

Can genomics help prevent metabolic diseases?

Research shows a potential link between genetics and certain diseases of transition cows.

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THE transition dairy cow (21 days before parturition to 21 days postpartum) must experience a series of complex metabolic and physiological changes as parturition approaches. As a result, periparturient disorders may occur and affect the future performance of these dairy cows.

Feed intake starts to drop a few weeks before parturition, with the lowest level occurring at calving. Simultaneously, nutrient demands rise due to the exponential growth of the fetus, mammary gland development, and the initiation of lactation. Accordingly, the cow typically undergoes a state of negative energy and protein balance and a characteristic fat mobilization from the adipose tissue stored in different areas of the body.

The role of fat

Extreme lipid mobilization leads to an increased release from adipose tissue of non-esterified fatty acids (NEFA) and excessive uptake of these by the liver with a potential pathologic accumulation in the form of triglycerides. However, in addition to being an energy source, adipose tissue also has immune, endocrine, regenerative, mechanical, and thermal functions. The extent of these fuel and nonfuel functions of adipose tissue varies depending on deposit size and body fat distribution.

Therefore, fat can be deposited under the skin (subcutaneous tissue) and around vital organs (kidney, omentum/visceral, and so forth), where it may play immunologically defensive and mechanically protective roles. Once activated, the adipose tissue may be inflamed and shift from storing to releasing NEFA. This is potentially driven in part through the release of local proinflammatory compounds called cytokines.

Regional differences in the precursors of fat-storing cells (preadipocytes), replication, differentiation, abundance, and gene expression may contribute to regional variation in fat tissue function. Indeed, variations in gene expression, which determine diverse specific and precise functions of the gene, between different fat deposits has been demonstrated in dairy cattle.

A displaced abomasum

Based on these findings in humans and lab animals, it is noteworthy that genetic studies have suggested that body fat distribution is associated with variation in genes involved during embryonic development. These associations with genetic variants may also occur in dairy cattle.

A New Zealand study found that their Holstein bloodlines had different fatty acid profiles in their adipose tissues and milk, which may affect the metabolic status of the adipose deposits differently. Other studies have demonstrated that the activity of fat metabolism-related enzymes, known

as lipases and desaturases, differ between abdominal and subcutaneous fat.

This supports the hypothesis of a preferential mobilization of abdominal fat in dairy cows, especially when they develop a left displaced abomasum. This may imply that some of the genes responsible for variation in abdominal fat accumulation are also related to variation in the risk of development of this digestive condition in Holstein cattle.

Interestingly, some bovine practitioners, myself included, have noted excessive abdominal fat during the surgical corrective procedure of displaced abomasums in cows with a normal body condition score (BCS). Therefore, identifying risk factors, such as genetic variants predisposing cows to this type of periparturient diseases and/or abdominal adiposity, would be beneficial to the dairy industry.

This might enable the identification of genetic markers that are predictive of variation in abdominal or visceral fat deposition. In turn, this could permit the establishment of proper management and selection strategies to prevent and control fat tissue related disorders (ketosis, fatty liver, displacement of the abomasum, and so forth) (Table 1).

It's in their genes

In order to contribute more information related to fat depositions in dairy cattle, we conducted a project entitled "Genome-wide study to detect SNPs associated with visceral and subcutaneous fat deposition in Holstein dairy cows." The objective was to assess the extent of genetic variation responsible for dif-

ferences in the degree of visceral or abdominal fat deposition in U.S. Holstein cows with normal body condition scores or subcutaneous fat depositions.

The study included adult Holstein cows sampled from a slaughterhouse. Only animals with a body condition score between 2.75 and 3.25 (scale of 1 to 5) were eligible to be sampled. The extent of abdominal fat (omental fat) at the level of the insertion of the lesser omentum over the pylorus area of the abomasum of the cow was assessed.

Two groups were sampled: 100 cows with an omental fold less than 5 millimeters (mm) in thickness and minimum fat deposition throughout the entire omentum, and 100 cows with an omental fold greater than or equal to 20 mm in thickness and with a marked fat deposit observed throughout the entire omentum.

A small piece of muscle from the neck was collected from each cow for DNA extraction. Samples were submitted to a commercial laboratory for interrogation of genome-wide genomic variation using the Illumina Bovine HD Beadchip.

A genome-wide association analysis was performed to test potential associations between fat deposition and genomic variation. Interestingly, 11 parts of the genome were found to be significantly associated with visceral fat deposition. Regions were located in chromosome 12 and 19 of the bovine species. As you can see in Table 2, potential genes that may differ in their expression between both genotypes are strongly related with very important cell functions and metabolic pathways in mammal cells.

We concluded that excessive omental or visceral fat in Holstein cows with normal body condition scores appears to be at least moderately heritable. Consequently, selection to reduce excessive omental fat is potentially conceivable, but it would require the generation of predicted transmitting abilities (PTA) from larger and random samples of Holstein cattle. That could help generate selection indexes to reduce the occurrence of excessive abdominal fat, which may prevent common metabolic diseases in dairy cattle. 🐄

Table 1. Incidence of displacement of abomasum, culling, fertility, and milk yield in normal cows and cows with subclinical ketosis (blood BHB > 1.2 mmol/L; fat-metabolism related diseases)

Condition	Normal	Subclinical ketosis	P-value
Displacement of abomasum	0.30%	6.50%	< 0.001
Early removal from herd	1.80%	5.40%	< 0.001
Conception to first service	40.00%	35.10%	0.55
Milk yield (lbs. per day)	77.2	74.6	0.006

Source: J. McArt, D. Nydam, G. Oetzel. Epidemiology of subclinical ketosis in early lactation dairy cattle. *Journal of Dairy Science*, 95:5056-5066, 2012.

Table 2. Function of potential genes within genomic regions that differed between cows with high and normal abdominal adiposity

Gene	Biological functions
CLTC	Maintenance of cellular vesicles; mitotic chromosome stabilization; cytoplasmic membrane trafficking and transport; tumorigenesis
DHX40	Production of ATP-dependent RNA helicases
FGF14	Embryonic development; cell growth; tissue repair; morphogenesis; tumorigenesis
GDPD1	Lipid metabolic activity
HOXB	Regulation of tissue differentiation; DNA-binding; embryonic patterning; organogenesis
PRAC2	Production of non-coding and nucleus-associated RNAs
PTRH2	Integrin signaling; mediation of cell survival and apoptosis; muscle development; regulation of myogenic differentiation
SKAP1	T-cell antigen receptor and integrin activation
VMP1	Vacuole membrane formation; autophagy regulation
YPEL2	Potential association with cell division

Source: P. Melendez, S. Poock, P. Pithua, P. Pinedo, D. Manriquez, S. Moore, J. Neal, and J. Taylor. 2019. Genome-wide study to detect SNPs associated with visceral and subcutaneous fat deposition in Holstein dairy cows. *Animal*, 13(3):487-494. doi: 10.1017/S1751731118001519.