

**Table S2.** ML estimates of the present models with the selective constraints based on mean energy increments due to an amino acid substitution (EI) for the 1-PAM substitution matrices of JTT, WAG, cpREV, and mtREV.

	JTT		WAG		cpREV		mtREV	
	EI-10 <sup>a</sup>	EI-11 <sup>a</sup>						
$-\hat{w}_0$	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
$1/\hat{\beta}$	2.50	2.60	1.78	2.14	2.15	2.26	2.14	2.29
$\hat{m}_{[tc][ag]}$	( $\rightarrow 0$ )	0.308	( $\rightarrow 0$ )	0.916	( $\rightarrow 0$ )	0.684	( $\rightarrow 0$ )	0.737
$\hat{m}_{tc ag}/\hat{m}_{[tc][ag]}$	2.51	2.22	1.82	1.58	2.82	2.24	4.21	3.06
$\hat{m}_{ag}/\hat{m}_{[tc][ag]}$	1.01	1.01	1.13	1.10	1.19	1.14	1.05	1.01
$\hat{m}_{ta}/\hat{m}_{[tc][ag]}$	1.02	1.07	1.26	1.22	0.992	1.14	1.48	1.44
$\hat{m}_{tg}/\hat{m}_{[tc][ag]}$	1.06	1.09	0.985	1.01	1.34	1.23	0.792	0.797
$\hat{m}_{ca}/\hat{m}_{[tc][ag]}$	0.937	0.891	1.04	0.949	0.974	0.925	1.17	1.08
$\hat{f}_{t+a}^{\text{mut}}$	0.582	0.565	0.516	0.486	0.376	0.405	0.359	0.403
$\hat{f}_t^{\text{mut}}/\hat{f}_{t+a}^{\text{mut}}$	0.522	0.525	0.603	0.575	0.647	0.642	0.671	0.646
$\hat{f}_c^{\text{mut}}/\hat{f}_{c+g}^{\text{mut}}$	0.432	0.450	0.495	0.511	0.450	0.462	0.388	0.404
$\hat{\sigma}$	3.20	0.918	11.7	0.998	7.26	0.969	5.25	0.339
$\hat{\tau}\hat{\sigma}$	0.0358	0.0217	0.0709	0.0204	0.0558	0.0211	0.0531	0.0185
#parameters	30	31	30	31	30	31	30	31
$\hat{I}_{KL}(\hat{\theta}) \times 10^8$ <sup>b</sup>	129885	126178	144772	126415	180379	169548	233525	222441
$\Delta\text{AIC}$ <sup>c</sup>	15435.7	14999.0	4801.8	4202.5	670.7	636.0	702.8	674.3
Ratio of substitution rates per codon								
the total base/codon	1.36	1.35	1.53	1.54	1.45	1.48	1.38	1.44
transition/transversion	1.09	1.11	0.803	0.834	1.08	1.13	1.34	1.41
nonsynonymous/synonymous <sup>d</sup>	2.09	2.13	2.48	2.82	2.45	2.65	1.75	1.92
Ratio of substitution rates per codon for $\sigma \rightarrow 0$								
total base/codon	1.0	1.18	1.0	1.38	1.0	1.31	1.0	1.37
transition/transversion	1.49	1.28	1.25	0.944	1.93	1.36	2.35	1.56
nonsynonymous/synonymous <sup>d</sup>	1.12	1.59	0.945	2.13	1.15	1.99	0.767	1.64
Ratio of substitution rates per codon for $w_{ab} = 0$ and $\sigma \rightarrow 0$								
total base/codon	1.0	1.28	1.0	1.59	1.0	1.48	1.0	1.59
transition/transversion	1.31	1.15	0.983	0.830	1.51	1.50	2.15	1.57
nonsynonymous/synonymous <sup>d</sup>	2.57	3.83	2.82	6.53	2.74	1.16	1.84	4.51

<sup>a</sup> In all models, equal codon usage ( $\hat{f}_t^{\text{usage}} = \hat{f}_a^{\text{usage}} = \hat{f}_c^{\text{usage}} = \hat{f}_g^{\text{usage}} = 0.25$ ) is assumed. If the value of a parameter is parenthesized, the parameter is not variable but fixed to the value specified.

<sup>b</sup>  $\hat{I}_{KL}(\hat{\theta}) = -(\ell(\hat{\theta})/N + 2.98607330)$  for JTT,  $-(\ell(\hat{\theta})/N + 2.97444860)$  for WAG,  $-(\ell(\hat{\theta})/N + 2.95801048)$  for cpREV, and  $-(\ell(\hat{\theta})/N + 2.85313622)$  for mtREV; see text for details.

<sup>c</sup>  $\Delta\text{AIC} \equiv 2N\hat{I}_{KL}(\hat{\theta}) + 2 \times \text{\#parameters}$  with  $N \simeq 5919000$  for JTT,  $N \approx 1637663$  for WAG,  $N \approx 169269$  for cpREV, and  $N \approx 137637$  for mtREV; see text for details.

<sup>d</sup> Note that these ratios are not the ratios of the rates per site but per codon; see text for details.