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Mini Review

Genomics of Lung Function

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Abstract

Lung function is a gold standard to diagnose Chronic Obstructive Pulmonary Disease (COPD), which is one of the leading causes of mortality in the world. Risk factors for COPD can cause one or more abnormal patterns of lung function, especially, environmental risk factors, like tobacco smoking, air pollutants, biomass fuel among which smoking is the primary risk factor but it is known that only 15-20% smokers develop COPD. With the advent of genome-wide association studies, several genetic variants related to lung function like *HHIP*, *HTR4*, *ADAM19*, *GPR126*, and *CHRNA3/5* have been discovered and replicated indicating their potential biological role in determining lung volumes. In this review, we have discussed about the latest developments in genomics of lung function.

Keywords: Lung function; Genomics; Public health; Chronic obstructive pulmonary disease

Introduction

Lung function reflects the physiological condition of airways and lungs [1] and acts as an important long term predictor of morbidity and mortality across the globe [2]. Lung volumes reaches its peak in early adulthood, followed by a plateau, and then subsequently declines which is likely to be influenced by genetic and environmental factors [3]. Spirometry is a standard technique used for measuring lung function, identifying respiratory illness (like Chronic Obstructive Pulmonary Disease (COPD)), and for monitoring the progression of lung disease [4]. The primary measures of lung volumes are Forced Vital Capacity (FVC) that approximates vital capacity, and Forced Expiratory Volume in 1st second (FEV_1). The ratio of FEV_1 to FVC is used to diagnose various respiratory diseases independent of lung size [5]. A reduced FEV_1/FVC ratio indicates airflow obstruction. In contrast, a reduced FVC suggests a restrictive ventilator defect, and acts as an independent (of other factors like age and smoking) and reliable predictor of mortality in the human population [6]. Lung function is considered as a complex phenotype influenced by multiple genetic and environmental factors and their interactions [7]. Twins and family based studies have provided consistent evidence of genetic contributions to lung function, with heritability estimates: as 85% for FEV_1, 91% for FVC, and 45% for FEV_1/FVC [8].

Genome-Wide Association Studies (Gwas)

In GWAS, we test for association between the frequency of each of thousands of common variants and a given phenotype, call significant SNPs (single nucleotide polymorphisms) that exceed a conservative genome-wide threshold for association (usually $P < 5\times10^{-8}$), and then test these for evidence of replication in independent cohorts [9]. GWAS have identified around 50 loci which have been associated with lung function [1-6,10-16]. Various GWAS studies have been conducted to confirm the association of different loci with lung function. Some of the identified loci have successfully been replicated in independent cohorts or populations. For example, *HHIP, FAM13A, DLEU7, CHRNA3/5, HLA-A, ADAM19, RARB, PID1, GPR126, CFDP1, BMP6, EFEMP1, PRDM11, AGER-PPT2, HTR4, INTS12-GSTCD-NPNT* were discovered by GWASs in relation to lung function and COPD [1,6,10-14,16]. Only few of them have been reported in more than one study, such as *HHIP, HTR4, ADAM19, GPR126*, and *CHRNA3/5*. In most of the studies, replication was not successful as it requires a large sample size [3,6,11-15,17].

Gene-Expression Studies

Gene expression studies analyzed 19 transcription sites in whole lung tissue, smooth muscles of airways, peripheral blood mononuclear cells and bronchial epithelial cells [2,3,5,6,13]. Out of 19 transcripts, 5 transcripts (*KCNJ2, BMP6, WWOX, PRDM11*, and *H2D17B12*) showed expression in all categories. Further, some of the loci were significantly related to lung function decline along with other variables and diseases, like variants at *MFAP2* were associated with decreased FEV_1/FVC, increased height as well as lung cancer; *KCNE2* was associated with myocardial infarction; *NCR3/AIF1* with neonatal lupus and systemic lupus erythematosus; *CDC123* with type 2 diabetes, *CFPD1* with type 1 diabetes; *MECOM* with blood pressure; *BMP6* and *EFEMP1* were also associated with height; an SNP in *ADCY2* was associated with increased risk for COPD [1,6,18].

Validation of Gwas Results

The validation of GWAS results in different human populations is an important task for establishing universal nature of identified genetic variants. For instance, SNPs in *IREB2* (rs13180), *CHRNA3/5* (rs8034191), *ADCY2* (rs11134242) and *HHIP* (rs13118928) were associated with lung function and COPD in Polish population [18,19]. Genetic variants at or nearby *THSD4-UACA-TLE3* and *C10 or f11* reached genome-wide significance with FEV_1/FVC in the combined (asthmatic and non-asthmatic) sample and in non-asthmatic subset of the Hutterite population (Europeans migrated to United States of America), respectively [8]. Further, carriers of *CHRNA3* had a significantly higher annual average decline of pre-FEV_1 (used for pre-bronchodilator FEV_1) than other genotypes and it was also correlated with COPD progression in a Chinese population [19]. Moreover, there are two casual SNPs (rs1051730 & rs8034191) of *CHRNA3* shared by lung cancer and COPD in European populations

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but were not associated with lung cancer risk in Chinese population [19]. Two genes *HTR4* and *TNS1* were validated in KARE (Korean Associated Resource) cohort from CHARGE Consortium studies and the SpiroMeta Consortium [20]. There were significant associations of FVC with *KCNJ2* in Koreans and with *EFEMP1* locus in African-Americans [6]. In India, there are small size validation studies related to COPD where investigators have also investigated association of selected polymorphisms with lung volumes in control samples among male smokers [21]. These observations suggest the relevance of validation of European findings in other human populations.

Gene-Environment Interaction Studies

Unexplained heritability has become a well-known phenomenon in genetic epidemiology and possible explanations include multiple effects of common variants, rare variants, gene-by-environment interactions, gene-gene interactions and epigenetic regulation-mechanisms that are not captured by existing GWAS platforms [6]. The interaction effect size for C allele of rs360563 (*CRISP2*) accelerated decline in FEV_1/FVC by 1.1% per Interquartile Range (IQR) change in PM10 (Particulate Matter having diameter 10μm) exposure over 11years. Similarly, G allele of rs2035268 (*SNCA*) was associated with an accelerated decline by 3.8% per allele and IQR change in exposure, whereas, genotypes of SNCA variant (GT and GG) showed FEV_1/FVC decline by 3.9% [22]. Further, influence of interaction of rs9931086 (*SLC38A8*) with occupational exposure was observed on FEV_1 suggesting the mediating pathways due to gene-environment interactions [23,24]. Overall, few number of large studies related to gene-environment interaction on respiratory health have been published [7] may be due to its requirement of large sample size, robust measurement of exposure and validated genetic variants.

Conclusion

Genome-wide approaches have helped in detecting several genetic variants associated with lung volumes in Western population groups and increased our understanding in their underlying genetic architecture. Gene-environment interaction studies are few in number due to its design related needs but such studies are important for estimating the effect of genetic variants in given environmental context. With very few validation studies in South East Asia, there is a need of research in populations with high diversity such as India, where limited number of genetic studies related to lung volumes are available (that too have used case-control design) rather than required population based studies.

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