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Epigenetic regulation of economically important traits in livestock: From molecular mechanisms to precision breeding

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ABSTRACT

Livestock production traits are complex phenotypes influenced by genetic variation, developmental processes, nutrition, environmental exposure, and management. Although conventional genetic and genomic approaches have substantially improved livestock breeding, DNA sequence variation alone does not fully explain phenotypic variation in economically important traits such as fertility, feed efficiency, disease response, milk production, meat quality, and environmental adaptation. Epigenetic mechanisms provide a dynamic regulatory interface between genotype and environment through DNA methylation, histone modifications, chromatin remodeling, non-coding RNAs, and RNA modifications. Increasing evidence in cattle, buffalo, sheep, and other livestock indicates that epigenetic mechanisms contribute to the regulation of growth, muscle development, adipogenesis, milk production, reproductive performance, immunity, and responses to environmental stress. Nutritional and maternal environments can modify epigenetic states during critical developmental windows, potentially contributing to persistent phenotypic programming. Sperm epigenomics has emerged as an important area of reproductive research, with studies identifying fertility-associated DNA methylation and histone modification patterns and exploring their potential as biomarkers for fertility prediction. Heat stress has also been associated with tissue- and context-specific epigenetic remodeling in livestock, although the direction and magnitude of these changes vary across tissues, breeds, and experimental conditions. Despite these advances, most livestock epigenomic studies remain associative, while differences in tissue, developmental stage, breed, environmental exposure, and analytical platforms limit cross-study comparison. Evidence for developmental programming is stronger than that for true transgenerational inheritance. This review critically examines epigenetic regulation of economically important livestock traits, emphasizing the transition from association to functional validation, replication, predictive utility, and integration with genomic selection. Epigenomics is considered a complementary layer of information rather than a replacement for conventional genomic breeding.

Keywords: Livestock, Epigenetics, DNA methylation, Histone modification, Non-coding RNA, Epigenomics, Fertility, Milk production, Meat quality, Heat stress, Precision breeding

1. Introduction

Livestock improvement is fundamentally based on exploiting genetic variation to enhance traits of economic and biological importance. Pedigree-based selection, quantitative genetics, marker-assisted selection, and genomic selection have progressively increased the accuracy and efficiency of genetic improvement. Nevertheless, traits such as fertility, disease response, feed efficiency, and environmental resilience remain challenging to improve because their expression is strongly influenced by physiological state, developmental history, nutrition, management, and environmental conditions (Ibeagha-Awemu *et al.*, 2015; Triantaphyllopoulos *et al.*, 2016; Thompson *et al.*, 2020; Wang *et al.*, 2021) [1, 2, 3, 4].

Epigenetics provides a molecular framework for understanding how developmental and environmental signals can influence gene activity without altering the underlying DNA sequence. DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs constitute major regulatory mechanisms through which cellular states are established, maintained, and modified (Ibeagha-Awemu *et al.*, 2015; Triantaphyllopoulos *et al.*, 2016; Goddard *et al.*, 2014) [1, 2, 5]. Increasing evidence has linked epigenetic variation with production, reproduction, health, development, and adaptive traits in livestock (Ibeagha-Awemu *et al.*, 2015; Triantaphyllopoulos *et al.*, 2016; Thompson *et al.*, 2020; Wang *et al.*, 2021) [1, 2, 3, 4]. The field has subsequently progressed from candidate-gene investigations toward genome-wide analyses of DNA methylation, chromatin accessibility, histone modifications, and regulatory RNA profiles.

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A defining feature of epigenetic information is its dynamic and context-dependent nature. Unlike inherited DNA sequence variants, many epigenetic states vary among tissues and can change with age, developmental stage, physiological status, nutrition, disease, and environmental exposure (Thompson *et al.*, 2020; Wang *et al.*, 2021) [3, 4]. This flexibility makes epigenomics particularly valuable for investigating genotype–environment interactions. At the same time, it presents challenges for its application in animal breeding because epigenetic profiles may be tissue-specific, temporally unstable, and sensitive to environmental conditions.

Recent studies and reviews suggest that epigenomic information may complement genomic selection by providing functional and environmentally responsive information, particularly for traits that are strongly influenced by environmental conditions [6, 7]. However, the practical value of an epigenetic marker depends on its reproducibility, biological relevance, stability, and ability to provide predictive information beyond genotype and conventional phenotypic records.

The present review examines the role of epigenetic regulation in economically important livestock traits, with particular emphasis on cattle and buffalo. It discusses major molecular mechanisms, growth and muscle development, adipogenesis and meat quality, milk production, reproduction and fertility, nutritional regulation, heat stress, developmental programming, immunity, feed efficiency, multi-omics integration, and emerging applications in precision breeding. Particular attention is given to the transition from descriptive associations toward functional validation and predictive applications.

2. Major epigenetic mechanisms in livestock

2.1 DNA methylation

DNA methylation is one of the most extensively investigated epigenetic mechanisms in livestock. It primarily involves the addition of a methyl group to cytosine residues, particularly at CpG sites, resulting in the formation of 5-methylcytosine. DNA methylation can influence transcription-factor binding, chromatin organization, and gene expression (Ibeagha-Awemu *et al.*, 2015; Goddard *et al.*, 2014) [1, 5]. Although promoter methylation is frequently associated with reduced transcription, this relationship is context-dependent. Methylation within gene bodies, enhancers, intergenic regions, and other regulatory elements can have different relationships with transcriptional activity. Therefore, the identification of a differentially methylated region (DMR) should not automatically be interpreted as evidence of transcriptional repression.

Genome-wide approaches such as whole-genome bisulfite sequencing (WGBS), reduced-representation bisulfite sequencing (RRBS), and targeted bisulfite sequencing have enabled high-resolution characterization of DNA methylation. However, methylation profiles are strongly influenced by tissue type, age, developmental stage, physiological condition, breed, and environmental exposure (Thompson *et al.*, 2020; Wang *et al.*, 2021) [3, 4]. Appropriate biological replication and careful control of these factors are therefore essential when interpreting livestock methylome studies.

2.2 Histone modifications

Histones package genomic DNA into chromatin and participate directly in the regulation of gene expression. Post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination can influence chromatin structure and the accessibility of transcriptional machinery (Triantaphyllopoulos *et al.*, 2016; Su *et al.*, 2026) [2, 8]. Different histone marks are associated with distinct chromatin states. For example, H_{3K4me3} is commonly associated with active promoters, H_{3K27ac} with active regulatory regions, whereas $H_{3K27me3}$ is frequently associated with transcriptional repression (Su *et al.*, 2026) [8].

Livestock studies have associated histone modifications with muscle development, adipogenesis, reproductive function, and other economically relevant phenotypes. Their dynamic nature makes histone modifications particularly relevant to developmental and environmental

regulation (Su *et al.*, 2026) [8]. However, interpretation requires consideration of tissue specificity, chromatin context, and the possibility that individual histone marks may have different functions depending on their genomic location.

2.3 Chromatin remodeling

Chromatin accessibility is an important determinant of whether regulatory DNA sequences can interact with transcription factors and other regulatory proteins. ATP-dependent chromatin-remodeling complexes can reposition nucleosomes and alter DNA accessibility. Technologies such as ATAC-seq, ChIP-seq, and CUT&RUN provide complementary information on chromatin organization and regulatory activity.

Integration of chromatin accessibility with DNA methylation and transcriptomic data can strengthen the interpretation of candidate regulatory regions [6, 8]. Such approaches may help distinguish epigenetic changes that are associated with altered cellular activity from those that are more directly involved in transcriptional regulation.

2.4 Non-coding RNAs

Non-coding RNAs comprise diverse regulatory molecules, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and piwi-interacting RNAs (piRNAs). These molecules can influence transcription, RNA stability, translation, chromatin organization, and cellular signaling.

miRNAs have been extensively investigated in livestock, particularly in relation to muscle development, adipogenesis, mammary-gland biology, and reproductive processes (Sun *et al.*, 2015; Dai *et al.*, 2016; Raza *et al.*, 2020; Wang *et al.*, 2014) [9, 10, 11, 12]. Differential miRNA expression has been associated with developmental stages and production phenotypes. However, computational prediction of miRNA targets alone does not establish a functional interaction. Experimental validation is required to demonstrate direct regulatory relationships and biological consequences.

2.5 Epitranscriptomic regulation

RNA modifications, particularly N6-methyladenosine (m6A), represent an expanding area of epigenetic and epitranscriptomic research. m6A can influence RNA stability, processing, localization, translation, and degradation. Compared with DNA methylation and histone modifications, epitranscriptomic research in livestock remains relatively recent. Nevertheless, increasing evidence indicates that RNA modifications may contribute to the regulation of production, reproduction, development, and environmental responses [6, 13].

Future studies integrating m6A profiling with transcriptomics and other epigenomic measurements may provide additional insight into post-transcriptional regulation of economically important traits.

3. Epigenetic regulation of growth and muscle development

Growth and skeletal muscle development involve coordinated regulation of satellite-cell proliferation, myoblast differentiation, protein synthesis, energy metabolism, and endocrine signaling. Epigenetic mechanisms can influence these processes through regulation of transcription factors and signaling pathways involved in myogenesis (Sun *et al.*, 2015; Dai *et al.*, 2016; Raza *et al.*, 2020; Wang *et al.*, 2014) [9, 10, 11, 12]. Bovine skeletal muscle has provided an important model for investigating relationships among DNA methylation, gene expression, and developmental stage. (Huang *et al.*) [14] characterized genome-wide DNA methylation patterns in bovine muscle and examined their relationships with mRNA and miRNA expression. Their findings demonstrated coordinated molecular changes associated with muscle development, supporting the importance of epigenetic regulation in muscle biology.

Several miRNAs, including miR-1 and miR-206, have been investigated in bovine muscle development and satellite-cell biology. These regulatory RNAs are associated with pathways controlling proliferation and differentiation (Dai *et al.*, 2016; Raza *et al.*, 2020) [10, 11].

Such findings indicate that non-coding RNAs can contribute to the molecular regulation of muscle formation. Early-life nutrition may further influence these regulatory pathways. (Nishino *et al.*) [15] reported that early high nutrition in Japanese Black cattle influenced growth and intramuscular fat deposition and was associated with changes in muscle metabolism involving epigenetic regulation. Their integrated analysis incorporated DNA methylation, gene expression, metabolites, and rumen-related measurements. Collectively, these findings support a model in which developmental nutrition can influence molecular pathways associated with muscle growth and composition. However, individual methylation differences should not be considered independent causal determinants unless supported by functional experiments.

4. Adipogenesis and meat quality

Intramuscular fat is an important determinant of beef quality and contributes to marbling, tenderness, juiciness, and sensory characteristics. Adipocyte differentiation is regulated by transcription factors such as PPARG, CEBPA, and SREBF1, together with genes involved in fatty acid synthesis, transport, and metabolism [16, 17, 18].

DNA methylation has been associated with the regulation of genes involved in lipid deposition and adipocyte differentiation. (Huang *et al.*) [14] demonstrated extensive relationships among DNA methylation, mRNA, and miRNA expression in bovine muscle, highlighting the interconnected nature of these regulatory layers. Other studies have examined epigenetic regulation of genes involved in lipid metabolism and intramuscular fat deposition.

A recent review emphasized the potential contribution of DNA methylation, histone modifications, and non-coding RNAs to intramuscular fat deposition in beef cattle (Abebe *et al.*, 2024) [16]. However, interpretation of bulk muscle epigenomic data is complicated by heterogeneous cellular composition. Muscle tissue contains myofibers, adipocytes, connective-tissue cells, vascular cells, and immune cells. Differences in the proportions of these cell types can therefore contribute to apparent epigenetic differences between animals or developmental stages. Future studies combining epigenomic profiling with single-cell approaches, histological measurements, and cell-type-specific analyses may help distinguish genuine regulatory changes from differences arising primarily from cellular composition.

5. Epigenetic regulation of milk production

Milk production depends on mammary epithelial-cell development, endocrine signaling, nutrient availability, cellular metabolism, and stage-specific regulation of mammary-gland function. Early studies proposed that epigenetic mechanisms could contribute to milk production through changes in mammary-gland gene expression (Singh *et al.*, 2010; Singh *et al.*, 2012) [19, 20]. Subsequent genome-wide studies have been increasingly combined DNA methylation and transcriptomic data. An integrated methylome and transcriptome analysis in dairy cattle identified differentially methylated regions and differentially expressed genes and highlighted candidate genes including DOCK1, PTK2, and PIK3R1 [21]. Such integrative studies provide stronger molecular evidence than methylation profiling alone because changes in DNA methylation can be examined alongside corresponding changes in gene expression.

Non-coding RNAs may also contribute to mammary-gland regulation. (Wang *et al.*) [22] demonstrated that *miR-152* can regulate DNA methyltransferase 1 and is involved in mammary-gland development and lactation in dairy cattle. Other investigations have identified stage-of-lactation-associated miRNA expression patterns (Wang *et al.*, 2012) [23]. However, interpretation of mammary epigenomic studies requires careful consideration of parity, lactation stage, nutritional status, udder health, production level, and mammary-cell composition. An epigenetic difference between high- and low-producing cows may represent a consequence of different physiological states rather than an upstream determinant of milk production. Longitudinal studies and functional validation are therefore essential for establishing temporal and biological relationships.

6. Epigenetic regulation of reproduction and fertility

Reproductive efficiency is one of the most economically important components of livestock production. Fertility is influenced by genetic background, endocrine status, nutrition, age, semen quality, reproductive management, and environmental stress. Sperm is particularly attractive for epigenomic research because it can be collected repeatedly and fertility phenotypes can be linked with large numbers of artificial-insemination records.

6.1 Buffalo sperm DNA methylation

(Verma *et al.*) [24] compared sperm DNA methylation profiles between high-fertility and subfertile buffalo bulls. The study included five bulls in each fertility group and used a custom buffalo CpG-island/promoter microarray. Ninety-six individual genes and an additional 55 CpG-island-associated genes were differentially methylated. The identified genes were associated with germ-cell development, spermatogenesis, capacitation, and embryonic development (Verma *et al.*, 2014) [24]. This study provided early evidence that sperm DNA methylation profiles can differ according to fertility status in buffalo and established a foundation for subsequent livestock sperm-epigenome research.

6.2 Histone modifications in buffalo sperm

(Verma *et al.*) [25] subsequently investigated genome-wide H_{3K4me2} and $H_{3K27me3}$ profiles in buffalo sperm. Eighty-four genes showed differential H_{3K4me2} enrichment, while 80 genes showed differential $H_{3K27me3}$ enrichment between high-fertility and subfertile bulls. Functional annotation implicated pathways associated with germ-cell development, spermatogenesis, and embryonic development (Verma *et al.*, 2015) [25]. These findings demonstrate that reproductive epigenetics extends beyond DNA methylation to chromatin-level regulation and suggest that multiple epigenetic layers may contribute to sperm quality and fertility.

6.3 Bovine sperm methylome and fertility

Subsequent studies in cattle have used RRBS and whole-genome methylation approaches to identify fertility-associated CpG sites and differentially methylated regions [26, 27, 28, 29, 30]. (Costes *et al.*) [26] examined 100 Montbéliarde bulls and identified 490 fertility-associated differentially methylated cytosines. Their study also demonstrated the feasibility of using sperm methylation profiles for fertility prediction through a Random Forest model. This represents an important progression from descriptive association toward biomarker development.

However, predictive performance within a study population does not establish generalizability. Independent validation across breeds, herds, geographic regions, and management systems is required before such biomarkers can be considered suitable for routine breeding applications. Whole-genome methylation studies have similarly identified candidate regions associated with bull fertility (Zhang *et al.*, 2023) [27]. Other investigations have reported associations between sperm methylation signatures and daughter fertility (Zhang *et al.*, 2023) [28], raising the possibility that paternal epigenomic information may be relevant to offspring reproductive outcomes. Such findings require cautious interpretation. An association between paternal sperm methylation and offspring fertility does not by itself demonstrate transgenerational inheritance because genetic relationships, paternal breeding value, maternal effects, and postnatal environmental factors may contribute to the observed association.

6.4 Sperm histone modifications and fertility

Histone modifications have also been investigated in bovine sperm. Studies have reported associations between H3K27 acetylation or methylation and bull fertility [29]. These findings support the broader concept that sperm chromatin organization may contribute to male reproductive quality. Recent reviews have emphasized that sperm epigenomics is developing rapidly but that reproducibility, breed specificity, assay standardization, sample size, and functional valida

tion remain important challenges (Sethi *et al.*, 2026; Bourassi *et al.*, 2026) [31, 32].

7. Nutritional regulation of the epigenome

Nutrition is an important environmental factor capable of influencing epigenetic regulation. Nutrients involved in one-carbon metabolism, including methionine, folate, choline, and betaine, can influence methyl-group availability and thereby potentially affect DNA methylation. Nutritional substrates can also alter cellular metabolites involved in the activity of chromatin-modifying enzymes [33, 34, 35]. However, nutritional epigenetic responses are highly context-dependent. They may vary according to nutrient dose, animal age, developmental stage, genotype, tissue type, physiological status, and baseline nutritional condition. Maternal nutrition is particularly important because fetal development represents a period of extensive epigenetic reprogramming.

(Amorín *et al.*) [36] investigated the effects of maternal diet on DNA methylation in skeletal muscle of beef calves and reported persistent methylation differences during postnatal development. Other studies have similarly demonstrated associations between maternal nutritional conditions and offspring molecular phenotypes [37, 38]. These findings support the concept of developmental programming but should not automatically be interpreted as evidence of inheritance. An epigenetic alteration that persists throughout the lifetime of an individual represents developmental programming unless evidence demonstrates transmission through subsequent generations.

8. Heat stress and epigenetic adaptation

Heat stress is a major environmental constraint affecting livestock productivity, particularly in tropical and subtropical production systems. Thermal stress can reduce feed intake, alter endocrine and metabolic pathways, impair reproductive performance, modify immune function, and reduce production efficiency. Epigenetic mechanisms are increasingly being investigated as potential molecular mediators connecting thermal exposure with altered gene regulation [39, 40, 41, 42, 43, 44].

8.1 Cattle methylome responses to heat stress

The study *Methylome Patterns of Cattle Adaptation to Heat Stress* compared Nellore and Angus bulls using RRBS and identified methylation differences associated with breed and thermal adaptation [39]. The findings provided evidence that cattle with different levels of heat adaptation may exhibit distinct epigenomic responses to thermal exposure. Indian cattle research has similarly investigated DNA methylation and stress-related gene expression in Sahiwal, Tharparkar, Hariana, and Vrindavani cattle [40]. Such studies are particularly relevant to tropical livestock production because indigenous *Bos indicus* cattle have evolved under environments characterized by relatively high thermal loads.

8.2 Tissue-specific and context-specific responses

Heat stress does not produce a single uniform epigenetic response. Methylation patterns may vary according to tissue, exposure duration, breed, age, physiological status, and environmental conditions. Recent reviews emphasize that DNA methylation represents only one component of heat-stress-related epigenetic regulation, alongside histone modifications, chromatin remodeling, and non-coding RNAs (Aravindh *et al.*, 2025) [41]. A recent systematic synthesis of cattle studies further highlighted substantial heterogeneity among experimental designs and biological contexts, making quantitative pooling of global methylation responses difficult (Bejaoui *et al.*, 2026) [42]. Therefore, heat stress should not be assumed to cause universal genome-wide hypermethylation or hypomethylation. Interpretation should instead focus on tissue-specific regulatory changes and their relationship with physiological and phenotypic responses.

8.3 Heat stress, oocytes, and embryos

Heat stress can influence reproductive processes even before conception. Recent experimental work has demonstrated effects of in vivo and in vitro heat stress on DNA methylation and hydroxymethylation in bovine oocytes and early embryos [43]. These findings are relevant because epigenetic states established during early development can influence embryonic competence and subsequent development. Nevertheless, molecular alterations should be interpreted alongside embryo-development outcomes rather than assumed to be directly causal.

9. Developmental programming and epigenetic inheritance

Developmental programming refers to persistent changes in an individual's phenotype resulting from environmental exposure during critical periods of development. Epigenetic regulation represents one potential molecular mechanism underlying such programming.

Livestock studies have reported associations between maternal nutrition, maternal heat exposure, and offspring molecular phenotypes [45, 46, 36, 37, 38]. However, developmental programming, intergenerational inheritance, and transgenerational inheritance are distinct concepts and should not be used interchangeably.

When a pregnant dam is exposed to an environmental factor, the fetus is directly exposed. In addition, developing germ cells within the fetus may also be exposed. Consequently, effects observed in the F_1 or F_2 generation do not necessarily represent true transgenerational inheritance.

True transgenerational inheritance requires persistence of the phenotype or molecular state in generations that were not directly exposed to the original environmental stimulus. (Laporta *et al.*) [46] reviewed evidence for intergenerational and transgenerational effects of heat stress and concluded that phenotypic evidence exists, whereas molecular evidence supporting true transgenerational inheritance remains limited.

Accordingly, livestock studies should apply inheritance terminology cautiously and provide evidence for molecular persistence across generations before classifying an observed effect as transgenerational.

10. Epigenetics, immunity, and disease

Immune responses involve rapid changes in gene expression, cellular differentiation, and inflammatory signaling, making epigenetic regulation particularly relevant to disease biology. DNA methylation, histone modifications, and non-coding RNAs can participate in inflammatory and immune pathways.

In livestock, these mechanisms are increasingly being investigated in mastitis, infectious diseases, and stress-associated immune responses. Mammary-gland disease provides an important example because immune activation can simultaneously influence epithelial-cell function and milk production.

However, interpretation of disease-associated epigenomic differences requires particular attention to cellular composition. Blood and tissue samples contain multiple cell types, and disease can alter the relative abundance of leukocytes and other immune populations. Consequently, apparent DNA methylation differences may reflect changes in cell composition rather than changes within individual cell types.

Single-cell RNA sequencing and single-cell chromatin profiling provide promising approaches for separating cell-composition effects from cell-specific regulatory changes.

11. Feed efficiency and metabolic traits

Feed efficiency is influenced by nutrient intake, digestion, rumen fermentation, energy metabolism, nutrient partitioning, and tissue-specific utilization of absorbed nutrients. Because metabolic intermediates can influence the activity of epigenetic enzymes, nutrition and epigenetic regulation are closely interconnected.

Integrated genomic and methylation analyses have identified candidate epigenetic contributions to residual feed intake and feed efficiency in cattle (Hu *et al.*, 2023) [47]. The work of (Nishino *et al.*) [15] further illustrates relationships among early nutrition, muscle metabolism, and epigenetic regulation.

In dairy sheep, integration of epigenomic and genomic information with machine-learning approaches has recently been explored for predicting feed efficiency traits [48]. Such studies represent an emerging approach for combining relatively stable genetic information with potentially dynamic epigenomic measurements.

However, predictive improvement should always be evaluated against genomic-only and phenotype-based models. The key question is whether epigenomic information provides meaningful incremental predictive value that is sufficient to justify its additional cost, complexity, and potential instability.

12. From epigenetic association to causal evidence

One of the central challenges in livestock epigenomics is distinguishing biological association from causation. The identification of a DMR associated with an economically important phenotype represents an important discovery, but it does not establish that the epigenetic change caused the phenotype.

A useful evidence hierarchy can be summarized as follows:

Evidence level	Description	Interpretation
1	Differential epigenetic mark	Association
2	Epigenetic mark associated with gene expression	Molecular concordance
3	Mark located within a plausible regulatory region	Regulatory plausibility
4	Experimental manipulation alters gene expression	Functional evidence
5	Manipulation alters the phenotype	Causal evidence
6	Independent replication	Reproducibility
7	Incremental predictive value beyond existing predictors	Predictive utility
8	Validation under field conditions	Practical application

DNA sequence → epigenetic state → chromatin accessibility → gene expression → protein activity → metabolites → physiology → economic phenotype

Consequently, future livestock studies should increasingly integrate genomic information with:

- DNA methylation;
- histone modifications;
- chromatin accessibility;
- RNA sequencing;
- miRNA and other non-coding RNA profiles;
- proteomics;
- metabolomics;
- microbiome data; and
- environmental measurements.

Multi-omics approaches can provide stronger biological evidence when multiple molecular layers converge on the same biological pathway.

For example, a candidate region supported by genetic association, differential methylation, altered chromatin accessibility, and corresponding RNA or protein changes provides a stronger mechanistic hypothesis than a methylation association alone. Such integrative approaches

Most livestock epigenomic studies currently fall within the early levels of this hierarchy. A DMR located within an economically relevant gene should therefore be regarded as a candidate regulatory marker, rather than as a causal variant equivalent to a functional DNA sequence mutation. Experimental approaches such as reporter assays, CRISPR/dCas9-based epigenome editing, targeted methylation manipulation, and gene perturbation can provide stronger evidence of causality [49, 50]. Combining these approaches with longitudinal phenotyping and independent replication will be important for translating epigenomic discoveries into useful biological and breeding applications.

13. Epigenomics and genomic selection

Genomic selection uses inherited DNA sequence information to predict breeding values. Epigenomic information differs fundamentally because it can respond to environmental and physiological conditions. Recent reviews therefore propose epigenomic information as a complementary component of genomic selection rather than a replacement for conventional genomic breeding [6, 7].

Potential applications include:

- fertility prediction;
- heat-stress response;
- disease response;
- feed efficiency;
- developmental programming;
- metabolic efficiency; and
- environmentally sensitive traits.

The critical question should be:

Does adding epigenomic information improve prediction beyond pedigree, genotype, phenotype, and environmental information?

This can be evaluated using nested cross-validation, independent validation populations, and direct comparisons between genomic-only and genomic-plus-epigenomic prediction models.

If epigenomic information does not provide sufficient incremental predictive value to justify its cost, measurement requirements, and potential instability, routine implementation may not be warranted.

14. Multi-omics integration

Epigenetic regulation represents one component of a multilayered biological system that can be conceptualized as:

may also help distinguish upstream regulatory changes from downstream consequences of altered physiology.

15. Single-cell epigenomics

Bulk tissue analysis averages molecular signals across multiple cell populations. This limitation is particularly relevant to tissues such as muscle, mammary gland, blood, liver, and reproductive tissues, where several functionally distinct cell types coexist.

Single-cell RNA sequencing can identify cellular populations and transcriptional states, whereas single-cell ATAC-seq can characterize cell-specific chromatin accessibility. Emerging single-cell methylation approaches may further resolve cellular heterogeneity in DNA methylation.

The development of scATAC-seq and other high-resolution epigenomic technologies has expanded the possibility of constructing cell-type-specific regulatory maps in livestock [6, 8].

However, the high cost of these technologies, substantial computational requirements, and limited availability of well-annotated livestock reference datasets currently restrict their routine application. Increasingly accessible single-cell datasets and standardized analytical pipelines will be important for broader adoption.

16. Artificial intelligence and machine learning

The high dimensionality of epigenomic datasets creates opportunities for machine-learning approaches in livestock research. Potential applications include fertility prediction, biomarker discovery, phenotype classification, feature selection, regulatory-network prediction, and multi-omics integration. The bull-fertility study by (Costes *et al.*) [26] demonstrated the feasibility of using Random Forest models based on sperm methylation profiles for fertility prediction. Such approaches illustrate how epigenomic information may eventually contribute to biomarker-based selection.

However, livestock epigenomic datasets often contain thousands of molecular features but relatively small numbers of animals, creating substantial risk of overfitting. Future studies should therefore report independent testing populations, nested cross-validation, calibration, feature-selection procedures, and comparisons with baseline genomic models. Importantly, high predictive accuracy should not be interpreted as evidence that the selected epigenetic features are biologically causal. Predictive utility and biological causality represent distinct forms of evidence.

17. Recommended experimental framework for livestock epigenomics

A robust livestock epigenomic study should ideally incorporate the following stages:

1. Clearly define the economically relevant phenotype.
2. Record breed, pedigree, genomic background, and relevant management factors.
3. Standardize environmental and nutritional conditions wherever possible.
4. Select biologically relevant tissues and sampling time points.
5. Ensure adequate biological replication and statistical power.
6. Perform genome-wide epigenomic profiling using an appropriate platform.
7. Integrate epigenomic data with transcriptomic information.
8. Investigate chromatin accessibility where biologically justified.
9. Account for cellular composition and tissue heterogeneity.
10. Validate candidate regions using independent molecular assays.
11. Perform functional experiments for high-priority candidates.
12. Replicate major findings in an independent population.
13. Compare epigenomic prediction with genomic and phenotype-based prediction.
14. Evaluate the economic feasibility of potential implementation.

This framework can help shift livestock epigenomics from exploratory association toward reproducible biological evidence and practical predictive applications.

18. Future perspectives

Future livestock epigenomics should increasingly move toward longitudinal, multi-environment, and integrative studies rather than isolated cross-sectional comparisons.

Breed-specific reference epigenomes could help distinguish conserved regulatory elements from population-specific adaptations. Accessible biological materials such as semen, blood, and milk may become useful sources for biomarker development if their epigenetic profiles can be reliably connected with biologically relevant tissues and phenotypes.

Integration of epigenomic information with genomic selection represents another important direction. However, the objective should not simply be to maximize the number of molecular features incorporated into prediction models. Greater emphasis should instead be placed on identifying stable, reproducible, biologically interpretable, and economically informative markers.

CRISPR/dCas9-based epigenome editing may provide valuable experimental tools for determining whether specific methylation or chromatin states have causal effects [49, 50]. At present, these approaches should primarily be regarded as research tools rather than established livestock breeding technologies.

Recent reviews suggest that future precision breeding will increasingly require integration of genetic, epigenetic, transcriptomic, metabolic, and environmental information rather than dependence on any single molecular layer [6, 7, 8]. Such integration could improve understanding of complex traits and help identify animals that are better adapted to specific production environments.

19. Conclusion

Epigenetic regulation represents a dynamic molecular interface connecting genetic variation, developmental history, nutrition, and environmental exposure with phenotypic expression. Evidence from cattle, buffalo, sheep, and other livestock demonstrates that DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs contribute to the regulation of economically important traits, including growth, muscle development, adipogenesis, milk production, fertility, feed efficiency, immunity, and environmental adaptation. These findings highlight the potential of epigenomics to provide biological information that is not captured by DNA sequence variation alone.

Among emerging applications, sperm epigenomics provides an important framework for investigating male fertility and identifying potential molecular biomarkers associated with reproductive performance. Similarly, research on maternal nutrition, developmental programming, and heat stress demonstrates that environmental conditions can influence epigenetic states during critical developmental periods. However, substantial variation among tissues, breeds, developmental stages, environmental conditions, and experimental approaches currently limits direct comparison across studies.

A major priority for future research is therefore to move beyond the identification of epigenetic associations and establish their reproducibility, biological function, temporal stability, and predictive value. Integration of epigenomic information with genomics, transcriptomics, proteomics, metabolomics, phenotypic records, and environmental data may provide a more comprehensive understanding of complex livestock traits.

At present, epigenomics should be viewed as a complementary layer to genomic selection rather than a replacement for conventional breeding approaches. Its greatest practical value is likely to emerge through validated biomarkers, integrated multi-omics strategies, environmentally informed prediction, and carefully designed experiments capable of establishing biological function and demonstrating meaningful improvement in prediction or selection efficiency.

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