Genetic Factors of Milk Yield in Dairy Cattle – Advances in the Quest for Universal Markers

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ABSTRACT

The current state of knowledge of milk-protein coding genes and prolactin is presented in this review. Genes encoding milk proteins (caseins and whey proteins) are discussed as well as the genes of the factors regulating expression milk protein genes, such as prolactin, prolactin receptor, and the genes of the somatotropic (somatotropin growth hormone) axis (growth hormone, GH-releasing hormone, Pit1 –Pituitary-specific Transcription Factor-1, growth hormone receptor, insulin-like growth factor 1, and STAT5A- Signal Transducers and Activators of Transcription). Also findings on diacylglycerol acyltransferase 1 and leptin genes are reviewed in terms of milk yield traits of dairy cattle.

Key words: Milk yield, genetics, dairy cattle, prolactin, somatotropic axis

INTRODUCTION

Milk yield in dairy cattle is governed both by genetic and environmental factors. Animals are subject to constant improvement for this quantitative trait, which is based on phenotype observations of cows and evaluation of the progeny and kins. These processes are both time-consuming and expensive. With the observed advances in molecular genetics, one may presume however that animal evaluation techniques based on differences at the DNA level will be available in the near future. Consequently this may dramatically accelerate genetic improvement of dairy cattle, especially due to genotyping of young animals.

The bovine genome was completely sequenced in 2007 (1). About 22,700 genes and about two million SNPs (single nucleotide polymorphisms) were found. The variability of the genotype caused by the simple polymorphisms of the substitution or insertions or deletions is great; however, only a small portion of these are of a functional character. Most associations between the polymorphism at a given locus and the phenotypic variability are virtually meaningless or appears in local populations only. Thus, the research in pursuit of a functional marker that would be of importance for selection, focuses mainly on protein-coding genes, involved in the processes of lactation, as well as the genes that regulate these complex processes.

This review presents a short characterization of milk-protein coding genes and prolactin.

GENES ENCODING MILK PROTEINS

Caseins

Casein content in bovine milk ranges from 2.4% to 2.6%, which represents about 78% of all milk proteins (2). There are four primary casein fractions of excellent nutritive value: αS1 (CASA1, CSN1S1), αS2 (CASA2, CSN1S2), β (CSN2, CASB), κ (CSN3, CASK) (2). These forms differ primarily in amino-acid composition, number of polymorphic variants, molecular weight, as well as in their content in milk and the amount of phosphorus. Caseins are encoded for by single autosomal genes that occupy approximately 200 Kbp on the sixth chromosome (2). The linked genes are present in the sequence: αS1, β, αS2, κ, which means that their expression

Table 1. Milk-yield associated bovine genes and their polymorphism

Gene	Product	Polymorphism	Alleles
CSN1S1, CASA1	αS1 casein	1) Transition *A/G*, exon XVII, change in polypeptide chain: E 192 G	*B, C* (*A, D, E, F*–rare)
		2) Transition *A/G*, region 5'UTR (-175); restriction endonuclease *Mae*III	*A, G*
CSN2, CASB	β casein	Transversion C/A, change in polypeptide chain: H67P (allel A^2), H106E (A^3), S122R (*B*)	A^1, A^2, A^3, *B*, (*D, E, C*)
CSN1S2, CASA2	αS2 casein	Transition *C/T*, promoter (-1084), restriction endonuclease *Mae*II	*C, T*
CSN3, CASK	κ casein	Double mutation in exon IV, changes in polypeptide chain: T36I, D 148 A, restriction endonuclease *Hind*III	*A, B* – most common
LGB, BLG	β-lactoglobulin	Double mutation *C/T*, *T/C*, changes in polypeptide chain D64G, V118A, restriction endonuclease *Hae*III	*A, B*
LTF	lactoferrin	1) Transversion *G/C*, region 3'UTR (+32)	*G, C*
		2) exon VI, restriction endonuclease *Eco*RI	*A, B*
PRL	prolactin	Transition *A/G* in exon III (or IV, see text). restriction endonuclease: *Rsa*I	*A, B*
PRLR	Prolactin receptor	Transversion *A/C*, intron 9 (209)	*A, C*
GHRH, STH-RH	Somatoliberin	Intron 2, restriction endonuclease: *Hae*III,	*A, B*
GH, STH	Somatotropin (growth hormone)	1) Transversion *G/C*, exon V, change in polypeptide chain: L 127 V, restriction endonuclease *Alu*I	*L, V*
		2) Simultaneous insertion and transition *TC/G*, restriction endonuclease: *Msp*I	*MspI(+), MspI* (-)
Pit1	Pit1 transcription factor	Transition *A/G*, exon VI, restriction endonuclease: *Hinf*I	*A, B*
GHR	Growth hormone receptor	1) Transversion *A/T*, region 5'UTR (-1182), restriction endonuclease: *Alu*I	+, -
		2) Transversion *T/A*, exon VIII, change in polypeptide chain F/Y	*Y, F*
IGF-I	Insulin-like growth factor 1	Transition *C/T*, restriction endonuclease: *Sna*BI.	*A, B*
STAT5A	STAT5A transcription factor	1) Transition *T/C*, exon XVI (12743), restriction endonuclease: *Ms*I	*C, T*
		2) Transition *A/G*, intron 9 (9501), restriction endonuclease: *Rsa*I, change in polypeptide chain V686A	*A, G*
DGAT1	Diacylglycerol acyltransferase 1	Dinucleotide substitution *AA/GC*, exon VIII (10433-10434), change in polypeptide chain: K232A	*K*, *A*
LPT	Leptin	1) Intron 2, restriction endonuclease: *Sau*AI	*A, B, C*
		2) Transition *C/T*, exon II, change in polypeptide chain: R/C, restriction endonuclease: *Kpn*2I	*C, T*
		3) Transition *C/T*, exon III, change in polypeptide chain: A/V, restriction endonuclease: *Hph*I	*C, T*

1), 2), 3) – Polymorphisms within the same gene

during lactation is regulated in a synchronic way. It is possible that a LCR (locus control region) exists for the casein genes.

The α-casein coding gene is 17508 bp in length and is built of 19 exons (2). Five genetic variants of CSN1S1 have been identified: *A*, *B*, *C*, *D*, and *E* (3). The allele *B* is of the highest frequency in *Bos taurus*, whereas *C* is the most common in *B. indicus* and *B. grunienns* (3). The allele B encodes glutamine whereas *C* encodes glycine, both at position 192. Table 2 presents the effects of particular variants on various milk performance parameters. Some authors studied mutations in the promoter of this gene and their possible effects on the performance of dairy cattle (Table 2).

The 8498-bp β-casein gene is composed of 9 exons. Seven variants of CSN2 were identified in cows, i.e. *A1, A2, A3, B, D*, and *E* (Table 1), of which *A* is the most common allele (2). Their associations with milk yield is described in Table 2.

The κ-casein coding gene is divided into 5 exons and is 13070 bp long (4). As a result of a double point mutation in exon IV at positions 136 (Thr/Ile) and 148 (Asp/Ala), the gene has two most commonly found alleles, *A* and *B* (4). The allele

Table 2. Effect of particular mutations on milk performance parameters

	Milk yield	Fat yield (kg)	Fat content (%)	Protein yield (kg)	Protein content (%)
CSN1S1	[+] *CC* (53, 52), [–] *BB* (54),[0] (55)			[+] *CC* (52)	
	[+] *AA* (55)			[+] *AG*, [–] *AA* (56), (no ind. *GG*)	[+] *AG*, [–] *AA* (56) (no ind. *GG*)
CSN2	[+] A^1A^1 (20, 57), [–] *BB* (57), [+] A^1A^3 (59)		[+] A^1B (58), [+] A^2A^3 (57)		[+] A^1B (58), [+] A^2A^3 (57), [–] A^1A^3 (59)
CSN1S2	[0] (60)	[0] (60)	[0] (60)	[0] (60)	[0] CC (60)
CSN3	[0] (61, 62), [–] *B* (63, 64, 65), [+] *B* (66, 67)	(0) (61, 62)	[0] (62), [+] *B* (68, 6, 69, 57)	[0] (61, 62)	[0] (61, 62), [+] *B* (68, 6, 69, 60)
LGB	[+] *AA* (58, 71, 72, 61), [0] (54, 57)	[0] (54, 57)	[+] *AA* (70, 71), [–] *BB* (58, 61), [0] (54, 57)	[0] (54, 57)	[+] *AA* (71), [–] *BB* (49), [0] (54, 57)
LTF	[+] *CC* (73)				[+] *CC* (73)
	[+] *AA* (74)				
PRL	[+] *AA* (18, 19, 72), [0] (8)	[0] (8)	[+] *AA* (18, 19), [0] (16)	[0] (16)	[+] *AA* (18), [0] (16)
PRL	[+] *CC* (25)				[+] *CC* (25)
GHRH	[0] (76)	[+] *AA* (38, 77), [0] (76)	[+] *AA* (38,78), [0] (76)	[0] (76)	[0] (76)
GH	[+] *LL* (53, 79), [+] *VV* (82), [0] (83)	[+] *LL* (80, 81, 79), [0] (83)	[+] *VV* (82, 80)	[+] *LL* (79), [0] (83)	
	[+] *Msp*I(+) (84)	[+] *Msp*I(–) (31, 85, 86), [–] *Msp*I(–) (84), [0] (38)	[+] MspI(+) (84)	[+] *Msp*I(–) (85), [–] *Msp*I(–) (84), [0] (38)	[+] *Msp*I(–) (31), [+] *Msp*I(+) (84)
Pit1	[+] *AA* (87, 88), [0] (89)	[0] (89)	[–] *AA* (88), [+] *AA* (90), [0] (89)	[+] *AA* (88), [0] (89)	[+] *AA* (88), [0] (89)
GHR	[0] ++ (91)	[0] ++ (91)	[+] ++ (38), [0] ++ (91)	[0] ++ (91)	[0] ++ (91)
	[+] *Y* (41, 83)	[+] *Y* (83)	[+] *Y* (41), [-] *Y* (92)	[+] *Y* (83) [-] *Y* (92)	
IGF 1	[0] (93), [+] *AB* (94), [+] *AA* (95)	[0] (93), [+] *AA* (95)	[0] (93), [+] *AB* (94)	[0] (93), [+] *AA* (95)	[0] (93), [+] *AB* (94)
STAT5A	[+] *TC* (no ind. *CC*) (45)	[0] (45)	[0] (45)	[0] (45)	[0] (45)
	[+] *GG* (96)		(+) *AA* (96)		
DGAT1	[–] *K* (47, 97, 98, 99, 100)	[+] *K* (47, 97, 98, 99, 100)	[+] *K* (47, 97, 98, 99), [0] (100)	[0] (100)	[–] *K* (47, 97, 98, 99, 100)
LPT	[+] *TT* (101), [0] (102)	[0] (102)	[0] (102)	[+] *TT* (55), [0] (20)	[0] (102)
	[+] *TT* (78, 103), [0] (20)	[0] (102)	[0] (102)	[+] *TT* (18), [0] (20)	[0] (102)
	[+] *TT* (102), [0] (101)			[+]*TT* (102), [0] (101)	

Explanation: effect of genotype/allele on the trait: [+] positive, [–] negative, [0] no effect; (1, 2, 3...)literature citation; "no ind." means no individuals of particular genotype

A frequency is higher compared to *B* in most studied cattle breeds. The polymorphism of this gene is reflected by a varied milk yield (Table 2). Some authors demonstrate that the milk BB homozygotes will yield 10% more curd in relation to milk of *AA* cows (5). A similar association was also found by other authors, although at a lower level, i.e. about 5% (6).

Whey proteins

Whey proteins represent 0.6-0.7% of the cow milk overall composition, of which albumins (beta lactoglobulin and al-

pha lactoglobulin) constitute about 75% of proteins, and the remaining represent immunoglobulins, lactoperoxidase, and lactoferrin (2). These proteins are very nutritious due to a high content of exogenous amino acids (2).

Whey proteins coding genes are shorter and more simple in their structure as compared with caseins genes (2). The beta-lactoglobulin (*LGB*, *BLG*) gene, located on the chromosome 11, is 4723 bp in length, whereas alpha-lactoglobulin gene in cattle has been mapped to the chromosome 5 (7). The most frequent *LGB* gene alleles are *A* and *B*. The previous allele encodes for aspartic acid at position 64 and valine at position 118, whereas the latter encodes for glycine and alanine at these positions, respectively. The effects of these alleles on milk performance of cows is presented in Table 2.

Lactoferrin (LF, also known as lactotransferrin (LTF)) is a multifunction protein primarily involved in a barrier against bacterial infections (8). The *LF* gene is located on chromosome 22 in cattle and includes 17 exons. An association of this gene with a risk of mastitis has drawn much attention (9). In 2008, 29 SNP mutations were found in the promoter region of the lactoferrin gene and 47 in exons (10). More than 140 SNPs in this gene have been identified, but none have been verified as a potential genetic markers (11). Such a high variability implies that a mastitis-resistance marker is very likely to exist within this gene, or possibly also a marker of milk yield.

GENES ENCODING FACTORS THAT REGULATE MILK PROTEIN EXPRESSION

Prolactin (PRL)

Prolactin is a peptide hormone released by the anterior pituitary; however, its secretion is also attributed to central nervous system, immunological system, and mammary gland (12). Prolactin, as a prohormone, consists of 227 amino acids, whereas the bovine proper hormone is composed of 199 amino acids (13). It is a multipurpose hormone, since more than 300 biological functions have been attributed to prolactin (12). The primary function of prolactin is initiation and maintenance of lactation, as it is responsible for synthesis of the main components of milk. Prolactin is involved in each stage of milk protein genes expression, i.e. transcription, mRNA stabilization, translation, and post-translational modifications of the proteins (2). The bovine prolactin gene, a 10 kbp sequence including five exons separated by four introns, is located on chromosome 23 (14). Much research has been carried out on the RFLP-*Rsa*I, a polymorphism in exon 3 which is a silent *A/G* transition at codon 103 that does not change the amino acid sequence of the resulting protein (15). The allele *A* is usually more frequent than *B* (16, 17, 18 19), although the associations between particular genotypes and milk yield of cows remain unclear (Table 2).

In 2005, another six SNP-type mutations were found; however, none of them affected the amino acid sequence of the prolactin polypeptide (17). Mutations at positions 8362, 8377, and 8398 were located in exon IV, those at positions 8307 and 8314 in intron 3, whereas that at 8510 in intron 4 (17). The authors (17) claim that the mutation at position 8398 represents a silent *A/G* transition described above and detected using the *Rsa*I restriction enzyme, which stands in contradiction with previous findings as to its location in exon III (17).

In 2008, 4 SNP mutations were detected at positions 6237, 6263, 6268, and 6297, two of which (6237 and 6268) change the amino acid sequence, which theoretically could affect the characteristics associated with the synthesis of milk, although such effects have not been confirmed yet (20).

Using the SSCP (Single Strand Conformation Polymorphism) method, several polymorphisms in the 5'-UTR region were also described, without showing a significant linkage of these mutations with milk performance of cows (21, 22).

1.1. Prolactin receptor (PRLR)

Prolactin interacts with target cells by binding to the PRL receptor located in the membrane. Prolactin receptor - PRLR, discovered more than 20 years ago, belongs to the class I cytokine receptor family, which shows a high homology with the growth hormone receptor (23). In cattle, two isoforms of PRLR have been found, resulting from alternative splicing: a long form, with a length of 557 amino acids, and a short one, with a length of 272 amino acids. The *PRLR* gene is mapped on the bovine chromosome 20q17 (24). The first polymorphism in the bovine prolactin receptor gene, identified in 2005, was an *A/C* transversion (205th nucleotide, intron 9) in the region involved in the alternative splicing of the transcript (25). In Jersey and Black-and-White cows, the allele *C* was of the lowest frequency, respectively 0.02 and

0.19, yielding much to the allele *A* (0.80) (25). The impact of this polymorphism on milk yield is presented in Table 2.

In Finnish Ayrshire cows, two other polymorphic sites in the bovine *PRLR* gene were discovered in 2006. The sites imply amino acid substitutions: in exon III, a *GT*/*AC* mutation of the frequency 0.86/0.14, and in exon VII, *T*/*C* transitions with the frequency 0.45/0.55 (26).

SOMATOTROPIC AXIS

GH-releasing hormone

Encoded by the gene *GHRH*, the growth-hormone-releasing hormone is a neuropeptide consisting of 44 amino acids, synthesized and released by the hypothalamus (27). GHRH triggers the production and release of growth hormone by the pituitary gland. The gene is mapped on chromosome 13 and contains five exons separated by four introns.

Due to the fact that administration of somatoliberin increases the level of GH in blood serum, thereby increasing milk production, the *GHRH* gene was considered a possible marker of that trait. The *GHRH* gene reveals a single, well-described polymorphism, recognized by *Hae*III restriction enzyme in intron 1 (Table 1). The frequencies of two possible alleles *A* and *B* vary greatly depending on the breed. The allele *A* is characterized by the highest frequency in the Angus breed of cattle (0.70), while the lowest in Hereford and Limousine (0.07) (28).

Growth hormone (GH)

Growth hormone is a pleiotropically acting polypeptide, whose pulsatile secretion of the anterior pituitary is regulated primarily by the antagonistic hypothalamic hormones: growth-hormone-releasing hormone and somatostatin (29). It consists of a single polypeptide chain, formed of 191 amino acids. At the N-end, the somatotropin molecule may have alanine or phenylalanine. The gene encoding bovine growth hormone is mapped on chromosome 19 of the genome and consists of five exons and four introns of a total length 1792 bp (30). Somatotropin plays a key role in the regulation of lactation, hence its gene (*GH*) seems to be an excellent marker for the genetic traits associated with milk yield. A number of polymorphisms in the bovine *GH* have been described (some examples appear in table 1), as well as their effect on the milk performance; the results of the research, however, are inconclusive. (Table 1)

Definitely the most intensively studied polymorphism is that at the beginning of exon V, detected by *Alu*I, and formed by a *G*/*C* substitution. Another polymorphism frequently studied consist in a simultaneous insertion and transition *TC*/*G* in intron 3, at position +838, first identified in 1993 (31). This region is recognized by *Msp*I and located in the vicinity of the potential binding transcription factor, coupled with the insertion / deletion of 0.9 kbp in the region 3'UTR, which also have potential binding sites for transcription factors (33).

As with the mutations described earlier, there are many reports on this polymorphism and its various effects on milk yield in cattle; however, these mutations have no major impact on the production traits. Also, a long list of polymorphisms have been described more or less accurately in introns 1, 2, and 3, as well as in the promoter and the regions 5' and 3' UTR.

Pit1 transcription factor

This factor regulates the expression of growth hormone and prolactin in the anterior pituitary gland (34). It belongs to the family of POU domain containing proteins (transcription factors, activating the expression of target genes). The Pit1 gene locus is located in the centromeric part of the first chromosome (34). The most common polymorphism in this gene and its effect on particular milk yield parameters is shown in Table 2.

Growth hormone receptor (GHR)

Growth hormone acts on target cells through a cytokine receptor, which is characterized by the presence of a transmembrane domain, co-operating with JAK tyrosine kinase (35). The kinase, activated by intracellular transmitters, phosphorylates the transcription factor STAT5. GH receptor is encoded by a single gene with a length of 110 kbp, consisting of 10 exons, mapped on chromosome 20. The gene of this receptor (*GHR*) is characterized by the presence of several exons whose transcripts undergo alternative splicing (36).

The amino acid sequence of a protein product is the same regardless of the variant of exon I. The place of transcripts splicing of all variants of exon I and exon II is located 9-11 nucleotides upstream of the start codon (37). Growth hormone activity depends on the receptor and therefore its gene may be a possible marker candidate. Particularly interesting

is the mutation in the region of 5' UTR due to the presence of LINE retrotransposon insertion with a length of 12 kbp in cattle. Three polymorphic sites have been located in the region of Holstein cattle using restriction enzymes (38). Exon X proved to be extremely polymorphic in the structural part of the gene, in which several SNPs have been located (26, 39, 40, 41).

Insulin-like growth factor 1 (IGF-1)

This factor, also known as somatomedin C, is a single polypeptide chain with a length of 70 amino acids (42). It mediates the action of growth hormone on target cells, mainly in the regulation of growth. The bovine *IGF*-1 gene was mapped on the long arm of chromosome 5 (43). It consists of seven exons, separated by long introns. Due to the alternative splicing of exon I and the presence of two different promoters, the transcript has a length of 1, 155 bp or 750 bp. The promoters did not reveal, however, the TATA or CCAAT motifs, characteristic for most promoters and conserved, or regions rich in GC residues. In all, 4 transcription start sites have been detected (44) and a number of mutations, although these have not been sufficiently studied so far – especially in terms of milk yield – these still wait for verification and extensive studies.

STAT5A transcription factor

The STATs (signal transducers and activators of transcription) are the family of proteins that transfer signals from cytokine receptors to the cell nucleus where they activate transcription (45). STAT5 proteins are important in the growth and differentiation of cells, since they mediate in the activity of GH and prolactin (main lactation regulators), therefore mutations in the genes encoding these hormones might modify their behavior (39). *STAT5A* and *STAT5B* have been mapped on chromosome 19, at q17, very closely to each other. The *STAT5A* gene is composed of 15947 bp, has 19 exons, and encodes for 794-amino-acid protein, being expressed mainly in the mammary gland, in which it differs from the *STAT5B* gene, whose expression was also found in the liver (46). Polymorphic studies on bovine *STAT5A* led to discoveries of a range of mutations, primarily SNPs, which demonstrates a rapid evolution of the sequence (47).

Diacylglycerol acyltransferase 1 (DGAT1)

DGAT1 is the key enzyme for the synthesis of triacylglycerols, the major fraction of milk fat compounds. Bovine *DGAT1* locus is found on chromosome 14. The often studied *AA*/*GC* dinucleotide substitution at positions 10433-10434 (exon VIII), which is potentially important for milk yield, results in a substitution of lysine in place of alanine at position 232 of the resulting protein. It has been proposed that the mutation, referred to as *K232A*, appeared at a very early stage of cattle domestication and is associated with milk fat content (48). The effects of this mutation on milk performance is presented in Table 2.

In Holstein-Fresian cows, the *AA* to *GC* ratio ranges between 0.40 and 0.60, with a total lack of *AA*/*AA* genotypes (49). In 2007, 5 VNTR (variable number tandem repeats) alleles were found in the DGAT1 promoter (48); it was also concluded that the effect of *K232A* polymorphism on milk yield should be considered jointly with the VNTR in the gene promoter (CCCGCC repeating motif). Other authors state that none of the VNTR alleles is useful as a QTL, and their results rather indicate that there is some other unrecognized polymorphism in the *DGAT1* gene which may be of importance in terms of milk productivity (50).

Leptin (LEP)

The leptin encoding gene is located on chromosome 4. Leptin is synthesized predominantly by adipocytes, i.e. fat tissue cells (51). Its blood level is a signal for the central nervous system on the energy resources of the body. Besides the maintenance of energy homeostasis, leptin also regulates endocrine processes and may take part in prolactin secretion regulation. The latter effect was demonstrated on mice with non-functional leptin genes, which had a lower PRL secretion (15). Lactation is accompanied by increased food intake, a shift in metabolism, and the employment of energy resources from the fat tissue, so the interaction between hormones regulating mammogenesis and milk production, as well as those that affect energy homeostasis and fat metabolism, gain in importance. It seems justified therefore to search for the genetic marker of milk yield within the leptin gene, as has been evidenced by previous studies (Table 1).

It should however be noted that milk yield also depends on the impact of other factors such as breed, population, herd, subsequent lactation, cow age, calving season, and other more or less specified factors. Applied statistical models, which are used to estimate associations between particular genotypes and milk yield, often miss the effects of these fac-

tors. Occasionally, a given genotype is represented by a few individuals in the population, which in consequence resulted in biased analysis results. It is hoped that this breakdown of research data will be taken into account in efforts aiming to determine various dependencies between genes and milk yield.

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