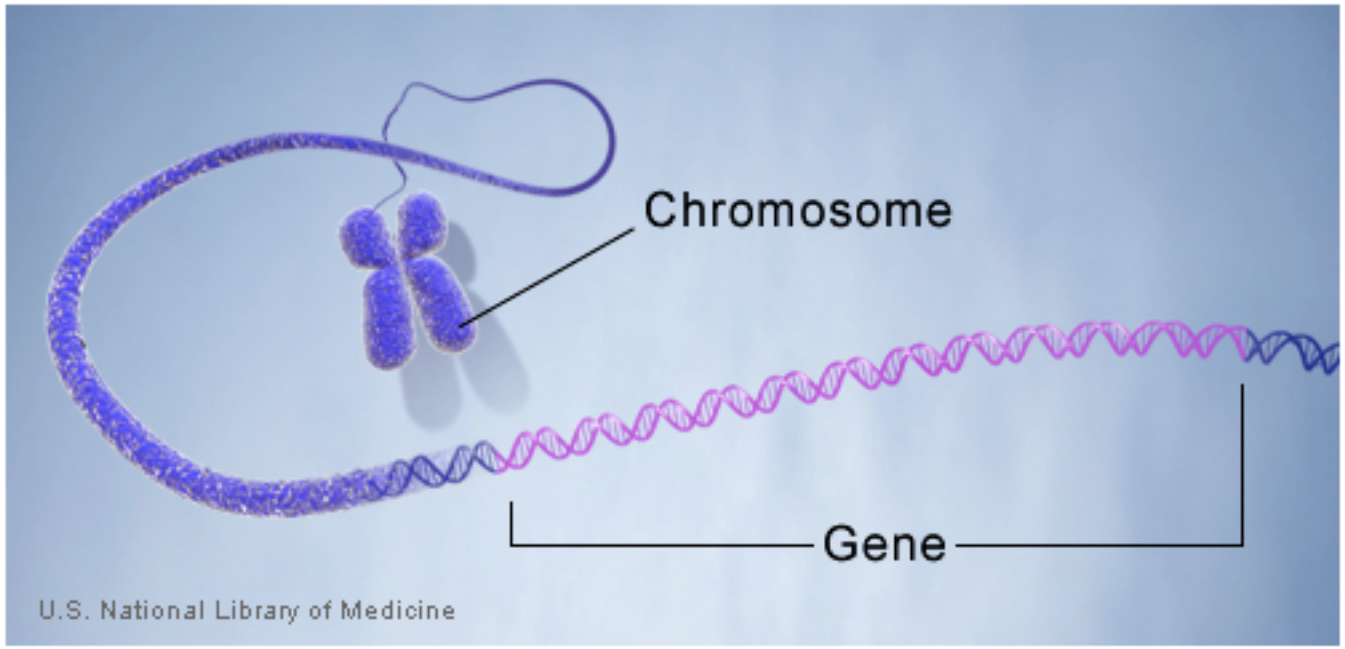
Introduction to Familial ILD

Katy Black

August 12, 2020

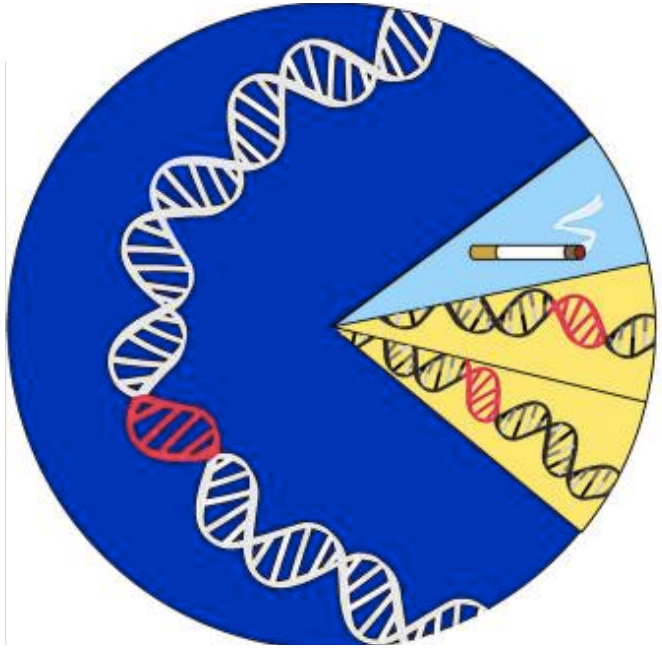
How genes work

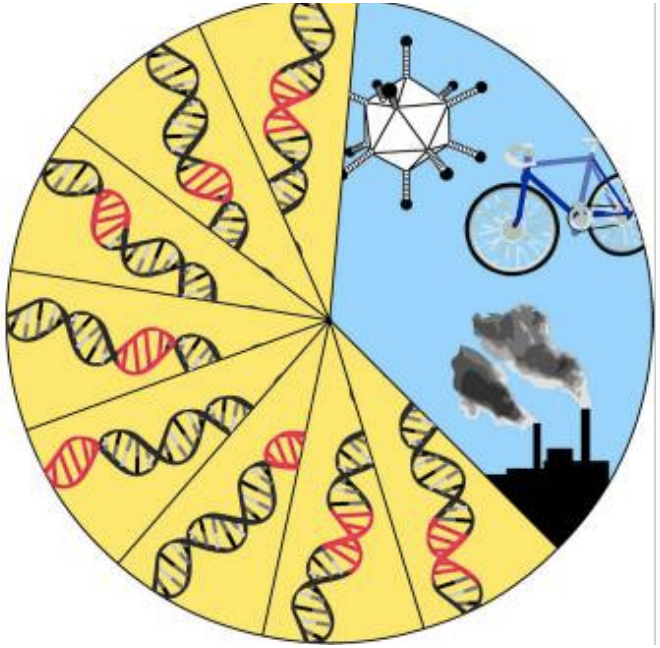
Genes are made up of DNA. Each chromosome contains many genes.



Credit: U.S. National Library of Medicine

Types of genetic disorders



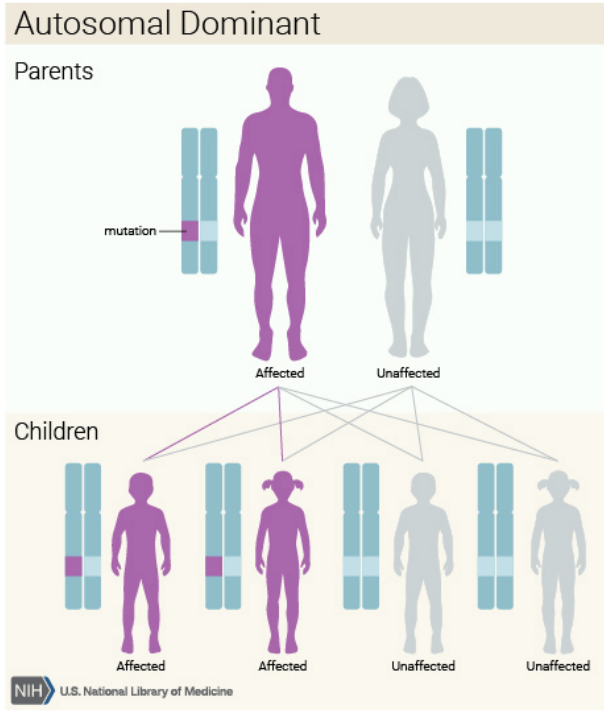


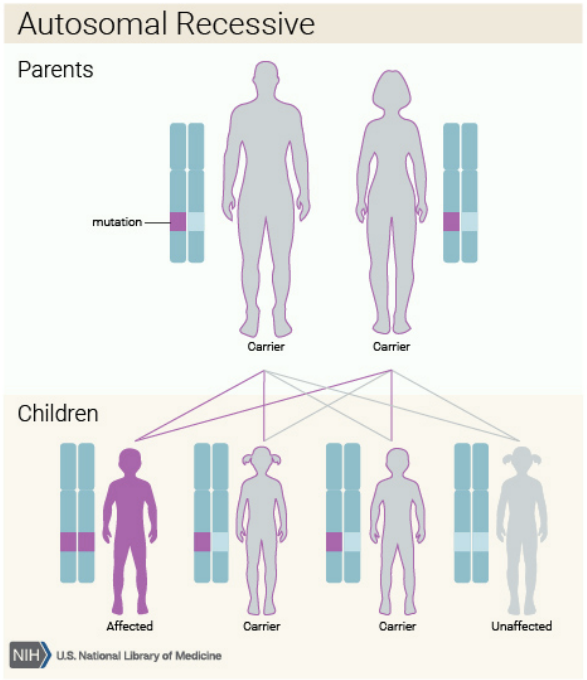
Single gene disorder: mostly one gene, mild effect from other genes and environment

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

https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns

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
Kaur, Mathai SK, Schwartz Front Med (Lausanne). 2017; 4: 154

Surfactant genes

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

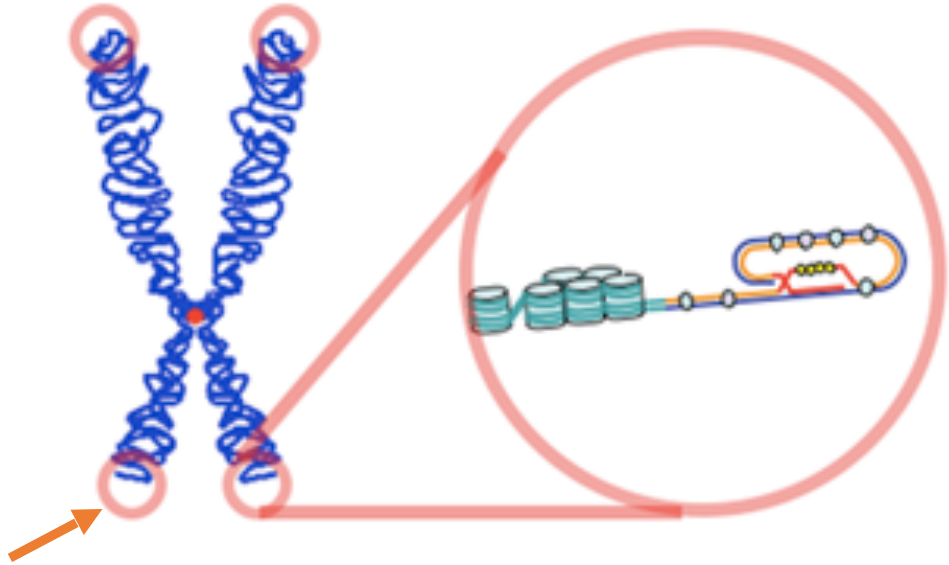
- **Surfactant protein-related genes**
  - keeps the air sac from collapsing
    - Surfactant protein C and A2, (SFTPC and SFTPA2)
    - ATP-binding cassette member A3 (ABCA3)

- **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

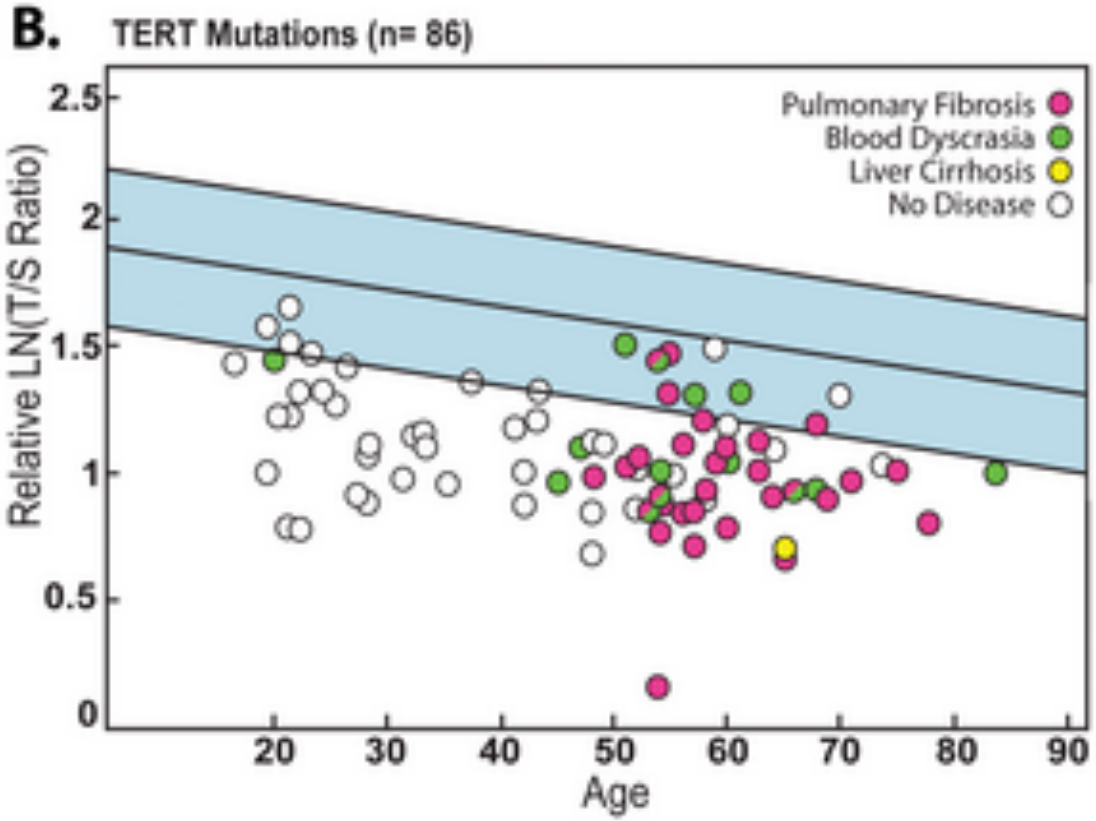
Aglet



Telomere

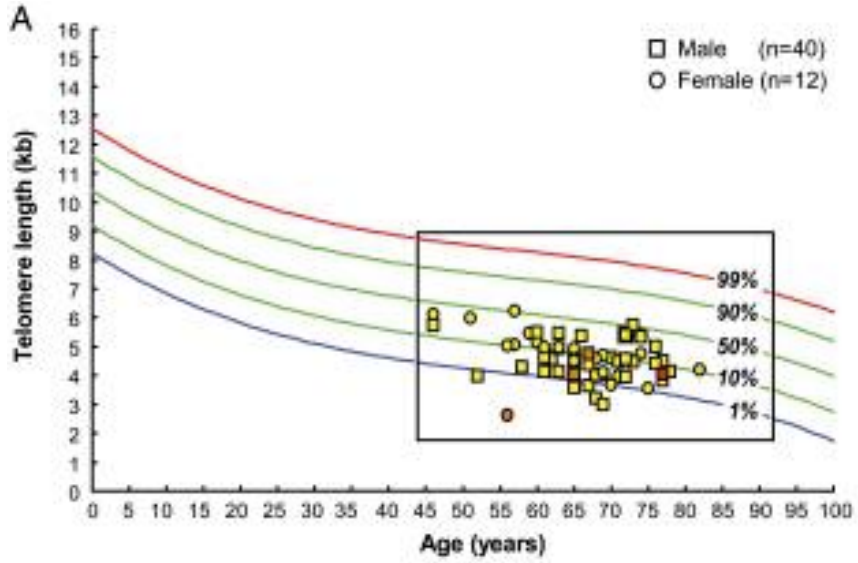
Telomeres are important all over the body

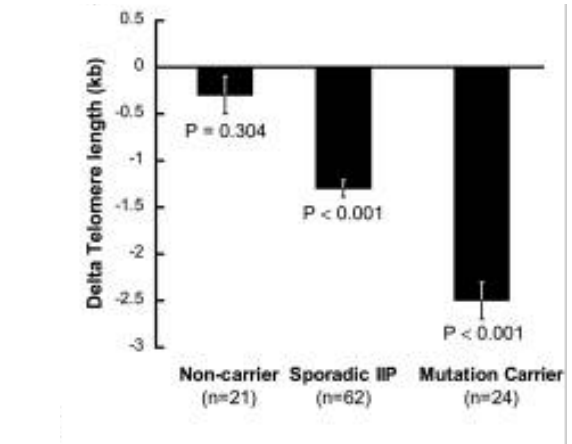
- Short telomeres associated with:
- Early graying of hair
  - Significant before age 30
- Bone marrow failure
  - “aplastic anemia”
- Liver fibrosis for no clear reason
  - Cryptogenic fibrosis

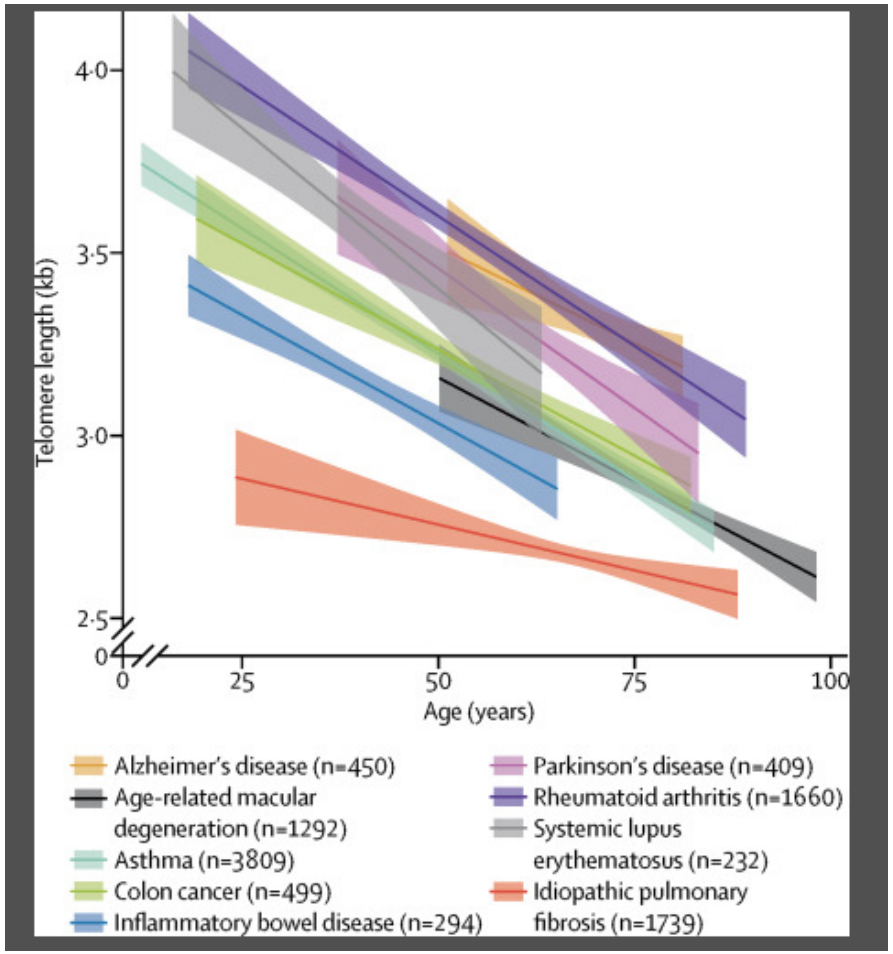


Diaz de Leon A..Christine K Garcia. (2010). PLoS ONE

Short telomeres in pulmonary fibrosis



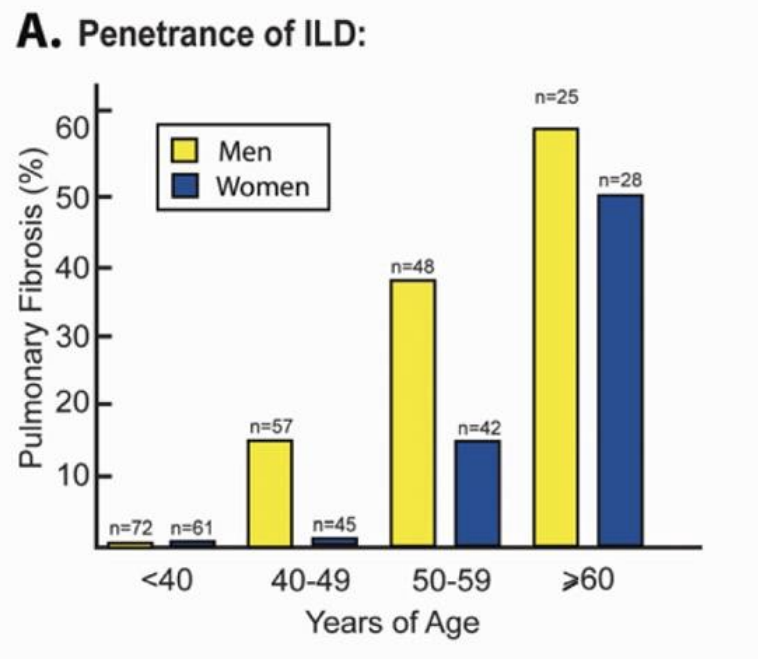




Dressen…Yaspan, Lancet Respir Med. 2018 Aug;6(8):603-614

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



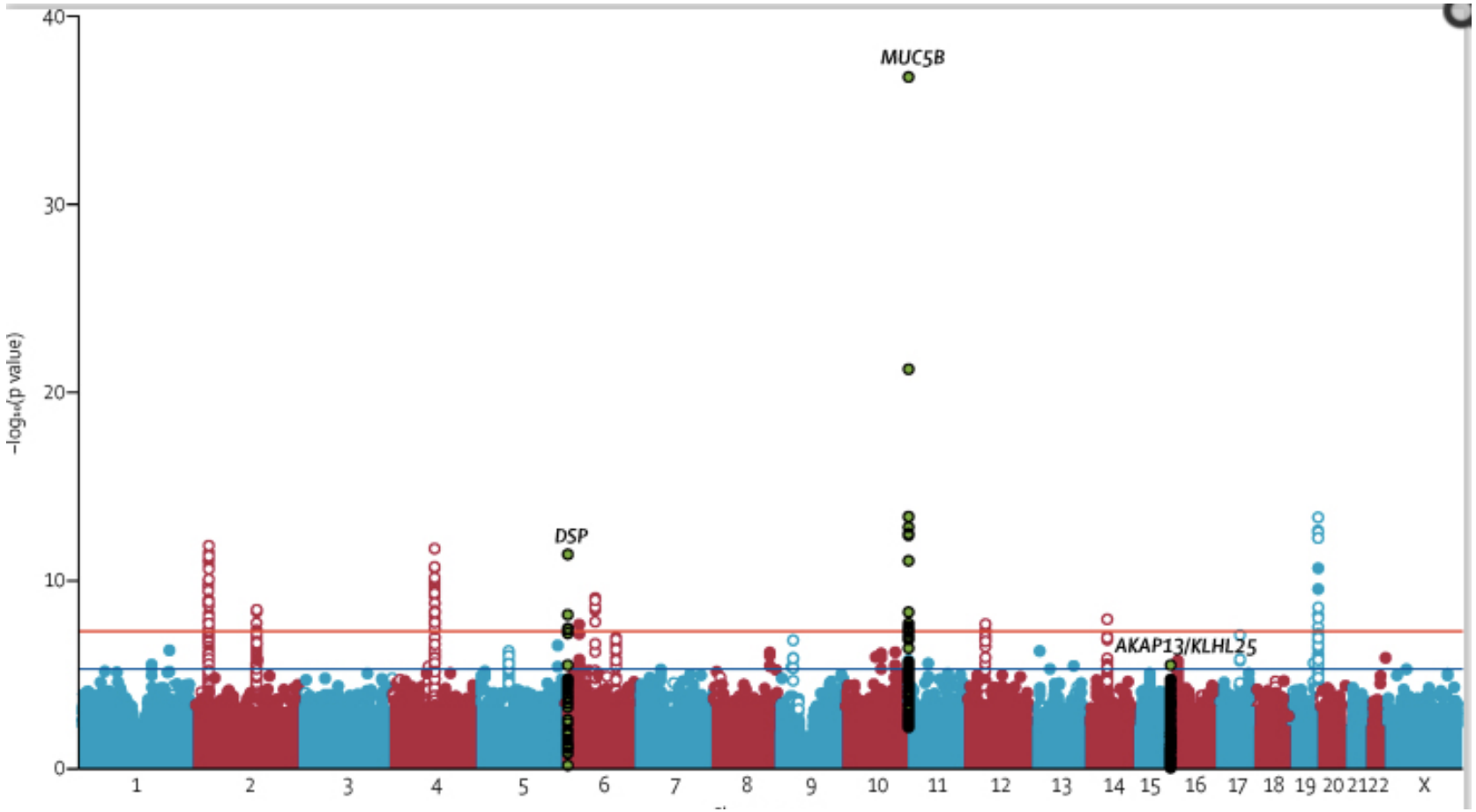
- Testing sporadic IPF patients with very short telomeres found a few new mutations (<5%)

Diaz de Leon A…CK Garcia PLoS ONE. 2010;

Devine & Gracia Clin Chest Med. 2012 Mar; 33(1): 95–11

Complex genetic disorders: look at all genes

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



Areas along the chromosome

Allen…Jenkins Lancet Respir Med. 2017 Nov;5(11):869-880.

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

Seibold MA, Wise AL, Speer MC, et al. N Engl J Med 2011; 364: 1503–1512
Fingerlin et al *Nat Genet 2013; 45: 613–620.*

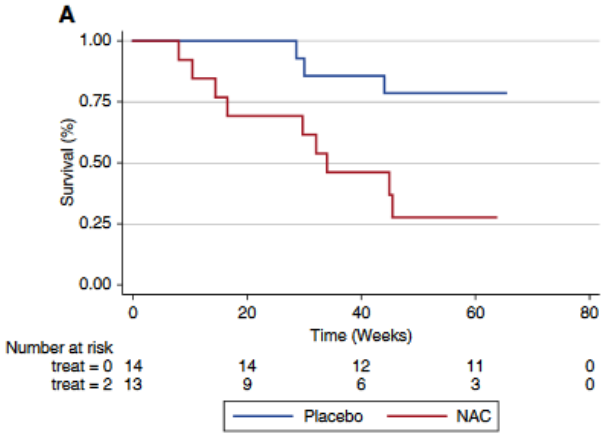
Common, milder variants: *TOLLIP*

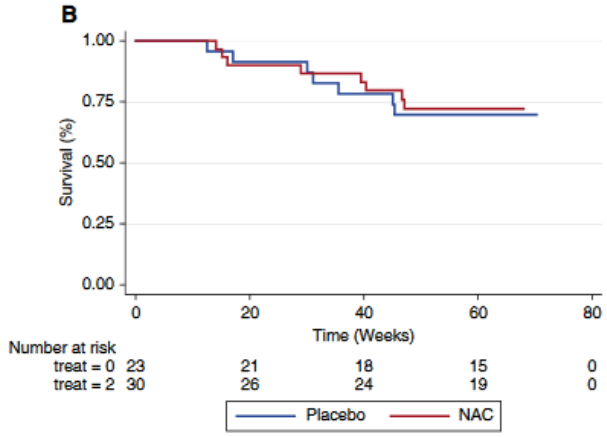
- TOLLIP Toll-interacting protein
- Three variants found with increased frequency in IPF
- One associated with faster progression

Noth et al. Lancet Respir Med. 2013 Jun;1(4):309-317.

TOLLIP may change response to therapy

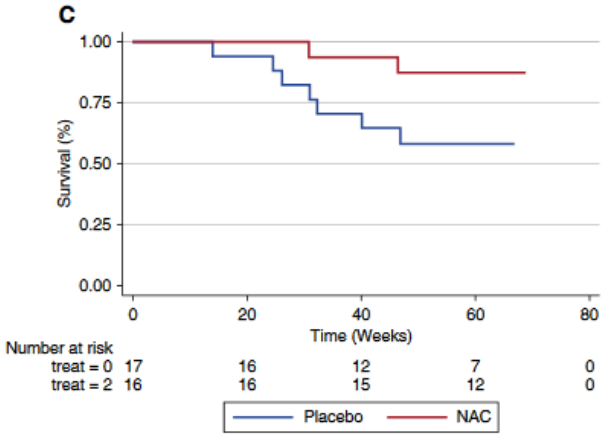
If *TOLLIP* variant "CC"
the drug was HARMFUL





If both
the drug was NEUTRAL

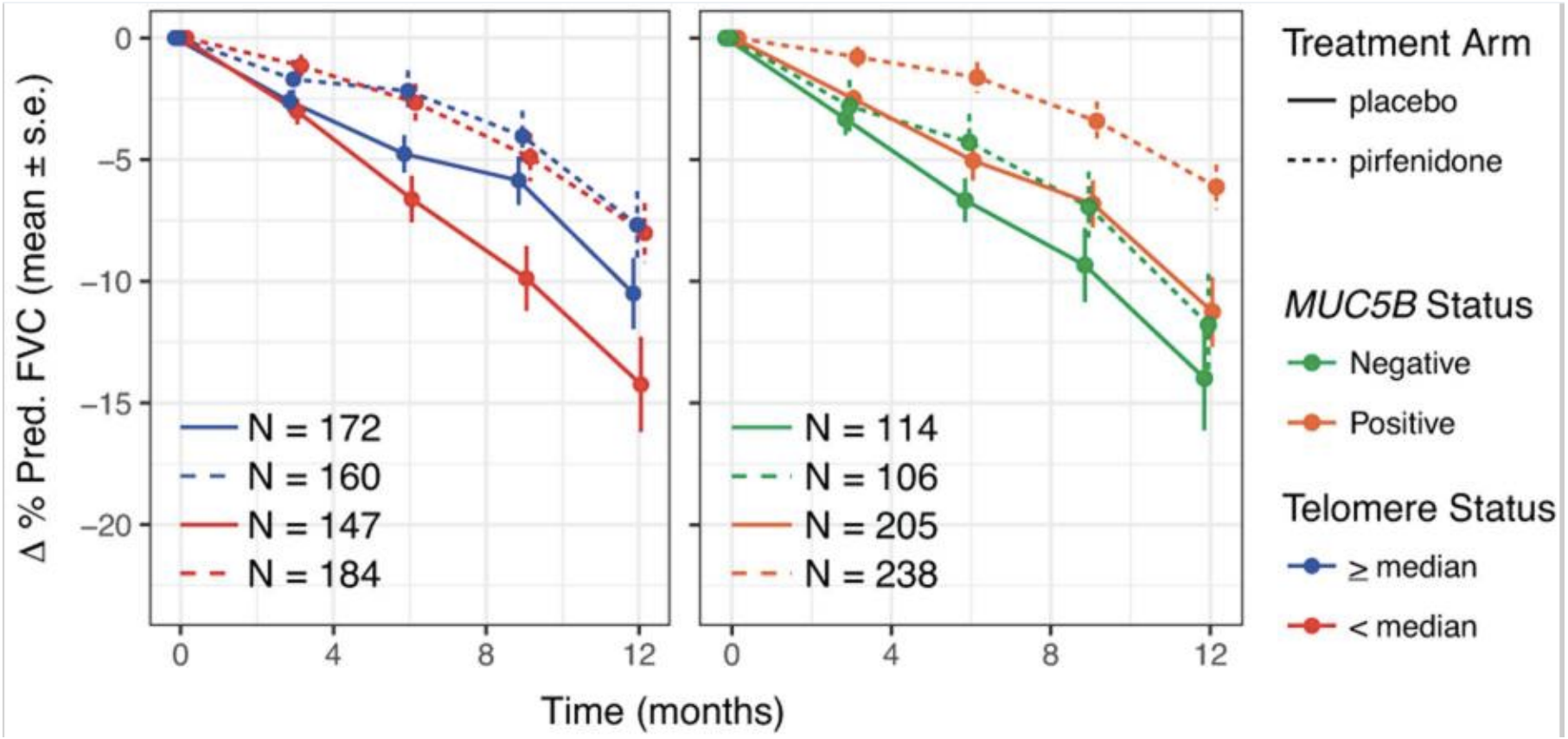
If *TOLLIP* variant "TT"
the drug was HELPFUL



Red = N-acetyl cysteine
Blue = placebo

Oldham et al. *Am J Respir Crit Care Med*. 2015 Dec 15;192(12):1475-82.

Telomeres, *MUC5B* and progression



Dressen…Yaspan, Lancet Respir Med. 2018 Aug;6(8):603-614

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)

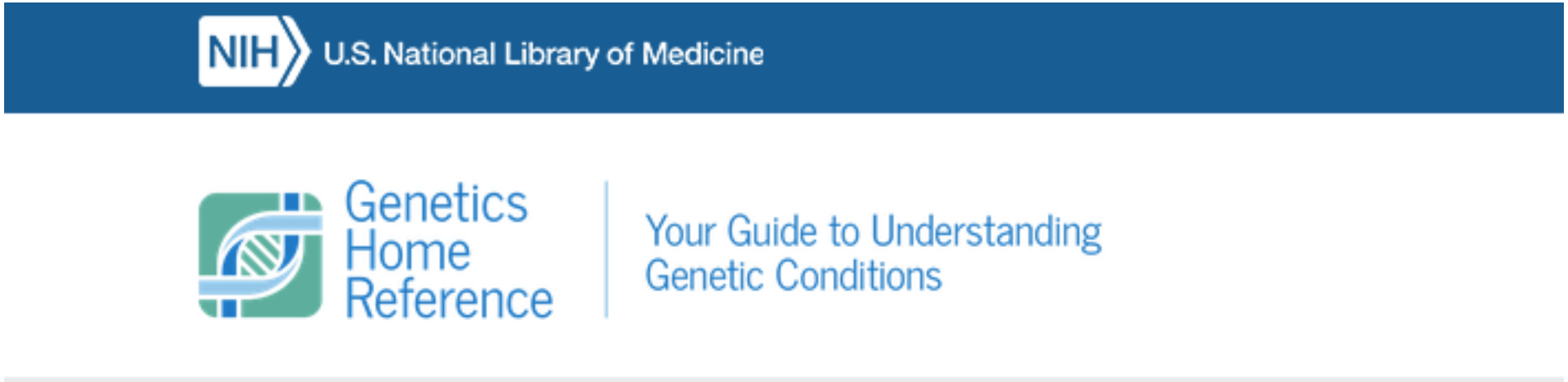
For specific questions: try the familial Pulmonary Fibrosis (FPF) Genetic Counseling Program

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



- https://ghr.nlm.nih.gov/

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