



## REVIEW

# Emerging coronaviruses: Genome structure, replication, and pathogenesis

Yu Chen<sup>1</sup> | Qianyun Liu<sup>1</sup> | Deyin Guo<sup>2</sup> <sup>1</sup>State Key Laboratory of Virology, Modern Virology Research Center, College of Life Sciences, Wuhan University, Wuhan, China<sup>2</sup>Center for Infection and Immunity Study, School of Medicine, Sun Yat-sen University, Guangzhou, China**Correspondence**

Yu Chen, Modern Virology Research Center, College of Life Sciences, Wuhan University, Wuhan 430072, China.

Email: [chenyu@whu.edu.cn](mailto:chenyu@whu.edu.cn)

Deyin Guo, Center for Infection and Immunity Study, School of Medicine, Sun Yat-sen University, Guangzhou 510080, China.

Email: [guodeyin@mail.sysu.edu.cn](mailto:guodeyin@mail.sysu.edu.cn)**Funding information**

China National Science and Technology Major Project, Grant/Award Number: #2018ZX10733403; National Natural Science Foundation of China, Grant/Award Number: #81620108020 &amp; #81672008; Shenzhen Science and Technology Program, Grant/Award Number: KQTD20180411143323605; Guangdong Zhujiang Talents Program, Grant/Award Number: 2017

**Abstract**

The recent emergence of a novel coronavirus (2019-nCoV), which is causing an outbreak of unusual viral pneumonia in patients in Wuhan, a central city in China, is another warning of the risk of CoVs posed to public health. In this minireview, we provide a brief introduction of the general features of CoVs and describe diseases caused by different CoVs in humans and animals. This review will help understand the biology and potential risk of CoVs that exist in richness in wildlife such as bats.

**KEYWORDS**

coronavirus, epidemiology, pathogenesis, respiratory tract, virus classification, zoonoses

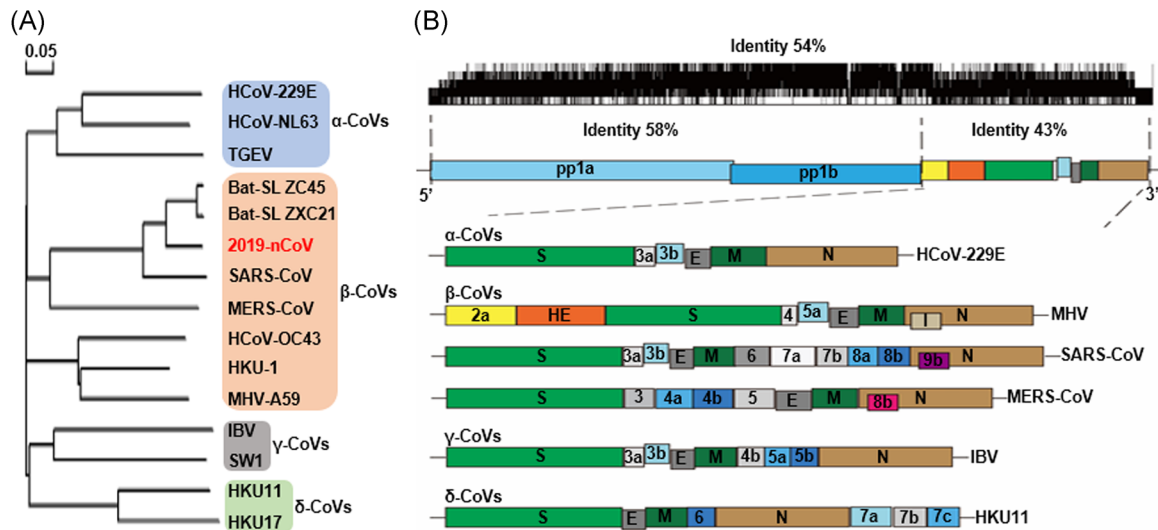
## 1 | INTRODUCTION

Coronaviruses (CoVs) are important pathogens for human and vertebrates. They can infect respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and many other wild animals.<sup>1-3</sup> The outbreaks of the severe acute respiratory syndrome (SARS) in 2002/2003 and the Middle East respiratory syndrome (MERS) in 2012 have demonstrated the possibility of animal-to-human and human-to-human transmission of newly emerging CoVs.<sup>4,5</sup> An outbreak of mystery pneumonia in Wuhan since December 2019 has been drawing tremendous attention around the world. Chinese government and researchers have been taking swift measures to control the outbreak and conduct the etiological studies. The causative agent of the mystery pneumonia has been identified as a novel coronavirus (nCoV) by deep sequencing and etiological investigations by at least five independent laboratories of China (<http://virological.org/> and <https://www.gisaid.org/>). On 12 January 2020, the World Health Organization temporarily named the new virus as 2019 novel coronavirus (2019-

nCoV). The sporadic emergence and outbreaks of new types of CoVs remind us that CoVs are a severe global health threat. It is highly likely that new CoV outbreaks are unavoidable in the future due to changes of the climate and ecology, and the increased interactions of human with animals. Thus, there is an urgent need to develop effective therapies and vaccines against CoVs.

## 2 | CORONAVIRAL GENOME STRUCTURE AND REPLICATION

CoVs belong to the subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales, and this subfamily includes four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (Figure 1A). The genome of CoVs is a single-stranded positive-sense RNA (+ssRNA) (~30 kb) with 5'-cap structure and 3'-poly-A tail. The genomic RNA is used as template to directly translate polyprotein 1a/1ab (pp1a/pp1ab), which encodes non-structural proteins (nsps) to form the replication-transcription complex



**FIGURE 1** The genomic structure and phylogenetic tree of coronaviruses. A, The phylogenetic tree of representative CoVs, with the new coronavirus 2019-nCoV highlighted in red. B, The genome structure of four genera of coronaviruses. Pp1a and pp1b represent the two long polypeptides that are processed into 16 nonstructural proteins. S, E, M, and N indicate the four structural proteins spike, envelope, membrane, and nucleocapsid. 2019-nCoV, 2019 novel coronavirus; CoVs, coronavirus; HE, hemagglutinin-esterase. Viral names: HKU, coronaviruses identified by Hong Kong University; HCoV, human coronavirus; IBV, infectious bronchitis virus; MHV, murine hepatitis virus; TGEV, transmissible gastroenteritis virus

(RTC) in a double-membrane vesicles (DMVs).<sup>6</sup> Subsequently, a nested set of subgenomic RNAs (sgRNAs) are synthesized by RTC in a manner of discontinuous transcription.<sup>7</sup> These subgenomic messenger RNAs (mRNAs) possess common 5'-leader and 3'-terminal sequences. Transcription termination and subsequent acquisition of a leader RNA occurs at transcription regulatory sequences, located between open reading frames (ORFs). These minus-strand sgRNAs serve as the templates for the production of subgenomic mRNAs.<sup>8,9</sup>

The genome and subgenomes of a typical CoV contain at least six ORFs. The first ORFs (ORF1a/b), about two-thirds of the whole genome length, encode 16 nsps (nsp1-16), except *Gammacoronavirus* that lacks nsp1. There is a -1 frameshift between ORF1a and ORF1b, leading to production of two polypeptides: pp1a and pp1ab. These polypeptides are processed by virally encoded chymotrypsin-like protease (3CL<sup>pro</sup>) or main protease (M<sup>pro</sup>) and one or two papain-like protease into 16 nsps.<sup>10,11</sup> Other ORFs on the one-third of the genome near the 3'-terminus encodes at least four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Besides these four main structural proteins, different CoVs encode special structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein (Figure 1B, lower panel). All the structural and accessory proteins are translated from the sgRNAs of CoVs.<sup>7</sup>

The genome sequence alignment of CoVs shows 58% identity on the nsp-coding region and 43% identity on the structural protein-coding region among different CoVs, with 54% at the whole genome level (Figure 1B, upper panel), suggesting the nsps are more conserved and the structural proteins are more diverse in need of adaptation to new hosts. Since the mutation rates in the replication of RNA viruses are much higher than that of DNA viruses, the genomes of RNA viruses are usually less than 10 kb in length. However, the CoV genome is much

larger, with roughly 30 kb in length, the largest known RNA viruses. The maintenance of such a large genome of CoVs may be related to the special features of the CoV RTC, which contains several RNA processing enzymes such as the 3'-5' exoribonuclease of nsp14. The 3'-5' exoribonuclease is unique to CoVs among all RNA viruses, probably providing a proofreading function of the RTC.<sup>12-14</sup> Sequence analysis shows that the 2019-nCoV possesses a typical genome structure of CoV and belongs to the cluster of *betacoronaviruses* that includes Bat-SARS-like (SL)-ZC45, Bat-SL ZXC21, SARS-CoV, and MERS-CoV. Based on the phylogenetic tree of CoVs, 2019-nCoV is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to SARS-CoV (Figure 1A).

### 3 | FUNCTIONS OF NONSTRUCTURAL AND STRUCTURAL PROTEINS IN CORONAVIRAL REPLICATION

Most of the nsps of nsp1-16 have been reported for their specific roles in the replication of CoVs. However, the functions of some of the nsps are unknown or not well understood. The known functions of the 16 nsps are summarized in Table 1.

Four structural proteins are essential for virion assembly and infection of CoVs. Homotrimers of S proteins make up the spikes on the viral surface and they are responsible for attachment to host receptors.<sup>50,51</sup> The M protein has three transmembrane domains and it shapes the virions, promotes membrane curvature, and binds to the nucleocapsid.<sup>52,53</sup> The E protein plays a role in virus assembly and release, and it involved in viral pathogenesis.<sup>54,55</sup> The N protein contains two domains, both of which can bind virus RNA genome via

**TABLE 1** The 16 nonstructural proteins of coronaviruses and their functions

nsp	Functions	References
nsp1	Cellular mRNA degradation, inhibiting IFN signaling	15,16
nsp2	Unknown	17,18
nsp3	PLP, polypeptides cleaving, blocking host innate immune response, promoting cytokine expression	19,20
nsp4	DMV formation	21,22
nsp5	3CL <sup>pro</sup> , M <sup>pro</sup> , polypeptides cleaving, inhibiting IFN signaling	23–25
nsp6	Restricting autophagosome expansion, DMV formation	26,27
nsp7	Cofactor with nsp8 and nsp12	28,29
nsp8	Cofactor with nsp7 and nsp12, primase	28–30
nsp9	Dimerization and RNA binding	31,32
nsp10	Scaffold protein for nsp14 and nsp16	33–36
nsp11	Unknown	37
nsp12	Primer dependent RdRp	28,38,39
nsp13	RNA helicase, 5' triphosphatase	40–42
nsp14	Exoribonuclease, N7-MTase	12,43–45
nsp15	Endoribonuclease, evasion of dsRNA sensors	46–48
nsp16	2'-O-MTase; avoiding MDA5 recognition, negatively regulating innate immunity	34,35,49

Abbreviations: 3CL<sup>pro</sup>, chymotrypsin-like protease; DMV, double-membrane vesicle; dsRNA, double-stranded RNA viruses; IFN, interferon; mRNA, messenger RNA; M<sup>pro</sup>, main protease.

different mechanisms. It is reported that N protein can bind to nsp3 protein to help tether the genome to RTC, and package the encapsidated genome into virions.<sup>56–58</sup> N is also an antagonist of interferon (IFN) and viral encoded repressor of RNA interference, which appears to be beneficial for the viral replication.<sup>59</sup>

### 3.1 | Diversity of CoV pathogenesis

Different CoVs display diverse host range and tissue tropism. Usually, *alphacoronaviruses* and *betacoronaviruses* infect mammals. In contrast, *gammacoronaviruses* and *deltacoronaviruses* infect birds and fish, but some of them can also infect mammals.<sup>4,60</sup> Before 2019, there were only six CoVs that were known to infect human and cause respiratory diseases. HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 cause only mild upper respiratory disease, and in rare cases some of them can cause severe infection in infants, young children and elders. SARS-CoV and MERS-CoV can infect lower respiratory tract and cause severe respiratory syndrome in human.<sup>56,61</sup> Some CoVs can infect livestock, birds, bats, mice, whales, and many other wild animals, and they can cause great economic loss. For example, in

2016, an HKU2-related bat CoV, swine acute diarrhea syndrome CoV, caused a large-scale outbreak of fatal disease in pigs in Southern China, and more than 24 000 piglets were dead.<sup>62</sup> This is the first documented spillover of a bat CoV that caused severe disease in livestock.<sup>4,63</sup>

The new CoV, 2019-nCoV, which belongs to *betacoronaviruses* based on sequence analysis (Figure 1A), can also infect the lower respiratory tract and cause pneumonia in human, but it seems that the symptoms are milder than SARS and MERS. Up to 20 January 2020, 291 cases in total have been confirmed in China by sequence analysis, clinical diagnosis and epidemiological examination, including 270 cases in Wuhan and 21 cases in Beijing, Shanghai, and Guangdong ([http://www.nhc.gov.cn/yjb/new\\_index.shtml](http://www.nhc.gov.cn/yjb/new_index.shtml)). In addition, four cases were confirmed in three other countries, including two cases in Thailand, one case in Japan, and one case in South Korea; all these patients had stayed in or visited Wuhan 2 weeks before the onset of the symptoms. Six deaths and 63 patients with severe symptoms were reported in Wuhan (<http://wjw.wuhan.gov.cn/>). Among the six death cases, four patients with published information are elder people of over 60 years old and have other illnesses before the infection, such as abdominal tumor and chronic liver disease, myocarditis and renal dysfunction, and cardiovascular disease.

Many of the patients have direct or indirect contact with the Wuhan Huanan Seafood Wholesale Market that is believed to be the original place of the outbreak of the 2019-nCoV. However, transmission of 2019-nCoV from fish to human is unlikely. The 2019-nCoV and fish CoVs such as Beluga Whale CoV/SW1 belong to different genera and apparently have different host ranges. As the Wuhan seafood market also sells other animals, the natural host of 2019-nCoV awaits to be identified. Due to the possibility of transmission from animal to human, CoVs in livestock and other animals including bats and wild animals sold in the market should be constantly monitored. In addition, more and more evidence indicate the new virus 2019-nCoV is spread via the route of human-to-human transmission because there are infections of people who did not visit Wuhan but had close contact with family members who had visited Wuhan and got infected (<http://www.cctv.com/>).

The major pathogenic CoVs are listed in Table 2 for better understanding the pathogenesis of CoVs.

## 4 | TREATMENT AND PREVENTION

At present, there is no single specific antiviral therapy for CoV and the main treatments are supportive. Recombinant IFN with ribavirin only has limited effects against CoVs infection.<sup>64</sup> After SARS and MERS epidemics, great efforts have been devoted to development of new antivirals targeting CoVs proteases, polymerases, MTases, and entry proteins, however, none of them has been shown to be efficacious in clinical trials.<sup>65–67</sup> Plasma and antibodies obtained from the convalescent patients have been proposed for use in treatment.<sup>68</sup>

In addition, various vaccine strategies, such as using inactivated viruses, live-attenuated viruses, viral vector-based

**TABLE 2** List of important pathogenic coronaviruses

Virus	Genus	Host	Symptoms
Human CoV-229E	Alpha	Human	Mild respiratory tract infections
Human CoV-NL63	Alpha	Human	Mild respiratory tract infections
PRCV/ISU-1	Alpha	Pig	Mild respiratory tract infections
TGEV/PUR46-MAD	Alpha	Pig	Diarrhea, with 100% mortality in piglets less than 2-wk-old
PEDV/ZJU-G1-2013	Alpha	Pig	Severe watery diarrhea
SeACoV-CH/GD-01	Alpha	Pig	Severe and acute diarrhea and acute vomiting
Canine CoV/TU336/F/2008	Alpha	Dog	Mild clinical signs, diarrhea
Camel alphacoronavirus isolate camel/Riyadh	Alpha	Camel	Asymptomatic
Feline infectious peritonitis virus	Alpha	Cat	Fever, vasculitis, and serositis, with or without effusions
Human CoV-HKU1	Beta	Human	Pneumonia
Human CoV-OC43	Beta	Human	Mild respiratory tract infections
SARS-CoV	Beta	Human	Severe acute respiratory syndrome, 10% mortality rate
MERS-CoV	Beta	Human	Severe acute respiratory syndrome, 37% mortality rate
Bovine CoV/ENT	Beta	Cow	Diarrhea
Equine CoV/Obihiro12-1	Beta	Horse	Fever, anorexia, leucopenia
MHV-A59	Beta	Mouse	Acute pneumonia and severe lung injuries
Beluga Whale CoV/SW1	Gamma	Whale	Pulmonary disease, terminal acute liver failure
IBV	Gamma	Chicken	Severe respiratory disease
Bulbul coronavirus HKU11	Delta	Bulbul	Respiratory disease (collected from respiratory tract of dead wild birds)
Sparrow coronavirus HKU17	Delta	Sparrow	Respiratory disease (collected from respiratory tract of dead wild birds)

vaccines, subunit vaccines, recombinant proteins, and DNA vaccines, have been developed but have only been evaluated in animals so far.<sup>69,70</sup>

Since there is no effective therapy or vaccine, the best measures now are to control the source of infection, early diagnosis, reporting, isolation, supportive treatments, and timely publishing epidemic information to avoid unnecessary panic. For individuals, good personal hygiene, fitted mask, ventilation, and avoiding crowded places will help to prevent CoVs infection.

## ACKNOWLEDGMENTS

This study was supported by the Natural Science Foundation of China (Grant No.: #81620108020 and #81672008), National Science and Technology Major Project (#2018ZX10733403), Shenzhen Science and Technology Program (Grant No.: KQTD20180411143323605) and Guangdong Provincial “Zhujiang Talents Program” (2017).

## ORCID

Deyin Guo  <http://orcid.org/0000-0002-8297-0814>

## REFERENCES

1. Wang LF, Shi Z, Zhang S, Field H, Daszak P, Eaton B. Review of bats and SARS. *Emerg Infect Dis.* 2006;12(12):1834-1840.

2. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature.* 2013; 503(7477):535-538.
3. Chen Y, Guo D. Molecular mechanisms of coronavirus RNA capping and methylation. *Viol Sin.* 2016;31(1):3-11.
4. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol.* 2019;17(3):181-192.
5. Cauchemez S, Van Kerkhove MD, Riley S, Donnelly CA, Fraser C, Ferguson NM. Transmission scenarios for Middle East respiratory syndrome coronavirus (MERS-CoV) and how to tell them apart. *Euro Surveill.* 2013;18(24):pii: 20503.
6. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, et al. Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. *J Virol.* 2006; 80(12):5927-5940.
7. Hussain S, Pan J, Chen Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. *J Virol.* 2005;79(9): 5288-5295.
8. Sawicki SG, Sawicki DL, Siddell SG. A contemporary view of coronavirus transcription. *J Virol.* 2007;81(1):20-29.
9. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol.* 2009;7(6):439-450.
10. Masters PS. The molecular biology of coronaviruses. *Adv Virus Res.* 2006;66:193-292.
11. Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. *J Gen Virol.* 2000;81(Pt 4): 853-879.

12. Eckerle LD, Becker MM, Halpin RA, et al. Infidelity of SARS-CoV Nsp14-exonuclease mutant virus replication is revealed by complete genome sequencing. *PLOS Pathog.* 2010;6(5):e1000896.
13. Ogando NS, Ferron F, Decroly E, Canard B, Posthuma CC, Snijder EJ. The curious case of the nidovirus exoribonuclease: its role in RNA synthesis and replication fidelity. *Front Microbiol.* 2019;10:1813.
14. Smith EC, Blanc H, Vignuzzi M, Denison MR. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. *PLOS Pathog.* 2013;9(8):e1003565.
15. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. *PLOS Pathog.* 2011;7(12):e1002433.
16. Tanaka T, Kamitani W, DeDiego ML, Enjuanes L, Matsuura Y. Severe acute respiratory syndrome coronavirus nsp1 facilitates efficient propagation in cells through a specific translational shutoff of host mRNA. *J Virol.* 2012;86(20):11128-11137.
17. Graham RL, Sims AC, Brockway SM, Baric RS, Denison MR. The nsp2 replicase proteins of murine hepatitis virus and severe acute respiratory syndrome coronavirus are dispensable for viral replication. *J Virol.* 2005;79(21):13399-13411.
18. Gadlage MJ, Graham RL, Denison MR. Murine coronaviruses encoding nsp2 at different genomic loci have altered replication, protein expression, and localization. *J Virol.* 2008;82(23):11964-11969.
19. Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: structures and functions of a large multi-domain protein. *Antiviral Res.* 2018;149:58-74.
20. Serrano P, Johnson MA, Chatterjee A, et al. Nuclear magnetic resonance structure of the nucleic acid-binding domain of severe acute respiratory syndrome coronavirus nonstructural protein 3. *J Virol.* 2009;83(24):12998-13008.
21. Beachboard DC, Anderson-Daniels JM, Denison MR. Mutations across murine hepatitis virus nsp4 alter virus fitness and membrane modifications. *J Virol.* 2015;89(4):2080-2089.
22. Gadlage MJ, Sparks JS, Beachboard DC, et al. Murine hepatitis virus nonstructural protein 4 regulates virus-induced membrane modifications and replication complex function. *J Virol.* 2010;84(1):280-290.
23. Stobart CC, Sexton NR, Munjal H, et al. Chimeric exchange of coronavirus nsp5 proteases (3CLpro) identifies common and divergent regulatory determinants of protease activity. *J Virol.* 2013;87(23):12611-12618.
24. Zhu X, Fang L, Wang D, et al. Porcine deltacoronavirus nsp5 inhibits interferon-beta production through the cleavage of NEMO. *Virology.* 2017;502:33-38.
25. Zhu X, Wang D, Zhou J, et al. Porcine deltacoronavirus nsp5 antagonizes type I interferon signaling by cleaving STAT2. *J Virol.* 2017;91(10):pii: e00003-17.
26. Angelini MM, Akhlaghpour M, Neuman BW, Buchmeier MJ. Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio.* 2013;4(4):pii: e00524-13.
27. Cottam EM, Whelband MC, Wileman T. Coronavirus NSP6 restricts autophagosome expansion. *Autophagy.* 2014;10(8):1426-1441.
28. Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun.* 2019;10(1):2342.
29. Zhai Y, Sun F, Li X, et al. Insights into SARS-CoV transcription and replication from the structure of the nsp7-nsp8 hexadecamer. *Nat Struct Mol Biol.* 2005;12(11):980-986.
30. te Velthuis AJ, van den Worm SH, Snijder EJ. The SARS-coronavirus nsp7+nsp8 complex is a unique multimeric RNA polymerase capable of both de novo initiation and primer extension. *Nucleic Acids Res.* 2012;40(4):1737-1747.
31. Egloff MP, Ferron F, Campanacci V, et al. The severe acute respiratory syndrome-coronavirus replicative protein nsp9 is a single-stranded RNA-binding subunit unique in the RNA virus world. *Proc Natl Acad Sci USA.* 2004;101(11):3792-3796.
32. Zeng Z, Deng F, Shi K, et al. Dimerization of coronavirus nsp9 with diverse modes enhances its nucleic acid binding affinity. *J Virol.* 2018;92(17):e00692-18.
33. Bouvet M, Lugari A, Posthuma CC, et al. Coronavirus Nsp10, a critical co-factor for activation of multiple replicative enzymes. *J Biol Chem.* 2014;289(37):25783-25796.
34. Chen Y, Su C, Ke M, et al. Biochemical and structural insights into the mechanisms of SARS coronavirus RNA ribose 2'-O-methylation by nsp16/nsp10 protein complex. *PLOS Pathog.* 2011;7(10):e1002294.
35. Decroly E, DeBarnot C, Ferron F, et al. Crystal structure and functional analysis of the SARS-coronavirus RNA cap 2'-O-methyltransferase nsp10/nsp16 complex. *PLOS Pathog.* 2011;7(5):e1002059.
36. Ma Y, Wu L, Shaw N, et al. Structural basis and functional analysis of the SARS coronavirus nsp14-nsp10 complex. *Proc Natl Acad Sci USA.* 2015;112(30):9436-9441.
37. Fang SG, Shen H, Wang J, Tay FPL, Liu DX. Proteolytic processing of polyproteins 1a and 1ab between non-structural proteins 10 and 11/12 of coronavirus infectious bronchitis virus is dispensable for viral replication in cultured cells. *Virology.* 2008;379(2):175-180.
38. Ahn DG, Choi JK, Taylor DR, Oh JW. Biochemical characterization of a recombinant SARS coronavirus nsp12 RNA-dependent RNA polymerase capable of copying viral RNA templates. *Arch Virol.* 2012;157(11):2095-2104.
39. te Velthuis AJW, Arnold JJ, Cameron CE, van den Worm SHE, Snijder EJ. The RNA polymerase activity of SARS-coronavirus nsp12 is primer dependent. *Nucleic Acids Res.* 2010;38(1):203-214.
40. Adedeji AO, Lazarus H. Biochemical characterization of Middle East respiratory syndrome coronavirus helicase. *mSphere.* 2016;1:5.
41. Hao W, Wojdyla JA, Zhao R, et al. Crystal structure of Middle East respiratory syndrome coronavirus helicase. *PLOS Pathog.* 2017;13(6):e1006474.
42. Jia Z, Yan L, Ren Z, et al. Delicate structural coordination of the severe acute respiratory syndrome coronavirus Nsp13 upon ATP hydrolysis. *Nucleic Acids Res.* 2019;47(12):6538-6550.
43. Bouvet M, Imbert I, Subissi L, Gluais L, Canard B, Decroly E. RNA 3'-end mismatch excision by the severe acute respiratory syndrome coronavirus nonstructural protein nsp10/nsp14 exoribonuclease complex. *Proc Natl Acad Sci USA.* 2012;109(24):9372-9377.
44. Chen Y, Cai H, Pan J, et al. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. *Proc Natl Acad Sci USA.* 2009;106(9):3484-3489.
45. Minskaia E, Hertzog T, Gorbalenya AE, et al. Discovery of an RNA virus 3'→5' exoribonuclease that is critically involved in coronavirus RNA synthesis. *Proc Natl Acad Sci USA.* 2006;103(13):5108-5113.
46. Bhardwaj K, Sun J, Holzenburg A, Guarino LA, Kao CC. RNA recognition and cleavage by the SARS coronavirus endoribonuclease. *J Mol Biol.* 2006;361(2):243-256.
47. Deng X, Hackbart M, Mettelman RC, et al. Coronavirus nonstructural protein 15 mediates evasion of dsRNA sensors and limits apoptosis in macrophages. *Proc Natl Acad Sci USA.* 2017;114(21):E4251-E4260.
48. Zhang L, Li L, Yan L, et al. Structural and biochemical characterization of endoribonuclease Nsp15 encoded by middle east respiratory syndrome coronavirus. *J Virol.* 2018;92(22):pii: e00893-18.
49. Shi P, Su Y, Li R, Liang Z, Dong S, Huang J. PEDV nsp16 negatively regulates innate immunity to promote viral proliferation. *Virus Res.* 2019;265:57-66.
50. Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. *Nat Struct Mol Biol.* 2006;13(8):751-752.

51. Delmas B, Laude H. Assembly of coronavirus spike protein into trimers and its role in epitope expression. *J Virol.* 1990;64(11):5367-5375.
52. Nal B. Differential maturation and subcellular localization of severe acute respiratory syndrome coronavirus surface proteins S, M and E. *J Gen Virol.* 2005;86(Pt 5):1423-1434.
53. Neuman BW, Kiss G, Kunding AH, et al. A structural analysis of M protein in coronavirus assembly and morphology. *J Struct Biol.* 2011;174(1):11-22.
54. DeDiego ML, Alvarez E, Almazan F, et al. A severe acute respiratory syndrome coronavirus that lacks the E gene is attenuated in vitro and in vivo. *J Virol.* 2007;81(4):1701-1713.
55. Nieto-Torres JL, DeDiego ML, Verdía-Báguena C, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. *PLOS Pathog.* 2014;10(5):e1004077.
56. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol.* 2015;1282:1-23.
57. Chang C, Sue SC, Yu T, et al. Modular organization of SARS coronavirus nucleocapsid protein. *J Biomed Sci.* 2006;13(1):59-72.
58. Hurst KR, Koetzner CA, Masters PS. Identification of in vivo-interacting domains of the murine coronavirus nucleocapsid protein. *J Virol.* 2009;83(14):7221-7234.
59. Cui L, Wang H, Ji Y, et al. The nucleocapsid protein of coronaviruses acts as a viral suppressor of RNA silencing in mammalian cells. *J Virol.* 2015;89(17):9029-9043.
60. Woo PCY, Lau SKP, Lam CSF, et al. Discovery of seven novel mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *J Virol.* 2012;86(7):3995-4008.
61. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.* 2016;24(6):490-502.
62. Zhou P, Fan H, Lan T, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature.* 2018;556(7700):255-258.
63. Simas PVM, Barnabé ACS, Durães-Carvalho R, et al. Bat coronavirus in Brazil related to appalachian ridge and porcine epidemic diarrhea viruses. *Emerg Infect Dis.* 2015;21(4):729-731.
64. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr H. Treatment of SARS with human interferons. *Lancet.* 2003;362(9380):293-294.
65. Chan JFW, Chan KH, Kao RYT, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect.* 2013;67(6):606-616.
66. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res.* 2015;115:9-16.
67. Wang Y, Sun Y, Wu A, et al. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. *J Virol.* 2015;89(16):8416-8427.
68. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211(1):80-90.
69. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol.* 2013;11(12):836-848.
70. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016;14(8):523-534.

**How to cite this article:** Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol.* 2020;92:418-423.  
<https://doi.org/10.1002/jmv.25681>