DOCUMENT SUMMARY

This document is a scientific commentary by Horsthemke (2018) that provides a critical perspective on **transgenerational epigenetic inheritance** in humans—the idea that epigenetic information (like DNA methylation) can be transmitted through the germline to affect subsequent generations. The author argues that while this phenomenon is observed in plants and some animals, conclusive proof in humans is scarce and controversial. The paper highlights the major challenges in studying this topic, such as confounding factors from **genetic, ecological, and cultural inheritance**, and explains how phenomena like "**fetal programming**" and "**secondary epimutations**" are often mistaken for true transgenerational epigenetic inheritance. The author concludes with a skeptical view, suggesting that for humans, the impact of cultural inheritance likely surpasses any detectable epigenetic effects.

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- **Related Docs**: This paper provides a critical perspective on the mechanisms of inheritance that are relevant to the discussions of trauma and neurodevelopment in "The Neuroscience of Autism" and "Rumball_2020_research_article_trauma_ptsd_autism."

FORMATTED CONTENT

A critical view on transgenerational epigenetic inheritance in humans

Bernhard Horsthemke

Transgenerational epigenetic inheritance refers to the transmission of epigenetic information through the germline. While it has been observed in plants, nematodes and fruit flies, its occurrence in mammals—and humans in particular—is the matter of controversial debate, mostly because the study of **transgenerational epigenetic inheritance** is confounded by genetic, ecological and cultural inheritance.

Defining transgenerational epigenetic inheritance

Although **epigenetics** deals only with the cellular inheritance of chromatin and gene expression states, it has been proposed that epigenetic features could also be transmitted through the germline and persist in subsequent generations. The

widespread interest in “**transgenerational epigenetic inheritance**” is nourished by the hope that epigenetic mechanisms might provide a basis for the inheritance of acquired traits. Yes, Lamarck has never been dead and every so often raises his head, this time with the help of epigenetics. Although acquired traits concerning body or brain functions can be written down in the **epigenome** of a cell, they cannot easily be transmitted from one generation to the next. For this to occur, these epigenetic changes would have to manifest in the germ cells as well, which in mammals are separated from somatic cells by the so-called **Weismann barrier**. Further, the chromatin is extensively reshaped during germ cell differentiation as well as during the development of totipotent cells after fertilization.

Fetal programming and intergenerational inheritance

Genetic inheritance alone cannot fully explain why we resemble our parents. In addition to genes, we inherited from our parents the environment and culture, which in parts have been constructed by the previous generations. A specific form of the environment is our mother's womb, to which we were exposed during the first 9 months of our life. The maternal environment can have long-lasting effects on our health. In the Dutch hunger winter, for example, severe undernourishment affected pregnant women, their unborn offspring and the offspring's fetal germ cells. The increased incidence of cardiovascular and metabolic disease observed in F1 adults is not due to the transmission of epigenetic information through the maternal germline, but a direct consequence of the exposure in utero, a phenomenon called "**fetal programming**" or if fetal germ cells and F2 offspring are affected—"**intergenerational inheritance**".

Secondary epimutations

Several studies... have reported the co-segregation of an abnormal DNA methylation pattern (called "epimutation") with a rare disease in two or more generations of certain families. In these cases, the abnormal DNA methylation of the gene under investigation was linked to a mutation in a neighboring gene... In contrast to a **primary epimutation**, which occurs independently of any DNA sequence change, this is a **secondary epimutation**, which strictly depends on the expression of the mutated neighboring gene. If this gene is expressed also in the germline... the epimutation is also found in germ cells, which should not be mistaken for **transgenerational epigenetic inheritance**.

Roadmap to proving transgenerational epigenetic inheritance

1. **Rule out genetic, ecological and cultural inheritance.** For studies in mice and rats, inbred strains and strictly controlled environments need to be used... In contrast with laboratory animals, it is impossible to rule out ecological and cultural inheritance in humans, but genetic effects should and can be excluded.
2. **Identify the responsible epigenetic factor in the germ cells.** Be aware that germ cell preparations may be contaminated with somatic cells or somatic DNA.
3. **Demonstrate that the epigenetic factor in the germ cells is responsible for the phenotypic effect in the next generation.** While RNA molecules can and have been extracted from sperm of exposed animals and injected into control

> zygotes, DNA methylation and histone modifications cannot easily be manipulated... and all of these experiments can hardly be done in humans.

Transgenerational inheritance in the light of evolution

In plants, nematodes and fruit flies, **transgenerational epigenetic inheritance** is well documented. It has been argued that this form of inheritance may permit a population to adapt to fluctuating environments. The question is whether this is also true for mammals and, particularly, humans. Almost all of the experimental mouse models and the few observations in humans concern deleterious traits (congenital malformations, anxiety, glucose intolerance, obesity, cardiovascular diseases, cancer and premature death)... this may, at least in part, be due to reporting bias... but overall casts doubt on an adaptive role of **transgenerational epigenetic inheritance** in these cases.

> That transgenerational inheritance of chromatin marks is so rarely observed in mammals may be a side effect of the extensive epigenetic reprogramming required for germ cell development and early embryogenesis in mammals, which could also serve as a mechanism to prevent the transmission of environmental insults that animals have encountered during their life.

In conclusion, in my opinion, even if the molecular mechanisms exist to transmit epigenetic information across generations in humans, it is very likely that the transgenerational transmission of culture by communication, imitation, teaching and learning surpasses the effects of epigenetic inheritance and our ability to detect this phenomenon. **Cultural inheritance** has certainly had an adaptive role in the evolution of our species, but the evidence for **transgenerational epigenetic inheritance**, as laid out above, is not (yet) conclusive. For now, I remain skeptical.