NOD2/CARD15 Mutations among Bedouin Arabs with Inflammatory Bowel Disease: Frequency and Phenotype Correlation

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ABSTRACT: **Background:** Inflammatory bowel disease (IBD) prevalence is increasing among Bedouin Arabs in Israel. This population is known to have a high rate of consanguinity. *NOD2/CARD15* mutations are well-studied in IBD.

Objectives: To investigate the frequency of *NOD2/CARD15* mutations in IBD Bedouin patients and their relevance to disease phenotype.

Methods: The IBD-Arab cohort in southern Israel included 68 patients, of whom 25 Crohn's disease (CD) patients and 25 ulcerative colitis (UC) patients consented to participate (72%). Blood samples were obtained from all participants who were genotyped for *NOD2/CARD15* variants Arg702Trp, Gly908Arg, and Leu1007fsinsC.

Results: The *NOD2/CARD15* mutation frequency was higher in CD than in UC patients. Carrier frequency for the Gly908Arg mutation in CD and UC patients was 8/25 (32%) and 3/25 (12%), respectively (P = 0.08). Neither the Arg702Trp nor Leu1007fsinsC mutation was found in our cohort. No homozygous/compound heterozygote mutations were found. Genotype-phenotype analysis revealed that CD patients carrying the Gly908Arg mutation were younger at diagnosis, 22.8 ± 4.5 vs. 28.82 ± 9.1 years (P = 0.04). All carriers were male, compared to 41.2% in non-carriers (P = 0.005). *NOD2/CARD15* mutation carriers with UC were older, 67.0 ± 24.5 years compared to 41.2 ± 12.3 years (P = 0.006). No other associations regarding disease localization or other clinical parameter were found.

Conclusions: The frequency of *NOD2/CARD15* gene mutations is high in CD and UC among Bedouin Arab IBD patients and is associated with younger age at onset in CD and male gender.

IMAJ 2018; 20: 695–699

KEY WORDS: Bedouin Arab, genetic predisposition, inflammatory bowel disease (IBD), *NOD2/CARD15* gene mutation, southern Israel

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract with two major forms: Crohn's disease (CD) and ulcerative colitis (UC). The Bedouin Arab population is a subgroup within the Muslim Arab population in Israel. The majority of Bedouin Arabs live in three regions in Israel: southern Israel (Negev desert), central Israel, and the Galilee. In southern Israel, there are approximately 240,000 Bedouin Arabs [1].

Our data from a previous report showed that there is an increase in the prevalence of IBD among the Bedouin population, which could be attributed to the urbanization and modernization process with far-reaching lifestyle changes [2].

The consanguinity rate among Bedouin Arabs in southern Israel is very high, a recently published report found 44.8% of consanguinity among Bedouin women who delivered in the maternity wards of the only hospital serving the Bedouin population [3]. As an unfortunate consequence of the high rate of consanguinity, a high prevalence of genetically determined diseases is observed in this population [4].

Diagnosis of IBD is based on a combination of clinical, radiological, endoscopic, and histological criteria. The *nucleotide-binding oligomerization domain 2* (*NOD2*) gene was identified in 2001. It is also known as *caspase recruitment domain* (*CARD15*) located on chromosome 16 [5,6].

The most common variants associated with Crohn's disease include one frameshift insertion leading to early truncation of the protein (Leu1007fsinsC) and two missense mutations (Arg702Trp, Gly908Arg). The presence of one polymorphism increased the risk for CD two- to threefold. The presence of two mutations or homozygosity increases the risk of CD 20- to 40-fold [6-10].

The frequency of *NOD2/CARD15* varies among different ethnic groups and geographical regions. The frequency among Caucasian CD patients ranges from 9–13% for Arg702Trp, 3–6% for Gly908Arg, and 7–16% for Leu1007fsinsC [11]. The frequency ranges among UC patients are 4–6%, 2%, and 2.5–3%, respectively [12-14]. Different reports in European

patients showed *NOD2/CARD15* mutation frequency ranging from 15.2–50% [7,8,15,16].

A mutation prevalence of 27% in CD and 7% in UC patients was reported for Jewish patients [17]. Several studies investigated the frequency of *NOD2/CARD15* mutations in the Arab population. A low frequency was found among Tunisian and Moroccan CD patients [18,19]. A higher frequency was found among Algerian patients with a frequency of 13% among CD patients, 5% in UC patients, and 8% among healthy control [20].

Karban et al. [21] found that 8.2% of Arab CD patients in northern Israel carried one *NOD2/CARD15* mutation, compared with 2.3% of controls.

A number of studies investigated the relationship between the occurrence of a *NOD2/CARD15* mutation and phenotype. Early age of disease onset and ileal involvement increased the likelihood of stricture formation. In addition, fibrostenotic behavior was reported [7-9,22]. A rapid and more aggressive form of CD with the trend of multiple surgical interventions and shorter time to surgery was found in another report [23].

The main objective of the present study was to determine the frequency of the three common *NOD2/CARD15* mutations among the Bedouin Arab IBD patients. A second objective was to assess the association between the presence of a *NOD2/CARD15* mutation and clinical features of the disease in this patient population.

PATIENTS AND METHODS

PATIENTS

Bedouin Arab patients with known CD or UC were included in the present study. Fifty of 68 Bedouin Arab IBD patients (73%) in southern Israel were available for genotyping. Written informed consent was obtained from all participants.

Data on demographics, the extent of disease, medical therapy, surgery, disease classification, complications, smoking history, and family history of IBD were obtained via questionnaires and reviews of patient records.

The Montreal classification was used for disease classification of CD and UC patients [24].

The study protocol was approved by the institution's Helsinki committee and by the health ministry committee.

DNA EXTRACTION AND GENOTYPING

Patients were genotyped for Leu1007fsinsC and Arg702Trp mutations using single tube allele-specific polymerase chain reaction (PCR) and for Gly908Arg using restriction enzyme digestion assay [5,7]. For detection of the R702W, sense primers: 5'-GAATTCCTTCACATCACTTTCCAGT-3' and 5'-GCGCATCTGAGAAGGCCCTGTTCT-3'; and antisense primers: 5'-GTCAACTTGAGGTGCCCAACATT-3' and 5'-CGCCCAGCGGGCACAGGCCTGGCACCG-3' were used.

For detection of 1007fs sense primers: 5'-CTGAGCCTTTGTT, GATGAGC-3', and 5'-CAGAAGCCCTCCTGCAGGCCCT-3; and antisense primers: 5'-TCTTCAACCACATCCCCATT-3' and 5'-CGCGTGTCATTCCTTTCATGGGGC-3' were used.

Multiplex PCR was performed with all four primers in one tube using the following conditions: 94°C for 10 minutes, 35 cycles (94°C for 30 seconds, 55°C for 1 minute, and 72°C for 1 minute), and an additional extension at 72°C for 10 minutes. PCR products were electrophoresed on 2% agarose and visualized with ethidium bromide. A restriction enzyme digestion assay was used for the detection of G908R as described by Karban and colleagues [25]. The amplification product of 380 bp was amplified from genomic DNA using the forward primer 5'-CCCAGCTCCTCCCTCTTC-3' and the reverse primer 5'-AAGTCTGTAATGTAAAGCCAC-3'. Products were digested with the enzyme HhaI for 1 hour at 37°C and analyzed on horizontal 2% agarose gel as restriction fragment length polymorphisms.

STATISTICAL ANALYSIS

The results are presented as the mean ± standard deviation for continuous variables and the percentage of total patients for categorical data. For the categorical variables, proportions were compared using *t*-test or chi-square, as appropriate.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). $P \leq 0.05$ was considered statistically significant.

RESULTS

We recruited 50 Bedouin Arab IBD patients, 25 diagnosed with CD and 25 diagnosed with UC. This total comprises 73% of the entire cohort of Bedouin Arab IBD patients in southern Israel.

NOD2/CARD15 MUTATION FREQUENCY

Table 1 shows the frequency of the three mutations of *NOD2/CARD15* in CD and UC patient. Of all IBD Bedouin patients included in the study, 22% carried at least one of the *NOD2/CARD15* mutations. All carriers had the mutation Gly908Arg. In the IBD Bedouin Arab cohort neither the Arg702Trp nor the Leu1007fsinsC mutations were found. However, the mutation

Table 1. Frequency of the *NOD2/CARD15* variants among Bedouin inflammatory bowel disease patients

	Crohn's disease mutation carrier, n	Ulcerative colitis mutation carrier, n	*P* value
Gly908Arg	8/25 (32%)	3/25 (12%)	0.08
Arg702Trp	0	0	–
Leu1007fsinsC	0	0	–

prevalence was significantly higher in CD patients than in UC patients. The mutation was observed in 8/25 (32%) of the CD patients and in 3/25 (12%) of UC patients.

GENOTYPE-PHENOTYPE ANALYSIS IN CD PATIENTS

Demographic and clinical data comparing the group of CD mutation carriers with the non-carriers are shown in Table 2.

The Gly908Arg mutation carriers were younger in age (31.38 ± 8.5 years vs. 38.88 ± 10.4 years; $P = 0.07$). The age at diagnosis was significantly lower among mutation carriers: 22.8 ± 4.5 years and 28.82 ± 9.1 years for non-carrier ($P = 0.04$). It is noteworthy to mention that all mutation carriers were male (100%), whereas in the non-carrier group only 41.2% were male ($P = 0.005$). When analyzing the disease location according to the Montreal classification, no association was found between the mutation carriers with the non-carriers. No relationship was found regarding other parameters including disease behavior, appendectomy history, family history of IBD, smoking history, treatment with anti-tumor necrosis factor (TNF), and surgery.

GENOTYPE-PHENOTYPE ANALYSIS IN UC PATIENTS

We analyzed the phenotypic characteristics presented by all 25 UC patients. Of the 25 UC patients, the Gly908Arg mutation was detected in three (12%). When comparing mutation carriers to non-carriers with regard to age, we found that Gly908Arg carriers are older than non-carriers (67.0 ± 24.5 years vs. 41.2 ± 12.3 years, $P = 0.006$, respectively). There was a trend toward older age at diagnosis (46.7 ± 16.1 years vs. 30.7 ± 12.7 years, $P = 0.06$). No significant associations were found regarding other parameters. Demographic and clinical data comparing the mutation carriers and non-carriers are shown in Table 3.

DISCUSSION

IBD prevalence in the Bedouin Arab population is increasing [2]. In the current study, we investigated the frequency of *NOD2/CARD15* mutations in this population and its association with the IBD phenotype. To the best of our knowledge, no data have been previously reported regarding these mutations in the Bedouin Arab population in southern Israel.

As expected, and in accordance with previous findings, we identified a higher frequency of *NOD2/CARD15* mutation in CD than UC, 32% vs.12%, respectively.

Interestingly, in our cohort only one of the three *NOD2/CARD15* variant mutations was found: the Gly908Arg mutation. No Arg702Trp or Leu1007fsinsC mutations were found among the Bedouin Arab IBD patients. In addition, no homozygotes/compound heterozygotes were observed.

The frequency of *NOD2/CARD15* mutations is relatively high among our population. The frequency is ethnic specific and varies in different reports and geographic region. However, most reports showed a prevalence of less than 30%. The frequency among Caucasian CD patients ranges from 3–16% for the different *NOD2/CARD15* mutations and 2–6% in UC patients [11-14].

There are limited reports from the Arab world regarding *NOD2/CARD15* mutations. There are several reports in different Arab populations in North Africa, Tunisia, Algeria, and Morocco as well as in the Arab population in another region

Table 2. Demographic, clinical characteristics and genotype-phenotype correlation in Crohn's disease patients

Characteristic	Gly908Arg carrier n=8 (32%)	Non-carrier n=17 (68%)	*P* value
Age, years, mean ± SD	31.38 ± 8.5	38.88 ± 10.4	0.07
Age at diagnosis, years, mean ± SD	22.8 ± 4.5	28.82 ± 9.1	0.04
Gender, male (%)	8 (100)	7 (41.2)	0.005
Appendectomy (%)	0	5 (33.3)	0.08
Family history of IBD (%)	1 (12.5)	4 (23.5)	0.47
Smoking history (%)	2 (25.0)	6 (35.3)	0.61
Anti-TNF treatment (%)	4 (50.0)	6 (37.5)	0.45
Surgery (%)	3 (37.5)	7 (41.2)	0.86
Disease duration, median, years (IQR)	5.5 (4–11.5)	6 (5–15)	0.63
Localization ileal (%)	2 (25)	7 (41)	0.43
L2 (%)	1 (12.5)	1 (5.9)	0.54
L3 (%)	4 (50)	8 (47)	0.61
L4 (%)	1 (12.5)	1 (5.9)	0.54
Non-stricturing, non-penetrating disease (%)	4 (50)	12 (71)	0.32
Stricturing-disease (%)	2 (25)	4 (24)	0.65
Penetrating-disease (%)	2 (25)	1 (5.9)	0.23

IBD = inflammatory bowel disease, IQR = interquartile range, SD = standard deviation, TNF = tumor necrosis factor

Table 3. Demographic, clinical characteristics and genotype-phenotype correlation in ulcerative colitis patients

Characteristic	Gly908Arg carrier n=3 (12%)	Non-carrier n=22 (88%)	*P* value
Age, years, mean ± SD	67.0 ± 24.5	41.2 ± 12.3	0.006
Age at diagnosis, years, mean ± SD	46.7 ± 16.1	30.7 ± 12.7	0.06
Gender, male (%)	1 (33.3)	11 (50.0)	0.53
Appendectomy (%)	0	0	–
Family history of IBD (%)	0	1 (4.5)	0.88
Smoking history (%)	0	5 (22.7)	0.49
Anti-TNF treatment (%)	0	0	–
Past surgery (%)	0	2 (10.0)	0.75
Proctitis (%)	1 (33.3)	4 (18.2)	0.50
Left colitis (%)	2 (66.7)	9 (40.9)	0.41
Pancolitis (%)	0	9 (41.1)	0.24

IBD = inflammatory bowel disease, SD = standard deviation, TNF = tumor necrosis factor

of Israel, which showed a lower frequency of mutation carriage and no more than 13%. The Bedouin Arab population is known to have a high rate of consanguinity marriage, which might explain the high prevalence of genetic disease [4].

In the current IBD Bedouin Arab cohort, there are two nuclear families; each includes four patients with IBD. This population could be an interesting population for further genetic investigation in the future.

There is a large number of reports regarding phenotype-genotype correlations of *NOD2*/*CARD15* in CD patients [5-10]. Our results, in agreement with other studies, showed a relationship between the *NOD2*/*CARD15* mutation and early age on onset, with the age of 22.8 ± 4.5 years in mutation carriers compared to 28.82 ± 9.1 years in non-carriers ($P = 0.04$). Similar findings were reported in previous studies [8,9,16,18]. An important finding of the present work is the gender relationship. Our results showed that 100% of the *NOD2*/*CARD15* mutation carriers were male, compared to 41% in the non-carrier group ($P = 0.005$). This finding has not been reported previously [6-9].

In our study, no association was found in other parameters, including disease location and behavior.

The present study included 25 patients with UC. We found the *NOD2*/*CARD15* mutation in three patients (12%), which is a relatively high-frequency rate compared with previously reported frequency in different ethnic groups [12-14].

In a genotype-phenotype analysis, age at diagnosis was higher among mutation carriers by about 15 years, but statistically non-significant (46.7 ± 16.1 years vs. 30.7 ± 12.7 years; $P = 0.06$) in the UC cohort. In our genotype-phenotype analysis, no other differences were found regarding demographic or clinical characteristics of the UC patients.

We have reported before that the incidence of IBD among Bedouin Arab is increasing [2], which may be attributed to the change of lifestyle, including urbanization and modernization with a Western lifestyle, particularly with regard to hygiene and nutrition. However, as we expected, we found a high prevalence of the *NOD2*/*CARD15* mutation in this specific population.

The Bedouin Arab population in southern Israel is a very young society, with 60% of the population younger than age 19 years [1]. The compensation of these aforementioned factors had led us to expect a continuation of the increase in IBD incidence and prevalence in the future. Also, educational activities are very important and could have an important impact. Preventive intervention that has been suggested includes dietary changes, reduction in the rate of smoking (which is very high among the population), and minimization of the consanguinity rate in the population. In addition, genetic counseling may be offerred to populations at high risk.

The limitations of the present study include the small number of patients. In addition, like most previous studies, our analysis included only the three most frequent mutations in the *NOD2*/*CARD15* gene and no sequencing of the gene was completed. Third, we did not include a healthy control cohort.

CONCLUSIONS

We found a high prevalence of *NOD2*/*CARD15* mutations in CD and UC patients among Bedouin Arab patients. In our cohort, only the Gly908Arg mutation was identified. *NOD2*/*CARD15* positivity was associated with younger age at diagnosis and male gender of CD patients.

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Capsule

Interleukin-1β has atheroprotective effects in advanced atherosclerotic lesions of mice

Despite decades of research, our understanding of the processes controlling late-stage atherosclerotic plaque stability remains poor. A prevailing hypothesis is that reducing inflammation may improve advanced plaque stability, as recently tested in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, in which post-myocardial infarction subjects were treated with an IL-1β antibody. **Gomesz** and colleagues performed intervention studies in which smooth muscle cell (SMC) lineage-tracing *Apoe-/-* mice with advanced atherosclerosis were treated with anti-IL-1β or IgG control antibodies. Surprisingly, they found that IL-1β antibody treatment between 18 and 26 weeks of Western diet feeding induced a marked reduction in SMC and collagen content, but increased macrophage numbers in the fibrous cap. Moreover, although IL-1β antibody treatment had no effect on lesion size, it completely inhibited beneficial outward remodeling. The authors also found that SMC-specific knockout of *Il1r1* (encoding IL-1 receptor type 1) resulted in smaller lesions nearly devoid of SMCs and lacking a fibrous cap, whereas macrophage-selective loss of IL-1R1 had no effect on lesion size or composition. Taken together, these results showed that IL-1β has multiple beneficial effects in late-stage murine atherosclerosis, including promotion of outward remodeling and formation and maintenance of an SMC- and collagen-rich fibrous cap.

Nature Med 2018; 24: 1418

Eitan Israeli

Capsule

Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis

Watad and colleagues, in a cross-sectional study, used the computerized databases of Maccabi Healthcare Services (MHS), which include up to 20 years of data on 2 million members. Women with Silicone breast implants (SBIs) were identified by procedure and diagnosis codes, clinical breast examinations, and mammography referrals. Autoimmune/rheumatic disorders were identified using the International Classification of Diseases 9th revision (ICD-9) codes. Multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95%CIs). A Cox proportional hazards model was used to calculate the hazard ratios (HRs) and 95%CIs among a subgroup of SBI recipients for whom the year of SBIs insertion was available. The authors included 24,651 SBI recipients and 98,604 matched SBI-free controls. The adjusted OR between SBIs and being diagnosed with any autoimmune/rheumatic disorders was 1.22 (95%CI 1.18–1.26). The strongest association with SBIs (OR › 1.5, P ‹ 0.001) was recorded for Sjögren's syndrome, systemic sclerosis (SSc), and sarcoidosis (OR 1.58, 1.63, and 1.98, respectively). Similar results were calculated when analysis was limited to women with no breast cancer history. A multivariable Cox regression model yielded an HR of 1.45 (95%CI 1.21–1.73) for being diagnosed with at least one autoimmune/rheumatic disorder in women with SBI compared to those without.

Int J Epidemiol 2018 Oct 16. doi: 10.1093/ije/dyy217

Eitan Israeli

"Learning without thought is labor lost; thought without learning inspiration does not come like a bols perilous"

Confucius, (551 BCE–479 BCE), Chinese philosopher