Review of: "Darwin, Gödel, Luria, Delbrück: Biomedical, Mathematical, and Metamathematical Perspectives on Attributes and Consequences of Random Somatic Mutations Subject to Selection"

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Potential competing interests: No potential competing interests to declare.

This manuscript presents important and relevant insights into approaches to quantitative behavioral genetic and molecular genetic research. A thorough examination of oversights regarding the relevance of mutations to the study of etiological factors contributing to the phenotype is crucial. However, I will confine my comments to one aspect of the manuscript that aligns with my expertise.

Specifically, I agree that the narrow heritability equation oversimplifies the estimation by considering only additive genotypic variance (VA) and phenotypic variance due to environmental factors (VE). This approach neglects other crucial genetic components, such as dominance effects and gene interactions, potentially leading to an incomplete understanding of the overall genetic influence on the phenotype. The broad heritability equation attempts to address this limitation by incorporating additional terms such as dominance effects (VD), gene interactions (VI), gene-environment interactions (VG×E), and covariance between genetic and environmental factors (COV(G, E)). While this expanded equation is more comprehensive, it introduces a new set of challenges.

The inclusion of terms like gene interactions and gene-environment interactions can be particularly problematic due to the difficulty in accurately measuring and interpreting these complex phenomena. The reliability of estimates for these components heavily relies on the assumptions made and the data available, which may not always be robust.

Moreover, the inclusion of multiple terms in broad heritability equation may lead to issues of multicollinearity, making it challenging to disentangle the unique contributions of each component.

Finally, while it is acknowledged that the estimation of heritability necessitates large sample sizes, the proposed equations introduce complexities that may undermine the accuracy and interpretability of the results. This can compromise the precision of parameter estimates and hinder the identification of the primary drivers of phenotypic variance. Furthermore, the article does not adequately address the statistical and computational challenges associated with estimating the parameters in the broad heritability equation. The complexity of the model may require sophisticated statistical methods and computational tools, and the article should provide a thorough discussion of the potential limitations and assumptions associated with these methods.

In conclusion, while the ambition to capture a more comprehensive picture of heritability through the broad heritability equation is commendable, the presented equations may introduce more challenges than solutions. I think they need to be considered in the manuscript.