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Should Genetics Be Blamed for High Incidence of Uterine Disease in Dairy Cows?[1]

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Introduction

Uterine diseases—such as metritis, clinical endometritis, and subclinical endometritis—are highly prevalent in high-producing dairy cows (Sheldon et al. 2006). These diseases have been associated with decreased pregnancy per artificial insemination (AI), extended interval to pregnancy, increased culling, and economic losses (Bartlett et al. 1986; Sheldon and Dobson 2004; Gilbert et al. 2005). Metritis affects about 20% of lactating dairy cows, with the incidence ranging from 8% to 40% in some farms (Curtis et al. 1985; Galvão et al. 2009; Goshen and Shpigel 2006). Clinical endometritis also affects about 20% of lactating dairy cows, with the prevalence ranging from 5% to 30% in some herds (Galvão et al. 2009; LeBlanc et al. 2002; McDougall et al. 2007). Subclinical endometritis is the most prevalent of all uterine diseases. It affects about 30% of lactating dairy cows, with the prevalence ranging from 11% to 70% in some herds (Barlund et al. 2008; Galvão et al. 2009; Gilbert et al. 2005; Cheong et al. 2011).

Figure 1. Dairy cows at the UF/IFAS Dairy Unit
Credit: Klibs Galvão

Traditionally, risk factors associated with metritis include primiparity, dystocia, twins, retained placenta (RP), stillbirth, abortion, prolapsed uterus, and ketosis (Markusfeld 1984; Curtis et al. 1985; Gröhn et al. 1990). Risk factors for endometritis include dystocia, twins, RP, stillbirth, abortion, metritis, problems with vulval conformation, male offspring, and ketosis (Gröhn et al. 1990; Galvão et al. 2009; Dubuc et al. 2010; Potter et al. 2010; Cheong et al. 2011).

Genetic selection for increased disease resistance in cattle has been proposed (Fisher et al. 2011; Mallard et al. 2011), and a recent study demonstrated that dairy cattle identified as high immune responders (i.e., individuals mounting a significant general antibody and cell-mediated immune response) were at lower risk of developing disorders such as mastitis, metritis, and retained placenta (Thompson-Crispi et al. 2012). Immune cells recognize pathogens through pattern-recognition receptors called toll-like receptors (TLR), and recognizing pathogens through the TLRs is the first step to eliminating them. At least 10 members of the TLR gene family are known to exist in mammals (Vasselon and Detmers 2002; Kaisho and Akira 2006).

The objective of this article is to present the results of a recent paper (Pinedo et al. 2013) that examined how alterations on the TLR genes affect the susceptibility to uterine diseases.

Evaluating the Effect of Alterations on the TLR Genes Regarding the Susceptibility to Uterine Diseases

The study was conducted within the University of Florida Dairy Unit (Gainesville, FL) with a cohort that consisted of 358 Holstein cows (164 primiparae; 194 multiparae). Metritis was defined as an abnormally enlarged uterus with reddish-brown fetid uterine discharge (with or without a fever) within 21 DIM. Clinical endometritis (CE) was characterized by the presence of purulent or mucopurulent vaginal discharge at 35±3 DIM. Subclinical endometritis (SCE) was characterized by the presence of = 10% neutrophils

in the endometrial cytology samples collected at 35±3 DIM. DNA was isolated from blood, and custom allele-specific genotyping assays derived from multiple bovine TLR sequencing studies were used. The association between specific TLR genotypes and each of the uterine diseases was evaluated by logistic regression with correction for confounding variables including calving season; parity; body condition score at calving, at enrollment (BCSEn), and at 35 DIM; dystocia; ketosis before and after 17 DIM; RFM; hypocalcemia; twins; calf dead on arrival; abortion; sire; and maternal grand sire.

Logistic regression models were constructed for each of the 29 variable sites. Four, two, and one SNPs (TLRs 2, 4, 6, 9) produced uncorrected P-values = 0.05, with respect to MET, CE, and CYE, but none of the SNP associations endured correction for multiple testing. Covariates included in the final model for MET comprised calving season, parity, dystocia, BCSEn, and ketosis at < 17 DIM. Covariates for CE were calving season, dystocia, ketosis at < 17 DIM and hypocalcemia. No covariates were retained for CYE.

Our analysis suggests that some TLR SNPs (TLRs 2, 4, 6, 9) may potentially elicit relatively small effects on uterine health in Holstein cows, and some confounding variables are actually more predictive for the incidence of disease than any genetic markers evaluated herein.

Conclusion

Uterine health is influenced by a number of environmental variables that make it difficult to accurately estimate the precise role of host genetic components. Our results indicated that known variation within seven bovine TLR genes does not modulate large effects on risk for uterine disease. Weak associations were observed between SNPs occurring in four bovine innate immune genes and uterine health in Holstein cows, suggesting that variation in innate immune genes may potentially modulate small effects on the incidence of uterine disease. Future studies employing whole-genome approaches are needed to help elucidate unknown genetic risk factors for uterine diseases in Holstein cows.

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