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Title: Candidate gene association study of chronic obstructive pulmonary disorder using a targeted high throughput sequencing approach

Dr. Joakim 29489 Klar joakim.klar@igp.uu.se [1], Dr. Hans 29490 Matsson Hans.Matsson@ki.se [2], Dr. Cecilia 29491 Söderhäll Cilla.Soderhall@ki.se [2], Dr. Helena 29492 Backman Helena.Backman@nll.se [3], Dr. Anne 29493 Lindberg ann.lindberg@nll.se MD [3], Dr. Eva 29513 Rönmark Eva.Ronmark@nll.se [3], Prof. Bo 29542 Lundbäck bo.lundback@gu.se MD [3] and Prof. Niklas 29559 Dahl niklas.dahl@igp.uu.se MD [1]. [1] Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden ; [2] Department of Biosciences and Nutrition, Karolinska Institute, Huddinge, Sweden and [3] The OLIN Studies, Sunderby Hospital of Norrbotten, Luleå, Sweden .

Body: Background: Genetic studies in humans and in animal models suggest that genes associated with lung developmental processes are also implicated in the development of COPD. Aim: We aim to investigating candidate genes, with emphasis on genes important for lung development, for genetic variants predisposing to the development of chronic obstructive pulmonary disease (COPD) using targeted enrichment in a cohort of COPD patients. Methods: Twelve patients with heterozygous loss of function mutations in a lung developmental gene, the fibroblast growth factor 10 (FGF10), was investigated for pulmonary functions and COPD was classified according to the ATS/ERS 2005 standard. To identify novel variants associated with COPD, we are currently conducting a candidate gene association approach using targeted enrichment (HaloPlex; Halo Genomics) and high throughput sequencing (Illumina) using patients and controls retrieved from the Swedish Obstructive Lung Disease in Norrbotten (OLIN) sample set. This strategy allows for the detection of all genetic variants in the enriched sequence, without the limitations when investigating known variants using SNP arrays. Results: Patients carrying mutations in FGF10 show a significant decrease in lung function parameters consistent with COPD. Based on these results, we are currently investigating in total 200 kb enriched sequence, including 22 genes implicated in lung development and 71 genes or regions previously associated to COPD. Conclusion: These findings support the idea that genetic variants affecting lung developmental genes are important determinants of adult lung function that may ultimately contribute to COPD.