

**Supplementary Table II**

PAML 'branch-site' analyses for evaluation of positive selection along specific lineages (see Fig. 5 for location of the branches in question; values in parentheses indicate percentage of codons falling in a particular  $\omega$  category)

	<b>PXR all sequences (11 sequences for full sequence and DBD only analyses; 13 sequences for LBD only analyses</b>	<b>Amino acid residues identified as likely targets of positive selection (residues indicated are human PXR corresponding residue; fraction is posterior probability for positive selection)</b>
<b>Branch a = foreground</b>		
<b>Full sequence<sup>b</sup></b>	$\omega = 0.032$ (58%), 0.24 (34%) $\omega_2 = \mathbf{2.49^a}$	Q406 (0.91), Q415 (0.91)
<b>DBD only</b>	No significant improvement over M3, K=2 model	None
<b>LBD only<sup>b</sup></b>	$\omega = 0.038$ (55%), 0.29 (36%) $\omega_2 = \mathbf{2.05}$	Q406 (0.91), Q415 (0.90)
<b>Branch b = foreground</b>		
<b>Full sequence<sup>c</sup></b>	$\omega = 0.025$ (46%), 0.20 (32%) $\omega_2 = \mathbf{1.60}$	I151 (0.93), F169 (0.92), L336 (0.90), L342 (0.93), S344 (0.93), P384 (0.92)
<b>DBD only</b>	No significant improvement over M3, K=2 model	None
<b>LBD only<sup>d</sup></b>	$\omega = 0.03$ (33%), 0.24 (23%) $\omega_2 = \mathbf{4.99}$	I151 (0.99), E153 (0.96), F169 (0.99), R265 (0.99), F281 <sup>e</sup> (0.93), C284 <sup>e</sup> (0.94), L336 (0.98), L342 (0.99), S344 (0.99), E378 (0.99), P384 (0.99), I403 (0.94)
<b>Branch c = foreground</b>		
<b>Full sequence<sup>d</sup></b>	$\omega = 0.027$ (27%), 0.21 (18%) $\omega_2 = \mathbf{4.73}$	F251 <sup>e</sup> (0.98), T290 (0.99), E309 (0.91), Q316 (0.99), K325 (0.95), E333 (0.99), A339 (0.99), S341 (0.96), T372 (0.98), L412 (0.98)
<b>DBD only</b>	No significant improvement over M3, K=2 model	None

<b>LBD only<sup>d</sup></b>	$\omega = 0.034$ (61%), $0.27$ (39%) $\omega_2 = 0.70$	None
<b>Branches a, b, and c = foreground Full sequence<sup>d</sup></b>	$\omega = 0.028$ (54%), $0.22$ (33%) $\omega_2 = 0.64$	None
<b>DBD only</b>	No significant improvement over M3, K=2 model	None
<b>LBD only<sup>c</sup></b>	$\omega = 0.033$ (48%), $0.28$ (28%) $\omega_2 = 0.55$	None

<sup>a</sup>  $\omega_2$  is  $\omega$  for sites along the specific foreground lineages.

<sup>b</sup>  $p < 0.05$  compared with M3, K=2 sites model (see Materials and Methods for further details).

<sup>c</sup>  $p < 0.005$  compared with M3, K=2 sites model.

<sup>d</sup>  $p < 0.001$  compared with M3, K=2 sites model.

<sup>e</sup> Human PXR amino acid residue identified as directly interacting with ligand (see Supplementary Figure 1).