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Letter to the Editor

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Common *SPINK-1* genetic mutations do not predispose to Crohn disease

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To the Editor,

Genetic factors may be important in Crohn disease (CD) risk and progression (1). The detection of linkage on chromosome 16 led to identification of the *CARD15/NOD2* gene as a susceptibility gene for CD (2).

Pancreatic secretory trypsin inhibitor, also known as serine protease inhibitor Kazal type 1 (SPINK-1), is a 56-amino acid peptide that protects the pancreas from autodigestion (3). SPINK-1 expression occurs in tissues other than the pancreas including the liver, the mucosa of the stomach, and the small and large intestines (4,5). The *SPINK-1* gene, located on chromosome 5q32, is close to one of the CD susceptibility loci (6). The association of pancreatic disorders with inflammatory bowel disease (IBD), the role of the SPINK-1 molecule in epithelial and mucosal protection, and the genetic location of the *SPINK-1* gene close to one of the CD susceptibility loci prompted us to perform *SPINK-1* gene genetic association analyses to ascertain its possible role in CD pathogenesis.

Patients admitted to the Ege University Inflammatory Bowel Disease Outpatient Clinic between January 2009 and January 2010 were evaluated and 56 CD patients and 80 healthy volunteers were included in the study. For each patient disease activity was assessed by the CD activity index (CDAI) and disease localization was classified according to the Vienna classification (7). Common genetic mutations in the third exon of the *SPINK-1* gene were analyzed by direct sequencing method as reported in the literature. The associations between phenotypic features of the disease and genotypic variations were evaluated (8). The study was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The mean age of CD patients at the time of diagnosis was 36.2 ± 15.2 years. Mean duration of CD disease was 6.5 ± 5 years when patients were included in the study. CD was located to the ileocolic segment in 24 (L3), the ileal segment in 21 (L1), and the colon in 10 patients (L2). The upper gastrointestinal system was affected in one subject (L4). Patients were receiving mesalazine and corticosteroids according to their disease location and activity. Three patients were on azothiopurine treatment due to steroid side effects. Nine patients had stricturing disease and 8 had penetrating disease. Extraintestinal manifestations including seronegative arthritis (n = 4), amyloidosis (n = 1), and erythema nodosum (n = 5) were diagnosed in 10 CD patients. None of the patients had acute or chronic pancreatitis. Neither N34S mutation nor P55S mutation was found in the *SPINK-1* gene third exon in CD patients. One control subject had a homozygous mutation at the N34S location (Figure). The allele frequency of N34S was 1% in healthy controls. No other rare mutations including D50E, Y54H, R65Q, and K66N of the *SPINK-1* gene were detected in the studied groups.

Susceptibility for CD is predominantly determined by genetic factors and the complex inheritance patterns suggest the interaction of multiple genes. Serine protease inhibitors synthesized within the gut maintain mucosal integrity and/or stimulate repair after injury (9). Despite the known role of the SPINK-1 molecule in epithelial and mucosal protection and the important genetic location close to the CD IBD5 susceptibility locus, our findings showed that common *SPINK-1* mutations are not found in CD patients in the Turkish population. However, the number of subjects in this study group was too small to rule out the association between *SPINK-1* mutations and CD. It is also suggested that *SPINK-1* mutations are rare in the healthy Turkish population. Extensions of genetic and expression analysis to all other serine protease inhibitors in different populations are warranted in further studies to clarify the possible role of SPINK molecules in CD.

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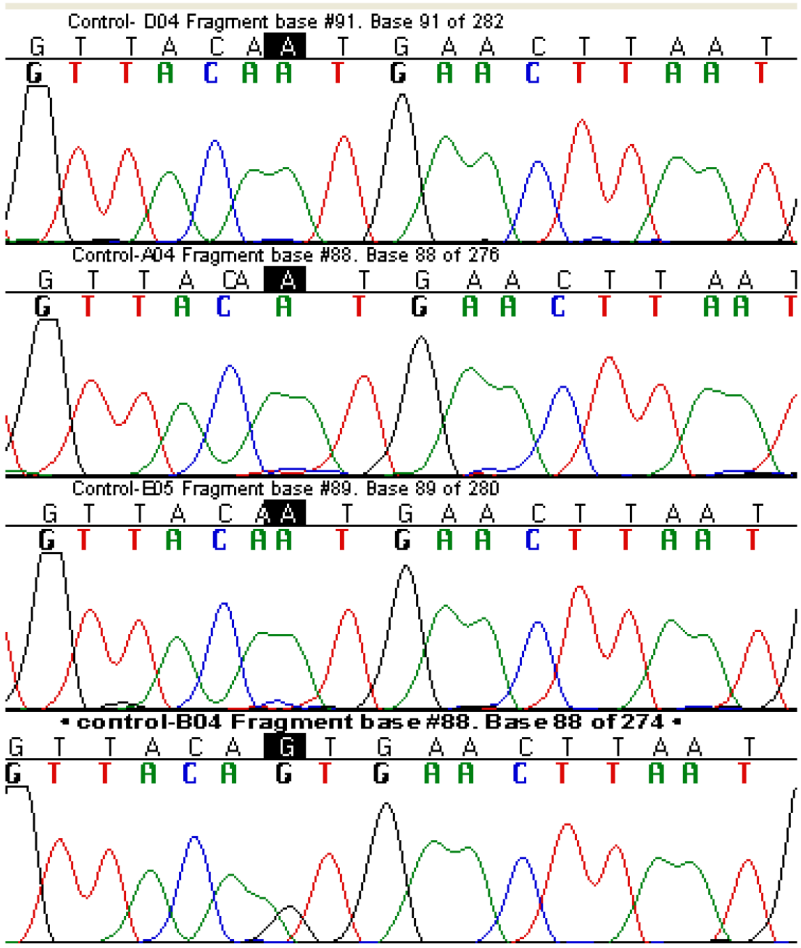

Figure. Sequence analysis of subjects: mutation at N34S is seen in one of the healthy controls.

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