Homozygosity for the CARD15 frameshift mutation 1007fs is predictive of early onset of Crohn's disease with ileal stenosis, entero-enteral fistulas, and frequent need for surgical intervention with high risk of re-stenosis

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OBJECTIVE
The identification of CARD15 as a susceptibility gene for Crohn's disease (CD) offers new possibilities for patient classification and risk assessment. The purpose of this study was to carry out a CARD15 sequence analysis in a large single-center IBD cohort and to investigate the impact of different genotypes on disease phenotypes.

MATERIAL AND METHODS
A total of 445 unrelated patients with IBD (68.1% CD, 28.5% ulcerative colitis (UC), 3.4% indeterminate colitis (IC)) were included in the study. Clinical data were recorded by detailed questionnaire and analysis of the charts. CARD15 variants (R702W, G908R, 1007fs (frameshift)) were identified by DNA sequence analysis.

RESULTS
CARD15 variants were found in 142 inflammatory bowel disease (IBD) patients (31.9%) including 120 CD patients (39.6%). In CD, the presence of two CARD15 variants was associated with ileal disease (p=0.008 versus wild-type (wt); OR 4.04; 95% CI 1.36-11.96) and a fibrostenotic phenotype (p=0.002 versus wt; OR 5.47; 95% CI 1.61-18.58). Subgroup analysis of 19 patients (4.3%) homozygous for the CARD15 variant 1007fs (3020ins C) revealed an association with onset of CD at an early age (p=0.014 versus wt), ileal involvement (p=0.001), and intestinal stenoses in all patients (p=0.001) frequently requiring surgery (73.7%; p=0.093). Of these patients 78.6% developed re-stenoses after surgical resection; 52.6% of the homozygotes were diagnosed as having entero-enteral fistulas.

CONCLUSIONS
Patients homozygous for the 1007fs mutation had an early disease onset with long-segment ileal stenoses and entero-enteral fistulas. They frequently needed surgical intervention and had a high risk of re-stenosis. Genotyping therefore appears to be an important diagnostic tool in identifying severely affected patients requiring individualized treatment strategies at an early stage of the disease.