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Epigenetics and its impact on Evolution : Evolution beyond Genome

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Abstract

The Extended Evolutionary Synthesis (EES) represents a paradigm shift in evolutionary biology by incorporating epigenetics, phenotypic plasticity, and non-genetic inheritance into evolutionary theory. While the Modern Synthesis (MS) emphasized genetic mutations and natural selection, EES challenges this framework by demonstrating that phenotypic changes can precede and influence genetic evolution. Epigenetic inheritance, developmental plasticity, and niche construction all play vital roles in shaping evolutionary trajectories. This review explores the foundational concepts of EES, contrasts them with MS, and examines the role of epigenetic modifications in species divergence, adaptation, and speciation. Key studies, such as epigenetic variation in Darwin's Finches, illustrate the role of epigenetic mechanisms in evolution. By integrating insights from evolutionary developmental biology (Evo-Devo) and reciprocal causation, EES offers a more comprehensive and dynamic understanding of evolutionary processes.

Additionally, this review delves into the role of transgenerational epigenetic inheritance (TEI) in adaptive evolution and speciation. TEI

allows environmentally induced epigenetic modifications to persist across generations, contributing to phenotypic plasticity and influencing speciation. The ability of epigenetic mechanisms to drive adaptation has been observed in various species, such as zebrafish and alligator weed, where epigenetic modifications enhance fitness and promote ecological diversification. We explore how TEI interacts with genetic assimilation, the Baldwin effect, and molecular constraints, shaping evolutionary outcomes. Furthermore, we examine the role of epigenetics in reproductive isolation and speciation, investigating how epigenetic modifications contribute to divergence hitchhiking, hybrid incompatibilities, and adaptive evolution. Emerging research on three-dimensional genomics and paleoepigenomics suggests that epigenetic reprogramming may have played a crucial role in past and present speciation events. By examining both theoretical models and empirical findings, this review underscores the evolutionary significance of epigenetic inheritance in shaping biodiversity.

Keywords: Adaptive Evolution, Darwinism, Epigenetics, Lamarckism, Modern Synthesis, Phenotypic plasticity, Speciation, Trans generational Epigenetic Inheritance.

Introduction

Evolutionary biology has traditionally been dominated by the Modern Synthesis (MS), which posits that genetic mutations and natural selection are the primary drivers of evolution. However, emerging research in epigenetics, developmental biology, and non-genetic inheritance suggests that additional factors contribute to evolutionary change. The Extended Evolutionary Synthesis (EES) expands upon MS by incorporating phenotypic plasticity, epigenetic modifications, and ecological interactions as key mechanisms in evolution.

This review examines the foundational principles of EES, emphasizing the role of epigenetics in inheritance, adaptation, and speciation. We explore historical perspectives, including Darwin's Pangenesis and Lamarckian

inheritance, and discuss how contemporary findings in epigenetics challenge traditional views of inheritance. Additionally, we highlight key concepts such as genetic assimilation, developmental constraints, and niche construction, which contribute to the broader understanding of evolutionary dynamics beyond genetic mutations alone.

Furthermore, this review explores the concept of transgenerational epigenetic inheritance (TEI) and its impact on evolutionary adaptation and speciation. TEI involves the transmission of environmentally induced epigenetic changes across multiple generations, influencing phenotypic traits, fitness, and reproductive isolation. We examine case studies, such as hypoxia resistance in zebrafish and the role of DNA methylation in Arabidopsis, that illustrate the importance of TEI in ecological adaptation. The interplay between TEI, phenotypic plasticity, and environmental stability provides insight into how organisms navigate changing environments and persist across generations. Additionally, we investigate the contribution of epigenetic mechanisms to speciation, focusing on reproductive isolation, divergence hitchhiking, hybrid incompatibilities, and the role of epigenetic drift in cryptic species formation. Emerging research in paleoepigenomics and three-dimensional genomics suggests that epigenetic factors have shaped speciation events throughout evolutionary history.

The Extended Evolutionary Synthesis

The Paradigm Shift occurred due to the intersection of the emerging field of Epigenetics and the established field of Evolutionary Biology, leading to the ultimate development of the "Extended Evolutionary Synthesis" (EES, Pigliucci and Müller, 2010). In 1942, Conrad Waddington was the pioneering scientist who first brought the concept of Epigenetics to prominence. Since the advent of Epigenetics, scientific advancements have significantly favored this field, prompting frequent consideration of how often the gene, the fundamental blueprint of our existence, is subject to daily rewriting. As we delve into the topic, we will emphasize Epigenetics as a pivotal component in the evolutionary process. We will also probe emerging factors driving Constructive evolution- an evolutionary framework that stands in dynamic contrast to the traditional

Modern Synthesis (MS, Huxley, 1942). Moreover, we will illuminate how once-overlooked theories have gained prominence, playing transformative roles in the development of a contemporary "*Unified theory of Evolution*" (Skinner *et al*., 2015). Starting from a Darwinian perspective, it is important to know that Darwin's view on Evolution was not exclusively centered on natural selection (Darwin, 1859). He himself supported the inheritance of acquired characteristics and introduced the concept of Pangenesis (Darwin, 1868. pp. 357-404; Skinner *et al.,* 2015). Lamarckism (1802), the concept that the environment can 'directly' alter the phenotype in a heritable manner, is often claimed to have resurfaced with the rise of Epigenetics, which explores the heritability of non-DNA sequence-based epigenetic information. However, this is a misleading conflation (Loison *et al*., 2018). Our current focus is on ideologies that advocate for cumulative evolution and those that investigate evolutionary trajectories beyond the genome (West- Eberhard, 2003; Jablonka and Raz, 2009; Pigliucci and Müller, 2010; James Shapiro, "Evolution: A View from the 21st Century" (FT Press Science, 2011); Felsenfeld, 2014; Jablonka, 2017). In this context, Darwinism remains a vital cornerstone for its introduction of natural selection; however, its limitation lies in focusing solely on this concept, while the field of evolutionary biology has since evolved and expanded beyond it. As our focus is primarily on Epigenetic inheritance, we will explore an evolutionary mechanism that transcends genomic sequences and dynamically interacts with environmental factors. Evidence reveals a divergence between phenotypic and genotypic mutation rates (Burger *et al.,* 2006), a variance that Epigenetics can elucidate (Skinner *et al*., 2015). A study on Darwin's Finches across the Galapagos Islands aimed to test whether epigenetic changes accumulate over long evolutionary periods, contributing to adaptation and ultimately, speciation. Five Darwin's Finches species, which evolved through adaptive radiation over 2-3 million years, varied in beak shape and size (Grant and Grant, 2008) were analyzed for genetic variation (via Copy Number Variation (CPV)) and Epigenetic variation (via differential DNA methylation). Given the role of epigenetics in

ecology and evolution (Richards *et al*., 2010), this groundbreaking genome-wide comparison revealed that epigenetic changes outpace genetic mutations, suggesting that these changes accumulate over time, playing a role in evolution (Michael K. Skinner, Carlos Gurerrero-Bosagna, M.Muksitul Haque, Eric E.Nilsson, Jennifer A.H. Koop, Sarah A. Knutie, and Dale H. Clayton, 2014).

A Lamarckian phenomenon would be feasible only if individual Epigenetic variations permitted the inheritance of acquired characteristics to contribute to unlimited evolutionary change. For this to occur, the inheritance of acquired characteristics (IAC) must function as a self-sufficient Evolutionary mechanism. However, evidence has demonstrated otherwise: IAC is not an intrinsic property of living organisms and is not supported as a comprehensive theory of Organic Evolution (Loison *et al*., 2018). The concept of cumulative evolution as outlined by the Extended Evolutionary Synthesis, broadens our understanding of evolutionary processes over millions of years. Before delving into the contemporary concept of the Extended Evolutionary Synthesis, it is essential to comprehend transformative impact of the Modern Synthesis (MS), (Neo-Darwinism is often erroneously conflated with the Modern Synthesis, despite being a distinct concept (Pigliucci and Müller 2010)), a paradigm introduced by Julian Huxley, (1942). The Modern synthesis views natural selection as the primary driver of evolution, with genetic mutations leading to gradual phenotypic changes. It emphasizes a gene- centered perspective, where genes are the sole basis of inheritance. (Mayr E. 1982; Arnold SJ. 2014, Laland KN, Uller T, Feldman MW, Sterelny K, Müller GB, Moczek A, Jablonka E, Odling-Smee J., 2015, Refer Table 1,2 & 3). Extended Evolutionary Synthesis suggests that phenotypic changes can precede and influence genotypic changes, thus, challenging Modern Synthesis through some key concepts: the inheritance of non-genetic traits (contrary to Modern Synthesis's gene-centric view), developmental constraints and affordances: Evo-Devo theory (Müller, 2007), evolvability, plasticity & phenotypic accommodation, Cyril Darlington's (1959) notion of soft

inheritance and Richard Lewontin's perspective of "niche construction"(Odling-Smee FJ *et al*, 2003), which are often marginalized in Modern Synthesis. Additionally, the Modern Synthesis tends to downplay macroevolution as merely an extrapolation of microevolution. Apart from being a constructive theory of evolution, EES endorses the idea of 'Reciprocal causation' that developing organisms are not solely products, but are also causes, of evolution (Laland KN, Uller T, Feldman MW, Sterelny K, Müller GB, Moczek A, Jablonka E, Odling-Smee J., 2015).

This era, marked by scientists advancing experiments, unveiling new models, and showcasing diverse living examples of Evolutionary processes, is termed by Arnold (2014) as the "Ongoing Synthesis"- a dynamic phase that has continued to gain momentum since 1963. (Ernst Mayr, 1963, *Population, Species and Evolution*; Arnold SJ., 2014, Am. Nat. 1836, 729–746). As Thomas Kuhn posited, when a dominant scientific paradigm fails to account for anomalies, it signals the need for a paradigm shift and the development of a new scientific framework (Kuhn, 1962). Many Darwinian proponents dismiss the Extended Evolutionary Synthesis through criticism of the evo-devo theory often stems from its characterization as 'developmental bias' and emphasizes natural selection as the primary driver of adaptation and speciation. Over years of scientific discourse, the debate about the Extended Evolutionary Synthesis has proven to be multifaceted, even in contemporary scholarly discussions (Murray JK, Benitez RA, O'Brien MJ, 2020; Dickens, 2021; Shan *et al.,*2024). Our primary focus is to examine how non-genetic or inclusive inheritance influences evolution within the framework of the Extended Evolutionary Synthesis and how it contrasts with the Modern Synthesis. In the Extended Evolutionary Synthesis, developmental processes work in tandem with natural selection, shaping the trajectory, pace of evolution, and the genesis of adaptation. Inheritance and variation extend beyond genetics, it also includes Epigenetic, Physiological, Ecological, Behavioral, and Cultural processes. Developmental changes often facilitate integrated functional responses to environmental shifts or other lifestyle-altering changes. In such instances, genes do not passively await

mutation; rather, they proactively engage in phenotypic adjustments (Jablonka *et al.,* 2017). Example of such phenomenon: Goats decreasing hindlimb stiffness when walking over compliant surfaces (Clites TR, Arnold AS, Singh NM, Kline E, Chen H, Tugman C, Billadeau B, Biewener AA, Herr HM, 2019). Cited by Nishikawa K., (2018) *"Environmental induction is a major initiator of adaptive evolutionary change. The origin and evolution of adaptive novelty do not await mutation; on the contrary, genes are followers, not leaders, in evolution."* (West-Eberhard *et al.*, 2003).

Extended Epigenetic Synthesis emphasizes organismal and developmental perspectives over a purely gene-centered approach. It is viewed as an evolutionary construct shaped by natural selection. (Haig D., 2007). We define epigenetics as the transmission of information beyond DNA sequences, occurring across cell divisions (Heard E, Martienssen RA., 2014), influencing gene regulation and the inheritance of epimutations. Epigenetic inheritance tends to remain consistent through cell divisions, as these traits are typically stable through mitosis, and in some instances, it also remains stable through meiosis, allowing transmission through the germline (Skinner *et al*.2010; Anway *et al*. 2005; Jirtle and Skinner 2007; Michael K. Skinner, Carlos Gurerrero-Bosagna, M.Muksitul Haque, Eric E.Nilsson, Jennifer A.H. Koop, Sarah A. Knutie, and Dale H. Clayton, 2014). Environmental factors have been found to enable the transmission of phenotypic variations across generations via epigenetic processes (Skinner *et al*., 2010). Inheritance, beyond the genome, also includes the transfer of developmental resources and non-genetic factors in influence the environment such as inheritance of behavioral patterns like maternal care in female rats, frequently licking and grooming their offspring during the first week postpartum (Liberman N. *et al.,* 2019). Offspring raised by mothers who forgo licking and grooming show elevated stress hormone levels and are less likely to engage in these behaviors with their own offspring. (Curley JP, Champagne FA, Bateson P, Keverne EB, 2008). Non-genetic inheritance can occur between soma cells, germ cells or between germ cells and soma cells. This process influences the expression

and retention of environmentally induced traits, impacting evolutionary rates. (Danchin E et al. 2011; Badyaev AV. 2009; Laland KN, Uller T, Feldman MW, Sterelny K, Müller GB, Moczek A, Jablonka E., Odling-Smee J., 2015). Epigenetic changes, such as DNA methylation, histone modifications, and RNA-mediated processes, occur beyond the DNA sequence and can be inherited across generations. DNA methylation plays roles in various processes, especially in heterochromatinization of the X chromosome, which takes place in the early developmental phase (Muyle et al., 2021). Traditionally, the Weismann barrier (Weismann, 1893) was seen as an impediment to epigenetic inheritance, but emerging evidence challenges this. For example, offspring can be influenced by the mother's epigenetic state via the placenta (Li CCY, Maloney CA, Cropley JE, Suter CM., 2010), and in humans, small RNAs absorbed during spermatogenesis by sperm cells may impact future generations (Ashe A, Whitelaw E. 2007). In zebrafish, while female methylation patterns are often reset, male methylation can be passed down, suggesting a more complex model of inheritance (Goll MG and Halpern ME., 2011). The Weismann Barrier is less effective in plants, *C. elegans*, and certain flies and mammals, allowing for epigenetic inheritance. Moreover, it is now understood that the difference between germline and somatic cells lies not in their chromosomal content, but in how they regulate and express the genome. This insight opens the door to transgenerational inheritance, revealing a more nuanced understanding of heredity. (Bline AP, Le Goff A, Allard P., 2020). For example, RNAi transgenerational inheritance in *C. elegans* (Li C, Bhagoutie PAW, Lao V, Saltzman AL., 2023), In *A. thaliana*, Transposable elements can sustain variations in DNA methylation states for at least eight generations, and likely even longer (Ashe A, Colot V, Oldroyd BP., 2021). The phenotypic variation measured in epigenetic recombinant inbred lines (epiRILs) (Zhang YY, Fischer M, Colot V, Bossdorf O., 2013) and variation encompasses various epigenetic markers inheriting across generations. Radish, which is subjected to heavy insect predation, increases the production of spines and toxins. The inheritance of these adaptive traits, which can vary in intensity, is known

as ‘adaptive transgenerational epigenetic inheritance” (Agrawal AA, Laforsch C, Tollrain R. 1999). Epigenetic mechanisms can unlock a spectrum of phenotypic variations from a single blueprint. Epimutations, which alter gene expression without modifying the sequence itself, offer a dynamic and reversible mechanism for shaping biological outcomes (Vogt G., 2022). In *Linaria vulgaris*, two phenotypes arise from the same genotypes due to differences in methylation patterns at the LSIC gene: the wild type with bilateral symmetry and the peloric mutant with radial symmetry. Offsprings from peloric mutants occasionally display wild-type flowers, demonstrating that the mutation is an epimutation, which is reversible. In contrast, genetic mutations would result in irreversible changes. (Fujimoto R, Sasaki T, Ishikawa R, Osabe K, Kawanabe T, Dennis ES., 2012)

From a historical perspective on evolution, certain theories that were previously overlooked are now gaining renewed interest with the emergence of epigenetics, making them increasingly relevant. Loison (2021), explains that while Genetic assimilation (Waddington, 1957, a trait shaped by environmental variability can eventually become genetically fixed within the genotype) and the Baldwin effect (Simpson, 1953) are closely related, they remain distinct processes and both processes can individually be reinforced by epigenetic inheritance. Genetic accommodation (West- Eberhard, 2003), alteration in the regulatory mechanisms governing trait expressions. To illustrate the simultaneous presence of genetic assimilation and genetic accommodation, an experiment was designed to reveal their tandem operation (Suzuki Y, Nijhout HF.,2006). ‘Phenotypic accommodation’ becomes pervasive and entrenched across generations, and can pave the way for genetic accommodation to occur. (Ashe A, Colot V, Oldroyd BP. 2021; Pigliucci M, Murren CJ, Schlichting CD., 2006).

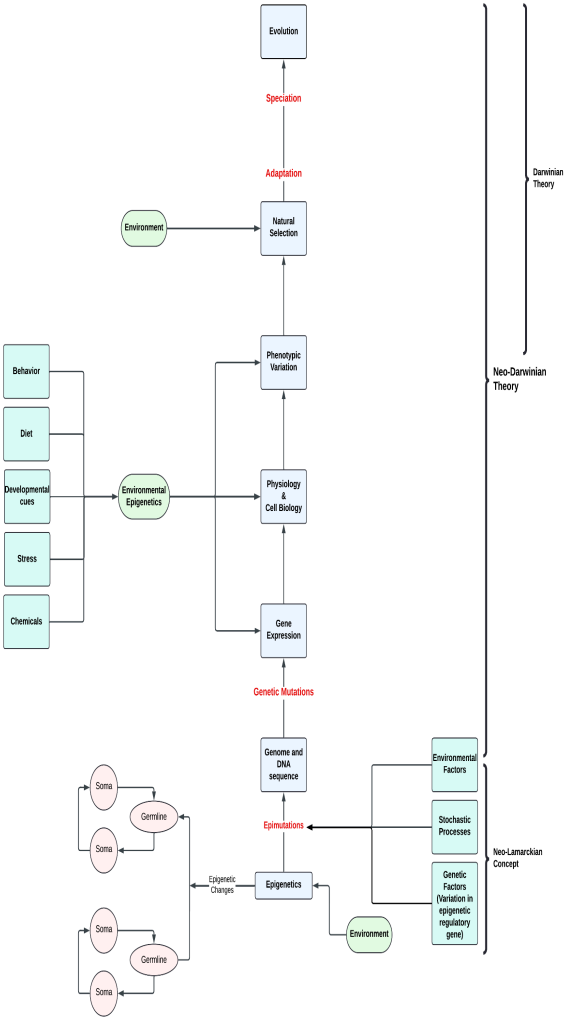

Fig: This diagram, originally introduced by Skinner *et al.* (2015), and subsequently refined by Skinner & Nilsson (2021), presents a modified version of the earlier flow charts, depicting the *"Unified Theory of Evolution"*. Environmental cues orchestrate epigenetic transformations that can travel through different biological pathways–soma-to-soma, soma-to-germline, and germline-to-germline–shaping phenotypic diversity. This process fuels genetic variation and adaptation, where specific

traits are selected, gene flow diminishes, and as phenotypic plasticity wanes, reproductive isolation intensifies. This cascading effect drives speciation and, ultimately, evolution.

Transgenerational Epigenetic Inheritance: Shaping Phenotypic Plasticity for Environmental Adaptation

Burggren (2016) emphasized that while epigenetic research often centres on individual mechanisms & diseases, the broader, evolutionary scope- particularly transgenerational epigenetics- remains underexplored. Our approach will bridge this gap, first unraveling the evolutionary impact of epigenetics before delving into its mechanisms and associated diseases. Building on our previous discussion of epigenetics, our focus now shifts to how these environmentally influenced changes are inherited and their potential role in adaptive evolution. Epigenetic changes are remarkably stable within an individual, persisting through mitotic divisions, and can be transmitted across generations via meiotic division. While genes themselves are reliably passed down through generations, the variations in how these genes are expressed are not always inherited. Yet, the ability to respond to environmental shifts is a trait that can be passed on (Debat and David, 2001; Angers *et al.,* 2010), a concept we will delve into shortly.

Perez and Lehler, 2019; Maximilian & Giacomo, 2022, delve deeply into intergenerational and transgenerational epigenetic inheritance (TEI). Intergenerational inheritance involves the passing of epigenetic changes from parents to offspring, typically affecting F1 or F2 generations. In mice, when a male is exposed to an environmental stimulus, the resulting epigenetic changes are passed to the F1 generation. If a pregnant female is exposed, these changes can extend to the F2 generation. This inheritance, whether from the mother or father, often stems directly from the parent's environmental exposure, particularly affecting the germline in pregnant females. TEI occurs when these changes persist across multiple generations, even in the absence of the original stimulus. Although intergenerational and transgenerational effects often share underlying mechanisms, the distinction between them remains subtle. To illustrate transgenerational epigenetic inheritance, consider the example of hypoxia

resistance in Zebrafish. This beneficial trait demonstrates how epigenetic changes can be passed across generations (Ho DH., 2010).
While DNA's accuracy ensures reliable genetic inheritance, eggs, and sperm also carry non-DNA molecules that transmit information across generations, involving Genome- associated mechanisms like covalent DNA and histone modifications and mechanism of transferring small noncoding RNAs (ncRNAs), present abundantly in sperm. Genome-independent mechanisms, like microbiome transfer. Despite the diversity of mechanisms contributing to epigenetic inheritance, it's important to recognize that these processes are less robust than DNA replication, resulting in a more limited duration of reliable information transfer (Perez & Lehner, 2019; Rando, O.J., 2015; Chen Q. *et al*., 2016; Sirkis F. *et al*, 2014).

Epigenetics: Linking Environment, Plasticity, and Selection. As our understanding of evolution deepens, environmental interactions are now seen as key factors in adaptive and non-adaptive plasticity, alongside non-epigenetic inheritance, rather than mere environmental errors (Waddington *et al*., 1942; Bonduriansky and Day, 2009; Lee U. *et al*, 2022).

Phenotypic plasticity in adaptation: In epigenetics, *Phenotypic Plasticity* (West-Eberhard, 1989) stands out as a key mechanism where a single genotype can produce diverse phenotypes through epigenetic shifts. This ability, shaped by the interplay between genetics and epigenetics, empowers organisms to adapt to their environments.
Plasticity in Environmental Shifts: Research by Lande (2009) and Ancel (2000) demonstrates that plasticity is crucial during significant environmental changes, aiding in adaptation without losing fitness peaks (Pal and Milkos, 1999; Lee U.,2022).
Speed and Flexibility: Epigenetic changes facilitate rapid adaptation and play a pivotal role in adaptive flexibility, while the genome anchors flexibility, with the epigenome guiding trait expression. Unlike the slower

pace of genetic mutations, epigenetic changes quickly adjust to stimuli, allowing adaptation within a single generation (Angers *et al*., 2022).
The adaptive Value of Plasticity: Phenotypic plasticity, is the ability to adjust traits in response to environmental changes. These changes can be inherited across generations, suggesting a potential role in adaptive evolution (Sentis A., 2018; Lee U., 2022; Brooker R., 2022). Alligator weed (*Alternanthera philoxeroides*) research indicates that the portion of epigenetic patterns persists for at least 10 generations, suggesting a stable inheritance of epigenetic marks that support environmental adaptation (Wen S. *et al.* 2019).

Phenotypic plasticity and *The Baldwin effect*: Simpson, 1953 suggests, that selection favors the flexibility of phenotypes rather than their specific traits, offering a key advantage in diverse environments (Crispo, 2007; Angers et al., 2010).
Furthermore, *Evolutionary legacy*: Traits that persist may also reflect evolutionary history, where features shaped by past pressures remain, even if not fully optimized for present conditions. For instance, winged aphids, which increased in response to predation, continued to be prevalent even in the absence of predators (Sentis A. *et al*., 2018). Examples like photoperiodism in *Arabidopsis* and predator-induced defenses in *Daphnia* highlight the role of TEI in adaptation (Harris KD, *et al.,* 2012). In *Arabidopsis*, epigenetic regulation of flowering time allows plants to adapt to changing seasons, optimizing reproductive success (Liu S. *et al.,* 2023). *Daphnia's* predator-induced traits, like helmet and neck teeth, suggest potential TEI, though further research is needed to confirm effects beyond the F2 generations (Agrawal A. A. *et al.,* 1999; Santos KF *et al.,* 2005; Harris KD *et al.,* 2012). However, the true adaptive nature of phenotypic plasticity is still questioned, underscoring the need for a deeper exploration of its evolutionary significance (Angers *et al*., 2010; Sentis A. *et al.,*2018; Lind & Spagopoulou, 2018; Brooker R. *et al*., 2022; Koolenka & Skinner, 2024;).

Molecular Noise and Topological Constraints: Lee U. (2022) cites Ramos et al., 2015, highlighting that managing molecular noise involves intricate topological constraints, indicating that inherent molecular variability persists in living systems, even if is not immediately adaptive. *Trade-offs in Plasticity Evolution*: Offspring optimized for current conditions may struggle with future environmental changes (Lee U. *et al*, 2022). *Genetic-plastic conflict influences plasticity*. Genic-plastic conflict occurs when varying mutation rates between genic and non-genic controls plasticity. Genetic conflict and network architecture can either constrain or promote mutations, depending on factors like pleiotropy and genomic mutability (Lee U.*et al*, 2022). Epigenetic variation fuels phenotypic diversity, shaping individual fitness and providing material for natural selection to act upon (Crews *et al*., 2007).

Two of the highly discussed models explaining the evolution of phenotypic plasticity are: *Bet-Hedging*: Cohen, 1966 suggests, that phenotypic variability, even if not immediately advantageous, might enhance survival in unpredictable environments, acting as a buffer against sudden changes (Carja et al., 2014; Furrow and Feldman, 2014; Lee U. *et al*., 2022; Stajic D. *et al*., 2022).

The West-Eberhard model (Eberhard, 2003) outlines three steps for evolving plastic traits: *responding to environmental cues, producing new phenotypes,* and *achieving genetic accommodation through natural selection*. This model suggests plasticity speeds adaptation in changing environments but can be wasteful in stable ones. (Lee U. *et al.,* 2022)

Epigenetics in fluctuating vs. Stable environments: Lee U. *et al*., 2022 highlights the significance of TEI in evolution, especially in dynamic environments. In rapidly changing conditions, epigenetic inheritance could provide an "epigenetic advantage" over genetic mutations (Burggren W. *et al.*, 2016). In fluctuating environments, phenotypic plasticity is advantageous, aligning with the Baldwin effect. However, genetic assimilation requires stability for an environmentally induced phenotype to become fixed and selected (Crispo, 2007; Pal,1998). For this to

succeed, the environment must remain stable from the time of induction to its eventual selection (Lachmann and Jablonka, 1996). Constantly shifting conditions may favor retaining induced phenotypes across generations, offering "preparedness" for future challenges, and blending flexibility with sustained adaptability (Jablonka *et al*., 1995; Angers *et al*., 2010). Striking the right balance means thriving in the present while staying ready for what lies ahead (Lee U. *et al.*, 2022). While the permanence of epigenetic changes is debated, their role in initiating adaptive evolution is undeniable, helping explore alternative phenotypes and broadening ecological niches (Crews *et al*., 2007; Angers *et al*., 2010). The adaptive potential of TEI is evident in *C. elegans,* where short life cycles enable rapid adaptation likely in humans (Perez and Lehner, 2019).

As we advance in the review, we will delve into the impact of TEI on evolutionary biology, examining how it influences different life stages and developmental phases, and what it ultimately contributes as a driving force.

DNA methylation influences variation: Before diving deeper into the inheritance perspective, we'll focus on the role of DNA methylation in phenotypic variation and transgenerational inheritance, particularly the impact of cytosine-to-tyrosine transitions, particularly called tertiary epimutation (Kusmartsev V. *et al.,* 2020).

Increased Mutation Rates: Elevated cytosine methylation can lead to higher mutation rates (Schorderet DF *et al*., 1992; Bateson P. *et al*., 2012; Burggren W. *et al*., 2016).

DNA Repair Inheritance: Methylation can hinder DNA repair mechanisms, leading to permanent genetic alterations (Meng H. *et al.*, 2015; Burggren W. *et al.*, 2016). *Transgenerational Effects*: Environmentally induced DNA methylation changes can be passed through sperm, leading to heritable mutations, as seen in studies on atrazine exposure in rats (McBirney M. *et al*., 2017; Legoff L. *et al*., 2019; Kusmartsev V. *et al*., 2020). Beyond DNA methylation, other epigenetic mechanisms, like histone modifications, also influence genetic variation.

The stability impact of these epimutations on evolution depends on their genomic context and species (Angers *et al*., 2010; Schuster-Böckler and Lehner, 2012; Graaf *et al*., 2015; Kronholm I. *et al*., 2016; Batte *et al*., 2017; Lind M.I. *et al*., 2018; Stajic D. *et al*., 2020; Fitz-James M. *et al*., 2022; Vogt G. *et al*., 2023).

DNA methylation acts as a crucial defense against **transposable elements**, which can move within the genome and cause mutations. By silencing these elements, methylation safeguards genomic stability and upholds heritable integrity, with profound evolutionary impact (Suzuki MM *et al.,* 2008).

While talking about DNA methylation patterns, not just hyper- or hypomethylation, determine gene activation or repression. In X chromosome inactivation, promoter methylation silences genes, but the active X has more gene body methylation, suggesting this pattern sustains gene activity rather than repressing it (Weaver ICG *et al.,* 2004; Hellman A. *et al.,* 2007)

Epigenetic erasure and Transgenerational Inheritance: The erasure of DNA methylation during embryogenesis is not absolute, leaving traces that impact transgenerational inheritance. While most DNA methylation patterns are reprogrammed during development, some regions retain these marks, potentially carrying epigenetic information across generations (Richards *et al*., 2006; Hitchins *et al*., 2007; Skinner MK *et al*., 2011, Korolenko A. *et al*., 2024). This incomplete erasure is more likely in genomic regions with low CpG density, whereas high-density CpG islands, associated with housekeeping genes, are typically erased. The selective retention of methylation appears to be a regulated process, influenced by specific factors and their timing (Moore LD, *et al*., 2013; Nilson EE *et al*., 2022; Mammar M. *et al*., 2023). As an example, In Zebrafish, paternal DNA methylation is retained throughout embryogenesis, while maternal patterns are gradually erased, allowing paternal epigenetic marks to be inherited and integrated into the maternal genome early in development (Jiang *et al.,* 2013). Although the

mechanisms of incomplete erasure are still under investigation, these retained methylation marks may have significant implications for phenotypic outcomes across generations. the extent to which these variations are inherited remains unclear (Jablonka *et al*., 2009; Kremsky, I. *et al*., 2020; Fitz-James M. *et al*., 2022). **Genomic imprinting**, where gene expression depends on parental origin, supports TEI. Histone modifications in sperm can be passed to offspring, influencing gene expression and enabling the inheritance of environmentally induced traits across generations (Wilkins JF *et al.,* 2005). The Dutch Hunger Winter of 1944-1945 offers a unique insight into the long-term exposure of prenatal famine exposure. Early development famine exposure led to significantly lower imprinted IGF2 gene methylation a decade later compared to their unexposed same-sex siblings (Lumey LH, *et al.,* 2007; Vaiserman A. *et al.,* 2021).

Parental Epigenetics and Adaptive Inheritance: Maternal and paternal epigenetics, influenced by diet and environmental exposures, play a crucial role in adaptation across generations (Korolenko *et al*., 2024).
Dietary Influence: Paternal diets can cause heritable metabolic changes in offspring. For instance, a high-fat diet in male rats led to glucose issues in their descendants, offering survival advantages in fluctuating environments (Ng SF *et al*. 2010; Burggren *et al.* 2016).
Environmental Exposures: Exposure to Toxins like glyphosate in rats can induce health issues in subsequent generations. Altered sperm methylation suggests glyphosate triggers adaptive epigenetic defenses.(Kubsad D. *et al.,* 2019; Korolenko, 2024).
Behavioral Conditioning: Maternal care, such as licking in rats, can lead to epigenetic change in offspring, influencing their stress responses and social behavior, vital for survival (Champagne A. *et al*., 2008; Vogt G. *et al*., 2023). Understanding adaptive evolution through epigenetics requires considering complexities beyond direct paternal transmission, including microbiome transfer and cryptic maternal effects (Perez and Lehner, 2019; Dion A., 2022)

Inbreeding Depression and Epigenetics Dynamics: Inbreeding can alter epigenetic marks, leading to disrupted gene expression.
Inbreeding depression & Epigenetic change: Inbreeding depression, marked by reduced viability in inbred organisms, influences epigenetic patterns significantly.
Inbreeding depression and alternate epigenetic mechanisms: This phenomenon often results in loss of cytosine methylation in models like *Drosophila* and *C.elegans*, revealing how inbreeding stress drives changes in epigenetic processes (Pennisi E. *et al*., 2011; Vergeer P. *et al*., 2012; Deepashree S. *et al*., 2018).
Interpreting Epigenetics Changes: The absence of cytosine methylation in inbred models, might stem from inbreeding depression rather than standard biological processes. These alterations highlight the need for caution when generalizing epigenetic features observed in inbred organisms (Korolenko A. *et al.*, 2014).
Evolutionary Implications: Epigenetics inheritance's role in inbreeding depression suggests it could be crucial in evolution and ecology. This indicates that epigenetic changes may offer an adaptive advantage amidst reduced genetic diversity due to inbreeding (Cheptou PO *et al*., 2013).

Epigenetics inheritance and the concept of Canalization: Canalization, Waddington (1942), refers to an organism's ability to maintain a stable phenotype despite genetic or environmental disturbances (Nanney *et al*., 1958; Walsh MR. *et al*., 2015). His *Drosophila* experiments revealed that ether and heat shock-induced wing changes persisted for generations, even after the stressors were removed (Waddington H., *et al.,* 1940; Waddington H., *et al.,* 1942). A concept that underscores how development tends to follow specific pathways, resisting deviations caused by genetic variability or environmental changes. (Jablonka *et al.*, 2009; Ashe A *et al*., 2012; Korolenko A. *et al*., 2024). Epigenetic inheritance plays a pivotal role in this process by buffering against environmental variations and ensuring

developmental consistency (Nanney *et al*., 1958; Whitelaw NC *et al*., 2008; Johannes F. *et al*, 2009).

Stabilizing phenotypic variation: Jablonka and Raaz (2009), states that epigenetics inheritance is influenced by genetic background and environmental factors, leading to varying levels of stability. However, epigenetics enables organisms to maintain consistent traits across generations, even amidst genetic mutations or environmental shifts when inherited stably (Johannes F. *et al*., 2009; Lee U. *et al*., 2022;).

Rapid Adaptation without genetic change: Epigenetic mechanism offers a crucial advantage for organisms with limited genetic diversity, enabling adaptation to new environments without solely depending on genetic mutations. These changes can revert once the environmental pressures subside, offering a flexible response mechanism that enhances survival (Johannes F. *et al*., 2009; Angers *et al*., 2010).

"Epigenetic Potential" as a Heritable Trait: phenotypic plasticity, governed by epigenetic mechanisms, can itself be subject to natural selection. Populations in stable environments might exhibit stronger canalization, while those in fluctuating ones may display greater epigenetic (Walsh MR *et al*., 2015; Vellichirammal NN *et al*., 2016; Burggren W. *et al*., 2016; Sentis A. *et al*., 2018).

Thibert-Plante and Hendry (2011) demonstrated that adaptive plasticity evolves rapidly when populations disperse across varied environments, enhancing the ability to colonize drastically different habitats (Smith G. *et al.*, 2013).

Phenotypic plasticity and Genetic assimilation: Long-term environmental pressures can transform these phenotypic changes into permanent, heritable genetic adaptations which are genetic assimilation, or fixation, of a trait. (Waddington, 1953; Debat & David, 2001; Jaenisch & Bird, 2003; Pigliucci *et al.,* 2006; Angers *et al*., 2010; Lee U. *et al.*, 2022). After colonizing new environments, populations may face divergent selection pressures on traits different from those that initially enabled their

survival, potentially leading to genetic accommodation or assimilation (Smith G. *et al.*, 2013).

The persistence of TEI across generations may be driven by factors like: Alterations in master genes like the pluripotency gene Pou5f1, with broad effects on gene regulation (Hao C., *et al.,* 2016), Epigenetic memory preservation through developmental reprogramming by TET1 (Hill, P.W.S., *et al.,* 2018) & Small RNAs acting as carriers of epigenetic information, exemplified by paramutation (Rassoulzadegan M., *et al.,* 2006; Chandler VL, *et al.,* 2007). Vogt G. (2024) cites studies on *Daphnia*, *C. elegans*, *Arabidopsis*, and *Chlamydomonas* which have shown epigenetic effects persisting for up to 200 generations. Despite these insights, more data is needed to fully grasp TEI's long-term persistence. While evidence for TEI impacting across a few generations is emerging, research extending beyond this is still sparse, exploring TEI beyond F3 generation across more species (Anastasiadi D. *et al.,* 2021; Burggren WW., *et al.,* 2010). Addressing these gaps will deepen our understanding of TEI's role in inheritance, adaptation, and evolution.

Epigenetics in Speciation

We have so far discussed how the environment shapes phenotypic plasticity and a form of inheritance that is distinct from genetic material, but crucial for adaptation- epigenetic inheritance. In the following, we will consider how these alterations can stimulate speciation by creating heritable differences that accommodate reproductive isolation. Therefore, with a detailed examination of incipient diverged species still being possible, Stankowski & Ravinet (2021) thus constructed and applied simulation models to ultimately provide the first necessary leap forward on what role, if any, may epigenetic variation contribute to speciation. Just to expand (we are talking about speciation here exclusively concerning bifurcation at the genetic loci, not epigenetic loci) (Greenspoon PB. *et al.*, 2022). Environmental induction of epigenetic marks may drive the

evolution of phenotypic plasticity, potentially facilitating ecological speciation (Pal & Miklós, 1999). Mayr E. 2001, presents a scenario where a genetically and epigenetically uniform species becomes separated by factors like geographic isolation or habitat fragmentation, leading to ecological divergence. The initial divergence, driven by epigenetic modifications, can then be reinforced by genetic changes over time, leading to more stable reproductive isolation (Pfenning DW. et al, 2010). The synergy between genetics and epigenetics shapes phenotypes, offering profound insights into the drivers of ecological Speciation. Phenotypic divergence primarily driven by transient modification might not represent a stable evolutionary phenomenon. On the other hand, higher stability of epigenetic markers also speeds up speciation except when there is no migration and epimutation is unbiased (Philip B.et al,2022).

As populations of a common ancestor diverge, gene flow diminishes, setting the stage for reproductive barriers and ultimately inability to interbreed (Dobzhansky *et al*, 1937). The barrier to gene flow produced by transgenerational epigenetic modifications functions analogously to selection against genetic variants, creating a localized reduction of gene flow around the epigenetic locus. The one that underpins speciation, referred to as reproductive isolation, comes about when barriers block the movement of genes between populations enabling them to evolve into different species (Vogt G. *et al,* 2015; Benjamin F. *et al*, 2012; Planidin NP *et al,* 2022). Populations may diverge to such a degree that they become reproductively isolated and ultimately speciation may result (David W.P et al, 2013).

Epigenetic modifications can act as drivers of evolutionary divergence by influencing adaptive traits, reducing gene flow, and accelerating the separation of populations into distinct species. Simulation models suggest that "adaptively biased epigenetic induction" can accelerate or slow down speciation, depending on the interaction between genotype, epigenotype, and phenotype (Greenspoon et al., 2022).

Epigenetic Induction: A double-edged sword in Speciation, particularly when it's adaptively biased, can have both positive and negative effects on the rate of speciation.

1. Epigenetic Variation as a Potential Accelerator of Speciation: Epigenetic modifications can influence adaptive traits, decreasing gene flow by reducing migrant and hybrid fitness, and accelerating divergence (Greenspoon PB *et al,*2022). Epigenetic variation can foster reproductive isolation by shaping traits linked to sexual selection, habitat choice, & mating behavior, leading to behavioral isolation and reduced gene flow (Mendelson TC. *et al*, 2003). Additionally, epigenetic drift, much like genetic drift, can also introduce random differences between populations, potentially driving speciation (Pfening *et al.*, 2013).

Epigenetic Modifications as Drivers of Divergence: Populations experience different ecological conditions, such as varying resource availability, climates, or predation pressures, they may undergo divergent epigenetic modifications that fine-tune their gene expression to better adapt to those environments (Smith G. *et* al, 2013; Vernaz G. *et* al, 2021; Vernaz G. *et al,* 2022). Epigenetic modifications with a considerable portion of species-specific epigenetic divergence potentially being established early in development when genetic changes lag. Early-life programming of distinct epigenetic patterns may contribute to the striking phenotypic diversity. For example, studies of cichlid fish from Lake Malawi (Vernaz G. *et al*, 2021) showed that ecologically divergent species exhibit distinct DNA methylation patterns, highlighting the role of epigenetics in adaptive diversification even without major genetic differences. (Vernaz G. *et al*, 2021; Benjamin F. *et al*, 2012; Vernaz G. *et al,* 2022; Smith TA. *et al*, 2016). Similarly, a study by Smith TA (2016) on *Etheostoma* darters found that within-species populations vary more in their methylomes than genomes, highlighting the key role of epigenetic shifts in the early stages of species divergence. Furthermore, research on crater lake cichlid fish (*Astatotilapia calliptera*) has shown extensive methylome divergence between ecomorphs inhabiting different depths and

having different diets, despite limited genetic differentiation (Vernaz G. *et al,* 2022).

Divergence hitchhiking, though often framed in terms of genetic variation, also extends to epigenetic modifications, which helps explain how selection acting on specific genes can drag along nearby neutral loci, creating "genomic islands" of reduced gene flow and enhanced differentiation (Feder JL *et al,* 2010; Via S. *et al,* 2008; Smith G. *et al*, 2013). Particularly in ecological speciation, divergent selection of traits for environmental adaptation reinforces these genomic islands (Smith G. *et al*, 2013; Feder JL *et al,* 2010). Emerging research (Vernaz G. *et al*, 2021; Vernaz G. *et al,* 2022) suggests that methylome divergence underpins epigenetic adaptation (Lauss K. *et al*, 2018). Epigenetic modifications, influence mutation rates and the recombination landscape, shaping genetic divergence patterns (Smith G. *et al*, 2013; Smith TA *et al,* 2016). Methylated cytosines, for example, are more prone to C>T mutations, while heterochromatin formation can suppress recombination (Smith G. *et al,* 2013). These interactions between epigenetic and genetic variation contribute to the patchwork of divergence across genomes. Although epigenetic changes are dynamic and reversible (Groszmann M *et al*, 2013; Greenspoon PB *et al,* 2022), they can initiate reproductive isolation. Over time, however, genetic differences must accumulate for long-term species persistence (Smith G. *et al,* 2013; Liu B. *et al,* 2003). In this way, epigenetically driven divergence hitchhiking can create favorable conditions for genetic differentiation, accelerating the speciation process (Via S *et al,* 2008; Feder JL *et al*, 2010; Greenspoon PB *et al,* 2022).

Epigenetics effects on gene flow: Epigenetic variations can serve as barriers to gene flow by reducing the fitness of **migrants and hybrids**, functioning as postzygotic isolating mechanisms (Michalak et al., 2008; Ishikawa et al., 2009; Smith et al., 2013; Greenspoon et al., 2022). Migrants arriving in a new environment with an epigenetic profile suited to their original habitat may struggle to adapt, leading to lower survival or

mating success, thus limiting their genetic contribution to the recipient population (Greenspoon et al.,2022). Environmental pressures in the new habitat may favor different epigenetic profiles, and if these profiles are maladaptive, the fitness of the migrants is compromised, which reduces gene flow (Vernaz et al., 2022; Andrew et al., 2004; Greenspoon et al., 2022).

Greenspoon et al. (2022) explore this through mathematical models, showing how epigenetic induction before migration can reduce fitness, thereby accelerating speciation.

Migrants adapted to one environment often exhibit reduced fitness in a different one, a key factor in ecologically dependent reproductive isolation (EDRI) (Butlin et al., 2010; Andrew et al., 2004). For instance, the evolution of sticklebacks exemplifies how adaptation to different environments lowers the survival rate and can drive reproductive isolation. (Herman, J.J. *et al.,* 2016; Thibert-Plante et al., 2011; Andrew et al., 2004). Ultimately, epigenetic profiles adapted to one environment may become maladaptive in another, limiting gene flow and fostering conditions that contribute to speciation (Greenspoon et al., 2022).

The timing of epigenetic induction, relative to migration, can significantly impact speciation. Epigenetic changes and phenotypic plasticity can shape the process of speciation, particularly depending on whether they happen before or after migration. If these changes occur after migration, the organisms can adapt to their new environment, increasing their chances of survival and reducing barriers to mating, which may slow the speciation process. On the other hand, if the changes occur before migration, the organisms are well-suited to their original environment, but when they move to a new habitat, their traits may no longer be advantageous. This mismatch between traits and environment can lead to lower fitness in the new setting, increasing reproductive isolation and promoting speciation (Thibert-plante X. *et al,* 2011; Greenspoon PB. *et al,* 2022)

Similarly, **hybrids** born from parents with divergent epigenetic backgrounds may experience fitness reductions due to epigenetic

incompatibilities (Brekke et al., 2016; Michalak et al., 2008; Kimatu et al., 2010; Smith et al., 2013). This is particularly evident in mammals, where disrupted genomic imprinting can lead to extreme growth defects (Brekke et al., 2016; Farideh et al., 2022). In deer mice, *Peromyscus* for instance, hybrid offspring show significant size differences depending on the direction of the cross, a result of misregulated imprinted genes (Vrana *et al.,* 1998; Michalak et al., 2008).

Epigenetic changes can also influence **hybrid vigor** or heterosis, where hybrids display increased biomass due to altered gene expression patterns, extensively used in crops such as maize (*Zea mays*), rice (*Oryza sativa*), canola (*Brassica napus*), and sorghum (*Sorghum bicolor*) (Greaves IK. *et al,*2015). This phenomenon is often driven by DNA methylation and trans-chromosomal methylation, which modifies gene expression between parental alleles (Lauss K. et al, 2018; Greaves et al., 2015; Groszmann et al., 2013). Additionally, small RNAs, such as 24-nucleotide siRNAs, play a critical role in shaping hybrid gene expression, further contributing to hybrid vigor (Greaves et al., 2015). On the flip side, epigenetic incompatibilities can cause detrimental effects in hybrids, such as plant hybrid necrosis, characterized by cell death and stunted growth (Kimatu et al., 2010). Hybridization can also activate transposons, triggering rapid genomic changes and reinforcing reproductive isolation, thus facilitating speciation (Kimatu et al., 2010).

As the evolution of reproductive isolation can accompany ecological divergence (i.e., ecological speciation, Nosil 2012), both the probability and rate of speciation may be reduced by gene flow. Epigenetic variation could kick-start the evolution of reproductive isolation like phenotypic plasticity (Pfennig et al. 2010).

Epigenetic variation, a crucial step in speciation influencing reproductive traits and mating behaviors can contribute to **reproductive isolation** (Ledón-Rettig CC *et al,*2012; Pfennig DW. *et al,* 2010; Thibert- Plante X. et al,2011; Smith TA. *et al,* 2016; Andrew H. *et al,* 2004). These changes may influence both pre-mating and post-zygotic barriers. For instance, epigenetic modifications can affect traits like coloration or pheromone

production, leading to assortative mating, where individuals with similar epigenetic profiles are more likely to reproduce together, thereby reducing gene flow between diverging populations (Benjamin, 2012; Smith, 2016). On the post-zygotic side, mismatches in methylation patterns or genomic imprinting can lead to hybrid sterility or inviability, strengthening reproductive barriers (Kimatu et al., 2010; Ondrej M. et al, 2009, Ishikawa R., 2009; Smith G., 2013 and Pfennig DW. et al, 2013). Empirical evidence (Smith TA. 2016; Smith G. 2013) supports the role of epigenetics in reproductive isolation. While epigenetic changes can initiate and contribute significantly to reproductive isolation, the long-term stability of distinct species often requires the accumulation of genetic differences (Pfenning DW. et al, 2013; Via S., 2008; Vernaz G., 2022; Greenspoon, 2022). This can occur through **genetic assimilation**. Epigenetics, by influencing gene flow and driving divergence, can set the stage for genetic assimilation (Pal & Miklos, 1999).

We have previous findings that both divergent natural selection and condition-dependent sexual selection promote speciation (Van Doorn et al, 2009). Epigenetic changes could act as a bridge between (selection pressures) natural and sexual selection during speciation. If epigenetic modifications influence genes underlying both ecological adaptation and reproductive traits. This linkage could accelerate speciation by aligning ecological divergence with assortative mating, as individuals with the advantageous epigenetic state would be favored by both natural and sexual selection (Jablonka, 2012b; Ledón-Rettig et al., 2013; Smith G. *et al,* 2013)

2. Epigenetic Variation as a Potential Decelerator of Speciation*:* When genetic changes dominate, especially in traits influenced by both genes and epigenetics, speciation may slow with an increase in gene flow. This is because epigenetics can offer an alternative route to adaptation, easing pressure on genetic evolution (Greenspoon PB *et al.,* 2013). Epigenetic changes can lead to genetic accommodation, fixing induced traits genetically. This can drive divergence but may also slow the genetic

differences needed for speciation (West- Eberhard *et al.,* 2003; Pfennig DW *et al.,* 2010). Gene flow can hinder divergence by *homogenizing* populations, spreading beneficial alleles, and complicating speciation (Greenspoon PB *et al.,* 2022). As Charlesworth B. & Charlesworth D. (2010), describes *Migration-selection balance*, maintains habitat-specific alleles but can slow speciation by reintroducing alleles and impeding divergence.

Epigenetics and the Balance: Heritable and stable epigenetics modifications can drive divergence by stabilizing new phenotypes, influencing the balance between gene flow and selection (Greenspoon PB. *et al.,* 2022). Epigenetics plays a vital role in shaping this balance with adaptive epigenetic induction either accelerating or decelerating speciation amid gene flow. This is due to epigenetics mechanisms offering rapid and flexible responses to environmental pressures (Shea N. *et al.*, 2011; Smith G. *et al.,* 2013).

The Intertwined Roles of Epigenetic Modifications and Genomic Elements in Driving Speciation: Transposable elements (TEs), capable of moving and replicating within a genome, are often perceived as drivers of genomic instability. They achieve this by introducing mutations and causing chromosomal rearrangements, both of which can potentially lead to reproductive isolation and, consequently, speciation (Rebollo R. *et al*, 2010; Rebollo R.et al, 2008; Fablet et al, 2009). In *Drosophila buzzatii*, the insertion of a TE causes an inversion on a chromosome, potentially contributing to reproductive isolation (Brown JD et al., 2010).

Chromosomal speciation, **Genetic Conflict, and Epigenetics:** Chromosomal speciation arising from changes like inversions or translocations – can be indirectly influenced by TEs. The activation of TEs, often regulated by epigenetic mechanisms, can trigger these chromosomal rearrangements (Geurts et al., 2006; Zhang et al., 2009). Rebollo R. *et al*, 2010 have provided some examples referring to the same,

the emergence of the invasive species *Spartina anglica*, characterized by significant genomic and epigenetic remodeling, exemplifies this interplay between TEs and chromosomal changes in speciation (Parisod et al., 2009). As observed by Ferree and Barbash, 2009 in Drosophila hybrids, hetero-chromatin, which is highly enriched in TEs and other repeats, also seems to play a role in speciation. Furthermore, bursts of transposition are not always associated with rapid speciation as no speciation has been observed in invaded natural populations of D. melanogaster (Robello R. *et al,* 2010). Rearrangements may reduce gene flow by suppressing recombination, allowing for the accumulation of incompatible alleles or locally adapted genes. This process can be influenced by genetic conflicts, such as meiotic drive, where certain genetic elements bias their transmission to offspring, leading to the fixation of rearrangements that might otherwise be detrimental (Malik HS et al, 2009; Malik HS, 2002).

Genetic Conflict and Epigenetics: The inherent conflict between selfish genetic elements, such as TEs, and the host genome often fuels the evolution of epigenetic mechanisms to suppress the activity of these elements (Michalak P. et al, 2008; Robello R. et al, 2010). These epigenetic mechanisms, including DNA methylation and histone modifications, aim to maintain genomic stability. However, hybridization or environmental stress can disrupt these mechanisms, potentially reactivating TEs (Ishikawa R. et al, 2009). In *Drosophila*, specific crosses between wild-caught males and laboratory-strain females result in hybrid dysgenesis, characterized by the mobilization of TEs (Girard and Hannon, 2008).

Epigenetics and Centromere Activity: Centromeres are often composed of repetitive DNA sequences. The centromere drive hypothesis suggests that these repetitive elements can evolve rapidly due to genetic conflict, leading to the preferential transmission of one parental chromosome over the other during meiosis (Brown JD et al, 2010). Neocentromeres, arising from epigenetic changes at new chromosomal locations, exemplify this

influence. The repositioning of centromeres through neocentromere formation can lead to reproductive isolation and speciation (Marshall OJ. et al,2008). For instance, in monkeyflowers (*Mimulus guttatus*), where a specific allele exhibits meiotic drive associated with divergent centromere repeats, contributes to reproductive isolation and speciation (Kinser TJ. et al, 2021).

Epigenetic Drift and Cryptic Species: Similar to genetic drift, stochastic changes in epigenetic marks could contribute to divergence. Such divergence, especially in ecologically relevant traits, might lead to the formation of cryptic species – morphologically similar but reproductively isolated groups (Fitzpatrick BM. et al, 2012). For example, Shah JM. et al, 2021, mentioned if an epimutation has occurred and changed the blooming time of a flower from day to night, it has created a reproductive barrier between this mutant and the rest of the population. Over the years, this mutant may also flourish and evolve into a new species that doesn't breed with its ancestral type in natural conditions. Turbek, 2021 reported an example where two different species of Seedeater birds, the Iberá Seedeater (*Sporophila iberaensis*) and Tawny-bellied Seedeater (*S. hypoxantha*), which lived in the same territory, have look-alike females, yet evolved into different species due to differences in the plumage color pattern of males and their song.

Epigenetic Variation and Allopolyploid Fitness: Allopolyploidy, often resulting from hybridization between species, frequently involves substantial epigenetic changes. Allopolyploidization can induce significant genomic shock (McClintock et al, 1984) leading to widespread changes in gene expression and epigenetic reprogramming (Yoo et al., 2013; Kinser TJ. et al, 2021; Bomblies K. et al, 2007). These changes can affect hybrid fitness and contribute to reproductive isolation between allopolyploids and their diploid progenitors. For instance, in *Arabidopsis suecica*, a natural allotetraploid, extensive non-additive changes in gene expression and epigenetic silencing have been observed (Wang J et al, 2004; Madlung A. et al, 2005). Furthermore, epigenetic changes may act

as a reservoir of heritable variation, influencing the evolutionary trajectory of allopolyploids long after their formation (Liu B. et al, 2003; Rieseberg, 2001). Polyploidy often leads to immediate reproductive isolation between polyploids and their diploid progenitors (Shah JM et al, 2022).

Paleoepigenomics and speciation: By comparing ancient epigenomes to those of contemporary populations, researchers can gain insights into the evolutionary history of epigenetic variation and its potential role in speciation (Brown JD., et al, 2010; Niiranen L. et al, 2022). A study by Gokhman and colleagues analyzed methylation maps from Denisovan and Neanderthal samples, comparing them to those of modern humans. They found over 1,000 differentially methylated regions (DMRs) and these DMRs were located near genes involved in various biological processes (Gokhman D. et al, 2014; Gokhman D. et al, 2020).
For example, hypermethylated regions within the *HOXD* gene cluster, involved in limb development, might explain the shorter limbs observed in Neanderthals compared to modern humans (Zakany, J et al, 2007; Weaver, T.D. et al, 2009). Some human-specific DMRs identified in these ancient specimens were also observed in Gambian children conceived during periods of food scarcity (Dominguez-Salas, P. et al, 2014; Waterland, R.A. et al, 2010). This suggests that dietary changes can have a significant impact on the human methylome and that these effects can persist across generations, as we discussed in earlier sections. Furthermore, epigenetic effects are responsible for human reproductive limitations in response to food scarcities (Lubinsky M. *et al,* 2018). Variation in DNA methylation patterns can lead to differences in gene expression, phenotypic variation, and consequently, speciation.

Three-Dimensional Genomics and Speciation: Three-dimensional genomics explores the spatial arrangement of the genome within a cell nucleus. This spatial organization is crucial for gene regulation and recombination. It is conceivable that changes in 3D genome structure could contribute to reproductive isolation and speciation. For instance, if

chromosome territories or chromatin loops differ between species, they might impact meiotic pairing or recombination frequencies, potentially contributing to speciation (Berdan E.L. *et al*, 2023; Mohan AV *et al,* 2024).

CONCLUSION

The Extended Evolutionary Synthesis provides a broader and more integrative framework for understanding evolutionary change, bridging the gap between genetics, epigenetics, and developmental processes. Unlike the Modern Synthesis, which emphasizes genetic determinism, EES highlights the interactive and reciprocal nature of evolution, where phenotypic changes can drive genetic modifications over time. Studies on epigenetic inheritance, such as those on Darwin's Finches, illustrate the profound impact of epigenetic modifications in shaping evolutionary outcomes.

Additionally, the role of transgenerational epigenetic inheritance in adaptive evolution and speciation underscores the importance of non-genetic inheritance in shaping biodiversity. TEI facilitates rapid adaptation to environmental pressures by allowing epigenetic modifications to persist across multiple generations. The integration of TEI into evolutionary theory enhances our understanding of phenotypic plasticity, reproductive isolation, and ecological speciation. Moreover, epigenetic divergence, hybrid incompatibilities, and divergence hitchhiking contribute significantly to the formation of new species. The study of paleoepigenomics and three-dimensional genomics offers new perspectives on how epigenetic modifications have historically influenced speciation events.

While EES does not entirely reject MS, it expands upon its limitations by incorporating additional layers of inheritance and adaptation. Future research should focus on exploring the stability of epigenetic modifications across generations, their role in long-term speciation, and their interaction with genetic mutations. By integrating epigenetics into

evolutionary theory, EES provides a dynamic and comprehensive perspective on how species evolve and adapt in changing environments.

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