Non-secretor FUT2 mutation associated with decreased risk of pediatric rotavirus gastroenteritis

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The concept that innate immunity to some enteric pathogens is related to histo-blood group antigens (HBGAs) is not new.

**Original Contributions**

**PREDISPOSITION FOR CHOLERA OF INDIVIDUALS WITH O BLOOD GROUP**

**POSSIBLE EVOLUTIONARY SIGNIFICANCE**

ROGER I. GLASS,†,‡ JAN HOLMGREN,§ CHARLES E. HALEY,∥ M. R. KHAN,∥ ANN-MARIE SVENNERHOLM,∥ BARBARA J. STOLL,∥ K. M. BELAYET HOSSAIN,∥ ROBERT E. BLACK,∥,‡ M. YUNUS,∥ and DHIMAN BARUA∥

**Attachment of Helicobacter pylori to Human Gastric Epithelium Mediated by Blood Group Antigens**

Thomas Borén,∥ Per Falk, Kevin A. Roth, Göran Larson, Staffan Normark

Helicobacter pylori is associated with development of gastritis, gastric ulcers, and adenocarcinomas in humans. The Lewis (Le) blood group antigen mediates H. pylori attachment to human gastric mucosa. Soluble glycoproteins presenting the Le antigen or antibodies to the Le antigen inhibited bacterial binding. Gastric tissue lacking Le expression did not bind H. pylori. Bacteria did not bind to Le antigen substituted with a terminal GalNAcα1-3 residue (blood group A determinant), suggesting that the availability of H. pylori receptors might be reduced in individuals of blood group A and B phenotypes, as compared with blood group O individuals.

**CONCISE COMMUNICATION**

Norwalk Virus Infection and Disease Is Associated with ABO Histo–Blood Group Type

Anne M. Hutson,∥ Robert L. Atmar,∥,‡ David Y. Graham,∥,‡ and Mary K. Estes∥,‡

Some people are resistant to Norwalk virus (NV) infection; however, the factor(s) responsible for resistance or susceptibility to NV infection has not been identified. This study investigated the relationship between a person’s ABO histo–blood group type and the risk of NV infection and symptomatic disease after clinical challenge. ABO phenotypes were identified by using serum samples from volunteers who participated in an NV challenge study (n = 51). Individuals with an O phenotype were more likely to be infected with NV odds ratio (OR), 11.8; 95% confidence interval (CI), 1.3–103), whereas persons with a B histo–blood group antigen had decreased risk of infection (OR, 0.096; 95% CI, 0.16–0.56) and symptomatic disease (OR, 0: 95% CI, 4–0.999). This is the first report demonstrating an association between a genetic factor and the risk of NV infection and symptomatic disease.
**FUT2 “secretor” gene**

- *FUT2* controls HBGA expression
- HBGA is a binding interface on mucosal epithelial cells
- If *FUT2* gene is inactivated, pathogen cannot bind to HBGA – it cannot enter cell and infection is prevented
- 20-25% of European descendants have a mutation inactivating *FUT2*

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**Blood cell**

**Gut cell**

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**FUT2 “secretor”**

**FUT2 “non-secretor”**
*(FUT2 gene is inactivated)*
Recent studies* have reported for the first time evidence of innate susceptibility to rotavirus through mechanisms involving host HBGAs

In a diverse, US pediatric population we studied the question: Does the \textit{FUT2} non-secretor mutation affect rotavirus gastroenteritis susceptibility?


Design/Methods:

Children <5 years old with diarrhea and/or vomiting (AGE) enrolled during hospitalizations and emergency department visits December 2011 through November 2012

Healthy controls having no AGE symptoms for 14 days were enrolled at well-child visits

DNA collected from saliva samples was analyzed by ImmunoChip microarray to determine FUT2 genotype and genetic ancestry

Whole stool was collected and analyzed for rotavirus by enzyme immunoassay (EIA) and genotyped
N= 1,428 children with AGE  
N= 810 healthy controls  
Secretor status and rotavirus test results

<table>
<thead>
<tr>
<th></th>
<th>Secretor</th>
<th>Non-Secretor (FUT2 mutation)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus Positive AGE</td>
<td>49 (100%)</td>
<td>0 (0%)</td>
<td>49</td>
</tr>
<tr>
<td>Rotavirus Negative AGE</td>
<td>1,121 (81%)</td>
<td>258 (19%)</td>
<td>1,379</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>631 (77%)</td>
<td>188 (23%)</td>
<td>819</td>
</tr>
</tbody>
</table>

100% of the AGE cases who were rotavirus positive were secretors (P<0.0001)  
Non-secretors appeared protected
The non-secretor *FUT2* mutation was rarely observed among those identified by genetic markers as being of MesoAmerican ancestry.

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>Secretors in rotavirus positive AGE subjects</th>
<th>Secretors in healthy controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>20 / 20 (100%)</td>
<td>252 / 336 (75%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Black</td>
<td>21 / 21 (100%)</td>
<td>293 / 394 (74%)</td>
<td>0.003</td>
</tr>
<tr>
<td>MesoAmerican</td>
<td>7 / 7 (100%)</td>
<td>74 / 77 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>1 / 1 (100%)</td>
<td>12 / 12 (100%)</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>49 / 49 (100%)</td>
<td>631 / 819 (77%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Rotavirus genotypes among secretors (n=49)

- G12,P8: 2%
- G3,P8: 6%
- G2,P4: 8%
- G1,P8: 84%
Comparison of *FUT2* secretor status for rotavirus positive AGE subjects and healthy controls among the subset of children receiving (any dose) rotavirus vaccine

<table>
<thead>
<tr>
<th></th>
<th>Secretors in vaccinated rotavirus positive AGE subjects</th>
<th>Secretors in vaccinated healthy controls</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>27 / 27 (100%)</td>
<td>486 / 631 (77%)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>
Conclusions

#1: Non-secretor \textit{FUT2} mutation appears protective against rotavirus infection (as it also does for norovirus)

#2: MesoAmericans rarely had the non-secretor \textit{FUT2} mutation, perhaps translating to higher risk of rotavirus infections

#3: All secretor rotavirus P-types were P[4] or P[8]

#4: All (100\%) vaccine failures in our sample were secretors (versus 77\% of healthy controls)
**FUT2 “secretor” gene**

- *FUT2* controls HBGA expression
- HBGA is a binding interface on intestinal epithelial and blood cells
- If *FUT2* gene is inactivated, pathogen cannot bind to HBGA – it cannot enter cell and infection is prevented

20-25% of European descendants have a mutation inactivating *FUT2*