

Ancestry-Based Differences in Norovirus Susceptibility: Implications for Understanding Global Infection Patterns

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(See the Major Article by Currier et al on pages 1631–8.)

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Noroviruses infect an estimated 21 million people annually and are a leading cause of acute gastroenteritis in the United States, making them a major health concern [1]. Despite the widespread prevalence of noroviruses, epidemiology of these viruses is poorly understood, even in the United States and European countries with active surveillance efforts. One critical factor that has been widely overlooked is whether geographic and ancestral differences among human populations impact outcomes such as local disease incidence, local norovirus genotype prevalence, and population-wide transmission patterns.

Previous work has demonstrated a link between human genetic factors and

norovirus susceptibility. Specifically, both histo-blood group antigen (HBGA) expression and secretor status (presence of a functional *FUT2* gene) have been shown to alter an individual's susceptibility to norovirus infection [2,3]. Although these factors have been recognized as susceptibility markers in individuals for more than a decade, their relationship to population-level norovirus epidemiology has not been characterized. In this issue of *Clinical Infectious Diseases*, Currier et al report results of a large-scale, multisite study that investigates the relationship between secretor status, norovirus susceptibility, and ancestry. This study takes an important step in exploring secretor status as it relates to ancestry in a pediatric population in the United States. The results of this study demonstrate ancestry-specific differences in norovirus susceptibility related to secretor status, suggesting that what is known about norovirus infection in white populations is not necessarily transferrable to other ethnic groups. To appreciate the global consequences of genetic diversity as it relates to norovirus infection and vaccine design, a better understanding of ancestry-specific genotypes and comprehensive, worldwide norovirus surveillance is necessary.

In their report, Currier et al present a well-constructed study utilizing robust control methodologies and novel testing procedures. This is the first norovirus susceptibility study to utilize the Immunochip, which is a high-throughput genotyping chip that allows for the determination of several genetic factors at once [4]. Here, it was used to detect single-nucleotide polymorphisms in the *FUT2* locus, genotype the ABO locus, and identify ancestry based on 1723 ancestral informative markers. HBGAs are a diverse family of carbohydrates that are genetically encoded and expressed in saliva and on mucosal surfaces of the human gut. They serve as binding ligands and putative receptors for the >30 different norovirus genotypes. Viral binding to these various HBGAs occurs in a strain-specific manner [5]. Previous work has demonstrated that individuals who express O-type HBGAs are more susceptible to GI.1 norovirus infection than those who express A and B-type HBGAs [2,3], although, for other genotypes, no association between infection and ABO expression was found [6].

In addition, susceptibility to norovirus is genetically mediated by the presence of a functional *FUT2* gene [2], as this enzyme is needed for the synthesis of ABO

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HBGAs. The percentage of individuals lacking a functional *FUT2* gene is generally cited as approximately 20% of the population; these individuals are known as “nonsecretors” because *FUT2*-dependent HBGAs are not expressed. Other individuals (approximately 80% of the population) carry at least 1 functional *FUT2* allele and are known as “secretors.” These percentages are based on studies evaluating white populations in the United States and Europe [7], and additional studies have determined that similar secretor frequencies are observed in Asian and African populations, although the inactivating mutations are diverse but often ancestry-specific [8, 9]. However, secretor phenotypes are not as well characterized in Mexico and in Central and South American countries. A recent norovirus infection study in an Ecuadorian birth cohort of 178 children found that nonsecretors made up 12% of the study population [10]. Another study in a Nicaraguan cohort demonstrated that nonsecretors made up only 6% of their uninfected control group and that all norovirus-infected patients in their study were secretors [11]. Unfortunately, despite Meso-American ancestry comprising approximately 70% of the population in both countries, neither study explicitly identified participant ethnicity, making it unclear if ancestry is a factor in the observed low prevalence of secretors in the study populations. At the very least, compared with other studies of secretor status, these results demonstrate that populations residing in distinct geographic areas can exhibit varying norovirus susceptibility characteristics.

In the present study, Currier et al specifically probed the relationship between genetic ancestry and norovirus susceptibility in children aged 14 days to 5 years from 6 geographically diverse study sites in the United States. They found that among the noninfected controls, 96% of people with Hispanic ancestry were secretors, compared with 74% and 73% of white and black participants, respectively. In addition, among norovirus-infected

participants, all 58 of Hispanic descent were secretors, compared with 111 of 128 (87%) of those who were black and 140 of 154 (91%) of those who were white. This strongly suggests that there are ancestry-based differences in norovirus susceptibility for genotypes that infect based on secretor status. Specifically, individuals with Hispanic ancestry may be more susceptible to certain norovirus genotypes.

How individual, ancestry-based differences in norovirus susceptibility may impact local and population-wide disease epidemiology in areas with high Hispanic populations is currently unknown, but it is an important question. Most of our knowledge of norovirus infection and epidemiology is based on large studies in the United States and in European countries, which may skew our understanding of norovirus characteristics toward the kinetics observed specifically in white populations. Small-scale epidemiological studies on norovirus disease incidence and outbreaks have been conducted in many countries, including those with primarily Hispanic populations, but differences in study design and research results make it hard to infer broader population-specific patterns from these findings in the absence of more consistent, long-term epidemiological surveillance.

Future work in this area should investigate both local and population-wide consequences of ancestry-based norovirus susceptibility differences. Larger studies in countries with large Hispanic populations should be conducted to confirm the high prevalence of the secretor phenotype found in this study. In addition, more comprehensive studies of other ethnic populations should be conducted. As the populations of many countries contain diverse ancestral backgrounds, the studies done to date probing secretor status of populations over large geographic areas may have been insufficient to detect specific ancestry-based differences. Other epidemiologically important questions to consider are whether populations that are composed of a high percentage of secretors

experience higher norovirus attack rates and whether the percentage of secretors in a population influences the prevalence of specific norovirus genotypes as a function of their ability to infect secretors vs nonsecretors.

Finally, as the authors discuss in their manuscript, ancestry-based norovirus susceptibility differences may affect both the design and recommended use of norovirus vaccines. The current bivalent vaccine in clinical trials covers GI.1 and GII.4 noroviruses [12–14]. The GII.4 genotype is responsible for approximately 70% of all norovirus outbreaks in the United States [15] and 51% of the cases in this study, and research to date has shown that this genotype almost exclusively infects secretor individuals [10, 16, 17]. More comprehensive epidemiological surveillance in regions with high secretor populations may uncover other genotypes that would be more important to include in the vaccine in place of GI.1 noroviruses, which make up a small percentage of norovirus infections. Furthermore, testing vaccines in populations with different ancestral backgrounds may uncover unknown associations between genetic diversity and vaccine effectiveness. To appreciate the impact of ethnicity-specific susceptibility differences on local and global norovirus infection patterns and how to best control norovirus disease worldwide, epidemiological studies and surveillance in diverse populations should be a priority in the future.

Notes

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