	1 20 40 60 80	
MN∨ HuNoV	GPPML PRPSGTYAGL PIADYGDAPPL STKTMF WRTSPE KLPPGAWE PAYL GSKDE RVD-GPSL QQVMRDQL KPYSE PRGLLGGGDSKGTYCGAPIL GPGSAPKL STKTKF WRSSTAPL PPGTYE PAYL GGKDPRVKGGPSL QQVMRDQL KPF TE PRGKI	Ρ
FMDV EV71	GLIVDTRDVEERVHVMFRKTKLAPTVAHGVFNPEFGPAALSNKDPRLNEGVVLDEVIFSKHKGDTKI GEIQWVKPNKETGRLSINGPFRTKLEPSVFHDVFEGNKEPAVLHSKDPRLEVDFEQALFSKYVGNTL	Υ
CV Identity	GE IEF IESSKDAGF PVINTPSKTKLEPSVFHQVFEGNKEPAVLRSGDPRLKANFEEAIFSKYIGNVN	Г
identity		-
MNV	82 100 120 140 PPQE IL DAVCDA IE NRLE NTLE - PQKPWTF KKACE SL DKNTSSGYPYHKQKSKDWTGSAF I GDL GDQA THANNM	Y
HuNoV FMDV		=
EV71	EPDEYIKEAALHYANQL-KQLEINTSQMSMEEACYGTENLEAIDLHTSAGYPYSALGIKKRDILDPTTRDVSKMKF	Y
CV Identity	HVDEYMLE AVDHYAGQL -ATL D I STE PMKLE DAVYGTE GLE AL DL TTSAGYPYVAL G I KKRD I L SKKTKDL TKL KE	5
laonaty	155 160 180 200 220	
MNV	EMGKSMRP I YTAAL KDEL VKPDK I YGK I KKRLL WGSDL GTM I RAARAF GPF CDAL KE T-C I F NP I RVGMSMNE DGPF I F ARH	
HuNoV FMDV	EE GKNMTPVYTGAL KDEL VKTDK I YGKIKKRLL WGSDL ATM I RCARAF GGL MDEL KTH-CVTL P I RVGMNMNE DGP I I FE RH ME KRE YKF ACQTFL KDE I RPME KV-RAGKTR I VDVL PVE H I L YTRMM I GRF CAQMHSNNGPQ I GSAVGCNPD VDWQRF GTHF	
EV71 CV	MDKYGL DL PYSTYV <mark>K</mark> DEL RSID <mark>KI-</mark> KKG <mark>KSR</mark> L I E ASSL NDSVYL RMAF GHL YE TF HANPGT I TGSAVGCNPD TF WSKL PILLI MDKYGL NL PMVTYVKDEL RSIE KV-AKGKSRL I E ASSL NDSVAMRQTF GNL YKTF HL NPGVVTGSAVGCDPDLF WSK I PVMLI	
Identity		_
	237 240 260 280 300	
MNV	NFRYHMDADYTRWDSTQQRAILKRAGDIMVRLSPEPDLARVVMDDLLAPSLLDVGDYKIVVEEGLPSGCPCTTQLNSLAH	
HuNoV FMDV	QYRNVWDVDYSAFDANHCSDAMNIMFEEVFRTEFGFHPNAEWILKTLVNTEHAYENKRITVEGGMPSGCSATSIINTILN	Ν
EV71 CV	GSLF AF DYSGYDASL SPVWF RALEL VL RE I GYSEE A I SL IE G I NHTHHVYRNKTYCVL GGMPSGCSGTS I F NSM I N GHL I AF DYSGYDASL SPVWF ACLKMLLE KL GYTHKE TNY IDYL CNSHHL YRDKHYF VRGGMPSGCSGTS I F NSM I N	
Identity		
	320 664 66: 340 687 688 360 380 4	00
MNV HuNoV	IL TL CAMVE VTRVDPD I VMQE SEF SF YGDDE VVSTNLEL DMVKYTMAL RRYGLL PTRADKEE GPLE RRQTL QG I SFL RRA I V LL TL CAL SE VTNL SPD I I QANSLF SF YGDDE I VSTD I KL DPE KL TAKL KE YGL KPTRPDK TE GPL V I SE DL NGL TFL RRTVT	
FMDV EV71	I YVL YAL RRHYE GVEL DTYTM I SYGDD I VVASDYDL DFE AL KPHF KSL GQT I TPADKSDKGF VL GHS I TDVTFL KRHF H I I I RALL I KTF KG I DL DEL NMVAYGDD VL ASYPF P I DCLEL AKTGKE YGL TMTPADKSPCF NE VNWDNATFL KRGFL	М
CV	I I I RTL ML KVYKGIDL DEL MW AT GODVL AS TPP PIDCLEL AK I GRE TGL IM TPADKSPCF NE VNWDNA TPL KAGPL I I I RTL ML KVYKGIDL DQF RM I AY GODVL AS TPP PIDCLEL AK I GRE TGL IM TPADKGE CF NE VTWTNA TFL KAGPL	
Identity		_
		79
MNV HuNoV		Ρ
FMDV EV71	DYGTGF Y-KPVMASKTLEAIL SFARRG-TIQEKLISVAGLAVHSGPDE YRRLFEPFQGL-FEII DEQFPFLIHPTMPMREIHESIRWTKDARNTQDHVRSLCLLAWHNGKQEYEKFVSTIRSVPVGRALAII	
CV	DE QYPFL VHPVMPMKD I HE S I RWTKDPKNTQDHVRSL CLL AWHNGE HE YEEF I RK I RSVPVGRCL TL I	P
Identity		
MNV	480 500 509 RHRSVL R-WVRF GTMDA-E TPQE RSAVF VNE DAAA	
HuNoV	RQE PMF R-WMRF SDL STWE GDRNL APSF VNE DGVE	
FMDV EV71	SYRSLYLRWVNAVCGDAAALE NYENLRRNWLELFE	
CV	AF STL RRKWLDSF	
identity		

**Figure S3. Sequence alignment of RdRp molecules.** Sequence alignments of RdRp from MNV, HuNV, FMDV, EV71, and CV are shown. Above the alignment, amino acid sequences are presented in blocks of 20 amino acids, and histograms below the alignment indicate the conservation level of amino acids. The catalytic residues GDD at the active site, involved in RNA binding are highlighted in yellow, and the residues involved in VPg binding are highlighted in the same color code as in Fig. 2C: MNV-1, EV71, FMDV, and CV in red, pink, blue, and cyan color, respectively.