Supplementary Figure S7: Examples of ORF pairs that are non-overlapping or unrelated in protein sequence.
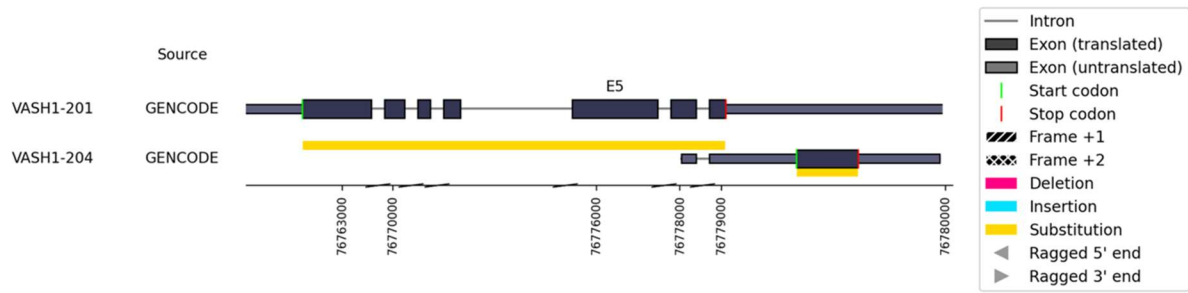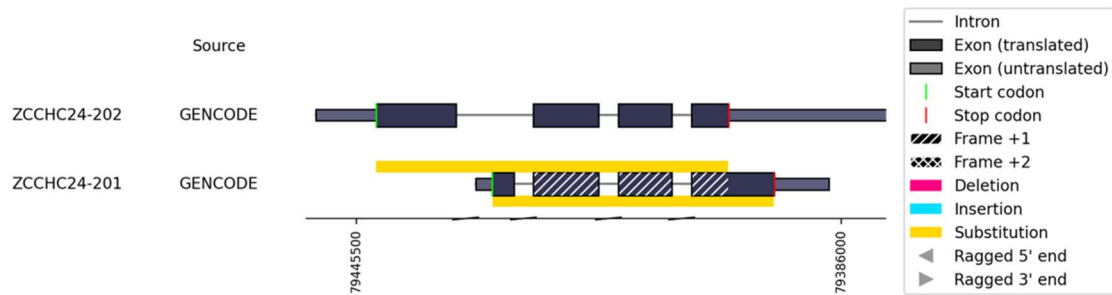
(A) An example (gene *VASH1*) of two ORFs that do not overlap in genome space. In this case, the input reference-alternative isoform pair would be compared, but since there is no overlap between ORFs in the genomic coordinate space, a single p-block substitution event would be reported. (B) Example (gene *ZCCHC24*) in which the ORF pair generates unrelated protein sequences. The two ORFs have at least some nucleotides overlapping in the genome space, but the corresponding protein isoform sequences are completely different due to a frameshift in all such overlapped regions. In other words, the entire reference isoform sequence is distinct from the alternative isoform sequence—even the overlapping regions produce very different polypeptide sequences due to the frameshift. Therefore, for such cases, a single "substitution" p-block, spanning the entire length of both the reference and alternative will be output.