A comparative phylogenomic analysis of peste des petits ruminants virus isolated from wild and unusual hosts

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Running title: Comparative phylogenomic analysis of peste des petits ruminants virus

Abstract

Peste des petits ruminants virus (PPRV) infects a wide range of domestic and wild ruminants, and occasionally unusual hosts such as camel, cattle and pig. Given their broad host-spectrum and disease endemicity in several developing countries, it is imperative to elucidate the viral evolutionary insights for their dynamic pathobiology and differential host-selection. For this purpose, a dataset of all available (n=37) PPRV sequences originating from wild and unusual hosts was composed and *in silico* analysed. Compared to domestic small ruminant strains of same geographical region, phylogenomic and residue analysis of PPRV sequences originating from wild and unusual hosts revealed a close relationship between strains. A lack of obvious difference among the studied sequences and deduced residues suggests that these are the host factors that may play a role in their susceptibility to PPRV infection, immune response, pathogenesis, excretion patterns and potential clinical signs or resistance to clinical disease. Summarizing together, the comparative analysis enhances our understanding towards molecular epidemiology of the PPRV in wild and unusual hosts for appropriate intervention strategies particularly at livestock-wildlife interface.

Key words: Peste des petits ruminants virus; wild and unusual hosts; molecular epidemiology; residue comparison; phylogenomic analysis

Introduction

Peste des petits ruminants (PPR) caused by peste des petits ruminants virus (PPRV) [1], is an OIE enlisted notifiable disease of domestic and wild ruminants that can spread across international borders [2]. Belong to genus *Morbillivirus* within the family *Paramyxoviridae*, PPRV also has potential to infect a wide range of susceptible host as is the characteristic of other morbillliviruses especially canine distemper virus (CDV) and rinderpest virus (RPV). Both viruses can potentially infect a wide range of susceptible hosts including wildlife, large ruminants, rodents and monkeys [3, 4]. Since, PPRV is closely related to CDV and RPV, and PPRV infection evidences have been reported in small ruminants, large ruminants, camel, wildlife species and pig [5, 6]. The potential of pig to act as virus amplifier and to shed virus in the environment indicates their role in the disease spread to small ruminants and other susceptible hosts [6].

The virus carries a negative sense, single stranded RNA genome of approximately 16 kb encoding six structural proteins; nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H) and polymerase (L) in an order of 3′-N-P-M-F-H-L-5′ [7]. The N protein is involved in ribonucleoprotein complex (RNP) formation for RNA encapsidation during viral transcription, replication and assembly. Together with P and L, N protein acts as a polymerase co-factor, which governs the virus replication [8]. Various domains and motifs in the N protein reduce the replication fitness of virus and thus carry potential to generate attenuated vaccine candidates from virulent field strains. Together with extensive use of N genes (due to transcriptional potential) and protein (due to transcription-gradient translation) in the detection of viruses using qualitative reverse-transcriptase polymerase chain reaction (qRT-PCRs) and enzyme linked immunosorbent assay (ELISA), respectively, greater and comparative assessments of the N protein are imperative. On the other hands, the H glycoprotein plays a prime role in tissue tropism by binding to two cellular receptors known

as poliovirus receptor-like 4 (Nectin-4) and signalling lymphocyte activation molecule (SLAM) [9, 10]. The SLAM receptors (also known as CD150 molecules) are immunoglobulin (Ig) superfamily glycoproteins and are expressed on the surface of many immune cells including primary B cells, virus-transformed B cells (B95a), T cells (activated, memory and clonal), and immature thymocytes [11]. The localization of these receptors determines host adaptation and correlates with virus-induced pathologies [9]. The H glycoprotein recognizes and uses overlapping regions to bind to these cellular receptors (SLAM and Nectin-4), which elicits conformational changes in the attachment protein to reveal a trigger sequence in its stem region that interact with the globular head of the fusion protein [12]. Taken together, these receptors are likely a major hurdle for morbilliviruses to cross the species-barrier and eventually require mutations in the receptor-binding regions of the H protein for host adaptation [12]. While extensive information has been made available on the H proteins, cellular factors that govern viral interactions with receptors in host-dependent manners are lacking. Understanding of these factors may highlight the virus jumps between hosts, and can explain the potential preference of the virus for specific hosts.

PPR is considered endemic in the Middle East, Africa and Asia. Four distinct lineages (I, II, III and IV) have been reported on the basis of partial *N* gene sequence with distinct geographical patterns [13]. Utilizing complete genome or partial gene sequencing (e.g. *N* gene), comparative molecular epidemiology and genetic variability of PPRVs in domestic small ruminants have widely been assessed in disease-endemic regions [14, 15]. Nevertheless, there is paucity on the phylogenetic relationship of PPRVs originating from wildlife and unusual hosts. Therefore, the current study was designed to explore genetic markers that allow an interpretation whether certain PPRV strains are more likely to be transmitted or disseminated from domestic to wild/unusual hosts or vice versa. Cumulative

outcome may facilitate the devising of appropriate intervention strategies particularly at livestock-wildlife interface for effective disease control in disease-endemic countries.

Materials and Methods

There is a paucity of genome sequence data for PPRV reported from wild and unusual hosts in public databases (http://www.ncbi.nlm.nih.gov/, accessed by June 2019). The available data is limited to five complete genome sequence and two complete and 30 partial nucleoprotein (*N*) gene sequences originating from various wild and unusual hosts. Therefore, selective data (n = 102) including *N* partial gene sequences of PPRVs from unusual and wild hosts origin (n = 37) and domestic small ruminants origin (n = 65) representing different lineages were used in this study. The sequences were aligned using ClustalW method in BioEdit® version 5.0.6 [16] and edited to equal length. To assess the phylogeny patterns, a tree was constructed using distance-based neighbour-joining model in MEGA® version 6.0 where reliability in topology of tree was assured with bootstrap replications (1,000) and *p*-distance substitution model [17]. The deduced amino acid sequences of complete *N*, *H* and *F* genes from wild and unusual hosts (n = 6)-origin PPRV were also compared with a strain originating from domestic small ruminants to determine substitution rations across the length of gene. To better elucidate a presumptive role of substitutions in host adaptation in wildlife or unusual hosts, sequences that were reported from domestic small ruminants during the same time period and geographical area were used in the analysis.

Results and discussion

Besides several important biological activities such as attachment, replication and induction of protective immune response in the host [13, 18, 19], the partial *N, F* and *H* genes sequences have been employed in a number of studies to determine the phylogeny and evolutionary relationship among circulating isolates worldwide [15, 18, 19]. Nonetheless, we

used only partial *N* gene sequences due to the fact that i) complete gene sequences for *N*, *F* and *H* genes were limited to a total of five isolates only and, when compared with corresponding genes originating from domestic small ruminants, their evolutionary relationship and deduced residue pattern was much alike, ii) a higher number of partial *N* gene sequences originating from diverse species are available in public database, and iii) the sequence and residue characteristics provide a distinctive resolution for PPRV epidemiology in disease endemic countries [13, 15].

Phylogenetic analysis clustered wild and unusual hosts-origin PPRV strains into five distinct clades. However, direct comparison of these PPRV with strains from small ruminants suggested their common origin. Clade-I included the camel-originated (Sudan origin) and wild-alpine goat-originated (Morocco origin) viruses that clustered close to domestic small ruminant-origin strains reported from Sudan and Morocco. Clade-II included cattle-, dog- and Asiatic lion- originated (India origin) PPRV strains that clustered together with small ruminant's originated viruses from India. Clade-III comprised of wild goat-originated (Iraq origin), Ibex-originated (Israel origin) and biting midges-originated (Turkey origin) strains that clustered with domestic small ruminants-originated PPRV strains isolated in Iran, Iraq and Turkey. Sequences from camel (Pakistan) and bharal (China) origin were included in clade-IV and clustered with small ruminants-originated strains isolated in Tibet, China and Pakistan. Likewise, PPRV isolates from ibex (UAE and China), antelope (India), wild goat (Iran) and camel (Pakistan) origin made together clade-V and clustered with domestic small ruminant-originated strains isolated in China, Iraq and Pakistan (Fig. 1).

The phylogenetic analysis revealed a close relationship between strains recovered from domestic and wild/unusual hosts of the same geographical region. For instance, camel-originated strains from Pakistan clustered close enough to those of domestic origin PPR viruses reported previously from Pakistan, Tibet and China. In disease endemic countries, the

125 virus can easily transmit from one animal to another due to sharing a common source of
126 water, food and vicinity or frequent contact particularly in areas where there are lack of well-
127 definite borders. Thus, it is not surprising that there is a close relationship between viruses
128 isolated from different host species in the same geographical area, likely reflecting a spill-
129 over from domestic animals to wildlife [20-22]. A few of such evidences include disease
130 outbreaks in Saudi Arabia [20], gazelle in UAE [21], ibex in Pakistan [22], bharal in Tibet
131 [23], and water-deer in China [24]. Additionally, due to extensive animal movements such as
132 in the Himalayas and Pamir region between Pakistan, Nepal, China, Afghanistan and
133 Tajikistan, potential inter-species transmission with a closely related virus is not unusual [25].
134 Also, there are few studies where sero-conversion in wild and unusual host while living in
135 close vicinity with domestic small ruminants has been reported [26, 27]. Although, the
136 frequent contact between domestic and non-domestic animals may play a crucial role in the
137 spread of virus, factors involved in the epidemiology of the PPRV at livestock-wildlife
138 interface is largely unknown.
139 In contrast to identification of PPRVs of all lineages (I-IV) in domestic small ruminants in
140 disease-endemic countries, viruses of only lineages II, III and IV have been reported to-date
141 from wild or unusual host and camels [Table 1; 28]. Usually, the lineage IV viruses were
142 predominantly found affecting a wide range of wild and unusual hosts in disease-endemic
143 countries. While the factors that predispose wildlife to lineage IV are not well defined, the
144 wider distribution of lineage IV and its potential to cause pathologies in small ruminants are
145 potential survival factors. Primarily, the lineage IV is the most dominant group of PPRV in
146 disease-endemic countries [22-25] and this dominance further supports its distribution in
147 susceptible hosts including wild and unusual animal species.
148 We have also conducted a comparative residue analysis of available complete *N*, *F* and *H*
149 gene of PPRV originating from wild and unusual hosts and domestic small ruminants because

residue substitutions in specific protein or a site leads to genetic variations either due to natural selection or adaptation to a novel host [29]. The deduced residues for *H* gene (1-610 aa), particularly the N-terminal proximal anchor (^{35}PYILLGVLLVMFLSLIGLLAIAG^{58}) and SLAM binding site (^{529}Y, ^{530}D, ^{533}R, ^{552}F, ^{553}Y, ^{554}P) were observed in a pattern similar to those of domestic small ruminants [14]. Although, SLAM receptors have significance for host adaptation however, the conserveness of its binding motif in *H* gene sequences obtained from PPRV-infected domestic and wildlife species indicated a lack of specific mutations that could be associated with the susceptibility of infection to a particular species, conclusively [30]. An influence on host adaptability and pathogenicity has previously been speculated upon the mutations/substitutions in *H* gene [19], the gained outcome should be cautiously interpreted because of limitation of sequences (n=6) available in the database. Interestingly, both the conservancy of SLAM binding motif and phylogenetic relationship of studied PPRVs strains to those of their respective host species (sheep and goats) anticipated that all these strains most likely evolved from a common ancestral virus indicating its intrinsic capacity to adapt novel host species [31].

The deduced residues across the whole length of *F* gene (1–547 aa) particularly the signal peptide (^{1}MTRVAILAFLFLFLNAVAC^{19}), the cleavage site (^{103}RRTRR^{108}), the fusion peptide (^{109}FAGAVLAGVALGVATAAQITAGVAL^{133}), and the leucine zipper domain (^{459}LGNAVTRLENAKELLDASDASDQIL^{480}) were found conserved. On the other hand, the nuclear export signal (^{4}LLKSLALF^{11}), nuclear localization signal (^{70}TGVMISML^{77}) and RNA binding motif (^{324}FSAGAYPLLWSYAMG^{338}) were conserved for *N* gene (1-526 aa). However, several substitutions were observed in the C-terminal regions of *N* gene and, therefore, could be considered as a hypervariable region without having any significant role in host adaptation reported so-far [14]. Substitutions at position 444(T/S→P/S), 446(P→Q), 464(S→G/I), 505(L/F→P/F/S), 510(S→P), 516(S→P) and 517(K→E) were consistent for

wild and unusual host than those reported for domestic small ruminants (Table 1). Although, the C-terminus of N protein is considered an important region for viral replication and substitutions in this region may have influence in the enhancement of persistency of virus infection for a long period [8], however, such substitutions have not influenced host adaptation. Based on the genomic similarities between PPRV sequences from small ruminant, camel and unusual host origin, the current study suggested that PPRV is promiscuous between host species without genomic alterations that may otherwise be required for adaptation to novel host/s. Though genomic and residue substitutions may have an influence on the evolution and adaptation of other morbilliviruses to novel hosts [31], however, it was not observed for PPRV in the current study.

Conclusion

The study provides an understanding towards the phylogenomics and evolutionary relationships among PPRV strains originating from domestic and wild/unusual hosts. Comparative genomic and residue analysis revealed a close relationship between study PPRV strains reported from the same geographical region. Since study data was limited to few of publically available sequences so far, there needs an abundant sequence dataset representing wild and unusual hosts to better elucidate underlying mechanisms on viral evolution in future. Most importantly, besides comparative sequence analysis, emphasis should be given to a range of host factors that may predispose adaptability and subsequent susceptibility of novel host to PPRV infection.

Author's contribution

AR, MZS apprehended the idea: AR, MM, MZS conceived and designed the work; AR, MZS did data analysis; AR, MM, MZS edited final draft.

Acknowledgment

None

Compliance with ethical standards

Conflict of interest: None

Ethical approval: This article does not contain studies with animals or humans performed.

Informed consent: No human or animals were involved.

Figure captions

Fig. 1 Phylogenetic analysis of 102 partial *N* gene nucleotide sequences (255bp) reported for PPRV. Black circle indicates the isolates reported from wild and unusual animals. Green colour of branches and isolates name indicate lineage IV while, blue indicates lineage II, Fuchsia indicates lineage I, and red indicates lineage III.

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Table 1 Comparative residue analysis of partial *N* genes of PPRV isolated from various wild and unusual hosts (available until June, 2019).

Lineage	Country	Host	Source of isolation	Year of isolation	Accession number	Residue positions at C-terminus						
						444	446	464	505	510	516	517
IV	India	Goat	Tissue	2008	GQ122189ǂ	**T**	**P**	**S**	**L**	**S**	**S**	**K**
		Chousingha	Tissue	2013	KY914553ǂ	**-**	**-**	**-**	**-**	**-**	**-**	**-**
		Cattle	Nasal swab	2007	EF641263	**P**	**Q**	**G**	**P**	**P**	**P**	**E**
		Dog	Nasal swab	2015	KT120060	**P**	**Q**	**G**	**P**	**P**	**P**	**E**
		Asiatic lion	Tissue	2007	JN632530	**P**	**Q**	**G**	**P**	**P**	**P**	**E**
		Asiatic lion	Tissue	2007	JN632532*	**P**	**Q**	**G**	**P**	**P**	**P**	**E**
	Pakistan	Goat	Nasal swab	2012	KJ398330ǂ	**T**	**P**	S	**L**	S	S	K
		Camel	Blood	2012	KC207882	**S**	**Q**	-	**F**	-	-	-
		Camel	Blood	2012	KC207883	**S**	**Q**	-	**F**	-	-	-
		Camel	Blood	2012	KC207884	**S**	**Q**	-	**F**	-	-	-
		Camel	Blood	2012	KC207885	**S**	**Q**	-	**F**	-	-	-
	China	Goat	Nasal swab	2014	MF443354ǂ	**T**	P	**S**	**L**	S	S	K
		Siberian ibex	Tissue	2014	KX664096ǂ	**S**	**-**	**-**	**-**	-	-	-
		Siberian ibex	Nasal-anal swab	2014	KX664098ǂ	**S**	**-**	**-**	**-**	-	-	-
		Siberian ibex	Tissue	2016	KX664100ǂ	**S**	**-**	**-**	**-**	-	-	-
		Goitered gazelle	Nasal-anal swab	2016	KX664097ǂ	**S**	**-**	**-**	**-**	-	-	-
		Argali	Tissue	2015	KX664099ǂ	**P**	**-**	**-**	**F**	-	-	-
		Ibex	Tissue	2015	KT633939**ǂ	**S**	-	-	**-**	-	-	-
		Wild bharal	Tissue	2008	JX217850**ǂ	**P**	-	-	**F**	-	-	-
		Wild bharal	Tissue	2008	EU815054ǂ	**P**	-	-	**F**	-	-	-
	Sudan	Sheep	Tissue	2008	HQ131931ǂ	P	**P**	S	L	S	S	K
		Camel	Tissue	2005	HQ131934	-	**Q**	-	-	-	-	-
		Camel	Tissue	2004	HQ131935	-	**Q**	-	-	-	-	-
		Camel	Tissue	2007	HQ131936	-	**Q**	-	-	-	-	-
		Camel	Tissue	2006	HQ131937	-	**Q**	-	-	-	-	-
		Camel	Tissue	2006	HQ131938	-	**Q**	-	-	-	-	-
		Camel	Tissue	2005	HQ131939	-	**Q**	-	-	-	-	-
		Camel	Tissue	2007	HQ131940	-	**Q**	-	-	-	-	-
		Camel	Tissue	2007	HQ131941	-	**Q**	-	-	-	-	-
		Camel	Tissue	2008	HQ131942	-	**Q**	-	-	-	-	-
		Camel	Tissue	2004	HQ131947	-	**Q**	-	-	-	-	-
		Camel	Tissue	2005	HQ131948	-	**Q**	-	-	-	-	-
	Iraq	Sheep	Nasal swab	2013	KF992797ǂ	**S**	**P**	S	L	S	S	K
		Wild goat	Nasal swab	2011	JF969755ǂ	**P**	**Q**	-	-	-	-	-
	Morocco	Goat	Not available	2015	KY885100	P	Q	S	**F**	S	S	K
		Alpine goat	Nasal swab	2008	KC594074**ǂ	-	-	-	**S**	-	-	-
	UAE	Sheep	Nasal swab	2013	KF992797ǂ	S	P	**S**	L	S	S	K
		Ibex	Tissue	2009	FJ795511ǂ	-	-	**I**	-	-	-	-
	Israel	Goat	Nasal swab	2016	DQ840191ǂ	**T**	P	**S**	L	S	S	K
		Nubian ibex	Tissue	2017	MF678816**ǂ	**P**	-	**-**	-	-	-	-
	Turkey	Lamb	Nasal swab	2016	MG744248	S	P	S	L	S	S	K
		Biting midges	Tissue	2015	KU325483	-	-	-	-	-	-	-
		Biting midges	Tissue	2015	KU175171	-	-	-	-	-	-	-
III	UAE	Goat	Nasal swab	1986	DQ840169ǂ	P	P	S	P	T	S	T
		Gazelle	Tissue	1986	KJ867545**ǂ	-	-	-	-	-	-	-
II	China	Vaccine strain	Not available	1975	X74443	P	P	S	L	S	S	K
		Water deer	Tissue	2016	KY196465*ǂ	-	-	-	-	-	-	-

Note: The domestic small ruminants originating PPRV isolates used for comparison were selected according the highest similarity to PPRV strains originating form wild/unusual hosts representing same geographical region and year of isolation. Random substitutions in individual isolate were also observed. Substitutions are bold in grey highlighted boxes. Identical residue denoted by "– ". ǂ = Isolation of virus from swabs and tissues samples from animal representing clinical infection, whereas except are the sequences of strain from apparently healthy animals.**Abbreviations:** T: Threonine, P: Proline, S: Serine, L: Leucine, K: Lysine, Q: Glutamine, F: Phenylalanine, P: Proline, E: Glutamic acid, I: Isoleucine, G: Glycine
**Complete genome sequence is available; *Complete *N* gene sequence is available