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ORIGINAL ARTICLE

Chronic Obstructive Pulmonary Disease (COPD): Making Sense of Existing GWAS Findings in Indian Context

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Abstract

To date, more than 1456 associations have been identified for Chronic Obstructive Pulmonary Disease (COPD) risk through Genome-Wide Association Studies (GWAS). However, target genes for COPD susceptibility in the Indian population and the mechanism underlying remains largely unexplored and no GWAS studies on COPD are available on the Indian population till now. This study was conducted using the existing public data on GWAS of different parts of the world, and the genetic polymorphisms to understand the possible mechanisms of these polymorphisms using available data from the Genotype-Tissue Expression (GTEx) project. We jotted down 16 important genes and 28 Single Nucleotide Polymorphisms (SNPs) in the Indian population from 1456 variants. Pathway analysis showed that these relevant genes are mostly associated with immune responses and activation, which is a key factor in COPD development. Our investigation revealed possible target genes associated with COPD in the context of the Indian population.

Key Words: *GWAS; GTEx; COPD; Indian population; Tissue-specific gene expression; cis-eQTL*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide [1] and the second leading cause of death in India [2], according to World Health Organization (WHO). It accounts for nearly 3 million deaths annually [3] and causes persistent respiratory problems and hyperimmune activities, including difficulties in breathing and phlegm. It is well known that smoking is one of the main risk factors for developing COPD [4], but only 20-30% of smokers in their lifetime develop COPD [5]. This indicates that other variations including genomics play a major role in COPD development. Apart from smoking, long exposure to harmful gases and particles, air pollution and occupational fumes and dust are also important risk factors for COPD [5].

Hypothesis-free genome wide association studies (GWAS) can reveal polymorphisms associated with COPD. But GWAS has several limitations, major being not able to find any

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causal mechanisms, rather finds association. Existing GWAS studies on COPD from different parts of the world have found several significant single nucleotide polymorphisms (SNPs) associated with COPD [6-12], many of them probably are spurious associations. Given all the associations throughout the genome are associated with COPD, making sense from these data are extremely difficult to translate to the patients. Apart from this, genetic polymorphism varies from one population to another. Till date, there is no GWAS study in India to the best of our knowledge. Hence genetic underpinning of COPD in the context of Indian population will be informative. This was made possible due to the availability of GenomeAsia100k project database [13], where whole genome data of 598 healthy Indians were made available along with other populations of Asia.

The expression quantitative trait loci (eQTL) can be used to find if any specific polymorphisms in the genome can alter the expression of nearby genes (cis-eQTL) or distant genes (trans-eQTL). Tissue-specific expression of genes and eQTL of polymorphisms can be checked using public databases of healthy individuals such as the Genotype-Tissue Expression (GTEx) project [14].

In this current manuscript, we took all the available associations throughout the world, taken from the EBI-GWAS catalog [15], and used some stringent criteria to pinpoint some of the most possible SNPs and their role in COPD. Their allele frequencies in the Indian population were checked using GenomeAsia100K project [13] to understand the India-specific risk allele frequencies of the significant polymorphisms found throughout the world. The eQTL of those polymorphisms was measured thereafter in different tissues including lung and whole blood.

Materials and Methods

All the significant polymorphisms and their summary statistics discovered in GWAS studies till 26/07/2021 were downloaded from the EBI-GWAS catalog [15]. A total of 1456 associations from 69 studies were found. They were sorted and trimmed or excluded based on the (a) excluding associated polymorphisms' p-value less than 10e-8; (b) variant id not defined properly or not in an internationally recognizable format, rsID or could not be annotated based on the variants identifier; (c) in case of repetitive rsID from different studies, the one with lesser p-value was taken or (d) excluded if the exact nucleotide polymorphisms with specifically mentioning the risk allele were not mentioned. By this, among 1456 associations, 549 associations remained. Further, using the GenomeAsia100K project database, allele frequencies of all the 549 associations in the Indian population were noted. They were further trimmed based on the allele frequencies of these polymorphisms. The associations were excluded if they were either not polymorphic (minor allele frequency 0) or rare allele (minor allele frequency <5%). Finally, after these steps, 200 associations remained in our analysis.

They were checked for tissue-specific cis-eQTL on the Genotype-Tissue Expression (GTEx) project and plots were generated. For this, 4 different tissue types, viz., lung, whole blood, kidney cortex, and cultured fibroblasts were taken. P-value was calculated after multiple testing corrections (FDR at 1%) and plots were generated in the GTEx portal [14]. Pathway analysis of these significant polymorphisms was carried out in Reactome version 78 [16].

Result

A total of 1456 associations from 69 studies were found in the EBI-GWAS catalog till 26th

July 2021 (Figure 1). After initial screening and exclusion, 549 variants remained. Risk allele frequencies (RAF) of these 549 variants in the Indian population were checked in the GenomeAsia100K Project database [13]. To understand the distribution of the RAF among the healthy Indian population and reported RAF in controls of respective GWAS, a scatter plot was generated (Figure 2), which clearly shows that RAFs are not the same among the GWAS control groups and Indian population. Many of the RAFs were very rare or non-polymorphic in the Indian population and thus they were removed from further analysis (excluded: minor allele frequency <0.05). After the removal of the rare and repetitive variants, 200 SNPs remained. They were again plotted to visualize the differences between RAFs among Indian and the GWAS control groups (Figure 3).

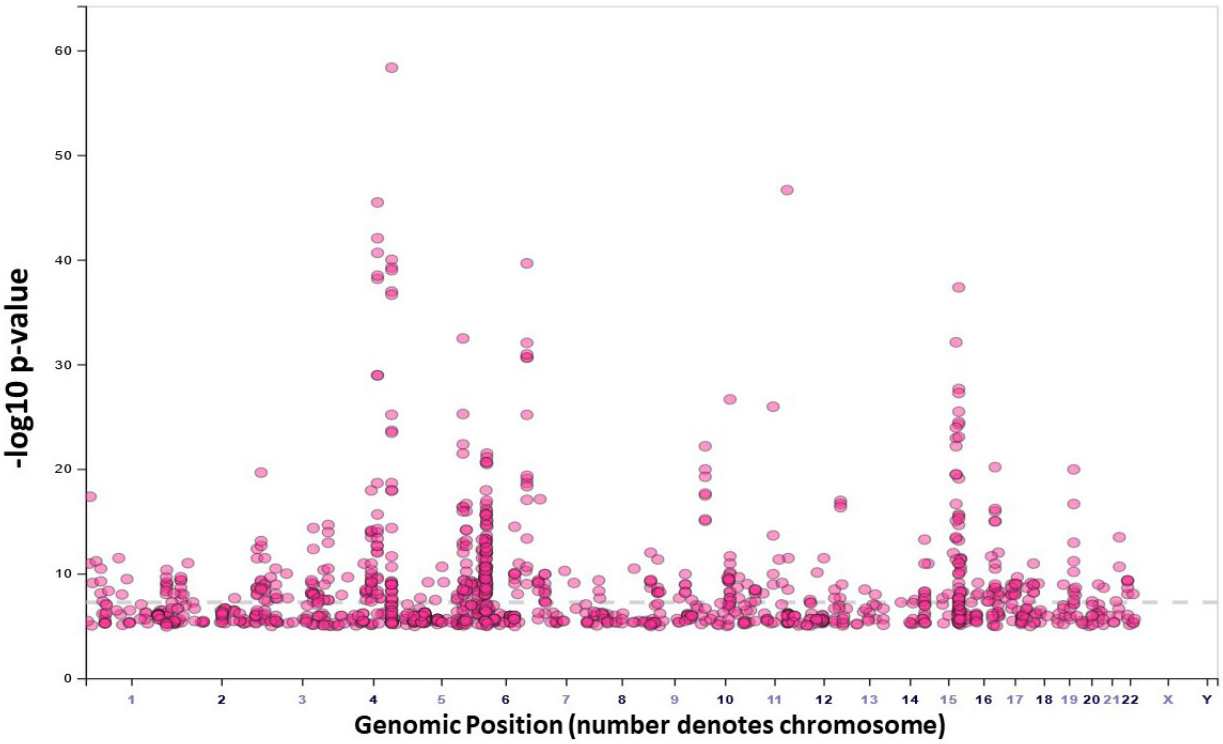

Figure 1) *Locus Zoom Plot of the GWAS studies. X-axis represents chromosomal positions and Y-axis is negative log10 of p-values. Threshold used here is 10e-8. Each dot in the plot is one SNP. Image is generated from the EBI-GWAS catalogue.*

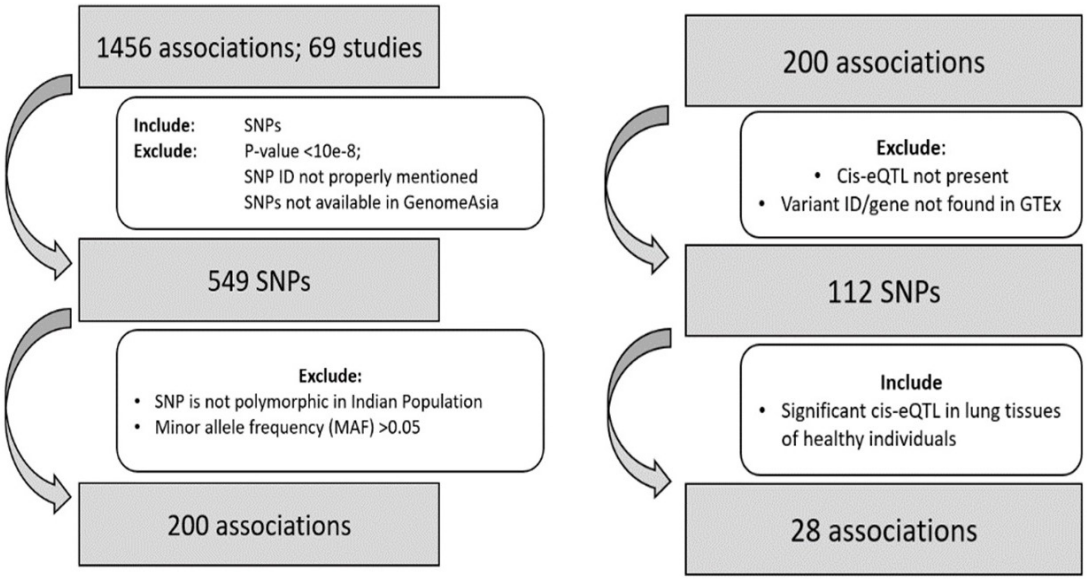

Figure 2) *Flow diagram of the selection of 28 SNPs from 1456 SNPs.*

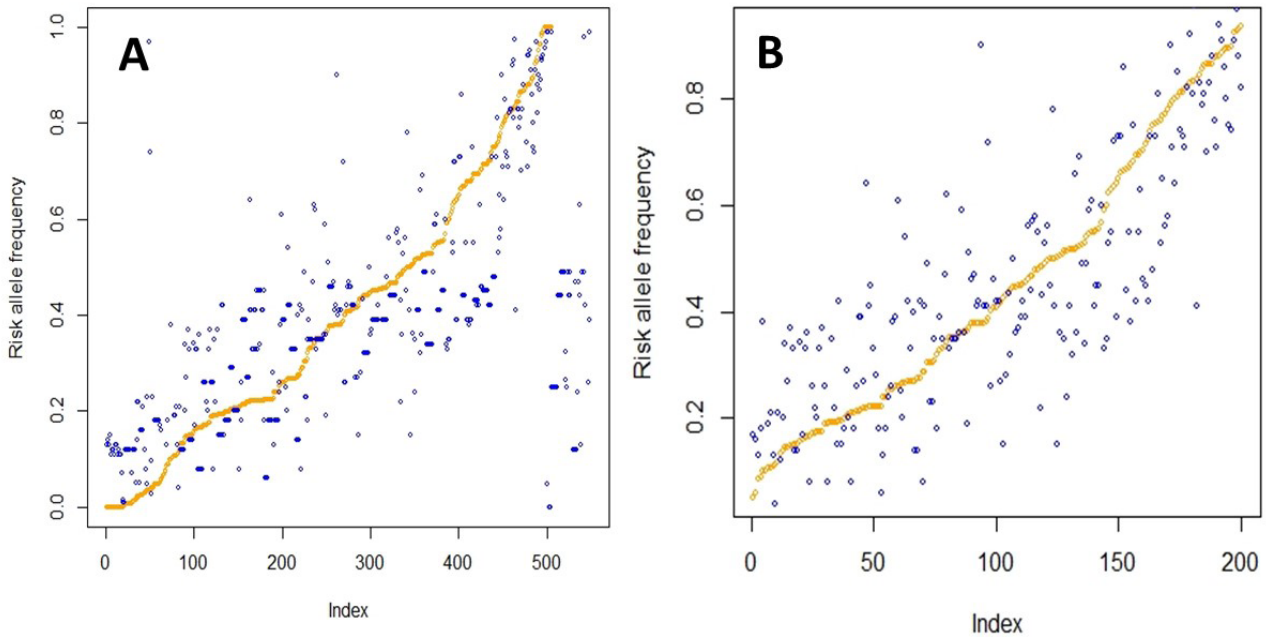

Figure 3) *Comparison of the Risk allele frequencies of the COPD associated SNPs in Indian population Vs. of the control study participants of the original GWAS study. The orange color represents RAF of the Indian population and blue color represents RAF of the original GWAS study control group. X-axis is the identity of a SNP and Y-axis is the allele frequency. Figure3A is for the selected 549 SNPs and Figure3B is for the later selected 200 SNPs in this study. This figure shows that risk allele frequency of the COPD associated SNPs are not same for India and other Western countries.*

Cis-eQTL of these 200 SNPs were checked in 4 healthy tissue types from GTEx, viz., lung, whole blood, cultured fibroblasts, and cortex kidney. Lung and whole blood were used as they are directly engaged in lung functioning and immune functioning. Cultured fibroblast and cortex kidney were used to understand the trend of cis-eQTL in other tissue types as well. In the case of intragenic variants, cis-eQTL analysis of the SNPs was performed with the same gene. And in the case of intergenic variants, cis-eQTL was performed on the nearest genes. Among the 200 SNPs, 28 of them showed significant differences in eQTL in the lung tissues due to the changes in risk or protective alleles in the healthy population (Table 1). These 28 SNPs were associated with 16 unique genes. Among 16 genes, FAM13A, ADAM19, CHRNA5, CFDP1, CCDC91 had more than 1 SNPs associated with COPD.

To understand what the pathways are associated with these genes, pathway enrichment (overrepresentation) analysis was performed on these genes against Reactome version 78 (https://reactome.org/). Genome-wide pathway enrichment analysis found the most significant 12 pathways at a false discovery rate (FDR) of 1% (Table 2).

Most of the significant pathways were found to be pathways related to the immune system, viz., antigen presentation, phagosome pathway, antigen processing, immunoregulatory interactions, interferon signaling, cytokine signaling, etc. (Figure 4). It is well known that hyperimmune activities are the major pathophysiology of COPD. The most relevant genes were also found to be associated with the immune system.

Discussion

Genetics contributes to the development of COPD to some extent along with other environmental factors. COPD is a key disease of concern worldwide and thus several genome-wide association studies were executed in different parts of the world. But to the best of our knowledge, no GWAS studies have been

TABLE 1
List of all the genes, associated variants, and their frequencies in the Indian population

Gene	Variant (SNP) ID and risk allele	Risk allele and frequency in India	Adjusted p-value (lung)	Adjusted p-value (whole blood)	Adjusted p-value (cultured fibroblasts)	Adjusted p-value (kidney cortex)
	rs1422795-C	0.3528	4.11E-17	5.21E-13	2.02E-14	ns
ADAM19	rs10866659-G	0.3528	4.11E-17	4.87E-13	3.09E-14	ns
	rs2277027-C	0.352	4.11E-17	4.87E-13	3.09E-14	ns
AGER	rs2070600-C	0.8804	4.68E-05	ns	ns	ns
CCDC91	rs11049386-T	0.8788	1.68E-08	ns	2.22E-13	ns
	rs11049488-G	0.8643	2.15E-07	ns	2.91E-13	ns
	rs7186831-A	0.4841	3.86E-05	4.47E-15	1.95E-42	ns
CFDP1	rs12449170-C	0.5167	5.90E-05	7.22E-15	6.27E-45	ns
	rs12930452-A	0.5498	5.90E-05	7.22E-15	6.27E-45	ns
	rs17486278-C	0.1923	3.95E-08	ns	1.16E-26	ns
CHRNA5	rs8192482-T	0.1472	5.02E-09	ns	5.74E-29	ns
	rs16969968-A	0.1480	5.02E-09	ns	5.74E-29	ns
DSP	rs2076295-T	0.6697	3.68E-75	ns	ns	ns
	rs2869966-T	0.5000	4.29E-05	ns	2.54E-04	ns
	rs2869967-C	0.3804	2.07E-05	ns	ns	ns
FAM13A	rs4416442-C	0.3794	8.49E-05	ns	ns	ns
	rs6837671-G	0.3792	4.29E-05	ns	ns	ns
	rs7671261-A	0.694	1.17E-04	ns	1.56E-06	ns
	rs7674369-A	0.3796	4.95E-05	ns	2.53E-04	ns
FLOT1	rs1064627-G	0.2057	8.00E-05	ns	2.87E-09	ns
HLA-C	rs2074488-T	0.1095	6.92E-18	8.20E-30	2.34E-06	ns
MED24	rs9303283-C	0.2684	2.00E-12	1.32E-16	2.29E-13	ns
MMP15	rs12926803-C	0.2517	9.27E-06	ns	ns	ns
RAB4B	rs2604894-A	0.4983	2.49E-05	ns	ns	ns
RIN3	rs72699855-G	0.8319	4.56E-05	ns	ns	ns
SFTPD	rs3923564-G	0.1129	1.57E-08	ns	ns	ns
SGF29	rs17707300-C	0.1756	4.45E-05	3.48E-13	ns	ns
TESK2	rs4660861-G	0.4682	5.03E-07	5.58E-25	5.90E-06	ns

TABLE 2
Significant pathways associated with COPD

Pathways	p-value	FDR
Antigen Presentation: Folding, assembly, and peptide loading of class I MHC	1.11E-16	1.89E-15
Endosomal/Vacuolar pathway	1.11E-16	1.89E-15
ER-Phagosome pathway	1.11E-16	1.89E-15
Antigen processing-Cross presentation	1.11E-16	1.89E-15
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	1.11E-16	1.89E-15
Interferon gamma signaling	1.11E-16	1.89E-15
Interferon alpha/beta signaling	1.11E-16	1.89E-15
Interferon Signaling	1.44E-15	2.16E-14
Class I MHC mediated antigen processing & presentation	5.32E-13	6.92E-12
Cytokine Signaling in Immune system	2.52E-10	3.02E-09
Adaptive Immune System	9.23E-10	1.02E-08
Immune System	4.43E-07	4.43E-06

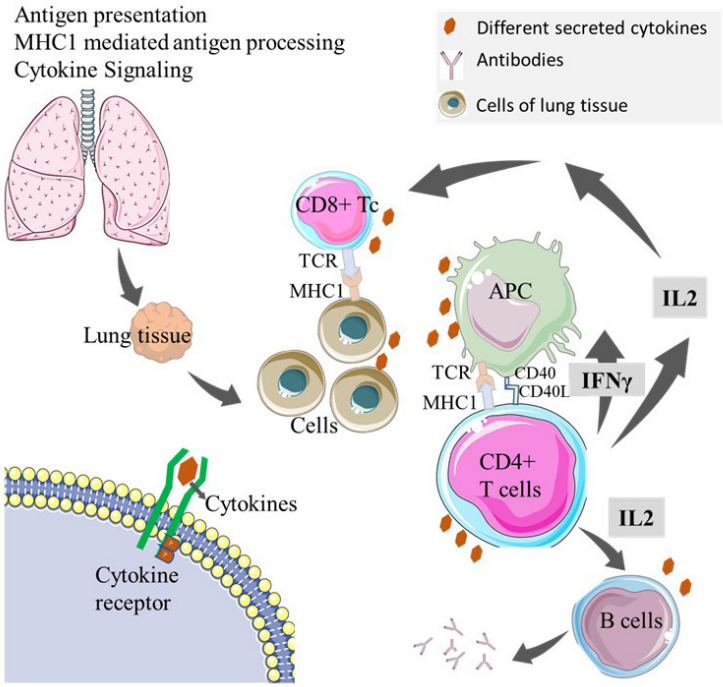

Figure 4) *A few significant pathways and their mechanisms associated with COPD, taking 16 genes important genes in the context of Indian population. Abbreviations: TCR: T-cell receptor; APC: Antigen-presenting cell; CD8+ Tc: CD8+ T cells; IL2: Interleukin-2; IFNγ: Interferon-gamma.*

performed on the Indian population. In this manuscript, we utilized publicly available data of different kinds to understand the possible genes and their variations that can potentially cause or enhance the possibility of COPD. We have comprehensively looked into all the single nucleotide polymorphisms (SNPs) associated with COPD. We then uncovered the SNPs relevant to the Indian population using the GenomeAsia100k database. The potential causality of these SNPs in terms of changes in the gene expression was checked using cis-eQTL from the GTEx portal. Initially, we started with 1456 associations from 69 different studies worldwide but came down to 26 associations affecting the expression of 16 genes in the lung

tissues. Among these 16 genes, almost all the genes are known to have some effects on lung functioning or immune activities; even some of the genes are associated with other chronic diseases and cancer.

From a comprehensive literature search conducted using the 'PubMed' and 'GWAS Catalogue' databases, and reviewing the literature available, only a limited number of studies were identified which had attempted to investigate the genetics of COPD and lung volumes, implying a considerable research gap, especially in the context of Indian population.

All the genes have some crucial role in normal functioning in humans and changes in their nucleotides can lead to different disease conditions. FAM13A is a protein-coding gene and one of the frequently replicated genes in COPD studies. Few studies have found associations and functional implications of this gene with COPD. FAM13A is known to mediate TGFβ-1 induced epithelial to mesenchymal transitions (EMT) in the small airway epithelium of patients having COPD [17]. It also induces increasing cell death in the lung by upregulating Reactive Oxygen Species (ROS) production. The advanced glycosylation end-product receptor (AGER) gene is a member of the immunoglobulin superfamily of cell surface receptors and is mainly expressed in lung tissues. It is a multiligand receptor, and besides AGE, interacts with other molecules implicated in homeostasis, development, inflammation, and certain diseases, such as diabetes and Alzheimer's disease [18]. A recent functional study by Allam *et al*. 2020 showed that AGER induces airway hyperresponsiveness [18]. HLA-C is one of the major genes associated with autoimmune diseases [19]. Previously this has also been found to be associated with COPD [20]. Surfactant protein D (SFTPD) is a lung-specific protein and has been found in COPD GWAS studies [21]. Several infectious and immune-mediated diseases have been shown to be associated with SFTPD. SAGA complex associated factor 29 (SFG29) is a subunit of two histone acetyltransferase complexes and is mainly involved in chromatin structure and organization. SGF29 was found to be significantly associated with COPD in a European GWAS study by Hobbs *et al*. 2017 [7].

Neuronal Acetylcholine Receptor Subunit alpha-5 (CHRNA5) is the protein encoded by CHRNA5. Its receptors are stimulated by nicotine, and polymorphisms in this gene could modulate its effects [10]. Carriers of CHRNA5 polymorphisms may be more susceptible to diseases related to tobacco consumption through nicotine dependence and exposure to oxidising microenvironment which produce molecular mechanisms like inflammation, a characteristic of COPD [22]. A study on transcript analysis of nAChR-α5 subunit by qRT-PCR has shown that nucleotide polymorphism of CHRNA5 gene influences airway remodeling in COPD both dependently and independently of smoking [23]. Testis associated actin remodelling kinase 2 (TESK2) is a serine/threonine protein kinase containing an N-terminal protein kinase domain. Previously a study has shown that TESK2 Low expression associates with poor survival of patients with lung adenocarcinoma [24]. TESK2 was also associated with COPD in a study by Sakornsakolpat *et al*. 2019 [6].

RIN3, a gene systematically found in this study, its protein product binds to the RAB5 small GTPases and functions as a guanine nucleotide exchange factor [25]. This gene has been associated with multiple disease conditions including Alzheimer's [26], pulmonary artery enlargement, and specific conditions for type-II diabetes, among others. Coiled-coil domain containing 19 (CCDC19) gene expresses mostly in the testis and lung. In normal physiological action, it is involved in flagellated sperm motility and enables AMP binding activity. Studies have shown that CCDC19 correlated with lung squamous cell carcinoma outcome [27]. Desmoplakin (DSP) protein anchors intermediate filaments to desmosomal

plaques. Polymorphisms in this gene have been associated with emphysema, a key component in COPD [28], pulmonary fibrosis, and lung cancer [29]. Whereas FLOT1 plays a role in vesicle trafficking and cell morphology. This gene is associated with several diseases including Alzheimer's Disease [30], tumor development, epithelial to mesenchymal transition (EMT) [31] and malignant phenotype in lung adenocarcinoma [32].

Mediator complex subunit 24 (MED24) is a transcriptional co-activator complex, involved in developmental process and disease conditions such as asthma [33]. Matrix metalloproteinase-15 (MMP15) is involved in extracellular matrix breakdown in normal physiological processes, such as tissue remodeling, development, as well as in disease conditions, such as metastasis and arthritis. It is involved in breast [34], hepatocellular [35] cancers, and in lung functioning [12]. RAB4B is a member of the RAS superfamily of small GTPases, involved in vesicular trafficking [36] and found to be associated with cancers. Variation (rs1422794) in a disintegrin and metalloproteinase domain 19 (ADAM19) gene was associated with a lower risk of suffering the most severe stages of COPD in a GWAS study by Pérez-Rubio *et al*., 2016 [37]. A SNP, rs2865531, located in the CFDP1 gene was found to be significantly associated with coronary artery disease (CAD) [38], and COPD was associated with an increased risk of coronary artery disease (CAD).

Pathway analysis of the 16 genes showed that these genes are associated with immunological processes which are a prime reason for hyperactivity in the lung and their gene expressions are significantly different due to the variants (SNPs) found in other COPD studies.

Conclusion

Functional analysis of 1546 SNPs is an absolute difficult task, most of which will not be showing any effect. Additionally, from a clinical perspective, genomic screening of 1500 SNPs is practically not feasible. But screening SNPs for 16 genes can be made possible for the prognosis of COPD. Genomics information is useful in the context of population and information from one population will not be as useful in another population. So, this study will be helpful for future functional studies on COPD in the Indian population. This can potentially also help in the risk assessment of individuals for prevention and personalized medicine. But authors also acknowledge that patient screening for these SNPs was not done, and by doing so, it would have become a comprehensive and compact finding. However, this study will enable the scientific community to gather information and plan genomic screening for COPD patients accordingly.

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Authors' Contributions

TD conceptualized, surveyed literature, aggregated data, generated plots, and graphs, wrote the manuscript partially, and interpreted results. AB arranged data, surveyed literature, independently gave inputs for betterment of the writing and interpretation of the results and wrote the manuscript partially.

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