



Figure S7. Models fitted to the KHG-derived amino acid substitution matrix. Each element $\log-O(\langle S \rangle(\hat{\tau}, \hat{\sigma}))_{ab}$ of the log-odds matrix of the model fitted to the 1-PAM KHG-derived amino acid substitution matrix (KHGaa) is plotted against the log-odds $\log-O(S^{\text{obs}}(1 \text{ PAM}))_{ab}$ calculated from KHGaa. Plus, circle, and cross marks show the log-odds values for 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.