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ⱸ Telomeropathy in Chronic Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an interstitial lung disease that develops after repeated exposure to a variety of inhaled environmental antigens, mainly organic. The disease is characterized by alveolitis, granulomas, and in some patients, chronic progressive fibrosis (i.e., chronic HP [CHP]) (1). The latter is quite often indistinguishable from idiopathic pulmonary fibrosis (IPF), as clinicians are quite often unable to distinguish pathognomonic imaging features that could differentiate it from IPF, and identification of an occult causative agent is unsuccessful in more than 60% of cases (2, 3). The rigid diagnostic criteria for HP highlight the diagnostic value of identifying the causal antigen, high-resolution computed tomography patterns, BAL fluid lymphocytosis, and in some cases, histopathological features (1–5).

Not all individuals exposed to HP-causative antigens develop disease, suggesting that genetic differences critically influence responsiveness to the offending antigen and play a role in susceptibility; however, the host cofactor(s) that play a role in susceptibility are unknown (6). According to a two-hit model, antigen exposure associated with genetic or environmental promoting factors provokes an immunopathological response (7).

Data on susceptibility genes and genetic prognosticators of disease progression and treatment response are still scarce. The identification of specific genetic fingerprints linked to HP development may be crucial not only for predicting clinical and therapeutic outcomes but also for preventing disease through avoidance of exposures to known HP inducers in high-risk individuals.

Today, much is known about the genetic predisposition to IPF, with MUC5B (Mucin 5B), rs35705950, and telomere shortening having well-documented genetic associations with the disease. In comparison, little is known about genetic associations in nonidiopathic forms of PF (8, 9).

Growing evidence demonstrates that a number of clinical disorders may be related to genetic defects in telomere replication and extension. Overall, these syndromes are referred to as "telomeropathies." Human telomere disease consists of a wide spectrum of disorders, including pulmonary and hepatic disorders, early graying of the hair, and bone marrow abnormalities (e.g., aplastic anemia and acute leukemia) (10).

In this issue of the *Journal*, Ley and colleagues (pp. 1154–1163) explore the role of rare protein-altering, telomere-related gene variants in patients with CHP (11). They used next-generation sequences from two CHP cohorts to analyze and identify variants in TERT (telomerase reverse transcriptase), TERC (telomerase RNA component), DKC1 (dyskerin 1), RTEL1 (regulator of telomere elongation helicase 1), PARN (poly[A]-specific ribonuclease), and TINF2 (TRF1 [telomere repeat–binding factor 1]-interacting nuclear

factor 2). They found that a substantial minority of patients with CHP presented with rare mutations in telomere-related genes leading to shorter telomeres and worse clinical outcomes. These findings support the role of telomere dysfunction in the pathogenesis and prognosis of a subset of patients with CHP.

This was a follow-up study of a previously published observation that patients with CHP ($n = 217$, two separate cohorts) with shorter telomere lengths exhibited worse survival (12). The authors performed whole-genome and exome sequencing in two individual cohorts (discovery and validation), comprising a total of 353 patients with CHP, and found that rare telomere-related genetic variants (mainly associated with TERT, RTEL1, and PARN genes) could clearly distinguish a subset of rapid progressors (11% and 8% in the discovery and replication cohorts, respectively) with similar demographic, functional, and radiological profiles.

This study has a number of significant attributes that should be highlighted:

1. This is the first study in the literature to link genetic anomalies in telomere homeostasis with the prognosis of CHP, suggesting pathogenic commonalities with IPF (13). Interestingly, this study highlights the necessity of assessing both telomere lengths and rare protein-altering genetic variants to stratify patients with CHP into prognostic subgroups.

2. The study enrolled highly characterized patients with sporadic cases of CHP derived from two separate cohorts (discovery and replication). Based on a recent consensus on diagnostic criteria for CHP, the majority of patients enrolled in both cohorts had a diagnosis of CHP with a degree of confidence of at least 70%, based on compatible high-resolution computed tomography patterns, history of exposure, and in the majority of cases ($n = 207$, 59%), histological evaluation. The study design was further enriched by stringent *a priori* criteria to assess the rarity of the studied genetic variants.

3. The criteria for rare protein-altering, telomere-related gene variants were established *a priori*, and sequences from both cohorts were processed using the same bioinformatics pipeline.

Although the above observations are cause for much enthusiasm, the study by Ley and colleagues also has a number of limitations, as elegantly highlighted by the authors. These can be summarized as follows: a limited follow-up period in the replication cohort (1.6 yr) to assess survival, lack of assessment of potential associations between genetic variants and treatment responses, quality of control cases, and methodological limitations with the use of quantitative PCR to assess telomere length.

In addition to its original attributes, the study by Ley and colleagues also provides data with potential implications. The identification of telomeropathy in peripheral blood leukocytes of patients with CHP implicates immunosenescence in disease pathogenesis and highlights the importance of peripheral blood cell counts as biomarkers of disease prognosis. This premise is in line with recent data showing that patients with IPF and increased numbers of monocytes (>0.95 K/µl) have worse survival (13). Future studies assessing the prognostic accuracy of the parameters of a complete blood cell count (including monocytes, eosinophils, platelets, red cell distribution width, and mean platelet volume) in

predicting CHP progression and survival will be of major interest. Such findings could also be in the context of extrapulmonary (e.g., hematological) abnormalities of short-telomere syndrome. Whether telomeropathy and short telomeres represent the inciting events of immune deregulation of CHP or simply exacerbate the disease process remains to be determined.

There is ongoing disagreement about what constitutes HP. In a previous study, agreement across multidisciplinary teams about an HP diagnosis was fair (κ = 0.24), whereas agreement about IPF (κ = 0.60) or connective tissue disease–associated interstitial lung disease (κ = 0.64) was moderate to good (14).

Large, prospective, collaborative studies in well-defined patients with CHP are sorely needed to overcome these limitations and allow firm conclusions to be drawn. ■

Demosthenes Bouros, M.D., Ph.D.
Argyrios Tzouvelekis, M.D., Ph.D.
Medical School
National and Kapodistrian University of Athens
Athens, Greece

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⮏ Mechanistic Insights into Lethal Lung Developmental Disorders
The Rare Informs the Common

At birth, the lung circulation undergoes a remarkable transition from a high-resistance vascular bed with low blood flow *in utero* to a low-resistance and high-flow state immediately after birth. This dramatic physiologic response allows the fetus to successfully navigate from its prenatal dependence on the placenta for gas exchange to successful postnatal adaptation for air breathing as the lung assumes its essential role as the organ of gas exchange. This singular event represents the culmination of a successful sequence of tightly orchestrated maturational changes that occur throughout normal lung growth, which ultimately lead to the development of a mature epithelium–vascular interface that is essential for normal gas exchange. Precise coordination of lung growth involving the airways and parenchyma, especially as related to vascular development, depends on diverse and highly interactive signaling pathways whose regulation remains incompletely understood (1, 2).

In some infants, the lung circulation fails to achieve or sustain the normal decrease in pulmonary vascular resistance, leading to hypoxemic respiratory failure with pulmonary hypertension, which is known as persistent pulmonary hypertension of the newborn. Despite advances in care, however, a subgroup of term or near-term infants present with persistent pulmonary hypertension of the newborn physiology that is poorly responsive to these interventions, and die in the first days of life with evidence of lethal congenital lung disease (3–6). In this highly fatal subgroup, lung biopsy or autopsy