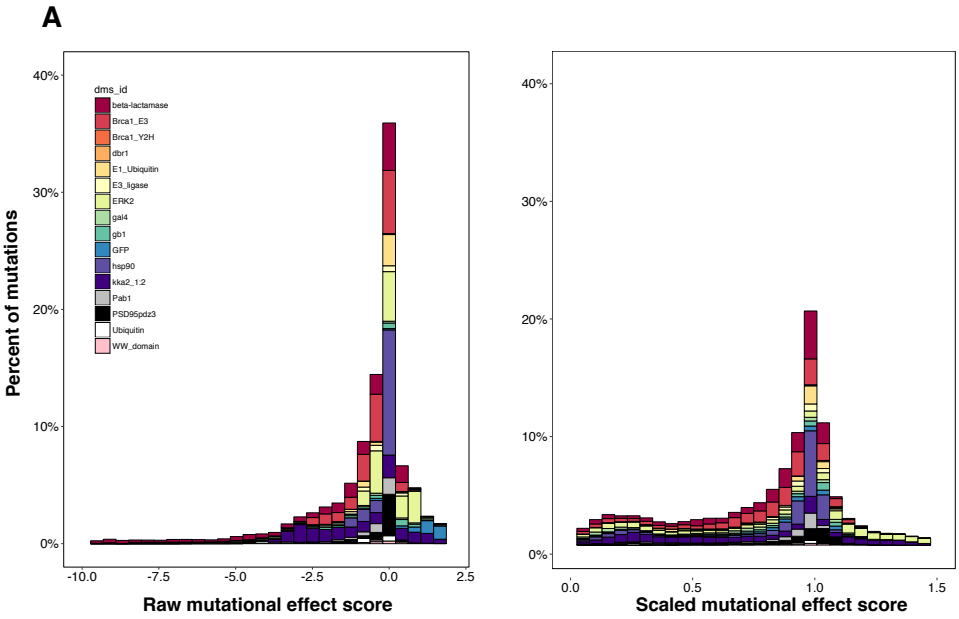
# Supplemental Figure Legends



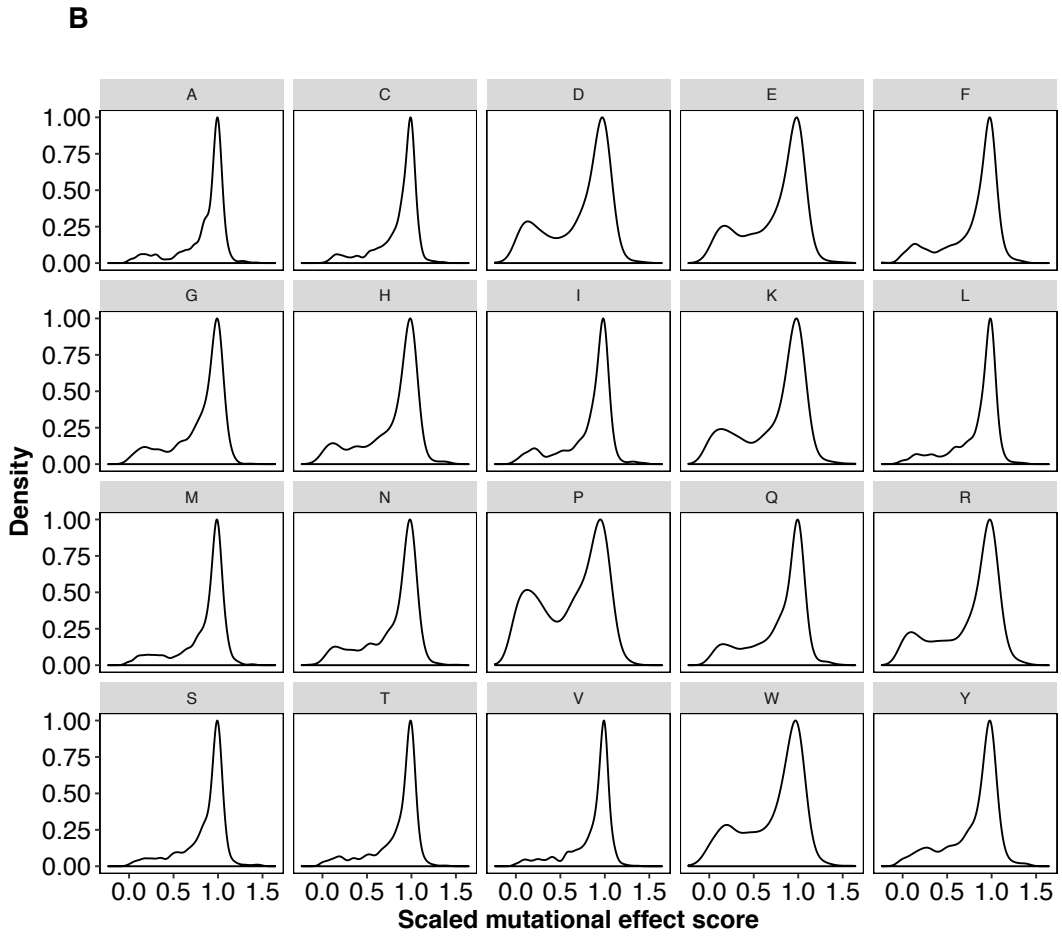



**Figure S1.** We curated large-scale mutagenesis data sets describing the effects of 34,373 mutations at 2,236 positions in fourteen proteins. To facilitate comparisons between each data set, we rescaled mutational effect scores for each protein by subtracting the median mutational effect score of all synonymous mutations in that protein from each nonsynonymous mutational effect score and then dividing that difference by the median of the bottom 1% of mutational effect scores (see **Methods**). (**A**) Stacked histograms of the original scores (**left panel**) and rescaled scores (**right panel**) are shown. (**B**) Density plots of the scaled mutational effect scores for each amino acid substitution are shown.

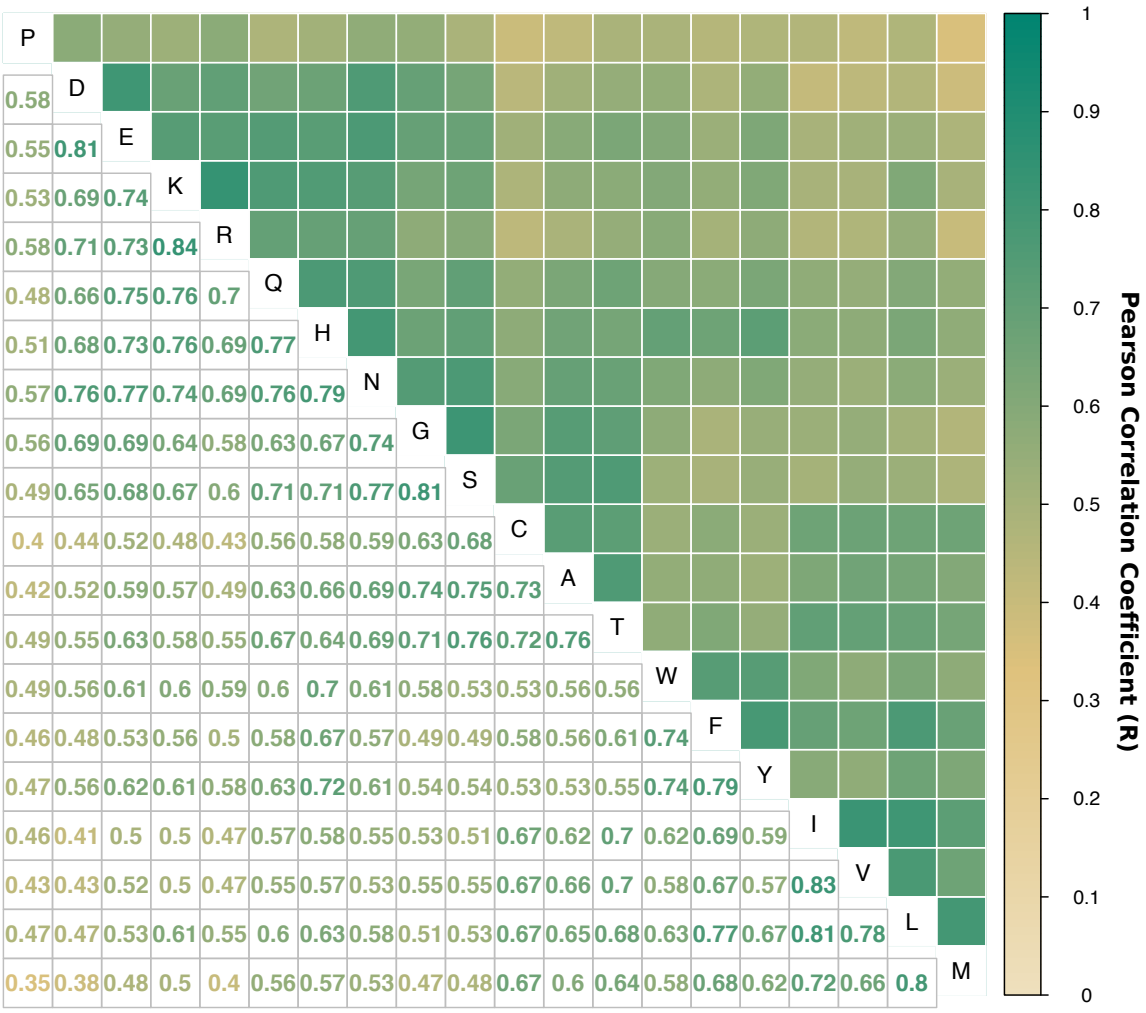



**Figure S2.** For each substitution, Pearson correlation coefficients were calculated for the mutational effect scores of that substitution with every other substitution at each position. A correlation plot of these Pearson coefficients is shown. Color indicates the Pearson correlation coefficient ranging from 0 (light brown) to 1 (green).

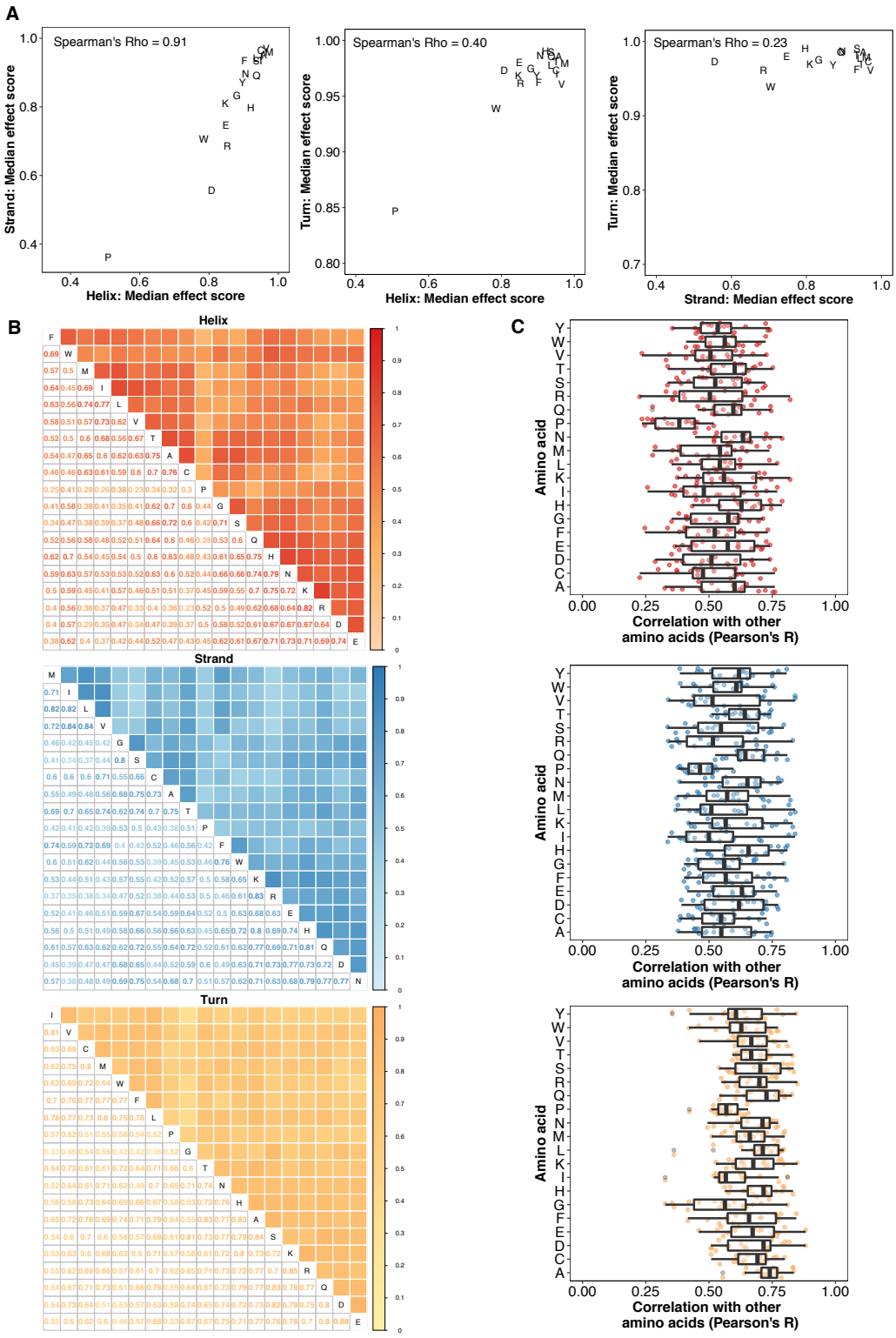

A
Spearman's Rho = 0.91
Strand: Median effect score
Helix: Median effect score
Spearman's Rho = 0.40
Turn: Median effect score
Helix: Median effect score
Spearman's Rho = 0.23
Turn: Median effect score
Strand: Median effect score
B
Helix
Strand
Turn
C
Amino acid
Correlation with other amino acids (Pearson's R)

**Figure S3.** (**A**) For each amino acid substitution, the median mutational effect score was calculated. The correlation between the median mutational effects for each substitution in helices, strand and turns are shown in scatterplots, and Spearman's Rho indicates the degree of rank correlation within each scatterplot. (**B**) Pearson correlation coefficients were calculated for the mutational effects of each substitution with every other substitution at every position. The Pearson correlation coefficient plots are shown separately for α-helices (top), β-sheets (middle), and turns (bottom). (**C**) Boxplots show the distribution of Pearson correlation coefficients for each amino acid type in three structural contexts.

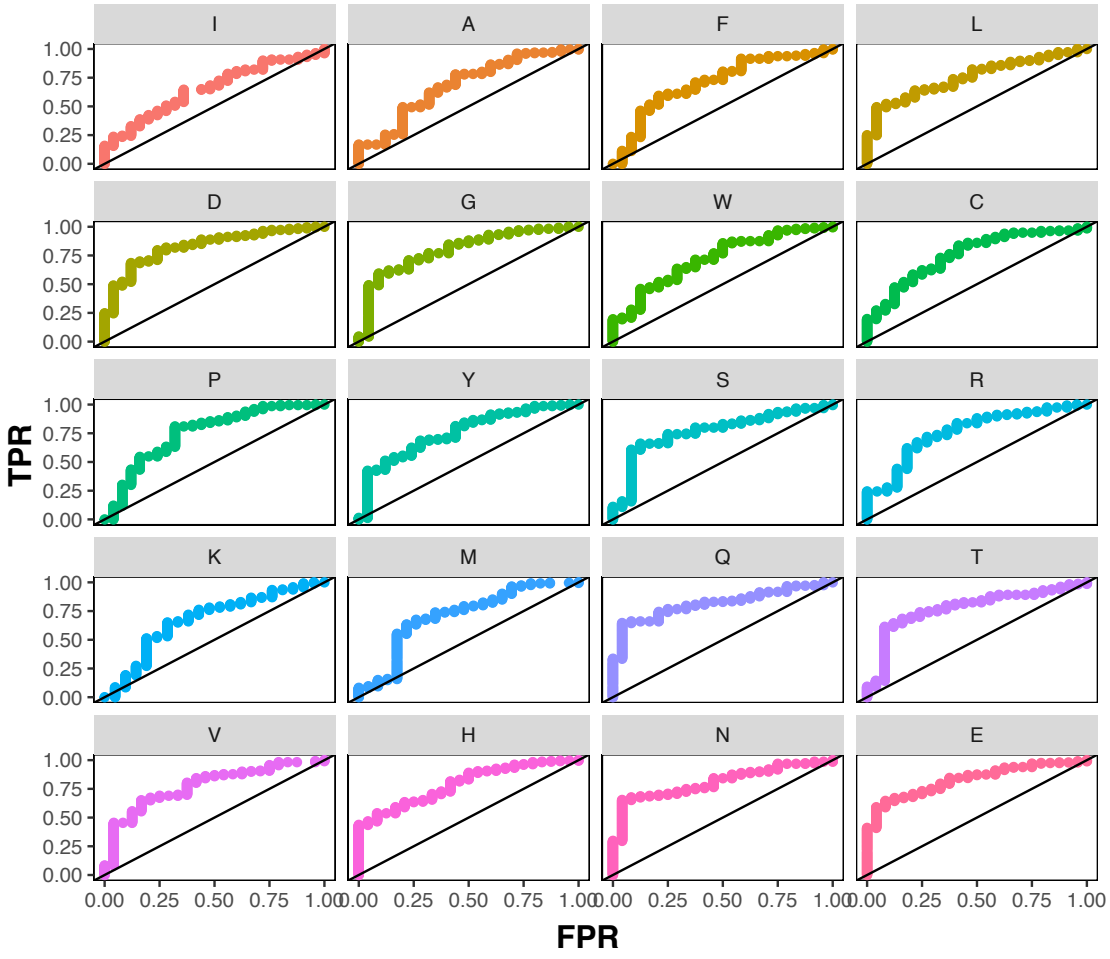



**Figure S4.** A mutational effect threshold was defined such that positions with a mutational effect score below the threshold were classified as “interface,” whereas positions with a mutational effect score above the threshold were classified as “non-interface.” ROC curves were generated by varying this threshold for each amino acid type in the four proteins with protein or DNA ligand-bound structures (hYAP65 WW domain, PSD95 pdz3 domain, Gal4 and BRCA1 RING domain (BARD1 binding)).

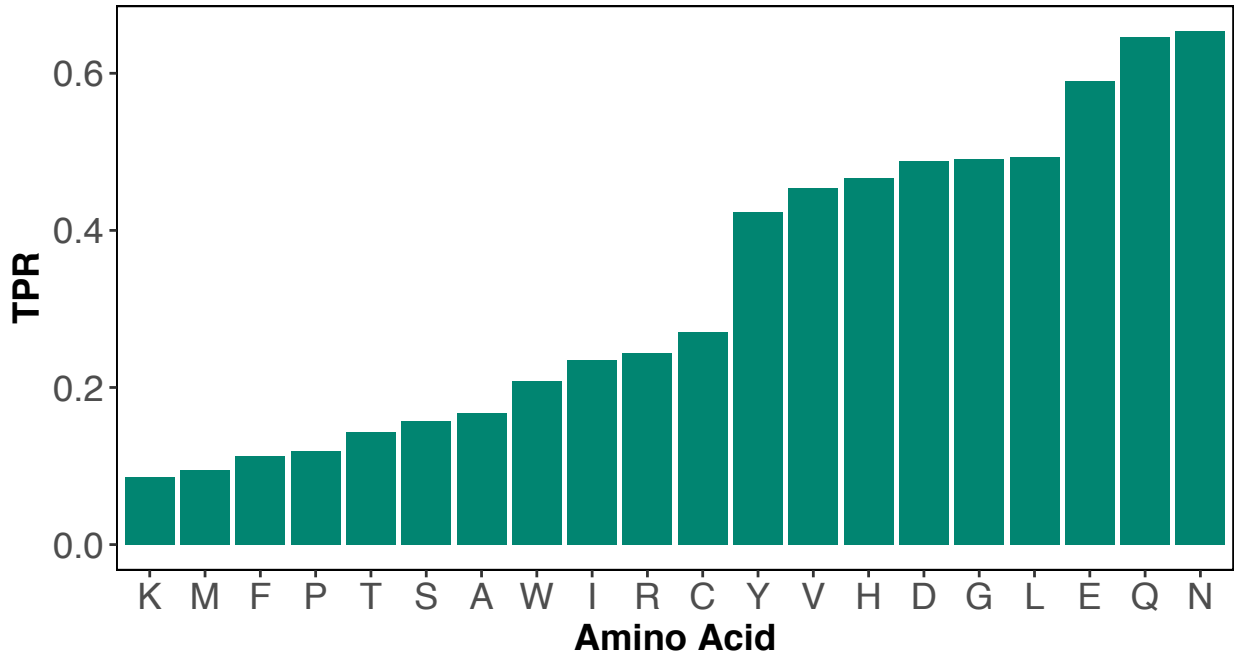



**Figure S5.** A mutational effect threshold was defined such that positions with a mutational effect score below the threshold were classified as "interface," whereas positions with a mutational effect score above the threshold were classified as "non-interface." A barplot shows each amino acid substitution's true positive rate (TPR) for detecting interface positions at a fixed, 5% non-interface position false positive rate.

**Supplemental Table**

**Table S1.** A table showing sample size, *p*-value and Bonferroni corrected *p*-value for paired, two-sided Wilcoxon rank sum tests of the position median effect scores versus each amino acid substitution's effect scores. This analysis was restricted to the 882 positions where the effects of all 19 possible substitutions were scored.