Genome Wide Association Study Identifies Locus Determining Genetic Heterogeneity Of Lung Function Decline In Asthmatic And Non-Asthmatic Adults


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Rationale: Previous genome-wide association studies (GWAS) have identified novel genetic factors associated with cross-sectional lung function reflecting lung function growth as well as decline. Accelerated lung function decline is associated with increased risk of mortality. We have conducted the first GWAS on age-related lung function decline stratifying all analyses by asthma status a priori.

Methods: We tested 2.5 million single nucleotide polymorphisms (SNPs) for associations with annual decline in FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and FEV1/FVC in three cohort studies of European ancestry (N=4’118, Epidemiological study on the Genetics and Environment of Asthma (EGEA), Swiss study on Air Pollution And Lung Disease In Adults (SAPALDIA) and European Community Respiratory Health Survey (ECRHS)). Standardized residuals, obtained from study-specific linear regressions of annual decline in FEV1, FEV1/FVC and FVC on age, height and centre in sex- and asthma status-specific strata, were used for genome-wide testing adjusted for ancestry-informative principal components. The study-specific regression coefficients for additive genetic effects were combined across cohorts in inverse-variance weighted fixed and random effects meta-analyses. Heterogeneity of genetic estimates between asthmatics and non-asthmatics was assessed using Cochran’s Q statistics. Thirty loci associated at P<10^{-5} in the discovery cohorts were followed-up by in silico replication in four replication cohorts (N=12’018, Atherosclerosis Risk in Communities (ARIC); Framingham Heart Study (FHS); Birth 1958 Cohort (BSBC); Dutch asthma study).

Results: The discovery phase asthma-stratified GWAS on decline in FEV1, FEV1/FVC, and FVC (asthmatics: N=1441, non-asthmatics: N=2677) identified a cluster of SNPs at 8p22 with FEV1/FVC decline restricted to asthmatics (P<10^{-7}). This locus did not replicate in asthmatics (n=1’160) and non-asthmatics (n=10’858). From the additional 29 loci with suggestive evidence for association with annual lung function decline, a SNP in a gene previously reported to be associated with height, replicated at P=0.026 for association with decline in FEV1 in non-asthmatics. Results did not differ by smoking status. SNPs previously associated with cross-sectional lung function were not associated with lung function decline.

Conclusions: This first GWAS on annual lung function decline in Caucasians found suggestive evidence for differences in genetic determinants that drive annual lung function decline in asthmatics and non-asthmatics. Consistent with the height gene HHIP identified as a locus for cross-sectional lung function, we identified another height-linked gene as potential genetic determinant of FEV1.

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