

**Table S1: Amino acid sequences at the C-terminus of HA-subtypes from Flu A, HA from Flu B and HEF From Flu C and Flu D**

	subtype	host	transmembrane domain										cytoplasmic tail											
Group-1	H1	A, H, P	V	S	L	G	A	I	S	F	W	M	C	S	N	G	S	L	Q	C	R	I	C	I
	H2	A, H, P	I	M	I	A	G	I	S	F	W	M	C	S	N	G	S	L	Q	C	R	I	C	I
	H5	A	I	M	V	A	G	L	S	L	W	M	C	S	N	G	S	L	Q	C	R	I	C	I
	H6	A	G	L	I	I	A	M	G	L	W	M	C	S	N	G	S	M	Q	C	R	I	C	I
	H8	A	I	L	I	A	G	G	L	I	L	G	M	Q	N	G	S	C	R	C	M	F	C	I
	H9	A	M	G	F	A	A	F	L	F	W	A	M	S	N	G	S	C	R	C	N	I	C	I
	H12	A	L	M	I	I	G	G	F	I	F	G	C	Q	N	G	N	V	R	C	T	F	C	I
	H11	A	A	I	I	M	G	F	I	F	W	A	C	S	N	G	S	C	R	C	T	I	C	I
	H13 gull	A	G	L	I	L	A	F	I	M	W	A	C	S	S	G	N	C	R	F	N	V	C	I
	H16 gull	A	G	L	I	L	A	F	I	M	W	A	C	S	S	G	N	C	R	F	N	V	C	I
	H17 bat	B	S	L	I	I	A	A	F	L	W	G	C	Q	K	G	S	I	Q	C	K	I	C	I
	H18 bat	B	L	I	I	L	A	A	I	E	W	G	C	F	K	G	N	L	Q	C	R	I	C	I
Group-2	H3	A, H, P,E	V	V	L	L	G	F	I	M	W	A	C	Q	K	G	N	I	R	C	N	I	C	I
	H4	A	A	L	L	L	A	F	I	L	W	A	C	Q	N	G	N	I	R	C	Q	I	C	I
	H7	A, E	A	I	A	M	G	L	V	F	I	C	I	K	N	G	N	M	R	C	T	I	C	I
	H10	A	A	V	I	M	G	L	V	F	F	C	L	K	N	G	N	M	R	C	T	I	C	I
	H14	A	A	L	I	L	G	F	V	L	W	A	C	Q	N	G	N	I	R	C	Q	I	C	I
	H15	A	A	I	A	M	G	L	I	F	M	C	V	K	N	G	N	L	R	C	T	I	C	I
	Flu B	H	L	M	I	A	I	F	I	V	Y	M	V	S	R	D	N	V	S	C	S	I	C	L
	toad	Am	A	I	T	I	A	A	G	I	M	F	L	C	K	N	G	R	C	T	I	C	I	
	eel	F	I	V	I	A	G	A	I	M	Y	M	G	K	S	G	N	I	R	C	N	I	C	L
	Flu C	H	L	A	A	L	V	I	S	G	I	A	C	R	T	K								
	Flu D	C, P	I	A	A	F	V	G	V	I	W	I	C	C	K	K								

Acylated cysteine residues are highlighted in yellow. Sequences are the consensus sequences calculated for each HA subtype and for HA of Flu B as described in Siche et al.

H17 and H18 are viruses from bats.

H17: A/little yellow-shouldered bat/Guatemala/060/2010(H17N10). Accession number:

AFC35438. H18: A/flat-faced bat/Peru/033/2010(H18N11); AGX84934:

Influenza C virus (C/Johannesburg/1/1966); UniProtKB - P07975.

Influenza D virus (D/bovine/France/2986/2012; NC\_026952.

Toad: Wuhan asiatic toad influenza virus, unclassified Orthomyxovirus; AVM87632

Eel: Wuhan spiny eel influenza virus, unclassified Orthomyxovirus; AVM87624

Hosts: A: avian, H: human, P: pig, B: bat, E: equine, C: cattle, Am: amphibia, F: fish

**Table S2: Accession numbers of HA sequences used to generate the phylogenetic tree in Fig.1**

Virus name	Subtype	No
A/WSN/1933(H1N1)	H1	U08903.1
A/semi-palmated sandpiper/Brazil/43/1990(H2N1)	H2	CY005413.1
A/mallard duck/ALB/26/1976(H3N1)	H3	CY005943.1
A/mallard/ALB/47/1998(H4N1)	H4	CY004925.1
A/turkey/England/50-92/91(H5N1)	H5	EU636692.1
A/gray teal/Australia/1/1979(H6N1)	H6	CY014623.1
A/chicken/Rostock/45/1934(H7N1)	H7	CY077420.1
A/turkey/Ontario/6118/1968(H8N4)	H8	CY014659.1
A/mallard/Alberta/11/1991(H9N2)	H9	CY005990.1
A/mallard/ALB/5/1995(H10N1)	H10	CY005997.1
A/black duck/Ohio/194/1986(H11N1)	H11	CY017765.1
A/mallard/Interior Alaska/9BM1907R1/2009(H12)	H12	CY079894.1
A/herring gull/DE/475/1986(H13N2)	H13	CY005914.1
A/blue-winged teal/Guatemala/CIP049H106-62/2011(H14N6)	H14	KJ195668.1
A/sooty tern/Western Australia/2190/1983(H15N9)	H15	CY006033.1
A/herring gull/DE/712/1988(H16N3)	H16	CY005933.1
A/little yellow-shouldered bat/Guatemala/153/2009(H17N10)	H17	CY103876.1
A/Artibeus lituratus/Brazil/2301/2012(H18N11)	H18	MH682203.1
B/Lee/40	FluB HA	DQ792897.1
C/Ann Arbor/1/50	FluC HEF	NC_006310.2
D/bovine/Texas/72/2017	FluD HEF	MT636473.1

**Table S3: Frequency of amino acids other than cysteine at position 50 of M2 of the indicated virus strains**

Virus host HA-subtype	Time period of collection date	Total M2 Sequences	Unique M2 Sequences	Percent of unique sequences not containing a Cys 50 Substituted by
<b>Avian M2</b>				
H1	1976-2018	945	158	<b>1,9%</b> Tyr, Ser
H2	1973-2018	541	109	<b>1,9%</b> Tyr
H3	1963-2019	2181	271	<b>2,2%</b> Tyr
H4	1956-2019	2012	224	<b>1,3%</b> , Tyr, Phe
H5	1995-2020	4208	845	<b>11,0%</b> Tyr
<i>H5N1</i>	1996-2019	2360	501	<b>10%</b> , Tyr
H6	1963-2018	1781	331	<b>8,5%</b>
H7	1902-2018	2163	344	<b>2,6%</b>
<i>H7N9</i>	2013-2017	623	94	<b>3,2%</b> , Tyr
H8	1967-2016	178	37	<b>11 %</b>
H9	1966-2019	2006	660	<b>12%</b>
H10	1949-2019	1281	144	<b>0,7%</b>
H11	1956-2019	767	135	<b>2,2%</b>
H12	1975-2018	349	62	<b>0</b>
H13	1977-2018	515	78	<b>2,5%</b>
H14	1982-2016	40	10	<b>0</b>
H15	1979-2015	10	1	<b>0</b>
H16	1975-2019	258	45	<b>0</b>
<b>Human M2</b>				
H1N1 „Spanish-Flu“	1918-1976	84	28	<b>0%</b>
H1N1 „Russian Flu“	1977-2008	1437	162	<b>74%</b> , Ser
H1N1 „Swine Flu“	2010-2020	11186	454	<b>0,2%</b> , Tyr
H2N2 „Asian Flu“	1957-1968	122	23	<b>0%</b>
H3N2 „Hongkong“	1968-2020	23232	905	<b>0,4%</b> , Tyr
H5 „bird Flu“	1997-2018	202	62	<b>24%</b> , Tyr, Phe
H7 „bird Flu“	1996-2018	127	36	<b>2,8%</b> , Tyr
<b>Porcine M2</b>				
H1N1	1930-2019	4050	934	<b>3,3%</b> , Tyr, Phe, Ser
H3N2	1978-2019	3030	620	<b>2,4%</b> , Tyr, Phe
H1N2	1980-2019	3174	676	<b>2,5%</b> , Tyr, Trp, Phe, Ser
<b>Equine M2</b>				
H7N7	1956-1977	15	7	<b>0%</b>
H3N8	1963-2017	200	45	<b>87%</b> , Phe
<b>Canine M2</b>				
H3N8	2003-2016	61	15	<b>87%</b> , Phe, Ser
H3N2	2006-2019	240	36	<b>0%</b>
<b>Bat M2</b>				
H17N10	2009-2010	2	2	<b>100%</b> , only Tyr
H18N11	2010-2011	2	2	<b>100%</b> , only Tyr

The NCBI database was searched for full-length M2 sequences (97 amino acids) present in a virus from a specific host, and having a specific HA (and partially NA) subtype as indicated. M2 sequences were aligned and the number of cysteines at position 50 calculated. The “time period of collection date” is the first and last year were the virus was isolated or sequenced.

Table S4: Amino acid sequences at the C-terminus of the spike protein of Coronaviruses

Genus	Subgenus	Species	Host	TMR	Cytoplasmic tail
Alpha	Pedacovirus	512/2005	Scoto. kuhlii	WYVWLAIVIALILVVSLLVF	CCISTGCCGCCGCGSCFSGCCRGTKLQHYEPIEKVHVQ
	Tegacovirus	Insavc-1	Canis lupus	WYVWLLIGLVVIFCIPILLF	CCCSTGCCGCIGCLGSCCHSICSRQGFESEYEPIEKVHVH
		FIPV	Felidae	WYVWLLIGLVVFCIPLLLF	CCFSTGCCGCIGCLGSCCHSICSRQGFESEYEPIEKVHVH
	Duvinacovirus	hCoV 229E	Homo sapiens	WWVWLCISVVLIFVVSMLLL	CCCSTGCCGFFSCFASSIRGCCSTKLPYYDVEKIHQ
	Setracovirus	hCoV NL63	Homo sapiens	WWVWLIISVVFVLLSLLVF	CCLSTGCCGCCNCLTSSMRGCCDCCGSTKLPYYEVEKVVHVQ
	Rhinacovirus	SADS	Sus scrofa	WAWWQWLLIFIALTLLAGLMLW	CCLATGCCGMCGLAATCASCCDCRGTKLQSYEIEKVVHVQ
Beta	Sarbecovirus	SARS2	Homo sapiens	WYIWLGFIAGLIAIVMTIML	CCMTSCCSCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
		RaTG13	R. affinis	WYIWLGFIAGLIAIMVTIML	CCMTSCCSCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
		Pangolin	M. javanica	WYIWLGFIAGLIAIMVTIML	CCMTSCCSCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
		SARS	Homo sapiens	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
		HKU3	R. sinicus	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
		Rp3/2004	R. spec	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
		279/2005	R. macrotis	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
		RsSHC014	R. sinicus	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
		Rs3367	R. sinicus	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
	Merbecovirus	MERS	Homo sapiens	WYIWLGFIAGLVALALCVFFI	LCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKVHVH
		HKU4	Tylo. pachypus	WYVWLGFIAGLVALLCVFFL	LCCTGCGTSCLGKMKCKNCCDSYEEYDVEKIHVH
		Neo	Neo. capensis	WYIWLGFIAGLLALALCVFFI	LCCTGCGTSCLGKLKCNRCCDKYEEYDLEPHKIHVH
		HKU5	Pip. abramus	WYIWLGFIAGLVALALCVFFI	LCCTGCGTSCLGKLKCNRCCDSYDEYEVEKIHVH
		133/2005	Tylo.pachypus	WYIWLGFIAGLVALLCVFFL	LCCTGCGTSCLGKMKCKNCCDSYEEYDVEKIHVH
	Embecovirus	hCoV HKU1	Homo sapiens	WYVWLLISFSFIIFLVLLFFI	CCCTGCGSACFSKCHNCCDEYGGHHDFVIKTSRDD
		hCoV OC43	Homo sapiens	WYVWLLICLAGVAMLVLLFFI	CCCTGCGTSCFKKCGGCCDDYTGYQELVIKTSRDD
		MHV	Mus musculus	WYVWLLIGLAGVAVCVLLFFI	CCCTGCGSCCFKKCGNCCDEYGGHQSIVIHNISSHED
		Quebec	Bos taurus	WYVWLLIGFAGVAMLVLLFFI	CCCTGCGTSCFKICGGCCDDYTGHQELVIKTSRDD
	Nobecovirus	HKU9	R.leschenaulti	WYVWLAMIAGIVGLVLAVIML	MCMTNCCSCFKGMCDCRRCCGSYDSYDDVYPAVRVNKKRTV
Gamma	Igacovirus	IBV	Gallus gallus	VWLAIATIIIFILIGWVFF	MTGCCGCCGCFGIMPLMSKCGKKSSYYTTFDNDVTEQ...
Delta	Andecovirus	HKU20	wigeon	WWVWLLIFLAICTFIIIVTIFL	CTGCCGCCGCFGCGGCCGLFSRVKHHEFSLPVEEQDGS...
	Herdecovirus	HKU19	Night heron	WYVWLAIALAFTGFVTILITIFL	CTGCCGCCGCFGCGGCCFGLFSKKIDPMRQYMNRYETPTSK...
	Buldecovirus	PDCoV	Sus scrofa	WYIWLAIALALIAFVTILITIFL	CTGCCGCCGCFGCGGCCFGLFSKKKRYTDDQPTPSFKFEW
Unclassified		GCWSCoV	Tro. sinicus	WWVWLIISIVWTIFFLLILM	CCCFGTGCCGICGCIARSARKRLDVEGGHFKYD

**Cysteine residues are highlighted in yellow; ...: indicate additional amino acids.**

**Accession numbers:** SARS-CoV2 (sp|P0DTC2), SARS-CoV (sp|P59594), MERS-CoV (sp|K9N5Q8), Bat coronaviruses; HKU3 (SARS-like coronavirus HKU3(sp|Q3LZX1), HKU4 (Bat coronavirus HKU4 (sp|A3EX94), HKU5 (Bat coronavirus HKU5(sp|A3EXD0), HKU9 (Bat coronavirus HKU9 (sp|A3EXG6), Rp3/2004 (Bat coronavirus Rp3/2004(sp|Q3I5J5), 133/2005 (Bat coronavirus 133/2005(sp|Q0Q4F2), 512/2005 (Bat coronavirus 512/2005(sp|Q0Q466), 279/2005 (Bat coronavirus 279/2005 (sp|Q0Q475), RaTG13 (Bat coronavirus RaTG13) (tr|A0A6B9WHD3), RsSHC014 (Bat SARS-like coronavirus RsSHC014 (tr|U5WLK5), Rs3367 (Bat SARS-like coronavirus Rs3367 (tr|U5WHZ7), NeoCoV (Coronavirus Neoromicia/PML-PHE1/RSA/2011(AGY29650.2), Human coronaviruses; HKU1 (human coronaviruses HKU1-isolate N1) (sp|Q5MQD0), 229E (Human coronavirus 229E) (sp|P15423), NL63 (Human coronavirus NL63) (sp|Q6Q1S2) and OC43 (Human coronavirus OC43) (sp|P36334), Quebec (Bovine coronavirus Quebec strain) (sp|P25193), Insavc-1 (canine coronavirus Insavc-1 strain) (sp|P36300), IBV (Avian infectious bronchitis virus)(sp|P11223), FIPV (Feline infectious peritonitis virus) (sp|P10033), MHV (Murine hepatitis virus) (sp|P11224), Pangolin coronavirus (tr|A0A6G6A2R8), HKU20 (Wigeon coronavirus HKU20 (tr|H9BR25), HKU19 (Night heron coronavirus HKU19) (tr|H9BR17), SADS (Swine acute diarrhea syndrome coronavirus)(tr|A0A2P1G7F5), PDCoV (Porcine deltacoronavirus)(tr|A0A140ESF1), GCWSCoV (Guangdong Chinese water skink coronavirus) (AVM87574).

**Table S5: Amino acid sequences at the C-terminus of the spike protein of newly discovered Coronaviruses with zoonotic potential**

Genus	Subgenus	Species	Host	TMR	Cytoplasmic tail
Alpha	Minunacovirus	Bat CoV 1	Miniopterus sp.	WYVWLAIAVTLIILVGPMWLW	CCLATGCCGCSCLVNSCSDCGGRRLQRYEIEKVHVQ
	Pedacovirus	512/2005	Scotophilus kuhlii	WYVWLAIVIALILVVSLLVF	CCISTGCCGCGCGSCFSGCCRGTKLQHYEPIEKVHVQ
	Unclassified	BtKY22/2006	Chaerephon sp.	WYVWLLIVVALTILAGIMLY	CCLATGCCGCSCLMTNTLDFRGRNLQRYEVEKVHVQ
Beta	Sarbecovirus	SARS-2	Homo sapiens	WYIWLGFIAGLIAIVMTIML	CCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
		SARS	Homo sapiens	WYVWLGFIAGLIAIVMTILL	CCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT
	Embecovirus	Longquan Aa	Apodemus agrarius	WYVWLLIGLAGVAVLVLLF...	CCCTGCGASCFFKCGSCDDYGGHQDIVVKTSRDD
	Merbecovirus	MERS	Homo sapiens	WYIWLGFIAGLVALALCVFFI	LCCGTGCGTNCMGKLKCNRCDDRYEEDYLEPHKVHVH
		SC2013	Vespertilio superans	WYIWLGFIAGLVALALCVF...	LCCGTGCGTNCMGKLKCNRCDDKYDDYDVEPHKIHVH
	Unclassified	BtKY24/2006	Eidolon helvum	WYAWLGMIAGLVGLAMAVFMLC	CCMTNCCSGLKGI CSCKQCQYDDYADVPAVRVSGKRTV
Unclassified		Rodent CoV	Myodes rufocanus	WYVWLLIGLAGVAVLVLLF...	CCCTGCGSSCFKKCGGDDYGGHQELVIKTSRDD

Cysteine residues are highlighted in yellow: ....dots indicate incomplete sequences

**Spike protein sequences** of Coronaviruses; BtKY22/2006 (Chaerephon bat coronavirus/Kenya/KY22/2006) (tr|F1DB20), Longquan Aa (Longquan Aa mouse coronavirus) (tr|A0A096XNE4), BtKY24/2006 (Eidolon bat coronavirus/Kenya/KY24/2006) (tr|F1DAZ1), Rodent CoV (Rodent coronavirus) (tr|A0A2H4MXV6), Bat CoV 1 (Miniopterus bat coronavirus 1) (tr|B1PHJ5), SC2013 (BtVs-BetaCoV/SC2013) (tr|A0A023Y9K3), 512/2005 (Bat coronavirus 512/2005) (sp|Q0Q466)

Animal hosts and their taxonomy: *Chaerephon* sp. Is belonging to the bat *Molossidae*, *Miniopterus* sp. to the family *Miniopteridae*, *Eidolon helvum* to the family *Pteropodidae* and the bats *Scotophilus kuhlii* and *Vespertilio sinensis* belong to the family *Vespertilionidae*. The rodents *Apodemus agrarius* belongs to the family *Muridae* and *Myodes rufocanus* to the family *Cricetidae*.

Table S6: Amino acid sequences at the C-terminus of the envelope protein of Coronaviruses

Genus	Subgenus	Species	Host	TMR	Cytoplasmic tail
Alpha	Pedacovirus	512/2005	Scoto. kuhlii	ILWLFLVLFVFLVISITFVQLI	NLCFTCHRLCNNVVYKPVGKVGKVSYSYMRIQPLTSDIIQV
	Tegacovirus	Insavc-1	Canis lupus	IFWFLIIIIILILFSIALLNII	KLCMVCCNLGRTVIIIVPARHAYDAYKNFMQIRAYNPDEALLV
		FIPV	Felidae	FFWLLLLIIIIILILFSIALLNVI	KLCMVCCNLGKTIIVLIPARHAYDAYKTFMQTKAYNPDEAFLV
	Duvinacovirus	hCov 229E	Homo sapiens	LLWCVLIVILLVCITIIKLI	KLCFTCHMFCNRTVYGPIKNVYHIYQSYMHDFFPKRVIDF
	Setracovirus	hCoV NL63	Homo sapiens	ILWLLVMIIFFVLAMTFIKLI	QLCFTCHYFFSRTLYQPVYKIFLAYQDYMQIAPVPAEVLNV
	Rhinacovirus	SADS	Sus scrofa	...VLWLLVLILVLLVAITVIKLI	QLCFSCHRLMSNTIYIPVYNAYLVYKSYMEVEPCPIINV
Beta	Sarbecovirus	SARS2	Homo sapiens	VNSVLLFLAFVVFLLVTLAIL	TALRLCAYCCNIVNVSLVKPSFYVYSRVKLNLSRVPDLLV
		RaTG13	R. affinis	...VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPSFYVYSRVKLNLSRVPDLLV
		Pangolin	M. javanica	...VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPSFYVYSRVKLNLSRVPDLLV
		SARS	Homo sapiens	VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		HKU3	R. sinicus	VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		Rp3/2004	R. spec	VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		279/2005	R. macrotis	VLLFFAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		RsSHC014	R. sinicus	...VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		Rs3367	R. sinicus	...VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKLNLSSEGVPDLLV
		MERS	Homo sapiens	FIFTVVCAITLLVCMAFLTAT	RLCVQCMTGFNTLLVQPALYLYNTGRSVYVKFQDSKPPLPP
		HKU4	Tylo. pachypus	FILTVVCAITLVVCLAILTAI	RLCVQCASGVNTLLFVPAFYIYNTGRNAYFKFQENRPPFP
		Neo	Neo. capensis	FIFTVVCAITLLVCMAFLTAT	RLCVQCITGVNTLLVQPAVYMYNTGRSVYVKFQESKPPLPP...
		HKU5	Pip. abramus	FILSVCAVTLVCLAILTAI	RLCVQCVSGCHTLVFLPAVHIYNTGRAAYVKFQESHPPYPP
		133/2005	Tylo. pachypus	FILTVVCAITLLVCLAVLTAI	RLCVQCASGVNTLLFVPAFYIYNTGRNAYFKFQENRPPFP
	Embecovirus	hCoV HKU1	Homo sapiens	LVLVLFCLISLIFVVAFLATI	KLCMQLCGFCNFFIISPSAYVYKRGMQLYKSYSEQVIPPTSD
		hCoV OC43	Homo sapiens	IFIVAICLLVTIVVVAFLATF	KLCIQLCGMCNTLVLSPSIYVFNRGRQFYEFYNDVKPPVLD
		MHV	Mus musculus	IFIFAVCLMVTIIVVAFLASI	KLCIQLCGLCNTLVLSPSIYLYDRSKQLYKYYNEEMRLPLLE
		Ontario	Bos taurus	IFIVAICLLVIIIVVVAFLATF	KLCIQLCGMCNTLVLSPSIYVFNRGRQFYEFYNDVKPPVLD
	Nobecovirus	HKU9	R. leschenaulti	LVLIIICLLVVIIVGCALLLIL	QFVFGVCGFVFKFVCKPTILVYNKFRNESLLNEREELL
Gamma	Igacovirus	IBV	Gallus gallus	NGSFLTALYIIIVGFLALYLLG	RALQAFVQAADA CCLFWYTWVVIPGAKGTAFVYKYTYGRK...
Delta	Andecovirus	HKU20	Wigeon	...PGSVVIAFLIVACCILLLLFI	KTCLAIFDCCSRSCTCVLDTVKPVYSFAYNLVPRFTPPYNP...
	Herdecovirus	HKU19	Night heron	...PAIYILVAVILLGCIVFLLLI	KTCLACCDFFTRTYT CILHTVKPIYVYLKPAPVVSKEDEYIK...
	Buldecovirus	PDCoV	Sus scrofa	GQYIIAILVVTICIGVALLFI	NTCLACVKLFYKCYLGAAYLVRPIIVYYSKPNPVPDEFVK...

**Cysteine residues are highlighted in yellow; ...: indicate additional amino acids**

**Accession numbers:** SARS-CoV2 (sp|P0DTC4), SARS-CoV (sp|P59637), MERS-CoV (sp|K9N5R3), Bat coronaviruses; HKU3 (SARS-like coronavirus HKU3)(sp|Q3LZW9), HKU4 (Bat coronavirus HKU4) (sp|A3EX99), HKU5 (Bat coronavirus HKU5) (sp|A3EXD5), HKU9 (Bat coronavirus HKU9) (sp|A3EXG8), Rp3/2004 (Bat coronavirus Rp3/2004) (sp|Q3I5J3), 133/2005 (Bat coronavirus 133/2005) (sp|Q0Q4E8), 512/2005 (Bat coronavirus 512/2005) (sp|Q0Q464), 279/2005 (Bat coronavirus 279/2005) (sp|Q0Q473), RaTG13 (Bat coronavirus RaTG13) (tr|A0A6B9WFI6), RsSHC014 (Bat SARS-like coronavirus RsSHC014) (tr|U5WI28), Rs3367 (Bat SARS-like coronavirus Rs3367) (tr|U5WLL8), NeoCoV (Coronavirus Neoromicia/PML-PHE1/RSA/2011) (AIG13101.1), Human coronaviruses; HKU1 (human coronaviruses HKU1-isolate N1) (sp|Q5MQC8), 229E (Human coronavirus 229E) (sp|P19741), NL63 (Human coronavirus NL63) (sp|Q6Q1S0) and OC43 (Human coronavirus OC43) (sp|Q04854), Ontario (Bovine coronavirus Ontario strain) (sp|P0C2Q6), Insavc-1 (canine coronavirus Insavc-1 strain) (sp|P36696), IBV (Avian infectious bronchitis virus)(sp|Q89894), FIPV (Feline infectious peritonitis virus) (sp|Q52PA5), MHV (Murine hepatitis virus) (sp|P0C2R0), Pangolin coronavirus (tr|A0A6G6A2K2), HKU20 (Wigeon coronavirus HKU20) (tr|H9BR26), and HKU19 (Night heron coronavirus HKU19) (tr|H9BR18), SADS (Swine acute diarrhea syndrome coronavirus)( tr|A0A2P1G6N3), PDCoV (Porcine deltacoronavirus)( tr|A0A0U2IVX8).



**Table S7: Amino acid sequences at the C-terminus of the envelope protein of newly discovered Coronaviruses with zoonotic potential**

Genus	Subgenus	Species	Host	TMR	Cytoplasmic tail
Alpha	Minunacovirus	Bat CoV 1	Miniopterus sp.	ILWLLFCVSVIIICCALIQLVQL...	QLCFICHRLCSNTVYKPVYKAYKIYQDYMQIEPLPVLNV
	Pedacovirus	512/2005	Scotophilus kuhlii	ILWLFLVFFVLVISITFVQLI	NLCFTCHRLCNNVVKPVGKVYGVYKSYMRIQPLTSDIIQV
	Unclassified	BtKY22/2006	Chaerephon sp.	LNLLLWLMICCAVIVICNAVI	QLIFTCHRFCSSTVYTPVYAVYRIYQNYMRIDPLPVIDV
Beta	Sarbecovirus	SARS2	Homo sapiens	VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPSFYVYSRVKNLNSSRPDLLV
		SARS	Homo sapiens	VLLFLAFVVFLLVTLAILTAL	RLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV
	Embecovirus	Longquan Aa	Apodemus agrarius	YVGQIILIVAICLLIIVIVVAA...	KLCIQLCGMCNTLVVSPSIYVYNRGRQFYKFYSDAKPP...
	Merbecovirus	MERS	Homo sapiens	FIFTVVCATLLVCMFLTAT	RLCVQCMTGFTLLVQPALYLYNTGRSVYVKFQDSKPPLPP
		SC2013	Vespertilio superans	FIVNFFIFTVACAIILLVCMA...	RLCVQCAIGLNALLVQPAIYVYNTGRSVYVKFQESKPP...
	Unclassified	BtKY24/2006	Eidolon helvum	LITNILLLVIASLLFVIVGCAL...	GACGCLANIVCKPTIILYRKFKYESLLNEQEDII
Unclassified		Rodent CoV	Myodes rufocanus	YVGQIIFIFAICLFVIVVVVAFLA	TFKLCVQLCGICNTLVLSPSIYVYNRGRQFYEFYQD...

Cysteine residues are highlighted in yellow: ... dots indicate incomplete sequences

**Envelope protein sequences** of Coronaviruses; BtKY22/2006 (Chaerephon bat coronavirus/Kenya/KY22/2006) (tr|F1DB22), Longquan Aa (Longquan Aa mouse coronavirus) (tr|A0A096XNF4), BtKY24/2006 (Eidolon bat coronavirus/Kenya/KY24/2006) (tr|F1DAZ3), Rodent CoV (Rodent coronavirus) (tr|A0A2H4N004), Bat CoV 1 (Miniopterus bat coronavirus 1) (tr|B1PHJ7), SC2013 (BtVs-BetaCoV/SC2013) (tr|A0A023Y9K8), 512/2005 (Bat coronavirus 512/2005) (sp|Q0Q464)

Animal hosts and their taxonomy: *Chaerephon* sp. is belonging to the bat *Molossidae*, *Miniopterus* sp. to the family *Miniopteridae*, *Eidolon helvum* to the family *Pteropodidae* and the bats *Scotophilus kuhlii* and *Vespertilio sinensis* belong to the family *Vespertilionidae*. The rodents *Apodemus agrarius* belongs to the family *Muridae* and *Myodes rufocanus* to the family *Cricetidae*.

**Table S8: Amino acid differences between human DHHC2 and DHHC2 of animal hosts of Flu A**

	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	5	15	25	35	45	55
Homo sapiens	-----	-----MA	PSGPGSS---	ARRRCRRVLY	WIPVVFITLL	LGWYYAYAI
Sus scrofa	-----	-----MA	PSGPGS----	VRRCRRVLY	WIPVVFISLL	LGWSYYAYAI
Gallus gallus	MRCGKMAAAA	P-----SAP	AAGAAGGWGG	VRRCQRLLY	WVPVLFISSI	LWSYYAYVT
Calidris pugnans	MRCEKMAAPP	PE--PPLPLP	PAGSAGTCMG	LRRRCQRLLY	WVPVLFISSI	LWSYYAYVT
Anas platyrhynchos	MRCGKMAAAP	PPVAAAGAAA	AAGAASGWGG	VRRCQRLLY	WVPVLFISSI	LWSYYAYVT
					<b>TMR1</b>	
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	65	75	85	95	105	115
Homo sapiens	QLCIVSMEN	GEQVVCLMAY	HLLFAMFVWS	YWKTIFTLPM	NPSKEFHLSY	AEKDLLEREP
Sus scrofa	QLCIVSMEN	GEQVVCLLAY	HLLFAMFVWS	YWKTIFTLPM	NPSKEFHLSY	AEKELLEREP
Gallus gallus	QLCLLTMTNI	GEKVVCLVAY	HIFFMLFVWS	YWKTIFTLPM	NPSKEFHLSY	SDKESLEREP
Calidris pugnans	QLCLLTMTNI	GEKVVCLVAY	HIFFMLFVWS	YWKTIFTLPM	NPSKEFHLSY	SDKESLEREP
Anas platyrhynchos	QLCLLTMTNI	GEKVVCLVAY	HIFFMLFVWS	YWKTIFTLPM	NPSKEFHLSY	SDKESLEREP
			<b>TMR2</b>			
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	125	135	145	155	165	175
Homo sapiens	RGEAHQEVLR	RAAKDLPIYT	RTMSGAIRYC	DRCLIKPDR	CHHCSVCDKC	ILKMDHHCPCW
Sus scrofa	RGEAHQEVLR	RAAKDLPIYT	RTMSGAIRYC	DRCLIKPDR	CHHCSVCDKC	ILKMDHHCPCW
Gallus gallus	RGESQQEVLR	RAAKDLPIYT	RTMSGAIRYC	DRCHLVKPDR	CHHCSVCDKC	ILKMDHHCPCW
Calidris pugnans	RGESQQEVLR	RAAKDLPIYT	RTMSGAIRYC	DRCHLVKPDR	CHHCSICDKC	ILKMDHHCPCW
Anas platyrhynchos	RGESQQEVLR	RAAKDLPIYT	RTMSGAIRYC	DRCHLVKPDR	CHHCSVCDKC	ILKMDHHCPCW
				<b>Zinc-binding</b>		<b>DHHC</b>
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	185	195	205	215	225	235
Homo sapiens	VNNCVGFSNY	KFFLLFLAYS	LLYCLFIAAT	DLQYFIKFWT	NGLPDTQAKF	HIMFLFFAAA
Sus scrofa	VNNCVGFSNY	KFFLLFLAYS	LLYCLFIAAT	DLQYFIKFWT	NGLPDTQAKF	HIMFLFFAAA
Gallus gallus	VNNCVGFSNY	KFFLLFLAYS	LLYCLFIAAT	DLQYFIKFWT	NGLPDTQAKF	HIMFLFFAAA
Calidris pugnans	VNNCVGFSNY	KFFLLFLAYS	LLYCLFIAAT	DLQYFIKFWT	NGLPDTQAKF	HIMFLFFAAA
Anas platyrhynchos	VNNCVGFSNY	KFFLLFLAYS	LLYCLFIAAT	DLQYFIKFWT	NGLPDTQAKF	HIMFLFFAAA
		<b>TMR3</b>				<b>TMR4</b>
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	245	255	265	275	285	295
Homo sapiens	MFSVSLSSLF	GYHCWLVSKN	KSTLEAFRSP	VFRHGTDKNG	FSLGFSKNMR	QVFGDEKKYW
Sus scrofa	MFSVSLSSLF	GYHCWLVSKN	KSTLEAFRSP	VFRHGTDKNG	FSLGFSKNMR	QVFGDEKKYW
Gallus gallus	MFSVSLSSLF	GYHCWLVSKN	KSTLEVFRAP	IFRHR	TDKNG	FSLGFSKNLR
Calidris pugnans	MFSVSLSSLF	GYHCWLVSKN	KSTLEVFRAP	IFRHR	TDKNG	FSLGFSKNLR
Anas platyrhynchos	MFSVSLSSLF	GYHCWLVSKN	KSTLEVFRAP	IFRHR	TDKNG	FSLGFSKNLR
			<b>TTXE</b>			<b>amphiphilic helix</b>
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....
	305	315	325	335	345	355
Homo sapiens	LLPIFSSSLGD	GCSFPTCLVN	QDPEQASTPA	GLNSTAKNLE	NHQFFAKPLR	ESQSHLLTDS
Sus scrofa	LLPIFSSSLGD	GCSFPTCLVN	QDPEQASTPA	GLNSTSKNPE	NHQFFAKPLR	ESQSHLLTDS
Gallus gallus	LLPVFSSSLGD	GCSFPTCLVN	QDPEQASTPG	GLNSTCKN-E	NHLPFAKPLR	DSQSHLLTDT
Calidris pugnans	LLPVFSSSLGD	GCSFPTCLVN	QDPEQASTPS	ALNSTSKN-E	NHLPFAKPLR	DSQSHLLTDT
Anas platyrhynchos	LLPVFSSSLGD	GCSFPTCLVN	QDPEQASTPG	GLNSTSKN-E	SLLFPFAKPLR	DSQSHLLTDT
		<b>End of model</b>		<b>unstructured</b>		
	..... .....	..... .....	..... .....			
	365	375	385			
Homo sapiens	QSWTESSINP	GKCKAGMSNP	ALTMENET			
Sus scrofa	QSWTESSTNP	GKCKSGMSNP	ALTMENET			
Gallus gallus	HSWSDIGAKA	EKGKVGMSNP	ALTMENET			
Calidris pugnans	PSWSETSGKA	EKGKVGMSNP	ALTMENET			
Anas platyrhynchos	QSWSDISAKA	EKGKIGMSNP	ALTMENET			

Amino acid alignment of DHHC2 of humans (*homo sapiens*), pigs (*sus scrofa*) and three avian species, chicken (*gallus gallus*), sandpiper (*Calidris pugnax*) and mallard duck (*Anas platyrhynchos*). The transmembrane regions are highlighted in grey, individual residues that contact the acyl chain in the cavity are highlighted in green and the two (S and T) that seal the cavity are highlighted in pink. The amphiphilic helix following TMR4 is also highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif (which is STLE in DHHC2) are highlighted in light blue. LVN is the end of the modeled structure and underlined is the part of the C-terminal region predicted to be unstructured.

Amino acid differences to human DHHC2 are highlighted in yellow in the sequence of the respective species and the non-conservative exchanges labeled in the 3D-structure of DHHC2 are in red.

Table S9: Amino acid differences between human DHHC15 and DHHC15 of animal hosts of Flu A

	5	15	25	35	45	55
Homo sapie	MRRGWKMALS	GGLRCCRRVL	SWVPVLVIVL	VVLWSYYAYV	FELCLVTVLS	PAEKVIYILIL
Sus scrofa	MRRGWKMALS	GGLRCCRRIL	SWVPVLVIVL	VVLWSYYAYV	FELCLVTVLS	PAEKVIYILIF
Gallus gal	-----MALS	RGLRCCQRAF	AWVPVLIITL	VVLWSYYAYV	CELCLMTLSN	PAEKVAYLII
Calidris p	-----MALS	RGLRCCQRAF	AWLPVLIITL	VVLWSYYAYV	CELCLVTLSN	PVEKVAYLII
Anas platy	-----MALS	RGLRCCQRAF	AWLPVLIIAL	VVLWSYYAYV	CELCLVTLSN	PVEKVAYLII
			<b>TMR1</b>			<b>TMR2</b>
	65	75	85	95	105	115
Homo sapie	YHAIFVFFTW	TYWKSIFTLP	QQPNQKFHLS	YTDKERYENE	ERPEVQKQML	VDMAKKLPVY
Sus scrofa	YHAIFVFFTW	TYWKSIFTLP	QQPNHKFHLS	YTDKERYENE	ERPEVQKQML	VDMAKKLPVY
Gallus gal	FHILFVLFVW	TYWKSIFTLP	VQPGKKYHMS	YADKERYENE	ERPEVQRQIL	AEIARKLPVY
Calidris p	FHILFVLFVW	TYWKSIFTLP	VQPGKKYHMS	YADKERYENE	ERPEVQRQIL	AEMARKLPVY
Anas platy	FHILFVLFVW	TYWKSIFTLP	VQPGKKYHMS	YADKERYENE	ERPEVQRQIL	AEIARKLPVY
			<b>Cysteine-rich domain</b>			
	125	135	145	155	165	175
Homo sapie	TRTGS GAVRF	CDRC HLIKPD	RCH HCSVCAM	CVLKMDH HCP	WVNNCIGFSN	YKFF LQFLAY
Sus scrofa	TRTGS GAVRF	CDRC HLIKPD	RCH HCSVCAM	CVLKMDH HCP	WVNNCIGFSN	YKFF LQFLAY
Gallus gal	TRTGS G GIRF	CDRC Q LIKPD	RCH HCSVCAT	CVLKMDH HCP	WVNNCIGFSN	YKFF L LFLAY
Calidris p	TRTGS G GIRF	CDRC Q LIKPD	RCH HCSVCAT	CVLKMDH HCP	WVNNCIGFSN	YKFF L LFLAY
Anas platy	TRTG N G GIRF	CDRC Q LIKPD	RCH HCSVCAT	CVLKMDH HCP	WVNNCIGFSN	YKFF L LFLAY
		<b>Zinc-binding</b>		<b>DHHC</b>		<b>TMR3</b>
	185	195	205	215	225	235
Homo sapie	SVLYCYLIAT	TVFSYFIKYW	RGELPSVRSK	FHVLFLLFVA	CMFFVSLVIL	FGYHCWLVS R
Sus scrofa	SVLYCLYIAT	TVFSYFIKYW	RGELPSVRSK	FHVLFLLFVA	CMFFVSLVIL	FGYHCWLVS R
Gallus gal	SLLYCLYIAA	TVFKYFIKYW	TGELTNGRSK	FHILFLLFLA	VMFFVSLMFL	FGYHCWLVS R
Calidris p	SLLYCLYIAA	TVFKYFIKYW	TGELTNGRSK	FHILFLLFLA	IMFFVSLMFL	FGYHCWLVS R
Anas platy	SLLYCLYIAA	TVFKYFIKYW	TGELTNGRSK	FHVLFLLFVA	VMFFVSLMFL	FGYHCWLVS R
	245	255	265	275	285	295
Homo sapie	NKT TLEAFCT	PVFTSGPEKN	GFNLGFIKNI	QQVFGDKKKF	WLPIPIGSSPG	DGHSFPMRSM
Sus scrofa	NKT TLEAFCT	PVFTSGPEKN	GFNLGFIKNI	QQVFGDNKKF	WLPIPIGSSPG	DGHSFPMRSM
Gallus gal	NRSTLEAFST	PVFQNGPDKN	GFNLGFVKNL	QQVFGEEKKL	WLLPIASSQG	DGHFFPMRAL
Calidris p	NRSTLEAFSA	PVFQNGPDKN	GFNLGFVKNL	QQVFGEEKKL	WLLPIASSQG	DGHFFPMRAL
Anas platy	NRSTLEAFSA	PVFQNGPDKN	GFNLGFVKNL	QQVFGEEKKL	WLLPIASSQG	DGHFFPMRAL
	305	315	325	335		
Homo sapie	NESQNPLLAN	EETWEDNEDD	NQDYPEG-SS	SLAVETET		
Sus scrofa	NESQNPLLAN	EEPWEDNEDD	NRDYPEG-SS	SLAVETET		
Gallus gal	CEAQNPLLSN	EEQWEDDGID	EEPHDSGEAA	SLAIETET		
Calidris p	CEAQNPLLAN	EEQWEDDGID	EEPHDSGEAS	SLAIETET		
Anas platy	CEAQNPLLAN	EEQWEDDGID	EEPHDSTEAS	SLAIETET		

Amino acid alignment of DHHC15 of humans (homo sapiens), pigs (sus scrofa) and three avian species: chicken (gallus gallus), sandpiper (Calidris pugnax) and mallard duck (Anas platyrhynchos). The transmembrane region is highlighted in grey, individual residues that contact the acyl chain in the cavity are highlighted in green and the two (S, Y) that seal the cavity are highlighted in pink. The amphiphilic helix following TMR4 is also highlighted in grey. Cys and His

residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue in the human sequence. NESQ is the end of the resolved structure. Amino acid differences to human DHHC15 are highlighted in yellow in the sequence of the respective species and the non-conservative exchanges labeled in the 3D-structure of DHHC15 are in red.

**Table S10: Amino acid differences between human DHHC8 and DHHC8 from animal hosts of Flu A**

	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	5	15	25	35	45	55								
Homo sapie	MPRSPGTRLK	PAKYIPVATA	AALLVGSSTL	FFVFTCPWLT	RAVSPAVPVY	NGIIFLFLVLA								
Sus scrofa	MPRSPGTRLK	PAKYIPVATA	AALLVGSSTL	FFVFTCPWLT	RAVSPAVPVY	NGILFLFLVLA								
Gallus gal	MPSTGKRFK	PTKYIPVSTA	AALLVGSTTL	FFVFTCPWLT	KAISPAIPVY	NGLVFLFLVLA								
Calidris p	-----	-----	-----	-----	-----	-----								
Anas platy	MPSTGKRFK	PTKYIPVSTA	AALLVGSTTL	FFVFTCPWLT	KAISPAIPVY	NGLVFLFLVLA								
			TMR1			TMR2								
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	65	75	85	95	105	115								
Homo sapie	NFSMATFMDP	GVFPRADEDE	DKEDDFRAPL	YKNVDVRGIQ	VRMKWCATCH	FYRPPRCSHC								
Sus scrofa	NFSMATFMDP	GVFPRADEDE	DKEDDFRAPL	YKNVDVRGIQ	VRMKWCATCH	FYRPPRCSHC								
Gallus gal	NFSMATFMDP	GVFPRADEDE	DKDDFRAPL	YKNVEIKGIQ	VRMKWCATCH	FYRPPRCSHC								
Calidris p	---MATFMDP	GVFPRADEDE	DKDDFRAPL	YKNVEIKGIQ	VRMKWCATCH	FYRPPRCSHC								
Anas platy	NFSMATFMDP	GVFPRADEDE	DKDDFRAPL	YKNVEIKGIQ	VRMKWCATCH	FYRPPRCSHC								
			Cysteine-rich domain		zinc-binding									
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	125	135	145	155	165	175								
Homo sapie	SVCDNCVEDF	DHHC	PWVNNC	IGRRNYRYFF	LFLLSLSAHM	VG	VVAFGLVY	VLN	HAEGLGA					
Sus scrofa	SVCDNCVEDF	DHHC	PWVNNC	IGRRNYRYFF	LFLLSLSAHM	VG	VVAFGLVY	VLN	HAEGLGA					
Gallus gal	SVCDNCVEDF	DHHC	PWVNNC	IGRRNYRYFF	LFLLSLS	THM	VG	VFTFGLIF	VLNHMEKLGA					
Calidris p	SVCDNCVEDF	DHHC	PWVNNC	IGRRNYRYFF	LFLLSLS	THM	VG	VFTFGLIF	VLNHMEKLGA					
Anas platy	SVCDNCVEDF	DHHC	PWVNNC	IGRRNYRYFF	LFLLSLS	THM	VG	VFTFGLIF	VLNHMEKLGA					
		DHHC		TMR3										
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	185	195	205	215	225	235								
Homo sapie	AHTTITMAVM	CVAGLFFIPV	IGLTGFHVVL	VTGR	TINEQ	VTGKFRGGVN	P	FTRG	CCGNV					
Sus scrofa	AHTTITMAVM	CVAGLFFIPV	IGLTGFHVVL	VTGR	TINEQ	VTGKFRGGVN	P	FTRG	CYGNV					
Gallus gal	AHTTITMAVM	CVAGLFFIPV	IGLTGFHIVL	VARGRTTNEQ	VTGKFRGGVN	P	FTRG	CCGNV						
Calidris p	AHTAITMAVM	CVAGLFFIPV	IGLTGFHIVL	VARGRTTNEQ	VTGKFRGGVN	P	FTRG	CCGNV						
Anas platy	AHTTITMAVM	CVAGLFFIPV	IGLTGFHIVL	VARGRTTNEQ	VTGKFRGGVN	P	FTRG	CCGNV						
			TMR4	TTXE				amphiphilic						
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	245	255	265	275	285	295								
Homo sapie	EHVLCSP	LAP	-----	-----	RYVVE	PPRLPLAVSL	KPPFLRPELL	DRAAPLKVKL						
Sus scrofa	EHVLCSP	LAP	-----	-----	RYVVE	PPRLPLAVRL	KPPFLRPELL	ERAPLKVKL						
Gallus gal	EHVLCSP	LAP	SLLHLPLQGS	CFMITRY	IIVE	P-KKKLAVSV	KPPFLRP	DLS	ER--QITVKI					
Calidris p	EHVLCSP	LAP	-----	-----	RYIIVE	P-KKKQAVSV	KPPFLRP	DLS	ER--QITVKI					
Anas platy	EHVLCSP	LAP	S-LHLPPQGS	CFMLTRY	IIVE	P-KKKQAVSV	KPPFLRP	DLS	ER--QITVKI					
		helix												
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	305	315	325	335	345	355								
Homo sapie	SDNGLKAGLG	RSKSKGSLDR	LDEKPLDLGP	PLPPKIEAGT	FSSDLQTPRP	GSAESALS	VQ							
Sus scrofa	SDNGLKAGLG	RSKSKGSLDR	LDEKPLDLGP	PLPPKAEAST	FGSD	LQTPRP	GSAESALS	AH						
Gallus gal	SDNGIQANLN	RSKSKISLEG	LEDKGM	DVQ	P	PLPPKGDQSK	Y-SELKGQLG	TSEESGLSPK						
Calidris p	SDNGIQANLN	RSKSKISLEG	LED	TSM	DVQ	P	PLPPKGDPSK	Y-SELKGQLG	TGEEGSLSPK					
Anas platy	SDNGIQANLN	RSKSKISLEG	LED	KSM	DVQ	P	PLPPKGDQSK	Y-SELKGQLG	TCEEGLSPK					
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	365	375	385	395	405	415								
Homo sapie	RTSPPTPAMY	KFRPAFPTGP	KVPFCGPGEQ	VPGPDSLTLG	---DDSI	RSL	DFVSEPS	LDL						
Sus scrofa	RTSPPTPAMY	KFRPNFPTGP	KAPFCGPGEQ	VTG	DSLTLG	---DDSI	HSL	DFASEPS	LDL					
Gallus gal	LISPTPAMY	KYRPAFSNNP	KVHYHAAAEQ	ITLQEGHSQ	ALIEED	DGRSL	DYQSEPS	LDI						
Calidris p	LISPTPAMY	KYRPAFSNNP	KVHYHATAEQ	ITMQEGHSQ	ALIEED	DGRSL	DYQSEPS	LDI						
Anas platy	LISPTPAMY	KYRPAFSNNP	KVHYHAAAEQ	ITMQEGHSQ	ALIEED	DGGS	DYQSEPS	LDI						
	..... .....	..... .....	..... .....	..... .....	..... .....	..... .....								
	425	435	445	455	465	475								
Homo sapie	PDYGP	GGLHA	AYPSPPLSA	SDAFSGALRS	LSLKASSRRG	GDHVALQPLR	SEGGPPTPHR							
Sus scrofa	PDY	P	GGLHA	AYPSPPLSA	AD	T	FSGALRS	LSLKAA	SRRG	GDHVALQPLR	SEGGPPTPHR			
Gallus gal	PSYRKSS	SLHK	TYQSSP	--LQ	IDSF	AIN	SRS	LSLK	SAGRRG	TDKV	PLHPIK	SEGA	A	ASTPYK
Calidris p	PSYRKSS	SLHK	TYQSSP	--LQ	IDSF	AIN	SRS	LSLK	SAGRRG	TEKV	PLHPIK	SEGA	A	ASTPYK
Anas platy	PSYRKSS	SLHK	TYQSSP	--LQ	IDSF	AIN	SRS	LSLK	SAGRRG	TDKV	PLHPIK	SEGA	A	ASTPYK

	485	495	505	515	525	535
Homo sapie	SIFAPHALPN	RNGSLSYDSL	LNPGPSGGHA	CPAHPAVGVA	GYHSPYLHPG	AT----GDPP
Sus scrofa	GLFAPHALPN	RNGSLSYDSL	LNPGPSGGHA	CPAHSSAGVP	GYRSPYLHTG	AV----GDPP
Gallus gal	SIFSPNSLSN	RNGSLSYDSL	LNPMPSPGRK	CVTHSAVSSV	GYHSPYLSAK	MCHLRGSELQ
Calidris p	SIFSPNSLSN	RNGSLSYDSL	LNPMPSPGRK	CTHSAVSSV	GYHSPYLSAK	MCHLRGSELQ
Anas platy	SIFSPNSLSN	RNGSLSYDSL	LNPMPSPGRK	CTAHSVSSV	GYHSPYLSAK	MCHLRGSELQ
	545	555	565	575	585	595
Homo sapie	RPLPRSFSVP	LG---PRPRE	PSPVRYDNLS	RTIMASIQR	KDREERERLL	RSQADSLFGD
Sus scrofa	RPPPRSFSVP	LG---PRPRE	PSPVRYDNLS	RTIMASIQR	KDREERERLL	RSQADSLFGD
Gallus gal	RQPPQSFSPV	LGGPAPHQRD	PSPVRYDNLS	KTIMASIQR	KEMEEREKLL	HSHPDSVFAD
Calidris p	RQPPQSFSPV	LGGPAPHQRD	PSPVRYDNLS	KTIMASIQR	KEMEEREKLL	HSHPDSVFAD
Anas platy	RQPPQSFSPV	LGGPAPHQRD	PSPVRYDNLS	KTIMASIQR	KEMEEREKLL	HSHPDSVFAD
	605	615	625	635	645	655
Homo sapie	SGVYDAPSSY	SLQQASVLSE	GPRGPALRYG	SRDDLAVAGPG	FGGARNPALQ	TSLSSLSSTV
Sus scrofa	SGVYDAPSSY	SLQQASVLSE	GPRGPVVRFG	SRDDLAVAGPG	FGGARNPALQ	ASLSSLSSTV
Gallus gal	SGVYDTIPSSY	SLQQVSTLSE	DPRSMAMRYG	SRDNLMAATS	FS-TRNPIIQ	SSVSSLSSAM
Calidris p	SGVYDTIPSSY	SLQQVSTLSE	DPRSMAMRYG	SRDNLMAATS	FS-TRNPIIQ	SSVSSLSSAM
Anas platy	SGVYDTIPSSY	SLQQVSTLSE	DPRSMAMR	-----	-----	-----
	665	675	685	695	705	715
Homo sapie	SRAPRTSSSS	LQADQASSN-	----APGPRP	SSGSHRSPAR	QGLPSPPGTP	HSPSYAGPKA
Sus scrofa	SRAPRTSSSS	LQADLANSS-	----APGARP	ASGSHRSPAR	QVPPSPPGTP	RSPSYAGPKA
Gallus gal	TRAPRTSTTS	LQADLANNNV	QTHQALQGRV	SNGSYKSPGH	QVPSSPTGMP	RSPSYGGPKA
Calidris p	TRAPRTSTTS	LQADLANNNV	QSHQALQGRV	SNGSFKSPGH	QVPSSPTGMP	RSPSYGGPKA
Anas platy	-----	-----	-----	-----	-----	-----
	725	735	745	755	765	775
Homo sapie	VAFIHTDLPE	PPPSLTVQRG	RIGTCTRGWG	RRGQPWVPPG	LHLCHLGRPE	DRPPLRAPWS
Sus scrofa	VAFIHTDLPE	PPPSLAVQRG	RIGTCSRGGW	RRGQPRVPPS	LHLCHLGLPE	DRPPLRAPWS
Gallus gal	ISFVNTVEIT	EVQSVGAQRD	DIQMKTPHKS	INGQP----	KGISRLG--S	TSSSQGTPVS
Calidris p	VSFVNTVEIT	EVQSVGAQRD	DMQLKTPHKS	INGQP----	KGISRLG--S	TSSSQGTPVS
Anas platy	-----	-----D	DMQLKTPHKS	INGQP----	KGISRLG--S	TSSSQGTPVS
	785	795	805	815	825	835
Homo sapie	QAAGAPPRGA	MCRLHLAASS	LFPSLSGP--	-----	-----	-----
Sus scrofa	BATGAPPRGA	VCRLHSAASS	LFPSLSGPQA	GHQVGDSGAQ	EARLPRTLGC	GLGSPLHQPH
Gallus gal	FAR----HSN	VKKVSGVGGT	TYEISV----	-----	-----	-----
Calidris p	FAR----HSN	VKKVSGVGGT	TYEISV----	-----	-----	-----
Anas platy	FAR----HSN	VKKVSGVGGT	TYEISV----	-----	-----	-----
Homo sapie	--					
Sus scrofa	Ld					
Gallus gal	--					
Calidris p	--					
Anas platy	--					

Amino acid alignment of DHHC8 of humans (homo sapiens), pigs (sus scrofa) and three avian species, chicken (gallus gallus), sandpiper (Calidris pugnax) and mallard duck (Anas platyrhynchos). The transmembrane regions and the amphiphilic helix following TMR4 are highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue. Most of the C-terminal region is predicted to be unstructured (underlined). Amino acid differences to human DHHC2 are highlighted in yellow in the sequence of the respective species.

**Table S11: Amino acid differences between human DHHC20 and DHHC20 of animal hosts of Flu A**

	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	5	15	25	35	45	55
Homo sapie	MAPWTLWRCC	QRVVGWVPVL	FITFVVVWSY	YAYVVELCVF	TIFGNEENGK	TVVYLVAFHL
Sus scrofa	MAPCTLWRCC	QRSVGWVPVL	FITFVVVWSY	YAYVVELCVF	TLGNGENGK	AVVYLVAFHL
Gallus gal	MAPSHVLKCC	QRVLAWVPV	FIALVVAWSY	YAYVVELCVF	TISSTAEEK--	-VVYLVI FHL
Calidris p	MAPSHVLKCC	QKVLAWVPVA	FIALVVAWSY	YAYVVELCMF	TISSTAEEK--	-VVYLVI FHL
Anas platy	MAPPR-VKCC	QKVLAWLPV	FIALVVAWSY	YAYVVELCLF	TISSTAEEK--	-VVYLVI FHL
			<b>TMR1</b>			<b>TMR2</b>
	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	65	75	85	95	105	115
Homo sapie	FFVMFVWSYW	MTIFTSPASP	SKEFYLSNSE	KERYEKEFSQ	ERQQEILRRA	ARALPIYTTS
Sus scrofa	FFVMFVWSYW	MTIFTSPASP	SKEFYLSSE	KERYEKEFSQ	ERQQEILRRA	ARGLPYTTS
Gallus gal	SFVMFVWSYG	KTIFTSPASP	SNEFCLS KAD	KEQYEKE ERP	ESQQEILRRA	AKDLPIYTTS
Calidris p	SFVMFVWSYW	KTIFTSPASP	SNEFCLS KAD	KEQYEKE ERP	ESQQEILRRA	AKDLPIYTTS
Anas platy	SFVMFVWSYW	KTIFTSPASP	SNEFCLS KAD	KEQYEKE ERP	EFQQEILRRA	AKDLPI TTT
			<b>Cysteine-rich domain</b>			
	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	125	135	145	155	165	175
Homo sapie	ASKTIRYCEK	CQLIKPDRAH	HCSACDS CIL	KMDHHC PWVN	NCVGFSNYKF	FLLFLLYSLL
Sus scrofa	ATQTIRYCER	CQLIKPDRAH	HCSACD ICVL	KMDHHC PWVN	NCVGFSNYKF	FLLFLLYSLL
Gallus gal	ASRAIRYCDR	CQLIKPDRCH	HCSACD ICVL	KMDHHC PWVN	NCVGFSNYKF	FLLFLMYSL
Calidris p	ASRAIRYCDR	CQLIKPDRCH	HCSACD ICVL	KMDHHC PWVN	NCVGFSNYKF	FLLFLMYSL
Anas platy	ASRAIRYCDR	CQLIKPDRCH	HCSACD ICVL	KMDHHC PWVN	NCVGFSNYKF	FLLFLMYSL
	<b>Acyl-CoA</b>	<b>Zinc-binding</b>		<b>DHHC</b>		<b>TMR3</b>
	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	185	195	205	215	225	235
Homo sapie	YCLFVAATVL	EYFIKFWTNE	LTDTRAKFHV	LFLFFVSAME	FISVLSLFSY	HCWLVGKNRT
Sus scrofa	YCLFVAATTVL	QYFIKFWTNE	LSDTRAKFHV	LFLFFVSTMF	FISVLSLFSY	HCWLVGKNRT
Gallus gal	YCLFVAATVL	QYFIKFWTNE	LPDTHAKFHV	LFLFFVAAMF	FISILSLFSY	HCWLVGKNRS
Calidris p	YCLFVAATVL	QYFIKFWTNE	LPDTHAKFHV	LFLFFVAAMF	FISILSLFSY	HCWLVS KNRS
Anas platy	YCLFVAATVL	QYFIKFWTKE	LTDAYAKYHI	LCLFFVA AIA	FIGIQWLFSY	HCWLVGKNRS
				<b>TMR4</b>		
	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	245	255	265	275	285	295
Homo sapie	TIESFRAPTF	SYGPDGNGFS	LGCSKNWRQV	FGDEKKYWLL	PIFSSLGDGC	SFPTRLVGMD
Sus scrofa	TIESFRAPTF	SYGPDGNGFS	LGCSKNWRQV	FGDEKKYWLL	PVFSSQGDGC	SFPTRLVGT
Gallus gal	TIETFRAPTF	RNGPDKNGFS	LGCSKNLREV	FGDEKKYWLL	PIFTSLGDGC	NFPTRLVIMD
Calidris p	TIETFRAPTF	RNGPDKNGFS	LGCSKNLREV	FGDEKKYWLL	PIFTSLGDGC	NFPTRLVIMD
Anas platy	TIESHRAPMF	RNGPDENGFS	LGYGKNLREV	FGDEKKYWLL	PIFTSLGDGC	NFPTRLVIMD
	<b>TTXE</b>		<b>amphiphilic helix</b>			
	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....
	305	315	325	335	345	355
Homo sapie	PEQASVTNQ	EYARSSGSNQ	PFPI-KPLSE	SKNRLLDSES	QWLENGAEEG	IVKSGTNNHV
Sus scrofa	PEQASVSNQS	ESGRS IGSNQ	PFPI-KPLSE	SKNRLLDSES	QWLEDGAEEG	VVRPGTNNHV
Gallus gal	PEQVTVSSQN	EPAKSSGANQ	PFPPTRPLSE	SNRLLASDS	QWVESGPEDE	NVKSGTKKHI
Calidris p	PEQLAVSSQN	EPAKSSGANQ	TFPP-RPLSE	SNRLLANDS	QWVESGPEEE	NVKSGAKKHI
Anas platy	PERVTVSTQT	EPAKSSGASQ	PFPP-QPLSE	SOVRLASDD	QWVEIDPEEE	NVK-----
	.... .					
	365					
Homo sapie	TVAIEN					
Sus scrofa	TVAIEN					
Gallus gal	IVSLES					
Calidris p	IVSLES					
Anas platy	-----					



Amino acid alignment of DHHC20 of humans (*homo sapiens*), pigs (*sus scrofa*) and three avian species, chicken (*gallus gallus*), sandpiper (*Calidris pugnax*) and mallard duck (*Anas platyrhynchos*). The transmembrane regions are highlighted in grey, individual residues that contact the acyl chain in the cavity are highlighted in green and the two (S and T) that seal the cavity are highlighted in pink. The amphiphilic helix following TMR4 is also highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue and basic residues involved in acyl-CoA binding are highlighted in green. LVGM is the end of the resolved DHHC20 structure. Amino acid differences to human DHHC2 are highlighted in yellow in the sequence of the respective species and the non-conservative exchanges labeled in the 3D-structure of DHHC20 are in red.

**Table S12: Amino acid differences between human DHHC8 and DHHC8 from animal hosts of  $\beta$ -CoVs**

10 20 30 40 50 60 70

Human MPRSPGTRLKPAKYIPVATAAALLVGSSTLFFVFT-----

Rhinolophus Sinicus MPRSPGTRLKPAKYIPVATAAALLVGSSTLFFVFT-----

Pipistrellus Kuhlii MPRSPGTRLKPAKYIPVATAAALLIGSSTLFFVFT-----

Camelus Dromedarius MPRSPGTRLKPAKYIPVATAAALLVGSSTLFFVFT-----

Manis Javanica MPRSPGTRLKPAKYIPVATAAALLVGSSALFFVFTLTWALLEALTVRPTSDFRGGRMSLSLTRPQAAGPE

TMR1

80 90 100 110 120 130 140

Human -----CPWLTRAVSPAVPVYNGIIFLFLVLANFSMATFMDPGVFPRADE

Rhinolophus Sinicus -----CPWLTRAVSPAVPVYNGIIFLFLVLANFSMATFMDPGIFPRADE

Pipistrellus Kuhlii -----CPWLTHAVSPAVPVYNGIIFLFLVLANFSMATFMDPGVFPRADE

Camelus Dromedarius -----CPWLTRAVSPAVPVYNGIIFLFLVLANFSMATFMDPGVFPRADE

Manis Javanica AAAPCQVPSPPSALLTAGALGSGTPALCPWLTRAVSPAVPVYNGIIFLFLVLANFSMATFMDPGVFPRADE

TMR2

150 160 170 180 190 200 210

Human DEDKEDDFRAPLYKNVDVRGIQVRMKWCATCHFYRPPRCHCSVCDNCVEDFDHHC PWVNNCIGRNYRY

Rhinolophus Sinicus DEDKEDDFRAPLYKNVDVRGIQVRMKWCATCHFYRPPRCHCSVCDNCVEDFDHHC PWVNNCIGRNYRY

Pipistrellus Kuhlii DEDKEDDFRAPLYKNVDVRGIQVRMKWCATCHFYRPPRCHCSVCDNCVEDFDHHC PWVNNCIGRNYRY

Camelus Dromedarius DEDKEDDFRAPLYKNVDVRGIQVRMKWCATCHFYRPPRC-PLQRCDNCAQDFDHHC PWVNNCIGRNYRY

Manis Javanica DEDKEDDFRAPLYKNVDVRGIQVRMKWCATCHFYRPPRCHCSVCDSCVEDFDHHC PWVNNCIGRNYRY

Zinc-binding DHHC DHHC domain

220 230 240 250 260 270 280

Human FFLFLLSLSAHMVGVAAGFLVYVLNHAEGLGAAHTTITMAVMCVAGLFFIPVIGLTGFHVVLVTRGRTTN

Rhinolophus Sinicus FFLFLLSLSAHMVGVAAGFLVYVLNHAEGLGAAHTTITMAVMCVAGLFFIPVIGLTGFHVVLVTRGRTTN

Pipistrellus Kuhlii FFLFLLSLSAHMVGVAAGFLVYVLNHAEGLGAAHTTITMAVMCVAGLFFIPVIGLTGFHVVLVTRGRTTN

Camelus Dromedarius FFLFLLSLSAHMVGVAAGFLVYVLHAEGLGAAHTTITMAVMCVAGLFFIPVIGLTGFHVVLVTRGRTTN

Manis Javanica FFLFLLSLSAHMVGVAAGFLVYVLNHAEGLGATHTTVTMAVMGVAGLFFIPVIGLTGFHVVLVTRGRTTN

TMR3 TMR4 TTXE

290 300 310 320 330 340 350

Human EQVTGKFRGGVNPFTRGCCGNVEHVLCSPLAPRYVVEPP-RLPLAVSLKPPFLRPELLDRAAPLKVKLSLSD

Rhinolophus Sinicus EQVTGKFRGGVNPFTRGCYGNVEHVLCSPLAPRYVVEPP-RLPLAARLKPPFLRPELLERAAPLKVKLSLSD

Pipistrellus Kuhlii EQVTGKFRGGVNPFTRGCYGNVEHVLCSPLAPRYVVEPPRLPLAARLKPPFLRPELLDRAAPLKVKLSLSD

Camelus Dromedarius EQVTGKFRGGVNPFTRGCYGNVEHVLCSPLAPRYVVRAA-RLPLAARLKPPFLRPELLERAAPLKVKLSLSD

Manis Javanica EQVTGKFRGGVNPFTRGCYGNVEHVLCSPLAPRYVVEPPQLPLATRLKPPFLRPELLGRAAPLKVKLSLSD

amphiphilic helix

	360	370	380	390	400	410	420
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	NGLKAGLGRSKSKGSLDRLDEKPLDLGPPLPPKIEAGTFSSDLQTPRPGSAESALSQVORTSPPTPAMYKF						
Rhinolophus Sinicus	NGLKASLGHSKSKGSLDRLDEKPLDLGPPLPPKAEAVTFSGDRQTPRPGSAESTLSAQRTSPPTPAMYKF						
Pipistrellus Kuhlui	NGLKAGLGRSKSKGSLDRLDEKPLDLGPPLPPKPEAGTFGGDRQTPRPGSAESALSAQRTSPPTPAMYKF						
Camelus Dromedarius	NGLKAGLGRSKSKGSLDRLDEKPLDLGPPLPPKAEAGTFASDLQTPRPGSAESALSAQRTSPPTPAMYKF						
Manis Javanica	NGLKASLGRSKSKGSLDRLDEKPLDLGPPLPSKVEVGTFGSNLQTPRPGSAESALKVQRTSPPTPAMYKF						
	430	440	450	460	470	480	490
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	RPAFPTGPKVPFCGPGEQVPGPDSLTLGDDSIIRSLDFVSEPSLDLPDYGGPG-LHAAYPPSPPLSASDAF						
Rhinolophus Sinicus	RPTTFPMGPKAPFCGPGEQVPGPDSLALGEDSIHSLDFTSEPNLDLPDYTPGG-LHTAYPPSPPLSASDTF						
Pipistrellus Kuhlui	RPAFPAGPKAPFCGPGEQVSGPDSLTLGEDSIHSLDFTSEPSLDLPDFAAGGGLHAPYAPSPPLGAADTF						
Camelus Dromedarius	RPAFPTGPKAPFCGPGEQVTGPDSLTLGEDSIHSLDFASEPSLDLPDYPPSG-LHAAYPPSPPLSATDTF						
Manis Javanica	RPAFFPMGPKSPFCGPGEQVPGPDSLTLGEDSVHGLDFTSEPHLDLPDYPPGG-LHAAYPPSPQLSVADTF						
	500	510	520	530	540	550	560
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	SGALRSLSLKASSRRGGDHVALQPLRSEGGPPTPHRSIFAPHALPNRNGSLSYDSLNNPGSPGGHACPAH						
Rhinolophus Sinicus	SGALRSLSLKAASRRGGDHTIALQSLRSEGGPPTPHRSIFAPHALSNRNGSLSYDSLNNPGSPSGHACPAH						
Pipistrellus Kuhlui	SGALRSLSLKAAGRRGGDHVALQPLRSEGGPPTPHRGVGFAPHALPNRNGSLSYDSLSPASPGGRACPAH						
Camelus Dromedarius	SGALRSLSLKAASRRGGDHMALQPLRSEGGPPTPHRSIFPSHALPNRNGSLSYDSLNNPGSPGGHTCPAH						
Manis Javanica	SGALRSLSLKAAGRGRGDHVALQPLRSEGGPPTPHRGIFAPHALPNRNGSLSYDSLDPGSPGGHACPAH						
	570	580	590	600	610	620	630
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	PAVG-VAGYHSPYLHPGATGDDPPRPLPRSFSPVLGPRPREPSPVRYDNLSTIMASIQERKDREERERLL						
Rhinolophus Sinicus	PSAG-MASYRSPYLHPGAVGDPPRPPRSFSPVLGPRPREPSPVRYDNLSTIMASIQERKDREERERLL						
Pipistrellus Kuhlui	PAAGGLAGYRSPYLHP---GDPPRPPRSFSPVLGPRPREPSPVRYDNLSTIMASIQERKDREERERLL						
Camelus Dromedarius	PSAG-VAGYRAPYLHAGAVGDPPRPPRSFSPVLGPRPREPSPVRYDNLSTIMASIQERKDREERERLL						
Manis Javanica	PPAG-MASYRSPYLHPGSVGDPPRPPRSFSPVLGSRPREPSPVRYDNLSTIMASIQERKDREEHQRLL						
	640	650	660	670	680	690	700
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	RSQADSLFGDSGVYDAPSSSYSLQQAS-VLSEGPRGPALRYGSRDDLAVAGPG---FGGARNPALQTSLSL						
Rhinolophus Sinicus	RSQADSLFGDSGVYDAPSSSYSLQQAS-VLSEGPRGPALHYGSRDDLAVAGPS---FRGARNPALQTSLSL						
Pipistrellus Kuhlui	RSQADSLFGDAGAYDAPGSYGLQQAAGALSEGPRGPAAARYGSRDDLAVAGPGGAGFGGARNPALQASVTS						
Camelus Dromedarius	RSQADSLFGDSGVYDAPSSSYSLQQAS-VLSEGPRGPALRYGSRDDLAVAGPG---FGGARNPALQASLSL						
Manis Javanica	RSQADSLFGDSGVYDAPSSSYSLQQAG-VLAEGPRGPVLRCGSRDDLAVAGPG---FGGARNPALQTSLSL						
	710	720	730	740	750	760	770
Human	..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....						
	S-----SSVSRAPRTSSSSSLQADQASSNAPGPRPSSGSHRSPARQGLPSPP-GTPHSPSYAGPKAVAFIH						
Rhinolophus Sinicus	S-----SAISRAPRTSSSSSLQADLANNNAPGPRPGSASQSRSPLRQGFPSP-STOPRSPFTFMGPKAVAFIH						
Pipistrellus Kuhlui	SGVAAAAAGSRAPRTSSSSSLQADLANNNAPGPRPGSGEHRSPLRQGAPSP-STOPRSPSYVGPKAVAFIH						
Camelus Dromedarius	S-----SAVSRAPRTSSSSSLQADLTNSSAPGTRPPSGSHRSPARQVFPSP-GTPRSPSYGGPKAVAFIH						
Manis Javanica	S-----SAVSRAPRTSSSSSLQADLANSNAPVPRPSSGSHRSPARQGLPSPP-GTPCSPSYFGPKAVAFVH						

	780	790	800	810	820	830	840
Human	..... ..... ..... ..... ..... ..... ..... .....						
Rhinolophus Sinicus	TDLPEPPPSLTVQ-----						
Pipistrellus Kuhlil	TDLPEPPPSLAVQ-----RG						
Camelus Dromedarius	SDLPEPPPSLAVQ-----RG						
Manis Javanica	TDLPEPPPSLAMQ-----RG						
	TDLPEPPPSLAVQSLCRPRASSSGDGGTDPVQENESGGHNPAANIPWVPGPWSRLGRTGPGSTRFPAQRG						

  

	850	860	870	880	890	900	910
Human	..... ..... ..... ..... ..... ..... ..... .....						
Rhinolophus Sinicus	-----RDHPQLKTP--PSKLNGQSPGLARLGATGPPGPSAS--PTRHTLVKKVSGVGGTTYEISV---						
Pipistrellus Kuhlil	RIGTCSRGWGRRGPPRVPPGLHLCHLGLPEDRPPPLRVWSPAAGVSPRGAVCRLHLAASSLFPRFSGPER						
Camelus Dromedarius	-----RDHPQLKNP--PSKLNGQSPGLARLGPTAGPPGPVTS--PARHTLVKKVSGVGGTTYEISV---						
Manis Javanica	WTGTCSRGWGRRGQPRAPPGLHLCHLGLPEDRPPALRASWSPAAGAPYRGAVCRLHSAASSLFPSLSGPER						
	RIGTCSRGWGRRGQPWAPPGLHLCHLGLPEDRPPPLQAPRSPATRMPSRGAVCRLHSAASSLFTGLSGPER						
	<u>PDZ ligand</u>						

  

Human	...
Rhinolophus Sinicus	DTK
Pipistrellus Kuhlil	---
Camelus Dromedarius	DTK
Manis Javanica	DTQ

Amino acid alignment of DHHC8 proteins from humans (homo sapiens), camel (camelus dromedaries, pangolin (manis javanica) and two bat species, Rhinolophus Sinicus (host of various  $\beta$ -CoVs including SARS-1 and presumably SARS-2) and Pipistrellus Kuhlil. The transmembrane regions and the amphiphilic helix following TMR4 are highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue. Most of the C-terminal region is predicted to be unstructured (underlined). Amino acid differences to human DHHC8 are highlighted in yellow in the sequence of the respective species.

Accession numbers: DHHC8 sequences of Human (NP\_037505.1), Rhinolophus Sinicus (XP\_019611479), Pipistrellus Kuhlil (XP\_036305544.1), Camelus\_Dromedarius (XP\_031299130) and Manis Javanica (XP\_036849239.1)

**Table S13: Amino acid differences between human DHHC9 and DHHC9 from animal hosts of  $\beta$ -CoVs**

Sequence logos for TMR1, TMR2, TMR3, TMR4, and TTXE across five species: Human, Rhinolophus Sinicus, Pipistrellus Kuhlii, Camelus Dromedarius, and Manis Javanica. The logos show conservation scores for each amino acid position (10-350). Key motifs are highlighted: Zinc-binding (residues 150-160), DHHC (residues 170-180), cysteine-rich domain (residues 200-210), and amphiliphic helix (residues 290-300).

**TMR1**

Human: MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTLFFAFECRYLAVQLSPAIPV  
Rhinolophus Sinicus: MSVIVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTLFFAFECRYLAVQLSPAIPV  
Pipistrellus Kuhlii: MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTLFFAFECRYLAVQLSPAIPV  
Camelus Dromedarius: MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTLFFAFECRYLAVQLSPAIPV  
Manis Javanica: MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTLFFAFECRYLAVQLSPAIPV

**TMR2**

Human: FAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGAVPQGRPPPRIKNFQINNQIVKLKY  
Rhinolophus Sinicus: FAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGIVPQGRPPPRIKNFQINNQIVKLKY  
Pipistrellus Kuhlii: FAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGAVPQGRPPPRIKNFQINNQIVKLKY  
Camelus Dromedarius: FAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGAVPQGRPPPRIKNFQINNQIVKLKY  
Manis Javanica: FAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGAVPQGRPPPRIKNFQINNQIVKLKY

**TMR3**

Human: CYTCKIFRPPRASHCSICDNCVERFDHHC PWVGN CVGKRNRYFYLFILSLSLLTIYVFAFNIVYVALKS  
Rhinolophus Sinicus: CYTCKIFRPPRASHCSICDNCVERFDHHC PWVGN CVGKRNRYFYLFILSLSLLTIYVFAFNIVYVALKS  
Pipistrellus Kuhlii: CYTCKIFRPPRASHCSICDNCVERFDHHC PWVGN CVGKRNRYFYLFILSLSLLTIYVFAFNIVYVALKS  
Camelus Dromedarius: CYTCKIFRPPRASHCSICDNCVERFDHHC PWVGN CVGKRNRYFYLFILSLSLLTIYVFAFNIVYVALKS  
Manis Javanica: CYTCKIFRPPRASHCSICDNCVERFDHHC PWVGN CVGKRNRYFYLFILSLSLLTIYVFAFNIVYVALKS

**TMR4**

Human: LKIGFLETCLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTGKNRVQNPYSHGNIV  
Rhinolophus Sinicus: LKIGFLETCLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTGKNRVQNPYSHGNIV  
Pipistrellus Kuhlii: LKIGFLETCLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTGKNRVQNPYSHGNIV  
Camelus Dromedarius: LKIGFLETCLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTGKNRVQNPYSHGNIV  
Manis Javanica: LKIGFLETCLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTGKNRVQNPYSHGNIV

**TTXE**

Human: KNCCEVLCGLPLPPSVLDRRGILPLEESGSRPPSTQETSSSLLPQSPAPTEHLNSNEMPEDSSTPEEMPPP  
Rhinolophus Sinicus: KNCCEVLCGLPLPPSVLDRRGILPLEESGSRPPSTQETSSSLLPQSPALTEHLSTNKMPEDTSTPAKMPPP  
Pipistrellus Kuhlii: KNCCEVLCGLPLPPSVLDRRGILPLEESGSRPPSTQETSSSLLPQSPVSPVPDFKILRALTEHLSSNEMPED  
Camelus Dromedarius: KNCCEVLCGLPLPPSVLDRRGILPLEESGSRPPSTQETSSSLLPQSPVPTDHLSSSEMPEDTSTPEEMPPP  
Manis Javanica: KNCCEVLCGLPLPPSVLDRRGILPLEESGSRPPSTQETSSSLLPQNAPTEHLSSNEMPEDTSTPEEMPPP

	360	370
	..... ..... ..... ..... .....	
Human	-----EPPEPPQEAAEAEK	
Rhinolophus Sinicus	-----EPPEPPQEVAEADK	
Pipistrellus Kuhlil	STPEEMPPEPPEPPQEVAEADK	
Camelus Dromedarius	-----EPPEPPQEGTEAEK	
Manis Javanica	-----EPPEPPQEMTEAEK	

Amino acid alignment of DHHC9 proteins from humans (homo sapiens), camel (camelus dromedaries, pangolin (manis javanica) and two bat species, Rhinolophus Sinicus (host of various  $\beta$ -CoVs including SARS-1 and presumably SARS-2) and Pipistrellus Kuhlil, host of MERS. The transmembrane regions and the amphiphilic helix following TMR4 are highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue. Most of the C-terminal region is predicted to be unstructured (underlined). Amino acid differences to human DHHC9 are highlighted in yellow in the sequence of the respective species.

Accession numbers: DHHC9 sequences of Human (NP\_001008223.1), Rhinolophus Sinicus (XP\_019572571.1), Pipistrellus Kuhlil (XP\_036299136.1), Camelus Dromedarius (XP\_031301040.1) and Manis Javanica (XP\_036872770.1)

**Table S14: Amino acid differences between human DHHC20 and DHHC20 from animal hosts of  $\beta$ -CoVs**

	10	20	30	40	50	60	70																																						
Human	MAPWTLWRCCQ	RVVGVWPVLF	ITFVVVWS	YYAYVVELCV	FTIFGNEENGK	TVVYLVAFH	LFFVMFVWSY																																						
Rhinolophus Sinicus	MAPGRFWRCCQ	RGVGVWPVLF	IAFVVAWS	YYAYVVELCV	FTLSGNGENGK	AVVYLVTFH	LSFVMFVWSY																																						
Pipistrellus Kuhlii	MAPGRFWRCC	LRGAGVWPVLF	ITFVAAWS	YYAYVVELC	LFTLSGNGENGK	AVAYLVAFH	LFFVMFVWSY																																						
Camelus Dromedarius	MAPGRFWRCCQ	RGVGVWPVLF	IAFVVAWS	YYAYVVELCV	FTLSGNGENGK	AVVYLVTFH	LSFVMFVWSY																																						
Manis Javanica	-----MFVWSY																																												
	TMR1																																			TMR2									
	80	90	100	110	120	130	140																																						
Human	MTIFTSPASPS	KEFYLSNSEK	ERYEKEFS	QERQQEIL	RRAARAL	PIYTTAS	KTI	RYCEK	CQLIK	PDRAH																																			
Rhinolophus Sinicus	MTIFTTPASPS	KEFYLSNSEK	ERYEKEFS	PERQQDIL	RRTARDLP	IYTTSGS	RRTIYRC	CER	CQLIK	PDRAH																																			
Pipistrellus Kuhlii	MTIFTSPAT	PSKEFYLSNSE	REHYEKEFS	QERQQEIL	RRTAKDL	PIYTTSGS	RRTIYRC	CER	CQLIK	PDRAH																																			
Camelus Dromedarius	MTIFTSPASPS	KEFYLSNSEK	ERYEKEFS	PERQQDIL	RRTARDLP	IYTTSGS	RRTIYRC	CER	CQLIK	PDRAH																																			
Manis Javanica	MTIFS	SHASPSKEFY	LSNSEKEHYE	KEFSQERQQE	ILRRAARD	LPIYTTAS	RRTIYRC	CER	CQLIK	PDRAH																																			
	Cysteine-rich domain																																			Acyl-CoA					Zinc-binding				
	150	160	170	180	190	200	210																																						
Human	HCSACDS	CILKMDHHC	PPWVNN	CVGFSNYK	FLLFL	LLYSLLY	CLFVAAT	VLEYFIK	FWT	-----																																			
Rhinolophus Sinicus	HCSACD	ICILKMDHHC	PPWVNN	CVGFSNYK	FLLFL	LLYSLLY	CLFVA	TTVLQYFIK	FWT	L	CHRRK	STES	C	PCQ																															
Pipistrellus Kuhlii	HCSACD	ICILKMDHHC	PPWVNN	CVGFSNYK	FLLFL	LLYSLLY	CLFVA	TTVLQYFIK	FWT	L	CHRRK	STES	C	PCQ																															
Camelus Dromedarius	HCSACD	ICILKMDHHC	PPWVNN	CVGFSNYK	FLLFL	LLYSLLY	CLFVA	TTVLQYFIK	FWT	L	CHRRK	STES	C	PCQ																															
Manis Javanica	HCSACD	ICILKMDHHC	PPWVNN	CVGFSNYK	FLLFL	LLYSLLY	CLFVAAT	VLEYFIK	FWT	L	CHRRK	STES	C	PCQ																															
	DHHC																																			TMR3									
	220	230	240	250	260	270	280																																						
Human	NELTDTRAK	FHVLFLFF	VSA	MFISVLSL	FSYHCWL	VGKNR	TTIES	SFRAPTFS	YSGPD	GN	GFSLG	SKN	WR																																
Rhinolophus Sinicus	NELPD	TRAKFHVL	FLFFVS	TMFFISVLS	SLFSYHCWL	VGKNR	TTIES	SFRAPTFS	YSG	QD	GN	GFSLG	YSKN	WR																															
Pipistrellus Kuhlii	NELTD	TRAKFHVL	FLFFVS	TMFFISVLS	SLFSYHCWL	VGKNR	TTIES	S	APTFS	YSGPD	GN	GFSLG	YSKN	WR																															
Camelus Dromedarius	NELPD	TRAKFHVL	FLFFVS	TMFFISVLS	SLFSYHCWL	VGKNR	TTIES	SFRAPTFS	YSG	QD	GN	GFSLG	HSKN	WR																															
Manis Javanica	NELSD	TRAKFH	ILFLFFVS	AMFFVSVLS	SLFSYHCWL	VG	RNRTTIES	SFRAPTFS	YSGPD	GN	GFSLG	YSKN	WR																																
	TMR4																																			TTXE									
	290	300	310	320	330	340	350																																						
Human	QVFGDEK	KYWLLPI	FSSSLG	DCSFPT	RLVGM	DPEQASV	TNQNEYAR	SSGSNQ	PFPIK	PLSE	SKN	RLLD	SE																																
Rhinolophus Sinicus	QVFGDEK	KYWLLPI	FSSSLG	DCSFPT	RLVGM	DPEQASV	TNQNEYAR	ISGN	PPFP	IR	PLSE	SKN	RLLD	SE																															
Pipistrellus Kuhlii	QVFGDEK	KYWLLPI	FSSSLG	DCSFPT	RLVGM	DPEQASV	TNQNEYAR	ISGN	QPPFIK	PLSE	SKN	RLLD	S	D																															
Camelus Dromedarius	QVFGDEK	KYWLLPI	FSSSLG	DCSFPT	RLVGM	DPEQASV	TNQNEYAR	ISGN	PPFP	VR	PLSE	SKN	RLLD	SE																															
Manis Javanica	QVFGDEK	KYWLLPI	FSSSLG	DCSF	ARLVGT	DPERASV	TSQNE	CARS	ISSNQ	PFPIK	PLSE	SKN	RLLD	SE																															

	360	370	380	390
	.... .... .... .... .... .... .... .... .... ....			
Human	SQWLENGAEEGIVKSGTNNHVTVAIEN	-----		
Rhinolophus Sinicus	<b>CQWTENGSEEGTV</b> RSGTNNHVTVAIEN	-----		
Pipistrellus Kuhlii	SQWTENGSEEDTIRSGINNFVTVAI	DKKVTCPLLLKKLDPEKSD		
Camelus Dromedarius	<b>CQWTENGSEEGTV</b> RSGTNNHVTVAIQN	-----		
Manis Javanica	SHWIENGSEEGIVRSGTNNHVTVAIEN	-----		

Amino acid alignment of DHHC20 proteins from humans (*homo sapiens*), camel (*camelus dromedaries*), pangolin (*manis javanica*) and two bat species, *Rhinolophus Sinicus* (host of various  $\beta$ -CoVs including SARS-1 and presumably SARS-2) and *Pipistrellus Kuhlii*, host of MERS. The transmembrane regions are highlighted in grey, individual residues that contact the acyl chain in the cavity are highlighted in green and the two (S and T) that seal the cavity are highlighted in pink. The amphiphilic helix following TMR4 is also highlighted in grey. Cys and His residues that coordinate zinc ions, the DHHC motif and the TTEX motif are highlighted in light blue and basic residues involved in acyl-CoA binding are highlighted in green. LVGM is the end of the resolved DHHC20 structure. Amino acid differences to human DHHC2 are highlighted in yellow in the sequence of the respective species and the non-conservative exchanges labeled in the 3D-structure of DHHC20 are in red.

Accession numbers: DHHC20 sequences of Human (NP\_001316988.1), Rhinolophus Sinicus (XP\_019571223.1), Pipistrellus Kuhlii (XP\_036313463.1), Camelus Dromedarius (XP\_031321583.1) and Manis Javanica (XP\_036857811.1).