



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

Pim Edelaar, Russell Bonduriansky, Anne Charmantier, Etienne Danchin, Benoit Pujol

► To cite this version:

Pim Edelaar, Russell Bonduriansky, Anne Charmantier, Etienne Danchin, Benoit Pujol. Response to Kalchhauser et al.: Inherited Gene Regulation Is not Enough to Understand Nongenetic Inheritance. Trends in Ecology & Evolution, 2021, 36 (6), pp.475-476. 10.1016/j.tree.2021.03.002 . hal-03414513

HAL Id: hal-03414513

<https://hal.science/hal-03414513>

Submitted on 8 Nov 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**RESPONSE TO KALCHHAUSER ET AL.: INHERITED GENE REGULATION IS NOT
ENOUGH TO UNDERSTAND NON-GENETIC INHERITANCE**

Pim Edelaar^{*1}, Russell Bonduriansky², Anne Charmantier³, Etienne Danchin⁴, Benoit Pujol^{5,6}

*: corresponding author; remaining authors in alphabetical order

1: Dept. Molecular Biology and Biochemical Engineering, University Pablo de Olavide,
41013 Seville, Spain (edelaar@upo.es; @Pim_Edelaar)

2: School of Biological, Earth and Environmental Sciences, University of New South
Wales, Sydney NSW 2052 Australia (r.bonduriansky@unsw.edu.au)

3: CEFÉ, Univ Montpellier, CNRS, EPHE, IRD, Univ Paul Valéry Montpellier 3,
Montpellier, France (anne.charmantier@cefe.cnrs.fr ; @AnneCharmantier)

4: Laboratoire évolution and Diversité Biologique (EDB UMR 5174), Université de
Toulouse Midi-Pyrénées, CNRS, IRD, UPS, 118 route de Narbonne, Bat 4R1, 31062
Toulouse cedex 9, France (etienne.danchin@univ-tlse3.fr).

5: PSL Université Paris: EPHE-UPVD-CNRS, USR 3278 CRIOBE, Université de
Perpignan, 52 Avenue Paul Alduy, 66860, Perpignan Cedex, France
(benoit.pujol@univ-perp.fr)

6: Laboratoire d'Excellence 'CORAIL', 58 avenue Paul Alduy, F-66360 Perpignan,
France

Key words: non-genetic inheritance, inherited gene regulation, epigenetics

In their Opinion article Adrian-Kalchhauser et al. [1] discussed the diverse molecular mechanisms underlying certain forms of non-genetic inheritance (see Box 1 for terminology). They propose embracing these mechanisms under the unifying concept of ‘inherited gene regulation’ (IGR). We think the article provides a valuable overview of several forms of non-genetically 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 non-genetic inheritance boil down to inherited gene regulation -- a conclusion that we regard as inconsistent with known features of many forms of non-genetic inheritance. Below, we clarify our concerns, and explain why we believe that non-genetically inherited variation cannot be understood solely in terms of variation in gene expression.

Several sentences in Adrian-Kalchhauser et al. [1] imply that non-genetic 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 non-genetic inheritance equates to inherited gene regulation. We argue that non-genetic inheritance is much broader than that.

The salient issue here is that many forms of non-genetic 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, 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 non-genetic 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 non-genetic 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 on the gene-regulatory aspects of non-genetic 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 non-genetic inheritance processes, the study of inherited gene regulation would not by itself allow us to grasp the full complexity of non-genetic inheritance. This is because although genes and epigenetic states are involved, non-genetic inheritance can nonetheless vary independently and be shaped by alternate mechanisms (e.g., ecological, social, etc.). Thus, reducing the study of epigenetics and non-genetic inheritance to inherited gene regulation would mean perpetuating the very limitation that we and many other biologists are now working to correct – limiting the study of inheritance to the study of genes only.

References:

1: Adrian-Kalchhauser, I. *et al.* (2020) Understanding 'Non-genetic' Inheritance:

Insights from Molecular-Evolutionary Crosstalk. *Trends Ecol. Evol.*

<https://doi.org/10.1016/j.tree.2020.08.011>

2:

2: Whiten A. (2019) Cultural evolution in animals. *Annu. Rev. Ecol. Evol. Syst.* 50, 27–

48

- 3: Creanza, N. *et al.* (2017) Cultural evolutionary theory: how culture evolves and why it matters. *Proc. Natl. Acad. Sci.* 114, 7782-7789
- 4: Fellous, S. *et al.* (2011) Adaptation due to symbionts and conflicts between heritable agents of biological information. *Nat. Rev. Genet.* 12, 663–663
- 5: Brucker, R.M. and Bordenstein, S.R. (2013) The hologenomic basis of speciation: gut bacteria cause hybrid lethality in the genus *Nasonia*. *Science* 341, 667-669
- 6: Pontarotti, G. (in press) Environmental inheritance: conceptual ambiguities and theoretical issues. *Biological Theory* <https://doi.org/10.1007/s13752-020-00348-5>
- 7: Jablonka, E. and Lamb, M.J. (2005) *Evolution in Four Dimensions. Genetic, Epigenetic, Behavioural, and Symbolic Variation in the History of Life*. Cambridge Massachusetts: MIT Press
- 8: Bonduriansky, R. and Day, T. (2018) *Extended Heredity: A New Understanding of Inheritance and Evolution*. Princeton and Oxford: Princeton University Press
- 9: Beisson, J. (2008) Preformed cell structure and cell heredity. *Prion* 2, 1-8
- 10: Danchin, É. *et al.* (2011) Beyond DNA: integrating inclusive inheritance into an extended theory of evolution. *Nat. Rev. Genet.* 12, 475-486
- 11 : Danchin, É. *et al.* (2019a) Early in life effects and heredity: reconciling neo-Darwinism with neo-Lamarckism under the banner of the inclusive evolutionary synthesis. *Phil. Trans. R. Soc. B* 374, 20180113
- 12 : Danchin, É. *et al.* (2019b) Epigenetically-facilitated mutational assimilation: epigenetics as a hub within the Inclusive Evolutionary Synthesis. *Biol. Rev.* 94, 259-282

Box 1: Genetic and non-genetic inheritance terminology

117

118 We use “inheritance” to mean the transmission of something from parent to offspring,
119 contributing to parent-offspring resemblance. “Genetic inheritance” is the transmission
120 of DNA sequence during reproduction. “Non-genetic inheritance” is then the
121 transmission of anything else from parent to offspring. This might also occur during
122 reproduction (e.g. small RNAs present in gametes), but other aspects like behaviour,
123 microbiomes and physical structures can be transmitted after reproduction and without
124 the involvement of gametes.

125 "Epigenetic inheritance" has historically been used in many different ways. We adhere
126 to the predominating narrow-sense use that refers to certain inherited molecular factors
127 that regulate gene expression. However, as explained above and in the text, these
128 molecular factors are only a sub-set of the kinds of elements that can mediate non-
129 genetic inheritance. Thus, the IGR framework encompasses only those forms of non-
130 genetic inheritance that involve parent-offspring transmission of narrow-sense
131 epigenetic factors, and leaves out other non-genetically inherited elements. Non-genetic
132 inheritance is broader than inherited gene regulation.

133