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Orf virus circulation in cattle in Turkey

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ABSTRACT

Orf virus (ORFV) causes contagious skin disease that mainly affects sheep and goats with zoonotic potential. However, there is not enough information about the association between ORFV and occurrence of skin disease in cattle. The present study describes outbreaks of ORFV infection in cattle in different provinces that are located in the Aegean, Central Anatolian and Mediterranean regions of Turkey. During the months of June and August 2017, vesicular fluid and scab samples were collected from cattle which had proliferative skin lesions. First, presence of lumpy skin disease virus (LSDV) and bovine herpesvirus 2 (BoHV-2, known as the causative agent of pseudo-lumpy skin disease) were investigated by real time PCR and PCR, respectively. Then, samples tested for the presence of parapoxviruses by PCR using primers specific to major envelope protein gene (B2L). Parapoxvirus DNA was detected in investigated samples whereas LSDV and BoHV-2 DNA were not detected. The analysis of the B2L gene sequences revealed that cattle were infected with ORFV. The isolates in the present study shared 100% sequence identity at the nucleotide and amino acid level when compared with previously characterised Turkish field ORFV isolates from goats in 2016. Results of the study show unusual infection of cattle with ORFV, and suggest that ORFV jumps the host species barrier from goats to cattle.

1. Introduction

Orf virus (ORFV) is an epitheliotropic virus, classified in the genus *Parapoxvirus* of the *Poxviridae* family, and is antigenically closely related to bovine papular stomatitis virus (BPSV), pseudocowpox virus (PCPV), squirrel parapoxvirus (SPPV) and parapoxvirus of red deer in New Zealand (PVNZ) [1]. Members of the *Parapoxvirus* genus are morphologically distinguished from other poxviruses by their ovoid shape and their relatively small size (about 260 nm in length) [1,2].

Parapoxviruses are enveloped, double-stranded DNA viruses, 130–150 kbp in length having 88 genes in the central region of their genome, and can infect both animals and humans [1,2]. BPSV and PCPV cause infection in cattle [3,4]. BPSV infection has been associated with lesions on the muzzle, lips and oral mucosa of young calves whereas PCPV is frequently associated with scabby lesions on the teats and udders of dairy cows [5]. ORFV mainly infects sheep and goats, and lambs and kids are more susceptible to disease than adults [6,7]. Additionally, clinical signs of ORFV infection have also been reported in Finnish and Norwegian reindeer, camels, Japanese serows, musk ox, dogs and cats [8–14].

Animals infected with ORFV develop contagious ecthyma that is characterized by the formation of papules, vesicles, and scabs on the lips, muzzles, gums, noses and teats [6,7]. ORFV infection is endemic in sheep and goat flocks in both the Anatolia and Thrace parts of Turkey and human cases have also been reported [15,16].

Skin diseases are important for cattle because they can cause significant discomfort and economic losses to the cattle industry. Viral skin diseases caused by lumpy skin disease virus (LSDV), BPSV and PCPV have been reported in cattle in Turkey [17–19]. However, before this study, there was no record of skin infection caused by the ORFV in cattle in Turkey. The present study describes outbreaks of ORFV infection in cattle in different provinces that are located in the Aegean, Central Anatolian and Mediterranean regions of Turkey.

2. Materials and methods

2.1. Study area and sample collection

This study was conducted during the months of June and August 2017 in the Afyonkarahisar Province in the Aegean, Isparta Province in the Mediterranean and Konya Province in the Central Anatolian regions of Turkey (Fig. 1). The cattle industry in these provinces is dominated by family-run small (1–10 cattle) and medium (11–50 cattle) dairy and beef herds. European breeds are the most common breed in these provinces. Among the investigated provinces, the first outbreak was reported from a medium dairy herd (n = 48) in the Konya Province in the Central Anatolian region of Turkey in June 2017. Skin lesions were noted in 7 cattle. Proliferative lesions of the skin (1–3 cm in diameter),

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Fig. 1. (A) Location of sampled region in Turkey. (B) Proliferative scabby lesions on the back of cattle.

mainly on the back and legs were the most common clinical signs. The age of the affected animals ranged from 15 to 60 months.

The second outbreak occurred in another medium dairy herd (n = 27) in the Afyonkarahisar Province in the Aegean region of Turkey in July 2017. Similar skin lesions were observed in 12–40 months cattle (n = 4). The third outbreak was reported from a small dairy herd (n = 9) in the Isparta Province in the Mediterranean region of Turkey in August 2017. Two of the 9 cattle, at 17 and 38 months of age, had skin nodules on their back.

Death was not recorded in these herds during the study period. Additionally, no human cases were reported in infected herds. Breeds of the infected cattle were Holstein and Brown Swiss (Table 1). Vesicular fluid and scab samples from cattle (n = 6) that had skin lesions were collected from 3 herds in the Konya, Afyonkarahisar and Isparta Provinces.

2.2. Viral DNA extraction

Scab samples were first homogenized in phosphate buffered saline (200 µl) using TissueRuptor (Qiagen, Hilden, Germany). DNA extraction was carried out from the vesicular fluid and scab homogenates using QIAamp Cador Pathogen Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions.

2.3. Real time PCR assay for LSDV

Real-time PCR assay was performed using capripoxvirus open reading frame of gene 074 specific primers and probe designed by Bowden et al. [20] with the LightCycler 480 Probes Master Kit (Roche Diagnostics, Mannheim, Germany). The assay was carried out in a 25 µl reaction mixture containing, 900 nM of each primer and 250 nM probe and 5 µl of DNA template. The reaction was run on the LightCycler 2.0 real time PCR machine (Roche Diagnostics, Mannheim, Germany) using the following amplification program: 50 °C for 2 min; 95 °C for 10 min; and 45 cycles of 95 °C for 15 s and 60 °C for 1 min.

2.4. BoHV-2 PCR assay

A PCR assay targeting UL29 gene which encodes the major DNA binding protein of BoHV-2 was used to detect viral DNA in investigated samples. The primers used for the amplification were previously described by d'Offay JM et al. [21]. PCR reaction was performed with Taq DNA Polymerase kit (Thermo Fisher, UK) in a final volume of 50 µl, which contained 1 µM of each primer and 5 µl of DNA template. Amplification was carried out in a MJ Research thermal cycler with the following conditions: initial denaturation of 94 °C for 3 min; followed by 40 cycles of 94 °C for 30 s, 68 °C for 1 min, and 72 °C for 30 s with a final extension of 7 min at 72 °C. Amplified PCR products were electrophoresed at 90 V for 1.5 h in 2% agarose gel and visualized by staining with GelRed (Biotium, USA).

2.5. Parapoxviruses PCR assay

Semi-nested PCR was performed with primers, described by Inoshima et al. [22], which amplify nucleotide sequences of the B2L gene of parapoxviruses. The first PCR was carried out in 50 µl reaction volume using 0.2 µM primers (PPP-1 and PPP-4), 5 µl DNA template and Taq DNA Polymerase kit (Thermo Fisher, UK). The second PCR was carried out with 5 µl of the first PCR product and PPP-3 and PPP-4 primers which amplify a 235 bp fragment on B2L gene. Amplification was carried out in a MJ Research thermal cycler with the following conditions: initial denaturation of 95 °C for 2 min; followed by 35 cycles of 94 °C for 35 s, 60 °C for 35 s, and 72 °C for 45 s with a final extension of 5 min at 72 °C. Amplified PCR products were electrophoresed at 90 V for 1.5 h in 1.5% agarose gel and visualized by staining with GelRed (Biotium, USA).

2.6. Sequencing of PCR products

The amplified DNA fragments were purified from gel with a High Pure PCR Product Purification Kit (Roche Diagnostics, Mannheim, Germany) and treated with ExoSAP-IT (ThermoFisher, Austin, USA) and sequenced with the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA) on an ABI 3500 DNA Analyser (Applied

Table 1
Epidemiological data of ORFV infected dairy herds in the study area.

Category	No. of cattle	No. of affected cattle	Affected breed	Morbidity rate (%)
Calf (0–6 months)	14	–	–	0
Heifer (1–2 years)	32	4	Holstein	12.5
Cow (3–8 years)	38	9	Holstein and Brown Swiss	23.7
Total	84	13		15.5

Biosystems, USA) in both the forward and reverse directions.

2.7. Sequence and phylogenetic analyses

Nucleotide and amino acid sequences were analysed using the Chromas Pro software version 1.7.5 (Technolysium Ltd, Tewantin, Australia). Phylogenetic tree was constructed for the B2L gene of parapoxviruses with additional sequences from GenBank using the MEGA software version 6, based on the genetic distances between different sequences calculated by Kimura two-parameter model. The confidence of the phylogenetic tree was assessed by bootstrapping, using 1000 replicates, and only values > 50% were reported.

Further, a phylogenetic network was carried out using the Network software version 5.0.1.1. (www.fluxus-engineering.com). B2L gene nucleotide sequence data were processed by star contraction algorithm [23] and then by median-joining (MJ) network algorithm [24].

3. Results

3.1. Detection of LSDV, BoHV-2 and parapoxviruses DNA

The analyses of viral DNA extracted from the vesicular fluid and scab homogenates from 6 cattle by parapoxvirus specific PCR assay identified the presence of parapoxvirus DNA in all investigated samples whereas LSDV and BoHV-2 DNA were not detected.

3.2. Sequence and phylogenetic analyses of the B2L gene of Parapoxviruses

The phylogenetic analysis of the B2L gene sequences showed that cattle were infected with ORFV (Fig. 2). Furthermore, analysis of the B2L gene sequences revealed that the nucleotide homology between the ORFV isolates from cattle in this study was 100% when compared with each other and 78.4–100% when compared with other parapoxvirus sequences from different regions. Amongst other parapoxvirus sequences, the highest sequence homology (100%) was observed with previously characterized Turkish field ORFV isolates from goats in 2016 (Konya/2016-ORFV1 and Aksaray/2016-ORFV2), and the lowest sequence homology (78.4%) was observed with a seal parapoxvirus isolate from Germany (AF414182). Furthermore, comparative nucleotide sequence analysis of the B2L gene of three isolates in this study revealed 81.8%–84.3% and 78.9%–95.5% identity with BPSV and PCPV isolates, respectively.

The deduced amino acid homology of the ORFV isolates in this study was 100%, whereas homology with other parapoxvirus isolates from Brazil, Bangladesh, Cameroon, China, Egypt, Ethiopia, Finland, France, Germany, India, Israel, Korea, Taiwan, Turkey and USA ranged between 60.2 and 100%. The highest amino acid homology (100%) was observed with previously characterized Turkish field ORFV isolates from goats in 2016 (Konya/2016-ORFV1 and Aksaray/2016-ORFV2). The deduced amino acid homology of the ORFV isolates in this study with BPSV and PCPV isolates from different countries ranged from 66.1%–70.5% and 72%–91.1%, respectively.

The network analysis based on B2L gene sequences showed that parapoxvirus species are separated from one another. ORFV isolates in this study formed a large node with previously characterized Turkish ORFV isolates and ORFV isolates from China, India and Taiwan (Fig. 3). A previously characterized Turkish ORFV isolate from a sheep (ORF1/1975 KC491189) and a Turkish ORFV isolate from a human (TR-S-Human/2011 JQ936990) differ from this node by two and five mutations, respectively.

4. Discussion

Skin diseases of cattle have economic impact due to poor hide quality. Viruses, bacteria, fungi, parasites, or non-infectious factors such as environmental and nutritional factors can cause skin disease in cattle [25]. The important viral agents that cause skin disease in cattle are LSDV, BoHV-2, BPSV, PCPV, cowpox virus and bovine papillomaviruses (BPVs) [26,27]. LSD becomes endemic in Turkey after first LSD outbreak was reported in 2013 [19]. BPSV, PCPV and BPVs infections have also been reported in cattle in Turkey [17,18,28].

Parapoxviruses may cause similar clinical symptoms, and clinical signs in cattle can look like many other diseases such as lumpy skin disease, pseudo-lumpy skin disease, foot and mouth disease and dermatophilosis [29–32]. Therefore, it is difficult to distinguish parapoxvirus infections from these diseases based on clinical signs. Histopathology and virus isolation are commonly used in the diagnosis of disease, but they are time and labour consuming. Molecular techniques have been proven the more rapid and sensitive for the diagnosis of parapoxvirus infections. DNA sequencing and PCR assay can be used together to distinguish among the different parapoxvirus species. Therefore, in this study semi-nested PCR which could detect low copy numbers of viral DNA in clinical samples [22] and sequence analysis were used.

The B2L gene that is highly conserved among divergent parapoxviruses was chosen because it has been widely used for molecular detection and genetic characterisation of species within the *parapoxvirus* genus [22,33]. The phylogenetic tree based on B2L gene sequences showed that cattle were infected with ORFV. Furthermore, in the B2L gene based network analysis, isolates in this study separated from BPSV, PCPV, PVNZ and sealpox isolates, and clustered in a taxon with previously characterized ORFV isolates. This conclusion is further strengthened by the fact that all isolates were obtained directly from skin lesions, and not from viruses that have been adapted to grow in cultured cells. Viruses often change genetically during the adaptive process in cell cultures [34]. To the best of my knowledge, this is the first report on the presence of the ORFV infection in cattle in Turkey.

Nucleotide and amino acid sequences demonstrated that Konya Cattle 2017-ORFV1, Afyonkarahisar Cattle 2017-ORFV2 and Isparta Cattle 2017-ORFV3 isolates obtained from three outbreaks in this study were closest (100%) to the Konya/2016-ORFV1 and Aksaray/2016-ORFV2 isolates obtained from the goats in the Konya and Aksaray Provinces in Turkey in 2016. The isolates of Konya/2016-ORFV1 and Konya Cattle 2017-ORFV1 were isolated from the same province (Konya Province). Furthermore, there is a movement of small ruminants and cattle between Konya, Aksaray, Afyonkarahisar and Isparta Provinces. It is therefore possible that same strain of ORFV was actively circulating during the 2016 and 2017 in the investigated regions and it was responsible for outbreaks.

Association between exposures to ORFV and skin disease in cattle is a rather rare event, with few reports [35,36]. Thus the present study reports unusual infection in cattle with ORFV. The gross lesions observed in the present study are similar to other descriptions of parapoxvirus infections in cattle (Fig. 1) [17,18,36]. In the present study, proliferative lesions were observed only on the back and legs of infected cattle, whereas skin lesions on the lips, oral mucosa, muzzles and nostrils are mostly seen in ORFV infected sheep and goats [7,16]. Although ORFV infection is most severe in young lambs, kids and immunodeficient animals [6,7], it was not seen in any cattle with severe disease. Possible explanations for this discrepancy may be the strain of virus and immune status of infected animals.

The morbidity of the ORFV infection in small ruminants can reach up to %100, although mortality rate is usually low (%1–%10), but it may reach up to 90% in lambs and kids due to secondary bacterial or fungal infections, environmental and host factors [6,37]. In the present outbreaks, overall morbidity rate was 15.5% but there was no mortality, and the morbidity rate was higher in cows (23.7%) than in calves and heifers (Table 1). This finding is in agreement with previous study that reported higher morbidity (93.2%) in cows co-infected with vaccinia virus and ORFV in Midwestern Brazil [36]. The observed higher morbidity rate in cows in this study can be explained by stress. It has been reported that cows under stress are more prone to infections [38].

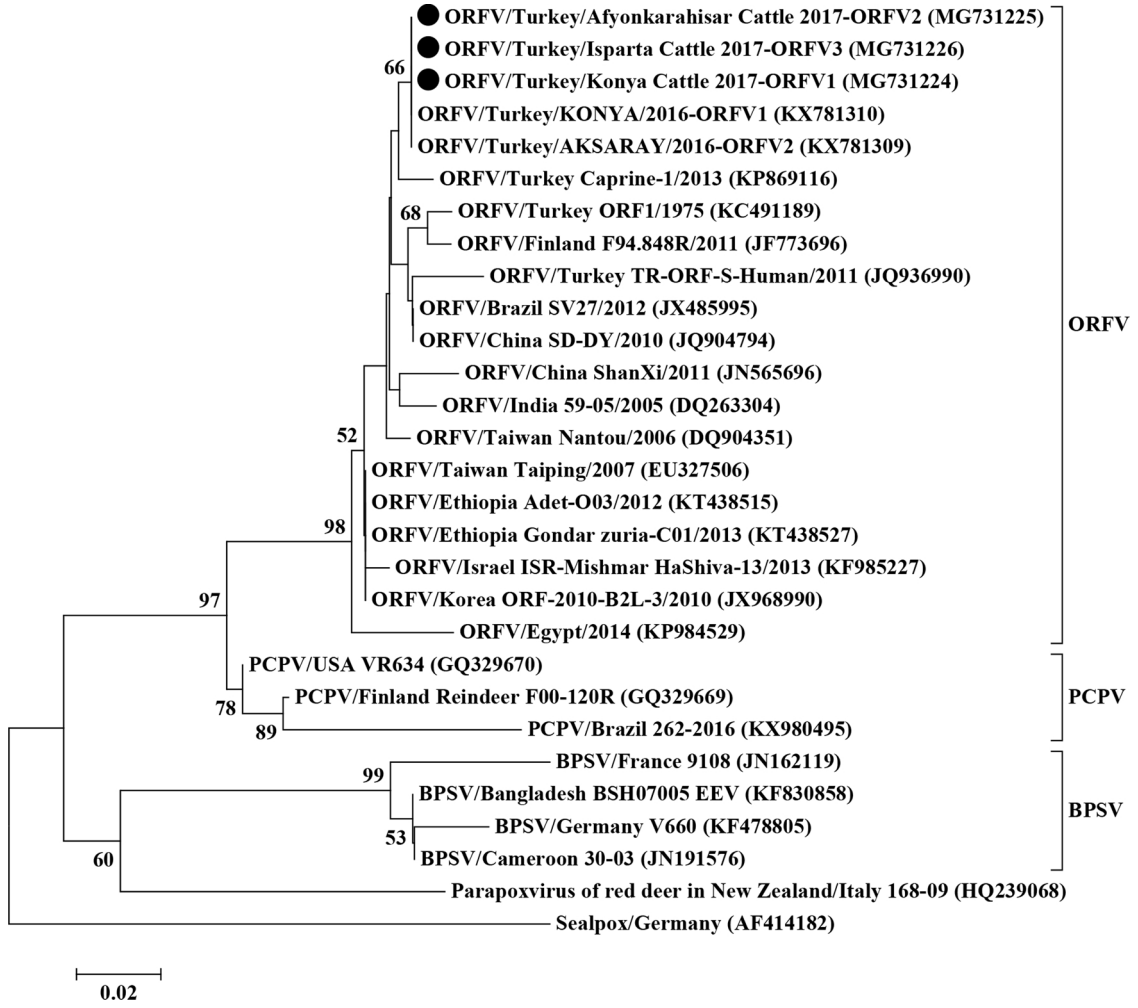

Fig. 2. Phylogenetic tree constructed based on nucleotide sequences of B2L gene showing the genetic relationships between parapoxvirus isolates. The sequences obtained in this study are marked with round black spot (●).

In the infected herds, farming practices to produce high milk yields could produce a stress response that makes cows susceptible to infections. Contaminated equipment and direct contact with each other may also have contributed to spreading the disease among cows. In addition, the morbidity rate was lower in this study than de Sant'Ana FJ et al.'s study. The observed lower morbidity rate in the cows can be explained by number of sampled animals and differences in herd management.

In this study, ORFV infection was not observed in calves and humans. Calves were kept away from other animals in separate pens in investigated herds, and there was no contact between calves and other animals. ORFV infection in humans occurs when the virus enters the body through broken skin [37]. Owners of the sampled herds reported that they wore gloves during milking and washed their hands after handling animals. These could explain why infection was not observed in calves and humans.

ORFV infection is generally seen during spring and summer [39]. In the present study outbreaks were recorded in summer season. Small ruminants and cattle use the pastures during this period, and contact between small ruminants and cattle is possible. The disease is transmitted through direct contact with an infected animal or indirect contact with contaminated environment [40]. After infection, some sheep and goats may also become carriers without clinical signs and serve as a source of infection [41]. Furthermore, ORFV is a hardy virus and can survive on the ground and farm material for months to years [42]. ORFV is endemic in sheep and goats in Turkey, and orf outbreaks in sheep and goats were reported in different regions of the study area during 2016 and 2017 [16,43]. It is therefore possible that ORFV transmitted among cattle by direct contact with infected sheep or goats whilst at pasture or indirectly from contaminated pastures.

In conclusion, results of the study indicate that the parapoxvirus that has caused skin disease in cattle belongs to the ORFV species. The origin of the outbreaks reported herein was unclear. One possibility was transmission from infected goat or sheep. Another possible explanation is the existence of subclinical parapoxvirus infection in cattle. It has been reported that parapoxviruses can cause persistent infections without clinical signs in cattle, and that the infection can be activated by stress and immunosuppressive factors [44]. Clinical outbreaks may be triggered by stress factors such as bad nutritional status and transport of animals. Further studies are needed to determine the exact mode of transmission of ORFV to cattle and possible zoonotic transmission.

Conflict of interest

The author declares that there are no conflicts of interest.

Acknowledgements

The part of the study was presented as an oral presentation in the 4rd International Symposium on EuroAsian Biodiversity in Kiev, Ukraine, July 3–6, 2018.

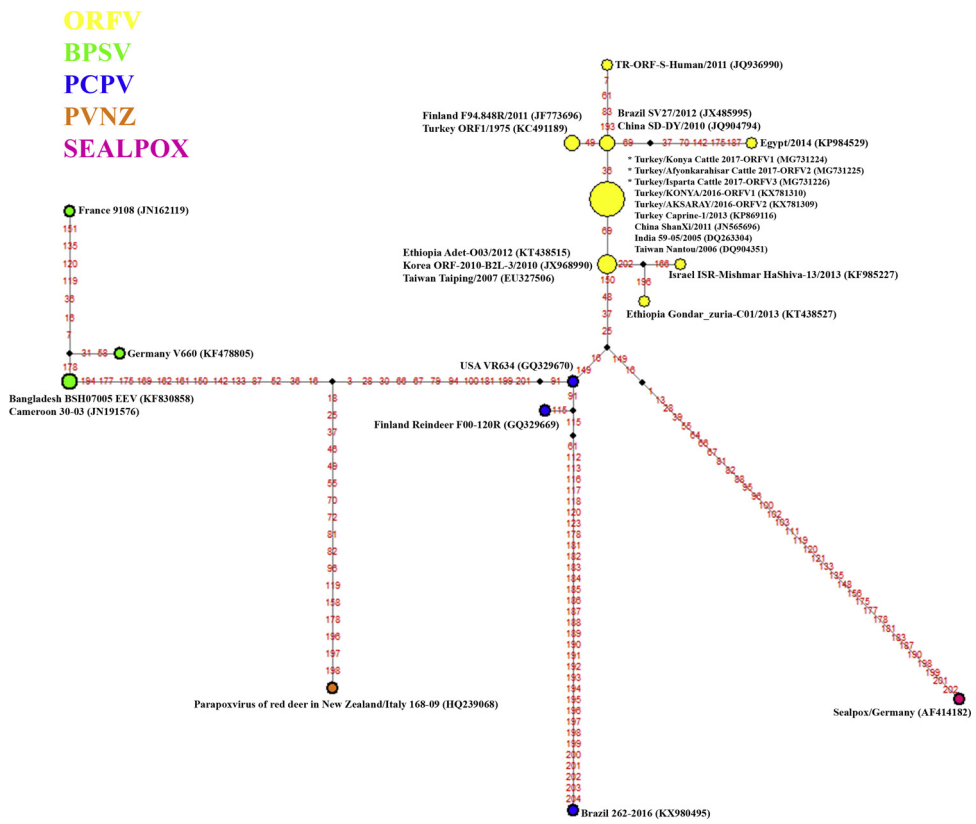

Fig. 3. Phylogenetic network analysis based on the B2L gene of the parapoxviruses. Numbers along the branches represent the nucleotide changes separating the nodes.

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