Supplementary Methods

Comparing motifs

Motif similarity is defined as the maximal Pearson's correlation of the PWM made into a 4xN vector across all offsets and both orientations, padding unmatched positions with N's (102). Motifs are considered a match if they have a similarity of at least 0.75; weak matches or variants are determined through manual inspection.

Collecting known motifs

Known motifs were collected from large scale data sets or databases. We collected human, mouse, and rat motifs from Transfac (version 11.3) (11), vertebrate motifs from Jaspar (version 2008) (12), and large scale systematic motifs generated using Protein Binding Microarrays (13, 14, 15) and high-throughput SELEX (16). HGNC gene names (103) were used to describe the names of motifs whenever possible.

Processing and naming of experimental data sets

Human protein binding peaks (excluding Pol2/Pol3) were taken from the January, 2011 freeze of ENCODE (8). The processing for these data sets is described in (104, 10) and the original data sets are available on the website accompanying this paper. To avoid potentially confounding issues, we excluded from our analysis: (1) the Y and mitochondrial chromosomes; (2) the hg19 rmsk and simple repeat tracks from UCSC (created on April 27, 2009) (105); and (3) protein coding regions, exons for non-coding genes, and 3' untranslated regions taken from GENCODE v4 (106). Like with the motif names, HGNC gene names (103) are used to describe the data sets.

Performing de novo motif discovery

Peaks were randomly partitioned into two data sets for the purpose of separating discovery and enrichment and limit over-fitting. The top 250 peaks for the first partition were used in motif discovery because high intensity peaks often have better enrichment for motifs (101). Five tools were run independently run on each data set: AlignACE (v4.0 with default parameters) (17), MDscan (v2004 with default parameters) (18), MEME (v3.5.7 with a maximum of 10 iterations and -maxw 10, 15, and 25 for the three motifs) (19), Weeder (v1.4.2 with option large) (20), and Trawler (v1.2 with 250 random intergenic blocks for background) (21). Any motifs beyond the top three for any method on one data set were discarded.

Computing enrichments of motifs

Motifs were matched against the genome using a PWM threshold corresponding to a p-value of 4^{-8} as determined by TFM-Pvalue (107), with the intent to imitate the frequency a fully specified 8-mer would match the genome.

Enrichments are always computed by taking a foreground region (i.e. bound regions for a data set) and comparing it to a background region (e.g. Intergenic non-repetitive regions) where regions in the foreground but not in the background are discarded. For a given motif, the fraction of matches that fall within the foreground is computed and divided by the corresponding fraction for shuffled control motifs (control motif generation details in (97)). To prevent spuriously high enrichments due to small counts, we compute a binomial confidence interval (with z=1.5) (108) around both motif and control fractions and take the extreme which leads to the enrichment closest to 1 (the software available on the website implements this enrichment metric).

For each factor group we order the motifs from all discovery programs by the enrichment in the second random partition for the discovery data set. For this step only, we restrict our analysis to 10% of the background regions to reduce the amount of computation. We then select discovered motifs for each factor by this rank order discarding any motif that matches a previous one with similarity greater than 0.75. We supplement these discovered motifs with the known motifs from the literature (described above) and rematch the motifs to the complete background regions and produce comparable enrichments for all data sets.

Supplementary Results

Robustness of motif similarity

While it has been shown that short motifs will sometimes have similar correlations just by chance (109, 110), this happens infrequently for the 0.75 similarity threshold with our database of motifs. When two motifs in the database match, scrambling one of the motifs 100 times leads to more than 5 matches only 6.4% of the time.

Moreover, a given motif in the database is 34.7 times more likely to match another motif in a database than a scramble. While this statistic is hard to interpret due to, on one hand, the significant redundancy in the database and, on the other, the partial exclusion of similar discovered motifs, it demonstrates that spurious motif matches should be relatively uncommon.

Effect of peak intensity on motif enrichment

While it has been shown that motif enrichment varies by peak intensity (101), we find that our results are largely robust to restricting to only the 1,000 strongest peaks per data set (89% of data sets have at least 1,000 peaks). The Pearson correlation of motif enrichment (for all motifs) for one data set when using all peaks or only the top 1,000 has a median of 0.89 (middle 50%: 0.85 to 0.95).

Moreover, the enrichment of the first discovered motif for a factor group has strong correlation between the complete and restrict data sets: for the 55 factor groups with at least two data sets and a discovered motif, the median correlation of the first discovered motif's enrichment is 0.97 (middle 50%: 0.81 to 1.00).

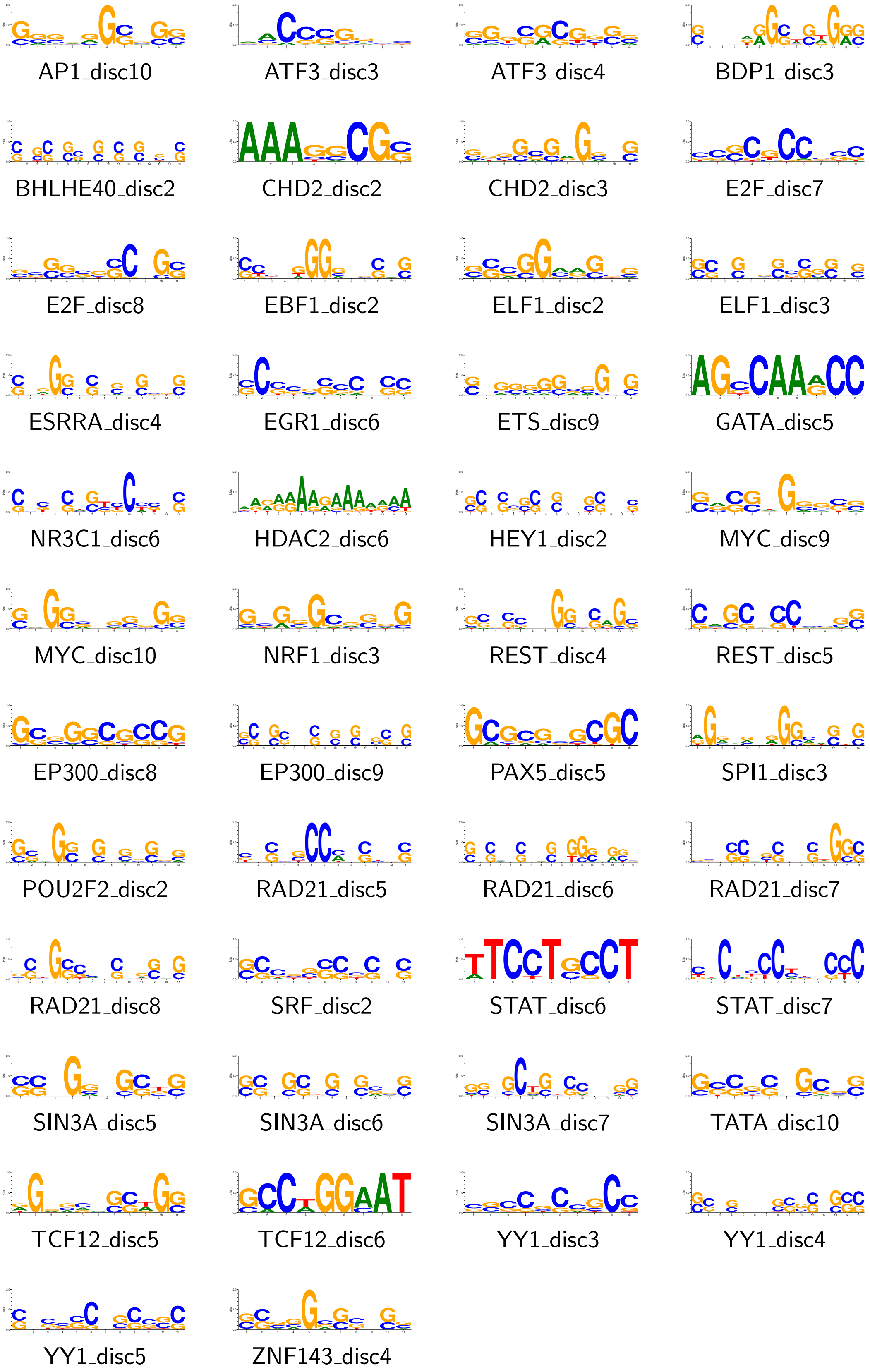


Table S1: Low complexity or weakly enriched motifs.

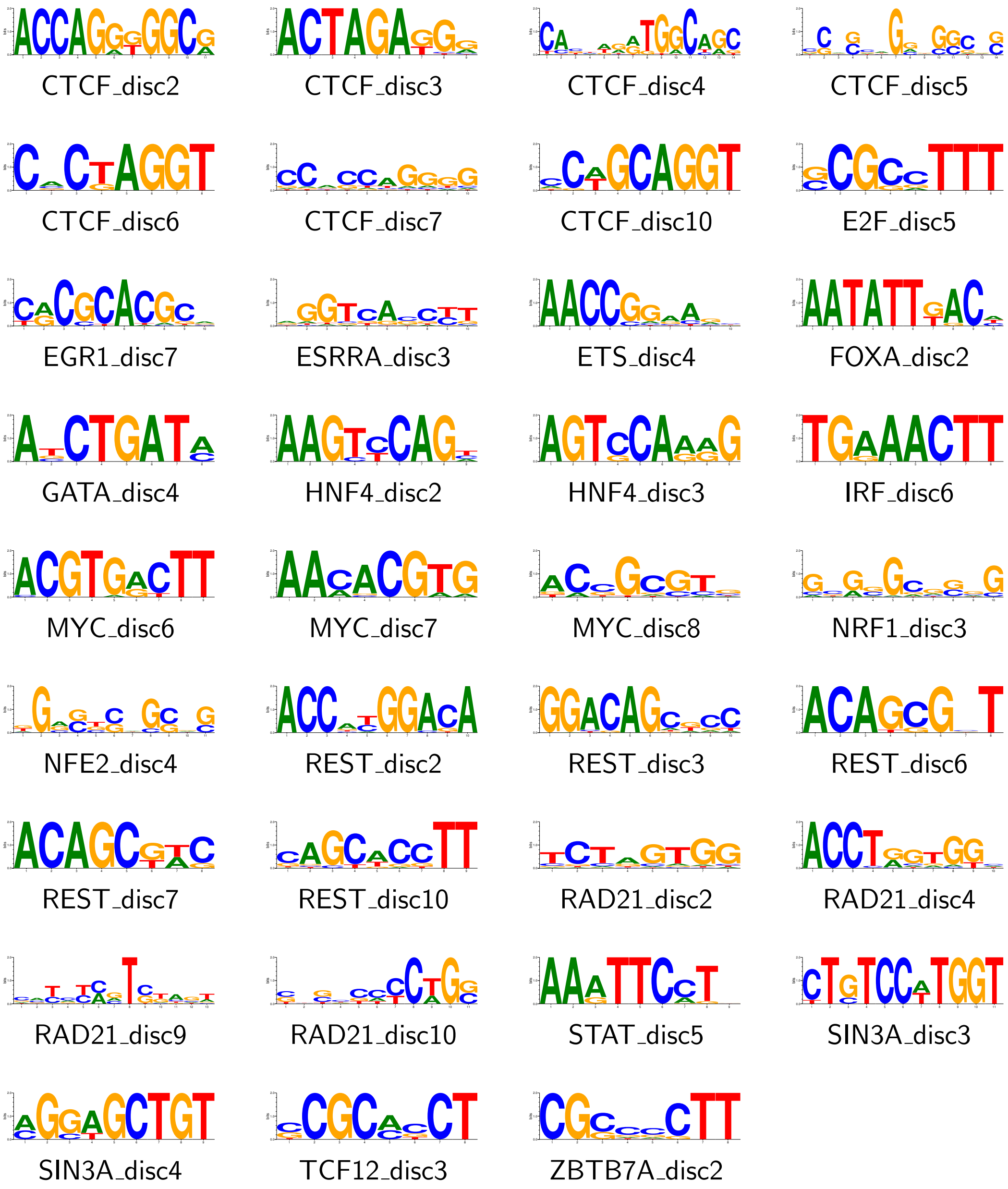
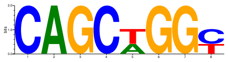
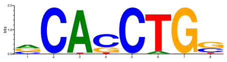
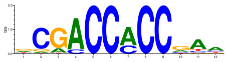
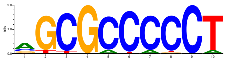
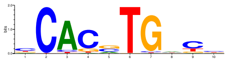
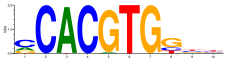
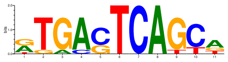
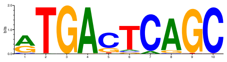
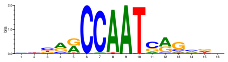
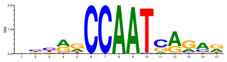
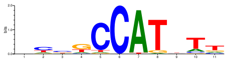
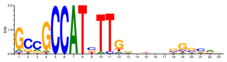
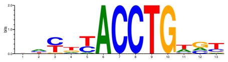
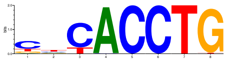
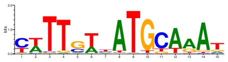
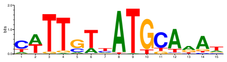


Table S2: Motifs with weak similarity to some other discovered motif. These occur frequently for factors with long known motifs that are amenable to breaking apart. We do not believe that these represent distinct motifs and are likely artifacts of the discovery process.

Known motif	Discovered motif
 TCF12_known1 3.0 (9.5)	 TCF12_disc1* 5.6 (11.2)
 ZBTB7A_known4 1.3 (10.0)	 ZBTB7A_disc1 2.2 (43.5)
 MXI1_known1 3.2 (9.6)	 MXI1_disc2* 4.4 (29.5)
 NFE2_known1 56.4 (78.8)	 NFE2_disc1* 75.9 (125.7)
 NFY_known6 72.6 (110.6)	 NFY_disc1 89.9 (84.7)
 YY1_known5 39.5 (38.6)	 YY1_disc1 47.5 (94.3)
 ZEB1_known1 4.9 (3.4)	 ZEB1_disc1 5.8 (11.1)
 POU5F1_known3 28.3 (22.7)	 POU5F1_disc1* 30.0 (24.8)

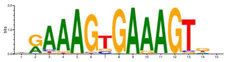
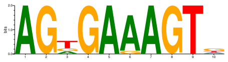
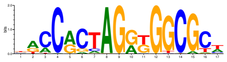
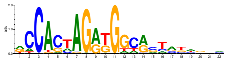
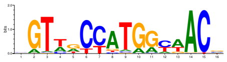
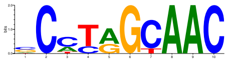
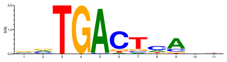
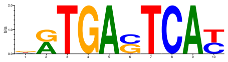
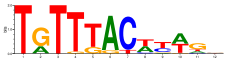
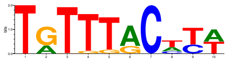
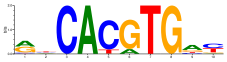
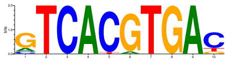
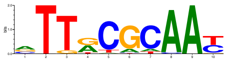
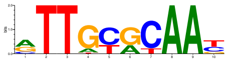
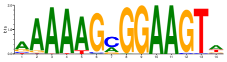
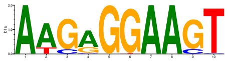
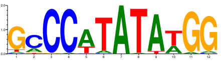
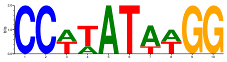
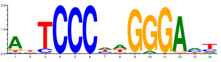
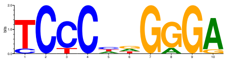
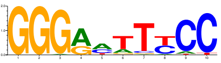
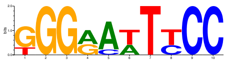
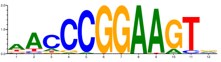
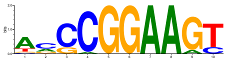
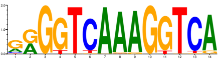
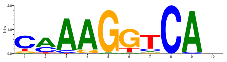
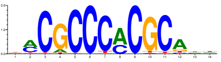
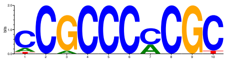
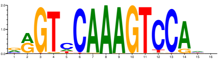
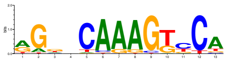
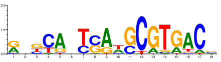
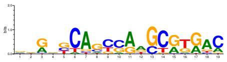
Known motif	Discovered motif
 PRDM1_known2 18.4 (23.3)	 PRDM1_disc1* 19.2 (25.1)
 CTCF_known2 78.0 (219.6)	 CTCF_disc1* 77.3 (118.5)
 RFX5_known6 28.6 (33.8)	 RFX5_disc1* 28.3 (60.7)
 AP1_known3 45.7 (52.5)	 AP1_disc3* 45.1 (82.0)
 FOXA_known6 19.9 (14.4)	 FOXA_disc1* 19.5 (11.2)
 MYC_known22 104.8 (334.2)	 MYC_disc1* 97.8 (139.5)
 CEBPB_known8 84.9 (100.6)	 CEBPB_disc1* 79.0 (91.4)
 SPI1_known4 26.5 (30.5)	 SPI1_disc1* 24.6 (37.0)

Table S3: Complete version of Figure 4, with all factors for which a discovered motif matching a known motif was found. When the discovered motif is not disc1, a better ranking motif was found that did not match a literature motif. * indicates that other discovered motifs were found, even after manual exclusion of weakly redundant and low complexity motifs.

Known motif	Discovered motif
 SRF_known7 126.6 (88.9)	 SRF_disc1 112.1 (93.8)
 EBF1_known4 8.7 (28.0)	 EBF1_disc1 7.3 (22.3)
 NFKB_known3 39.8 (78.5)	 NFKB_disc1 30.3 (45.7)
 ELF1_known2 22.9 (68.8)	 ELF1_disc1 17.0 (105.9)
 RXRA_known10 9.6 (12.4)	 RXRA_disc1* 7.0 (8.2)
 EGR1_known8 11.9 (299.6)	 EGR1_disc1* 8.6 (238.1)
 HNF4_known18 28.0 (34.2)	 HNF4_disc1* 20.0 (30.2)
 PAX5_known5 20.5 (78.2)	 PAX5_disc1* 14.3 (47.3)

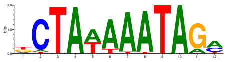
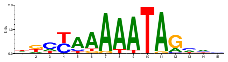
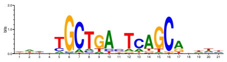
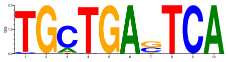
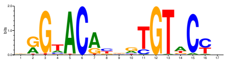
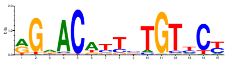
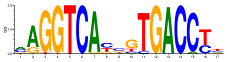
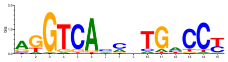
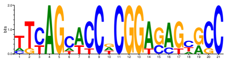
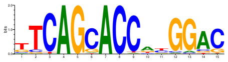
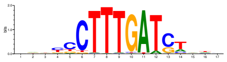
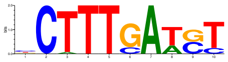
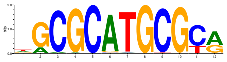
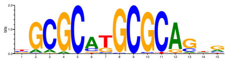
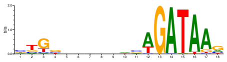
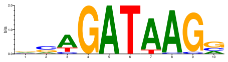
Known motif	Discovered motif
 MEF2_known12 12.0 (6.8)	 MEF2_disc1* 7.9 (6.7)
 MAF_known7 57.8 (68.2)	 MAF_disc1 37.1 (50.1)
 NR3C1_known17 33.5 (49.4)	 NR3C1_disc1* 20.8 (25.0)
 ESRRA_known6 35.6 (60.4)	 ESRRA_disc1* 21.0 (39.0)
 REST_known2 66.9 (188.9)	 REST_disc1 39.4 (115.6)
 TCF7L2_known5 10.9 (7.8)	 TCF7L2_disc2* 6.0 (9.0)
 NRF1_known2 84.7 (1196.5)	 NRF1_disc1* 41.3 (969.7)
 GATA_known14 23.8 (31.3)	 GATA_disc1* 6.9 (23.4)

Table S3 (continued)

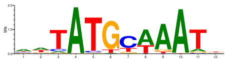
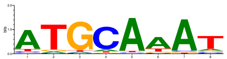
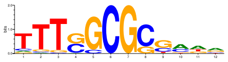
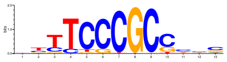
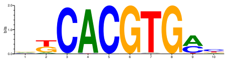
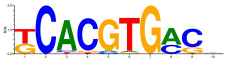
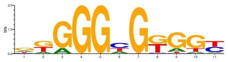
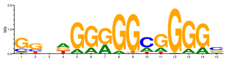
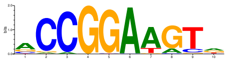
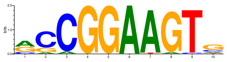
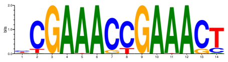
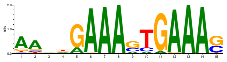
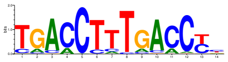
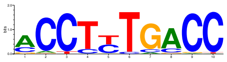
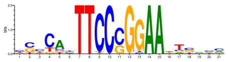
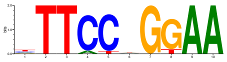
Known motif	Discovered motif
 POU2F2_known15 21.1 (5.3)	 POU2F2_disc1 6.1 (11.0)
 E2F_known9 12.1 (127.5)	 E2F_disc3* 3.1 (71.2)
 BHLHE40_known4 70.2 (168.4)	 BHLHE40_disc1 17.3 (167.0)
 SP1_known8 5.8 (37.7)	 SP1_disc3* 1.0 (8.8)
 ETS_known18 53.9 (306.1)	 ETS_disc2* 8.0 (330.6)
 IRF_known20 61.0 (74.1)	 IRF_disc3* 8.8 (15.4)
 NR2C2_known1 53.4 (51.8)	 NR2C2_disc2* 4.0 (33.4)
 STAT_known2 116.3 (131.0)	 STAT_disc1* 2.4 (56.1)

Table S3 (continued)

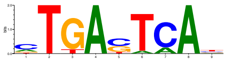
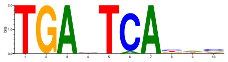
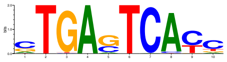
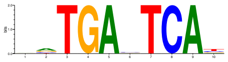
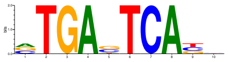
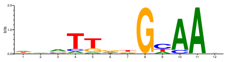
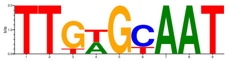
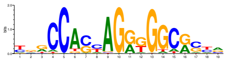
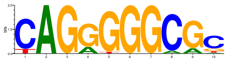
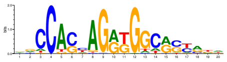
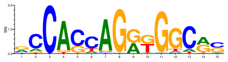
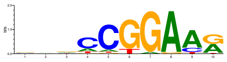
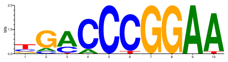
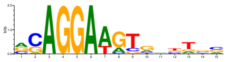
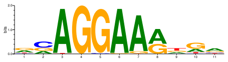
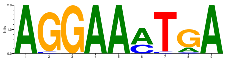
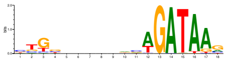
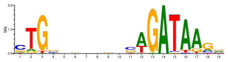
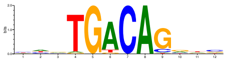
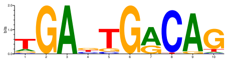
Factor	Matching discovered motifs		
 AP1_known5 (TRE)	 GATA_disc2 (32)	 SMARC_disc1 (34)	 STAT_disc2 (46)
	 TCF7L2_disc1 (35)		
 CEBPB_known7	 STAT_disc4* (47)		
 CTCF_known1	 CTCFL_disc1* (64)	 RAD21_disc1* (62)	 SMC3_disc1 (63)
 ETS_known7	 NR2C2_disc1 (51)		
 ETS_known4	 GATA_disc3 (49)	 MEF2_disc2 (50)	
 GATA_known14	 TAL1_disc1 (66, 67)		
 MEIS1_1	 PBX3_disc2 (65)		

Table S4: Selected shared motifs with literature support. Shown are the motifs that match a known motif for the indicated factor along with relevant citations. Details in the text. * indicates motif is reverse complemented for comparison purposes.

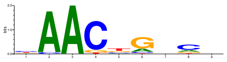
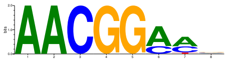
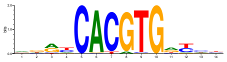
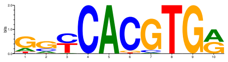
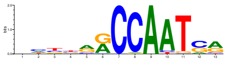
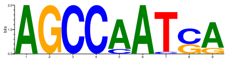
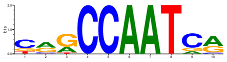
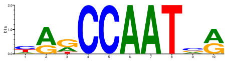
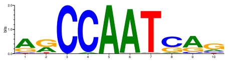
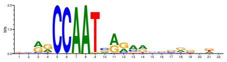
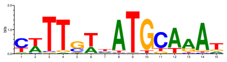
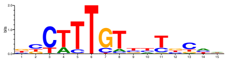
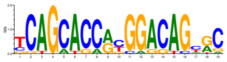
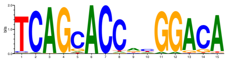
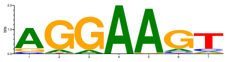
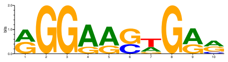
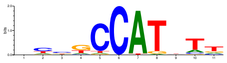
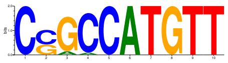
Factor	Matching discovered motifs		
 MYB_4	 ETS_disc8 (54)		
 MYC_known3	 SIN3A_disc2 (38)		
 NFY_known5	 CEBPB_disc2 (43)	 E2F_disc4* (45)	 IRF_disc1 (40)
	 RFX5_disc2 (42)	 SP1_disc1* (44)	
 POU5F1_known3	 NANOG_disc2* (57, 58)		
 REST_known3	 SIN3A_disc1* (37)		
 SPI1_known2	 IRF_disc5 (41)		
 YY1_known5	 THAP1_disc2 (55, 56)		

Table S4 (continued)

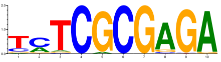
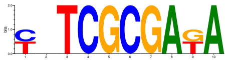
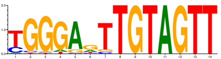
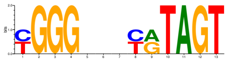
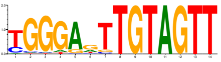
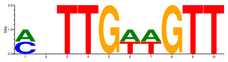
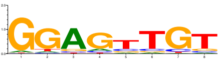
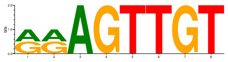
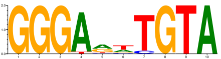
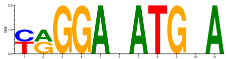
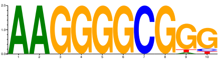
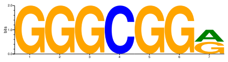
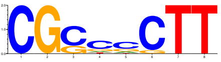
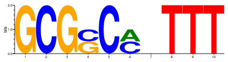
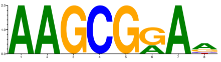
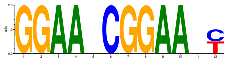
Discovered motif	Motif from (85)
 BRCA1_disc1 (Novel1)	 M8
 ETS_disc1 (Novel2)	 M4
 ETS_disc1 (Novel2)	 M108/FAC1
 ETS_disc5 (Novel2)	 M129
 SIX5_disc2 (Novel2)	 M75/STAT1
 SP2_disc3 (Novel3)	 M6/SP1
 ZBTB7A_disc2 (Novel3)	 M164
 TATA_disc5 (Novel6)	 M21

Table S5: Novel motifs matching those found using systematic conservation measures in four mammals by Xie et al. (85). One representative motif is shown for each putative novel motif when multiple match the same motif. Each motif from (85) is named using the provided identifier and annotation.

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