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Research article

The genetic diversity of genogroup I noroviruses causing acute gastroenteritis outbreaks in Beijing between 2014 and 2023

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ABSTRACT

Background: In the past decade, we have continuously conducted sporadic monitoring and outbreak detection of norovirus (NoV), which causes human acute gastroenteritis (AGE) in the capital of China. Accumulated data have shown that genogroup I (GI) NoVs not only cause sporadic cases but also cannot be ignored during outbreaks. This study aimed to update the genetic diversity of GI NoVs in the capital of China from 2014 to 2023.

Methods: Fecal or anal swab samples were collected from AGE outbreaks triggered by GI NoVs in Beijing Chaoyang District from 2014 to 2023. Both the partial coding genes of RNA-dependent RNA polymerase (RdRp) (~283 bp) and viral protein 1 (VP1) (~303 bp) were amplified via reverse transcription polymerase chain reaction (RT-PCR) and sequenced, followed by genotyping and phylogenetic analysis.

Results: A total of 421 fecal or anal swab samples were collected from 59 AGE outbreaks caused by GI NoVs. Genetic diversity was observed, with nine genotypes reported, including recombinant strains of GI.6[P11] and GI.3[P13], as well as multiple subtypes that cocirculated. In addition, we also reported a shift in the dominant genotype, with GI.6 [P11] in 2015–2018, GI.3 [P13] in 2019–2021, and GI.4 [P4] in 2023. Furthermore, alterations in amino acids were indirectly indicated through single nucleotide polymorphisms (SNPs) in certain VP1 areas of strains GI.3 [P13] and GI.6[P11]. Epidemiologically, the peak of infection induced by GI NoVs occurs from March to May.

Conclusions: The sustained circulation and obvious genotype shift of GI NoVs in this region cannot be ignored, and GI.4[P4] NoVs are highly likely to become the main epidemic strain in the following years.

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1. Introduction

Human norovirus (NoV) has been identified as the main cause of viral acute gastroenteritis (AGE) worldwide [1–5]. Annually, approximately 2–5.7 million children contract NoV in the United States and Europe, and 89 % of children contract NoV within their initial two years in Asia and Africa [6–9]. Likewise, NoVs contribute significantly to the disease burden in China [10].

NoVs can be divided into at least 10 different genogroups (GI-GX). The main human infections were GI and GII. On the basis of the RNA-dependent RNA polymerase (RdRp) and VP1 regions, NoVs are divided into 60 and 49 genotypes, with GI and GII containing 14/37 RdRp genotypes and 9/27 VP1 genotypes, respectively [11,12]. Globally, GII is most commonly associated with NoV infection and remains the dominant strain [1,2,13–16], whereas GI is mainly responsible for sporadic infections.

However, GI NoVs cannot be ignored during AGE outbreaks. A systematic review of NoV epidemics in China between 2000 and 2018 revealed that GI was responsible for 30 out of the 266 outbreaks [17]. The recombinant strain GI.6[P11] was responsible for 1.3 % of NoV outbreaks in China between 2016 and 2018 and 2.6 % in Beijing between 2014 and 2017 [18,19]. The main genotype of GI-induced AGE was GI.6 [P11] in Beijing and Argentina from 2014 to 2019 and GI.3 in Taiwan from 2015 to 2019 [19–21]. GI.3 [P13] NoV was also detected in two outbreaks in 2018 and 2020 in Argentina [22].

In addition, the contamination of GI NoVs in water and food indicates a high risk of human infection. Several reports indicate that the detection rates of GI and GII NoVs in wastewater are comparable in different regions [23–26], and even the detection rate of GI NoVs in vegetables is high worldwide [27], one of the reasons that GI NoVs should receive more attention.

Moreover, natural GII infection provides little immunity acquired against infection and no evidence of protection from GI infection [28]. An effective vaccine should provide sufficient acquired immune protection for different genogroups. Therefore, it is extremely important to clarify the variants of the GI and GII genogroups for the selection and compatibility of vaccine strains. Several candidate vaccines containing GI and GII NoV VLPs are currently in development [29], but the genotypes of these vaccines vary annually. In addition, the research hotspots have focused mostly on the GII genotype rather than the GI genotype.

In the past decade, we have been continuously conducting sporadic monitoring and outbreak detection of NoVs that cause human acute gastroenteritis (AGE) in the capital of China. Our previous report described the genetic diversity of GI NoVs causing sporadic cases [30]. Here, we monitored the epidemiological trends and genetic characteristics of NoV GIs during AGE outbreaks from 2014 to 2023 to provide valuable information for accurate diagnosis of circulating strains, herd immunity and potential vaccine development, as well as more accurate scientific data for NoV control.

2. Methods

2.1. Definitions

We followed the requirements of the Beijing Centre for Disease Control and Prevention. AGE cases are defined as patients who have diarrhea (three or more loose stools in 24 h) and/or vomiting (one or more episodes). Outbreaks of AGE are defined by the occurrence of three or more epidemiologically relevant cases of AGE within 3 days. After meeting the inclusion criteria for AGE, the outbreak is confirmed to be induced by NoV when two or more cases test positive for NoV by real-time polymerase chain reaction (PCR) [31].

2.2. Sampling and data collection

The Chaoyang District Center for Disease Control and Prevention (CDC) carries out AGE surveillance within the AGE epidemic surveillance network established by the municipal CDC and follows relevant guidance. Briefly, from 2014 to 2023, AGE cases that occurred in schools, kindergartens and other institutions were first reported to community health centers and then reported to the Chaoyang District CDC [19]. An investigation will be conducted within 24 h after receiving the report. Moreover, fecal samples or anal swabs from AGE-treated patients should be collected within 48 h after the investigation.

2.3. Laboratory detection

The samples were qualitatively confirmed to be NoV positive via a commercial dual-channel real-time PCR kit (DAAN GENE, Guangzhou, China). If there is no amplification curve or a Ct value > 38 in both the FAM and VIC channels, the sample can be judged as negative for the NoV GI/GII type. If the Ct value of the FAM or VIC channel is no more than 38 with a clear amplification curve, the sample can be judged to be positive for NoV GI or GII if positive and confirmed to be GI, the GI NoV-specific primer pair MON432/G1SKR was used to amplify part of the coding gene of RdRp (283 bp) and viral protein 1 (VP1) (303 bp) through reverse transcription PCR, followed by Sanger sequencing.

2.4. Genotyping and phylogenetic analysis

All sequences were genotyped via the Fundamental Tool for Local Alignment Search (BLAST; https://blast.ncbi.nlm.nih.gov/Blast.cgi)) and an online NoV genotyping tool (http://www.rivm.nl/mpf/norovirus/typingtool/). The genome sequence most closely resembling our input sequence is chosen for reference. Using the MegAlign module in MEGA software (version 7.0, MEGA Limited, Auckland, New Zealand), the sequences of this study were compared with reference sequences to examine their differences.

To assess the genetic evolution link between this study's sequences and references, we retrieved the complete or segmented VP1 and RdRp sequences of various genotypes from GenBank to conduct phylogenetic analysis. The alignment of sequences utilized MegAlign, and Mega version 7.0 developed a maximum-likelihood (ML) tree employing the optimal model T92 + G (T92: Tamura-Nei model, G: Gamma distribute) for RdRP and VP1. The phylogenetic tree's statistical relevance was assessed through a bootstrap analysis involving 1000 duplicates.

3. Results

3.1. Epidemiological distribution of GI NoVs in AGE outbreaks

In the past decade (2014–2023), 969 AGE outbreaks have occurred in Beijing Chaoyang District, among which 555 (57.3 %) were laboratory-confirmed resulting from NoVs. There were 59 outbreaks caused by NoV GI and 496 caused by NoV GII. After genotyping, 84.7 % (50/59) were attributed to the GI genotype, even though the GII genotype still predominated (89.9 %, 446/496) [32–34]. The predominant genotype of NoV GII was GII.2 [P16] (40.0 %, 182/446). The main season for outbreaks in which NoV GII was genotyped was spring (59.19 %, 264/446), and the main place of occurrence was kindergarten (74.4 %, 332/446).

Although AGE outbreaks caused by GI NoVs are relatively rare, they still occur every year. Most GI NoV outbreaks occurred in the spring season (64.5 %, 38 of 59), followed by the fall season (15.2 %, 9 of 59), summer (11.8 %, 7 of 59), and winter (8.5 %, 5 of 59) (Fig. 1). Most GI NoV outbreaks occurred in primary schools (61.0 %, 36 of 59) or kindergartens (35.6 %, 21 of 59), followed by junior high schools (3.4 %, 2 of 59) (Table 1). Among the GI NoV outbreaks, modes of transmission were identified, with person-to-person transmission being the most prevalent (58/59, 98.3 %), followed by water transmission (1/59, 1.7 %). A total of 421 fecal samples or anal swabs were collected from 59 GI NoV-induced AGE outbreaks. After laboratory detection, 250 samples were determined to be GI NoV positive. The median number of individuals affected per NoV-GI AGE outbreak was 4 (range: 3–19). The median age of positive individuals was 8 years (range: 1–15 years), with the highest infection rate in the 8-year age group (15.2 %, 38/250, 95 % CI: 9.22–21.2 %), followed by the 5-year age group (12.0 % (30/250, 95 % CI: 6.02–18.0 %) and the 7-year age group (10.4 % (26/250, 95 % CI: 4.42–16.4 %) (Table 2). There are notable statistical variances in the number of individuals of infected age ($\chi^2 = 90.068$, $P < 0.001$, IBM SPSS 20, chi-square test). The sex ratio (male/female) was 1.21. There was no significant difference between males and females ($\chi^2 = 2.304$, $P = 0.129$; IBM SPSS 20; chi-square test).

3.2. Genotyping of GI NoVs in AGE outbreaks

The genetic diversity of GI NoVs that cause AGE outbreaks was analyzed. Parts of the RdRp and VP1 genes were successfully amplified and sequenced in a total of 123 samples from 50 outbreaks. Unfortunately, sequence information for several samples has not been obtained due to low viral loads.

Finally, nine genotypes belonging to the GI genogroup were identified, including GI.1[P1], GI.2[P2], GI.3[P3], GI.3[P13], GI.4 [P4], GI.5[P4], GI.5[P12], GI.6[P6] and GI.6[P11]. In general, the recombinant strains of GI.3[P13] (36.0 %, 18/50) were the predominant strains, followed by the recombinant strains of GI.6[P11] (22.0 %, 11/50) and GI.4[P4] (20.0 %, 10/50), whereas the other genotypes accounted for no more than 10 % each in the past decade. In addition, the annual composition of genetic diversity significantly differed.

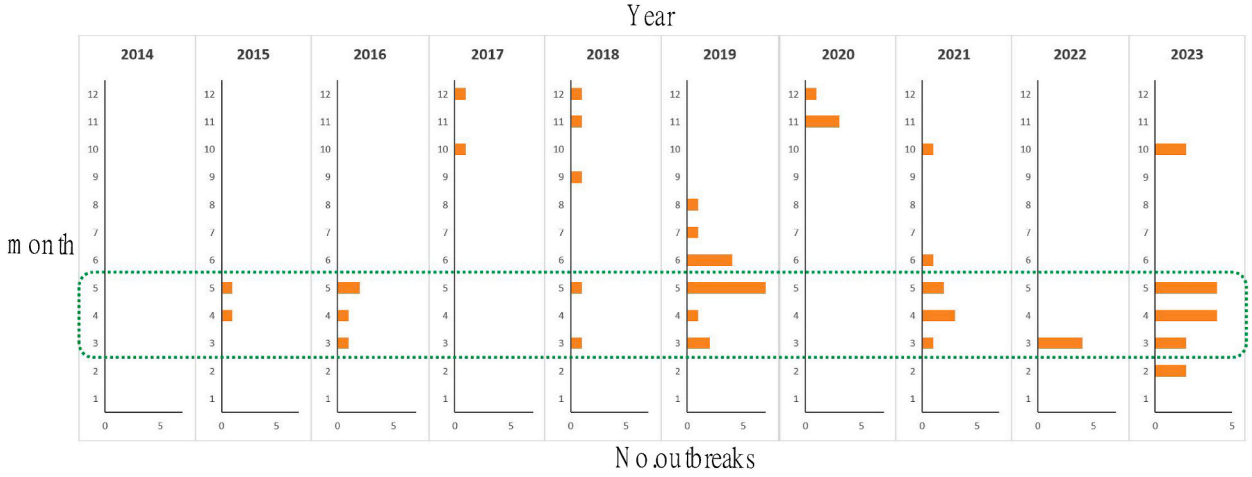

Fig. 1. Monthly distribution of AGE outbreaks caused by GI NoVs in Beijing Chaoyang District from 2014 to 2023. **Note:** The number of AGE outbreaks is represented by a bar chart year by year from 2014 to 2023. The horizontal axis represents the number of AGE outbreaks, whereas the vertical axis represents the month. Most GI NoV outbreaks occurred in the spring season (enclosed by the green dashed line).

Table 1
Association between distribution and transmission mode and outbreaks of the norovirus GI in Beijing from 2014 to 2023.

	GI (N = 59)	χ^2	*P*-value
School			
kindergarten	21	29.525	<0.001
primary school	36		
junior high school	2		
Transmission mode			
person-to-person	58	55.068	<0.001
water	1		

Table 2
Association between sex, age and cases of AGE outbreaks of norovirus GI in Beijing from 2014 to 2023.

	GI (N = 250) n(%)	χ^2	*P*-value
Gender			
male	137 (54.8)	2.304	0.129
female	113 (45.2)		
Age group (yrs)			
1~	3 (1.2)	90.608	<0.001
2~	0 (0.0)		
3~	14 (5.6)		
4~	24 (9.6)		
5~	30 (12.0)		
6~	25 (10.0)		
7~	26 (10.4)		
8~	38 (15.2)		
9~	24 (9.6)		
10~	19 (7.6)		
11~	16 (6.4)		
12~	12 (4.8)		
13~	10 (4)		
14~	9 (3.6)		
15~16	0 (0.0)		

3.3. Phylogenetic and evolutionary analysis of NoV outbreaks

Phylogenetic trees were constructed on the basis of all partial RdRp (Fig. 4A) and VP1 (Fig. 4B) gene sequences obtained from NoV GI AGE outbreaks in Beijing from 2014 to 2023. Partial GI.6[P11] RdRp fragments were highly homologous (98.6%–100.0 %) to those of reference strains from 2016 to 2019 in China and from 2019 to 2020 in South Korea. The partial nucleotide acid similarity of the GI.6 [P11] VP1 region ranged from 88.1 % to 100.0 %. These sequences were highly homologous to those of reference strains from 2015 to 2018 in China and 2016 to 2017 and 2019 in South Korea. Analysis of the phylogenetic tree revealed that these sequences grouped into two distinct clades, whereas the second clade was further divided into three smaller subclades (Fig. 4A and B). The primary detection period for clade 1 spans 2015 and 2016, whereas the evolutionary branch of clade 2 is predominantly observed from 2016 to 2021. A total of 36 single nucleotide polymorphism (SNP) sites were pinpointed (Fig. 5A and B).

Partial RdRp sequences in GI.3 [P13] presented high similarity (93.5%–100 %) with those of reference strains from Japan, South Korea, Taiwan, and Thailand in 2019. The partial nucleotide acid similarity of the GI.3[P13] VP1 region ranged from 92.7 % to 100.0 %. Analysis of the phylogenetic tree revealed that these sequences grouped into two distinct clades (Fig. 4A and B). Similarly, 14 SNPs (Fig. 5A and B) were found.

4. Discussion

NoVs are considered major agents of viral AGEs at all ages worldwide, which leads to high morbidity and even mortality due to serious infections, particularly in elderly individuals and children [10]. Prior to 2017, 72.8 % of AGEs induced by NoV were classified as GII.4 [10]. Nonetheless, the abrupt appearance of novel GII.17[P17] variants, which are prevalent in various Asian nations such as China and Japan, along with the rise of recombinant strains of GI.6[P11] and GI.3[P13], the shared recombinant strains causing NoV GI epidemiological outbreaks in China and Taiwan, underscore the necessity and significance of investigating alternative nonnative variants [17,21,31,35,36].

Initially, our analysis focused on the seasonal patterns, environments, modes of transmission, and fundamental traits of 59 AGE outbreaks of NoV GI in Beijing, China, from 2014 to 2023. This research revealed that outbreaks of NoV GI occurred mainly during the colder months, similar to earlier findings in Beijing, the USA, and Australia [19,37–39], likely because many Chinese kindergartens and primary schools start their school year in the spring and autumn. Importantly, the NoV GI outbreaks in the AGE showed notable statistical variance across months ($\chi^2 = 65.000$, $P < 0.001$, IBM SPSS 20, chi-square test). In particular, NoV GI usually initiates AGE

outbreaks between March and May in most years, with the exception of a short-lived spike from October to December in certain years (Fig. 1).

Since 2016, a variety of genotypes have emerged concurrently, predominantly GI.6 [11], GI.3[P13], and GI.4[P4] (Fig. 2). Notably, the changes in the dominant strains have gone through three distinct time stages. The predominant genotype in Beijing's Chaoyang District between 2015 and 2018 was GI.6 [P11] (46.2 %, 6/13), which aligns with the global prevalence from 2016 to 2019 [18,20,31,40] and Beijing's epidemic genetic makeup from 2014 to 2017 [19]. From 2019 to 2022, it became GI.3 [P13] (34.4 %, 11/32). Research indicates that from 2018 to 2019, this particular genotype rose to prominence in Taiwan [21] and subsequently in Chaoyang District. Our findings indicate that outbreaks caused by NoV GI.3 mainly occurred in kindergarteners (31.6 %, 6/19) and elementary schools (68.4 %, 13/19), similar to NoV outbreaks in Beijing in 2014–2019 and China in 2012–2016 [19,31,41], indicating the need to focus on new strains circulating in Asia or elsewhere. It appeared in 2017, and it is inferred that there may be a low prevalence in Beijing before 2019. Because research on GI is rare, GI.3 has increased, and GI.6 has decreased over a wide range, which may be the result of system evolution in recent years. In 2023, there was an abrupt increase in GI.4[P4] levels, but the changes in sequences were not noticeable, with GI.4[P4] (50.0 %, 7/14) circulating in conjunction with GI.3[P13] (35.7 %, 5/14) (Fig. 3), in stark contrast to the epidemics of the GI.6[P11] or GI.3[P13] genotypes noted both within the country and abroad [19,21,31]. It is suggested that we pay attention to the dynamics of GI.4[P4] in the future to observe whether it will become a new dominant genotype.

To identify the relationships detected in this study with some of the previously reported NoV GI RdRp genes and VP1 genes, we selected reference sequences from GenBank and performed phylogenetic analysis (Fig. 4A and B). Our study included the creation of evolutionary trees with incomplete RdRp and VP1 sequences to demonstrate similarity with other reference strains, suggesting that NoV evolution can be revealed through incomplete genome sequences. The GI.6[P11] strain grouped with China from 2015 to 2018, indicating a possible widespread occurrence of this genotype during that period, which aligns with our observations. Within clade 1, this study's sample sequence showed 99.48 % similarity with MG871408 from China and MK280882 from Australia. In this study, the samples of the GI.6[P11] sequence were grouped with KU724080 in China, LC726060 in Japan, and MZ021891 and MN421716 in South Korea in subclade 2.1, with a homology range of 98.95%–100.00 %. Within subclade 2.2, the grouping included OM899811 from Spain, OR857077 from China, and OQ880477 from Japan, which exhibited a homology range of 98.95%–100.00 %. Studies have shown that the amino acid sequence at the Histo Blood Group Antigens (HBGA) binding site of GI.6 [P11] in Beijing remained unchanged from 2016 to 2019 [34]. Nonetheless, a total of 10 unique amino acid alterations were observed in Beijing. SNPs were obtained through a process of partial sequence alignment, indicating signaling changes in these amino acids.

These GI.3[P13] sequences were highly homologous to those of reference strains from 2018 to 2020 in South Korea and from 2018 to 2019 and 2022 in Japan and 2020 in China. In this study, the sample of GI.3[P13] sequences was grouped with MN922719 from Taiwan, OR792774 from China, LC573330 from Thailand, MT491999 from Spain, and MN421663 from Korea in the first clade, showing a homology between 99.48 % and 100.00 %. Within clade 2, the grouping included LC769710 from Japan, MZ021896 from Korea, MT492003 from Spain, and PP564824 from Thailand, which exhibited homology between 98.95 % and 100.00 %. Owing to the high affinity of GI.3 [P13] for many parts of Asia, as well as the occurrence of successive epidemics, this suggests the need to be vigilant against rising epidemic genotypes in other regions. Research indicates that GI.3 fails to attach to the immune sera of different genotypes [13,42–44], potentially making GI.3 the primary contributor to the epidemic, with SNPs indirectly suggesting alterations in amino acids.

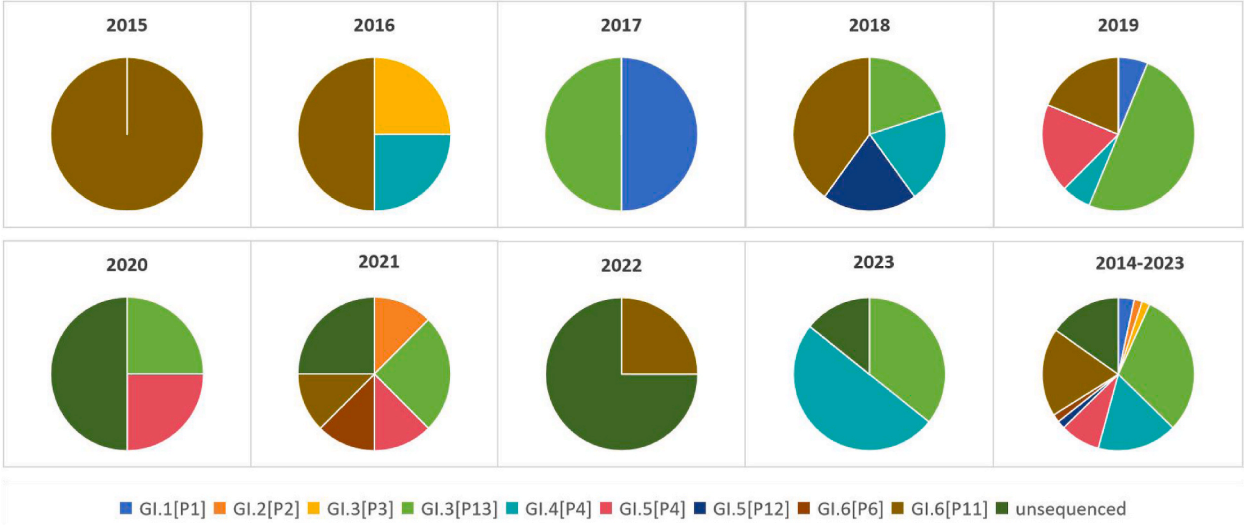

Fig. 2. Annual distribution of AGE outbreaks caused by GI NoVs by genotype in Beijing Chaoyang District from 2014 to 2023. **Note:** The composition of each recombinant subtype and unsequenced strain is shown via a percentage circular chart annually from 2015 to 2023 and combined (the last graph).

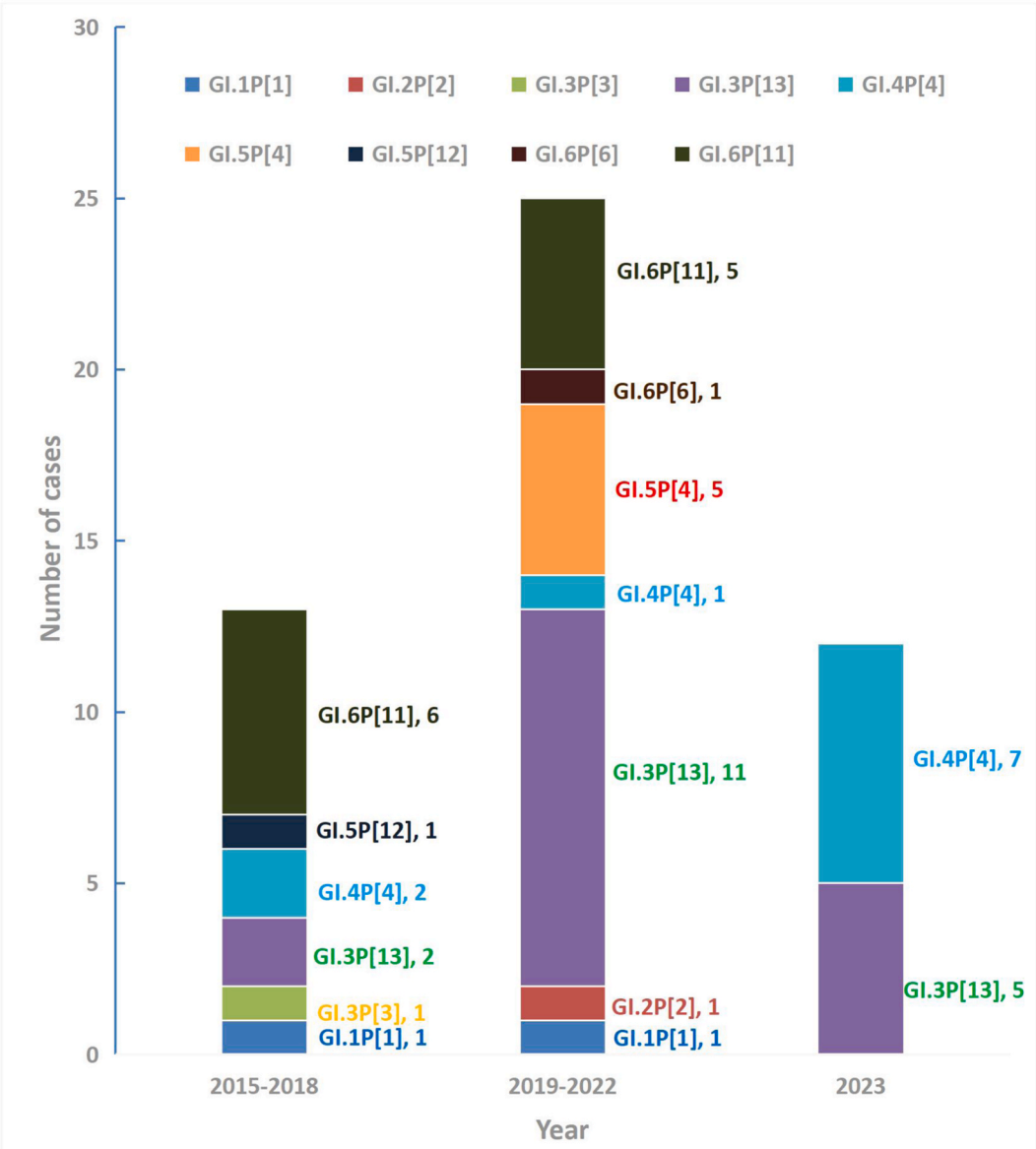

Fig. 3. Distribution of the genotypes across three distinct time intervals. **Note:** We divided the past decade into three time periods (2015–2018, 2019–2022, 2023) to show the changes in the dominance and diversity of NoV strains. The predominant genotype in Beijing Chaoyang District between 2015 and 2018 was GI.6 [P11]. During 2019–2022, it became GI.3 [P13]. In 2023, there was an abrupt increase in GI.4 [P4] in conjunction with GI.3 [P13].

5. Conclusion

In summary, the findings of our research reveal a shift in three primary genotypes of NoV GI in the capital of China, with the GI.6 [P11] recombinant genotype emerging as the leading genotype, succeeded by the GI.3[P13] recombinant genotype and the GI.4[P4] genotype rising in 2023, potentially explaining the recent surge in diarrhea cases and outbreaks of GI. These findings also suggest that the dominant strains of the NoV GI genotype changed in different years. Therefore, molecular epidemiological surveillance of the NoV GI strain should be strengthened in the future, and changes in the dominant strain should be detected in time to provide a basis for early warning, prediction and control of the epidemic.

CRediT authorship contribution statement

Xiangyu Hu: Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Lingli Sun:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding

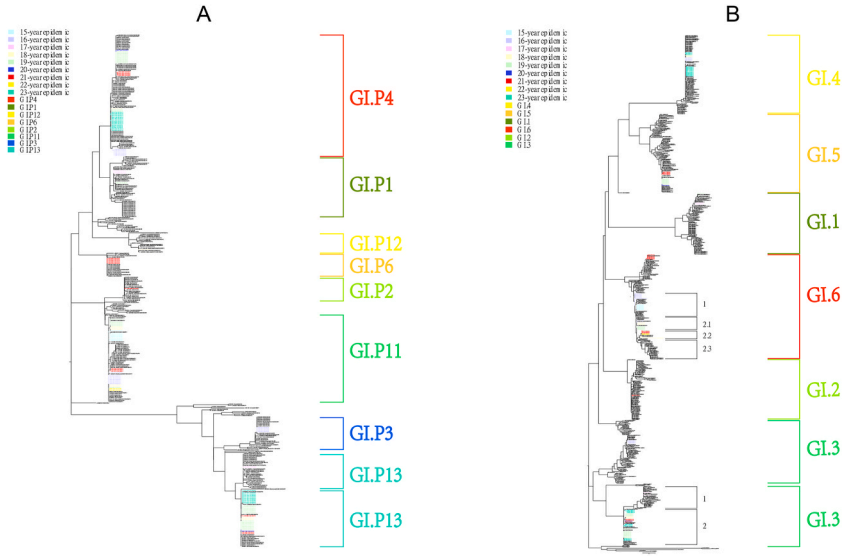

Fig. 4. Phylogenetic analysis of NoV based on the RdRp and VP1 nucleotide sequences. Note: A. Phylogenetic tree based on the partial nucleotide sequence (147 bp) of the NoV RdRp region; B. phylogenetic tree based on the partial nucleotide sequence (191 bp) of the NoV capsid region. The NoV strains obtained from Beijing Chaoyang District from 2014 to 2023 are indicated with different colors. The phylogenetic tree was constructed via the neighbor-joining method with 1000 iterations of the bootstrap test.

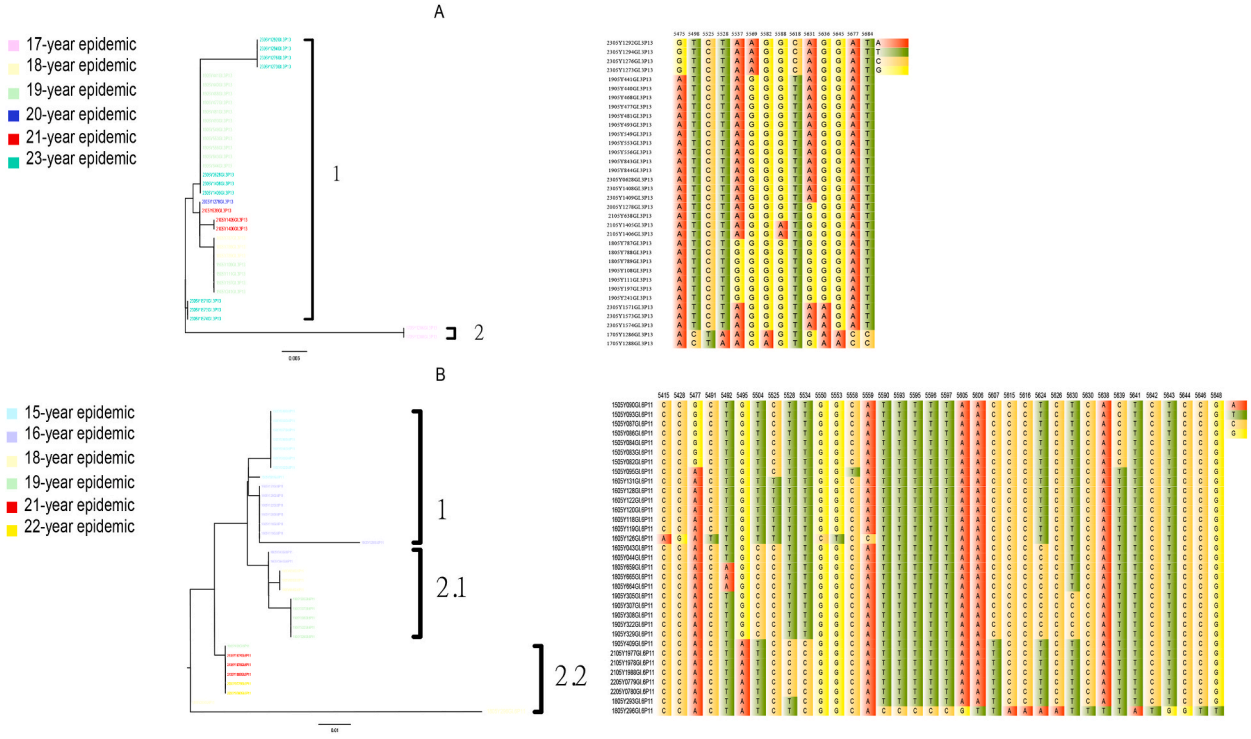

Fig. 5. Comparison of variation sites. **Note:** Various hues symbolize samples from the respective years of this research. A denotes the phylogenetic tree and nucleotide location analysis of incomplete GI.3 sequences from GI.3 [P13], whereas B represents the phylogenetic tree and nucleotide location analysis of partial GI. sequences from GI.6 [P11] in this research.

acquisition, Conceptualization. **Taoli Han:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Jianhong Zhao:** Supervision, Project administration, Methodology, Conceptualization. **Xiao Qi:** Project administration, Methodology, Investigation. **Yue Zhang:** Supervision, Investigation. **Pan Lu:** Supervision, Data curation. **Jiaxin Zhao:** Supervision, Data

curation. **Yan Gao:** Supervision, Project administration, Data curation. **Zheng Zhang:** Methodology, Conceptualization. **Beibei Li:** Supervision, Investigation. **Jialiang Du:** Writing – review & editing, Methodology, Conceptualization. **Yang Jiao:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Ethics statement

The study was approved by the ethical committee of the National Institutional for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (No. IVDC2017NO.023). Every participant gave their written, informed agreement. In cases where minors are younger than 18, the consent document is signed by a parent or guardian, and these minors give further verbal agreement.

Availability of data and materials

The data associated with the study have not been deposited into a publicly available repository and are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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