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JOURNAL CLUB

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ARTICLE

The Role of Genetic Testing in Pulmonary Fibrosis: A Perspective From the Pulmonary Fibrosis Foundation Genetic Testing Work Group, Chest, 2022, ISSN 0012-3692, https://doi.org/10.1016/j.chest.2022.03.023.

CLINICAL QUESTION

How should genetic testing inform clinical practice in the setting of familial pulmonary fibrosis?

SUMMARY

This working group perspective was commissioned by the Pulmonary Fibrosis Foundation in response to the current lack of guidance surrounding genetic testing in familial pulmonary fibrosis (FPF). The group was comprised of expert pulmonologists, geneticists, and genetic counselors from the United States. This work identifies high-yield clinical scenarios in which the results of genetic testing are likely to inform clinical decision-making. The article reviews common and rare variants along with their significance in the setting of familial fibrosis and appropriate laboratory methods for genetic testing.

Gene variants in pulmonary fibrosis are categorized as common or rare based on the allele frequency within the general population. Common variants occur more frequently within the general population and may infer risk for pulmonary fibrosis but are generally not themselves causative of disease. Rare variants, on the other hand, occur infrequently in the general population but tend to occur within coding regions of disease-associated genes. These variants cosegregate with disease within families and can alone be causative of disease. Genetic testing in familial fibrosis focuses on identification of *rare* inheritable variants.

Currently, rare variants in two biologic pathways – surfactant metabolism and telomere maintenance – are known to contribute to the genetic heritability of FPF. Specifically, six surfactant gene variants and nine telomere gene variants have been identified as pathogenic in the development of pulmonary fibrosis. By far the most commonly affected gene in FPF is *TERT* which is found in 20-30% of kindreds.

The role of telomere length (TL) testing is reviewed in this summary. TL is best utilized in a complimentary fashion to genetic testing. TL is influenced by age and specific telomere gene variants, therefore the presence of telomere shortening alone should be interpreted with caution. However, in clinical scenarios highly suggestive of a short telomere syndrome (pulmonary fibrosis, bone marrow dysfunction, premature graying of hair, liver dysfunction, pulmonary emphysema), TL may have a reasonably high negative predictive value above the 50th percentile. The prognostic utility of telomere length measurement in any patient with pulmonary fibrosis is a point of clinical interest; further investigation is needed to determine whether this should routinely be incorporated into clinical practice.

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Laboratory methods for gene sequencing and TL testing are reviewed along with specific clinical scenarios in which clinicians should and should not consider genetic testing for both affected proband and family members. The authors ultimately recommend that panel-based gene sequencing should be considered in any individual meeting the criteria for familial pulmonary fibrosis. The authors generally do not advise genetic testing in sporadic pulmonary fibrosis.

GROUP OPINION

Genetic testing in familial fibrosis has historically occurred at specialized centers for genetic testing, often with specialists who have little to no clinical experience or knowledge of fibrotic lung disease. Formal clinical guidelines informing how and when to incorporate genetic testing into practice for the non-geneticist pulmonologist are lacking. This summary perspective provides guidance with respect to appropriate patient candidates for genetic testing in pulmonary fibrosis, the potential clinical utility of genetic testing in FPF, guidance on specific testing methods, and scenarios in which testing is not advised. This review, while not itself a formal guideline statement brings attention to the growing body of knowledge regarding genetics in FPF and introduces a framework for incorporating genetic testing more readily into patient care.

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