Multigenerational Effects

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KEYWORDS

- Epigenetics • Nutrition • Growth • Reproduction
- Genetic by environment interaction

KEY POINTS

- A large body of data is accumulating that provides evidence of epigenetic mediation of environmental influences on physiologic traits in humans and other species.
- Epigenetic mediation of gene expression may be transferred (inherited) across generations.
- Potential exists for using epigenetic approaches on a population or herd-wide basis to improve production efficiency in limited nutritional environments.
- Epigenetic mediation of gene expression can alter estimates of genetic sources of variation (genetic by environment interactions).

INTRODUCTION

The idea that environmental alterations of a phenotype are transferred across generations has existed for centuries.[1] In 1809, Lamarck postulated environmentally induced changes in a phenotype were passed on to subsequent generations. In 1859, Darwin proposed the concept of natural selection, in which the best-fit phenotype for a specific environment maintained a reproductive or survival advantage in that environment. Debates about whether inheritance of acquired characteristics or survival of the fittest was correct ensued throughout the nineteenth century. Weismann's experiment in the late 1800s showing that amputation of mice tails over 20 generations failed to alter tail length was considered strong evidence against the inheritance of acquired characteristics theory. In addition, the rediscovery of Mendel's work in the early 1900s provided insight into the mechanisms of inheritance and focused subsequent research toward understanding the genetic control of a phenotype. This resulted in the discovery of DNA and its role as the blueprint for life. Ultimately, genome sequencing ensued as the final step in understanding phenotypic diversity. However,

the high levels of DNA sequence homology, within and across species, and lower than expected numbers of genes identified for numerous species has raised questions about whether DNA sequence variation is sufficient to explain the existing phenotypic variation or if other mechanisms may be contributing.

Data accumulated over the last 20 years support the concept that epigenetics mediates environmentally induced changes in a phenotype across generations. Epigenetic modification of the genome over and above alterations in nucleotide sequence is now considered a major factor contributing to different patterns of gene expression in different cell groups.[2] Inheritance of epigenetic modifications of gene expression across generations provides for phenotypic plasticity in the face of fixed genotype. Better understanding of epigenetic actions has resulted in a unified theory of evolution. This theory considers genotypic and epigenetic pathways for mediating environmental changes in a phenotype.[3] Although most epigenetics research has focused on the detrimental effects of nutritional deficiencies or environmental toxins, the natural role for epigenetics is adaptation to environment. Greater understanding and characterization of epigenetic responses to various management practices can enhance livestock production efficiency. This article briefly summarizes research on generational inheritance and provides examples of how this process may enhance the efficiency of beef cattle production.

Epigenetics Mediates Multigenerational Impacts of Environment

"Intergenerational factors may be defined as those factors, conditions, exposures, and environments experienced by one generation that relate to the health, growth, and development of the next generation."[4] Environmental factors may alter a phenotype via direct effect on the animal (first generation), direct or maternally mediated effects on the fetus (second generation), or gonadal cell lines of the fetus (third generation) when pregnant animals are exposed to environmental factors (fetal programming), and through inheritance across generations.[2,5] Epigenetic mediation of gene expression is a process contributing to the transfer of environmental impacts across generations.

In fetal programming, in which exposure of pregnant females to environmental stimuli influences the phenotypic traits observed in the fetus and the subsequent generation, the epigenetic change observed may be due to a direct or maternally mediated effect on the fetus and germ cells within the fetus, and not due to cross-generational inheritance.[5] In addition, the physiologic processes influenced by fetal programming depend on when exposure to environmental stimuli occurs with respect to conception or stage of embryonic or fetal development, and embryonic or fetal sex.[3,6,7]

Obviously, the generational interval of a species markedly influences the capacity to study the mutigenerational impacts of environmental factors. Much of the research evaluating multigenerational effects has focused on nutritional deficiencies, diseases, and other undesirable responses. Research demonstrating generational impacts on human offspring from populations subjected to extreme nutritional stress led to the thrifty phenotype hypothesis.[8] This hypothesis proposes that mothers subjected to nutritional deficiencies forecast the environment their offspring will be born in, thereby providing their offspring with a survival advantage. Exposure of females to severe nutritional deficiency during pregnancy results in altered metabolism and provides enhanced capacity for caloric storage in offspring later in life. This hypothesis has led to many studies using laboratory and domestic animals as models to facilitate tight control of dietary treatments at specific stages of pregnancy. These studies provide insight into the physiologic mechanisms that mediate the impact of undernutrition

and overnutrition during fetal development at specific time points later in life.[9–11] Although the thrifty phenotype hypothesis implied survival advantage in nutritionally limited environments, the metabolic changes identified in these studies resulted in undesirable health consequences in offspring existing in ample nutrient environments.[8] For example, indigenous populations that evolved under seasonal periods of feast and famine exhibit high instances of metabolic disorder after changing to a more sedentary lifestyle.[2]

Although it is logical that the thrifty phenotype hypothesis would apply to wild animal populations,[12] the extent that it may apply to the more highly managed livestock industry has not been thoroughly evaluated. Animals within a herd are all subjected to similar environmental stimuli throughout the production cycle; any stimuli resulting in epigenetic modification may result in herd-wide changes. The cumulative effects of herd-wide exposure and generational inheritance are rapid changes in phenotypic characteristics of the population when compared with the rate of phenotypic change brought about by genetic selection.

Relative to the poultry, swine, and dairy industries, beef and lamb production occurs with less management of the production environment. Therefore, species managed under pastoral grazing systems may be more influenced by epigenetic alterations of gene expression. At present, the impact of epigenetics in any of the livestock industries has not been well-described. However, increased awareness of the potential generational effects associated with epigenetics has led to greater consideration about how relatively small nutritional differences imposed under common production practices may lead to metabolic programming that alters the production characteristics of the offspring.[7,13] Due to long generation intervals, much of this research has been limited to evaluating the impacts of uterine programming on the postnatal characteristics of the gestating fetus or the direct effects of nutritional impacts during postnatal development. Studies following the multigenerational effects are scarce. The limited studies on cattle populations managed under extensive environments for long periods of time indicate a metabolic adaptive response, resulting in their ability to function below National Research Council (NRC)[14] requirements.[15] Collectively, the research indicates the potential to propagate desired characteristics in the livestock industry through epigenetic pathways.

An example of how long-term differences in nutritional management may result in differences in multigenerational responses to nutritional restriction is provided by Vonnahme and colleagues.[16] These researchers evaluated response to nutritional restriction in ewes originating from a common genetic population but managed for several generations under very different nutritional environments. Ewes maintained in a relatively sedentary lifestyle with a diet that always met or exceeded NRC recommendations exhibited greater loss in bodyweight and body condition score (BCS), and greater suppression in placental efficiency and fetal growth in response to nutritional restriction, than ewes from a herd maintained in an extensive, semiarid range environment. Thus, long-term differences in nutritional management resulted in a divergence in response to short-term nutritional restriction. Whether these differences are driven by divergence in selection or epigenetic modulation is not known. These results support the concept that management under divergent nutritional environments alters nutritional requirements and response to nutritional limitations in subsequent generations.

Example of Multigenerational Effects in Cattle from a Lifetime Productivity Study

In 2001, a long-term research project was initiated at the US Department of Agriculture, Agriculture Research Service, Fort Keogh Livestock and Range Research

Laboratory, Miles City, Montana, to study the lifelong impact of feeding 1 of 2 levels of protein supplementation to cows grazing dormant winter pasture during the last trimester of gestation. It was hypothesized that management with lesser inputs over time would provide selection pressure for more efficient cows. Two possible modes of action leading to support of the hypothesis would be (1) a change in genetic composition of the herd or (2) a metabolic adaptation to function with less input. Genetic change would require a long period of time compared with metabolic adaptation. The adaptation process could also result in altered uterine function, bringing about epigenetic changes in the offspring.

Detailed description of the study and the most recent summary of results are available from Roberts and colleagues[13] (2016). Following is a brief description of the treatments and some of the previously published results. In December of each winter, cows were divided into their lifelong assigned treatment group, which was predicted to provide a marginal (MARG) or adequate (ADEQ) level of protein supplementation based on NRC requirements. They were supplemented with either 1.1 kg/d (MARG, n = 138 cows and 21 bred heifers) or 1.8 kg/d (ADEQ, n = 92 cows and 19 bred heifers) of alfalfa hay. To remain in the population, cows were required to get pregnant and wean a calf each year. When analyzed over 9 years, differences in the supplemental feed levels resulted in the ADEQ-supplemented cows gaining more weight during supplementation than MARG-supplemented cows (least squares means for age-adjusted differences over 9 years were 25 ± 1.3 vs 22 ± 1.2 kg weight change for ADEQ vs MARG levels, P<.05). This difference was accompanied by differences in BCS at precalving between the ADEQ-supplemented cows (4.98 ± 0.04) and the MARG-supplemented cows (4.86 ± 0.03, BCS scale of 1 = extremely thin to 9 = extremely fat, P<.02). Pregnancy rates over the 2002 to 2007 breeding seasons were 92 plus or minus 1.9% and 91 plus or minus 1.6% for the ADEQ and MARG level groups, respectively (P = .8).[13] Thus, the difference in supplementation resulted in a small divergence in weight change over the last trimester of pregnancy but did not affect pregnancy rates. For subsequent discussion, animals from this portion of the study are referred to as the first generation.

Heifers born in the study from 2002 to 2011 were allotted by weaning weight within dam treatment to be fed to appetite (control, n = 656) or fed at 80% of that consumed by control heifers at a common bodyweight basis (restricted, n = 655) over a 140-day period between weaning and first breeding. Heifers were exposed for breeding and pregnant heifers were retained for replacement. As with the first generation, the replacement females grazed dormant winter forage each year. Control heifers were supplemented each winter with 1.8 kg/d protein supplement and restricted heifers were provided 1.1 kg/d treatments, corresponding to the ADEQ and MARG levels of supplement, respectively. These females represented daughters of the first generation, as well as subsequent generations. With 1 exception, previous analyses of the data have been limited to the classification by individual treatment and dam treatment (ie, 2 × 2 for most recent generations).[13] Thus, previously published results did not differentiate between second and third generation females (see later discussion). In previous analyses, the main effects of dam treatment during the last trimester of pregnancy were observed for bodyweights on daughters at 3 years of age and older. Females born to MARG-supplemented dams were heavier at the start of breeding at 3 years and older, and had greater BCS than females from the ADEQ-supplemented dams. The difference in weight at 3 years of age was associated with greater retention (less loss due to reproductive failure) between 3 and 4 years of age. Interaction of dam treatment and individual treatment were observed for the calves produced by the cows, the only third-generation trait previously analyzed. Restricted cows from

MARG-supplemented dams produced lighter calves at birth and weaning than their contemporary herd mates.

For statistical purposes, in the remaining portion of this article, the differentiation of second-generation and third-generation females is accomplished by treatment coding of the maternal granddam (MGD). Animals were considered second-generation females if their MGD was not subjected to the different supplementation levels, whereas any female whose MGD was subjected to either ADEQ or MARG winter supplementation was classified as a third-generation female. Note that this classification method for the third generation does not differentiate between females with treatments applied for more than 3 generations. This classification process allowed analysis of the generational effects of the 2 treatment levels applied to the last 3 generations (individual treatment, dam treatment, and MGD treatment). In addition, sires used on this population were produced by females in the study, providing an opportunity to evaluate the impact of the supplement level provided to the sire's dam on each of the sire's daughters (ie, the paternal granddam [PGD] effect).

As previously discussed, earlier analyses indicated that the MGD treatment by dam treatment interaction on offspring weight at birth and weaning, in which offspring from MARG-supplemented dams out of MARG-supplemented dams, produced calves slightly smaller at birth and weaning when compared with other dam treatment by MGD treatment classifications.[13] These interactions were also evident in the most recent analyses conducted for this article (**Table 1**, analyzed for males and females). The current analyses indicate these lighter weights at birth and weaning were associated with shorter hip height in daughters at 1 year of age (see **Table 1**). The supplement level provided to the MGDs influenced the loin muscle area of granddaughters at 1 year of age (measured by carcass ultrasound) and weight at prebreeding at approximately 14 months of age. Heifers descending from the MARG-supplemented MGDs had smaller loin muscle area and were 5 kg lighter than heifers from the ADEQ-supplemented MGDs (see **Table 1**). A trend was also observed for the effect of dam treatment on heifer offspring weight at 14 months of age, with heifers out of the MARG-supplemented dams weighing 4 kg less than heifers out of the ADEQ-supplemented dams. As expected, the prebreeding weight of heifers was altered by the feeding level (control vs restricted) during postweaning development. Restricted feeding resulted in lighter prebreeding weights than control feeding (restricted and control are designated as MARG and ADEQ, respectively, in **Table 1**, based on winter supplementation level). The prebreeding weight of cows 5 years of age and older was influenced by interactions of MGD and dam treatments, and MGD and individual treatments (see **Table 1**). In previous analyses that did not include the MGD effects, the main effect of dam treatment and individual treatments were observed.[13] Cows out of MARG-supplemented dams were heavier than cows out of the ADEQ-supplemented dams. Animals receiving the ADEQ supplement each winter were heavier than cows given the MARG supplement (ie, direct effect of supplement level). The current results indicate an increase in mature weight occurred with MARG supplementation to either the MGD or dam, and that MGD treatment is important when evaluating the direct effect of supplement levels on weight change. Animals supplemented at the same level as their MGD were heavier than animals that received the opposite of the supplement treatment that their MGD received.

The supplement level provided to the PGD influenced heifer (granddaughter) intramuscular fat at 1 year of age, in which heifers descending from MARG-supplemented PGDs had greater intramuscular fat than heifers from the ADEQ-supplemented PGDs (see **Table 1**). The prebreeding weight of cows 5 years and older was influenced by the interaction of PGD and individual treatments (see

Table 1
Effect of supplementation level provided to paternal granddam, maternal granddam, dam, or individual on growth and ultrasound carcass measurements

MGD Treatment	MARG[a]		ADEQ[a]			
Dam treatment	MARG	ADEQ	MARG	ADEQ	SE	P
Birth weight[b], kg	33.8[d]	34.5	34.3	34.5	0.17	.08
Weaning weight[b], kg	201[d]	215	214	214	1	<.01
Hip height at 12 mo age, cm	116[d]	118	117	117	0.3	<.01
MGD treatment	MARG	ADEQ				
Loin muscle area at 12 mo age, cm²	52.9	54.2	—	—	0.3	.01
PGD treatment	MARG	ADEQ				
Intramuscular fat at 12 mo age, %	3.7	3.5	—	—	0.02	.03
Weight at 14 mo age, kg	MARG	ADEQ				
Effect of MGD treatment	301	306	—	—	2	.03
Effect of dam treatment	302	306	—	—	2	.10
Effect of Individual treatment	296	311	—	—	2	<.01
MGD treatment	MARG		ADEQ			
Dam treatment	MARG	ADEQ	MARG	ADEQ		
Mature weight[c], kg	517	512	518	500[d]	5	.09
MGD treatment	MARG		ADEQ			
Individual treatment	MARG	ADEQ	MARG	ADEQ		
Mature weight[c], kg	524	505[d]	502[d]	516	5	<.01
PGD treatment	MARG		ADEQ			
Individual treatment	MARG	ADEQ	MARG	ADEQ		
Mature weight[c], kg	506[d]	514[d,e]	520[e]	507[d]	5	<.01

[a] Animals were provided either 1.1 kg/d (MARG) or 1.8 kg/d (ADEQ) alfalfa hay as supplement while grazing dormant native range during the last trimester of pregnancy. Rows with 4 values depict means for interactions of treatments indicated in preceding two rows. Rows with 2 values depict means for main effect of treatment indicated in preceding row.
[b] Some of these data were analyzed and reported previously.[13]
[c] Weight of cows 5 years and older taken before start of breeding, approximately 3 mo after ending the winter supplement treatment.
[d] Means in same row without similar superscripts differ (P<.05).
[e] Means in same row without similar superscripts differ (P<.05).

Table 1). Weight rankings in the PGD by individual treatment interaction are opposite of ranking in the MGD by individual treatment interaction. Cows fed the same level of supplement as their PGD were lighter than cows fed the opposite supplement treatment of their PGD.

The expanded model applied in the current analyses indicates transgenerational effects and a parental path of inheritance (ie, MGD vs PGD) must be considered when evaluating direct treatment effects on individuals, as well as carryover effects from dam treatments. The magnitude of differences reported in **Table 1** reflects a 2% to 4% difference in weight. This magnitude of difference is much lower than differences reported for many studies evaluating severe nutrition deficiencies.[2] Exposure of 2 successive generations to MARG supplementation resulted in offspring exhibiting reduced weights at birth through at least 1 year of age; however, weights later in life were greater in offspring descending from cows subjected to 1 or 2 generations of MARG supplementation. Although not presented, the differences in BCS paralleled

the differences in mature weights, in which heavier weights were associated with a greater BCS. So, differences in weight reflect differences in body composition and not necessarily a change in body size. These results would be consistent with metabolic changes that result in a caloric storage advantage (see previous discussion), which may provide a reproductive advantage in limited environments.

Pregnancy rates at 3 years of age were influenced by the interaction of the MGD treatments by dam treatments (**Table 2**), with the lowest pregnancy rates occurring in cows coming from the ADEQ-supplemented dams and the ADEQ-supplemented MGDs. The pregnancy rate at 5 years of age was influenced by MGD treatment by individual treatment interaction (see **Table 2**), with the lowest pregnancy rates occurring in the ADEQ-supplemented cows from the ADEQ-supplemented MGDs. Although these results reflect positively for MARG supplementation, pregnancy success at specific ages is not independent from pregnancy rates at earlier ages. Rebreeding rates of 2-year-old females was decreased by the direct effect of MARG supplementation.[13] This potentially influences the population structure progressing to the next age, whereby less fit females may be culled out earlier in life under a MARG level of supplementation but not until older ages when managed under ADEQ supplementation. Continued data collection will provide greater insight into the generational impact on longevity. However, it is interesting to speculate that generational inheritance of environmentally stimulated changes in gene expression may be contributing to the genetic by environment interaction recently reported for stayability (measure of longevity) in cattle.[17]

Consideration of Epigenetics in Genetic by Environmental Interactions

Several livestock traits are under the control of genetic and environmental factors and their interaction. In today's application of genetics in the livestock industry, genetic by environment interactions are not generally considered. However, with the continued accumulation of data concerning how epigenetics may mediate environmental effects on gene expression, accounting for such effects is needed. Genetic by environment interactions have been widely studied. However, few studies have explored the effects of nutritional environments on the genetics of the animals and their offspring. Studying the effects of the environment on the genetic merit of the animal quantitatively could be carried out through 2 approaches. The first is a multitrait model that treats each observation of a given trait in a certain environment as different and assumes genetic correlations.[18–21] The second approach is using a reaction norm model that requires a continuous environmental gradient. This approach allows the characterization of the trajectory of animal performance across the environment.[22–26]

Table 2
Interaction of supplement level provided to maternal granddam and dam, or maternal granddam and individual, on pregnancy rate

MGD treatment	MARG[a]		ADEQ[a]			P
Dam treatment	MARG	ADEQ	MARG	ADEQ	SE	MGD × dam
% Pregnant at 3 y age	84[b,c]	85[b]	88[b]	75[b,c]	4	.065
Individual treatment	MARG	ADEQ	MARG	ADEQ	SE	MGD × individual
% Pregnant at 5 y age	93[b]	99[b]	96[b,c]	89[b,c]	3	.03

[a] Animals were provided either 1.1 kg/d (MARG) or 1.8 kg/d (ADEQ) alfalfa hay as supplement while grazing dormant native range during the last trimester of pregnancy.
[b] Means in same row without similar superscripts differ ($P<.05$).
[c] Means in same row without similar superscripts differ ($P<.1$).

Exploring how nutrition affects the genetics of an animal and its offspring was conducted by Hay and Roberts[27] (2018) using these 2 approaches. Results indicated genetic estimates for postweaning average daily gain (ADG) were subject to the interaction of nutritional environment imposed on the dam during pregnancy (ie, genetic by environment interaction, where environment was classified as ADEQ or MARG treatments; see previous discussion). Results indicated that the genetic estimate for ADG differed depending on prenatal environment. The results also indicated a higher impact of genetic by nutritional environment interaction on phenotypes with lower heritability. Genetic breeding values of the offspring showed a change in magnitude across the ADEQ and MARG treatments and, in some cases, reranking. Furthermore, the indirect genetic response to selection differed between the environments and, in some cases, lower nutritional input environments resulted in a higher genetic response. Although not directly established, differences resulting from fetal programming may account for the observed results. Unpublished results from a study by Hay and Roberts showed a change of single nucleotide polymorphisms (SNPs) effects in the offspring across the dam's nutritional environments (ADEQ and MARG supplementation). The percentage of maternal genetic variance explained by each SNP for birth weight differed between the MARG and the ADEQ supplemented groups. This difference was greatest for a SNP located on 24Mb on chromosome 14. This chromosome has been reported to harbor many genes and quantitative trait loci, controlling growth and metabolism.

With the existence of genetic by environment interaction, it is sensible to have environment-specific breeding programs. However, in beef cattle, most genetic evaluations are based on phenotypic data from a limited range of environments and seldom on animals having offspring in very different environments. Genomics could help with this issue because SNP could be used to compute genomic breeding values in different environments, which, in turn, could be used for selection and mating decisions. However, this would require a large genomic reference dataset spanning various environments.

SUMMARY

Environmental influences resulting in epigenetic mediation of gene expression can affect multiple generations via a direct effect on the animal; direct or maternally mediated effects on the fetus, or gonadal cell lines of the fetus when pregnant animals are exposed; and through inheritance across generations. Although much of the research on multigenerational effects has focused on nutritional deficiencies, diseases, and other undesirable responses, tremendous potential exists to use epigenetics as a tool to improve production efficiency. Because animals within a herd are all subjected to similar environmental stimuli throughout the production cycle, any stimuli resulting in epigenetic modification may result in herd-wide changes. Beef production occurs with less management of the production environment than swine, poultry, and dairy. This indicates beef production may be influenced to a greater extent by epigenetic alterations of gene expression than industries incorporating greater environmental control. Production practices that result in herd-wide exposure to specific nutritional environments, resulting in generational inheritance of desirable characteristics, will be much more rapid than pursuing phenotypic change through genetic selection. At present, the impact epigenetics has had in the livestock industry is not well-described. However, significant potential exists to propagate desired characteristics in the livestock industry through epigenetic pathways and these pathways may alter estimates of genetic variance (ie, expected

progeny differences), thereby resulting in genetic by environment interactions that will need to be taken into consideration when using traditional genetic selection.

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