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## Calculation of dN/dS

Multiple-sequence alignments from each gene family were back-translated into codon alignments to reconstruct phylogenetic trees using FastTree2 with default parameters. The entire workflow was executed using ETE3 (ref. [64](#)) with options `ete3 build --nt-switch-threshold 0.0 --noimg --clearall --nochecks -w clustalo_default-none-none-none --no-seq-rename`. For calculation of selective pressure per family we ran HyPhy using the BUSTED model<sup>[65](#)</sup> with default parameters, codon-based nucleotide alignment and the phylogenetic tree generated previously, retrieving the dN/dS ratio under the full codon model. We discarded gene families with dN/dS values higher than 0.5.

Article | [Open access](#) | [Published: 18 December 2023](#)

## Functional and evolutionary significance of unknown genes from uncultivated taxa

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REAL

IQCF1

BUSTED-E (error corrected) results

NOT REAL

KRT8

$\omega_1=0.4063$  (1.5589%)  
 $\omega_2=0.4076$  (93.816%)  
 $\omega_3=11.09$  (4.6249%)+  
0.0% error

$\omega_1 = 0.00001848$  (11.039%)  
 $\omega_2 = 0.04232$  (75.696%)  
 $\omega_3 = 1.000$  (12.675%)+  
0.58% error ( $\omega_e > 10^6$ )

14 sequences in the alignment	475 codon sites in the alignment	1 partitions
25 median branches/partition used for testing	3 classes non-synonymous rate variation	3 classes synonymous rate variation
0.0000043 p-value for episodic diversifying selection	10 Sites with ER≥10 for positive selection	N/A:N/A Multiple hit rates (2H:3H)
15 (branch, site) pairs with EBF ≥ 100	10 Sites contributing most signal to EDS detection	N/A:N/A Expected fractions of MH subs (2H:3H)

11 sequences in the alignment	1516 codon sites in the alignment	1 partitions
18 median branches/partition used for testing	3 classes non-synonymous rate variation	3 classes synonymous rate variation
0.50 p-value for episodic diversifying selection	0 Sites with ER≥10 for positive selection	N/A:N/A Multiple hit rates (2H:3H)
N/A (branch, site) pairs with EBF ≥ 100	N/A Sites contributing most signal to EDS detection	N/A:N/A Expected fractions of MH subs (2H:3H)

