

# Effect of recombinations on changes in genotype proportions between norovirus seasons in Japan

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## ARTICLE INFO

### Keywords:

Genotype proportion  
Norovirus  
Recombination  
RNA-dependent RNA polymerase  
Viral protein 1

## ABSTRACT

**Background:** Norovirus (NoV) is an etiological agent of acute gastroenteritis in humans. Genomic recombinations in NoV occur mainly at the junction of the genes encoding the RNA-dependent RNA polymerase (RdRp) and the major capsid protein (viral protein 1, VP1), which may produce strains with novel combinations of VP1- and RdRp-genotypes.

**Methods:** Here the effect of recombinations on changes in the proportions of VP1-genotypes was examined through analysis of the observed frequencies of VP1-genotypes in Japan from season 2006/2007 to 2019/2020 reported in the Infectious Agents Surveillance Report (IASR) and the nucleotide sequences for 2788 GI and 19,782 GII strains deposited in the International Nucleotide Sequence Database (INSD).

**Results:** Positive correlation was identified between the observed frequency in the IASR and the number of nucleotide sequences in the INSD for individual VP1-genotypes in each season. In addition, acquisition of novel RdRp-genotypes was associated with an increase in the observed proportion of VP1-genotypes.

**Conclusions:** Recombinations creating strains with novel combinations of VP1- and RdRp-genotypes may be an adaptive mechanism for NoV.

## 1. Introduction

Norovirus (NoV) is an etiological agent of acute gastroenteritis in humans, causing 685 million cases of diarrhea, which correspond to 18% of all cases of diarrhea, resulting in 212 thousand deaths worldwide annually (Kirk et al., 2010; Lopman, 2015; Pires et al., 2015). Notably, NoV is more prevalent in developed (20%) and low-mortality developing countries (19%) than in high-mortality developing countries (14%), suggesting that improvements in sanitation and hygiene are not sufficient for control and prevention of NoV (Patel et al., 2008; Ahmed et al., 2014). In the current situation without anti-NoV drugs, it is demanded to develop vaccines against NoV.

NoV belongs to the genus *Norovirus* in the family *Caliciviridae*, having a virion of a non-enveloped icosahedron with the size of 38 nm in diameter and a genome of a linear, non-segmented, single-stranded RNA of positive polarity with the length of 7.5 kb (Clarke et al., 2012). ORF1, ORF2, and ORF3 are located in this order from the 5'-end to the 3'-end of the genome. ORF1 encodes non-structural proteins (NS) including the RNA-dependent RNA polymerase (RdRp). ORF2 encodes the major capsid protein (viral protein 1, VP1), with or without an overlap of ORF4 in an alternative reading frame, which encodes virulence factor 1 (VF1).

ORF3 encodes the minor capsid protein (VP2).

VP1 is the determinant of antigenicity and the target of neutralizing antibodies against NoV. Based on the similarity in the amino acid sequence of VP1, NoV strains are divided into genogroups GI-GX, among which GI, GII, GIV, GVIII, and GIX strains infect humans (Zheng et al., 2006; Vinje, 2015; Chhabra et al., 2019). GI, GII, and GIV strains are further classified into VP1-genotypes GI.1-GI.9, GII.1-GII.27, and GIV.1 and GIV.2, respectively (Kroneman et al., 2013; Vinje, 2015). NoV strains with different VP1-genotypes within the same genogroups appear to be antigenically related in various degrees (Hansman et al., 2006; Parra et al., 2017).

Reportedly, genomic recombinations occur mainly at the junction of ORF1 and ORF2 between NoV strains within the same genogroup (Katayama et al., 2002; Bull et al., 2007; Ludwig-Begall et al., 2018). Therefore, based on the similarity in the nucleotide sequence encoding the RdRp, GI and GII strains are also classified into RdRp-genotypes GI-P1-GI-P14 and GII-P1-GII-P41, respectively, although no strains have been assigned to GII-P9, GII-P14, and GII-P19 (Chhabra et al., 2019). Thus, GI and GII strains are dually genotyped, as designated in the form of VP1-genotype[RdRp-genotype], such as GI.1[P1].

In Japan, the NoV season is defined such that season 2006/2007

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<https://doi.org/10.1016/j.mgene.2021.100934>

Received 3 March 2021; Received in revised form 23 May 2021; Accepted 31 May 2021

Available online 2 June 2021

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represents the period between September 2006 and August 2007. NoV strains with various VP1-genotypes have been observed to co-circulate every season changing their proportions (Suzuki et al., 2016; Thongprachum et al., 2016). Since cross-immunity against NoV strains with different VP1-genotypes appears to be limited and may even promote their infections (Chhabra et al., 2020), it is desirable to develop multi-valent vaccines against NoV for each target season by formulating the composition of VP1-genotypes in the seed strains to match that in the dominant strains in the target season, which may be facilitated by predicting the proportions of VP1-genotypes (Suzuki et al., 2016, 2019). Such a prediction may also be useful for selecting human populations to be vaccinated, because VP1-genotypes appear to be related to preferences on human ages for infection and transmission modes of NoV (Mathijs et al., 2012).

For predicting the proportions of VP1-genotypes, it is critical to understand evolutionary mechanisms for NoV. Reportedly, the herd immunity in humans drives changes in the proportions of NoV strains (Ruis et al., 2020). However, outbreaks of NoV sometimes appear to be caused by recombinants with novel combinations of VP1- and RdRp-genotypes, suggesting a possibility that recombinations creating strains with novel combinations of VP1- and RdRp-genotypes may be an adaptive mechanism for NoV (Mahar et al., 2013; Parra, 2019; Cates et al., 2020). The purpose of the present study was to evaluate this possibility by examining whether acquisition of novel RdRp-genotypes was associated with an increase in the observed proportion of VP1-genotypes during evolution of NoV in Japan.

## 2. Materials and methods

### 2.1. Epidemiological data

In Japan, the prevalence of VP1-genotypes in NoV has been surveyed by the National Institute of Infectious Diseases (NIID), Japan. The observed frequencies of VP1-genotypes have been reported in the Infectious Agents Surveillance Report (IASR) from season 2006/2007 to 2019/2020 (supplementary Table S1). GI and GII strains with various VP1-genotypes, but no GIV, GVIII, or GIX strains, have been identified in these seasons. For the VP1-genotypes with the sum of the observed frequencies over the entire period greater than ten, the observed frequencies were converted into the observed proportions in each season for GI (supplementary Table S2) and GII (supplementary Table S3) strains.

### 2.2. Sequence data

Nucleotide sequences containing ORF2 for GI and GII strains of NoV were retrieved from the International Nucleotide Sequence Database (INSD) on November 11, 2020, using TBLASTN (version 2.2.26) (Ye et al., 2006). In TBLASTN, the amino acid sequences of VP1 for GI (strain name: Hu/GI.1/8FIIa/1968/USA, INSD accession number: JX023285) and GII (Hu/GII.4/MD120-12/1987/USA, JX289821) strains were adopted as the query. The Norovirus Genotyping Tool (version 2.0) (Kroneman et al., 2011) was used for determining the VP1-genotype for the nucleotide sequences of 2788 GI and 19,782 GII strains that were provided with the information on the isolation year and month in the INSD entry file (supplementary Table S4). Among these strains, 115 GI and 932 GII strains were isolated before season 2006/2007, and the remaining 2673 GI and 18,850 GII strains were isolated from season 2006/2007 to 2019/2020.

### 2.3. Data analysis

In the evolutionary studies for the proportion of viral strains, it has often been assumed that the abundance of nucleotide sequences deposited in the INSD reflects the prevalence of viral strains in humans (Luksza and Lassig, 2014; Suzuki, 2015). To evaluate this assumption in

NoV, the nucleotide sequences for 2673 GI and 18,850 GII strains that were isolated from season 2006/2007 to 2019/2020 and VP1-genotyped above were classified according to the isolation season and the VP1-genotype (supplementary Table S5). In addition, after discarding the nucleotide sequences for NoV strains isolated in Japan as well as those with unknown geographical origin, the nucleotide sequences for 2615 GI and 17,311 GII strains were classified according to the isolation season and the VP1-genotype (supplementary Table S6). The number of nucleotide sequences in the INSD (supplementary Tables S5 and S6) was compared with the observed frequency in the IASR (supplementary Table S1) for individual VP1-genotypes in each season by drawing the scatter plot and computing the correlation coefficient.

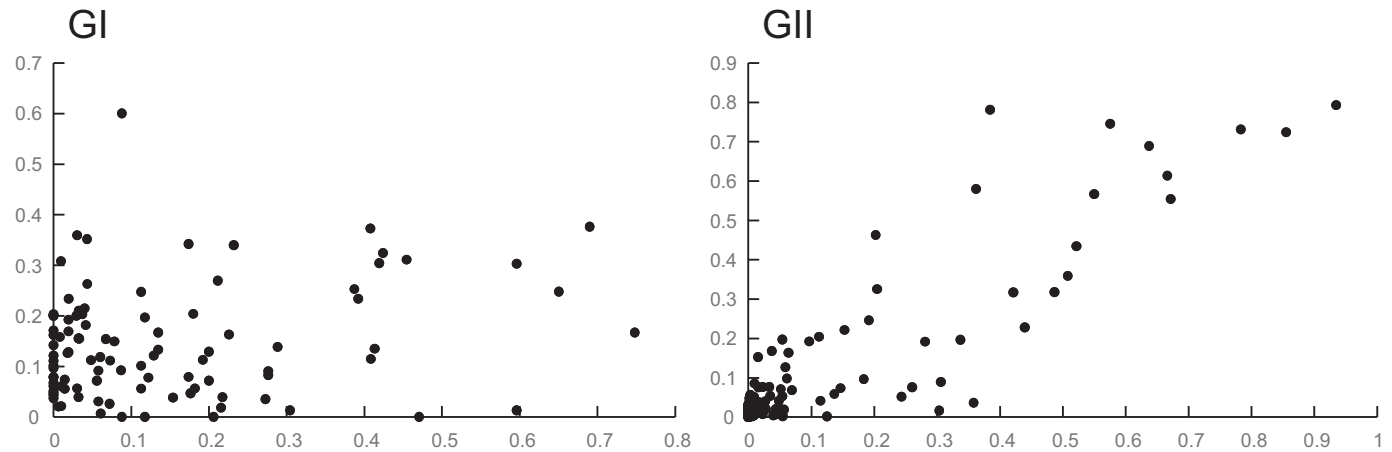
To evaluate the possibility that recombinations creating strains with novel combinations of VP1- and RdRp-genotypes may be an adaptive mechanism for NoV (Mahar et al., 2013; Parra, 2019; Cates et al., 2020), a further analysis was conducted for examining whether acquisition of novel RdRp-genotypes was associated with an increase in the observed proportion of VP1-genotypes. Among the nucleotide sequences for 2788 GI and 19,782 GII strains that were VP1-genotyped above, the RdRp-genotype was also determined for 572 GI and 4770 GII strains using the Norovirus Genotyping Tool (version 2.0) (Kroneman et al., 2011) (supplementary Table S7). The dually genotyped sequences were classified according to the isolation season and the VP1-genotype, for identifying the RdRp-genotypes combined with individual VP1-genotypes in each season as well as the seasons in which acquisition of novel RdRp-genotypes occurred in individual VP1-genotypes (supplementary Table S8). For each of the seasons with or without acquisition of novel RdRp-genotypes (season  $t$ ), the observed proportion of VP1-genotypes ( $p_t$ ) was compared with those in seasons  $t - 1$  ( $p_{t-1}$ ) and  $t + 1$  ( $p_{t+1}$ ) (supplementary Tables S2 and S3). Season  $t$  was considered to be involved in an increase in the observed proportion of VP1-genotypes if  $p_t - p_{t-1}$  or  $p_{t+1} - p_t$  exceeded a threshold value (0.05, 0.10, or 0.15). All of the seasons with or without acquisition of novel RdRp-genotypes were categorized according to whether they were involved or uninvolved in an increase in the observed proportion of VP1-genotypes. The rate of involvement in an increase in the observed proportion of VP1-genotypes was compared between the seasons with and without acquisition of novel RdRp-genotypes by Fisher's exact test.

## 3. Results

### 3.1. Correlation between the observed frequency in the IASR and the number of nucleotide sequences in the INSD

The nucleotide sequences for 2673 GI and 18,850 GII strains that were isolated from season 2006/2007 to 2019/2020 and VP1-genotyped were classified according to the isolation season and the VP1-genotype (supplementary Table S5). In the scatter plot generated using the observed frequency in the IASR (supplementary Table S1) and the number of nucleotide sequences in the INSD (supplementary Table S5) for individual VP1-genotypes in each season, the correlation coefficient was 0.357 for GI strains ( $P = 3.10 \times 10^{-4}$  by the  $t$  test) and 0.807 for GII strains ( $P = 1.07 \times 10^{-36}$ ) (supplementary Fig. S1). In addition, when the observed frequency and the number of nucleotide sequences were converted into proportions, the correlation coefficient became 0.264 for GI strains ( $P = 8.64 \times 10^{-3}$ ) and 0.907 for GII strains ( $P = 1.74 \times 10^{-59}$ ) (supplementary Fig. S2).

It should be noted that in the above analysis the correlation coefficient may be overestimated because the nucleotide sequences for the NoV strains that were isolated for obtaining the observed frequencies of VP1-genotypes in the IASR may be deposited in the INSD. To avoid this problem, the nucleotide sequences for the NoV strains isolated in Japan as well as those with unknown geographical origin were discarded, and the nucleotide sequences for 2615 GI and 17,311 GII strains were classified according to the isolation season and the VP1-genotype (supplementary Table S6). In the scatter plot generated using the observed



**Fig. 1.** Scatter plot generated using the observed proportion in the IASR (abscissa) and the relative number of nucleotide sequences in the INSD (ordinate) for individual VP1-genotypes in each season for GI and GII strains. In Japan, the observed frequencies of VP1-genotypes have been reported in the IASR from season 2006/2007 to 2019/2020. For the VP1-genotypes with the sum of the observed frequencies over the entire period greater than ten, the observed frequencies were converted into the observed proportions in each season for GI and GII strains. In addition, nucleotide sequences containing ORF2 for GI and GII strains of NoV were retrieved from the INSD. After discarding the nucleotide sequences isolated in Japan as well as those with unknown geographical origin, the VP1-genotype was determined for the nucleotide sequences of 2615 GI and 17,311 GII strains that were isolated from season 2006/2007 to 2019/2020. The numbers of nucleotide sequences for individual VP1-genotypes were converted into the relative numbers in each season for GI and GII strains. The correlation coefficient was 0.232 for GI strains ( $P = 2.13 \times 10^{-2}$  by the  $t$  test) and 0.900 for GII strains ( $P = 4.50 \times 10^{-57}$ ).

**Table 1**

The  $2 \times 2$  contingency tables for the numbers of seasons with or without acquisition of novel RdRp-genotypes and involved or uninvolved in an increase in the proportion of VP1-genotypes setting the threshold value to be 0.05, 0.10, or 0.15.

| Threshold <sup>a</sup> | GI    |       |       | GII   |       |       |
|------------------------|-------|-------|-------|-------|-------|-------|
|                        | >0.05 | ≤0.05 | Total | >0.05 | ≤0.05 | Total |
| With acquisition       | 4     | 3     | 7     | 9     | 15    | 24    |
| Without acquisition    | 31    | 23    | 54    | 17    | 82    | 99    |
| Total                  | 35    | 26    | 61    | 26    | 97    | 123   |
| Threshold              | >0.10 | ≤0.10 | Total | >0.10 | ≤0.10 | Total |
|                        |       |       |       |       |       |       |
| With acquisition       | 2     | 5     | 7     | 9     | 15    | 24    |
| Without acquisition    | 21    | 33    | 54    | 13    | 86    | 99    |
| Total                  | 23    | 38    | 61    | 22    | 101   | 123   |
| Threshold              | >0.15 | ≤0.15 | Total | >0.15 | ≤0.15 | Total |
|                        |       |       |       |       |       |       |
| With acquisition       | 0     | 7     | 7     | 6     | 18    | 24    |
| Without acquisition    | 18    | 36    | 54    | 12    | 87    | 99    |
| Total                  | 18    | 43    | 61    | 18    | 105   | 123   |

<sup>a</sup> The VP1- and RdRp-genotypes were determined for the nucleotide sequences of 572 GI and 4770 GII strains retrieved from the INSD. The dually genotyped sequences were classified according to the isolation season and the VP1-genotype, for identifying the RdRp-genotypes combined with individual VP1-genotypes in each season as well as the seasons in which acquisition of novel RdRp-genotypes occurred in individual VP1-genotypes. For each of the seasons with or without acquisition of novel RdRp-genotypes (season  $t$ ), the observed proportion of VP1-genotypes ( $p_t$ ) was compared with those in seasons  $t-1$  ( $p_{t-1}$ ) and  $t+1$  ( $p_{t+1}$ ). Season  $t$  was considered to be involved in an increase in the observed proportion of VP1-genotypes if  $p_t - p_{t-1}$  or  $p_{t+1} - p_t$  exceeded a threshold value (0.05, 0.10, or 0.15). All of the seasons with or without acquisition of novel RdRp-genotypes were categorized according to whether they were involved or uninvolved in an increase in the observed proportion of VP1-genotypes.

frequency in the IASR (supplementary Table S1) and the number of nucleotide sequences in the INSD (supplementary Table S6) for individual VP1-genotypes in each season, the correlation coefficient was 0.324 for GI strains ( $P = 1.15 \times 10^{-3}$ ) and 0.805 for GII strains ( $P = 1.71 \times 10^{-36}$ ) (supplementary Fig. S3). In addition, when the observed frequency and the number of nucleotide sequences were converted into

proportions, the correlation coefficient became 0.232 for GI strains ( $P = 2.13 \times 10^{-2}$ ) and 0.900 for GII strains ( $P = 4.50 \times 10^{-57}$ ) (Fig. 1). These results suggested that the observed frequency in the IASR and the number of nucleotide sequences in the INSD were positively correlated. The correlation was stronger in GII strains than in GI strains, which may be because the observed frequency and the number of nucleotide sequences were greater and thus subject to smaller stochastic errors in GII strains than in GI strains.

### 3.2. Effect of recombinations on changes in genotype proportions between norovirus seasons in Japan

The VP1- and RdRp-genotyped sequences for 572 GI and 4770 GII strains were classified according to the isolation season and the VP1-genotype, for identifying the seasons in which acquisition of novel RdRp-genotypes occurred in individual VP1-genotypes (supplementary Table S8). All of the seasons with or without acquisition of novel RdRp-genotypes were categorized according to whether they were involved or uninvolved in an increase in the observed proportion of VP1-genotypes setting the threshold value to be 0.05, 0.10, or 0.15. When the threshold value was set to be 0.05, the rate of involvement in an increase in the observed proportion of VP1-genotypes was significantly greater in the seasons with acquisition of novel RdRp-genotypes than in the seasons without acquisition in GII strains ( $P = 0.0478$ ) (Table 1).

In contrast, the rate was not significantly different between the seasons with and without acquisition of novel RdRp-genotypes in GI strains (Table 1), which may be because the observed frequency and the number of nucleotide sequences were relatively small and thus subject to relatively large stochastic errors, so that the seasons with or without acquisition of novel RdRp-genotypes and involved or uninvolved in an increase in the observed proportion of VP1-genotypes may not be identified correctly.

Similar results were obtained when the threshold value was set to be 0.10, in which the rate was significantly greater in the seasons with acquisition of novel RdRp-genotypes than in the seasons without acquisition in GII strains ( $P = 0.0139$ ) (Table 1). However, the statistical significance disappeared when the threshold value was set to be 0.15, due to a reduction in the number of seasons involved in an increase in the observed proportion of VP1-genotypes (Table 1).

Additionally, a similar analysis was conducted for examining

whether acquisition of novel RdRp-genotypes was associated with a decrease in the observed proportion of VP1-genotypes, setting the threshold value to be  $-0.05$ ,  $-0.10$ , or  $-0.15$ . However, the rate of involvement in a decrease in the observed proportion of VP1-genotypes was not significantly different between the seasons with and without acquisition of novel RdRp-genotypes in GI and GII strains (supplementary Table S9). These results suggested that acquisition of novel RdRp-genotypes was associated with an increase in the proportion of VP1-genotypes in GII strains.

#### 4. Discussion

In the present study, the effect of recombinations on changes in the proportions of VP1 genotypes between NoV seasons in Japan was examined through the analysis of the observed frequencies of VP1-genotypes reported in the IASR and the nucleotide sequences of NoV strains deposited in the INSD. It was found that the observed frequency in the IASR and the number of nucleotide sequences in the INSD were positively correlated, suggesting that the abundance of nucleotide sequences in the INSD may reflect the prevalence of NoV strains in humans. Thus, the relative number of nucleotide sequences in the INSD may be used as a proxy for the proportion of NoV strains in humans when the number of nucleotide sequences is relatively large (Luksha and Lassig, 2014; Suzuki, 2015).

In addition, it was found that acquisition of novel RdRp-genotypes was associated with an increase in the proportion of VP1-genotypes in GII strains. This may be because the fitness effect of a relatively large alteration in the amino acid sequence of RdRp accompanied by a change in the RdRp-genotype may be greater than that of a relatively small alteration unaccompanied by a change in the RdRp-genotype (Lindsmith et al., 2011), so that an increase in the proportion of VP1-genotypes may be more evident with acquisition of novel RdRp-genotypes than without acquisition when progeny strains survive. The fitness effect may be related to the function or the antigenicity of RdRp. However, in the previous study for predicting the proportions of VP1-genotypes, the prediction accuracy was not improved by incorporating the herd immunity against NS and VP2 in addition to VP1 (Suzuki et al., 2016, 2019), supporting the idea that VP1-derived virus-like particles (VLP) and VP1-P domain-derived P-particles may be suitable as vaccines (Hansman et al., 2006; Kocher and Yuan, 2015). These results suggested that the fitness effect derived from acquisition of novel RdRp-genotypes may be related to the function of RdRp.

#### 5. Conclusions

In conclusion, recombinations creating strains with novel combinations of VP1- and RdRp-genotypes may be an adaptive mechanism for NoV. Therefore, acquisition of novel RdRp-genotypes may be an indicator of an increase in the proportion of VP1-genotypes, which may be instructive in predicting the proportions of VP1-genotypes in NoV.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mgene.2021.100934>.

#### Declaration of Competing Interest

The author declares no conflict of interest.

#### Acknowledgements

The author thanks anonymous reviewers for valuable comments. This work was supported by JSPS KAKENHI Grant Number JP19K12221 and AMED Grant Number JP20fk0108120h0701 to Y.S.

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