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Letter: Biological Sciences: Evolution

Reply to Halanych *et al.*: Ctenophore misplacement is corroborated by independent datasets.

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In their letter, Halanych *et al.* (1) criticize our recent assertion (2) that the phylogenetic placement of ctenophores as the sister group to all other animals (the Ctenophora-sister hypothesis) in three previous studies (3–5) was an artifact caused by undetected systematic error.

Halanych *et al.* claim we used no “objective criteria” to identify sources of systematic error. In fact, we used an objective comparison of Bayesian cross-validation scores to select the best-fitting substitution model, since poorly-fitting models are a frequent source of systematic error. Halanych *et al.* point out that this comparison did not include partitioned site-homogeneous models. However, they did not mention that only one of the studies we addressed (3) used this approach, and that multiple site-homogeneous partitions still do not account for within-partition site-heterogeneous biochemical constraints, which our results showed had a major impact on model fit and the tree topology.

Halanych *et al.* also incorrectly suggest that our model-selection procedure relied on circular assumptions about the position of sponges. No such assumptions were made to demonstrate the better fit of site-heterogeneous models. In fact, our cross-validation tests were conservative in favor of Ctenophora-sister, because we “trained [all models] under the tree topology favored by WAG [Ctenophora-sister], thus making the test conservative in favor of the WAG model [and consequently Ctenophora-sister]” (Methods in (2)).

Halanych *et al.* further claim our conclusions rested extensively on unconverged analyses. In reality, our conclusions about the position of Ctenophora were based solely on converged analyses, with two unconverged analyses mentioned only for completeness in one case, or to demonstrate weak phylogenetic signal in the other (reanalysis of (5)).

The main criticism of Halanych *et al.* is that we arbitrarily preferred results obtained using only closely-related outgroups. In fact, our results simply showed weaker average support

for Ctenophora-sister under better-fitting models. When only holozoan (not just choanoflagellate) outgroups were included, support for Ctenophora-sister did deteriorate (Figure 2B-C in (2)), or support for Porifera-sister emerged (Figure 2A in (2)), and this effect became more pronounced when using only choanoflagellates. This sensitivity of the position of Ctenophora to model choice after excluding distant outgroups suggests these outgroups exacerbate systematic error by obscuring the effect of better-fitting models.

The final comment (1) about the questionable use of gene content data is unjustified. The observation that “gene content varies greatly within phyla” is evidence that it contains phylogenetic signal. Accordingly, analysis of gene content (corrected for ascertainment bias) recovered well-established bilaterian relationships (Figure 3 in (2)), and corroborated non-bilaterian relationships inferred from amino acid data (Figure 1 in (2)).

Finally, Halanych *et al.* claim that our conclusions mistreated complex traits as single characters and ignored the position of Placozoa. In fact, we acknowledged that “Future studies [...] will help to clarify the relationship between the homology of similar structures and their underlying genetic mechanisms”, and “resolving the exact phylogenetic positions of Ctenophora and Placozoa [...] will be crucial to reconstruct the evolution of key characters, such as nervous systems, muscles, and digestive tracts, in more detail” (2).

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