Abstract

TITLE: CYTOKINE GENOTYPES AND CYSTIC FIBROSIS PHENOTYPE. CYTOKINE GENE POLYMORPHISMS AND SEVERITY OF CYSTIC FIBROSIS LUNG DISEASE

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ABSTRACT BODY: Abstract Body: Background: The search for modifier genes to explain inconsistencies in cystic fibrosis (CF) genotype-phenotype relationships has yielded mixed results. In a previous cross-sectional study (2002) from our centre the clinical effect (as described by FEV1, BMI z-score, admitted days and NIH score) of single nucleotide polymorphisms (SNPs) of four cytokine genes (interleukin-8, TNF-α, interleukin 1β and interleukin-10) was examined in 158 children with CF. No association between cytokine genotype and any biological outcome measure was found. In this present study a cross-sectional and longitudinal examination of this relationship was undertaken to test the hypothesis that pro-inflammatory SNPs would affect longitudinal changes in CF lung disease.

Methods: Using the cohort examined in our earlier study we performed both longitudinal and cross-sectional data analyses examining the relationship between SNPs (TNF-α, interleukin-8, interleukin-10 and interleukin-1β) and clinical outcome measurements. In the first part of this current study, lung function data (annual decline of FEV1 percent predicted) was compared with the cytokine genotype over a 13 year period. In the second part of this current study multiple regression was used to assess associations between clinical outcomes (best FEV1 percent predicted and BMI at the age of 10 years) and alleles of cytokine genes, adjusting for gender, CF genotype and lung infection status.

Results: A total of 152 patients with CF were analyzed in the longitudinal study and data from 130 patients at the age of 10 yrs were analyzed in the cross-sectional study. There was evidence for an association between pro-inflammatory SNPs of the interleukin-8, interleukin-10 and interleukin-1β gene and more severe lung disease. Multiple regression of the longitudinal data with a total of 10956 lung function measurements showed an additional annual decline of the percentage predicted FEV1 of -1.15 (interleukin-8, p<0.001), -0.24 (interleukin-10, p=0.049) and -0.41 (interleukin-1β, p<0.001) for patients with any of the pro-inflammatory alleles. None of the cross-sectional data showed a significant association between the cytokine genotypes and the clinical outcomes.

Conclusion: Pro-inflammatory alleles of three cytokine genotypes, interleukin-8, interleukin-10 and interleukin-1β, have been identified which appear to be associated with slightly more severe lung disease in patients with CF over a 13 year period. Further studies are required to exclude influence of confounders on the severity of lung disease.