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Review Article

β-Lactoglobulin Gene Polymorphisms in Sheep and Effects on Milk Production Traits: A Review

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Abstract | β-lactoglobulin is the main whey protein of milk from different species. To date, β-lactoglobulin gene (*BLG*) is one of the most investigated in ruminants including sheep. β-lactoglobulin was the first protein, in which polymorphism was found. Polymorphisms of *BLG* gene have been detected in several sheep breeds, but studies on the effects of *BLG* genetic variants on milk production traits and cheese making ability have given conflicting results. Therefore, this paper represents a detailed and updated review on β-lactoglobulin gene polymorphisms in many sheep breeds worldwide. Moreover, the associations among *BLG* polymorphisms and milk yield and composition as well as milk coagulation properties were reported to offer a complete overview on these topics.

Keywords | Sheep, β-lactoglobulin, Gene polymorphisms, Milk production, Milk coagulation

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INTRODUCTION

Milk and dairy products from small ruminant species represent a significant part of the agricultural economy worldwide especially in marginal areas. However, goat and sheep milks have peculiar composition and properties and, as a consequence, specific productive destinations (Selvaggi et al., 2014a). In fact, sheep milk is used mainly for cheese production (Selvaggi and Tufarelli, 2012; Selvaggi et al., 2014b). There is a strong association among milk protein polymorphisms and milk yield, composition and technological aspects. So, it is necessary to make available in-depth information regarding genetic polymorphisms of milk proteins in ovine species also considering the great genetic biodiversity of sheep breeds.

β-lactoglobulin is the main whey protein of cow, sheep, goat and horse milk; it is lacking in milk from human, rodents, rabbits and camels in which, instead, another major whey protein (whey acidic protein) is found (Perez and Calvo, 1995). The whey proteins showed a high nutritive value being a precious source of digestible proteins. Sheep milk whey proteins account for 17–22% of total proteins. Whey obtained from sheep milk is particularly rich in proteins with a high β-lactoglobulin and low α-lactalbumin content (Moatsou et al., 2005). β-lactoglobulin is a globular protein member of the lipocalin family, small proteins with many properties, such as the ability to bind small hydrophobic molecules. Although its biological function is still unclear, β-lactoglobulin provides amino acids to the offspring and a possible role in the transport of retinol and fatty acids has been suggested (Perez and Calvo, 1995). β-lactoglobulin was the first protein in which polymorphism was found; it consists of 162 amino acids and forms stable dimers in milk having a molecular weight of 18 kDa per monomer (Kontopidis et al., 2004).

POLYMORPHISMS OF *BLG* GENE

β-lactoglobulin is encoded by the *BLG* gene that has been mapped on chromosome 3 in sheep (Hayes and Petit, 1993). This gene is expressed in the mammary gland in a tissue-specific manner during pregnancy and lactation (Clark, 1998). β-lactoglobulin gene is highly polymorphic in ruminants: in cattle, 12 polymorphic variants of this protein are known, with variants A and B being the most frequent and commonly related to differences in milk protein yield and quality (Lunden et al., 1997; Yang et al., 2012). In sheep, β-lactoglobulin polymorphism was widely investigated in many breeds worldwide. Three co-dominant alleles (A, B and C) have been reported in this species differing by one or more amino acid changes. The genetic variant A differs from variant B in the amino acid sequence at position 20 (Tyr→His) (Bell and McKenzie, 1967; Kolde and Braunitzer, 1983; Ali et al., 1990). Later, Erhardt (1989) found a new and rare variant indicated as C that is a subtype of variant A with a single amino acid exchange at position 148 (Arg→Gln). Variants A and B are the most common and have been detected in many breeds (see Table 1, 2 and 3). The rare variant C was detected only in few

Table 1: Summary of published allelic frequencies of β-lactoglobulin gene in different sheep breeds with different purpose from Asia

Breed	Purpose	A	B	C	References
Nagdi	Meat	-	1.000	-	El-Shazly et al., 2012
Harry	Meat	-	1.000	-	El-Shazly et al., 2012
Muzzafarnagri	Meat, Carpet wool	0.100	0.900	-	Arora et al., 2010
Zel	Meat	0.140	0.860	-	Yousefi et al, 2013
Jalauni	Meat, Carpet wool	0.160	0.840	-	Arora et al., 2010
Magra	Carpet wool	0.193	0.807	-	Arora et al., 2010
Rampur Bushair	Carpet wool	0.273	0.727	-	Arora et al., 2010
Mandya	Meat	0.273	0.727	-	Arora et al., 2010
Garole	Meat	0.277	0.723	-	Arora et al., 2010
Ganjam	Meat, Carpet wool	0.326	0.674	-	Arora et al., 2010
Afshari	Meat	0.340	0.660	-	Elyasi et al., 2010
Awassi	Dairy	0.348	0.352	-	Anton et al., 1999
Moghani	Meat	0.360	0.640	-	Elyasi et al., 2010
Changthangi	Carpet wool	0.386	0.614	-	Arora et al., 2010
Patanwadi	Carpet wool	0.410	0.590	-	Jyotsana et al., 2014
Jaisalmeri	Carpet wool	0.425	0.575	-	Arora et al., 2010
Kheri	Meat, carpet wool	0.472	0.528	-	Arora et al., 2010
Arkharmerino	Fine wool	0.480	0.520	-	Elyasi et al., 2010
Kendrapada	Meat	0.480	0.520	-	Jyotsana et al., 2014
Sonadi	Meat, carpet wool	0.499	0.501	-	Arora et al., 2010
Dekkani	Meat, coarse wool	0.500	0.500	-	Arora et al., 2010
Madgyal	Meat	0.500	0.500	-	Jyotsana et al., 2014
Kurdi	Meat	0.510	0.490	-	Nassiry et al., 2007
Malpura	Wool	0.510	0.490	-	Jyotsana et al., 2014
Makoei	Meat, Carpet wool	0.530	0.470	-	Elyasi et al., 2010
Chhotanagpuri	Carpet wool	0.531	0.469	-	Arora et al., 2010
Ghezel	Meat, Carpet wool	0.560	0.440	-	Elyasi et al., 2010
Morkaraman	Meat, Carpet wool	0.560	0.440	-	Çelik and Özdemir, 2006
Marwari	Carpet wool	0.562	0.438	-	Arora et al., 2010
Chokla	Carpet wool	0.569	0.431	-	Arora et al., 2010
Awassi	Dairy	0.630	0.370	-	Çelik and Özdemir, 2006
Nali	Carpet wool	0.630	0.370	-	Jyotsana et al., 2014
Karakul	Pelt, wool, meat	0.714	0.286	-	Kevorkian et al., 2008
Gökçeada	Dairy, meat, wool	0.763	0.237	-	Elmaci et al., 2006
Kivircik	Meat, wool, dairy	0.776	0.224	-	Elmaci et al., 2006
Dumba	Carpet wool	0.950	0.050	-	Jyotsana et al., 2014
Sakiz	Dairy, wool, meat	0.976	0.024	-	Elmaci et al., 2006
Noami	Meat	1.000	-	-	El-Shazly et al., 2012
Sawakni	Meat	1.000	-	-	El-Shazly et al., 2012

Sheep breeds in which the associations among polymorphism and milk traits where investigated are highlighted in bold

Table 2: Summary of published allelic frequencies of β-lactoglobulin gene in different sheep breeds with different purpose from Europe

Breed	Purpose	A	B	C	References
Sarda	Dairy	0.274	0.726	-	Pietrolà et al., 2000
Churra	Dairy	0.310	0.690	-	Gutiérrez-Gil et al., 2001
Rhön	Meat	0.324	0.676	-	Erhardt, 1989
Carranzana	Dairy	0.350	0.640	0.010	Calavia, 1997
Valle del Belice	Dairy	0.350	0.650	-	Giaccone et al., 2000
Valachian	Dairy, wool, meat	0.353	0.647	-	Miluchová et al., 2011
Black Merino	Fine wool	0.392	0.607	0.001	Ramos et al., 2009
Romanian Rusty Tsigai	Dairy, wool, meat	0.420	0.580	-	Kusza et al., 2015
Romanov	Meat, wool	0.430	0.570	-	Mácha and Novackova, 1974
Gyimesi Racka	Dairy, wool, meat	0.460	0.540	-	Kusza et al., 2015
White Merino	Fine wool	0.464	0.535	0.001	Ramos et al., 2009
Lacha	Dairy	0.470	0.530	-	Recio et al., 1997
Bosnian Pramenka	Dairy	0.470	0.530	-	Kusza et al., 2015
Lacaune	Dairy	0.473	0.527	-	Anton et al., 1999
Polish Merino	Fine wool	0.480	0.520	-	Kaweka and Radko, 2011
Polish Merino	Fine wool	0.498	0.502	-	Mroczkowski et al., 2004
Polish Mountain	Carpet wool, dairy	0.500	0.500	-	Kaweka and Radko, 2011
Lacha	Dairy	0.500	0.490	0.010	Calavia, 1997
Comisana	Dairy	0.500	0.500	-	Chiofalo et al., 1986
Hungarian Tsigai	Dairy	0.510	0.490	-	Kusza et al., 2015
Lithuanian Blackface	Meat, wool	0.520	0.480	-	Kučinskiene et al., 2005
Massese	Dairy	0.520	0.480	-	Mele et al., 2007
Pleven	Dairy	0.528	0.472	-	Erhardt, 1989
Slovakian Tsigai	Dairy, wool, meat	0.540	0.460	-	Kusza et al., 2015
Bergschaf	Meat, coarse wool	0.550	0.450	-	Kaweka and Radko, 2011
Serbian Cokanski Tsigai	Dairy, wool, meat	0.550	0.450	-	Kusza et al., 2015
Merinoland	Fine wool	0.579	0.246	0.175	Erhardt, 1989
Spanish Merino	Fine wool	0.580	0.410	0.010	Recio et al., 1997
Croatian Tsigai	Dairy, wool, meat	0.580	0.420	-	Kusza et al., 2015
Manchega	Dairy	0.610	0.390	-	Martínez et al., 1993
Gentile di Puglia	Wool, meat	0.613	0.387	-	Chessa et al., 2003
Serra da Estrela	Dairy	0.620	0.378	0.002	Ramos et al., 2009
Altamurana	Dairy	0.625	0.375	-	Dario et al., 2005
Lacaune	Dairy	0.630	0.370	-	Barillet et al., 1993
Leccese	Dairy	0.630	0.370	-	Dario et al., 2008
Racka	Dairy, wool, meat	0.640	0.360	-	Kusza et al., 2015
Friesian	Dairy	0.660	0.340	-	Kaweka and Radko, 2011
Bulgarian Tsigai	Dairy, wool, meat	0.680	0.320	-	Kusza et al., 2015
Merino	Fine wool	0.684	0.316	-	Corral et al., 2010
Lithuanian Native Coarsewooled	Meat, wool	0.690	0.310	-	Kučinskiene et al., 2005
East Friesian	Dairy	0.690	0.310	-	Staiger et al., 2010

Sheep breeds in which the associations among polymorphism and milk traits where investigated are highlighted in bold

breeds such as: Merinoland, Lacha, Carranzana, Spanish Merino, Serra da Estrela, White Merino, and Black Merino (Erhardt, 1989; Calavia, 1997; Recio et al., 1997; Ramos et al., 2009). Erhardt (1989) suggested that the allele C perhaps originated from the Spanish Merinos considering that both Merinoland and Hungarian Merino, in which the allele C was detected, contain blood from Spanish Merinos. This hypothesis may be strengthened by the allele C detection in Black Merino and White Merino (Ramos et al., 2009). As reported in Table 1, four sheep breeds from Saudi Arabia were found monomorphic: in particular, in Noami and Sawakni breeds only the allele A was found; whereas Nagdi and Harry breeds were genotyped as BB (El-Shazly et al., 2012). Moreover, most of sheep breeds from India showed a prevalence of B allele; as a consequence, Arora et al. (2010) suggested that the B allele could possibly be considered the ancestral variant of *BLG* in Indian sheep. In fact, in many breeds from India, the frequency of allele B was higher than that reported in breeds from Southwest Asia, Eastern and Central Europe and Mediterranean countries (Table 1 and 2). In addition, only few investigations on *BLG* polymorphisms were carried out in countries other than Europe and Asia; sheep breeds from Africa, America and Oceania showed a frequency of A allele ranging from 0.704-0.950, and no evidence of C allele was found (Table 3).

RELATIONSHIP BETWEEN GENETIC VARIANTS OF *BLG* GENE AND MILK PRODUCTION TRAITS

Polymorphisms of *BLG* gene may be helpful as informative molecular markers for milk yield and composition as well as for rheological properties of milk. However, the influence of *BLG* polymorphism on milk yield and composition and cheese-making properties is controversial, indicating superiority of either the A or B allele or no relationship with quantitative traits.

In Valle del Belice ewes, the AA genotype was associated with greater milk production (Giaccone et al., 2000). A similar result was found in Sarda breed; in this case, animals carrying AA and AB genotypes had higher milk yield than BB ewes (Nudda et al., 2000, 2003). In East Friesian sheep, it was observed a higher milk yield during the first lactation in individuals carrying AA genotype; whereas BB genotype ewes had the highest milk yield in the following lactations (Schmoll et al., 1999). In Portuguese dairy sheep studied by Ramos et al. (2009), homozygous AA ewes presented lower values of milk yield and no differences between AB and BB genotypes were found. No differences in terms of milk production among genotypes were found in Sarda (Pietrolà et al., 2000), East Friesian (Staiger et al., 2010), Polish Mountain, Polish Merino, East Friesian, and Bergschaf (Kaweka and Radko, 2011) and in West African sheep (Aranguren-Méndez et al., 2012). Some investigations assessed the superiority of the B allele (Rampilli et al., 1997; Bolla et al., 1989). Later, this result was confirmed by Corral et al. (2010) in Merino sheep breed.

As for milk quality, recently Corral et al. (2010) demonstrated that Merino ewes genotyped as AA were those that produced the highest fat and protein percentages. Moreover, heterozygous Serra da Estrela animals presented higher milk fat content than those carrying genotype BB. Besides, AA Merino ewes had higher milk protein content than animals with genotype AB (Ramos et al., 2009). A positive association was found between AB genotype and fat and lactose percentages in milk from Iranian indigenous Zel sheep breed (Yousefi et al., 2013). Previous findings by Dario et al. (2005, 2008) in Altamurana and Leccese breeds reported a superiority of AA and AB genotypes for fat and whey protein percentages in milk. Martínez et al. (1993) pointed out a highly significant and positive effect of AA and AB genotypes on milk protein and casein contents in Manchega sheep. On the other hand, Giaccone et al. (2000) reported a positive effect of BB genotype on milk protein and fat contents, and Mroczkowski et al. (2004) found a positive relationship between BB genotype and milk protein content in comparison with both AA and AB genotypes in Polish Merino. No association among milk composition traits and *BLG* genotypes was found in Polish Mountain, Polish Merino, East Friesian, Bergschaf (Kaweka and Radko, 2011), Massese (Mele et al., 2007), Sarda (Nudda et al., 2000, 2003), Merino (Recio et al., 1997), and Churra (Gutiérrez-Gil et al., 2001). As reported by Rampilli et al. (1997) in Massese breed, the BB variant of *BLG* could be related to a higher milk production with

Table 3: Summary of published allelic frequencies of β-lactoglobulin gene in different sheep breeds with different purpose from other countries

	Breed	Purpose	A	B	C	References
Africa	Barki	Carpet wool, meat	0.704	0.296	-	Othman et al., 2012
	Ossimi	Carpet wool, meat	0.828	0.172	-	Othman et al., 2012
	Rahmani	Carpet wool, meat	0.950	0.050	-	Othman et al., 2012
America	**West African**	Meat	0.900	0.100	-	Aranguren-Méndez et al., 2012
Oceania	Border Leicester×Merino	Meat, wool	0.750	0.250	-	Thomas et al., 1989
	Hyfer	Meat, wool	0.840	0.160	-	Thomas et al., 1989

Sheep breeds in which the associations among polymorphism and milk traits where investigated are highlighted in bold lower casein content and greater overall amount of whey proteins. At the same time, the AA and AB genotypes showed higher β-lactoglobulin and total casein contents and were related to a better quality of milk also in terms of rennetability. To date, only one investigation reported the relationship between *BLG* genotypes and milk fatty acid composition in sheep; in particular, milk from AB individuals had the lowest concentration of medium-chain fatty acids and the highest level of trans fatty acids, monounsaturated fatty acids and long-chain fatty acids, with no significant differences regarding the polyunsaturated fatty acids level (Mele et al., 2007).

Many investigations have shown a superiority of milk from AA ewes for cheese processing thanks to its shorter clotting time, a better rate of curd firming and a favourable cheese yield (Lopez Galvez et al., 1993; 1994; 1998; Rampilli et al., 1997; Gutierrèz-Gil et al., 2001). In addition, Garzón et al. (1993) reported a superiority of AA and AB genotypes, in comparison to BB homozygotes, in terms of curdling time, medium and maximum firmness, rate of firming, and curd yield in Manchega breed. These results conflict with data reported by Pilla et al. (1995) who found that the B allele positively affected the rennet coagulation properties of milk. No association between *BLG* polymorphism and milk renneting properties (clotting time, curd firming time and curd firmness) was found by Recio et al. (1997) in Merino ewes and by Nudda et al. (2000) in Sarda breed. More recently, Çelik and Özdemir (2006) investigated the association between *BLG* genetic variants and rennet clotting time in milk belonging to Awassi and Morkaraman breeds without statistical significant differences.

CONCLUSIONS

It is noteworthy that the available literature provides no conclusive remarks about the effects of different β-lactoglobulin genotypes on milk production traits and coagulation properties in ovine species. Sometimes, results from different investigations are not comparable with each other for many reasons: population size, breed, frequency of the considered genotypes, statistical models used for data analysis. Moreover, the conflicting reports on the association of genetic variants of *BLG* with milk production traits may be due to the lack of knowledge of the relatedness of the studied animals. Despite these controversial results, to include molecular genetic markers in selection to improve livestock productive performance is also a target in sheep breeding to enhance the economy of dairy sheep production worldwide. To improve the local farms productivity in developing countries and in marginal areas of developed countries is a strategy to limit the off-farm migration and safeguard the current wide animal biodiversity. However, the fact remains that to sustain the economy of rural and marginal areas is also a crucial target in developed countries.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHORS CONTRIBUTION

All authors contributed equally to the manuscript.

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