

Bronchial Variation: Anatomical Abnormality May Predispose Chronic Obstructive Pulmonary Disease

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Abstract: Noxious particulate matter in the air is a primary cause of chronic obstructive pulmonary disease (COPD). The bronchial tree acts to filter these materials in the air and preserve the integrity of the bronchi. Accumulating evidence has demonstrated that smoking and air pollutants are the most prominent risk factors of COPD. Bifurcations in the airway may act as deposition sites for the retention of inhaled particles, however, little is known concerning the impacts of abnormalities of the bronchial anatomy in the pathogenesis of COPD. Studies have reported significant associations between bronchial variations and the symptoms in COPD. In particular, it has been shown that bronchial variations in the central airway tree may contribute to the development of COPD. In this review, we identified three common types of bronchial variation that were used to formulate a unifying hypothesis to explain how bronchial variations contribute to the development of COPD. We also investigated the current evidence for the involvement of specific genes including fibroblast growth factor 10 (*Fgf10*) and bone morphogenetic protein 4 (*Bmp4*) in the formation of bronchial variation. Finally, we highlight novel assessment strategies and opportunities for future research of bronchial variations and genetic susceptibility in COPD and comorbidities. Our data strongly highlight the role of bronchial variations in the development, complications, and acute exacerbation of COPD.

Keywords: chronic obstructive pulmonary disease, bronchial variation, fibroblast growth factor 10, bone morphogenetic protein 4

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and in 2015 showed an increasing prevalence of 174.5 million cases worldwide.¹ The inhalation of toxic particles and smoking are the primary risk factors for COPD. However, only 10–20% of chronic heavy cigarette smokers develop symptomatic COPD. Whilst several factors have been associated with COPD including asthma, genetic inheritance, maternal smoking during pregnancy, low birth weight and lower respiratory tract infections during childhood,^{2,3} the precise risks of COPD remain to be fully understood. Also, bronchial anatomy abnormalities may be involved in the pathogenesis of COPD.

In 2018, Smith and colleagues reported that one-quarter of the normal population have variations in bronchial anatomy that may contribute to the development and progression of chronic respiratory diseases, particularly COPD. These variations are also associated with *Fgf10* mutations.⁴ The findings provide new insights

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into the anatomical and genetic basis of COPD. In this review, we discuss the role of bronchial variations in the pathogenesis and comorbidities of COPD.

Bronchial Variation Subtypes and Identification

Bronchial variations present of absent, displaced, or accessory origin in the bronchi and can occur either simultaneously or successively. The three most common subtypes of bronchial variations are tracheal bronchus, accessory cardiac bronchus, and bridging bronchus (Table 1).⁵ Tracheal bronchus was first described by Sandifort et al in 1785 and originates from the trachea towards the upper lobes, as mentioned in a paper by Aktas et al.⁶ Accessory cardiac bronchus was first defined by Brock et al in 1946 and is short or long diverticulum arising medially from the main bronchus or the right bronchus intermedius.⁷ Finally, bridging bronchus was first described by Gonzalez-Crussi et al in 1976 and appears as variations originating from the left main bronchus that cross over to the right bronchus.⁸ Uncommon bronchial variations include tracheal diverticulum and bronchial isomerism. Clinically, bronchial variations are typically combined with other congenital deformities such as tracheal stenosis, cardiovascular malformations, and Down syndrome.

Multi-detector CT (320-slices) with 3D reconstruction and multi-planar reconstruction (MPR) can be used to measure the lengths and diameters of the variant bronchi.⁹ Magnetic resonance imaging (MRI) with surface shaded

display (SSD), and virtual endoscopy (VE) can be used to observe the transaxial, coronal and sagittal sections of the bronchi. These approaches display the bronchial performance and protrusion outside the lumen and can detect deviations within 10%.¹⁰ 3D O₂-enhanced MRI has strong capabilities for both ventilation and perfusion assessment that can be used to improve the classification of clinical stages in COPD.¹¹ Endobronchial optical coherence tomography (EB-OCT) is useful in the assessment of small airway disorders (diameter < 2 mm, 9th generation bronchi) and in COPD as it can display the mucosal, submucosal, smooth muscle, and cartilage layers of the airway structure. The mean luminal diameter, inner luminal area and the airway wall area of the 3rd-6th generation bronchi are known to correlate with forced expiratory volume in one second (FEV₁) in percent of predicted (FEV₁%) ($r=0.731$, $p<0.001$).¹² Also, EB-OCT shows a more accurate and comprehensive assessment of small airway remodeling than traditional CT assessment. Recently, artificial intelligence (AI) has been used to quantify emphysema automatically and this approach may also be applicable to identify bronchial variations in future research.¹³

Bronchial Variation and COPD Development

COPD is characterized by partially irreversible lung air-flow obstruction and has several major risk factors including cigarette smoking. Smith and colleagues first reported

Table 1 Three Common Bronchial Variation Subtypes and Clinical Abnormalities

Sites	Origin	Develop	Variation Subtypes	Clinical Abnormalities
Trachea Bronchus	Trachea	Directs to the UL	a) Displaced (a branch of the RUL missing) b) rudimentary (tracheal diverticulum) c) supernumerary (normal trifurcation in RUL) d) anomalous RUL bronchus (duplication of RUL)	Tracheal stenosis, bronchostenosis, Down syndrome, VACTERL syndrome (vertebral variations, anal atresia, cardiac abnormalities, tracheoesophageal fistula and or esophageal atresia, renal agenesis and dysplasia, limb defects)
Accessory Cardiac Bronchus	Right main bronchus, intermediate bronchus	Towards the mediastinum, parallel to the RMB toward pericardium	a) Short (blind-ending diverticulum) b) intermediate (branching with alveolar) c) terminal sprigs (undeveloped lobulus)	Bronchial fistula, diverticula, adenoid recess and tumor
Bridging Bronchus	Left main bronchus	Crossing over the mediastinum	a) Subtype 1 (normal trachea bifurcating into RB) b) subtype 2 (absent or short diverticulum of RB)	Hypoplastic lungs, left PA sling, imperforate anus, absent coccyx, horseshoe kidney and cardiovascular malformations

Note: Data from Wooten et al.⁵

Abbreviations: PA, pulmonary artery; RUL, right upper lobe; RB, right bronchus; RMB, right middle bronchus; UL, upper lobes.

accessory subsuperior bronchial variations associated with an increased risk of COPD prevalence (OR=1.64, 95% CI: 1.18–2.29, $p=0.004$). The patients with accessory subsuperior variation tended to have an increased incidence of emphysema (apparent diffusion coefficients 0.19, 95% CI: 0.07–0.30).⁴

Bronchial variation may contribute to COPD in several ways. Firstly, airway bifurcations may provide deposition sites in which inhaled particles can aggregate. At displaced or accessory bronchi, goblet cell proliferation may be destroyed by the abnormal distribution of mucosa glands and cilia. The disordered movement of cilia promotes the dysfunction of mucociliary clearance (MCC). Consequently, impaired MCC allows bacterial pathogens and toxic particles to gain a foothold in the lower respiratory tract which increases mucus secretion and decreases lung clearance. The colonization of pathogens and particles contributes to chronic airway inflammation by altering the host adaptive immune response via TLR3 triggering of the IFNs pathways and bronchopulmonary damage.¹⁴ The loss of the mucus barrier covering the bronchial epithelium during frequent airway infection is associated with the acute exacerbation of COPD (AECOPD). Thus, the bifurcation anomalies induce more bacterial and particle deposits resulting in the release of chemokines and cytokines; both of which serve to promote local inflammation and contribute to COPD and AECOPD.¹⁵ Secondly, the lengths and diameters of airways can affect the development of COPD. Smith found that the cumulative length of the absent right lower lobe medial-basal bronchial variation was 29.0% longer but with 6.9% smaller subsegments calibers compared to normal bronchi. In contrast, the accessory right lower lobe sub-superior bronchial variation presented 7.3% shorter length and 26.3% larger calibers with a higher percentage of emphysema.⁴ The observed decreased bronchial diameters contribute to airflow limitation and airway remodeling which are the major causes of dyspnea in COPD patients. Thirdly, most patients who are born with bronchial variations are asymptomatic but suffer from respiratory tract infections throughout life particularly adenovirus bronchiolitis, pneumonia and bronchiectasis. Based on these observations, the extent of pathological changes in the different bronchial variations are specific to individual COPD patients.

It is well known that early exposure to either particulate matter or pathogens promotes abnormal changes during lung development. Continuous exposure to dust from birth to 28 days postnatally increases the expression of

transforming growth factor (TGF)- β 1 and matrix metalloprotease (MMP)-9.¹⁶ Pregnant rats maintained at under 11.5% O₂ from gestation show greater anatomical variation in airway lumen area (0.205 ± 0.009 vs 0.187 ± 0.002 , $\sqrt{\text{area}/P_{\text{bm}}}$) and have a heterogeneous distribution of airway lumen caliber in adulthood.¹⁷ Also, respiratory tract infections are an important factor in the growth and development of children. Respiratory syncytial virus (RSV) can spread across the placenta from the respiratory tract of the mother to the fetus.¹⁸ Childhood exposure to RSV is a risk factor for adult RSV illness (OR=2.38; 95% CI: 1.03–5.51).¹⁹ RSV infection and pneumonia during infancy (OR=3.59; 95% CI: 1.41–9.14) and nitrogen oxide exposure during at less than 1 year of age (OR=3.08; 95% CI: 1.11–8.51) are independent risk factors for the irreversible airflow limitation.²⁰ This may be due to epigenetic alterations in gene regulation, modulation of the immune response, aberrant molecular signaling, and growth factors involved in lung development.

The increased risk of COPD at 53 years of age is related to the early accelerated decline in FEV₁ z-scores (OR=35.0, 95% CI: 19.5–64.0), persistently low FEV₁ z-scores (OR=9.5, 95% CI: 4.5–20.6) and below average FEV₁ z-scores (OR=3.7, 95% CI: 1.9–6.9) in children. These factors contribute to 75% of COPD burden and make patients susceptible to damage from smoking, particle matter or pathogens.²¹ Patients with bronchial variations may be born with impaired lung function, or experience respiratory tract infection at birth, in childhood and adolescence, with sustained and accelerated airflow limitations. These individuals suffer from COPD at an early age under the combined effects of genetic and environmental factors (Figure 1). These alterations are more likely to occur during early life and even in utero suggesting that there is a susceptibility window during which genetics can disrupt normal bronchial development.^{22,23}

Genetic Variation and Bronchial Variation in COPD

Fgf10 and *Bmp4* Participate in the Development of Bronchial Variation

To elucidate the effects of bronchial variation in COPD, we recognize that the bronchial variations originate during tracheobronchial embryonic development. The patterns of bronchial architecture develop based on the reciprocal interactions and morphological changes between the airway epithelium and the mesenchyme if environmental exposure is not taken into account. The

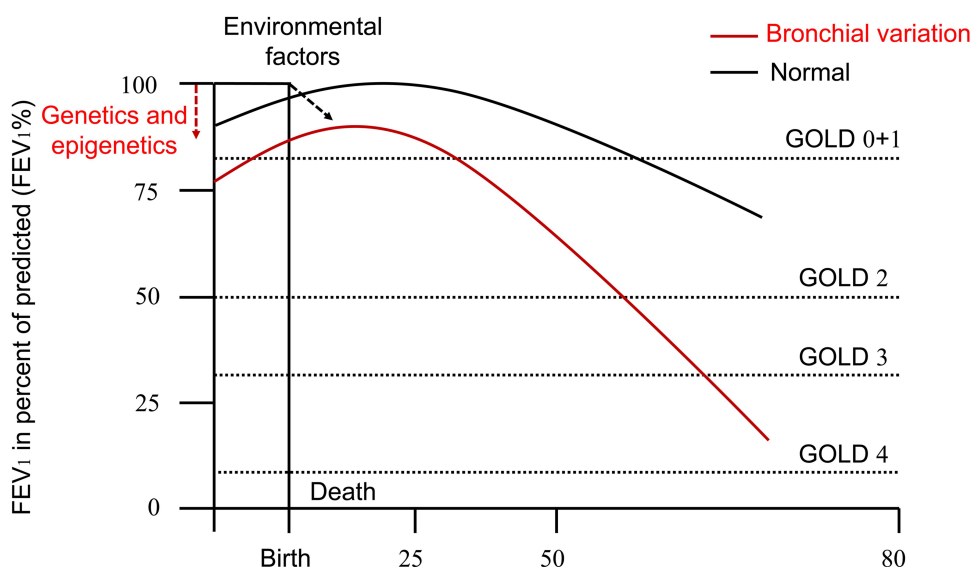


Figure 1 Rate of decline in FEV₁ with genetic and environmental factors. This downtrend of FEV₁ over a lifetime is determined by genetics and epigenetics before birth. Then the different curves decline in different rates dependent on organ development/repair (aging) and environmental factors (smoking and air pollutions) after birth. The lung function of people with bronchial variations is worse than that of normal people at birth. The risk of COPD is higher and earlier if environmental exposure is not taken into account.

Abbreviation: FEV₁, forced expiratory volume in one second.

branch pattern and lineage of the bronchial variations result from the imbalanced development between the epithelium and the mesenchyme under genetic control mechanisms.^{24,25} These processes are controlled by two highly conserved families, fibroblast growth factors (*Fgfs*) and bone morphogenetic proteins (*Bmps*), both of which are involved epithelial and mesenchymal differentiation. *Fgf10* is expressed in the early distal mesenchyme, whilst *Bmp4* is expressed in the endodermal buds. Epithelial cells begin to grow during lung bud formation resulting in branched growth by regulating the balance between *Fgf10* and *Bmp4*. *Fgf10* produced at the tip of the epithelial cells promotes endoderm proliferation and its outward movement acts to inhibit budding. This process exerts opposing effects against *Bmp4* during lung bud morphogenesis.²⁶ In *Fgf10* knockout mice, lung bud development is completely abolished and can be rescued by ubiquitous overexpression of *Fgf10*. These data indicate that the precise localized expression of *Fgf10* is required for lung branching morphogenesis in vivo.²⁷ In *Bmp4* specific *Smad* knockout mice, *Fgf10* upregulates the expression of *Nkx2-1* in foregut development towards primitive lung buds (E9.25d) and exhibits an undifferentiated single lumen on E10.5–11.5d without extension.²⁸ The opposing effects of *Fgf10* and *Bmp4* may induce imbalances in the development of the bronchial epithelium and the mesenchyme that

contributes to abnormal bronchial location and bifurcation (Figure 2). Based on these data, we hypothesize that genetic variations encoding bronchial variations can promote the development of COPD.

Fgf10 and *Bmp4* Participate in COPD and Comorbidity

Currently, over twenty genetic loci with single nucleotide polymorphisms (SNPs) associated with COPD-related phenotypes, such as emphysema, chronic bronchitis and hypoxemia, have been demonstrated by genome-wide association studies (GWAS).^{29–31} *ORM1*, *SERPING1* and *C3* were identified as a panel of AECOPD-specific immunomodulatory determinants.³² A clinical study found that the frequencies of *Fgf10* gene SNP sites rs2973644 and rs10473352 were significantly increased in COPD patients of the Han population in North China ($\chi^2=6.021-6.213$, $p<0.05$).^{33,34} *Bmp4* is up-regulated in the airway epithelium of asymptomatic patients and COPD smokers (1.0×10^{-2} vs 7.2×10^{-5} , control group: 0.1 ± 0.2). *Smad* signaling mediated by *Bmp4* significantly disrupts the beating of cilia and secretory cell function by regulating basal cell hyperplasia and squamous cell differentiation.³⁵ Thus, the opposing effects of *Fgf10* and *Bmp4* signaling may contribute to bronchial variations and may participate in dysregulating the biology of the human airway relevant to both smoking and COPD.

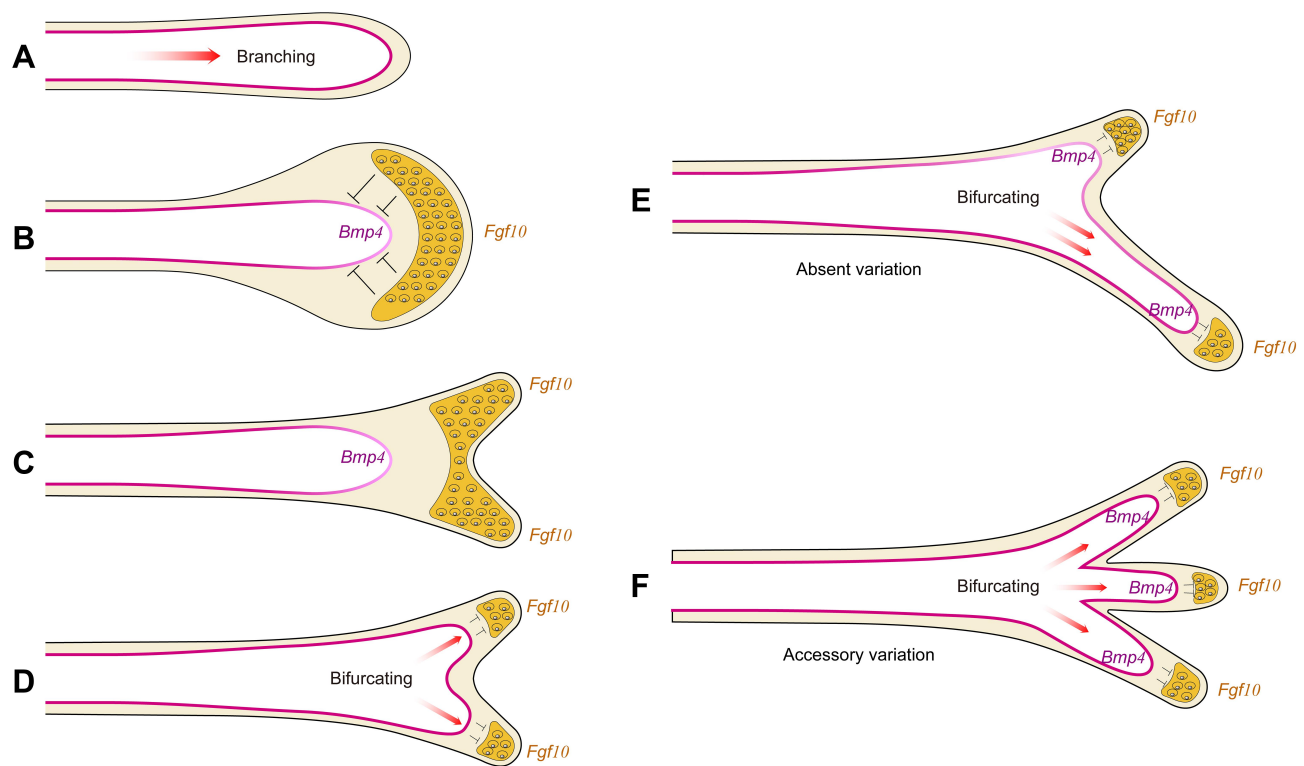


Figure 2 A model for the opposing effect of *Fgf10* and *Bmp4* in lung bud morphogenesis. An extending bud is shown schematically. Purple and yellow denote *Bmp4* and *Fgf10* expression. (A) Throughout bronchial development, *Bmp4* is expressed in the epithelium and *Fgf10* in the adjacent mesenchyme. *Fgf10* promotes lung endoderm proliferation and migration. *Bmp4* antagonizes *Fgf10*-mediated outgrowth of lung endoderm. The balance between the expression of *Fgf10* and *Bmp4* exists during branching, keeping the normal development of bronchus. (B) As the expression of *Fgf10* increased, distal mesenchyme has shown hypertrophic morphologically and inhibited the expression of *Bmp4* in the epithelium to stop branching. (C) Restricted by the traction of the internal epithelium, the expression of *Fgf10* on both sides increased gradually, and lateral buds appeared symmetrically which represented as bifurcating. (D) Once the lung buds have been initiated, the expression of *Bmp4* increased, and the expression of *Fgf10* was inhibited. Epithelium grew along the distal mesenchyme towards lateral buds. The cycle of promotion of mesenchymal proliferation and outgrowth of endoderm begins again. (E) We considered the alternative hypothesis that the expression of *Fgf10* at the tip of one lung bud increased excessively and downregulated *Bmp4* expression. Then this bud formed a blind end or diverticulum with only another bud growing which was called absent variation (eg RMB or RLB in bridging bronchus). (F) When *Bmp4* was more predominantly expressed than *Fgf10*, endothelial growth was faster than mesenchyme differentiation. Then more than three buds appeared at the bifurcation which was called accessory variation (eg tracheal bronchus, accessory cardiac bronchus).

Abbreviations: *Bmp4*, bone morphogenetic protein 4; *Fgf10*, fibroblast growth factor 10; RMB: right middle bronchus, RLB: right lower bronchus.

Fgf10 attenuates particulate matter 10 (PM10) induced airway inflammation by inhibiting apoptosis and increasing cell proliferation in bronchial epithelial (BEAS-2B) cells.³⁶ The reduction in submucosal gland branching in *Fgf10* heterozygous mice was not rescued in the adult mice.³⁷ Knockdown of *Bmp4* by siRNA increased lipopolysaccharide and tumor necrosis factor- α (TNF- α) induced IL-8 expression levels in human airway epithelial cells. Also, *Bmp4* heterozygous mice presented with more severe lung inflammation.³⁸ These data suggest that *Fgf10* and *Bmp4* may be involved in the pathogenesis of AECOPD via dysregulation of airway homeostasis.

The *Fgf10* and *Bmp4* signaling pathways are crucial for the dynamic communication between the epithelium and the mesenchyme during bronchial development (Figure 2). Epithelial-mesenchymal transition (EMT) is a process during which epithelial cells gradually transform

into mesenchymal cells without epithelial function and characteristics. The reverse of this process can also occur via mesenchymal-epithelial transition (MET). Both EMT and MET can be in a balanced state during lung development. In human bronchial epithelial cells derived from patients, partial or excessive MET is found in COPD, whilst excessive EMT is detected in lung cancer, during metastatic colonization and in idiopathic pulmonary fibrosis.^{39,40} *Fgf10* siRNA decreased GSK3 β levels by 96% which plays an important role in EMT in breast cancer cells.^{41,42} However, the roles of the *Fgf10* and *Bmp4* signaling pathways in MET and COPD remain unclear.

In a *Fgf10*^{-/-} model of bronchopulmonary dysplasia, the loss of vessels was associated with an increase in poorly muscularized vessels.^{43,44} These abnormalities in bronchopulmonary structure increased the pulmonary

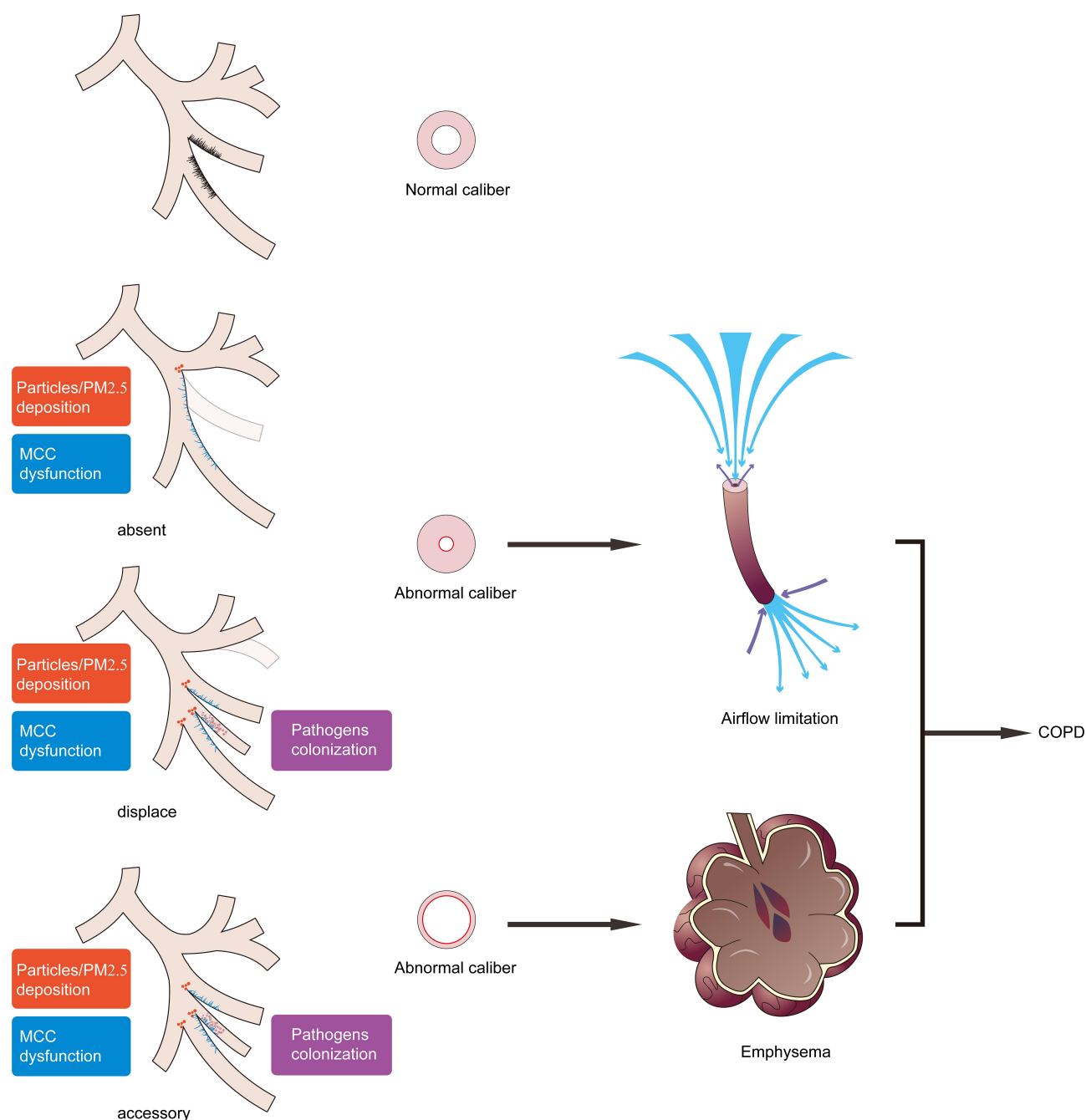


Figure 3 Schematic representation of bronchial variations in the development of COPD. Bronchial variations participate in the pathogenesis of COPD as anatomical determinants and promote abnormal bifurcations with more particles deposition. Abnormal variant bronchus covered cilia with movement and distribution dysfunction (MCC dysfunction) allowed more pathogens colonization. Absent or displaced bronchial variation presents bronchial wall thickening and caliber shorter, resulting in airflow limitation. Accessory or displaced bronchial variation accompanied by bronchial wall thinning and lumen enlargement results in emphysema. These are two common pathophysiological development patterns of COPD.

Abbreviations: COPD, chronic obstructive pulmonary disease; MCC, mucociliary clearance.

vascular resistance evaluated as pulmonary hypertension throughout childhood, adolescence and young adults.^{45,46} The induction of oxidative stress and inflammation by the particles in the lung trigger pulmonary vascular remodeling and pulmonary capillary bed destruction in COPD with pulmonary hypertension.

Conclusion

In summary, bronchial variations may be involved in the development of COPD and contribute to complications and acute exacerbation of COPD. Studies in vitro and in vivo have shown that *Fgf10* and *Bmp4* may contribute to both bronchial variations and COPD through the

regulation of epithelial and mesenchymal growth. These observations may have far-reaching consequences in the comprehensive evaluation of COPD via anatomical and genetic assessment. Adults with bronchial variations should be alerted to the development of COPD whether they smoke or not. For COPD patients with bronchi variations, more attention should be paid to sputum drainage and the prevention of infection. *Fgf10* and *Bmp4* may serve as heritable biomarkers to inform phenotype-specific COPD and high-risk COPD patients for lung cancer and pulmonary hypertension screening.

Hypothesis

We hypothesize that abnormal airway bifurcations may provide deposition sites for inhaled particles and MCC dysfunction to promote the colonization of pathogens and particles. Bronchial variations also characterized as abnormal airways and alveoli caliber contribute to the airflow limitations and emphysema during the pathogenesis of COPD (Figure 3).

We are planning to conduct a retrospective clinical study to evaluate the incidence of bronchial variations in COPD patients in the Chinese population, especially COPD patients with emphysema or lung cancer. Bronchial variations on CT can be observed for different locations and bifurcations and estimate the percentage of regional emphysema, variant bronchial lengths and inner diameters. Bronchoscopy may be performed to obtain biopsy samples along with bronchoalveolar lavage that could be used to determine the expression of key genes including *Fgf10* and *Bmp4*, lower respiratory tract microbial pathogens and ciliary function. Further stratified and risk factor analyses should also be conducted.

Abbreviations

AECOPD, acute exacerbation of COPD; AI, artificial intelligence; *Bmp4*, bone morphogenetic protein 4; COPD, chronic obstructive pulmonary disease; EB-OCT, endobronchial optical coherence tomography; EMT, epithelial-mesenchymal transition; FEV₁, forced expiratory volume in one second; FEV₁%, FEV₁ in percent of predicted; *Fgf10*, fibroblast growth factor 10; FVC, forced vital capacity; GWAS, genome-wide association studies; MCC, mucociliary clearance; MET, mesenchymal-epithelial transition; MMP-9, matrix metalloproteinase-9; MPR, multi-planar reconstruction; MRI, magnetic resonance imaging; PA, pulmonary artery; RB, right bronchus; RMB, right middle bronchus; RLB, right lower bronchus; RSV, respiratory syncytial virus; RUL, right upper lobe; SNPs, single nucleotide

polymorphisms; SSD, surface shaded display; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; UL, upper lobes; VE, virtual endoscopy.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in association with the present study.

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