

Heavy Chain V-gene

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-----FR1----- CDR H1 -----FR2----- CDR H2 -----FR3-----
IGHV4-59 QVQLQESGPGLVKPSSETLSLTCTVSGGSIS SYYWSWIRQPPGKGLEWIGYIYSGSTN YNPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYC
H7.HK1 QVQLQESGPGLVKPSSETLSLTCSVSGGSI N SYYWTWIRQPPGKGLEWVGYIYHSGSTS YNPSLKSRITISVAPSKNHFSLELTSMTAADTAVYYCAR
H7.HK2 QVQLQGSGPGLLRPSETLSLTCSVSGVSIN SYYWSWVRQPPGKALEWIGYIYSGNTN YNPSLESRVTISVDRSKNQFSLKMTSVTAADTARYFCAR
IGHV7-4-1 QVQLVQSGSELKPKGASVKVSCKASGYTFT SYAMNWRQAPGQGLEWMGWINTNTGNPTYAQGFTRGRVFSLDTSVSTAYLQICSLKAEDTAVYYC
H7.HK3 QVQLVQSGSELKRPGASVKVSCRASGYTFT SYTINWVRQAPGQGLEWMGWINTSTGDPTYAQGFTRGRVFSLDTSVSTAYLEISRLKAEDTAVYYCAR
IGHV4-61 QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGSYWSWIRQPPGKGLEWIGYIYSGSTN YNPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYC
H7.HK4 QVQLQESGPGLVKPSSETLSLTCTVSGGSVRSASYAWSWIRQPPGKGLEWIGDIYSGTTN YNPSLKSRTLSVDTAKNRFSLRLRSVTAADTAVYHCAR
  
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Light Chain V-gene

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-----FR1----- CDR L1 -----FR2----- CDRL2 -----FR3-----
IGKV2-28 DIVMTQSPSLPVPTEGEPASISCRSSQSLLSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
H7.HK1 DIVMTQSPVSLPVTPGEPASISCNSSQSLLSNGYALDWYLQKPGQSPKLMIYLGLNRAFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
H7.HK2 DIVMTQSPSLPVPTEGEPASISCRSNQSLQHSNGYVLDWYRQKPGQSPHLLIYLGFNRASGVPDRFSGGGSGTDFTLKISRVEAEDVGVYYC
IGKV1-5 DIQMTQSPSTLSASVGDRTITCRASQSI SSWLA WYQQKPGKAPKLLIYDASSLESQVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
H7.HK3 DIQMTQSPSTLSASVGDRTITCRASQSI SSWLA WYQQKPGKAPKLLIKASSLESQVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
IGKV1-16 DIQMTQSPSSLSASVGDRTITCRASQGI SNYLA WFQQKPGKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC
H7.HK4 DIQMTQSPSSLSASVGDRTITCRASQGI RNYLA WFQQKPGQAPKSLIFAASSLHTGVPSRFSGSGSGTDFTLTISLQPEDFATYYC
  
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CDR3

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      CDR H3      ----FR4----      CDR L3 ----FR4----
H7.HK1 LGGHGDYGSDY  WGQGTLVTVSS      MQALQTPFTFGPGTRVDIK
H7.HK2 QGIFGDYGSDY  WPGGTLVTVSS      MQGLQTPFTFGPTTVDLK
H7.HK3 AFGLTVVRGGIVGVWGQGTTVTVSS      QQYNSYSQTFGQGTKVEIK
H7.HK4 ERYYYGSSGDFDY  WQQGTLVTVSS      QHYNSYPPTFGQGTKLEIK
  
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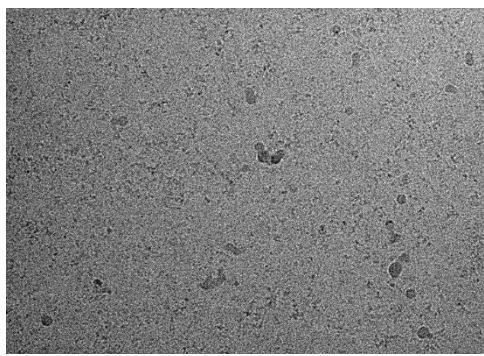
Supplementary Fig. 1 H7.HK mAb sequences. Protein sequences of the heavy and light chain variable regions of the H7.HK mAbs are aligned to the putative germline V-genes at top, with amino acid substitutions in red, and in magenta for substitutions shared between the clonally related mAbs H7.HK1 and H7.HK2. Spaces are added to maintain alignment; framework regions (FR) and complementarity-determining regions (CDRs) are indicated based on the Chothia nomenclature. Highlighted in yellow are the mAb residues (paratopes of H7.HK1 and H7.HK2) contacting the H7 antigen. The putative N-linked glycosylation sites on the light chain CDR L1 of H7.HK1 and H7.HK2 and the heavy chain CDR H2 of H7.HK3 are underlined.

A

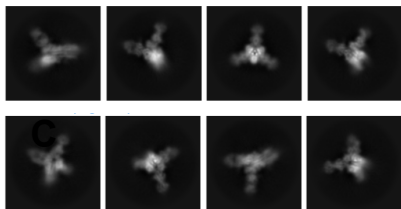
H7.HK1



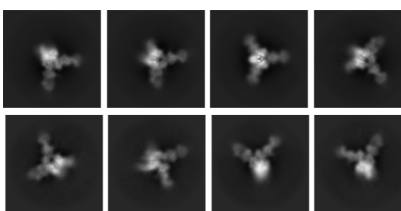
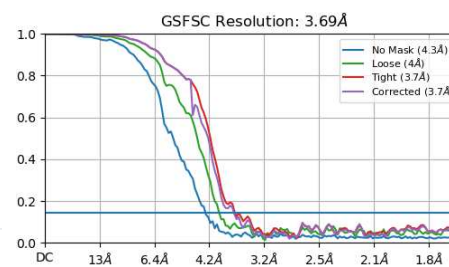
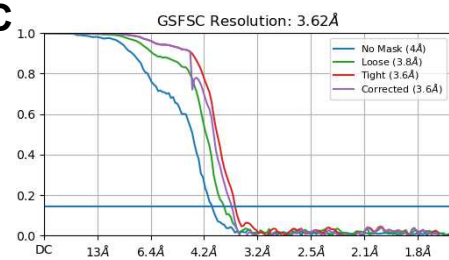
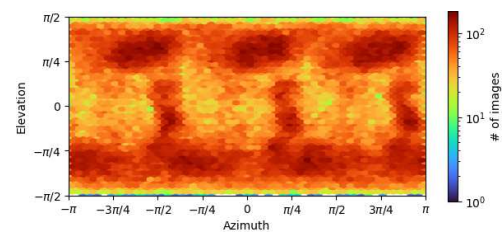
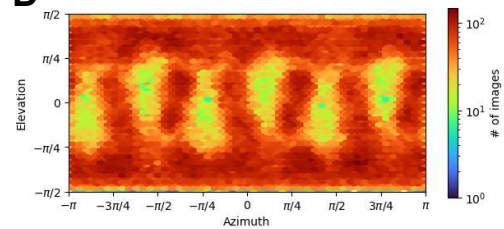
H7.HK2

**B**

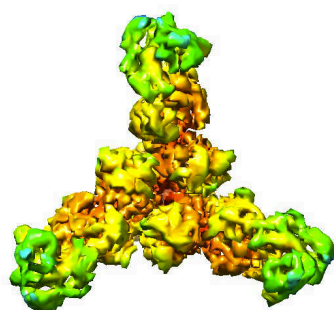
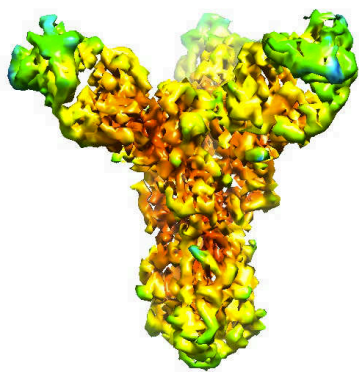
H7.HK1



H7.HK2

**C****D****E**

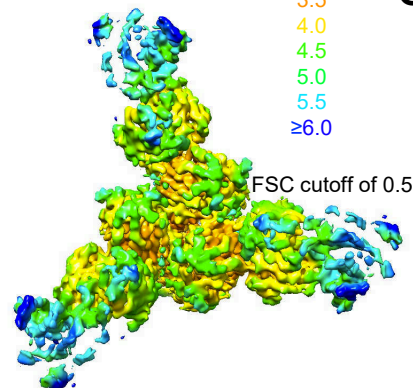
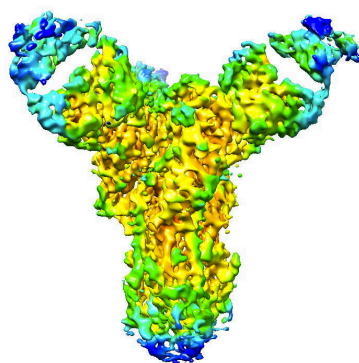
H7.HK1



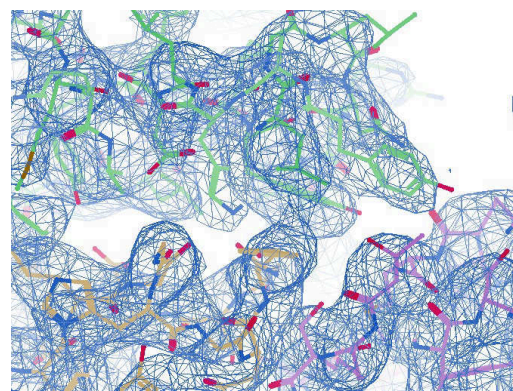
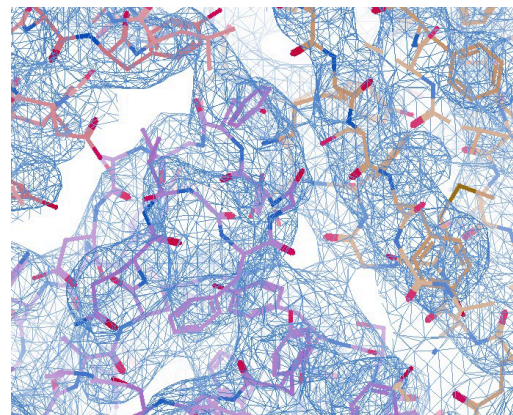
Local Resolution (Å)

≤3.0
 3.5
 4.0
 4.5
 5.0
 5.5
 ≥6.0

H7.HK2

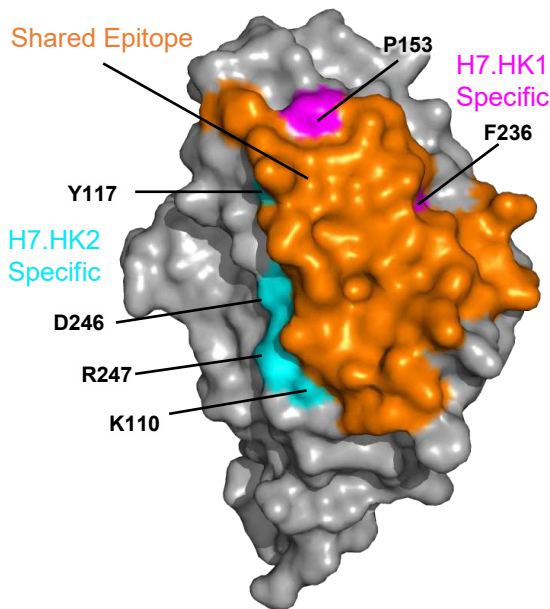


FSC cutoff of 0.5

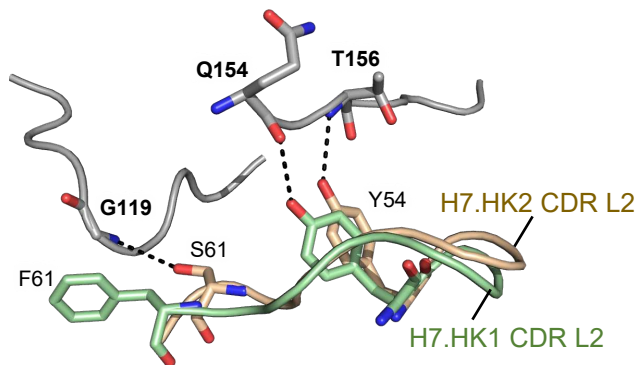
F**G**

Supplementary Fig. 2 Cryo-EM details of H7.HK1 and H7.HK2 in complex with H7 SH13 DS2 6R HA trimer.

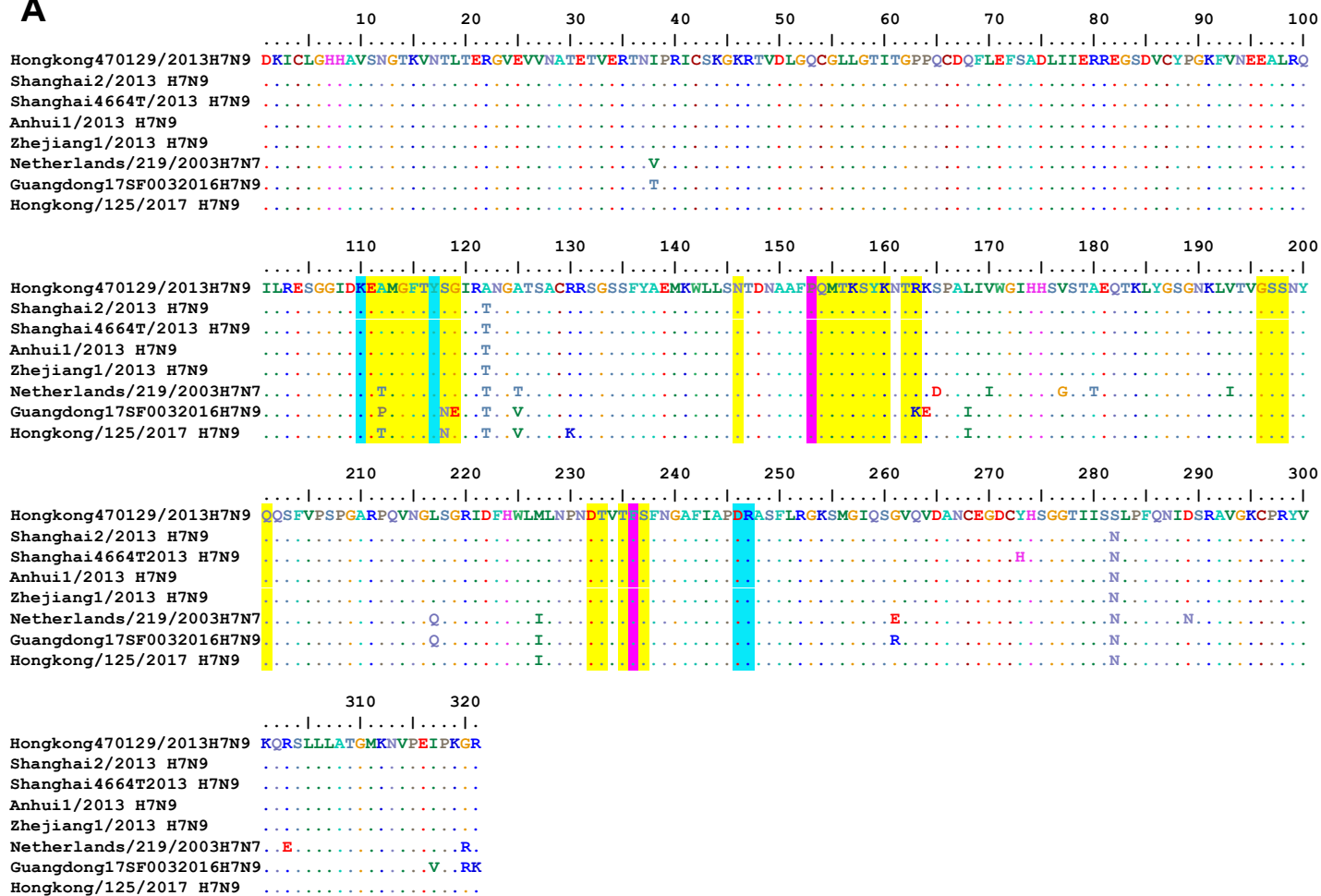
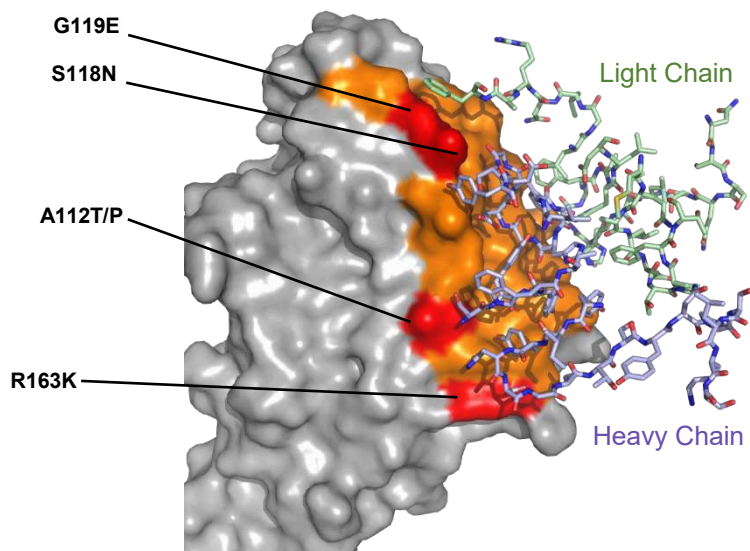
(A) Representative micrograph of H7.HK1 (left) and H7.HK2 (right). (B) Representative 2D class averages of H7.HK1 and H7.HK2. (C) The gold-standard Fourier Shell Correlation (FSC) resulted in a resolution of 3.62 Å for the overall map of H7.HK1 and 3.69 Å for the overall map of H7.HK2. Non-uniform refinement with C3 symmetry was used for both reconstructions. (D) The orientations of all particles used in the final refinement are shown as a heatmap. (E) The local resolution of the final overall map is shown contoured at 0.0989 for both structures. Resolution estimation was generated through cryoSPARC using an FSC cutoff of 0.5. (F) Representative density is shown for the interface of H7.HK1 heavy chain, light chain, and H7 HA. (G) Representative density is shown for the interface of H7.HK2 heavy chain, light chain, and H7 HA.

A**B**

	<u>H7.HK1</u> : <u>H7</u>	<u>H7.HK2</u> : <u>H7</u>
Heavy Chain	Y52 : E111	Y52 : Y159
H Bonds	R97 : G114	R97 : G114
	G102 : S158	G102 : S158
	D103 : T116	D103 : T116
	Y104 : T156	Y104 : T156
	Y104 : S158	Y104 : S158
	S106 : T116	S106 : T116
Heavy Chain		
Salt Bridge	H53 : E111	
Light Chain		
H Bonds	Y54 : Q154	Y54 : T156
		S61 : G119

C

Supplementary Fig. 3 Comparison of H7.HK1 and H7.HK2 binding to H7. (A) Differences in epitopes of H7.HK1 and H7.HK2. Majority of surface contacts are conserved, shown in orange. H7.HK1 specific surfaces are shown in magenta, and H7.HK2 specific surfaces are shown in cyan. (B) Hydrogen bonds and salt bridges formed by H7.HK1 and H7.HK2 with H7. (C) Differences in CDR L2 binding to H7 by H7.HK1 and H7.HK2 as a result of F61S substitution in H7.HK2. S61 forms an additional hydrogen bond with G119 of H7. Additionally, position of Y54 is shifted so that it forms a hydrogen bond with T156 for H7.HK2 instead of Q154 for H7.HK1.

A**B**

Supplementary Fig. 4 Antigenic drift of H7 HA1 in 2016-2017. (A) H7 HA1 protein sequences from the indicated viral isolates are aligned to the 2013 Hong Kong H7N9 autologous isolate at top, with identical amino acids shown in dots. Highlighted in yellow are the H7 residues (epitope) forming contacts with both mAbs H7.HK1 and H7.HK2. H7.HK1 specific epitopes are in magenta; H7.HK2 specific epitopes are in cyan. (B) Surface presentation of the H7 HA1 domain highlighting the epitopes (orange) of mAbs H7.HK1 and H7.HK2, with four mutations in red that appeared in the 2016-2017 viral isolates of H7N9. The sticks are interacting CDRs of mAb H7.HK1 heavy and light chains.

Supplementary Table 1 Cryo-EM data collection, refinement, and validation statistics for H7 SH13 DS2 6R HA in complex with H7.HK1 and H7.HK2 Fabs.

	H7 SH13 DS2 6R H7.HK1 (EMD-41422) (PDB: 8TNL)	H7 SH13 DS2 6R H7.HK2 (EMD-41441) (PDB: 8TOA)
Data collection and processing		
Magnification	105000	105000
Voltage (kV)	300	300
Electron exposure (e-/Å ²)	58	58
Defocus range (µm)	0.8-2	0.8-2
Pixel size (Å)	0.83	0.83
Symmetry imposed	C3	C3
Initial particle images (no.)	5713957	2339643
Final particle images (no.)	178347	191469
Map resolution (Å)	3.62	3.69
FSC threshold	0.143	0.143
Refinement		
Initial model used (PDB code)	6IDD	8TNL
Model resolution (Å)	3.62	3.69
FSC threshold	0.143	0.143
Model composition		
Non-hydrogen atoms	16487	15570
Protein residues	2112	2109
Ligands	7	11
<i>B</i> factors (Å ²)		
Protein	39.71	58.34
Ligand	58.78	48.38
R.m.s. deviations		
Bond lengths (Å)	0.005	0.007
Bond angles (°)	1.121	1.231
Validation		
MolProbity score	1.65	2.23
Clashscore	5.45	12.08
Poor rotamers (%)	0.06	1.62
Ramachandran plot		
Favored (%)	94.86	92.30
Allowed (%)	5.14	7.41
Disallowed (%)	0.0	0.29