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Letter

Response to Kalchhauser *et al.*: Inherited Gene Regulation Is not Enough to Understand Nongenetic Inheritance

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In their Opinion Adrian-Kalchhauser *et al*. [1] discussed the diverse molecular mechanisms underlying certain forms of nongenetic inheritance (see Box 1 for terminology). They proposed embracing these mechanisms under the unifying concept of inherited gene regulation (IGR). We think the article provides a valuable overview of several forms of nongenetically inherited gene regulation and their interactions with genetic variation. However, we are concerned that this article might lead readers to conclude that all forms of nongenetic inheritance boil down to IGR – a conclusion that we regard as inconsistent with known features of many forms of nongenetic inheritance. In the following text, we clarify our concerns, and explain why we believe that nongenetically inherited variation cannot be understood solely in terms of variation in gene expression.

Several sentences in Adrian-Kalchhauser *et al.* [1] imply that nongenetic inheritance can be reduced to IGR, including: 'We provide a more precise basis for integrating "non-genetic" modes of inheritance into evolutionary and ecological studies. The key shared features of these mechanisms can be clarified by the unifying concept of IGR', and 'Recognizing the common effect of highly diverse molecular mechanisms as IGR is a first step toward identifying general features of non-genetic inheritance systems'. While specific interpretation of these quotes is open for discussion and they are taken out of context, we do think they could give readers the idea that nongenetic inheritance equates to inherited gene regulation. We argue that nongenetic inheritance is much broader than that.

The salient issue here is that many forms of nongenetic inheritance cannot be meaningfully understood as only involving changes in gene regulation. For instance, many behaviours are learned by offspring from watching their parents [2]. A culturally transmitted behaviour such as a preference for a given food might be associated with altered gene expression, but this does not mean that it is useful to redefine culture in terms of variation in gene expression: cultural inheritance is better understood as the transmission of behavioural traditions via social learning [3].

Similarly, parental microbiomes can be inherited by offspring [4,5], and so can other aspects of the environment (e.g., physical constructions, food stores, chosen habitats, territories, hosts, and social environments), known as ecological inheritance [6]. Even at the molecular level, prions and chaperone molecules can be transmitted and have phenotypic effects, while not operating via gene regulation [7,8]. Likewise, structural inheritance involves template-like processes that operate during cell division but do not depend on changes in gene expression [9]. All these other forms of nongenetic inheritance might be associated with changes in gene expression, but there is no reason to assume that gene expression plays a causal role in these processes. They cannot be usefully boiled down to inherited variation of gene regulation because changes in gene expression need not give rise to the variation in question nor mediate its transmission across generations.

While Adrian-Kalchhauser *et al.* are most certainly aware of these additional forms of nongenetic inheritance, their paper unfortunately does not explicitly mention that their concept of inherited gene regulation does not cover these additional forms. We agree with the authors that, 'A key contemporary research challenge is incorporating inheritance mechanisms beyond DNA sequence into evolutionary and ecological investigations', and even that 'Some simplification of these dauntingly diverse and functionally complex mechanisms is reasonable and indeed necessary for this effort'. However, if our aim is 'Understanding non-genetic inheritance: ...' (their title), we argue that this cannot be wholly done by focussing exclusively

Box 1. Genetic and Nongenetic Inheritance Terminology

We use inheritance to mean the transmission of something from parent to offspring, contributing to parent–offspring resemblance. Genetic inheritance is the transmission of DNA sequence during reproduction. Nongenetic inheritance is then the transmission of anything else from parent to offspring. This might also occur during reproduction (e.g., small RNAs present in gametes), but other aspects like behaviour, microbiomes, and physical structures can be transmitted after reproduction and without the involvement of gametes.

Epigenetic inheritance has historically been used in many different ways. We adhere to the predominating narrow-sense use that refers to certain inherited molecular factors that regulate gene expression. However, as explained above and in the text, these molecular factors are only a subset of the kinds of elements that can mediate nongenetic inheritance. Thus, the IGR framework encompasses only those forms of nongenetic inheritance that involve parent–offspring transmission of narrow-sense epigenetic factors, and leaves out other nongenetically inherited elements. Nongenetic inheritance is broader than IGR.

on the gene-regulatory aspects of nongenetic inheritance. Instead, a broader (inclusive) view of heredity is necessary [2–12].

There is no doubt that genes are involved in epigenetics (see Box 1 for terminology). However, limiting ourselves solely to the study of genes would not allow us to grasp the full complexity of epigenetics [8,11,12]. The same holds for inherited gene regulation. Although it is likely that it is involved in most nongenetic inheritance processes, the study of IGR would not by itself allow us to grasp the full complexity of nongenetic inheritance. This is because although genes and epigenetic states are involved, nongenetic inheritance can nonetheless vary independently and be shaped by alternate mechanisms (e.g., ecological, social, etc.). Thus, reducing the study of epigenetics and nongenetic inheritance to IGR would mean perpetuating the limitation that we and many other biologists are now working to correct – limiting the study of inheritance to the study of genes only.

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