



**Figure S10. The LG-ML91+-12 model fitted to the 1-PAM KHG codon substitution matrix.** Each element  $\log-O(\langle S \rangle(\hat{\tau}, \hat{\sigma}))_{\mu\nu}$  of the log-odds matrix corresponding to (A) single, (B) double, and (C) triple nucleotide changes in the LG-ML91+-12 model fitted to the 1-PAM KHG codon substitution matrix is plotted against the log-odds  $\log-O(S^{\text{KHG}}(1 \text{ PAM}))_{\mu\nu}$  calculated from KHG. Upper triangle, plus, circle, and cross marks show the log-odds values for synonymous pairs and one-, two-, and three-step amino acid pairs, respectively. The dotted line in each figure shows the line of equal values between the ordinate and the abscissa.