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Understanding the genetics of chronic obstructive pulmonary disease, α1-antitrypsin deficiency, and implications for clinical practice

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Understanding the genetics of COPD, α1-Antitrypsin Deficiency (AATD), and implications for clinical practice

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Abstract

Cigarette smoking and poor air quality are the greatest risk factors for developing COPD, but growing evidence indicates genetic factors also affect predisposition to and clinical expression of disease. With the exception of α1-Antitrypsin deficiency (AATD), a rare autosomal recessive disorder that is present in 1-3% of individuals with COPD, no single gene is associated with the development of obstructive lung disease. Instead, a complex interplay of genetic, epigenetic, and environmental factors are the basis for persistent inflammatory responses, accelerated cell aging, cell death, and fibrosis, leading to the clinical symptoms of COPD and different phenotypic presentations. In this brief review, we discuss current understanding of the genetics of COPD, pathogenetics of AATD, epigenetic influences on development of obstructive lung disease, and how classifying COPD by phenotype can influence clinical treatment and patient outcomes.

Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 6.4% of the U.S. adult population. It is the third leading cause of death worldwide, with estimated U.S. direct costs of 49 billion dollars annually (National Center for Health Statistics, 2016). Cigarette smoking and poor air quality are the greatest risk factors for COPD (GBD Chronic Respiratory Disease Collaborators, 2017), but there is growing evidence that genetic factors affect predisposition to and clinical expression of disease. Having a family history (FH) of COPD markedly increases an individual's risk of developing disease, especially in people who smoke. Compared to smokers without FH of COPD, smokers whose parents had COPD were three times as likely to develop disease, but non-smokers with FH of COPD had *no* increased risk compared to non-smokers without FH (Zhou et al., 2013). Thus, development of COPD is attributable to a combination of environmental *and* genetic factors.

Genetics

With the exception of α1-Antitrypsin deficiency (AATD), which occurs in 1-3% of patients with COPD, no single gene is associated with the development of obstructive lung disease (Sakornsakolpat et al., 2019). AATD is a rare disorder typically seen in people of European ancestry. Among people with AATD, Pulmonary disease occurs primarily as a result of abnormally shaped α1-Antitrypsin proteins (AAT) synthesized by the liver, rather than from environmental exposures. Normally, AAT protects lung tissue from being damaged by cytotoxic enzymes secreted by roaming neutrophils, a subset of white blood cells that act as first-responders in non-specific immunity. However, in AATD, the abnormal proteins do not function correctly and are instead retained in the liver, causing cirrhosis and progressive lung damage through loss of neutrophil elastase inhibition (Strnad, McElvaney, & Lomas, 2020).

Misfolded AAT proteins are created due to a single DNA point mutation (change in one nucleotide base pair) at the allele *SERPINA1,* located on chromosome 14. An allele is a gene pair, with one gene derived from each parent. AAT alleles can be *homozygous* (same genetic sequence on chromosome 14) or *heterozygous* (different genetic sequences). These variations are called protease inhibitor (PI*) types, and are used to classify AATD. The unusual taxonomy is based on nomenclature created prior to the identification of the *SERPINA1* allele (Stoller, Hupertz, & Aboussouan, 2020).

PI*M is the predominant (normal) AAT allele, whereas PI*Z is the most common pathologic allele, followed by variants of PI*S, PI*I, and PI*F (Miravitlles et al., 2017). Homozygous individuals *without* AATD would thus have the genotype PI*MM (i.e. two normal PI*M genes). Because AATD is an autosomal *recessive* disorder, an individual must have *two* abnormal genes to express disease. Therefore, an individual without clinical disease could also have genotype PI*MZ or PI*MS (one normal and one disease allele). Similarly, an individual with AATD could have genotype PI*ZZ, PI*ZS, or any other combination of two disease alleles. AATD ranges from mild to severe, depending on the pathogenic variant of the PI* mutations. For heterozygous individuals with one normal gene (PI*M), risk of developing obstructive lung disease may still be elevated, even though clinical AATD is not present.

For the preceding reasons, in addition to usual COPD management, AATD should be treated with intravenous infusion of plasma-purified AAT protein to promote correct immune functioning and to slow the progression of emphysema (Miravitlles et al., 2017). Thus, while a rare disorder, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that all individuals with COPD should be tested for AATD to facilitate identification

and proper treatment of affected individuals (Global Initiative for Chornic Obstructive Lung Disease, 2021).

Like asthma and other complex diseases, COPD is otherwise genetically heterogenous, with wide variability in genes, disease expression, progression, and subjective symptomatology (Corlateanu et al., 2020). Prior to the advent of economical whole-genome sequencing, studies in COPD genetics focused primarily on identifying discrete, shared DNA variations specific to affected, related individuals (i.e. linkage studies). This was done by examining a series of "candidate genes" thought to be related to COPD. However, linkage studies were unsuccessful in finding any monogenic patterns of heredity, as occurs in other respiratory conditions like AAT and cystic fibrosis.

With increasingly economical whole-genome sequencing, research into COPD genetics transitioned from linkage studies to *genome-wide association studies* (GWAS), which enable the examination of subtle variations in DNA across the entire genome, along with associations between genetic patterns, clinical traits, and treatment responsiveness (Visscher et al., 2017). Researchers using this approach have identified 156 different genes at 82 significant loci, of which >15% overlap with asthma and pulmonary fibrosis (Sakornsakolpat et al., 2019).

The importance of genetics for COPD lies in the fact that inflammatory responses, which modulate disease progression and clinical presentation, are driven by DNA. Genetic code defines how and when inflammatory mediators are created, and how noxious stimuli (e.g. particulates) are perceived and processed. Cigarette smoking, the primary cause of COPD, exposes lung tissue to elevated levels of *reactive oxygen species* (ROS). Excess ROS damages DNA and leads to increased expression of genes that control inflammation through altered activity of intracellular mediators, most commonly *Nuclear factor E2-related factor* (*Nrf2)*. *Nrf2*

regulates hundreds of genes downstream, and is central to cellular management of oxidative stress and inflammation. With dysregulation of *Nrf2*, cellular stress and aging are greatly accelerated. These intracellular changes cause the release of *pro-inflammatory mediators* into the extracellular space. Chemical messengers then attract other inflammation-regulating cells (e.g. macrophages, neutrophils, T-helper cells), which precipitate the release of additional cytotoxic chemokines and cytokines (commonly interleukins), further damaging surrounding tissues. Cumulatively, these processes form a reinforcing cycle of damage, inflammation, accelerated cell death, and fibrosis (Hikichi, Mizumura, Maruoka, & Gon, 2019). It is also worth noting that like asthma, inflammation in COPD can be mediated by different T-helper (Th) pathways. Inflammation in COPD typically follows *Th1* and *Th17* pathways (also known as Type 1 non-allergic airway inflammation), but may also be mediated by *Th2* pathways. This has been referred to as Type 2 (allergic) airway inflammation or Type 2 COPD (Oishi, Matsunaga, Shirai, Hirai, & Gon, 2020). It has been suggested that the inflammatory mechanism via different T-helper pathways may underlie variable responsiveness to treatments; *Th2* pathways are susceptible to use of inhaled corticosteroids (ICS), whereas *Th1* and *Th17* pathways have poor ICS-responsiveness.

Epigenetics

Early stage evidence indicates that epigenetic influences also play an important role in COPD development through a secondary process called DNA methylation (He, Tang, Huang, & Li, 2020). Methylation occurs when a histone molecule becomes entangled with a portion of DNA, blocking translation and effectively "silencing" that section of genetic code. (This can be conceptualized as bubble gum tangled in a strand of hair.) Methylation is actually a normal process and acts as an essential on/off switch for gene expression during growth and

development. However, abnormal methylation causes increased down-regulation of *protective* genes, contributing to accelerated cellular aging and death (Du et al., 2019). Furthermore, evidence indicates that prenatal smoke exposure might also increase risk for later developing COPD through epigenetic mechanisms, as hyper-methylated DNA has been observed in the cord blood of infants exposed to cigarette smoke *in utero* (Krauss-Etschmann, Meyer, Dehmel, & Hylkema, 2015). This suggests that exposure to environmental toxins could have prolonged epigenetic effects contributing to development of disease. Because methylation is reversible, it is hypothetically amenable to targeted drug therapy, and is therefore an area of active pharmaceutical research.

Clinical Phenotypes

Consistent with the complex underlying genetics, clinical presentation of COPD is also highly variable. Once treated as a single entity, COPD is now considered to be an umbrella term with several distinct phenotypes (Sakornsakolpat et al., 2019). Phenotypes are essentially sub-groups within COPD that have shared clinical characteristics of obstructive lung disease, but also have clinically important between-group differences, such as who is typically affected, patterns of symptoms and disease progression, and variable responsiveness to treatments. Classifying and treating COPD by phenotype can help to predict outcomes and improve clinical management.

The first phenotypic classification system for COPD was proposed in 1989, and included chronic bronchitis, emphysema, and asthma (Snider, 1989). Since then, multiple taxonomies have been proposed, with currently accepted phenotypes including AATD, chronic bronchitis, emphysema, frequent exacerbator and rare exacerbator (Corlateanu et al., 2020). Asthma and COPD are now considered fully-distinct diseases entities, albeit sharing common characteristics,

and the use of "Asthma-COPD overlap" is no longer encouraged (Global Initiative for Chornic Obstructive Lung Disease, 2021). Emerging evidence points to additional phenotypic variations that may include a "no smoking COPD" group or overlap with other co-morbidities such as bronchiectasis.

Implications for Practice

Since 2011, GOLD guidelines for pharmacologic management of COPD have capitalized on four broad phenotypic groupings to determine the most appropriate first line therapy, based on responsiveness to treatment (Global Initiative for Chornic Obstructive Lung Disease, 2021). These phenotypes (GOLD Group A, B, C, D) are clustered by two clinical characteristics: risk of exacerbation with or without hospitalization (low risk/high risk) versus overall symptom burden (low symptoms/high symptoms). While spirometric classification is assessed (grade of $FEV1_{\%\ predicted}$), it is not used as a sole factor in treatment selection, as there is no evidence to support efficacy. Serum eosinophil counts (>100-300 cell/μL) can be predictive of ICS responsiveness and Type 2 airway inflammation, and can help to determine if inhaled or oral corticosteroids could be beneficial. At present, biomarkers, genomic, and pharmacogenetic testing are not recommended for clinical management, with the exception of AATD testing, which should be performed once for all patients with COPD (ICD-10-CM code E88.01). If not covered by insurance, free confidential DNA test kits are available to providers or patients directly (Alpha-1 Foundation, n.d.). Similarly, most contemporary direct-to-consumer genetic testing services can identify *SERPINA1* variants (Hersh, Campbell, Scott, & Raby, 2019; Horton et al., 2019).

Conclusion

In conclusion, COPD is a common, preventable inflammatory disease that occurs due to a complex interplay of genetic and environmental factors. Current understanding of COPD supports use of broad phenotypic categories to inform clinical management and predict outcomes. Increased understanding of genetic and epigenetic factors will likely result in increasingly targeted treatment options over time.

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