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Titel des Beitrags: Large-scale genome-wide association studies and meta-analyses of longitudinal change in adult lung function.

Abstract: Genome-wide association studies (GWAS) have identified numerous loci
influencing cross-sectional lung function, but less is known about genes influencing longitudinal change in lung function. We performed GWAS of the rate of change in forced expiratory volume in the first second (FEV1) in 14 longitudinal, population-based cohort studies comprising 27,249 adults of European ancestry using linear mixed effects model and combined cohort-specific results using fixed effect meta-analysis to identify novel genetic loci associated with longitudinal change in lung function. Gene expression analyses were subsequently performed for identified genetic loci. As a secondary aim, we estimated the mean rate of decline in FEV1 by smoking pattern, irrespective of genotypes, across these 14 studies using meta-analysis. The overall meta-analysis produced suggestive evidence for association at the novel IL16/STARD5/TMC3 locus on chromosome 15 (P = 5.71 × 10(-7)). In addition, meta-analysis using the five cohorts with >=3 FEV1 measurements per participant identified the novel ME3 locus on chromosome 11 (P = 2.18 × 10(-8)) at genome-wide significance. Neither locus was associated with FEV1 decline in two additional cohort studies. We confirmed gene expression of IL16, STARD5, and ME3 in multiple lung tissues. Publicly available microarray data confirmed differential expression of all three genes in lung samples from COPD patients compared with controls. Irrespective of genotypes, the combined estimate for FEV1 decline was 26.9, 29.2 and 35.7 mL/year in never, former, and persistent smokers, respectively. In this large-scale GWAS, we identified two novel genetic loci in association with the rate of change in FEV1 that harbor candidate genes with biologically plausible functional links to lung function.