

Identification of the novel Kawasaki 2014 GII.17 human norovirus strain in Italy, 2015

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Surveillance of noroviruses in Italy identified the novel GII.17 human norovirus strain, Kawasaki 2014, in February 2015. This novel strain emerged as a major cause of gastroenteritis in Asia during 2014/15, replacing the pandemic GII.4 norovirus strain Sydney 2012, but being reported only sporadically elsewhere. This novel strain is undergoing fast diversification and continuous monitoring is important to understand the evolution of noroviruses and to implement the future strategies on norovirus vaccines.

During the winter season 2014/15, a novel GII.P17-GII.17 norovirus (NoV) strain emerged in Asian countries [1-4]. Since its emergence, this novel NoV strain, named Kawasaki 2014, has replaced the previously dominant GII.4 genotype Sydney 2012 variant in Asia, and it has been detected in a limited number of cases on other continents [1-5]. This epidemiological trend is also reflected in the GenBank database, with the vast majority of the Kawasaki 2014 GII.17 NoV sequences generated in studies from the Asian continent.

Here we report the detection of the Kawasaki 2014 GII.17 strain during the 2014/15 winter season in Italy. As sequence information on Kawasaki 2014 GII.17 NoVs detected outside the Asian continent is limited [5], we determined the sequence of a large portion of the genome, including the full-length capsid gene of the GII.17 Kawasaki NoV strain circulating in Italy, and analysed the virus sequence with similar GII.17 NoV sequences available in the GenBank database.

Genotyping

The NoV genome contains three open reading frames (ORFs). ORF1 encodes non-structural proteins including the RNA-dependent RNA polymerase (RdRp), while ORF2 and ORF3 encode the major capsid protein VP1 and a minor structural protein VP2, respectively [6].

NoVs are classified in at least six genogroups, GI to GVI [6]. NoV genogroups are further divided in various genotypes based on differences in the RdRp region (polymerase genotype, or pol type) and in the VP1 (capsid genotype, or cap type) [7]. NoV genotyping was performed using standardised sequence analysis web-based tools developed and maintained by the NoroNet [8].

Surveillance of noroviruses in Italy

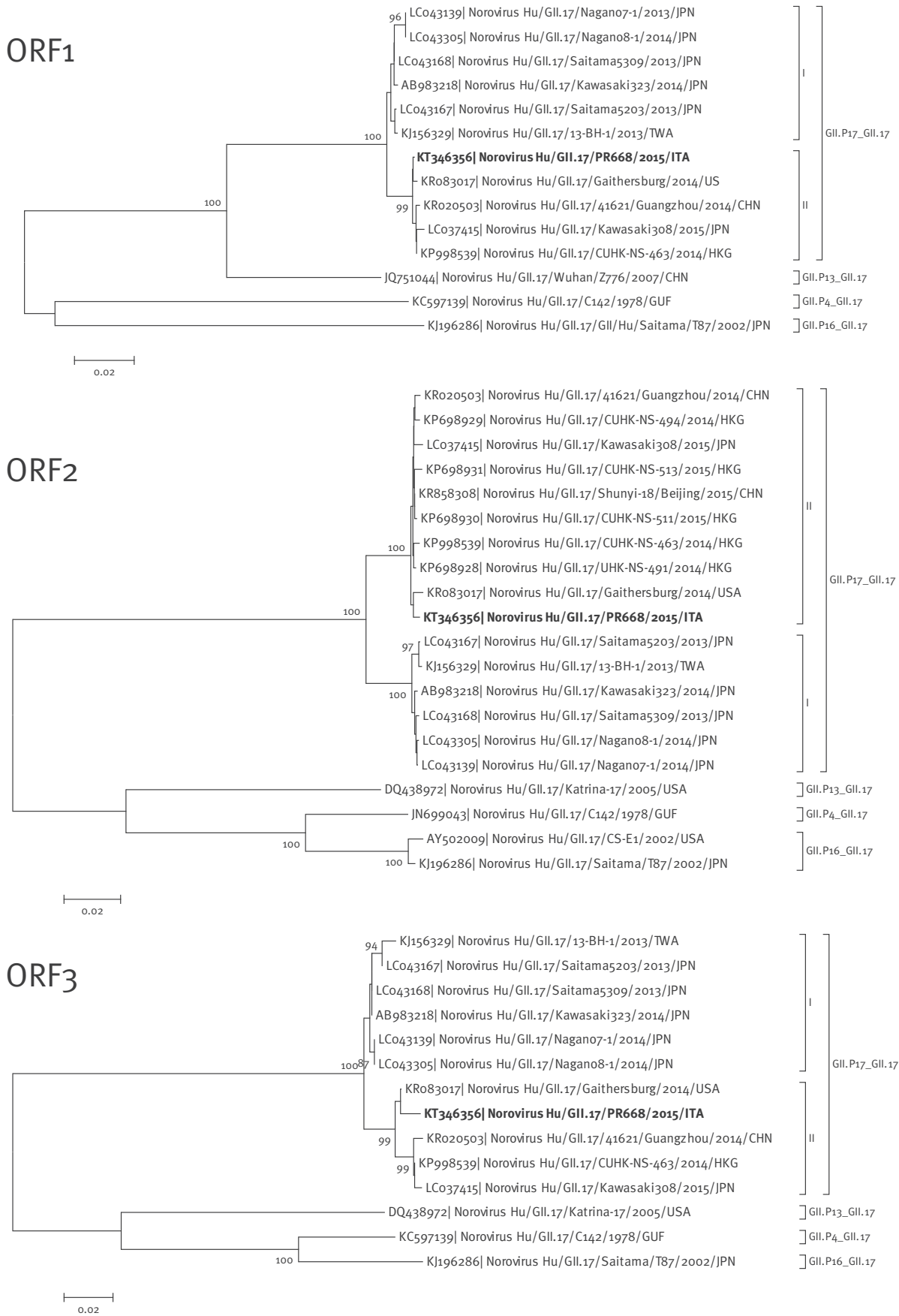
The Italian Study Group for Enteric Viruses (ISGEV; <http://isgev.net>) monitors the epidemiology of enteric viruses in children through hospital-based surveillance. A subset of about half of the NoV-positive samples is systematically genotyped in both region A (ORF1, RdRp) and region C (ORF2, capsid). From September 2014 to March 2015, NoV prevalence was 12% (137/1,144) and NoVs were typed in 81 cases (59%). GII.P17-GII.17 NoV strains were detected in two sporadic cases of acute severe gastroenteritis in young children hospitalised in February 2015 in two distinct Italian regions.

Sequence analysis

Upon direct sequencing of the RT-PCR amplicons, the two strains, PR668/2015/ITA and BA603-6/2015/ITA, were found to be identical in the short diagnostic regions A and C. We determined the sequence of a large portion (3.2 kb) of the genome at the 3' end for strain PR668/2015/ITA. Viral RNA was extracted from 140 µl of stool suspension using the QIAmp viral RNA kit (Qiagen, GmbH, Hilden, Germany). A 3'-rapid amplification of cDNA ends (RACE)-PCR protocol was used to generate the 3.2-kb amplicon encompassing the 3' end of ORF1, the full-length ORF2 and ORF3, and the 3' untranslated region (UTR) until the poly(A) tail, using the reverse primer VN3T20 [9] and the forward primer JV12Y [10]. The RACE product was cloned and the

FIGURE 1

Phylogenetic analysis based on partial ORF1, full ORF2 and full ORF3 sequences of GII.17 NoV, Italy, February 2015



The Italian GII.P17_GII.17 strain is indicated in bold. Trees were built with the maximum-likelihood method, and bootstrapped with 1,000 repetitions. Bootstrap values >80% are indicated. The scale bar indicates the number of nucleotide substitutions per site.

FIGURE 2

Amino acid substitutions in the VP1 sequence of norovirus GII.17 norovirus strains, 1978–2015

Strain	Country	Year	Amino acid number (P2 domain amino acids 279-405)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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7	4251	4255	4259	4263	4267	4271	4275	4279	4283	4287	4291	4295	4299	4303	4307	4311	4315	4319	4323	4327	4331	4335	4339	4343	4347	4351	4355	4359	4363	4367	4371	4375	4379	4383	4387	4391	4395	4399	4403	4407	4411	4415	4419	4423	4427	4431	4435	4439	4443	4447	4451	4455	4459	4463	4467	4471	4475	4479	4483	4487	4491	4495	4499	4503	4507	4511	4515	4519	4523	4527	4531	4535	4539	4543	4547	4551	4555	4559	4563	4567	4571	4575	4579	4583	4587	4591	4595	4599	4603	4607	4611	4615	4619	4623	4627	4631	4635	4639	4643	4647	4651	4655	4659	4663	4667	4671	4675	4679	4683	4687	4691	4695	4699	4703	4707	4711	4715	4719	4723	4727	4731	4735	4739	4743	4747	4751	4755	4759	4763	4767	4771	4775	4779	4783	4787	4791	4795	4799	4803	4807	4811	4815	4819	4823	4827	4831	4835	4839	4843	4847	4851	4855	4859	4863	4867	4871	4875	4879	4883	4887	4891	4895	4899	4903	4907	4911	4915	4919	4923	4927	4931	4935	4939	4943	4947	4951	4955	4959	4963	4967	4971	4975	4979	4983	4987	4991	4995	4999	5003	5007	5011	5015	5019	5023	5027	5031	5035	5039	5043	5047	5051	5055	5059	5063	5067	5071	5075	5079	5083	5087	5091	5095	5099	5103	5107	5111	5115	5119	5123	5127	5131	5135	5139	5143	5147	5151	5155	5159	5163	5167	5171	5175	5179	5183	5187	5191	5195	5199	5203	5207	5211	5215	5219	5223	5227	5231	5235	5239	5243	5247	5251	5255	5259	5263	5267	5271	5275	5279	5283	5287	5291	5295	5299	5303	5307	5311	5315	5319	5323	5327	5331	5335	5339	5343	5347	5351	5355	5359	5363	5367	5371	5375	5379	5383	5387	5391	5395	5399	5403	5407	5411	5415	5419	5423	5427	5431	5435	5439	5443	5447	5451	5455	5459	5463	5467	5471	5475	5479	5483	5487	5491	5495	5499	5503	5507	5511	5515	5519	5523	5527	5531

sequence was determined. Phylogenetic analysis was performed using MEGA v. 6.0 [11].

The 3.2-kb sequence of the Italian NoV GII.P17-GII.17 strain has been deposited in GenBank under accession number KT346356. The partial sequence of ORF1 (807 nt), and the full-length sequences of ORF2 (1,621 nt) and ORF3 (849 nt) of strain PR668/2015/ITA were analysed with NoV GII.P17-GII.17 sequences available in the GenBank database (Figure 1).

The topology of the trees in the multi-target phylogenetic analysis was conserved, with the GII.P17-GII.17 Kawasaki 2014 NoV forming a monophyletic branch and further segregating into two genetic subclades. The first subclade containing the Italian PR668/2015/ITA strain clustered with GII.P17-GII.17 NoVs detected in China and Hong Kong during 2014 and 2015, and was genetically related (99.9%) to a GII.P17-GII.17 strain detected in the United States (US) in November 2014. The second subclade included GII.P17-GII.17 NoV detected in Japan and Taiwan during 2013 and 2014. The viruses of the two subclades showed a moderate degree of nucleotide and amino acid divergence in the ORF2 and ORF3 sequences (1–1.9% nucleotide and 0–0.4% amino acid differences in ORF1, 0.4–4.1% nucleotides and 0.9–6.2% amino acids in ORF2, and 0.5–3.3% nucleotides and 1–4.9% amino acids in ORF3). Interestingly, the GII.17 capsid sequences of the two genetic subclades differed markedly from the oldest GII.17 capsid sequence available in GenBank database, dating back to 1978 (23.3–24.8% nucleotide and 14.2–16.6% amino acid differences in ORF2, and 19.4–27% nucleotide and 22.1–22.9% amino acid differences in ORF3).

Several changes in the VP1 sequence were observed between the two Kawasaki 2014 subclades, mostly, but not exclusively, affecting the antibody blockade sites, i.e. the putative epitopes (A-E) located in the capsid protruding hypervariable P2 domain (Figure 2). In the 543 amino acid VP1 protein, 17 amino acid changes (3.1% divergence) and four insertions separate the two Kawasaki 2014 subclades, while 38 amino acid changes (7% divergence) and several insertions/deletions separate the Kawasaki 2014 GII.17 NoV and the former GII.17 recombinant forms.

Discussion

NoVs are a major cause of acute gastroenteritis in both children and adults, with sporadic cases and outbreaks in various epidemiological settings [6]. Although more than 30 cap genotypes within genogroups GI, GII, and GIV may infect humans [7], a single genotype, GII.4, has been associated since the mid-1990s with the majority (ca 70–80%) of NoV-associated cases of gastroenteritis worldwide [12]. GII.4 NoV strains undergo a continuous process of genetic/antigenic diversification and periodically generate new strains via accumulation of point mutations or recombination, with one novel GII.4 variant emerging every two to three years [12,13] and

becoming predominant globally. NoV vaccines based on GII.4 NoV strains are currently under development [14].

In the winter season 2014/15, the GII.P17-GII.17 NoV strain Kawasaki 2014 emerged in Asia, replacing the previously dominant GII.4 genotype Sydney 2012 variant [1-4]. A signature of the Kawasaki 2014 variant is a novel pol type GII.P17, combined with a GII.17 ORF2 gene. Previously, NoVs with a GII.17 cap genotype possessed a GII.P4, GII.P3, GII.P13 or GII.P16 pol genotype [15-18]. Although being predominant in several Asian countries, this novel GII.P17-GII.17 strain has been detected in a limited number of cases on other continents [1-5]. The epidemiological trends exhibited by the Kawasaki 2014 NoV variant are considered unique, as, so far, this is the only non-GII.4 NoV strain to have shown such epidemic pattern. The emergence of the novel GII.P17-GII.17 NoV strain in the Asian countries has been associated with increased NoV activity, i.e. with increased incidence of NoV-induced acute gastroenteritis, in the 2014/15 winter season, compared to the previous (2013/14) winter season [1-3]. This pattern has been observed, but not consistently, during the worldwide spread of NoV GII.4 variants [19]. Based on current literature on GII.17 NoVs, there is no indication on the clinical severity of the novel GII.17 virus [1-5]. Likewise, our study did not assess whether Kawasaki 2014 NoVs are associated with increased severity of the clinical symptoms.

Hospital-based surveillance for NoV identified the emergence of GII.P17-GII.17 strains in Italy at the end of the 2014/15 winter season, in February 2015. The viruses were genetically closely related to GII.17 NoVs identified in the US and Asia in 2014 and 2015 [3,5], forming a distinct subclade of the Kawasaki 2014 GII.17 NoV variant. Co-circulation of two subclades of Kawasaki 2014 GII.17 NoV with several amino acid changes in the putative capsid epitopes could suggest that this novel strain is undergoing fast diversification, mirroring what was seen globally for the epidemic GII.4 variants [12].

In addition, the emergence and spread of the novel GII.17 variant Kawasaki 2014 could represent a challenge for the efficacy of the candidate NoV vaccines [14], that target the globally predominant GII.4 NoV, as it is not known whether vaccine immunity elicited to GII.4 NoV is cross-reactive with GII.17 viruses. Continuous monitoring of the epidemiology of human NoV is important to understand the evolution of NoV and to implement the future strategies on NoV vaccines.

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Conflict of interest

None declared.

Authors' contributions

Conceived and designed the experiments: MCM, FT, VM; analysis of samples: MCM, FT, MC, GMG, SDG, VM; analysed and interpreted the data: MCM, FT, VM; wrote the manuscript: MCM, FT, VM; critical revision of the manuscript: AC, MC, GMG, SDG, MCA, FDC, CC; approved the final version: MCM, FT, AC, MC, GMG, SDG, MCA, FDC, CC, VM.

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