Title: Genetic variant of the nicotinic receptor gene and the long term prognosis of smokers

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Body: Study objective: Polymorphisms in the nicotinic acetylcholine receptor gene (CHRNA3/A5 locus) has been associated with several smoking related traits such as nicotine dependence, cigarette consumption, smoking cessation, lung cancer and the development of COPD. Our aim was to study one of the polymorphisms (rs1051730) in long term prognosis among smokers. Subjects and methods: Genotyping was done in two longitudinal cohorts: Finnish COPD patients (N=575, 74% men) among which several clinical variables are available and among smoking men (N=1911) to whom only basic demographic information was available. The analyses were done using multivariate logistic regression model and Cox proportional hazards model. Additive model was used in all analyses and OR and HR values are given for minor homozygote. Finnish Health2000 population cohort (N=1728) was used for control for estimating the risk of COPD. Results: The genetic variant increased the risk of COPD when compared to the Finnish population at large (OR=1.4, p=3.2 x 10-5). Among COPD patients the minor allele was associated with cancerous diseases (adjusted OR 2.4 CI 1.00-5.67), in smoking men with pack years (adjusted OR 1.4 CI 1.09-1.96) and in both cohorts with all-cause mortality. Adjusted hazards ratios for mortality in COPD patients and in smoking men were HR 2.2, CI 1.22-3.82 and HR 1.2, CI 1.09-1.50, respectively. Conclusions: Genetic variance found in the CHRNA3/A5 locus may be associated with long-term prognosis among smokers.