How should we compare different genomic estimates of the strength of inbreeding depression?

Marty Kardos[a,1], Pirmin Nietlisbach[b], and Philip W. Hedrick[c]

Yengo et al. (1) evaluate the ability of genomic measures of inbreeding to quantify inbreeding depression. The authors conclude that a measure of inbreeding based on "runs of homozygosity" (F_{ROH}) had low power and upwardly biased estimates of the amount of inbreeding depression compared with F_{HOM} (a measure of homozygosity relative to Hardy–Weinberg proportions) and F_{UNI} (correlation between uniting gametes; similar to F_{HOM} but with strong weight given to homozygous rare alleles). However, differences among these measures of inbreeding, and how their simulations were parameterized, invalidate these conclusions.

Yengo et al. (1) assume that regressions of phenotype (y) against F_{ROH} are comparable to regressions of y against F_{UNI} or F_{HOM}. This is incorrect because of the different properties of these measures of inbreeding. F_{ROH} ranges from 0 to 1 (like the pedigree inbreeding coefficient F_P), and estimates the fraction of the genome in ROH, where identical-by-descent chromosome copies coalesce in a "recent" ancestor. F_{ROH} can be interpreted as a probability of identity-by-descent and used to estimate lethal equivalents (2). F_{UNI} and F_{HOM} include negative values and frequently have substantially higher variance than F_P and F_{ROH} (3–6).

Steeper slopes for F_{ROH} are expected, and incorrectly interpreted as upward bias, when F_{ROH} has a lower variance than F_{UNI} (7). For example, when the variance of F_{UNI} is twice the variance of F_{ROH}, regressions of y vs. F_{ROH} are expected to be 1.41 times steeper than regressions of y vs. F_{UNI}, assuming equal correlations of y with F_{ROH} and F_{UNI}. Measures of inbreeding with different variances should first be standardized (z-transformed) to equitably compare estimates of inbreeding depression by regression (7).

y was simulated as a function of F_{QTL} (1), which measures inbreeding relative to Hardy–Weinberg proportions at causal loci. F_{QTL} is thus expected to have a similar variance to F_{UNI} and F_{HOM}, depending on the simulated dominance effects. Simulating y as a function of F_{QTL} means that tests of inbreeding depression based on F_{UNI} and F_{HOM} are expected a priori to have lower bias and higher power than F_{ROH} when analyzing the simulated data.

Yengo et al. (1) detected inbreeding depression for more traits in humans with F_{UNI} than with F_{ROH}. This could be because F_{UNI} is more powerful than F_{ROH}, or because F_{UNI} captured variation in inbreeding due to distant ancestors, while F_{ROH} measured inbreeding due only to recent ancestors by excluding short ROH. F_{ROH} can incorporate short ROH arising from distant ancestors when millions of SNPs are analyzed (8, 9). Doing so would mean that F_{ROH} and F_{UNI} estimate similar parameters and would make for a more equitable comparison of the performance of these measures of inbreeding.

Comparisons of inbreeding metrics with different variances should focus on correlations or regressions of y versus standardized inbreeding coefficients. Correlation is a useful alternative measure of the strength of inbreeding depression, and is unaffected by differences in variance among measures of inbreeding. F_{ROH} was previously shown to be more strongly correlated with the homozygous mutation load (4), and F_{ROH} thus appears to be preferable for studies of inbreeding depression.

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[a]Flathead Lake Biological Station, University of Montana, Polson, MT 59860; [b]Department of Zoology, University of British Columbia, Vancouver, BC V6T 1Z4, Canada; and [c]School of Life Sciences, Arizona State University, Tempe, AZ 85192

Author contributions: M.K., P.N., and P.W.H. wrote the paper.

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[1]To whom correspondence should be addressed. Email: martykardos@gmail.com.

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