Epidemiology and Genetics of Inflammatory Bowel Disease in Turkey

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Falk Symposium 159, İstanbul
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  - American Hospital.
  - Haydarpaşa Numune Hospital,
  - İstanbul University.
  - Marmara University.

• **İZMİR:**
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  - Ege University
  - Izmir Atatürk Hospital

• **MERSİN:**
  - Mersin University

• **TRABZON:**
  - Karadeniz Teknik University
Epidemiology of IBD in Turkey

• No population-based study has been performed

• To investigate IBD epidemiology, IBD Society designed a research protocol based on hospital data
Epidemiology of IBD in Turkey

- 19 medical centers involved
- These centers were included if
  - The medical center was a university hospital or grade A tertiary hospital
  - Diagnostic facilities for high quality endoscopy, radiology, and pathology were available
- A standard protocol was adopted for data collection and analysis
Material and Methods

- All previous data of IBD patients were recorded on patient forms created in the website of the IBD Society (www.ibhd.org.tr) from September 1, 2004 to April 1, 2007 (which was the prevalence date)
Material and Methods

• Incidence and prevalence was calculated from 3 of 10 cities
• In these 3 cities, all gastroenterology clinics participated in the study
  - Ankara, İzmir, Edirne
• Demographic and clinical data presented herein are taken from the records of all patients from all 10 cities
Material and Methods

Data included
- Demographics
- Smoking history
- History of appendectomy and tonsillectomy
- Family history of IBD
- Disease location and behavior
- Extraintestinal manifestation
Material and Methods

- Statistical analysis was performed by SPSS
- Numeric variables were compared by t-test,
- Nominal variables were compared by chi-square tests
- Significance was set as 0.05
Results
IBD Patients

- Ulcerative colitis 2938
- Crohn's disease 975
- Indeterminate colitis 41
- IBD 3954
Prevalence rates

- IBD: 44.7%
- UC: 39.7%
- CD: 25.4%
- 36%
- 30.2%
- 33.3%
- 19%
- 25.5%
- 10.4%
- 2.4%

Ankara
Edirne
İzmir
Total
## Prevalence rates

<table>
<thead>
<tr>
<th></th>
<th>Patient number</th>
<th>Population</th>
<th>Prevalence (10^5)</th>
</tr>
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<tr>
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<tr>
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<tr>
<td>CD</td>
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<td>159</td>
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</table>
IBD prevalence according to age (per 100000)

10-19
20-29
30-39
40-49
50-59
Over 60
Mean age at diagnosis

UC: 38.4 ± 13 and CD: 34.3 ± 13
## Male to Female Ratio

<table>
<thead>
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<th>Patients</th>
<th>Female</th>
<th>Male</th>
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<tr>
<td></td>
<td>n</td>
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<tr>
<td>Ulcerative colitis</td>
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<td>Crohn’s disease</td>
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<td>44.1</td>
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</table>

**Note:** Male/Female ratio indicates the ratio of male patients to female patients.
Risk Factors
Genetic Factors In Turkish IBD Patients

- Family history of IBD
- HLA tissue groups
- CARD15 / NOD 2 studies
- Prothrombotic gene mutations in IBD
- Cytokine gene mutations
Family History

![Bar chart showing family history percentages for UC and CD.

- UC: 4.3%
- CD: 4.2%

Legend:
- Blue: Family history (+)
- Green: Family history (-)
The distribution of HLA-DRB alleles in ulcerative colitis patients in Turkey

- A positive association with the HLA-DRB1*1502 allele
- A negative association with the DRB1*13 allele
- HLA-DRB1*0701 was significantly increased in pANCA positive UC patients compared with pANCA negative patients

Genetic Factors

- The most important gene of interest to date is the CARD15/NOD2 gene polymorphism.
- They are associated with:
  - the terminal ileum location of CD
  - the stricturing phenotype and
  - the familial form of disease.
Genetic Factors

- There are two studies that have investigated CARD15/NOD2 in IBD in Turkey.
Aims: to investigate polymorphism in the
- NOD2/CARD15
- NOD1/CARD4
- ICAM-1 genes
NOD2/CARD15, NOD1/CARD4, and ICAM-1 gene polymorphisms in Turkish patients with inflammatory bowel disease

• The study group
  - 70 Crohn’s disease patients
  - 120 ulcerative colitis patients
  - 106 healthy controls

• Individuals were genotyped for the three variants by RFLP-PCR technique

## Genotype and allele distributions of NOD2/CARD15 genes

<table>
<thead>
<tr>
<th></th>
<th>Genotype</th>
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<th>Allele frequencies (%)</th>
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<td>-/-</td>
<td>-/+</td>
<td>+/+</td>
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<td></td>
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<td>Controls</td>
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## Genotype and allele distributions of NOD1/CARD4

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<th>Allele frequencies (%)</th>
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<tr>
<td></td>
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### Genotype and allele distributions of ICAM-1 genes

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<td>UC</td>
<td>30</td>
<td>86</td>
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<tr>
<td></td>
<td>Controls</td>
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<td>67</td>
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Results

- The three previously described Crohn’s disease predisposing variants of the NOD2/CARD15 gene and the polymorphism examined in the NOD1/CARD4 and ICAM-1 genes were not found to be associated with UC and CD.

Distribution of common CARD15/NOD2 variants in patients with Crohn’s disease from Turkey

• **The study group**
  - 56 Crohn’s disease patients
  - 100 healthy controls

• **Individuals were genotyped for the three variants by RFLP-PCR technique**

## Genotype and allele frequencies of CARD15/NOD2 variants in CD

<table>
<thead>
<tr>
<th>Variant</th>
<th>Genotype</th>
<th>Allele frequencies (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
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<td>-/+</td>
<td>+/+</td>
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<tr>
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</tr>
<tr>
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<tr>
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<td>48</td>
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<tr>
<td>Controls</td>
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</tr>
<tr>
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<td>54</td>
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<tr>
<td>Controls</td>
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Prothrombotic Gene Mutations in IBD

Factor V Leiden, prothrombin G20210A and MTHFR gene mutations in inflammatory bowel disease

Murat TÖRÜNER¹, Özlem ERKAN², İrfan SOYKAN³, Mithat BOZDAYI⁴, Hulya ÇETINKAYA⁵, Cihan YURDAYDIN⁶, Özden ÜZUNALIMOĞLU⁷, Ali ÖZDEN⁸

A comprehensive analysis of 12 thrombophilic mutations and related parameters in patients with inflammatory bowel disease: data from Turkey

Şerif Yılmaz · Karim Bayana · Yelda Tüzün · Sabri Buta · Abdullah Altıntaş

Gastrointestinal - 03789

Prothrombotic Gene Mutations and Crohn’s Disease; Is There Any Association?

Hülya Özer-Özkoçak MD¹, Neslihan Altaci PHD¹, Filiz Türe², Canan Alkım MD³

Hepato-Gastroenterology 2005; 52:1467-1469

| TABLE 2 Frequency of FV Leiden Mutations in CD Patients Compared with Controls (p > 0.05) |
|---|---|---|---|
| n  | Normal | Heterozygous | Homozygous |
| CD  | 44   | 40 (90.8%) | 3 (6.8%)  | 1 (2.3%) |
| Controls | 43   | 41 (95.3%) | 2 (4.7%)  | 0 (0%) |

| TABLE 3 Frequency of Prothrombin G20210A Mutations in CD Patients Compared with Controls (p > 0.05) |
|---|---|---|---|
| n  | Normal | Heterozygous | Homozygous |
| CD  | 44   | 42 (95.4%) | 2 (4.6%)  | 0 (0%) |
| Controls | 43   | 42 (97.7%) | 0 (0%)  | 1 (2.3%) |
Prothrombotic Gene Mutations in IBD

- The prevalence of prothrombin G20210A gene and factor V Leiden gene mutations was found to be statistically insignificant between CD patients and the control group.

Prothrombotic Gene Mutations in IBD

• There was a statistical difference between the proportions of the mutated allele frequencies of Beta-Fibrinogen-455G-A, MTHFR A1298C and ACE-I/D in IBD

Aim: To examine the allelic polymorphisms that may determine the immune response level in
- TNFα,
- IL-1β,
- IL-10 and
- IL-1RN cytokine genes
which have a role in the inflammatory pathway in IBD
Cytokine gene polymorphisms in Turkish patients with inflammatory bowel disease

- **Results**
  - No significant differences were found in the allele and genotype frequencies of the polymorphisms in TNFα, IL-1β, IL-10 and IL-1RN genes between patients with UC and CD and healthy controls

Celik Y, Dağıl Ü, Kılıç MY. Scand J Gastroenterol 2006; 41: 559-65
Environmental Risk Factors in IBD in Turkey

- Appendec.
- Tonsillec.
- Measles
- Amebiasis
- Smoking

Comparison of UC vs. CD with P values:
- Appendec.: P = 0.001
- Tonsillec.: P = 0.001
- Measles: P = 0.001
Clinical Characteristics
Distribution of UC patients according to localization

- Proctitis: 29%
- Pancolitis: 26%
- Left sided: 45%
Distribution of CD patients according to localization

- Ileocecum: 18%
- Ileocolon: 34%
- Colon: 25%
- Small bowel: 22%
- GI: 1%
- Isolated upper: 
Distribution of CD patients according to disease type

- Non-penet. non strict. 52%
- Stricturing 30%
- Penetrating 18%
# Extraintestinal Manifestations of IBD

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<tr>
<th></th>
<th>UC</th>
<th>CD</th>
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<td>%</td>
</tr>
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<tr>
<td>Skin diseases</td>
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<td>Eye complications</td>
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<td>1.14</td>
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<td>Hepatobiliary</td>
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<td>3.13</td>
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<tr>
<td>Musculoskeletal</td>
<td>155</td>
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<tr>
<td>Genitourinary</td>
<td>40</td>
<td>1.37</td>
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</table>
Extraintestinal Manifestations of IBD

- The most common findings were
  - peripheral arthropathy and sacroiliitis in both groups,
  - followed by cholecystopathy
Conclusions

• The prevalence of IBD in Turkey is lower than other European country prevalences but is higher than data from Asian populations

• The peak age of IBD onset in Turkey is similar to that in both the east and west
  - The majority of IBD cases are diagnosed in middle-aged patients, with male predominance
Conclusions

• The most common clinical form of UC is left-sided colitis, and of CD is ileo-colonic form
• The proportion of patients having extraintestinal manifestations in Turkey is also similar to that of Western and Eastern series
Conclusions

- The studies regarding association with mutations of the NOD2/CARD15 gene in the Turkish population are controversial.
- A large population-based study in this regard is needed.
- According to the results of the genetic studies available thus far, genetic factors may not be important risk factors in susceptibility to IBD in the Turkish population.
Thanks to

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- Dr. Nurdan Tözün
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- Dr. Belkıs Ünsal

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