FUT2 secretor genotype and susceptibility to infections and chronic conditions in the ALSPAC cohort [version 1; referees: 1 approved with reservations]

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Abstract

Background: The FUT2 (fucosyltransferase 2) gene encodes alpha (1,2) fucosyltransferase, which determines blood group secretor status. Being homozygous for the inactive “non-secretor” rs601338(A) allele appears to confer resistance to certain infections (e.g. Norovirus, Rotavirus and Helicobacter pylori) and susceptibility to others (e.g. Haemophilus influenza and Streptococcus pneumonia). Non-secretors also have an increased risk of type 1 diabetes and inflammatory bowel disease. We aimed to determine the association of the FUT2 secretor genotype with infections and chronic conditions in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC).

Methods: This study included 7,582 pregnant women from the ALSPAC pregnancy cohort. Personal history of infections (measles, mumps, chicken pox, whooping cough, cold sores, meningitis, genital herpes, gonorrhoea and urinary infections) and chronic conditions (kidney disease, hypertension, diabetes, rheumatism, arthritis, psoriasis, hay fever, asthma, eczema and various allergies) were self-reported by standardized questionnaire. FUT2 secretor status was determined from the rs601338 genotype.

Results: Overall, 1920 women (25.3%) were homozygous for the FUT2 non-secretor allele (AA). Secretor status was associated with mumps, with 68% of non-secretors experiencing this infection, compared to 48% of secretors (RR, 1.40; 95% CI, 1.34–1.46; p<0.0001). A weaker association was observed for measles infection (76% vs. 72%; RR, 1.05; 95% CI, 1.02–1.09; p=0.0008). Non-secretors also experienced a 39% increased risk of kidney disease (5.4% vs. 3.9%; RR, 1.39; 95% CI, 1.11–1.75; p=0.004). For some conditions, including gonorrhoea and arthritis, FUT2 heterozygosity (GA) appeared to confer an intermediate phenotype. There was no strong evidence of association between FUT2 secretor status and other infections or chronic conditions, although statistical power was limited for rare outcomes.

Conclusion: Our results identify an association between FUT2 secretor status and kidney disease, and confirm a recently reported association with susceptibility to mumps infection. The clinical implications of these associations warrant further investigation.

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This article is included in the Avon Longitudinal Study of Parents and Children (ALSPAC) gateway.

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Introduction

The FUT2 (fucosyltransferase 2) gene encodes the alpha (1,2) fucosyltransferase, which determines blood group secretor status. About 20% of Caucasians are homozygous for the nonsense mutation W143X (rs601338G>A), encoding a stop codon that inactivates the FUT2 enzyme. Individuals who are homozygous for this “non-secretor” allele (AA) are unable to secrete histo-blood group antigens into bodily fluids, or express them on mucosal surfaces.

Non-secretors have a lower risk of diarrheal illness and ear infections in childhood. The non-secretor phenotype also confers resistance to specific pathogens that require FUT2-dependent antigens to infect host cells, including Norovirus and Rotavirus and Helicobacter pylori. By contrast, the non-secretor phenotype has been associated with increased susceptibility to other pathogens, including Candida, Haemophilus influenzae, Neisseria meningitidis and Streptococcus pneumoniae. Most recently, in a genome-wide association study (GWAS) of common infections, Tian et al. reported an increased susceptibility to mumps in non-secretors. In addition, non-secretors appear to be at increased risk for certain autoimmune diseases, including type 1 diabetes, psoriasis and inflammatory bowel disease.

The above associations have not been simultaneously examined in a single population and several have not been independently replicated. Moreover, the association of FUT2 secretor status with other infectious and chronic diseases has not been widely studied. Finally, previous studies have typically only considered the secretor phenotype as dichotomous, assuming the non-secretor allele to be recessive. In this study, we characterized the association of FUT2 secretor status with a variety of infectious and chronic diseases in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC), and uniquely examined the impact of heterozygosity for the non-secretor allele.

Methods

Study design and population

This study accessed data from the ALSPAC cohort. ALSPAC recruited 14,541 pregnant women resident in the former county of Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. The current analysis included a subset of 7,582 women who selected and provided written informed consent for genotyping analysis, and reported their personal medical history during pregnancy. The ALSPAC website contains details of all the data that is available through a fully searchable data dictionary at http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Genotyping

ALSPAC mothers were genotyped using the Illumina human660W-quad array at Centre National de Génopède (CNG) (Evry, France) and genotypes were called with Illumina GenomeStudio. PLINK (v1.07) was used to carry out quality control (QC) measures on an initial set of 10,015 participants and 557,124 directly genotyped single nucleotide polymorphisms (SNPs). SNPs were removed if they displayed more than 5% missingness or a Hardy-Weinberg equilibrium P value of less than 1.0×10^-6. Additionally, SNPs with a minor allele frequency of less than 1% were removed. Samples were excluded if they displayed more than 5% missingness, had indeterminate X chromosome heterozygosity or extreme autosomal heterozygosity. Samples showing evidence of population stratification were identified by multidimensional scaling of genome-wide identity by state pairwise distances using the four HapMap populations as a reference, and then excluded. Cryptic relatedness was assessed using an identity by descent (IBD) estimate of more than 0.125, which is expected to correspond to roughly 12.5% alleles shared IBD or relatedness at the first cousin level. Related participants that passed all other QC thresholds were retained during subsequent phasing and imputation. In total, 9,048 mothers and 526,688 SNPs passed these QC filters.

Imputation

A total of 477,482 SNP genotypes in common between the sample of mothers described above and a second sample of 9,115 children were combined. SNPs with genotype missingness above 1% due to poor quality (N=11,396 SNPs) were removed and a further 321 participants were removed due to potential ID mismatches. This resulted in a dataset of 17,842 participants, containing 6,305 duos and 465,740 SNPs (112 were removed during liftover and 234 were out of HWE after combination). Haplotypes were estimated using ShapeIT (v2.r644), which utilizes relatedness during phasing. The phased haplotypes were then imputed to the Haploype Reference Consortium (HRC) panel of approximately 31,000 phased whole genomes using Impute V3. For this study, we excluded the mothers who had removed consent, leaving 8,698 eligible mothers. We further excluded those who did not provide personal medical history, leaving 7,582 for analysis.

Exposure: FUT2 genotype

FUT2 secretor status was defined based on the rs601338 SNP, where G is the wild-type “secretor” allele and A is the nonsense “non-secretor” allele. Following previous studies, we considered the A allele to be recessive and dichotomized secretor status, combining the GA and GG genotypes as secretors and comparing them to the homozygous AA non-secretors. In addition, we explored the impact of GA heterozygosity at this locus.

Outcomes: infections and chronic conditions

Infections and chronic conditions were self-reported using a standardized questionnaire during pregnancy. Women were asked if they had ever had various infections (measles, mumps, chicken pox, whooping cough, cold sores, meningitis, genital herpes, gonorrhea and urinary infections) or chronic conditions (diabetes, hypertension, kidney disease, rheumatism, arthritis, psoriasis, hay fever, asthma, eczema, and any allergies, including cat, dust, pollen, insect bites or ‘other’).

Statistical analysis

Demographic characteristics were summarized with descriptive statistics and compared between non-secretors (AA) and secretors (GA or GG combined) using t-tests for continuous variables and chi-square tests for categorical variables.
or chi-squared tests for categorical variables. For each outcome, the relative risk (RR) and 95% confidence interval (95% CI) was calculated for non-secretors versus secretors. A multivariable model was used to determine whether the association of FUT2 secretor status and kidney disease was independent of measles, mumps and urinary tract infections. To explore the potential impact of FUT2 heterozygosity, a three group analysis was also conducted, considering the AA, GA and GG genotypes separately and using homozygous secretors (GG) as the reference group. All statistical analyses were performed in SAS (version 9.4, Cary, NC, US).

Results
Overall, 1920 women were homozygous for the FUT2 non-secretor allele (AA, 25.3%), 1906 were homozygous for the secretor allele (GG, 25.1%) and 3756 were heterozygous (GA, 49.5%). Almost half (46%) were first-time mothers, 21% were unmarried, 21% smoked, and 14% had a university degree. The mean (± standard deviation) age was 26.9 (± 5.9) years and the mean body mass index was 22.9 (± 3.7) kg/m². These demographic characteristics were not associated with FUT2 secretor status (Table 1). The lifetime prevalence of infections ranged from <1% for meningitis to 87% for chicken pox, while the prevalence of chronic conditions ranged from 1% for diabetes to 43% for allergies.

Dichotomous FUT2 secretor status and infections
The homozygous AA non-secretor genotype was associated with mumps infection, with 68% of non-secretors experiencing this infection, compared to 48% of secretors (RR, 1.40; 95% CI, 1.34–1.46; p<0.0001) (Table 2). Weaker associations were observed for measles infection (76% vs. 72%; RR, 1.05; 95% CI, 1.02–1.09; p=0.0008) and urinary infections (57% vs. 55%; RR, 1.05; 95% CI, 1.00–1.10; p=0.05). There was no strong evidence of association between FUT2 secretor status and whooping cough, chicken pox or cold sores (Table 2).

Dichotomous FUT2 secretor status and chronic conditions
Homozygous AA non-secretors experienced a 39% increased risk of kidney disease compared to secretors (5.4% vs. 3.9%; RR, 1.39; 95% CI, 1.11–1.75; p=0.004) (Table 2). This association was essentially unchanged in a multivariable model controlling for mumps, measles and urinary infections (adjusted RR, 1.39; 95% CI, 1.10–1.75; p=0.005). Directionally consistent results were also observed for diabetes (RR, 1.23; 95% CI, 0.76–2.00; p=0.40), rheumatism (RR 1.19, 95%CI: 0.94-1.51, p=0.14) and arthritis (RR, 1.21; 95% CI, 0.93–1.57; p=0.15), although power was lacking for these relatively rare outcomes. There was no strong evidence of association between FUT2 secretor status and hypertension, hay fever, asthma or allergies (Table 2).

FUT2 heterozygosity
Compared to homozygous GG secretors, GA heterozygotes experienced a similar risk of mumps infection (RR, 0.97; 95% CI, 0.91–1.02; p=0.24) and kidney disease (RR, 0.99; 95% CI, 0.75–1.30; p=0.93), suggesting that increased susceptibility to these conditions (as described above) is likely to be a recessive trait experienced only in homozygous AA non-secretors. Similar evidence was found for measles, urinary infections and eczema, where disease risk was comparable for individuals with GG and GA genotypes. However, this pattern was not consistent across all conditions. For example, the risk of gonorrhea was similarly elevated in GA heterozygotes (1.4%) and AA non-secretors (1.5%) compared to GG secretors (1.0%), and the risk of arthritis was lower in GA heterozygotes (3.0%) compared to either homozygous genotype (4.0% in AA, 3.8% in GG), although statistical evidence of association was weak for these relatively rare outcomes (Figure 1).

Discussion
Our findings from the population-based ALSPAC cohort confirm and extend previous research associating the FUT2 genotype with susceptibility to infections and chronic diseases. Specifically, we confirmed a recently reported association with mumps infection and identified an association with kidney disease. We also evaluated a number of other common conditions (e.g. whooping cough, chicken pox and asthma) but found no strong evidence of association with FUT2 secretor status, indicating that FUT2

Table 1. Demographics of mothers in the ALSPAC cohort according to FUT2 secretor status.

<table>
<thead>
<tr>
<th>Secretor Status (rs601338 genotype)</th>
<th>Non-Secretors (AA)</th>
<th>Secretors (GG or GA)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1920</td>
<td>N=5662</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>26.9 ± 5.9</td>
<td>26.9 ± 5.8</td>
<td>0.94</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8 ± 3.6</td>
<td>23.0 ± 3.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Married</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>423 (22.4)</td>
<td>1173 (21.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Yes</td>
<td>1468 (77.6)</td>
<td>4364 (78.8)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>861 (46.3)</td>
<td>2539 (46.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>1</td>
<td>641 (34.4)</td>
<td>1957 (35.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>264 (14.2)</td>
<td>738 (13.4)</td>
<td></td>
</tr>
<tr>
<td>3 or more</td>
<td>95 (5.1)</td>
<td>259 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1480 (78.8)</td>
<td>4324 (77.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Yes</td>
<td>397 (21.2)</td>
<td>1229 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;O level</td>
<td>457 (24.6)</td>
<td>1418 (25.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>O level</td>
<td>642 (34.5)</td>
<td>1946 (35.4)</td>
<td></td>
</tr>
<tr>
<td>A level</td>
<td>461 (24.8)</td>
<td>1306 (23.8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or n (%). AA, homozygous for non-secretor alleles; GG, homozygous for secretor alleles; GA, heterozygous; ALSPAC, Avon Longitudinal Study of Parents and Children; BMI, body mass index. Comparisons by t-test for continuous variables or chi-squared test for categorical variables.
Table 2. Lifetime incidence and relative risk of infectious and chronic conditions among mothers in the ALSPAC cohort according to dichotomized FUT2 secretor status.

<table>
<thead>
<tr>
<th>Condition</th>
<th>FUT2 Secretor Status (rs601338 genotype)</th>
<th>Relative Risk Non-Secretors vs. Secretors</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Secretors (AA)</td>
<td>Secretors (GA or GG)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>N=1920</td>
<td>N=5662</td>
<td></td>
</tr>
<tr>
<td>cases (%)</td>
<td>cases (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measles</td>
<td>1458 (75.9)</td>
<td>4076 (72.0)</td>
<td>1.05 (1.02, 1.09)</td>
</tr>
<tr>
<td>mumps</td>
<td>1299 (67.7)</td>
<td>2734 (48.3)</td>
<td>1.40 (1.34, 1.46)</td>
</tr>
<tr>
<td>chicken pox</td>
<td>1656 (86.3)</td>
<td>4925 (87.0)</td>
<td>0.99 (0.97, 1.01)</td>
</tr>
<tr>
<td>whooping cough</td>
<td>222 (11.6)</td>
<td>638 (11.3)</td>
<td>1.03 (0.89, 1.18)</td>
</tr>
<tr>
<td>cold sores</td>
<td>843 (43.9)</td>
<td>2458 (43.4)</td>
<td>1.01 (0.95, 1.07)</td>
</tr>
<tr>
<td>meningitis</td>
<td>15 (0.8)</td>
<td>61 (1.1)</td>
<td>0.73 (0.41, 1.27)</td>
</tr>
<tr>
<td>genital herpes</td>
<td>45 (2.3)</td>
<td>108 (1.9)</td>
<td>1.23 (0.87, 1.73)</td>
</tr>
<tr>
<td>gonorrhea</td>
<td>29 (1.5)</td>
<td>70 (1.2)</td>
<td>1.22 (0.80, 1.88)</td>
</tr>
<tr>
<td>urinary infection</td>
<td>1095 (57.0)</td>
<td>3085 (54.5)</td>
<td>1.05 (1.00, 1.10)</td>
</tr>
<tr>
<td>Chronic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kidney disease</td>
<td>103 (5.4)</td>
<td>218 (3.9)</td>
<td>1.39 (1.11, 1.75)</td>
</tr>
<tr>
<td>hypertension</td>
<td>272 (14.2)</td>
<td>804 (14.2)</td>
<td>1.00 (0.88, 1.13)</td>
</tr>
<tr>
<td>diabetes</td>
<td>23 (1.2)</td>
<td>55 (1.0)</td>
<td>1.23 (0.76, 2.00)</td>
</tr>
<tr>
<td>rheumatism</td>
<td>93 (4.8)</td>
<td>230 (4.1)</td>
<td>1.19 (0.94, 1.51)</td>
</tr>
<tr>
<td>arthritis</td>
<td>77 (4.0)</td>
<td>188 (3.3)</td>
<td>1.21 (0.93, 1.57)</td>
</tr>
<tr>
<td>psoriasis</td>
<td>59 (3.1)</td>
<td>213 (3.8)</td>
<td>0.82 (0.62, 1.08)</td>
</tr>
<tr>
<td>hay fever</td>
<td>573 (29.8)</td>
<td>1742 (30.8)</td>
<td>0.97 (0.90, 1.05)</td>
</tr>
<tr>
<td>asthma</td>
<td>215 (11.2)</td>
<td>652 (11.5)</td>
<td>0.97 (0.84, 1.12)</td>
</tr>
<tr>
<td>eczema</td>
<td>469 (24.4)</td>
<td>1271 (22.4)</td>
<td>1.09 (0.99, 1.19)</td>
</tr>
<tr>
<td>any allergies</td>
<td>837 (43.6)</td>
<td>2412 (42.6)</td>
<td>1.02 (0.97, 1.09)</td>
</tr>
</tbody>
</table>

AA, homozygous for non-secretor alleles; GG, homozygous for secretor alleles; GA, heterozygous; ALSPAC, Avon Longitudinal Study of Parents and Children; RR, relative risk; CI, confidence interval.

*Self-reported during pregnancy: “Have you ever had...?”

Influences pathogen- or disease-specific processes, rather than overall innate or adaptive immunity. Finally, our results suggest that FUT2 heterozygosity may confer an intermediate phenotype for certain conditions, although further research is required to replicate these findings.

Our results confirm the association reported in a recent GWAS for common infections among 23andMe research participants by Tian et al., where the FUT2 rs516316(C) allele was associated with mumps infection (odds ratio, 1.25; 95% CI, 1.24–1.27). This risk allele is in complete linkage disequilibrium with the non-secretor rs601338(A) allele evaluated in our study, where a strong association was also observed (RR, 1.40; 95% CI, 1.34–1.46). Tian et al. hypothesized that non-secretors are more susceptible to mumps infection because binding of the mumps virus to host cell sialic acid receptors is enhanced in the absence of FUT2-dependent antigens on the cell surface. Indeed, using x-ray crystallography and functional assays, Kubota et al. recently showed that mumps virus preferentially uses a trisaccharide containing α2,3-linked sialic acid in unbranched sugar chains as a receptor. Our results provide further evidence that susceptibility to mumps infection is modulated by FUT2 secretor status.

Our study also provides new evidence of a predisposition to kidney disease among non-secretors (RR, 1.39; 95% CI, 1.11–1.75). Notably, this association was not related to urinary or other infections. To our knowledge, the FUT2 genotype has not previously been associated with kidney disease in the general population, although one study found that renal scarring in patients...
with recurrent pyelonephritis was more common in non-secretors than secretors and renal tissue is known to secrete soluble ABO antigens in a FUT2-dependent manner\textsuperscript{2,28}.

Consistent with previous studies\textsuperscript{19-21}, we observed a trend towards an increased risk of arthritis, rheumatism and diabetes among non-secretors, although we lacked statistical power for the analysis of these relatively uncommon autoimmune disorders.

Finally, we examined disease risk among GA heterozygotes, who are typically considered secretors because the non-secretor rs601338\textsuperscript{A} allele is assumed to be recessive. Our results for mumps and kidney disease support this assumption, as increased susceptibility was only seen in homozygous AA non-secretors. However, we observed different patterns of association for some other conditions, including a potentially increased risk of gonorrhea and reduced risk of arthritis among GA heterozygotes, although our effect estimates were imprecise for these relatively rare conditions. Further research is warranted to replicate these observations in larger populations, and explore whether heterozygosity may impart an intermediate risk or unique protection from certain conditions.

Limitations of this work include the reliance on self-reported medical histories and low power for rare outcomes (such as meningitis, diabetes and other autoimmune diseases). Our analysis of the ALSPAC pregnancy cohort was limited to women, so the results may not be generalizable to men, and potential sex differences could not be investigated.

In conclusion, our results identify a novel association between FUT2 non-secretor status and increased risk of kidney disease, and confirm a recently-reported association with increased susceptibility to mumps infection. The clinical implications of these associations warrant further investigation.

Data availability
The ALSPAC data management plan (http://www.bristol.ac.uk/alspac/researchers/data-access/documents/alspac-data-management-plan.pdf) describes in detail the policy regarding data sharing, which is through a system of managed open access. The steps below highlight how to apply for access to the data included in this paper and all other ALSPAC data. The datasets used in this analysis are linked to ALSPAC project number B3047; please quote this project number during your application.

1. Please read the ALSPAC access policy (PDF, 627kB) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.
2. You may also find it useful to browse the fully searchable ALSPAC research proposals database, which lists all research projects that have been approved since April 2011.

3. Please submit your research proposal for consideration by the ALSPAC Executive Committee. You will receive a response within 10 working days to advise you whether your proposal has been approved.

If you have any questions about accessing data, please email alspac-data@bristol.ac.uk.

Competing interests
No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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References


The manuscript by Azad *et al.* describes the search for associations between the FUT2 genotype (or secretor phenotype) with several infectious diseases or chronic conditions from the ALSPAC cohort. Analysis of the rs601338 SNP from over 7500 women of the cohort revealed several significant associations, the two most striking ones linking the nonsecretor phenotype (AA genotype) to mumps and kidney disease. The relationship between the FUT2 AA genotype and mumps may be explained by the use of alpha2,3sialylated motifs as receptors for the MuV that would be hidden by the prior transfer of a fucose, as hypothesized earlier by Tian *et al.*. This constitutes an important independent replication study for that particular association.

Specific comments:

- The Tian *et al.* study also described an association between mumps and the ABO genotype. Since the A and B blood group enzymes act in concert with the FUT2 enzyme, it would be interesting to analyse the ABO polymorphism in combination with the FUT2 genotype in order to get a better understanding of the genetics of susceptibility to mumps. This would be a significant improvement to the manuscript.

- A weakness of the study lies in the loosely defined clinical conditions that may limit the ability to uncover significant associations with the FUT2 status. Thus, a borderline association only was observed with non-defined urinary infection although a strong association between the nonsecretor phenotype and recurrent urinary tract infection caused by *E. coli* uropathogenic strains has been described several times. Likewise, the very interesting association observed between the FUT2 AA genotype and kidney disease leaves the reader unsatisfied since one would like to know the nature of the associated kidney diseases. Considering the above-mentioned infections by *E. coli* uropathogenic strains, an association with pyelonephritis would be expected. This limitations to the study should be discussed.

- From a methodological point of view, although I am not a statistician, I wander if a correction for multiple testing would not be necessary since the authors tested for associations between the FUT2 status and 19 independent infectious or chronic conditions. This should be checked and the corrected analysis performed if required.

**References**

1. Tian C, Hromatka B, Kiefer A, Eriksson N, Noble S, Tung J, Hinds D: Genome-wide association and
HLA region fine-mapping studies identify susceptibility loci for multiple common infections. *Nature Communications*. 2017; 8 (1). Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.