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Epigenetics as a mediator of genome x environment interactions

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Abbreviated Title: G×E and epigenetics

Summary
Epigenetic mechanisms, defined as heritable changes in gene function that cannot be explained by changes in the DNA sequence, may play a role in the genotype × environment interaction. Here we briefly show how epigenetics can interact with the environment, how these mechanisms are linked to genetics, and to what extent they can mediate the G×E interaction. The classical genetic selection model decomposes the phenotype into genetic and environmental effects, poorly taking into account their interaction. But this decomposition may be improved. Given the constraints faced by livestock breeding today, especially due to climate change, a better understanding of the epigenetic mechanisms governing the genome's responses to changing environments could provide new routes for improving selection for a wide range of traits.

Key words: Epigenetics, Genotype, Environment, GxE interaction, Breeding

Introduction

Animals in livestock systems face multiple constraints during life and have to adapt to different challenges such as changes in the rearing environment, feed transitions, climate variations, or diseases. These potentially stressful events can have a strong effect on production, health and welfare, the magnitude of which varies among individuals, particularly according to their genotype (Nauta *et al.* 2006, Cardoso and Tempelman 2012). Over the last decades genetic selection has contributed to greatly improve livestock performance: in poultry breeding the increase in performance has been remarkable both in broilers and layers (see (Aggrey *et al.* 2020)). The genetic selection model considers that phenotype is decomposed into genetic (G) and environmental (E) effects, and eventually the interaction between the two (G×E). We know nowadays that this decomposition of components affecting phenotypes is over simplistic. G×E interaction has been known for a long time to influence phenotypes, but the classical selection methods were not able to take it precisely into account. Furthermore, breeding conditions were often

quite standardised and its intra-breed impact was not so important. However, with the agro-ecological transition due to climate change, breeding systems are evolving. For example, there is a tendency to lengthen the production careers of females (dairy cattle, layers), the animals being of varying ages and more exposed to varying environments during their lives. In addition, the conditions in which animals are reared may be less uniform with sometimes extreme variations, for example heat waves. So, understanding the G×E component could be important to be able to breed better adaptable genotypes.
There are growing evidences that the environment experienced by the animal may also induce long-term modifications of non-genetic inherited factors that have an impact on phenotype and thus should be taken into account in the phenotype decomposition (see David *et al.* 2019a). Indeed, the environment contributes to a large fraction of the variability of complex traits, notably through epigenetic phenomena: the activation and inactivation of genes that underlay expression variation are partly regulated by epigenetic marks, in part triggered by the environment. These phenomena are therefore part of the mechanisms underlying Genotype × Environment interactions.

1 - Epigenetics

What is epigenetics?

Several definitions of epigenetics coexist, the most widely used being "The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Riggs *et al.* 1996). Epigenetics can be considered as one of the conductors that contribute to regulate gene expression, for example by adding small chemical modifications to the DNA. In order to enter the restricted space of the cell nuclei, DNA is compacted in the form of a double helix surrounded by nucleosomes, small units made up of particular proteins, the histones. These proteins can undergo numerous chemical modifications (acetylation, methylation, etc.) which contribute to increase or decrease the accessibility of the DNA molecule to the cellular machinery of gene expression. The DNA itself can be modified by the addition of a methyl group on certain bases (mostly cytosines in a 'cytosine - guanine' environment, CG, in vertebrates). This multitude of chemical tags are all epigenetic marks that act as turning genes on or off and controlling the level of gene expression. Transcription of non-coding RNA interacting with DNA is an additional mechanism capable of regulating gene expression. All these marks constitute the epigenome, which is established during the embryonic development when cells become specialized, and differs according to cell type and tissue specificity. Epigenetic marks are involved in various mechanisms such as cell differentiation, inactivation of an X chromosome in female mammalian cells, parental genomic imprinting, or differentiation between monozygotic twins.
These marks are partially reversible, which makes them an effective lever for supporting the genome's response to environmental variation (Feil and Fraga 2011).

What links between epigenetics and environment?

As well as the genome of an organism influences its response to the environment, the environment can also modify the expression of genes through epigenetic mechanisms. Biotic disturbances (changes in the quality or quantity of nutrients, hormone levels...) or abiotic stresses (heat waves...) during prenatal development can induce modifications of

these marks, ensuring a dynamic regulation of gene expression (Feil and Fraga 2011). These same disturbances during the productive life, notably for species with long production careers, can also change epigenetic marks, resulting in phenotype variation during the animal lifetime. These epigenetic marks are then partially transmitted during cell division and, when maintained, represent a persistent chemical memory of previous disturbances (Skinner 2011).

In plants, the importance of epigenetics in responses to environmental variations is well established, for instance with the vernalization process (Friedrich *et al.* 2019). In animals, epigenetic modifications can also mediate the variation of gene expression due to environmental effects such as nutrition, (see Langley-Evans 2015, Chavatte-Palmer *et al.* 2016). A recent study in capelin (*Mallotus villosus*), a marine fish, showed that variations in reproductive strategy triggered by the environment (different life histories, in particular low and stable temperature vs high and variable temperature) are more likely governed by epigenetic changes than by genetic modifications (Cayuela *et al.* 2021). Other famous examples of environmentally induced epigenetic mechanisms are the fate of bee larvae that evolve into queens or workers depending on the diet they receive, and the sex determination in turtles, which depends on the temperature during egg incubation (Ge *et al.* 2018, Wojciechowski *et al.* 2018). In the well-known viable yellow agouti model in mice, it has been shown that dietary supplementation with genistein, a phytoestrogen known to modify DNA methylation, can modify phenotypes by altering the epigenome (Dolinoy *et al.* 2006).

In poultry, epigenetic analyses of environmental influences on phenotype are scarce, but several examples can be found in studies about nutrition or thermal manipulation during early life or incubation (see Buyse *et al.* 2020). Histone post-translational modifications in the chicken hypothalamus have been shown to be impacted by embryonic thermal manipulation, and may be ultimately involved in the thermal acclimation of adult birds (David *et al.* 2019b). Recent examples demonstrate the association between DNA methylation and incubation conditions (Corbett *et al.* 2020), detrimental early life conditions (Pértille *et al.* 2017) or chronic stress (Pértille *et al.* 2020). These examples highlight the fact that the exposure to unfavorable specific environmental conditions lead to epigenetic changes which could serve as stress related biomarkers, but they do not contribute to understand if these epigenetic changes are the causative factors of phenotype variability. Of note, favorable environments, as for example exercise training in human, can also trigger changes in epigenetic marks that lead in particular to a better protection from diseases (see Denham 2018, and below).

Part of this environmental memory may be transmitted along generations, a phenomenon whose extent is debated but which may improve genetic selection models if taken into account. The actual contribution of epigenetics to phenotypic variation is scarcely assessed. Studies in quail have estimated epigenetic heritability for body weight and egg quality traits, showing that epigenetic heritability was 0.10 for body weight at 7 days of age, and close to zero for the other traits studied (Paiva *et al.* 2018a, Paiva *et al.* 2018b). The authors concluded that including the epigenetic effect in the animal model helped to explain the residual and non-Mendelian variability of initial body weight.

To know the role of genetics and epigenetics in the construction of phenotypes would allow to improve models used in genetic selection. Similarly, to know the effect of the parental

environment on the offspring performance and health will contribute to improve farming systems in order to favor epigenomes that have positive effects on performance and adaptive capacity.
While, as illustrated above, both genetics and epigenetics contribute to phenotypes, they are not two completely unrelated processes.

What links between epigenetics and genetics?
It is now well established that DNA polymorphisms can affect epigenetic marks (Bell *et al.* 2011, Do *et al.* 2017). For example, deGoede et al recently showed that 67.3% of all human annotated lncRNA genes had their expression significantly associated with at least one DNA variant in at least one tissue (de Goede *et al.* 2021). Similarly, up to 80% of the variation in DNA methylation can be explained by the genotype (Gertz *et al.* 2011). A large sample-sized study in human demonstrated the association of long-range regulation of CpG methylation with genetic polymorphisms (Lemire *et al.* 2015). Do et al. have reviewed many studies revealing the existence of a large genetic-driven epigenetic variability (Do *et al.* 2017). This can affect DNA methylation, detected through allele-specific methylation or meQTLs (QTLs responsible for CpG methylation level variability), and chromatin conformation, identified by allele-specific chromatin accessibility. One mechanism explaining this influence of genotypes on epigenetic state is the fact that DNA sequence at specific binding sites can affect the binding of transcription factors, some of these transcription factors being able to modify the DNA methylation level nearby (Feldmann *et al.* 2013).
On the other side, mutation rates can also be affected by epigenetic states: CpG dinucleotides have a mutation rate about 12 times higher than other transition types, because methylcytosines are hypermutable (Sved and Bird 1990), and CpG content may even affect non-CpG mutation rate (Walser and Furano 2010). More generally, associations between chromatin structure and mutation rates have been reported (Makova and Hardison 2015). Thus, environmental exposures could not only select, but also play a direct role on DNA polymorphisms, even if the currently published studies rely on correlations, non-demonstrative for a causative action. These phenomena, when triggered by the environment for generations through epigenetic marks leading to genetic modifications, have been called the "epigenetically facilitated mutational assimilation" (Danchin *et al.* 2019).
Having observed that epigenetic mechanisms are linked to the environment and to the genetics of an organism, the question is to what extent they can mediate the G×E interaction.

2 - Genotype × Environment interactions from an epigenetic perspective

When is "G×E" referred to?
Genotype × environment interactions determine how individuals with different genotypes will respond differently to different environments. Environments can be different in term of biotic (hormone concentration during development, disease, etc) or abiotic (temperature, exposure to chemical contaminants, etc) factors. These interactions may modify the ranking, according to performances, of different individuals when exposed to different environments (Haldane 1946) (Figure 1).

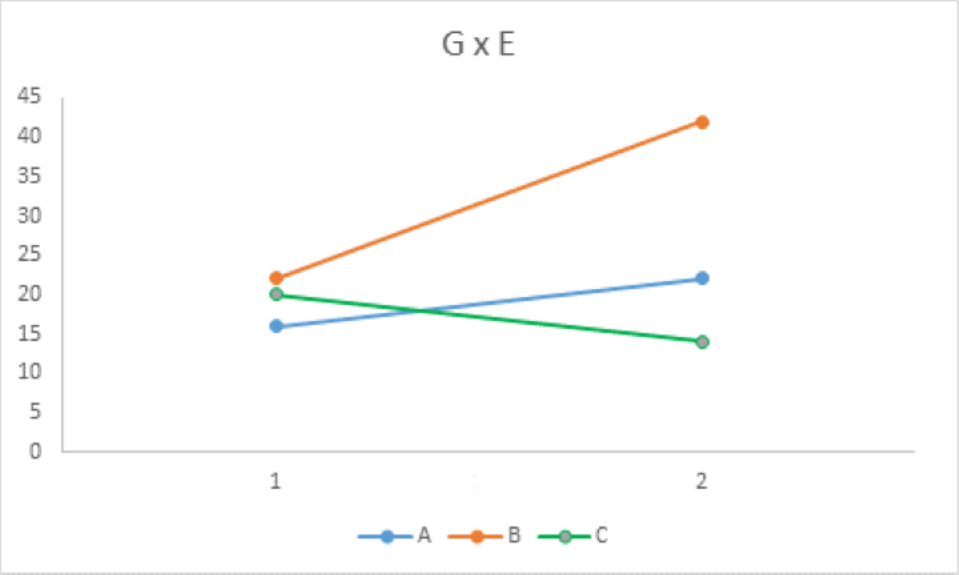

Figure 1: Example of genotype by environment interaction analysis
Arbitrary unit for the phenotypic value of a quantitative trait showing GxE (3 genotypes: A, B, C in 2 environments: 1 and 2)

G×E interactions have been thoroughly studied in cattle (e.g. Hayes *et al.* 2009, Bernabucci *et al.* 2014). While re-ranking of sires in dairy cattle may be limited (Calus and Veerkamp 2003), G×E interaction was shown to affect milk production traits (Hayes *et al.* 2003). In beef cattle, bull re-ranking was shown to occur mostly in restrictive environments, highlighting the importance of evaluating the consequences of a mismatch between selection and production environments (Corrêa *et al.* 2010, Santana *et al.* 2013). In breeding programs such as those encountered in pig and poultry, a loss in genetic gain due to G×E interaction can also be observed (Mulder and Bijma 2005). G×E interaction has been observed for several traits both in broiler (slow-growing, N'Dri A *et al.* 2007) and laying hen (Mathur and Horst 1994) productions. In laying hens, QTL × diet and QTL × age interactions were shown to affect different production traits (Romé *et al.* 2015).

As described by Lillehammer et al (Lillehammer *et al.* 2009) in dairy cattle, genetic polymorphisms can cause this G×E interactions. Some alleles may affect both production and environment susceptibility, and those maintaining or improving production while reducing environmental sensitivity could be good candidates for marker-assisted selection for robustness. Other genes may contribute to the change in animal ranking under various environments. In this case, the selection for the improving allele in one environment may cause a loss in performance under a different environment. An example of this mechanism involving different genes in different environments is found for feed efficiency in poultry (Mignon-Grasteau *et al.* 2010): with an easily digested corn-soya diet, the genetic component of digestive efficiency will be little involved in the variability of feed efficiency, whereas with a diet that is difficult to digest, this digestive component will be more important, and will involve different metabolic pathways, and therefore different genes.

It has been shown that most genes have a positive correlation between general production and environmental sensitivity with the consequence that environmental sensitivity increases with selection for high performance (Rauw and Gomez-Raya 2015). This detrimental link may be due to trade-off between functions (Friggens *et al.* 2017).

Breeders are thus faced with the challenge of how to manage these possible changes in rank: is it preferable to select the best animals in a given environment taking the risk that their performances will be highly modified if environmental conditions are changing or is it preferable to select animals with more modest performances but stable over a wide variety of environments?

In the case of poultry, while the importance of G×E is quite limited for the selected pure lines that are kept under a standardized housing system, it becomes relevant for the crossbred commercial lines reared for human consumption, as commercial breeding companies operate in a global context and distribute their breeding stock worldwide. This is even more accurate for alternative productions (organic, label), which are reared with an outdoor access, whereas the breeding stock is reared in closed pens. The quantification of the interaction between genetics and environment becomes therefore necessary to improve the prediction accuracy of the models across different environments and to supply breeding stocks that are able to express their optimal performances under a wide range of production environments. To achieve this, one strategy would be to account for field performance of crossbred birds in pure line genetic improvement (Esfandyari *et al.* 2016, Duenk *et al.* 2019). An alternative way can be to take advantage of the pyramid structure of breeding (Hiemstra and Napel 2013): pure lines are bred in a controlled environment, and parents of the commercial offspring are bred in the different places/climates where the commercial animals will be bred. The adaptation of the animals for one generation should lead to better performance of the final offspring. Unravelling the impact of the environment on phenotypic variation, largely mediated by interactions between genetic and non-genetic components, is therefore necessary to reach the ultimate goal of improved prediction of an animal's phenotype based on genotypic and environmental information.

The interaction between genome and environment is thus a phenomenon that has been known for a long time, but studies trying to decipher the molecular mechanisms underlying G x E interactions are scarce.

What molecular mechanisms underlying G×E?

Observation of allele-specific responses to different environments

Several studies have already demonstrated the existence of genomic regions that respond differently to the environment depending on the allele carried.

The existence of environmental "susceptible" or "resistant" alleles is well illustrated by the influence of physical activity on the effects of risk alleles of the fat mass and obesity associated gene (*FTO*) on obesity: the effects of these detrimental alleles are significant only in people with low physical activities (Rampersaud *et al.* 2008).

By using different cell types and different treatments, Moyerbrailean et al. identified 215 genes whose ASE (allele-specific expression) was triggered by the environment, half of which had been identified by GWAS as associated with complex traits (Moyerbrailean *et al.* 2016).

The concept of "response-eQTL" (reQTL) has been developed to qualify eQTLs whose effects depend on the environment, for instance differing according to different immune stimuli (Kim-Hellmuth *et al.* 2017). Kim-Hellmuth et al. identified 417 reQTLs in human monocytes that were differentially responding to various immune stimulations, thus demonstrating the interaction between infectious stimuli and genetic predisposition to

diseases (Kim-Hellmuth *et al.* 2017). Alasoo et al. detected reQTLs and "conformation accessibility" QTLs in human macrophages in response to stimulation by IFNγ and/or Salmonella, with a probable impact on the binding of cell-type-specific transcription factors (Alasoo *et al.* 2018).
These allele-specific responses may be the result of environment-specific gene expression or of allelic effects that vary from one environment to another (Rauw and Gomez-Raya 2015). Studies trying to decipher the underlying molecular mechanisms are rather scarce, notably because it requires a larger number of individuals to highlight an interaction between two factors than to demonstrate the effects of a single factor on a given trait. Nevertheless, a growing number of studies have shown that these interactions can be triggered by epigenetic mechanisms, as illustrated by the examples below.

G×E mechanisms observed at specific genomic positions
Allele-specific DNA methylation as a mechanism of genotype × environment interaction was demonstrated in mice. Holland et al. showed that the DNA methylation level at a specific CpG explained why a low-protein diet during development could induce a decrease in weight in adult mice that depends on the individual genotype. It was found that weaning weight in mice exposed to prenatal protein restriction was inversely related to the level of methylation of a specific CpG, 133 bp upstream of the transcription start site of the rDNA locus, but only for animals carrying the A allele at the genomic position 104 bp upstream of the TSS. Methylation of the CpG-133 was unaffected by environment for animals carrying the C allele. This epigenetic response to the environment, in interaction with genetics, is correlated with transcriptional and phenotypic results (Holland *et al.* 2016).
A notable example is also found in studies of psychiatric disorders related to childhood trauma (see Klengel and Binder 2015). An allele in intron 2 of the *FKBP5* gene - involved in the regulation of the glucocorticoid complex governing the stress response - has been shown to alter chromatin conformation and increase gene expression by bringing the promoter closer to an enhancer when associated to the glucocorticoid receptor (GR). This increase in *FKBP5* expression impairs the feedback effect that reduces blood cortisol levels inducing an altered physiological response to stress. Strikingly, the risk allele significantly increases the possibility of psychological disorders when the individual is subjected to trauma in early life, while it does not when the trauma occurs in adulthood. The underlying G×E mechanism seems to be epigenetic in nature: a severe stress in childhood in individuals carrying the risk allele determines a stronger stress-induced cortisol response that in turn induces an allele-specific demethylation at a GRE (Glucocorticoid Response Element) site in intron 7 of *FKBP5*. This demethylation is retained in adulthood and increases the risk of developing psychiatric disorders such as major depression and post-traumatic stress disorder. The same allele-specific epigenetic mechanism in interaction with the environment was also found in patients with psychosis in a recent study (Mihaljevic *et al.* 2021).
These examples illustrate the way by which the environment may act on the regulation of gene expression through epigenetic mechanisms: CpG methylation plays a major role in regulating gene expression, directly through modifying DNA conformation, and through governing the accessibility of transcription factors (TF). Depending on the TF, its ability to bind to its TF binding site (TFBS) is decreased (most often) or increased (notably for

developmental TFs) according to the level of DNA methylation of the region (Yin *et al.* 2017). Therefore, a modification in the level of DNA methylation at specific sites triggered by the environment may change the expression of specific genes.

G×E genome-wide analyses

Few studies have analysed the epigenotype as a mediator of the G×E interaction on a genome-wide scale.

In human, Teh et al identified 1423 regions whose methylation levels were highly variables between individuals, by analyzing umbilical cord samples from 237 babies (Teh *et al.* 2014). While the methylation level of 25% of these regions were explained by the genotype, 75% were explained by the interaction between genotype and prenatal environment (maternal age, body mass index, smoking, depression, etc.). The environment alone, independently of the genotype, had no significant influence. These findings were recently confirmed in a larger study including 2365 newborns (Czamara *et al.* 2019). The association of genetic variability with prenatal environment is thus the best predictor of DNA methylation variability.

In fish, Lallias et al. used several rainbow trout isogenic lines, characterized by a lack of genetic variability within lines, to study genetic differences in the impact of environmental variation on DNA methylation (Lallias *et al.* 2020). By incubating eggs at two different temperatures (11°C and 16°C), they showed that the magnitude of the environment-induced modifications of DNA methylation profiles was dependent on the genetic background.

Structural characteristics of genomic regions showing G×E interactions

Current research suggests that environmentally-responsive epigenetic regions may show specific characteristics (Law and Holland 2019). Correlated regions of systemic interindividual variation have been observed, often associated with transposable elements and subtelomeric regions (Gunasekara *et al.* 2019). These regions are remarkably independent of the overall tissue specificity of DNA methylation levels, as when observed in one tissue, they are predictors of DNA methylation levels of other tissues in the same region. They are partly governed by genetic variation, and partly associated with the early life environment.

Genes showing G×E interactions seem to bear longer intergenic lengths, high motif concentration, and mid-range expression levels (Grishkevich *et al.* 2012). In addition, genes with G×E interactions are more often associated with distant-acting loci than genes without G×E interaction (Smith and Kruglyak 2008).

Conclusion

Although the chicken was the first species of agronomic importance to be sequenced, less experiments than in mammals have been conducted in birds to study epigenetic processes, despite their possible influence on economically important phenotypes. Given the likely evolution of the climate in the near future, there is a need to improve the adaptive capacities of animals to climatic and dietary changes. A better understanding of the epigenetic mechanisms governing the genome responses to changing environments could open up new avenues for improving selection for a large range of traits including animal

welfare. Deciphering the contribution of epigenetic effects to G×E interactions is therefore a promising area of research, not only for the understanding of the molecular mechanisms involved, but also for its possible applications in livestock production. With the ongoing technological developments in genomics and epigenomics and the decreasing costs of sequencing, it is possible that future breeding strategies will not only use genetic information but also epigenetic analyses.

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