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Review Article

Epigenetics and its Implications in Animal Breeding and Livestock Production: Mechanisms, Environmental Interactions and Prospective Applications

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ABSTRACT

Epigenetic regulation plays a central role in shaping how livestock genomes respond to environmental and developmental signals without altering the underlying DNA sequence. In recent years, growing evidence has demonstrated that epigenetic mechanisms contribute significantly to variation in economically important traits, including growth performance, reproduction, immunity, productivity, and environmental adaptability. Despite this expanding body of knowledge, the practical integration of epigenetic information into livestock breeding programs remains limited. This narrative review synthesizes current research on epigenetic mechanisms in livestock species and critically examines their emerging applications in animal breeding and production systems. A comprehensive literature search was conducted using PubMed, Scopus, and ScienceDirect, with emphasis on studies published between 2010 and 2024 that investigated epigenetic processes, environmental interactions, and breeding-related outcomes in farm animals. The evidence indicates that DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs function as dynamic regulatory interfaces linking the genome to external factors such as nutrition, thermal stress, and management. Environmental exposures during sensitive developmental periods can induce persistent epigenetic changes, some of which may be transmitted across generations and influence offspring phenotypes. Epigenome-wide association studies have identified epigenetic markers associated with production traits, disease resistance, and climate resilience, highlighting their potential value in complementing genomic selection. In parallel, advances in CRISPR-based epigenome editing technologies now enable targeted modulation of gene expression without permanent genetic modification, opening new avenues for precision livestock improvement. Although challenges related to cost, tissue specificity, and incomplete understanding of epigenetic heritability remain, rapid technological progress and declining sequencing costs are improving feasibility. Overall, integrating epigenetic information into breeding strategies holds considerable promise for enhancing selection accuracy, sustainability, and adaptive capacity in livestock production under changing environmental conditions.

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1.0 INTRODUCTION

The concept of epigenetics was first introduced by Conrad Hal Waddington in the mid-twentieth century (Waddington, 2012) to describe the processes through which genetic information interacts with developmental and environmental factors to produce observable phenotypes. Since then, epigenetics has evolved into a well-established field concerned with heritable changes in gene activity that occur without modification of the DNA nucleotide sequence (Bird, 2007; Feil & Fraga, 2012). These regulatory processes provide organisms with a mechanism for integrating environmental cues into stable yet reversible patterns of gene expression, thereby allowing phenotypic flexibility while preserving genomic integrity (Jablonka & Raz, 2009).

In livestock species, epigenetic regulation has gained increasing attention as a key contributor to variation in traits of economic and biological importance (Ibeagha-Awemu & Zhao, 2015; González-Recio et al., 2015). Characteristics such as growth rate, feed efficiency, milk yield, reproductive performance, disease resistance, and tolerance to environmental stressors are shaped not only by DNA sequence variation but also by epigenetic modifications that influence when, where, and to what extent genes are expressed. Accumulating evidence from cattle, sheep, pigs, and poultry demonstrates that epigenetic mechanisms respond dynamically to nutrition, management practices, thermal conditions, and health challenges, often with lasting consequences for animal performance and welfare.

At the molecular level, epigenetic regulation in mammals is mediated through several interconnected mechanisms, including DNA methylation, post-translational modification of histone proteins, chromatin remodeling, and the action of non-coding RNAs (Bird, 2002; Kouzarides, 2007; Esteller, 2011; Bannister & Kouzarides, 2011). Together, these processes determine chromatin structure and accessibility, thereby modulating transcriptional activity across the genome. Importantly, epigenetic states are not static; they change across developmental stages and can be reprogrammed in response to environmental inputs, particularly during critical windows such as gametogenesis, embryonic development, and early postnatal life.

Conventional livestock improvement programs have achieved substantial genetic gains through selective breeding and, more recently, through genomic selection approaches that use dense DNA marker information to predict breeding values (Meuwissen et al., 2001; VanRaden, 2008). While genomic selection has markedly improved the accuracy and rate of genetic progress, sequence-based models typically explain only a proportion of the observed phenotypic variation (Manolio et al., 2009). This so-called "missing heritability" is especially pronounced for complex traits that are strongly influenced by environmental conditions. Epigenetic variation has therefore been proposed as a complementary source of information that may help bridge the gap between genotype and phenotype, particularly for traits characterized by developmental plasticity and genotype-by-environment interactions (González-Recio et al., 2015; Gutiérrez-Gil et al., 2022).

An additional dimension of epigenetic regulation with particular relevance to livestock production is the possibility of epigenetic inheritance across generations (Guerrero-Bosagna & Skinner, 2012; Skinner, 2015). Although extensive epigenetic reprogramming occurs during gametogenesis and early embryogenesis, certain epigenetic marks can escape complete erasure and influence offspring phenotypes. Experimental and observational studies suggest that environmental exposures experienced by parents such as nutritional status, thermal stress, or health challenges may leave epigenetic imprints that affect growth, metabolism, and resilience in subsequent generations. While the extent and stability of such transgenerational effects remain under active investigation, their potential implications for breeding strategies are considerable.

Technological advances over the past decade have transformed the study of epigenetics in livestock. High-throughput sequencing techniques, including whole-genome bisulfite sequencing, chromatin immunoprecipitation sequencing, and RNA sequencing, now enable genome-wide profiling of epigenetic marks at increasingly affordable costs (Lister et al., 2009; Zhou et al., 2018). These tools have facilitated the

identification of epigenetic variants associated with production traits and adaptive responses, as well as the characterization of tissue- and stage-specific epigenomic landscapes. In parallel, the development of CRISPR-based epigenome editing systems has introduced the possibility of precisely modifying gene expression through targeted manipulation of epigenetic marks without altering DNA sequence, opening new avenues for functional studies and precision breeding (Hilton et al., 2015; Liu et al., 2016; Pulecio et al., 2017).

Despite these advances, the application of epigenetic knowledge in practical livestock breeding remains in its early stages. Challenges related to cost, tissue specificity, data integration, and incomplete understanding of epigenetic stability and heritability continue to limit widespread adoption. Consequently, there is a need for critical synthesis of existing research to clarify the biological significance of epigenetic variation, evaluate its potential utility in breeding programs, and identify key gaps that must be addressed to enable effective implementation.

This review provides a comprehensive overview of epigenetic mechanisms in livestock species, with particular emphasis on their interaction with environmental factors, roles in reproduction and development, and emerging applications in breeding and production systems. By integrating findings across molecular biology, animal genetics, and production science, this article aims to highlight both the opportunities and limitations of incorporating epigenetic information into livestock improvement strategies and to outline future directions for research and application in this rapidly evolving field.

2.0 Materials and Methods

This review article was developed through an extensive literature survey using databases such as PubMed, Scopus, and ScienceDirect. The review prioritizes recent studies from 2010–2024 focusing on epigenetic mechanisms, environmental effects, and applications in livestock production systems.

2.1 Fundamental Epigenetic Mechanisms in Livestock

Epigenetic regulation in livestock operates through a set of interrelated molecular processes that collectively determine how genetic information is expressed across tissues and developmental stages. Unlike DNA sequence variation, which is relatively stable across an individual's lifetime, epigenetic marks are dynamic and responsive to both internal developmental cues and external environmental conditions. Understanding these mechanisms is therefore essential for interpreting phenotypic variation in livestock and for assessing how epigenetic information might be leveraged in breeding and management systems.

2.2 DNA Methylation

DNA methylation is the most extensively characterized epigenetic modification in mammalian genomes and has been studied widely in livestock species (Jones, 2012; Smith & Meissner, 2013). It involves the covalent addition of a methyl group to the fifth carbon of cytosine residues, predominantly within cytosine–guanine dinucleotide (CpG) contexts. This modification is established and maintained by a family of DNA methyltransferase enzymes, with DNMT3A and DNMT3B responsible for de novo methylation and DNMT1 ensuring faithful propagation of methylation patterns during DNA replication (Bestor, 2000; Okano et al., 1999).

In mammalian genomes, the majority of CpG sites are methylated, whereas CpG-rich regions located near gene promoters commonly referred to as CpG islands often remain unmethylated to permit active transcription (Deaton & Bird, 2011). When methylation occurs within promoter regions, it is generally associated with transcriptional repression. This effect arises through the recruitment of methyl-binding proteins and associated chromatin-modifying complexes that promote chromatin compaction and restrict access of transcriptional machinery (Jones & Takai, 2001; Klose & Bird, 2006).

In livestock, DNA methylation plays essential roles in processes such as genomic imprinting, X-chromosome inactivation, suppression of transposable elements, and tissue-specific gene regulation during development (Li et al., 1993; Reik & Walter, 2001; Yoder et al., 1997). Genome-wide analyses in cattle, sheep, and pigs have revealed that methylation patterns vary substantially across tissues and developmental stages, reflecting functional specialization (Salilew-Wondim et al., 2015; O'Doherty et al., 2012). Dynamic reprogramming of DNA methylation occurs during gametogenesis and

early embryonic development, highlighting the sensitivity of this mechanism to both intrinsic and environmental influences.

Recent advances in high-throughput methylation profiling, including reduced representation bisulfite sequencing and whole-genome bisulfite sequencing, have enabled the identification of differentially methylated regions associated with economically important traits (Li et al., 2019; Zhu et al., 2021; Wang et al., 2022). Studies have linked methylation variation in growth-related pathways to feed efficiency and body composition, while tissue-specific methylation patterns in the mammary gland have been associated with lactation performance (Singh et al., 2010; Chen et al., 2020). These findings underscore the potential relevance of DNA methylation as a molecular mediator between genotype, environment, and phenotype in livestock production.

2.3 Histone Modifications

Histone proteins form the structural core of nucleosomes, around which DNA is wrapped to create chromatin (Luger et al., 1997). The amino-terminal tails of histones are subject to a wide array of post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination (Kouzarides, 2007; Bannister & Kouzarides, 2011). These modifications influence chromatin structure and function by altering histone–DNA interactions or by serving as docking sites for regulatory proteins.

Among histone modifications, acetylation is generally associated with transcriptional activation (Grunstein, 1997; Sterner & Berger, 2000). The addition of acetyl groups by histone acetyltransferases reduces the positive charge on histone tails, weakening their interaction with negatively charged DNA and resulting in a more open chromatin conformation. In contrast, histone deacetylases remove these acetyl groups, promoting chromatin condensation and transcriptional repression (Yang & Seto, 2008). In livestock tissues, changes in histone acetylation patterns have been linked to developmental stage, physiological state, and environmental stress. The most well-characterized activating marks are histone H3 lysine 9 acetylation (H3K9ac) and H3 lysine 27 acetylation (H3K27ac), both associated with active promoters and enhancers (Creyghton et al., 2010; Kharchenko et al., 2011).

Histone methylation exhibits more complex functional outcomes, as its effects depend on the specific residue modified and the degree of methylation (Martin & Zhang, 2005). Certain marks, such as trimethylation of histone H3 at lysine 4 (H3K4me3), are characteristic of transcriptionally active promoters, whereas others, including methylation at lysine 9 or lysine 27 (H3K9me3 and H3K27me3), are associated with gene silencing and heterochromatin formation (Barski et al., 2007; Guenther et al., 2007; Lachner et al., 2001; Cao et al., 2002). Genome-wide profiling studies in livestock have demonstrated that these marks are dynamically regulated during embryogenesis, tissue differentiation, and physiological transitions such as lactation.

Evidence from assisted reproductive technologies further highlights the importance of histone modifications in livestock. Aberrant histone modification patterns in embryos produced through in vitro fertilization or somatic cell nuclear transfer have been associated with reduced developmental competence, indicating that proper epigenetic reprogramming is essential for normal development (Whitworth et al., 2011; Wang et al., 2020). In dairy cattle, histone H3 acetylation patterns in mammary tissue vary across lactation stages and correlate with expression of milk protein genes (Singh et al., 2012). Furthermore, heat stress in livestock has been shown to alter histone modification patterns in immune cells, affecting cytokine expression and immune function (Slimen et al., 2016; Weng et al., 2022). These observations reinforce the functional significance of histone-based regulation in both natural and managed reproductive contexts.

2.4 Non-Coding RNAs

Non-coding RNAs constitute a diverse group of regulatory molecules that influence gene expression at transcriptional and post-transcriptional levels (Esteller, 2011; Mattick & Makunin, 2006). Among these, microRNAs have been most extensively studied in livestock. These short RNA molecules (~22 nucleotides) regulate gene expression by binding to complementary sequences in target messenger RNAs, leading to translational repression or mRNA degradation

(Bartel, 2009; Ambros, 2004). Through this mechanism, a single microRNA can influence multiple biological pathways simultaneously (Friedman et al., 2009).

In livestock species, microRNAs have been implicated in muscle development, adipogenesis, lactation, reproduction, and immune responses (Chen et al., 2017; Huang et al., 2018). Tissue-specific expression patterns of microRNAs have been documented in skeletal muscle, adipose tissue, mammary gland, and reproductive organs, often correlating with key production traits. For example, miR-21 and miR-143 play critical roles in bovine adipocyte differentiation and intramuscular fat deposition, traits important for meat quality (Jin et al., 2010; Li et al., 2011). In lactating dairy cows, mammary gland-specific miRNAs such as miR-26a, miR-30a, and let-7 family members regulate milk protein and fat synthesis by targeting key metabolic genes (Wang et al., 2016; Do et al., 2017). Circulating microRNAs detected in blood and milk have also attracted interest as potential non-invasive biomarkers of health status and productive performance (Liang et al., 2017; Pratt et al., 2020).

Long non-coding RNAs, which exceed 200 nucleotides in length, add another layer of regulatory complexity (Ponting et al., 2009; Rinn & Chang, 2012). These molecules participate in gene regulation through diverse mechanisms, including chromatin remodeling, transcriptional interference, and modulation of RNA stability. Some lncRNAs serve as scaffolds that recruit chromatin-modifying complexes to specific genomic loci, while others act as molecular decoys or guides (Wang & Chang, 2011; Bassett et al., 2014). In livestock, emerging evidence links long non-coding RNAs to processes such as muscle fiber differentiation, fat deposition, and reproductive function (Koufariotis et al., 2015; Zhang et al., 2019). For instance, the lncRNA H19 influences muscle fiber composition and growth in cattle and pigs, while HOTTIP regulates adipogenesis through interactions with chromatin remodeling complexes (Cao et al., 2018; Liu et al., 2020). Although functional characterization remains incomplete for many of these transcripts, their tissue-specific expression patterns suggest important regulatory roles.

2.5 Chromatin Remodeling

Chromatin remodeling refers to ATP-dependent processes that reposition, eject, or restructure nucleosomes to regulate DNA accessibility (Clapier & Cairns, 2009; Narlikar et al., 2013) (Table 1). These processes are mediated by multi-subunit chromatin remodeling complexes that alter chromatin architecture without modifying histones or DNA directly. By controlling nucleosome positioning, these complexes influence the ability of transcription factors and regulatory proteins to access genomic regions. These complexes are classified into four main families based on their ATPase subunit: SWI/SNF (switch/sucrose non-fermentable), ISWI (imitation switch), CHD (chromodomain helicase DNA-binding), and INO80 (inositol requiring 80) (Hargreaves & Crabtree, 2011; Becker & Workman, 2013).

Table 1. Major Epigenetic Mechanisms in Mammals and their Functional Implications

Epigenetic Mechanism	Description	Functional Implications	Reference
DNA Methylation	Addition of methyl groups to cytosine in CpG islands	Gene silencing or activation	Biermann & Steger, 2007
Post-Translational Histone Modifications	Acetylation, methylation, phosphorylation of histone tails	Chromatin structure & transcription regulation	Rajender et al., 2011
Chromatin Remodeling	ATP-dependent repositioning of nucleosomes	DNA accessibility to transcription factors	Narlikar et al., 2013
Small Non-Coding RNAs	miRNAs and siRNAs regulating gene expression post-transcriptionally	Gene silencing, development regulation	Bartel, 2009

SWI/SNF complexes are particularly important in mammalian development, cell differentiation, and DNA repair (Ho & Crabtree, 2010; Wilson & Roberts, 2011). These complexes can slide, eject, or replace nucleosomes, creating nucleosome-depleted regions that facilitate transcription factor binding (Cairns, 2009). In livestock, chromatin remodeling is particularly critical during early embryonic development, when extensive restructuring of chromatin accompanies the transition from maternal to embryonic control of gene expression (Eckersley-Maslin et al., 2018; Kobayashi & Kurumizaka, 2019). Disruptions in chromatin remodeling during this period have been linked to developmental arrest and reduced embryo viability (Jiang et al., 2014; Canovas et al., 2017).

Advances in chromatin accessibility profiling using ATAC-seq (Assay for Transposase-Accessible Chromatin) have revealed cell-type-specific patterns of open and closed chromatin that correspond closely with gene expression profiles in different tissues (Halstead et al., 2020; Yu et al., 2021) (Figure 1).

Collectively, DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling operate as an integrated regulatory network that governs gene expression in livestock. These mechanisms provide a molecular basis for developmental plasticity and environmental responsiveness, positioning epigenetics as a critical interface between genetics, management, and production outcomes

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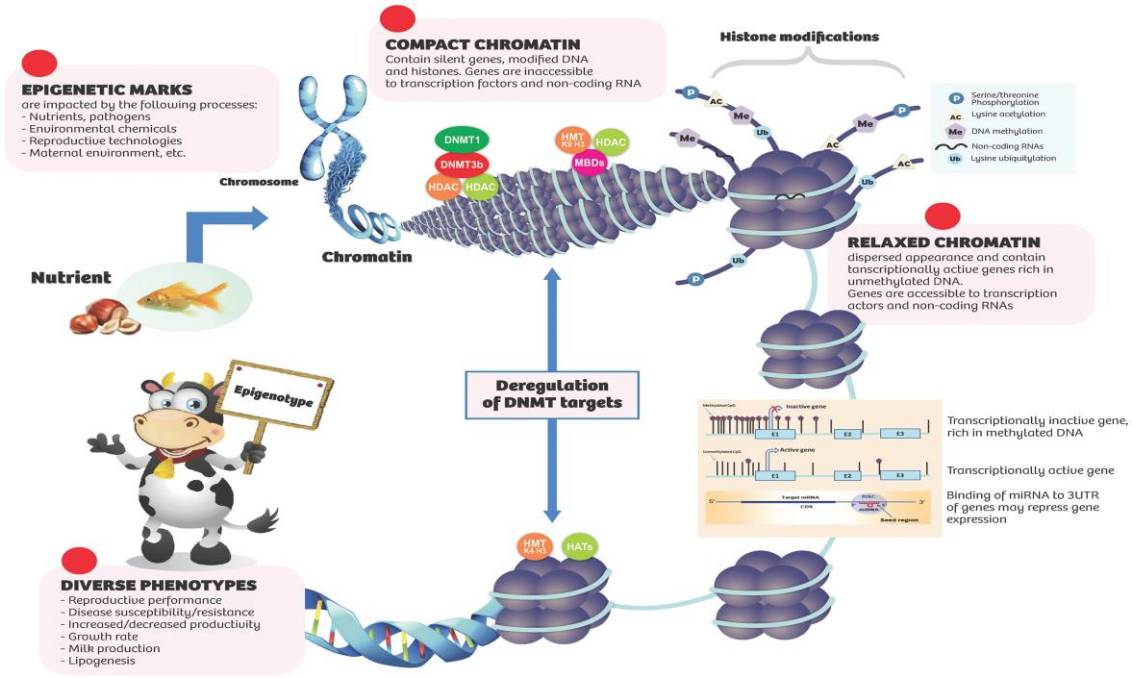

Figure 1. Chromatin States and their Functional Differences

Side-by-side view of compact (heterochromatin) vs. relaxed (euchromatin) chromatin, showing transcriptional activity. The left panel shows tightly packed chromatin (heterochromatin) with limited transcription factor access, associated with gene silencing. The right panel shows loosely organized chromatin (euchromatin) with open accessibility to transcription factors, associated with active gene expression. Histones are depicted as protein complexes around which DNA (shown as a double helix) wraps to form nucleosomes.

Source: Ibeagha-Awemu & Zhao (2015)

3. Environmental Influences on Epigenetic Landscapes

Environmental conditions play a decisive role in shaping epigenetic patterns in livestock by modulating gene expression in response to external stimuli (Feil & Fraga, 2012). Unlike genetic variation, which is inherited and relatively fixed, epigenetic regulation provides a flexible mechanism through which animals can adapt to changing nutritional, climatic, and

management environments. These environmentally induced epigenetic changes are particularly relevant in livestock production systems, where animals are frequently exposed to variable feeding regimes, thermal stress, disease challenges, and management interventions.

3.1 Nutritional Programming and Metabolic Epigenetics

Nutrition is one of the most extensively studied environmental factors influencing epigenetic regulation in livestock (Anderson et al., 2012; Waterland & Michels, 2007). Nutrients and dietary components supply essential substrates and cofactors required for epigenetic modifications, including methyl donors such as methionine, choline, folate, and vitamins involved in one-carbon metabolism (Crider et al., 2012; Ly et al., 2020) (Table 2). Alterations in dietary composition can therefore influence DNA methylation and histone modification patterns, with downstream effects on gene expression and phenotype.

Table 2. Examples of Nutritional Epigenetic Alterations in Livestock

Nutrient/Diet Intervention	Epigenetic Effect	Species	Reference
Folate and Vitamin B12	Increased global DNA methylation	Sheep	Sinclair *et al.,* 2007
Betaine Supplementation	Altered PEPCK1/PEPCK2 methylation	Pigs	Cai *et al*., 2014
Zinc Supplementation	Hypomethylation and gene upregulation	Hens	Li et al., 2015
Protein Restriction	Gene-specific hypermethylation	Cattle	Juchem *et al*., 2012

The epigenetic consequences of maternal nutrition during gestation on offspring phenotype are covered in detail in Section 4.2, which focuses on fetal epigenetic programming.

In pigs, maternal betaine supplementation during gestation has been shown to alter DNA methylation of PEPCK1 and PEPCK2 genes, key regulators of gluconeogenesis in offspring liver, correlating with improved glucose homeostasis (Cai et al., 2014). Similarly, protein restriction during pregnancy in cattle induces gene-specific hypermethylation in fetal liver, affecting metabolic pathways that persist into adulthood (Juchem et al., 2012; Paradis et al., 2017).

Postnatal nutrition also contributes to epigenetic variation, particularly in tissues with high metabolic activity such as liver, muscle, and adipose tissue. In dairy cattle, early-life feeding strategies influence DNA methylation in mammary tissue, with potential long-term effects on milk production capacity (Laporta et al., 2020). Micronutrient supplementation, particularly zinc, has been shown to modulate DNA methylation and gene expression in poultry, affecting growth and immune function (Li et al., 2015; Zhu et al., 2019). Differences in feeding intensity, energy density, and protein composition have been linked to changes in methylation and histone modification profiles that regulate pathways involved in muscle accretion, fat deposition, and energy utilization. These findings highlight the potential for nutritional management to influence livestock performance through epigenetic mechanisms, complementing traditional genetic and nutritional approaches (Dunn & Bale, 2011; Padmanabhan et al., 2016).

3.2 Thermal Stress and Climatic Adaptation

Heat stress represents a major challenge in livestock production, particularly as global temperatures rise due to climate change (Bernabucci *et al*., 2010; Polsky & von Keyserlingk, 2017). Thermal stress imposes substantial physiological burdens, reducing feed intake, impairing reproductive performance, compromising immune function, and decreasing milk yield and meat quality (Bernabucci *et al*., 2014; Osei-Amponsah *et al.,* 2020). Importantly, heat stress induces epigenetic alterations that may contribute to these phenotypic effects and can be transmitted to offspring.

In dairy cattle, maternal heat stress during late gestation negatively affects calf birth weight, immune development, and subsequent production performance effects that persist beyond the period of direct thermal exposure (Tao et al., 2012; Monteiro et al., 2016). Mechanistic studies have revealed that in utero heat stress alters DNA methylation patterns in bovine offspring liver and mammary glands, affecting pathways related to immune function, cell proliferation, and metabolism (Skibiel et al., 2018; Laporta et al., 2020). Specifically, genes involved in heat shock response, inflammatory

signaling, and metabolic regulation exhibit differential methylation and expression in heat-stressed animals.

Heat stress also affects the male germline, with studies in bulls showing that elevated testicular temperatures alter sperm DNA methylation and histone modification patterns, potentially compromising embryo development and offspring health (Rahman *et al*., 2011; Simmons *et al*., 2020). Similarly, heat stress in laying hens disrupts DNA methylation in liver tissue, affecting lipid metabolism genes and egg production (Varasteh *et al*., 2018).

Epigenetic mechanisms may also underlie breed differences in heat tolerance. Thermotolerant livestock breeds, such as Brahman cattle and indigenous sheep and goat breeds in tropical regions, exhibit distinct epigenetic signatures compared to heat-sensitive breeds, suggesting that epigenetic variation contributes to adaptive differences (Srikanth *et al*., 2017; Gim *et al*., 2020) (Figure 2) Identifying these epigenetic markers could facilitate breeding for climate resilience.

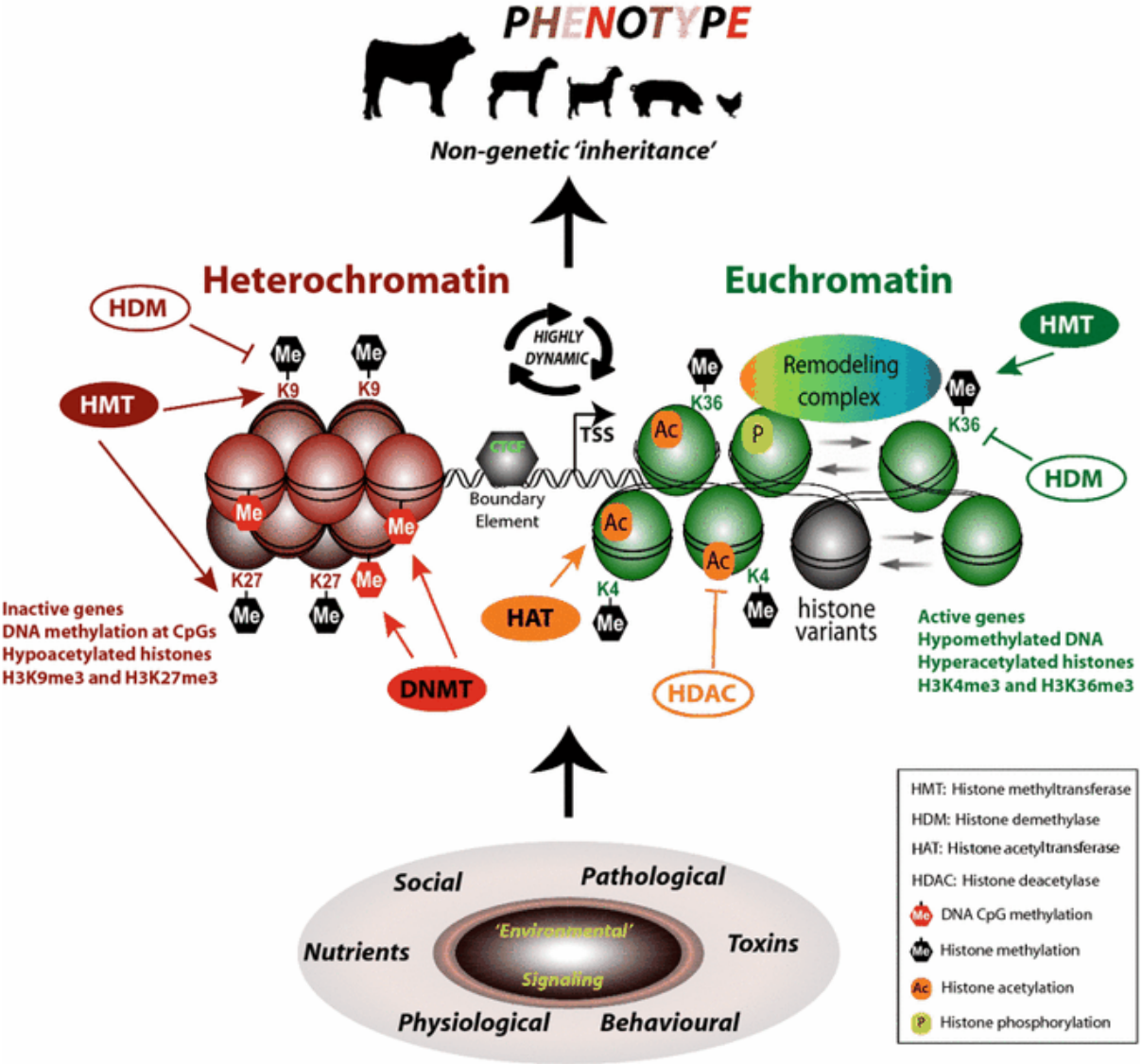

Figure 2. Chromatin Modifications and Phenotypic Regulation in Livestock
Diagram showing how environmental factors lead to chromatin remodeling and impact gene expression. The flowchart illustrates: (1) Environmental stressors (heat stress, nutritional changes, toxins, pathogens)

at the top, (2) Signal transduction pathways leading to the nucleus, (3) Recruitment of chromatin modifying enzymes (DNMTs, HATs, HDACs, HMTs), (4) Changes in chromatin structure showing transition from open (euchromatin) to closed (heterochromatin) states or vice versa, (5) Altered gene expression patterns, (6) Downstream phenotypic outcomes including changes in: growth rate, immune response, reproduction, milk production, and stress tolerance. Arrows indicate the cascade of molecular events from environmental stimulus to phenotypic response.
Source: Triantaphyllopoulos *et al*. (2016)

3.3 Management Practices and Production Systems

Management practices, including housing conditions, stocking density, handling procedures, and health interventions, also contribute to shaping epigenetic landscapes in livestock (Merlot et al., 2008; Rutherford et al., 2012). Stressful management conditions can activate neuroendocrine pathways that influence epigenetic regulation of genes involved in stress response, immunity, and behavior (Champagne & Meaney, 2006; Harlow et al., 2016). Chronic stress exposure has been associated with altered methylation patterns in regulatory regions of stress-related genes, potentially affecting animal welfare and productivity.

In pigs, maternal stress and poor welfare conditions during gestation have been associated with altered DNA methylation in offspring brain regions that regulate stress responses and behavior (Otten et al., 2015). Similarly, early weaning stress in cattle calves induces changes in DNA methylation of immune-related genes, potentially affecting disease susceptibility (Tao et al., 2019). Research in poultry has demonstrated that prenatal stress through corticosterone exposure alters DNA methylation in the hypothalamus and affects fearfulness and stress coping behaviors in adulthood (Goerlich et al., 2012).

Differences between intensive and extensive production systems have been linked to distinct epigenetic profiles, reflecting variation in environmental complexity, social interactions, and exposure to pathogens. For instance, animals reared in enriched or pasture-based systems may exhibit epigenetic patterns that support enhanced immune competence and adaptive behavior, whereas those in highly controlled environments may display different regulatory signatures. Although disentangling the effects of individual management factors remains challenging, these observations underscore the sensitivity of epigenetic regulation to production context.

Assisted reproductive technologies, including in vitro fertilization, embryo culture, and somatic cell nuclear transfer, represent a category of management intervention with pronounced epigenetic consequences that are discussed in detail in Section 4.3.

3.4 Health, Disease, and Immune Challenges

Health status and exposure to pathogens constitute additional environmental influences on epigenetic regulation in livestock (Netea et al., 2016; Penney et al., 2022). Infection and immune activation trigger epigenetic remodeling in immune cells, enabling rapid and coordinated transcriptional responses to pathogenic threats. DNA methylation and histone modification changes in immune-related genes have been associated with variation in disease resistance and recovery across individuals and breeds.

In cattle, mastitis, a common udder infection is associated with differential DNA methylation in mammary tissue and peripheral blood leukocytes, affecting expression of inflammatory and antimicrobial genes (Wang et al., 2013; Jensen et al., 2020). Similarly, viral infections such as bovine viral diarrhea virus (BVDV) and infectious bovine rhinotracheitis (IBR) alter miRNA expression profiles, which regulate antiviral immunity (Jin et al., 2014; Lawless et al., 2013).

Emerging evidence suggests that epigenetic mechanisms may contribute to immune memory and trained immunity in livestock, whereby prior exposure to pathogens or vaccines induces lasting changes in immune responsiveness (Bhatia & Dahiya, 2015; Scharer et al., 2019). Such epigenetic imprinting could have implications for disease management strategies and selective breeding for enhanced resilience. However, the stability and heritability of disease-associated epigenetic marks remain areas of active investigation.

Collectively, environmental influences interact with epigenetic mechanisms to generate phenotypic diversity in livestock populations. By mediating the effects of nutrition, climate, management, and health challenges on gene expression, epigenetic regulation provides a biological framework for understanding how animals adapt to production environments. These insights reinforce the importance of integrating environmental context into epigenetic studies and highlight the potential for management-based epigenetic modulation as a complement to genetic selection.

4. Epigenetics in Reproduction and Development

Reproduction and early development represent critical phases in the livestock life cycle during which epigenetic regulation exerts particularly strong and lasting effects (Reik, 2007; Smith et al., 2012). During these periods, extensive epigenetic reprogramming occurs to establish cell- and tissue-specific patterns of gene expression that guide embryonic development, organ formation, and postnatal growth. Because these processes coincide with heightened sensitivity to environmental influences, epigenetic regulation in reproduction and development has important implications for fertility, offspring performance, and long-term productivity in livestock systems.

4.1 Epigenetic Reprogramming During Gametogenesis and Early Embryogenesis

Gametogenesis and early embryonic development are characterized by profound remodeling of epigenetic marks (Seisenberger et al., 2012; Hackett et al., 2013). In mammalian species, including livestock, DNA methylation patterns are largely erased and subsequently re-established during these stages, allowing the formation of totipotent and pluripotent cell states. This reprogramming process is essential for normal development, as it resets epigenetic information while preserving parent-of-origin–specific marks associated with genomic imprinting (Smallwood & Kelsey, 2012).

Genomic imprinting is an epigenetic phenomenon whereby certain genes are expressed exclusively from one parental allele based on differential DNA methylation established during gametogenesis (Ferguson-Smith, 2011; Barlow & Bartolomei, 2014). Imprinted genes play critical roles in placental development, fetal growth, and postnatal metabolism (Fowden et al., 2006). Disruption of imprinting can result in severe developmental abnormalities and pregnancy complications, as seen in overgrowth syndromes like large offspring syndrome (LOS) in ruminants (Young et al., 1998; Chen et al., 2015).

In sperm and oocytes, distinct epigenetic landscapes are established that reflect their specialized biological roles. Following fertilization, the paternal and maternal genomes undergo asymmetric epigenetic remodeling, with the paternal genome typically experiencing rapid demethylation and extensive chromatin reorganization (van der Heijden et al., 2005; Guo et al., 2014). Disruptions to these tightly regulated processes can impair embryonic development and reduce fertility, emphasizing the importance of precise epigenetic control during the earliest stages of life.

Studies in cattle, sheep, and pigs have demonstrated that deviations in DNA methylation and histone modification patterns during early embryogenesis are associated with reduced blastocyst quality, altered gene expression, and compromised implantation success (Salilew-Wondim et al., 2015; O'Doherty et al., 2012). In livestock, epigenetic reprogramming errors in gametes are associated with reduced fertility and embryonic mortality. Studies in bulls have identified DNA methylation aberrations in sperm associated with subfertility, suggesting that sperm epigenetic profiles could serve as biomarkers for male reproductive potential (Perrier et al., 2018; Lambert et al., 2018). Similarly, oocyte epigenetic quality is influenced by maternal age, ovarian environment, and metabolic status, affecting subsequent embryo development (Hao et al., 2018; Ghoneim et al., 2021). These findings highlight epigenetic reprogramming as a key determinant of reproductive efficiency and developmental competence in livestock.

4.2 Maternal Environment and Fetal Epigenetic Programming

The intrauterine environment plays a central role in shaping the epigenetic profile of the developing fetus. Maternal nutrition, metabolic status, stress exposure, and health during pregnancy influence the availability of substrates

and signaling molecules that regulate epigenetic modifications (Barker, 2007; Fleming et al., 2018). As a result, environmental conditions experienced by the dam can induce epigenetic changes in the fetus that persist beyond birth.

In livestock species, maternal undernutrition or overnutrition during gestation has been linked to altered DNA methylation at genes involved in growth regulation, energy metabolism, and endocrine signaling (Sinclair et al., 2007; Yan et al., 2013). These epigenetic modifications have been associated with variation in birth weight, postnatal growth trajectories, body composition, and metabolic efficiency. Such findings are consistent with the concept of developmental programming, whereby early-life conditions exert long-term effects on phenotype through epigenetic mechanisms.

Maternal stress and disease during pregnancy have also been shown to influence fetal epigenetic regulation, particularly in pathways related to immune function and stress responsiveness. These effects may contribute to differences in disease susceptibility and resilience among offspring, with potential consequences for animal health and productivity under commercial production conditions.

4.3 Assisted Reproductive Technologies and Epigenetic Stability

Assisted reproductive technologies (ART), including in vitro fertilization, embryo culture, and somatic cell nuclear transfer, are widely used in livestock breeding programs to accelerate genetic progress and disseminate superior genetics (Sirard, 2018; Lonergan & Fair, 2016). However, these technologies involve manipulation of gametes and embryos during periods of extensive epigenetic reprogramming, raising concerns about epigenetic stability (Denomme & Mann, 2012; Chen & Zhang, 2022).

Numerous studies have reported that embryos produced through ART can exhibit aberrant DNA methylation and histone modification patterns compared with their in vivo–derived counterparts (Young et al., 2001; Urrego et al., 2014). Such epigenetic alterations have been linked to reduced developmental competence, abnormal fetal growth, and increased incidence of developmental disorders. In ruminants, for example, altered epigenetic regulation has been implicated in large offspring syndrome, a condition characterized by excessive fetal growth and perinatal complications (Chen et al., 2015; Canovas et al., 2017).

Somatic cell nuclear transfer, used for animal cloning, is particularly prone to epigenetic errors, as the donor nucleus must be comprehensively reprogrammed from a differentiated somatic state to a totipotent embryonic state (Yang et al., 2007; Matoba & Zhang, 2018). Incomplete erasure of somatic epigenetic memory results in low cloning efficiency and high rates of developmental abnormalities (Bourc'his et al., 2001; Santos & Dean, 2004). Histone modifications, particularly histone acetylation, have been identified as critical barriers to successful nuclear reprogramming, and treatment with HDAC inhibitors has been shown to improve cloning outcomes in multiple species (Kishigami et al., 2006; Whitworth et al., 2011).

Efforts to optimize ART protocols have increasingly focused on minimizing epigenetic disruption. Improvements in culture media composition, oxygen tension, and timing of embryo manipulation have been shown to partially restore normal epigenetic patterns and improve developmental outcomes (Bissoondath et al., 2009; Milroy et al., 2021). These findings underscore the need to consider epigenetic consequences when implementing and refining reproductive technologies in livestock systems.

4.4 Transgenerational Epigenetic Effects

Beyond their immediate impact on individual development, epigenetic changes arising during reproduction may influence subsequent generations (Guerrero-Bosagna & Skinner, 2012; Skinner, 2015). Although most epigenetic marks are reprogrammed during gametogenesis and early embryogenesis, some modifications can evade complete erasure and be transmitted to offspring. Evidence for such transgenerational epigenetic effects has been reported in several livestock species, particularly in relation to nutritional and environmental exposures.

Parental experiences, including dietary restriction, thermal stress, or disease challenge, have been associated with epigenetic alterations in gametes that correlate with phenotypic changes in progeny (Dunn & Bale, 2011; Padmanabhan et al., 2016). While the magnitude and stability of these effects remain subjects of debate, their

potential implications for breeding strategies are substantial. If environmentally induced epigenetic variation contributes to heritable differences in performance or resilience, it may represent an additional layer of inheritance beyond DNA sequence variation.

Figure 3, following fertilization, the early mammalian embryo undergoes dynamic epigenetic remodeling characterized by active and passive DNA demethylation, histone variant exchange, and chromatin restructuring (Eckersley-Maslin et al., 2018; Wu & Zhang, 2017). This reprogramming is essential for establishing pluripotency and enabling embryonic genome activation (EGA), the critical transition from maternal to embryonic transcriptional control.

In cattle, EGA occurs between the 8-cell and 16-cell stages, requiring precise coordination of chromatin remodeling and transcription factor activity (Graf et al., 2014; Jiang et al., 2014). Aberrant epigenetic reprogramming during pre-EGA stages is a major cause of developmental arrest and embryonic mortality in both in vivo and in vitro systems (Dahl et al., 2016; Canovas et al., 2017).

Histone modifications undergo dramatic changes during early embryogenesis. For example, paternal chromatin undergoes rapid protamine-to-histone exchange and active demethylation shortly after fertilization, while maternal chromatin experiences passive demethylation through DNA replication. Histone H3K4me3 and H3K27me3 marks establish bivalent chromatin domains at developmental genes, poising them for subsequent activation during differentiation (Rugg-Gunn et al., 2010; Xiang et al., 2020).

Non-coding RNAs, particularly maternal miRNAs and long non-coding RNAs deposited in oocytes, play regulatory roles during oocyte maturation and early embryogenesis (Svoboda et al., 2015; Arun et al., 2020). Dysregulation of these ncRNAs compromises embryo developmental competence, highlighting their importance in reproduction.

Overall, epigenetic regulation in reproduction and development provides a mechanistic link between parental environment, early-life conditions, and long-term phenotypic outcomes in livestock. Recognizing and managing these epigenetic influences may enhance reproductive efficiency, improve offspring performance, and support more sustainable livestock production systems.

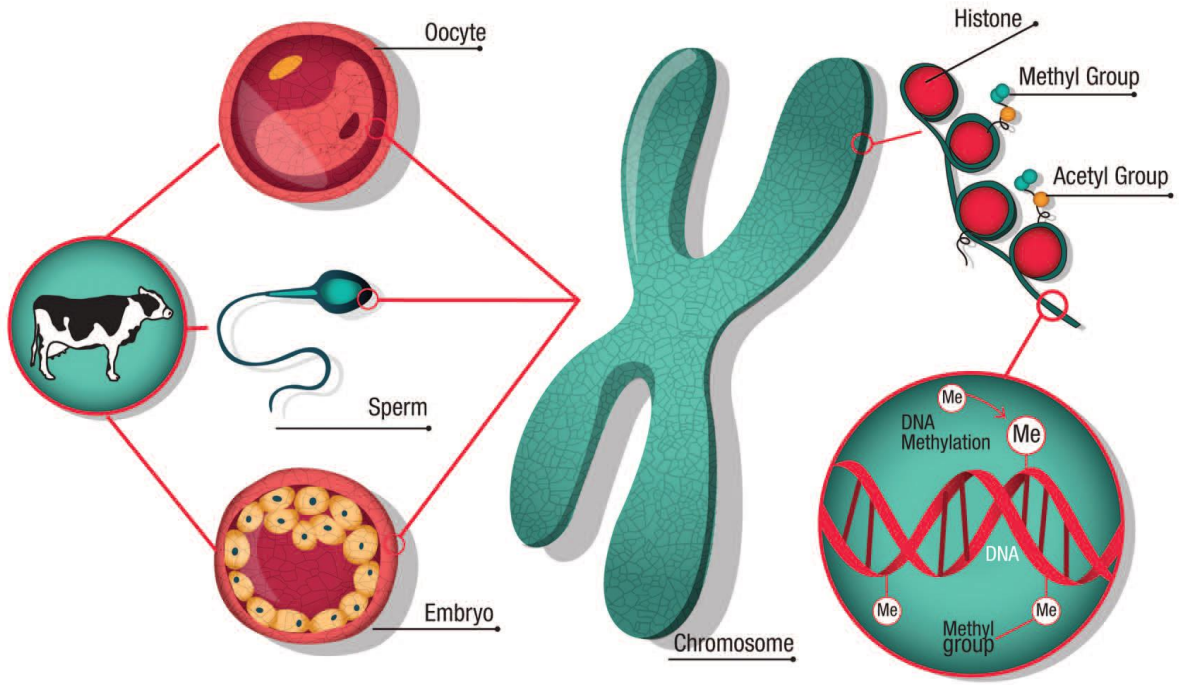

Figure 3. Epigenetic Landscape During Embryo Development

A diagram showing gamete and early embryo development stages, with major epigenetic changes. The illustration depicts: (1) Parental gametes (sperm and oocyte) with established epigenetic marks, (2) Fertilization leading to zygote formation, (3) Early cleavage stages showing progressive DNA demethylation (active in paternal genome, passive in maternal genome), (4) Morula stage with minimal methylation, (5) Blastocyst stage showing initiation of de novo methylation and chromatin remodeling, (6) post-implantation embryo with tissue-specific methylation patterns. Key epigenetic events are labeled including: erasure of gametic methylation patterns, maintenance of imprinted genes, histone modifications (H3K4me3, H3K27me3), and chromatin accessibility changes.

Source: Urrego *et al*. (2014)

5. Epigenetic Biomarkers and Applications in Livestock Breeding

The growing recognition that epigenetic variation contributes to phenotypic diversity in livestock has stimulated interest in the identification and application of epigenetic biomarkers for animal breeding (González-Recio et al., 2015; Gutiérrez-Gil et al., 2022). Unlike DNA sequence polymorphisms, epigenetic markers capture information about gene regulation and environmental responsiveness, offering a potential means of linking genotype, management conditions, and observed performance. As such, epigenetic biomarkers represent a promising but still emerging tool for enhancing selection strategies in livestock improvement programs.

5.1 Epigenome-Wide Association Studies in Livestock

Epigenome-wide association studies (EWAS) have become a central approach for identifying epigenetic variation associated with complex traits in livestock (Rakyan et al., 2011; Flanagan, 2015). By examining genome-wide patterns of DNA methylation or other epigenetic marks, EWAS aim to detect differentially modified regions correlated with phenotypic variation. In cattle, sheep, pigs, and poultry, EWAS have identified epigenetic signatures associated with growth performance, feed efficiency, carcass traits, milk production, fertility, disease resistance, and thermal tolerance (Fang et al., 2017; Dechow et al., 2020).

Many of these studies have highlighted tissue-specific epigenetic markers, reflecting the functional specialization of different organs. For example, methylation patterns in muscle tissue have been associated with meat quality and growth rate, while epigenetic variation in the mammary gland has been linked to lactation performance (Li et al., 2019; Yang et al., 2021; Chen et al., 2020; Wang et al., 2022). Similarly, epigenetic profiles in immune-related tissues have been correlated with disease susceptibility and immune responsiveness. These findings emphasize the importance of selecting appropriate tissues and developmental stages when identifying candidate epigenetic biomarkers.

Despite their promise, EWAS in livestock face several methodological challenges. Sample sizes are often limited due to the cost and complexity of epigenomic profiling, reducing statistical power and reproducibility (Langevin & Kelsey, 2013). In addition, epigenetic variation can be influenced by age, tissue composition, and environmental history, complicating causal interpretation. Addressing these challenges will require standardized experimental designs, larger datasets, and integration of epigenetic information with genomic and phenotypic data.

5.2 Integration of Epigenetic Information into Breeding Programs

Table 3, incorporating epigenetic markers into breeding programs represents a conceptual extension of genomic selection (González-Recio, 2012; Paiva et al., 2019). While genomic selection relies on DNA sequence variation to predict breeding values, epigenetic information may provide complementary insight into regulatory processes that influence trait expression, particularly for traits with strong environmental sensitivity. Several theoretical and empirical studies have suggested that combining genomic and epigenomic data could improve prediction accuracy for complex traits.

One potential application involves the use of epigenetic markers as auxiliary predictors in genomic evaluation models. By capturing environmentally induced regulatory variation, these markers may help explain phenotypic differences not accounted for by DNA sequence alone. Several modeling approaches have been explored, including:

Epigenetic Relationship Matrices (ERM): Analogous to genomic relationship matrices (GRM), ERMs capture similarity among individuals based on DNA methylation profiles rather than DNA sequence variants (van Dongen et al., 2016).

Multi-Omics Prediction Models: Integrating genomic, epigenomic, transcriptomic, and metabolomic data into unified prediction frameworks to capture multiple layers of biological variation (Xu et al., 2021; Wang et al., 2023).

Reaction Norm Models: Using epigenetic markers as indicators of environmental exposure to model genotype-by-environment interactions more accurately (González-Recio et al., 2015).

This approach may be particularly relevant for traits such as fertility, disease resistance, and heat tolerance, where genotype-by-environment interactions play a prominent role.

Another application lies in early-life selection. Because epigenetic patterns can reflect developmental programming, profiling epigenetic markers at early stages may provide predictive information about later-life performance. However, the temporal stability of such markers remains a critical consideration, as epigenetic states can change over time in response to management and environmental conditions.

Pilot studies in dairy cattle and pigs have demonstrated modest improvements in prediction accuracy when epigenetic data are included alongside genomic data, particularly for production traits and disease resistance (Fang et al., 2017; Dechow et al., 2020). However, widespread implementation is currently limited by the cost and technical complexity of epigenome profiling, as well as the need for large reference populations with both phenotypic and epigenomic data.

Potential breeding strategies that explicitly account for environmental responsiveness and developmental plasticity include (Ibeagha-Awemu & Zhao, 2015; Murdoch et al., 2016):

Selection for Epigenetic Stability: Identifying individuals with robust epigenomes that maintain stable gene expression across diverse environmental conditions, potentially enhancing resilience (Zhang & Meaney, 2010).

Epigenetic Heterosis: Exploiting epigenetic complementarity in crossbreeding programs, where hybrid offspring may exhibit favorable epigenetic configurations that enhance heterosis effects (Greenberg & Bourc'his, 2019).

Environmentally-Targeted Selection: Selecting animals based on epigenetic profiles that predict superior performance in specific production environments, such as heat tolerance or disease-prevalent regions (Osei-Amponsah et al., 2020).

Transgenerational Epigenetic Effects: Considering maternal and paternal epigenetic contributions when designing mating schemes, particularly for traits influenced by developmental programming (Skinner, 2015; Padmanabhan et al., 2016).

Table 3. Genome to Epigenome Relationships in Livestock

Genetic Feature	Epigenetic Feature	ES Cells	Differentiated Cells	Notes
CpG Islands	DNA methylation-free	Strong	Moderate	Some CpG islands methylated with age
Transposon Regions	H3K27 Methylation	Strong	Moderate	Varies with tissue type
Repetitive Elements	H3K9, H4K20 Methylation	Variable	Variable	Epigenetic silencing mechanism

Source: Langevin & Kelsey (2013)

5.3 Epigenetic Biomarkers for Health and Resilience

Beyond production traits, epigenetic biomarkers hold potential value for improving animal health and resilience (Bhat et al., 2019; Pratt et al., 2020). Epigenetic regulation plays a central role in immune function, stress response, and adaptation to environmental challenges. As a result, epigenetic signatures associated with disease resistance or stress tolerance could be used to identify animals with superior resilience under commercial production conditions.

Circulating epigenetic markers, including cell-free DNA methylation patterns and non-coding RNAs detectable in blood or milk, have attracted particular interest due to their potential for non-

invasive sampling (Liang et al., 2017; Nolte et al., 2019). Such biomarkers could facilitate routine monitoring of animal health and physiological status, enabling earlier intervention and more targeted management. In dairy cattle, plasma miRNA profiles differ between healthy cows and those with mastitis, metabolic disease, or reproductive disorders, suggesting diagnostic potential (Lai et al., 2020; Zhao et al., 2021). Similarly, DNA methylation patterns in peripheral blood leukocytes have been associated with immune competence and disease resistance in cattle and pigs (Wang et al., 2013; Jensen et al., 2020).

Epigenetic age—biological age estimated from DNA methylation patterns—represents an emerging biomarker for health status and longevity (Horvath & Raj, 2018). Epigenetic clocks have been developed for several livestock species and may predict productive lifespan and reproductive longevity (Lowe et al., 2022; Prado et al., 2023). However, further validation is needed to establish the robustness and specificity of these markers across breeds, environments, and production systems.

5.4 Practical Constraints and Future Perspectives

Despite growing interest, several practical barriers currently limit the widespread adoption of epigenetic biomarkers in livestock breeding. Epigenomic assays remain more expensive and technically demanding than standard genotyping, and their interpretation requires careful consideration of tissue specificity and environmental context (Murdoch et al., 2016; Zentner & Henikoff, 2015). Moreover, the extent to which epigenetic variation is stably inherited across generations remains incompletely understood, raising questions about its long-term utility in selection programs.

Nevertheless, rapid technological advances are improving the feasibility of epigenetic applications. Declining sequencing costs, improved bioinformatic pipelines, and increasing availability of multi-omics datasets are facilitating more comprehensive analyses of epigenetic regulation (Zhou et al., 2018). As understanding of epigenetic stability and heritability improves, epigenetic biomarkers may become an increasingly valuable complement to genomic selection, particularly in the context of sustainable and climate-resilient livestock production.

6. Epigenome Editing and Future Directions

Recent advances in genome engineering have extended beyond DNA sequence modification to include precise manipulation of epigenetic states, giving rise to the field of epigenome editing (Hilton et al., 2015; Kungulovski & Jeltsch, 2016). Unlike conventional genetic engineering, which introduces permanent changes to the genome, epigenome editing targets regulatory marks that control gene expression without altering the underlying DNA sequence (Pulecio et al., 2017; Thakore et al., 2016). This distinction has important implications for livestock breeding, where public acceptance, regulatory frameworks, and long-term biological consequences remain critical considerations.

6.1 CRISPR-Based Epigenome Editing Technologies

CRISPR-associated systems have been adapted to enable targeted epigenetic modification through the use of catalytically inactive Cas proteins fused to epigenetic effector domains (Qi et al., 2013; Gilbert et al., 2014). These programmable complexes can be directed to specific genomic loci using guide RNAs, where they deposit or remove epigenetic marks such as DNA methylation or histone modifications. By modulating chromatin accessibility and transcriptional activity, epigenome editing allows precise control of gene expression without introducing double-strand breaks or sequence mutations.

Several effector domains have been successfully fused to dCas9 for epigenome editing applications:

dCas9-DNMT3A: Induces targeted DNA methylation at specific CpG sites, enabling gene silencing without DNA sequence changes (Liu et al., 2016; Stepper et al., 2017).

dCas9-TET1: The TET1 catalytic domain promotes DNA demethylation, allowing targeted gene activation at methylated loci (Xu et al., 2016; Morita et al., 2016).

dCas9-HAT (p300/CBP): Histone acetyltransferase domains increase histone acetylation at target genes, activating transcription from promoters and enhancers (Hilton et al., 2015; Klann et al., 2017).

dCas9-HDAC/KRAB: Histone deacetylases or KRAB repressor domains induce chromatin compaction and gene silencing (Thakore et al., 2015; Gilbert et al., 2013).

In livestock research, CRISPR-based epigenome editing has primarily been applied in experimental settings to investigate gene function and regulatory architecture. Proof-of-concept studies have demonstrated the ability to activate or repress target genes involved in growth, metabolism, and immune response by altering local epigenetic states (Ruan et al., 2018; Zhang et al., 2020; Wang et al., 2020). These approaches provide valuable insight into causal relationships between epigenetic regulation and phenotype, complementing observational studies such as epigenome-wide association analyses.

6.2 Potential Applications in Livestock Improvement

From a breeding perspective, epigenome editing presents intriguing opportunities for fine-tuning gene expression in ways that may enhance performance, resilience, or adaptability. For example, targeted activation of genes associated with stress tolerance or immune competence could improve animal robustness under challenging environmental conditions. Similarly, modulation of regulatory regions controlling metabolic pathways may influence feed efficiency or body composition without altering the genetic code.

Epigenome editing may also offer advantages in addressing traits that are difficult to improve through conventional selection due to antagonistic genetic correlations or strong environmental dependence. By selectively modifying regulatory networks rather than coding sequences, it may be possible to achieve more nuanced phenotypic outcomes. However, translating these experimental possibilities into practical breeding tools will require substantial validation to ensure stability, specificity, and absence of unintended effects.

Beyond epigenome editing, base editing and prime editing technologies enable precise nucleotide changes without double-strand breaks (Komor et al., 2016; Anzalone et al., 2019). While these modify DNA sequence rather than epigenetic marks, they offer complementary approaches for precision breeding by correcting deleterious mutations or introducing beneficial alleles with minimal off-target effects (Porto et al., 2020; Menchaca et al., 2021). Base editors have been successfully applied in livestock to introduce specific mutations associated with desirable traits or disease resistance (Xie et al., 2019; Zhou et al., 2020). Prime editors enable targeted insertions, deletions, and all 12 possible base-to-base conversions (Anzalone et al., 2019; Jin et al., 2021).

6.3 Biological, Technical and Ethical Considerations

Despite its promise, epigenome editing raises several biological and technical challenges. Epigenetic states are inherently dynamic and context-dependent, and the persistence of engineered epigenetic modifications across cell divisions and developmental stages remains uncertain. Tissue specificity represents another major constraint, as epigenetic editing in one tissue may not produce equivalent effects in others, limiting whole-animal applicability.

Off-target effects, while generally less severe than those associated with DNA editing, remain a concern, particularly when manipulating regulatory networks with widespread downstream consequences. Rigorous validation and long-term monitoring will be essential to assess the safety and reliability of epigenome-edited animals.

Ethical and regulatory considerations further complicate the adoption of epigenome editing in livestock production (Van Eenennaam, 2019; Bruce & Whitelaw, 2021). Although epigenome editing does not involve direct alteration of DNA sequence—potentially distinguishing it from conventional genetic modification, regulatory frameworks remain unclear in most jurisdictions (Doudna, 2020; Sprink et al., 2016).

Public acceptance of gene-edited livestock products varies by region and editing approach, with surveys indicating greater acceptance for health-related applications (e.g., disease resistance) than production traits (Mielby et al., 2021; Galyean et al., 2022). Transparent communication about benefits, risks, and regulatory oversight will be essential for responsible implementation of these technologies.

6.4 Future Research Directions

Future research on epigenome editing in livestock should prioritize a deeper understanding of

epigenetic stability, inheritance, and interaction with environmental factors. Longitudinal studies examining the durability of engineered epigenetic changes and their effects on performance across the lifespan are particularly needed. In addition, integrating epigenome editing with multi-omics approaches: including genomics, transcriptomics, and metabolomics will provide a more comprehensive view of regulatory networks and their phenotypic consequences.

In the near term, the most immediate value of epigenome editing is likely to lie in functional genomics and proof-of-concept studies rather than direct commercial application. By enabling precise manipulation of gene regulation, epigenome editing can help clarify the causal roles of epigenetic mechanisms identified through association studies and inform the development of more effective breeding and management strategies.

Overall, epigenome editing represents a powerful addition to the toolkit of animal genetics and breeding research. While significant scientific, technical, and societal challenges remain, continued advances in this field have the potential to reshape understanding of gene regulation and open new pathways toward sustainable and resilient livestock production.

7. Epigenetics and Climate Change Adaptation

Climate change poses substantial challenges to livestock production, including increased frequency of heat waves, altered precipitation patterns, expanded disease vector ranges, and shifts in feed availability (Thornton et al., 2009; Rojas-Downing et al., 2017). Epigenetic mechanisms may facilitate rapid adaptation to these changing conditions, complementing longer-term genetic selection (Burggren, 2016; Rey et al., 2020).

7.1 Epigenetic Mechanisms of Heat Tolerance

Heat stress induces epigenetic alterations that affect stress response, metabolism, and immunity (Skibiel et al., 2018; Weng et al., 2022). Importantly, some heat stress-induced epigenetic marks can be transmitted to offspring, potentially preparing them for similar thermal challenges a phenomenon termed predictive adaptive responses or anticipatory maternal effects (Gluckman et al., 2005; Burggren, 2016).

Research in poultry has demonstrated that embryonic thermal conditioning brief heat exposure during incubation, improves heat tolerance in adult birds through epigenetic programming of thermoregulatory genes (Loyau et al., 2016; Piestun et al., 2017). Similar approaches could be explored in mammals to enhance climate resilience.

As discussed in Section 3.2, comparative epigenomic studies between thermotolerant breeds such as Brahman cattle and thermosensitive breeds have identified candidate epigenetic markers associated with heat adaptation (Srikanth et al., 2017; Gim et al., 2020). Incorporating these markers into breeding programs could accelerate selection for heat tolerance, which is particularly important given that traditional genetic improvement for this trait is slow due to low heritability and unfavorable genetic correlations with production traits (Carabaño et al., 2019).

7.2 Nutritional Resilience and Feed Efficiency

Climate change affects feed quality and availability, requiring livestock to maintain productivity on sub-optimal diets (Thornton et al., 2009). Epigenetic mechanisms influencing metabolic efficiency and nutrient partitioning may be targets for enhancing nutritional resilience (Yan et al., 2013; Paradis et al., 2017). Studies have shown that early nutritional programming through strategic feeding of dams or neonates can induce favorable epigenetic modifications that improve feed efficiency and metabolic health in offspring (Laporta et al., 2020; Cai et al., 2014). Understanding these mechanisms could inform management practices that prime animals for efficient resource utilization under variable nutritional conditions.

7.3 Disease Resistance in Changing Environments

Climate change is altering disease epidemiology in livestock, with expanding ranges of pathogens and vectors (Rojas-Downing et al., 2017). Epigenetic regulation of immune function, including trained immunity offers potential mechanisms for enhanced disease resistance (Netea et al., 2016; Penney et al., 2022).

Vaccination strategies that leverage epigenetic reprogramming of immune cells to establish long-lasting protective immunity are being investigated (Scharer et al., 2019). Additionally,

nutritional interventions that support immune epigenetics, such as supplementation with immunomodulatory fatty acids or polyphenols, may enhance disease resistance (Dechow et al., 2020; Han et al., 2021).

8. Challenges and Future Directions

Despite substantial progress, several challenges must be addressed to fully realize the potential of epigenetics in livestock breeding and production.

8.1 Technical and Economic Challenges

High Costs: Comprehensive epigenome profiling remains expensive compared to genomic genotyping, limiting large-scale application (Murdoch et al., 2016; Zentner & Henikoff, 2015). While sequencing costs continue to decline, the bioinformatic analysis and interpretation of epigenomic data require specialized expertise and computational resources (Zhou et al., 2018).

Tissue Specificity: Epigenetic patterns are highly tissue-specific, creating challenges for accessible sampling in live animals (Langevin & Kelsey, 2013). Blood-based epigenetic markers are convenient but may not accurately reflect epigenetic states in economically relevant tissues like muscle, mammary gland, or reproductive organs (Guintivano et al., 2013). Developing surrogate tissue approaches or identifying tissue-shared epigenetic marks is a research priority.

Temporal Dynamics: Epigenetic marks change over developmental stages, ages, and in response to environmental fluctuations, requiring careful consideration of sampling timing and standardization of protocols (Hannum et al., 2013; Horvath & Raj, 2018).

Reference Populations: Large, well-phenotyped reference populations with comprehensive epigenomic profiling are needed to develop accurate prediction models and identify robust biomarkers (González-Recio et al., 2015; Paiva et al., 2019). Building such populations requires substantial investment and coordination among breeding organizations and research institutions.

8.2 Biological Complexity

Epigenetic Stability and Heritability: The stability and heritability of epigenetic marks across generations remain incompletely understood in livestock (Skinner, 2015). While some environmentally-induced epigenetic changes can be transmitted transgenerationally, many are reset during gametogenesis and early development (Heard & Martienssen, 2014). Distinguishing heritable from transient epigenetic variation is essential for breeding applications.

Epigenotype-Environment Interactions: Epigenetic patterns result from complex interactions between genetic background, developmental history, and environmental exposures (Feil & Fraga, 2012). Disentangling these factors to identify causal epigenetic variants is methodologically challenging and requires sophisticated experimental designs and statistical approaches (van Dongen et al., 2016; Xu et al., 2021).

Functional Interpretation: Many epigenetic variants identified through EWAS are correlative associations rather than causal determinants of phenotypes (Flanagan, 2015). Functional validation through experimental manipulation, such as epigenome editing, is needed to establish causality but is resource-intensive (Pulecio et al., 2017).

8.3 Integration into Breeding Programs

Data Management and Infrastructure: Integrating epigenomic data into existing breeding databases and genetic evaluation systems requires substantial infrastructure development (Paiva et al., 2019). Standardized data formats, quality control procedures, and analytical pipelines must be established.

Industry Adoption: Convincing breeding organizations and producers to adopt epigenetic technologies requires clear demonstration of economic value, practical feasibility, and return on investment (Van Eenennaam, 2019). Pilot projects that quantify the added value of epigenetic information for specific traits and production systems will be crucial.

Education and Training: Capacity building in epigenetics, bioinformatics, and data science is needed within the livestock genetics community (Gutiérrez-Gil *et al.,* 2022). Training programs for breeders, geneticists, and technicians will facilitate technology transfer and implementation.

8.4 Future Research Priorities

Key research priorities for advancing epigenetics in livestock include:

Multi-Generational Studies: Longitudinal studies tracking epigenetic patterns across multiple generations to elucidate transgenerational

inheritance and stability (Skinner, 2015; Guerrero-Bosagna & Skinner, 2012).

Functional Epigenomics: Systematic functional characterization of epigenetic variants through epigenome editing and other experimental approaches (Hilton et al., 2015; Liu et al., 2016).

Integration with Other Omics: Combining epigenomic data with genomic, transcriptomic, proteomic, and metabolomic information in systems biology frameworks to capture biological complexity (Xu et al., 2021; Wang et al., 2023).

Computational Methods: Developing advanced machine learning and artificial intelligence approaches for analyzing high-dimensional epigenomic data and improving prediction accuracy (Eraslan et al., 2019; Zou et al., 2019).

Comparative Epigenomics: Cross-species comparative analyses to identify conserved epigenetic regulatory mechanisms and accelerate knowledge transfer from model organisms to livestock (Xiang et al., 2020).

Applied Validation: On-farm validation studies demonstrating practical utility and economic benefits of epigenetic technologies in commercial production systems (González-Recio et al., 2015).

9. CONCLUSION

Epigenetics represents a paradigm-shifting field that bridges genetics, environment, and phenotype in livestock production. The mechanisms of DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation collectively enable dynamic, reversible modulation of gene expression in response to developmental signals and environmental inputs. This molecular flexibility allows animals to adapt to diverse production conditions, though it also creates vulnerability to adverse environmental exposures during critical developmental windows.

Evidence demonstrates that epigenetic variation contributes substantially to phenotypic diversity in economically important traits, including growth, reproduction, milk production, meat quality, feed efficiency, and disease resistance. Environmental factors, particularly nutrition, thermal stress, and pathogen exposure induce epigenetic alterations that can have lasting consequences for individual performance and, potentially, offspring phenotypes through transgenerational inheritance.

The integration of epigenomic information into livestock breeding programs holds considerable promise for enhancing genetic gain, improving environmental adaptation, and addressing the challenges posed by climate change. Epigenome-wide association studies are identifying biomarkers that could complement genomic selection, while advanced technologies like CRISPR-based epigenome editing offer unprecedented precision for modulating gene expression without permanent genetic modifications. These tools may enable the development of climate-resilient, disease-resistant, and highly efficient livestock adapted to diverse and changing production environments.

However, realizing this potential requires overcoming substantial technical, economic, and knowledge gaps. The high cost and complexity of epigenome profiling, tissue-specific nature of epigenetic patterns, incomplete understanding of transgenerational stability, and challenges in functional interpretation all present barriers to widespread implementation. Additionally, regulatory frameworks and public acceptance of epigenetically-modified livestock products remain uncertain.

Despite these challenges, the trajectory of epigenetics research in livestock is promising. Declining sequencing costs, advancing bioinformatic tools, growing datasets, and increasing recognition of epigenetics' importance are converging to make integration into breeding programs increasingly feasible. As the field matures, epigenetic information is likely to become a standard component of comprehensive genetic evaluation systems, complementing DNA sequence-based selection and enabling more holistic approaches to livestock improvement.

Looking forward, the application of epigenetics in livestock production aligns with broader goals of sustainable agriculture producing more food with fewer resources while minimizing environmental impact and enhancing animal welfare. By harnessing epigenetic mechanisms that underlie environmental responsiveness and phenotypic plasticity, the livestock industry can develop animals better suited to future production challenges, ultimately contributing to global food

security in an era of climate change and resource constraints.

The coming decades will determine whether epigenetics transitions from an emerging research field to a practical tool embedded within commercial breeding programs. Success will require continued investment in fundamental research, development of cost-effective profiling technologies, validation of economic benefits, and collaborative efforts among researchers, breeders, and policymakers. As our understanding deepens and technologies mature, epigenetics is poised to play an increasingly central role in shaping the future of livestock production.

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