Genetics and Pulmonary Fibrosis

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National Jewish Health, Denver CO
InformedDNA®
Introduction and Disclosures

• InformedDNA®
  – Senior Genetic Counselor
  – Oncology, Ocular, Neuro and Pulmonary Fibrosis
  – Dec. 2015-present

• National Jewish Health
  – August 2003 to present (various roles)
  – Advisor to the ILD program and Institution

• Pulmonary Fibrosis Foundation
  – Medical Advisory Board Member
  – Ambassador
Who we are

The Pulmonary Fibrosis Foundation mobilizes people and resources to provide access to high quality care and leads research for a cure so people with pulmonary fibrosis will live longer, healthier lives.  www.pulmonaryfibrosis.org

Our signature programs include:
• PFF Care Center Network
• PFF Patient Registry
• PFF Patient Communication Center
• PFF Ambassador Program
• PFF Support Group Leader Network
• PFF Disease Education Webinar Series
• PFF Summit
• PFF Daughters
Agenda

• Interstitial Lung Disease (ILD)
  – Idiopathic Pulmonary Fibrosis (IPF)
  – Familial Pulmonary Fibrosis (FPF)

• Genetics Primer

• Genetics of FPF/IPF

• Genetic Testing/Issues for FPF

• Using genetics in precision medicine (trials/treatments)

• Screening/Surveillance

• Genetic Services for FPF/IPF
Clinically heterogeneous (>100 disorders)

Interstitial lung disease

Known cause or association:
- Connective tissue diseases
- Occupational causes
- Drug side effects

Idiopathic interstitial pneumonias

Granulomatous:
- Sarcoidosis
- Hypersensitivity pneumonitis
- Infections

Other forms of ILD:
- Lymphangioleiomyomatosis
- Pulmonary Langerhans' cell histiocytosis
- Eosinophilic pneumonia
- Pulmonary alveolar proteinosis

Idiopathic pulmonary fibrosis
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Lymphocytic interstitial pneumonia

Non-specific interstitial pneumonia
- Respiratory bronchiolitis-ILD
- Acute interstitial pneumonia
Identification of Genes in PF

• Define causative factors
• Improve understanding of pathogenesis
• Aid in diagnosis
• Clinical utility
• Identify individuals at risk
• Suggest potential treatment options
• Clinical trials/treatment
• Personalize medicine

www.lyon.k12.nv.us
Sporadic IPF Pedigree
Familial Pulmonary Fibrosis Pedigrees
## Genetic Variation

### Rare Variants
- < 1% of the population
- Mendelian traits
  - Hereditary patterns (AD, AR, X-linked)
- Associated with classic genetic syndromes
  - Cystic Fibrosis
  - Breast cancer (BRCA)
- Stronger effect in risk of disease
- Variants along the entire gene

### Common Variants
- > 1% of the population
- Can be inherited
- Associated with disease risk
  - Heart disease, diabetes, cancer, PF
- Smaller effect in risk of disease
- Therapeutic targets
- “23andMe”, ancestry tests, pharmacogenomics
- “Hot spots” same in all carriers
IPF: Genetic-Allelic Spectrum

Alder, Kropski, Fingerlin, Seibold

Effect Size

Large

Very Rare

MAF < 0.1%

MAF > 5%

Small

Common variants (CV):

- SFTPC, ABCA3
- SFTPA1/A2, NKX2-1
- TERT, TERC
- RTEL1, PARN
- DKC1, TINF2, NAF1
- ZCCHC8

Rare variants (RV):

- DSP, TOLLIP, MAPT, DPP9, others
- TERMT, TERC
- RTEL1, PARN
- DKC1, TINF2, NAF1
- ZCCHC8

Personal Genome Next-Generation Sequencing (NGS)

Common variants (CV):

- MUC5B

Genome-wide Association Studies (GWAS)
Multifactorial Genetic Disease

- Usually common variants
- Combination of factors
  - Genetics
  - Environmental/Lifestyle
- Complex
- Can recur in families
- Not usual patterns of inheritance (dominance, recessive)
- Increased risk

www.familialpulmonaryfibrosis.org
IPF

Sporadic
75-80%

Familial IPF
~20%

Hereditary
~5%
Hermanksy Pudlak Syndrome (HPS)

- Oculocutaneous albinism
- Bleeding diathesis
- PF in some individuals
- Autosomal Recessive
- Pulmonary Fibrosis by 3rd decade
- At least 10 genes associated
- Specific variants in HPS1, HPS4 and AP3B1 genes in Puerto Rican population for PF
- Remaining genes thus far not associated with PF
- Prevalence: 1-9/1,000,000

hpsnetwork.org
Dyskeratosis Congenita DC

- 11 genes to date (GeneReviews 2016)
- Classic features skin, nails, mouth
- Bone marrow failure syndrome
- Head/neck cancers
- Bone development/hair/teeth
- Pulmonary Fibrosis
- Liver disease
- XL, AD, AR, some genes AD/AR
- Premature Aging syndrome
- 400 families known in the world
- “Short Telomere Syndrome”

https://www.ncbi.nlm.nih.gov/books/NBK22301/
Telomere Diseases

Calado, 2009
Telomere Length Varies

- Variations occur between
  - Organism Level
    - Age
    - Family
    - Individual
    - Male vs. Female
  - Cellular Level
    - Cell/tissue type
    - Cell
    - Chromosomes

Slide source: Carolyn Applegate, Johns Hopkins
Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis

Mary Y. Armanios, M.D., Julian J.-L. Chen, Ph.D., Joy D. Cogan, Ph.D.,
Jonathan K. Alder, B.A., Roxann G. Ingersoll, B.S., Cheryl Markin, B.S.,
William E. Lawson, M.D., Mingyi Xie, B.S., Irma Vulto, B.S., John A. Phillips III, M.D.,
Peter M. Lansdorp, M.D., Ph.D., Carol W. Greider, Ph.D., and James E. Loyd, M.D.
Telomere Length

Alder et al, 2018
CHARACTERISTICS OF RARE FPF GENES

• **Telomerase** pathway genes ~ 20-30% (STS)
  - Liver disease
  - Bone marrow failures (AA, MDS, AML)
  - Premature greying (20s/30s)
  - Pulmonary Fibrosis
  - Biallelic presents more severe in pediatric
  - Up to 60% detection in telomeropathy pedigree

• **Surfactant** Protein C ~ 1-3%
  - Childhood onset usually occurs
  - Earlier age of onset (e.g. <50)
  - Prolonged course - decades

• **Rare syndromic, neonate/childhood onset/biallelic**
  - Hermansky Pudlak (HPS)
  - Brain-Lung-Thyroid Syndrome
  - Dyskeratosis Congenita
Impact of Genetic Information

• Role of genetics
• Genetic testing
• Cost
• Medical impact
• Clinical trials?
• Risks to relatives
• Confidentiality
• Insurability
• Psychosocial impact
• Services
Genetic Testing

• Right test for right patient
• Few genes available for testing
• Cost
  – $$ for initial test on affected family member
  – ~$ for other family members once mutation is known
  – May or may not be covered by insurance
  – Costs are coming down
• Test results can be complex
• Genetic testing for IPF not routine
• Genetic counseling highly recommended for any genetic testing
Result Interpretation

- No Mutation (Negative)
- VUS-Likely Benign
- Uncertain Significance (VUS)
- VUS-Likely Pathogenic
- Pathogenic Mutation (Positive)

A NEGATIVE result =

UNINFORMATIVE

If no mutations are identified:
1) The technology used today could have missed it (low likelihood but does happen!)
2) The testing performed did not look at the gene(s) involved in the family
3) The gene(s) involved have not been discovered yet
4) There is a non-genetic component to the lung fibrosis in the family

1) Rely on family history to dictate screening and management
2) Consider testing other affected family members
Clinical Management

• Clinical utility ?

• Telomerase genes
  – Liver tests
  – Hematological monitoring
  – Lung transplant

• Survival information (MUC5B, TOLLIP)

• Future
  – Therapies based on genotype (personalized medicine)
Diagnostic Importance in Management and Treatment

- Lung transplant: higher risk for complications due to bone marrow suppression and infections
  - If short telomeres and/or telomerase mutation
  - 7 out of 8 patients needed platelet transfusion
- Certain drugs contraindicated
- Donor selection for bone marrow transplant
- Bone marrow transplant timing

Slide source: Carolyn Applegate, Johns Hopkins
### IPF: Genetic-Allelic Spectrum

**Effect Size**
- **Large**: SFTPC, ABCA3, SFTPA1/A2, NKX2-1
  - **TERT**, **TERC**, **RTEL1**, **PARN**, **DKC1**, **TINF2**, **NAF1**
  - **MUC5B**

**Rare variants (RV):**
- Personal Genome Next-Generation Sequencing (NGS)

**Common variants (CV):**
- Genome-wide Association Studies (GWAS)

**Variant Frequency**
- **Very Rare**: TERT
- **MAF <0.1%**: DSP, TOLLIP, MAPT, DPP9, others
- **MAF > 5%**: TERT
- **Common**: ZCCHC8

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Alder, Kropski, Fingerlin, Seibold
New $22M Study to Use Sequencing, Proteomics to Investigate Pulmonary Fibrosis

Nov 04, 2019 | staff reporter

NEW YORK — The Pulmonary Fibrosis Foundation (PFF) announced today the start of a study, supported by $22 million in funding from the National Institutes of Health and philanthropic organization Three Lakes Partners, using genomics and other technologies to diagnose and treat idiopathic pulmonary fibrosis (IPF).

The study — called Prospective Treatment Efficacy in IPF Using Genotype for Nac Selection, or PRECISIONS — is being led by Cornell University’s Fernando Martinez and the University of Virginia’s Imre Noth, who will use samples from the PFF’s patient registry and biorepository to help determine whether N-acetyl-cysteine is effective in IPF patients with a particular genetic mutation that is found in about 25 percent of people with the lung disease.
Goals of PRECISIONS

• Determine if NAC is effective for patients w/IPF with a TOLLIP variant (plays a role lung immunity)
• Develop blood-based assays to distinguish IPF from other lung diseases with same symptoms
• Identify genetic variants that influence a person’s risk of developing IPF
MUC5B

- Linkage analysis in 82 families – Chromosome 11
- Mucin Gene, MUC5B
- Variant in promoter region of MUC5B (G>T)
  - AGTCT
  - Single nucleotide polymorphism “SNP”
  - Associated with IPF and FPF
  - Found in 19% of controls (common variant)

<table>
<thead>
<tr>
<th>MUC5B</th>
<th>FPF</th>
<th>IPF</th>
<th>Healthy Controls</th>
</tr>
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<tbody>
<tr>
<td>Variant</td>
<td>59%*</td>
<td>67%*</td>
<td>19%*</td>
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*Estimated Carrier Frequency in IPF, FPF, and control populations from study

MUC5B SNP

• Dysregulated MUC5B expression may be involved in pathogenesis of IPF
  – Excess mucin impairing mucosal defense?
  – Interfering with alveolar repair?
  – Directly causing lung injury?

• Odds Ratios for Heterozygotes/Homozygotes
  – 6.8 and 20.8 fold risk in FIP
  – 9.0 and 21.8 fold risk in IPF

MUC5B SNP

– Significantly associated with improved survival in carriers amongst patients with IPF\(^1\)

– Found to be associated with ILD in general population\(^2\)
  • Framingham Heart Study
  • More apparent in older persons (age >50)
  • Not influenced by cigarette smoking

Risk to Relatives

- Family history = risk
- Risk appears greater to relatives in FPF
  - Dominant w/reduced penetrance
  - X-linked, recessive
- Common variants: increased risk to relatives
  - sporadic
  - familial cases
Screening for those at-risk

- **No** established guidelines
- Baseline and subsequent regular screening for at risk asymptomatic family members
  - Pulmonary function tests
  - HRCT scan to detect early abnormalities
  - Standard questionnaire measuring dyspnea
  - 14% had early ILD on CT
  - 35% had abnormal tbbx
- Minimizing risks:
  - Smoking cessation
  - Maintain healthy BMI and lifestyle
  - Minimize known exposures
Psychosocial Impact

• Recognition of familial disease by clinician

• Awareness of diagnosis
  – Depression and anxiety
  – Frequently a former caregiver is now the patient

• Desire genetic information

• Take action: research, clinical trials

• Great concern for risk to relatives
Risks and Benefits of Genetic Testing

• Risks
  – Learning genetic status
  – Emotional and psychological
  – Monetary
  – Genetic Discrimination?
    • affected
    • unaffected

• Benefits
  – Learning genetic status
  – “Knowing” risk
  – Reproductive planning
  – Prevention plan (?)
  – Screening for disease
  – Peace of mind
Genetic Discrimination

• Mostly fear-based
• Genetic Information Non-Discrimination ACT (GINA)
  – Signed into law May 21, 2008
  – Augments individual state laws
  – Applies only to health insurance and employment
• GINA has relieved many fears for genetic discrimination
What Does GINA Do?

• **Health Insurance**
  – Prohibits requirement of genetic testing
  – Prohibits use of genetic information to
    • Set premiums, coverage, rates
    • Determine eligibility
    • Be used as a pre-existing condition
  – Prohibits health insurers from requesting genetic information on
    • The individual
    • The individual’s family members (including family history alone)

• **Employment**
  – Prohibits genetic information use by employers in decisions
    • Hiring
    • Firing
    • Job assignments
    • Promotions
    • Prohibits employers from requiring, requesting or purchasing genetic information about an individual or family member
What Won’t GINA Do?

• Does not extend to elective insurances (life, disability)
• Does not mandate coverage for tests or treatment
• Does not apply
  – Military
  – Federal employees
  – The Indian Health Service
• Does not protect the manifestation of disease (different from predisposition)
  – GINA protects the genetic information, not the disease itself
Resources for Patients and Families

www.pulmonaryfibrosis.org

DNA banking:
Prevention Genetics

GINA information
www.ginahelp.org
Familial Pulmonary Fibrosis
Genetic Counseling Service

- Telephone-based Genetic Counseling
- Inception February 2008
- Provide genetic information/advisement to providers, patients and family members
- Supported by
  - Pulmonary Fibrosis Foundation
  - Private donations
- Toll-free number

National Jewish Health
Janet Talbert, MS, CGC
1-800-423-8891 ext. 1097
talbertj@njhealth.org
Genetic Counseling-Find a GC

• National Society of Genetic Counselors (nsgc.org)
• American Board of Genetic Counselors (abgc.net)
• Telehealth companies (e.g. InformedDNA®, others)
Research options

• Clinical Trials
  – www.clinicaltrials.gov

• Familial Pulmonary Fibrosis Research at National Jewish Health and University of Colorado Denver

• National Enrollment:
  – Contact: Julie Powers, MHS
    Instructor
    University of Colorado
    12631 E 17th Ave
    Aurora, CO 80045
    Office: 303-724-6539
    julia.powers@ucdenver.edu
Summary

• A familial/hereditary component exists in IPF (small)
• No single gene
  – Multiple genes identified, may depend on family
  – Rare variants vs. common variants
  – Multiple environmental factors
• Increased risk to unaffected 1st-degree relatives (parent, sibling, child) is perceived
• Most families exhibit dominant pattern, reduced penetrance
• Baseline screening as a tool for family members at risk
• Patients/Families need recognition, support and resources
• Genetic Counseling is vital in understanding these issues
Thank You!
References

- www.ginahelp.org
- Dr. Christine Garcia, slide (Genetic/Allelic PF spectrum)
- Kropski et al Am J Respir Crit Care Med. 2015 Feb 15;191(4):417-26
- Kropski et al Am J Respir Crit Care Med. 2017 Jun 1;195(11):1423-1428