CASE REPORT

Personalized genetic testing and norovirus susceptibility

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BACKGROUND: The availability of direct-to-consumer personalized genetic testing has enabled the public to access and interpret their own genetic information. Various genetic traits can be determined including resistance to norovirus through a nonsense mutation (G428A) in the *FUT2* gene. Although this trait is believed to confer resistance to the most dominant norovirus genotype (GII.4), the spectrum of resistance to other norovirus strains is unknown. The present report describes a cluster of symptomatic norovirus GI.6 infection in a family identified to have norovirus resistance through personalized genetic testing.

CASE PRESENTATION: In January 2013, four members of a family determined by a direct-to-consumer genetic test to be homozygous for the norovirus resistance trait (A/A genotype for single nucleotide polymorphism rs601338) developed symptoms consistent with acute viral gastroenteritis. Stool and vomitus samples were submitted for enteric viral pathogen testing. Samples were positive for norovirus GI.6 in three of the four cases.

CONCLUSIONS: The present report is the first to describe norovirus GI.6 infection in patients with the G428A nonsense mutation in *FUT2*; this cluster of cases suggests that the G428A mutation in *FUT2* may not confer resistance to norovirus GI.6. Direct-to-consumer genetic testing is empowering members of the public to identify novel associations with their genetic traits. Expert consultation is important for the interpretation of personalized genetic test results, and follow-up laboratory testing can confirm any potentially novel associations.

Key Words: *Direct-to-consumer genetic testing; Norovirus; Norovirus resistance*

Les tests génétiques personnalisés et la susceptibilité au norovirus

HISTORIQUE : Les tests génétiques personnalisés destinés directement aux consommateurs permettent au public d'accéder eux-mêmes à l'information génétique et à l'interpréter. Il est ainsi possible de déterminer divers traits génétiques, y compris la résistance au norovirus par une mutation non-sens (G428A) dans le gène *FUT2*. Même si on pense que ce trait confère une résistance au génotype du norovirus le plus dominant (GII.4), on n'en connaît pas le spectre de résistance à d'autres souches de norovirus. Le présent rapport décrit une grappe d'infection symptomatique au norovirus GI.6 au sein d'une famille dont la résistance au norovirus avait été établie au moyen de tests génétiques personnalisés.

PRÉSENTATION DU CAS : En janvier 2013, quatre membres d'une famille qui, d'après un test génétique destiné directement au consommateur, étaient homozygotes au trait de résistance au norovirus (génotype A/A du polymorphisme de nucléotide simple rs601338) ont présenté des symptômes évocateurs d'une gastroentérite virale aiguë. Des coprocultures et des prélèvements de vomissures ont été soumis à un test pour déceler un virus entéropathogène. Dans trois des quatre cas, les prélèvements étaient positifs au norovirus GI.6.

CONCLUSIONS : Le présent rapport est le premier à décrire l'infection à norovirus GI.6 chez des patients présentant la mutation non-sens G428A dans le gène *FUT2*. Ce groupe de cas laisse croire que la mutation G428A dans le gène *FUT2* ne confère pas de résistance au norovirus GI.6. Les tests génétiques destinés directement aux consommateurs permettent aux membres du public d'établir de nouvelles associations avec leurs traits génétiques. Il est important de consulter un expert pour en interpréter les résultats, et des tests de laboratoire effectués en suivi peuvent confirmer ces associations potentielles.

Worldwide, norovirus is the most common cause of acute viral gastroenteritis in adults (1). Multiple host and viral factors contribute to the persistence of noroviruses in the human population, including the environmental stability of the virus, resistance to some disinfecting agents, low infectious dose and postinfection shedding, lack of long-term cross-protective immunity after infection and frequent replacement of the predominant circulating strain due to the existence of multiple genotypes and strains, and antigenic drift (2-5). Noroviruses are spread predominantly through the fecal-oral route, but aerosolization through vomitus is another possible route of transmission (6). The rates of norovirus infection follow a seasonal pattern, with higher rates during winter months in temperate regions (7). In addition to numerous sporadic cases in the community, outbreaks are commonly reported in many public settings including long-term care facilities, hospitals, daycares, schools and cruise ships (2).

The norovirus genome is a linear, positive-sense, single-stranded RNA molecule approximately 7.5 kb in length (8). Noroviruses are members of the *Caliciviridae* family and are genetically classified into six genogroups (GI, GII, GIII, GIV and GV) according to their capsid proteins (9). Each genogroup is further subdivided into multiple genotypes (10). The capsid proteins also play a role in determining host specificity and affect host immunological response. The majority of noroviruses that infect humans belong to genogroups I and II. In the past decade, the genogroup II, genotype 4 viruses (GII.4) have been the most dominant worldwide (11).

Epidemiological evidence, in vitro binding studies and viral challenge studies in volunteers have all shown that inherited host factors

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also play a role in host susceptibility to noroviruses. In particular, secretor status or the ability to express histo-blood group antigens on mucosa is likely correlated with the risk of developing symptomatic norovirus infection. Most GII.4 and some GI.1 (Norwalk virus) noroviruses have been shown to require binding to histo-blood group antigens and, thus, nonsecretors are believed to be resistant to infection by these genotypes (12,13). One of the common mutations affecting secretor status is the G428A nonsense mutation in the *FUT2* gene, which encodes for the fucosyltransferase-2 enzyme (14-16). Individuals who are homozygous for the G428A mutation in *FUT2* are nonsecretors. In clinical studies, it has been shown that these individuals are resistant to symptomatic infection by norovirus GI.1 (15) and most GII.4 strains (17,18). In one reported outbreak of norovirus GI.3, nonsecretor status was not protective against norovirus infection (19). The full extent of the norovirus resistance that is conferred by the G428A mutation against different genotypes and strains of norovirus is not currently known.

The introduction of direct-to-consumer genetic testing has enabled the public to examine their own genetic traits and ancestry. While there is ongoing debate regarding whether these tests require the same regulatory oversight as other medical tests, hundreds of thousands of consumers have undergone these tests and, in some cases, they are using the test results to change health behaviours and even alerting their physicians to the results (20). These tests allow the public to potentially identify novel genetic associations at the individual and family level, and some test providers even allow customers to crowdsource and conduct their own community-based genetic research. One company alone, 23andMe (USA), has currently tested close to 500,000 individuals, creating a large genetic database with the potential to make valuable discoveries (21,22). These tests are most useful for the determination of monogenic traits such as secretor status. We describe a cluster of norovirus GI.6 in four family members that was identified by direct-to-consumer genetic testing as being homozygous for the G428A mutation in *FUT2*.

CASE PRESENTATION

A family in British Columbia had undergone genetic testing through 23andMe and all four individuals were determined to be "norovirus resistant" (A/A genotype for SNP rs601338). During the 2012-2013 norovirus season, all the family members developed an illness consistent with viral gastroenteritis. The index case (patient A) was a six-year-old girl who presented with nausea, vomiting and diarrhea. On day 2, the mother of the index case (patient B, a 46-year-old woman) presented with nausea and mild diarrhea, but did not experience any vomiting. On day 3, the 10-year-old brother of the index case (patient C) developed symptoms of nausea, vomiting and diarrhea. Later on day 3, the father of the index case (patient D, a 46-year-old man) also developed nausea, vomiting and diarrhea. There were no other people living within the household. All members of the family cluster resolved their symptoms within two days of illness onset without medical intervention. On day 3, stool samples were collected from patients A, B and D and a vomitus sample was collected from patient C. On day 4, samples were submitted for enteric virus testing.

Two of the three stool samples (patients A and D) and the vomitus sample (patient C) tested positive for norovirus genogroup I by reverse-transcriptase polymerase chain reaction. Total nucleic acid was extracted from stool and vomitus using NucliSENS easyMag (bioMerieux, USA) and tested in a duplex real-time reverse-transcriptase polymerase chain reaction targeting norovirus genogroups I and II (23). Sequencing of the capsid VP1 region (region C) determined that these noroviruses belonged to genotype GI.6 (Genbank accession numbers KJ569103-5) (24). Norovirus outbreak surveillance for British Columbia showed that 20% of gastroenteritis outbreaks reported to the British Columbia Public Health Microbiology and Reference Laboratory were due to norovirus GI.6 during the 2012-2013 norovirus season (25). This is significantly higher than in the previous norovirus season (0% detected in 2011-2012). An increased incidence of norovirus GI.6 in 2012 was also reported in Alberta and in the United States (26,27).

CONCLUSIONS

Direct-to-consumer genetic testing has the potential to increase public awareness of genetically determined traits such as disease risk and response to drugs. However, genetic information can also be misinterpreted without an overall understanding of the clinical and scientific knowledge associated with these genetic traits. Many phenotypes are determined by multiple genes or by a complex combination of genetic, environmental and other factors. Currently, the most popular direct-to-consumer genetic tests target single nucleotide polymorphisms (SNPs) found throughout the human genome. These SNP-based tests are most useful for genetic traits that are monogenic (or mostly monogenic). Results from these tests are often relayed to the consumers through a website rather than through a health care professional with expertise in medical genetics.

The 23andMe online report for norovirus resistance explains that this trait is highly heritable. Individuals with two copies of the 'A' SNP (G428A) are "resistant to infection by the most common strain of norovirus". The website also explains that there may be other genetic determinants of norovirus resistance that may confer resistance in those who do not have the 'AA' genotype. Individuals who are not familiar with the diversity of norovirus genotypes and strains may not understand that norovirus resistance from the G428A mutation may not protect them from all norovirus infections. Furthermore, for genetic traits associated with resistance or susceptibility to infectious agents, it is important that genetic test vendors update their databases frequently to reflect the rapid evolution and strain replacements associated with infectious agents. Consumers should be informed that new information may lag behind the emergence of new strains and variants.

Conversely, some individuals, including those with more knowledge, may be able to use such genetic information to aid identification of previously unappreciated disease susceptibility and other novel associations with genetic traits. In the present report, we show that norovirus GI.6 was able to cause symptomatic infection in four individuals who were determined to be homozygous for the G428A mutation in *FUT2* through direct-to-consumer genetic tests, including two adults with different genetic backgrounds. Although we were unable to perform independent confirmation of the G428A mutation, it is unlikely that the SNP would be incorrectly assigned in all four individuals because the concordance of direct-to-consumer genetic testing is high (>99.6%) and the homozygous mutation in the children matched that of the parents (28). While we issue caution on the interpretation of direct-to-consumer genetic testing results and the need for expert consultation, we also demonstrate the potential of these tests to allow individuals to accelerate the process of identifying new associations between host genetic traits and phenotypes.

DISCLOSURES: The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS: PT and FB collected the clinical and genetic data. NP, BA and JIR analyzed the norovirus genotyping results. NP and PT drafted the manuscript. All authors have read, edited and approved the manuscript.

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