conserved and non-conserved amino acid residues involved in PGN recognition. These results provide new insight into the molecular function and regulation of NOD2 and related NOD family proteins.

M1562

Evaluation of SNPs in TNF (C-857T) and MDR1 (C3435T) As Susceptibility Factors for IBD

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Background: Recently, association of the TNF C-857T and MDR1 (C3435T) polymorphism with inflammatory bowel disease (IBD) has been reported. Strong association of TNF C-857T with ulcerative colitis (UC) was seen, but with Crohn disease (CD) only after removal of individuals carrying the disease predisposing CARD15 mutations. Objective: To replicate and explore the nature of these associations a German (629 CD patients, 320 UC patients) and UK cohorts (164 CD, 87 UC). Methods: The association of TNF C-857T and MDR1 (C3435T) with IBD, CD and UC was tested in samples using family-based and case-control association tests. Univariate TDT analyses examined association with clinical sub-traits. Results: In case-control analyses, the TNF C-857T CC genotype was over represented relative to controls in German trios and German families for CD ($P=0.011$). No association with UC was observed ($P=0.470$). TDT analyses indicated that the C allele was over-transmitted in both CD and UC (IBD; German families and trios $P=0.0025$). Over-transmission in a British family sample was not significant when this sample was considered independently. No evidence of association was detected between the C3435T MDR1 polymorphism and the IBD, CD or UC phenotypes in any analysis. Conclusions: The TNF C-857T polymorphism exhibits a complex association with IBD. The T allele may protect against complications of IBD including stenosis, fistulae and arthritis, but may also be due to linkage disequilibrium with other loci within the MHC region.

M1563

TNF-Alpha and IL-10 Snps Act Together to Predict Disease Behaviour in Crohn's Disease

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Introduction: TNF-alpha and IL-10 are cytokines that have both been implicated in the pathogenesis of Crohn's disease (CD). There are limited data on the effects of both cytokines on disease phenotype in the same population. Certain single nucleotide polymorphisms (SNPs) within the promoter region of the IL-10 (-1082-G allele) and TNF-alpha (-308-A allele, -857-C allele) genes are associated with significantly higher levels of circulating IL-10 and TNF, respectively. Aims: to investigate 4 SNPs in the promoter region of both genes in a well-characterized CD cohort by case-control analysis. To examine whether there are significant associations with disease phenotype. Methods: 275 consecutive CD cases from the IBD database and 217 healthy controls were genotyped for 2 TNF-alpha (-308 and -857) and 2 IL-10 (-592 and -1082) SNPs, by PCR-RFLP. All clinical data were obtained from the database. Genotype-phenotype analysis was only performed for SNPs that attained $P<0.2$ in case-control analysis. Results: genotype analysis showed a significant difference between cases and controls for IL-10 (-1082) ($P=0.03$) and a trend for TNF(-857) ($P=0.16$), but not for the other 2 SNPs. Both IL-10 (-1082) and TNF-alpha (-857) were associated with disease behaviour ($P=0.02$ and $P=0.04$ respectively), with patients carrying the IL-10 G allele having a greater risk of stricturing disease, and those carrying the TNF C allele having a greater risk of stricturing or penetrating disease. When both SNPs were analyzed together, patients carrying both these alleles showed an even stronger association with stricturing behaviour which persisted after multivariate analysis ($P=0.008$). There was also a weaker association with familial CD ($P=0.03$). These findings were unchanged after stratification for NOD2 genotype (SNPs 8,12 and 13). Conclusion: specific SNPs in the TNF-alpha and IL-10 genes may help to predict CD behaviour. This may be clinically useful in shaping treatment of the disease at an earlier stage. The above results will need to be verified in an independent ethnically similar cohort using the same methods of assessment of disease-related variables as in this study.

M1564

TLR4 Asp299Gly, Inflammation and Response to Infliximab in CD

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INTRODUCTION. Crohn's disease (CD) is a chronic inflammatory disorder. An excessive immune response to the intestinal bacterial flora, plays a role in the pathogenesis of the disease. This is underscored by the association between CARD15 and Toll-like receptor (TLR)-4 polymorphisms and CD. Binding of lipopolysaccaride (LPS) of Gram negative bacteria to TLR4 results via the NF-kB signalling pathway in the transcription of many inflammatory genes among which TNF-alpha. The functional Asp299Gly polymorphism in TLR4 impairs the efficacy of LPS signalling. Chimeric monoclonal antibodies against TNF-alpha (Infliximab) are a very effective treatment for CD, however 20-30% of patients are refractory. It has been shown that patients with more inflammation at baseline (as defined by high CRP levels) respond better to Infliximab. METHODS & AIMS. We studied the effect of TLR4 Asp299Gly on inflammation and both the biological and clinical response to Infliximab. 300 CD patients were collected in a prospective trial to evaluate response to Infliximab. Patients received Infliximab in an on demand schedule. CRP and CDAI were evaluated before infusion and at week 4 or 10 following Infliximab (for luminal and fistulizing disease respectively). Clinical response and remission were defined as a decrease of CDAI of 100 points and a drop below 150 points. Biological response and remission as a 50% decrease of CRP levels and drop below 3 mg/L respectively. Genotyping was done by PCR RFLP. Groups were compared using Chi-square test and t-test. RESULTS. There was no difference in CRP levels at baseline between patients with and without TLR4 mutations. Median decrease in CDAI and CRP was 97 points (IQR 35.5-206) and 7.4 mg/l (IQR 0-23.6). A clinical response was seen in 65% of the patients and 49% of these entered clinical remission. Biological response and remission were seen in 69% and 37% of the patients respectively. We did not find a significant difference in response to Infliximab treatment between patients with (16%) and without the TLR4 Asp299Gly rare allele (84%). CONCLUSION. Although the functional TLR4 Asp299Gly polymorphism results in less translocation of NF-kB upon stimulation with LPS, we did not find a association between this SNP and both clinical and biological response to Infliximab in CD. Similar results have been obtained for CARD15 and suggest that innate immunity genes do not seem to influence response to Infliximab.

M1565

A Polymorphism in Insulin-Like Growth Factor Gene May be Associated with Early Fistulizing Behaviour in Colonic Crohn's Disease

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Crohns disease (CD) is a heterogeneous multifactorial polygenic disease. Genetic background may influence the phenotype. Insulin-like Growth Factors (IGF), potentially involved in fibrosis and apoptosis regulation are increased in CD. Our aim was to study the association between several polymorphisms described in IGFs or IGF receptors (RIGF) and phenotypes of CD, essentially anatomic behaviour. Methods: A 2 cohorts study was set up. Five polymorphisms in IGF1, IGF2, RIGF1 and RIGF2 were studied in a first cohort of 145 CD and 126 controls. Genotype frequencies were compared between CD and controls as well as between behaviours of CD defined according to Vienna classification determined at diagnosis and after 5 years. Positive results (with a $p<0.1$) were then checked on a second cohort of 323 CD. A multivariate analysis was then performed including clinical and demographic variables potentially influencing CD behaviour. Results: In the first cohort, there was no significant difference in genotypes frequencies between CD and controls as well as between various CD behaviours except for a functionally significant polymorphism, characterized by a variable number of a simple sequence repeat in the promoter of IGF1. Homozygotes for the most common allele (4/4), were significantly less frequent in penetrating (B3) than in structuring (B2) or uncomplicated (B1) behaviours both at diagnosis (26.5%, 65% and 42.1%; $p=0.045$) and after 5 years (23.3%, 56.5% and 51.6%; $p=0.034$). Such significant difference was not confirmed in the second cohort, but the trend mainly for disease behaviour 5 years after diagnosis was still present (30.9% of 4/4 in B3, 41.4% in B2 and 38.6% in B1) and the difference remained significant when grouping the two cohorts together (28.6% 4/4 in B3, 45.7% in B2 and 42.6% in B1; $P=0.038$). Multivariate analysis selected disease location and IGF1 genotype as independent parameter associated with CD behaviour at 5 years ($p<0.001$), and when looking at genotypes in patients stratified for disease location, the lower frequency of 4/4 genotype in B3 patients was not found in pure ileal disease, but essentially in colonic and ileocolonic disease (18.3% of 4/4 in B3 vs 48.2% in B1 and B2; $P=0.0004$, $RR=2.6$, 1.5-4.7). Conclusion: An association seems to exist between this functionally significant polymorphism in the promoter of IGF1gene and the inclination to develop early fistulizing disease, particularly in colonic CD.

M1566

Increased Frequency of a Single Nucleotide Polymorphism in Hypothetical Gene FLJ21425 in Patients with Crohn's Disease in a Louisiana Population

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The purpose of this study was to test the hypothesis that polymorphisms in FLJ21425, a cDNA encoding a hypothetical protein that we have found to be underexpressed in the mucosa of patients with newly diagnosed, active Crohn's disease, are associated with susceptibility to Crohn's disease. To test this hypothesis, we sequenced genomic DNA at the LSU Core Gene Sequencing Laboratory from 60 patients with Crohn's disease and 100 unrelated controls from a genetically similar population using DNA amplified with gene-specific primers designed from a 2726 base pair Incyte cDNA sequence. At base pair 2473, we detected a single nucleotide polymorphism (SNP) resulting in a cytosine to thymine substitution (C2473T) that was present in 45% ($n=27$) of patients with Crohn's but in only 27% ($n=27$) of normals ($X^2=5.43$, $p=0.02$). When only unrelated patients were included in the analysis, 42% ($n=20$) of patients and 27% ($n=27$) controls had the SNP ($X^2=3.08$, $p<0.10$). These data suggest that a SNP in the 3'end of FLJ21425 may be associated with increased risk of Crohn's disease. DNA from more patients is being analyzed to determine if FLJ21425 is a disease-associated gene or is in linkage disequilibrium with a disease-associated gene.

M1567

Genetic Crohn's Disease. A Different Entity Than Sporadic. A Study in Monozygotic Twins

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Background and Aims: Crohn's disease (CD) may be divided into a familial form in contrast to sporadic CD, the former being mainly genetically determined while the latter should mainly be caused by environmental factors. Using the Vienna classification the familial form consists most often of ileal (L1) or ileocolonic (L3) disease while colonic location (L2) is more common in sporadic. The aim of the present study was to test this hypothesis by comparing monozygotic (MZ) twins concordant for CD with pairs discordant for CD. Concordant pairs were then regarded as familial CD with a strong genetic influence, while discordant pairs were looked upon as sporadic CD, which by chance affected a MZ twin, and where environmental factors were most important etiologically. Methods: The twins derived from a Swedish population based cohort of twins with inflammatory bowel disease (IBD) and were clinically phenotyped by retrospective scrutiny of their medical notes, in CD using the Vienna classification. All MZ twins were invited to participate in a study of