

# Chapter 12

## Classical Coronaviruses



Nitesh Kumar Jaiswal and Shailendra K. Saxena 

**Abstract** In the last week of December 2019, few patients with the history of pyrexia of unknown origin and symptoms of lower respiratory tract infections were detected in Wuhan, a well-known area as the largest metropolitan city located in the province of Hubei, China. On further investigation, a novel coronavirus was identified as the causative pathogen, which later on provisionally named as 2019 novel coronavirus (2019-nCoV). Coronaviruses are predominantly found in warm-blooded animals and birds and cause various respiratory complications and multiorgan failure in the immunocompromised individuals. Human coronaviruses were first identified in 1965 and are responsible for the respiratory tract infections in major proportion of population worldwide; at least five new human coronaviruses have been identified, including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The background related to the origin and classification of coronaviruses is reviewed here.

**Keywords** 2019-nCoV · MERS-CoV · SARS-CoV · Strain 229E · Strain OC43 · Coronavirus

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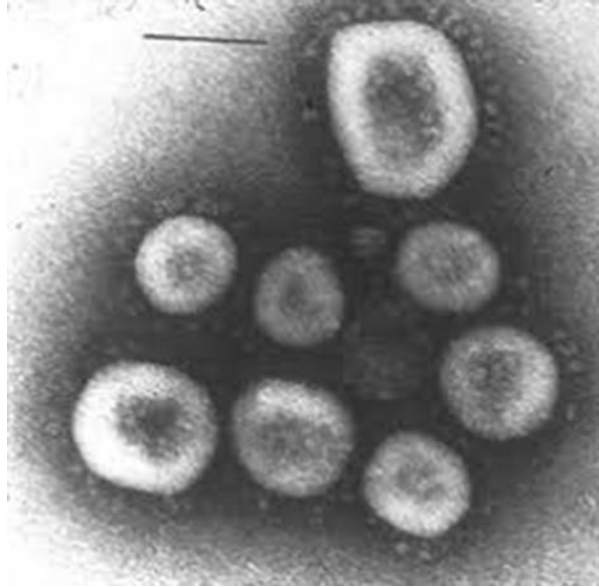
## 12.1 Introduction

Coronaviruses isolated from several species consist of a group of large, enveloped, single plus stranded RNA viruses, and these viruses are earlier known to cause acute rhinitis and diarrhea in humans (Drosten et al. 2003a; Chen et al. 2020). A human coronavirus named SARS-CoV (severe acute respiratory syndrome coronavirus) was associated with the SARS outbreak in the year 2002–2003 (Zhong et al. 2003; Drosten et al. 2003b; Fouchier et al. 2003; Ksiazek et al. 2003). Similarly 10 year after SARS outbreak, another deadly human coronavirus [Middle East respiratory syndrome coronavirus (MERS-CoV)] emerged in the Middle East nations (Zaki et al. 2012). Recently, a new coronavirus named 2019-nCoV (belonging to the family *Coronaviridae* and subfamily *Orthocoronavirinae*) has erupted in the region of Wuhan (China) with severe respiratory tract infections in human. This virus is distinct from MERS-CoV and SARS-CoV; animal-to-human transmission has been considered as the origin of this outbreak, as most of the patients had a history to visit a local fish and wild animal market in Wuhan during the epidemic (Chan et al. 2020; Huang et al. 2020; Zhu et al. 2020). Animal-to-human and inter-human transmissions of this viral infection through respiratory route were established by certain group of scientists (Lu et al. 2020; Ji et al. 2020). Patient isolation and accurate timely diagnosis are the hallmarks to control this new epidemic. It is also important to acquire knowledge from the history and evolution of coronaviruses. Phylogenetic analysis and its relation with different natural hosts of these viruses can help one to estimate its genetic variability which in turn has important applications for the viral etiopathogenesis, clinical manifestations, and vaccine development.

## 12.2 Origin and Evolution of Coronaviruses

In the mid-1930s, a severe respiratory infection of chicken was considered to be the earliest known disease by coronaviruses, infection presently known as avian infectious bronchitis, caused by avian infectious bronchitis virus (IBV). The era of human coronaviruses began in the year 1965 when Tyrrell and Bynoe observed that they could serially sub-passage a virus in tissue culture while doing research on human participants at the Common Cold Unit close to Salisbury, UK; they named this virus as B814 (Tyrrell and Bynoe 1966). Their experiment demonstrated that common colds could be transmitted by nasal secretion that did not contain rhinoviruses, and further *in vitro* experiments of nasal swabs from these participants had been inoculated onto organ cultures obtained from respiratory tract cell lines. They discovered the presence of enveloped RNA viruses with the feature morphology of coronaviruses similar to the previously defined infectious bronchitis virus. They were unable to grow the virus in tissue culture at that time. Subsequently in the year 1966, Hamre and Procknow succeeded in growing a new virus (229E) of unexpected

**Fig. 12.1** Coronavirus OC16 (McIntosh et al. 1967a)



tissue culture properties from a medical graduate with symptoms of common cold (Hamre and Procknow 1966).

Both B814 and 229E were ether sensitive and required a lipid-containing coat for infectivity. These two viruses were unassociated with any known orthomyxoviruses. McIntosh et al. (1967a) had used the similar technique of Tyrrell and Bynoe to extract the multiple strains of ether-susceptible agents from human volunteers. These viruses were designated OC as they were grown in the organ culture of respiratory tract. In the year 1967, Almeida and Tyrrell were able to demonstrate the similar morphology of B814 and IBV under the electron microscopy of the fluid obtained from the inoculated organ culture. The virus particles were of size around 80–150 nm, pleomorphic, enveloped with membrane coating, and multiple club-shaped surface projections (Almeida and Tyrrell 1967). All of these (229E, OC, B814, and IBV) along with the virus causing mouse hepatitis and transmissible gastroenteritis infection of swine had a similar morphology under electron microscopy (McIntosh et al. 1967b; Witte et al. 1968) (Fig. 12.1). The new group of these viruses was named coronavirus in 1968 (corona means the crown-like structure with surface projection), reflecting their morphology in the electron microscope, and further Coronaviridae was accepted as their family name in 1975 (Tyrrell et al. 1975).

229E and OC 43 were the only two human coronaviruses discovered before the outbreak of SARS-CoV. Both of them were recognized as less pathogenic causing mild flu-like infection, thus not being explored further in the research field. SARS emerged in the late 2002 from South East Asia with an epicenter of China and spread expeditiously all over the world. Taking after the acknowledgement that SARS was caused by a new human coronavirus (SARS-CoV), it was found to be more

pathogenic and causes serious respiratory complications (Li et al. 2005; Ren et al. 2008; Peiris et al. 2003). The genomic sequencing of SARS-CoV was comfortably achieved as it had the capacity to grow readily in tissue culture. Two other modern human coronaviruses, NL63 and HKU-1, were also found in association with respiratory disease.

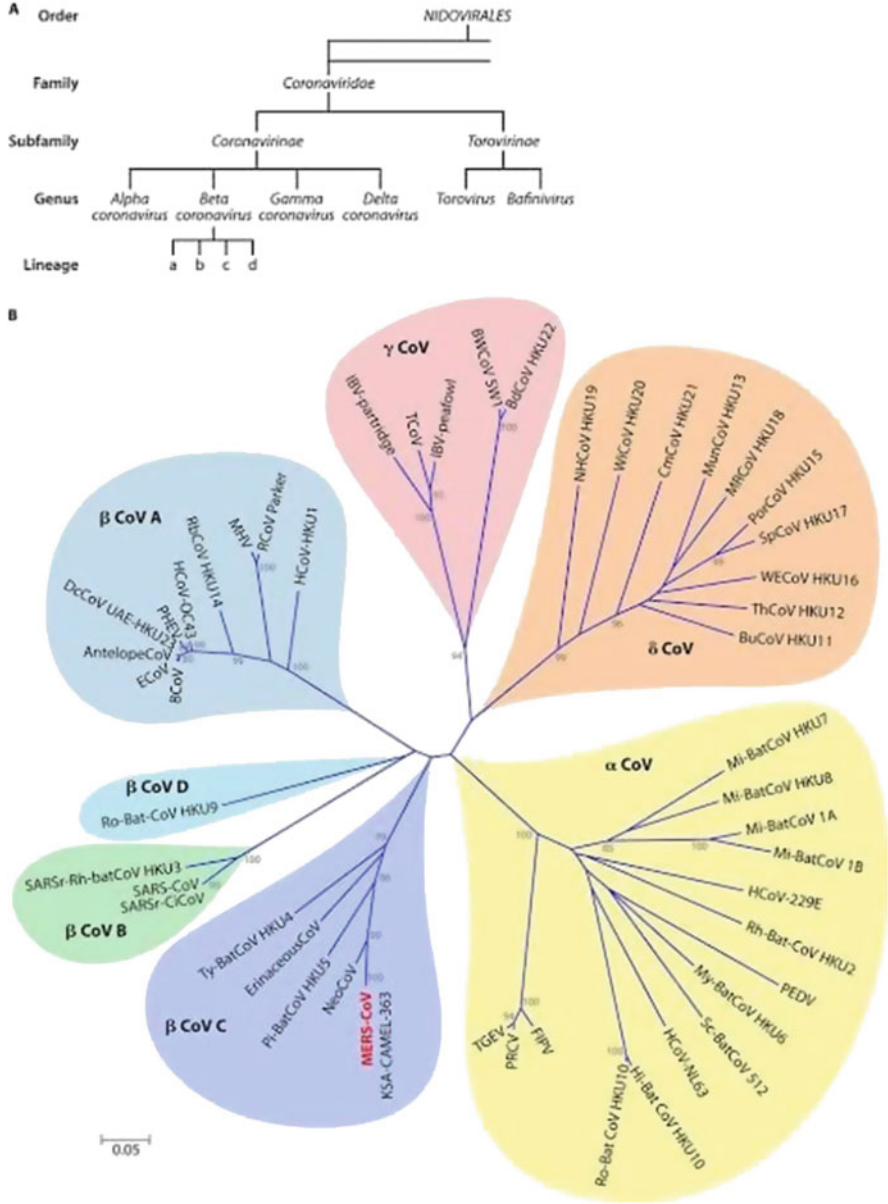
Ten years after SARS, yet another profoundly pathogenic condition, Middle East respiratory syndrome or MERS appeared that took its heaviest toll on wealthy urban area of Middle East nations (Zaki et al. 2012). SARS-CoV and MERS-CoV were transmitted directly to people from feline animals (civet) and dromedary camels, respectively (Guan et al. 2003; Alagaili et al. 2014; Hemida et al. 2013). Extensive research studies of these two viruses have helped to know about the biological properties and exceptional perception of human coronaviruses.

In late December 2019, few patients with the history of unexplained fever and symptoms of lower respiratory tract infections were detected in Wuhan, an area avowed as the largest metropolitan city located in the Hubei province of China. The etiology of this unknown respiratory infection was not being able to be established; it was classified as pneumonia of unknown etiology initially. Further investigation by the local authority of Chinese Center for Disease Control and Prevention identified the causative pathogen and provisionally named 2019 novel coronavirus (2019-nCoV). On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, announced that the disease caused by this new coronavirus is COVID-19 which is the acronym of “coronavirus disease 2019.” The WHO raised the threat to this CoV epidemic in the category of “very high” level in February 2020. Various organizations throughout the globe are working to establish countermeasures to prevent possible devastating effects from this new human coronavirus.

The reestablished intrigued in this bunch of infections has driven to the disclosure of a plenty of coronaviruses and their capacity to jump over different animal species over a period of time.

### 12.3 Classification

The International Committee on Taxonomy (ICT) of viruses has classified coronaviruses under family *Coronaviridae* and order *Nidovirales*. Toroviruses and coronaviruses are the two representative genera of the family *Coronaviridae*; they have been further classified in subfamily *Coronavirinae*. On the basis of rooted and unrooted genetic trees and partial nucleotide sequence of RNA-dependent RNA polymerase, subfamily *Coronavirinae* has been recognized and classified into four genera—alpha ( $\alpha$ ) coronavirus, beta ( $\beta$ ) coronavirus, gamma ( $\gamma$ ) coronavirus, and delta ( $\delta$ ) coronavirus (Woo et al. 2009, 2012a). The  $\alpha$  coronaviruses and  $\beta$  coronaviruses infect only warm-blooded animals. The  $\gamma$  coronaviruses and  $\delta$  coronaviruses infect birds, but some of them can also infect mammals. Phylogenetic relationship of various human and animal coronaviruses and the list of known



**Fig. 12.2** Phylogenetic classification of coronaviruses. (Source: Cui J., Lei F and Shi ZL. Review: Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology, December 2018)

coronaviruses are shown in Fig. 12.2 and Tables 12.1, 12.2, and 12.3, respectively. Infection with  $\alpha$  coronaviruses and  $\beta$  coronaviruses leads to respiratory disorders in human and gastrointestinal disorders in animals (Su et al. 2016; Forni et al. 2017; Gorbalenya et al. 2006). Currently available genetic sequence databases of all human

**Table 12.1** Coronaviruses under different genera

Genus	Species
Alpha coronavirus	Human coronavirus 229E, human coronavirus NL63, Miniopterus bat coronavirus 1, Miniopterus bat coronavirus HKU8, porcine epidemic diarrhea virus, Rhinolophus bat coronavirus HKU2, Scotophilus bat coronavirus 512
Beta coronavirus	Beta coronavirus 1, human coronavirus HKU1, murine coronavirus, Pipistrellus bat coronavirus HKU5, Roussettus bat coronavirus HKU9, Severe acute respiratory syndrome-related coronavirus, Severe acute respiratory syndrome coronavirus 2, Tylonycteris bat coronavirus HKU4, Middle East respiratory syndrome-related coronavirus, human coronavirus OC43, hedgehog coronavirus 1 (EriCoV)
Gamma coronavirus	Infectious bronchitis virus (IBV), beluga whale coronavirus SW1, infectious bronchitis virus
Delta coronavirus	Bulbul coronavirus HKU11, porcine coronavirus HKU15

**Table 12.2** Coronaviruses and their different natural hosts

Natural host	Coronaviruses	Abbreviation
Chicken	Infectious bronchitis virus	IBV
Cattle	Bovine coronavirus	BCoV
Dog	Canine enteric coronavirus	CCoV
Cat	Feline coronavirus	FCoV
Cat	Feline infectious peritonitis virus	FIPV
Humans	Human coronavirus 229E	HCoV-229E
Humans	Human coronavirus NL63	HCoV-NL63
Humans	Human coronavirus OC43	HCoV-OC43
Humans	SARS-coronavirus	SARS-CoV
Humans	Human enteric coronavirus	HECoV
Mouse	Murine hepatitis virus	MHV
Rat	Rat coronavirus	RtCoV
Rat	Sialodacryoadenitis virus	SDAV
Pig	Porcine epidemic diarrhea virus	PEDV
Pig	Transmissible gastroenteritis virus	TGEV
Pig	Porcine hemagglutinating encephalomyelitis virus	HEV
Pig	Porcine respiratory coronavirus	PRCoV
Turkey	Turkey coronavirus	TCoV
Pheasant	Pheasant coronavirus	PhCoV
Shearwater	Puffinosis coronavirus	PCoV

coronaviruses reveal with its animal origins: Viruses of the family *Coronaviridae* are listed, with their abbreviations and natural animal reservoir (Cavanagh 1997) (Table 12.2). Domestic animals can act as an intermediate host to transmit these viruses from their reservoir host to the humans. Sometimes domestic animal may acquire infection with closely related zoonotic coronaviruses (Woo et al. 2009, 2012a). Extensive research study on the source of infection of SARS-CoV and

**Table 12.3** List of human and animal coronaviruses

Human coronaviruses	Animal coronaviruses
HCoV-229E (human coronavirus 229E)	Antelope CoV (Sable antelope coronaviruses)
HCoV-HKU1 (human coronavirus HKU1)	BCoV (bovine coronaviruses)
HCoV-NL63 (human coronavirus NL63)	BdCoV HKU22 (bottlenose dolphin coronavirus HKU22)
HCoV-OC43 (human coronavirus OC43)	BuCoV HKU11 (bulbul coronavirus HKU11)
SARS-CoV (SARS coronavirus)	BWCoV-SW1 (beluga whale coronavirus SW1)
MERS-CoV (Middle East respiratory syndrome coronavirus)	CMCoV HKU21 (common-moorhen coronavirus HKU21)
	DcCoV UAE-HKU23 (dromedary camel coronavirus UAE-HKU23)
2019-nCoV (COVID 19)	ECoV (equine coronavirus)
	ErinaceousCoV (beta coronavirus <i>Erinaceus</i> )
	FIPV (feline infectious peritonitis virus)
	Hi-BatCoV HKU10 ( <i>Hipposideros</i> bat coronavirus HKU10)
	IBV-partridge (avian infectious bronchitis virus partridge isolate)
	IBV-peafowl (avian infectious bronchitis virus peafowl isolate)
	KSA-CAMEL-363 (KSA-CAMEL-363 isolate of Middle East respiratory syndrome coronavirus)
	MHV (murine hepatitis virus)
	Mi-BatCoV 1A ( <i>Miniopterus</i> bat coronavirus)
	Mi-BatCoV 1B ( <i>Miniopterus</i> bat coronavirus 1B)
	Mi-BatCoV HKU7 ( <i>Miniopterus</i> bat coronavirus HKU7)
	Mi-BatCoV HKU8 ( <i>Miniopterus</i> bat coronavirus HKU8)
	MRCoV HKU18 (magpie robin coronavirus HKU18)
	MunCoV HKU13 (munia coronavirus HKU13)
	My-BatCoV HKU6 ( <i>Myotis</i> bat coronavirus HKU6)
	NeoCoV (coronavirus <i>Neoromicia</i> )
	NHCoV HKU19 (night heron coronavirus)
	PEDV (porcine epidemic diarrhea virus)
	PHEV (porcine hemagglutinating encephalomyelitis virus)
	Pi-BatCoV-HKU5 ( <i>Pipistrellus</i> bat coronavirus HKU5)
	PorCoV HKU15 (porcine coronavirus HKU15)
	PRCV (porcine respiratory coronavirus)
	RbCoV HKU14 (rabbit coronavirus HKU14)
	RCoV parker (rat coronavirus Parker)
	Rh-BatCoV HKU2 ( <i>Rhinolophus</i> bat coronavirus HKU2)
	Ro-BatCoV-HKU9 ( <i>Rousettus</i> bat coronavirus HKU9)

(continued)

**Table 12.3** (continued)

Human coronaviruses	Animal coronaviruses
	Ro-BatCoV HKU10 ( <i>Rousettus</i> bat coronavirus HKU10)
	SARSr-CiCoV (SARS-related palm civet coronavirus)
	SARSr-Rh-BatCoV HKU3 (SARS-related <i>Rhinolophus</i> bat coronavirus HKU3)
	Sc-BatCoV 512 ( <i>Scotophilus</i> bat coronavirus 512)
	SpCoV HKU17 (sparrow coronavirus HKU17)
	TCoV (turkey coronavirus)
	TGEV (transmissible gastroenteritis virus)
	ThCoV HKU12 (thrush coronavirus HKU12)
	Ty-BatCoV-HKU4 ( <i>Tylonycteris</i> bat coronavirus HKU4)
	WECov HKU16 (white-eye coronavirus HKU16)
	WiCoV HKU20 (wigeon coronavirus HKU20)

MERS-CoV has found bat as a reservoir, and it has laid to the better understanding of coronavirus microbiology. At present, seven species of  $\alpha$  coronavirus and four species of  $\beta$  coronavirus have been identified only in bats (Su et al. 2016; Lau et al. 2013; Perlman and Netland 2009; Woo et al. 2012b; Graham et al. 2013; Hu et al. 2015; de Wit et al. 2016; Wang et al. 2018; Lin et al. 2017).

## 12.4 Future Perspectives

As we deal with the thriving pandemic of novel highly contagious human coronavirus disease (Covid-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the human race is locked in a battle against it. Genomic sequences of closely related viruses silently circulate in bats. The molecular epidemiological information reveals that a virus of bat origin infecting unidentified animal species sold in Wuhan sea food markets could be the possible source of this infection. Several research studies have focused on the evaluation of the zoonotic potentials of animal coronaviruses since the outbreak of SARS-CoV and MERS-CoV. The high diversity of coronaviruses detected in bats and their genomic variability increases the risk of interspecies transmission. 2019-nCoV highlights the importance of bats as a reservoir for new viruses causing infection in humans, and it can also be used as a good model to design studies and strategies to prevent future emergence of new zoonotic diseases. It is important to increase the efforts to characterize viral genome of different animal coronaviruses and also to look for the viral evolution and adaptation to their natural hosts. The possibility to predict the interspecies transmission can be helpful in planning of specific surveillance programs and act quickly in an outbreak. Therefore, extensive research studies in finding experimental models for the emerging zoonotic viral diseases are absolutely mandatory.



### Executive Summary

- Classical coronaviruses consist of a group of large, enveloped, RNA viruses.
- Recently, a new coronavirus named 2019-nCoV (belonging to the family *Coronaviridae* and subfamily *Orthocoronavirinae*) has erupted in the South East Asian country.
- Subfamily *Coronavirinae* consists of four genera—alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus.
- Alpha coronaviruses and beta coronaviruses cause respiratory disorders in human and gastrointestinal disorders in animals.
- Animal-to-human and inter-human transmissions are frequently seen in these group of viruses.

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