Identification of novel rare genetic variants associated with COPD in the general population

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Abstract

There are large differences in individual susceptibility to develop COPD, which cannot be explained by common genetic variants. Rare genetic variants, occurring in <1% of the general population, can potentially explain this individual risk to develop COPD. Here, we aim to identify rare genetic variants associated with COPD.

Whole genome sequencing was performed on 36 subjects with COPD (FEV₁/FVC<70% and FEV₁%pred<90) from the LifeLines general population cohort who had never smoked and were not exposed to environmental smoke or occupational exposures. Rare genetic variants in coding regions with predicted pathogenic effect were selected with the GAVIN algorithm. Variants present in ≥3 subjects were compared with healthy, non-exposed subjects (N=1846) within LifeLines (GoNL imputed data), using a chi² test. Next, frequencies of significant variants were further tested in the general population, irrespective of exposures, between healthy (N=10,560) and COPD subjects (N=2,101) from the LifeLines cohort and replicated in the Rotterdam Study (10,897 healthy and 599 COPD subjects).

We identified 7,357 predicted pathogenic variants in 5,196 unique genes of which 318 rare genetic variants were carried by ≥3 subjects. 127 of the 318 variants could be imputed in LifeLines and the frequency of 45 variants was significantly different between non-exposed COPD versus non-exposed healthy controls. Next, 5 variants were significantly associated with COPD in the LifeLines population and 2 of these variants, present in ARAP3 and KIF27, were replicated in the Rotterdam study.

Our study is the first to identify rare genetic variants associated with COPD in the general population.

Footnotes

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