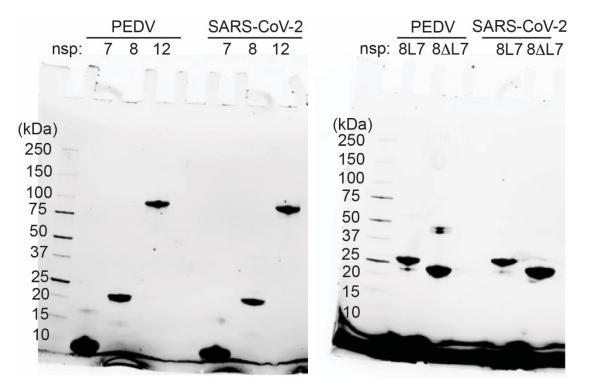
EMDB	29779
PDB	8G6R
Microscope	Talos Arctica
Voltage (kV)	200
Detector	K3 direct electron detector (Gatan)
Dose Rate (e <sup>-</sup> /pixel/sec)	12
Exposure Time (sec)	3.5
Electron Exposure (e <sup>-</sup> /Å <sup>2</sup> )	60
Frames (no.)	60
Defocus Values	-0.7 to -2.5
Sample Tilt (°)	25
Data Collection Mode	EFTEM, Counting, CDS
Nominal Magnification	105,000x
Pixel Size (Å)	0.834
Symmetry Imposed	C1
Movies Collected (no.)	1,261
Initial Particle Images (no.)	710,143
Final Particle Images (no.)	74,367
Map Resolution (Å) – GSFSC	3.3
Initial Model Used (PDB ID)	7CYQ
Non-hydrogen Atoms	9,410
Protein Residues	1075
Nuceic Acid Residues	40
R.M.S. Deviations	
Bond Lengths (Å)	0.004
Bond angles (°)	0.556
MolProbity Score	1.64
Clashscore	7.19
Ramachandran Plot	
Favored (%)	96.34
Allowed (%)	3.66
Disallowed (%)	0

**Table S1: cryo-EM data collection and refinement.** Information provided is for the cryo-EM data collection, and processing that produced the electron density map of the PEDV polymerase complex. Additionally, validation statistics for the polymerase complex coordinate model built into the reconstruction are provided.

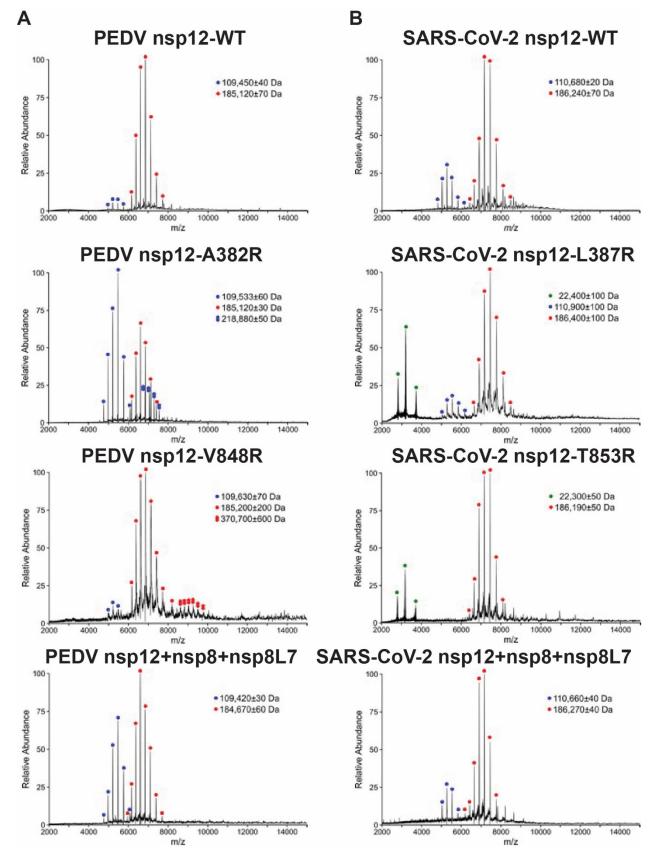
	Desolvation Parameters			
Sample	Capillary Temperature (°C)	In-source Trapping (V)		
PEDV nsp12+8+7	250	-150		
PEDV A382R-nsp12+8+7	200	-300		
PEDV V848R-nsp12+8+7	200	-200		
PEDV nsp12+8+8L7	250	-300		
SARS-CoV-2 nsp12+8+7	200	-150		
SARS-CoV-2 L387R- nsp12+8+7	200	-150		
SARS-CoV-2 T853R- nsp12+8+7	200	-160		
SARS-CoV-2 nsp12+8+8L7	250	-150		

**Table S2, native mass spectrometry desolvation parameters:** Parameters listed were optimized for each sample to remove as many adducts as possible without disrupting the complex(es) of interest.

**Supplemental video 1, 3D variability analysis of PEDV core complex:** The movie displays a series of 3D volumes (in gray) determined by 3D variability analysis (cryoSPARC v3.3.1). The movie begins by oscillating between the extremes of variability within the volume series. Docking our PEDV core complex model (nsp12 – light purple, nsp7 – green, nsp8 – red, primer – neon green, template – dark purple) into the densities reveals the flexibility of dsRNA leaving the active site. We predict that this movement results in the lack of complete reconstruction of our dsRNA and nsp8<sub>1</sub> N-terminal extension in our final map and model.



**Figure S1, SDS-PAGE of viral proteins:** Samples of purified proteins used for *in vitro* studies were run on pre-cast, stain-free, 4-20% SDS-PAGE gels (BioRad) and imaged using UV fluorescence. Expected molecular weights for different proteins are nsp7 – 9 kDa, nsp8 – 22 kDa, nsp12 – 110 kDa, nsp8L7 – 31 kDa, and nsp8 $\Delta$ L7 – 25 kDa. The far-left lane of each gel is a protein ladder protein MWs labeled.



**Figure S2**, **native mass spectrometry of coronavirus polymerase complexes**. Native mass spectra for all coronavirus polymerase complexes tested with major mass populations labelled for each. Single and double red dots are monomeric and dimeric full intact complexes, respectively. Single and double blue dots are monomeric and dimeric solo nsp12, respectively. Green dots are free nsp8. A) SARS-CoV-2 complexes, top to

bottom: wildtype, L387R, T853R, nsp8L7. **B)** PEDV complexes, top to bottom: wildtype, A382R, V848R, nsp8L7.

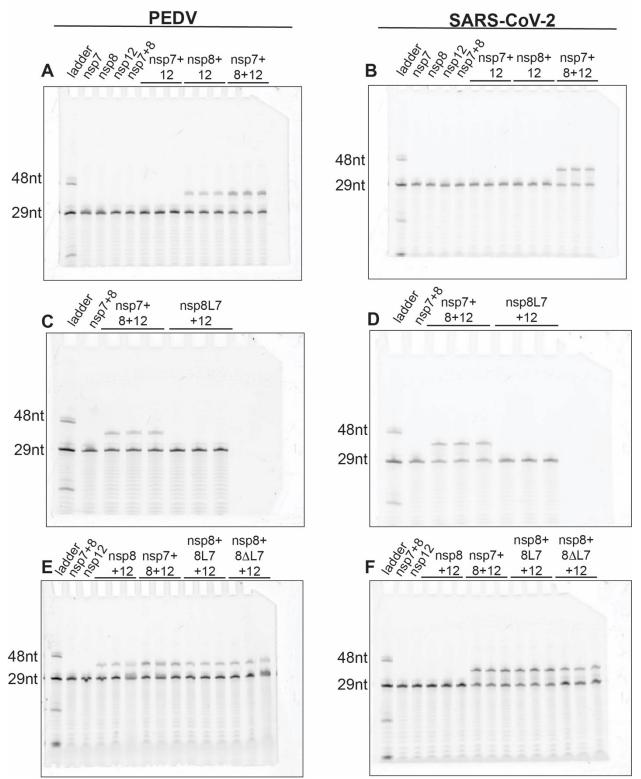
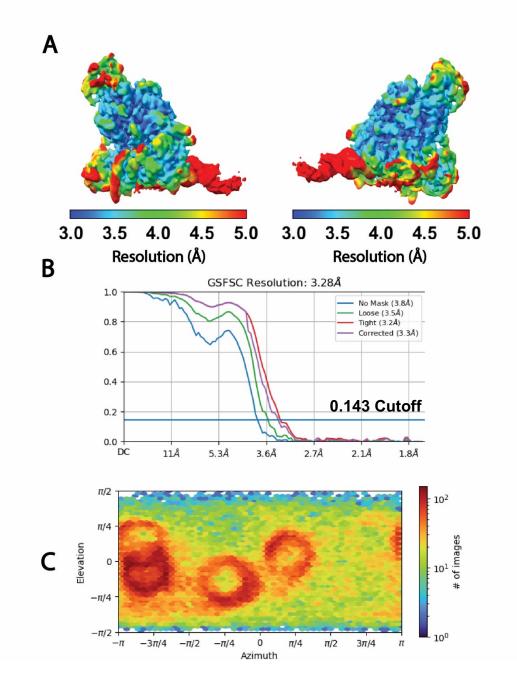


Figure S3, full gel images for piecewise and fusion protein primer extensions: Primer extensions assess the activity of nsp12 by its ability to extend an RNA primer (29 nucleotides or nt) to the length of its RNA template (38 nt) pair. A) PEDV piecewise primer extension revealing optimal nsp12 activity in the presence of both nsp7 and nsp8, and reduced activity with just nsp8. B) SARS2 piecewise primer extensions showing nsp12 is only active in the presence of both cofactors. Nsp8L7 does not individually activate nsp12 (C is PEDV, D is SARS-CoV-2). Nsp8L7 and nsp8 $\Delta$ L7 activate nsp12 with free nsp8 present (E is PEDV, F is SARS-CoV-2), indicating polymerase activities requirement for nsp8<sub>1</sub>, while nsp8<sub>2</sub>'s helical extension is not essential for activity.



**Figure S4, cryo-EM validation:** A) Cryo-EM reconstruction filtered by local resolution according to the color key. B) Gold-standard Fourier shell correlation plot determined in cryoSPARC. The solid blue line marks the 0.143 cutoff. C) Particle orientation distribution plot for the final reconstruction. "# of images" indicates number of projections at a particular orientation (Elevation x Azimuth).

0	HKU19	-LGYSSNQNNSYLNRVKGSS-DARLEPCTSDNRPDVVVRAFNIYNNATAGIFKSTKNN	56	
δ	HKU11	NSPYLNRVTGSS-GARLEPQQPGVTPDAVKRAFHVHNNTTSGIFLSTKTN	49	
	PDCV	NSAYLNRVTGSS-DARLEPLQPGTQPDAVKRAFHVHNDTTSGIFLSTKSN	49	
	FCoV_65F	GTTVDQSYLNRVRGSS-AARLEPCN-GTDPDHVSRAFDIYNKDVACIGKFLKTN	52	
	HCoV_229E	SFDSSYLNRVRGSS-AARLEPCN-GTDIDYCVRAFDVYNKDASFIGKNLKSN	50	
α	HCoV_NL63	SVDISYLNRARGSS-AARLEPCN-GTDIDKCVRAFDIYNKNVSFLGKCLKMN	50	
	HKU8	SLDNNYLNRVRGSS-AARLEPCN-GTEPEHVIRAFDIYNKDVACIGKFVKVN	50	
	PEDV	STDMAYLNRVRGSS-AARLEXCN-GTDTQHVYRAFDIYNKDVACLGKFLKVN	50	
γ	HKU22	SVPQNYLNRVRGLS-EARLRPCASGLLPDVVKRAFDLYNSNTAGMYASLKHN	51	
	IBV	SVAVASGFDKNYLNRVRGSS-EARLIPLANGCDPDVVKRAFDVCNKESAGMFQNLKRN	57	
	HCoV_OC43	SKDTNFLNRVRGASVDARLVPCASGLSTDVQLRAFDIYNASVAGIGLHLKVN	52	
	HCoV_HKU1	SKDLNFLNRVRGTSVNARLVPCASGLSTDVQLRAFDICNTNRAGIGLYYKVN	52	
	MHV	SKDTNFLNRVRGTSVNARLVPCASGLDTDVQLRAFDICNANRAGIGLYYKVN	52	
0	MERS	SKDSNFLNRVRGSIVNARIEPCSSGLSTDVVFRAFDICNYKAKVAGIGKYYKTN	54	
β	HKU4	SKDTNFLNRVRGSSVNARLEPCSSGLTTDVVYRAFDICNFKARVAGIGKYYKTN	54	
•	HKU5	SKDSNFLNRVRGSIVNARIEPCASGLTTDVVFRAFDICNYKAKVAGIGKYYKTN	54	
	HKU9	AKDECFLNRVRGTSGVARLVPLGSGVQPDIVLRAFDICNTKVAGFGLHLKNN	52	
	SARS-CoV-2	SADAQSFLNRVCGVS-AARLTPCGTGTSTDVVYRAFDIYNDKVAGFAKFLKTN	52	
	SARS-CoV	SADASTFLNRVCGVS-AARLTPCGTGTSTDVVYRAFDIYNEKVAGFAKFLKTN	52	
		:***. * **: . : ***.: * : : * *		
	HKU19	CTRFKSTRPGSIINKPVRTIETFFVTKQCTENVFRAEEQCYNMLPKSIVSTDDKFSCVAY	116	
δ	HKU11	CSRFRTTKQNLPLP-NKGSVELYFVSKQCSQQVFEIEETCYNMFDDSLKSTPEKFGVLAR	108	
	PDCV	CARFKTTRSALPLP-NKGEVELYFVTKQCAAKVFEIEEECYNALSTELYTTDDTFGVLAK	108	NUDAN
	FCoV_65F	CSRFRNLDSGAVAE	94	NIRAN
	HCoV_229E	CVRFKNVDKDDAFYIVKRCIKSVMDHEQSMYNLLKGCNAVAK	92	Motif A <sub>N</sub>
α	HCoV_NL63	CVRFKNADSGALAE	92	
	HKU8	CVRFKNADKHDAFYVVKRCTKSVMEHEQSIYDALKDCGAVSP	92	
	PEDV	CVRLKNLDKHDAFYVVKRCTKSAMEHEQSIYSRLEKCGAVAE	92	
γ	HKU22	CARFQELDENDDEIDSFFVVKQTTPHNFEHEEKCYLDLKADCVAV	96	
'	IBV	CARFQEVRDTEDGNLEYCDSYFVVKQTTPSNYEHEKACYEDLKSEVTAD	106	
	HCoV_OC43	CCRFQRVDENGDKLDQFFVVKRTDLTIYNREMKCYERVKDCKFVAE	98	
	HCoV_HKU1	CCRFQRIDDDGNKLDKFFVVKRTNLEVYNKEKTYYELTKSCGVVAE	98	
	MHV	CCRFQRVDEDGNKLDKFFVVKRTNLEVYNKEKECYELTKECGVVAE	98	
0	MERS	TCRFVELDDQGHHLDSYFVVKRHTMENYELEKHCYDLLRDCDAVAP	100	
β	HKU4	TCRFVQVDDEGHKLDSYFIVKRHTMSNYELEKRCYDLLKDCDAVAI	100	
	HKU5	TCRFVEVDDEGHRLDSFFVVKRHTMENYELEKRCYDLVKDCDAVAV	100	
	HKU9	CCRYQELDADGNQLDSYFVVKRHTESNYLLEQRCYEKLKDCDVVAR	98	
	SARS-CoV-2	CCRFQEKDEDDNLIDSYFVVKRHTFSNYQHEETIYNLLKDCPAVAK	98	
	SARS-CoV	CCRFQEKDEEGNCPAVAV	98	
		* :::*: * * *		
	HKU19	HDFFKFDGVNNVVRRHLTKYTLLDLVYALRHLSTS-QEIIQEILTTMCGTSEE	168	
2			160	
δ	HKU11 PDCV	TEFFKFDKI <mark>PNVNRQFLTKYTLLDLAYA</mark> LRHLSTS-RDVIKEILITICGTTEE TEFFKFDKI <mark>PNVNRQYLTKYTLLDLAYA</mark> LRHLSTS-KDVIQEILITMCGTPED	160	
i	FCoV 65F	HDFFLYKEGRCEFGNVARKDLTKYTMMDLCYAIRNFDEKNCEVLKEILVTLGACNES	151	NIRAN
	HCoV 229E	HDFFTWHEGRTIYGNVARADITKITMMDLCFALRNFDEKDCGVFKEILVIIGACNES	149	Motif B <sub>N</sub>
α	HCoV NL63	HDFFTWKDGRVIYGNVSRQDHTKITHEDLETALKALDLKDEGVIKLINGEGALD HDFFTWKDGRVIYGNVSRHNLTKYTMMDLVYAMRNFDEONCDVLKEVLVLTGCCDNS	149	N.
C.	HKU8	HDFFVWKDGRSVY <mark>GNIARHDLTKYTMMDLVHA</mark> LRNFDEKNCETLKEILVISGACDSS	149	
	PEDV	HDFFTWKDGRAIYGNVCRKDLTEYTMMDLCYALRNFDENNCDVLKSILIKVGACEES	149	
	HKU22	HDFFRFE-GMYNICRORLTKYTMMDLCYAFRHFDPNDCDVLKEILVVKGCCEWD	149	
γ	IBV	HDFFVFNKNIYNISRQRLTKYTMMDFCYALRHFDPKDCEVLKEILVTYGCIEDYHPK	163	
- i	HCoV OC43	HDFFFFRAN HINISKAATKIIMADFCHARANFDFROEVLALIVIIGETEDINFK HDFFFFDVEGSRV <mark>PHIVRKDLTKYTMLDLCYA</mark> LRHFDRNDCMLLCDILSIYAGCEQS	155	
	HCoV_HKU1	HDFFTFDIDGSRVPHIVRRDBIRITHEDECTALRHFDRNDCSILCEILCEYADCKES	155	
	MHV	HEFFTFDVEGSRVPHIVRRADSKIMLDLCIALRHFDRNDCSTLCEILLLYAECEES	155	
	MERS	HDFFIFDVEGSKVFHIVRDESKFIMEDLETALANFDRADESTEREIDETTREEES HDFFIFDVDKVKTPHIVRQRLTEYTMMDLVYALRHFDQN-SEVLKAILVKYGCCDVT	156	
β	HKU4	HDFFIFDVDKVKTFHIVRQSLTEYTMMDLVJALRHFDQN SEVERATUVKIGCCDVI HDFFIFDVDKTKTPHIVRQSLTEYTMMDLVYALRHFDQNNCEVLKSILVKYGCCEQS	150	
Ч	HKU5	HDFFIFDVDKIKIPHIVRQSLIEITHADLVIALRHFDQNNCEVLKSILVKIGCCDAS	157	
	HKU9	HDFFKFNIEGVMTPHVSRERLTKYTMADLVYSLRHFDNNNCDTLKEILVLRGCCTVD	155	
	SARS-CoV-2	HDFFKFRIDGDMVPHISRQRLTKYTMADLVYALRHFDEGNCDTLKEILVTYNCCDDD	155	
	SARS-CoV	HDFFKFRVDGDMVPHISRQRLTKYTMADLVYALRHFDEGNCDTLKEILVTYNCCDDD	155	
		:** : :: *. *:::*: ::::::::::::::::::::		

			226	
2	HKU19 HKU11	WFVDGWYDPIENPTFYDEFHKLGSLINNCVVMANKFADTCKTVGLVGILTADNQDLGG WFGDSWFDPIENPTFYREFHKLGSVLNRCVLNANAFAKACSELGIVGILTPDNQDLLG	226 218	
δ	PDCV	WF-GENWFDFIENFFFFIREFIREGSVENRCVENARAFARACSELGIVGILTPDNQDLLG WF-GENWFDPIENPSFYKEFHKLGDILNRCVLNANKFASACIDAGLVGILTPDNQDLLG	218	
j	FCoV 65F	-FFENKDWFDPVENEAIHEVYARLGPIVANAMLKCVAFCDAIVEKGYIGIITLDNODLNG	210	NIRAN
	HCoV 229E	-YFEMKNWFDPIENEDIHRVYAALGKVVANAMLKCVAFCDEMVLKGVVGVLTLDNQDLNG	208	Motif C <sub>N</sub>
α	HCoV NL63	-YFDSKGWYDPVENEDIHRVYASLGKIVARAMLKCVALCDAMVAKGVVGVLTLDNODLNG	208	
U.	HKU8	-YFDNKNWYDPVENEDIHRVYAKLGCVVANAMLKCVALCDAMVAKGVVGVLTLDNQDLNG	208	
	PEDV	-YFNNKVWFDPVENEDIHRVYALLGTIVSRAMLKCVKFCDAMVEQGIVGVVTLDNQDLNG	208	
	HKU22	-YFDQPNWYDPVENPDWFSLISRLGPIFQRALIKVAEFCDLMVEKGYIGVVTLDNQDLNG	208	
γ	IBV	WFEENKDWYDPIENPKYYAMLAKMGPIVRRALLNAIEFGNLMVEKGYVGVITLDNQDLNG	223	
i	HCoV OC43	-YFTKKDWYDFVENPDIINVYKKLGPIFNRALVSATEFADKLVEVGLVGVLTLDNQDLNG	214	
	HCOV HKU1	-YFSKKDWYDFVENPDIINIYKKLGPIFNRALLNTVIFADTLVEVGLVGVLTLDNQDLYG	214	
	 MHV	-YFQKKDWYDFVENPDIINVYKKLGPIFNRALLNTAKFADALVEAGLVGVLTLDNQDLYG	214	
	MERS	-YFENKLWFDFVENPSVIGVYHKLGERVRQAILNTVKFCDHMVKAGLVGVLTLDNQDLNG	215	
β	HKU4	-YFDNKLWFDFVENPSVIGVYHKLGERIRQAMLNTVKMCDHMVKSGLVGVLTLDNQDLNG	216	
М	HKU5	-YFDNKLWFDFVENPNVISVYHKLGERIRQAVLNTVKFCDQMVKSGLVGVLTLDNQDLNG	216	
	HKU9	-YFDRKDWYDPVENPDIIRVYHKLGETVRKAVLSAVKMADAMVEQGLIGVLTLDNQDLNG	214	
	SARS-CoV-2	-YFNKKDWYDFVENPDILRVYANLGERVRQALLKTVQFCDAMRNAGIVGVLTLDNQDLNG	214	
ļ	SARS-CoV	-YFNKKDWYDFVENPDILRVYANLGERVRQSLLKTVQFCDAMRDAGIVGVLTLDNQDLNG	214	
		: *:* :** :* * <mark>:*::* ***** *</mark>		
	HKU19	QIYDFGDFVVTQPGNGCIEMDAYLSYIMPSMSMTHMLKCECLDDNGSYKDYSIYQY	282	
δ	HKU11	QIYDFGDFIITQPGNGCVDLSSYYSYLMPIMSMTHMLKCECYDNDGNEIDYDGFQY	274	
	PDCV	QIYDFGDFIITQPGNGCVDLASYYSYLMPIMSMTHMLKCECMDSDGNPLEYDGFQY	274	NIRAN
	FCoV_65F	NFYDFGDFVKTAPGFGCACVTSYYSYMMPLMGMTSCLESENFVKSDIYGSDYKQYDLLAY	270	Motif C <sub>N</sub>
	HCoV_229E	NFYDFGDFVLCPPGMGIPYCTSYYAYMMPVMGMTNCLASECFMKSDIFGQDFKTFDLLKY	268	
α	HCoV_NL63	NFYDFGDFVVSLPNMGVPCCTSYYSYMMPIMGLTNCLASECFVKSDIFGSDFKTFDLLKY	268	
	HKU8	NFYDFGDFTIGIPGVGVPLATSYYSYLMPVMGMTNCLARECFVKSEIFGSDFKTYDLLEY		$\alpha$ CoV unique loop,
	PEDV	DFYDFGDFTCSIKGMGIPICTSYYSYMMPVMGMTNCLASECFVKSDIFGEDFKSYDLLEY	268	PEDV 249-268
γ	HKU22	NFYDFGDFKKVLPGCGVPVTTSYYSYMPCLTACDALASERFFEFKA-TSGYKQYDLTKY	267	
	IBV	KFYDFGDFQKTAPGAGVPVFDTYYSYMMPIIAMTDALAPERYFEYDV-HKGYKSYDLLKY	282	
	HCoV_OC43	KWYDFGDYVIAAPGCGVAIADSYYSYIMPMLTMCHALDCELYVNNAYRLFDLVQY	269	
	HCoV_HKU1	QWYDFGDFIQTAPGFGVAVADSYYSYMMPMLTMCHVLDCELFVNDSYRQFDLVQY	269	
	MHV	QWYDFGDFVKTVPGCGVAVADSYYSYMMPMLTMCHALDSELFVNGTYREFDLVQY	269	
0	MERS	KWYDFGDFVITQPGSGVAIVDSYYSYLMPVLSMTDCLAAETHRDCDF-NKPLIEWPLTEY	274	
β	нки4 нки5	KWYDFGDFVITQPGAGVAIVDSYYSYLMPVLSMTNCLAAETHKDCDF-NKPLIEWPLLEY	275 275	
	HKU9	KWYDFGDFVITQPGAGVAIVDSYYSYLMPVLSMTNCLAAETHRDCDL-TKPLIEWPLLEY	275	
	SARS-CoV-2	QWYDFGDFIEGPAGAGVAVMDTYYSLAMPIYTMTNILAAECHVSGDL-CNLKRVLDIFKY NWYDFGDFIOTTPGSGVPVVDSYYSLLMPILTLTRALTAESHVDTDL-TKPYIKWDLLKY	273	
	SARS-COV-2	NWIDFGDFIQIFFGGGVFVVDSIISLEMFILITRALAAESHVDIDL-IKFIIKWDLLKI NWYDFGDFVQVAPGCGVFIVDSYYSLLMFILITRALAAESHMDADL-AKPLIKWDLLKY	273	
	JARS-COV	****** * * ** ** * * * * *	215	
1	HKU19	DFTDYKMELFNKYFRHWSQTYHPNCVDCVDDRCIVHCANFNILFAMCLPNTCFGNLCSQA	342	
δ	HKU11	DFTDFKLSLFSKYFTYWDRPYHPNTVDCPDDRCVLHCANFNVLFAMCIPSTAFGNLCSQA	334	
V	PDCV	DFTDFKLGLFEKYFKYWDRPYHPNTVECPDDRCVLHCANFNVLFAMCIPNTAFGNLCSRA	334	
!	FCoV_65F	DFTDHKEKLFEKYFKHWDRTYHPNCSDCTSDDCIIHCANFNTLFSMTIPNTAFGPLVRKV	330	
	HCoV_229E	$\label{eq:constraint} DFTEHKEVLFNKYFKYWGQDYHPDCVDCHDEMCILHCSNFNTLFATTIPNTAFGPLCRKV$	328	
α	HCoV_NL63	$\label{eq:constraint} DFTEHKENLFNKYFKHWSFDYHPNCSDCYDDMCVIHCANFNTLFATTIPGTAFGPLCRKV$	328	
~	HKU8	$\label{eq:constraint} DFTEHKLGLFNKYFKHWDLDYHPNCSDCYDEMCVIHCANFNALFATTIPDTSFGPLCRKV$	328	
ļ	PEDV	$\label{eq:constraint} DFTEHKTALFNKYFKYWGLQYHPNCVDCSDEQCIVHCANFNTLFSTTIPITAFGPLCRKC$	328	
$\gamma$	HKU22	$\label{eq:constraint} DFTEEKLQLFMKYFKYWDRTYHPNCVECIDDRCLIHCANFNILFATLFPQTAFGCLCKRV$	327	
¥ I	IBV	${\tt DYTEEKQDLFQKYFKYWDQEYHPNCRDCSDDRCLIHCANFNILFSTLVPQTSFGNLCRKV$	342	
j	HCoV_OC43	DFTDYKLELFNKYFKHWSMPYHPNTVDCQDDRCIIHCANFNILFSMVLPNTCFGPLVRQI	329	
	HCoV_HKU1	DFTDYKLELFNKYFKYWGMKYHPNTVDCDNDRCIIHCANFNILFSMVLPNTCFGPLVRQI	329	
	MHV	DFTDFKLELFTKYFKHWSMTYHPNTCECEDDRCIIHCANFNILFSMVLPKTCFGPLVRQI	329	
	MERS	$\label{eq:constraint} DFTDYKVQLFEKYFKYWDQTYHANCVNCTDDRCVLHCANFNVLFAMTMPKTCFGPIVRKI$	334	
β	HKU4	DYTDYKIGLFNKYFKYWDQTYHPNCVNCSDDRCILHCANFNVLFSMVLPNTSFGPIVRKI	335	
		DYTDYKIGLFEKYFKXWDQQYHPNCVNCTDDRCVLHCANFNVLFSMTLPGTSFGPIVRKI	335	
P	HKU5			
P	НКU5 НКU9	$\verb"YYTQFKYSLFSNYFKYWDMQYHPNCVACADDRCILHCANFNILFSMVLPNTSFGPLVQKI"$	333	
μ		YYTQFKYSLFSNYFKYWDMQYHPNCVACADDRCILHCANFNILFSMVLPNTSFGPLVQKI DFTEERLKLFDRYFKYWDQTYHPNCVNCLDDRCILHCANFNVLFSTVFPPTSFGPLVRKI	333 333	
P	HKU9			

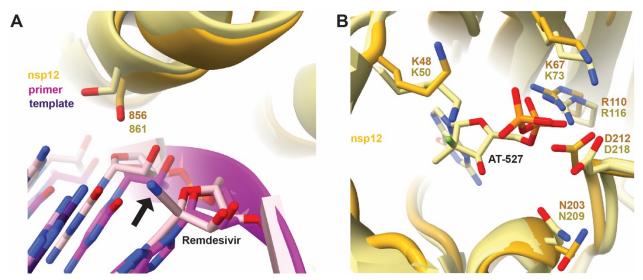
1	HKU19	TVDGHPIVQTVGLHSKELGIVMNQDVNNHMSNINMPTLLRLVGDPTTMCSVADACLDLRT	402	
δ	HKU11	TVDGHKIIQTVGVHLKELGIVLNQDVNTHMSNINLNTLLRLVGDPTTIASVSDKCLDFRT	394	
v I	PDCV	${\tt TVDGHLVVQTVGVHLKELGIVLNQDVTTHMANINLNTLLRLVGDPTTIASVSDKCVDLRT$	394	
	FCoV_65F	$\tt HIDGVPVVVTAGYHFKQLGIVWNLDVKLDTMKLTMTDLLRFVTDPTLLVASSPALLDQRT$	390	
	HCoV_229E	${\tt FIDGVPVVATAGYHFKQLGLVWNKDVNTHSTRLTITELLQFVTDPTLIVASSPALVDKRT$	388	
α	HCoV_NL63	$\tt FIDGVPLVTTAGYHFKQLGLVWNKDVNTHSVRLTITELLQFVTDPSLIIASSPALVDQRT$	388	PEDV nsp12
0.	HKU8	${\tt FIDGVPVVTTAGYHFKQLGLVWNKDLNTHSTRLTINELLRFVTDPALLVASSPALFDQRT$	388	1
	PEDV	$\tt WIDGVPLVTTAGYHFKQLGIVWNNDLNLHSSRLSINELLQFCSDPALLIASSPALVDQRT$	388	C370
~	HKU22	$\tt YIDGVPFISTTGYHSKELGVLLNKDNSMSFSKMSIGELMRFAADPSLLVSASDAFVDLRT$	387	A382
γ	IBV	FVDGVPFIATCGYHSKELGVIMNQDNTMSFSKMGLSQLMQFVGDPALLVGTSNKLVDLRT	402	V384
i	HCoV_OC43	FVDGVPFVVSIGYHYKELGIVMNMDVDTHRYRLSLKDLLLYAADPALHVASASALYDLRT	389	
	HCoV_HKU1	FVDGVPFVVSIGYHYKELGVVMNLDVDTHRYRLSLKDLLLYAADPAMHVASASALLDLRT	389	
	MHV	FVDGVPFVVSIGYHYKELGVVMNMDVDTHRYRLSLKDLLLYAADPALHVASASALLDLRT	389	
	MERS	FVDGVPFVVSCGYHYKELGLVMNMDVSLHRHRLSLKELMMYAADPAMHIASSNAFLDLRT	394	
β	HKU4	FVDGVPFIVSCGYHYKELGLVMNMDFNIHRHRLALKELMMYAADPAMHIASASALWDLRT	395	
Р	HKU5	FVDGVPFVISCGYHYKELGLVMNMDVSLHRHRLSLKELMMYAADPAMHIASASALWDLRT	395	SARS-CoV-2 nsp12
	HKU9	YVDGVPFVVSTGYHYRELGVVMNQDVRQHAQRLSLRELLVY <u>A</u> ADPAMHVAASN <u>ALS</u> DKRT	393	A375
	SARS-CoV-2	FVDGVPFVVSTGYHFRELGVVHNQDVNLHSSRLSFKELLVYAADPAMHAASGNLLLDKRT	393	L387
	SARS-CoV	FVDGVPFVVSTGYHFRELGVVHNQDVNLHSSRLSFKELLVYAADPAMHAASGNLLLDKRT	393	L389
		:** .: : * * ::**: * * .: : * * **: * **		
1	HKU19	PCQTIASIASGATKQSVKPGHFNAHFYEHALESGILSEDSGIDIRHFYYMQDGEAAIKDY	462	
δ	HKU11	PCQTLATMSSGITKQSVKPGHFNQHFYKHLLDSDILN-QLGIDLKHFYYMQDGEAAITDY	453	
0	PDCV	PCQTLATMSSGIAKQSVKPGHFNQHFYKHLLDSNLLD-QLGIDIRHFYYMQDGEAAITDY	453	
1	FCoV_65F	VCFSIAALSTGVTYQTVKPGHFNKDFYDFITERGFFEEGSELTLKHFFFAQGGEAAMTDF	450	
	HCoV_229E	VCFSVAALSTGLTSQTVKPGHFNKEFYDFLRSQGFFDEGSELTLKHFFFTQKGDAAIKDF	448	
α	HCoV_NL63	ICFSVAALSTGLTNQVVKPGHFNEEFYNFLRLRGFFDEGSELTLKHFFFAQNGDAAVKDF	448	
~	HKU8	VCFSVAALGTGLTKQTVKPGHFNKEFYDFLCAQGFFDEGSELTLKHFFFAQKGDAAIRDF	448	
	PEDV	VCFSVAALGTGMTNQTVKPGHFNKEFYDFLLEQGFFSEGSELTLKHFFFAQKGDAAVKDF	448	
~	HKU22	SCFSLSALSTGLTYQTVKPGHFNEDFYNFAEKKGFFKEGSSIPLKHFFYIQDGNAAIADF	447	
γ	IBV	SCFSVCALASGITHQTVKPGHFNKDFYDFAEKAGMFKEGSSIPLKHFFYPQTGNAAINDY	462	
i	HCoV_OC43	CCFSVAAITSGVKFQTVKPGNFNQDFYDFVLSKGLLKEGSSVDLKHFFFTQDGNAAITDY	449	
	HCoV HKU1	CCFSVAAITSGIKFQTVKPGNFNQDFYEFVKSKGLFKEGSTVDLKHFFFTQDGNAAITDY	449	
	MHV	CCFSVAAITSGVKFQTVKPGNFNQDFYEFILSKGLLKEGSSVDLKHFFFTQDGNAAITDY	449	
	MERS	SCFSVAALTTGLTFQTVRPGNFNQDFYDFVVSKGFFKEGSSVTLKHFFFAQDGNAAITDY	454	
β	HKU4	PCFSVAALTTGLTFQTVRPGNFNKDFYDFVVSRGFFKEGSSVTLKHFFFAQDGHAAITDY	455	
Р	HKU5	PCFSVAALTTGLTFQTVRPGNFNKDFYDFVVSKGFFKEGSSVTLRHFFFAQDGHAAITDY	455	
	HKU9	VCMSVAAMTTGVTFQTVKPGQFNEDFYNFAIKCGFFKEGSTISFKHFFYAQDGNAAISDY	453	
	SARS-CoV-2	TCFSVAALTNNVAFQTVKPGNFNKDFYDFAVSKGFFKEGSSVELKHFFFAQDGNAAISDY	453	
	SARS-CoV	TCFSVAALTNNVAFQTVKPGNFNKDFYDFAVSKGFFKEGSSVELKHFFFAQDGNAAISDY	453	
		* ::.:: * *:**:** .**::. : ::**:: * *.**: *:		
]	HKU19	SYYRYNTPTMVDIKQFLFVMEVADKYLSFYDGGCIPAETVVVNNL <mark>DKSAGYPFNKLGKAR</mark>	522	
δ	HKU11	SYYRYNTPTMVDIKMFLFVLEVADKYLQPYEGGCLNAQSVVVNNL <mark>DKYAGYPFNKLGKAR</mark>	513	
	PDCV	SYYRYNTPTMVDIKMFLFCLEVADKYLEPYEGGCINAQSVVVSNL <mark>DKSAGYPFNKLGKAR</mark>	513	Polymerase
	FCoV_65F	NYYRYNRVTVLDICQAQFVYKIVCKYFDCYDGGCINAREVVVTNY <mark>DKSAGYPLNKFGKAR</mark>	510	Motif G
	HCoV_229E	DYYRYNRPTILDIGQARVAYQVAARYFDCYEGGCITSREVVVTNL <mark>NKSAGWPLNKFGKAG</mark>	508	
α	HCoV_NL63	DFYRYNKPTILDICQARVTYKIVSRYFDIYEGGCIKACEVVVTNL <mark>NKSAGWPLNKFGKAS</mark>	508	
	HKU8	DFYRYNRPTVLDICQARVAYHVVKRYFDIYEGGCIAARDVVVTNL <mark>NKSAGYPLNKFGKAS</mark>	508	
	PEDV	DYYRYNRPTVLDICQARVVYQIVQRYFDIYEGGCITAKEVVVTNL <mark>NKSAGYPLNKFGKAG</mark>	508	
γ	HKU22	DYYRFNKPTMVDIQQFLFCFEVTDKYFEQYDGGCIPANQVVVTNL <mark>DKSAGYPFNKFGKAR</mark>	507	
1	IBV	DYYRYNRPTMFDIRQLLFCLEVTSKYFECYEGGCIPASQVVVNNL <mark>DKSAGYPFNKFGKAR</mark>	522	
	HCoV_OC43	NYYKYNLPTMVDIKQLLFVLEVVYKYFEIYDGGCIPASQVIVNNY <mark>DKSAGYPFNKFGKAR</mark>	509	
	HCoV_HKU1	NYYKYNLPTMVDIKQLLFVLEVVYKYFEIYDGGCIPASQVIVNNY <mark>DKSAGYPFNKFGKAR</mark>	509	
	MHV	NYYKYNLPTMVDIKQLLFVLEVVNKYFEIYEGGCIPATQVIVNNY <mark>DKSAGYPFNKFGKAR</mark>	509	
~	MERS	NYYSYNLPTMCDIKQMLFCMEVVNKYFEIYDGGCLNASEVVVNNL <mark>DKSAGHPFNKFGKAR</mark>	514	
β	HKU4	SYYAYNLPTMVDIKQMLFCMEVVDKYFDIYDGGCLNASEVIVNNL <mark>DKSAGHPFNKFGKAR</mark>	515	
	HKU5	SYYAYNLPTMCDIKQMLFCMEVVDRYFEIYDGGCLNASEVIVNNL <mark>DKSAGHPFNKFGKAR</mark>	515	
	HKU9	DYYRYNLPTMCDIKQLLFSLEVVDKYFDCYDGGCLQASQVVVANYDKSAGFPFNKFGKAR	513	
	SARS-CoV-2	DYYRYNLPTMCDIRQLLFVVEVVDKYFDCYDGGCINANQVIVNNLDKSAGFPFNKWGKAR	513	
	SARS-CoV	DYYRYNLPTMCDIRQLLFVVEVVDKYFDCYDGGCINANQVIVNNLDKSAGFPFNKWGKAR	513	
		.:* :* *: **:. :*:. *:*** : *:* * <mark>:* ** *:**</mark>		

	HKU19	NYYD-LTYAEQNAMFEYTKRNVLPTVTQMN <mark>LKYAISAKDRAR</mark> TVAGVSIISTMTNRQYHQ	581	
δ	HKU11	NYYD-MTYAEQNQLFEYTKRNVLPTLTQMN <mark>LKYAISAKDRAR</mark> TVAGVSIISTMTNRQYHQ	572	
0	PDCV	NYYD-MTHAEQNQLFEYTKRNVLPTLTQMN <mark>LKYAISAKDRAR</mark> TVAGVSIISTMTNRQYHQ	572	Polymerase
	FCoV_65F	LYYETLSYEEQDAIFALTKRNVLPTMTQMN <mark>LKYAISGKARAR</mark> TVGGVSLLSTMTTRQYHQ	570	Motif F
	HCoV_229E	LYYESISYEEQDAIFLLTKRNILPTMTQLN <mark>LKYAISGKERAR</mark> TVGGVSLLATMTTRQFHQ	568	WOULL
α	HCoV_NL63	LYYESISYEEQDALFALTKRNVLPTMTQLN <mark>LKYAISGKERAR</mark> TVGGVSLLSTMTTRQYHQ	568	
	HKU8	LYYESLSYEEQDALYALTKRNVLPTMTQLN <mark>LKYAISGKERAR</mark> TVGGVSLLSTMTTRQFHQ	568	
	PEDV	LYYESLSYEEQDELYAYTKRNILPTMTQLN <mark>LKYAISGKERAR</mark> TVGGVSLLSTMTTRQYHQ	568	
γ	HKU22	LYYESLSYAEQDQLFELTKRNILPTITQIN <mark>MKYAISAKSRAR</mark> TVAGVSILSTMTNRQFHQ	567	
1	IBV	LYYE-MSLEEQDQLFESTKKNVLPTITQMN <mark>LKYAISAKNRAR</mark> TVAGVSILSTMTNRQFHQ	581	
	HCoV_OC43	LYYEALSFEEQDEIYAYTKRNVLPTLTQMN <mark>LKYAISAKNRAR</mark> TVAGVSILSTMTGRMFHQ	569	
	HCoV_HKU1	LYYEALSFEEQNEIYAYTKRNVLPTLTQMN <mark>LKYAISAKNRAR</mark> TVAGVSILSTMTGRMFHQ	569	
	MHV	LYYEALSFEEQDEIYAYTKRNVLPTLTQMNLKYAISAKNRARTVAGVSILSTMTGRMFHQ	569	
0	MERS	VYYESMSYQEQDELFAMTKRNVIPTMTQMNLKYAISAKNRARTVAGVSILSTMTNRQYHQ	574	
β	HKU4	VYYESMSYQEQDELFAVTKRNVLPTITQMNLKYAISAKNRARTVAGVSILSTMTNRQYHQ	575	
	HKU5	VYYESLSYQEQDELFAMTKRNVLPTITQMNLKYAISAKNRARTVAGVSILSTMTNRQYHQ	575	
	HKU9	LYYESLSYADQDELFAYTKRNVLPTITQMNLKYAISAKNRARTVAGVSIASTMTNRQFHQ	573	
	SARS-CoV-2	LYYDSMSYEDQDALFAYTKRNVIPTITQMNLKYAISAKNRARTVAGVSICSTMTNRQFHQ	573	
	SARS-CoV	LYYDSMSYEDQDALFAYTKRNVIPTITQMNLKYAISAKNRARTVAGVSICSTMTNRQFHQ	573	
		**: :: :*: **:*::**:** <mark>:*****</mark> ** **********		
	HKU19	KLLKSISVARNQTIVIGTTKFYGGWDNMLRNLMANINN <mark>PKLAGWDYPKCDRSM</mark> PNLLRIT	641	
6	HKU11	KMLKSISLARNOTIVIGTIKFIGGWDNMLRRLMNGINNPILVGWDYPKCDRSMPNMLRIA	632	
δ	PDCV	KMLKSISLARNQTIVIGTIKFIGGWDNMLRRLMCNINN <mark>PILVGWDYPKCDRSM</mark> PNMLRIA	632	_
i	FCoV 65F	KHLKSIAATRNATVVIGTTKFYGGWDNMLKNLMRDVDN <mark>GCLMGWDYPKCDRAL</mark> PNMIRMA	630	Polymerase
	HCoV 229E	KCLKSIVATRNATVVIGTTKFYGGWDNMLKNLMADVDDPKLMGWDYPKCDRAMPSMIRML	628	Motif A
~	HCoV NL63	KHLKSIVNTRNATVVIGTTKFYGGWNNMLRTLIDGVENPMLMGWDYPKCDRALPNMIRMI	628	
α	HKU8	KHLKSIVNTRNATVVIGTTKFYGGWDNMLRNLMDGVDNACLMGWDYPKCDRALPNMIRMI	628	
	PEDV	KHLKSIVNTRGASVVIGTTKFYGGWDNMLKNLIDGVEN PCLMGWDYPKCDRALPNMIRMI	628	
	HKU22	KCLKSIVNTRNATVVIGTTKFYGGWDNMLRNLMRGVED <mark>PVLMGWDYPKCDRAM</mark> PSLLRLS	627	
γ	IBV	KILKSIVNTRNAPVVIGTTKFYGGWDNMLRNLIQGVED <mark>PILMGWDYPKCDRAM</mark> PNLLRIA	641	
i	HCoV OC43	KCLKSIAATRGVPVVIGTTKFYGGWDDMLRRLIKDVDN <mark>PVLMGWDYPKCDRAM</mark> PNLLRIV	629	
	HCoV HKU1	KCLKSIAATRGVPVVIGTTKFYGGWDDMLRHLIKDVDN <mark>PVLMGWDYPKCDRAM</mark> PNILRIV	629	
	MHV _	KCLKSIAATRGVPVVIGTTKFYGGWDDMLRRLIKDVDS <mark>PVLMGWDYPKCDRAM</mark> PNILRIV	629	
	MERS	KMLKSMAATRGATCVIGTTKFYGGWDFMLKTLYKDVDN <mark>PHLMGWDYPKCDRAM</mark> PNMCRIF	634	
β	HKU4	KMLKSMAATRGATCVIGTTKFYGGWDFMLKTLYKDVES <mark>PHLMGWDYPKCDRAM</mark> PNMCRIL	635	
P	HKU5	KMLKSMAATRGSTCVIGTTKFYGGWDFMLKTLYKDVDN <mark>PHLMGWDYPKCDRAM</mark> PNMCRIF	635	
	HKU9	KMLKSIAAARGASVVIGTTKFYGGWNRMLRTLCEGVDN <mark>PHLMGWDYPKCDRAM</mark> PNLLRIF	633	
	SARS-CoV-2	KLLKSIAATRGATVVIGTSKFYGGWHNMLKTVYSDVEN <mark>PHLMGWDYPKCDRAM</mark> PNMLRIM	633	
ļ	SARS-CoV	KLLKSIAATRGATVVIGTSKFYGGWHNMLKTVYSDVET <mark>PHLMGWDYPKCDRAM</mark> PNMLRIM	633	
		* ***: :*. ****:*****. **: : .:: * ********		
			300	
6	HKU19	SSLLLARKH-ACCTHSQRFYRLANECAQVLSEIVVSGNVMYVKPGGTSSGDATTAYANSV	700	
δ	HKU11 PDCV	ASCLLARKH-TCCNQSQRFYRLANECCQVLSEVVVSGNNLYVKPGGTSSGDATTAYANSV	691	
i	FCoV 65F	ASCLLARKH-TCCNQSQRFYRLANECCQVLSEVVVSGNNLYVKP <mark>GGTSSGDATTAYANSV</mark> SAMVLGSKHIGCCTHSDRFYRLSNELAOVLTEVVHCTGGFYIKP <mark>GGTTSGDGTTAYANSA</mark>	691 690	Polymerase
	HCoV 229E	SAMVLGSKHIGCCIHSDRFIRLSNELAQVLIEVVHCIGGFIIRGGIISGDGIIAIANSA SAMILGSKHVTCCTASDKFYRLSNELAQVLIEVVYSNGGFYFKPGGTISGDATTAYANSV	688	Motif B
α	HCoV NL63	SAMUGSKHVICCTATDRFYRLGNELAQVLTEVVISNGGFIFKPGGTTSGDASTAYANSI	688	
<i>u</i>	HKU8	SAMILGSKHVNCCTNSDRYYRLCNELAQVLTEVVISNGGFYMKP <mark>GGTTSGDATTAYANSV</mark>	688	
	PEDV	SAMILGSKHTTCCSSTDRFFRLCNELAQVLTEVVYSNGGFYLKP <mark>GGTTSGDATTAYANSV</mark>	688	
	HKU22	ASLILARRHKGCCDWNERIYRLANEAAQVLSEVALSNGGLYVKPGGTSSGDATTAYANSA	687	
γ	IBV	ASLVLARKHTNCCTWSERVYRLYNECAQVLSETVLATGGIYVKPGGTSSGDATTAYANSV	701	
i	HCoV OC43	SSLVLARKHETCCSQSDRFYRLANECAQVLSEIVMCGGCYYVKP <mark>GGTSSGDATTAFANSV</mark>	689	
	HCoV HKU1	SSLVLARKHEFCCSHGDRFYRLANECAQVLSEIVMCGGCYYVKP <mark>GGTSSGDATTAFANSV</mark>	689	
	MHV	SSLVLARKHDSCCSHTDRFYRLANECAQVLSEIVMCGGCYYVKP <mark>GGTSSGDATTAFANSV</mark>	689	
	MERS	ASLILARKHGTCCTTRDRFYRLANECAQVLSEYVLCGGGYYVKP <mark>GGTSSGDATTAYANSV</mark>	694	
β	HKU4	ASLILARKHSTCCTNSDRFYRLANECAQVLSEYVLCGGGYYVKP <mark>GGTSSGDATTAYANSV</mark>	695	
٣	HKU5	ASLILARKHSTCCTNTDRFYRLANECAQVLSEYVLCGGGYYVKP <mark>GGTSSGDATTAYANSV</mark>	695	
	HKU9	ASLILARKHSTCCNASERFYRLANECAQVLSEMVLCGGGFYVKP <mark>GGTSSGDSTTAYANSV</mark>	693	
	SARS-CoV-2	ASLVLARKHTTCCSLSHRFYRLANECAQVLSEMVMCGGSLYVKP <mark>GGTSSGDATTAYANSV</mark>	693	
	SARS-CoV	ASLVLARKHNTCCNLSHRFYRLANECAQVLSEMVMCGGSLYVKP <mark>GGTSSGDATTAYANSV</mark>	693	
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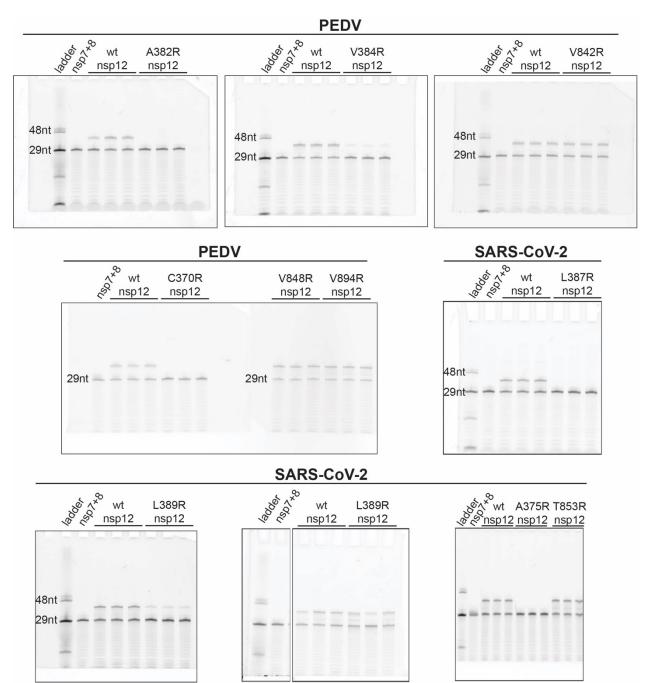
	HKU19	FNILQVVSANIARFMSTSAATHHDVDVMHLHRQIYDDIYRGNSNDSVAIQSFYEHLQKY <mark>F</mark>	760	
δ	HKU11	FNILQVVSANVATFLSTSSHNSREIADLHRNLYEDIYRGDSNNTTIIDQFYQHLQKYF	751	
Ŭ	PDCV	FNILQVVSANVATFLSTSTTTHLNKDIADLHRSLYEDIYRGDSNDITVINRFYQHLQSY <mark>F</mark>	751	Polymerase
	FCoV_65F	FNIFQAVSANVNKLLGVDSNTCNNVTVKSIQRKIYDNCYRSSSVDDDFVVEYFSYLRKH <mark>F</mark>	750	Motif B
	HCoV_229E	FNIFQAVSSNINCVLSVNSSNCNNFNVKKLQRQLYDNCYRNSNVDESFVDDFYGYLQKH <mark>F</mark>	748	Motif C
α	HCoV_NL63	FNIFQAVSSNINRLLSVPSDSCNNVNVRDLQRRLYDNCYRLTSVEESFIDDYYGYLRKH <mark>F</mark>	748	
	HKU8	FNIFQAVSANINRILGI <mark>NSNTCNNLAVKSLQRMLYDNCYRSSAVDPGFVDTFYGYLRKH</mark> F	748	
	PEDV	FNIFQAVSANVNKLLSVDSNVCHNLEVKQLQRKLYECCYRSTTVDDQFVVEYYGYLRKH <mark>F</mark>	748	
$\gamma$	HKU22	FNLFQATAANVAQLLATPTSRIYVEEVRALQHELYTQVYRRDKPDMDFVYTFYAYLNKH <mark>F</mark>	747	
γ	IBV	FNIIQATSANVARLLSVITRDIVYDDIKSLQYELYQQVYRRVNFDPAFVEKFYSYLCKN <mark>F</mark>	761	
- 1	HCoV OC43	FNICQAVSANVCALMSCNGNKIEDLSIRALQKRLYSHVYRSDKVDSTFVTEYYEFLNKH <mark>F</mark>	749	
	HCoV HKU1	FNICQAVTANVCSLMACNGHKIEDLSIRNLQKRLYSNVYRTDYVDYTFVNEYYEFLCKH <mark>F</mark>	749	
	MHV	FNICQAVSANVCSLMACNGHKIEDLSIRELQKRLYSNVYRADHVDPAFVSEYYEFLNKH <mark>F</mark>	749	
	MERS	FNILQATTANVSALMGANGNKIVDKEVKDMQFDLYVNVYRSTSPDPKFVDKYYAFLNKH <mark>F</mark>	754	
β	HKU4	FNILQATTANVSALMSANGNTIIDREIKDMQFDLYINVYRKVVPDPKFVDKYYAFLNKH <mark>F</mark>	755	
P	HKU5	FNILQATTANVSALMGANGNTIVDEEVKDMQFELYVNVYRKSQPDPKFVDRYYAFLNKH <mark>F</mark>	755	
	HKU9	FNICQAVSANLNTFLSVDGNKIYTTYVQELQRRLYLGIYRSNTVDNDLVLDYYNYLRKH <mark>F</mark>	753	
	SARS-CoV-2	FNICQAVTANVNALLSTDGNKIADKYVRNLQHRLYECLYRNRDVDTDFVNEFYAYLRKHF	753	
	SARS-CoV	FNICQAVTANVNALLSTDGNKIADKYVRNLQHRLYECLYRNRDVDHEFVDEFYAYLRKHF	753	
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	HKU19	GLMILSDDGVACIDQEAAKQGMVADLDDFRDVLFYQNNVYMSDSKCWIETDMSKGPHEFC	820	
δ	HKU11	GLMILSDDGVACIDTEAAASGVVSNLDGFRDILFYQNNVYMADSKCWTETDMTVGPHEFC	811	
0	PDCV	GLMILSDDGVACIDSAVAKAGAVADLDGFRDILFYQNNVYMADSKCWTETDMNVGPHEFC	811	Polymerase
	FCoV 65F	SMMILSDDGVVCYNKDYADLGYVADISAFKATLYYQNNVFMSTAKCWVEPDLNVGPHEFC	810	Motif C
	HCoV 229E	SMMILSDDGVVCYNKTYAELGYIADISAFKATLYYQNGVFMSTAKCWTEEDLSIGPHEFC	808	
α	HCoV NL63	SMMILSDDGVVCYNKDYAELGYIADISAFKATLYYQNNVFMSTSKCWVEEDLTKGPHEFC	808	Motif D
0.	HKU8	SMMILSDDGVVCYNKEYASLGYVADINAFKATLYYQNNVFMSTSKCWVEEDLTKGPHEFC	808	Motif E
	PEDV	SMMILSDDGVVCYNNDYASLGYVADLNAFKAVLYYQNNVFMSASKCWIEPDINKGPHEFC	808	
~	HKU22	SLMILSDDGVVCYNSDYAEAGMVASIASFREVLFYQNNVFMADSKCWTEEDVKIGPHEFC	807	
γ	IBV	SLMILSDDGVVCYNNTLAKQGLVADISGFREVLYYQNNVFMADSKCWVEPDLEKGPHEFC	821	
ĺ	HCoV OC43	SMMILSDDGVVCYNSDYASKGYIANISAFQQVLYYQNNVFMSESKCWVEHDINNGPHEFC	809	
	HCoV HKU1	SMMILSDDGVVCYNSDYASKGYIANISVFQQVLYYQNNVFMSESKCWVENDITNGPHEFC	809	
	MHV	SMMILSDDGVVCYNSEFASKGYIANISAFQQVLYYQNNVFMSEAKCWVETDIEKGPHEFC	809	
	MERS	SMMILSDDGVVCYNSDYAAKGYIAGIQNFKETLYYQNNVFMSEAKCWVETDLKKGPHEFC	814	
β	HKU4	SMMILSDDGVVCYNSDYAAKGYVASIQNFKETLYYQNNVFMSEAKCWVETNLEKGPHEFC	815	
Р	HKU5	SMMILSDDGVVCYNSDYATKGYIASIQNFKETLYYQNNVFMSEAKCWVETDLKKGPHEFC	815	
	HKU9	SMMILSDDGVVCYNADYAQKGYVADIQGFKELLYFQNNVFMSESKCWVEPDITKGPHEFC	813	
	SARS-CoV-2	SMMILSDDAVVCFNSTYASQGLVASIKNFKSVLYYQNNVFMSEAKCWTETDLTKGPHEFC	813	
	SARS-CoV	SMMILSDDAVVCYNSNYAAQGLVASIKNFKAVLYYQNNVFMSEAKCWTETDLTKGPHEFC	813	
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	HKU19	SQHTVLAEYDGEPCYYPYPDVSRILGACIFVNETEKTDPVQNLERYISLAIDAYPLTKVD	880	
δ	HKU11	SQHTVLAEHEGKPYYLPYPDVSRILGACIFVDDVNKADPIQNLERYISLAIDAYPLTKVD	871	
	PDCV	SQHTVLAEHDGKPYYLPYPDVSRILGACIFVDDVNKADPVQNLERYISLAIDAYPLTKVD	871	Polymerase
	FCoV_65F	SQHTLQIVGADGDYYLPYPDPSRILSAGVFVDDIVKTDNVIMLERYVSLAIDAYPLTKHP	870	Motif E
	HCoV_229E	SQHTMQIVDENGKYYLPYPDPSRIISAGVFVDDVTKTDAVILLERYVSLAIDAYPLSKHP	868	
α	HCoV_NL63	SQHTMQIVDKDGTYYLPYPDPSRILSAGVFVDDVVKTDAVVLLERYVSLAIDAYPLSKHP	868	
	HKU8	SQHTMQIVDGDGTYYLPYPDPSRILSAGVFVDDVIKTDAVVLLERYVSLAIDAYPLSKHP	868	PEDV nsp12
	PEDV	SQHTMQIVDKDGTYYLPYPDPSRILSAGVFVDDVVKTDAVVLLERYVSLAIDAYPLSKHE	868	V842
γ	HKU22	SQHSMLVEIDGEMRYLPYPDPSRILGACVFVDDVEKTEPVVVMERYVALAIDAYPLIYHE	867	V848
1	IBV	SQHTMLVEVDGEPRYLPYPDPSRILCACVFVDDLDKTESVAVMERYIALAIDAYPLVHHE	881	
	HCoV_OC43	SQHTMLVKMDGDDVYLPYPNPSRILGAGCFVDDLLKTDSVLLIERFVSLAIDAYPLVYHE	869	
	HCoV_HKU1	SQHTMLVKIDGDYVYLPYPDPSRILGAGCFVDDLLKTDSVLLIERFVSLAIDAYPLVYHE	869	
	MHV	SQHTMLVKMDGDEVYLPYPDPSRILGAGCFVDDLLKTDSVLLIERFVSLAIDAYPLVYHE	869	
	MERS	SQHTLYIKDGDDGYFLPYPDPSRILSAGCFVDDIVKTDGTLMVERFVSLAIDAYPLTKHE	874	
β	HKU4	SQHTLYIKDGDDGYFLPYPDPSRILSAGCFVDDIVKTDGTVMMERYVSLAIDAYPLTKHD	875	
	нки5	SQHTLFIKDGDDGYFLPYPDPSRILSAGCFVDDIVKTDGTLMVERFVSLAIDAYPLTKHD	875	
	нки9	SQHTMLVEMNGEKVYLPYPDPSRILGAGCFVDDLLKTDGTLMMERYVSLAIDAYPLTKHA	075	SARS-CoV-2 nsp12
	SARS-CoV-2	SQHTMLVKQGDDYVYLPYPDPSRILGAGCFVDDIVKTDGTLMIERFVSLAIDAYPLTKHP	873	1847
	SARS-CoV	SQHTMLVKQGDDYVYLPYPDPSRILGAGCFVDDIVKTDGTLMIERFVSLAIDAYPLTKHP	873	T853
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δ	HKU19 HKU11 PDCV FCoV 65F	-NKKGKVFYVLLDYIRKLANELQEGIMDAFQTSTDTSYINNFVTENFYSDMYAKAPVLQ -PIKGKVFYLLLDYIRILAQELQDGILDTFQSMTDMSYVNNFVQEAFYAQMYEQSPTLQ -PIKGKVFYLLLDYIRVLAQELQDGILDAFQSLTDMSYVNNFMNEAFYAQMYEQSPTLQ KPAYQKVFYALLDWVKHLQKTLNAGILDSFSVTMLEDGQDKFWSEEFYASLYEKSTVLQ	938 929 929 929	
α	HCoV_229E HCoV_NL63 HKU8	KPEYRKVFYALLDWVKHLNKTLNEGVLESFSVTLLDEQESKFWDESFYASMYEKSTVLQ NSEYRKVFYVLLDWVKHLNKNLNEGVLESFSVTLLDNQEDKFWCEDFYASMYENSTILQ NPEYRKVFYVLLDWVKHLNNTLNQGVLESFSVTLLEDASSKFWDESFYANLYEKSAVLQ	927 927 927	PEDV nsp12
γ	PEDV HKU22 IBV HCoV OC43	NPEYKKVFYULLDWVKHLYKTLNAGULESFSVTLLEDSTAKFWDESFYANMYEKSAVLQ NEEYGKVFYLLLSYIQTLYQRLSNDMLMDYSFVMNIDTSSKFWEEDFYRQMYESSPTLQ NEEYKKVFFVLLSYIRKLYQELSQNMLMDYSFVMDIDKGSKFWEQEFYENMYRAPTTLQ NEEYQKVFRVYLAYIKKLYNDLGNQILDSYSVILSTCDGQKFTDESFYKNMYLRSAVMQ	927 926 940 928	V894
β	HCoV_HKU1 MHV MERS HKU4 HKU5	NEEYQKVFRVYLEYIKKLYNDLGTQILDSYSVILSTCDGLKFTEESFYKNMYLKSAVMQ NPEYQNVFRVYLEYIKKLYNDLGNQILDSYSVILSTCDGQKFTDETFYKNMYLRSAVLQ DIEYQNVFWVYLQYIEKLYKDLTGHMLDSYSVMLCGDNSAKFWEEAFYRDLYSSPTTLQ DTEYQNVFWVYLQYIEKLYKDLTGHMLDSYSVMLCGDDSAKFWEEGFYRDLYSSPTTLQ DPEYQNVFWVYLQYIEKLYKDLTGHMLDSYSVMLCGDNSAKFWEESFYRDLYTAPTTLQ	928 928 933 934 934	
	HKU9 <b>SARS-CoV-2</b> SARS-CoV	DPEYQNVFWCYLQYIKKLHEELTGHLLDTYSVMLASDNASKYWEVDFYENMYMESATLQ NQEYADVFHLYLQYIRKLHDELTGHMLDMYSVMLTNDNTSRYWEPEFYEAMYTPHTVLQ NQEYADVFHLYLQYIRKLHDELTGHMLDMYSVMLTNDNTSRYWEPEFYEAMYTPHTVLQ .** *::.*: *: :: :: :: ** :*	932 932 932	

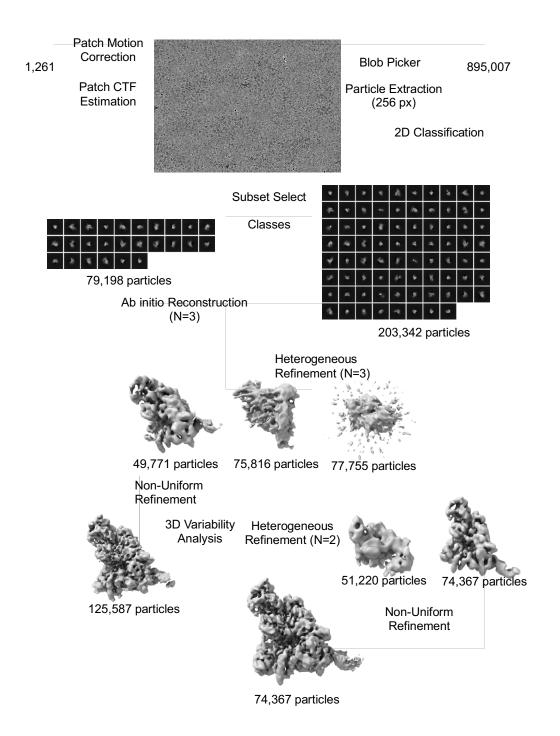
**Figure S5, Multiple sequence alignment of coronavirus nsp12s.** Alignment of nsp12 from the alpha- (FCoV-65F, HCoV-229E, HCoV-NL63, HKU8, PEDV), beta- (HCoV-OC43, HKU1, MHV MERS, HKU4, HKU5, HKU9, SARS-CoV, SARS-CoV-2), gamma (HKU22, IBV), and delta- (HKU19, HKU11, PDCV) coronavirus genera. Global alignment was done using Clustal Omega [2]. Residues marked with "\*" are conserved, ":" are very similar, and "." are moderately similar residues.



**Figure S6: possible cross-effectiveness of CoV antivirals.** In each figure PEDV nsp12 is shown in dark yellow and the RNA primer in dark pink, superimposed are SARS-CoV-2 models in lighter, matching colors. **A)** The antiviral Remdesivir's 1'-cyano group (black arrow) is believed to clash with SARS-CoV-2 nsp12 S861 in the +4 extension position. Remdesivir incorporated into a nascent primer at +3 is shown (PDB ID: 7B3C). Due to the sequence and spatial homology of S856 in PEDV we predict Remdesivir would have similar effectiveness against PEDV. **B**) The dual action antiviral AT-527 was shown to bind and inhibit the NiRAN domain of SARS-CoV-2 nsp12 (PDB ID: 7ED5). Several residues important for drug binding are conserved in PEDV, shown are K48, K67, R110, N203, and D212.



**Figure S7, full gel images for mutant nsp12 primer-extension assays:** Primer extension results for complexes with mutant nsp12s for PEDV and SARS-CoV-2. For each experiment wildtype (wt) and mutant polymerase reactions were done in triplicate. Viral cofactors, nsp7 and nsp8, were always provided in excess to nsp12 (wt or mutant). Each experiment included one negative control reaction lacking nsp12.



**Figure S8, cryo-EM processing pipeline:** Workflow for the processing of cryo-EM data starting with 1,261 movies. All data processing was performed in cryoSPARC [1]. Poor particles were removed through multiple rounds of 2D classification, then a subset of polymerase classes were used to generate initial models for subsequent heterogenous refinement with all remaining particles. Particles from classes resembling polymerases were merged for further 3D refinement and a final round of heterogenous refinement into nsp12 alone and polymerase complex maps. The complex map was further refined to our final 3.3 Å reconstruction.

## Supplemental References:

- 1. Punjani, A., et al., *cryoSPARC: algorithms for rapid unsupervised cryo-EM structure determination.* Nat Methods, 2017. **14**: p. 290-296.
- 2. Sievers, F., et al., *Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega.* Mol Syst Biol, 2011. **7**: p. 539.