

**Table S1: Selection pressure analysis of unique and novel *E* gene substitutions found in different clades**

Serotype	Clade	Substitution	Selection pressure analysis method <sup>‡</sup>				
			SLAC	FEL	IFEL	FUBAR	MEME
DENV-2	Cosmopolitan (clade a)	E-K160T	Neutral (0.473)	Neutral (0.866)	Neutral (0.75)	Neutral (0.612)	0.06
	Cosmopolitan (clade b)	E-H346Q	Negative (0.004)	Neutral (0.057)	Neutral (0.13)	Negative (0.98)	0.53
	Cosmopolitan (clade a)	<b>E-I379V</b>	<b>Negative (0.0001)</b>	<b>Negative (&lt;0.05)</b>	<b>Negative (0.01)</b>	<b>Negative (1)</b>	0.30
DENV-3	Genotype I (clade c)	<b>E-L430I</b>	<b>Negative (0.046)</b>	<b>Negative (0.002)</b>	Neutral (0.08)	<b>Negative (0.997)</b>	>1.00
DENV-4	Genotype II (clade b)	E-D274E	Neutral (0.653)	Neutral (0.543)	Neutral (0.60)	Neutral (0.608)	0.23

<sup>‡</sup>Implemented in HyPhy software package implemented in the Datamonkey web-server [39]. Residues under purifying (negative) selection are shown in bold letters. These non-neutral residues were confirmed by at least three methods (significant levels were defined as posterior probability value of  $\Rightarrow 0.9$  for FUBAR and p-values  $\Rightarrow 0.05$  for the remaining methods). FEL=fixed effects likelihood; IFEL=internal fixed effect likelihood; FUBAR=fast unbiased Bayesian approximation; MEME=mixed effect model of evolution; SLAC= Single likelihood ancestor counting.