European Respiratory Society
Annual Congress 2012

Abstract Number: 2658

Publication Number: P4795

Abstract Group: 12.3. Genetics and Genomics

Keyword 1: COPD - mechanism **Keyword 2:** Genetics **Keyword 3:** Epidemiology

Title: Heterozygosity for E292V in ABCA3, lung function and COPD in 64,000 individuals

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Body: Recessive mutations in the ATP-binding-cassette-member A3 (ABCA3) gene are associated with chronic lung disease in childhood, but frequency of chronic lung disease due to ABCA3 mutations in the general population is unknown. We tested the hypothesis that individuals heterozygous for ABCA3 mutations have reduced lung function and increased risk of COPD in the general population. We resequenced 760 individuals and identified three novel (H86Y, A320T, A1086D) and four previously described mutations (E292V, P766S, S1262G, R1474W) in ABCA3. We genotyped the entire Copenhagen City Heart study (n=10,604) to assess the clinical importance of these mutations. To validate our findings we genotyped an additional 54,395 individuals from the Copenhagen General Population Study for the E292V mutation. In the Copenhagen City Heart Study E292V heterozygotes had 5% reduced FEV_1% predicted (t-test: p=0.008) and 3% reduced FVC % predicted compared with noncarriers (p=0.04) and an increased odds ratio for COPD of 1.9 (95% CI: 1.1-3.1). In contrast, the A1086D mutation was associated with increased FEV_1% predicted (p=0.03) and FVC % predicted (p=0.008) in the Copenhagen City Heart Study. None of the other ABCA3 mutations associated with lung function or COPD risk. In the larger Copenhagen General Population Study, and in the two studies combined, E292V heterozygotes did not have reduced lung function or increased risk of COPD ($p \geq 0.11$), while this was the case for the positive controls, surfactant protein-B 121ins2 heterozygotes and α_1-antitrypsin ZZ homozygotes. Our results indicate that partially reduced ABCA3 activity due to E292V is not a major risk factor for reduced lung function and COPD in the general population.