Figure s1

a. Gene track showing alignment of the 24 BACs chosen for the BAC MPRA to hg38. **b**. Bar plot showing the total number of bins with a pval.mad ≤ 0.05 in the BAC MPRA for Neurons and HEKs, as well as a reduced count where consecutive bins were merged into a single active region. **c.** Bar plot showing the total number of oligos with a pval.mad ≤ 0.05 in the Oligo MPRA, as well as a reduced count where consecutive and overlapping oligos were merged into a single active region.

Figure s2

a–f. Gene tracks of CREs for *MAPT* identified in Rogers et al.[39] where variant effects were found in our MPRA. Regions are labeled as in Rogers et al.[39] as distance from the *MAPT* promoter. Variant effects shown are in Neurons. Adj. p. values for variants are: **a.** chr17:45219428:C:T = 0.0456, chr17:45219449:T:A = 0.0401, **b.** chr17:45241205:C:T = 0.0467, chr17:45241344:C:G = 0.0246, chr17:45241498:G:A = 8.16×10^{-4}, chr17:45241588:C:T = 3.74×10^{-4}, chr17:45241965:C:T = < 2.2×10^{-16}, chr17:45242096:C:T = 0.0246, chr17:45242183:G:GA = 0.0165, **c.** chr17:45429574:G:A = 0.0175, chr17:45429600:C:T = 5.82×10^{-4}, chr17:45429596:T:C = 3.17×10^{-13}, chr17:45429616:G:T = 2.82×10^{-5}, chr17:45429635:C:T = 2.04×10^{-3}, chr17:45429804:T:G = 2.64×10^{-3}, **d.** chr17:45431618:C:G = 0.0222, chr17:45431806:C:T = 1.17×10^{-4}, chr17:45432539:C:T = 0.0476, chr17:45432576:C:T = 7.80×10^{-3}, chr17:45432583:C:T = 0.0255, chr17:45432606:G:T = < 2.2×10^{-16}, chr17:45432617:G:T = 1.88×10^{-4}, chr17:45432652:A:ACCCTT = 4.32×10^{-3}, **e.** chr17:45848799:G:GC = 0.0312, chr17:45849095:A:G = 1.88×10^{-4}, chr17:45849813:C:T = 5.08×10^{-3}, **f.** chr17:45873854:T:G = 7.38×10^{-3}, chr17:45873875:G:A = 0.0237.

Figure s3

a. Gene track of the *MAPT* promoter saturation mutagenesis region showing variant effects observed in HEK293FT cells (pval.mad ≤ 0.05 and |logFC| > 0.1). The top row of the heatmap represents the centered 5 bp deletion sequences, and the bottom 3 rows represent each alternate base at that position. Red lines represent variants with a gain of activity and blue lines represent a loss of activity. **b.** Correlation plot of logFC of variant effects observed in Neurons and HEK293FT cells (pval.mad ≤ 0.05 and a |logFC| of at least 0.1). Blue dots represent variant effects in HEK293FT cells, pink represent variant effects in Neurons, and purple are variant effects in both cell types. (logFC Spearman's $\rho = 0.336$, approximate $p < 2.2 \times 10^{-16}$)

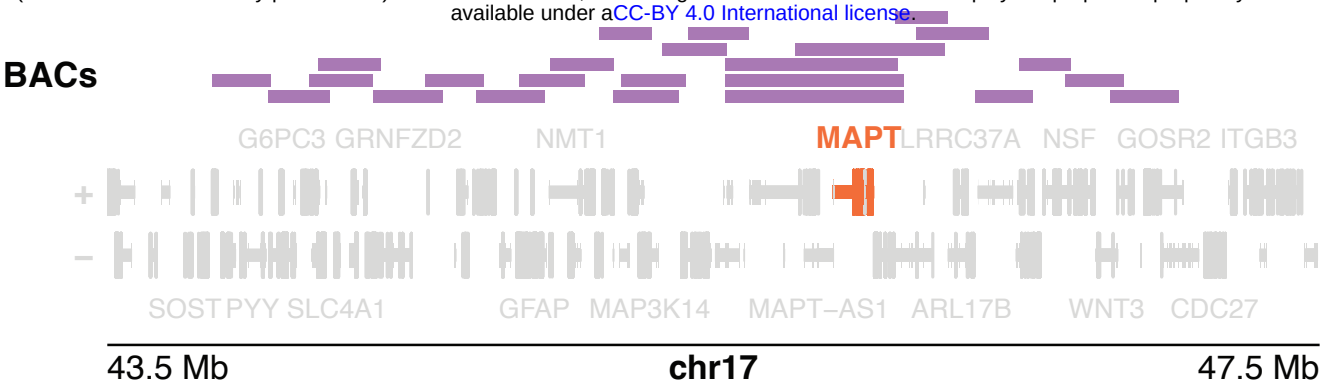
Figure s4

a. Correlation plots of AlphaGenome raw scores and MPRA logFC from the *MAPT* promoter mutagenesis. (Spearman's $\rho = 0.0277$, approximate $p = 0.0321$) **b.** Same as a. except only variants with an adj. p. value ≤ 0.05 in the Neuron MPRA by bcalm are plotted. (Spearman's $\rho = 8.71 \times 10^{-9}$, approximate $p = 8.71 \times 10^{-4}$) **c.** Correlation plots of PromoterAI scores and MPRA logFC from the *MAPT* promoter mutagenesis. (Spearman's $\rho = 0.482$, approximate $p = 1.89 \times 10^{-4}$) **d.** Same as in c except only variants with an adj. p. value ≤ 0.05 in the Neuron MPRA by bcalm are plotted. (Spearman's $\rho = 0.2924$, approximate $p = 1.10 \times 10^{-9}$) **e.** Correlation plot of

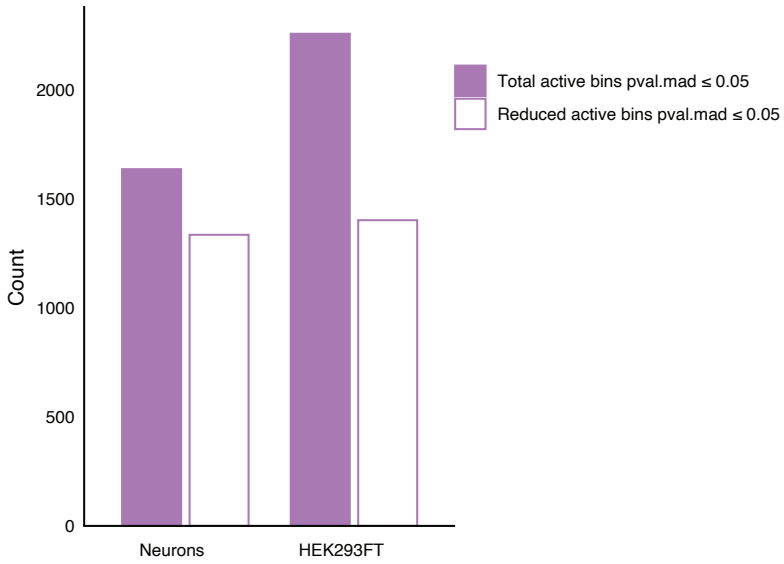
AlphaGenome raw scores and PromoterAI scores for each SNV in the saturation mutagenesis MPRA (Spearman's ρ = 0.153, approximate $p < 2.2 \times 10^{-16}$). For all plots, the best fit line is a linear regression of the data.

Figure s1

a.



b.



c.

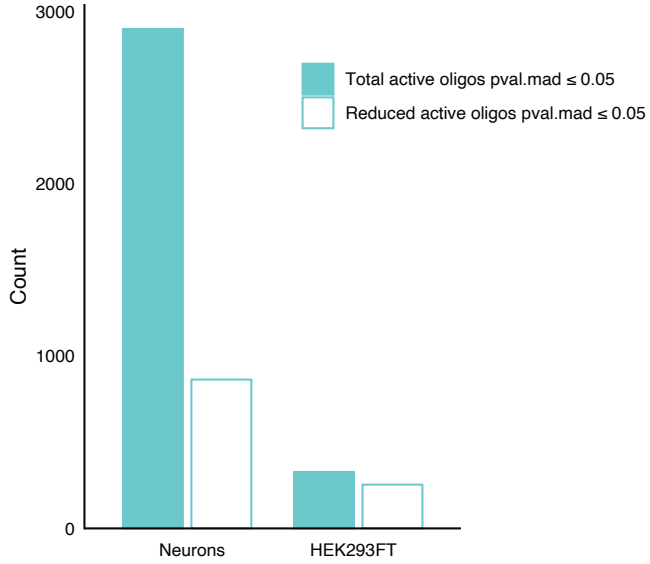


Figure s2

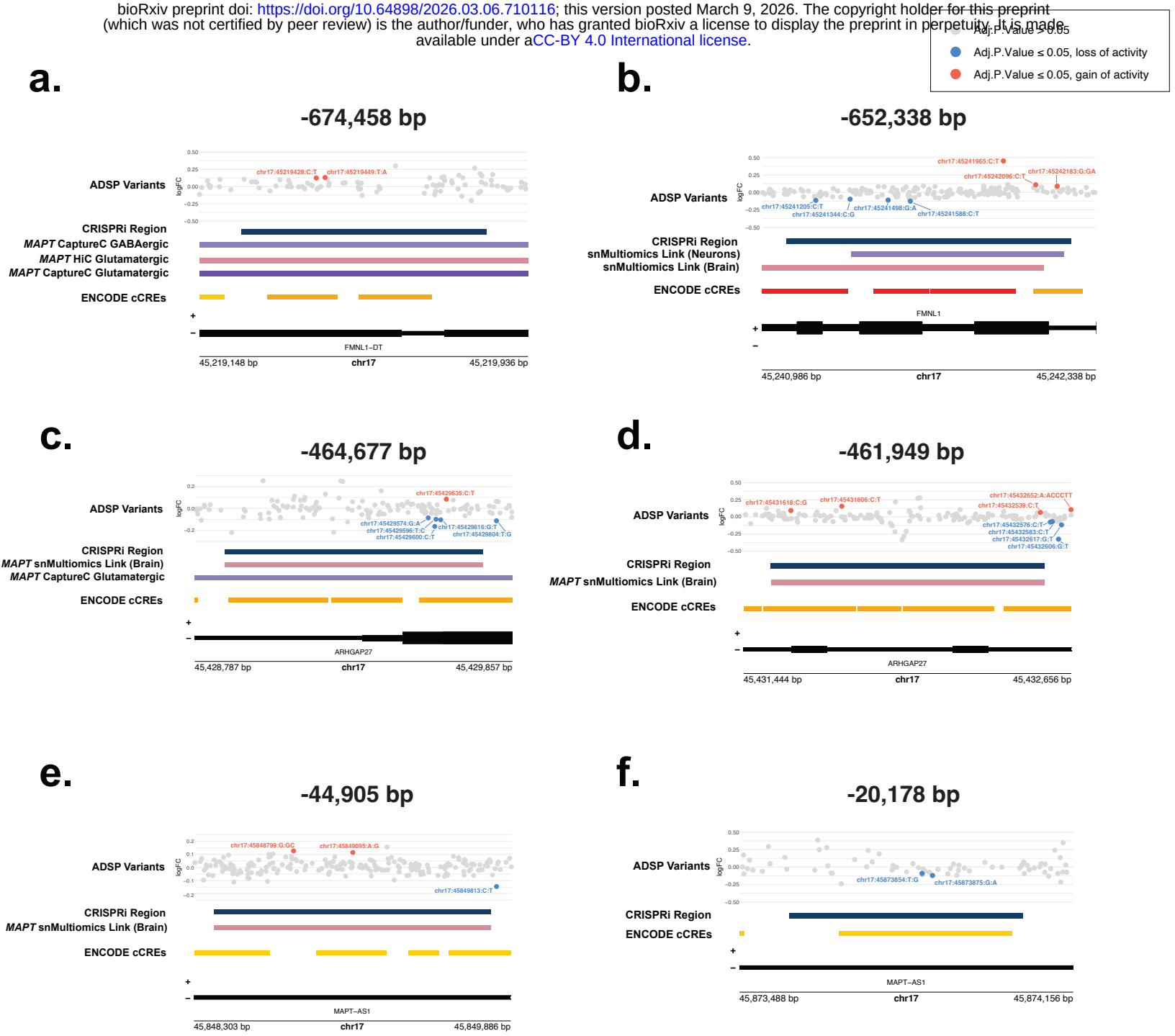
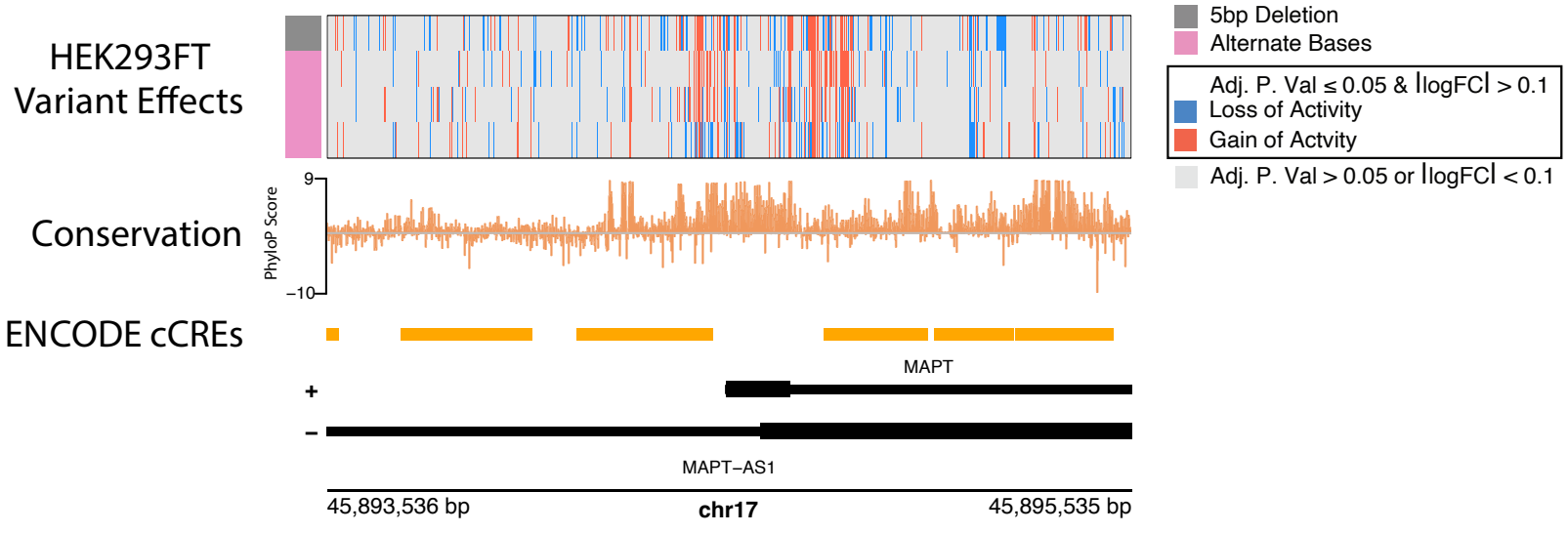


Figure s3

a.



b.

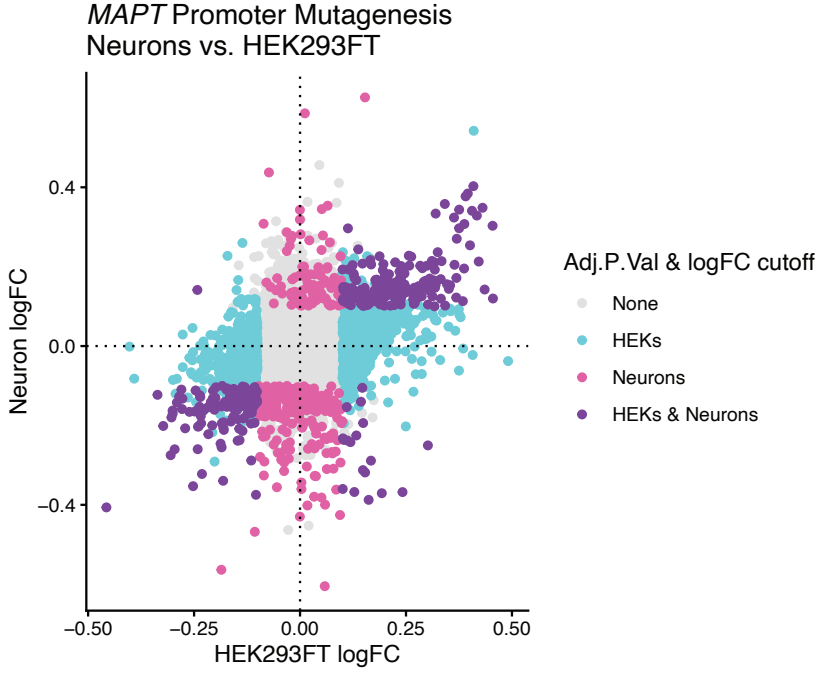
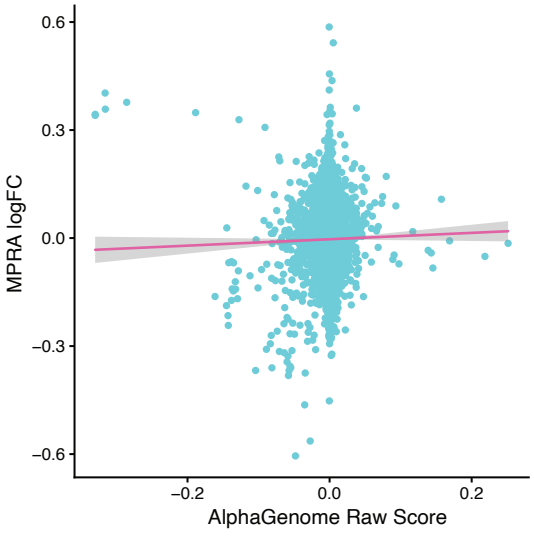
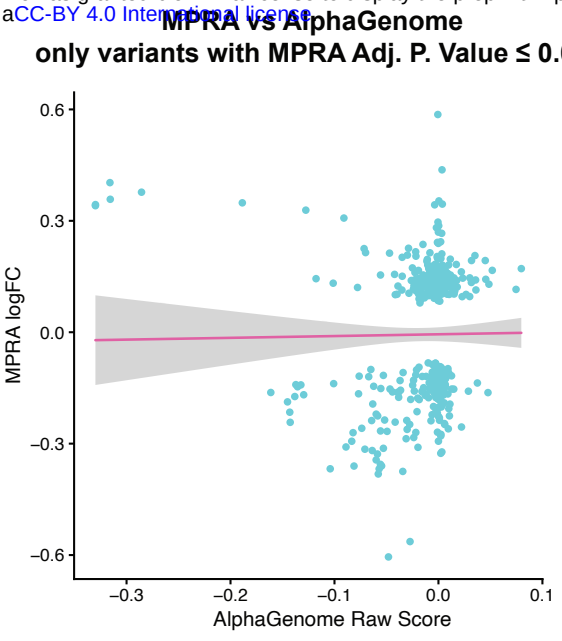


Figure s4

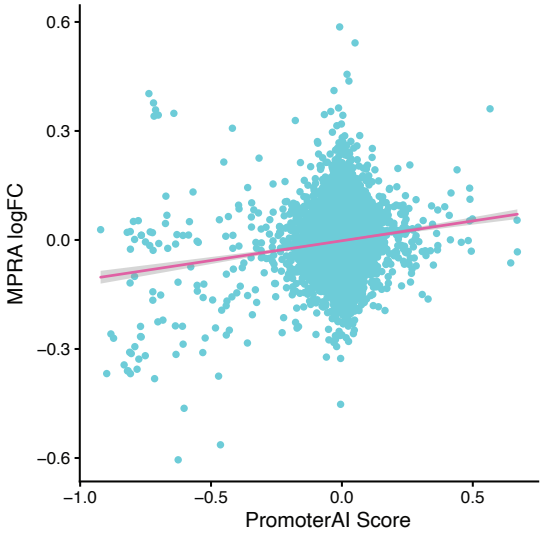
a.



b.



c.



d.

e.