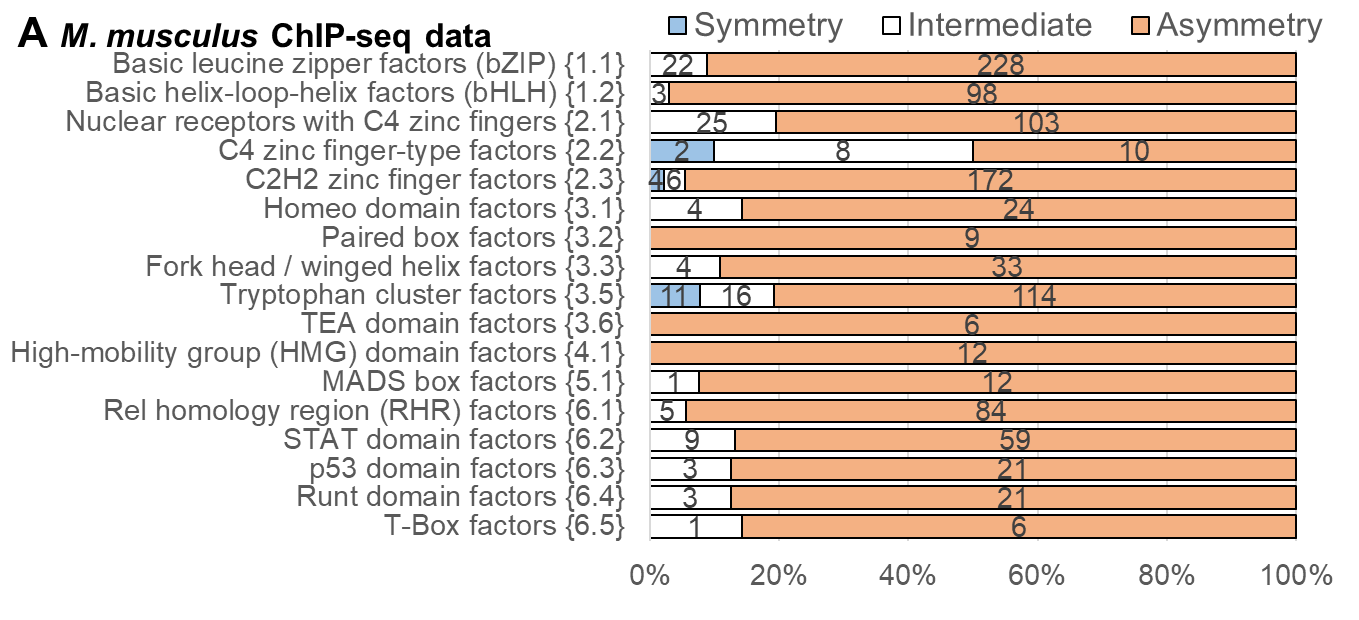
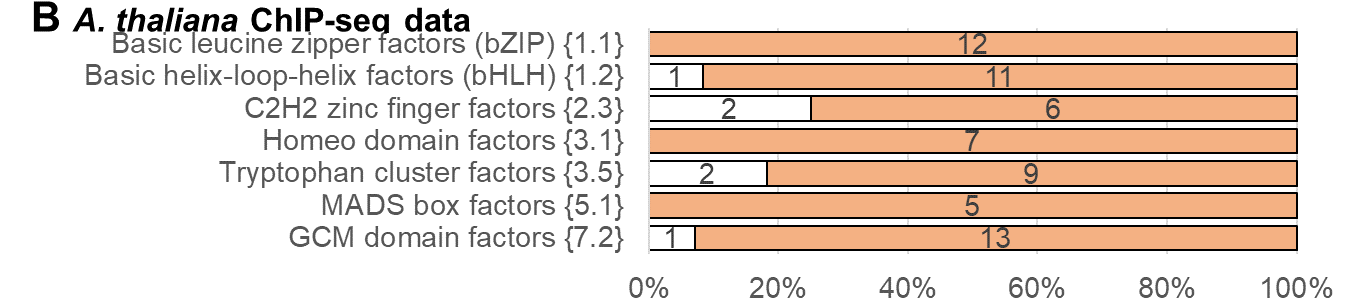
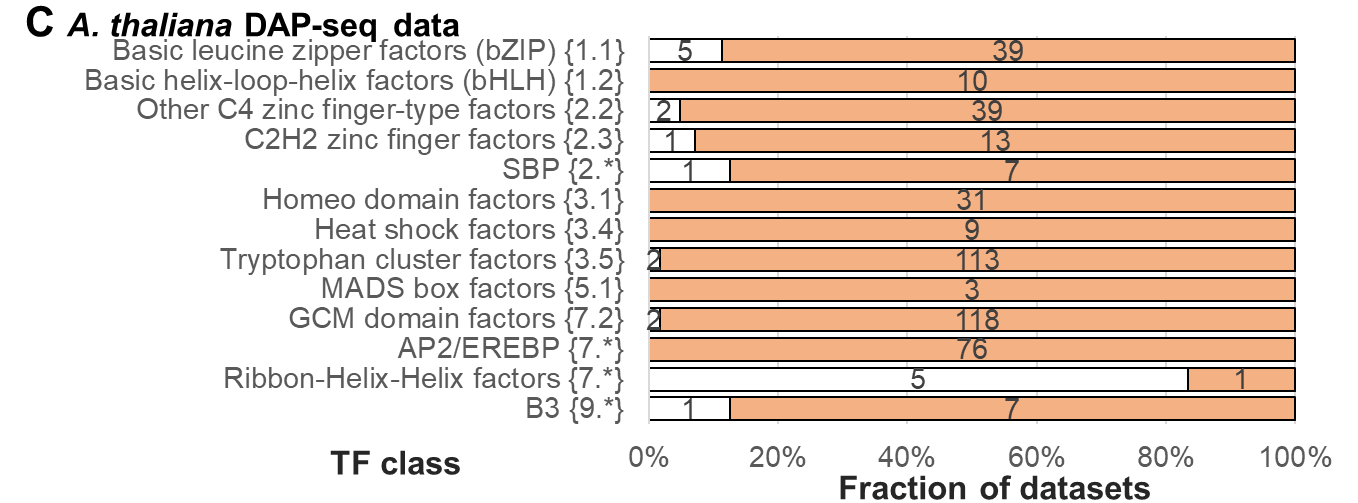
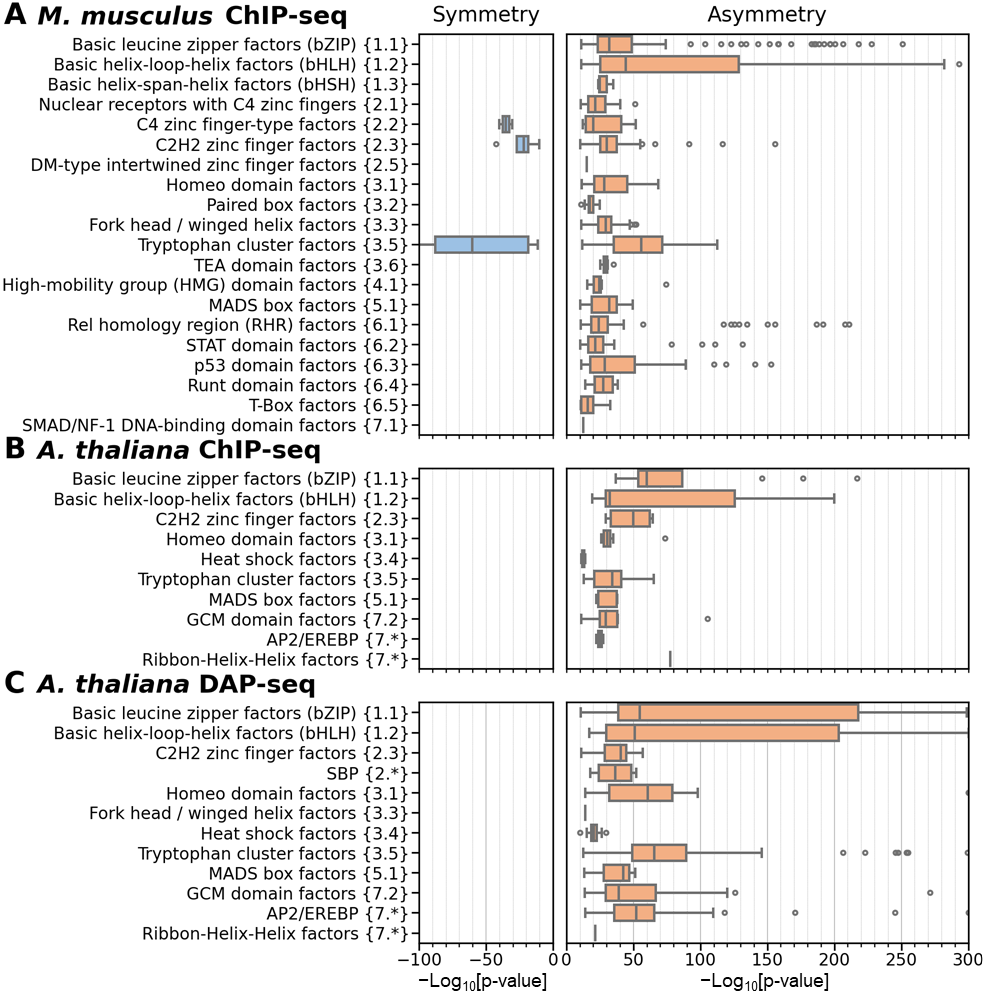
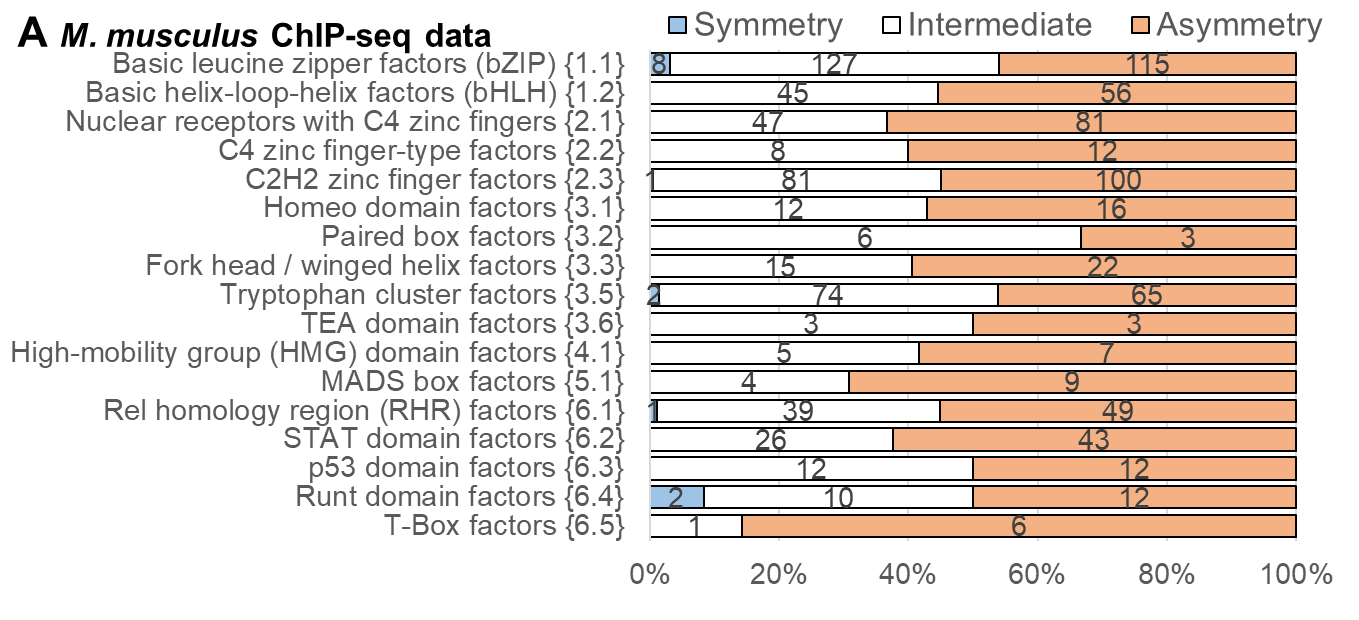
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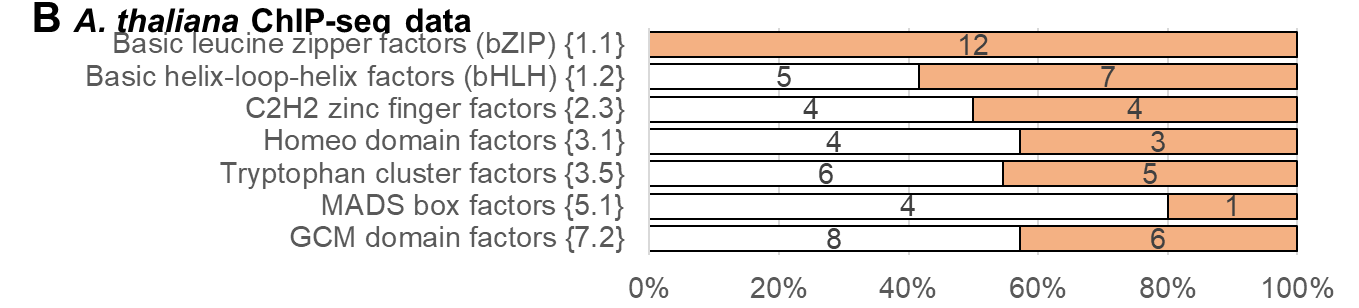
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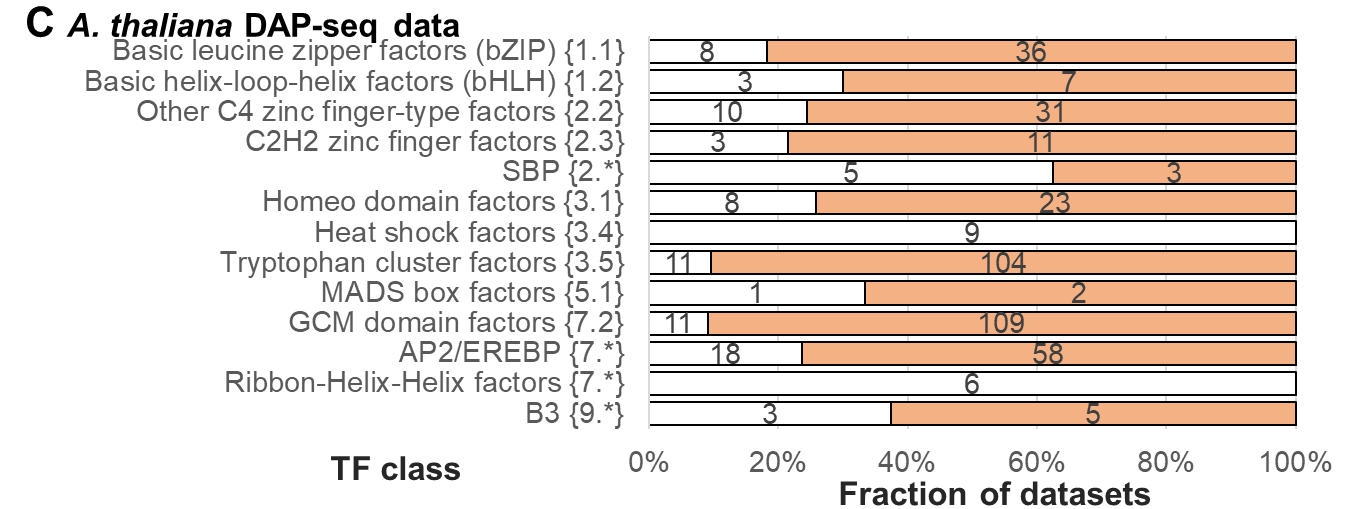
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**Figure S1.** Abundances of homotypic asymmetric/symmetric CEs in the benchmark collections of ChIP-seq and DAP-seq data. TAR value of 1.1 was applied to compute the significance of asymmetry within homotypic CEs. (**A**) ChIP-seq data for *M. musculus.* (**B**) ChIP-seq data for *A. thaliana.* (**C**) DAP-seq data for *A. thaliana.* Axes X show the number of datasets in a TF class. Blue/brown colors count datasets possessing a high significance of enrichment within homotypic symmetric/asymmetric CEs, p < 1E-10. White color respects absence of a high significance, p > 1E-10, neither symmetric nor asymmetric CEs have high significance. Axes Y display TF classes according to TFClass [7,8] (**A**) and Plant-TFClass [11], (**B**) and (**C**).

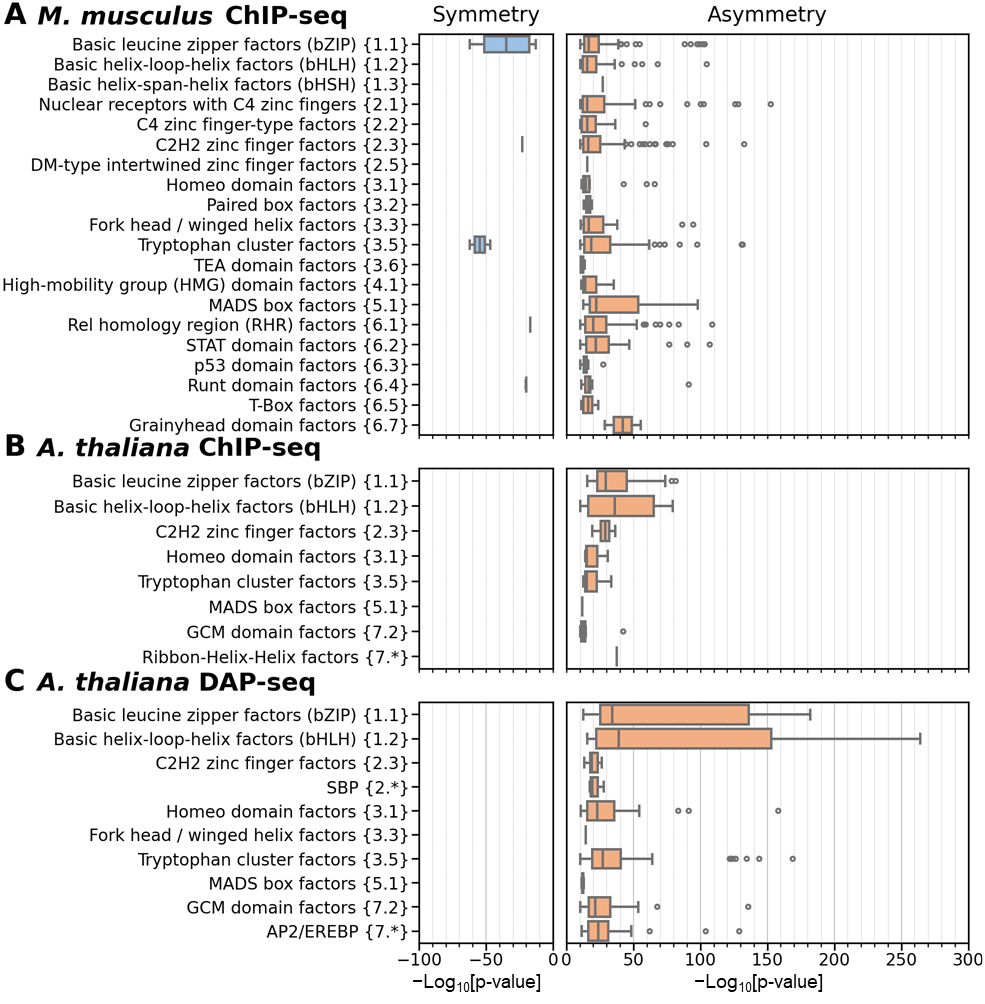
**Figure S2.** Distribution of the significance of enrichment of homotypic asymmetric/symmetric CEs as a function of the DBD structure of target TFs. TAR value of 1.1 was applied to compute the significance of asymmetry within homotypic CEs. (**A**) ChIP-seq data for *M. musculus.* (**B**) ChIP-seq data for *A. thaliana.* (**C**) DAP-seq data for *A. thaliana.* Hierarchical classifications of *M. musculus* and *A. thaliana* target TFs by the structure of DBDs were derived from TFclass [7,8] and Plant-TFclass [11], see Section 4.1. Axes X mark the significance of enrichment by Fisher exact test (Figure 1E), −Log10(p-value), calculated by MCOT [26,31,32]. Brown/blue colors imply enrichment towards asymmetry/symmetry, for each TF class we considered only datasets possessing the significant enrichment towards asymmetry or symmetry according to the results from Figure 4. Axis Y mark TF classes. The boxplots depict the distributions of the Q1, Q2 and Q3 quartiles of the fractions of the considered datasets with certain values of the significance, −Log10(p-value). Whiskers on either side of the Q1/Q3 respect the minimum/maximum values if they were located within 1.5 interquartile ranges (IQR = Q3 – Q1) from Q1/Q3, otherwise they are equal to {Q1 - 1.5 \* IQR} / {Q3 + 1.5 \* IQR}, respectively. In the latter case, we marked all other points as outliers.



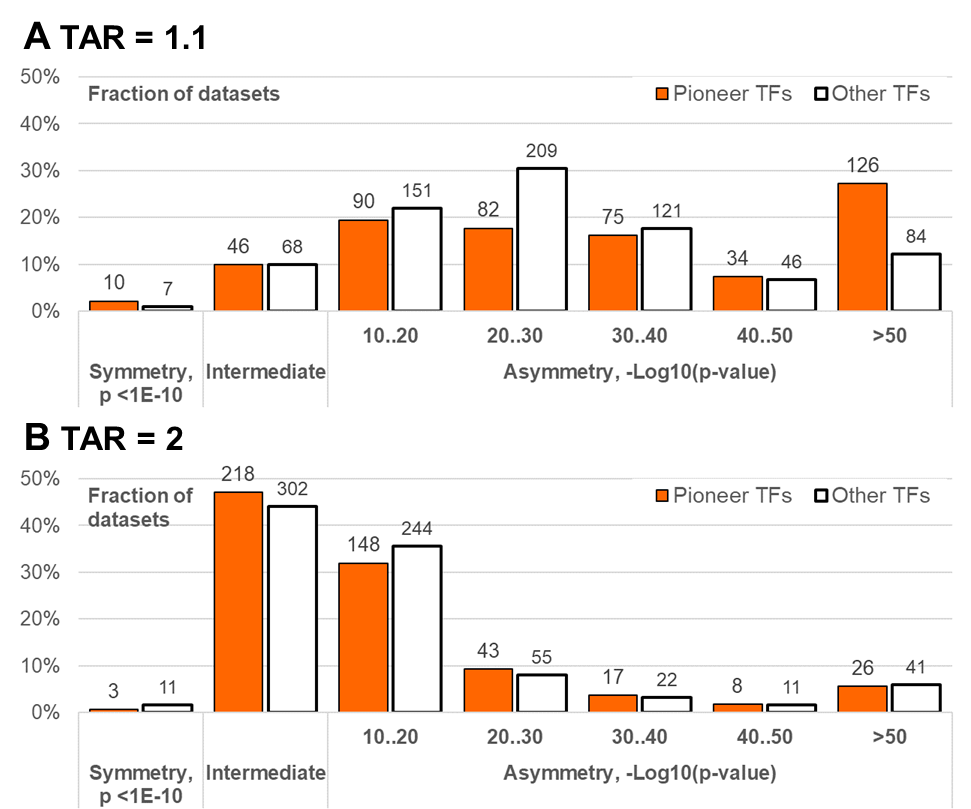




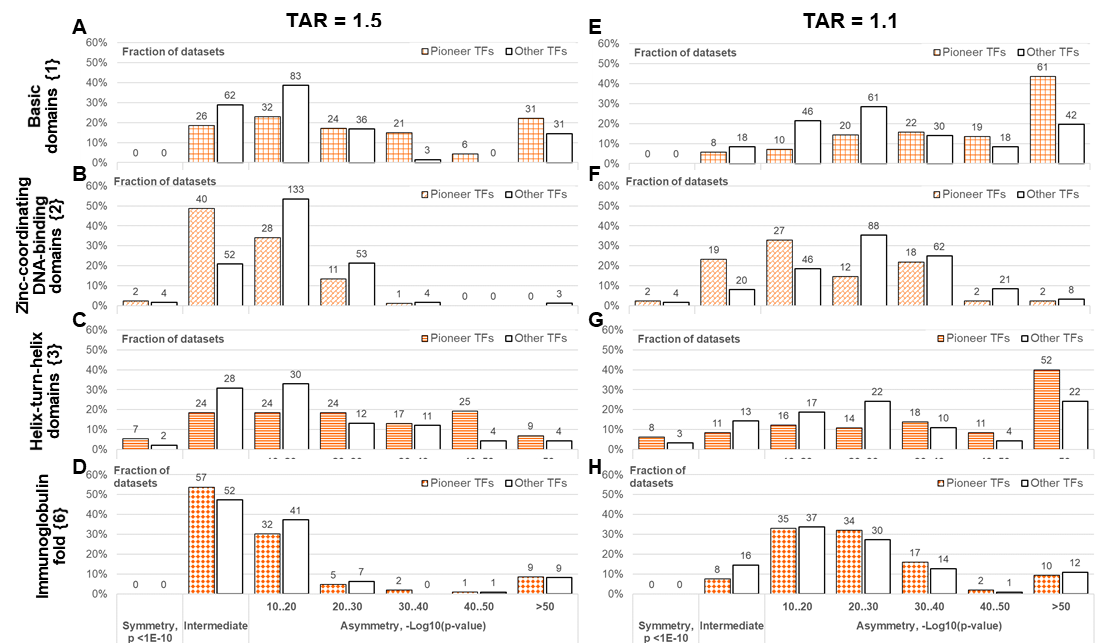
**Figure S3.** Abundances of homotypic asymmetric/symmetric CEs in the benchmark collections of ChIP-seq and DAP-seq data. TAR value of 2 was applied to compute the significance of asymmetry within homotypic CEs. (**A**) ChIP-seq data for *M. musculus.* (**B**) ChIP-seq data for *A. thaliana.* (**C**) DAP-seq data for *A. thaliana.* Axes X show the number of datasets in a TF class. Blue/brown colors count datasets possessing a high significance of enrichment within homotypic symmetric/asymmetric CEs, p < 1E-10. White color respects absence of a high significance, p > 1E-10, neither symmetric nor asymmetric CEs have high significance. Axes Y display TF classes according to TFClass [7,8] (**A**) and Plant-TFClass [11], (**B**) and (**C**).

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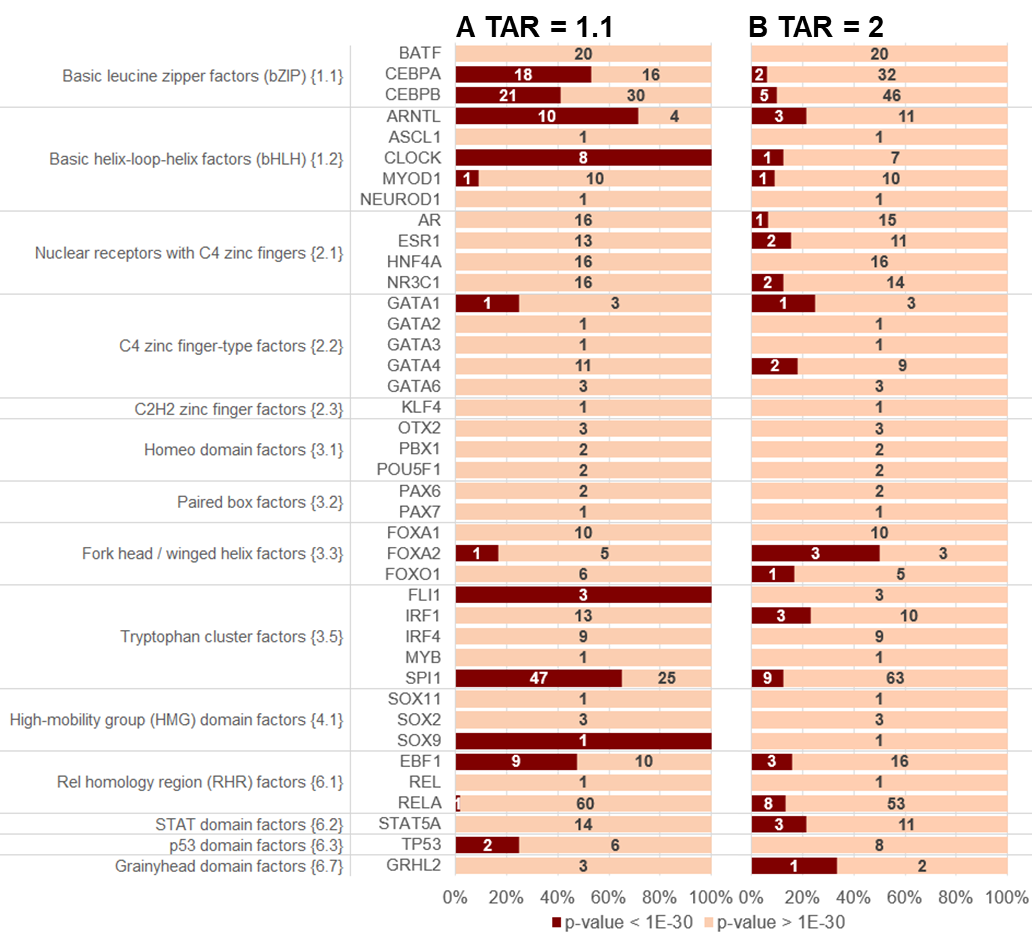
**Figure S4.** Distribution of the significance of enrichment of homotypic asymmetric/symmetric CEs as a function of the DBD structure of target TFs. TAR value of 2 was applied to compute the significance of asymmetry within homotypic CEs (**A**) ChIP-seq data for *M. musculus.* (**B**) ChIP-seq data for *A. thaliana.* (**C**) DAP-seq data for *A. thaliana.* Hierarchical classifications of *M. musculus* and *A. thaliana* target TFs by the structure of DBDs were derived from TFclass [7,8] and Plant-TFclass [11], see Section 4.1. Axes X mark the significance of enrichment by Fisher exact test (Figure 1E), −Log10(p-value), calculated by MCOT [26,31,32]. Brown/blue colors imply enrichment towards asymmetry/symmetry, for each TF class we considered only datasets possessing the significant enrichment towards asymmetry or symmetry according to the results from Figure 4. Axis Y mark TF classes. The boxplots depict the distributions of the Q1, Q2 and Q3 quartiles of the fractions of the considered datasets with certain values of the significance, −Log10(p-value). Whiskers on either side of the Q1/Q3 respect the minimum/maximum values if they were located within 1.5 interquartile ranges (IQR = Q3 – Q1) from Q1/Q3, otherwise they are equal to {Q1 - 1.5 \* IQR} / {Q3 + 1.5 \* IQR}, respectively. In the latter case, we marked all other points as outliers.



**Figure S5.** Homotypic asymmetric CEs of pioneer TFs. Target TFs from the benchmark collection for *M. musculus* ChIP-seq data were considered. TAR values of 1.1 (**A**) and 2 (**B**) were applied to compute the significance of asymmetry within homotypic CEs. Distributions of the significance of asymmetry within CEs for ChIP-seq datasets of target TFs with and without proven pioneer activity. Orange and white colors mark TFs with proven pioneer activity and the other TFs. Axis X denotes the significance of enrichment. The groups Symmetry, Intermediate, Asymmetry 10..20, Asymmetry 20..30, etc. imply the significant enrichment towards symmetric CEs (p-value < 1E-10), lack of pronounced significance in either direction (p > 1E-10), the significant enrichment towards asymmetric CEs (1E-10 < p-value < 1E-20, 1E-20 < p-value < 1E-30, etc.) , respectively. Axes Y mean fractions of datasets, labels above columns show the number of datasets.



**Figure S6.** Homotypic asymmetric CEs of pioneer TFs from the superclasses Basic domains {1}, Zinc-coordinating DNA-binding domains {2}, Helix-turn-helix domains {3}, and Immunoglobulin fold {6} (rows). Target TFs from the benchmark collection for *M. musculus* ChIP-seq data were considered. TAR values of 1.5 (left, **A**-**D**) and 1.1 (right, **E**-**H**) were applied to compute the significance of asymmetry within homotypic CEs. Distributions of the significance of asymmetry within CEs for ChIP-seq datasets of target TFs with and without proven pioneering activity. Orange and white colors mark TFs with proven pioneer activity and the other TFs. Axis X denotes the significance of enrichment. The groups Symmetry, Intermediate, Asymmetry 10..20, Asymmetry 20..30, etc. imply the significant enrichment towards symmetric CEs (p-value < 1E-10), lack of pronounced significance in either direction (p > 1E-10), the significant enrichment towards asymmetric CEs (1E-10 < p-value < 1E-20, 1E-20 < p-value < 1E-30, etc.). Axes Y mean fractions of datasets, labels above columns show the numbers of datasets.



**Figure S7.** Homotypic asymmetric CEs of pioneer TFs. Target TFs from the benchmark collection for *M. musculus* ChIP-seq data were considered. TAR values of 1.1 (**A**) and 2 (**B**) were applied to compute the significance of asymmetry within homotypic CEs. Distributions of the significance of asymmetry within CEs for ChIP-seq datasets of target TFs with proven pioneering activity. Axis X marks the number of ChIP-seq datasets. Axis Y shows TF classes and TF names. The maroon color indicates the high significance of asymmetry in homotypic CEs, p-value < 1E-30; the apricot color implies all remaining cases, p-value > 1E-30.