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BRIEF REPORT

Molecular epidemiology of noroviruses associated with sporadic gastroenteritis in Guangzhou, China, 2013-2015

Liang Xue[1,2] · Ruimin Dong[3] · Qingping Wu[1,2] · Yonglai Li[4] · Weicheng Cai[1,2] · Xiaoxia Kou[1,2] · Jumei Zhang[1,2] · Weipeng Guo[1,2]

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Abstract Norovirus diarrhea is a great threat to public health worldwide. To characterize the prevalence of circulating noroviruses associated with sporadic gastroenteritis cases in Guangzhou, 215 stool specimens were collected during two consecutive cold seasons in 2013-2015. Noroviruses were detected in 25 (11.63 %) samples, and GII.4 (6/9) and GII.17 (10/16) were identified as the most predominant variants of each of those seasons. The remaining strains belonged to the genotypes GII.P12/GII.3, GII.2, and GI.Pb/GI.6. The phylogenetic relationships of the GII.17 strains were analyzed based on their capsid protein sequences. This study suggests a significant shift of predominant variants associated with sporadic gastroenteritis in Guangzhou.

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✉ Qingping Wu
wuqp203@163.com

[1] State Key Laboratory of Applied Microbiology Southern China, Guangdong Institute of Microbiology, No. 100, Xianlie Zhong Road, Guangzhou 510070, People's Republic of China

[2] Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Guangdong Open Laboratory of Applied Microbiology, Guangzhou 510070, People's Republic of China

[3] Department of Cardiology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, People's Republic of China

[4] Laboratory Department, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, People's Republic of China

Noroviruses (NoVs) are regarded as the leading cause of non-bacterial gastroenteritis worldwide [1]. NoVs infect humans of all age groups and are responsible for almost half of foodborne gastroenteritis outbreaks and 75 %–90 % of non-bacterial gastroenteritis outbreaks [2, 3]. As a member of the family *Caliciviridae*, NoV has a single-strand, positive-sense RNA genome that is approximately 7.5 kb to 7.7 kb in size, with three open reading frames (ORFs). NoVs are classified into six genogroups (GI to GVI) based on phylogenetic analysis of major capsid protein sequences, of which the GI, GII, and GIV strains infect humans [4–6]. Furthermore, GII NoVs have been subdivided into 31 genotypes based of the RdRp gene and 21 genotypes based on the capsid gene [7]. However, only GII.4 has been identified as a predominant genotype globally, and it was the cause of 70 % to 80 % of all NoV outbreaks in the USA, Australia, and most European countries during the past two decades [8–10]. New GII.4 variants have emerged every two to three years and have become the dominant strains in subsequent seasons, and GII.4_Sydney_2012 was identified as the latest predominant GII.4 variant circulating worldwide [11–14]. In addition, recombination is also regarded as a significant driving force in NoV evolution, and an increasing prevalence of recombinant NoV strains has been found in many countries, including China [14–17]. Recently, a new GII.17 variant was reported as the predominant genotype in some Asian countries and regions [18, 19]. Genetic information about the new predominant variant is still limited, and it is not certain whether the GII.17 virus is more virulent than the former GII.4 variants. Therefore, NoV surveillance needs to be carried out for a long time in order to detect any increase in the frequency of NoV epidemics caused by the emerging GII.17 variant.

Table 1 Genotype distribution of norovirus-positive samples detected in Guangzhou, China, based on phylogenetic analysis of a portion of the polymerase region and the capsid N/S domain

Year	No. of samples collected	No. of positive samples	Genotype (RdRp/capsid)	No. of NoV isolates
2013/2014	135	9 (6.7%)	GII.Pe/GII.4_Sydney_2012	5
			GII.P12/GII.3	2
			GII.P4-2006b /GII.4-2006b	1
			GI.Pb/GI.6	1
2014/2015	80	16 (20%)	GII.P17/GII.17	10
			GII.Pe /GII.4_Sydney_2012	2
			GII.P4-2006b/GII.4_Sydney_2012	2
			GII.P12/GII.3	1
			GII.P2/GII.2	1
Total	215	25 (11.7%)	//	25

NoV gastroenteritis is also a common public health problem in China. During the past decade, NoV was identified as the second-most significant etiological agent in outpatients with acute gastroenteritis, and different GII.4 variants were found as the predominant genotypes at different times, including GII.4_Hunter_2004, GII.4-2006b, GII.4_New Orleans_2009 and GII.4_Sydney_2012 [12, 20, 21]. Similarly, China was one of the main regions where the new GII.17 variant was emerging and circulating widespread recently [18, 22]. Therefore, in this study, we aimed to perform continuous molecular surveillance to determine the prevalence and genetic diversity of NoVs in sporadic gastroenteritis cases in Guangzhou, China.

The study was approved by the Research Ethics Committee at the Third Affiliated Hospital of Sun Yat-sen University and the Institutional Review Board (IRB) at the Chinese CDC for the protection of human subjects (project approval number 2013(2)-76). Fecal specimens were collected from 215 patients with acute gastroenteritis at the Third Affiliated Hospital of Sun Yat-sen University in Guangzhou during two consecutive winter seasons (from November 2013 to March 2014 and from November 2014 to March 2015), and all specimens were stored at -80 °C until further analysis.

Viral RNA was extracted from 140 μl of supernatant of 10 % (w/v) fecal suspension using a QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). One-step reverse transcription polymerase chain reaction (RT-PCR) was then employed for NoV detection (TAKARA, Dalian, China) [23, 24], and a negative control containing RNase-free water and a positive control containing NoV RNA were included in each run. The purified RT-PCR products were subjected to direct sequencing at both ends with amplification primers, and sequencing was performed on an automated sequencer (ABI 3730 DNA Analyzer, Applied Biosystems), which was carried out by Majorbio Co., Ltd (Shanghai, China). A total of 25 fecal specimens were found to be NoV positive, but the prevalence of this virus in two seasons was not consistent (Table 1). Specifically, 9/135 (6.7 %) of samples tested positive for NoVs during November 2013 to March 2014, and the NoV detection rate in the ensuing season increased to 20 % (16/80). All nucleotide sequences were deposited in the GenBank database under accession numbers KR869037-KR869086. The results indicated that NoVs were still an important cause of sporadic gastroenteritis in the winter seasons in Guangzhou.

To identify the genotypes of the detected NoVs, partial nucleotide sequences of the polymerase region (nucleotide position 4279-4605, with respect to Hawaii virus, GenBank accession number HCU07611) and the capsid N/S domain (nucleotide position 5046-5389, with respect to Hawaii virus, GenBank accession number HCU07611) were employed for phylogenetic analysis. All NoV nucleotide sequences with NoV reference sequences of different genotypes were first aligned using the ClustalX algorithm version 1.83 [25], and phylogenetic trees were then produced by the neighbor-joining method with the Kimura two-parameter model in MEGA Version 6.0 [26]. All nucleotide sequences were also submitted to the NoV automated genotyping tool (http://www.rivm.nl/mpf/norovirus/typingtool) to verify phylogenetic analysis results [7]. The result showed that all NoV strains were clustered with viruses belonging to the GII genogroup except for one strain, GZ2013-L57, which belonged to GI (Fig. 1 and Table S1). In detail, the major genotype was found to be GII.4 (6/9) in the first season, followed by GII.P12/GII.3 and GI.Pb/GI.6. For GII.4 variants, strains in most samples (5/6) belonged to the predominant variant GII.Pe/GII.4_Sydney_2012 (5/6). The remaining strain was identified as the former predominant variant GII.4-2006b, which was detected in an adult aged 82. In the subsequent

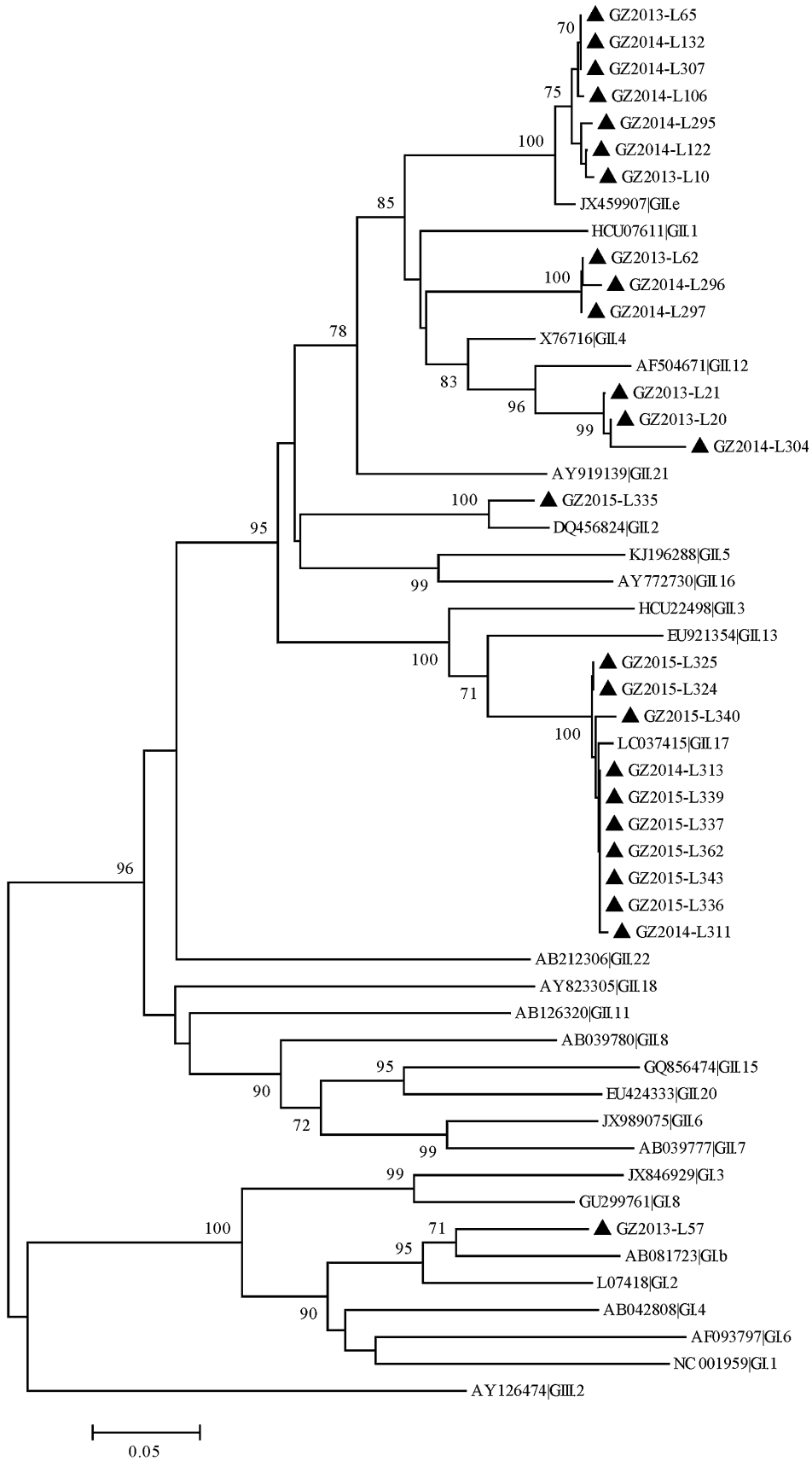
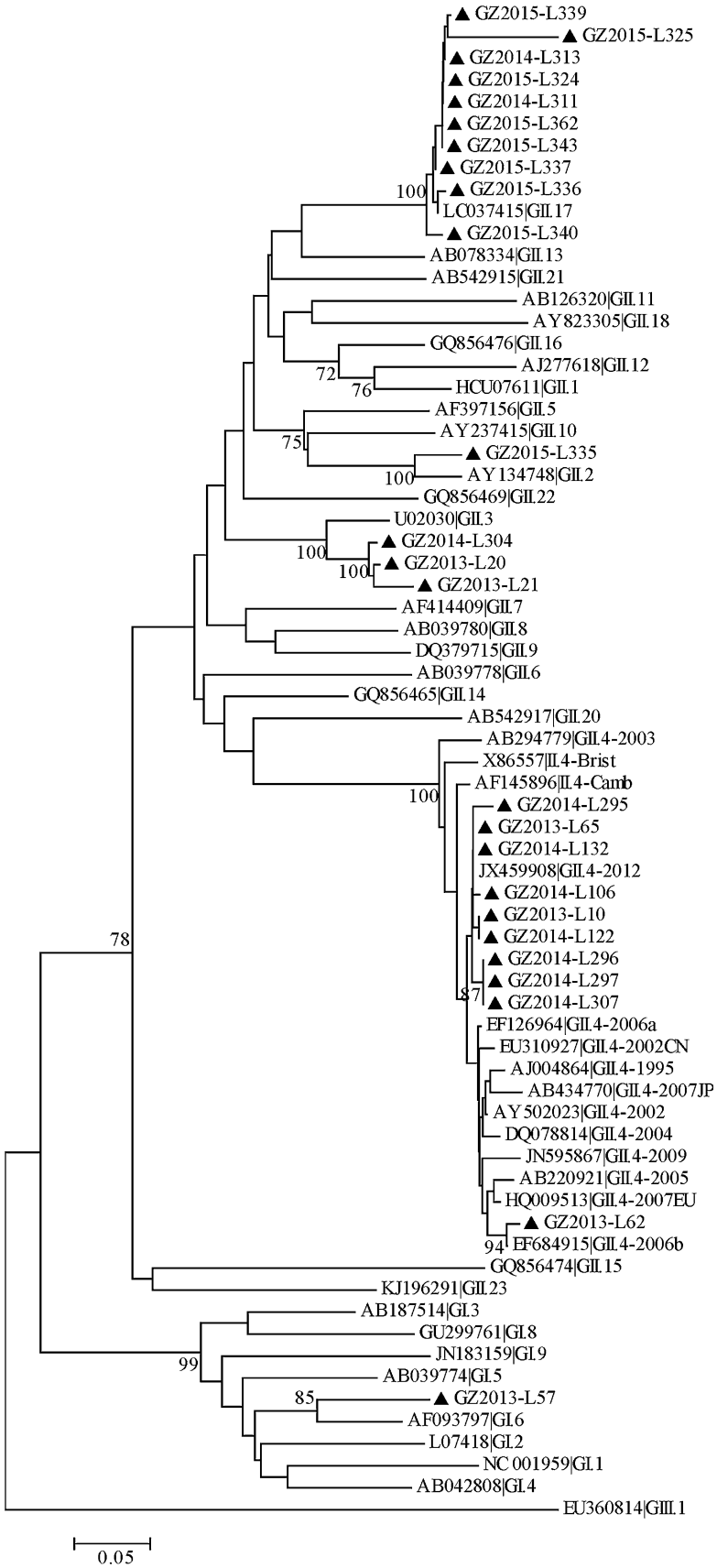


Fig. 1 Phylogenetic trees of norovirus detected in Guangzhou based on (A) a portion of the polymerase region and (B) the capsid N/S domain. The dendrogram was constructed by the neighbor-joining method with the Kimura two-parameter model in MEGA (version 6.0). Numbers at the nodes indicate supporting bootstrap values (%) for 1000 resampled datasets; only values greater than 70 % are shown. Local NoV strains (GenBank accession nos. KR869037-KR869086) are designated by location, year, and identification number (indicated by black triangles). Reference sequences are indicated by their accession numbers and genotypes. The scale bar represents the unit for the expected number of substitutions per site

Fig. 1 continued



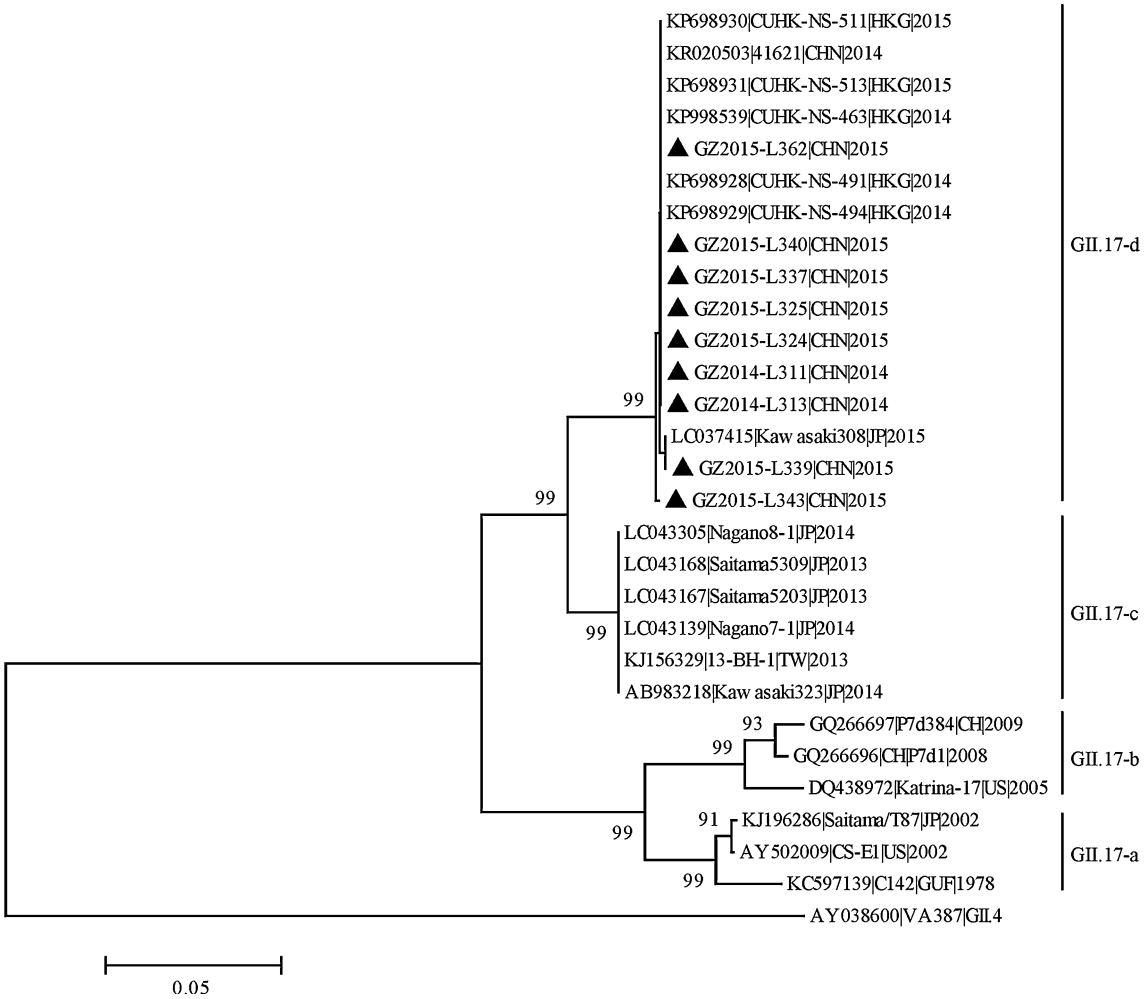


Fig. 2 Phylogenetic analysis based on the predicted amino acid sequences of GII.17 NoVs. The neighbor-joining trees were constructed using MEGA (version 6.0). Bootstrap values higher than 70 % are shown at the corresponding branches. The scale bar represents the unit for the expected number of substitutions per site. Local NoV strains (GenBank accession nos. KT149168-KT149176) are designated by location, year, and identification number (indicated by black triangles)

season, the predominant genotype turned out to be GII.17 (10/16), and four other variants were also noted, including GII.Pe/GII.4_Sydney_2012, GII.P4-2006b/GII.4_Sydney_2012, GII.P12/GII.3 and GII.2. The first GII.17-positive sample was collected in December 2014, and after that, almost all of the NoV-positive samples detected were identified as GII.17 (except GZ2015-L335). Two strains were detected in children (6 months and 1 year old, respectively), and eight GII.17 NoVs were found in adults (24 to 57 years old).

It is novel that a non-GII.4 NoV variant has emerged as the predominant genotype in China since its global epidemic in the mid-1990s. To further characterize these novel GII.17 strains, nine full-length VP1 sequences were obtained using the primers NV2of2 and GV132 (accession numbers KT149168-KT149176). In addition, nineteen VP1 sequences of GII.17 NoVs available in GenBank, collected in Hong Kong, Taiwan, the Chinese mainland, Japan, Switzerland, French Guiana and the USA, were also included as reference sequences (accession numbers and strain names are KR020503|41621, KP698928|CUHK-NS-491, KP698931|CUHK-NS-513, KP698930|CUHK-NS-511, KP998539|CUHK-NS-463, KP698929|CUHK-NS-494, LC043305|Nagano8-1, LC043167|Saitama5203, LC043139|Nagano7-1, LC043168|Saitama5309, LC037415|Kawasaki308, KJ156329|13-BH-1, AB983218|Kawasaki 323, KJ196286|Saitama/T87, KC597139|C142, GQ266696|P7d384, GQ266697|P7d1, DQ438972|Katrina-17, AY502009|CS-E1; see also Table S2). Phylogenetic analysis of these 28 sequences was performed, and a clade was defined as a group of at least two homologous NoV strains based on viral capsid protein VP1 that was phylogenetically well separated from others. As a result, all GII.17 sequences could be clustered into four clades (designated

as a, b, c, and d), and nine Guangzhou strains in this study all belonged to the clade GII.17-d, with seven GII.17 strains reported in Japan and the Hong Kong region since 2014 (Fig. 2).

NoV is still known to cause a considerable burden of acute gastroenteritis worldwide, and long-term surveillance of epidemics caused by this highly variable virus is necessary in many countries, including China [27]. In this study, long-term persistence of NoV in human populations was verified in cases of sporadic acute gastroenteritis in Guangzhou, and an emerging GII.17 variant was identified as the new predominant genotype.

A high degree of genetic diversity is a major feature of NoVs worldwide [28]. Of the different viral genotypes, GII.4 NoV has been found to be the predominant one in outbreaks and sporadic infections for about two decades [29, 30]. During this NoV surveillance for sporadic gastroenteritis in Guangzhou, the predominant variant in the first season (November 2013 to March 2014) was identified as GII.4_Sydney_2012 NoV, which was first reported in March 2012 in Australia [11]. In other surveys for sporadic infections, the GII.4 genotype was also identified as the predominant variant, causing 57.9 % to 79.2 % of the reported NoV infections associated with global epidemics in 2012-2014 [14, 15, 31–33]. A shift in the predominant variants occurred in the subsequent season (November 2014 to March 2015), with GII.17 NoV being found in most samples. This genotype was also documented in other countries and regions, including Hong Kong, Taiwan, and Japan [19, 34]. From November 2014 to January 2015, this genotype was also detected as the major cause of NoV outbreaks in Guangdong [18]. Although genetic information for this genotype is still insufficient, all reported GII.17 strains ($n = 28$) with full-length capsid protein sequences could be clustered into four clades. The first GII.17 NoV was isolated in 1978 (JN699043 and KC597139) [35], but only new emerging GII.17 variants caused an epidemic of acute gastroenteritis since late 2014. In the future, it should be explored whether GII.17 NoVs can become a global variant after a nearly forty-year period of stasis.

In addition to accumulating point mutations associated with error-prone RNA replication, recombination between NoV strains also occurs frequently as a mechanism by which they evolve and increase their genetic diversity [16]. In this study, several recombinant NoV variants were detected, including GII.P12/GII.3, GII.P4-2006b/GII.4_Sydney_2012 and GI.b/GI.6. Based on current literature, it is difficult to assess the significance of NoV recombination, but it is obvious that it is a very common event. Currently, partial RdRp and capsid VP1 sequences are regularly investigated to detect recombinants, and a dual nomenclature system using both two sequences has been proposed to better recognize recombinant viruses [36]. With the development of sequencing technologies, more and more genome sequences are accumulating, and these can be used to identify NoV recombinants [37–40]. During a recent surveillance in Chongqing, China, the recombinant GII.P12/GII.3 was found to have been a predominant genotype between 2011 and 2013 [14], and an interesting finding of that study was the potential for increased virulence of NoV recombinants. As the predominant genotype, GII.4 NoVs have kept evolving, mainly through point mutations, for almost four decades, but recombination between different GII.4 variants has also been detected [17]. In addition, the recombinant GI.Pb/GI.6 was also detected with a low prevalence rate in China and Australia [41], and this variant was even found in the intestinal contents of a wild Norway rat [42]. Thus, recombination requires increased attention during NoV surveillance, and future investigations are required to focus on understanding the trends in molecular evolution of NoV genomes [37, 43].

Despite the relatively small number of samples analyzed, the emergence of GII.17 NoV in Guangzhou was detected in this study, and recombination between different genotypes was also verified. The rapid replacement of GII.4 NoVs by the novel GII.17 variant in Asia suggests a potential for GII.17 NoV strains to become pandemic [34]. Therefore, continuous NoV surveillance is still warranted, and it is also of importance that data on these strains can be rapidly shared via global NoV networks in order to improve existing prevention and intervention strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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