Novel Chinese pseudorabies virus variants undergo extensive recombination and rapid interspecies transmission

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Abstract

Chinese PRV variants have frequent recombination and preferential interspecies transmission. So far, 23 confirmed PRV-infected human cases have been reported. In this letter, we discussed the significance of PRV recombination and its public health issue as an occupational zoonosis.

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Dear Editor,

We have some comments related to the recently published paper in *Transboundary and Emerging Diseases* titled "Genetic evolution analysis of novel recombinant pseudorabies virus strain in Sichuan, China" (Huang et al., 2020). A Chinese pseudorabies virus (PRV) isolate named FJ62 was reported to be a natural recombination of PRV genotype 1 from wild boar and genotype 2 from domestic pigs. Specifically, the gB gene of PRV FJ62 shared the highest homology (100%) with Japanese MY-1 strain from wild boar, which shared the same nucleotide sequences with European and American PRV strains. By contrast, gC, gD and gE genes of PRV FJ62 were closely related to Chinese PRV variants in domestic pigs that were far removed from the reference strains in Europe and USA.

Genetically, PRVs could be classified into two genotypes based on genomic sequence or viral gC gene. PRV strains in China belong to genotype 2, whereas PRV isolates from other countries belong to genotype 1. Within genotype 2, Chinese PRV isolates are further divided into two subgenotypes: classical PRV (PRV isolates before 2011) in subgenotype 1 and PRV variants isolated since 2011 in subgenotype 2. As a large DNA virus, the mutation and recombination rates of PRV are theoretically slow. However, frequent inter-genotype and intra-genotype recombinations have been reported. In a recent study, He et al (2019) reported that 29 PRVs had undergone recombination, with more inter- than intra-genotype recombinations found.

The mutation and recombination of viral glycoproteins - such as gB, gC, gD and some other undefined protective immunity-elicited proteins - might partially explain the incomplete protection provided by PRV vaccine strains.

Besides frequent recombination, Chinese PRV variants undergo preferential interspecies transmission including cows, dogs, cats, sheep, minks, foxes, racoons, and even humans (Wong et al., 2019, Li et al., 2020). PRV utilizes its glycoprotein gD to bind to cells via the nectin-1 receptor, which shares conserved amino acid residues among different species (Li et al., 2017). Zheng et al recently reported a human severe pseudorabies encephalitis in *Transboundary and Emerging Diseases* (Zheng et al., 2019). Besides that, another 22 PRV variants-infected human cases have been reported (Table 1). There are several distinct characteristics of patients infected with PRV variants versus those infected with classical PRV. First, humans infected with classical PRV had fever, weakness and pruritus before progressing to neurological signs, including dysphagia and paresthesia. The clinical signs of patients can last several months, but all eventually recovered without any treatment. By contrast, humans infected with PRV variants suffered severe central nervous system disorders and fatal encephalitis. Besides encephalitis, 12 out of 23 patients also suffered from endophthalmitis, causing loss of vision. How PRV variants invade the ocular nerve system and leads to endophthalmitis warrants further investigation. Second, humans infected with classical PRVs had close contact with diseased dogs, cats or cattle (Wong et al., 2019). By contrast, all patients infected with PRV variants had close contact with pigs. This suggested that pigs have become the etiological source of PRV for human infection. Third, PRV variants have been successfully isolated on cells from cerebrospinal fluid samples of patients. Most recently, human PRV hSD-1/2019 strain was, for the first time, isolated from cerebrospinal fluid samples on PK-15 cells (Liu et al., 2020). The virus was shown to be a PRV variant by next-generation sequencing; it induced acute neurological signs in pigs, and caused high mortality.

The above reported cases suggest that PRV could be an important neglected occupational zoonotic pathogen in humans. Therefore, PRV should be screened for in unexplained fever and encephalitis cases in human, especially when patients have a history of close contact with pigs or pig products. The mechanisms by which PRV variants lead to encephalitis and endophthalmitis should be further explored in non-human primate models.

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CONFLICT OF INTEREST

The author declares no conflict of interest relevant to this article.

ETHICAL APPROAL

Not applicable to this comment.

Data Availability Statement

There is no experimental data available in this letter.

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Table 1 . Summary of reported human PRV cases.

Case	Year	Sex	Age	Province	Occupation	Clinical signs	Clinical signs	Outcome
						Encephalitis	Endophthalmitis	
1	2018	Male	25	Hubei	Veterinary	Yes	Yes	Survived
2	2019	Male	35	Henan	Pig butcher	Yes	No	Survived
3	2019	Male	49	Henan	Pig butcher	Yes	No	Survived
4	2018	Male	43	Shandong	Veterinary	Yes	No	Survived
5	2018	Male	Mid-aged	Shandong	Butcher	Yes	No	Died
6	2018	Male	Mid-aged	Hebei	Swineherd	Yes	Yes	Survived
7	2018	Male	Young	Guangdong	Driver	Yes	Yes	Survived
8	2011	Female	Young	Beijing	Pork dealer	Yes	No	Died
9	2017	Male	55	Inner Mongolia	Pork dealer	Yes	Yes	Died
10	2017	Male	51	Inner Mongolia	Cook	Yes	No	Died
11	2017	Male	38	Shandong	Butcher	Yes	No	Survived
12	2016	Female	42	Hebei	Unknown	Yes	Yes	Survived
13	2019	Male	44	Anhui	Pork dealer	Yes	Yes	Survived
14	2019	Male	44	Shandong	Pork dealer	Yes	Yes	Survived
15	2018	Male	50	Shandong	Pig slaughterer	Yes	No	Survived
16	2018	Female	50	Shandong	Pork cutter	Yes	No	Survived
17	2018	Male	43	Shandong	Pig handler	Yes	Yes	Survived
18	2018	Male	59	Shandong	Pork cutter	Yes	No	Survived
19	2018	Male	50	Shandong	Pork cutter	Yes	Yes	Survived
20	2018	Male	59	Hebei	Swineherd	Yes	Yes	Survived
21	2019	Male	43	Shandong	Veterinary	Yes	No	Survived
22	2019	Male	49	Anhui	Pig slaughterer	Yes	Yes	Survived
23	2017	Female	46	Jiangxi	Swineherd	Yes	Yes	Survived