Commentary

Do we Understand Heredity an Evolution? No

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Genetics has long been regarded as the cornerstone of biological understanding—explaining how life reproduces, evolves, and sustains human health. Mendelism, including Johannsen's 1911 genotype conception, which posits that 'genes are the units of heredity', supplanted Galton's earlier phenotype-based statistical law of ancestral heredity. Yet, this shift was not the result of decisive empirical validation.

Evidence accumulated over the past three decades challenges the genotype conception. In 1992, the discovery of radiation-induced genomic instability and the bystander effect undermined the assumption that heritable change is strictly gene-dependent. In 2009, genetic variance failed to account for the fitness trajectory observed in the Long-Term Evolution Experiment (LTEE) with *E. coli*. By 2013, it became evident that evolution in the LTEE was thermodynamically—not genetically—driven.

This paper traces the historiography of heredity from 1880 onwards, critically re-evaluates Mendelism, and reviews recent empirical findings. It concludes that Mendelism fails as a scientific framework. Consequently, there is no valid consensus underpinning the life sciences, human health, or evolutionary theory. This represents a profound failure in twentieth-century biology.

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1. Introduction

For over a century, the molecular genetic paradigm—anchored in Johannsen's genotype conception and Mendelian inheritance—has dominated biological thought. Yet this framework increasingly fails to account for a growing body of empirical evidence that challenges its foundational assumptions. Phenomena such as genomic instability, the bystander effect, and findings from the Long-Term

Evolution Experiment (LTEE) reveal a persistent disconnect between genotype and phenotype. These developments suggest that genes are neither the sole nor the primary units of heredity.

In response to this disconnect, we introduced the concept of the cellular phenotype manifest as a dynamic attractor state—not merely as a descriptive term, but as a paradigm-shifting principle [1]. The cellular phenotype represents the integrated, dynamic state of the cell, shaped by both genetic and non-genetic factors, and capable of transmitting heritable traits independently of DNA sequence. This reframing challenges the assumption that inheritance is solely gene-dependent and opens the door to a systems-level understanding of biological continuity.

Complementing this, we proposed the concept of "rules of engagement"—a novel framework describing the efficient cause of cellular behaviour [1]. These rules govern how cellular components interact, self-organise, and maintain functional coherence, independent of genotypic instruction. To our knowledge, this causal category has not been previously articulated in the literature and offers a new explanatory dimension in cell biology, distinct from genetic determinism, epigenetics, and environmental triggers.

This commentary builds on these foundations to argue that heredity and evolution are better understood through the lens of cellular dynamics and thermodynamics, rather than molecular genetics alone [2]. To demonstrate the need for such a radical revision of cellular biology, we begin by reviewing the historiography of inheritance—showing that Galton's law of ancestral heredity, which was abandoned in favour of Mendelism, (1) provides a sound description of the heredity process, (2) was not displaced through rigorous scientific evaluation, and (3) that Johannsen's pure line experiments do not validate the genotype conception.

2. A Brief and Selective Historiography of the Foundations of Heredity (1880-1906)

This section does not aim to provide a comprehensive account of the events between 1880 and 1906, as many historians have already examined these developments (e.g. [3][4][5][6]). Instead, it highlights key episodes that shaped the conceptual foundations of heredity and led to the eventual dominance of Mendelism.

2a. The Law of Ancestral Heredity

Francis Galton, Darwin's cousin, pioneered the application of statistics to biology, particularly in the study of heredity. His work addressed phenomena such as regression to the mean [7] and culminated in the publication of *Natural Inheritance* in 1889 [8]. In 1897, Galton proposed the law of ancestral inheritance, which quantified the average contributions of multiple generations of ancestors to the phenotype of offspring [9]. This law, based on direct transmission of phenotypic traits, was later described by Pearson [10] as a statistical description of inheritance rather than a biological theory.

The law served two key purposes:

- It demonstrated that including ancestral data beyond the immediate parents improved predictive accuracy.
- It enabled probabilistic estimation of offspring traits based on phenotypic data from parents and ancestors.

Galton's law was grounded in empirical studies of human families and animal breeding records, using both qualitative and quantitative traits such as height, eye colour, and coat colour.

In parallel, Galton developed a theory of heredity based on Darwin's pangenesis, which he termed the "hypothesis of parts," involving the transfer of 'stirp' via germ cells. Bulmer [11] notes that Galton saw compatibility between his statistical law and the germline mechanism, quoting Galton:

"The person may be accepted on the whole as a fair representative of the germ, and, being so, the statistical laws which apply to the persons would apply to the germs also, though with less precision in individual cases."

Bulmer concludes that Galton viewed the ancestral law as a logical necessity requiring empirical verification.

2b. The Birth of Mendelism

In 1900, Mendel's 1866 work on *Pisum sativum* was rediscovered by Hugo de Vries, Carl Correns, and Erich von Tschermak. British biologist William Bateson quickly became Mendel's leading advocate in England, promoting the theory through lectures and his book *Mendel's Principles of Heredity – A Defence* [12]. However, even the rediscoverers expressed doubts about the general applicability of Mendel's laws [13].

W. F. R. Weldon, co-founder of *Biometrika*, used the journal to highlight experimental results that contradicted Mendelian dominance [14]. This sparked the well-known Mendelian–biometrician dispute (1902-1906), chronicled by Provine [4].

A pivotal moment occurred at the 1904 meeting of the British Association's Zoological Section in Cambridge. Despite expectations of a rigorous scientific debate, the meeting did not produce a decisive endorsement of Mendelism. Weldon accused Bateson of adjusting Mendel's theory to fit experimental data [15], and Pearson noted that observed traits in humans and animals could not be reconciled with Mendelian principles [10].

A key experiment involving mice was conducted by Weldon's student A. D. Darbishire, to test Mendelism. Initially, Darbishire's results on eye colour inheritance did not support Mendel's ideas. In 1904, he published findings that he considered a "grave challenge to the future of Mendelism" [4]. Bateson, however, identified flaws in Darbishire's data and pressured him not to disclose the inaccuracies publicly. Darbishire, caught between loyalty to Weldon and Bateson's demands, ultimately presented ambiguous results at the Cambridge meeting, stating that some findings supported Mendelism while others aligned with ancestral inheritance [16].

Darbishire's ambivalence is captured in his unpublished allegorical fable *The Laying Bare of the Marvel*, in which he portrays himself as a neutral figure rejected by both camps [17]. Bateson refused private dialogue, insisting that any communication be public [4]. Weldon died in 1906 before completing a review of horse breeding data, and Pearson shifted his focus to eugenics.

Thus, Mendelism "slipped under the fence"—not through decisive scientific validation, but through attrition and strategic advocacy. As Omholt later observed:

> "Geneticists have invented several additional concepts to describe statistically inferred patterns in their data... All these concepts are in active use... and in terms of underlying mechanisms they are all far from well understood." [18]

Phillip Ball similarly notes that Mendelian traits are the exception rather than the rule, and that teaching genetics through Mendel may give a false impression of gene function [19].

Despite Bateson's efforts—some arguably unprofessional—Mendelism was never endowed with robust scientific credibility.

2c. The Genotype Conception

In 1911, Wilhelm Johannsen published *The Genotype Conception of Heredity* [20], based on his earlier pure line breeding experiments with *Phaseolus vulgaris* (haricot beans), conducted in 1901–1902 and detailed in his 1903 monograph [21]. His genotype conception posits that inheritance is determined by the genotypes present in parental gametes, which in turn determine the phenotype of the offspring. This conception underpins modern genetics.

Johannsen emphatically rejected the biometricians' view of heredity as the direct transmission of phenotypes and dismissed any influence of ancestry. He wrote:

> "Ancestral influence! As to heredity, it is a mystical expression for a fiction. The ancestral influences are the 'ghosts' in genetics, but generally the belief in ghosts is still powerful."

Johannsen's pure line breeding approach, pioneered earlier by Louis de Vilmorin, involved isolating self-fertilised bean lines and measuring the average weight of their progeny. In 1901, he sowed market-purchased beans (F_0), isolated each plant, and produced 19 pure lines. In 1902, he selected beans of varying individual weights from these lines (F_1), sowed them, and harvested their progeny (F_2). He observed that the F_2 beans exhibited phenotypes characteristic of their line, rather than those of the selected F_1 parents—indicating that selection within pure lines was ineffective.

Norwegian historian Nils Roll-Hansen [22] interprets Johannsen's experiment as "crucial" not for validating the genotype conception, but for resolving the debate over continuous versus discontinuous variation. The biometricians, following Darwin, argued for continuous variation, while de Vries and the Mendelians favoured discontinuity. Johannsen's finding—that fluctuating variation was not heritable—supported the latter view.

Importantly, Roll-Hansen does not regard Johannsen's experiment as a test of the genotype versus phenotype conceptions. The genotype conception is not discussed in Johannsen's 1903 paper, and Roll-Hansen, arguably Johannsen's foremost interpreter, does not attribute significant weight to it.

Given the empirical success of Galton's law of ancestral heredity, which relies on direct transmission of phenotypes, Johannsen's claim that his pure line experiments validate the genotype conception warrants scrutiny. Johannsen adopted Mendelism, asserting that it supported the genotype conception:

> "The genotype conception, initiated by Galton and Weismann... now revised as an expression of the insight won by pure line breeding and Mendelism, is in the least possible

degree a speculative conception." [20]

According to Provine [4], Johannsen's theory gained traction in America, where de Vries' mutation theory was already popular. Following his 1911 paper, Johannsen toured the United States, lecturing on pure line theory, which gradually faced less criticism.

However, Johannsen's experimental system—based on self-fertile plants with identical parental genotypes—cannot test the process of heredity. It proves that fluctuating variation is not heritable, but it cannot confirm or refute the genotype conception. Ancestral influence is inherently excluded from such a system. Thus, Johannsen's pure line experiments are too simplistic to support the genotype conception as a general principle of heredity.

2d. Summary of the Historical Evidence

Galton and Pearson's law of ancestral heredity offers two key strengths: it provides a robust description of the inheritance process and enables probabilistic predictions of offspring phenotypes based on parental and ancestral traits. Despite these merits, it was displaced by Mendelism around 1906—without a rigorous scientific evaluation of the competing frameworks.

Experimental evidence has repeatedly failed to support Mendel's laws. The theory has been continuously adjusted to accommodate conflicting data [18], and genome-wide association studies have struggled to identify the genes presumed responsible for common genetic disorders such as schizophrenia [23].

Johannsen's genotype conception, which underpins modern genetics, was not validated by his pure line experiments. These experiments demonstrated that fluctuating variation is not heritable, but they were incapable of testing the broader process of heredity. The experimental system was too simple to assess ancestral influence or genotype–phenotype causality.

Taken together, the historical record reveals that Mendelism gained prominence through advocacy and institutional momentum rather than empirical superiority. The genotype conception, while foundational to molecular genetics, lacks universal applicability and remains unproven in key biological contexts.

3. Review of Recent Evidence Regarding Mendelism and the Genotype Conception

3a. Radiation-Induced Genomic Instability and the Bystander Effect

Ionising radiation is well known to induce DNA mutations, potentially altering genotypes and leading to disease phenotypes. However, two phenomena—genomic instability and the bystander effect—demonstrate that heritable phenotypic changes can occur without direct genotypic alteration, thereby violating the genotype conception.

In 1992, Kadhim et al. reported chromosomal instability in mouse bone marrow cells irradiated with ^238Pu alpha particles. These karyotypic changes persisted across multiple post-irradiation generations [24]. That same year, Nagasawa and Little demonstrated the bystander effect in Chinese hamster cells: a dose of just 0.31 mGy caused increased sister chromatid exchanges in 30% of cells, even though fewer than 1% were directly hit by alpha particles [25].

These effects have since been observed in human zygotes and foetuses [26], and extensively reviewed by Schofield and Kondratowicz [27]. They are now recognised as “radiation-induced non-targeted effects” and have been documented in international research programmes spanning 1995-2012. Similar effects are triggered by other environmental stressors, such as air pollution.

Further evidence comes from Huumonen et al. [28], who compared gene expression in two populations of *C. elegans* descended from irradiated and sham-irradiated ancestors. After several generations, the irradiated lineage showed significant upregulation of 28 probes and downregulation of 375, with increased heterogeneity in gene expression. These changes were not attributable to genotypic damage, further undermining the genotype conception.

In practice, it is not possible to prove that inheritance of gamete genotypes alone determines offspring phenotype. These findings demonstrate that the genotype conception is not universally valid—if it applies at all.

3b. The Long-Term Evolution Experiment (LTEE)

The LTEE, initiated by Lenski, has tracked over 70,000 generations of *E. coli* across 12 replicate populations derived from a genetically uniform founder strain [29]. Each day, bacteria are transferred to

fresh nutrient media, and researchers periodically measure fitness (growth rate), cell size, and DNA sequence changes.

By 2009, after 20,000 generations, researchers observed a linear accumulation of mutations but a highly non-linear fitness trajectory [30]. By 50,000 generations, fitness across all replicates followed an identical power-law curve [31], while cell size trajectories varied significantly. This disconnect between genomic and phenotypic evolution contradicts Fisher's foundational model, which links fitness change to genetic variance [32].

To explain the power-law behaviour, researchers invoked statistical constructs such as "diminishing-returns epistasis" and "clonal interference". However, Baverstock [33] argues that these explanations are insufficient. If epistasis governs fitness, it should also affect cell size—but it does not. Moreover, for clonal interference to produce identical fitness trajectories across 12 independent cultures, beneficial mutations would need to occur with implausible frequency.

In 1998, Lenski estimated that only one in a million mutations in *E. coli* is beneficial. Thus, the observed fitness pattern cannot plausibly be explained by mutation-driven mechanisms. The LTEE data suggest that evolution is governed by thermodynamic constraints and cellular dynamics—not genetic variation alone.

3c. The evolution of bacteria with minimised genomes

Recent findings on the evolution of the minimal cell [34] further support this thermodynamic interpretation. The authors correctly observe that the rate of adaptation is independent of genome size. This is expected if evolution is a thermodynamic rather than a genetic process. If fitness gains were driven by genetic variance, then—given that the mutation rate per gene is independent of genome length—the minimized genome would exhibit greater variance per unit of genome, and thus a higher rate of fitness increase. Yet this is not observed. Instead, both minimized and non-minimized cells adapt at comparable rates. This suggests that the rate of evolution is not constrained by genetic architecture, but rather by the availability of free energy (nutrients) to support replication. Under the culture conditions used in this experiment, that energetic requirement was met—supporting the view that evolutionary adaptation is governed by thermodynamic principles.

4. Conclusion and Implications for the Life Sciences

The historical and empirical evidence presented here undermines the foundational assumptions of Mendelism and the genotype conception. Galton's law of ancestral heredity, though statistically descriptive rather than mechanistic, offers a more accurate account of inheritance than Mendelian genetics. Its predictive power and recognition of ancestral influence stand in contrast to the continual need to adjust Mendelian theory to fit discordant data.

Johannsen's genotype conception, while influential, was not validated by his pure line experiments. These experiments demonstrated that fluctuating variation is not heritable, but they were incapable of testing the broader mechanisms of heredity. The simplicity of the system excluded ancestral influence and rendered it unsuitable for evaluating genotype–phenotype causality.

Recent empirical findings further challenge the genotype conception. Radiation-induced genomic instability and the bystander effect demonstrate that heritable phenotypic changes can occur independently of DNA sequence alterations. The Long-Term Evolution Experiment reveals that fitness trajectories are governed by thermodynamics and cellular dynamics, not genetic variation alone.

Together, these findings suggest that the molecular genetic paradigm is insufficient to explain heredity, evolution, and biological continuity. The cellular phenotype—defined as the integrated, dynamic state of the cell—offers a more robust framework. It accommodates both genetic and non-genetic influences and provides a systems-level understanding of inheritance.

This paradigm shift has profound implications. It calls into question the scientific foundations of human health, evolutionary theory, and the life sciences more broadly. A re-evaluation of biological causality is urgently needed—one that moves beyond genetic determinism and embraces the complexity of cellular organisation and thermodynamic constraint.

In response to challenges to the central premise of population genetics—the genotype conception—we previously introduced two novel concepts: the cellular phenotype as a dynamic attractor state, and the rules of engagement [1]. The former assumes the role traditionally attributed to the genotype, not only in transmitting parental information to offspring but also in regulating cellular behaviour. It does so by activating information encoded in the virtual rules of engagement, thereby fulfilling the requirement for two distinct sources of information—rules and genes—to define the cellular state. This dual-source framework circumvents the limitations implied by Gödel's incompleteness [35]. Within this paradigm, the genotype plays a passive role as the material cause of cellular function. The observed combination of

stability and plasticity in biological cells thus emerges from the interplay of these two independent informational sources, culminating in a dynamic attractor state that defines cellular characteristics.

The failure of Mendelism to account for the full complexity of heredity, and the inability of the genotype conception to withstand empirical scrutiny, demand a fundamental rethinking of biological causality. The cellular phenotype—dynamic, integrative, and responsive to both genetic and non-genetic influences—offers a more coherent and empirically grounded framework. This shift is not merely academic: it has profound implications for how we understand disease, evolution, and the continuity of life. If the life sciences are to remain scientifically credible and socially relevant, they must move beyond the constraints of genetic determinism and embrace a systems-level biology rooted in cellular dynamics and thermodynamic principles. The time has come to revise the foundations.

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