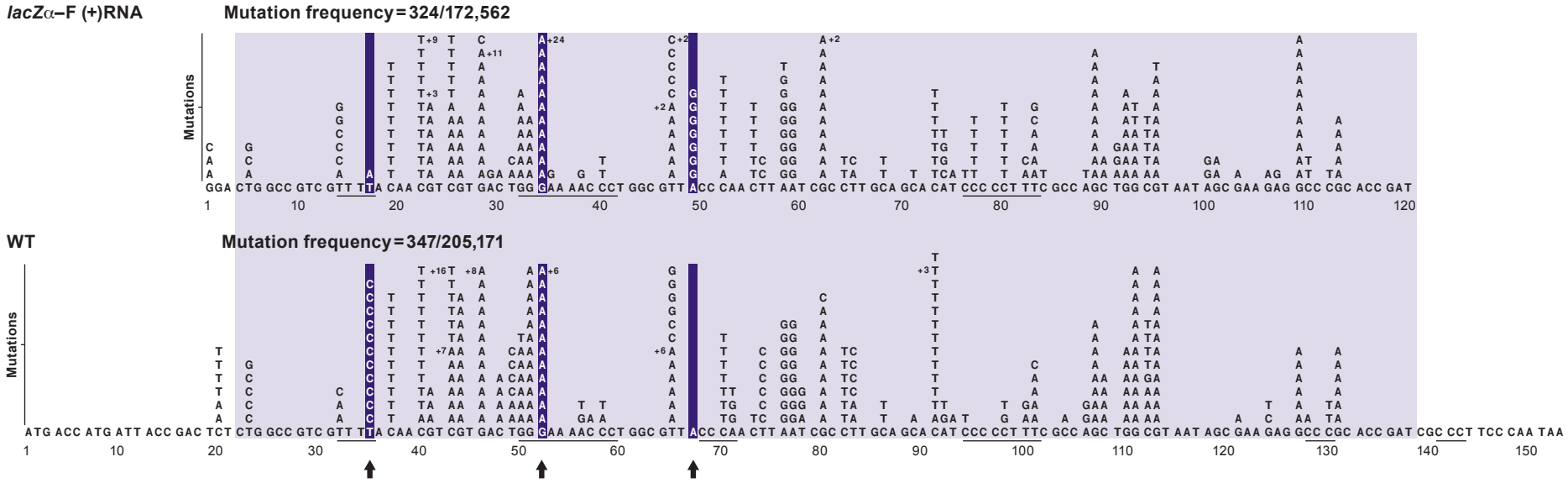
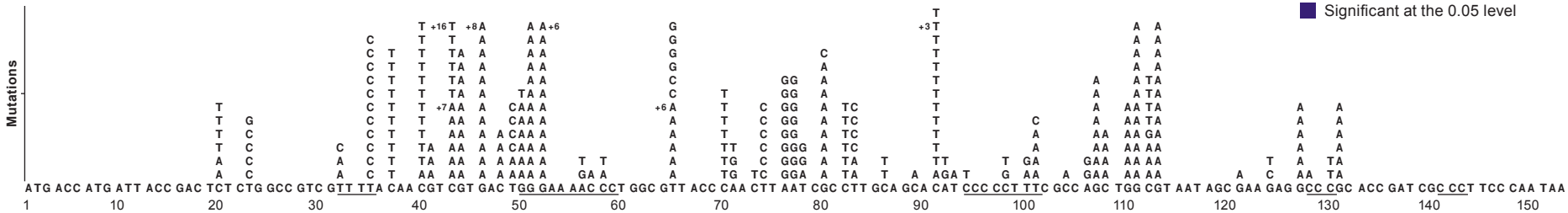


Supplementary Figure 1. A comparison of the missense mutations that arose during the replication the old vector [2], shown at the top, and numbered 1-120, and the vector used in the experiments described in this paper, lower, numbered 1-154. The differences in the sequences surrounding the essential region of *lacZα* are described in the text. Runs of nucleotides in *lacZα* are underlined. The number and nature of the missense mutations at each position are indicated above the sequence. In cases in which the number of mutations at a particular position is greater than can be depicted, the additional mutations are indicated by a number at the top of the column. The positions at which there were statistically significant differences in the missense mutations are indicated by arrows and color coded. Orange, significant at the 0.0001 level, red, significant at the 0.001 level, brown, significant at the 0.01 level, blue, significant at the 0.05 level. In all cases, because the data involved multiple comparisons, the Benjamini-Hochberg correction was used to calculate the reported significance.

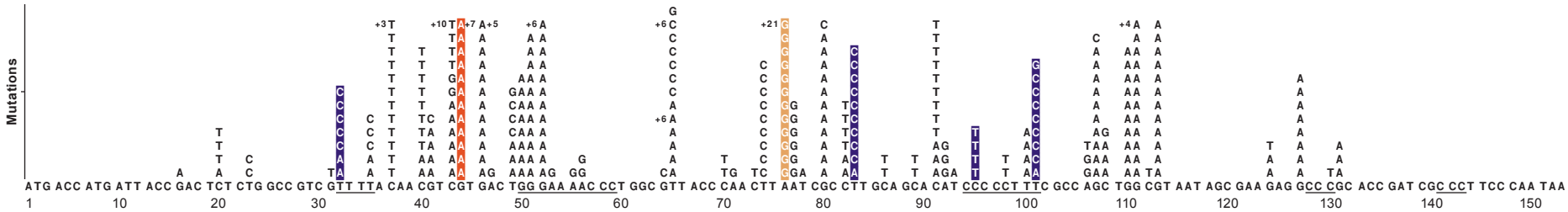
Class I: Missense mutations

Significant at the 0.0001 level
Significant at the 0.001 level
Significant at the 0.01 level
Significant at the 0.05 level

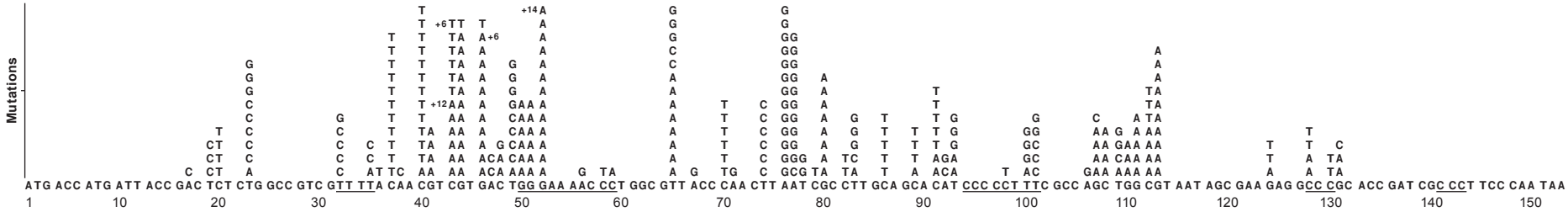
WT Mutation frequency = 347/205,171

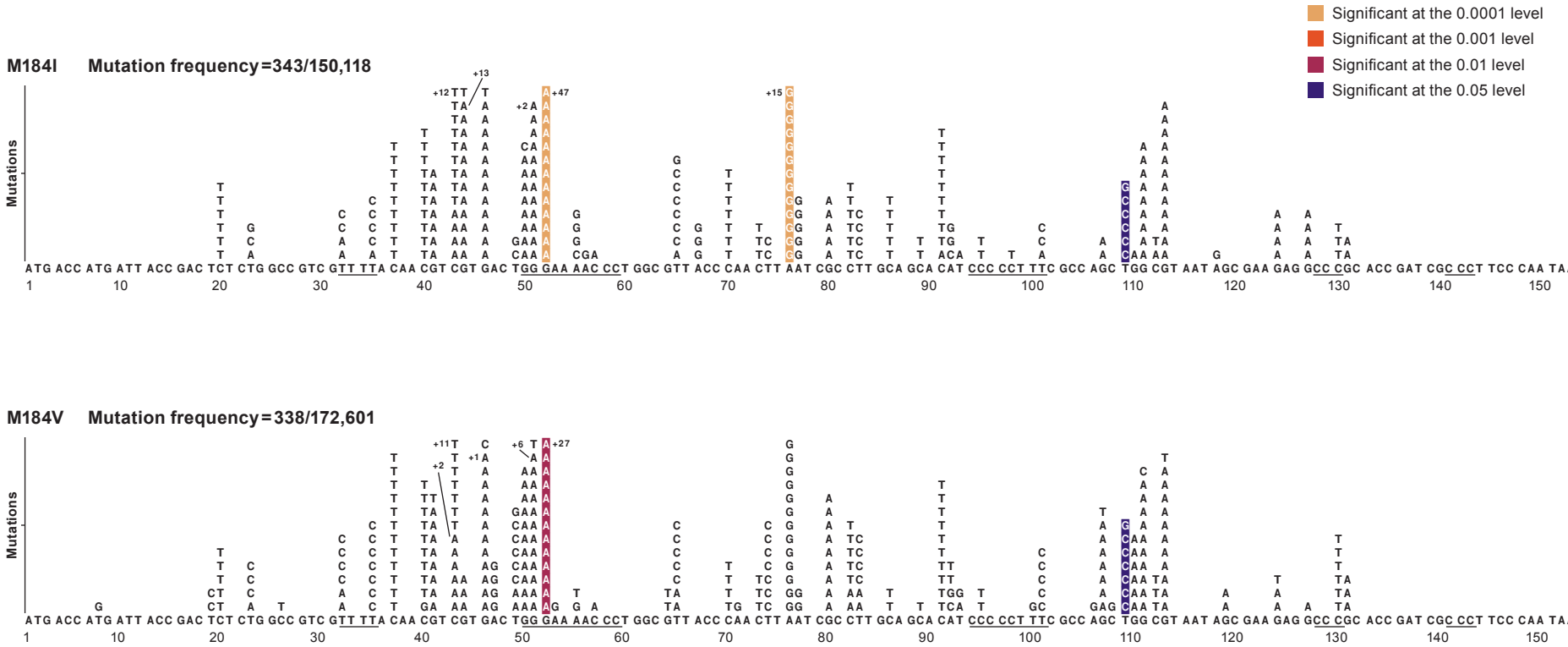


Y115F Mutation frequency = 372/93,727



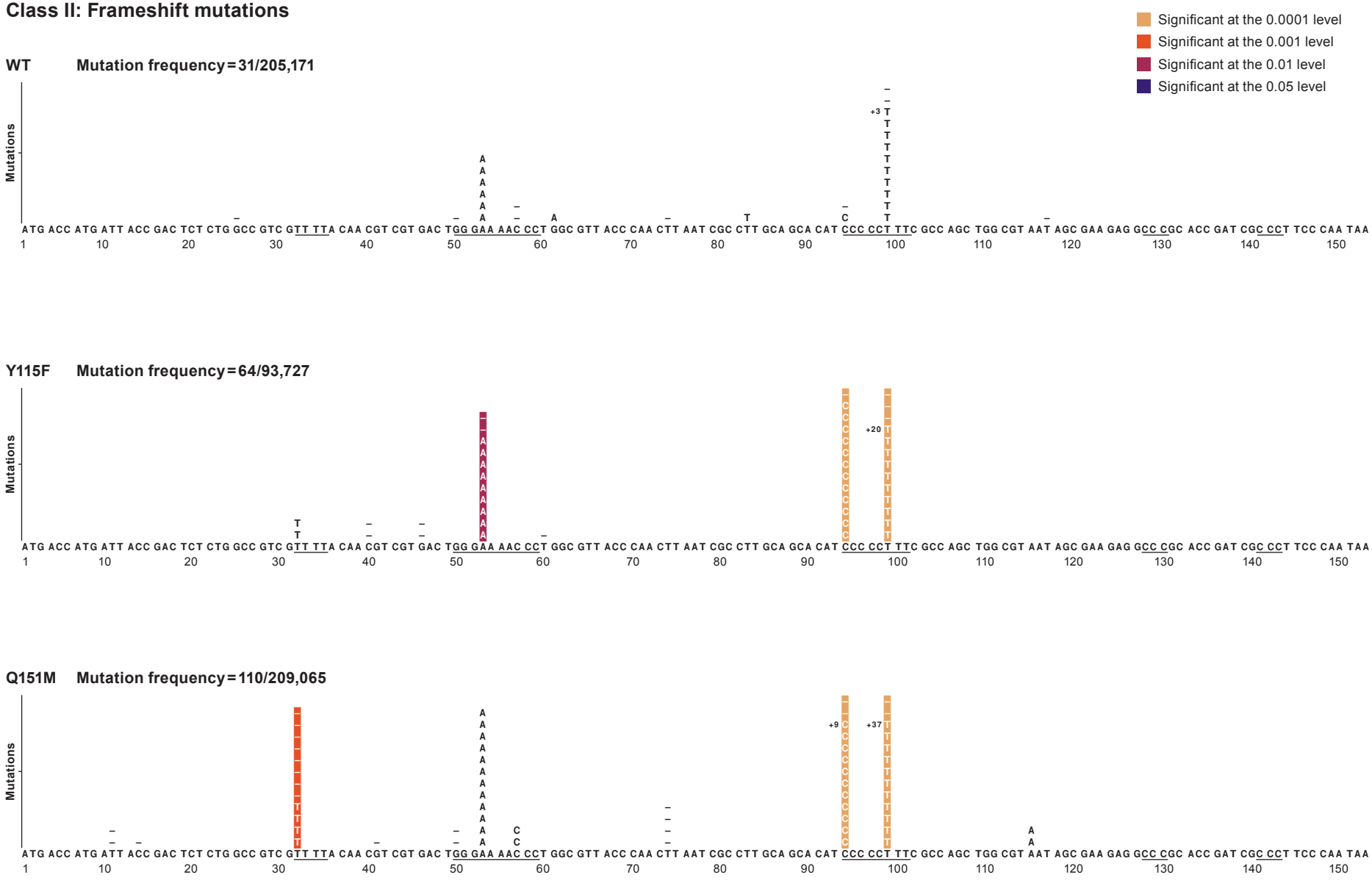
Q151M Mutation frequency = 329/209,065

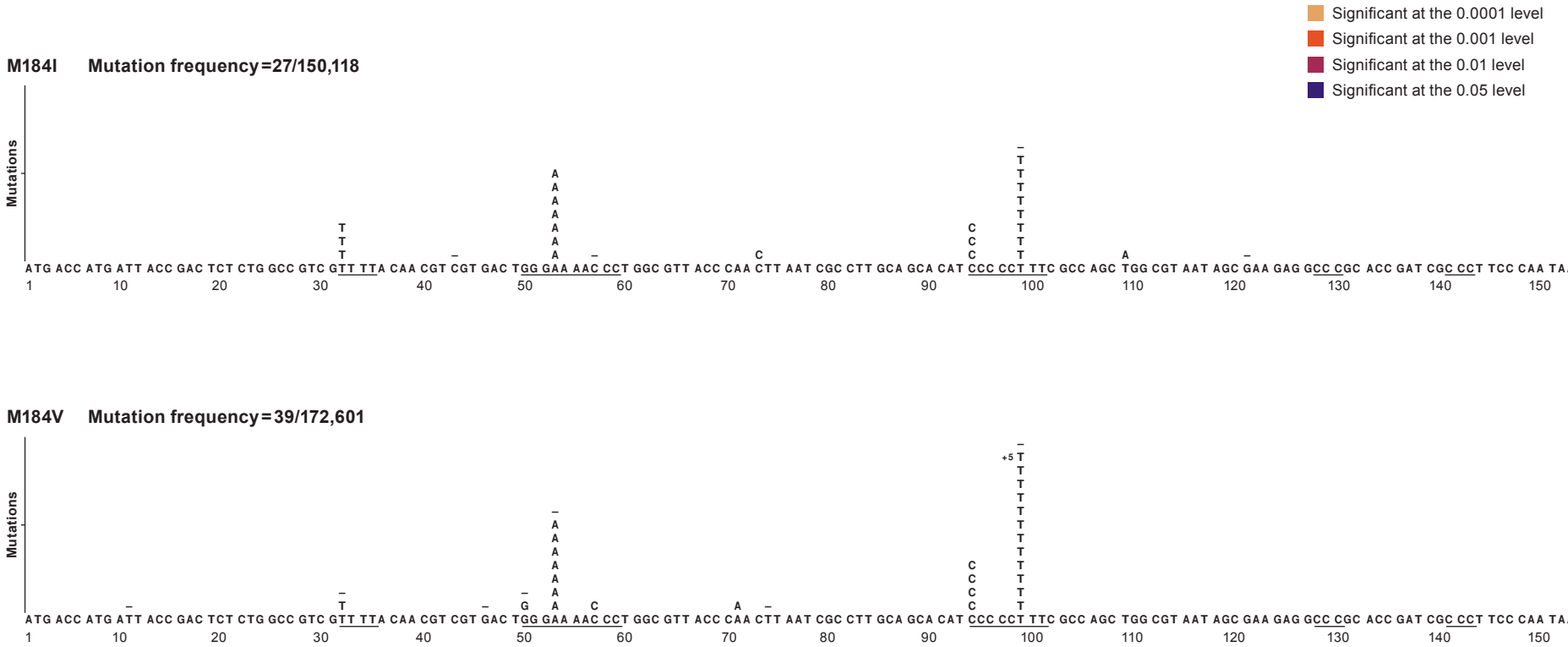




Supplementary Figure 2. Missense mutations that arose during the replication of the vector that carried WT RT and each of the RT mutants. The presentation of the data is similar to that used in Supplementary Figure 1. For the data derived using the RT mutants, the number of *lacZα* mutations at each position were compared to WT, and the Benjamini-Hochberg corrected significance was calculated.

Class II: Frameshift mutations





Supplementary Figure 3. Frameshift Mutations. This figure is similar to Supplementary Figures 1 and 2, except that it shows frameshift mutations instead of missense mutations. Because it is not possible to determine where in a run a frameshift mutation occurred, all of the mutations in runs are shown at the first nucleotide of the run. Insertions are shown as the letter that corresponds to the inserted nucleotide; deletions are shown as dashes.