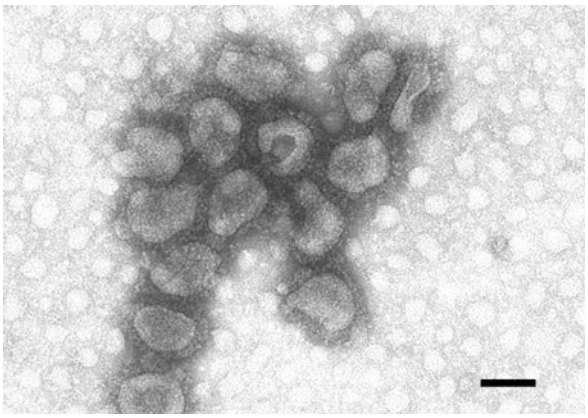
Betacoronavirus[‡]

Coronaviridae

Nicola Decaro



Betacoronavirus-1 (BCoV). Fig. 1
Transmission electron micrograph, negative staining of purified virus. Length of bar (nm): 100 (Courtesy of Dr. A. Lavazza, Istituto Zooprofilattico di Lombardia ed Emilia Romagna, Italy)

Virion

Morphology:	Spherical
Envelope:	Yes
Diameter (nm):	120–160
Length (nm):	
Structural components:	Core, capsid, envelope
Buoyant density (g/mL):	1.23–1.24
Buoyant density method:	CsCl
Lipid composition:	Envelope lipids are derived from cytoplasma membrane of host cell
Additional information:	Surface projections made by the spike (S) protein; some strains contain a second layer of surface projections made of HE protein

[‡]This chapter was reprinted from the first edition of the Springer Index of Viruses. Taxonomy and classification of the virus species described in this chapter may have changed.

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Genome

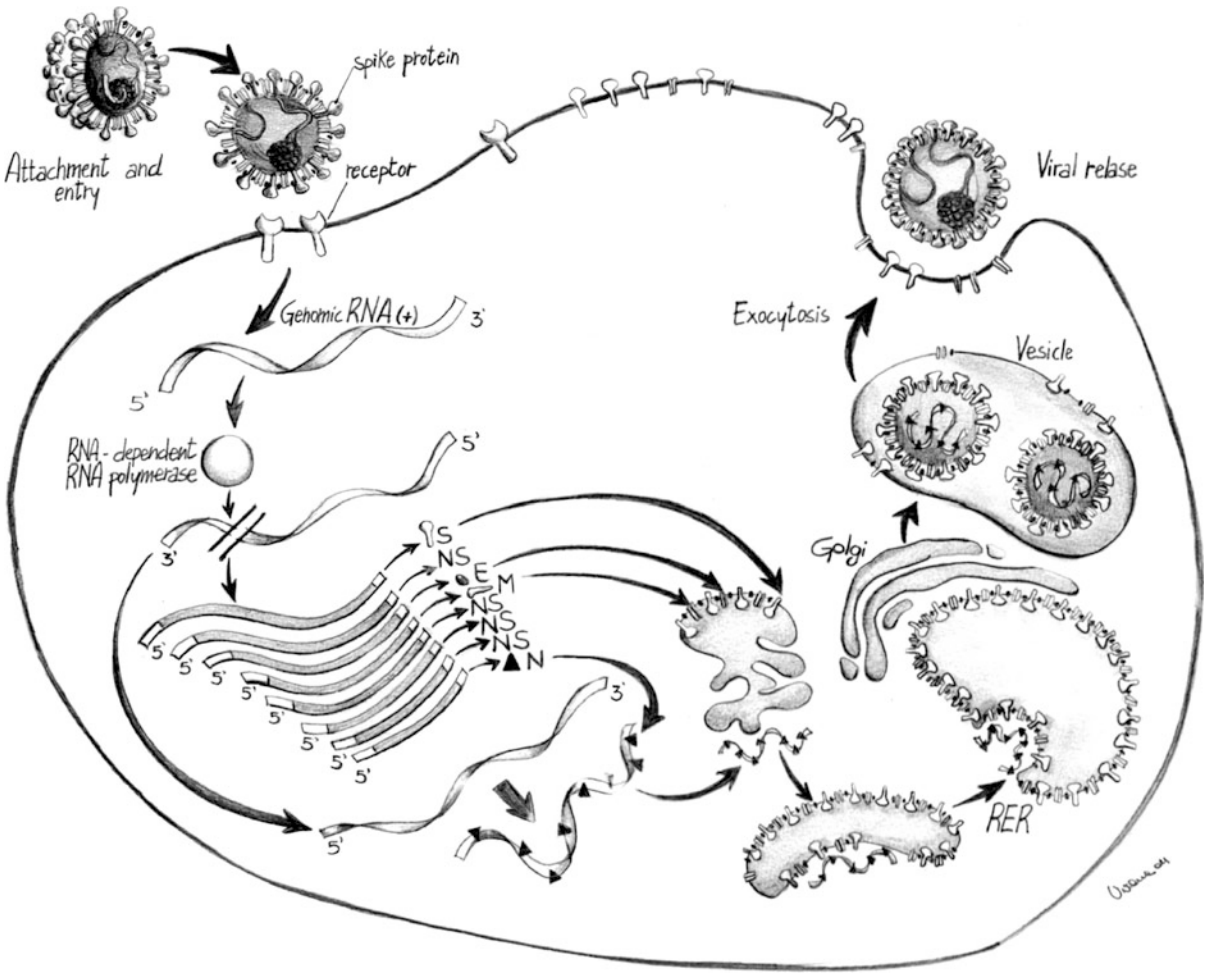
Nucleic acid:	RNA	
Strandedness:		
Polarity:		
Configuration:		
Segment organization:	Segment no. 1 (kb):	29.0–31.4
	One segment(s):	29–31.4 (kb) total (calculated)
G + C content (%):	37.6–41.8	
mRNA transcripts:	7–10	
Open reading frames:	7–10	
Additional information:	The genome contains a leader at the 5′ end and a poly(A) tail; genes are arranged in the order 5′-replicase-(HE)-S-E-M-N-3′, with a variable number of other genes that are believed to be non-structural	

Replication

Entry mechanism:	Receptor-mediated endocytosis
Site of transcription:	Cytoplasm
Transcriptase:	Virus-encoded RNA-dependent RNA polymerase
Site of genome replication:	Cytoplasm
Replicase:	Virus-encoded RNA-dependent RNA polymerase
Replication intermediate:	Negative-strand RNA intermediate
Site of virion assembly:	Cytoplasm, the intermediate compartment
Egress mechanism:	Budding through the pre-Golgi and Golgi to the basolateral (MHV) surface
Additional information:	Only the membrane (M) and envelope (E) proteins are required for the production of virus-like particles (VLPs)

History

Year of event	Event	References
1949	Murine hepatitis coronavirus (MHV) associated with encephalomyelitis in mice	Cheever et al (1949)
1967	HCoV-OC43 isolated from patients with common cold	McIntosh et al (1967)
1968	Electron microscopy reveals that BCoV has a second, short surface protein (HE)	Bridger et al (1978)
1975	ICTV approves Coronaviridae family with one genus, Coronavirus	Tyrrell et al (1975)
1981	Spike protein shown to be responsible for membrane fusion	Holmes et al (1981)
1982	Leader sequence at 5′ of mRNAs is from 5′ of genome (MHV)	Lai et al (1982)



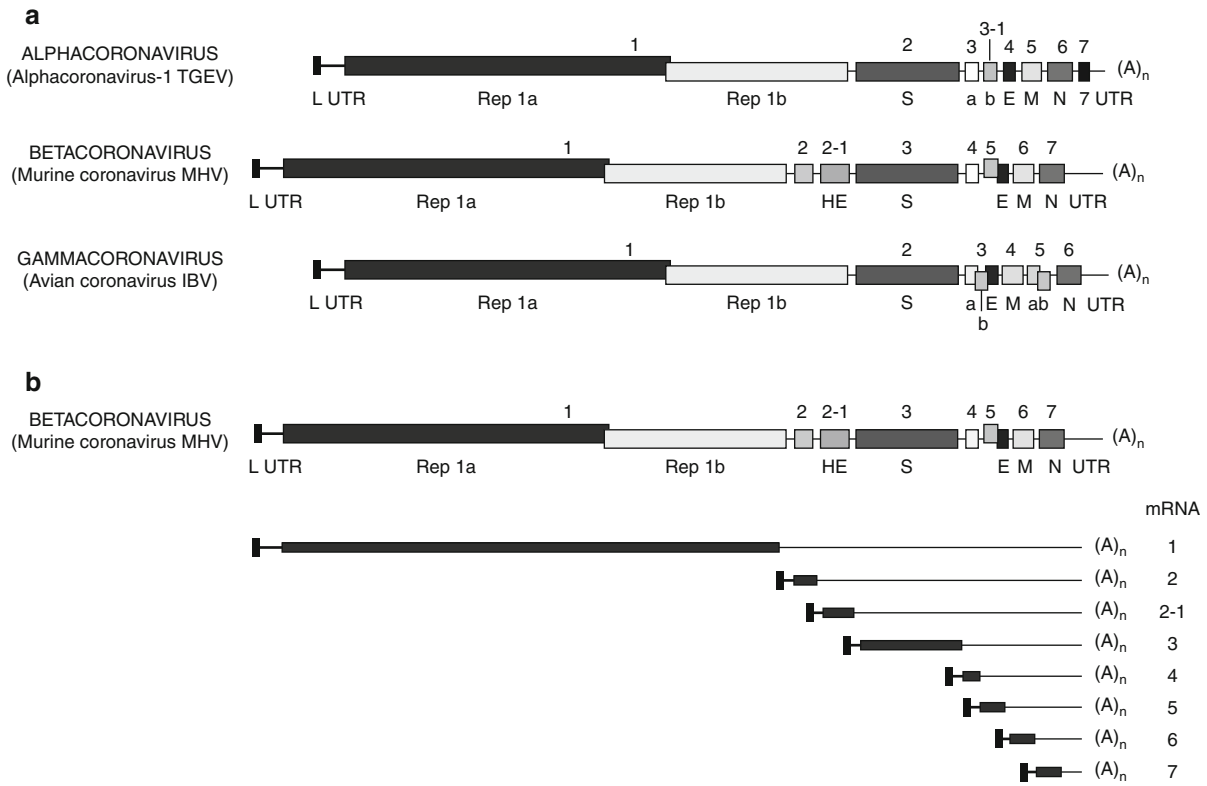
Alpha-, Beta-, and Gammacoronavirus replication cycle. Fig. 2
HE protein is present only in some Betacoronaviruses (Courtesy of Dr Viviana Tarallo, Department of Veterinary Public Health, Valenzano, Italy)

Year of event	Event	References
1982	First coronavirus gene (N) sequenced (MHV)	Skinner and Siddell (1982)
1983	Leader-primed transcription model proposed (MHV); discontinuous transcription during positive strand synthesis	Lai et al (1983)
1984	M protein (MHV) is located in Golgi membranes	Tooze et al (1984)
1985	Near start of genes is a sequence similar to 3′ end of the leader RNA at 5′ end of the genome (MHV)	Budzilowicz et al (1985)
1985	Coronavirus defective RNAs discovered (MHV)	Makino et al (1985)
1985	Homologous recombination achieved with MHV	Lai et al (1985)

Year of event	Event	References
1991	Cell susceptibility to MHV conferred by a receptor of the carcinoembryonic antigen family	Dveksler et al (1991)
1996	ICTV recognises Coronaviridae as containing 2 genera: Coronavirus and Torovirus	Cavanagh et al (1997)
1996	ICTV recognises the order Nidovirales containing families Coronaviridae and Arteriviridae	Cavanagh et al (1997)
1996	M and E proteins sufficient for the formation of virus-like particles	Bos et al (1996); Vennema et al (1996)
1997	Insertion of gene for green fluorescent protein into genome of MHV by recombination	Fischer et al (1997)
2000	In-vitro construction of chimeric coronaviruses that cross the species barrier	Kuo et al (2000)
1999	Insertion of a transcription control sequence into MHV by recombination	Hsue and Masters (1999)
2002	A novel coronavirus (SARS-CoV) recognised as aetiological agent of severe acute respiratory disease (SARS) in humans in Guandong Province, China	Drosten et al (2003); Ksiazek et al (2003); Peiris et al (2003)
2003	Angiotensin-converting enzyme 2 recognised as functional receptor for SARS-CoV	Li et al (2003)
2003	SARS-like CoVs identified in wild carnivores sold at live markets in Guandong Province, China	Guan et al (2004); Tu et al (2004)
2005	Bats recognised as natural reservoirs of SARS-like CoVs	Lau et al (2005); Li et al (2005)
2005	Specific changes detected in the spike protein and accessory proteins 3a and 8 of SARS-CoV	Song et al (2005)
2005	Human coronavirus HKU1 identified in the nasopharyngeal aspirates of patients with pneumonia in Hong Kong	Woo et al (2005)
2005	Design of wide-spectrum inhibitors of coronavirus main protease	Yang et al (2005)
2005	Transcriptomics and proteomics approaches proposed for coronaviral infections	Jiang et al (2005)
2006	A common ancestor is recognised for BCoV, HCoV-OC43 and PHEV	Vijgen et al (2006)
2007	Identification of coronavirus interferon antagonist proteins	Ye et al (2007)
2009	ICTV recognises the family Coronaviridae as containing two subfamilies, Coronavirinae and Torovirinae, with the former including three genera	Carstens (2010)
2009	According to the new taxonomy, genus Coronavirus is replaced by genera Alpha-, Beta- and Gammacoronavirus, corresponding to the old antigenic groups	Carstens (2010)
2009	BCoV, HCoV-OC43, PHEV, CRCoV and related viruses are recognised as host variants of a unique species, Betacoronavirus-1, of the genus Betacoronavirus	Carstens (2010)
2009	SARS-CoV and bat SARS-CoVs are recognised as host variants of a unique species, SARSr-CoV, of the genus Betacoronavirus	Carstens (2010)
2010	An important role in the coronavirus lyfe cycle is assigned to the ubiquitin-proteasome system	Raaben et al (2010)

Genus Members

Species name	Synonyms	Wild-type strains/ isolates	Natural host range	Experimental host range	Membership status
Murine coronavirus	Murine hepatitis virus (MHV); Rat coronavirus (Rat sialodacryoadenitis coronavirus) (RtCoV [SDAV]); Puffinosis coronavirus (PCoV)	MHV: A59, JHM; RtCoV: Parker, SDAV-681	Mice (MHV), rats (RtCoV); Manx shearwater (PCoV)	Mice (PCoV)	Type species
Betacoronavirus 1	Bovine coronavirus (BCoV); Human coronavirus OC43 (HCoV-OC43); Human enteric coronavirus (HECoV); Porcine hemagglutinating encephalomyelitis virus (PHEV); Canine respiratory coronavirus (CRCoV); Equine coronavirus (ECoV); Bubaline coronavirus (BuCoV); Giraffe coronavirus (GiCoV); Sable antelope coronavirus (SACoV); Sambaar deer coronavirus (SDCoV); Waterbuck coronavirus (WbCoV); White-tailed deer coronavirus (WtDCoV); Elk coronavirus (EkCoV)	BCoV:Mebus; DB2; HCoV-OC43: VR759;VA; PHEV: Minnesota; CRCoV:4182; BuCoV:179/07-11; GiCoV:US/OH3/ 2003	Cattle, humans, swine, dogs, horses, ruminants	Turkeys,dogs (BCoV); mice (HCoV-OC43); cattle(HECoV)	Approved member
Human coronavirus HKU-1 (HCoV-HKU1)		N5P8; Caen; LZ20	Humans		Approved member
Pipistrellus bat coronavirus HKU5 (Pi-BatCoV-HKU5)		HKU5-1 LMH03f	Bats (Pipistrellus spp.)		Approved member
Rousettus bat coronavirus HKU9 (Ro-BatCoV-HKU9)		HKU9-1 BF_005I	Bats (Rousettus spp.)		Approved member
SARS-related coronavirus (SARSr-CoV)	Severe acute respiratory syndrome coronavirus (SARS-CoV); Severe acute respiratory syndrome-related Rhinolopus bat coronavirus (SARSr-Rh-BatCoV); Severe acute respiratory syndrome-related Rhinolopus bat coronavirus 273 (SARSr-Rh-BatCoV-273); Severe acute respiratory syndrome-related Rhinolopus bat coronavirus HKU3 (SARSr-Rh-BatCoV-HKU3)	SARS-CoV: Urbani; Toronto; GDO3	Humans, wild carnivores (SARS-CoV); bats	Mice, hamsters, cats, ferrets, non-human primates	Approved member
Tylonycteris bat coronavirus HKU4 (Ty-BatCoV-HKU4)		HKU4-1 B04f	Bats (Tylonycteris spp.)		Approved member



Genome organization of Alpha-, Beta-, and Gammacoronavirus prototypes (A) and transcription map of Murine coronavirus MHV (B). Fig. 3

Numbers above *bars* ORFs, *L* leader, *UTR* untranslated region, *Rep* replicase, *(A)n* poly A (Modified from Springer Index of Viruses, 1st edition, with permission)

Nucleotide Sequences

Genomic region	Species	Strain	Nucleotides	Access number	References
Complete genome	Murine coronavirus (MHV)	A59-C12	31,357	AF029248	Leparc-Goffart et al (1997)
Complete genome	Murine coronavirus (Rt-CoV)	Parker	31,250	NC_012936	Spiro et al (2009) direct submission
Complete genome	Ty-BatCoV-HKU4	HKU4-1 B04f	30,286	NC_009019	Woo et al (2007)
Complete genome	Pi-BatCoV-HKU5	HKU5-1 LMH03f	30,482	NC_009020	Woo et al (2007)
Complete genome	Ro-BatCoV-HKU9	HKU9-1 BF_005I	29,114	NC_009021	Woo et al (2007)
Complete genome	HCoV-HKU1	N5P8 genotype A/B	29,755	DQ339101	Woo et al (2006)
Complete genome	Betacoronavirus-1 (BCoV)	DB2	31,023	DQ811784	Spiro, et al (2006) direct submission

Genomic region	Species	Strain	Nucleotides	Access number	References
Complete genome	Betacoronavirus-1 (PHEV)	VW572	30,480	DQ011855	Vijgen et al. (2006)
Complete genome	Betacoronavirus-1 (SACoV)	US/OH1/2003	30,995	EF424621	Zhang et al (2007) direct submission
Complete genome	Betacoronavirus-1 (GiCoV)	US/OH3/2003	31,002	EF424623	Hasoksuz et al (2007)
Complete genome	Betacoronavirus-1 (ECoV)	NC99	30,992	EF446615	Zhang et al (2007)
Complete genome	Betacoronavirus-1 (HECoV)	4408	31,029	FJ415324	Zhu et al (2008) direct submission
Complete genome	Betacoronavirus-1 (HCoV-OC43)	87309 Belgium 2003	30,723	AY903459	Vijgen et al (2005)
Complete genome	Betacoronavirus-1 (SDCoV)	US/OH-WD388/1994	30,997	FJ425189	Alekseev et al (2008)
Complete genome	Betacoronavirus-1 (WbCoV)	US/OH-WD358/1994	30,962	FJ425186	Alekseev et al (2008)
Complete genome	Betacoronavirus-1 (WtDCoV)	US/OH-WD470/1994	31,020	FJ425187	Alekseev et al (2008)
Complete genome	SARSr-CoV (SARS-CoV)	HKU-39849	29,742	AY278491	Zeng et al (2003)
Complete genome	SARSr-CoV (SARSr-Rh-BatCoV HKU3)	HKU3-2	29,687	DQ084199	Lau et al (2005)
Complete genome	SARSr-CoV (SARSr-Rh-BatCoV 273)	BtCoV/273/2005	29,704	DQ648856	Tang et al (2006)
Genomic 3′ end	Betacoronavirus-1 (BuCoV)	Italy/179/07-11	9,679	EU019216	Decaro et al (2008)
Genomic 3′ end	Betacoronavirus-1 (CRCoV)	240/05	9,686	EU999954	Lorusso et al (2009)
N protein gene	Murine coronavirus (PCoV)		1,728	AJ544718	Wu et al (2003) direct submission

Proteins

Protein name	Protein name abbreviation	Number of amino acids	Molecular weight (kDa)	Time of expression	Accession numbers	Additional information
Polyprotein 1ab (replicase complex)	pp1ab	6793–7241	740–800	Throughout	AAR91584; AAP13442; ADE34721; ADE34822; ABG47068; YP_001039961; ADM33557; YP_001039952; BAF75628; YP_459949; YP_003038518; AAT84359; YP_001671996; ADI59786; YP_003029844; ABD75543	Encoded by two ORFs, 1a and 1b; pseudoknot involved in frameshifting; cleaved to several products, including an RNA-dependent RNA polymerase

Protein name	Protein name abbreviation	Number of amino acids	Molecular weight (kDa)	Time of expression	Accession numbers	Additional information
Hemagglutinin esterase	HE	386–439	65	Throughout	D00764; AAT98579; AAY68296; YP_209232; ABP38257; NP_937949	Present in all members of the genus except SARSr-CoV, Ro-BatCoV-HKU9, Ty-BatCoV-HKU4, Pi-BatCoV-HKU5; non-essential
Spike glycoprotein	S	1241–1376	150–220	Throughout	AAM77000; ACJ66971; ACJ67012; AAF25499; YP_003038522; ACJ66977; CAA83661; AAQ67205; AAF69334; AAF97738; ABD75545; ABN10857; ABG47052; ADM33574; ABN10911; YP_001039962; ADE34733; ACU31051; AAV97986	Highly glycosylated; forms homotrimers; cleaved to S1 and S2 subunits
Membrane protein	M	219–230	23–25	Throughout	AF220295; ABP38308; ABG78752; AAY68301; AAT84357; AAF36439; AAD33106; ABD75508; ABN10854; YP_729208; ABN10890; ADM33569; ABD75325; ADE34793; AAP41041; AAU04653	N-linked or O-linked glycans; triple-spanning
Envelope protein	E	75–88	9–12	Throughout	AAR01017; AAM77003; NP_150081; ABG78751; YP_003029850; ACN89766; ABD75515; ABN10889; ABN10862; YP_729207; ABD75324; ACZ72168; AAP41040	Essential for virion assembly; E plus M forms virus-like particles
Nucleocapsid protein	N	417–470	50–60	Throughout	AAA66397; ACL13001; ABP38321; AAR01019; ACH72650; ABP87995; ACN89747; AAD33104; ABD75581; ABN10900; ABN10939; ABG47067; AAZ41337; ADK66848; ABN10855; AAP50495; ACZ72030	Highly basic phosphoprotein; forms a helical nucleocapsid
Non-structural protein 2a (32 kDa)	ns2a (ns2 or ns32kDA)	194–278	30–32	Throughout	AAF25507; ABV74052; ABG78746; ABP87988; AAA74377; ACN89750; AAU06354; AAF97736; YP_459950	Unique to Betacoronavirus-1 and Murine coronavirus; ns2a in murine coronavirus; ns2 or ns32kDa in Betacoronavirus-1; gene between pp1ab and HE genes

Protein name	Protein name abbreviation	Number of amino acids	Molecular weight (kDa)	Time of expression	Accession numbers	Additional information
Non-structural protein 4	ns4	106–139	15	Throughout	AAF97739; YP_003029849; YP_209234; ACN89764	Unique to Murine coronavirus; two distinct ORFs (4a, 4b) in Betacoronavirus-1; not essential; may be truncated in some strains
Non-structural protein 4a (4.9 kDa)	ns4a (ns4.9 kDa)	29–44	4.9	Throughout	AAF25500; AAF25510; AAG40624; ABV74055; ACL12997; ACJ35490	Unique to Betacoronavirus-1; not essential for replication; may be truncated in some strains
Non-structural protein 4b (4.8 kDa)	ns4b (ns4.8 kDa)	43–45	4.7–4.8	Throughout	AAF25501; AAG60546; AAL40402; ACJ35491	Unique to Betacoronavirus-1; not essential for replication; may be truncated in some strains
Non-structural protein 5 (12.7 kDa)	ns5 (ns5a or ns12.7 kDa)	107–112	12.6–13.1	Throughout	AAF19390; NP_068672; AAF97740; YP_173239; YP_003038502; AAF25502; ACX46843	Unique to Murine coronavirus/ Betcoronavirus-1/HCoV-HKU1; ns5 in MHV; ns12.7 kDa in BCoV; ns4 in HCoV-HKU1; not essential; may be truncated in some strains
Internal protein	I (N2)	136–220	23	Throughout	ACN89765; ACN89684; ACT11047; AAF25516; ABG78754; AAY68303; ABP87996; NP_937955; ACT11037; ABC70724	Unique to Murine coronavirus/ Betacoronavirus-1/HCoV-HKU1; ORF is within the N gene; not essential; may be truncated in some strains
SARS-CoV 3a protein	Sars3a	274	30.9	Throughout	ACZ72036; ACZ72226; ACQ82726; ADE34813; ADE34734; ABD75316; AAU04635	Unique to SARSr-CoV; O-glycosylated, triple membrane spanning; forms homotetramers; not essential for replication
SARS-CoV 3b protein	Sars3b	114–154	12.8–17.7	Throughout	ACZ71978; ACB69862; ACB69907; AAU04636; YP_001382387; ABD75317	Unique to SARSr-CoV; not essential for replication
SARS-CoV 6 protein	Sars6	63	7.5	Throughout	ABA02272; ACZ72098; ACZ71861; AAP13448; AAU04639; ABD75318; ADE34737; ADE34805	Unique to SARSr-CoV; not essential for replication
SARS-CoV 7a protein	Sars7a	122	13.9	Throughout	ACQ82731; ACZ72041; ACZ72128; ACZ72216; ACZ72260; NP_828857	Unique to SARSr-CoV; type I transmembrane protein; not essential for replication

Protein name	Protein name abbreviation	Number of amino acids	Molecular weight (kDa)	Time of expression	Accession numbers	Additional information
SARS-CoV 7b protein	Sars7b	44	5.3	Throughout	CAJ15124; ABA02274; ABA02274; ACZ71953; BAC81397; AAS44625; ACQ82732; AAU04656; YP_001382367; ABD75329; ADE34728	Unique to SARSr-CoV; not essential for replication
SARS-CoV 8 protein	Sars8	122–123	13.8	Throughout	AAZ67036; ABG47066; AAU04657; AAZ67036; AAV91639	Unique to some SARSr-CoVs (early human and animal SARS-CoVs); present as two distinct ORFs (8a and 8b) in human SARS-CoV due to a 29-nt deletion
SARS-CoV 8a protein	Sars8a	39	4.3	Throughout	NP_849176; ACZ72058; ACZ72277; ACZ71804; ACZ71969	Unique to most human SARSr-CoVs; originating from a 29-nt deletion in ORF8; not essential for replication
SARS-CoV 8b protein	Sars8b	84	9.5	Throughout	CAJ15126; NP_849177; ACZ72059; BAC81413; AAP41046; ACZ71805	Unique to most human SARSr-CoVs; originating from a 29-nt deletion in ORF8; not essential for replication
SARS-CoV 9b protein	Sars9b	97–98	10.8	Throughout	ACB69891; AAR87585; BAC81401; AAP69659; ACB69857; AAU04659; ADE34821; ADE34810; AAZ67037	Unique to SARSr-CoV; gene located within N gene; not essential for replication
SARS-CoV 14 protein	Sars14	70	7.8	Throughout	ACZ72047; ADC35508; ACZ72207; ACZ72032; AAU04674; YP_001382371; AAZ67042; AAZ67045	Unique to SARSr-CoV; also known as ORF10 protein; not essential for replication

Biology

Species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Murine coronavirus (MHV)	Sac(−), L2, DBT, RK13, 17Cl-1	Intestine, liver, CNS	Syncytia with several cell types	Tropism is virus strain dependent
Murine coronavirus (RtCoV)	L2, LBC, RBL-02	Respiratory tract, parotid gland	Syncytia formation	Infects laboratory rats at high prevalence
Murine coronavirus (PCoV)	NCTC-1469	Skin, lung, blood	Cell rounding and detachment, syncitya formation	

Species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Betacoronavirus-1 (BCoV)	HRT-18, PK15, PK3, MDBK, BEK-1	Intestine, respiratory tract	Cell lysis; syncytia if trypsin present	No genetic differences between enteric and respiratory strains
Betacoronavirus-1 (HCoV-OC43)	HRT-18, MA-321, DRG-N	Upper respiratory tract	Cytoplasm vacuolisation, degeneration of monolayer	Infects astrocytes and microglial cells; some strains replicate in the enteric tract
Betacoronavirus-1 (HECoV)	HRT-18; HFI; J774; C6/36	Intestinal epithelium	Formation of giant cells and small syncytia	
Betacoronavirus-1 (PHEV)	Pk-15, IBRS2, SK, SK-K	Intestine and CNS	Syncytia formation	Also replicates in respiratory tract
Betacoronavirus-1 (CRCoV)	HRT-18	Respiratory tract	No evident cytopathic effect	Also replicates in the intestine
Betacoronavirus-1 (ACoV)	HRT-18	Intestinal epithelium	Cell rounding and detachment	
Betacoronavirus-1 (ECoV)	HRT-18	Intestinal epithelium	Round refractile cells, syncytia formation	
Betacoronavirus-1 (BuCoV)	HRT-18	Respiratory tract	Syncytia formation and subsequent cell lysis	Poor growth in MDBK cells
Betacoronavirus-1 (GiCoV, SACoV, SDCoV, WbCoV, WtDCoV, EkCoV)	HRT-18	Intestinal epithelium	Rounded cells and syncytia formation	
HCoV-HKU1	None	Upper and lower respiratory tract	Not applicable	A certain replication has been obtained using human ciliated airway epithelial cell cultures
SARSr-CoV (SARS-CoV)	Vero-E6; FRhK-4; Caco-2; LLC-Mk2; HuH7; RK-13; MA-104; CV-1	Lower respiratory tract (pneumocytes/ macrophages)	Cell rounding, refractivity and cell detachment	Also grows on lymphoid cell cultures causing a non-lytic infection

Diseases

Disease	Causative agent	Affected organisms	Disease characteristics	Transmission route/vector	Treatment	Geographic distribution
Mouse hepatitis and encephalitis	Murine coronavirus (MHV)	Mice	Hepatitis, diarrhoea, acute or chronic demyelinating encephalomyelitis	Faecal-oral	None	Worldwide
Rat pneumonia and sialodacryoadenitis	Murine coronavirus (RtCoV, SDAV)	Rats	Pneumonia, rhinitis, sialodacryoadenitis	Aerosol	None	Worldwide

Disease	Causative agent	Affected organisms	Disease characteristics	Transmission route/vector	Treatment	Geographic distribution
Puffinosis	Murine coronavirus (PCoV)	Manx shearwater (Puffinus puffinus)	Blisters on the webs of the feet, conjunctivitis and locking of the ankle joint of the legs	Likely aerosol	None	South-west coast of Wales
Bovine enteritis and respiratory disease	Betacoronavirus-1 (BCoV)	Cattle	Acute enteritis in newborns, wynter dysentery in adults, respiratory disease in all ages	Faecal-oral, aerosol	Only symptomatic	Worldwide
Human common cold	Betacoronavirus-1 (HCoV-OC43)	Humans	Common cold (sneezing, coughing, nasal discharge)	Aerosol	Only symptomatic	Worldwide
Human enteritis	Betacoronavirus-1 (HECoV)	Humans	Diarrhoea	Faecal-oral	Only symptomatic	A single case reported in the USA
swine encephalomyelitis, vomiting and wasting disease	Betacoronavirus-1 (PHEV)	Swine	vomiting, weight loss, encephalomyelitis	Faecal-oral	Only symptomatic	Worldwide
Canine respiratory disease	Betacoronavirus-1 (CRCoV)	Dogs	Cough, nasal discharge, tracheobronchitis	Aerosol	Only symptomatic	Worldwide
Equine enteritis	Betacoronavirus-1 (ECoV)	Horses	Enteritis	Faecal-oral	Only symptomatic	USA, Japan
Buffalo enteritis	Betacoronavirus-1 (BuCoV)	Water buffaloes (Bubalus bubalis)	Enteritis	Faecal-oral	Only symptomatic	Italy, Bulgaria
Alpaca enteritis	Betacoronavirus-1 (ACoV)	Alpacas (Vicugna pacos)	Enteritis, fever	Faecal-oral	Only symptomatic	USA
Wild-ruminant enteritis	Betacoronavirus-1 (GiCoV, SACoV, SDCoV, WbCoV, WtDCoV, EkCoV)	Wild ruminants (giraffes, sable antelopes, sambaar deer, waterbuck, white-tailed deer, elks)	Enteritis	Faecal-oral	Only symptomatic	USA
Human respiratory disease	HCoV-HKU1	Humans	Fever, cough, coryza, sore throat, bronchiolitis, bronchitis, pneumonia and croup	Aerosol	Only symptomatic	Worldwide
Severe acute respiratory disease	SARSr-CoV (SARS-CoV)	Humans	Flu-like prodrome, fever, dry cough, non–respiratory symptoms e.g. diarrhoea, myalgia, headache and chills/rigors	Aerosol	Symptomatic, antivirals	East Asia with further spreading to many countries

Diagnosis

Method	Species	Sample material	Detection target	References
Electron microscopy	Murine coronavirus (MHV)	Liver, brain	Particle morphology	Dumitrescu et al (1962)
DBT cell culture and immunofluorescence assay	Murine coronavirus (MHV)	Liver, brain	Viral antigens	Hirano et al (1976)
Immunoshostochemistry	Murine coronavirus (MHV)	Liver, brain	Viral antigens	Knobler et al (1981)
RT-PCR amplification of the membrane protein gene	Murine coronavirus (MHV, RtCoV)	Tissues	Viral RNA	Homberger et al (1991)
Nested PCR amplification of the nucleocapsid protein gene	Murine coronavirus (MHV)	Faeces	Viral RNA	Yamada et al (1998)
Real-time RT-PCR amplification of the membrane protein gene	Murine coronavirus (MHV, RtCoV)	Tissues, faeces, cage swipes	Viral RNA	Besselsen et al (2002)
HRT-18, MDBK or PK15 cell culture and immunofluorescence assay	Betacoronavirus-1 (BCoV, HCoV-OC43, PHEV, CRCoV, BuCoV, GiCoV, ECoV, ACoV, SACoV, WbCoV, SDCoV, WtDCoV, EkCoV)	Faeces, intestine, respiratory specimens	Viral antigens	Peterson et al (1976)
Electron microscopy	Betacoronavirus-1 (BCoV, HCoV-OC43, PHEV, CRCoV, BuCoV, GiCoV, ECoV, ACoV, SACoV, WbCoV, SDCoV, WtDCoV, EkCoV)	Faeces, intestine, respiratory specimens	Particle morphology	Chasey and Lucas (1977)
Protein A-colloidal gold immunoelectron microscopy	Betacoronavirus-1 (BCoV, HCoV-OC43, PHEV, CRCoV, BuCoV, GiCoV, ECoV, ACoV, SACoV, WbCoV, SDCoV, WtDCoV, EkCoV)	Faeces, intestine, respiratory samples	Viral antigens	Dea and Garzon (1991)
Haemagglutination using mouse or chicken erytrocytes	Betacoronavirus-1 (BCoV, HCoV-OC43, PHEV, CRCoV, BuCoV, GiCoV, ECoV, ACoV, SACoV, WbCoV, SDCoV, WtDCoV, EkCoV)	Faeces, intestine, respiratory specimens	Viral haemagglutinin	Storz et al (1992)
Monoclonal antibody ELISA	Betacoronavirus-1 (BCoV)	Faeces, intestine, respiratory specimens	Viral antigens	Thorns et al (1992)
Immunoistochemistry	Betacotonavirtus-1 (BCoV)	Paraffin-embedded, formalin-fixed intestines	Viral antigens	Zhang et al (1997)
Microimmunodot blot assay	Betacoronavirus-1 (BCoV)	Faeces, intestine, respiratory specimens	Viral antigens	Gaber and Kapil (1999)
Nested RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (BCoV)	Faeces, intestine, respiratory specimens	Viral RNA	Cho et al (2001)
Internally-controlled nested RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (BCoV)	Faeces, intestine, respiratory specimens	Viral RNA	Takiuchi et al (2006)

Method	Species	Sample material	Detection target	References
Real-time RT-PCR amplification of the membrane protein gene	Betacoronavirus-1 (BCoV, BuCoV, CRCoV)	Faeces, intestine, respiratory specimens	Viral RNA	Decaro et al (2008)
Nested RT-PCR amplification of the spike protein gene	Betacoronavirus-1 (PHEV)	Brain, faeces, intestine, respiratory specimens	Viral RNA	Sekiguchi et al (2004)
Real-time RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (CRCoV)	Respiratory specimens	Viral RNA	Mitchell et al (2009)
Immunofluorescence assay	Betacoronavirus-1 (HCoV-OC43)	Nasopharyngeal smears	Viral antigens	McIntosh et al (1978)
Monoclonal time-resolved fluoroimmunoassay	Betacoronavirus-1 (HCoV-OC43)	Respiratory specimens	Viral antigens	Hierholzer et al (1994)
Enzyme immunoassay	Betacoronavirus-1 (HCoV-OC43)	Respiratory specimens	Viral antigens	Hierholzer et al (1994)
Nested RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (HCoV-OC43)	Respiratory specimens	Viral RNA	Vabret et al (2001)
Real-time RT-PCR amplification of the membrane protein gene	Betacoronavirus-1 (HCoV-OC43)	Respiratory specimens	Viral RNA	Vijgen et al (2005)
Microarray using standard amplification and hybridization techniques	Betacoronavirus-1 (HCoV-OC43)	Respiratory specimens	Viral RNA	Lodes et al (2007)
RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (HCoV-OC43), HCoV-HKU1	Respiratory specimens	Viral RNA	Dominguez et al (2009)
Nested PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (HCoV-OC43), HCoV-HKU1	Respiratory specimens	Viral RNA	Gaunt et al (2010)
Multiplex real-time RT-PCR amplification of the nucleocapsid protein gene	Betacoronavirus-1 (HCoV-OC43), HCoV-HKU1	Respiratory specimens	Viral RNA	Gaunt et al (2010)
Vero or FRhK cell culture and immunofluorescence assay	SARSr-CoV (SARS-CoV)	Respiratory specimens	Viral antigens	Ksiazek et al (2003)
Electron microscopy	SARSr-CoV (SARS-CoV)	Respiratory specimens	Particle morphology	Ksiazek et al (2003)
Nested RT-PCR amplification of the RdRp (nsp1ab) gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Drosten et al (2003)
RT-PCR amplification of the RdRp (nsp1ab) gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Peiris et al (2003)
Real-time RT-PCR amplification of the RdRp (nsp1ab) gene	SARSe-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Poon et al (2003)

Method	Species	Sample material	Detection target	References
Real-time RT-PCR amplification of the RdRp (nsp1ab) gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Kuiken, et al (2003)
Real-time RT-PCR amplification of the nucleocapsid protein gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Kuiken, et al (2003)
Immunohistochemistry	SARSr-CoV (SARS-CoV)	Formalin-fixed, paraffin-embedded tissues	Viral antigens	Kuiken et al (2003)
Indirect immunofluorescence assay	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Kuiken et al (2003)
ELISA test using whole virus	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Ksiazek et al (2003)
RT-PCR amplification of the nucleocapsid protein gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Bermingham et al (2004)
Virus neutralising antibody test	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Zheng et al (2004)
Immunochromatographic test	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Wu et al (2004)
Western blot	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Wu et al (2004)
Dot blot enzyme-linked immunosorbent assay	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Chow et al (2004)
ELISA test using recombinant nucleocapsid protein	SARSr-CoV (SARS-CoV)	Serum	Anti-viral antibodies	Guo et al (2007)
Nucleocapsid-based human coronavirus immunoassay	SARSr-CoV (SARS-CoV)	Serum	Anti-nucleocapsid protein antibodies	Severance et al (2008)
Internally-controlled real-time RT-PCR amplification of the RdRp (nsp1ab) gene	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral RNA	Yu et al (2008)
Localized surface plasmon coupled fluorescence (LSPCF) fiber-optic biosensor	SARSr-CoV (SARS-CoV)	Serum	Viral antigens (nucleocapsid protein)	Huang et al (2009)
Surface plasmon resonance (SPR)-based biosensor	SARSr-CoV (SARS-CoV)	Serum	Anti-SARS-CoV surface antigen antibodies	Park et al (2009)
Enzyme-linked immunosorbent assay using chemiluminescence	SARSr-CoV (SARS-CoV)	Respiratory specimens, faeces	Viral antigens (nucleocapsid protein)	Fujimoto et al (2008)

Vaccine Strains

Strain	Attenuation process	Additional information	References
Betacoronavirus-1 BCoV many strains	Inactivated vaccines	Do not prevent respiratory diseases	Saif (2010)
Betacoronavirus-1 BCoV many strains	Passage in cell culture	Do not prevent respiratory disease	Saif (2010)
SARSr-CoV SARS-CoV strain Utah	Double-inactivated, whole-virus vaccine	Not yet licenced; reached the phase 1 clinical trial testing	Spruth et al (2006)
VRC-SRSDNA015-00-VP vaccine containing the spike gene of SARS-CoV strain Urbani	DNA vaccine expressing the spike protein	Not yet licenced; reached the phase 1 clinical trial testing	Martin et al (2008)

Vector Constructs

Vector name	Backbone strain	Application	Insertion capacity (kb)	Additional information	References
p25HE	Murine coronavirus MHV-JHM	Expression	1.4	Helper-dependent expression system	Liao et al (1995)
MHV-GFP	Murine coronavirus MHV-A59	Expression	0.5	Genome vector generated by recombination	Fischer et al (1997)
pMH54	Murine coronavirus MHV-A59	Reverse genetics	10.2	Used for targeted RNA recombination to obtain chimeric MHVs	Kuo et al (2000)
pJHM	Murine coronavirus MHV-JHM	Reverse genetics	10.2	Used for targeted RNA recombination to obtain chimeric MHVs	Ontiveros et al (2001)
icMHV-A59	Murine coronavirus MHV-A59	Reverse genetics	31.5	Full-length genome infectious clone constructed through ligation of seven inserts	Yount et al (2002)
icSARS-CoV	SARsr-CoV SARS-CoV Urbani	Reverse genetics	29.7	Full-length genome infectious clone constructed through ligation of six inserts	Yount et al (2003)
vMHV-inf-1	Murine coronavirus MHV-A59	Reverse genetics	31.4	Recombinant vaccinia virus containing the full-length genome of MHV	Coley et al (2005)
pBAC-SARS-CoV	SARSr-CoV SARS-CoV Urbani	Reverse genetics	30	Infectious bacterial artificial chromosome	Almazan et al (2006)
pBAC-OC43(FL)	Betacoronavirus-1 HCoV-OC43	Reverse genetics	30	Infectious bacterial artificial chromosome	St-Jean et al (2006)

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