**Figure S7.**—Vast majority of substitutions are effectively neutral, even those that substantially repattern binding. Each small plot corresponds to one enhancer (replicates pooled) and shows the selection coefficient (vertical axis) of each substitution as a function of the Euclidean distance (horizontal axis) between the binding profiles of the background haplotype and the haplotype newly formed by the substitution. Substitutions shown are those on the lineage leading from the initial haplotype to the most frequent haplotype at the end of each simulation. The gray region spans from $-2 < Ns < 2$, which corresponds to effectively neutral mutations (fixations probabilities in this region range from 0.3 to 2.3 times the neutral fixation probability).