Qeios

Peer Review

Review of: "Do We Understand Heredity and Evolution? No"

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Keith Baverstock is to be congratulated on his careful analysis of the history of the process by which many biologists ended up “Chasing Mendel” (Joyner & Prendergast, 2014), instead of identifying the many processes by which inheritance occurs, including those over and above the genome. These must include processes and factors that are not represented in DNA. Genes, in that very restricted DNA sequence sense, are clearly “not the Blueprint for life.” (Noble, 2024). The information in an egg cell, over and above that contained in its DNA, when digitised from its analogue imaging, is even greater than the 3 billion base pairs in a human genome (Noble, 2008). I therefore wholeheartedly agree with Baverstock that “attractor states can, in response to larger perturbations, transition in the cell’s state, causing new phenotypic properties.” Sun et al (2005) showed 20 years ago in fish how much the cytoplasm influences the development of an embryo over and above what is transmitted in its nuclear DNA.

When these cellular processes are taken into account, it becomes much easier to understand the shocking outcome of attempting to predict disease states from polygenic scores (Hingorani et al 2023). That this was to be expected was shown by Wald et al (1999) way back in 1999. Yet, we have still to see from any of the Human Genome Project leaders a serious acknowledgement that the expected clinical outcomes of the Human Genome Project have simply not happened.

Instead, we find publications endlessly rearranging the association score data using various kinds of manipulation of the association score data. It cannot be emphasised more strongly that association is far from equivalent to causation. This is like rearranging the deck chairs on the Titanic.

I have not been able to comment earlier on Baverstock’s important article because my focus recently has been directed at publishing a book (Noble, 2025a) and an article (Noble, 2025b) outlining in detail how causation can be measured in physiology and how it is generally very different from association. Even a

doi.org/10.32388/6LU8H2

zero association score (and most associations are indeed abysmally small) can hide *massive* levels of causation.

It is indeed true that "The time has come to revise the foundations."

Hingorani AD, Gratton J, Finan C, et al 2023. Performance of polygenic risk scores in screening, prediction, and risk stratification: secondary analysis of data in the Polygenic Score Catalog. BMJ Medicine 2023;2:e000554. doi: 10.1136/bmjmed-2023-000554

Joyner & Prendergast, 2014, Chasing Mendel: five questions for personalized medicine. *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2014.272336

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Wald, N, Hackshaw, A.K. & Frost.C.D. 1999. When can a risk factor be used as a worthwhile screening test? *British Medical Journal*. 319 11 December 1999.

Declarations

Potential competing interests: No potential competing interests to declare.