Introduction to Familial ILD

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How genes work

Genes are made up of DNA. Each chromosome contains many genes.
Types of genetic disorders

**Single gene disorder:** mostly one gene, mild effect from other genes and environment

**Complex genetic disorder:** lots of genes and the environment each have a mild effect

Manolio, TA Brooks LD, Collins FC JCI 2008
Single gene disorder: rare variant with dramatic effect

**Cystic fibrosis:**
Mutations in BOTH copies of the *CFTR gene* ("cystic fibrosis transmembrane conductance regulator") lead to severe disease; seen in 25% of children of carriers.

Genetics of ILD

• “Familial” idiopathic pneumonia – ILD with no clear reason in at least two related family members
• ~10% of IPF patients have a family history of the disease
• ~20% of patients with familial disease have a rare variant “mutations” in a known gene

9 genes known to cause pulmonary fibrosis
  • 6 genes controlling telomeres
  • 3 genes controlling surfactant in the lung alveoli (air sacs)

Kropski..Loyd Am J Respir Crit Care Med. 2017 Jun
Surfactant genes

• Mix of oils and proteins that is critical in keeping alveoli open
  • Surfactant proteins A, B, C, D mix with lipids

• May cause disease at any age
  • Many surfactant protein mutations cause severe disease in infancy

• Early onset disease may be associated with surfactant genes
Rare, significant variants

- **Surfactant protein-related genes**
  - keeps the air sac from collapsing
    - Surfactant protein C and A2, (SFTPC and SFTPA2)
    - ATP-binding cassette member A3 (ABCA3)

- **Telomere function:** caps on chromosomes
  - telomerase reverse transcriptase, TERT
  - human telomerase RNA component, hTR
  - dyskerin, DKC1
  - telomere interacting factor 2, TINF2
  - Regulator of telomere elongation helicase, RTEL1
Telomeres

- Genes related to telomeres - the aglets of chromosomes
  - Cap the ends of chromosomes and allow continued cell division
Telomeres are important all over the body

- Short telomeres associated with:
  - Early graying of hair
    - Significant before age 30
  - Bone marrow failure
    - “aplastic anemia”
  - Liver fibrosis for no clear reason
    - Cryptogenic fibrosis

Short telomeres in pulmonary fibrosis

Dressen...Yaspan, Lancet Respir Med. 2018 Aug;6(8):603-614
Several genes build telomeres

- TERT, TERC, RTEL, PARN build “telomerase”
- Common variant in TERT also found more commonly in IPF
- “incomplete penetrance”
- Not everyone gets disease
  - More with age
  - 95% of smokers

- Testing sporadic IPF patients with very short telomeres found a few new mutations (<5%)

Diaz de Leon A...CK Garcia PLoS ONE. 2010;
Complex genetic disorders: look at all genes

Likelihood an area on the chromosome is different in people with and without a disease.

Common, milder variants: **MUC5B**

- Found in airway cells that make mucus
- Single gene variation “SNP“rs3570590” : a 6-8 x risk of IPF
- Found in 34% of familial interstitial pneumonia, 38% in idiopathic pulmonary fibrosis, and 9% controls
- Somewhat better prognosis than other IPF patients

Common, milder variants: **TOLLIP**

- TOLLIP Toll-interacting protein
- Three variants found with increased frequency in IPF
- One associated with faster progression

TOLLIP may change response to therapy

If TOLLIP variant “CC”
the drug was HARMFUL

If TOLLIP variant “TT”
the drug was HELPFUL

If both
the drug was NEUTRAL

Red = N-acetyl cysteine
Blue = placebo

Telomeres, *MUC5B* and progression

Should every patient get genetic testing?

Information is useful – but currently we don’t know how to use this

- no clear treatment changes

If no known gene is found, could be reassuring for family

- not all important genes are known

If gene with better disease course could be reassuring

- unclear what the meaning is for a given person

- concerns for insurance coverage of family members
Who should be tested?

• Targeted genetic testing currently recommended:

  • If family history of ILD AND liver and bone marrow problems -> could test telomere length. If short (<10th percentile) consider genetics

  • If family history of very early ILD, could consider testing for surfactant gene mutation (less data)

  • Some lung transplant programs test telomere length
How could you get genetic testing?

• Ask your doctor
  • Clinically available

• Join a clinical study
  • Free!
  • Genetic counseling typically included
  • Does not go into medical record
  • Help build learning
What about families?

• Remind family to be vigilant about symptoms and not to smoke

• If you have a family history of pulmonary fibrosis, consider enrolling in a study
  • ? could consider CT scan in 50s (no data to support)

For specific questions: try the familial Pulmonary Fibrosis (FPF) Genetic Counseling Program
1.800.423.8891 ext. 1097 or email Janet Talbert at talbertj@njhealth.org.
Take home

• Several genes are known to increase risk of ILD
  • Some have a large effect – found in a few families
  • Some have a small effect – found in many people

• Common variants may change the course of the disease

• Common variants may change the effect of a drug

• Future drug trials will likely collect and analyze genetic information
Learn more about genetic diseases

Programs doing research on familial ILD

Columbia/NIH: The Families At-Risk for Interstitial Lung Disease (FAR-ILD) [NCT03641742](#)
- Anyone with ILD who has a parent or sibling with it
- Could include CT scan, pulmonary function testing, blood draw from a vein, bronchoscopy, & return visits.
- Atif Choudhury: 212-342-4551 / mac2463@cumc.columbia.edu

National Jewish Health (Denver, CO) **Pulmonary Fibrosis & Genetic Factors**
- Research coordinator Julie Powers 303.724.6539
Vanderbilt Familial ILD study

Enrollment Criteria:
– Family members between ages 40-70 years
– Family members who have no known serious diseases
– Multiple members of your family have had pulmonary fibrosis, including a parent or sibling

Study coordinators (Cheryl.Markin@vumc.org or Katrina.Douglas@vumc.org) or phone toll free 1-888-898-1550.

https://medsites.mc.vanderbilt.edu/pulmonaryfibrosis/familial-interstitial-lung-disease-program