

Host Genetic Susceptibility to Enteric Viruses: A Systematic Review and Metaanalysis

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(See the Major Article by Costantini et al on pages 1–10.)

Background. Norovirus and rotavirus are prominent enteric viruses responsible for severe acute gastroenteritis disease burden around the world. Both viruses recognize and bind to histo-blood group antigens, which are expressed by the fucosyltransferase 2 (*FUT2*) gene. Individuals with a functional *FUT2* gene are termed “secretors.” *FUT2* polymorphisms may influence viral binding patterns and, therefore, may influence host susceptibility to infection by these viruses.

Methods. We performed a systematic review of the published literature on this topic. Data were abstracted and compiled for descriptive analyses and metaanalyses. We estimated pooled odds ratios (ORs) for infection using random-effects models.

Results. We found that secretors were 9.9 times (95% confidence interval [CI], 3.9–24.8) as likely to be infected with genogroup II.4 noroviruses and 2.2 times as likely to be infected with genogroup II non-4 noroviruses (95% CI, 1.2–4.2) compared with nonsecretors. Secretors were also 26.6 times more susceptible to infections from P[8]-type rotaviruses compared with nonsecretors (95% CI, 8.3–85.0).

Conclusions. Our analyses indicate that host genetic susceptibility to norovirus and rotavirus infection may be strain specific. As strain distribution and the proportion of genetic phenotypes vary in different countries, future studies should focus on differences in susceptibility among various ethnicities. Knowledge of innate susceptibility to rotavirus and norovirus can lead to improved understanding of both vaccine performance and individual risk of disease.

Keywords. norovirus; rotavirus; *FUT2*; histo-blood group antigen.

Enteric viruses, specifically norovirus and rotavirus, are a leading cause of diarrheal illness worldwide. Rotavirus has been associated with more than 450 000 deaths per year among young children, with disproportionately high levels of mortality in Asia and sub-Saharan Africa [1]. It is estimated that norovirus is associated with approximately 18% of all cases of acute gastroenteritis [2]. In populations with widespread rotavirus vaccination, norovirus has been recognized as the predominant cause of acute gastroenteritis in children [3, 4].

Noroviruses are a genetically diverse group of RNA viruses, consisting of at least 6 genogroups (G) [5]. Two genogroups, GI and GII, are responsible for the majority of human illnesses; together, these groups include more than 30 genotypes. Most outbreaks are caused by GII.4 noroviruses, which undergo rapid antigenic evolution, giving rise to a new predominant strain every 2 to 4 years [6, 7]. Novel GII.4 strains are often associated with increased morbidity and mortality [8, 9]. There are currently no licensed vaccines available for protection against norovirus. However, one vaccine is entering phase III clinical

trials, and other potential vaccines are in various stages of development [10–12].

Rotaviruses are double-stranded RNA viruses with a genome consisting of 11 segments. They are classified according to the genes that code for 2 surface proteins, VP7 (or G, glycoprotein) and VP4 (P, protease sensitive) [13]. Gene reassortment of these proteins can lead to several strains of rotavirus. However, 3 P-genotypes, P[8], P[6], and P[4], are responsible for the majority of human rotavirus infections [13]. Two rotavirus vaccines have been licensed and are used throughout the world; both vaccines contain a P[8] component [14].

Both norovirus and rotavirus recognize and bind to histo-blood group antigens (HBGA), which are oligosaccharides found in the epithelial cells of the gastrointestinal and respiratory tracts, as well in saliva and other secretions [15, 16]. The expression of HBGA on the gut surface epithelium is controlled by the fucosyltransferase 2 (*FUT2*) gene, which encodes alpha (1, 2) fucosyltransferase in order to generate H-antigens. In turn, H-antigens are catalyzed by enzymes to produce A or B blood group antigens. Numerous polymorphisms exist on the *FUT2* gene; for example, the nucleotide 428 (G > A) nonsense mutation is most commonly found in European populations, while a missense mutation found at nucleotide 385 (A > T) predominantly occurs in Asian populations [17]. Individuals with such polymorphisms are known as “nonsecretors” and make up about 20% of the European population; the remaining 80% have the functional

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FUT2 gene and are known as “secretors.” Similarly, the *FUT3* gene encodes alpha (1, 3) or (1, 4) fucosyltransferase in order to generate Lewis antigens [18]. Approximately 6%–8% of the European population is Lewis negative compared with about 32% of the African population [19, 20].

Results from challenge and outbreak studies support a correlation between infection with norovirus or rotavirus and HBGA phenotypes. Immunity to either virus is suggested to occur, to a degree, in a genotype- or strain-dependent manner [21, 22]. Here, we aimed to systematically describe host-genetic associations with the risk of rotavirus or norovirus by conducting a metaanalysis of the current literature.

METHODS

We performed a systematic review of the PubMed database to obtain peer-reviewed publications reporting data on norovirus or rotavirus cases and their potential association(s) with HBGA phenotypes [23, 24]. The full search strategy is detailed in the [Supplementary Appendix \(Supplementary Table 1\)](#). Briefly, our search included terms such as “histo blood group antigens,” “secretor,” “*FUT2*,” and other related terminology. Titles and abstracts were screened for relevance before assessment of full-text articles. Publications were included if they presented data on the number of infected or symptomatic individuals as well as uninfected or asymptomatic individuals among any of the following categories: secretor status, Lewis phenotype, and ABO blood group. We excluded publications that presented secondary data analysis or nonhuman data, those written in a language other than English, and those without a control group. We did not restrict our search strategy by study design or year of publication; we included all publications identified through 1 December 2014. Additional publications were identified through reference lists from included papers.

Data Abstraction and Variable Definition

Data on the following variables were abstracted from each publication, when available: last name of first author, title and year of publication, journal name, study type and setting, pathogen type (ie, norovirus or rotavirus), race and age of study participants, the specific *FUT2* mutation under analysis, and the number of cases and controls. When publications presented multiple control groups, we compared cases with the pooled controls. Data on the number of infected and uninfected individuals were abstracted for the following groups: secretors and nonsecretors, Lewis positives and negatives (abstracted by genotype where presented), and blood types A, B, O, and AB. Data were stratified by pathogen genotype or serotype; studies that presented data on multiple genotypes were represented by multiple data lines.

Cases were defined as individuals with a laboratory-confirmed infection of norovirus or rotavirus, and controls were defined as those without a laboratory-confirmed infection. However, in studies in which norovirus and rotavirus cases were not

laboratory tested (ie, outbreak summaries), symptomatic illness was considered as a proxy for infection, and asymptomatic or unexposed individuals were considered as controls.

Control group data were required for inclusion. However, due to the paucity of data on rotavirus, we included data from 1 publication on rotavirus that presented results from 2 separate study sites, only 1 of which had control group data. For data from the study site without control group data, cases infected with 1 strain were compared with cases infected with other strains to determine odds of strain-specific infection (eg, P[4] infections were compared with P[6] and P[8] infections).

All individuals with *FUT2* mutations were grouped as nonsecretors, regardless of the type of mutation. Homozygous carriers of the missense mutation found at nucleotide 385 (A > T), commonly recognized as “weak secretors,” were included in the nonsecretor category for analytic purposes. Additionally, since the categorization of secretor status varied among studies, with most studies presenting data only on secretors and nonsecretors, partial secretors (ie, heterozygous individuals) were classified as secretors.

Statistical Analyses

Our primary objective was to determine if the odds of norovirus or rotavirus infection were associated with mutations in the *FUT2* gene. All publications identified through our systematic review were included in the metaanalysis. We estimated pooled odds ratios (ORs) for infection (vs no infection) between secretors and nonsecretors by using a random-effects model stratified by genotype. When calculating ORs for study data that included zero individuals in any group, 0.5 was added to all groups in that study. Statistical significance was determined by the 95% confidence interval (CI). For analysis of norovirus infections, we classified genotypes into the following 3 groups: GI, GII non-4 (not including GII.4), and GII.4. For the rotavirus analysis, strains were separated into the following 3 groups based on the VP4 gene: P[4], P[6], and P[8]. We assessed the amount of residual heterogeneity by calculating the I^2 statistic. Publication bias was assessed using Egger’s regression test.

We conducted 2 additional analyses to determine the odds of norovirus infection between Lewis-positive and Lewis-negative individuals and between individuals with O blood type and those with non-O blood types (A, B, and AB). Pooled ORs and 95% CIs for the additional analyses were generated through random-effects models.

To examine differences by study design among the norovirus studies, we conducted a meta-regression analysis that included both genotype and study design. All analyses were conducted using the metafor package in R [25, 26].

RESULTS

We identified 72 publications, of which 39 full-text articles were assessed for inclusion (Figure 1). In total, 23 publications met

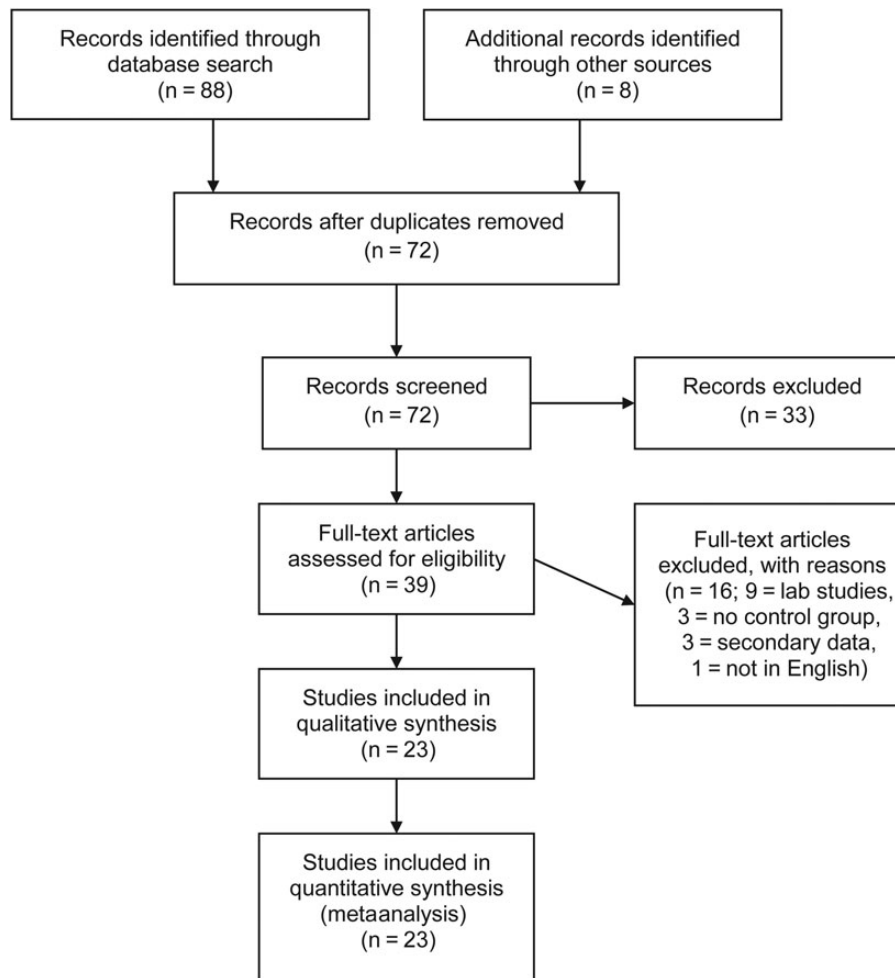


Figure 1. Study selection.

our inclusion criteria; almost all were published between 2002 and 2014 (2 articles were pending acceptance at the time of our search and were subsequently accepted in early 2015) (Supplementary Tables 2 and 3). Of 23 publications from which data were abstracted, 19 (86%) contained data only on norovirus, while 3 (9%) included data on rotavirus and 1 (5%) included data on both viruses. Publications included data on a total of 4584 individuals from 12 countries and on age groups ranging from children aged <5 years to the elderly. Associations between rotavirus or norovirus and secretor status were assessed in 22 studies (96%), with blood group in 10 studies (46%) and with Lewis phenotype in 5 studies (23%). Of those studies that reported associations, 16 (72%), 4 (40%), and 2 (40%) publications reported a significant positive association ($P < .05$) between infection and secretor status, O blood type, or Lewis epitope, respectively.

Norovirus

Overall, among 18 norovirus studies that presented data on associations with secretor status, secretors had 4.2 times the odds

of infection when compared with nonsecretors (95% CI, 2.3–7.9; I^2 statistic, 73%; Figure 2). Secretors were 9.9 times more frequently infected with GII.4 noroviruses (95% CI, 3.9–24.8; I^2 statistic, 38%) and 2.2 times more frequently infected with GII non-4 noroviruses than nonsecretors (95% CI, 1.2–4.2; I^2 statistic, 34%). When examined overall, secretors had higher odds of infection with GI (OR, 3.4; 95% CI, .7–16.7; I^2 statistic, 87%) noroviruses, though the effect was nonsignificant. There was evidence of publication bias in the norovirus outcome studies taken as a whole ($P < .001$).

Controlling for genotype, challenge studies were significantly associated with increased odds of infection ($P < .001$). Exclusion of challenge studies from the model did not yield a substantial difference among the GII.4 and GII non-4 groups. When challenge studies were excluded from the GI group, secretors had lower odds of infection (OR, 0.8; 95% CI, .5–1.3; I^2 statistic, 0%); this effect was nonsignificant.

Neither blood type O (compared with A, B, or AB blood type; OR, 1.5; 95% CI, .9–2.6; I^2 statistic, 64%; Figure 3) or

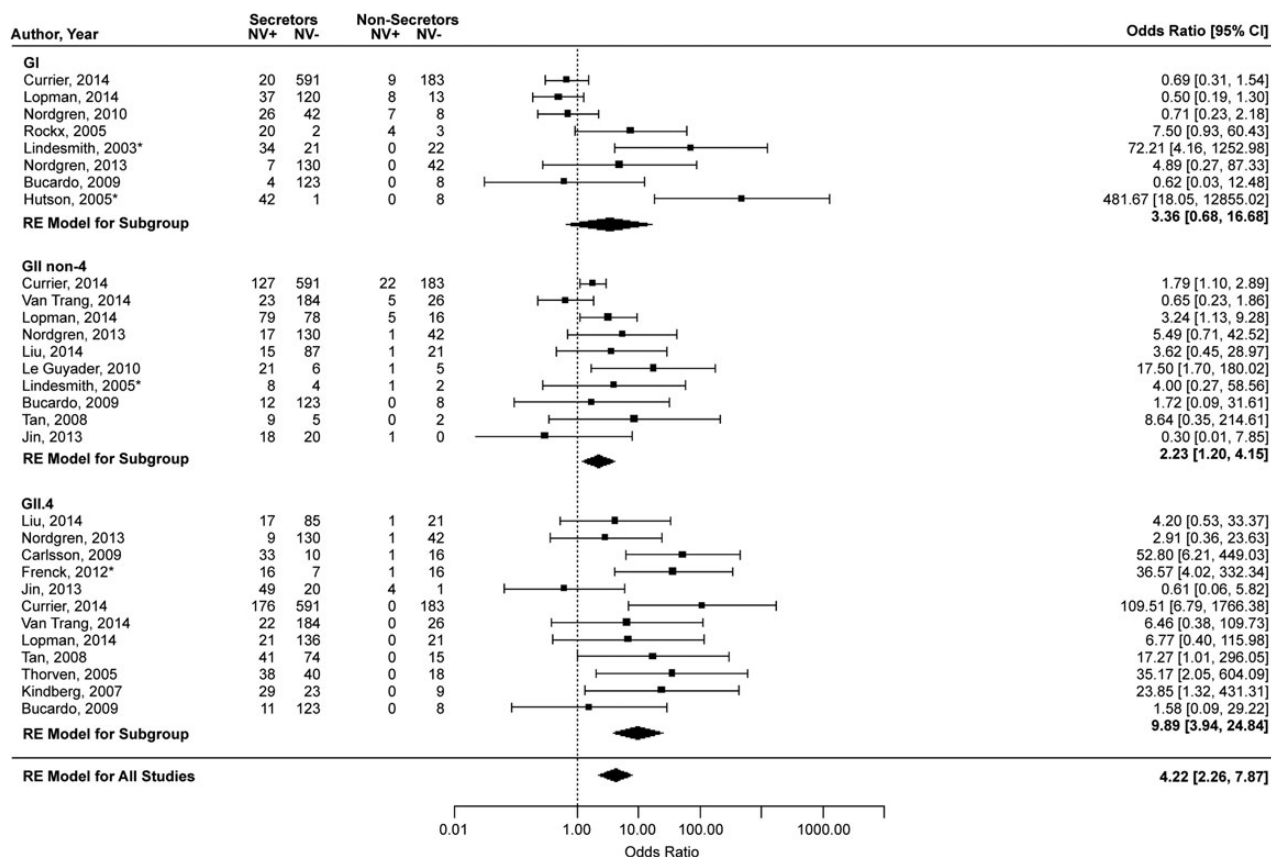


Figure 2. Susceptibility to norovirus infection based on secretor status, by genotype. Studies that presented data on multiple genotypes compared with 1 control group were stratified by genotype and compared with the same control group. *Challenge studies are denoted with an asterisk. Abbreviations: CI, confidence interval; NV+, norovirus positive; NV-, norovirus negative; RE, random effects.

Lewis-positive individuals (compared with Lewis negative; OR, 1.1; 95% CI, .6–1.8; I^2 statistic, 0%; Figure 4) had greater odds of norovirus infection. No evidence of publication bias was found for either analysis.

Rotavirus

Among 4 studies that presented data on associations between rotavirus and secretor status, secretors had 4.2 times the odds of infection (95% CI, 1.1–15.8; I^2 statistic, 70%) with rotavirus overall compared with nonsecretors (Figure 5). Secretors were significantly more likely to have P[8] infections than nonsecretors (OR, 26.6; 95% CI, 8.3–85.0; I^2 statistic, 0%). This result was highly consistent for all studies that reported an association between secretor status and rotavirus. Secretor status was not significantly associated with susceptibility to either P[6] (OR, 0.4; 95% CI, .0–4.1; I^2 statistic, 71%) or P[4] (OR, 3.6; 95% CI, .7–19.6; I^2 statistic, 0%) infections. There was no evidence of publication bias in the rotavirus studies.

DISCUSSION

Our analysis revealed consistent associations between secretor status and susceptibility to both norovirus and rotavirus

infection. Secretors had increased likelihood of norovirus infection, and this risk was driven by susceptibility to GII norovirus infections, most importantly, GII.4 noroviruses. We did not find a significantly increased risk of infection with GI noroviruses among secretors. Interestingly, the 2 studies that reported strong associations with GI were both GI.1 volunteer challenge studies, supporting the notion that GI.1 viruses have secretor-dependent binding properties distinct from contemporary GI viruses. When these challenge studies were excluded from the model, the risk of GI infection dropped substantially, suggesting that any association between secretor status and susceptibility to GI infections overall may be driven by GI.1 noroviruses, which no longer commonly cause outbreaks [27]. While there is mechanistic evidence that Lewis phenotype and ABO blood type also play a role in susceptibility to norovirus [16], we did not observe a clear association with infection for either. Based on the limited data on rotavirus, we found a similarly increased risk of infection for secretor-positive individuals, driven by a substantially heightened risk for P[8] rotavirus infection.

Despite the different study designs and populations, we found a good deal of consistency between studies. After controlling for genotype in the meta-regression model, only challenge

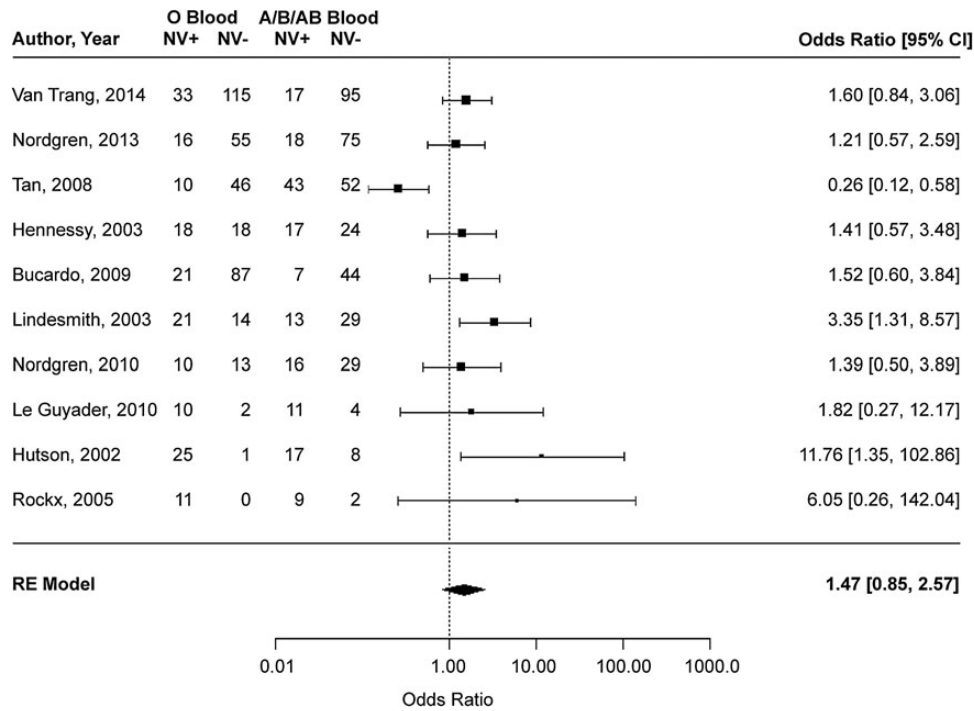


Figure 3. Susceptibility to norovirus infection based on blood type. Abbreviations: CI, confidence interval; NV+, norovirus positive; NV-, norovirus negative; RE, random effects.

studies were significantly associated with increased odds of infection; exclusion of these studies did not yield a considerable difference in the effect among the GII.4 and GII non-4 groups. After accounting for different genotype profiles, most groups

had little to no heterogeneity, as measured by the I^2 statistic. The rotavirus studies had a similar pattern; however, studies on P[6] had a significant amount of heterogeneity. More studies on associations with P[6] rotavirus would help ascertain susceptibility

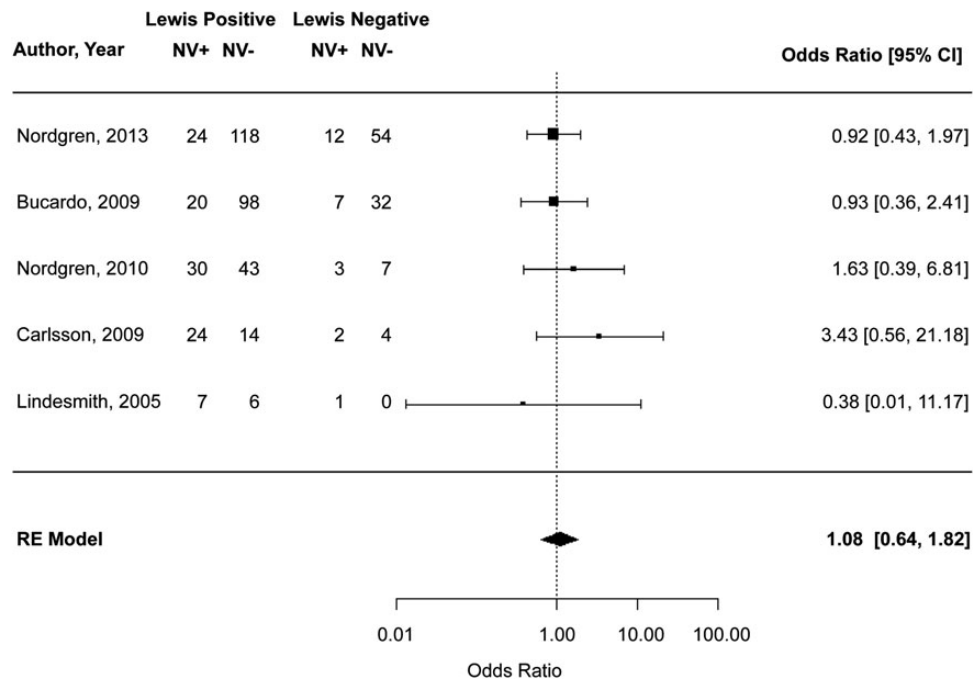


Figure 4. Susceptibility to norovirus infection based on Lewis status. Abbreviations: CI, confidence interval; NV+, norovirus positive; NV-, norovirus negative; RE, random effects.

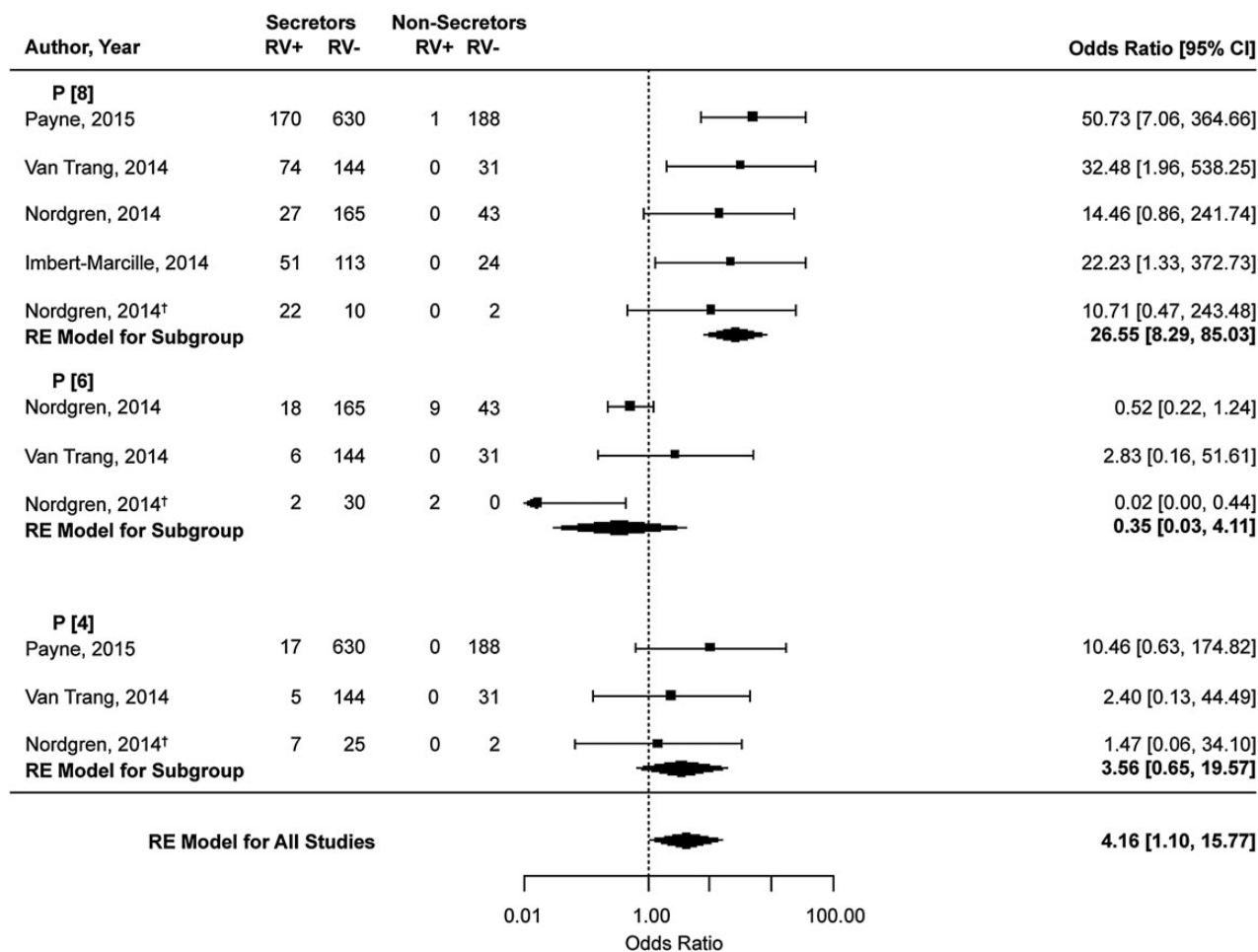


Figure 5. Susceptibility to rotavirus infection based on secretor status, by genotype. [†]Cases infected with 1 strain were compared with cases infected with other strains to determine odds of strain-specific infection (eg, P[4] infections were compared with P[6] and P[8] infections). Abbreviations: CI, confidence interval; RE, random effects; RV+, rotavirus positive; RV–, rotavirus negative.

to this type of rotavirus. Some of the observed heterogeneity among both the rotavirus and norovirus studies might be explained by variation among ethnicities and associated single nucleotide polymorphisms. For example, homozygous carriers of the 385 (A > T) missense mutation are considered “weak” secretors, as they express low levels of H-antigen, as opposed to “nonsecretors” with the 428 (G > A) nonsense mutation who do not secrete H-antigen. As the 2 mutations are different in functionality, they may also cause differences in susceptibility to specific strains.

Similarly, there was evidence of publication bias in the norovirus studies when examined as a whole. This may suggest that some negative results (ie, studies finding a lack of association) are not being published. This has clear implications; in order to develop a complete understanding of host susceptibility, data on negative associations with genetic predictors are as important as data on positive associations, as they may reveal variation among groups such as ethnicity.

Several limitations must be considered in conjunction with our findings. First, the publications included in our analysis

represented differences in the way infected individuals and uninfected individuals were defined. For example, in outbreak studies, symptomatic individuals are considered as infected cases, even in circumstances where not all infections were laboratory confirmed, and therefore may have been the result of an unrelated etiology. Similarly for outbreak studies, the classification of controls may include some who were not truly exposed to the virus, as well as those who were infected but were asymptomatic. In contrast, challenge studies use both seroconversion as well as detection of viral RNA in stool samples to identify cases, resulting in a more sensitive and specific diagnosis for all infected individuals, including those who were asymptomatic. Another advantage of challenge studies compared with observational studies is that all participants are known to have an exposure. Because all participants in challenge studies are exposed to the virus, individuals defined as uninfected are truly uninfected.

Second, all of the rotavirus studies are hospital-based and, as a result, may have only captured severe illness. Thus, our

findings may reflect susceptibility to severe illness, rather than susceptibility to infection. To some degree, this might have also impacted the norovirus results, though results from community and challenge studies appeared to be consistent.

Another limitation was the small number of published studies that examined innate susceptibility to rotavirus. While we were able to assess susceptibility to norovirus based on secretor status, Lewis status, and blood type, we were only able to analyze the relationship between secretor status and rotavirus. Additional studies that focus on the association with rotavirus are needed to fully assess variations in susceptibility as a result of *FUT2* and *FUT3* mutations.

Finally, there was incomplete geographical representation in the studies included in our metaanalysis. More than a quarter of the studies we included were conducted in the United States, and a similar number originated from European countries. Conversely, there were little to no data from Asian populations, specifically those of Polynesian descent, as well as Middle Eastern and South Asian populations. Study participants from Central and South American countries were also underrepresented; these countries often include large indigenous populations.

The lack of wide geographical representation is especially important to the topic of *FUT2* and *FUT3* polymorphisms, the proportion of which varies among different ethnicities, potentially leading to differences in risk of infection among those populations. Some examples include the predominance of the missense mutation at nucleotide 385 (A > T) among East Asian populations and of the Lewis-negative phenotype among African populations [17, 28]. Notably, one study suggested that a Lewis-negative predominant African population in Burkina Faso was naturally protected from P[8] rotavirus infections [21]. Since individuals from several regions are underrepresented, we cannot extrapolate our results to individuals of all ethnicities, and future research should focus on these populations in order to determine to what extent susceptibility based on secretor status may vary among different ethnic groups. Research should also include consideration of the interaction between enteric bacteria and viruses in determining susceptibility; a recent study demonstrated that depletion of intestinal flora significantly reduced murine norovirus titers [29].

The results of our analysis suggest the potential for pharmaceutical and other therapeutic interventions that block the binding of norovirus and rotavirus to HBGA glycans, which would impede the first step of the virus infection process. Studies have shown that human breast milk from mothers with the secretor phenotype contains fucosylated oligosaccharides, which can act as such a blockade against the binding of norovirus virus-like particles [30, 31].

These results also have implications for vaccine development and study design. As our analysis indicates, some individuals may be protected against infection and, further, may not respond to the vaccine. A recent GII.4 norovirus vaccine trial

included secretor status as a criterion for eligibility in order to ensure susceptibility to the challenge virus [10]. Results of vaccine efficacy studies should be interpreted while bearing in mind the proportion of individuals in the study population with *FUT2* or *FUT3* polymorphisms. Differences in susceptibility to P[8] rotaviruses may also suggest that nonsecretors respond less well to vaccination. However, current evidence shows that both vaccines are effective against heterotypic and homotypic strains [32].

In conclusion, analysis of the existing literature suggests a strong association between the *FUT2* gene and risk of infection with GII.4 noroviruses and P[8] rotaviruses. Future observational studies in Asia and South and Central America and among various ethnicities in these regions are needed in order to understand differences in innate susceptibility to enteric viruses. Further, it is important to understand the potential contribution of commensal bacteria in order to determine susceptibility to these viruses. Understanding patterns of susceptibility may be useful for the development of norovirus vaccines and therapeutics and the application of both norovirus and rotavirus vaccines among populations with an increased or decreased likelihood of infection.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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Potential conflict of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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