Mutation in a Lordsdale Norovirus Epidemic Strain as a Potential Indicator of Transmission Routes

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An increase in norovirus outbreaks was reported internationally during 2002 and 2003 and was also observed in Oxfordshire (United Kingdom) hospitals. To understand their epidemiological relationships, viruses from 22 outbreaks (15 from one hospital) were subjected to nucleotide sequencing. The 3′-terminal 3,255 nt or complete genomes were determined for 49 viruses. All outbreaks were caused by a genogroup II norovirus related to the Lordsdale virus (GI 4), common in healthcare settings. The norovirus mutation rate was sufficiently high that the 3,255-nucleotide sequences allowed separate and potentially connected outbreaks to be identified, since all outbreaks with identical sequences were temporally or geographically linked. The high mutation rate was further indicated by four mutations and three microheterogeneities in 3,255 nucleotides during 17 days of norovirus shedding by an immunocompromised patient. The data suggested that multiple virus introductions from the community, occasional transmission among wards, and one instance of ongoing environmental contamination had occurred. The accumulation, or lack, of mutations within an outbreak was also used to indicate the predominant transmission route. In an outbreak where person-to-person spread was thought to predominate, six mutations were detected throughout the genome, whereas one mutation was detected when point source infection was suspected. This norovirus epidemic strain differed from its closest previously described relative by 11.4 to 13.6% in the outer P2 domain of the capsid, which also had a single-amino-acid insertion. Alterations to the capsid structure compared to previous noroviruses may explain the increased number of outbreaks during 2002 and 2003.

Noroviruses are recognized as a worldwide cause of epidemic acute nonbacterial gastroenteritis. They are members of the family Caliciviridae, having a single-stranded RNA genome with positive polarity ~7.5 kb long. Noroviruses frequently cause outbreaks of gastroenteritis in settings where people congregate, such as hospitals, hotels, cruise ships, and schools (4, 12, 19, 21). Transmission occurs fecal-orally via aerosols, fomites, food, or water, and the attack rate is high, with the virus affecting all age groups (5). Outbreak control is hampered by the low infectious dose and environmental persistence of the virus (14). It is estimated that in the United States 23,000,000 infections, 50,000 hospitalizations, and 300 deaths are caused by noroviruses each year (23).

An unusual increase in the number of norovirus outbreaks was reported in Europe and the United States during the winter of 2002-2003 (2, 3, 16, 32). Outbreaks are a significant problem in healthcare institutions (8, 18), and 68% of the 2002-2003 increase in the United Kingdom involved elderly patients in such a setting (3). Hospitals and care homes accounted for 79% of 1,877 reported general outbreaks in England and Wales from 1992 to 2000 (18).

Nucleotide sequence data for norovirus strains collected over 30 years have demonstrated high levels of genetic diversity. Two genogroups infect humans (genogroup I [GI] and GII) (9, 15), and each can be subdivided into up to 10 phylogenetic clades (1, 30). In contrast to the wider community, outbreaks in healthcare settings are usually caused by a small number of GII strains (18), with a Lordsdale virus-like GII strain (GII clade 4 [GI 4]) predominating (7, 8, 10, 20). Lordsdale virus was identified following a United Kingdom hospital outbreak in March 1993 (6). Studies to track transmission among hospital outbreaks have often used short fragments of nucleotide sequence (150 to 300 bp) from the relatively conserved RNA polymerase region. However, the predominance of the Lordsdale virus-like strain limits their utility, as many hospital outbreak strains collected over a short period are identical in this region (20).

Since noroviruses have an RNA genome and replicate rapidly using a polymerase that lacks proofreading activity, they would be expected to mutate quickly. This was demonstrated by Nilsson et al. (24), who found 32 amino acid changes in the capsid protein of a norovirus shed chronically over 1 year by an immunocompromised patient. Longer nucleotide sequences could therefore allow the relationships among outbreaks in healthcare settings to be determined by detecting the small numbers of mutations which occur over short periods of time. The objectives of this study were, first, to obtain sufficient sequence data to clarify the relationships among multiple outbreaks in a single hospital during 2002 and 2003 and to compare the viruses to those in outbreaks from six surrounding hospitals and, secondly, to find a possible explanation for the increase in outbreaks during 2002 and 2003.
TABLE 1. Locations, dates, samples, and sequences obtained from norovirus outbreaks

<table>
<thead>
<tr>
<th>Outbreak location</th>
<th>Start date&lt;sup&gt;a&lt;/sup&gt;</th>
<th>End date&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration (days)</th>
<th>No. symptomatic&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No. of positive samples (RNA Pol&lt;sup&gt;c&lt;/sup&gt; RT-PCR)</th>
<th>RNA Pol&lt;sup&gt;c&lt;/sup&gt; sequence variant</th>
<th>No. of 3′-terminal sequences (3,255 nt)</th>
<th>No. of genome sequences (7,558 nt)</th>
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</thead>
<tbody>
<tr>
<td>Hosp A, ward 7E</td>
<td>9/25/02</td>
<td>10/2/02</td>
<td>7</td>
<td>20</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>10/7/02</td>
<td>10/14/02</td>
<td>8</td>
<td>14</td>
<td>2/4</td>
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<td>4</td>
<td>14</td>
<td>1/2</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Hosp A, ward 7A</td>
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<td>10/30/02</td>
<td>6</td>
<td>22</td>
<td>5/7</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
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<td>Hosp A, ward 7D</td>
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<td>11/4/02</td>
<td>10</td>
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<td>3/5</td>
<td>2</td>
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<td>11/4/02</td>
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<td>1</td>
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<td>9</td>
<td>7/10</td>
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<td>1</td>
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<td>10/5/02</td>
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<td>25</td>
<td>8/8</td>
<td>1</td>
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<tr>
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<td>14</td>
<td>1/3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
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<td>12/21/02</td>
<td>1/10/03</td>
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<td>30</td>
<td>2/3</td>
<td>1</td>
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<td>2/26/03</td>
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<td>3/3</td>
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<td>16</td>
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<td>4/15/03</td>
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<td>12</td>
<td>1/1</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>75/130</td>
<td>49</td>
<td></td>
<td></td>
</tr>
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</table>

<sup>a</sup> Month/day/year.

<sup>b</sup> Number symptomatic includes patients, staff and relatives. Start and end dates refer to the dates restrictions on patient and staff movements were imposed by hospital infection control.

<sup>c</sup> Pol, polymerase.

<sup>d</sup> Three isolates from one immunocompromised patient.

<sup>e</sup> Hosp, hospital.
Nucleotide sequence accession numbers. The complete genome sequences (7,558 nt) of eight norovirus strains were submitted to GenBank. The accession numbers are AY581254 and AY587983 to AY587989. The 3'-terminal 3,255-nt sequences extending from the RNA polymerase within open reading frame 1 (ORF1) through ORF2 and ORF3 to the 3'-terminal 136 nt and no indication of multiple changes at particular sites. The same change was frequently present in more than one outbreak.

RESULTS

Outbreaks, samples, and strain identification. Noroviruses from a total of 22 outbreaks in seven different Oxfordshire (United Kingdom) hospitals were included in the study (Table 1). Most outbreaks selected (n = 15) occurred in a single hospital, referred to as hospital A. The outbreaks lasted between 3 and 20 days, and 9 to 48 people were affected (Table 1).

Norovirus-positive stools were identified by reverse transcription-PCR using previously published oligonucleotide primers that bind conserved sequences within the RNA polymerase region to amplify a 327-bp fragment (29). A total of 75 positive stool samples were identified among 130 tested. Nucleotide sequencing of this amplicon demonstrated that all the viruses were very closely related, many having identical sequences within an RNA polymerase fragment (variant 1) (Table 1 and Fig. 1). Four additional closely related sequences were found (Fig. 1). Comparison to previously described viruses revealed that the five variants were closely related to Lordsdale virus, a member of GII (GII 4). However, they were distinct from previously described variants.

Norovirus mutation as a tool for defining outbreaks and transmission routes. The relationships among the majority of outbreaks could not be determined from the short fragments of RNA polymerase sequence, so longer sequences were obtained to increase the resolution. The 3'-terminal 3,255-nt sequences of 49 noroviruses from 18 of the 22 outbreaks were determined (Table 1). This sequence included part of the RNA polymerase gene, the entire capsid, ORF3, and the 3'-terminal 200 nt 3'. The same change was frequently present in more than one outbreak.

Sequence identity was considered a likely indicator that outbreaks (defined in Materials and Methods) could be con-
The level of identity between outbreaks was assessed using a neighbor-joining tree constructed from the 49 sequences (Fig. 2). Eight outbreaks with unique virus sequences were identified, indicating that they were not connected. The remaining 10 outbreaks formed three clusters. Cluster 1 included three outbreaks from late September and October 2002. Two occurred in hospital A and differed by one point mutation, and a third occurred in nearby hospital B. Cluster 2 included concurrent outbreaks on two hospital A wards. Therefore, the outbreaks that had identical virus sequences were temporally or geographically linked, i.e., part of larger outbreaks involving more than one ward.

To examine the predominant transmission routes within two different outbreaks, the accumulation of virus mutations was investigated in different patients infected over the course of each outbreak. If person-to-person spread predominated, many accumulated mutations would be expected, as they are inherited by consecutive hosts. Conversely, in a common-source outbreak, fewer accumulated mutations would be expected, since each patient develops his or her own mutations in the virus received from the common source. The two outbreaks were chosen on the basis of observations made by infection control staff. Patients tended to develop symptoms consecutively in one outbreak (hospital B, ward L; 29 September to 5 October 2002), but more cases occurred together in the other outbreak (hospital A, ward 7C; 26 October to 4 November 2002) (Table 1). Both outbreaks affected 25 people; the former lasted 7 days with 6 positive fecal samples available, and the latter lasted 10 days with 10 samples available.

The complete genome sequences of the viruses in the six samples from the hospital B, ward L, outbreak were determined. A total of six mutations occurred gradually during the 7-day outbreak (Table 2). Eight viruses were identical in the 3′-terminal 3,255 nt; two differed at the same position. The complete genome sequences of viruses collected at the start and end of the outbreak demonstrated no further differences. These data support the idea that prolonged person-to-person transmission may be indicated by the accumulation of mutations during an outbreak, as they are inherited by consecutive hosts.

The rapid norovirus mutation rate was further indicated by 3′-terminal 3,255-nt sequences obtained 17 days apart from an immunocompromised patient who had received a bone marrow transplant. Four mutations and three nucleotide microheterogeneities (the presence of two different nucleotides at the same position within a sequence chromatogram) were detected (Fig. 2, hospital A, ward 5E outbreak).

Identification of a new norovirus strain. The relationship of the GII strain identified in the present study to previous strains was assessed using capsid sequences obtained from GenBank.

![FIG. 2. Neighbor-joining tree showing relationships among 49 strains from 18 outbreaks within the 3′-terminal 3,255 nt. The strains and outbreaks are indicated as follows: hospital (Hosp), plus ward where more than one outbreak from one hospital was included; date of sample collection (month/day/year); and sample number. ∗, variants shed over 17 days by an immunocompromised patient.](image)

**TABLE 2. Mutations accumulated in virus genome in six patients infected during an outbreak**

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Sample date &amp;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mutation at position (within 7,558-nt genome) &amp;&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>B4S2</td>
<td>9/25/02</td>
<td>1015 T C T T T T A</td>
</tr>
<tr>
<td>B4S5</td>
<td>9/27/02</td>
<td>1015 T C T T T T A</td>
</tr>
<tr>
<td>B4S6</td>
<td>9/27/02</td>
<td>1015 T C T T T T T A</td>
</tr>
<tr>
<td>B4S4</td>
<td>10/1/02</td>
<td>1015 T C T T T T G</td>
</tr>
<tr>
<td>B4S7</td>
<td>10/1/02</td>
<td>1015 T C T T T A</td>
</tr>
<tr>
<td>B4S1</td>
<td>10/3/02</td>
<td>1015 T C T T T A</td>
</tr>
</tbody>
</table>

<sup>a</sup> Month/day/year.
<sup>b</sup> Accumulated mutations are indicated by boldface type.
The Oxfordshire viruses formed a unique cluster within the Lordsdale virus-like group (GII 4). Previous strains in this group formed two additional clusters. One occurred from 1987 to 1994, and the other occurred from 1995 to 2001. The three clusters did not overlap temporally. This observation was repeated when neighbor-joining trees were constructed for ORF1 and ORF3 (data not shown), so no evidence of recombination was detected.
The norovirus most closely related to the Oxfordshire variant was identified by a BLAST search of the GenBank database. It was 004/95 M-14/1995/AU (GenBank accession number AF080551), which occurred in Australia during 1995 (25). An alignment was constructed using the capsid sequences of (i) a representative of the Oxfordshire viruses (Hu/NLV/Oxford/B5S22/2003/UK), (ii) strain 004/95 M-14/1995/AU, and (iii) Norwalk virus, the only norovirus for which the capsid crystal structure is known (26) (Fig. 4). The regions of the Lordsdale virus-like capsids which corresponded to the Norwalk virus capsid were estimated from the alignment. The majority of capsid amino acid differences between the Oxford virus and its closest relative from 1995 occurred within the outer P2 domain (11.4% divergence), followed by the P1 domain (2.2% divergence), the S domain (1.1% divergence), and the amino-terminal arm (0% divergence) (Fig. 4). A single-amino-acid insertion (glycine) was present in the P2 regions of all the Oxfordshire viruses sequenced.

**FIG. 4.** Alignment of the capsid amino acid sequences of the representative Oxfordshire variant Hu/NV/Oxford/B5S22/2003/UK (GenBank AY881254), its closest previously described relative (004/95 M-14/1995/AU [GenBank AF080551]), and Norwalk virus (GenBank M87661). The different subdomains of the capsids, estimated using the previously described crystal structure of the Norwalk virus capsid (26), are indicated. The majority of amino acid sequence changes between the new strain and its previous closest relative occurred in the outer P2 subdomain of the capsid and are highlighted in boxes.

The norovirus most closely related to the Oxfordshire variant was identified by a BLAST search of the GenBank database. It was 004/95 M-14/1995/AU (GenBank accession number AF080551), which occurred in Australia during 1995 (25). An alignment was constructed using the capsid sequences of (i) a representative of the Oxfordshire viruses (Hu/NLV/Oxford/B5S22/2003/UK), (ii) strain 004/95 M-14/1995/AU, and (iii) Norwalk virus, the only norovirus for which the capsid crystal structure is known (26) (Fig. 4). The regions of the Lordsdale virus-like capsids which corresponded to the Norwalk virus capsid were estimated from the alignment. The majority of capsid amino acid differences between the Oxford virus and its closest relative from 1995 occurred within the outer P2 domain (11.4% divergence), followed by the P1 domain (2.2% divergence), the S domain (1.1% divergence), and the amino-terminal arm (0% divergence) (Fig. 4). A single-amino-acid insertion (glycine) was present in the P2 regions of all the Oxfordshire viruses sequenced.

**DISCUSSION**

Gastroenteritis outbreaks in healthcare settings are often caused by Lordsdale virus-like noroviruses (18), also referred to as GII 4 strains. Their relatively high level of genetic identity makes the epidemiological relationships between outbreaks difficult to discern, particularly over the short term. The reported increase in norovirus outbreaks during the winter of 2002-2003 (2, 3, 16, 32) also occurred in Oxfordshire hospitals. Twenty-two of these outbreaks formed the basis of the present study. All the outbreaks were caused by a Lordsdale virus-like
strain, and most outbreaks could not be distinguished using a short fragment of RNA polymerase sequence (Table 1 and Fig. 1). However, noroviruses mutate rapidly (24), and this characteristic, together with longer sequences from each outbreak, was exploited to identify those that were potentially linked.

Nucleotide sequencing of the 3′-terminal 3,255 nt of 49 strains was applied successfully to determine the relationships of 18 outbreaks representing seven Oxfordshire hospitals. The definition of outbreaks on a per-ward basis by infection control staff was verified as correct by molecular data in 8 of the 18 outbreaks. However, the remaining 10 outbreaks occurred in three clusters of two or more outbreaks with identical sequences (Fig. 2). The outbreaks in each of these clusters were temporally or geographically linked, being (i) concurrent in wards of the same or a nearby hospital, i.e., areas sharing frequent patient and staff movements (clusters 1 and 3), or (ii) in the same location as a previously identical strain but 18 days later (cluster 2). The latter suggests ongoing environmental contamination by the virus, since no mutations occurred over the interval between outbreaks. The temporal and/or spatial links between identical viruses suggest that the norovirus mutation rate is sufficiently high for sequence identity in the 3′ 3,255 nt to indicate potentially connected outbreaks.

To determine whether mutation accumulation could be used to infer the predominant transmission route within an outbreak, two outbreaks were studied in greater detail, using 3′-terminal 3,255-nt and complete genome sequences. In one outbreak where person-to-person transmission was considered likely, six mutations gradually accumulated in the virus genome over time (Table 2). In contrast, a single point mutation was detected in an outbreak where many patients developed symptoms closer together, suggesting a greater role for simultaneous infection.

Combined with precise epidemiological data, this approach could allow the relative importance of different transmission routes in particular healthcare settings to be determined and could assist infection control procedures. The data described here suggest that the 18 outbreaks variously involved (i) multiple virus introductions, (ii) transmission among wards, (iii) person-to-person transmission, (iv) simultaneous infection of a large number of patients, and (v) environmental contamination over an extended period.

The Oxfordshire outbreaks included in the present study were part of a global increase which took place during 2002 and 2003, beginning in January 2002, with an unusually high number of outbreaks continuing into the summer (17). A national epidemic of Lordsdale virus at this time was reported in the United Kingdom (32). A new strain associated with the Europe-wide outbreak increase has also been identified as a Lordsdale virus-like strain on the basis of short RNA polymerase sequences containing a motif (AATCTG) which differed by 2 nt from certain previous GII 4 strains (16). All five of the RNA polymerase variants in the present study contained this hexamer (Fig. 1).

The mutations detected within the 3′-terminal 3,255 nt of 49 viruses included in this study were predominantly transitions (93%). Only four mutations were observed in 550 nt spanning the junction between ORF1 and ORF2, and none were observed in the 3′-terminal 136 nt of 49 viruses. The absence of mutations from certain regions of the genome may indicate areas where conservation of secondary structure is particularly important.

A comparison of the Oxfordshire strain capsid amino acid sequence to those of other Lordsdale-like viruses indicated that it differed by 11.4 to 13.6% in the outer P2 domain, in which it also had a single-amino-acid insertion. This strain may have been sufficiently distinct antigenically to evade previous host immunity, leading to the increased number of outbreaks. Capsid structural changes have been predicted as a result of only eight cumulative amino acid changes in the P2 domain (24), and the Oxfordshire viruses differed from their closest relative by 16 amino acids within this region.

The sequences obtained in the present study were combined with data obtained from GenBank to allow three clusters to be identified within the Lordsdale virus-like group (Fig. 4). None of the three had cocirculated, and all of the groups had similar levels of divergence within the capsid P2 domain. This further confirms that the predominant Lordsdale virus-like strain is replaced periodically by a new, antigenically distinct variant (13, 25).

The P2 domain was the region of the capsid in which the majority of amino acid changes occurred during chronic norovirus shedding by an immunocompromised patient (24). During the present study, an immunocompromised patient (a bone marrow transplant recipient) who was infected nosocomially shed norovirus for at least 17 days. Four mutations occurred within the 3,255-nt sequence determined, and there were three microheterogeneities. Long-term shedders may be the source of new human norovirus strains which are pathogenic to others (24), since an animal reservoir has not been identified. The demonstration of norovirus shedding for extended periods in immunocompromised patients has important implications for hospital infection control. Our data suggest that the effectiveness of infection control procedures can be monitored using molecular data, which can also indicate the predominant transmission routes.

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REFERENCES


