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Letter to the Editor

Low prevalence of NOD2/CARD15 and TLR4 gene polymorphisms, ASCA and pANCA in inflammatory bowel disease patients from northwest Greece participating in the EC-IBD Study Group cohort

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TO THE EDITOR: Sir, during the last decade various genetic and serological markers have been reported in association with inflammatory bowel disease (IBD).

Among genetic markers, single nucleotide polymorphisms (SNPs) in the NOD2/CARD15 gene have been involved in the pathogenesis of Crohn's disease (CD) while the Asp299Gly polymorphism in the lipopolysaccharide (LPS) receptor TLR4 has been reported to be associated with CD and ulcerative colitis (UC). This last polymorphism is associated with impaired responsiveness to LPS and enhanced susceptibility to gram-negative bacteria.

Among serological markers, ASCA and pANCA have been associated with the diagnosis of CD and ulcerative colitis (UC) respectively. The majority of such studies originate from northern European populations and centers while studies from southern European population are scarce.[1,2]

The aim of this short communication is to report the prevalence of these genetic and serologic markers in a well-defined IBD population in northwest Greece, which was recruited during the period 1992-1993 and was followed up prospectively for a 10-year period during the study of the European Collaborative Inflammatory Bowel Disease Group (EC-IBD Study Group).

Diagnosis of IBD was made using standard clinical, endoscopic, histologic and radiologic criteria. Blood samples from 36 IBD patients [32 with ulcerative colitis (88.9%), 4 with Crohn's disease (11.1%)] were analyzed. Of these patients, 17 were men (47.2%) and 19 women (52.8%) with a mean age of 49.8±14.6 (range 28-80 years). Ulcerative colitis location was in 26 patients (72.2%) left sided, in 3 patients (8.3%) pancolitis and in 3 patients (8.3%) proctitis. Crohn's disease was located in terminal ileum in 3 cases (8.3%) and ileum and colon in one case (2.8%). All patients attended the study after signing an informed consent.

We also analysed samples from 36 age and sex matched healthy controls originating from the same geographical region. All individuals were analysed for CARD15 R702W, G908R and L1007fs, for TLR4 aAsp299Gly and for ASCA and pANCA.

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Abbreviations:

ASCA=Anti-saccharomyces cerevisiae antibodies
CARD=Caspase activating recruiter domain
CD=Crohn's disease
EC-IBD = European Collaborative Inflammatory Bowel Disease
IBD=Inflammatory bowel disease
LPS= lipopolysaccharide
pANCA=Anti-neutrophil cytoplasmic autoantibodies
SNP(s)=Single nucleotide polymorphisms
TLR=Toll-like receptor
UC=ulcerative colitis

All laboratory testing was performed at the Laboratory of Gastroenterology, University Hospital Gasthuisberg, Leuven Belgium, which was the central Laboratory for all the EC-IBD Study Group samples. Serum and DNA was extracted from peripheral blood using classical methods. The PCR-RFLP method in agarose gels was used for CARD15 and TLR4 polymorphisms, ASCA were determined by ELISA and pANCA by indirect immunofluorescence.

We observed a zero frequency of CARD15 variants in our IBD cohort, as compared to 8.5% (3/35) in controls (p=0.7). TLR4 mutated alleles were present in two IBD patients (one CD, one UC) and in 3 controls (p=0.6). ASCA was not detected in any of IBD patients or any of the control individuals. For pANCA, prevalence was 7.4% in UC (2/27) compared to 0% in CD and 0% in controls (all p=NS). Within EC-IBD study group cohort the figures our center were of the lowest reported together with these of Portugal and Israel.[3]

To summarize results, we found no CARD15 variants while the prevalence of TLR4 gene polymorphism did not differ between patients and control groups. ASCA was not detected in any sample and pANCA was present only in two UC patients.

Despite of the restricted number of individuals analysed which may have underpowered our results, real differences in these markers may exist among our area and other areas of Greece or Europe as it has already been shown in epidemiological studies.[4]

In fact, ASCA has been associated with CARD15, ileal disease and a more severe disease type (surgery, penetrating behaviour).[5] It is noteworthy to mention that IBD seems to have a milder course in our area compared to other areas of Greece and northern Europe with UC prevalence being four to eight fold higher compared to CD prevalence.[6] Fianally, it is of interest that all four CD patients were diagnosed with ileal involvement.

To conclude, in this unselected consecutive IBD cohort from northwest Greece genetic and laboratory markers, which have been reported of remarkable frequency in other centers, seem to be much less frequent.

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