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What is Familial Pulmonary Fibrosis?

Pulmonary fibrosis (PF) is a disease that describes a variety of disorders that lead to the same endpoint: progressive scar accumulation in the lung. This can be the result of occupational, environmental, autoimmune diseases, other specific diseases (e.g. Sarcoidosis) or rare inherited conditions where pulmonary fibrosis is a feature (e.g. Dyskeratosis Congenita or Hermansky Pudlak syndrome). These are considered known causes of pulmonary fibrosis. Often times, the cause is unknown, and is then classified as idiopathic. Pulmonary fibrosis is considered sporadic when there are no known relatives with the diagnosis, However, when 2 or more blood relatives are affected, this is considered familial pulmonary fibrosis (FPF). Currently, it is estimated that up to 20% of people with pulmonary fibrosis have familial pulmonary fibrosis (FPF). Disease causing (pathogenic) genetic variants have been discovered in up to 10 genes in approximately 20-30% of families with FPF.

What is a gene?

Genes are units of genetic information that are passed from parents to children. A gene provides the directions to make our body's proteins, and these proteins carry out certain functions in our bodies (such as making our eyes blue or brown). Each of us receive a full set of about 20,000 genes from each of our parents. Therefore, we have a pair of genes, one from each parent, to make each protein.

What is a variant?

We all have small changes in each of the 20,000 genes that make us different from each other, even within families. These changes are called variations (also known as variants or mutations). Variation in genes is normal and part of the evolutionary process. Variants in any gene can be benign, protective, neutral, or harmful, of which the latter are associated with disease. If one copy of the gene stops working, we have a backup. Most of the time, the backup copy is enough to keep the protein working. In this case, a person would be considered to be a "carrier" for a disorder, like in Cystic Fibrosis. This is also called "recessive

inheritance". Sometimes though, the backup copy is not enough, or the 2nd copy gets knocked out and there is no protein made at all. This is when a disease may manifest since no protein can be made. When it takes only one copy of a harmful variant to cause risk for disease, it is known as "dominant".

What causes FPF?

We are still learning about all the possible causes of FPF. It is important to know that there is not simply one gene or one variant that causes FPF. Inherited gene variants in two important pathways are known to be related to FPF. The more frequent variants are in genes that are related to protecting the telomeres. Telomeres are specialized structures located at the ends of chromosomes that serve to protect our chromosomes throughout our lifetime. Variants in several of telomere regulatory genes (TERT, TERC, PARN, DKC1, NAF1, RTEL1, ZCCHC8, and TINF2) have been discovered and account for 20-30% of FP cases. Variants in genes of another pathway, the surfactant genes (SFTPA1, SFTPA2, SFTPC, ABCA3 and NKX2-1) are less common and account for 1-3% of familial cases.

In patients with sporadic IPF who do not have a family history of PF, rare cases of telomerase gene variants have been reported in approximately 1-5% of patients. However, common variants in multiple genes have been associated. Common variants are defined as being present in 5-10% of healthy individuals, but are found more frequently in patients with IPF. While these variants can also be passed down in families, they are thought to have a lesser effect in development of IPF compared to the rare variants in the genes listed previously. For the scope of this document we will focus on the rare variants only as those are more strongly associated with FPF.

How is FPF inherited?

A harmful variant in only one copy (either mother or father) of the pair of known genes is enough to cause or increase risk for FPF in a person. When a parent has a variant in a gene that can cause FPF, each child has a 50% chance to inherit the abnormal gene, or a 50% chance to inherit the normal gene. If a child inherits the abnormal disease gene, that does not necessarily mean they will develop FPF but the risk increases significantly. This is known as "reduced penetrance", where a person can carry a gene variant, but may never develop the disease. Reduced penetrance can make a disease appear to "skip" generations. Different families have different gene variants. Knowing which specific variant is present in a family is critical in helping genetic testing for any other person in that family. Testing one specific gene for a known variant is far easier than testing for all the possible genes.

Genetic Testing Overview

Patients with FPF or likely genetic forms of pulmonary fibrosis should be seen for a genetic evaluation and counseling to determine what, if any genetic testing is appropriate and to educate the patient about risks and benefits of genetic testing.

What testing is available for people at risk for FPF?

Genetic testing is laboratory testing of DNA, usually from a blood or saliva specimen. It searches for a variant in a known gene implicated in FPF. The results of genetic testing can help understand the cause of the disease in a family and if there is risk for another family member to develop FPF.

How can I get genetic testing for FPF?

Because there can be unexpected risks, counseling by experts (genetic counselors) is recommended to be fully informed. Counselors can identify which genes should be tested, what tests are available, assist in ordering and

teach you about the benefits and limitations of genetic testing. Variations in genes can be confusing and may not provide a simple answer to whether this is the reason a person has FPF. Even negative results do not rule out an inherited risk. Costs of genetic tests can be variable and insurance may not always cover these costs. In addition, elective type insurances (e.g. life, disability, etc) could potentially discriminate against a person based on their genetic test result. This does NOT apply to health insurance per the Genetic Information and Nondiscrimination Act (GINA).

Who should be tested for genes in FPF?

If genetic testing is considered to be beneficial for the patient, it is recommended to test the person with a diagnosis of FPF instead of an unaffected family member. It is important to remember that, currently, a gene variant responsible for FPF will only be found in 20-30% of patients with FPF. Therefore, up to 80% of patients with FPF will test negative for the current genes known. There are other genes yet to be discovered that run in families. Further, testing is not recommended in patients without FPF, asymptomatic family members or in minors.

Since many of the genes implicated in FPF are telomere regulatory genes, one other test consideration is the measurement of telomere length as a first line screen.

Telomeres naturally shorten over time as we age. For instance, a baby has longer telomeres than a 70-year-old. This test measures the length of a patient's telomeres from their DNA, compares them to healthy patients of the same age and the results are given in percentiles (50th percentile is average for age). It is important to note that telomeres can be shorter than average across most interstitial lung diseases (and other diseases like COPD), especially in IPF whether familial or sporadic. The shorter the telomeres are, the more suspect it is that there will be an identifiable gene mutation, but not always. This is an option to supplement DNA results, to help inform treating providers about the value of DNA testing or for patients who are not sure if they desire DNA testing. Of note, telomere length testing for FPF and IPF is a specialized test that should be targeted and performed by laboratories with expertise in telomere biology disorders.

RESOURCES:

- Genetics Home Reference- Learn about genetics <https://ghr.nlm.nih.gov/>
- National Society of Genetic Counselors (NSGC) (find a counselor): www.nsgc.org
- American Board of Genetic Counselors (ABGC) (find a counselor): www.abgc.net
- Telehealth genetic counselors: www.informeddna.com or other telehealth companies (search "telehealth genetics counseling")
- Clinical Trials: www.clinicaltrials.gov
- DNA banking: www.preventiongenetics.com