Livestock Studies, 2020; 60 (2): 68-73
http://doi.org/10.46897/livestockstudies.846425

RESEARCH PAPER

LIVESTOCK STUDIES

Evaluation of two SNP markers in DPPA2 and SYTL3 genes for association with host response against Visna/Maedi infection in Turkish sheep

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Article History

Received: 06 March 2020
Accepted: 13 November 2020
First Online: 25 December 2020

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Keywords

Visna/maedi
Genetic association
Genetic resistance/susceptibility

Abstract

Visna/maedi (VM) is an incurable viral disease of sheep causing serious production losses across the globe. Classical control measures against VM such as screening and culling are costly and time-consuming. Breeding VM resistant sheep could provide an opportunity for struggling with the VM and decreasing the economic loss. In this study, we aimed to investigate possible associations between two previously reported single nucleotide polymorphisms (SNPs) in the ovine DPPA2 and SYTL3 genes and VM serostatus, and evaluate implementation of selective breeding strategies against VM in Karacabey merino, Kivircik, Imroz, and composite breeds; Bandirma, Hampshire crosses (HAMP), Ramlic and Black-headed German mutton crosses (SBA) which are reared in Marmara region of Turkey. For this purpose, we genotyped the sheep which VM serostatus were determined previously. The genotyping results showed that these SNPs in the DPPA2 and SYTL3 genes are polymorphic. We have conducted an association analysis with an experimental design using case-control matched pairs. Finally, a power analysis was performed to determine the power of the statistical analysis. According to our findings, within our detection limits (the minimum odds ratio 2.5 to 2.8; CI 95; statistical power 0.96; p-value < 0.05), there was no significant association between the SNPs in the DPPA2 and SYTL3 genes and VM serostatus. Therefore, these SNP markers are not useful to selective breeding against VM in Turkish sheep.

Introduction

Visna/maedi (VM) is a viral infection in sheep caused by lentiviruses and characterized with a long incubation period, slow progression, weight loss and eventually death. Although it is a multisystemic disease, there are two main manifestations of VM: visna (progressive inflammation of the central nervous system) and maedi (respiratory form characterized by interstitial pneumonia). Because of pathogenic and genetic similarity between VM virus and Caprine arthritis encephalitis virus (CAEV), both viruses called to be small ruminant lentiviruses (SRLV) (Gomez-Lucia *et al*., 2018). Furthermore, VMV share common features such as genome organization, virus replication mode, and latency with HIV virus that is causative agent of Acquired immunodeficiency syndrome (AIDS) in humans (Andrésdóttir, 2018). The main transmission route of VMV is from mother to lamb via colostrum and milk, however aerosol route either in close contact or up to several meters is another common mode of transmission (Peterhans *et al*., 2004). There is no effective treatment and also a commercial vaccine not available for VM (Gomez-Lucia *et al*., 2018), thus, disease control strategies generally are based on serological screening and culling infected animals (Pépin *et al*., 1998).

VM is distributed in sheep industry across the globe and responsible for serious production loss. VM prevalence have been reported as 24.8% in Spain (Lago *et al*., 2012), 71% in Lebanon (Tabet *et al*., 2017), from 10.5 to 21.6% in Ethiopia (Ayalet *et al*., 2001), 28.8% in Germany (Huttner *et al*., 2017), from 20 to 60% in the UK (Ogden *et al*., 2019), 34.8% in Kosovo (Cana *et al.,* 2020), and

from 3.3 to 96.7% in Canada (Heinrichs *et al*., 2017). In Turkey prevalence of VM was reported between 2.7 to 77.9% (Burgu and Toker, 1990; Yavru *et al*., 2012; Muz *et al*., 2013).

Due to no available treatment and/or immunization to struggle with VM, efforts turned towards genetic research to identify the underlying host genetic factors against VM. Various studies have proposed a number of candidate loci to be associated with VM disease status (Herrmann-Hoesing *et al*., 2008; White *et al*., 2009; Larruskain *et al*., 2010; Sarafidou *et al*., 2013). However, a major gene (TMEM154) was reported to be associated with host susceptibility/resistance to VM in a genome-wide association (GWA) study using case-control design (Heaton *et al*., 2012), and this result was confirmed by subsequent independent studies (Molaee et at., 2018; Molaee *et al*., 2019; Yaman *et al*., 2019). Moreover, SNP markers in the ovine DPPA2 and SYTL3 genes were reported by another GWA study to be potential co-receptors for VM infection White *et al*., 2012).

The aim of present study was to investigate whether there is an association between SNP markers in the DPPA2 and SYTL3 genes and VM serostatus in Turkish sheep. To this end, a retrospective cohort study was performed to determine serostatus of sheep which have been reared at Sheep Breeding and Research Institute (SRI) in the same environmental and management conditions. A case-control matched pairs panel was constructed and samples were genotyped using single nucleotide primer extension (SNuPE) assay. Finally, a McNemar's test (McNemar, 1947) for correlated proportions was conducted to determine any significant association between SNPs of interest and VM serostatus in Turkish sheep.

Material and Methods

Animals

Native Turkish sheep; Karacabey merino, Kivircik, Imroz, and composite breeds; Bandirma, Hampshire crosses (HAMP), Ramlic and Black-headed German mutton crosses (SBA) were used to study of which serological VM status were previously determined with indirect-ELISA in 2017 (Yaman *et al*., 2019). All sheep were from a research flock that have been bred in SRI. For genetic analysis, a tube of peripheral whole blood with EDTA was collected from V. jugularis in aseptic conditions. Sampled animals were two years old or older. A case-control matched pairs panel was constructed, and genetic analysis performed on matched pairs.

DNA isolation was conducted using commercial spin-column kits according to the manufacturer's manual. Primers were designed using primer blast online tool (https://www.ncbi.nlm.nih.gov/ tools/primer-blast/). A multiplex polymerase chain reaction (PCR) was employed to amplify the regions of the ovine DPPA2 and STYL3 genes covering the target SNPs. Single nucleotide primer extension (SNuPE) experiment was designed to genotype target SNPs at the same time. Briefly, extension primers without fluorescent tag were designed for each SNP in different lengths (18 vs 26bp) to bind one base prior to the target SNP. Then, SNaPshot™ Multiplex Kit (Thermo Fisher Scientific Inc., USA) was used for SNuPE assay in standard thermal cycler. Throughout the SNuPE reaction, it was expected that the fluorescently labeled ddNTPs bind exactly to the target nucleotide and chain termination reaction occurs. Finally, after incubation with shrimp alkaline phosphatase (SAP) for enzymatic purification, reaction products were subjected to capillary electrophoresis with fragment analysis protocol on ABI 3500 sequencer platform. Amplification primers, extension primers and a summary of the genotyped SNPs are provided in Table 1. Chromatograms were visualized using GeneMapper v6 software. To confirm the SNuPE results, approximately 10% of the samples were sequenced for each SNP.

Genetic association studies require maximum control of other factors, particularly for disease traits. Exposure intensity and exposure duration are two major factors affecting the disease status. Additionally, breed effect (population stratification or population structure) is another major factor on the results of association analyses. To account for exposure duration, exposure intensity and breed effect, case-control matched pairs were constructed. Briefly, a seropositive ewe matched with a seronegative from the same breed (for breed effect), the same age (for exposure duration) and the same flock (for exposure intensity), and statistical analysis was performed over case-control matched pairs. For DPPA2, 127 matched pairs (127 case and 127 control; n= 254) and for STYL3, 131 matched pairs (131 cases, 131 controls; n= 262) were constructed. Matched pairs panel according to breed and ages are given in Table 2. To determine whether there is any association between interested SNPs and VM serostatus a McNemar's test for correlation proportion was conducted. Association analysis was performed for three heritability model:1-exactly one copy of allele provides genetic risk or protection, 2-one or two copies of allele provides genetic risk or protection, and 3- exactly two copy of allele provides genetic risk or protection. Matched pairs were assigned to be (1;1), (1;0), (0;1), and (0;0) where in (1;1) pairs, either case and control members of the pair have the risk/protection factor, in (1;0) pairs, the case has the risk/protective factor but control does not, in (0;1) pairs, the case does not have the risk/protection factor

but the control has, and in (0,0) pair, neither of the case nor the control have the risk/protection factor. Assigned pairs were manually arranged and McNemar's test was perfomed an online tool (https://www.graphpad.com/quickcalcs/McNemar1.cfm) using number of each assigned pairs. It is expected for a significant association, the sum of discordant pairs (1;0 and 0;1) must be greater than 25. Finally, a power analysis using G*Power v3.1.9.4 (Faul *et al*., 2009) software was conducted to check the statistical power of the study for each SNP marker.

Table 1. A summary of amplification and extension primers

Primer ID	Amplification primers	PCR Size	Extension primers	Size (bp)	SNP	rs
styl3-F	GCTTCTCAATTCCGCCCTTTC	791	CTTTGAAGACGGCTGCTT	18	A/C/T	rs413063847
styl3-R	CTAGGCGCTATGGTGAGCTG					
dppa2-F	TGAAGTTACCACCTCAACCGT	884	GTGATGATTTAGGAATAT ACTGCAAA	26	C/T	rs411941451
dppa2-R	GATCTCTGGTGCTTGGAACA					

Table 2. Distribution of matched pairs according to breeds and ages

	DPPA2								STYL3							
	Ages								Ages							
Breeds	8	7	6	5	4	3	2	Total	8	7	6	5	4	3	2	Total
Karacabey merino	-	2	3	2	3	4	1	15	-	3	2	2	3	3	1	14
Kivircik	-	7	11	9	7	4	-	38	-	9	12	9	7	4	-	41
Imroz	-	-	6	6	2	2	1	17	-	-	6	6	2	2	1	17
Bandirma	3	11	11	14	9	3	-	51	4	13	12	14	8	3	-	54
HAMP	-	-	2	-	1	-	-	3	-	-	2	-	1	-	-	3
SBA	-	-	-	-	-	2	-	2	-	-	-	-	-	2	-	2
Ramlic	-	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-
Total	3	20	34	31	22	15	2	127	4	25	34	31	21	14	2	131

Results

SNuPE assay results revealed that each SNP marker in the DPPA2 and STYL3 genes were polymorphic for all breeds except Ramlic. Only two matched pair were available from Ramlic ewes for the SNP in DPPA2 gene, nevertheless these four sheep were monomorphic regarding this SNP. Minor allele frequency (MAF) for the SNP in DPPA2 ranked from 0.13 (SBA) to 0.50 (Imroz) and for the SNP in STYL3 ranked from 0.25 (SBA) to 0.44 (Imroz, Table 3). For the SNP in DPPA2 in Imroz and Ramlic and for the SNP in STYL3 in Karacabey merino and Hampshire crosses minor alleles have turned to be a major allele. Sequence results for 10% of the samples for each SNP were in 100% concordance with SNuPE assay.

Table 3. Allele distribution of DPPA2 and STYL3 SNPs according to breeds

	DPPA2				STYL3			
Breeds	*n*	HW	MAF	Alleles	*n*	HW	MAF	Alleles
Karacabey merinos	30	0.52	0.20	T/C	28	1.00	0.42	T/C
Kivircik	76	0.53	0.35	T/C	82	0.42	0.43	C/T
Imroz	34	0.44	0.50	C/T	34	1.00	0.44	C/T
Bandirma	102	0.84	0.24	T/C	108	0.36	0.27	C/T
HAMP	6	1.00	0.08	T/C	6	0.48	0.42	T/C
SBA	4	1.00	0.13	T/C	4	1.00	0.25	C/T
Ramlic	2	1.00	-	C/T	-	-	-	0
Total	254				262			

McNemar's test for correlated proportion revealed that number of discordant pairs were greater than 25 for all three scenario (exactly one allele, one or two allele, and exactly two allele provide risk or protection factor) except "one or two allele" model for STYL3 gene. Statistical power analysis was performed over real percent of discordant pairs and sample size. Detection limits of the study were determined to have statistical power as 0.96, minimum odds ratio as 2.5; CI as 95; p-value < 0.05 for the SNP in DPPA2, and statistical power as 0.96, minimum odds ratio as 2.8, CI as 95; p-value < 0.05 for the SNP in STYL3. Statistical analysis did not indicate any significant association between the SNP markers in DPPA2 and STYL3 with VM serostatus within our statistical limits (Table 4).

Table 4. McNemar's test for VM association with *DPPA2* and *STYL3* SNP markers.

		SNP ID	
McNemars pair status and test statistics[a]	**McNemar's quadrants and equations[b]**	***DPPA2***	***STYL3***
Exactly one copy of risk or protective allele			
1,1	"a"	29	23
1,0	"b"	35	27
0,1	"c"	34	32
0,0	"d"	29	49
Total pairs	a+b+c+d	127	131
Discordant pairs	b+c	69	59
OR	b/c	1.0	0.8
CI95 Lower	-	0.6	0.5
CI95 Upper	-	1.7	1.4
McNemar's $\chi 2^{d}$	$(\|b - c\| - 1)^2/(b + c)$	0.0	0.3
p-value	-	0.19	0.17
One or two copies of risk or protective allele			
1,1	"a"	53	105
1,0	"b"	24	10
0,1	"c"	33	13
0,0	"d"	17	3
Total pairs	a+b+c+d	127	131
Discordant pairs	b+c	57	23
OR	b/c	0.7	0.8
CI95 Lower	-	0.4	0.3
CI95 Upper	-	1.2	1.8
McNemar's $\chi 2$	$(\|b - c\| - 1)^2/(b + c)$	1.1	0.2
p-value	-	0.10	0.27
Exactly two copies of risk or protective allele			
1,1	"a"	3	35
1,0	"b"	10	30
0,1	"c"	20	28
0,0	"d"	94	38
Total pairs	a+b+c+d	127	131
Discordant pairs	b+c	30	58
OR	b/c	0.5	1.1
CI95 Lower	-	0.2	0.6
CI95 Upper	-	1.1	1.8
McNemar's $\chi 2$	$(\|b - c\| - 1)^2/(b + c)$	2.7	0.0
p-value	-	0.06	0.20

[a]Each member of a case-control pair is assigned a value of "1" or "0" depending on whether the risk/protective factor is present (1) or absent (0). Briefly, in (1,1) pairs, either case and control members of the pair have risk/protection factor, in (1,0) pairs, case has risk/protective factor but control not, in (0,1) pairs, case not has risk/protection factor but control have, and in (0,0) pair neither of case and control have risk/protection factor.
[b]These are quadrants from the McNemar's contingency table for classifying pairs.

Discussion

VM is among the most prevalent disease in sheep industry worldwide. Only Australia and New Zealand have been considered to be MV free, but not for the CAEV, the goat type of the SRLV. Furthermore, while Japan has also been considered free from MV, recent studies showed the presence of the VM virus in this country (Gomez-Lucia *et al*., 2018). In addition to having no treatment or vaccine, vertical transmission via colostrum from ewe to lamb makes it much more difficult to struggle with VM. Moreover, control measures such as screening, culling and restocking have been found to be expensive and time consuming (Pépin *et al*., 1998; Berriatua *et al*., 2003; Ruiz-Fons *et al*., 2014). Nevertheless, it should be kept in mind that even if MV eradication is achieved by classical control measures, the flocks will remain susceptible against VM, thus, possibility of new infection by vectors or by infected ewes joining the herd from other flocks will remain as a threat for sheep herds.

On the other hand, breeding for VM resistant sheep could provide an opportunity to struggle with VM. For this reason, a variety of research on molecular mechanisms underlying host genetic factors against VM have been conducted. Herrmann-Hoesing et al. (2008) tested the possible association between DRB1 gene in Ovar-MHC II loci and provirus level of Ovine Progressive Pneumonia (OPP) that is counter part of VM, and they found that DRB1*0403 or DRB1*07012 alleles were associated with lower proviros level of OPP (Herrmann-Hoesing et al., 2008). Another report seeking the association between DRB1 and VM status revealed that the DRB1*0325 allele associated with susceptibility to VM (Larruskain *et al*., 2010). White *et al*. (2009) reported that a 4-base deletion in the promoter domain of CCR5 gene significantly reduced the provirus level in homozygous. Another reported deletion variant in ZNF389 gene also reported to be associated with provirus level of VM infection (White *et al*., 2013). Sarafidou *et al*. (2013) proposed that G520R mutation in ovine TLR9 coding region associated with VM serostatus. Nevertheless, there is no published data from independent studies to confirm the effect of these loci.

In a recent study, however, specific haplotypes in TMEM154 gene proposed to be major gene regarding genetic resistance/susceptibility to VM (Heaton *et al*., 2012), and it is repeatedly reported by subsequence studies that TMEM154 variants can explain the big proportion of the VM serostatus variations in North American (Leymaster *et al*., 2013; 2015), German (Molaee *et al*., 2018), Turkish (Yaman *et al.*, 2019), and Iranian (Molaee *et al*., 2019) sheep. But it might be hypothesized that different co-receptors encoded by other genomic locations are quite possible.

In a recent genome-wide association study, White *et al*. (2012) reported that multiple SNPs located within or near the various genes might be involved in host immune response to VM. They have also reported one SNP within DPPA2 and one SNP within STYL3 genes significantly associated with VM status. In the present study, the possible effect of these two SNPs was tested in Turkish sheep with an experimental design including case-control matched pairs. However, the results of White *et al*. (2012) have not been confirmed in Turkish sheep. The reasons for not being confirmed for these results might arise from differences in experimental design of the studies, different subtypes of the VM viruses, and gene-environment interaction.

In conclusion, within our detection limits, no association was detected between VM serostatus and previously reported two SNPs located in the ovine DPPA2 and the ovine STYL3 genes. These SNPs are not useful for selective breeding in Turkish sheep. Further studies might be required to elusive involved co-receptors in the host immune response to the VM virus.

Acknowledgements

This research has been funded by the Republic of Turkey Ministry of Agriculture and Forestry, General Directorate of Agricultural Research and Policies (Project number: TAGEM/HAYSÜD/15/A01/P02/02-02).

Ethical statement

All animal procedures in the study were reviewed and approved by the local ethics committee of Sheep Breeding and Research Institute (Approval Number: 1282412).

Conflict of interests

The author declares no conflicts of interest.

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