

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

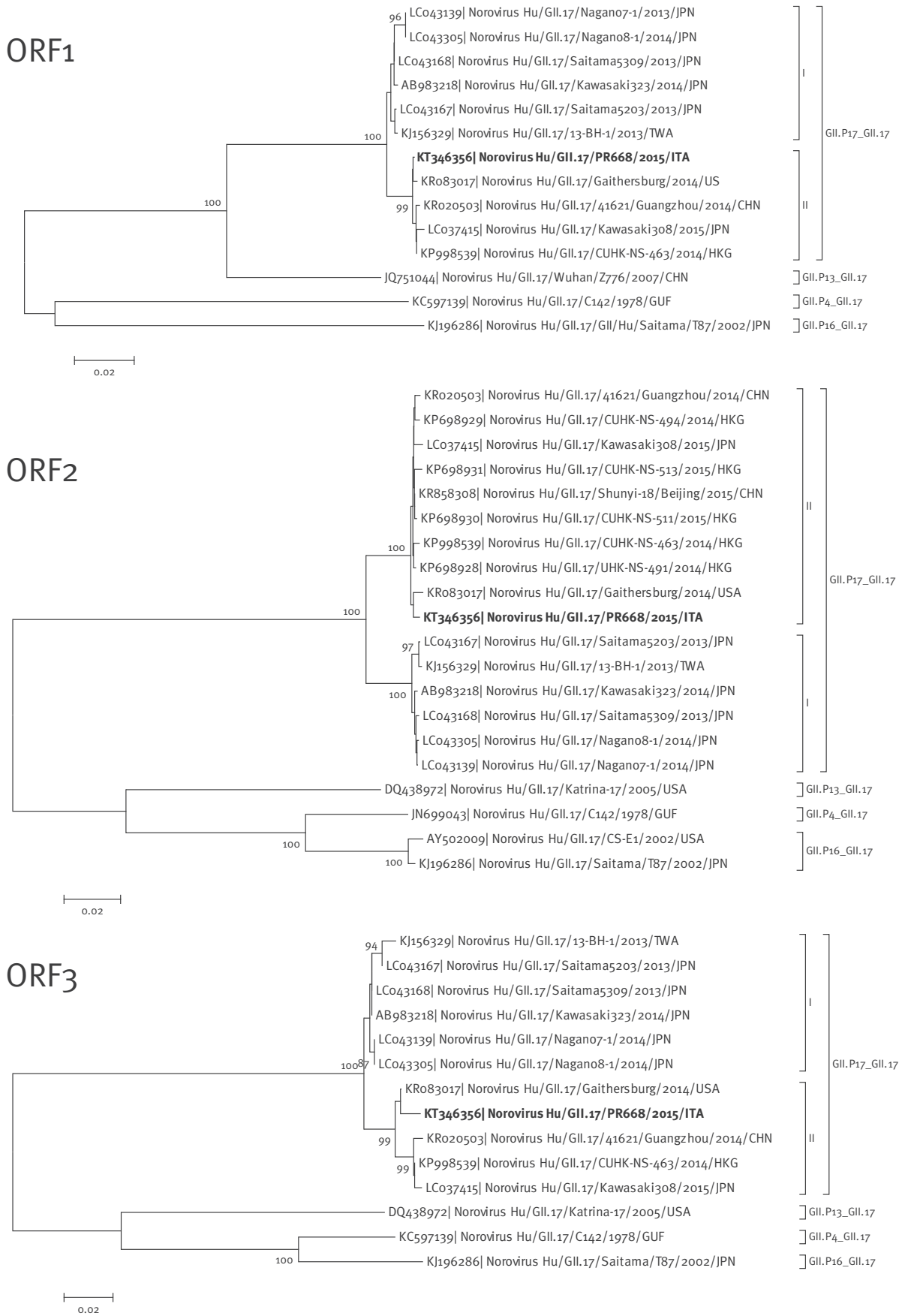
The Italian Study Group for Enteric Viruses (ISGEV; <http://isgev.net>) monitors the epidemiology of enteric viruses in children through hospital-based surveillance. A subset of about half of the NoV-positive samples is systematically genotyped in both region A (ORF1, RdRp) and region C (ORF2, capsid). 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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8	5243	5248	5253	5258	5263	5268	5273	5278	5283	5288	5293	5298	5303	5308	5313	5318	5323	5328	5333	5338	5343	5348	5353	5358	5363	5368	5373	5378	5383	5388	5393	5398	5403	5408	5413	5418	5423	5428	5433	5438	5443	5448	5453	5458	5463	5468	5473	5478	5483	5488	5493	5498	5503	5508	5513	5518	5523	5528	5533	5538	5543	5548	5553	5558	5563	5568	5573	5578	5583	5588	5593	5598	5603	5608	5613	5618	5623	5628	5633	5638	5643	5648	5653	5658	5663	5668	5673	5678	5683	5688	5693	5698	5703	5708	5713	5718	5723	5728	5733	5738	5743	5748	5753	5758	5763	5768	5773	5778	5783	5788	5793	5798	5803	5808	5813	5818	5823	5828	5833	5838	5843	5848	5853	5858	5863	5868	5873	5878	5883	5888	5893	5898	5903	5908	5913	5918	5923	5928	5933	5938	5943	5948	5953	5958	5963	5968	5973	5978	5983	5988	5993	5998	6003	6008	6013	6018	6023	6028	6033	6038	6043	6048	6053	6058	6063	6068	6073	6078	6083	6088	6093	6098	6103	6108	6113	6118	6123	6128	6133	6138	6143	6148	6153	6158	6163	6168	6173	6178	6183	6188	6193	6198	6203	6208	6213	6218	6223	6228	6233	6238	6243	6248	6253	6258	6263	6268	6273	6278	6283	6288	6293	6298	6303	6308	6313	6318	6323	6328	6333	6338	6343	6348	6353	6358	6363	6368	6373	6378	6383	6388	6393	6398	6403	6408	6413	6418	6423	6428	6433	6438	6443	6448	6453	6458	6463	6468	6473	6478	6483	6488	6493	6498	6503	6508	6513	6518	6523	6528	6533	6538	6543	6548	6553	6558	6563	6568	6573	6578	6583	6588	6593	6598	6603	6608	6613	6618	6623	6628	6633	6638	6643	6648	6653	6658	6663	6668	6673	6678	6683	6688	6693	6698	6703	6708	6713	6718	6723	6728	6733	6738	6743	6748	6753	6758	6763	6768	6773	6778	6783	6788	6793	6798	6803	6808	6813	6818	6823	6828	6833	6838	6843	6848	6853	6858	6863

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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