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# Unusual BA222-like strains of *Rotavirus A* (Sedoreoviridae: Rotavirus: Rotavirus A): molecular and genetic analysis based on all genome segments

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### Abstract

Introduction. Rotavirus infection is the major cause of severe dehydrating diarrhea requiring hospitalization in young children worldwide. Due to their segmented genome, rotaviruses are capable of gene reassortment, which makes the emergence and spread of genetically novel strains possible. The purpose of this study was to search for unusual rotaviruses circulating in Nizhny Novgorod in 2021-2023 and their molecular genetic characterization based on all genome segments.

Materials and methods. Rotavirus-positive stool samples of children were examined by PCR genotyping and electrophoresis in PAAG. cDNA fragments of each of the 11 genes (VP1-VP4, VP6, VP7, NSP1-NSP5), 570 to 850 nucleotide pairs in length were sequenced for the selected strains. The phylogenetic analysis was performed in the MEGA X program.

Results. In the study period 2021-2023, 11 G[P] combinations with a predominance of G3P[8] (59.5%) were identified. Six atypical Rotavirus A (RVA) strains were identified: 2 strains of the G2P[4] genotype (G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E2-H3, G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E3-H2) and 4 G3P[9] strains (all strains had the genotype G3-P[9]-I2-R2-C2-M2-A3-N2-T3-E3-H3). Phylogenetic analysis based on all genes showed an evolutionary relationship between rotaviruses similar to rotaviruses of cats and dogs (BA222-like) and unusual strains of the G2P[4] genotype, for which a mixed combination of genotypes was identified and characterized for the first time. Discussion. The results obtained expand the understanding of the diversity of reassortant RVAs, as well as complement the data on the genotypic structure of the rotavirus population in Nizhny Novgorod.

Conclusion. The wide genetic diversity of reassortant RVA can help rotaviruses overcome the immunological pressure provided by natural and vaccine-induced immunity. In this regard, to control the emergence of new variants and assess changes in the virulence of rotaviruses after reassortment processes, continuous molecular monitoring for circulating RVA is necessary.

Keywords: Rotavirus A; genotyping; full genotype; phylogenetic analysis; genetic variants; genetic diversity; reassortment

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### ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

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# Необычные BA222-подобные штаммы Rotavirus A (Sedoreoviridae: Rotavirus: Rotavirus A): молекулярно-генетический анализ на основе всех сегментов генома

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### Резюме

**Введение.** Ротавирусная инфекция является основной причиной тяжелых дегидратирующих диарей, требующих госпитализации, у детей младшего возраста во всем мире. Благодаря сегментированному геному ротавирусы способны к реассортации генов, что делает возможным появление и распространение генетически новых штаммов.

**Цель исследования –** поиск необычных ротавирусов, циркулировавших в Нижнем Новгороде в 2021–2023 гг., и их молекулярно-генетическая характеристика на основе всех сегментов генома.

**Материалы и методы.** Ротавирус-положительные образцы стула детей исследовали методами ПЦР-генотипирования и электрофореза в полиакриламидном геле. Для отобранных штаммов были секвенированы фрагменты комплементарной ДНК каждого из 11 генов (VP1–VP4, VP6, VP7, NSP1–NSP5) длиной от 570 до 850 пар нуклеотидов. Филогенетический анализ проводили в программе MEGA X.

Результаты. В исследуемый период 2021–2023 гг. было идентифицировано 11 G[P]-комбинаций с преобладанием G3P[8] (59,5%). Выявлено 6 нетипичных штаммов ротавируса А (PBA): 2 штамма генотипа G2P[4] (G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E2-H3, G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E3-H2) и 4 штамма G3P[9] (все штаммы имели генотип G3-P[9]-I2-R2-C2-M2-A3-N2-T3-E3-H3). Филогенетический анализ на основе всех генов показал эволюционное родство между ротавирусами, подобными ротавирусам кошек и собак (BA222-подобными), и необычными штаммами генотипа G2P[4], для которых смешанная комбинация генотипов была выявлена и охарактеризована впервые.

Заключение. Полученные результаты расширяют представления о разнообразии реассортантных PBA, а также дополняют данные о генотиповой структуре популяции ротавирусов на территории Нижнего Новгорода. Результаты исследования в совокупности с полученными ранее данными расширяют представление о генетическом разнообразии ротавирусов и роли реассортантов в его поддержании, что важно для создания новых ротавирусных вакцин и понимания эволюционных процессов в популяции PBA.

Ключевые слова: ротавирус А; генотипирование; полный генотип; филогенетический анализ; генетическое разнообразие; реассортанты

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Локальным этическим комитетом ФБУН «Нижегородский НИИ эпидемиологии и микробиологии им. академика И.Н. Блохиной» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека (Роспотребнадзор) (Протокол № 6 от 24.03.2021).

### Introduction

Currently, most intestinal infections of established etiology are caused by viral pathogens. The spectrum of intestinal viruses is very diverse, but the leading cause of incidence among children is Rotavirus A (RVA, *Ro*- *tavirus* genus, *Sedoreoviridae* family, *Reovirales* order, *Resentoviricetes* class, *Duplornaviricota* type). Rotavirus infection (RVI) accounts for approximately 228,000 deaths worldwide each year, including approximately 128,500 among children under 5 years of age [1, 2].

The greatest burden of RVI is among children living in low- and middle-income countries, especially because of unfavorable living conditions, limited supply of clean drinking water and poor sanitation [3]. In Russia, despite the annually increasing number of children vaccinated against RVI, the vaccination coverage of the target cohort remains extremely low to influence the epidemic process (2020 – 3.68%; 2021 – 6.23%; 2022 – 7.15%; 2023 – 12.7%) [4, 5].

A distinctive feature of rotaviruses (RVs) is a segmented genome consisting of 11 segments of doublestranded RNA with a total length of about 18,555 nucleotides encoding 6 structural (VP1-VP4, VP6-VP7) and 6 non-structural (NSP1–NSP6) proteins [6–8]. RVs are characterized by a wide antigenic and genetic diversity. The VP4 and VP7 genes have been most fully characterized, on the basis of which G- and P-genotypes are determined using binary classification [9]. To date, 42 G-genotypes and 58 P-genotypes are known for RVA [10]. The most common in the world, including Russia, are considered to be 6 combinations of G[P]-types of RVA: G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P[8], which account for approximately 90% of cases of RVA infection [11, 12]. The number of less common G[P]-variants is much larger, but they account for only 4.9% of infections. For example, they include such genotypes as G9P[4], G9P[9], G8P[8], G2P[8], G4P[4], G3P[9], and others [13–16].

The binary classification system focuses only on the VP4 and VP7 gene segments and does not provide information on the diversity of other genes. Therefore, to better understand the epidemiology and evolution of RV, a full-genome classification system was proposed to assign each segment of the virus genome to a specific genotype. To describe the complete genotype, the label Gx-P[x]-Ix-Rx-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx is used for genes encoding VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5/NSP6 proteins, respectively [17]. Determination of the complete genotype facilitates the detection of rare and unusual RVA and provides a better understanding of the origin and diversity of strains, which, in turn, is important for successful prediction of the epidemic situation and assessment of the impact of vaccine prophylaxis on the pathogen population.

Based on whole-genome typing, 3 genetic groups are distinguished among RVAs. Worldwide, the frequently occurring combinations of G1, G3, G4, G9, G12, and P[8] are usually associated with the Wa-like (1st) genetic (G1/G3/G4/G9-P[8]-I1-R1-C1-M1-A1-N1group T1-E1-H1), which is distantly related to porcine RVs [18, 19]. Such RVs are characterized by a long migration profile of genome segments in polyacrylamide gel electrophoresis (PAGE). G2P[4] genotype strains, in turn, belong to the DS-1-like (2nd) genetic group (G2-P[4]-I2-R2-C2-M2-A2-N2-T2-E2-H2), evolutionarily related to bovine RVs [17, 19]. They have a short genomic segment migration profile. There is a 3rd, minor, AU-1-like genetic group (G3P[9]-I3-R3-R3-C3-M3-A3-A3-N3-T3-E3-H3), which includes strains similar to cat and dog RVs characterized by a broad segment migration profile

[20, 21]. Strains with a pure AU-1-like combination are rarely found in humans, while variants with a mixed set of AU-1-like and DS-1-like genes are more common. They are usually assigned to a separate group, the prototype for which is RVA strain VA222 (G3-P[9]-I2-R2-R2-C2-C2-M2-A2-A3-N1-T3-E2-H3) isolated from a domestic cat in Italy in 2005 [22, 23].

The presence of a segmented genome determines the ability of RV to exchange segments (reassortment) when two or more strains simultaneously infect a cell, which allows genes with different specificity to group independently of each other, thus maintaining diversity in the population. The spread of epidemically significant reassortant strains of RVA, which carry genetic material of several genetic groups, has been increasingly observed worldwide [9, 24, 25].

In this regard, the **aim of this study** was to search for unusual RVs in Nizhny Novgorod and their molecular genetic characterization based on all genome segments.

# Materials and methods

Stool samples from children hospitalized in a children's infectious disease hospital in Nizhny Novgorod with symptoms of acute intestinal infection in the period 2021–2023 were used.

Nucleic acid extraction and polymerase chain reaction (PCR) with reverse transcription (RT-PCR) were performed using RIBO-prep and REVERTA-L reagent kits (Central Research Institute of Epidemiology of Rospotrebnadzor (CRIE), Russia). Rotavirus RNA was detected using AmpliSense Rotavirus/Norovirus/Astrovirus FL and AmpliSense Viro-Screen-FL real-time PCR test systems (CRIE). Additionally, viral RNA was analyzed by polyacrylamide gel electrophoresis (RNA-PAAG) [26].

G[P]-genotype of RV was determined by multiplex PCR based on primers specific for genotypes G1–G4, G6, G8, G9, G12, P[4], P[6], P[8], and P[9] [26–32]. Results were detected by electrophoresis in agarose gel containing ethidium bromide.

For each gene, one complementary DNA (cDNA) fragment of 570 to 850 nucleotide pairs in length was obtained using primers published previously [32]. The cDNA fragments were sequenced along two strands using forward and reverse primers on a Nanofor 05 instrument (Institute of Analytical Instrumentation (IAP), Russian Academy of Sciences, Russia) using the BigDye Terminator v3.1 sequencing kit (Thermo Fisher Scientific, USA). Nucleotide sequences are available in the GenBank database under the numbers PP475712–PP475777.

The search for related sequences was performed using the BLAST online service. For phylogenetic analysis, nucleotide sequences of 11 RV genes circulating in different countries, including Russia (Novosibirsk, Omsk and Moscow), as well as RV sequences from Nizhny Novgorod obtained earlier, were retrieved from GenBank. The GenBank registration numbers of these strains are given in the names of the isolates on the phylogenetic trees. Nucleotide sequence alignment and analysis were performed in the MEGA X program

version 10.0.5. Phylogenetic trees were constructed using the Maximum Likelihood method [33, 34]. Bootstrap analysis was performed based on 1000 random samples. The percentages of nucleotide sequence similarity were calculated using the Pairwise Distances method. The affiliation of the studied strains to phylogenetic lineages and sublineages was determined based on clustering of isolates on phylogenetic trees with a node support index of more than 75 and a high level of nucleotide sequence similarity (98.5–100.0% for different genes). Phylogenetic lineages and sublineages were designated according to the classification accepted in the literature [32, 35–40].

The study protocol was approved by the Local Ethical Committee of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare (Rospotrebnadzor) (Protocol No. 6 of 24.03.2021).

### Results

### Characterization of the spectrum of G[P]-genotypes of RVA in Nizhny Novgorod

A total of 3715 stool samples from children hospitalized in an infectious disease hospital with symptoms of acute gastroenteritis between 2021 and 2023 were examined for the presence of rotavirus RNA. In 1085 cases (29.2%), RV RNA was detected, which was further used for G/[P]-genotyping by RT-PCR and/or sequencing. In 792 samples (72.9%), the G[P]-genotype of RV was determined. In 192 samples (17.7%), the G- or P-genotype was partially determined. The results of genotyping carried out on two genes (VP4 and VP7) showed that RVAs circulating in Nizhny Novgorod were characterized by high diversity. The spectrum of RV G-genotypes identified by PCR included 4 widely spread in the world (G1, G2, G3 and G9), and 2 rare for Russia (G6 and G8). The set of P-genotypes included 4 types, among which were frequently occurring P[4], P[8], and rare P[6] and P[9]. A total of 11 G/P combinations were detected:



- **Fig. 1.** Distribution of RVA strains of the main G[P]-genotypes in Nizhny Novgorod in the season 2021–2023 (in %).
- Рис. 1. Распределение штаммов РВА основных G[P]-генотипов в Нижнем Новгороде в сезон 2021–2023 гг. (в %).

widespread G3P[8], G9P[8], G2P[4], G1P[8], and rare G8P[8], G3P[9], G9P[4], G3P[6], G2P[8], G6P[9] and G3P[4] (**Fig. 1**).

The dominant position during the study period was occupied by strains of the G3P[8] genotype (59.5%), followed by strains of the G9P[8] genotype (10.8%). The other genotypes showed low share contribution: G9P[4] - 2.1%, G1P[8] - 1.3%, G2P[4] - 1.6%, G3P[4]-1.3%, G8P[8]-1.1%, G3P[6]-0.8%, G3P[9]-1.0%, G2P[8] - 0.8%, G6P[9] - 0.1%.

# Identification of reassortant rotaviruses and determination of their complete genotypes

Examination of RVA-containing samples by RNA-PAGE revealed 6 strains (2 strains of genotype G2P[4] and 4 strains of genotype G3P[9]) that exhibited so-called broad (AU-1-like) genomic segment migration profiles in PAGE (slowly migrating segment 5, rapidly migrating segments 6 and 11) (**Fig. 2**).

Strains were sequenced for 11 genes (VP1-VP4, VP6, VP7, NSP1-NSP5/6) to determine their complete genotypes: G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E2-H3, G2-P[4]-I2-R2-C2-M2-A3-N2-T3-E3-H2  $\mu$  G3-P[9]-I2-R2-C2-M2-A3-N2-T3-E3-H3. The studied strains had a mixed set of genes from two different genetic groups, DS-1-like (genotypes numbered 2) and AU-1-like (genotypes numbered 3), indicating their reassortant origin.

# Phylogenetic analysis of rotaviruses based on all genome segments

The nucleotide sequences of 11 genes were used to study the phylogenetic relationships of the 6 identified RV genotypes G2P[4] and G3P[9]. Phylogenetic analysis allowed us to study the intragenotype diversity of the studied strains at the lineage and sublineage level. The adapted trees are shown in **Fig. 3**, **4**.

For each gene, the studied strains were included in 1 or 2 clusters. The genes *VP4*, *VP7*, *NSP4* and *NSP5/6* showed the highest diversity (**Table**).

# Strains similar to feline rotavirus BA222

The 4 strains of genotype G3P[9] identified in this study belonged to a group of RVs similar to strain VA222 isolated from a cat. These strains (2853/21, 2885/21, 347/22, and 2619/21) were similar in 9 genes (*VP1–VP4*, *VP6*, *VP7*, *NSP1*, *NSP3*, *NSP5/6*) to the prototypical RV strain VA222, but differed from it in the *NSP2* and *NSP4* genes, which possessed other genotypes. The highest level of nucleotide sequence similarity was found for the *VP2*, *VP3*, *VP7*, *NSP1*, *NSP3*, and *NSP5/6* genes and amounted to 98.7–100.0%. A lower level of homology was shown for *VP1*, *VP4* and *VP6* genes, ranging from 96.3–98.1%.

Also, the studied strains were related to the Nizhny Novgorod VA222-like RV genotypes G3P[9] (NN148/17, NN2748/18) and G6P[9] (NN1061-16) detected earlier, in 2016–2018. With isolates of genotype G3P[9] (NN148/17 and NN2748/18), the tested strains had a high level of nucleotide sequence homology for all 11 genes (99.1–100.0%). The strain of genotype G6P[9] (NN1061/16) showed the closest affinity

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for 8 genes (*VP1–VP4*, *NSP1–NSP3*, *NSP5/6*) with a level of nucleotide sequence similarity of 98.7–100.0%. A lower level of similarity was established for the *VP6* gene (96.0%). The *VP7* and *NSP4* genes had a different genotype.

# Atypical strains of the G2P[4] genotype

The two RVA strains of genotype G2P[4] (1473/21 and 2924/21) identified in the present work had a mixed set of genes. They carried a VA222-like base, while the *VP4*, *VP7* genes and in one case the *NSP5/6* gene were obtained as a result of reassortment from typical representatives of the DS-1-like genetic group.

The most closely related by divergent genes (VP4, VP7 and in one case NSP5/6) were strains of genotype G2P[4] from Nizhny Novgorod identified earlier in 2018 (NN560/18, NN96/18 and NN425/18). The level of nucleotide sequence similarity was quite high at 98.7–99.9%.

The rest of the genes (*VP1–VP3*, *VP6*, *NSP1–NSP5/6*) were closely related to the VA222-like group of RVs. Directly with prototypic VA222, samples 1473/21 and 2924/21 were most related to the prototypic VA222 by 3 genes: *VP2*, *NSP3*, *NSP4* and *VP2*, *VP3*, *NSP3*, respectively. The nucleotide sequence similarity in the case of these genes reached 98.6–99.8%, while for the other genes it was lower, 95.2–97.6%.

The relatedness of the studied strains of genotype G2P[4] with the Nizhny Novgorod RVs of genotypes G3P[9] G6P[9] (NN1061/16, and NN148/17, NN2748/18), identified earlier, was also established for all VA222-like genes. Thus, the studied strain 1473/21 shared the highest number of genes (8 out of 11) with strain NN148/17 (G3P[9]) (VP1-VP3, VP6, NSP1-NSP3, NSP5/6), showing high nucleotide sequence similarity, 99.1-99.9%. It shared 7 genes (VP1-VP3, NSP2-NSP5/6) with strain NN1061/16 (G6P[9]) with a nucleotide sequence similarity level of 98.6-99.8%. Five genes were related to those of strain NN2748/18 (G3P[9]) (VP1, VP2, VP6, NSP2, NSP3). The homology of their nucleotide sequence was estimated at 98.7-99.7%.

Similarly, strain2924/21 had close phylogenetic relatedness with strain NN148/17 (G3P[9]) for 8 genes (*VP1–VP3*, *VP6*, *NSP1–NSP4*), showing high nucleotide sequence similarity of 98.8–99.8%. With strain NN2748/18 (G3P[9]), it shared 6 genes (*VP1–VP3*, *VP6*, *NSP2*, *NSP3*) with a homology level of 98.5–99.5%. In the case of strain NN1061/16 (G6P[9]), it showed close affinity for 5 genes (*VP1–VP3*, *NSP2*, *NSP3*) with a high level of nucleotide sequence similarity, 99.1–99.8%.

### Discussion

This paper characterizes the diversity of RVA genotypes circulating in Nizhny Novgorod in 2021–2023. The spectrum is represented by 11 types dominated by G3P[8] (59.5%), followed by G9P[8] (10.8%). By June 2021, there was a decrease in the proportion of G9P[8] genotypes in the Nizhny Novgorod RV population, with a subsequent change of the dominant genotype to G3P[8] in July 2021. [41]. The data obtained serve as an addition





- \* an unusual position of the segment relative to typical representatives of DS- and Wa-like gene groups.
- Рис. 2. Профили миграции сегментов днРНК типичных представителей DS-1-/Wa-подобных ротавирусов и исследуемых штаммов генотипов G2P[4] и G3P[9] в ПААГ.

 необычное положение сегмента относительно типичных представителей DS- и Wa-подобных геногрупп.

to the information on genetic rearrangements in the RV population during their long-term circulation in Nizhny Novgorod, observations of which have been carried out since 1984 [13, 26, 32, 40–44].

The presented results also supplement the available data on the genotype structure of RV populations in Russia. According to the data of the reference center of monitoring for acute intestinal infections, in the winterspring period of 2021 in the territory of the Russian Federation (Moscow, Tomsk, Irkutsk, Sverdlovsk, Novosibirsk regions, the Republic of Dagestan, Khabarovsk Territory and Kamchatka Territory), the dominance of the G9P[8] genotype remained, but a gradual increase in the proportion of the G3P[8] genotype was already observed. In 2022, there was a significant

Genome segments / Сегменты генома Strains № Штаммы VP4 VP7 VP6 VP1 VP2 VP3 NSP1 NSP2 NSP3 NSP4 NSP5/6 Feline-like strains / Штаммы, подобные PB кошек 1 BA222 G3-3-e P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N1 T3 E2-XVII H3 2 NN1061/16 G6-I P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI Т3 E2-XVII H3 3 NN148/17 G3-3-e P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 E3 H3 NN2748/18 G3-3-e P[9] I2-XIV M2-XI N2-XVI Т3 4 R2-XIII C2-IX A3 E3 H3 Typical DS-1-like strains / Типичные Ds-1-подобные штаммы 5 NN96/18 G2-IVa-3 P[4]-IV-b I2-V-1 R2-V-1 C2-IVa-1 M2-VII A2-IVa-1 N2-V-1 T2-V-1 E2-VI H2-IVa-1 6 NN425/18 G2-IVa-3 P[4]-IV-b I2-V-1 R2-V-1 C2-IVa-1 M2-VII A2-IVa-1 N2-V-1 T2-V-1 E2-VI H2-IVa-1 7 NN437/18 G2-IVa-1 P[4]-IV-b I2-V-1 R2-V-1 C2-IVa-1 M2-VII A2-IVa-1 N2-V-1 T2-V-1 E2-VI H2-IVa-1 C2-IVa-2 8 NN560/18 G2-IVa-2 P[4]-IV-a I2-V-2 R2-V-2 M2-V A2-IVa-2 N2-V-2 T2-V-2 E2-VII H2-IVa-2 Strains obtained in this work / Штаммы, полученные в данной работе 9 2853/21 G3-3-e P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 E3 H3 10 2885/21 G3-3-e P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 E3 H3 347/22 G3-3-e P[9] I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 E3 H3 11 G3-3-e M2-XI E3 2619/22 P[9] I2-XIV R2-XIII C2-IX A3 N2-XVI **T**3 H3 12 1473/21 E2-XVII H3 13 G2-IVa-3 P[4]-IV I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 14 2924/21 G2-IVa-3 P[4]-IV I2-XIV R2-XIII C2-IX M2-XI A3 N2-XVI T3 E3 H2-IVa

 Table. Subgenotype-level genomic constellations of rotaviruses from Nizhny Novgorod

 Таблица. Геномные констелляции ротавирусов Нижнего Новгорода на уровне субгенотипов

Note. The studied strains are highlighted in bold. DS-1-like alleles are marked in red, alleles of RV cats are blue, and Wa-like alleles are green.

*Примечание.* Исследуемые штаммы выделены жирным шрифтом. Красным цветом отмечены DS-1-подобные аллели, голубым – аллели PB кошек, зеленым – Wa-подобные аллели.

decrease in the frequency of occurrence of the G9P[8] genotype and the prevalence of the G3P[8] genotype was shown to prevail in the RV circulation in the territory of the Russian Federation, which remained in 2023. [4, 5]. This information is consistent with the data obtained in the present study.

RVs of the G3 genotype of the VP7 gene have a wide host range and are found in most susceptible animal species (including humans, rabbits, monkeys, pigs, birds, cats, dogs, horses, mice, cows and lambs) [7, 45, 46]. In human  $\overline{RV}$ , it is mostly associated with the  $\overline{P[8]}$  genotype of the VP4 gene, but is less frequently found in combination with the P[9] genotype [47–49]. The G3P[9] combination is prevalent mainly in RVs of cats and dogs [50], but due to reassortment, strains similar to animal RVs can occur in humans [51]. RVs of genotype G3P[9] were first detected in humans in 1982 in Japan and Israel [17, 22, 52]. Later, their appearance was registered in Thailand and Spain [53–59]. In the territory of Nizhny Novgorod, G3P[9] strains have been sporadically observed in the population since 1984. In early studies, they were studied on the basis of single genes (VP4, VP6, VP7, NSP4) [60, 61]; the first study of these strains on the basis of all genome segments was conducted in 2023 [40].

G3P[9] RVs are sporadically found in humans, forming a separate genetic group, isolated from Wa-like and DS-1-like viruses [49, 59, 62–64]. For human G3P[9], the possibility of at least 8 different combinations of complete genotypes has been shown: G3-P[9]-I3-R3-C3-M3-A3-N3-N3-T3-E3-H3 [9, 17], G3-P[9]-I3-R3-C3-M3-A3-N3-T3-E3-H6 [16, 22, 51], G3-P[9]-I2-R2-C2-M2-A3-N2-T1-E2-H3 [46, 52], G3-P[9]-I2-R2-C2-M2-A3-N1-T6-E2-H3, G3-P[9]-I2-R2C2-C2-M2-A2-A3-N2-N2-T6-E2-H3 [65], G3-P[9]-I2-R2-C2-C2-M2-A2-A3-N1-T3-E2-H3 [66, 67], G3-P[9]-I3-R3-C2-C2-M3-A3-N1-T6-E3-H3 [68, 69], and G3-P[9]-I2-R2-C2-M2-A2-A3-N2-T3-E3-H3 [68, 70]. Interestingly, the NSP1 gene of all G3P[9] strains of animal and human origin invariably possesses the A3 genotype, whereas the genotype of the other genes can vary (VP6 - I2/I3; VP1 - R2/R3; VP2 - C2/C3; VP3 - M2/M3; NSP2 - N1/N2/N3; NSP3 - T1/T3/T6; NSP4 - E2/E3; NSP5/6 - H3/H6).

The G3P[9] RVAs identified and investigated in the present study possessed a combination of G3-P[9]-I2-R2-C2-M2-M2-A3-N2-T3-E3-H3 genotypes. Phylogenetic analysis showed that they shared 9 genes (*VP1–VP4*, *VP6*, *VP7*, *NSP1*, *NSP3*, *NSP5/6*) with feline RV VA222 (Italy, 2005). Out of all of these, *VP2*, *VP3*, *VP7*, *NSP1*, *NSP3*, and *NSP5* genes had a high percentage of nucleotide sequence similarity (98.7–100.0%), while *VP1*, *VP4*, and *VP6* had a lower percentage (96.3–98.1%). The Nizhny Novgorod strains differed from type VA222 in the *NSP2* and *NSP4* genes, which possessed other genotypes.

The results obtained show close relatedness of the studied RVs with earlier strains of genotype G3P[9] from Nizhny Novgorod. In the period 2016–2018, 3 similar RVA strains of genotype G3P[9] [40] were identified and studied on the basis of all genome segments. Their nucleotide sequences were used for phylogenetic analysis in the present work. The similarity of Nizhny Novgorod G3P[9] strains of different years amounted to 99.7–100.0% for different genes.

Intergroup reassortants based on the VA222-like combination were previously found in South Korea. S. Jeong et al. (2014) investigated RVA of genotype G3P[9]





**Рис. 3.** Филогенетическое дерево, построенное на основе нуклеотидных последовательностей структурных генов (*VP1–VP4, VP6, VP7*) штаммов ротавируса А.

■ - штаммы, полученные в данной работе; □ - нижегородские штаммы, взятые из GenBank.



Fig. 4. Phylogenetic trees based on nucleotide sequences: nonstructural genes (NSP1-NSP5/6) of rotavirus strains A.

- **Рис. 4.** Филогенетическое дерево, построенное на основе нуклеотидных последовательностей неструктурных генов (*NSP1–NSP5/6*) штаммов ротавируса А.
  - – штаммы, полученные в данной работе; □ нижегородские штаммы, взятые из GenBank.

isolated in 2012 from an unvaccinated 9-year-old girl with symptoms of severe gastroenteritis. The strain studied had the genotype G3-P[9]-12-R2-C2-C2-M2-M2-A2-A3-N2-T3-E3-H3. Phylogenetic analysis showed that it shared 9 genes (*VP1–VP4*, *VP6*, *VP7*, *NSP1*, *NSP3*, *NSP5/6*) with prototype VA222 strain, with different levels of nucleotide sequence similarity. Clustering of the studied strains with typical DS-1-like human RVs was established for the *NSP2* gene, and for *NSP4* – with an Australian strain of cat and dog RVs. This strain had a complex evolutionary origin, potentially involving reassortment events between cat RVs and DS-1-like human RVs [70].

Similar data were obtained by a group of researchers from China. M. Cao et al. examined 2 strains of G3P[9] genotype isolated in 2020 and 2023 from a 12-month-old girl and a 16-month-old boy, respectively. Both strains had the combination of genotypes: G3-P[9]-I2-R2-C2-M2-M2-A3-N2-T3-E3-H3. Phylogenetic analysis established that both studied RVAs shared 8 genes (*VP1– VP4, VP7, NSP1, NSP3*, and *NSP4*) with RVAs similar to cat and dog RVAs, with varying levels of nucleotide sequence similarity (99.3–99.6%). The remaining 3 genes (*VP6, NSP2*, and *NSP5/6*) were associated with typical DS-1-like human RVs (99.3–100.0%) [68].

This study shows the circulation of unusual strains that had the genotypes G2-P[4]-I2-R2-C2-C2-M2-A2-A3-N2-T3-E2-H3 and G2-P[4]-I2-R2-C2-C2-M2-A2-A3-N2-T3-E3-H2. The VP1-VP3, VP6, NSP1, NSP3-NSP5/6 genes of one of them and VP1-VP3, VP6, NSP1, NSP3, *NSP4* genes of the other were related to the prototype strain VA222 of RVA (Italy, 2005). The remaining genes (namely VP4, VP7 and in the case of one NSP5/6 strain) originated from human DS-1-like strains of genotype G2P[4]. Strains with this combination of genotypes were identified and characterized by sequencing all genome segments for the first time. In Russia and in the world, no reports on the detection of similar G2P[4] strains have been previously noted. In all genes, both BA222 and DS-1-like, these strains had close relatives from Nizhny Novgorod, which suggests their local origin.

The reassortant strains characterized in this study could not be detected by G/[P]-genotyping by PCR, which is routinely used to study RV. This emphasizes the importance of using a full-genome classification system and modern sequencing methods to monitor the circulation of this pathogen.

# Conclusion

The results of the study in combination with previously obtained data expand the understanding of the significant genetic diversity of RV and the role of reassortants in its maintenance. This information is important for the development of new rotavirus vaccines, understanding of evolutionary processes in the RVA population, and indicates the relevance of studying the genetic evolution of rare and novel virus strains. To control the emergence of new variants, continuous molecular monitoring for circulating RVA using full genomic classification is a necessity.

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