

**Table S1.** ML estimates of the present models without selective constraints on amino acids for the 1-PAM substitution matrices of JTT, WAG, cpREV, and mtREV.

id no.	parameter	JTT		WAG		cpREV		mtREV	
		No-Constraints- <sup>a</sup>		No-Constraints- <sup>a</sup>		No-Constraints- <sup>a</sup>		No-Constraints- <sup>a</sup>	
		1	10	1	10	1	10	1	10
0	$-\hat{w}_0$	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
1	$1/\hat{\beta}$	( $\infty$ )	( $\infty$ )	( $\infty$ )	( $\infty$ )	( $\infty$ )	( $\infty$ )	( $\infty$ )	( $\infty$ )
2	$\hat{m}_{[tc][ag]}$	( $\rightarrow 0$ )	$\rightarrow 0$	( $\rightarrow 0$ )	0.279	( $\rightarrow 0$ )	0.0455	( $\rightarrow 0$ )	0.0405
3	$\hat{m}_{tc ag}/\hat{m}_{[tc][ag]}$	2.16	2.20	1.61	1.54	2.17	2.62	2.32	3.24
4	$\hat{m}_{ag}/\hat{m}_{tc ag}$	(1.0)	1.28	(1.0)	1.36	(1.0)	1.50	(1.0)	1.47
5	$\hat{m}_{ta}/\hat{m}_{[tc][ag]}$	(1.0)	0.629	(1.0)	0.687	(1.0)	0.480	(1.0)	0.595
6	$\hat{m}_{tg}/\hat{m}_{[tc][ag]}$	(1.0)	0.708	(1.0)	0.622	(1.0)	0.775	(1.0)	0.373
7	$\hat{m}_{ca}/\hat{m}_{[tc][ag]}$	(1.0)	1.28	(1.0)	1.45	(1.0)	1.64	(1.0)	1.96
8	$\hat{f}_{t+a}^{\text{mut}}$	(0.5)	0.495	(0.5)	0.401	(0.5)	0.279	(0.5)	0.226
9	$\hat{f}_t^{\text{mut}}/\hat{f}_{t+a}^{\text{mut}}$	(0.5)	0.486	(0.5)	0.503	(0.5)	0.563	(0.5)	0.583
10	$\hat{f}_c^{\text{mut}}/\hat{f}_{c+g}^{\text{mut}}$	(0.5)	0.335	(0.5)	0.354	(0.5)	0.306	(0.5)	0.223
14	$\hat{\sigma}$	( $\rightarrow 0$ )	1.76	( $\rightarrow 0$ )	1.58	( $\rightarrow 0$ )	2.96	( $\rightarrow 0$ )	2.46
	$\hat{\tau}\hat{\sigma}$	0.0137	0.0228	0.0136	0.0206	0.0139	0.0296	0.0149	0.0296
	#parameters	21	30	21	30	21	30	21	30
	$\hat{I}_{KL}(\hat{\theta}) \times 10^8$ <sup>b</sup>	729533	207260	1156393	233841	1014962	249448	945289	305500
	$\Delta\text{AIC}$ <sup>c</sup>	86428.1	24595.5	37917.6	7719.1	3478.0	904.5	2644.1	901.0
	Ratio of substitution rates per codon								
	the total base/codon	1.0	1.30	1.0	1.47	1.0	1.40	1.0	1.35
	transition/transversion	1.13	1.00	0.848	0.752	1.11	1.02	1.24	1.10
	nonsynonymous/synonymous <sup>d</sup>	2.75	4.15	2.84	5.77	2.60	4.91	2.09	3.30
	Ratio of substitution rates per codon for $\sigma \rightarrow 0$								
	the total base/codon	1.0	1.0	1.0	1.21	1.0	1.04	1.0	1.02
	transition/transversion	1.13	1.20	0.848	0.853	1.11	1.43	1.24	1.45
	nonsynonymous/synonymous <sup>d</sup>	2.75	2.83	2.84	4.26	2.60	3.19	2.09	2.08

<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,  $N \simeq 1637663$  for WAG,  $N \simeq 169269$  for cpREV and  $N \simeq 137637$  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.