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EPIGENETICS: REGULATION OF GENE EXPRESSION

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Abstract: Livestock genetics is currently navigating through a genomic era promoted by advances in DNA technologies. There is however a promising field that has not yet been tackled in livestock breeding and genetics: **Epigenetics**. Epigenetics is the study of heritable changes in gene expression and other genomic functions without altering the underlying "DNA" sequence. Epigenetics introduces a level of genetic regulation independent to the DNA sequence. These changes play a role in short-term adaptation of individuals and include reversibility. It can be transmitted somatically or inherited through modification of DNA regions and allows organisms on a multigenerational scale to switch between phenotypes. Epigenetic alterations in gene expression result from 'environmental' effects, both via external surroundings of an organism and via internal conditions. Epigenetic shows potential benefits and possibility of changes in the livestock industry. Economically important traits such as milk yield and milk quality, backfat thickness, body weight and growth seem to be associated with imprinted and X-linked QTL. These perspectives make epigenetics an interesting area of research at this time.

Keywords: Epigenetics, DNA methylation, genomic imprinting.

INTRODUCTION

Livestock genetics is currently navigating through a genomic era promoted by advances in DNA technologies. New advances continue, and efforts are currently placed in whole genome sequencing (e.g., in species such as cattle and swine) for its implementation future implementation to improve accuracy of genomic selection or mapping new QTL of interest (Gonzalez, 2008; Meuwissen and Goddard, 2010). There is, however, a promising field that has not yet been tackled in livestock breeding and genetics: **Epigenetics.** The modern definition of epigenetics is the study of heritable changes in gene expression and other genomic functions without altering the underlying "DNA" sequence. Hence the name **"epi"** – (derived from the Greek word meaning "over, above, outer" – combined with **genetics**

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(Richards, 2006). Molecular biological studies often define 'epigenetics' in terms of underlying mechanisms (Ho and Burggren, 2010).

Epigenetics Changes in gene expressions caused by mechanisms other than changes in the underlying DNA sequence. These changes play a role in short-term adaptation of individuals, and include reversibility. It can be transmitted somatically or inherited through modification of DNA regions and allows organisms, on a multigenerational scale, to switch between phenotypes. Epigenetics is the partial hereditary variation in genomic activity without any alterations of the DNA sequence. Inheritance refers to the memory of such activity; transferred between cellular generations through mitosis, and between organismal generations through meiosis (Esteller, 2011).Other examples of epigenetic processes are the essential developmental mechanisms of gametogenesis, aging, embryo genome activation, X chromosome inactivation and genomic imprinting (Attig *et al.,* 2010). The major difference between genetics and epigenetics is explained in **Table 1.**

Table 1: Major difference between genetics and epigenetics

Genetics	Epigenetics
Blueprint (DNA) for development	Additional instructions (chemical tags on chromatin)
Stable (rarely reversed)	Reversible (imprinting)
Resistant to environmental influences (except mutagens)	Potentially susceptible to environmental perturbation

MAJOR MECHANISMS OF EPIGENETIC GENETIC EXPRESSION

Two epigenetic processes involving chromatin remodeling have received much attention in the last decade. DNA methylation comprises the addition of a methyl group to nucleotides, which typically silences gene expression (Coolen *et al.,* 2011; Adrian, 2007; Cheung and Lau, 2005). Histone modification is the acetylation and/or methylation of chromosome packaging proteins. The amino-terminal tails of histones protrude from the nucleosome and are subject to chemical modifications including phosphorylation, acetylation, and methylation. These modifications of histones affect the access of regulatory factors and complexes to chromatin and influence gene expression. Also different processes of post-translational histone modifications include deacetylation**,** histone phosphorylation and sumoylation (Yutaka *et al.,* 2003). Non-coding RNA activity, involving small RNAs, microRNAs and large RNAs, has also been shown to play an important role in modulating

protein activity *via* regulation of translation, transcription or protein structure (Daniel and Danesh, 2015; Ho and Burggren, 2010).

IMPORTANCE OF EPIGENETICS

(a) Genomic imprints

Genomic imprinting is the mechanism where one allele's expression differs depending on which parent it was inherited from. Mammalian genomes have an additional layer of epigenetic information referred to as genomic imprints, so called because they carry a molecular memory of parental origin that is acquired in the germ line. Germ line cells contain small RNA known as Piwi-associated interfering RNA (piRNA). Mammalian spermatocytes are filled with piRNA, and similar RNA occurs in oocytes as well. In mammals, it is in fact paternal imprinting which prevents parthenogenesis, ensuring that paternal contribution is obligatory for descendants. Because epigenetic reprogramming occurs during folliculogenesis and embryogenesis, any disturbance of the normal natural environment during these critical phases could cause epigenetic alterations (Werner and Flueck, 2011).

Quantitative Traits Loci associated with imprinting in livestock

Newer studies have identified an IGF2 sequence associated to meat traits and body weight inbeef cattle (Bagnicka *et al.,* 2010). Studies have reported conflicting data on IGF2 gene sequences that supposedly result both in increase of average daily weight gain as well as lighter birth weight. A correlation between milk protein gene expression and DNA methylation in mammary gland and other tissues has also been detected (Jammes *et al.,* 2011). There is a significant correlation between IGF2 and milk yield and milk protein yield. The gene was negatively associated with milk protein percentage. Other studies have shown an indication of IGF2 correlating with a QTL for milk production traits and one study demonstrated an association between IGF2 and estimated breeding values for milk yield, milk fat yield and milk protein yield in Holstein-Friesian bulls. There have been few studies conducted on imprinting in avian species, most are conflicting. In poultry, imprinted QTLs have been found for traits such as egg weight, age at first egg, feed intake, egg quality and body weight; all economically important traits. Traits in poultry that have shown reciprocal effects are thought to originate from sex-linked genes, maternal effects or parent-of-origin specific expression (Tuiskula-Haavisto, 2004).

(b) X chromosome inactivation

The hallmark of both X-chromosome inactivation (X inactivation) and genomic imprinting is monoallelic gene expression. X inactivation is random in somatic cells, whereas the

expression of imprinted genes and X inactivation in the extraembyonic lineages are dictated by parental origin. Indeed, the epigenetic mechanisms that are involved in X inactivation and genomic imprinting share some marked similarities. Genes located on the X chromosome are subjected to X-inactivation, another type of mono-allelic expression. In females one copy of each X chromosome is silenced and in contrast to imprinting this copy is supposedly randomly selected. Subsequently, this will regulate the number of X chromosomes working in the cell (Dijana, 2012).

X-linked Quantitative Traits Loci

In pigs a QTL for backfat thickness has been reported on the X-chromosome. Harlizius *et al.* (2000) also found an area on the porcine X-chromosome to harbor loci that significantly influence backfat thickness and intramuscular fat content in both genders; supporting the theory of key genes for obesity and carcass composition in pigs demonstrating non-Mendelian inheritance and expression. X-linked QTL affecting adiposity and weight of individual fat depots in male mice have also been detected as well as X-linked QTL affecting obesity strictly in males. In commercial pig breeding different purebred lines are used to produce high quality pork (de Koning, 2011).

ROLE OF ENVIRONMENT IN EPIGENETICS REGULATION

Epigenetics is attractive for animal breeding because it may help finding part of the missing causality and missing heritability of complex traits and diseases. DNAm (methylation) patterns are modified along the life of an individual by environmental forces like diet, stress, drugs or pollution among many others (Petronis, 2010). Furthermore, the environment may affect the methylation pattern of up to three generations cohabiting under the same specific circumstances at a given time during pregnancy: the productive female, the fetus and the fetus' germ cells. Nijland *et al*. (2008) recently showed a similar pattern in sheep: diet of pregnant ewes had some effect on the weight of their grand-daughters. Epigenetics also results from other important cultural interactions like social learning, symbolic communication, imitation and through diet. Thus, epigenetic heredity of feeding and drinking behaviour during pregnancy can influence the appetite for certain foods like alcohol in offspring of rats (Daxinger and Whitelaw, 2012).

METHODS FOR STUDYING EPIGENETIC MODIFICATIONS

It is important to detect which DNA base sequence in the genome have been methylated in order to know the epigenetic conditions as well as the diagnostic marker for diseases such as cancer in the future. However, ordinary genetic tests can not detect methylated regions. In

recent years, various methods have been developed to detect methylation. The most well known method is **bisulfite sequencing**, which determines the DNA sequence through bisulfate preparation of a DNA fragment to change the base (Patterson, 2011). Recently, the identification of DNAm is possible using some state-of-the-art technologies based on **second generation sequencing**, which provide signals of DNAm on a genome-wide basis. These technologies allow obtaining different DNAm measurements with different levels of coverage and resolution. The **third generation technology** for sequencing is expected to bring deeper and more accurate knowledge on the epi-genomic base modification, and may help to develop specific bead-arrays for its use in livestock (Meyer and Liu, 2014; Emes and Farrell, 2012).

OPPORTUNITIES IN LIVESTOCK

a) Selection for productive traits has led to amazing genetic gains in most livestock species during the last decades. Animals with concentrate and uni-feed diet systems are expected to be differently methylated than animals in a less intensive system based on a pasture feeding systems. It will be important to detect what practices are associated to favorable methylation patterns that affect disease resistance and other economically important traits. Finding this missing causality would assist in rising animals under favorable circumstances and reduce unfavorable methylation patterns.

b) Breeding companies may also detect what genotypes are more susceptible to (un)favorable methylation patterns to select animals with a reduced susceptibility to unfavorable methylation patterns.

c) Farms could use epigenetic information to reduce disease incidence and the use of antibiotics in animal production. Personalized medicine using methylation on DNA is currently carried out on cancer research in humans and seems to be a promising strategy for veterinary medicine as well (Gomez and Ingelman-Sundberg, 2009).

d) Economically important traits such as milk yield and milk quality, backfat thickness, body weight and growth seem to be associated with imprinted and X-linked QTL. IGF2 and H19 play a vital role in several valuable traits such as muscle mass, fat deposition, meat and milk production has been studied extensively.

CONCLUSION AND FUTURE PERSPECTIVES

Considering all above points, imprinting could become an important factor to be noted in future breeding schemes. Future study on the effects of imprinting on chicken and sheep could also be economically beneficial if more imprinted genes are found and possibly utilized

in breeding schemes. The study of epigenetic variation is an attractive challenge during the next decade. First efforts should focus on proving that DNAm marks contribute to variation of traits of interest in the livestock populations. Then research efforts should focus on (1) the development of technology to detect DNAm on individuals in an affordable manner (2) the development of statistical tools to accommodate genome-wide epigenetic information in the phenotype decomposition equation, and (3) an efficient implementation of epi-genomic selection in breeding and management programs.

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