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Digest

Digest: Few new mutations are recessive lethal

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Abstract

When a new mutation arises, what is the probability that it is recessive lethal? Wade et al. find that fewer than 1% of nonsynonymous mutations in humans and *Drosophila melanogaster* are recessive lethal. The authors show that methods based on site frequency spectrum (SFS) analyses, though generally robust in their estimations of the nonlethal distribution of fitness effects (DFE), are unable to accurately estimate the fraction of recessive lethal mutations.

The distribution of fitness effects (DFE) of new mutations has been a hotly debated topic with direct ties to the long-standing neutralist versus selectionist debate in theories of molecular evolution. Additionally, the prevalence of recessive lethal mutations is critical to understanding phenomena such as inbreeding depression and lethal Mendelian diseases. In theory,

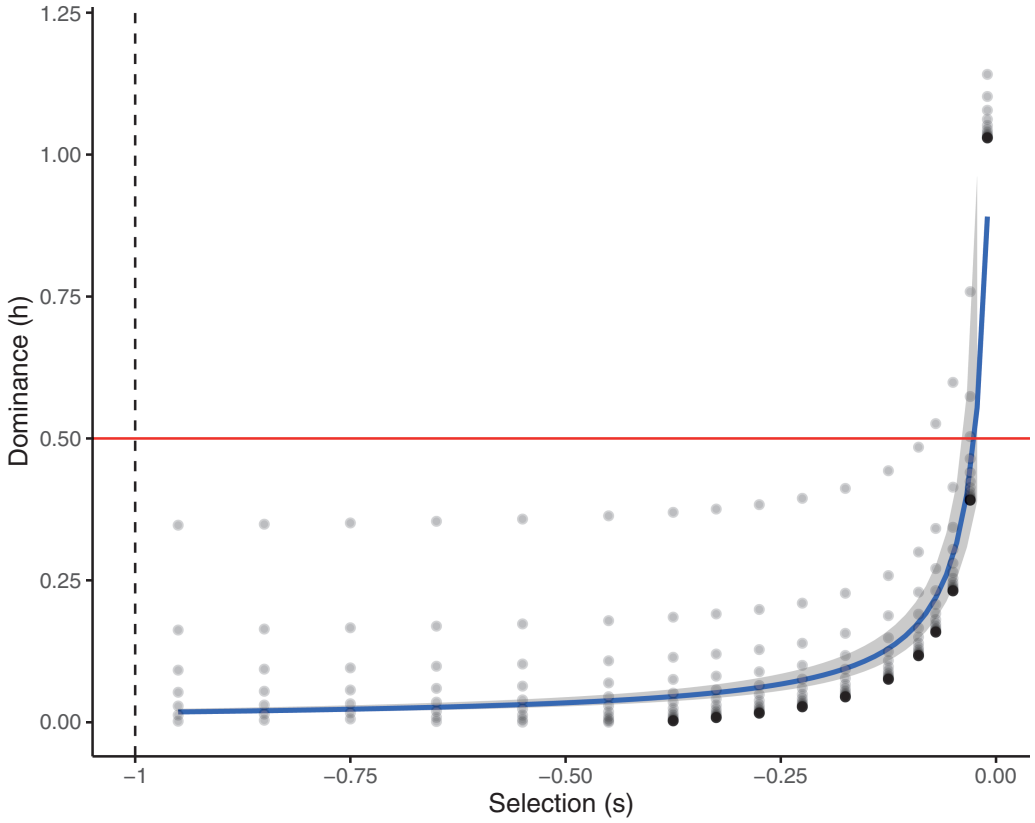

Figure 1. Predicted relationship between dominance (h) and selection (s) for deleterious mutations based on findings by Agrawal and Whitlock (2011). Red horizontal line indicates the assumed dominance of deleterious mutations under common methods such as Fitðaðl. The mismatch between the assumed and true dominance of lethal mutations (indicated by the dashed vertical line) explains the inability of most SFS-based methods to accurately predict the fraction of new recessive lethal mutations.

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a well-specified model could accurately estimate the DFE given accurate estimates of relevant parameters, and many studies have empirically derived parameters such as genome size, recombination rates, effective population size (N_e), and mutation rate, among many others (Keinan & Clark, 2012; Li, 2011; Rice et al., 2015).

Wade et al. (2023), using estimated and empirically determined values of genomic parameters to build their models, evaluated two approaches to determine the proportion of new mutations that are recessive lethal. The authors tested different methods on datasets generated by the forward-in-time simulator SLiM 3 (Haller & Messer, 2019). The first approach, an established method called Fit∂a∂i, analyzes the site frequency spectrum (SFS) of the genetic data sets and then outputs which DFEs best fit the observed allele frequencies in the population. The authors found that Fit∂a∂i failed to accurately predict the prevalence of recessive lethal mutations due to underlying assumptions of the model. For the second approach, Wade et al. (2023) applied models of mutation–selection–drift balance, which combine population genetic models of mutation, selection, and drift processes to estimate the proportion of recessive lethal mutations that best fit the empirically determined numbers of segregating lethal mutations. Models where less than 1% of new nonsynonymous mutations were recessive lethal provided the best fit for both humans and *D. melanogaster*. Their findings show that, in contrast to Fit∂a∂i, mutation–selection–drift balance models can accurately estimate the fraction of recessive lethal mutations.

The fraction of new mutations that are recessive lethal has implications for modeling inbreeding depression. The direct effects of recessive lethals can be extreme: an early study of inbreeding depression in *D. melanogaster* found that recessive lethals account for about half of the reduction in viability due to inbreeding (Simmons & Crow, 1977). Having accurate estimates of inbreeding depression is particularly key for endangered species as such models can be used to guide effective management strategies; therefore, better estimations of recessive lethals may aid in conservation efforts (Hedrick & Kalinowski, 2000).

Many current approaches for inferring the DFE assume new mutations are entirely additive. Studies show that more deleterious mutations tend to be less additive (Figure 1) and, therefore, models that assume additivity are less accurate at inferring the dynamics of more deleterious mutations (Agrawal & Whitlock, 2011; Balick et al., 2015; Simmons & Crow, 1977). Structural proteins follow the opposite correlation, further complicating the relationship between dominance and selection coefficients (Phadnis & Fry, 2005). Fortunately, Wade et al. (2023) ultimately find that this assumption does not significantly affect estimates of nonlethal mutations, meaning SFS-based methods are robust to the presence of recessive lethal mutants.

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