

# Familial Pulmonary Fibrosis Research Study Newsletter

## National Jewish Health Becomes the Main Study Site and Data Coordinating Center of the Familial Pulmonary Fibrosis (FPF) Study

In May 2008, David A. Schwartz, MD, his research team and the Familial Pulmonary Fibrosis Study moved to National Jewish Health in Denver, Colorado. National Jewish Health has been ranked the #1 respiratory hospital in the nation the last eleven years in a row (1998-2009) by *U.S. News and World Report*. The mission of National Jewish Health since 1899 is to heal, to discover and to educate as a preeminent health care institution. “Science Transforming Life” is our promise to patients to use a proactive, preventive approach to medicine. National Jewish Health physicians and researchers are at the forefront of a new era in healthcare that embraces a personalized, preventive approach to medicine.

National Jewish Health has been involved in the Familial Pulmonary Fibrosis Project for the past decade and has the clinical and research expertise to coordinate the diverse activities that are involved in this research program. Moreover, the Familial Pulmonary Fibrosis Program is consistent with the development of a Personalized Medicine Program at National Jewish Health where the investigators and clinicians are attempting to understand the environmental and genetic factors that facilitate the diagnosis and care of patients with chronic lung diseases, including Familial Pulmonary Fibrosis. Our view is that the Familial Pulmonary Fibrosis Research Program will flourish at National Jewish Health.

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### What does this change mean for study enrollees?

All FPF study materials including medical records, biopsy slides, consent forms, questionnaires, X-rays and blood samples have been transferred to National Jewish Health to accommodate this change. These materials remain stored in a confidential and secure manner. The FPF Study enrolling sites include National Jewish Health, Duke University, Vanderbilt University, and the Landspítali University Hospital in Reykjavik, Iceland.

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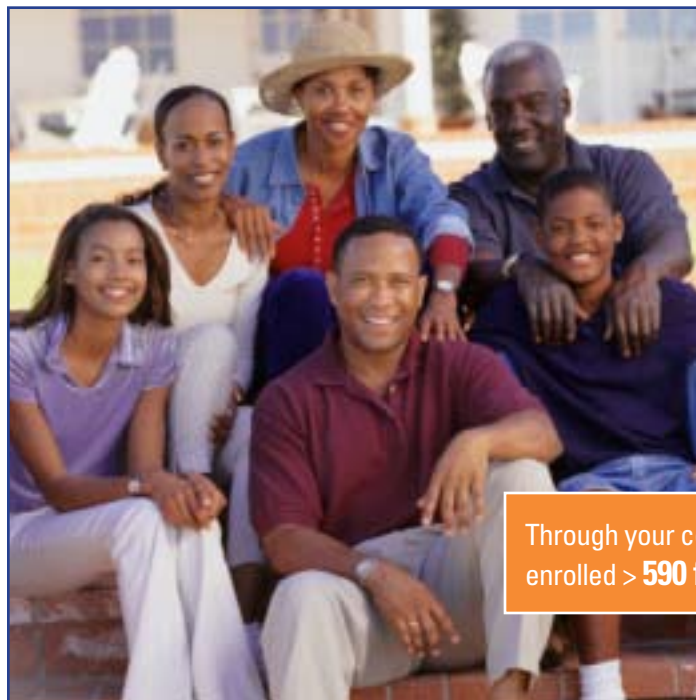


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### FPF Study Progress

We continue to lead a highly coordinated research team searching for the genetic basis of Familial Interstitial Pneumonia (FIP), also known as FPF. Through your contributions to this study, we have enrolled > 590 families over the past 10 years that have  $\geq 2$  cases of Idiopathic Interstitial Pneumonia (IIP). Of those families, 183 families had confirmed FIP that included two cases of IIP with at least one diagnosis of Idiopathic Pulmonary Fibrosis (IPF). Of the 183 families, there are 82 families that have had DNA linkage analysis performed. Linkage studies allow researchers to narrow down regions of the human genome to find candidate genes for disease utilizing family DNA information.

We have identified regions on chromosomes 10, 11, and 12 that likely contain genes contributing to familial forms of IIP. On chromosome 11 in particular, we have two genes of interest, MUC5AC and MUC2, which are mucin genes. Of the two, we are taking a closer look at MUC5AC, which may be related to the development of pulmonary fibrosis.



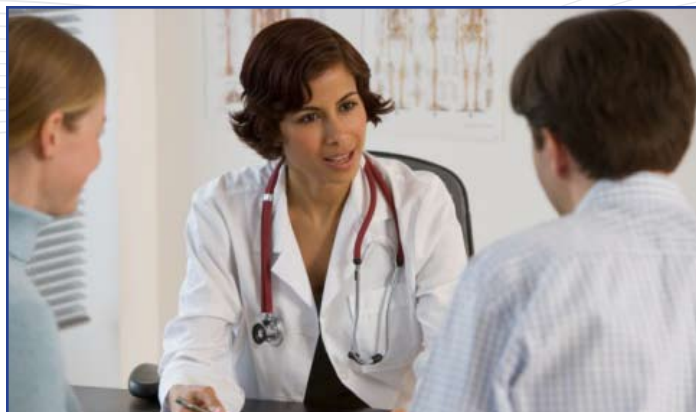
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### Mucin Genes

Mucins are what give mucus its gel-like properties providing lubrication, protection, and transport functions within the body. Specifically, mucus in the lungs acts to trap and remove inhaled foreign particles from the airways. MUC2, MUC5AC and MUC5B are the main gel-forming mucins in human airways.

Our studies have identified genetic changes (polymorphisms) in MUC5AC that are associated with pulmonary fibrosis in both families and individual patients with no family history of the disease. One of these changes is located in a region of the gene that is thought to be involved with binding individual mucins together to form long chains that give the mucus its gel-like property. Thus, these changes may affect the ability of the mucin to clear particles out of the lungs potentially leading to a higher risk of pulmonary fibrosis due to an increase in damage to the lungs. Mouse models also support this idea showing that mice that do not have the MUC5AC gene have a decreased ability to clear particles out of the lungs and increased signs of fibrosis after exposure to a drug known to cause lung damage (bleomycin).

We are currently in the process of publishing these findings. Unfortunately, we are unable to provide any study subject with individual results. Research genetic testing does not include the very strict guidelines that are included in clinical diagnostic laboratory genetic testing, and because of this difference, we are not permitted to share our research results with you. However, once a clinical laboratory test is developed, we will provide this information to you so that you, or a family member of yours, can be tested.



## David A. Schwartz, MD Becomes Director of the Genetics and Therapeutics Center at National Jewish Health

The Center for Genetics and Therapeutics is dedicated to understanding the genetic basis of diseases that are common in patients cared for at National Jewish Health. This new Center will build on the scientific and clinical strengths at National Jewish Health by developing programs to understand how genes work in biological systems, how genetic variants contribute to the development of disease, and why individuals with the same disease have very different results due to the treatment.

The FPF study is part of this new center, as we continue the search for genetic factors in this disease. Dr. Schwartz remains committed to this study and has assembled expert physician-scientists and researchers in the field of pulmonary fibrosis to continue work on this project.

## Current Knowledge of Genetic Factors for Sporadic Cases of Pulmonary Fibrosis

At this time, a single gene has not been identified to be causative of pulmonary fibrosis. However, there has been progress in genetic research for pulmonary fibrosis that is aiding researchers in their quest. The following is currently known:

- Mutations in the genes TERT and TERC have recently been reported to be associated with the development of pulmonary fibrosis in 10% of FPF and 2% of sporadic cases of idiopathic pulmonary fibrosis (IPF).
- Mutations in the gene encoding surfactant protein C are associated with the development of an inflammatory form of pulmonary fibrosis in one family and what appears to be both idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) in another large family. In sporadic cases of IPF, surfactant protein C mutations appear to be rare.
- In a Mexican cohort, mutations in the genes encoding surfactant protein A1 and surfactant protein B have been shown to be associated with IPF in non-smoking and smoking populations, respectively.
- ELMOD2 was identified as a candidate gene for FPF in a genomic screen of six multiplex families from southeastern Finland.
- Genetic changes in structures critically involved in the immune system have been reported to be associated with the development of IPF

Gene discovery for FPF/IPF remains challenging and complex, as the findings above indicate that not only one gene may be responsible for FPF, but multiple genes may play a role.

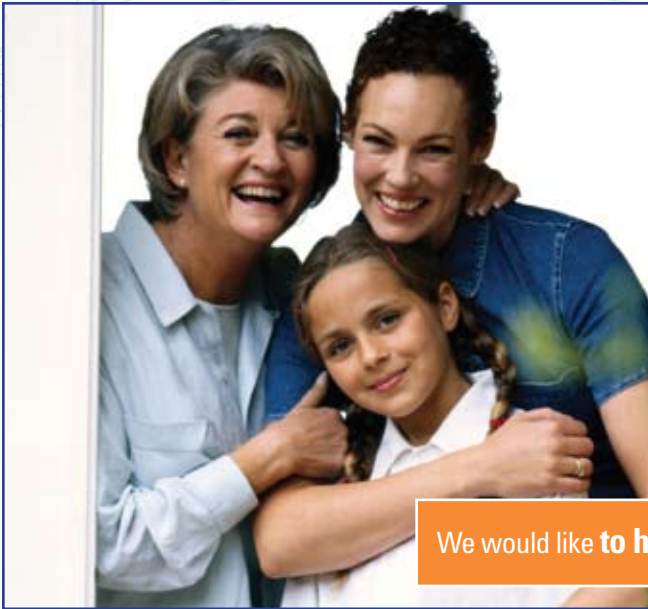
## Future Directions

### Molecular Phenotyping Grant Awarded to National Jewish Health

David Schwartz and his lab have received a grant to research the molecular signatures of pulmonary fibrosis. The overall goal of this project is to combine gene expression data and genomic findings in patients with idiopathic interstitial pneumonia (IIP) to develop and validate molecular signatures that serve to refine the diagnostic criteria for this group of complex diseases.

### Upcoming Research

Our group has submitted a comprehensive proposal to the National Institutes of Health (NIH) to study the relationship between every human gene and the risk of developing pulmonary fibrosis. We are also submitting a proposal with Vanderbilt University and Duke University to study the interaction between genes and environmental factors in the development of pulmonary fibrosis.



We would like **to hear from you.**

## Please Keep Us Updated

Now that we are once again enrolling families in the FPF study, we would like to hear from you. We continue to enroll new families as well as members of existing families that may not have initially enrolled. Please let your family members know that the study is continuing to enroll and have them contact a coordinator at one of the sites (listed to the right). If you or another family member has been diagnosed with pulmonary fibrosis after initially enrolling, please let us know. Knowing of a change in health status is critical in order for the analysis of the data to be accurate and powerful as possible. In addition, if other members of your family are newly diagnosed, please ask them to contact us so that we can offer to enroll them into the study as well.

We would also like to hear from additional families who have multiple members diagnosed with pulmonary fibrosis. We greatly appreciate any referrals of new families interested in our research. Please have them contact one of our coordinators listed to the right.

Please keep us updated on any address, email or telephone number changes so that we will have the most current contact information for you.

You may also contact us through our online form at [www.njhealth.org/FPFtrial](http://www.njhealth.org/FPFtrial). This will allow you to submit contact information through a secure and confidential manner.

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