Association of fucosyltransferase 2 gene variants with ulcerative colitis in Han and Uyghur patients in China

Ainyinuer Aheman, He-Sheng Luo, Feng Gao

AIM: To investigate the contribution of fucosyltransferase 2 (FUT2) variants to the genetic susceptibility and clinical heterogeneity of ulcerative colitis (UC) between Han and Uyghur patients in Xinjiang, China.

METHODS: A total of 102 UC patients (53 Han patients including 22 men and 31 women, and 49 Uyghur patients including 25 men and 24 women; aged 48 ± 16 years) and 310 age- and sex-matched healthy controls were enrolled from January 2010 to May 2011 in Xinjiang People’s Hospital of China. UC was diagnosed based on the clinical, endoscopic and histological findings following Lennard-Jones criteria. Blood samples were collected and genomic DNA was extracted by the routine laboratory methods. Polymerase chain reaction-sequence-based typing method was used to identify FUT2 variants rs281377, rs1047781, rs601338 and rs602662. Genotypic and allelic frequencies were documented and compared between the UC patients and the healthy controls. Genotypic frequencies were also compared between Han and Uyghur patients. Potential association of genetic variation and UC between Han and Uyghur patients was examined.

RESULTS: rs281377 was found significantly associated with UC in the Han population as compared with the controls (P = 0.011) while rs281377 was not associated with UC in the Uyghur population (P = 0.06). TT homozygous rs281377 frequencies were higher in the UC groups than in the controls (88.7% vs 68.7% and 55.1% vs 50.3%). rs1047781 was specifically associated with UC in the Uyghur population (P = 0.001), but not associated with UC in the Han population (P = 0.13). TT homozygous rs1047781 frequencies were lower in the UC groups than in the controls (9.5% vs 11.8% and 4.0% vs 6.7%). rs601338 was statistically related to UC in both populations (Han, P = 0.025; Uyghur, P = 8.33 × 10^-5). AA homozygous rs601338 frequencies were lower in the UC groups than in the controls (0% vs 1.8% and 12.2% vs 13.4%). No association was found between rs602662 and UC in both Han and the Uyghur populations. Allelic analysis showed that rs281377 allele was significantly associated with UC in the Han population as compared with the controls [P = 0.001, odd ratio (OR) = 0.26], however, it was not associated with UC in the Uyghur population (P = 0.603, OR = 1.14), and rs1047781 allele was associated with UC in the Uyghur population (P = 0.001, OR = 0.029) while it was not associated with UC in the Han population (P = 0.074, OR = 0.62). Moreover, rs601338 was associated with UC in both Han (P = 0.005, OR = 0.1) and Uyghur populations (P = 0.002, OR = 0.43). Meta analysis showed that rs1047781 and rs601338 conferred risk of UC as compared with the controls [P = 0.005, OR = 0.47; P = 0.0003, OR = 0.35; 95% confidence interval (CI) = 0.31-0.72 and 0.21-0.58], but rs281377 and rs602662 showed no statistically significant differences between
patients with UC and controls ($P = 0.10, OR = 0.71$; $P = 0.68, OR = 0.09$; $95\% \ C I = 0.47-1.07$ and $0.56-1.47$).

**CONCLUSION:** Functionally relevant $FUT2$ gene variants are associated with UC, suggesting that they play a potential role in the pathogenesis of UC and may contribute to the clinical heterogeneity of UC between Han and Uyghur patients.

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**Key words:** Ulcerative colitis; Fucosyltransferase 2; Gene polymorphisms; Han; Uyghur

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**INTRODUCTION**

Ulcerative colitis (UC) and Crohn’s disease are often characterized as chronic inflammatory bowel diseases (IBD). Clinical features in both disorders include abdominal pain, diarrhea, weight loss and increased risk of developing colorectal cancer. The etiology of UC is thought to be multifactorial, such as genetic, environmental, immune, and gut barrier factors. Genetic factors involved in the regulation of the immune system are considered to play a significant role in the pathogenesis of IBD. Much progress has been achieved in recent years regarding the genetic etiology of IBD. Studies have found that disease distribution and phenotypic appearance differ significantly between ethnic groups and even within populations. Apart from varying environmental factors that affect susceptible individuals, genetic heterogeneity between different populations itself plays an important role in IBD. Previously compared the clinical characteristics of UC between the Han and Uyghur populations residing in the Xinjiang Uyghur Autonomous Region of China. We found differences between the Uyghur and Han populations living in the same region, where Uyghur population had a higher prevalence of UC, a younger age of onset, an increased prevalence of the chronic persistence and acute outbreak type, more moderate and severe forms, a higher complication rate, and an increased frequency of positive anti-neutrophilic cytoplasmic antibodies (pANCA). However, the genetic heterogeneity related to UC between these two ethnic groups need to be investigated.

Secretor/non-secretor phenotypes [determined by the fucosyltransferase 2 ($FUT2$) gene] are associated with some metabolic and infectious diseases, and ABO glyco-
syltransferase activity has been shown to be involved in the pancreatic cancer risk. Genetic variation in $FUT2$ has been implicated in susceptibility to Helicobacter pylori infection, Norovirus (Norwalk virus) progression of human immunodeficiency virus, recurrent urinary tract infections, the development of vaginal candidiasis, gram-negative sepsis in infants, and cholera. Carriers of non-secretor variants have higher plasma vitamin B12 levels than carriers of the secretor genotypes. In addition to the genetic associations mentioned above, non-secretion of ABO blood group antigens into body fluids has been shown to be associated with rheumatic fever and Crohn’s disease, but not associated with UC. Earlier studies have shown differences in the intestinal microbiota between the UC patients and healthy subjects and alterations in the microbiota of IBD patients are related to changes in the $FUT2$ genotype. The $FUT2$ gene codes for an α (1,2)-fucosyltransferase and regulates the expression of ABH antigens in body secretions and the intestinal mucosa. The $FUT2$ gene is located on chromosome 19q13.34 (chromosome 19: 49, 199, 228-49, 209, 207) and consists of two exons. The cDNA is 3.1 kb long and encodes a polypeptide of 332 amino acid residues. The gene determines the secretion status of the ABO antigens with secretors having at least one functional $FUT2$ allele, whereas non-secretors are homozygous for nonfunctional $FUT2$ allele.

rs601338 nonsense mutation (Trp143stop) in the $FUT2$ gene of non-secretors has been reported in Caucasians (Europeans and Iranians) and Africans and was found in approximately 1% of Chinese. The frequency of non-secretors among east Asians is similar to Europeans and Africans, but east Asians are homozygous for a different weak-activity allele resulting from a rs1047781 gene polymorphism. In Portuguese, two $FUT2$ polymorphisms, rs602662 and T839C, are associated with decreased or absent $FUT2$ enzyme activity.

**MATERIALS AND METHODS**

**Patients and controls**

A total of 102 consecutive patients with UC (53 Han and 49 Uyghur, 47 men and 55 women, aged 18-78 years) and 310 age- and sex-matched healthy controls (161 Han and 149 Uyghur, 137 men and 173 women, aged 18-75 years) were enrolled from January 2010 to May 2011 in the De-
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Department of Gastroenterology and the Physical Examination Center, Xinjiang People's Hospital of China. UC was diagnosed based on the clinical, endoscopic and histological findings following the Lennard-Jones criteria\(^{[1]}\). The extent of the disease was assessed by colonoscopy at the initial diagnosis and during follow-up. Extensive colitis was defined as lesions located beyond the splenic flexure. Distal colitis was defined as lesions limited to the region distal to the spleen flexure\(^{[2,3]}\). The study protocol was approved by the Ethics Committee of Xinjiang People's Hospital. Selected patients with UC and healthy controls are Chinese Han and Uygur from Urumqi, Xinjiang, China. Informed consent was obtained from all the subjects.

**Extraction of DNA**

Genomic DNA was purified using a QIAamp DNA Blood Midi kit (Qiagen, Germany). Purified genomic DNA from blood donors was stored frozen in microtitre plates (10 ng/μL in TE buffer) until analyzed.

**Polymerase chain reaction and sequencing primers**

Primers for the polymerase chain reaction (PCR) amplification and sequencing were designed using conventional standard criteria. Primer specificity was checked with published nucleotide sequences using Basic Local Alignment Search Tool and analyzed for the risk of primer-dimer formation and secondary structures using Oligo 6.0 Software. The following pair of primers was used for the FUT2 (forward, 5′-AGCGCCCCGGGCCTCCATCTC C-3′; reverse, 5′-GGAACCATGTGTGCTTCTCAT GCCCCG-3′). The same forward and reverse primers were used for sequencing.

**PCR and PCR product purification**

Water of 17.3 μL, 0.5 μL 20 μmol/L forward primer, 0.5 μL 20 μmol/L reverse primer, 2.5 μL PCR buffer, 1 μL dNTPs, 2 μL MgCl₂ and 0.2 μL TaqGold (Applied Biosystems, Branchburg, New Jersey, United States) were added to 1 μL DNA (≥ 50 ng). Amplification conditions for the FUT2 PCR were: one cycle of 5 min at 95 °C followed by 10 cycles of 20 s at 95 °C and 40 s at 78 °C and 23 cycles of 10 s at 95 °C, 10 s at 62 °C and 2 min at 72 °C, and finally one cycle of 5 min at 72 °C and 4 °C. The PCR was performed by a GeneAmp PCR system 9700 from the Applied Biosystems. PCR products were purified using the SAP-Exon method.

**PCR product sequence**

Twelve μL water, 1 μL 10 μmol/L forward primer, 2 μL BigDye sequencing buffer, 4 μL Big dye (BigDye® Terminator v3.1 Cycle Sequencing Kit) were added to 1 μL PCR product (≥ 50 ng). Cycle sequencing conditions for the FUT2 were: one cycle of 1 min at 96 °C followed by 25 cycles of 10 s at 96 °C, 5 s at 50 °C and 4 min at 60 °C and 4 °C. The PCR was performed by a GeneAmp PCR system 9700 from Applied Biosystems. DNA sequencing was performed using an automated sequencer (ABI 3730XL, Applied Biosystems). Chromas software version 2.0 was used to analyze the raw sequence data. The FUT2 genotyping method was established in accordance with the polymorphism (Figure 1). The frequencies of the genotypes were calculated by direct counting.

**Statistical analysis**

Hardy-Weinberg disequilibrium was assessed with χ² test and clinical records including age were analyzed with t test. Allelic and genotypic association analyses were performed using the Pearson’s 2 × 2 or 2 × 3 table χ² test. Odd ratio (OR) and 95% confidential interval (95% CI) were also calculated by Pearson’s 2 × 2 χ² test. To adjust for the multiple tests performed and obtain an empirical null distribution of the association test P values (P empirical), we conducted 10,000 permutations in the case-control samples. Tests for the heterogeneity of effect size between Han and Uygur populations were carried out using Cochran’s Q test, and P < 0.05 indicated that heterogeneity existed. When heterogeneity was found, random-effects model was applied using Cochran-Mantel-Hansel test to calculate the overall genetic effect of single nucleotide polymorphisms by combining the data from Han and Uygur populations; otherwise, fixed-effects model was applied. The above analyses were performed using PLINK v.1.07 (http://pngu.mgh.harvard.edu/purcell/plink/).
RESULTS

Clinical characteristics of UC patients

DNA was obtained from 102 consecutive UC patients and 310 healthy individuals who were well matched by sex and age. The main clinical characteristics of the UC patients are summarized in Table 1. UC patients included 47 women and 55 men with 53 Han and 49 Uyghur, and their average age at onset was 48 ± 16 years. Among the 310 healthy controls, there were 161 Han and 149 Uyghur including 137 men and 173 women, and their average age was 47 ± 14 years. There were no significant differences in sex ratio and the average age between the UC patients and healthy controls (P = 0.74 and P = 0.801).

Comparison of FUT2 genotype and allelic variants between UC patients and healthy controls

The genotype frequencies of the FUT2 gene variants of the UC patients and the healthy controls are presented in Table 2. rs281377 was only associated with UC in Han population (P = 0.011), while rs1047781 was associated specifically with UC in Uyghur population (P = 0.001). rs601338 was statistically related to UC in both Han and Uyghur populations (Han, P = 0.025; Uyghur, P = 8.33 × 10−5). rs602662 was not associated with UC in both Han and Uyghur populations. TT homozygote of rs281377 was compared between the two ethnic UC groups and controls. Its frequencies were higher in the UC groups than in the controls (88.7% vs 68.7% and 55.1% vs 50.3%, respectively). TT homozygous rs1047781 frequencies (9.5% vs 11.8% and 4.0% vs 6.7%) and AA homozygous rs601338 frequencies (0% vs 1.8% and 12.2% vs 13.4%) were both lower than in the controls.

In allelic analysis as shown in Table 3 and Figure 2, rs281377 was found associated with UC only in the Han population (P = 0.001, OR = 0.26). rs1047781 was associated specifically with UC in Uyghur population (P = 0.001, OR = 0.29), whereas rs601338 was associated with UC in both Han and Uyghur populations (Han, P = 0.005, OR = 0.10; Uyghur, P = 0.002, OR = 0.43) and rs602662 was not associated with UC in both Han and Uyghur populations (Han, P = 0.985; Uyghur, P = 0.652, Figure 1).

The comparison between Han and Uyghur UC patients and controls revealed that genotype and allele rs281377 and rs601338 in the Han population were significantly associated with UC while in the Uyghur population, rs1047781 and rs601338 were significantly associated with UC.

Meta-analysis showed that rs1047781 and rs601338 conferred risk of UC as compared with the controls, (P = 0.005, OR = 0.47; P = 0.0003, OR = 0.35; 95% CI = 0.31–0.72 and 0.21–0.58) while rs281377 and rs602662 were not significantly different statistically between patients with UC and controls (P = 0.100, OR = 0.71; P = 0.680, OR = 0.90; 95% CI = 0.47–1.07 and 0.56–1.47).

DISCUSSION

UC is thought to fundamentally represent an altered interaction between the intestinal microbiota and the intestinal immune system[13]. The intestinal microbiota interacts with luminal enterocytes via host cell surface molecules, including oligosaccharides synthesized by glycosyltransferases[14]. Previous studies have shown that the allele polymorphism with a synonymous mutation rs281377, including the nonsense mutation rs601338, and missense mutation rs1047781 and rs602662, is almost inactive and is responsible for some instances of non-secretor status[15]. Non-secretor phenotypes in the population occurring as the absence of particular carbohydrate molecules in the mucosa may have conferred protection against some pathogens. It is demonstrated that FucT2-null mice do not express fucosyl glycolipid FGA1 in the colon, whereas normal mice do[16]. Commensal bacteria and probiotics may exert their protective effects via preventing adherence, or even displacing pathogenic bacteria[17], which is consistent with the notion that FUT2 and non-secretor may affect the status of the gastrointestinal microbiota. Furthermore, changes in the microflora of IBD patients have been documented.

Our study indicated that the genetic polymorphisms of the FUT2 gene were correlated with UC, and the associations differed between Han and Uyghur people in China. We analyzed four variants of FUT2 gene, the frequency of three variants of the FUT2 genotype (rs281377, rs1047781 and rs601338) showed significant associations with UC (P < 0.05), however, the associations differed between the two ethnic groups. In the Han population, genotype and allele of rs281377 and rs601338 were significantly associated with UC whereas in the Uyghur population, genotype rs1047781 and rs601338 were associated with UC.

We also compared the TT homozygote of rs281377 between the two ethnic UC groups and controls. Its frequencies were higher in the UC groups than in the controls (88.7% vs 68.7 and 55.1% vs 50.3%, respectively). TT homozygous rs1047781 (9.5% vs 11.8 and 4.0% vs 6.7%) and AA homozygous rs601338 frequencies (0% vs 1.8% and 12.2% vs 13.4%) were both lower than in the controls.

A limitation of the present study was the relatively

| Table 1 Clinical characteristics of the study subjects |
|-----------------------------------------------|
| Items                                      | Han population | Uyghur population | Total |
|-----------------------------------------------|
| UC patients                                  | 53             | 49               | 102   |
| Gender (male/female)                         | 22/31          | 25/24            | 47/35 |
| Age of onset (yr)                            | 52 ± 15        | 46 ± 15          | 48 ± 16 |
| Extensive colitis                            | 20 (0.38)      | 30 (0.61)        | 50 (0.49) |
| Distal colitis                               | 33 (0.62)      | 19 (0.39)        | 52 (0.53) |
| Mild and moderate                            | 47 (0.89)      | 40 (0.82)        | 87 (0.85) |
| Severe                                      | 6 (0.11)       | 9 (0.18)         | 15 (0.15) |
| Healthy controls                             | 161            | 149              | 310   |
| Gender (male/female)                         | 67/94          | 70/79            | 137/173 |
| Age of onset (yr)                            | 48 ± 15        | 49 ± 13          | 47 ± 14 |

Data are shown as mean ± SD or n (%). UC: Ulcerative colitis.
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Table 2  Genotypic association of four single nucleotide polymorphisms with ulcerative colitis in Han and Uyghur populations  a (%)

| SNPs | Allele | Groups | UC cases | Controls | \( \chi^2 \) | P |
|------|--------|--------|----------|----------|---------|-----|
| rs281377 | C/T | Han | 0 (0)/6 (11.3)/47 (88.7) | 9 (5.6)/42 (26.1)/110 (68.4) | 9.091 | 0.011 |
| C/T | Uyghur | 10 (20.4)/12 (24.5)/27 (55.1) | 15 (10.1)/59 (39.6)/75 (50.3) | 5.633 | 0.060 |
| rs1047781 | T/A | Han | 5 (9.5)/13 (24.5)/35 (66.0) | 19 (11.8)/61 (37.9)/81 (50.3) | 4.077 | 0.130 |
| T/A | Uyghur | 2 (4.0)/4 (8.2)/43 (87.8) | 10 (6.7)/50 (33.6)/89 (59.7) | 13.480 | 0.001 |
| rs601338 | A/G | Han | 0 (0)/1 (1.9)/52 (98.1) | 3 (1.8)/23 (14.3)/135 (83.9) | 7.382 | 0.025 |
| A/G | Uyghur | 6 (12.2)/9 (18.4)/34 (69.4) | 20 (13.4)/76 (51.0)/33 (35.6) | 18.790 | 8.33 \times 10^{-4} |
| rs602662 | A/G | Han | 0 (0)/3 (5.7)/50 (94.3) | 0 (0)/9 (5.6)/152 (94.4) | NA | NA |
| A/G | Uyghur | 5 (10.2)/15 (30.6)/29 (59.2) | 11 (7.4)/61 (40.9)/77 (51.7) | 1.776 | 0.412 |

UC: Ulcerative colitis; SNPs: Single nucleotide polymorphisms; Pobs: Observed P value; Pemp: Empirical null distribution of the association test P values; P(Q): Heterogeneity test, was calculated by Cochran’s Q test; Poverall: Meta-analysis P value, was calculated by Mantel-Haenszel test under fixed-effects or random-effects model; OR: Odd ratio; 95% CI: 95% confidential interval.

Table 3  Allelic association of four single nucleotide polymorphisms with ulcerative colitis in Han, Uyghur and combined populations

| SNPs | Groups | Risk allele | Frequency (case/control) | \( \chi^2 \) | Pobs | Pemp | OR (95% CI) | P(Q) | Poverall | OR (95% CI) |
|------|--------|------------|--------------------------|---------|-------|------|-------------|------|-----------|-------------|
| rs281377 | Han | C | 0.057/0.186 | 10.290 | 0.001 | 0.002 | 0.26 (0.11-0.63) | 0.003 | 0.100 | 0.71 (0.47-1.07) |
| Uyghur | C | 0.327/0.299 | 0.270 | 0.603 | 0.636 | 1.14 (0.70-1.86) |
| rs1047781 | Han | T | 0.217/0.308 | 3.203 | 0.074 | 0.106 | 0.62 (0.37-1.05) | 0.100 | 0.005 | 0.47 (0.31-0.72) |
| Uyghur | T | 0.082/0.235 | 10.950 | 0.001 | 0.002 | 0.29 (0.13-0.63) |
| rs601338 | Han | A | 0.009/0.090 | 7.954 | 0.005 | 0.102 | 0.10 (0.01-0.72) | 0.140 | 0.0003 | 0.35 (0.21-0.58) |
| Uyghur | A | 0.214/0.389 | 9.979 | 0.002 | 0.002 | 0.43 (0.25-0.73) |
| rs602662 | Han | A | 0.026/0.028 | 0.000 | 0.985 | 1.000 | 1.01 (0.27-3.81) | 0.860 | 0.680 | 0.90 (0.56-1.47) |
| Uyghur | A | 0.255/0.279 | 0.204 | 0.652 | 0.699 | 0.89 (0.53-1.49) |

SNPs: Single nucleotide polymorphisms; Pobs: Observed P value, was calculated by \( 2 \times 2 \chi^2 \) test; Pemp: Empirical null distribution of the association test P values; P(Q): Heterogeneity test, was calculated by Cochran’s Q test; Poverall: Meta-analysis P value, was calculated by Mantel-Haenszel test under fixed-effects or random-effects model; OR: Odd ratio; 95% CI: 95% confidential interval.

UC: Ulcerative colitis; SNPs: Single nucleotide polymorphisms; NA: Not available.

SNPs: Single nucleotide polymorphisms; Pobs: Observed P value, was calculated by \( 2 \times 2 \chi^2 \) test; Pemp: Empirical null distribution of the association test P values; P(Q): Heterogeneity test, was calculated by Cochran’s Q test; Poverall: Meta-analysis P value, was calculated by Mantel-Haenszel test under fixed-effects or random-effects model; OR: Odd ratio; 95% CI: 95% confidential interval.

Figure 2  Allelic analysis of fucosyltransferase 2 variants and ulcerative colitis in Han and Uyghur populations.

 Darren, with his technical assistance.

In conclusion, our study found that the functional FUT2 variants might not only play a role in the pathogenesis of UC, but also contribute to the different clinical manifestations of UC between Han and Uyghur patients in north-west China. The effects of the different genotypes on the intestinal microbiota of normal controls and patients with UC are still unknown and likely represent a potentially productive area for future research in the quest to better understand the pathogenesis and treatment of UC.

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COMMENTS

Background

Earlier studies have shown differences in the intestinal microbiota between the ulcerative colitis (UC) patients and healthy subjects, and alterations in the microbiota of inflammatory bowel diseases (IBD) patients are related to changes in the fucosyltransferase 2 (FUT2) genotype. In this study, the authors examined whether polymorphism of the FUT2 gene differed between the Han and Uyghur patients with UC.

Research frontiers

FUT2 and non-secretor may affect the status of the gastrointestinal microbiota. Studies have found that disease distribution and phenotypic appearance differ significantly between ethnic groups and even within populations. The association of the genetic heterogeneity of UC between two ethnic groups, Chinese Han and Uyghur, were investigated.
Innovations and breakthroughs

This study found that the functional FUT2 variants might not only play a role in the pathogenesis of UC, but also contribute to the different clinical manifestations of UC between Han and Uygur patients in North-West China.

Applications

The effects of the different genotypes on the intestinal microbiota of normal controls and patients with UC are still unknown and likely represent a potentially productive area for future research in the quest to better understand the pathogenesis and treatment of UC.

Terminology

UC is a form of IBD. It is a refractory, chronic, and nonspecific disease which usually occurs in the rectum and the entire colon. FUT2 encodes the α(1,2) fucosyltransferase that determines blood group secretor status, and synthesizes the H-type 1 antigen in saliva and mucosa.

Peer review

The author investigated the contribution of FUT2 variants to the genetic susceptibility and clinical heterogeneity of UC between Han and Uygur patients. This manuscript contains potentially interesting findings.

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