

Published in final edited form as:

*J Infect Dis.* 2019 February 15; 219(5): 836–843. doi:10.1093/infdis/jiy582.

## ***FUT2* gene variants and reported respiratory and gastrointestinal illnesses during infancy**

Sheila J. Barton, PhD<sup>1</sup>, Robert Murray, PhD<sup>2</sup>, Karen A. Lillycrop, PhD<sup>2,4</sup>, Hazel M Inskip, PhD<sup>1,3</sup>, Nicholas C Harvey, MA, MB, BChir, PhD, FRCP<sup>1,3</sup>, Cyrus Cooper, OBE, DL, FMedSci<sup>1,3</sup>, Neerja Karnani, PhD<sup>5,6</sup>, Irma Silva Zolezzi, PhD<sup>7</sup>, Norbert Sprenger, PhD<sup>7</sup>, Keith M. Godfrey, BM FRCP PhD<sup>1,2,3</sup>, Aristeia Binia, PhD<sup>7</sup>

<sup>1</sup>MRC Lifecourse Epidemiology Unit, University of Southampton, UK <sup>2</sup>Human Development and Health Academic Unit, University of Southampton, UK <sup>3</sup>NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, UK <sup>4</sup>School of Biological Sciences, University of Southampton, Southampton General Hospital, UK <sup>5</sup>SO16 6YD <sup>6</sup>Singapore Institute for Clinical Sciences, A\*STAR, Singapore <sup>7</sup>Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore <sup>7</sup>Nestlé Research Center, Lausanne, Nestec S.A., Switzerland

### **Abstract**

**Background**—*FUT2* controls the production on digestive and respiratory epithelia of histo-blood group antigens involved in the attachment of pathogens. The aim of our study was to relate *FUT2* variants to reported gastrointestinal and respiratory illnesses in infancy.

**Methods**—In the UK Southampton Women’s Survey, *FUT2* genetic variants (rs601338, rs602662) were genotyped in 1831 infants and related to infant illnesses adjusting for sex, breastfeeding duration and potential confounders.

**Results**—For *FUT2* SNP rs601338, the risk ratios for 1 bout of diarrhoea from ages 6-12 and 12-24 months per additional risk (G) allele were 1.23 (95%CI 1.08-1.4,  $p=0.002$ ) and 1.41 (1.24-1.61  $p=1.7\times 10^{-7}$ ), respectively; the risk ratio for 1 diagnoses of lower respiratory illnesses

---

**Correspondence to:** Dr Aristeia Binia, Nestlé Research Center, P.O. Box 44, Vers-chez-les-Blanc, CH-1000 Lausanne 26, Phone: +41-21-785-8278, aristeia.binia@rdls.nestle.com.

Part of this work was presented in a poster presentation during “The International Society for Developmental Origins of Health and Disease” conference in 2017.

**Conflict of interest:**

Dr Barton is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone

Dr Murray is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone

Dr Lillycrop is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone

Prof Inskip has no conflicts of interest

Dr Harvey has no conflicts of interest

Dr Cooper has no conflicts of interest

Dr Karmani is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone

Dr Silva Zolezzi, is an employee of Nestec S.A

Dr Sprenger is an employee of Nestec S.A

Prof Godfrey has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone

Dr Binia is an employee of Nestec S.A

(pneumonia or bronchiolitis) from 12-24 months per additional G allele was 2.66 (1.64-4.3,  $p=0.00007$ ). Similar associations were found between rs602662 and gastrointestinal and respiratory illnesses, due to the high linkage disequilibrium with rs601338 ( $R^2=0.92$ ). Longer breastfeeding duration predicted a lower risk of diarrhoea independent of infant *FUT2* genotype.

**Conclusions**—We confirmed that *FUT2* G-alleles are associated with a higher risk of infant gastrointestinal illnesses and identified novel associations with respiratory illnesses. *FUT2* locus variants need consideration in future studies of infantile gastrointestinal and respiratory illnesses.

## Keywords

*FUT2* variants; gastrointestinal and respiratory illnesses; paediatric illnesses

---

## Introduction

Diarrhoea and respiratory illnesses are major causes of morbidity and mortality in young children less than five years of age, with over 2 million deaths per year[1]. Preventive measures and improved disease management have reduced mortality, but it remains particularly substantial in low or middle-income countries[1], accounting for 30% of early childhood deaths worldwide[2]. Mortality is especially high in young children with multiple episodes per year[3, 4]. In developed countries, gastroenteritis cases are mainly due to rotavirus (in unvaccinated children), norovirus, adenovirus and *Salmonella*, with the first two accounting for half and a third of the cases, respectively, and the last two approximately 10%. In young children, rotavirus and norovirus infections are highly prevalent, with a peak age between 3 months and two years[5]. For acute lower respiratory infection in young children, human respiratory syncytial virus (RSV) is the most common causal pathogen[6]. Breastfeeding is proposed as a protective factor against both diarrhoea and respiratory infections, suggesting that early cessation of lactation and the benefits delivered to the infants might contribute to the avertable infections [7, 8].

Host characteristics are known to impact the susceptibility to early childhood infections. Recent studies have reported that genetic polymorphisms affecting the production of histo-blood group antigens (HBGA), which can act as attachment sites for specific pathogens, are associated with incidence of diarrhoea [9–11]. The *FUT2* (FUT2 [MIM: +182100]) gene encodes for  $\alpha$ 1,2-fucosyltransferase 2, which catalyzes the addition of a fucose to the H-type 1 precursor, generating the H-type antigen in saliva and on digestive and respiratory epithelia, producing the secretor phenotype. Inactivating polymorphisms in *FUT2* give rise to the non-secretor status, characterized by the absence of H-type antigen in mucosal tissues and secretions[12]. The objective of our study was to assess the genetic risk that *FUT2* contributes to infant morbidities in a UK mother-offspring cohort study (the Southampton Women's Survey (SWS)); given the presence of H-type antigen on respiratory epithelia, our particular focus was on respiratory illnesses which have not previously been related to *FUT2* variants in population-based studies.

## Methods

### Study Population

Offspring of participants in the SWS were studied [13]. Between 1998 and 2007, 3158 infants were born and data were collected on them both during the pregnancy and after the birth. Infant health outcomes (chest wheezing, cough, pneumonia or bronchiolitis, croup, diarrhoea, vomiting and ear infections) were assessed by nurse-led questionnaires 6, 12 and 24 months after birth (Questions asked by research nurses on infant health outcomes are listed in Supplementary Table 2). Detailed information about breastfeeding was also obtained by nurse-led questionnaires administered at 6, 12 and 24 months after the birth of the child. Maternal smoking during pregnancy was assessed by questionnaire in early and late pregnancy. Visits were placed at short intervals (6, 12 and 24 months) and trained research nurses familiar with infant health outcomes administered all questionnaires to minimise recall bias.

**Patient Consent and Ethical Approval**—All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Southampton and South West Hampshire Research Ethics Committee approved all procedures (276/97, 307/97). Informed consent was obtained from all individual participants included in the study.

**Research Reporting Checklist**—The STROBE guideline checklist (<http://www.strobe-statement.org/index.php?id=strobe-home>) was used in the preparation of this manuscript.

### DNA extraction

A 5-10 cm segment was cut from the mid portion of each cord, immediately following delivery, flushed with saline to remove fetal blood, flash-frozen in liquid nitrogen and stored at  $-80^{\circ}\text{C}$  until required for DNA isolation. Genomic DNA was prepared from umbilical cord and cord blood by a standard high salt method [14], and from adipose tissue using the QIAamp DNA mini kit (Qiagen, Germany).

### Genotyping of FUT2 variants

1831 offspring and their mothers from the SWS cohort with infant health outcomes and available DNA were genotyped for 2 polymorphisms, rs601338 and rs602662, in the *FUT2* gene located on chromosome 19. The genomic region containing rs601338 and rs602662 was amplified by PCR following manufacturer's guidelines (HotStarTaq Plus DNA Polymerase, Qiagen, 203605) (Supplementary Table 1). SNP genotyping was carried out on a Pyromark MD.

**Statistical Analysis**—Statistical procedures were performed in Stata version 13 (StataCorp, Texas, USA) and SPSS version 21 (IBM, Armonk, New York). The small number of offspring ( $n=83$ ) whose mothers were recorded as having non-white ethnicity were excluded from analysis to ensure genetic homogeneity in the study population.

Genotypes were coded according to the additive model (0, 1 or 2 copies of the G allele). Infant health outcomes were coded as dichotomous variables indicating whether the child had suffered one or more episodes of the health outcome or not

Binary regressions were completed with each genotype individually used as a predictor variable for each infant health outcome, adjusting for child's sex, parity, mode of delivery (vaginal or Caesarean), maternal SES and length of breastfeeding split into 3 groups (never,  $\leq 3$  months,  $> 3$  months). Analyses of infant diarrhoea, from 6 to 12 and 12 to 24 months (which do not commonly result in a doctor's prescription of antibiotics) were additionally adjusted for infant antibiotic use to reduce the likelihood of any observed associations resulting from antibiotic use rather than an infective episode. Infant antibiotic use from 6 to 12 months was also examined to see if it was associated with episodes of diarrhoea from 12 to 24 months. Regressions showing association between offspring *FUT2* SNPs and health outcomes were additionally adjusted for matching maternal genotype where available, and for preterm birth ( $< 37$  weeks). Results from binary regression are expressed as risk ratios per unit increase in number of risk alleles. A Benjamini-Hochberg procedure with a False Discovery Rate (FDR) of 10% was applied to account for multiple testing.

## Results

Supplementary Table 3 shows genotype distributions for white and other ethnicities in the SWS cohort. Chi squared tests show that there were associations between rs602662 and ethnicity ( $p=0.004$ ) and between rs601338 and ethnicity ( $p=0.025$ ). Expected values show that whites had fewer *g/g* genotypes and more *a/a* genotypes than other ethnicities. Therefore analysis was restricted to white infants only due to insufficient numbers of other ethnicities in the SWS cohort.

Both SNPs, rs601338 and rs602662 in *FUT2*, were in Hardy-Weinberg equilibrium in the infants with white ethnicity (chi squared  $p$ -value $>0.05$ ). rs601338 had a minor allele frequency of 48.7% (A) and rs602662 had a minor allele frequency of 48.6% (G). rs602662 is in high Linkage Disequilibrium (LD) with rs601338 in Caucasian populations ( $R^2=0.92$ ; Ensembl).

Analysis of infant health outcomes was based on 1831 SWS singleton births with available phenotype data from birth to 24 months and genotype for at least one SNP. Table 1 shows summary statistics for the study sample from the SWS cohort ( $n=1831$ ). A comparison of infants included ( $n=1831$ ) and not included ( $n=1327$ ) in the study is shown in Supplementary Table 4.

Figure 1 shows risk ratios and 95% Confidence Intervals for each copy of the risk allele (G) for rs601338 and all infant health outcomes tested.

For *FUT2* SNP rs601338, infants who possessed the G allele were more likely to suffer infant vomiting, diarrhoea, pneumonia/bronchiolitis and nocturnal cough than infants possessing A alleles. Thus, *FUT2* SNP rs601338 showed a significant association with one or more episodes of diarrhoea from birth to 6 months (risk ratio 1.20 (95%CI 1.03-1.4),  $p=0.017$ ), 6 to 12 months (risk ratio 1.15 (1.04-1.26),  $p=0.004$ ) and 12 to 24 months (risk

ratio 1.29 (1.17-1.43),  $p=3.27 \times 10^{-7}$ ). rs601338 was associated with one or more episodes of vomiting from 6 to 12 months (risk ratio 1.23 (1.08-1.4),  $p=0.002$ ) and from 12 to 24 months (risk ratio 1.41 (1.24-1.61)  $p=1.7 \times 10^{-7}$ ). rs601338 was also associated with one or more diagnoses of lower respiratory illness (pneumonia or bronchiolitis) between 12 to 24 months (risk ratio 2.66 (1.64-4.3),  $p=0.00007$ ) and with nocturnal cough between 12 to 24 months (risk ratio 1.16 (1.02-1.33),  $p=0.029$ ). No significant associations were observed between rs601338 and croup, wheezing, ear infections, atopic eczema or atopy from birth to 24 months (Figure 1). Similar results were observed for rs602662 as the two SNPs are in high Linkage Disequilibrium ( $R^2=0.92$ ) (Supplementary Figure 1).

Antibiotic use from 6 to 12 months was associated with increased episodes of diarrhoea from 12 to 24 months ( $p=0.006$ ).

Length of breastfeeding (>3 months compared to never breastfed) was also a significant predictor of infant diarrhoea and pneumonia/ bronchiolitis from 12 to 24 months ( $p=0.042$ ). Longer breastfeeding duration lowered the risk of diarrhoea and pneumonia/bronchiolitis independent of infant *FUT2* genotype. Maternal *FUT2* genotype was not found to be a significant predictor of infant health outcomes when infant *FUT2* genotype was included in the model. Preterm birth was not a significant predictor of infant health outcomes with a Benjamini and Hochberg FDR of 10%.

## Discussion

Our study showed significant associations of *FUT2* SNPs rs601338 and rs602662 with the risks of reported respiratory and diarrhoeal illnesses, as well as vomiting and nocturnal cough from birth to 24 months in infants in a population based study. The risk of diarrhoeal infections was significantly higher in the infants possessing the G allele compared to those with the A alleles in *FUT2* SNPs. The result was consistent from birth to 6 months, to 12 months and up to 24 months. Prevalence rates for one or more reported bouts of diarrhoeal lasting more than 2 days were highest between 6 and 12 months of age, being reported for 36% of infants. Reported pneumonia or bronchiolitis was less frequent in this population, ranging from 2.9% between birth and age 6 months to 4.3% between ages 12 and 24 months. G alleles on both *FUT2* SNPs tested conferred higher risk of pneumonia or bronchiolitis in this population. Other comorbidities potentially linked to infectious diseases, like vomiting lasting more than 2 days and nocturnal cough, were also associated with these *FUT2* SNPs at 6 to 12 months and at 24 months respectively. The direction of the association was the same, with a lower risk of illness in the carriers of G alleles.

Our main findings are in line with existing literature on diarrhoeal infections and host genetic susceptibility. *FUT2* genetic variations have been associated with susceptibility to diarrheal infections in several studies [9, 10, 15, 16]. SNP rs601338 (W154X) was identified as the possible causal variant in recent meta-analysis of birth cohorts studies consisting of >5,000 young children [9]. The strongest association was found for at “at least one episode of diarrhoea” reported around age 1 year but strong results were also reported for other time-points. Similarly, in our study, a reduced risk of diarrheal episodes with rs601338 SNP was consistently reported from 6 to 24 months but with a stronger association for diarrheal

episodes from 12 to 24 months. A community-based birth study from Ecuador assessed the associations of norovirus gastroenteritis with secretor status at first 3 years of life and identified that secretor children were more susceptible to norovirus GII.4 genotype infections, whereas non-secretors were susceptible to non-GII.4 infections. [17]. Another study in China of children with acute diarrhoea was in line in these findings, although the detection of cases of norovirus GII.4 and GII.3- associated diarrheal infections in non-secretors showed that these children are not fully protected [18]. Our data did not include information on the specific diarrheal aetiology or identification of pathogens; it is however known that norovirus and rotavirus infections are the commonest among children and they are influenced by *FUT2* genotype [10, 16, 19]. Previous studies suggest that most probably a direct association between secretor phenotype or *FUT2* genotypes and incidence of norovirus or rotavirus-identified infection outbreaks exists, with non-secretor or carriers of *FUT2* non-functional mutations having protection against these infections [10, 16, 19] (Figure 2). *FUT2* genetic variations or secretor status, as parts of the innate host genetic factors have been also shown to interact with intestinal microbiota [20–22]. In light of this, a recent study aimed to investigate the interactions of among *FUT2* genotypes, gut microbiota and viral infections typically linked to norovirus and rotavirus [23]. The study however could not confirm significant differences in intestinal microbial composition between *FUT2* genotype groups, suggesting that these associations may be specific to the disease context or environmental exposures [24, 25]. Whether there is a direct link of association between risk of diarrheal infections and *FUT2* genotypes, or if intestinal microbiota are interacting with host genetics to modulate risk of infections, is not well understood.

Our novel findings on reported respiratory illnesses are in the same direction as in the recent study by Taylor *et al.*, 2017, in which secretor patients with non-cystic fibrosis bronchiectasis had an increased susceptibility to *Pseudomonas aeruginosa*-dominated airway infection compared to non-secretors among other disease outcomes [26]. It would be important to confirm these observations in future studies of children with known aetiology of the respiratory infections and other comorbidities.

*FUT2* is highly polymorphic with different inactivating mutations in particular ethnic groups, but with this genetic heterogeneity giving rise to similar proportions of the non-secretor phenotype; for example, approximately 20% of Europeans and 22% of East Asians are non-secretors [27]. American populations of Hispanic ancestry are less likely to be non-secretors compared to non-Hispanic populations, highlighting the low prevalence of the *FUT2* inactivating mutations in Amerindian populations [15]. Non-secretors are characterized by an absence of H antigen in salivary secretions and on mucosal surfaces of the body. In European and African populations, the most common inactivating variant is rs601338 (W154X), whereas in Asian populations the missense SNP rs1047781 (I140F) leads to a truncated protein with weak bioactivity [28]. G risk allele in our study on rs601338 encodes the secretor phenotype, whereas the A allele the non-secretor. The second *FUT2* variant included in our analysis, rs602662, is a missense SNP (G258S) in high LD with rs601338, as shown in our results. This SNP was included in our study, as it has been shown to lead independently of rs601338 to the expression of a *FUT2* enzyme with very low activity and thus might influence the expression of H antigen as well [29]. HBGA groups like the H antigen may mediate the attachment of pathogens, leading to infection. In the case of

rotavirus, the cell attachment viral spike protein VP8\* can recognize A-type HBGA, perhaps leading to increased susceptibility of secretors compared to non-secretors to specific rotavirus strains[30, 31].

Our study showed an association of *FUT2* SNPs with reported pneumonia or bronchiolitis and nocturnal cough from age 12 to 24 months. A single previous study reported that secretors had increased susceptibility to respiratory infections of influenza viruses A and B, rhinoviruses, respiratory syncytial viruses and echoviruses, however, further evidence for the role of *FUT2* genetic polymorphisms in respiratory illnesses is scarce, with none in population-based studies [32]. We acknowledge with caution the findings on reported pneumonia or bronchiolitis, as the number of episodes in our population within the specific time periods were low (Table 1) but a clear association was nonetheless observed.

Breastfeeding was identified as an independent protective exposure in our results, raising the possibility that some of the factors in human milk may reduce the risk of infections independently. The *FUT2* enzyme also controls the production of specific human milk oligosaccharides by adding a fucose molecule to lactose in an  $\alpha$ 1,2-fucosylation activity to generate more complex oligosaccharides such as 2'-fucosyllactose (2'FL) and lacto-N-fucosylpentaose I (LNFP1). These human milk oligosaccharides are present in the milk of all secretors mothers and are absent in the milk of non-secretor mothers. Previous studies have demonstrated a specific protective effect of these oligosaccharides against diarrheal infections in a cohort of Mexican mothers and infants[33]. In that study, where infants were predominantly breastfed, it was postulated that the presence of these indigested oligosaccharides could compete with the attachment of pathogens to the intestinal epithelial surfaces by inhibiting their colonization and subsequent infection. Using this paradigm, a hypothesis could be proposed that presence of these  $\alpha$ 1,2-fucosylated human milk oligosaccharides provided by a secretor lactating mother to her secretor infant might attenuate the increased risk that these infants inherently have to specific strains of viruses (like rotavirus or norovirus), considering that the glycan structures present in both human milk oligosaccharides and the epithelial epitopes are similar. Our study examined the association of maternal secretor status in relation with the risk of infections but no independent effect was found. However, many of the population of mothers and infants we studied were not exclusively breastfed and samples were not available to analyze the presence of oligosaccharides in the mother's breast milk. We might also expect differences in the causal pathogens between our study and the previous Mexican study[33]. Future studies will need to assess this hypothesis by determining both infant secretor status and sequencing for *FUT2* variants, as well as analyzing the presence of  $\alpha$ 1,2-fucosylated human milk oligosaccharides in a predominantly breast fed population.

The main strength of our study was the relatively large population, providing statistical power to examine a number of associations with *FUT2* genotypes. The main limitations are first, that information was not available on the aetiology of the illnesses, and available data on both reported illnesses and genotyping information were available only for a part and not for the entire SWS cohort[13]. Despite the large size of our population, we also did not have the power to analyse subpopulations with different ethnicity. Infant outcomes were self-reported by the mothers through questionnaires administered by research nurses, and could

possibly be affected by recall bias; this was however minimised by short intervals between visits and by trained research nurses administering the questionnaires. Despite this lack of phenotypic specificity we identified significant associations, consistent through time and in the same direction. Second, we could not accurately measure the level of exposure to pathogens, because our study could assess neither the level of exposure to these pathogens in the population, nor variations in hygiene between the *FUT2* subgroups analysed.

## Conclusion

Our study has highlighted the consistent association of *FUT2* variants with risk of diarrhoea in infants, as well as describing novel associations with respiratory illnesses related and comorbidities in a large population of infants. Host genetic susceptibility to infections needs to be accounted in future epidemiological and interventional studies investigating these outcomes, alongside studying the protective role of early life factors such as breastfeeding.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding

This work was supported by different research grants and funding from Nestec S.A. The Southampton Women's Survey is funded through the UK Medical Research Council (as part of an MRC award to the MRC Lifecourse Epidemiology Unit), British Heart Foundation, Food Standards Agency, Arthritis Research UK, National Osteoporosis Society, International Osteoporosis Foundation and Cohen Trust. Funding for the *FUT2* genotyping and associated analysis has been provided by Nestec S.A. under a Research Agreement with the University of Southampton, Auckland UniServices Ltd., Singapore Institute for Clinical Sciences, National University Hospital Singapore PTE Ltd., National University of Singapore. Prof Godfrey is supported by the UK Medical Research Council (MC\_UU\_12011/4), the National Institute for Health Research (as an NIHR Senior Investigator (NF-SI-0515-10042) and through the NIHR Southampton Biomedical Research Centre) and the European Union's Erasmus+ Capacity-Building ENeASEA Project and Seventh Framework Programme (FP7/2007-2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977.

## Abbreviation

<b>FDR</b>	False Discovery Rate
<b>2'FL</b>	2'-fucosyllactose
<b>FUT2</b>	$\alpha$ 1,2-Fucosyltransferase 2
<b>HBGA</b>	Histo-blood group antigens
<b>HMO</b>	Human Milk Oligosaccharide
<b>HWE</b>	Hardy-Weinberg Equilibrium
<b>LD</b>	Linkage Disequilibrium
<b>LNFP1</b>	Lacto-N-fucosylpentaose I
<b>MAF</b>	Minor Allele Frequency
<b>RSV</b>	Respiratory syncytial virus

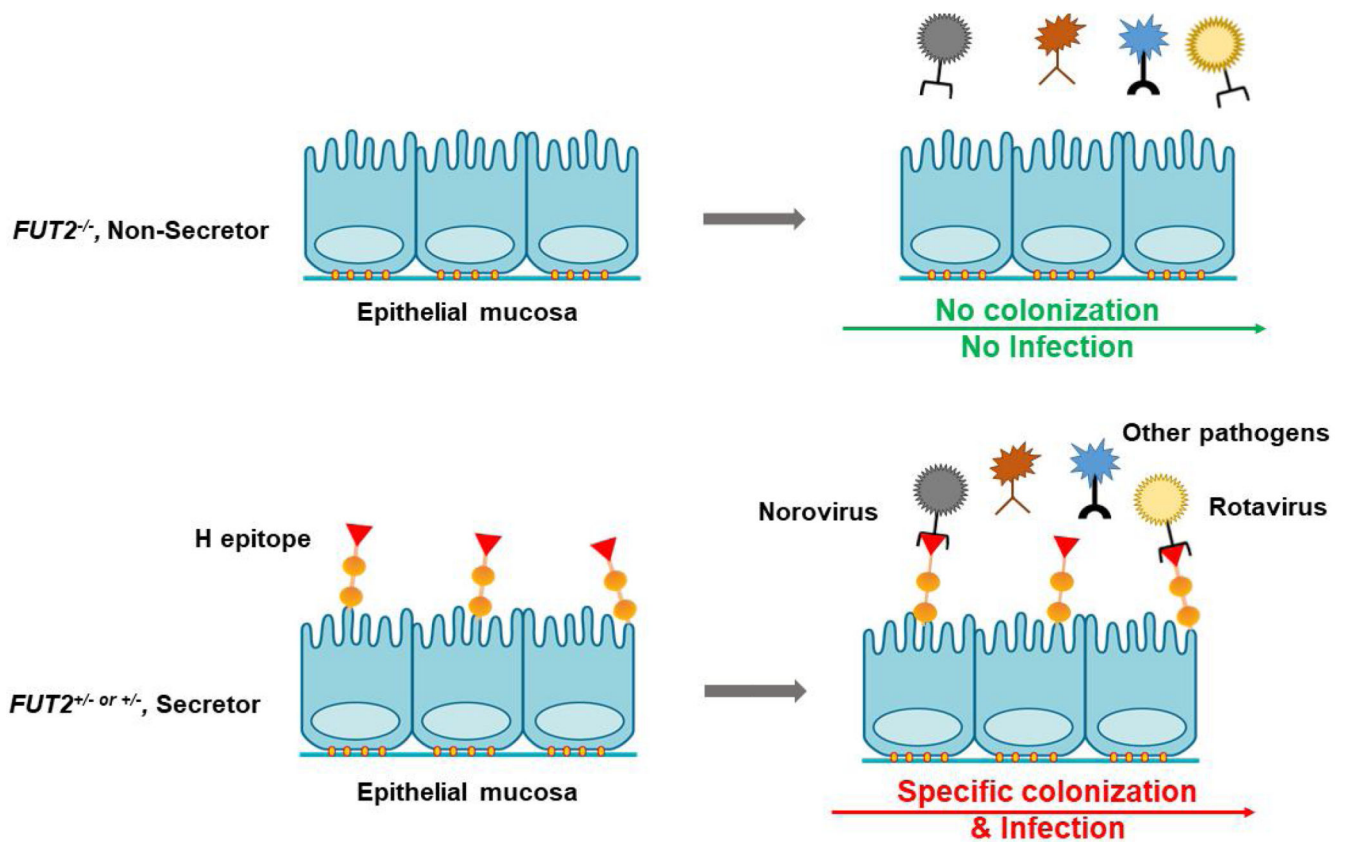


<b>SNP</b>	Single nucleotide polymorphism
<b>SWS</b>	Southampton Women's Survey

## References

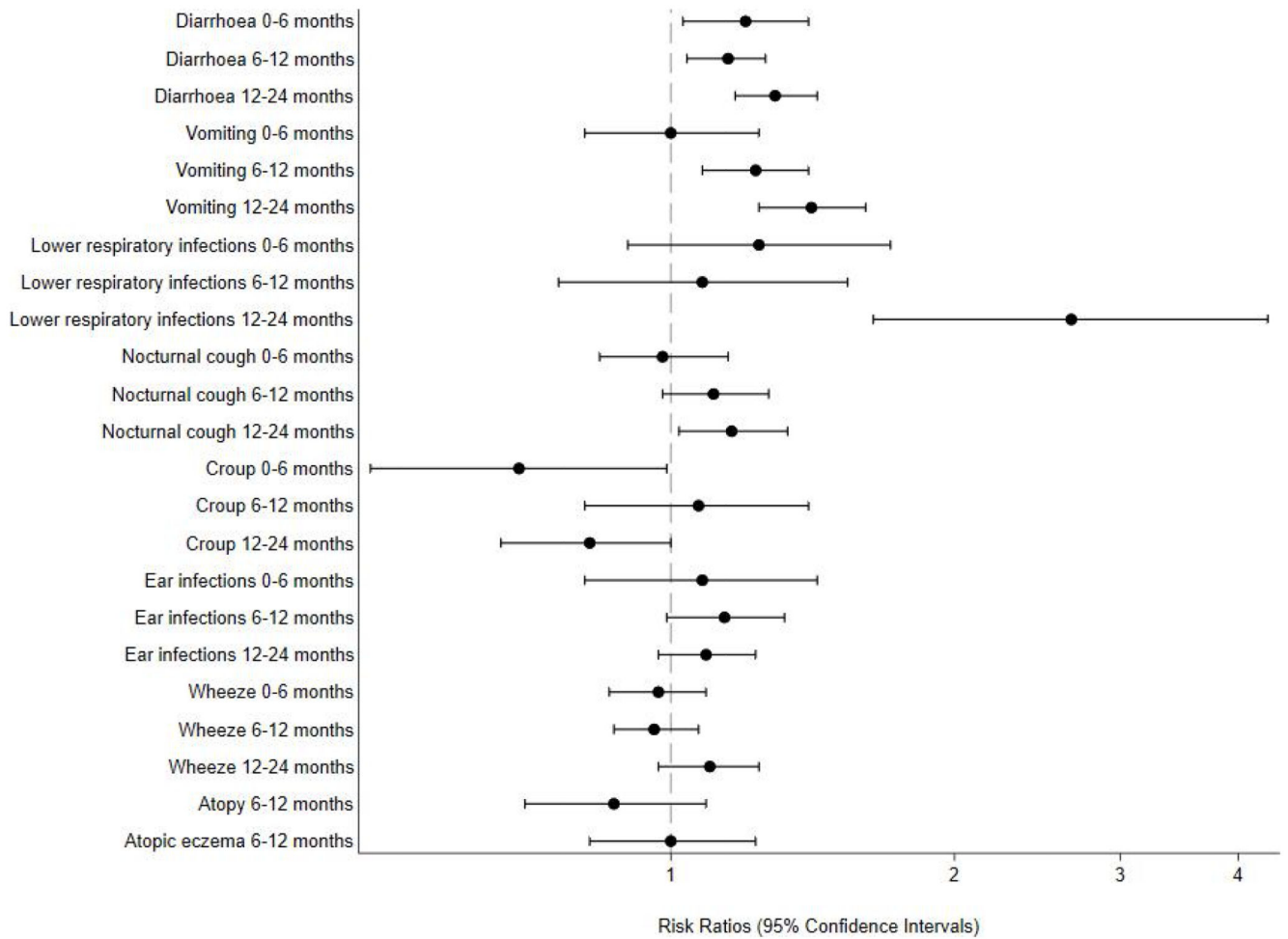
1. Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013; 381:1405–16. [PubMed: 23582727]
2. Keusch, GT, Walker, CF, Das, JK, Horton, S, Habte, D. Diarrheal Diseases Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities. Third Edition. Black, RE, Laxminarayan, R, Temmerman, M, Walker, N, editors. Vol. 2. Washington (DC): 2016.
3. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet*. 2017; 390:946–58. [PubMed: 28689664]
4. Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health*. 2012; 12:220. [PubMed: 22436130]
5. Wiegering V, Kaiser J, Tappe D, Weissbrich B, Morbach H, Girschick HJ. Gastroenteritis in childhood: a retrospective study of 650 hospitalized pediatric patients. *Int J Infect Dis*. 2011; 15:e401–7. [PubMed: 21489842]
6. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010; 375:1545–55. [PubMed: 20399493]
7. Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics*. 2010; 126:e18–25. [PubMed: 20566605]
8. Prameela KK, Vijaya LR. The importance of breastfeeding in rotaviral diarrhoeas. *Malays J Nutr*. 2012; 18:103–11. [PubMed: 23713234]
9. Bustamante M, Standl M, Bassat Q, et al. A genome-wide association meta-analysis of diarrhoeal disease in young children identifies FUT2 locus and provides plausible biological pathways. *Human molecular genetics*. 2016; 25:4127–42. [PubMed: 27559109]
10. Kindberg E, Akerlind B, Johnsen C, et al. Host genetic resistance to symptomatic norovirus (GGII. 4) infections in Denmark. *J Clin Microbiol*. 2007; 45:2720–2. [PubMed: 17537929]
11. Kambhampati A, Payne DC, Costantini V, Lopman BA. Host Genetic Susceptibility to Enteric Viruses: A Systematic Review and Metaanalysis. *Clin Infect Dis*. 2016; 62:11–8. [PubMed: 26508510]
12. Koda Y, Tachida H, Pang H, et al. Contrasting patterns of polymorphisms at the ABO-secretor gene (FUT2) and plasma alpha(1,3)fucosyltransferase gene (FUT6) in human populations. *Genetics*. 2001; 158:747–56. [PubMed: 11404338]
13. Inskip HM, Godfrey KM, Robinson SM, et al. Cohort profile: The Southampton Women's Survey. *International journal of epidemiology*. 2006; 35:42–8. [PubMed: 16195252]
14. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic acids research*. 1988; 16:1215. [PubMed: 3344216]
15. Payne DC, Currier RL, Staat MA, et al. Epidemiologic Association Between FUT2 Secretor Status and Severe Rotavirus Gastroenteritis in Children in the United States. *JAMA Pediatr*. 2015; 169:1040–5. [PubMed: 26389824]
16. Thorven M, Grahn A, Hedlund KO, et al. A homozygous nonsense mutation (428G-->A) in the human secretor (FUT2) gene provides resistance to symptomatic norovirus (GGII) infections. *J Virol*. 2005; 79:15351–5. [PubMed: 16306606]
17. Lopman BA, Trivedi T, Vicuna Y, et al. Norovirus Infection and Disease in an Ecuadorian Birth Cohort: Association of Certain Norovirus Genotypes With Host FUT2 Secretor Status. *J Infect Dis*. 2015; 211:1813–21. [PubMed: 25505295]
18. Liu P, Wang X, Lee JC, et al. Genetic susceptibility to norovirus GII.3 and GII.4 infections in Chinese pediatric diarrheal disease. *Pediatr Infect Dis J*. 2014; 33:e305–9. [PubMed: 25037042]

19. Imbert-Marcille BM, Barbe L, Dupe M, et al. A FUT2 gene common polymorphism determines resistance to rotavirus A of the P[8] genotype. *J Infect Dis.* 2014; 209:1227–30. [PubMed: 24277741]
20. Wacklin P, Tuimala J, Nikkila J, et al. Faecal microbiota composition in adults is associated with the FUT2 gene determining the secretor status. *PLoS One.* 2014; 9:e94863. [PubMed: 24733310]
21. Wacklin P, Makivuokko H, Alakulppi N, et al. Secretor genotype (FUT2 gene) is strongly associated with the composition of Bifidobacteria in the human intestine. *PLoS One.* 2011; 6:e20113. [PubMed: 21625510]
22. Kolde R, Franzosa EA, Rahnavard G, et al. Host genetic variation and its microbiome interactions within the Human Microbiome Project. *Genome Med.* 2018; 10:6. [PubMed: 29378630]
23. Rodriguez-Diaz J, Garcia-Mantrana I, Vila-Vicent S, et al. Relevance of secretor status genotype and microbiota composition in susceptibility to rotavirus and norovirus infections in humans. *Sci Rep.* 2017; 7
24. Davenport ER, Goodrich JK, Bell JT, Spector TD, Ley RE, Clark AG. ABO antigen and secretor statuses are not associated with gut microbiota composition in 1,500 twins. *BMC Genomics.* 2016; 17:941. [PubMed: 27871240]
25. Rausch P, Rehman A, Kunzel S, et al. Colonic mucosa-associated microbiota is influenced by an interaction of Crohn disease and FUT2 (Secretor) genotype. *Proc Natl Acad Sci U S A.* 2011; 108:19030–5. [PubMed: 22068912]
26. Taylor SL, Woodman RJ, Chen AC, et al. FUT2 genotype influences lung function, exacerbation frequency and airway microbiota in non-CF bronchiectasis. *Thorax.* 2017; 72:304–10. [PubMed: 27503233]
27. Ferrer-Admetlla A, Sikora M, Laayouni H, et al. A natural history of FUT2 polymorphism in humans. *Mol Biol Evol.* 2009; 26:1993–2003. [PubMed: 19487333]
28. Silva LM, Carvalho AS, Guillon P, et al. Infection-associated FUT2 (Fucosyltransferase 2) genetic variation and impact on functionality assessed by in vivo studies. *Glycoconj J.* 2010; 27:61–8. [PubMed: 19757028]
29. Serpa J, Mendes N, Reis CA, et al. Two new FUT2 (fucosyltransferase 2 gene) missense polymorphisms, 739G-->A and 839T-->C, are partly responsible for non-secretor status in a Caucasian population from Northern Portugal. *Biochem J.* 2004; 383:469–74. [PubMed: 15250822]
30. Hu L, Crawford SE, Czako R, et al. Cell attachment protein VP8\* of a human rotavirus specifically interacts with A-type histo-blood group antigen. *Nature.* 2012; 485:256–9. [PubMed: 22504179]
31. Liu Y, Huang P, Tan M, et al. Rotavirus VP8\*: phylogeny, host range, and interaction with histo-blood group antigens. *J Virol.* 2012; 86:9899–910. [PubMed: 22761376]
32. Raza MW, Blackwell CC, Molyneaux P, et al. Association between secretor status and respiratory viral illness. *BMJ (Clinical research ed).* 1991; 303:815–8.
33. Morrow AL, Ruiz-Palacios GM, Jiang X, Newburg DS. Human-milk glycans that inhibit pathogen binding protect breast-feeding infants against infectious diarrhea. *J Nutr.* 2005; 135:1304–7. [PubMed: 15867329]



**Fig 1.**

Risk Ratios (RR) and 95% Confidence Intervals (CI) for each copy of the risk allele (G) for rs601338 and all health outcomes tested. The dashed line shows the risk ratio of null effect; confidence intervals crossing this line shows that the outcome is not associated with *FUT2* SNP rs601338.

**Fig 2.**

The proposed mechanism of interaction between H epitope defined by *FUT2* and pathogens. *FUT2* inactivating mutations (rs601338 (W154X) and rs1047781 (I140F)) leading to non-secretor phenotype are associated with reduced susceptibility to the risk of infections.

**Table 1**  
**Summary statistics for the study sample.**

<b>Mother</b>	<b>N</b>	<b>Percent</b>
Maternal smoking during pregnancy status	1798	
Smoking during pregnancy	300	16.7
Non-smoker during pregnancy	1498	83.3
Parity	1829	
First born child	901	49.3
Second or higher birth	928	50.7
Mode of delivery	1811	
Vaginal delivery	1395	77
Caesarean Section	416	23
<b>Child</b>	<b>N</b>	<b>Percent</b>
Male/Female	951/ 880	51.9 /48.1
Breastfeeding status	1759	
Never tried	322	18.3
<=3 months	739	42
>3 months	698	39.7
Wheezing: birth to 6 months	1814	24.4
Nocturnal cough: birth to 6 months	1816	15.3
Pneumonia or bronchiolitis: birth to 6 months	1817	4.3
Croup: birth to 6 months	1817	3.7
Vomiting: birth to 6 months	1817	9.7
Diarrhoea: birth to 6 months	1817	16.8
Ear infection: birth to 6 months	1817	5.7
Wheezing: 6 to 12 months	1743	30.2
Nocturnal cough: 6 to 12 months	1742	21.9
Pneumonia or bronchiolitis: 6 to 12 months	1743	4
Croup: 6 to 12 months	1743	6.7
Vomiting: 6 to 12 months	1740	22.4
Diarrhoea: 6 to 12 months	1742	36
Ear infection: 6 to 12 months	1742	19.3
Atopic eczema 6 to 12 months	1743	10.7
Atopy 6 to 12 months	1466	11.1
Wheezing: 12 to 24 months	1681	26.4
Nocturnal cough: 12 to 24 months	1680	22.5
Pneumonia or bronchiolitis: 12 to 24 months	1682	2.9
Croup: 12 to 24 months	1682	11.3
Vomiting: 12 to 24 months	1682	24.5

<b>Mother</b>	<b>N</b>	<b>Percent</b>
Diarrhoea: 12 to 24 months	1681	34.9
Ear infection: 12 to 24 months	1681	26

(N: Number)