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RESEARCH ARTICLE

Investigation of Polymorphisms on ABCG2, AA-NAT and FABP3 Genes in the Kıvırcık Sheep Reared in Three Different Provinces of Turkey [1]

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Summary

In this study mutations located in intron 5 of *ABCG2,* exon 3 of *AA-NAT* and exon 2 of *FAB3* genes were investigated by PCR based methods in the Kıvırcık sheep sampled from Bursa, Manisa, and İstanbul provinces of Turkey. All loci investigated were found as polymorphic. While in the *ABCG2* and *FABP3* loci two alleles and three genotypes were found, in the *AA-NAT* locus two alleles and two genotypes were detected. In *ABCG2* locus allele "- ", in *AA-NAT* allele A, in *FABP3* locus allele G were observed as predominant. The frequency values of the predominat alleles at *ABCG2, AA-NAT* and *FABP3* loci were found 0.60, 0.87 and 0.58, respectively. While the whole population investigated exhibits deviation from the Hardy- Weinberg equilibrium for *ABCG2* and *FABP3* loci, was found at Hardy-Weinberg equilibrium for *AA-NAT* locus.

Keywords: *ABCG2, AA-NAT, FABP3, Polymorphism, Sheep*

Türkiye'nin Üç Faklı İlinde Yetiştirilen Kıvırcık Koyunlarda ABCG2, AA-NAT ve FABP3 Genlerindeki Polimorfizmlerin İncelenmesi

Özet

Bu çalışmada Türkiye'nin Bursa, Manisa ve İstanbul illerinden örneklenen Kıvırcık koyunlarında *ABCG2* geninin 5.intron, *AA-NAT* geninin 3. ekzonunda ve *FABP3* geninin 2. ekzonunda bulunan mutasyonlar PCR tabanlı yöntemlerle incelenmiştir. İncelenen tüm lokuslar polimorfik bulunmuştur. *ABCG2* ve *FABP3* lokuslarında iki allel ve üç genotip belirlenirken, *AA-NAT* lokusunda iki allel ve iki genotip belirlenmiştir. *ABCG2* lokusunda "- " alleli, *AA-NAT* lokusunda A alleli ve *FABP3* lokusunda G allellinin predominant olduğu gözlenmiştir. *ABCG2, AA-NAT* ve *FABP3* lokuslarındaki predominant allelerin frekans değerleri sırasıyla 0.60, 0.87 ve 0.58 olarak bulunmuştur. İncelenen populayonun tamamı *ABCG2* ve *FABP3* lokusları bakımından Hardy-Weinberg dengesinden sapma gösterirken *AA-NAT* lokusu bakımından dengede bulunmuştur.

Anahtar sözcükler: *ABCG2, AA-NAT, FABP3, Polimorfizm, Koyun*

INTRODUCTION

Kıvırcık is the one of the most important native sheep breed of Turkey that constitutes almost seven percent of total sheep population. It is a multipurpose breed and it has higher meat quality when compare with the other native sheep breeds in the country [1].

In Turkey some efforts have been began by General Directorate for Agricultural Research and Policies (GDAR) to improve yield characteristics of Kıvırcık sheep in 2005 with Communiqué 2005/13 based on Cabinet Decision with number 2005/8503. It is well known that genetic improvement of the livestock species is an expensive and time consuming process. To increased genetic gain by selection a gene has major affect can be used for selection criteria in the breeding schema. Genetic polymorphisms are used by selection of carrier animals of causal mutations with desirable effects on the economic traits in farm animals such as Broola mutation for reproduction or PrP

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gene for scrapie resistant in sheep [2]. In goat predicted advantage of casein assisted selection over traditional selection based on performance was 18% for protein content [3]. In Turkey lack of production records is a limiting factor to analyze this kind of associations. On the other hand investigations of allelic frequencies of economically important traits loci have been increased among Turkish native livestock species as cattle, goat and sheep, in recent years [4-6]. It is assumed that mutations occur on *ABCG2*, *AA-NAT* and *FABP3* genes have effects on some economically important traits and can be thought as molecular markers.

The ATP-binding casette sub-family G member 2 (*ABCG2*) is a member of a protein family responsible for transport of various molecules across cell membranes [7,8]. *ABCG2* is expressed several tissue including mammary gland and it is reported that the level of expression is elevated in lactation period in some monogastrics, goats and dairy cows [9-11]. Due to its function and near chromosomal location to an important QTL region effects on milk production traits in cattle [12,13], researches have been focused on associations between mutations occur in the *ABCG2* gene and milk production traits. Thus several relationships between mutation located in this gene and milk yield, protein and fat percentage, and somatic cell score (SCC) in dairy cows were revealed [14-17]. Number of studies carried out in ovine is very limited when compare with studies focused on bovine. Relationships between a microsatellite locus located with *ABCG2* on ovine chromosome 6 and some production traits were highlighted [18]. In a recent study [19] mutations in ovine *ABCG2* gene and their relationship with some economically important traits were investigated and 13 SNPs and a single 35 bp insertion/deletion were revealed in different region of the gene. They also reported significant relationship with a T→C transition and protein percentage as well, 35 bp insertion/deletion and SCC.

Arylalkylamine N-acetyltransferase (*AA-NAT*) is an important enzyme in Melatonin (MLT) biosynthesis by acting on serotonin for MLT regulating the animal seasonal breeding [20-23]. Due to its critical role in melatonin production it has been suggested that genetic mutation of the gene may also important in seasonal reproduction in sheep [22]. Researches on *AA-NAT* polymorphism have been focused on human [24-26]. Although *AA-NAT* is very important for animal reproduction, there are a limited number of studies carried out on *AA-NAT* in farm animals. Majority of these studies have been realized on associations between *AA-NAT* gene polymorphisms and meat production traits in cattle [27,28]. Recently 1142 bp of ovine *AA-NAT* gene has been investigated to reveal mutations occurred in this gene and their relationship with seasonality in Chinese sheep breeds [22]. The authors reported an A→G transition located at exon 3 and important differences in distribution of genotype frequencies among seasonal and non-seasonal sheep breeds [22]. The GG genotype was higher in non-seasonal breeds while the GA genotype was higher in seasonal sheep breeds [22]. Mutations, occur in goat *AA-NAT* gene, were also reported that may be used for improvement of litter size [23].

Fatty acid-binding proteins (FABPs) involve in fatty acid transport from the plasma membrane to the sites of ß-oxidation and triacylglycerol or phospholipid synthesis [29]. Among FABPs the *FABP3*, also known as Heart FABP (H-FABP), is mainly expressed in cardiac and skeletal muscle [30]. Fatty acid-binding protein (*FABP*) gene is an important candidate gene for both meat quality and milk product properties as cheese making because of its possible effects on milk fat content [31]. It is reported that *FABP3* genetic variants affect on intramuscular fat content both sheep and pigs [30-32]. Ovine *FABP3* gene and its chromosomal location were analyzed at 2002 [33]. 13 SNPs, one CTC insertion/deletion and a variable polyA tract were detected. Afterward two of these SNPs located in exon 2 and intron 13 were analyzed for association studies and heterozygous genotypes for both SNPs were found related to milk fat content.

Due to their possible affects on economically important traits they can be thought as molecular markers in breeding scheme after verify the associations. In order to realize this kind of selection it should be known frequencies of the molecular marker. This study aimed to investigate distribution of allele frequencies of *ABCG2*, *AA-NAT* and *FABP3* genes in native Kıvırcık Sheep from breeding populations.

MATERIAL and METHODS

The study was approved by the Ethics Committee of Uludag University (UÜHADYEK), (approval date: 10.07.2012; no: 2012-08/5).

In this study 100 animals from Kıvırcık sheep breed investigated for polymorphisms located in *ABCG2* and *FABP3* gene. Due to some analytic problems *AA-NAT* polymorphism was analyzed in 98 sheep. Blood samples were collected from six distinct farms in Bursa (n=30), six distinct farms in Manisa (n=34) and only single farm (this flock was constitute different flocks from Thrace at different time) in İstanbul (n=36) provinces. Total DNA was extracted using a genomic DNA purification kit (K0512, Fermentas, Lithuania) according to the instructions provided in the manual.

While PCR-RFLP analyzes to investigate polymorphisms of *FABP3* [33] and *AA NAT* [22] loci, PCR was performed to genotyping *ABCG2* locus [19]. Primers and restriction enzymes used in the study are given in *Table 1*. The restriction fragments were directly analyzed by electrophoresis in 2% and 2.5% agarose gels in 1 TBE buffer, stained with ethidium bromide, and visualized under UV light.

Table 1. *Primers and restriction enzymes used in the study*
Tablo 1. *Çalışmada kullanılan primerler ve restriksiyon enzimleri*

Locus Name	Genomic Region	Primers (5′→ 3′)	Enzymes
ABCG2	Intron 5	GCCTCTTCTCCCATACGTC AAAC CAGTTGTGGGCTCATC	-
AA-NAT	Exon 3	AGCGTCCACT GCCTGAAAC GGGATGGAAGCCAAACCTC	*Sma*I
FABP3	Exon 2	GGTTTTGCTACCAGGCAGGT TTCCCTATTCCCCTTCAGGG	*BsaJ*I

Direct counting was used to estimate genotype and allele frequencies of the genetic variants for all loci. The chi-square test ($\chi 2$) was used to check whether the populations were in Hardy-Weinberg equilibrium. All calculations and the $\chi 2$ analyses were carried out using PopGene32 software [34].

RESULTS

Electrophoretic analysis revealed two alleles and three genotypes for *ABCG2* and *FABP3* loci while two alleles and two genotypes detected at the *AA-NAT* locus. PCR products and RFLP fragment size of alleles are given in *Table 2* and electroforograms are shown in *Fig. 1*.

Table 2. *Sizes of PCR products and RFLP fragments obtained from electrophoretic analysis*
Tablo 2. *Elektroforetik analizlerden elde edilen PCR ürünleri ile RFLP fragmanlarının büyüklükleri*

Locus Name	PCR Product	Allele Size	Allele Name
ABCG2	267 bp (if deletion not present) 232 bp (if deletion present)	267 bp	+
		232 bp	-
AA-NAT	1142 bp	255 bp, 371 bp and 516	A
		183 bp, 255 bp, 333 bp and 371 bp	G
FABP3	222 bp	186, 36 bp	A
		143, 43, 36 bp	G

Allele and genotype frequencies at each locus for each Kıvırcık population from different provinces and overall Kıvırcık population are given in *Table 3*. Observed and expected heterozygosity values for all loci in investigated populations also given in *Table 4*.

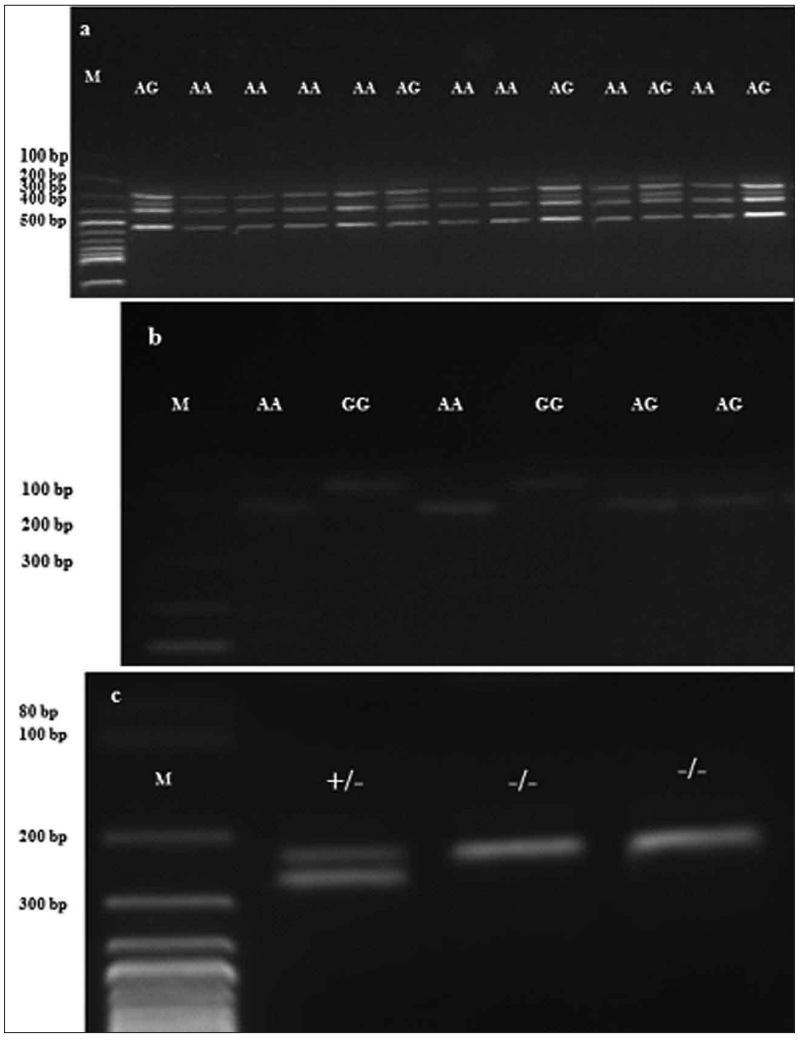

Fig 1. a- Electrophoretic image of *AA-NAT* genotype (M: Bio Basic MSM34DNA ladder), **b-** Electrophoretic image of *FABP3* genotype (M:Bio Basic MSM34 DNA ladder), **c-** Electrophoretic image of *ABCG2* genotype (M: Fermentas SM0243, GeneRuler)

Şekil 1. a- *AA-NAT* genotiplerinin elektroforetik görüntüsü (M: Bio Basic MSM34DNA ladder), **b-** *FABP3* genotiplerinin elektroforetik görüntüsü (M:Bio Basic MSM34 DNA ladder)**, c-** *ABCG2* genotiplerinin elektroforetik görüntüsü (M: Fermentas SM0243, GeneRuler)

Table 3. *Distribution of allele and genotype frequencies among populations, overall population and χ2 values*
Tablo 3. *Populasyonlar arasında, populasyonlar genelinde allel ve genotip frekanslarının dağılımı ile χ2 değerleri*

LOCUS	Alleles	Genotypes	KIV-BURSA			KIV-MANİSA			KIV-İSTANBUL			OVERALL		
			Genotype Freq. (%)	Allele Freq.	χ2	Genotype Freq. (%)	Allele Freq.	χ2	Genotype Freq. (%)	Allele Freq.	χ2	Genotype Freq. (%)	Allele Freq.	χ2
ABCG2	-	-/-	50.0	0.65	3.86*	41.7	0.67	0.45	35.3	0.5	6.19*	42.0	0.60	5.34*
	+	+/-	30.0	0.35		50.0	0.33		29.4	0.5		37.0	0.40	
		+/+	20.0			8.3			35.3			21.0		
AA-NAT	A	AA	79.3	0.90	0.32	80.0	0.90	0.37	64.7	0.82	1.41	74.5	0.87	2.00
	G	AG	20.7	0.10		20.0	0.10		35.3	0.18		25.5	0.13	
FABP3	A	AA	23.4	0.40	3.13	19.0	0.33	5.49*	47.0	0.53	20.63**	30.0	0.42	26.27**
	G	AG	33.3	0.60		28.0	0.67		11.8	0.47		24.0	0.58	
		GG	43.3			53.0			42.2			46.0		

** significant, P<0.05; ** significant, P<0.01*

Table 4. *Observed and expected heterozygosity values for all loci in investigated populations*
Tablo 4. *İncelenen populasyonlardaki beklenen ve gözlenen heterozigotluk değerleri*

LOCUS	KIV-BURSA		KIV-MANİSA		KIV-İSTANBUL		OVERALL	
	Obs-Het	Exp-Het	Obs-Het	Exp-Het	Obs-Het	Exp-Het	Obs-Het	Exp-Het
ABCG2	0.3000	0.4627	0.5000	0.4507	0.2941	0.5075	0.3700	0.4804
AA-NAT	0.2069	0.1887	0.2000	0.1826	0.3529	0.2950	0.2551	0.2237
FABP3	0.3333	0.4881	0.2778	0.4507	0.1176	0.5057	0.2400	0.4896

DISCUSSION

All loci investigated were found as polymorphic in Kıvırcık population. There are few number of studies carried out with these mutations investigated in the present study [19,22,31-33]. Allelic frequencies obtained from analysis are not consistence with the previous studies carried out for *ABCG2* [19] while frequency distributions of the *FABP3* and *AA-NAT* alleles are found similar to those of some Spanish sheep breeds and Chinese seasonal reproduction breeds, respectively [22,33]. For *FABP3* locus the G allele was also found as predominant majority of breeds investigated and frequencies of A allele was ranged from 1 (in Mouflon) and 0.26 (in Raza Aragonesa) [33]. The authors suggested that the wild allele of the *FABP3* locus investigated could be A allele and a subsequent mutation followed by selection may have increased the frequency of the G allele in domestic sheep breeds [33]. In the later study of the same authors heterozygous genotypes for this mutation was found related to milk fat content and it seems as a candidate gene for the marker assisted selection studies [19].

At *ABCG2* locus the "–" allele was found as predominant and its frequency differed from 0.50-0.65 in the present study and for all over the population it was found as 0.60 *(Table 3)*. On the contrary the "+"allele was found as predominant in a previous study [19]. Otherwise they found to be related the "–" allele and higher SCC. The high frequency of this allele is an unfavorable event in Kıvırcık breeding populations.

In the case of *AA-NAT* it can be said that our findings are concordance with the results obtained from Chinese sheep breeds [22]. The study carried out in these Chinese sheep breeds revealed that frequencies of the *AA-NAT*-G are higher in non-seasonal reproduction breeds while found quite lower in the seasonal reproduction breeds [22]. It is well known that Turkish sheep breeds are generally seasonal reproduction breeds thus in our study G allele frequencies showed quite low. On the other hand G allele frequency obtained Kıvırcık populations was lower than allelic frequency of G allele frequencies obtained Chinese seasonal reproduction breeds. In the present study we are not found any heterozygous genotypes for this locus which may a negative situation when the locus is needed for marker assisted selection.

Furthermore chi-square test (χ2) revealed that allelic frequencies in *ABCG2* loci Kıvırcık populations from Bursa and İstanbul are in disequilibrium ($P<0.05$) and in the *FABP3* locus Kıvırcık- Manisa ($P<0.05$) and Kıvırcık- İstanbul the frequencies are also in disequilibrium ($P<0.01$). It should be kept in mind that these populations are breeding populations and there may strong selection pressures across populations and this situation probably due to selection acting on these loci in these populations, which are being selected for milk production or resistance to mastitis.

Genetic improvement of the livestock species is an expensive and time consuming process. Instead of or beside of classical selection methods for economically important traits they may be used genes have major effect on the traits for selection criteria. Kıvırcık is one of the most important sheep breed in animal production of Turkey. Molecular markers may be used in studies on genetic improvement of Kıvırcık sheep breed when efforts are continued in this field. Studies should be increased to reveal genetic structure of this breed for genes affect on economically important traits. On the other hand frequencies of these kinds of genes investigated routinely and further investigations should be carried out to ensure the relationships with the genes and the traits.

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