The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease

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BACKGROUND
We investigated the influence of 2 common Toll-like receptor 4 (TLR4) polymorphisms on susceptibility and disease characteristics of Crohn's disease (CD).

METHODS
Genomic DNA from 204 patients with CD and 199 unrelated controls was analyzed for the presence of 2 single nucleotide polymorphisms in the TLR4 gene, resulting in the amino acid substitutions Asp299Gly and Thr399Ile. In addition, the carrier status for the 3 common CD-associated CARD15/NOD2 gene mutations, Arg702Trp, Gly908Arg, and 1007fs, was determined. The frequency of the different genotypes was compared, and a detailed genotype-phenotype correlation was performed.

RESULTS
An almost 2-fold increase in the frequency of the TLR4 Asp299Gly phenotype was observed in patients with CD (14.2%) compared with healthy controls (7.5%, \( P = 0.038 \), odds ratio = 2.03). The prevalence of a stricture phenotype was increased in patients heterozygous for 1 of the TLR4 polymorphisms studied (Asp299Gly, 34.5%; Thr399Ile, 36.7%) compared with patients with wild-type TLR4 (17.1% and 16.7%; \( P = 0.04 \) and 0.02, respectively). The presence of the Asp299Gly polymorphism in the absence of CARD15/NOD2 mutations was a particularly strong predictor of the stricture phenotype that was present in 47.4% of the patients with Asp299Gly+/NOD2- compared with 10.1% of the patients with the Asp299Gly-/NOD2+ status (\( P = 0.0009 \); \( P = 0.0004 \) for Thr399Ile+/NOD2- versus Thr399Ile-/NOD2+). In contrast, there was a trend toward a higher prevalence of the penetrating phenotype in the TLR4-/NOD2+ group (71.6%) compared with the TLR4+/NOD2- group (47.4%, \( P = 0.059 \)).

CONCLUSIONS
The TLR4 Asp299Gly polymorphism is a risk factor for CD. TLR4 and CARD15/NOD2 mutations may contribute to distinct disease phenotypes.