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

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22 In their Opinion article Adrian-Kalchhauser et al. [1] discussed the diverse molecular
23 mechanisms underlying certain forms of non-genetic inheritance (see Box 1 for
24 terminology). They propose embracing these mechanisms under the unifying concept of
25 ‘inherited gene regulation’ (IGR). We think the article provides a valuable overview of
26 several forms of non-genetically inherited gene regulation and their interactions with
27 genetic variation. However, we are concerned that this article might lead readers to
28 conclude that all forms of non-genetic inheritance boil down to inherited gene
29 regulation -- a conclusion that we regard as inconsistent with known features of many
30 forms of non-genetic inheritance. Below, we clarify our concerns, and explain why we
31 believe that non-genetically inherited variation cannot be understood solely in terms of
32 variation in gene expression.

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

43 The salient issue here is that many forms of non-genetic inheritance cannot be
44 meaningfully understood as only involving changes in gene regulation. For instance,
45 many behaviours are learned by offspring from watching their parents [2]. A culturally

46 transmitted behaviour such as a preference for a given food might be associated with
47 altered gene expression, but this does not mean that it is useful to redefine culture in
48 terms of variation in gene expression: cultural inheritance is better understood as the
49 transmission of behavioural traditions via social learning [3].

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

62 While Adrian-Kalchhauser et al. are most certainly aware of these additional forms of
63 non-genetic inheritance, their paper unfortunately does not explicitly mention that their
64 concept of inherited gene regulation does not cover these additional forms. We agree
65 with the authors that “*A key contemporary research challenge is incorporating*
66 *inheritance mechanisms beyond DNA sequence into evolutionary and ecological*
67 *investigations*”, and even that “*Some simplification of these dauntingly diverse and*
68 *functionally complex mechanisms is reasonable and indeed necessary for this effort*”.
69 However, if our aim is “Understanding Non-genetic Inheritance: ...” (their title), we

70 argue that this cannot be wholly done by focussing exclusively on the gene-regulatory
71 aspects of non-genetic inheritance. Instead, a broader (inclusive) view of heredity is
72 necessary [2-12].

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

84

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115

116 **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