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Deciphering Idiopathic Bronchiectasis One Gene at a Time

Bronchiectasis, defined as permanent dilatation of the airways (1), is a sign of disease, a common end point of myriad respiratory conditions. Thus, when patients present with bronchiectasis, it is important to investigate the causes that have led to this finding.

Bronchiectasis often results from repeated insults to the airways, leading to a vicious cycle of damage and repair and ultimately abnormal remodeling and loss of airway integrity (1). The causes of bronchiectasis are many and vary by age, region, and genetic background (2). It is often seen in common conditions such as chronic obstructive pulmonary disease (3). Bronchiectasis is disproportionately prevalent in areas that are resource restricted, where infections and healthcare disparity are often blamed for the development of bronchiectasis among endogenous populations around the world (4, 5). Moreover, an increased burden of childhood respiratory illnesses and exposures to environmental pollutants may be a culprit in different regions (5). Genetic conditions such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and immunodeficiency, which lead to ineffective mucociliary clearance or an increased burden of bacteria, are known causes of bronchiectasis in children and young adults (6, 7).

Despite the significant strides made in identifying the etiology leading to bronchiectasis, many remain without an identifiable cause (2, 8). These cases of idiopathic bronchiectasis are possibly the result of undiagnosed genetic conditions. Although the concept of gene–disease relationship is entrenched in the education and care philosophy of pediatric care providers, seeking a unifying genetic cause is still lacking in adult patient care. In the case of PCD, for instance, both the American Thoracic Society and the European Respiratory Society guidelines include recommendations to pursue genetic studies if available. However, we still struggle to obtain these tests for adult patients, outside the realm of research. This is due to unawareness by the care team of the many rare genetic conditions contributing to chronic pulmonary diseases, the unfounded concept that identifying a genetic cause may not lead to a change in management, or inaccessibility of the required tests, whether as a result of lack of resources or denial of medical insurance in resource-affluent areas.

In the study by Dougherty and colleagues (pp. 63–76) reported in this issue of the *Journal* (9), a collaborative group of researchers spanning multiple institutions across several continents evaluated cases of idiopathic bronchiectasis. All patients presented to their physicians with diffuse bronchiectasis, chronic rhinosinusitis, and nasal polyposis, features that are common in CF and PCD. Patients underwent careful evaluation, including testing for CF and PCD, which included functional studies of CFTR, mucus rhinology, and cilia motility studies. Samples from all patients underwent next-generation sequencing, which identified pathogenic variants in *WFDC2* in 11 individuals from 10 unrelated families. It is interesting that patients with variants in *WFDC2* also had low concentrations of nasal nitric oxide, a finding that is well established as a screening method for PCD (10). Low nasal nitric oxide is also encountered in patients with CF and immunodeficiency (11).

WFDC2 (also known as HF4) belongs to the WAP four-disulfide core domain family of proteins, which function as protease inhibitors. WFDC2 is a small, secreted protein that has been identified as a biomarker for several conditions, including inflammatory myopathies, ovarian cancer, and other solid tumors (12, 13). WFDC2 has also been reported to have antibacterial activity including against *Pseudomonas aeruginosa* (3).

The authors confirmed loss of expression of *WFDC2* in primary culture airway cells from patients and provide compelling evidence that *WFDC2* is expressed in secretory airway cells and in serous and ductal cells from the submucosal glands. Patients were found to have low amounts of secreted WFDC2 in their saliva, airway secretions, and serum compared with healthy volunteers. Analysis of the protein makeup of saliva from patients showed altered expression of several serine protease inhibitors that were previously linked to chronic sinusitis, including SPINK5 (14). Altogether, these findings suggest

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that WFDC2 may play a role in the immune modulatory response of the airways.

Interestingly, WFDC2 concentrations were high in the patients with CF or PCD, two other conditions that lead to chronic rhinosinusitis and bronchiectasis. As WFDC2 is a secreted protein and is low in the sera of patients, its concentration can be used as a diagnostic tool in patients with idiopathic bronchiectasis.

This new association between WFDC2 and idiopathic bronchiectasis emphasizes the need to evaluate patients with idiopathic bronchiectasis for genetic causes of disease, mostly because our patients deserve a definite diagnosis but also because some of these conditions might require a different management approach that can have an impact on disease progression and prognosis. ■

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To Boldly Go into Molecular Endotypes of Bronchiectasis Exacerbations

Exacerbations are bad events in bronchiectasis. They result in acute physician visits, medication costs, emergency room visits, and hospitalizations. As a result, exacerbations are the primary driver of the high healthcare costs associated with bronchiectasis (1). The economic toll levied by bronchiectasis exacerbations is a global problem (2), and it affects children (3) and adults alike (4). Furthermore, the unpredictable nature of exacerbations imposes an unsettling uncertainty on the lives of patients with bronchiectasis and robs them of quality of life. Given the importance of bronchiectasis exacerbations, they are the standard outcome measure in clinical trials of desperately needed therapeutic drugs for patients with bronchiectasis. The importance of exacerbations, however, is matched by their complexity. Bronchiectasis is arguably the most heterogeneous of all diseases, with most cases occurring for unknown reasons. It involves complex pathophysiologic connections and manifests varied endotypes (5). Therefore, it is not surprising that bronchiectasis exacerbations are themselves multifarious. Even though there is a published consensus definition of bronchiectasis exacerbations (6), they are often elusive targets in the vastly heterogeneous pool of patients with bronchiectasis. From the standpoint of the clinician caring for patients with bronchiectasis, there is a tremendous desire to understand exacerbations so we can treat our patients with accuracy and improve their lives.

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