2 Supplementary Notes

2.1 Supplementary Note 1

To understand this non-additive behavior in ABE1.1(L84F) we again rely on our entropy-based analysis. As residues 84 and 108 are in direct contact (see the three-dimensional structure of TadA* in (Figure 3F)), we speculate that each of these residues may encode useful information regarding the nature of the other. To test this hypothesis, we define the covariance of two residue sites i and j using mutual information as:

$$\text{Mutual Information} \;=\; \text{MI}_{i,j} \;=\; H_i + H_j - H_{i,j} \tag{8}$$

where H_i and H_j are the self-entropy scores calculated using Equation 1, and $H_{i,j}$ is the joint entropy for the occurrence of a certain pair of amino acids at sites i and j. This computation leads to a mutual information score between residues 84 and 108, $MI_{84,108}$, equal to 0.245. In the context of all the MI values calculated for the entire sequence of TadA, $MI_{84,108}$ is in the 74th percentile (Figure S16), indicating a somewhat weak correlation between the two sites. However, it should be noted that in our dataset site 84 is never encountered to be a phenylalanine (Figure 3D). Thus, there is no combination of 84F and 108N in our dataset. This indicates that mutual information is not the appropriate metric to understand the nature of the interaction between residues 84 and 108.

2.2 Supplementary Note 2

An additional `-UACG-` motif was identified within the RNA editing Site 1 amplicon (referred to as Site 1′ henceforth) which was previously unreported.[35] Editing levels at this site are much lower than the other six sites, but otherwise follow the same patterns when treated with the different ABE variants (Figure S3. Interestingly, there is a drastic difference in editing levels at this site between ABE0.1 and ABE1.1. Introduction of the L84F mutation to ABE1.1 drastically lowers editing levels, and even lower editing is seen with ABE7.10. The secondary structure for Site 1′ is highlighted in Figure S4.