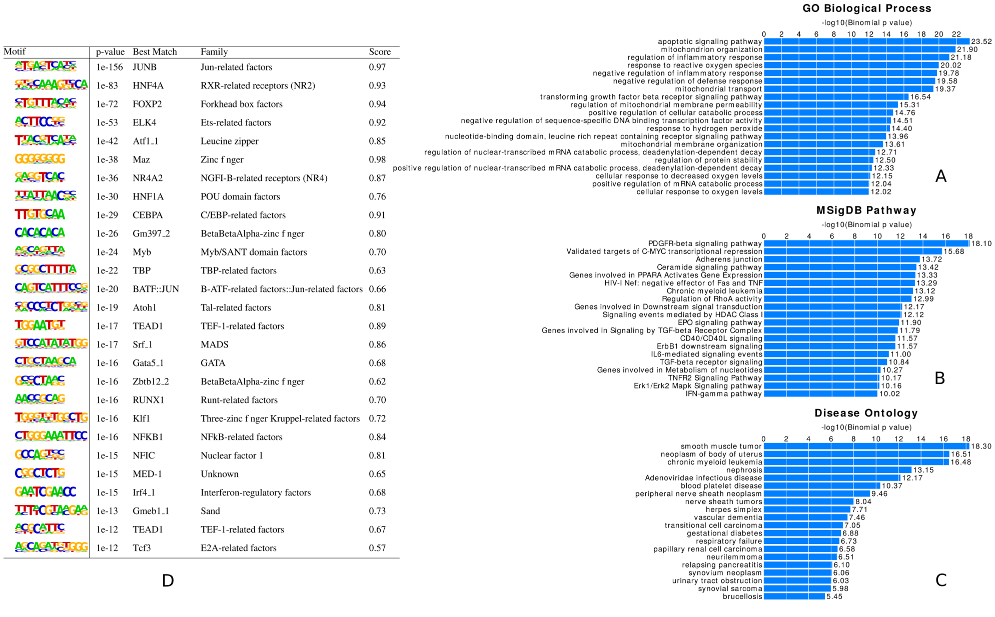
Motif	p-value	Best Match	Family	Score
	1e-413	FOS, JUN	Fos-related factors, Jun-related factors	0.97
	1e-79	KLF5	Three-zinc finger Kruppel-related factors	0.95
	1e-61	CEBPA	C/EBP-related factors	0.91
	1e-46	bZIP_CREB/G-box-like_subclass	CREB-related factors	0.84
	1e-45	FLI1	Ets-related factors	0.91
	1e-32	CTCF	More than 3 adjacent zinc finger factors	0.87
	1e-30	FOXD1	Forkhead box factors	0.82
	1e-30	Sp4_2	BetaBetaAlpha-zinc finger	0.82
	1e-26	REL	NFkB-related factors	0.92
	1e-24	SP1	Three-zinc finger Kruppel-related factors	0.73
	1e-24	Hoxc9	HOX-related factors	0.73
	1e-22	NFIC	Nuclear factor 1	0.78
	1e-22	Zbtb12_2	BetaBetaAlpha-zinc finger	0.64
	1e-20	TEAD1	TEF-1-related factors	0.79
	1e-19	Foxo1	Forkhead box factors	0.72
	1e-19	Hand1::Tcfe2a	Helix-Loop-Helix	0.62
	1e-18	ETS::E-box	Ets::bHLH	0.79
	1e-16	CEBPA	C/EBP-related factors	0.69
	1e-16	TBP	TBP-related factors	0.73
	1e-16	NFIC::TLX1	Nuclear factor 1::NK-related factors	0.65
	1e-16	Tcfap2e_2	Helix-Loop-Helix	0.76
	1e-15	Gata4	GATA-type zinc fingers	0.88
	1e-14	NFIC	Nuclear factor 1	0.60

Figure S18: Functional and motif analysis of the DECRES NiA enhancers on cell line HelaS3. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: families of best-matched TFs. Column 5: best match scores.



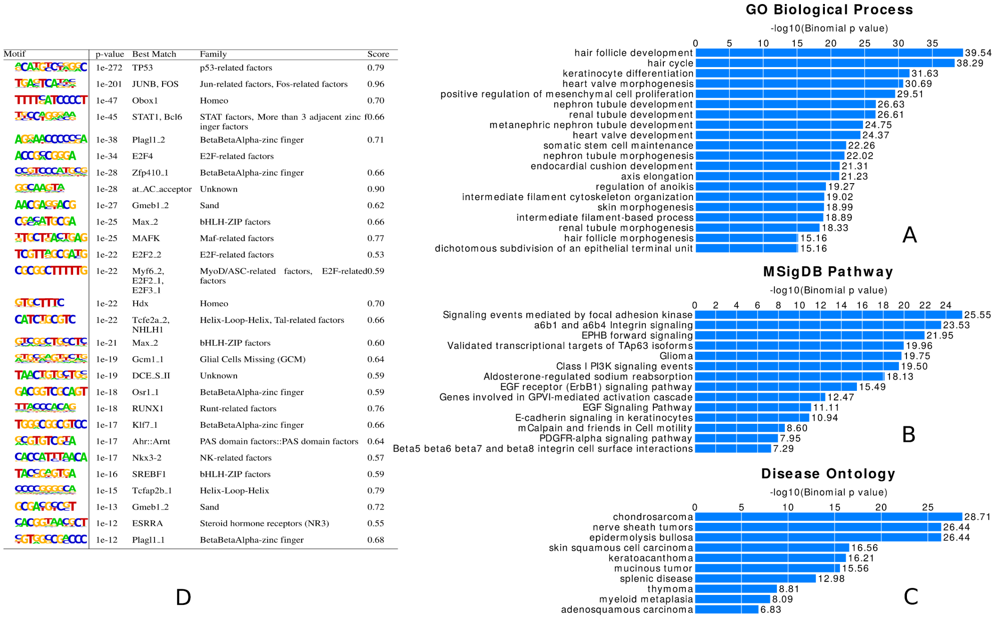
Motif	p-value	Best Match	Family	Score
	1e-3527	HNF4A, HNF4G	RXR-related receptors (NR2)	0.97
	1e-2261	FOXA1, Foxa2	Forkhead box factors	0.98
	1e-969	REST	Factors with multiple dispersed zinc fingers	0.82
	1e-571	REST	Factors with multiple dispersed zinc fingers	0.78
	1e-480	CTCF	More than 3 adjacent zinc finger factors	0.92
	1e-455	Esrrb	Steroid hormone receptors (NR3)	0.95
	1e-453	HNF1B, HNF1A	POU domain factors	0.89
	1e-366	bZIP_cEBP-like_subclass	C/EBP-related factors	0.92
	1e-337	Arid5a_1	ARID-related factors	0.67
	1e-283	Nuclear_Receptor_class	Unknown	0.78
	1e-206	TEAD1	TEF-1-related factors	0.90
	1e-161	TCF7L2	TCF-7-related factors	0.91
	1e-144	Tcf7l2_2	TCF-7-related factors	0.76
	1e-110	ELF1	Ets-related factors	0.92
	1e-108	JUND, FOS	Jun-related factors, Fos-related factors	0.97
	1e-78	Zfp691_1	BetaBetaAlpha-zinc finger	0.60
	1e-74	SP1	Three-zinc finger Kruppel-related factors	0.92
	1e-67	Smad3_1	SMAD factors	0.55
	1e-65	Zfp161_2	BetaBetaAlpha-zinc finger	0.71
	1e-61	Atoh1	Tal-related factors	0.75
	1e-55	Nkx2-5(var.2)	NK-related factors	0.59
	1e-46	DCE_S_II	Unknown	0.63

Figure S19: Functional and motif analysis of the DECRES genome-wide predictions on cell line HepG2. A,B,C: Top enriched biological processes,pathways and diseases, respectively, in the predicted cell-specific CRRs. D: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.



Motif	p-value	Best Match	Family	Score
	1e-156	JUNB	Jun-related factors	0.97
	1e-83	HNF4A	RXR-related receptors (NR2)	0.93
	1e-72	FOXP2	Forkhead box factors	0.94
	1e-53	ELK4	Ets-related factors	0.92
	1e-42	Atf1_1	Leucine zipper	0.85
	1e-38	Maz	Zinc finger	0.98
	1e-36	NR4A2	NGFI-B-related receptors (NR4)	0.87
	1e-30	HNF1A	POU domain factors	0.76
	1e-29	CEBPA	C/EBP-related factors	0.91
	1e-26	Gm397_2	BetaBetaAlpha-zinc finger	0.80
	1e-24	Myb	Myb/SANT domain factors	0.70
	1e-22	TBP	TBP-related factors	0.63
	1e-20	BATF::JUN	B-ATF-related factors::Jun-related factors	0.66
	1e-19	Atoh1	Tal-related factors	0.81
	1e-17	TEAD1	TEF-1-related factors	0.89
	1e-17	Srf_1	MADS	0.86
	1e-16	Gata5_1	GATA	0.68
	1e-16	Zbtb12_2	BetaBetaAlpha-zinc finger	0.62
	1e-16	RUNX1	Runt-related factors	0.70
	1e-16	Klf1	Three-zinc finger Kruppel-related factors	0.72
	1e-16	NFKB1	NFkB-related factors	0.84
	1e-15	NFIC	Nuclear factor 1	0.81
	1e-15	MED-1	Unknown	0.65
	1e-15	Irf4_1	Interferon-regulatory factors	0.68
	1e-13	Gmeb1_1	Sand	0.73
	1e-12	TEAD1	TEF-1-related factors	0.67
	1e-12	Tcf3	E2A-related factors	0.57

Figure S20: Functional and motif analysis of the DECRES NiA enhancers on cell line HepG2. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: families of best-matched TFs. Column 5: best match scores.



Motif	p-value	Best Match	Family	Score
	1e-272	TP53	p53-related factors	0.79
	1e-201	JUNB, FOS	Jun-related factors, Fos-related factors	0.96
	1e-47	Obox1	Homeo	0.70
	1e-45	STAT1, Bcl6	STAT factors, More than 3 adjacent zinc finger factors	0.66
	1e-38	Plagl1_2	BetaBetaAlpha-zinc finger	0.71
	1e-34	E2F4	E2F-related factors	
	1e-28	Zfp410_1	BetaBetaAlpha-zinc finger	0.66
	1e-28	at_AC_acceptor	Unknown	0.90
	1e-27	Gmeb1_2	Sand	0.62
	1e-25	Max_2	bHLH-ZIP factors	0.66
	1e-25	MAFK	Maf-related factors	0.77
	1e-22	E2F2_2	E2F-related factors	0.53
	1e-22	Myf6_2, E2F2_1, E2F3_1	MyoD/ASC-related factors, E2F-related factors	0.59
	1e-22	Hdx	Homeo	0.70
	1e-22	Tcfe2a_2, NHLH1	Helix-Loop-Helix, Tal-related factors	0.66
	1e-21	Max_2	bHLH-ZIP factors	0.60
	1e-19	Gcm1_1	Glial Cells Missing (GCM)	0.64
	1e-19	DCE_S_II	Unknown	0.59
	1e-18	Osr1_1	BetaBetaAlpha-zinc finger	0.59
	1e-18	RUNX1	Runt-related factors	0.76
	1e-17	Klf7_1	BetaBetaAlpha-zinc finger	0.66
	1e-17	Ahr::Arnt	PAS domain factors::PAS domain factors	0.64
	1e-17	Nkx3-2	NK-related factors	0.57
	1e-16	SREBF1	bHLH-ZIP factors	0.59
	1e-15	Tcfap2b_1	Helix-Loop-Helix	0.79
	1e-13	Gmeb1_2	Sand	0.72
	1e-12	ESRRA	Steroid hormone receptors (NR3)	0.55
	1e-12	Plagl1_1	BetaBetaAlpha-zinc finger	0.68

Figure S21: Functional and motif analysis of the DECRES genome-wide predictions on cell line HMEC. A,B,C: Top enriched biological processes,pathways and diseases, respectively, in the predicted cell-specific CRRs. D: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.

Motif	p-value	Best Match	Family	Score
GAATGACTCATT	1e-288	FOS, JUN	Fos-related factors, Jun-related factors	0.95
TCACTTCCTGTC	1e-70	Erg	Ets-related factors	0.92
CCCCGCCC	1e-33	KLF5	Three-zinc finger Kruppel-related factors	0.92
GGAATGTT	1e-30	TEAD1	TEF-1-related factors	0.87
TGACGTCACA	1e-30	Atf1_1	Leucine zipper	0.92
ACTGATTACA	1e-24	FOXO3	Forkhead box factors	0.68
TAACCACG	1e-23	RUNX1	Runt-related factors	0.70
CCAGTGACTAAA	1e-21	Zbtb3_2	BetaBetaAlpha-zinc finger	0.69
GGTGTGGC	1e-21	Klf1	Three-zinc finger Kruppel-related factors	0.75
TGGCAACCGG	1e-20	RFX5	RFX-related factors	0.73
TTGTGCAA	1e-19	CEBPA	C/EBP-related factors	0.86
GCTGTTACGT	1e-19	Rhox11_2	Paired-related HD factors	0.69
TGTGTGTGTG	1e-19	Gm397_2	BetaBetaAlpha-zinc finger	0.77
CAGGCAGCCT	1e-19	Osr1_2	BetaBetaAlpha-zinc finger	0.61
AAGCCGCA	1e-18	Gcm1_1	Glial Cells Missing (GCM)	0.64
TTCGTAAG	1e-17	Gmeb1_1	Sand	0.66
TCTGAGCG	1e-15	INR	Unknown	0.61
GCAAATATGC	1e-14	FOXI1	Forkhead box factors	0.65
TTTTTTTTTCC	1e-14	Srf_2	MADS	0.87
ATCTGCGCTG	1e-14	DCE_S_II	Unknown	0.70
AAAAGCCTCG	1e-14	Nr2e3	RXR-related receptors (NR2)	0.60
TCCTTAAAAGGC	1e-13	TBP	TBP-related factors	0.72
CCGATTTA	1e-13	Hoxc9	HOX-related factors	0.72

D

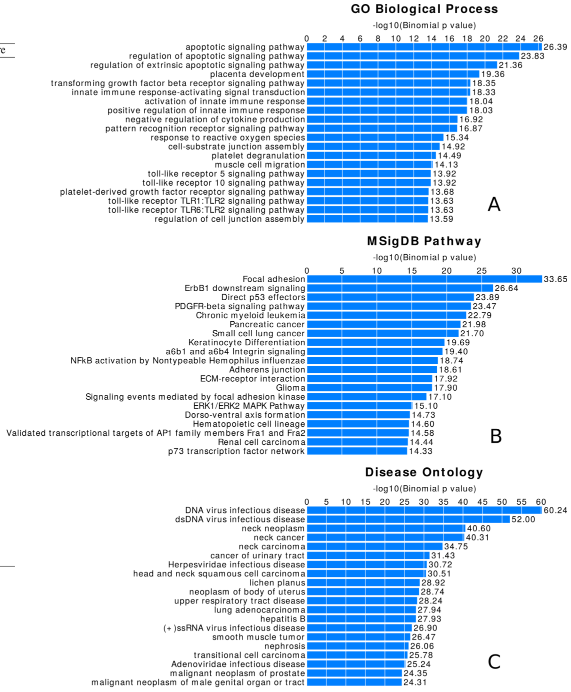


Figure S22: Functional and motif analysis of the DECRES NiA enhancers on cell line HMEC. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: families of best-matched TFs. Column 5: best match scores.

Motif	p-value	Best Match	Family	Score
ATGACTCATC	1e-999	JUNB, JUND, FOS, FOSL2	Jun-related factors, Fos-related factors	0.97
ACAGGAAGTG	1e-689	FEV, FLI1	Ets-related factors	0.93
TCGGAAGGAA	1e-142	ELF5	Ets-related factors	0.69
GCCATTGTTT	1e-64	SOX9	SOX-related factors	0.93
CTGAGATAAG	1e-48	GATA3, Gata4, Gata1	GATA-type zinc fingers	0.96
GTGTTTCCTTTG	1e-44	Foxa2, FOXA1	Forkhead box factors	0.74
GCTGGTTTCCTC	1e-43	SPIB	Ets-related factors	0.65
CCACGTGC	1e-35	Mycn	bHLH-ZIP factors	0.96
TGTTTATACAGC	1e-31	Foxa2	Forkhead box factors	0.75
AAAGTAAGTCTG	1e-30	EHF	Ets-related factors	0.55
GCGAGTCAGC	1e-29	Mafb	Maf-related factors	0.77
TGGCTGCCCTCC	1e-24	Hic1_1	BetaBetaAlpha-zinc finger	0.67
TGTTATCAGAAC	1e-23	Gata5_1	GATA-type zinc fingers	0.70
CAGGAAGAAC	1e-23	EHF	Ets-related factors	0.70
CTCTGGCA	1e-21	NFIC	Nuclear factor 1	0.86
CCACTTCACG	1e-19	Nkx3-1_1	NK-related factors	0.71
GAGCGGCAAGGC	1e-18	E2F6	E2F-related factors	0.60
GGCCGCCGGC	1e-15	Tcfap2b_2	Helix-Loop-Helix	0.72
GCGCCGCGGA	1e-13	MZF1	More than 3 adjacent zinc finger factors	0.63
TGTGTCTTTCTC	1e-12	SMAD2 ::SMAD3 ::SMAD4	SMAD factors	0.62

D

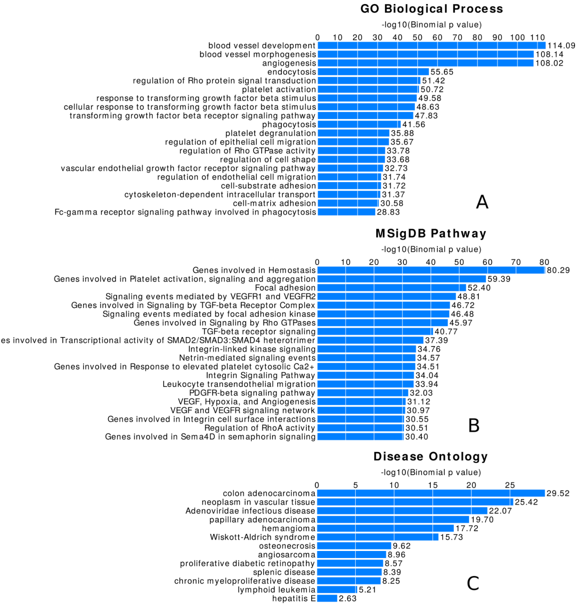
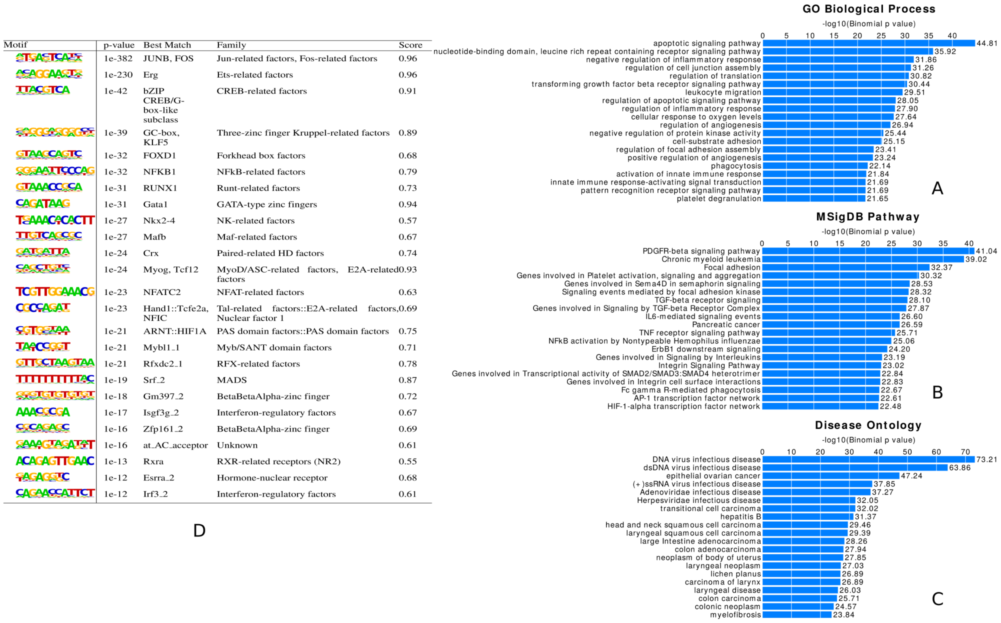
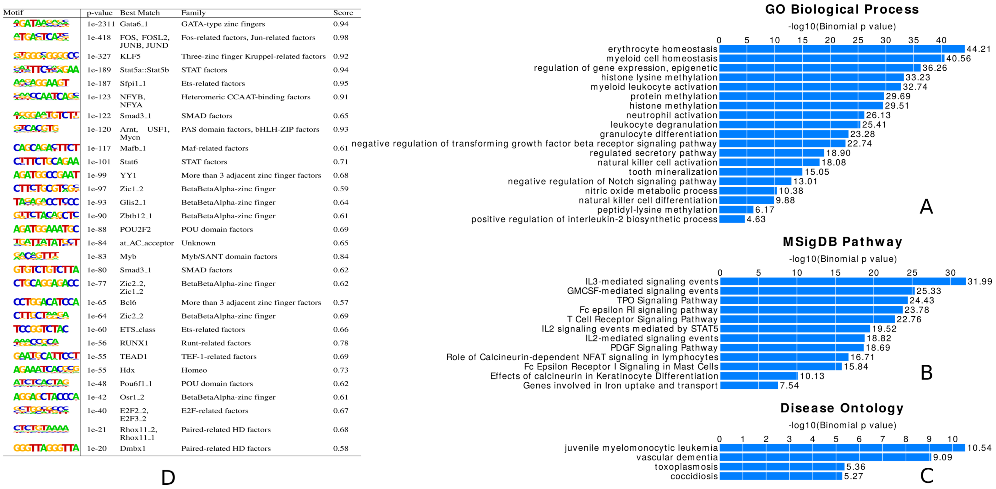


Figure S23: Functional and motif analysis of the DECRES genome-wide predictions on cell line HUVEC. A,B,C: Top enriched biological processes,pathways and diseases, respectively, in the predicted cell-specific CRRs. D: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.



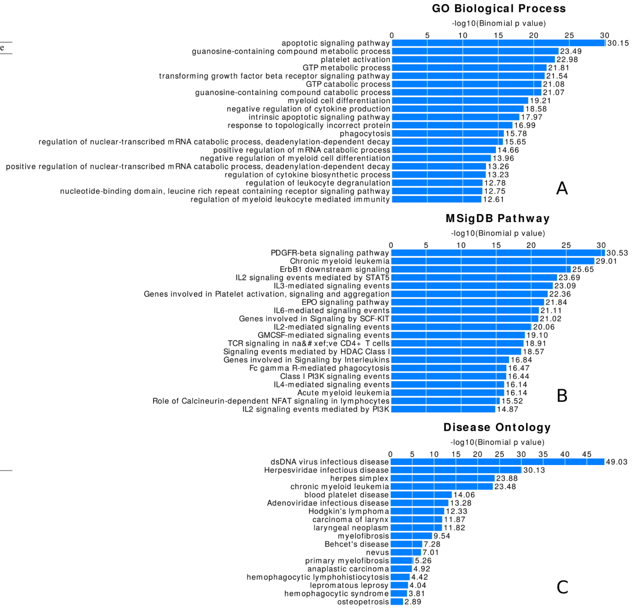
Motif	p-value	Best Match	Family	Score
ATGASTCATC	1e-382	JUNB, FOS	Jun-related factors, Fos-related factors	0.96
ACAGGAAGTG	1e-230	Erg	Ets-related factors	0.96
TTACGTCA	1e-42	bZIP CREB/G-box-like subclass	CREB-related factors	0.91
GAGGGAGGGGCC	1e-39	GC-box, KLF5	Three-zinc finger Kruppel-related factors	0.89
GTAAGCAGTC	1e-32	FOXD1	Forkhead box factors	0.68
GGGAATTCCCAG	1e-32	NFKB1	NFkB-related factors	0.79
GTAAACCGCA	1e-31	RUNX1	Runt-related factors	0.73
CAGATAAG	1e-31	Gata1	GATA-type zinc fingers	0.94
TGAAACACACTT	1e-27	Nkx2-4	NK-related factors	0.57
TTGTCAGCGC	1e-27	Mafb	Maf-related factors	0.67
GATGATTA	1e-24	Crx	Paired-related HD factors	0.74
CAGCTGTC	1e-24	Myog, Tcf12	MyoD/ASC-related factors, E2A-related factors	0.93
TCGTTGGAAACG	1e-23	NFATC2	NFAT-related factors	0.63
CGCCAGAT	1e-23	Hand1::Tcfe2a, NFIC	Tal-related factors::E2A-related factors, Nuclear factor 1	0.69
CGTGGTAA	1e-21	ARNT::HIF1A	PAS domain factors::PAS domain factors	0.75
TAACCGGT	1e-21	Mybl1_1	Myb/SANT domain factors	0.71
GTTGCTAAGTAA	1e-21	Rfxdc2_1	RFX-related factors	0.78
TTTTTTTTTTAC	1e-19	Srf_2	MADS	0.87
GGGTGTGTGTGT	1e-18	Gm397_2	BetaBetaAlpha-zinc finger	0.72
AAACGCGA	1e-17	Isgf3g_2	Interferon-regulatory factors	0.67
CGCAGAGC	1e-16	Zfp161_2	BetaBetaAlpha-zinc finger	0.69
GAAAGTAGATAT	1e-16	at_AC_acceptor	Unknown	0.61
ACAGAGTTGAAC	1e-13	Rxra	RXR-related receptors (NR2)	0.55
TAGAGGTC	1e-12	Esrra_2	Hormone-nuclear receptor	0.68
CAGAACCATTCT	1e-12	Irf3_2	Interferon-regulatory factors	0.61

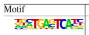
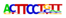
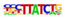
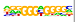
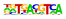
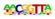
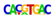
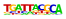
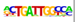
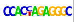
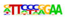
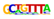
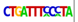
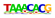
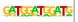
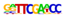
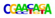
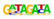
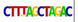
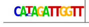
Figure S24: Functional and motif analysis of the DECRES NiA enhancers on cell line HUVEC. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: families of best-matched TFs. Column 5: best match scores.



Motif	p-value	Best Match	Family	Score
AGATAAGAGC	1e-2311	Gata6_1	GATA-type zinc fingers	0.94
ATGASTCATC	1e-418	FOS, FOSL2, JUNB, JUND	Fos-related factors, Jun-related factors	0.98
GTGGGCGGGGCC	1e-327	KLF5	Three-zinc finger Kruppel-related factors	0.92
GATTTCTCAGAA	1e-189	Stat5a::Stat5b	STAT factors	0.94
AAGAGGAAGT	1e-187	Sfpi1_1	Ets-related factors	0.95
GAACCAATCAGC	1e-123	NFYB, NFYA	Heteromeric CCAAT-binding factors	0.91
AGGGAATGTCTT	1e-122	Smad3_1	SMAD factors	0.65
GTCACGTG	1e-120	Arnt, USF1, Mycn	PAS domain factors, bHLH-ZIP factors	0.93
CAGCAGACTTCT	1e-117	Mafb_1	Maf-related factors	0.61
CTTTCTGCAGAA	1e-101	Stat6	STAT factors	0.71
AGATGGCCGAAT	1e-99	YY1	More than 3 adjacent zinc finger factors	0.68
CTTCTGCGTCGC	1e-97	Zic1_2	BetaBetaAlpha-zinc finger	0.59
TAGAGACCTCCC	1e-93	Glis2_1	BetaBetaAlpha-zinc finger	0.64
GTTCTACAGCTC	1e-90	Zbtb12_1	BetaBetaAlpha-zinc finger	0.61
AGATGGAAATGC	1e-88	POU2F2	POU domain factors	0.69
TGATTATATGCT	1e-84	at_AC_acceptor	Unknown	0.65
GACAGTTT	1e-83	Myb	Myb/SANT domain factors	0.84
GTGTCTGTCTTA	1e-80	Smad3_1	SMAD factors	0.62
CTGCAGGAGACC	1e-77	Zic2_2, Zic1_2	BetaBetaAlpha-zinc finger	0.62
CCTGGACATCCA	1e-65	Bcl6	More than 3 adjacent zinc finger factors	0.57
CTTGCTAAGA	1e-64	Zic2_2	BetaBetaAlpha-zinc finger	0.69
TCCGGTCTAC	1e-60	ETS_class	Ets-related factors	0.66
AAACCGCA	1e-56	RUNX1	Runt-related factors	0.78
GAATGCATTCCT	1e-55	TEAD1	TEF-1-related factors	0.69
AGAAATCACGCG	1e-55	Hdx	Homeo	0.73
ATCTCACTAG	1e-48	Pou6f1_1	POU domain factors	0.62
AGGAGCTACCCA	1e-42	Osr1_2	BetaBetaAlpha-zinc finger	0.61
GCTGGCGCCC	1e-40	E2F2_2, E2F3_2	E2F-related factors	0.67
CTCTGTAAAA	1e-21	Rhox11_2, Rhox11_1	Paired-related HD factors	0.68
GGGTTAGGGTTA	1e-20	Dmbx1	Paired-related HD factors	0.58

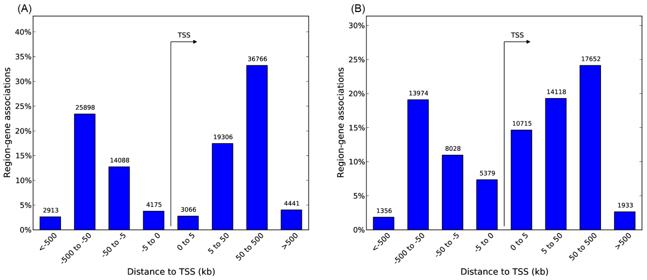
Figure S25: Functional and motif analysis of the DECRES genome-wide predictions on cell line K562. A,B,C: Top enriched biological processes,pathways and diseases, respectively, in the predicted cell-specific CRRs. D: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.

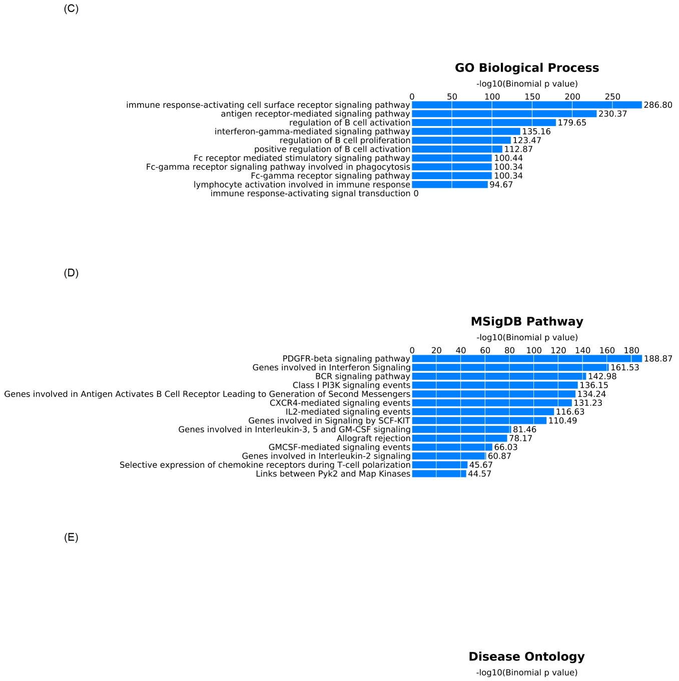


Motif	p-value	Best Match	Family	Score
	1e-203	JUNB, FOSL2	Jun-related factors, Fos-related factors	0.98
	1e-109	Sfpi1_1, ELF1, Erg, FLI1	Ets-related factors	0.93
	1e-104	Gata1	GATA-type zinc fingers	0.94
	1e-61	KLF5, SP1	Three-zinc finger Kruppel-related factors	0.97
	1e-44	Atf1_1, Jundm2_1	(Leucine zipper), CREB-related factors, Jun-related factors	0.91
	1e-43	TRP(MYB)_class	Myb/SANT domain factors	0.85
	1e-38	USF1	bHLH-ZIP factors	0.96
	1e-34	bZIP_cEBP-like_subclass	C/EBP-related factors	0.67
	1e-33	NFYB	Heteromeric CCAAT-binding factors	0.91
	1e-29	CTCF	More than 3 adjacent zinc finger factors	0.85
	1e-28	Stat5a::Stat5b, STAT1	STAT factors	0.91
	1e-28	Foxo1	Forkhead box factors	0.75
	1e-20	Pou2f2	POU domain factors	0.68
	1e-20	Forkhead_class	Forkhead box factors	0.76
	1e-19	Pbx1	TALE-type homeo domain factors	0.64
	1e-18	Irf4_1	Interferon-regulatory factors	0.68
	1e-16	Tcf3_2	E2A-related factors	0.55
	1e-16	SMAD2::SMAD3::SMAD4	SMAD factors	0.71
	1e-12	Hmbox1	POU domain factors	0.56
	1e-12	NFYB	Heteromeric CCAAT-binding factors	0.65

D

Figure S26: Functional and motif analysis of the DECRES NiA enhancers on cell line K562. A,B,C: Top 20 enriched biological processes, pathways, and diseases, respectively, in the NiA enhancers. D: Enriched *de novo* motifs in the NiA enhancer regions. Column 4: families of best-matched TFs. Column 5: best match scores.





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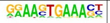
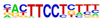
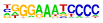
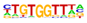
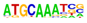
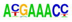
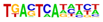
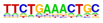
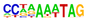
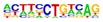
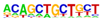
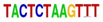
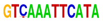
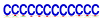
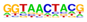
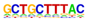
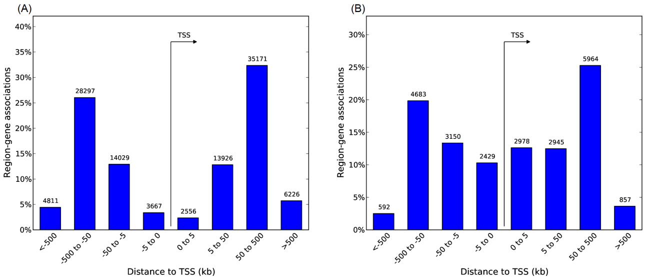
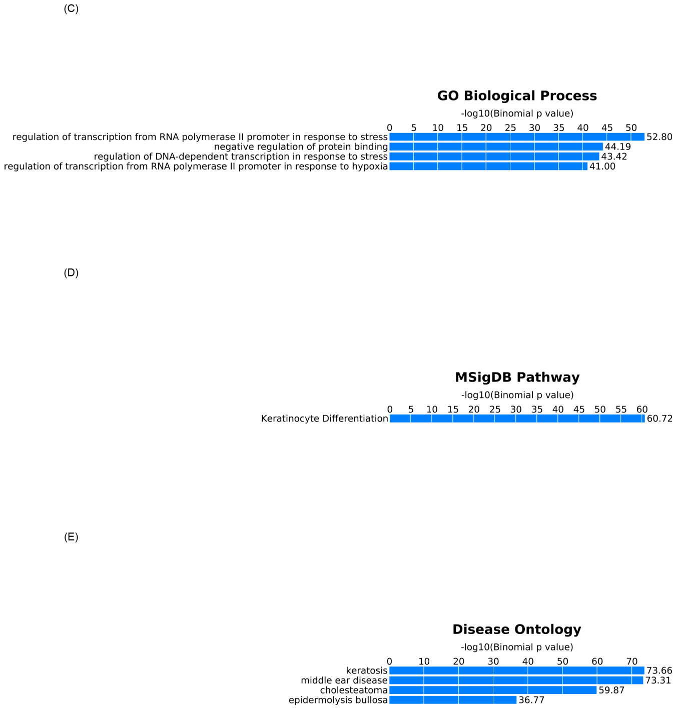
Motif	*p*-value	Best Match	Family	Score
	1e-1757	IRF1	Helix-turn-helix domains	0.955
	1e-702	Sfpi1	Helix-turn-helix domains	0.933
	1e-504	NFkB-p65	Immunoglobulin fold	0.972
	1e-371	RUNX1	Immunoglobulin fold	0.973
	1e-163	POU2F2	Helix-turn-helix domains	0.935
	1e-150	IRF4	Helix-turn-helix domains	0.843
	1e-129	BATF::JUN	Basic leucine zipper factors (bZIP)	0.939
	1e-100	CHR	Not available	0.671
	1e-89	Mef2a	alpha-Helices exposed by beta-structures	0.922
	1e-71	Meis1	Helix-turn-helix domains	0.764
	1e-54	MyoD	MyoD / ASC-related factors	0.818
	1e-33	NKX3-1	Helix-turn-helix domains	0.604
	1e-24	Sox17	Other all-alpha-helical DNA-binding domains	0.673
	1e-22	Zfp281	Zinc-coordinating DNA-binding domains	0.920
	1e-22	Rfx4	Helix-turn-helix domains	0.823
	1e-18	Osr2	Zinc-coordinating DNA-binding domains	0.594

Figure S27: Functional and motif analysis of the Combined genome-wide predictions on cell line GM12878. A: Distance from the predicted A-Es to gene TSSs. B: Distance from the predicted A-Ps to gene TSSs. C,D,E: Top 20 enriched biological processes, pathways, and diseases, respectively, in the predicted cell-specific CRRs. F: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.





(F)

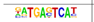
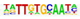
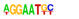
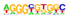
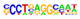
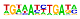
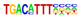
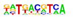
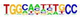
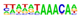
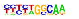
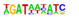
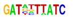
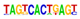
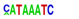
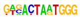
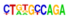
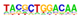
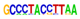
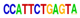
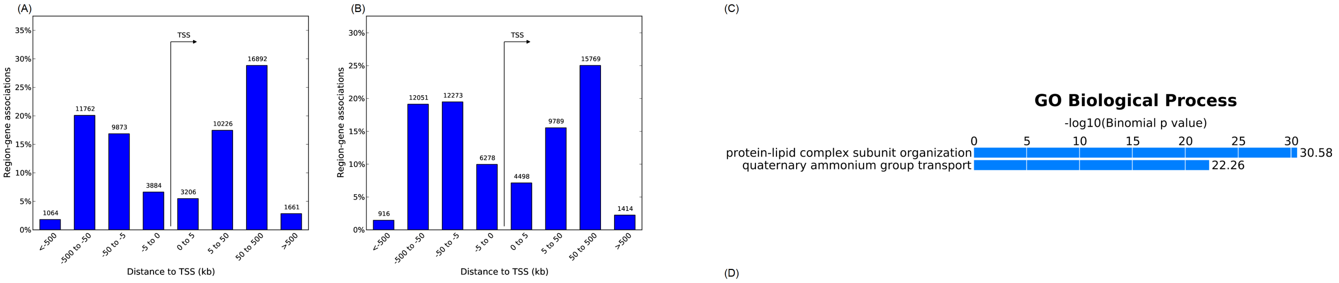
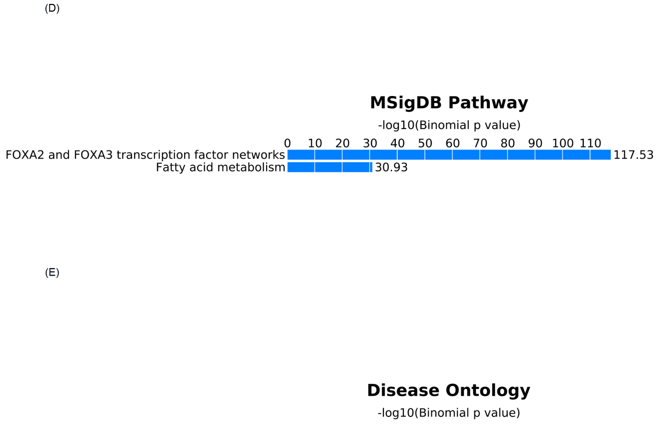
Motif	*p*-value	Best Match	Family	Score
	1e-6754	BATF	Basic leucine zipper factors (bZIP)	0.987
	1e-564	CEBPA	C/EBP-related	0.974
	1e-464	TEAD	Helix-turn-helix domains	0.966
	1e-399	KLF5	Zinc-coordinating DNA-binding domains	0.962
	1e-280	AP-2gamma	Zinc-coordinating DNA-binding domains	0.949
	1e-267	Six1	Helix-turn-helix domains	0.925
	1e-257	Nur77	Zinc-coordinating DNA-binding domains	0.900
	1e-243	Atf1	Basic leucine zipper factors (bZIP)	0.941
	1e-233	Tlx?	Not available	0.883
	1e-222	Forkhead_-class	Not available	0.940
	1e-169	NF1-halfsite	Zinc-coordinating DNA-binding domains	0.863
	1e-156	GATA	Zinc-coordinating DNA-binding domains	0.913
	1e-109	GATA	Zinc-coordinating DNA-binding domains	0.861
	1e-84	Nkx3.1	Helix-turn-helix domains	0.611
	1e-79	Hoxc9	Helix-turn-helix domains	0.904
	1e-73	Isl1	Helix-turn-helix domains	0.691
	1e-73	Hand1::Tcfe2a	Twist-like factors	0.776
	1e-51	NFATC2	Immunoglobulin fold	0.633
	1e-46	Zfp128	Zinc-coordinating DNA-binding domains	0.580
	1e-45	STAT5	Immunoglobulin fold	0.611

Figure S28: Functional and motif analysis of the Combined genome-wide predictions on cell line HelaS3. A: Distance from the predicted A-Es to gene TSSs. B: Distance from the predicted A-Ps to gene TSSs. C,D,E: Top 20 enriched biological processes, pathways, and diseases, respectively, in the predicted cell-specific CRRs. F: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.





(F)

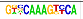
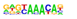
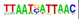
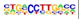
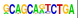
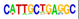
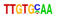
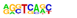
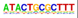
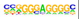
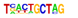
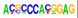
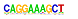
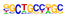
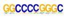
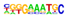
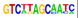
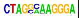
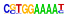
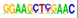
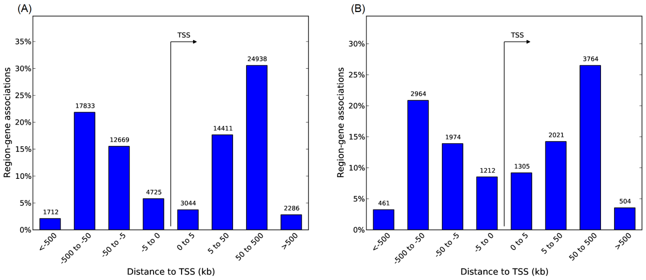
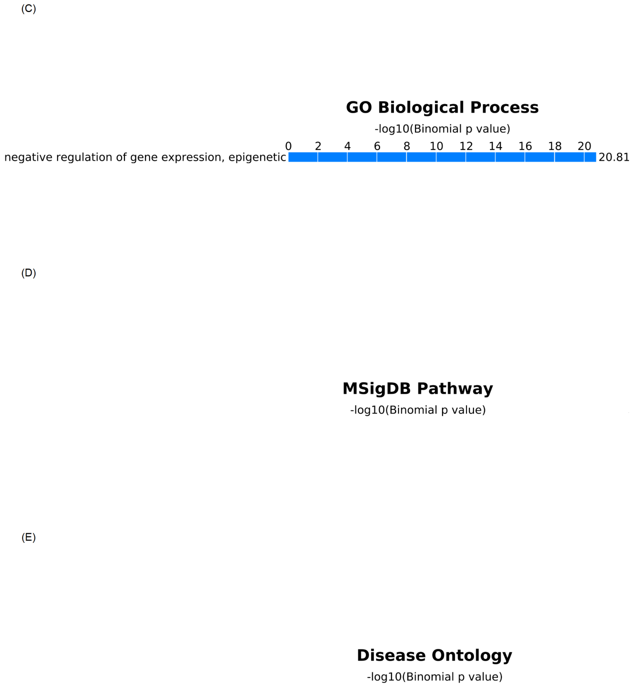
Motif	*p*-value	Best Match	Family	Score
	1e-1086	HNF4A	Zinc-coordinating DNA-binding domains	0.968
	1e-423	Fox:Ebox	Helix-turn-helix domains	0.904
	1e-352	Hnf1	Helix-turn-helix domains	0.949
	1e-101	Nr5a2	Zinc-coordinating DNA-binding domains	0.876
	1e-87	Six1	Helix-turn-helix domains	0.592
	1e-74	MafA	Basic leucine zipper factors (bZIP)	0.632
	1e-68	CEBPA	C/EBP-related	0.901
	1e-63	Nuclear_Receptor_class	Not available	0.786
	1e-61	Pou6f1	Helix-turn-helix domains	0.576
	1e-60	KLF5	Zinc-coordinating DNA-binding domains	0.875
	1e-56	T	Basic helix-loop-helix factors (bHLH)	0.653
	1e-49	Egr2	Zinc-coordinating DNA-binding domains	0.691
	1e-48	EWS:ERG-fusion	Helix-turn-helix domains	0.744
	1e-48	Tlx?	Not available	0.658
	1e-47	Tcfap2e	Basic domains	0.715
	1e-43	NFKB1	Immunoglobulin fold	0.733
	1e-42	Rfx3	Helix-turn-helix domains	0.670
	1e-42	at_AC_acceptor	Not available	0.575
	1e-41	NFATC2	Immunoglobulin fold	0.892
	1e-40	DCE_S_I	Not available	0.637

Figure S29: Functional and motif analysis of the Combined genome-wide predictions on cell line HepG2. A: Distance from the predicted A-Es to gene TSSs. B: Distance from the predicted A-Ps to gene TSSs. C,D,E: Top 20 enriched biological processes, pathways, and diseases, respectively, in the predicted cell-specific CRRs. F: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.





(F)

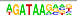
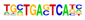
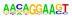
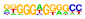
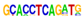
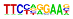
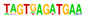
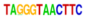
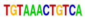
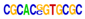
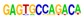
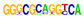
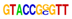
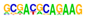
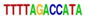
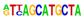
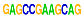
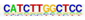
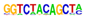
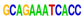
Motif	*p*-value	Best Match	Family	Score
	1e-2706	Gata2	Zinc-coordinating DNA-binding domains	0.980
	1e-630	Bach2	NF-E2-like factors	0.974
	1e-238	Sfpi1	Helix-turn-helix domains	0.921
	1e-227	KLF5	Zinc-coordinating DNA-binding domains	0.921
	1e-202	CREB	CREB-like factors	0.600
	1e-176	STAT5	Immunoglobulin fold	0.948
	1e-175	Six1	Helix-turn-helix domains	0.581
	1e-173	Spz1	Not available	0.667
	1e-170	Myb	Helix-turn-helix domains	0.763
	1e-166	Zfp161	Zinc-coordinating DNA-binding domains	0.602
	1e-163	Tbox:Smad	Not available	0.805
	1e-140	RXR	Zinc-coordinating DNA-binding domains	0.711
	1e-133	Nkx3-1	Helix-turn-helix domains	0.546
	1e-130	DCE_S_I	Not available	0.613
	1e-128	Zfp187	Zinc-coordinating DNA-binding domains	0.593
	1e-126	Pou2f3	Helix-turn-helix domains	0.639
	1e-121	DCE_S_I	Not available	0.611
	1e-116	E2F2	Helix-turn-helix domains	0.632
	1e-111	DCE_S_II	Not available	0.614
	1e-109	Hdx	Helix-turn-helix domains	0.749

Figure S30: Functional and motif analysis of the Combined genome-wide predictions on cell line K562. A: Distance from the predicted A-Es to gene TSSs. B: Distance from the predicted A-Ps to gene TSSs. C,D,E: Top 20 enriched biological processes, pathways, and diseases, respectively, in the predicted cell-specific CRRs. F: Enriched *de novo* motifs in the predicted cell specific CRRs. Column 4: families of best-matched TFs. Column 5: best match scores.

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