



Discovery, diversity and evolution of novel coronaviruses sampled from rodents in China



Wen Wang^{a,b,1}, Xian-Dan Lin^{c,1}, Wen-Ping Guo^{a,b,1}, Run-Hong Zhou^a, Miao-Ruo Wang^d, Cai-Qiao Wang^a, Shuang Ge^a, Sheng-Hua Mei^d, Ming-Hui Li^{a,b}, Mang Shi^{a,e}, Edward C. Holmes^{a,e}, Yong-Zhen Zhang^{a,b,*}

^a State Key Laboratory for Infectious Disease Prevention and Control, Department of Zoonoses, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Changping, Beijing, China

^b Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China

^c Wenzhou Center for Disease Control and Prevention, Wenzhou, Zhejiang Province, China

^d Longquan Center for Disease Control and Prevention, Longquan, Zhejiang Province, China

^e Marie Bashir Institute of Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Biological Sciences and Sydney Medical School, The University of Sydney, Sydney, New South Wales 2006, Australia

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ABSTRACT

Although rodents are important reservoirs for RNA viruses, to date only one species of rodent coronavirus (CoV) has been identified. Herein, we describe a new CoV, denoted Lucheng Rn rat coronavirus (LRNV), and novel variants of two *Betacoronavirus* species termed Longquan Aa mouse coronavirus (LAMV) and Longquan Rl rat coronavirus (LRLV), that were identified in a survey of 1465 rodents sampled in China during 2011–2013. Phylogenetic analysis revealed that LAMV and LRLV fell into lineage A of the genus *Betacoronavirus*, which included CoVs discovered in humans and domestic and wild animals. In contrast, LRNV harbored by *Rattus norvegicus* formed a distinct lineage within the genus *Alphacoronavirus* in the 3CL^{pro}, RdRp, and Hel gene trees, but formed a more divergent lineage in the N and S gene trees, indicative of a recombinant origin. Additional recombination events were identified in LRLV. Together, these data suggest that rodents may carry additional unrecognized CoVs.

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Introduction

Coronaviruses (CoVs; family *Coronaviridae*) are the etiological agent(s) of respiratory, enteric, hepatic, and neurological diseases in animals and humans. The first coronavirus (infectious bronchitis virus) was isolated in chicken embryos in 1937 (Beaudette and Hudson, 1937), with subsequent viral isolations in rodents, domestic animals, and humans. However, until the emergence of severe acute respiratory syndrome (SARS) in China in 2002/3 (Drosten et al., 2003; Woo et al., 2009), coronaviruses had been of greater concern to agriculture than public health. Since the discovery of SARS-CoV intense scientific efforts have been directed toward characterizing additional coronaviruses in humans and other animals (Drexler et al., 2010; Guan et al., 2003; Lau et al., 2005; Li et al., 2005; Quan et al., 2010; van der Hoek et al., 2004; Woo

et al., 2012). As a consequence, the number of coronaviruses identified has increased rapidly (Woo et al., 2009, 2012). Of particular importance was the recent discovery of a new severe respiratory illness with renal failure (Middle East Respiratory Syndrome, MERS) caused by a novel coronavirus (MERS-CoV) (Bermingham et al., 2012; van Boheemen et al., 2012), and which is also a zoonosis (Annan et al., 2013; Azhar et al., 2014; Reusken et al., 2013). It is highly likely that there are additional unrecognized coronaviruses circulating in animals.

Rodentia (rodents) is the largest order of mammals with approximately 2277 species worldwide, representing some 42% of all mammalian species (Wilson and Reeder, 2005). Rodents are a major zoonotic source of human infectious diseases (Meerburg et al., 2009; Luis et al., 2013), particularly as they often live at high densities and hence may harbor high levels of microbial diversity (Moya et al., 2004). In addition, some rodent species live in close proximity to humans, such that they represent an important zoonotic risk. To date, however, only one species of coronavirus – Murine coronavirus – has been associated with rodents (de Groot et al., 2011). The prototype virus, which was named mouse hepatitis virus (MHV), was first isolated in mice in 1949

* Corresponding author at: Department of Zoonoses, National Institute of Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Changping Liuzi 5, Beijing 102206, China. Tel.: +86 10 58900782.

E-mail address: zhangyongzhen@icdc.cn (Y.-Z. Zhang).

¹ Contributed to this work equally.

(Cheever et al., 1949), with a variant then identified in rats in 1970 (where it was termed rat sialodacryoadenitis coronavirus) (Parker et al., 1970). No other rodent-associated CoVs have been discovered since this time.

Although RNA viruses are often characterized by their high rates of mutation, recombination may also be of evolutionary importance, and has been associated with such characteristics as the ability to infect new hosts and alter virulence (Holmes, 2013). Recombination appears to be commonplace in coronaviruses (Graham and Baric, 2010; Jackwood et al., 2012; Keck et al., 1987; Woo et al., 2006), and which may facilitate their emergence. For example, two types of feline CoVs (FCoV) – FCoV type I and II – have arisen by double recombination events between FCoV types I and canine Coronavirus (CCoV) (Herrewegh et al., 1998). Similarly, recombination generated the three genotypes (A, B and, C) of

human coronavirus HKU1 (Woo et al., 2006), and homologous recombination has occurred in the evolutionary history of SARS-CoV (Graham and Baric, 2010).

To explore the diversity and evolution of CoVs in rodent populations we screened rodents collected from rural regions of Zhejiang province, China. This revealed a remarkable diversity of CoVs circulating in rodents, along with evidence for cross-species transmission and recombination.

Results

Collection of rodents, and the identification of coronaviruses

A total of 1465 rodents representing 10 different species were captured from three locations in Zhejiang province, China during 2011–2013 (Table 1 and Fig. 1). RT-PCR targeting a conserved sequence of the viral RdRp (RNA-dependent RNA polymerase) gene was performed to detect coronaviruses. PCR products of the expected size were recovered from 10 *Apodemus agrarius*, 4 *Rattus norvegicus*, 14 *R. lossea*, 1 *R. tanezumi*, and 1 *Niviventer confucianus*, such that approximately 2% of rodents were positive for CoV (Table 1). The classification of these viruses as CoVs (Family *Coronaviridae*, Genus *Alpha-* and *Beta-*) was confirmed by genetic analyses (see below).

Genetic characterization of viral sequences

To better characterize the rodent CoVs discovered here, complete viral RdRp gene sequences were recovered from 21 (70%) of the RNA positive rodent samples described above. Additionally, 1 complete and 4 near complete (> 98%) viral genome sequences were successfully recovered from five positive CoV samples (Table S1). Genetic analysis indicated that two CoVs sampled from *R. norvegicus* in Lucheng and Longquan shared 50.6%–71.7% nucleotide sequence similarity with alpha coronaviruses; 15 CoVs from 13 *R. lossea*, 1 *R.*

Table 1
Prevalence of coronaviruses in rodents in Zhejiang Province, China.

Species	Longquan		Wencheng		Lucheng	Total
	Residential	field	Residential	field	Residential	
<i>Apodemus agrarius</i>	–	10/427	–	0/17	–	10/444
<i>Mus musculus</i>	0/3	–	0/4	–	–	0/7
<i>Microtus fortis</i>	0/44	0/261	–	–	–	0/305
<i>Micromys minutus</i>	–	0/2	–	–	–	0/2
<i>Niviventer confucianus</i>	–	1/58	–	0/27	–	1/85
<i>Rattus norvegicus</i>	3/214	–	0/31	–	1/17	4/262
<i>R. lossea</i>	–	14/300	–	0/1	–	14/301
<i>R. tanezumi</i>	0/25	1/7	0/18	–	0/3	1/53
<i>R. fulvescens</i>	0/1	0/3	–	–	–	0/4
<i>R. edwardsi</i>	–	–	–	0/2	–	0/2
Total	3/287	26/1058	0/53	0/47	1/20	30/1465

Note: CoV RNA positive specimens/total specimens; “–” no animals were captured.



Fig. 1. A map of Zhejiang province, China showing the location of trap sites in which rodents were captured and surveyed for coronaviruses.

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