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Communication

Indels and Host-Derived Sequences in Rat Hepatitis E Virus Genomes

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Abstract: Rat hepatitis E virus genotype 1 (rHEV) is an emerging zoonotic pathogen found globally in commensal rodents and is a significant cause of hepatitis, especially in immunocompromised populations. We systematically analyzed 99 rHEV genomes and identified multiple insertions and deletions predominantly within the macro X domain of *ORF1*, including a recurrent deletion of a 7−39 amino acid region in a large cluster of subtype II.b. Significant homology to human gene fragments was detected in 14% of genomes, including sequences related to transcription factors and phosphatases. This marks the first evidence of host genome-derived gene insertions in rHEV, expanding the understanding of rHEV genome plasticity, and highlights the need for further functional studies to elucidate the role of these variants in viral pathogenesis and zoonotic adaptation.

Keywords: hepatitis E; zoonoses; evolution; recombination

1. Introduction

Rat hepatitis E virus genotype 1 (rHEV) is an emerging zoonotic pathogen primarily found in commensal street rodents worldwide [1,2]. It is a member of the Hepeviridae family alongside the clinically significant *Paslahepevirus balayani* species. rHEV is antigenically highly divergent to *P. balayani* genotypes, and was initially considered as a rodent-restricted virus, but has increasingly been identified as a cause of hepatitis E infection in humans, particularly in immunocompromised individuals [3].

HEV, like other RNA viruses, exhibits high genomic variability, with studies estimating its evolutionary rate to be approximately 1.3×10^{-3} substitutions/site/year [4]. During infection, this results in the consistent production of quasispecies. While this variation is mainly driven by point mutations—insertion, deletion, and recombination events have been reported in *P. balayani* genotype 3, which contribute to the virus's evolution [5–7]. Notable genetic adaptations include insertions derived from host genes within the viral genome's polyproline region (PPR), which have been linked to enhanced replication capacity and expanded host range. While extensive evidence documents insertions and duplications within the PPR of *P. balayani* genotype 3 genomes, such rearrangements have yet to be reported in rHEV. Given the rising recognition of rHEV as a zoonotic threat and the growing number of human infections, understanding its genomic diversity and mechanisms of adaptation is crucial for assessing viral evolution, host range expansion, and potential impacts on disease severity and transmission. This study aims to address this knowledge gap by systematically analyzing near-complete rHEV genomes to characterize insertion and deletion events and identify sequences of potential host origin.

2. Methods

A BLASTn search of the core nucleotide database (core_nt) was performed to identify (near-)complete rHEV genomes (≥95% coverage to GU345042.1) [8]. Genomes were split into open reading frame (ORF) sequences based on GU345042.1's start and stop codons, and aligned using MACSE [9] to produce a frameshift-aware amino acid multiple sequence alignment. Alignments were visualized using Jalview [10] and genomes containing insertions or deletions (indels) with respect to GU345042.1 were manually identified. rHEV ORFs were also compared to the human and rat genomes (hg38 and RGSC 6.0/rn6) using the Blast-Like Alignment Tool (BLAT) [11], with a BLAT score threshold of 20.

Whole genome multiple sequence alignment was performed with MAFFT's E-INS-i algorithm [12], and a maximum likelihood phylogeny was inferred with IQ-TREE [13] using the GTR+F+I+R4 nucleotide substitution model. The resulting phylogeny was visualized with TreeViewer [14]. Multiple sequence alignments were visualized with ImageGP 2 [15].

3. Results

Using the BLASTn algorithm, we retrieved 99 near-complete rHEV genomes (≥95% coverage to GU345042.1). They were then split into ORF sequences and aligned using MACSE, a codon and frameshift-aware alignment tool. Within *ORF1*, all identified indels were located within the macro X domain (829−866 aa of GU345042.1) (Tables 1 and 2). In total, 15 insertions in 15 genomes were manually identified in *ORF1* (Figure 1). The longest insertion was a 9 aa sequence (RHMPGPLAE) identified in LC573546.1 (843−851 aa) (Figure 1A and Table 1). This sequence may be derived from the human immunoglobulin heavy chain junction region (MBN4537926), but it is difficult to confidently predict the origin of such a short sequence (BLAST E value = 0.2). Two other insertions were each only found in one rHEV genome, a 6-aa insertion in OP947211.1 (LSDVGL; 863-868 aa) and a 5-aa insertion in PP533468.1 (LSPRG; 868−872 aa). At 863 aa of GU345042.1, two genomes (LC549186.1 and LC549187.1) had a 6-aa insertion (VAGSDG), and five genomes (LC573546.1, LC549184.1, PQ537341.1, PQ537343.1, and PQ537342.1) contained a 5-aa insertion (consensus of AGTSG). At 864 aa of GU345042.1, 5 genomes (PP533467.1, PP533469.1, PP533470.1, PP533465.1, and PP533466.1) had a 5-aa insertion (consensus of DSHPE) (Figure 1B). A 7-10 aa deletion was identified in 33 genomes between amino acids 844−854 of GU345042.1 (Figure 1C and Table 2). Four of these genomes—ON644869.1, ON887282.1, ON887283.1, and PX667109.1—had extended deletions in this region ranging from 23−39 aa in length. The majority of the genomes containing this deletion are phylogenetically related, with 28 genomes forming a cluster within subtype II.b, whilst four genomes belong to subtype I.d, and one genome is located in subtype I.a. In *ORF2*, only one insertion was identified, a 13-aa sequence in PX667111.1 at 352−364 aa (EQDVHLAGNNGVG) (Figure 2A). This sequence is a duplication of the 13-aa directly upstream, except the first aa, methionine, has been replaced with a glutamate. A 29-aa deletion was also identified in MH729810.1 (455−483 aa of GU345043.1) (Figure 2C). No indels were identified in *ORF3*.

To directly compare the rHEV genomes to the human and rat genomes, we employed BLAT, an alignment tool that can align short sequences with both mismatch and gap tolerance. In total, 14 rHEV genomes (13.9%) had significant alignment to human genes, whilst no matches to rat-derived genes were identified (Table 3). Each rHEV genome only contained a single human gene hit, although the same human genes were often identified in multiple rHEV genomes. For example, a 75-nt section of the *KMT2C* gene was identified in the PPR of five rHEV genomes, all of which are rodent-derived strains in subtype II.b (Figure 3). However, these five genomes do not phylogenetically cluster together within their subtype. Other conserved gene sequences include a 78-nt section of *EGLN3* in *ORF3* (2 rHEV genomes) and a 75-nt novel transcript sequence in the macro X domain (3 rHEV genomes), which were only found in subtype II.b human-derived genomes from Hong Kong. Human gene fragments were also identified in the macro X domain of rodent-derived rHEV genomes belonging to subtype I.a (*BCL11A, KLHL30*, and *PPM1F*) and II.f (*PLEC*).

Table 1. Inserted sequences identified in rat hepatitis E virus genomes compared to the reference genome GU345042.1.

Accession	rHEV Subtype	Country	Host	Reference Amino Acid Region	Inserted Sequence
LC549184.1	II.b	Mainland China	*Rattus norvegicus*	863	PRGLS
LC549186.1	I.d	Japan	*Sucus murinus*	863	VAGSDG
LC549187.1	I.d	Mainland China	*Homo sapiens*	863	VAGSDG
LC573546.1	II.b	Japan	*Rattus rattus*	840	RHMPGPLAE
LC573546.1	II.b	Japan	*Rattus rattus*	863	IGGGH
OP947211.1	II.b	Mainland China	*Rattus norvegicus*	862	LSDVGL
PP533465.1	II.b	Mainland China	*Rattus norvegicus*	864	DSHPE
PP533466.1	II.b	Mainland China	*Rattus norvegicus*	864	DSHPE
PP533467.1	II.b	Mainland China	*Rattus norvegicus*	864	GSHPE
PP533468.1	II.b	Mainland China	*Rattus norvegicus*	865	LSPRG
PP533469.1	II.b	Mainland China	*Rattus norvegicus*	864	DSHPE
PP533470.1	II.b	Mainland China	*Rattus norvegicus*	864	DSHPE
PQ537341.1	I.a	Spain	*Rattus norvegicus*	863	AGTSG
PQ537342.1	I.a	Spain	*Rattus norvegicus*	863	AGTSG
PQ537343.1	I.a	Spain	*Rattus norvegicus*	863	AGTSG

Table 2. Deleted sequences identified in rat hepatitis E virus genomes compared to the reference genome GU345042.1.

Accession	rHEV Subtype	Country	Host	Deleted Reference Amino Acid Region	Deleted Reference Amino Acid Sequence
AB847307.1	II.b	Indonesia	*Rattus rattus*	845−852	PPPTTPAP
PX667111.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PX667109.1	II.b	Hong Kong, China	*Homo sapiens*	834−854; 858−874	AHQDGLPASPPPPPTTPAPSP; PPAGPSGGADEGSVPTS
JX120573.1	II.b	Vietnam	*Rattus tanezumi*	845−854	PPPTTPAPSP
LC549185.1	II.b	Mainland China	*Rattus losea*	845−852	PPPTTPAP
MG813927.1	II.b	Hong Kong, China	*Homo sapiens*	844−852	PPPPTTPAP
MN450851.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
MN450852.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
MN450854.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
MN450855.1	II.b	Hong Kong, China	*Rattus norvegicus*	845−851	PPPTTPA
MT210621.1	II.b	Mainland China	*Rattus norvegicus*	845−851	PPPTTPA
ON644869.1	I.a	Netherlands	*Rattus rattus*	838−861	GLPASPPPPPTTPAPSPPGPPPAG
ON887282.1	I.d	Mainland China	*Rattus tanezumi*	825−863	RSWRAQAGAAGQDGLPASPPPPPTTPAPSPPGPPPAGPS
ON887283.1	I.d	Mainland China	*Rattus tanezumi*	825−828; 833−836; 839−861; 866−873	RSWR; AAGQ; LPASPPPPPTTPAPSPPGPPPAG; ADEGSVPT
OP947210.1	II.b	Mainland China	*Rattus norvegicus*	845−852	PPPTTPAP
OQ715538.1	II.b	Mainland China	*Rattus losea*	845−854	PPPTTPAPSP
PP533449.1	I.d	Mainland China	*Rattus tanezumi*	845−852	PPPTTPAP
PP533452.1	II.b	Mainland China	*Rattus rattus*	845−852	PPPTTPAP
PP533454.1	II.b	Mainland China	*Bandicota bengalensis*	845−852	PPPTTPAP
PP533455.1	II.b	Mainland China	*Rattus tanezumi*	845−852	PPPTTPAP
PP533456.1	II.b	Mainland China	*Rattus tanezumi*	845−852	PPPTTPAP
PP533458.1	II.b	Mainland China	*Sucus murinus*	845−852	PPPTTPAP
PP533459.1	II.b	Mainland China	*Rattus tanezumi*	845−852	PPPTTPAP
PP533460.1	II.b	Mainland China	*Bandicota bengalensis*	845−852	PPPTTPAP
PP533461.1	I.d	Mainland China	*Rattus rattus*	845−851	PPPTTPA
PP533463.1	II.b	Mainland China	*Rattus tanezumi*	845−852	PPPTTPAP
PQ488551.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PQ488552.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PQ488553.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PQ488556.1	II.b	Hong Kong, China	*Homo sapiens*	845−851	PPPTTPA
PQ488557.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PQ488558.1	II.b	Hong Kong, China	*Homo sapiens*	845−852	PPPTTPAP
PQ488560.1	II.b	Hong Kong, China	*Rattus norvegicus*	845−852	PPPTTPAP

Table 3. Significant rat hepatitis E virus genome BLAT hits to human genome (Hg38).

Accession	rHEV subtype	Country	Host	BLAT Score	ORF	rHEV region (aa)	Identity (%)	Hg38 Chrom-osome	Hg38 Region	Hg38 Span (nt)	Hg38 gene hit
PQ541187.1	I.a	Sierra Leone	*Rattus rattus*	36	ORF1	845−856	100	chr2	60,553,837−60,553,872	36	BCL11 transcription factor A (BCL11A)
AB847308.1	I.a	Indonesia	*Rattus rattus*	24	ORF1	843−858	75	chr2	238,142,821−238,142,868	48	Kelch-like protein 30 (KLHL30)
LC145325.1	II.b	Indonesia	*Rattus rattus*	28	ORF1	590−614	96.7	chr7	152,262,135−152,262,209	75	Lysine methyltransferase 2C (KMT2C)
LC225388.1	II.b	Indonesia	*Rattus rattus*	28	ORF1	590−614	96.7	chr7	152,262,135−152,262,209	75	Lysine methyltransferase 2C (KMT2C)
MH729812.1	II.b	Mainland China	*Rattus losea*	28	ORF1	574−598	96.7	chr7	152,262,135−152,262,209	75	Lysine methyltransferase 2C (KMT2C)
PP533455.1	II.b	Mainland China	*Rattus tanezumi*	31	ORF1	590−614	97	chr7	152,262,135−152,262,209	75	Lysine methyltransferase 2C (KMT2C)
PP533456.1	II.b	Mainland China	*Rattus tanezumi*	28	ORF1	590−614	96.7	chr7	152,262,135−152,262,209	75	Lysine methyltransferase 2C (KMT2C)
PQ488553.1	II.b	Hong Kong, China	*Homo sapiens*	28	ORF1	830−854	88.9	chr5	608,282−608,356	75	Novel transcript
PQ488557.1	II.b	Hong Kong, China	*Homo sapiens*	28	ORF1	830−854	88.9	chr5	608,282−608,356	75	Novel transcript
PQ488558.1	II.b	Hong Kong, China	*Homo sapiens*	28	ORF1	830−854	88.9	chr5	608,282−608,356	75	Novel transcript
MG600417.1	II.f	Vietnam	*Rattus argentiventer*	30	ORF1	864−879	81.3	chr8	143,924,726−143,924,773	48	Plectin (PLEC)
OR500096.1	I.a	South Korea	*Rattus norvegicus*	25	ORF1	833−860	74.60%	chr22	21,938,247−21,938,330	84	Protein phosphatase 1F (PPM1F)
MG813927.1	II.b	Hong Kong, China	*Homo sapiens*	24	ORF3	44−69	65.40%	chr14	34,205,264−34,205,341	78	Egl-9 Family Hypoxia Inducible Factor 3 (EGLN3)
MN450851.1	II.b	Hong Kong, China	*Homo sapiens*	24	ORF3	44−69	65.40%	chr14	34,205,264−34,205,341	78	Egl-9 Family Hypoxia Inducible Factor 3 (EGLN3)

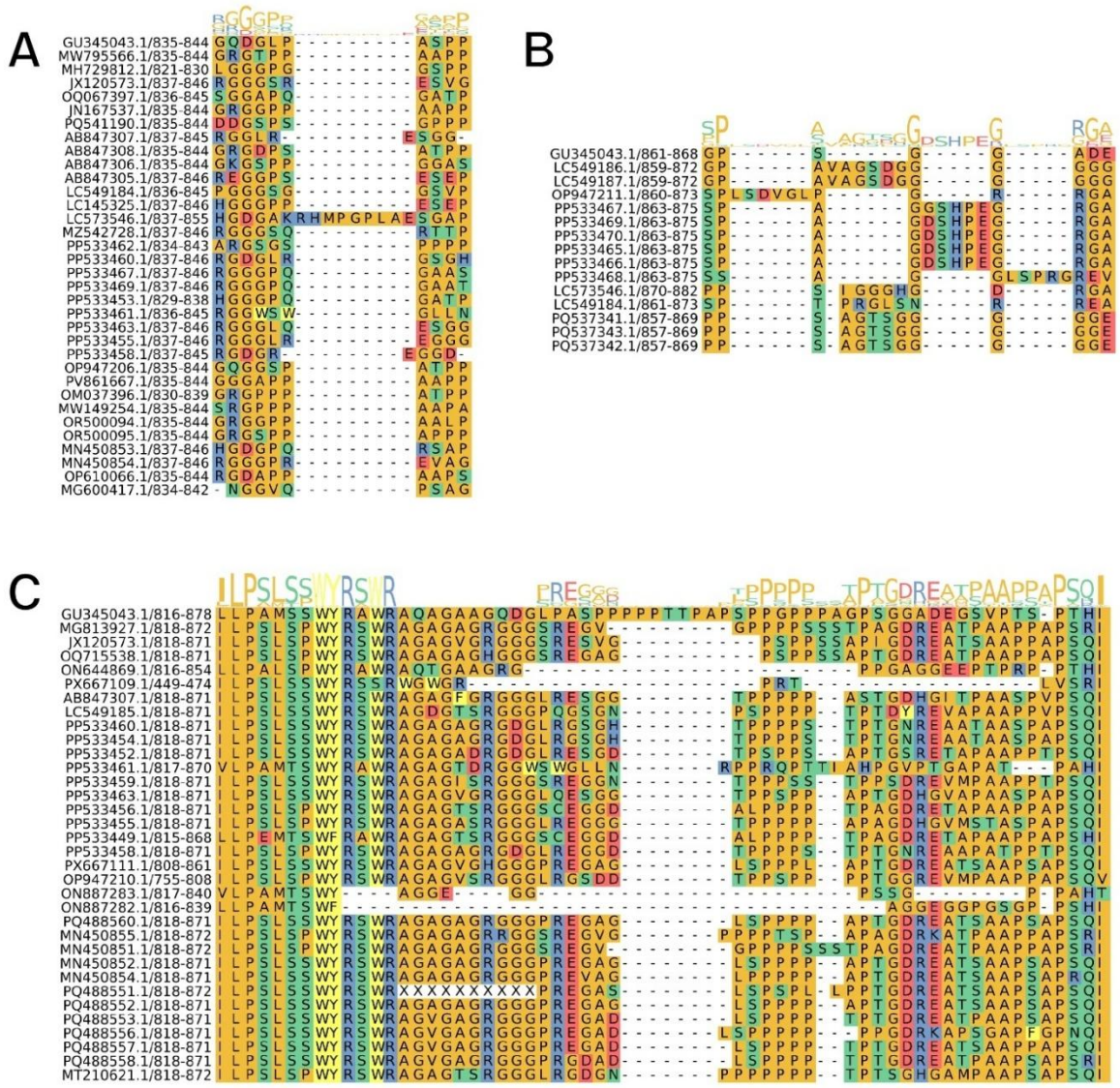

Figure 1. Insertion and deletion sequences identified in open reading frame 1. (**A**) A 9-amino acid sequence in LC573546.1 inserted at amino acid 840 with respect to GU345043.1. A random selection of other genomes was included for visualisation. (**B**) A series of insertions in multiple genomes in the region between amino acids 862−865 with respect to GU345043.1. (**C**) Deletions of 7−39 amino acids between the amino acids 844−854 with respect to GU3450423.1.

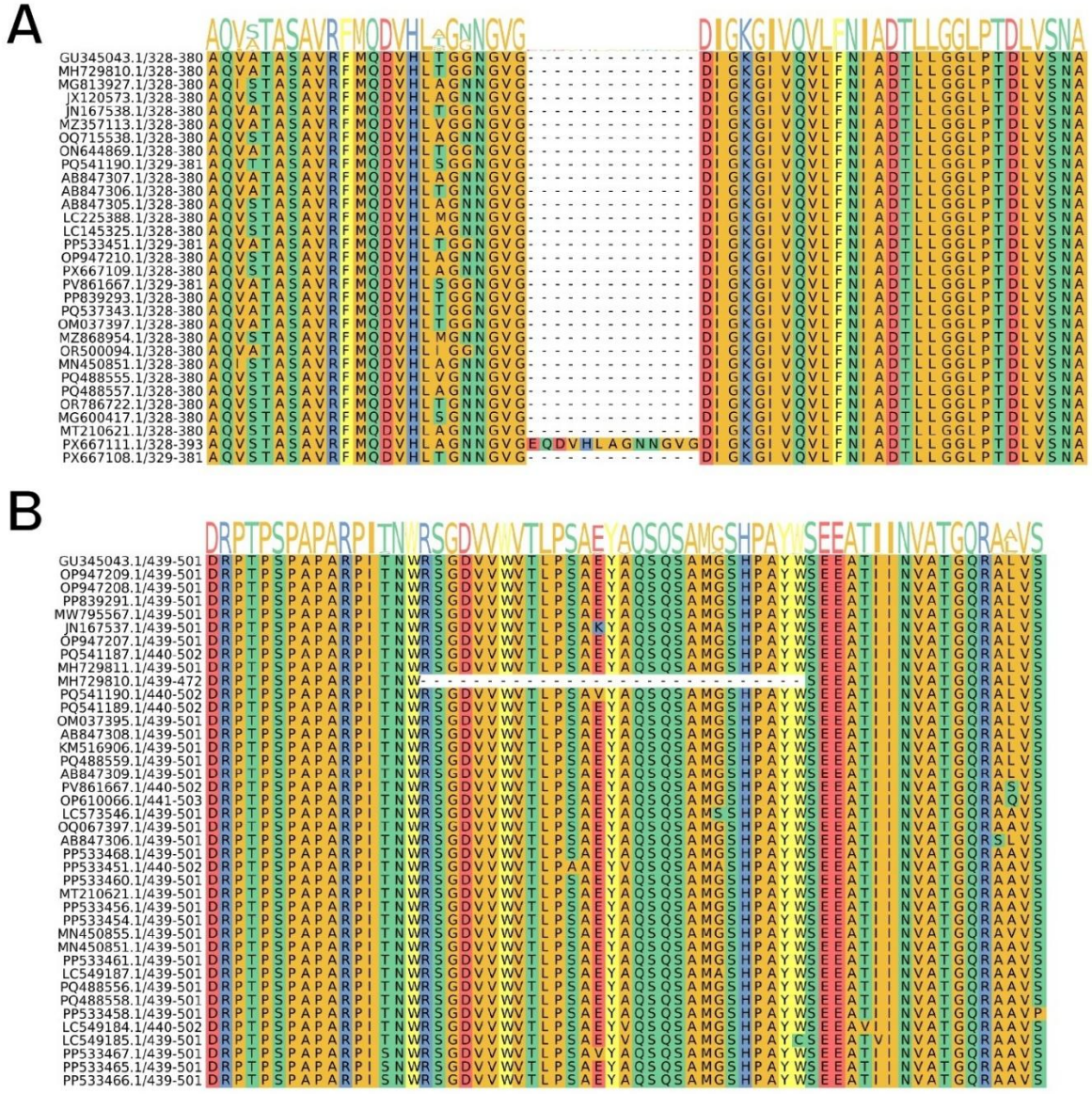

Figure 2. Insertion and deletion sequences identified in open reading frame 2. (**A**) A 13-amino acid sequence in MH729810.1 inserted at amino acid 351 with respect to GU345043.1. (**B**) A 29-amino acid deletion between amino acids 455−483 with respect to GU345043.1. A random selection of other genomes was included for visualization.

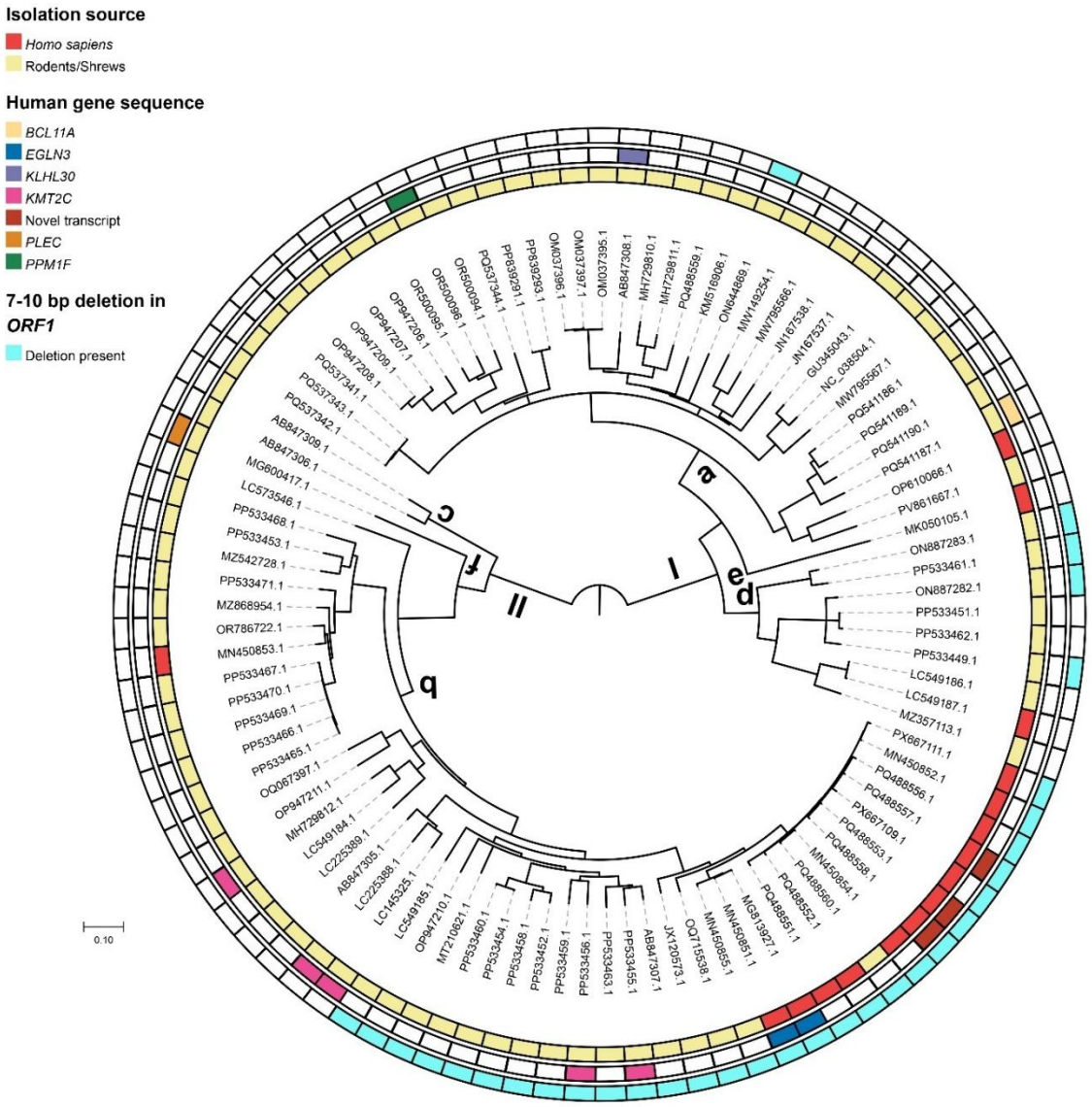

Figure 3. Phylogenetic clustering of human gene sequences and deletions in rat hepatitis E virus. Maximum likelihood phylogeny was inferred using 97 rat hepatitis E virus genomes with IQ-Tree. Human gene sequences were identified using the BLAST-like alignment tool (BLAT).

4. Discussion

The identification of indels and human gene sequences within rHEV genomes expands our understanding of the genetic complexity and evolutionary dynamics of this emerging zoonotic pathogen. Similar to observations in zoonotic *P. balayani* genotype 3, where host-derived insertions and genome duplications have been linked to fitness and replicative advantages, our findings demonstrate for the first time that rHEV genomes also harbor indels. However, in contrast to *P. balayani* genotype 3, these insertions and deletions were predominantly found within the macro X domain of *ORF1* and not the PPR.

The localization of all observed indels and the majority of human gene sequences to the macro X domain raises intriguing questions about the functional impact of these variations. Whilst the function of this domain is still unclear, it is thought to play a role in virus translation, replication, and pathogenicity through multiple pathways [16,17]. It has previously been suggested that the high genetic variation of the PPR and the X domain may be associated with the persistence of *P. balayani* in acute and chronic infection [18]. Therefore, these insertions and deletions that we have identified may affect viral fitness, host range, or immune evasion, although further experimental validation is required. The recurrent detection of a 7−39 aa deletion in the macro X domain of many rHEV genomes, including a large cluster of subtype II.b, which encompasses the Hong Kong patient supercluster, highlights possible lineage-specific evolutionary pressures or adaptation pathways within rodent hosts or during zoonotic transmission. It is unclear why this deletion is also present in one member of subtype I.a

and 4/9 members of subtype I.d, although the latter were all isolated in Mainland China, which may be indicative of localized evolutionary niches.

Our BLAT analysis revealed multiple rHEV genomes containing sequences with significant homology to human genes, including those encoding a histone methyltransferase (*KMT2C*), a transcription factor (*BCL11A)*, and a phosphatase (*PPM1F)*. This is a novel observation for rHEV and parallels the insertions that have been described in human-infecting *P. balayani* genotype 3 strains. The functional consequences of captured human gene fragments in rHEV genomes remain to be elucidated. It is plausible that these human-derived sequences in rHEV might influence viral replication efficiency, host tropism, or immune modulation, but functional assays will be needed to validate their impact. Given that immunocompromised patients are particularly vulnerable to chronic rHEV infection, understanding the role of these insertions may provide insights into viral persistence and pathogenesis in humans.

This study documents, for the first time, the presence of human-derived gene sequences and indels in rHEV genomes, expanding the knowledge of HEV genome plasticity and host-virus genetic interplay. This underscores the dynamic nature of this pathogen's genome and its potential to acquire and repurpose host genetic material. These findings emphasize the importance of monitoring viral genetic adaptations that may facilitate zoonotic spillover and adaptation to human hosts. Future studies should explore the mechanistic basis and phenotypic effects of these insertions, ideally through reverse genetics and in vitro replication models, to clarify their contribution to viral evolution and clinical outcomes.

Author Contributions

S.F.S.H. and S.S. conceived the study. S.F.S.H. conducted all bioinformatics analyses. S.F.S.H. and S.S. prepared and reviewed the manuscript. All authors agree to the authorship of this manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The genome sequences used in this study are available from NCBI GenBank and the accession numbers for the individual sequences are provided in Tables 1−3.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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