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Review

# Epigenetics: An Unusual Pattern of Inheritance

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## Abstract

*Epigenetics is an emerging field of research that has attracted much interest in genetic studies of various diseases and disorders. It plays a significant role in various biological phenomena such as gene expression in early embryonic development, silencing, and imprinting of transposons, etc. Recently, it has been shown that epigenetic effects can be inherited from one generation to the next. An individual is exposed to a certain kind of environment its entire life which is capable of triggering chemical changes which can activate or silence genes. For example, diet, exercise, stress, seasonal changes, exposure to therapeutic drugs, etc. are capable of bringing out beneficial or detrimental epigenetic changes that can affect metabolism, health, and development. All these factors can alter the epigenetic profile of an individual permanently.*

**Keywords:** Epigenetics, Genetics, Inheritance, Livestock

## Introduction

In early 1940s, British Biologist Conrad Waddington coined the term “Epigenetics” blending the terms Epigenesis and Genetics, to interpret how genes interact with their surroundings to produce a phenotype. Since then, accumulative research has improved our understanding of this field and also expanded the meaning of the term epigenetics. Epigenetics broadly describes the study of stable heritable changes in gene function that occur without any alteration of the DNA sequences. Epigenetic processes are essential for development and cellular differentiation and are also responsible for the aging and development of several diseases, including cancer. Evidence indicates that both cellular (endogenous) and environmental factors influence epigenetic processes. These processes include DNA methylation, histone modifications, and micro RNAs, and they can help to explain how cells with identical DNA can differentiate into different cell types (Maiti, 2012).

In life science, epigenetics may be defined as the study of heritable phenotype changes that do not include alterations in the DNA sequence. The Greek prefix epi- (ἐπι- "over, outside of, around") means "on top of" or "in addition to" the classical genetic basis for inheritance. Epigenetics usually includes those alterations which affect the activity and expression of the gene but this term may also be applied to any heritable phenotypic change. These effects on cellular and physiological phenotypic traits may arise from external or environmental factors, or through normal development. The standard definition of epigenetics necessitates these alterations to be heritable in the next generation of either cells or organisms (Jaenisch and Bird, 2003).

Epigenetics shows that not all genetic information is in the DNA sequence but also in some modifications that occur along the epigenome, particularly DNA methylation (DNAm) in which a methyl group is added to the 5’ position of the Cytosine -Pyrimidine ring (Gonzalez-Recio, 2012). The genome defines the complete set of genetic information contained in DNA residing within the cell of each organism. The epigenome on the other hand comprises the complex modifications associated with genomic DNA imparting a unique cellular and developmental identity. Cytokines, growth factors, alterations in hormonal levels as well as the release of stress-response and neurotropic factors are some examples of molecules that are modulated by the environment and which come under the category of epigenome modifiers. Ultimately, the environment presents these various factors to the individual that influence the epigenome, and the unique epigenetic and genetic profile of each individual also modulates the specific response to these factors (Kanherkar *et al.*, 2014).

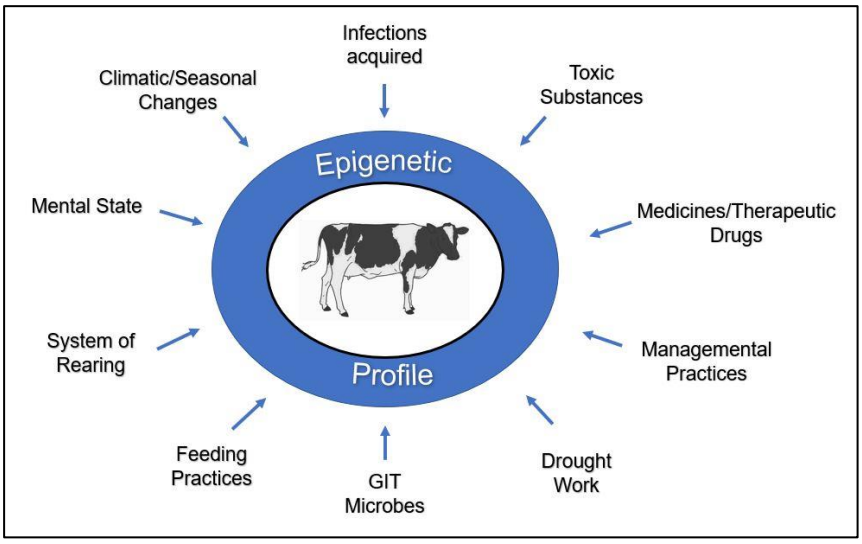


**Fig.1**: Factors that may affect the epigenetic profile of an organism

In this way, in comparison with the genome the epigenome gets affected by lots of factors such as intracellular stimulus as well as extracellular stimulus, through intercellular communication, by neighboring cells, by physiology, or completely by the environment which is provided to the organism. A compilation of epigenetic influences on cattle has been shown in Fig.1.

## Epigenetics in Livestock Production

There are various examples of epigenetic modifications in livestock and living beings as well. One of the examples of epigenetic changes in eukaryotic biology is the process of cellular differentiation. Totipotent stem cells differentiate into the various pluripotent cell lines of the embryo at the time of morphogenesis and these cell lines result in entirely differentiated cells. In other words, a single fertilized egg cell becomes the zygote and then continues to divide, the resulting daughter cells give rise to different kinds of cells in an organism, including neurons, muscle cells, epithelium, endothelium of blood vessels, etc. by activating or by inhibiting the expressions of some genes (Reik, 2007).

The classical example of a solitary mutant sheep that was named 'Solid Gold' illustrates beautifully that low epigenetic changes can influence the inheritance of a trait, which is primarily controlled by a protein-coding gene. 'Solid Gold' was a ram (male sheep) that was born in an Oklahoma sheep ranch in 1983 (Oklahoma is a city in the USA) and had a prodigiously large rear end (the so-called 'big bottom' or 'beautiful buttocks'), which was a muscle hypertrophy. The trait was later described as a 'callipyge' phenotype, since the locus for this trait was named 'callipyge' (CLPG), meaning beautiful buttocks (Charlier *et al.*, 2001). Due to its heavy meaty buttocks, the mutant ram 'Solid Gold' was considered to be a money-making entity (due to increased yield of meat) and was therefore promptly selected for multiplication. 'Solid Gold' transmitted this muscle hypertrophy to an estimated 15% of its offspring. However, further matings performed between hypertrophied male (the 'callipyge' phenotype) descendants of 'Solid Gold' and unrelated wild-type ewes gave a 1:1 sex-independent segregation ratio. This is what one would expect, if the trait is dominant in nature and if the callipyge phenotype was heterozygous and the wild type is homozygous recessive for the gene controlling this trait. However, the inheritance was found to be much more complex, when studied in detail and the unexpected results were explained on the basis of (i) epigenetic changes involved in genome imprinting, and (ii) the ncRNA causing gene silencing (Gupta, 2013).

The results of reciprocal crosses involving callipyge and normal phenotype in sheep have been illustrated in fig. 2 (a, b) and 03 (a, b)**.** As mentioned in these figures, a cross between hypertrophied male (with callipyge phenotype) descendants of the 'Solid Gold' and unrelated wild-type ewes gave a 1:1 ratio between the mutant and the wild-type (Fig.2 a). The ratio was sex-independent (i.e. 1:1 ratio both in male and female progeny), suggesting that the trait was apparently autosomal dominant. However, in the progeny of the reciprocal cross (callipyge female x normal male), none of the offspring was callipyge, as if callipyge switched from the dominant to become a recessive trait (Fig.2 b) but these normal-looking offspring did include carriers of callipyge trait (as confirmed through the use of molecular markers). When the normal-looking ewes (females), which were carriers of the mutation callipyge, were crossed with non-carrier normal rams (males), the carrier female did not transmit the trait and the lambs were normal (Fig.3 a). But when the normal-looking carrier's males were crossed with non-carrier normal females, 1:1 segregation was observed (Fig.3 b). This suggested that the trait appeared only when the sheep inherited the gene for the trait from the sires (male parent) and not when it is inherited from the dams (female parent) (Gupta, 2013).

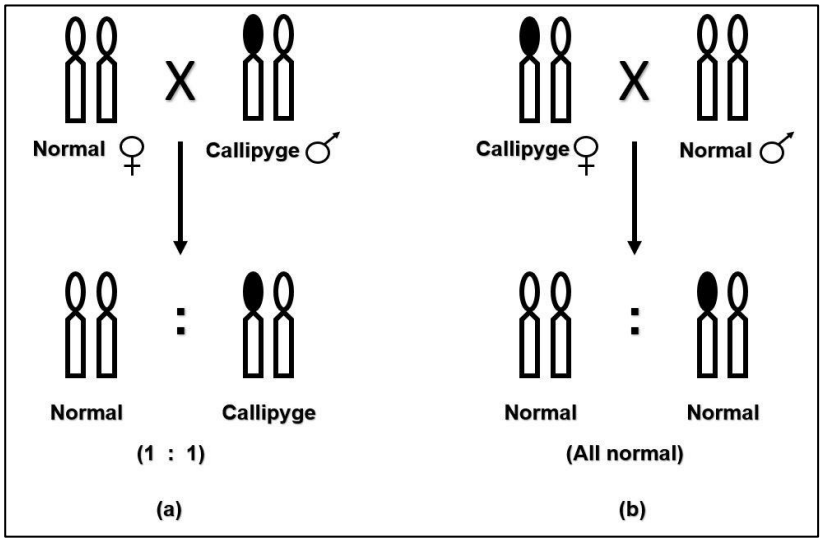


**Fig.2**: Reciprocal crosses of callipyge and normal phenotype in sheep

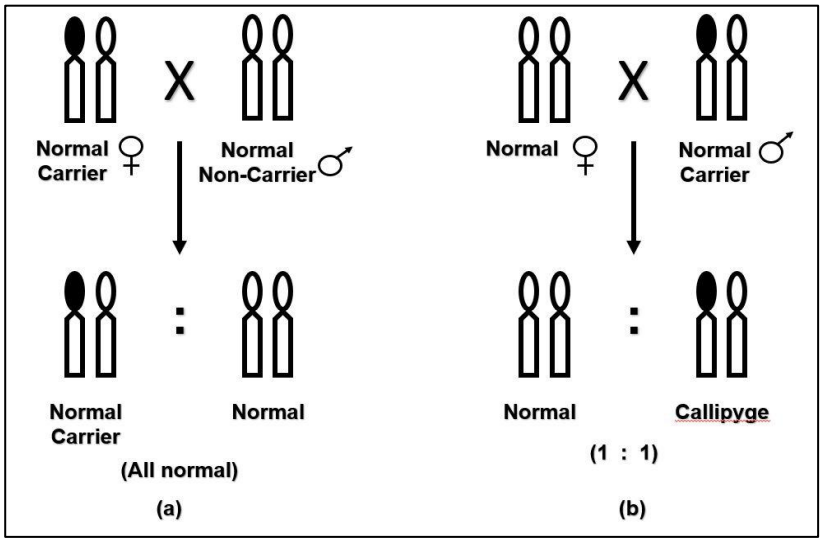


**Fig.3**: Reciprocal crosses involving normal carriers for callipyge with normal non carriers in sheep

The most surprising results were obtained from the cross *callipyge* ewe x *callipyge* ram (both assumed to be heterozygous), where the ratio was neither 3:1 (expected due to an autosomal dominant trait) nor was it 1:1 (expected from an imprinted paternally expressed gene); instead, the ratio was close 1:3 (callipyge: wild-type).

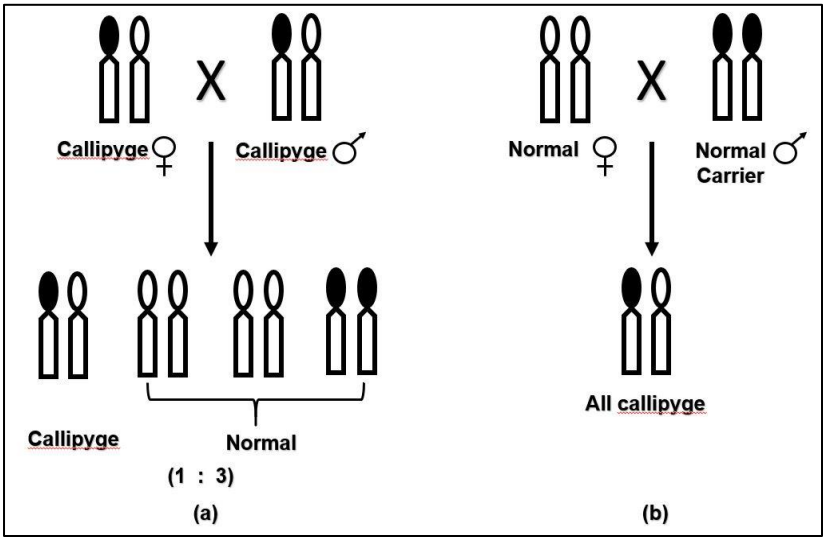


**Fig.4**: Results of crosses involving (a) callipyge x callipyge; (b) normal non-carrier female x normal carrier male (homozygous for callipyge)

Even more surprising was the observation that even the homozygotes for *callipyge* dominant allele (CLPG/CLPG) as determined with the help of associated molecular markers had wild phenotype and not the expected callipyge phenotype (Fig.4 a). This suggested that the only sheep which develop big bottoms are those that receive just one copy of the mutation from the father and none from the mother. This phenomenon was described as polar overdominance. When the rams that were homozygous for the mutant allele were crossed with normal females, all the progeny was callipyge (Fig.4 b), since both homologous chromosomes (each carrying CPLG) had a male imprint (Charlier *et al.*, 2001 and Gupta, 2013).

## Mechanism Underlying Epigenetics

An identical genome is carried by each cell in an organism but the ultimate phenotype of an organism does not fix despite the stability of these instructions, and deviation may arise due to changes in gene expression in response to environmental cues. DNA methylation, histone modification, and RNA-associated silencing are the major ways these changes are controlled (Kanherkar *et al.*, 2014).

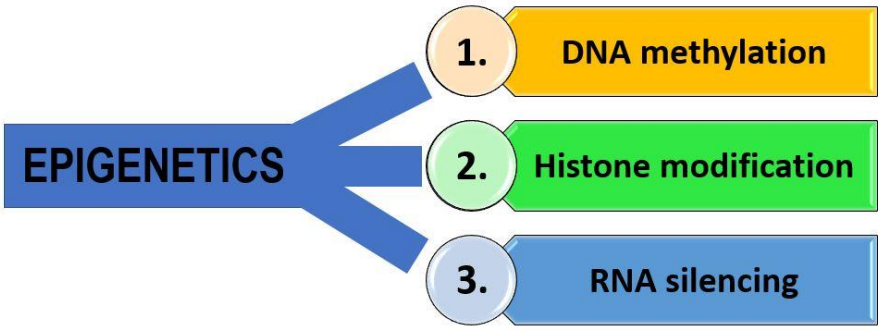


**Fig. 5**: Mechanism underlying epigenetics

### *a. DNA Methylation*

The genomic distribution of methylated DNA sequence present in a cell is known as methylome, this methylome has got the ability to undergo alterations with respect to the environment or the developmental stage. DNA methylation includes the addition of a methyl group covalently at 5' of the Pyrimidine ring of Cytosine that is represented as 5-methyl C or CMe (Fig.5).

The sites, where promoters rich in CG sequences are found, lead to the transcription of most protein-coding genes in mammals. At these sites, cytosine is positioned next to a guanine nucleotide linked by a phosphate called a CpG site. These short stretches of CpG-dense DNA are identified as CpG islands. Chromatin structure adjacent to CpG island promoters facilitates transcription, while methylated CpG islands impart tight compaction to chromatin that prevents the onset of transcription and gene expression (Kanherkar *et al.*, 2014).

### *b. Histone Modification*

Histones are the highly basic proteins and core components of chromatin complexes. These protein molecules provide a structural backbone around which DNA wraps at regular intervals, packages as nucleosomes, and generates chromatin. The nucleosome makes the first level of chromatin organization and is composed of two of each histones H2A, H2B, H3, and H4, these histones arrange in an octameric core with DNA tightly wrapped around the octamer. Histones regulate DNA packaging with immense influence on the degree of chromatin compaction, influencing transcriptional activity as well as transcriptional silencing (Luger *et al*., 1997).

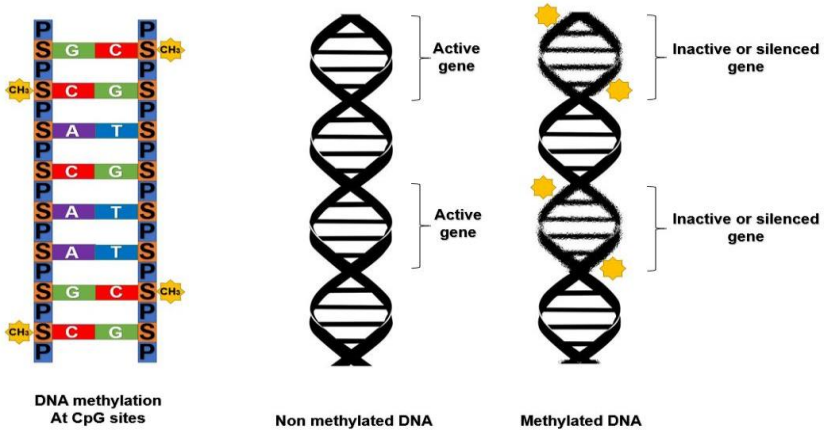


**Fig.6**: Simple representation of the effect of methylated DNA

Histone modifications are post-translational modifications on the histone tails, which are flexible stretches of N or C terminal residues extending from the globular histone octamer. Modifications of histones involve acetylation of lysine residues, methylation of lysine and arginine residues, phosphorylation of serine and threonine residues, and ubiquitination of lysine residues present on histone tails as well as sumoylation and ADP ribosylation. All of these changes affect DNA transcription. The addition or removal of methyl groups on DNA and histones and acetyl groups on histones are the prime mechanisms of changing the epigenetic landscape (Cedar and Bergman, 2009).

### *c. RNA Silencing*

Unlike histone modifications, RNA silencing is a post-transcriptional gene modification during which the expression of one or more genes is downregulated or suppressed by small non-coding stretches of RNA, which are described as microRNAs (miRNA) and small interfering RNAs (siRNA). These RNAs can act as switches and modulators, exerting extensive influence within the cell and beyond (Kanherkar *et al.*, 2014). These RNAs fine-tune the gene expression as they act as specific modulators based on the cell-type specificity of the organism during development as well as pathological conditions (Giraldez *et al*., 2005; Girardot *et al*., 2012; Baer *et al*., 2013). Also, miRNAs have been known to play a role in tumor suppression, apoptosis, cellular proliferation, and cell movement which suggests that they can be manipulated in treating epigenetic diseases like cancer (Kala *et al*., 2013).

## Endogenous and Exogenous Factors Regulating Epigenetic Profile of Gene

There are various genes, expressions of which are governed by various exogenous and endogenous factors. To illustrate the endogenous factors regulating the expression of a gene, let us consider an example of the OCT4 gene. OCT4 is the master pluripotency gene, which is regulated through different stages of human development and its activation is necessary for maintaining pluripotency, whereas it must be silenced in order for a cell to differentiate (Kellner and Kikyo, 2010). In this way, the OCT4 gene remains in an active state in embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and neoplastic cells, however, it remains inactive in fully differentiated cells of an organism. The primary reasons behind the inactivation of the OCT4 gene in differentiated cells involve all three types of mechanisms underlying epigenetics which are illustrated above i.e., DNA methylation, histone modification, and RNA silencing.

Now to understand the impact of various exogenous factors on the expression of the OCT4 gene. Vitrification, done for cryopreservation is found to be associated with the change in the methylation patterns of the OCT4 gene. Milroy *et al*. (2011) and Zhao *et al*. (2012) reported that vitrification resulted in decreased methylation of the OCT4 promoter causing reduced gene expression in mouse blastocysts and the same was observed for mouse oocytes that underwent vitrification followed by in vitro maturation. Simply, in these cases reduction in temperature due to cryopreservation was the epigenetic factor that caused a change in the expression of the OCT4 gene.

## Epigenetics and Lamarckism

Cytosine methylation of DNA is also influenced by the diet of an individual because there are enzymes that take methyl molecules from the basic nutrients such as folic acid and vitamin B12 and transfer them to the cytosine of DNA (Gupta, 2013).

Coat colour in mice is one of the classical examples of it. Normally, the fur of agouti mice is yellow, brown or a calico-like mixture of the two. The trait is under the control of a transposon which is highly methylated thus rendering them inactive. In a study from Duke University (NC, USA) published in 2003 when pregnant mice were fed with methyl-rich diet (including folic acid, vitamin B12, and other methyl-rich compounds) they developed mostly brown fur whereas mice without a methyl-rich diet gave birth to mostly yellow pups with a higher susceptibility to obesity, diabetes, and cancer (Fig.7).

This was despite the fact that all offspring inherited exactly the same agouti gene (i.e., with no nucleotide differences). The transposon located at the 5’ end of the agouti locus gets methylated and shuts off the expression of the agouti gene not just in the recipient mouse but even in offspring. The above study in mice suggests that environmental factors such as nutritional supplements can have a dramatic impact on inheritance not by changing the DNA sequence of a gene or via single nucleotide polymorphism but by changing the methylation of that gene. This also explains why identical twins can have dramatically different phenotypes in different environments (Gupta,

2013).

Hsp90 regulates the gene in *Drosophila*. Hsp90 is a heat shock protein folding over 100 different proteins. Evidence collected in the late 1990s suggested that Hsp90 also functions in chromatin remodeling involved in regulating gene expression. For instance, it has been shown that Hsp90 increases the activity of H3 lysine-4 (H3K4) methyltransferase, SMYD3. Sometimes, Hsp90 can also mask epigenetic variation so that if Hsp90 activity is suppressed (due to a mutation or due can also mask epigenetic variation so that if Hsp90 activity is suppressed (due to a mutation or due to inhibition by a drug, or due to environmental stress) heritable epigenetic variation is released (Gupta, 2013).

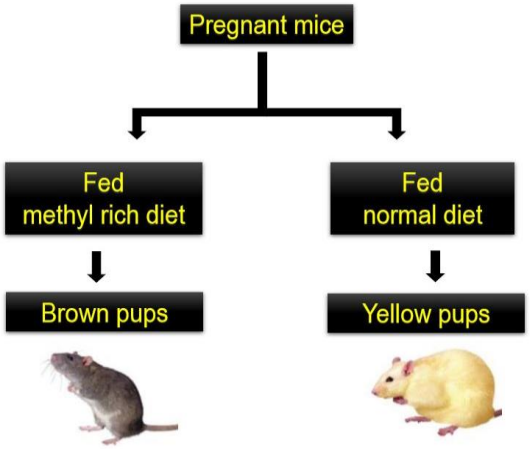


**Fig.7**: Effect of methyl rich diet on pregnant agouti mice

An important environmentally induced heritable epigenetic change involving alterations in Hsp90 is the morphological variation noticed in *Drosophila* eye (appendages-like structure sticking out of the eye) caused by chromatin remodeling. This is one of the most convincing pieces of evidence that epigenetic variation is really heritable and that Hsp90 alterations are Lamarckism. It can therefore be concluded that genetics and epigenetics go 'hand in hand and both along with environmental effects control the phenotype (Gupta, 2013).

## Opportunities in Livestock Production

DNA patterns are modified along the life of an individual by environmental forces like diet, stress, drugs, or pollution among many others (Petronis, 2010). Thus, Epigenetics is an attractive and emerging field for livestock breeding because it may help find part of the missing causality and missing heritability of various quantitative traits and diseases.

Some particular environments are more likely to increase certain kinds of methylation patterns and these patterns would contribute to the phenotypic variation between individuals. Removing this disturbance from the phenotype decomposition equation (infinitesimal model) might help to estimate parameters more accurately. The environment may affect the methylation pattern of up to three generations cohabiting under similar environmental conditions at a given time during pregnancy: the pregnant female, the fetus, and the fetus' germ cells. Nijland *et al.*, (2008) have reported in their studies on sheep that the diet offered to the pregnant ewes had some impact on the birth weight of their granddaughters. Thus, what happens to an animal during its lifetime may have consequences for future generations (Gonzalez-Recio, 2012).

On the basis of research done in humans, we could assume that all these exogenous and endogenous factors also affect the methylation patterns of the genome. For example, animals with concentrated and unique feed diets in intensive systems of rearing are expected to be differently methylated than animals reared in the semi-intensive or extensive system based on pasture feeding. It will be very crucial to find out what practices are associated with favorable methylation patterns that affect disease resistance and other economic traits in livestock. Farms could use epigenetic information to reduce disease incidence and the use of antibiotics in animal production (Gonzalez-Recio, 2012).

## Epigenetics in Livestock Breeding

Environment and environmental stressors are important to understanding evolutionary forces in natural populations (Charmantier and Garant, 2005). Nowadays, Accurate prediction of environmental variations that affect the progeny cannot be done. In cattle, where only 32–80 % of the additive genetic variance can be explained by genetic variation (SNPs, substitutions, etc.) (Haile-Mariam, *et al.,* 2013). Thus, there is a 'missing heritability' component (Yang *et al., 2010*). However, it is highly likely that it is also affected by environmental and epigenetic factors. If the environment in which livestock is being reared is recorded properly within their epigenomes, then definitely it will give more accurate and precise estimation of phenotypic variance which cannot be done by considering genetic variance only. Now, there are methods to estimate epigenetic contribution to the covariance between relatives (Tal *et al*., 2010) and we can begin to analyze the epigenetic variation (Slatkin, 2009).

Despite the hurdles associated with livestock studies, distinguishing epigenetic effects (heritable or not) would provide a great benefit to animal science, husbandry, etc., resulting in improved accuracy of prediction of breeding values (González-Recio, 2012). Single nucleotide polymorphisms (SNPs) and stable epimutations under linkage disequilibrium (LD), could be accounted for in the same way that LD is estimated for the DNA variations alone (Goddard and Whitelaw, 2014).

## Epigenetic Therapies in Livestock Health

Alterations in epigenomic profiles have the potential to change the expression of any gene and consequently may result in various modified physiological states, and in many cases diseases such as type 1 diabetes. Unlike DNA mutations, it must be more straightforward to reverse changes within a 'diseased' epigenome back to a non-diseased state. This has obvious implications for livestock health.

Now it is reported that DNA methylation induced by aging, diet, and heavy metals, etc. can induce neoplasm in cells (Richardson, 2003; Bailey and Fry, 2014). Global changes in histone acetylation levels are also observed in malignancies and there are numerous examples of coding mutations (*e. g. p300/CBP*) and recurrent chromosomal translocations (*e.g.* MLL-CBP) involving histone acetyltransferases. The expression levels of various HDACs (Histone deacetylase) are altered in certain cancers; however, coding mutations are very rare. Histone methylations as well as other modifications are also similarly linked to cancer (Dawson and Kouzarides, 2012).

If the disease status such as cancer is described in terms of epigenetic status then the fact should be noticed that drugs used to cure such pathological state target the epigenetic machinery. These can be classified into two classes: (1) those that target epigenetic enzymes and (2) those that target 'readers' of epigenetic modifications. The majority of drugs, currently approved for clinical use, target DNA methylation and histone acetylation levels by inhibiting the DNA methyltransferases and HDACs (Mirabella *et al*., 2016). Drugs such as azacitidine and Decitabine have shown good results by inhibiting enzymes, such as DNA methyltransferases against myelodysplastic syndromes (MDS).

Chromatin 'readers' are proteins with specialized domains that selectively recognize and bind to modifications on specific histones. An example is, bromodomain-containing protein 4 (BRD4) which contains two tandem bromodomains, termed BD1 and BD2, that bind to acetylated lysine within histone H4 (Devaiah and Singer, 2013). A number of reports have validated BRD4 as a good target for therapeutic intervention and this led to the development of inhibitors, which bind to the bromodomains of BRD4, thereby preventing chromatin association and transcriptional activity. These intelligently designed inhibitors have already shown good efficacy against cancers, such as MLL- translocated acute myeloid leukemias (Dawson *et al*., 2011).

In addition to anti-cancer activity, epigenetic inhibitors possess other interesting characteristics. For instance, BRD4 inhibitors effectively suppress murine cardiomyocyte hypertrophy, in vitro and pathological cardiac remodeling, in vivo (Anand *et al.,* 2013). In this way, the variety of physiological responses achieved through a single inhibitor of disease-causing epigenetic factors highlights how beneficial this approach is going to be inhuman as well as livestock health.

## Challenges in Livestock

One of the major challenges in livestock breeding is to track epigenetic details that alter across the generations. Although, now it has been known for some time that a significant proportion of the phenotypic variance is explained by paternally imprinted loci where one allele's expression differs from the other because expression depends on the parent from whom it was inherited (Monk *et al.,* 2006).

The present livestock upgradation strategies assume that the phenotypic expression of desirable traits is dependent on parental origin. The overall phenotypic expression of these traits is due to various combined genetic and environmental factors. According to livestock breeding theory, most of the traits are affected by a large number of genes but each individual gene contributes only very little to the overall phenotypic variance of the trait (Triantaphyllopoulos *et al*., 2016).

Thus, the effect of an individual gene is of much importance from the aspect of inheritance of quantitative traits. The loci of such genes are referred to as quantitative trait loci (QTL), show parent-of-origin-specific effects, and comprise imprinted loci. This asymmetric allelic expression is established through epigenetic mechanisms during the development of germ cells into sperm or ovum. An imprinted gene is in effect heterozygotic, making it more vulnerable to negative mutational effects that are often connected to disease (Table 01). Thus, a single mutation can have dramatic phenotypic effects. Earlier it was thought that dosage compensation does not occur in the bird. But now it has been reported that many Z-linked genes in the chicken are indeed dosage compensated. The process does not involve sex chromosome inactivation typical of mammals but rather some unknown mechanism. In poultry, it has been suggested that QTLs for economically important traits, such as egg weight, age at first egg, feed intake, egg quality, and body weight with parent-of-origin-specific expression, could be the result of genomic imprinting, which is often assumed to be unique to mammals (Triantaphyllopoulos *et al*., 2016).

Technological advances such as genome-wide next-generation sequencing, dynamic imaging of genomic loci, quantitative proteomics, and computational analyses have facilitated detail mapping of DNA methylation and its derivatives (e.g. 5hmC), captured histone modifications in single cells, and they have significantly contributed to chromatin accessibility studies, such as chromosome conformation capture (3C) technologies (Kubiak *et al*., 2015).

## Conclusions

The investigation of epigenetic forces is a complex mystery to researchers. Epigenetics shows some limitless possibilities for the betterment of livestock health and production. There is still a need to acquire more information to understand the relevance of various epigenetic mechanisms like DNA methylation on genome-wide prediction and enlighten the impact of various epigenetic forces on the state of nature for complex traits. The association among genome, epigenome, and phenotype is to be investigated and the information about epigenome may undrape some additional facts on the relationship between genotype and phenotype. Thus, it will be crucial to find out the managemental practices associated with favorable methylation patterns which enhance the overall health production in livestock farming.

## Contribution by authors

All the authors contributed equally to writing the manuscript. The final manuscript was read by all others and consented to publication.

## Conflict of Interests

There is no conflict of interest.

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## References

1. Anand, P., Brown, J.D., Lin, C.Y., Qi, J., Zhang, R. & Artero, P.C. (2013). Bromodomains mediate transcriptional pause release in heart failure. *Cell*, 154, 569–582.

2. Bailey, K.A. & Fry, R.C. (2014). Arsenic-associated changes to the epigenome: what are the functional consequences? *Current Environmental Health Reports*, 1, 22–34.
3. Cedar, H. & Bergman, Y. (2009). Linking DNA methylation and histone modification: patterns and paradigms. *Nature Review Genetics*, 10, 295-304.
4. Charlier, C., Segers, K., Karim, L., Shay, T., Gyapay, G., Cockett, N. & Georges, M. (2001). The callipyge mutation enhances the expression of coregulated imprinted genes in cis without affecting their imprinting status. *Nature Genetics*, 27(4), 367-369.
5. Charmantier, A. & Garant, D. (2005). Environmental quality and evolutionary potential: lessons from wild populations. *Proceedings of the Royal Society B*, 272, 1415–1425.
6. Dawson, M.A. & Kouzarides, T. (2012). Cancer epigenetics: from mechanism to therapy. *Cell*, 150, 12–27.
7. Dawson, M.A., Prinjha, R.K., Dittmann, A., Giotopoulos, G., Bantscheff, M. & Chan, W.I. (2011). Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. *Nature*, 478, 529–533.
8. Devaiah, B.N. & Singer, D.S. (2013). Two faces of BRD4: mitotic bookmark and transcriptional lynchpin. *Transcription*, 4, 13–17.
9. Doherty, R. & Couldrey, C. (2014). Exploring genome wide bisulfite sequencing for DNA methylation analysis in livestock: a technical assessment. *Frontier in Genetics*, 5, 126.
10. Giraldez, A.J., Cinalli, R.M., Glasner, M.E., Enright, A.J., Thomson, J.M. & Baskerville, S. (2005). MicroRNAs regulate brain morphogenesis in zebrafish. *Science*, 308, 833–838.
11. Girardot, M., Cavaille, J. & Feil, R. (2012). Small regulatory RNAs controlled by genomic imprinting and their contribution to human disease. *Epigenetics*, 7, 1341–1348.
12. Goddard, M.E. & Whitelaw, E. (2014). The use of epigenetic phenomena for the improvement of sheep and cattle. *Frontier in Genetics*, 5, 247.
13. Gomez, D., Shankman, L.S., Nguyen, A.T. & Owens, G.K. (2013). Detection of histone modifications at specific gene loci in single cells in histological sections. *Nature Methods*, 10, 171–177.
14. Gonzalez-Recio, O. (2012). Epigenetics: a new challenge in the post-genomic era of livestock. *Frontiers in Genetics*, 106(2), 1-4.
15. Gupta, P.K. (2013). *Genetics Classical to Modern*, Meerut, Uttar Pradesh: Rastogi Publications.
16. Haile-Mariam, M., Nieuwhof, G.J., Beard, K.T., Konstatinov, K.V. & Hayes, B.J. (2013). Comparison of heritability's of dairy traits in Australian Holstein-Friesian cattle from genomic and pedigree data and implications for genomic evaluations. *Journal of Animal Breeding and Genetics*, 130, 20–31.
17. Jaenisch, R. & Bird, A. (2003). Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. *Nature Genetics*, 33, 245-254.
18. Jenuwein, T. & Allis, C. (2001). Translating the histone code. *Science*, 293, 1074–1080.
19. Kala, R., Peek, G.W., Hardy, T.M. & Tollefsbol, T. O. (2013). MicroRNAs: an emerging science in cancer epigenetics. *Journal of Clinical Bioinformatics*, 3(6), 1-8.
20. Kanherkar, R.R., Bhatia-Dey, N. & Csoka, A.B. (2014). Epigenetics across the human lifespan. *Cell and Developmental Biology*, 49(2), 1-19.
21. Kellner, S. & Kikyo, N. (2010). Transcriptional regulation of the Oct4 gene, a master gene for pluripotency. Histology and Histopathology, 25, 405-412.
22. Kelm, S.C., Freeman, A.E. & Kehrli, M.E. (2001). Genetic control of disease resistance and immune-responsiveness. *Veterinary Clinics of North America*: *Food Animal Practice*, 17, 477–493.
23. Kubiak, M. & Lewandowska, M.A. (2015). Can chromatin conformation technologies bring light into human molecular pathology? *Acta Biochimica Polonica*, 62, 483–489.
24. Luger, K., Mader, A.W., Richmond, R.K., Sargent, D.F. & Richmond, T.J. (1997). Crystal structure of the nucleosome core particle at 2.8 A resolution. *Nature*, 389, 251–260.
25. Maiti, A. (2012). Mechanism of active DNA demethylation: Recent progress in Epigenetics. *Journal of Bioresearch Communications*, 1(2), 1-2
26. Milroy, C., Liu, L., Hammoud, S., Hammoud, A., Peterson, C.M. & Carrell, D.T. (2011). Differential methylation of pluripotency gene promoters in in-vitro matured and vitrified, in vivo-matured mouse oocytes. *Fertility and Sterility*, 95, 2094–2099.
27. Mirabella, A.C., Foster, B.M. & Bartke, T. (2016). Chromatin deregulation in disease. *Chromosoma*, 125, 75–93.
28. Monk, D., Arnaud, P., Apostolidou, S., Hills, F.A., Kelsey, G. & Stanier, P. (2006). Limited evolutionary conservation of imprinting in the human placenta. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 6623–6628.
29. Nijland, M.J., Ford, S.P. & Nathanielsz, P.W. (2008). Prenatal origins of adult disease. *Current Opinion in*

*Obstetrics and Gynecology*, 20, 132–138.
30. Nino-Soto, M., Heriazon, A., Quinton, M., Miglior, F., Thompson, K. & Mallard, B.A. (2008). Differential gene expression of high and low immune responder Holstein dairy cattle. *Developmental Biology*, 132, 315–320.
31. Noberini, R., Sigismondo, G. & Bonaldi, T. (2016). The contribution of mass spectrometry-based proteomics to understanding epigenetics. *Epigenomics*, 8, 429–445.
32. Petronis, A. (2010). Epigenetics as a unifying principle in the etiology of complex traits and diseases. *Nature*, 465, 721–727.
33. Reik, W. (2007). Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature*, 447(7143), 425–432.
34. Richardson, B. (2003). Impact of aging on DNA methylation. *Ageing Research Reviews*, 2, 245–261.
35. Slatkin, M. (2009). Epigenetic inheritance and the missing heritability problem. *Genetics*, 182, 845–850.
36. Small, E.C., Xi, L., Wang, J.P., Widom, J. & Licht, J.D. (2014). Single-cell nucleosome mapping reveals the molecular basis of gene expression heterogeneity. *Proceedings of the National Academy of Sciences of the United States of America*, 111, E2462–2471.
37. Tal, O., Kisdi, K. & Jablonka, E. (2010). Epigenetic contribution to covariance between relatives. *Genetics*, 184, 1037–1050.
38. Triantaphyllopoulos, K.A., Ikonomopoulos, I. & Bannister, A.J. (2016). Epigenetics and inheritance of phenotype variation in livestock. *Epigenetics and Chromatin*, 31(9), 1-18.
39. Varon, L., Munilla, S., Mouresan, E.F., Gonzalez-Rodriguez, A., Moreno, C. & Altarriba, J. (2015). A bayesian model for the analysis of transgenerational epigenetic variation. *G3 (Bethesda)*, 5, 477–485.
40. Yang, J., Beben, B., McEvoy, B.P., Gordon, S., Henders, A.K. & Nyholt, D.R. (2010). Common SNPs explain a large part of the heritability for human height. *Nature Genetics*, 42, 565–569.

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