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REGULARIZED LEAST SQUARES CLASSIFIERS MAY PREDICT CROHN'S DISEASE FROM PROFILES OF SONGLE NUCLEOTIDE POLYMORPHISMS

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Background and Aims: Association studies strategy provides a limited view of complex genetic disorders like Crohn's disease (CD) in which one gene is neither necessary nor sufficient to develop the disease. Moreover, they do not take into account gene-gene interactions and the correlation between groups of genes and phenotype. We focused on the prediction of CD susceptibility by analyzing SNPs profiles of a number of defined or candidate genes by using well-founded methods and procedures developed in the field of statistical learning theory.
Methods: A sample generated by a case-control study composed of 178 CD patients [mean age 38±18 yrs (range 5-86; 99 males; mean age at diagnosis 28±15)], and 127 healthy controls (84 males; mean age 43±11 yrs) was investigated. The genetic profile of each subject was characterized by 16 genetic variants distributed over 11 genes (CARD15, OCTN1/2, DLG5, MYO9B, PTPN22, IBD5 locus, TNFα, MCP1, MDR1, FcGIIIA and NFκB) evaluated by DHPLC, RFLP, TaqMan, and direct sequencing techniques. Analysis was performed by mean of the regularized least-squares (RLS) classifier methodology; the prediction accuracy was measured by the leave-k-out cross validation (LKOCV) procedure with 500 random splits of the data in training and test sets.
Results: The three CARD15 SNPs showed the highest values of specificity indicating that more than 90% of controls lack of these variants. These SNPs also showed the lowest values of sensitivity pointing out that only the 28% of CD patients carry at least one variant. The G908R variant of CARD15 provided the highest value of positive predictive value (PPV), however its accuracy in CD prediction was similar to chance (47%). RLS classifiers predicted CD with a statistically significant accuracy (A) (62%; p = 0.018), significantly increasing the diagnostic accuracy of at least 10% compared to that obtained with the evaluation of CARD15 gene. No interaction between the investigated genes was demonstrated.
Conclusions: RLS methodology has been able to increase the diagnostic accuracy of CD prediction by contemporary evaluating a large number of gene polymorphisms and their possible interactions. This approach might be particularly useful in large-scale population screening program, and when evaluating large data set of gene polymorphisms (i.e. chip, microarray). Moreover it could shield more light in selecting possible candidate genes with a weak genetic contribution and evaluating gene-gene and gene-phenotype interactions by analyzing populations with an affordable small sample size.

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DOES HEALTH-RELATED QUALITY OF LIFE CHANGE IN FOLLOW-UP IN ULCERATIVE COLITIS AND CROHN DISEASE?

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Background: Health-related Quality of Life (HRQoL) is currently being used as surrogate marker of disease behaviour in most interventional studies on Inflammatory Bowel Disease (IBD). The IBSEN cohort (Inflammatory Bowel South Eastern Norway) have previously presented HRQoL in IBD patients five years after initial diagnosis and identified variables that influence HRQoL.
Aim: To determine HRQoL 10 years after diagnosis in patients with ulcerative colitis and Crohn disease. Further to compare HRQoL data five and 10 years after initial diagnosis in the IBSEN cohort.
Methods: All patients alive had an invitation to participate in a standardized 10 year follow-up. In addition to collection of clinical data, patients where asked to complete HRQoL-questionnaires: the Inflammatory Bowel Disease Questionnaire (N-IBDQ, a Norwegian disease specific and validated quality of life questionnaire) and the SF-36 (a generic quality-of-life questionnaire).
Results: At 10 years there was HRQoL-data on 340 IBD patients, of these there were additional data from the 5 year follow up in 265 (78%); mean age 45.6 years (SD ± 13.4), 50.5%women and 65% with ulcerative colitis. HRQoL based on N-IBDQ was constant, the overall score was 185 at 10 years compared to 184 at five years. Categorized by diagnosis and sex there was somewhat larger difference between men with ulcerative colitis and women with Crohns disease at 10 years compared to five years. HRQoL by SF-36 demonstrate some of the same difference, women with Crohns disease scores least while men with ulcerative colitis have the highest score.
Conclusion: HRQoL 10 years after diagnosis determined by the N-IBDQ was unchanged compared to five years data. We do find that women with Crohns disease report the most inferior HRQoL at 10 years as well as at five years. Results from the SF-36 questionnaire support these findings.

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EVALUATION OF NUCLEAR PREGNANE X RECEPTOR (NR1I2) IN PEDIATRIC PATIENTS WITH IBD

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Background & Aims: The nuclear pregnane X receptor (PXR) is an important component of the body's adaptive defense mechanism against toxic substances including foreign chemicals (xenobiotics). Genetic variations in the PXR encoding gene NR1I2 on chromosome 3q were found in adults with inflammatory bowel disease (IBD) exhibiting a strong genotype-phenotype correlation. Therefore the aim of this study was to investigate the association of NR1I2 polymorphisms with disease in a pediatric IBD cohort.
Methods: We performed a case-control study examining the single nucleotide polymorphism (SNP) at the -28385 locus, which has previously been associated with altered activity of PXR-regulated genes in a German cohort including 115 children with IBD (79 Crohn's disease, 31 ulcerative colitis, 5 colitis indeterminata) and 120 ethnically matched healthy adult controls.
Results: We observed no significant association of the -25385 SNP with IBD patients, with the following frequency for the -25385C allele: n=142 (61.74%) versus n=143 (59.58%) in controls (p=0.6325, OR=1.09, CI 0.74-1.61). Moreover, no significant association could be found when IBD subgroups were tested. Crohn's disease showed an allele frequency of 59.49% (n=94 with p=0.98, OR=0.99,CI=0.64-1.53), whereas ulcerative colitis showed an allele frequency of 67.74% (n=42 with p=0.24, OR=1.42, CI=0.75-2.68).
Conclusions: Our results indicate that the -25385 SNP is not associated with pediatric IBD. There is no significant difference between the allele frequency of this NR1I2 susceptibility variant in the German pediatric IBD population compared to healthy controls.

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GENETIC MARKERS AND THE RISK OF COMPLICATED DISEASE BEHAVIOUR IN CROHN'S DISEASE PATIENTS

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Introduction & aims: The majority of Crohn's disease (CD) patients develop complications (fistulae or strictures) in the course of the disease and often require surgery. It is important to identify patients who are at high risk to develop complications early, as this may have therapeutic implications. We investigated if CD-associated genes may influence time to onset of complications and need for abdominal surgery, and if a risk model for disease progression could be identified.
Methods: A cohort of 505 patients with CD (41.2% male; median age at diagnosis 24.4y (IQR 19.2-31.3) was genotyped for variants in NOD2/CARD15, TUCAN/CARD8, NOD1/CARD4, TLR1, TLR2, TLR4, TLR6, OCTN1, OCTN2 and DLG5, and were reviewed for age and smoking at diagnosis, disease loca-