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BRIEF REPORT

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Maedi Visna virus infection and *TMEM154* genotypes in Valle del Belìce sheep breed

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ABSTRACT

Maedi Visna (MV) is a viral infection in sheep caused by *Lentivirus* and characterised by a long incubation period, slow progression, weight loss and eventually death. *TMEM154* was reported in the ovine as major candidate gene associated with host susceptibility/resistance. The aim of this study was to verify the prevalence of MV infection within Sicilian herds of Valle del Belìce breed using an ELISA serological test and to estimate the frequencies of the resistant/susceptible genotypes to the *TMEM154* gene. Finally, we investigated the association between *TMEM154* E/K genotype and MV infectious status. A total of 1,083 animals from different flocks were tested. The ELISA method showed 15.33% ($n = 166$) of infected individuals. Analyses of the sequences showed the presence of both K and E alleles with frequencies of 0.151 and 0.849, respectively. On the total individuals, only 23 carried KK genotype while 280 were heterozigous EK, and 780 homozygous EE. The locus was in Hardy-Weinberg equilibrium in the breed (p-value <0.05) and observed and expected heterozygosity values were 0.258 and 0.256, respectively. Moreover, a significant association (p-value < 0.001) between *TMEM154* genotypes and seroprevalence status (positive vs. negative) was found. This study allowed us to know the prevalence of MV infection in Sicilian flocks of Valle del Belìce breed and could be helpful in establishing selection programs aimed at controlling and eradicating this virus.

HIGHLIGHTS

- We verified the prevalence of Maedi Visna virus within Sicilian herds of Valle del Belìce sheep.
- The results indicate that no individuals with resistant genotype were seropositive.
- Our findings represent a starting point for the creation of mating programs by using animals carrying resistant genotype.

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Introduction

Maedi Visna virus (MVV) or Ovine Progressive Pneumonia is a *Lentivirus* belonging to the Retroviridae family and is part of the Small Ruminants *Lentivirus* (SRLV) group (Sigurdsson et al. 1952; Straub 2004). This group has been included by the World Health Organisation (OIE) on the list of notifiable terrestrial animal diseases due to their economic impact on the international trade of animals and their products (OIE 2018). Common symptoms of MVV infection in sheep included interstitial pneumonia with dyspnoea, indurative mastitis, and cachexia (Pritchard and Dawson 2000; Clawson et al. 2015; Minguijón et al. 2015).

MVV infection is also referred to as 'adult sheep disease', since it is characterised by a rather long preclinical stage in which the animal does not show symptoms of the disease (Jones 2014). Infection takes place through colostrum/milk consumption from infected ewes (vertical transmission), and/or by direct contact with respiratory secretions from infected animals (horizontal transmission) (Blacklaws et al. 2004; Preziuso et al. 2004; Peterson et al. 2008; Ramírez et al. 2021). Due to no available treatment and/or immunisation to struggle with MVV, efforts turned towards genetic research to identify the underlying host genetic factors against MVV. Several studies proposed different candidate genes associated with MVV disease status (Rodrigues et al. 2023), such as: *ovar-*

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DRB1 (Herrmann-Hoesing et al. 2008; Larruskain et al. 2010), *CCR5* (White et al. 2009), *DPPA2/DPPA4* and *SYTL3* (White et al. 2012), *TLR9* (Sarafidou et al. 2013), and *ZNF389* (White et al. 2014). However, *TMEM154* (Transmembrane Protein Gene 154) was reported in the ovine species as major candidate gene associated with host susceptibility/resistance (Heaton et al. 2012), and this result was confirmed by independent studies (e.g. Molaee et at. 2018; Yaman et al. 2019; Tumino et al. 2022). The polymorphism involved in resistance/-susceptibility is located in the portion of the gene encoding the extracellular part of the protein and is characterised by the substitution, at position 35 of the protein, of glutamate (E) amino acid with lysine (K) one (Heaton et al. 2012; 2013). The resistance occurred only in homozygous KK animals, while heterozygous EK and homozygous EE were susceptible to disease. However, some authors reported that KK genotype was not fully protective depending on several factors as viral dose, route of infection, type and number of MVV strains involved (Heaton et al. 2013).

To the best of our knowledge, few studies have been conducted in local sheep breeds to identify gene variants involved in the genetic resistance to MVV (Molaee et al. 2019; Yaman et al. 2019; Arcangeli et al. 2021; Tumino et al. 2022). Moreover, these studies used a relatively low number of animals per breed and reported that the frequencies of the protective *TMEM154* alleles are significantly low or absent in some indigenous populations. Furthermore, several studies suggested the influence of breed on the susceptibility to MVV (Molaee et al. 2019; Moretti et al. 2022).

The Valle del Belìce sheep is an economically important dairy breed whose milk is used to produce typical dairy products. In this study, the prevalence of Maedi Visna virus infection was investigated in several flocks of this breed, located in different Sicilian provinces. Moreover, we estimated the allele and genotype frequencies of E35K substitution in *TMEM154* encoding protein. Finally, we analysed *TMEM154* E/K genotype association with MVV infectious status.

Material and methods

Animals and samples

A total of 1,083 individuals (1,055 ewes and 28 rams) were sampled from nine flocks of Valle del Belìce sheep located in three different geographical areas of Sicily: Agrigento (AG), Palermo (PA) and Trapani (TP) provinces. Only animals older than two years were considered, therefore number of sampled individuals ranged from 15 to 230 per herd. Individual blood and milk samples were collected from each animal by veterinarians during routine controls.

Serological analyses for MVV status

Serological tests were performed on whole milk (for ewes) and plasma blood samples (for rams) using the commercial ELISA assay ID Screen® MVV/CAEV Indirect Screening test (IDvet, Grabels, France), following the manufacturer's instructions. At the final step, the plates were loaded at 450 nm wavelength by an ELISA plate reader. The cut-off value was defined based on the corrected optical density (OD) ratio between sample and positive control (S/P%) at a wavelength of 450 nm. According to the manufacturer's instructions, samples were considered negative with S/P% value $\leq$50% and positive with S/P% value $\geq$60%.

DNA extraction and genotyping

Genomic DNA was extracted from 200 µl of whole blood following the PureLink Genomic DNA kit protocol (Invitrogen). The quantification of the extracted DNA was performed by Nanodrop ND-1000 (Thermo Fisher Scientific) and samples were normalised at 50 ng/uL.

A 470 bp fragment containing exon 2 of the ovine *TMEM154* gene (NM_001306112) was amplified using primers FW-GTTTCTCGCTGGATGCATGG and REV-AGATCCTTGGCTAGAGGGCT. The amplification protocol aimed to identify the polymorphism G→A at position 103 of the *TMEM154* mRNA, which leading to mutation of GAA codon in AAA one. This substitution causing change at position 35 of encoding protein in which E amino acid was replaced by K one. Therefore, mutated individuals with AA genotype represented KK resistant animals, while heterozygous GA and homozygous GG were both susceptible to infection.

The PCR amplifications were performed on Veriti PCR System thermal cycler (Applied Biosystems) in a final volume of 10 µL containing 100 ng of genomic DNA, 0.2 µM of each primer, 1X QIAGEN PCR Master Mix (Qiagen). Amplification conditions were 95 °C for 15 min, 30 cycles of 94 °C for 30 sec, 61 °C for 1 min and 30 sec, 72 °C for 1 min and 30 sec, and a final extension at 72 °C for 10 min. The amplified fragments were purified using ExoSAP-IT Express PCR Product Cleanup reagent following manufacturer's protocol (Thermo Fisher Scientific). The sequencing reaction was performed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) following

by purification with BigDye XTerminator Purification Kit (Applied Biosystems). Finally, sequencing analyses were performed on 3500xl Genetic Analyser (Applied Biosystems).

Statistical analysis

The obtained nucleotide sequences were checked using Sequencing Analysis v5.3.1 software (Applied Biosystems) and then analysed with SeqScape v2.5 software (Applied Biosystems). The polymorphic site containing the G→A mutation was confirmed by visual examination of the electropherograms for all samples.

The allelic and genotypic frequencies at the *TMEM154* gene, and the deviations from the Hardy-Weinberg equilibrium were estimated using the Popgene software (Yeh and Boyle 1997). Fisher's exact test was performed to compare observed frequencies of seropositive samples across AG, PA and TP provinces. Moreover, the test was also conducted to assess the association between genotypes and seroprevalence. Statistical analyses and tests were performed using R software v4.2.1.

Result

The results from ELISA analyses showed on a total of 1,083 individuals, 166 seropositive and 917 seronegative animals (15.33% and 84.67%, respectively). Table 1 showed the percentage of positive individuals in the different provinces which ranged from 6.45% to 17.03%, with the highest prevalence in Palermo province, probably due to different livestock management strategies.

Sequencing analysis and alignment of the obtained sequences showed the presence of both K and E amino acids, with frequencies of 0.151 and 0.849, respectively (Table 2). On the total individuals, only 23 carried KK genotype, while the most frequent genotype was EE (780 animals), followed by EK (280 animals). The *TMEM154* locus was in Hardy-Weinberg equilibrium in the Valle del Belìce breed (p-value < 0.05) and observed and expected heterozygosity values were 0.258 and 0.256, respectively.

Table 1. Seroprevalence of Maedi Visna virus per geographical area.

Province	N of individuals	N of seropositive	Seroprevalence
PA	769	131	17.03%[a]
AG	190	27	14.21%[b]
TP	124	8	6.45%[c]

[abc]Different lower-case letters indicate significant differences among geographical area (p-value < 0.05).
PA: Palermo; AG: Agrigento; TP: Trapani; N: Number.

A significant association (p-value < 0.001) between *TMEM154* genotypes at position 35 and seroprevalence status (positive vs negative) was found in Valle del Belice breed. It was observed that all MVV positive individuals showed susceptible genotypes (EK and EE), and individuals with homozygous resistant genotype KK were negative (Table 2).

Discussion

MV is among the most prevalent disease in sheep industry worldwide. After the results reported by Heaton et al. (2012), the importance of *TMEM154* gene and its E35K amino acid mutation have been widely recognised in sheep (Heaton et al. 2013; Clawson et al. 2015; Molaee et al. 2019; Yaman et al. 2019; Murphy et al. 2021; Ramírez et al. 2021; Rodrigues et al. 2023), but few studies regarding the frequencies of genetic variants (Arcangeli et al. 2021; Moretti et al. 2022; Tumino et al. 2022) are available on the Italian breeds. In this study, the presence of Maedi Visna virus infection and the genotype and allele frequencies of the *TMEM154* gene were assessed in Valle del Belìce sheep breed. Moreover, we investigated the association between *TMEM154* E/K genotype with MVV infectious status.

The serological tests showed a seroprevalence of 15.33% on total analysed individuals. Different prevalence rates of MVV, ranging from very low to very high, have been recorded in sheep breeds. For example, Pavlak et al. (2022) reported a seroprevalence of 10% in Croatian breeds, whereas a seroprevalence of 1% was observed in Polish breeds (Junkuszew et al. 2016). Similar results to those observed for Valle del Belìce breed are reported for Turkish breeds, with a seroprevalence that ranged from 10.05% (Ameen and Karapinar 2018) to 16% (Azkur et al. 2011; Gezer et al. 2021), while in Spanish breeds it ranged from 25% (Lago et al. 2012) to 52.8% (Pérez et al. 2010). In other Italian sheep breeds, seroprevalence was about 26% (Moretti et al. 2022; Tumino et al. 2022).

Consistent with our study, other previous authors (Gezer et al. 2021; Pavlak et al. 2022) reported statistically significant differences between seroprevalence and geographical areas. In Sicily, differences in management strategies among provinces could be the reason of observed statistically significant differences.

We observed a statistically significant (p-value < 0.001) association between animal genotypes and seropositivity. An interesting result was that no individuals with homozygous KK genotype were seropositive in our study, confirming this genotype as

Table 2. Genotype and allele frequencies at *TMEM154* locus in Valle del Belìce sheep breed.

	TMEM154 Allele Frequencies		*TMEM154* Genotype Frequencies				TMEM154 GENOTYPE		
Total Sheep	E	K	EE	EK	KK	MVV Status	EE	EK	KK
1,083	0.849	0.151	0.720	0.259	0.021	Positive (166)[a]	148	18	0
						Negative (917)[b]	780	114	23

[ab]Different lower-case letters indicate a significant association among MV status and genotype (p-value < 0.001).

resistant/protective. In a recent study on Sicilian local sheep breeds (Tumino et al. 2022), the association between *TMEM154* genotype and MVV susceptibility was also observed; moreover, some of these analysed breeds (Comisana, Barbaresca and Pinzirita) showed high frequency of the resistant K allele, while Valle del Belice breed showed high frequency of the susceptible E allele (0.88), in agreement with our results. Moretti et al. (2022), in a study on three different Italian sheep breeds (Biellese, Delle Langhe and Bergamasca), observed that susceptible allele (E) frequencies ranging from 18.3% to 32.95%, and resistant (K) ones ranging from 67.95% to 81.7%. Ramírez et al. (2021), showed different genotype frequencies depending on the considered breed (Navarra, Latxa, Assaf and Churra). The protective genotype (KK) was predominant in Navarra (80.7%), Latxa (69.1%), and Churra (74.3%) breeds, except for the Assaf breed in which susceptible heterozygous EK was most prevalent (43.2%), followed by EE (36.5%) and KK (20.3%). Finally, Molaee et al. (2018) in a study on the Merinoland breed, showed low frequency of susceptible genotypes EE and EK (null and 0.26, respectively) compared with the resistant genotype KK. Therefore, these results suggest and confirm that the allelic and genotypic differences are related to the breed.

Conclusion

Our data allowed us to know the prevalence of MVV infection in Sicilian flocks of Valle del Belìce breed and could be helpful in establishing selection programs aimed at controlling and eradicating this virus. Further investigations will be needed, also on other sheep populations, with the final aim to adopt and to implement mating programs by using animals carrying resistant variants; this could also reduce economic losses from the disease.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available upon request from the corresponding author.

Ethical approval

The animal study protocol was approved by the Bioethics Committee of the University of Palermo: protocol code UNPA-CLE–98597. All procedures involving animal sample collection followed the recommendation of directive 2010/63/EU.

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