Figure S1  Localization of 8-mers in human promoters. A) Localization Factor (LF), a measure of non-random distribution of a DNA sequence, for 32,896 continuous 8-mers (X₄-N₀-X₄). For each 8-mer, the distribution in 17,143 human promoters (-1,000 bp to +500 bp) aligned relative to the TSS was determined and plotted in the most abundant 20 bp bin. Some sequences are preferentially localized near the TSS. B) Probability (p=10⁻⁴) that an 8-mer have a non-random distribution is plotted in the most abundant bin for all 8-mers.
Figure S2  A) Distribution of the CRE 8-mer TGACGTCA in human promoters. B) LF for CRE 8-mer with insert length ranging from 0-bps to 30-bps (TGAC-\(N\_0\)-30-GTCA). C) Distribution of the ETS TFBS (CCGGAACT) in promoters counting occurrence in 20 bp bins. D) LF for ETS 8-mer (CCGG-\(N\_0\)-30-AAGT) with insert length ranging from 0-bps to 30-bps. The 8-mer CCGGAAGT preferentially localize in promoters when the two 4-mers are abutted. High LF values are also observed at additional insert
length, including CCGG-\textsubscript{N\_6}-AAGT, which represents the ETS\textsuperscript{\leftrightarrow}ETS motif and CCGG-\textsubscript{N\_2}\textsubscript{3}-AAGT. E) Distribution of the split 8-mer CGCC-\textsubscript{N\_2}\textsubscript{4}-TATA in promoters. F) LF for CGCC-\textsubscript{N\_0,30}-TATA with insert length ranging from 0-bps to 30-bps. G) Distribution of the split 8-mer CAAT-\textsubscript{N\_2}\textsubscript{4}-CCGC in human promoters. The most localizing motif is the split 9-mer CCAAT-\textsubscript{N\_2}\textsubscript{4}-CCGC marked in red. H) LF for CAAT-\textsubscript{N\_0,30}-CCGC with insert length from 0-bps to 30-bps. I) Distribution of the split 8-mer GGGA-\textsubscript{N\_4}-TAGT and more localizing split 10-mer GGGA-\textsubscript{N\_2}-TGTAGT. J) Occurrences of split 8-mer GGGA-\textsubscript{N\_0,40}-TAGT with insert length ranging from 0-bps to 40-bps. The reverse order of the two 4-mers TAGT-\textsubscript{N\_0,40}-GGGA is shown with negative values.
Figure S3  A) Distribution of the two ETS TFBS (CCGGAA and GCGGAA).  B) Distribution of the two split 8-mers GCGG-N$_2$-ACGT and CCGG-N$_2$-ACGT representing the ETS$\leftrightarrow$CRE motif.  C) Color representation of the sequences surrounding the 134 ETS$\leftrightarrow$CRE 11-mers that occur in housekeeping DHSs with C=blue, G=yellow, A=green and T=red. The core part of the ETS$\leftrightarrow$CRE motif is shown in inset. Sequences were grouped based on the nucleotides as shown by numbers in bold: 1CGGAAGTACG2345 where the numbers represent the order of grouping.
Figure S4  A) Occurrence in mouse promoters compared to the genome of all split 8-mer containing two CGs separated by 4-bps (N-CG-N$_4$-CG-N$_3$) as is observed in the ETS$\leftrightarrow$ETS motif which is labeled. B) Occurrence in mouse promoters compared to the genome of all split 8-mer containing two CGs separated by 7-bps CG-N$_7$-CG-N) as is observed in the ETS$\leftrightarrow$CRE motif which is labeled C-F) Methylation status in mouse dermal fibroblasts of the 4 ETS$\leftrightarrow$CRE 13-mers / CGGAAGTGACGT / GCGGAAGTGACGT / CGGAAGTGACGT / CGGAAGTGACGT. Percent methylations of 1st and 2nd CpGs are plotted for each 4 motifs. The majority of occurrences have no CpG methylation on either CpG. G) Methylation of 1st and 2nd CGs for the 13-mer CACGCACACACCG with pairs of CpG separated by 7-bps showing both the CpGs in the motif are mostly methylated in dermal fibroblasts.
Figure S5  A-D) Methylation status in mouse primary keratinocytes of the 4 ETS<->CRE 13-mers \texttt{CGGAAGTGACGT}. Percent methylations of 1st and 2nd CpGs are plotted. The majority of occurrences have no CpG methylation on either CpG. E) Methylation of 1st and 2nd CGs for the 13-mer \texttt{CACGCACACCCG} with pairs of CpG separated by 7-bps showing both the CpGs in the motif are mostly methylated in keratinocytes.
Figure S6  A-D) Comparison in methylation status of both the CpGs in 4 ETS-CRE 13-mers\(^{\text{GGGAGTGGACGT}}\) in mouse dermal fibroblasts and keratinocytes.  E) Methylation of 1st and 2nd CGs for the 13-mer CACGCACACCCCG in primary dermal fibroblasts and keratinocytes.
Table S1  The Localization Factor (LF) for all continuous \(X_4-N_0-X_4\) and split 8-mers \(X_4-N_2-X_4\) was determined. Next, the probability of a non-random distribution was determined and the top 20 for different insert length was determined. For column \(X_4-N_2-X_4\), the insert length that produced the highest LF is presented. The most localized split 8-mers are further extended to determine the TFBS or overlapping TFBS and are presented in the column next to the sequence motifs. Two sequences representing the ETS⇔ETS motif and the ETS motif and the ETS motif are highlighted in red.

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<th>Predicted TFBS</th>
<th>P-value</th>
<th>Sequence</th>
<th>Predicted TFBS</th>
<th>P-value</th>
<th>Sequence</th>
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Table S2  Occurrence of different length of ETS⇔CRE motifs in the human genome, promoters, proximal promoters, CpG Islands and housekeeping DNase hypersensitive sites.

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<th>Motifs</th>
<th>N-mers</th>
<th>DNA sequence</th>
<th>Whole Genome</th>
<th>Promoter</th>
<th>Proximal Promoter</th>
<th>CpG Islands</th>
<th>House-keeping DHS</th>
<th>All DHS</th>
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<td># Unmasked (100%)</td>
<td>(-1000...500) (0.8%)</td>
<td>(-200...60) (0.1%)</td>
<td>(0.7%)</td>
<td>(0.2%)</td>
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<td>(8.7%)</td>
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<tr>
<td>ETS</td>
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<td>1,761 (10%)</td>
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<td>465 (10%)</td>
<td>298 (6%)</td>
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<td>343 (7%)</td>
<td>1,456 (31%)</td>
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<tr>
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<td>1,030</td>
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<td>162 (16%)</td>
<td>227 (22%)</td>
<td>180 (17%)</td>
<td>458 (44%)</td>
<td>278 (27%)</td>
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<td>ETS⇔CRE</td>
<td>11-mer</td>
<td>CGGAAGTGACG</td>
<td>226</td>
<td>157 (69%)</td>
<td>124 (55%)</td>
<td>164 (73%)</td>
<td>134 (59%)</td>
<td>186 (82%)</td>
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<td>17 (52%)</td>
<td>25 (76%)</td>
<td>19 (58%)</td>
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<td>15 (83%)</td>
<td>12 (67%)</td>
<td>18 (100%)</td>
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<td>6 (86%)</td>
<td>4 (57%)</td>
<td>7 (100%)</td>
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<td>234 (1%)</td>
<td>451 (3%)</td>
<td>279 (2%)</td>
<td>2,647 (15%)</td>
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<td>212 (5%)</td>
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<td>176 (11%)</td>
<td>236 (15%)</td>
<td>190 (12%)</td>
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<td>124 (55%)</td>
<td>164 (73%)</td>
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<td>186 (82%)</td>
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<td>30 (91%)</td>
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<td>2 (100%)</td>
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<td>2 (100%)</td>
<td>0 (0%)</td>
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Table S3  Enriched GO terms (P<0.05) for the human genes that have one of the 4 ETS⇔CRE 12-mer or 13-mers (C/GCGGAAGTGACGC) in promoters. There are no enriched GO terms with P-value <0.05 for the genes with C/GCGGAAGTGACGC in their promoters.

<table>
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<th>Sequence</th>
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<th>Backgound count</th>
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Table S4  Occurrence of unmethylated versions of the ETS⇔CRE motifs in the mouse genome with 24,273 promoters and proximal promoters and 16,026 CpG Islands. Unmethylated occurrences are presented in parenthesis.

<table>
<thead>
<tr>
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<th>N-mers</th>
<th>DNA sequence</th>
<th>Whole Genome (# Unmethylated)</th>
<th>Promoter (-1000...500) (#Unmethylated)</th>
<th>Proximal Promoter (-200...60) (#Unmethylated)</th>
<th>CpG Islands (#Unmethylated)</th>
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<td></td>
<td></td>
<td></td>
<td>(100%)</td>
<td>(1.18%)</td>
<td>(0.19%)</td>
<td>(0.34%)</td>
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<td>1261 (990)</td>
<td>704 (643)</td>
<td>1362 (1286)</td>
</tr>
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<td>CRE</td>
<td>8-mer</td>
<td>TGACCGTCA</td>
<td>14297 (1561)</td>
<td>578 (432)</td>
<td>315 (268)</td>
<td>599 (569)</td>
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<tr>
<td>ETS&lt;sup&gt;⇔&lt;/sup&gt;CRE</td>
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<td>CGGAAGTGACGGT</td>
<td>89 (67)</td>
<td>37 (36)</td>
<td>31 (31)</td>
<td>60 (60)</td>
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<td>12-mer</td>
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<td>82 (68)</td>
<td>35 (35)</td>
<td>33 (33)</td>
<td>68 (67)</td>
</tr>
<tr>
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<td>21 (21)</td>
<td>10 (10)</td>
<td>7 (7)</td>
<td>19 (19)</td>
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