Predictions were made using SNAP (Screening for Non-Acceptable Polymorphisms), a neural network based method for prediction of functional effects of single amino acid substitutions. By default, for each submitted substitution, SNAP reports a single binary prediction (Neutral/Non-neutral), which is associated with an RI (reliability index, range 0-9) and a value of “expected accuracy” (0-100%; in testing, the accuracy of SNAP predictions at the given RI). The SNAP RI scores are computed by taking a mean of ten neural nets trained on different data sets – the raw score. Unfortunately, none of these values map directly to percentage change in proliferation rate. As we reported in the original SNAP paper, increased scores indicate better prediction accuracy. Thus, we used the raw score to estimate our “standard deviation”– 0.01 for scores of 60 and above, 0.15 for scores of 0, and the rest pro-rated accordingly. The predictions themselves were coarsely estimated from testing of other experimentally determined mutants: SNAP>=37, 1.0 (severe effect), SNAP => 27, 0.8 (moderate effect), SNAP -> 16, 0.6 (mild effect)

Overall, it is important to note that while we can attempt to adapt SNAP output to the various prediction challenges, accounting for all possible variations on the theme is nearly impossible. Thus, it is more realistic to leave the interpretation of mutation neutrality to the expert experimentalists working with the protein at hand.