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Review

Genetics of bovine abomasal displacement

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ABSTRACT

Displacement of the abomasum (DA) is a common inherited condition in Holstein cows. This article reviews the genetics of DA including risk factors, genetic parameters and molecular genetic results. Breeds other than Holsteins affected by DA include Guernseys, Jerseys, Brown Swiss, Ayrshires and Simmental-Red Holsteins. In most DA cases, left displacements of the abomasum (LDA) are seen. Lactation incidence rates are higher for DA in first lactation Holsteins compared to later lactations. For Holstein cows, heritability estimates for DA are between 0.03 and 0.53. Genetic correlation estimates among DA and milk production traits range from positive to negative.

Genome-wide significant genomic regions associated with LDA are located on bovine chromosomes (BTA) 1, 3, 11, 20 and 23. *Motilin*-associated single nucleotide polymorphisms on BTA23 exhibit a functional relationship with LDA. Pathways for deposition of calcium, insulin-dependent diabetes mellitus and synaptic transmission are significantly related to LDA in Holsteins. Deciphering the DA-associated genomic regions and genes may be an important step in the quest to understand the underlying disease-causing mechanisms and in unravelling mutations with a causal relationship to DA.

Introduction

Displacement of the abomasum (DA) is a condition in many dairy cattle breeds and is of increasing concern in terms of both animal welfare and economics. Most DA cases occur around the time of parturition and may be associated with concurrent metabolic and reproductive disease. A higher risk of involuntary culling is often the consequence of DA in dairy cows.

This article briefly reviews the published incidences, risk factors, heritability estimates for DA and the genetic correlations between DA and milk production traits. In addition, we summarise the results of molecular genetic research in identifying quantitative trait loci (QTLs) and associated single nucleotide polymorphisms (SNPs). The results of linkage analyses, association studies and candidate gene analyses as well as perspectives for further research are also presented.

Incidence and risk factors

DA is a common condition in many dairy cattle breeds. Holstein cows are particularly predisposed to DA with lactation incidence rates (LIRs) of 1.6–5% (Detilleux et al., 1997; Wolf et al., 2001; LeBlanc et al., 2005; Koeck et al., 2013). Dairy cows are mostly affected, but DA also occurs infrequently in calves and young cattle of both sexes (Constable et al., 1992). LIRs are highest in third to fifth lactation cows in German Holsteins (Wolf et al., 2001) whereas in the US Holsteins first lactation cows show the highest incidence at 4.1% (Appuhamy et al., 2009; Koeck et al., 2013).

Left displacement of the abomasum (LDA) is much more frequently found in cows than displacement to the right abdominal wall (RDA) (Espersen, 1961; Geishauser et al., 1998b; Wolf et al., 2001; Stengärde and Pehrson, 2002). Most cases of LDA are observed around the time of calving (Constable et al., 1992) whereas RDA cases seem to be unrelated to calving time (Doll, 2007). Despite successful veterinary treatment, milk production decreases over the course of the concurrent lactation (Geishauser et al., 1998b; Hamann et al., 2004). Subsequent disease and reduced conception rates decrease survival probabilities for cows after they have experienced DA (Ricken et al., 2005).

Abomasal hypomotility is the main prerequisite of DA (Nelson et al., 1995; Geishauser et al., 1998a; Wittek et al., 2005, 2007; Doll et al., 2009) and electromyography recordings have demonstrated abomasal atony in LDA-affected dairy cows (Nelson et al., 1995). The depth of the abdomen and the vertical distance between the ventral abdomen and the duodenum are greater in cows with a previous history of LDA than in those without, and this may further decrease the rate of abomasal emptying, particularly in the presence of abomasal atony (Wittek et al., 2007). This hypothesis seems to be further substantiated by the prokinetic effects of erythromycin seen on abomasal emptying rate in dairy cows (Wittek et al., 2008; Constable et al., 2012).

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Possible risk factors that have been identified for DA include calving problems, twin births, a high body condition score before calving, overfeeding in the dry period, decreased feed intake, endotoxaemia, hypocalcaemia, hypokalaemia, metabolic alkalosis and concurrent diseases such as ketosis and metritis (Markusfeld, 1986; Constable et al., 1992; Massey et al., 1993; Geishauser, 1995; Fürll and Krüger, 1999; Rohrbach et al., 1999; Stengärde and Pehrson, 2002; Van Winden et al., 2003; Pravettoni et al., 2004; LeBlanc et al., 2005; Ricken et al., 2005; Zebeli et al., 2011; Zurr and Leonhard-Marek, 2012; Lyons et al., 2014).

Metritis and elevated β-hydroxybutyrate (BHB) serum concentrations in the first week following calving were found to be the most important risk factors for DA in Canadian Holstein cows (LeBlanc et al., 2005). Cows with serum BHB concentrations ≥1.0 mmol/L in the first week after calving had a 13.6-fold odds ratio (OR) of developing DA than cows with lower values (Seifi et al., 2011). A study including 528 dairy herds from 10 European countries indicated that cows with BHB concentrations >1.6 mmol/L during the first 2–15 days in milk had a 6.9 times greater OR for developing DA than cows with lower BHB concentrations (Suthar et al., 2013).

In DA-affected dairy cows, insulin-like growth factor-1 concentrations are significantly lowered compared to controls (Lyons et al., 2014). Increased production of nitric oxide in the enteric nervous system, a lowered sensitivity to acetylcholine and/or a lowered concentration of substance P in the abomasal wall may also increase the risk of DA (Geishauser et al., 1998a; Sickinger et al., 2008). Doll et al. (2009) concluded that abomasal hypomotility, especially due to dysfunctions of the enteric nervous system, seems to be a key event underlying the pathogenesis of DA.

Breeds at risk

It is evident that there is a considerable genetic disposition of cows to DA. The condition is prevalent in German Holsteins (Hamann et al., 2004; Sickinger et al., 2008), Holstein Friesians (Ozturk et al., 2013), Jerseys (Jubb et al., 1991; Constable et al., 1992), Guernseys, Ayrshires, Brown Swiss (Constable et al., 1992; Eicher et al., 1999) and Simmental-Red Holsteins (Eicher et al., 1999), with Holsteins and Guernseys at highest risk (Constable et al., 1992; Eicher et al., 1999). The disease is rarely observed in beef cattle (Constable et al., 1992) and the dual-purpose German Fleckvieh (Simmental) (Doll, 2007; Doll et al., 2009). Heritability estimates for LDA and DA are higher than for other dairy cattle diseases (Zwald et al., 2004a; Neuenschwander et al., 2012; Parker Gaddis et al., 2014) for which low heritabilities (<0.05) have been generally reported (Distl, 1992; Uribe et al., 1995; Zwald et al., 2004a; Heringstad, 2010; Koeck et al., 2010).

Heritability

Most genetic studies have been performed in Holsteins. The heritability estimates based on threshold models are between 0.03 and 0.53 for DA, LDA and RDA (Table 1). Summarising heritabilities across studies, the corresponding estimates are 0.20, 0.30 and 0.22, respectively. The differences between these estimates may be explained by diverse ways of recording DA-cases, the estimation methods used and the populations investigated. Koeck et al. (2013) used first-lactation records only; in the study by Zwald et al. (2004a), data from first lactation yielded higher heritabilities than for all lactations (0.18 vs. 0.15). Similar results for first (0.22) and later lactation records (0.12) were obtained by Parker Gaddis et al. (2014). Genomic data for 7883 sires, based on common SNPs from the Illumina Bovine SNP50 BeadChip, were employed to construct a relationship matrix combining the pedigree and genomic relationships for a threshold sire model analysis. This single-step genomic analysis increased heritability estimates of DA for first (0.32) and later lactation records (0.17) (Parker Gaddis et al., 2014).

Table 1
Heritability estimates for all displacements of the abomasum (DA), to the left (LDA) and right side (RDA) in Holstein cows.

Number of cows	Heritability			Method	Lactation records	Reference	Country
	DA	LDA	RDA				
7416	0.28			STM	All	Uribe et al. (1995)	Canada
9315	0.36	0.51	0.19	LAM	All	Wolf et al. (2001)	Germany
9315		0.53	0.09	LAM	All	Hamann et al. (2004)	Germany
3578	0.18	0.11	0.39	LAM	All	Ricken et al. (2004)	Germany
75,252	0.18			STM	First	Zwald et al. (2004a)	USA
75,252	0.15			STM	All	Zwald et al. (2004a)	USA
44,839	0.03			S-MGS	All	Appuhamy et al. (2009)	USA
80,882		0.21		STM	All	Neuenschwander et al. (2012)	Canada
63,763	0.27			LAM	First	Koeck et al. (2013)	Canada
134,226	0.22			STM	First	Parker Gaddis et al. (2014)	USA
100,635	0.12			STM	2–5	Parker Gaddis et al. (2014)	USA

LAM, linear animal model and transformation onto the liability scale; STM, sire threshold model; SMGS, bivariate linear-threshold sire–maternal grandsire model.

For DA and ketosis there was found to be a moderate genetic correlation (0.45 ± 0.16) in first-lactation US Holstein cows (Zwald et al., 2004b). Genetic correlations with mastitis, lameness, cystic ovaries and metritis were positive (0.07–0.17) but not significantly different from zero due to large standard errors. An even higher genetic correlation between LDA and ketosis (0.58 ± 0.13) was shown in Canadian Holstein cows by Neuenschwander et al. (2012).

Molecular genetics

Linkage and association studies

Molecular genetic studies focus only on LDA because approximately 75% of all DA cases have a displacement to the left and because LDA may have a different genetic background to RDA (Wolf et al., 2001; Ricken et al., 2004). In order to detect genomic regions that contain genes that have an influence on LDA, linkage and association studies are performed. A whole-genome scan in 14 paternal daughter groups with 360 German Holstein cows, 221 microsatellites and a further 85 microsatellites for fine-mapping 14 chromosomes showed two genome-wide and three chromosome-wide significant QTLs for LDA (Mömke et al., 2008). These QTLs are located on bovine chromosomes (BTA) 1 and 3, and on BTA21, 23 and 24, respectively. Furthermore, 11 LDA-QTLs specifically linked within grandsire families are mapped on BTA5, 6, 10, 12, 15, 16, 17, 19, 23 and 26 (Table 2).

A genome-wide association study (GWAS), using the Illumina Bovine SNP50 BeadChip with 225 cases and 629 controls and 36,226 informative SNPs, revealed 36 LDA-associated SNPs on 17 bovine chromosomes; a putative influence of these SNPs on LDA was assumed because a nominal significance level of $P < 0.001$ had been chosen (Mömke et al., 2013). Correcting for multiple testing allowed the authors to deduce genome-wide significance levels. Two of these SNPs reached genome-wide significance at $-\log_{10}P$-values >4.6. These SNPs were found to be located on BTA11 within the gene *IL1RN* (*interleukin-1 receptor antagonist*) and on BTA20 close to the gene *IPO11* (*importin 11*). A pathway analysis using all 36 putatively associated LDA-SNPs and a significance threshold of $P < 0.01$ revealed deposition of calcium and insulin-dependent diabetes mellitus as