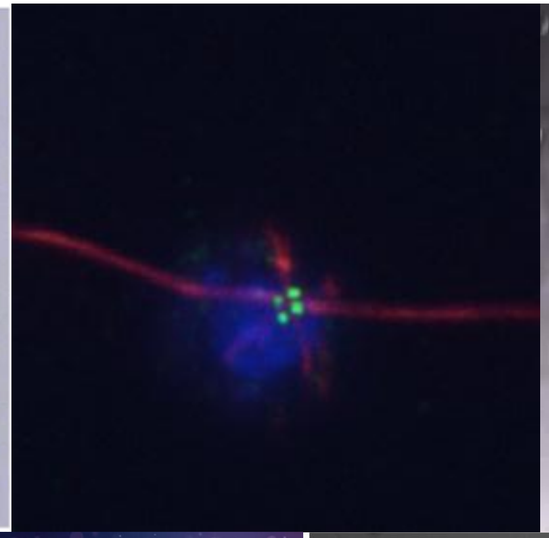
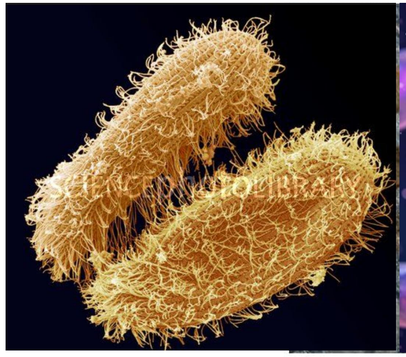
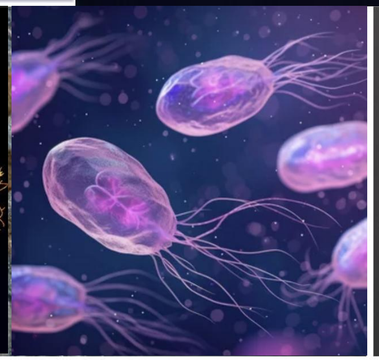
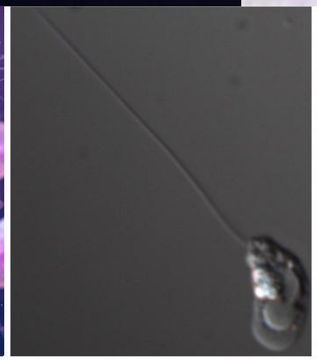
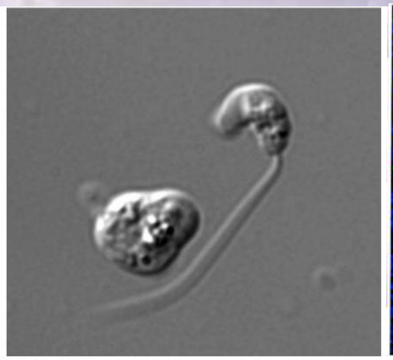
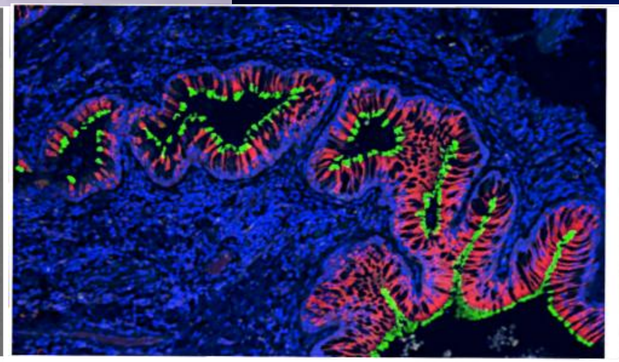
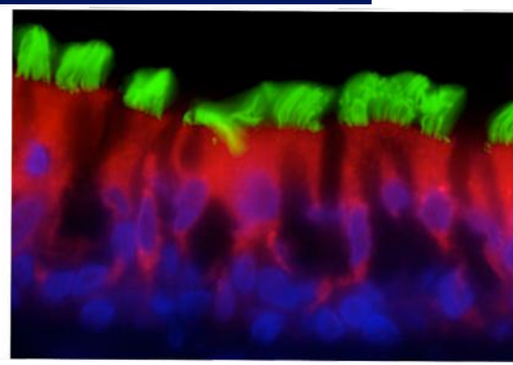
From Pond Scum to Human Disease

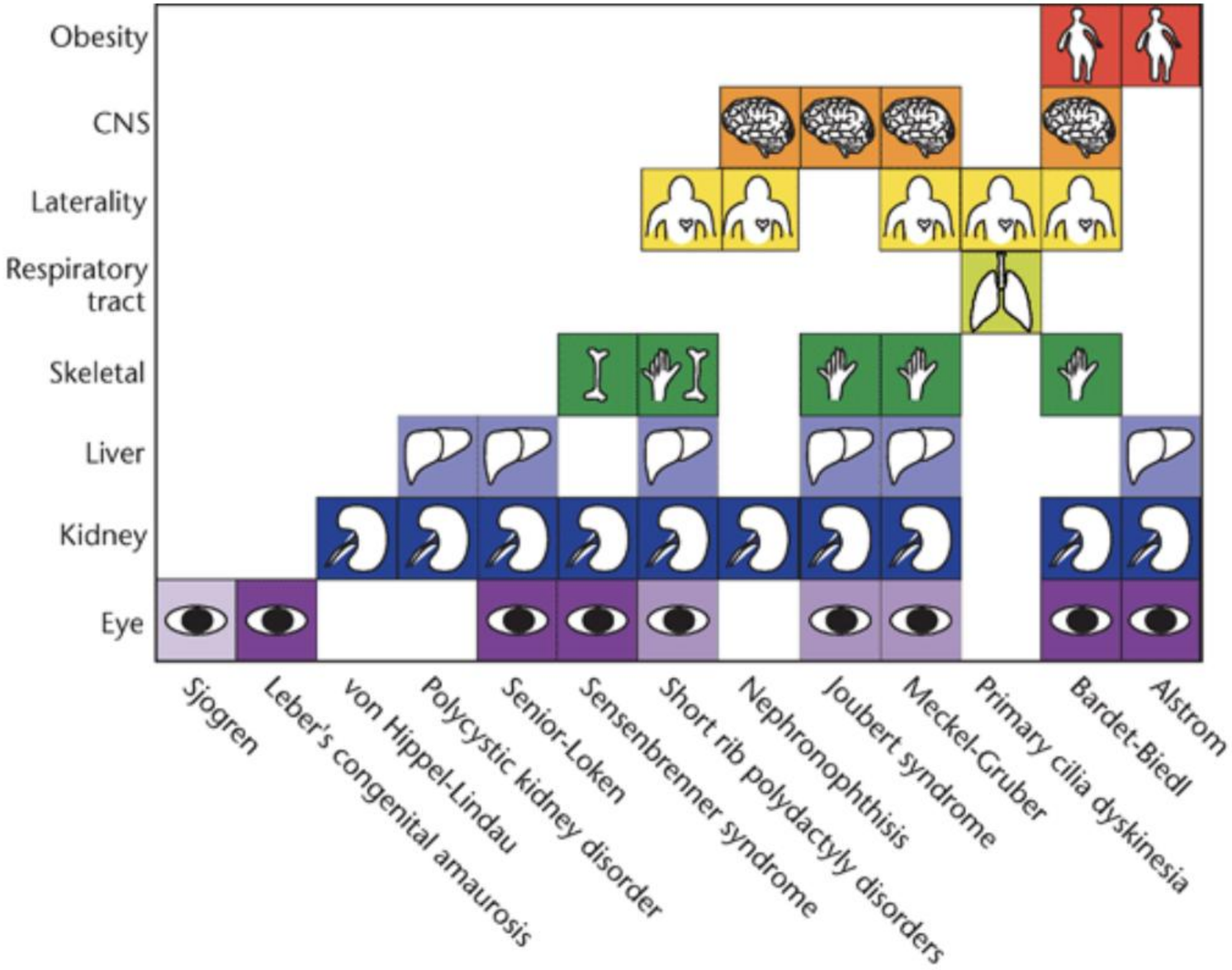








Susan K. Dutcher
Department of Genetics
Washington University School of Medicine

WashU Medicine

From Pond Scum to Human Disease

William Peck, MD.
Dean, Washington University Medical School



Acknowledgements

Washington University Cilia and C

Steve Brody
Adult
Pulmonary

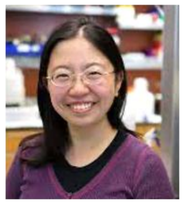
Amjad Horani
Pediatric
Pulmonary

Phil Bayly
Mechanical
Engineering

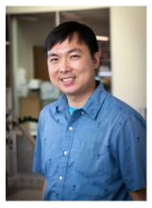
Rui Zhang
Biochemistry

Amber Stratman
Cell Biology

Jenn Strahle
Pediatric
Neurosurgery



Jenn Wang
Biology



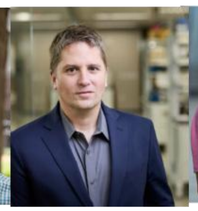
Peter Jin
Genetics

Polina Lishko
Cell Biology

Moe Mahjoub
Nephrology

Phil Williams
Ophthalmology

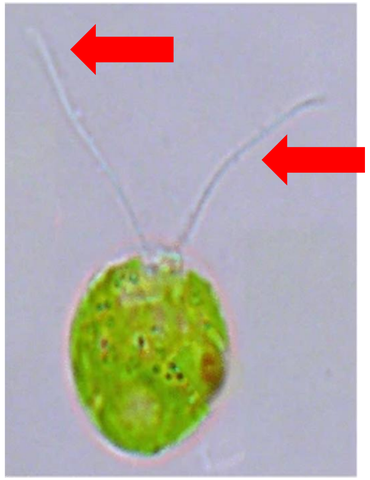
Louis
Woodhams



Ben Major
Cell Biology

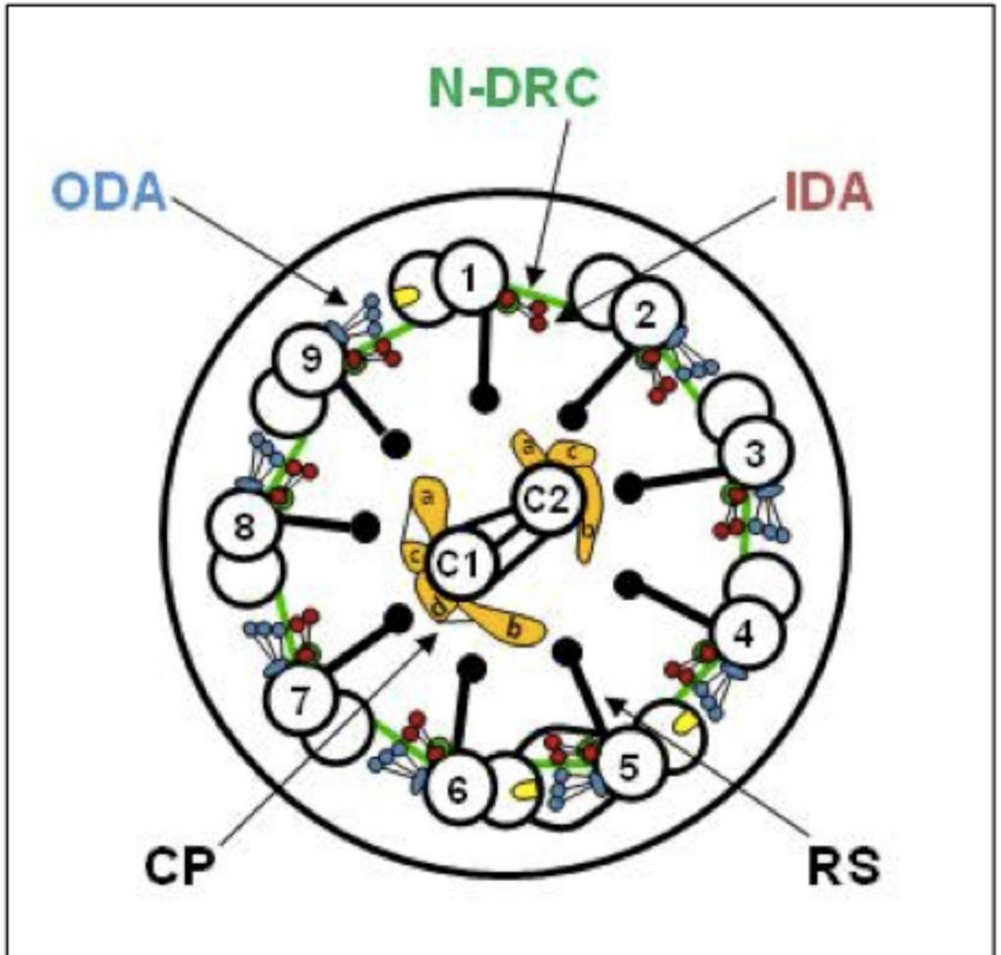
Yao Chen
Neuroscience

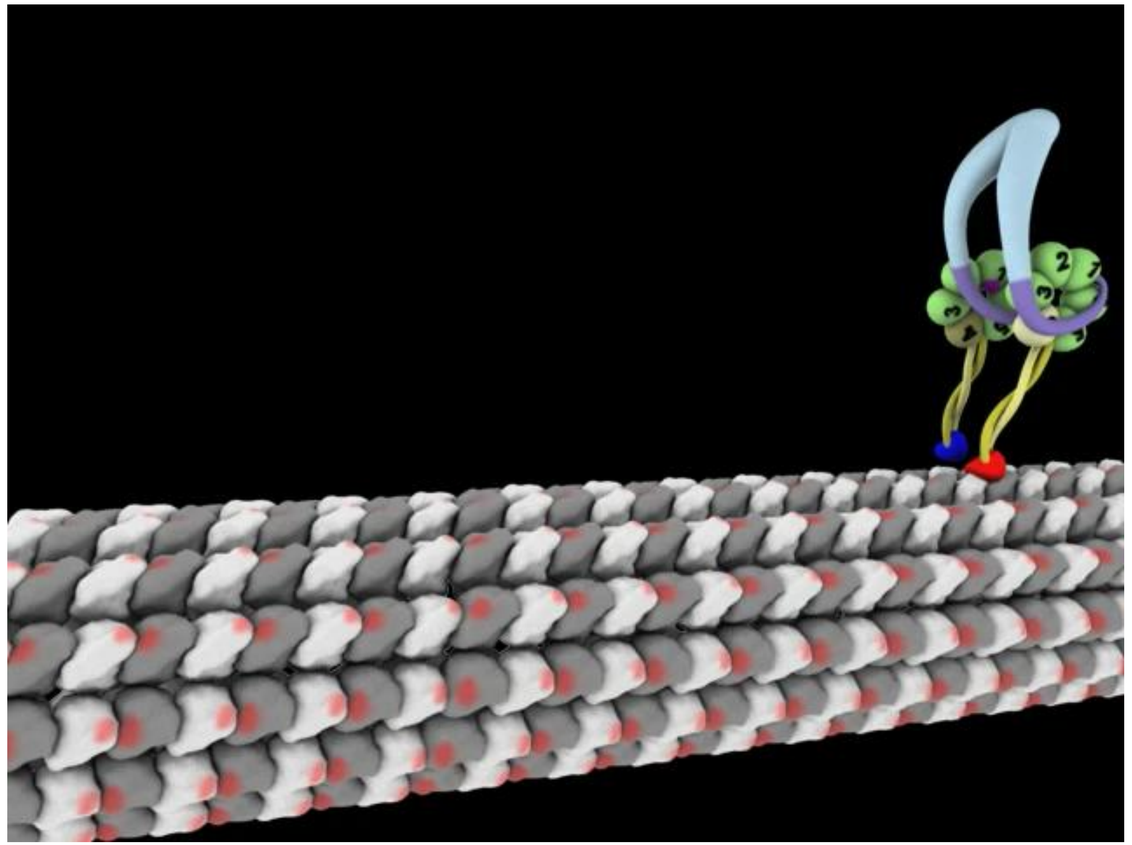
Celia Santi
Ob/Gyn



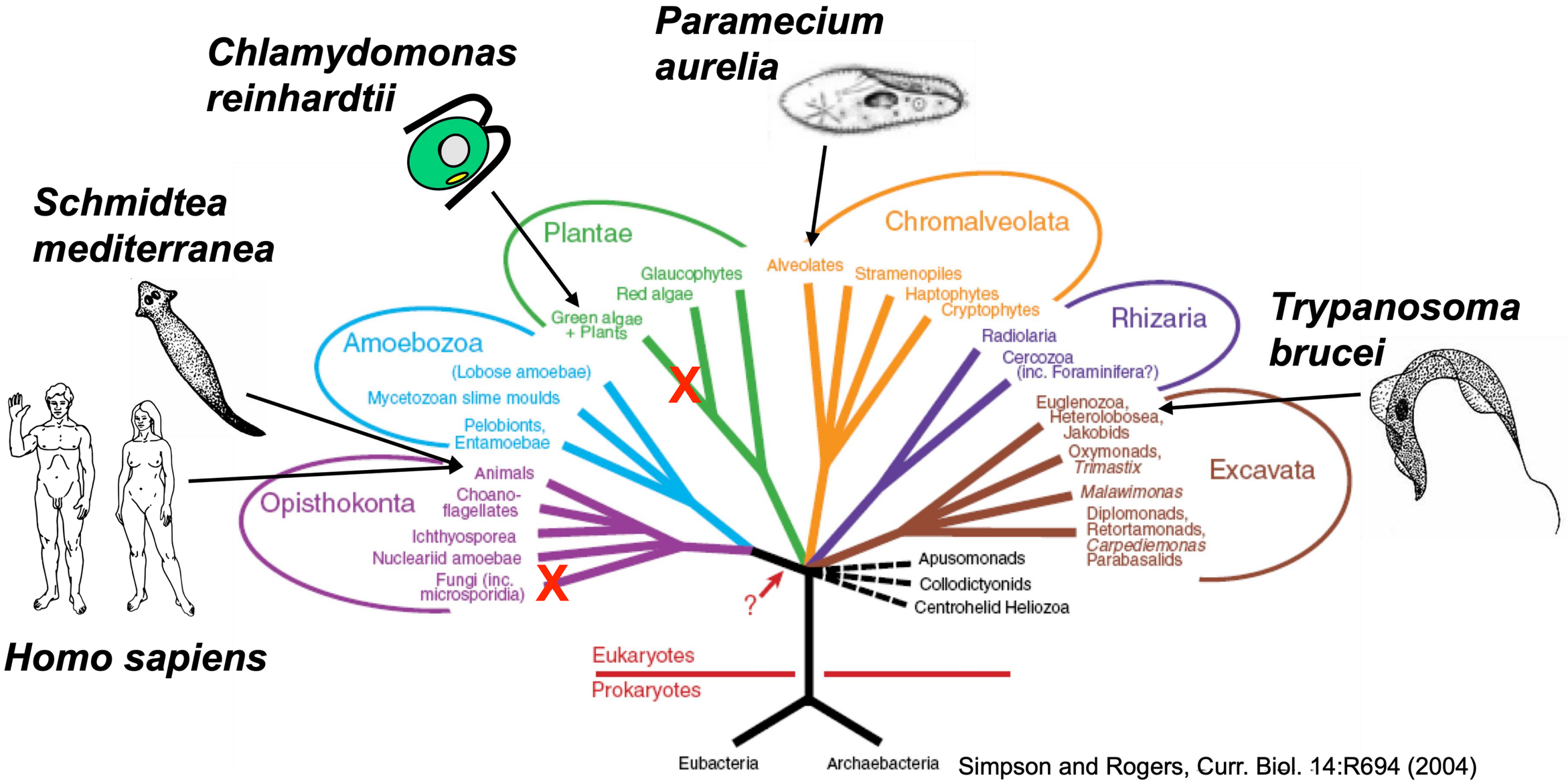
Chlamydomonas

Amherst MA 1942



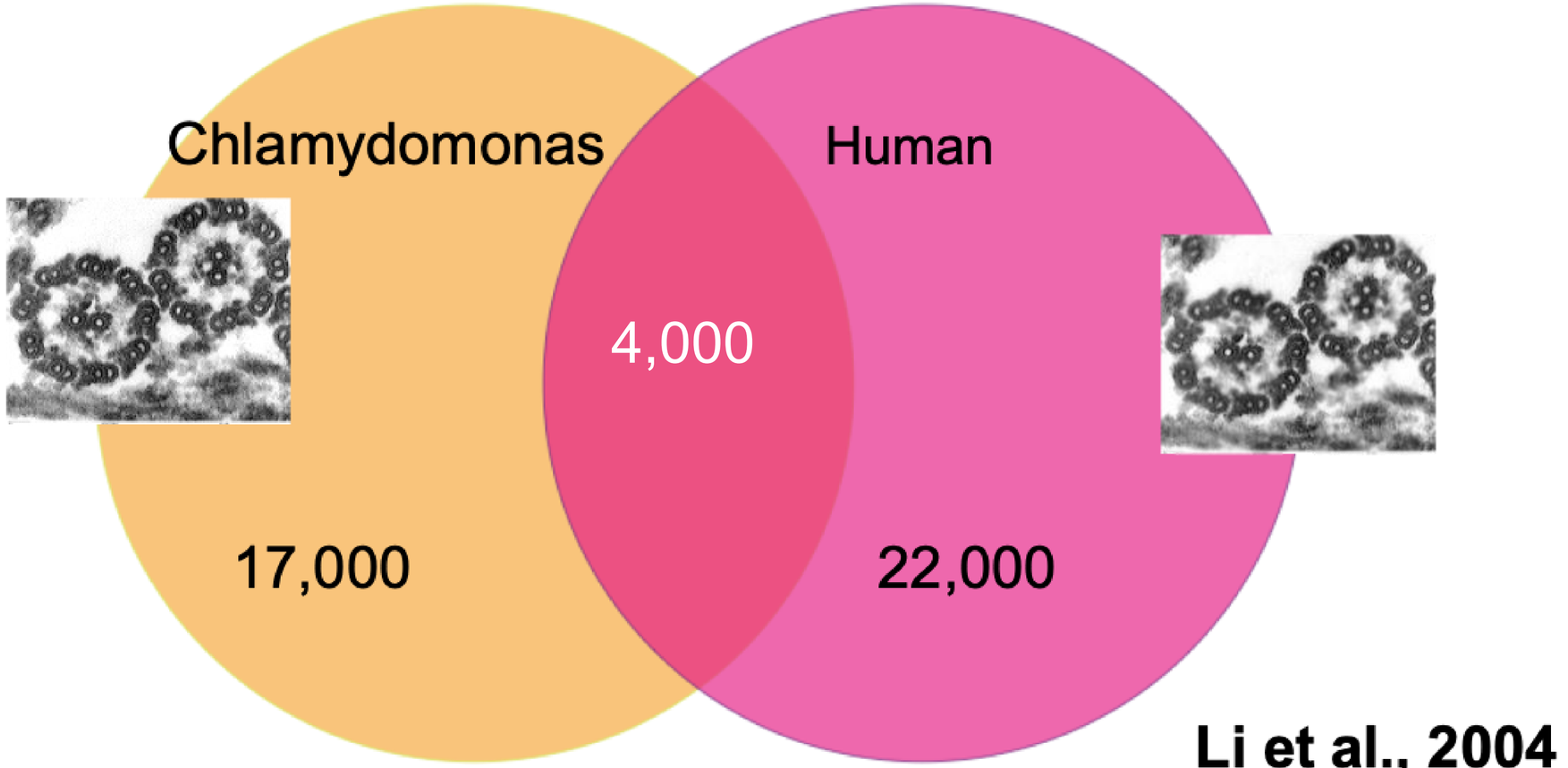


Cilia in Eukaryotes



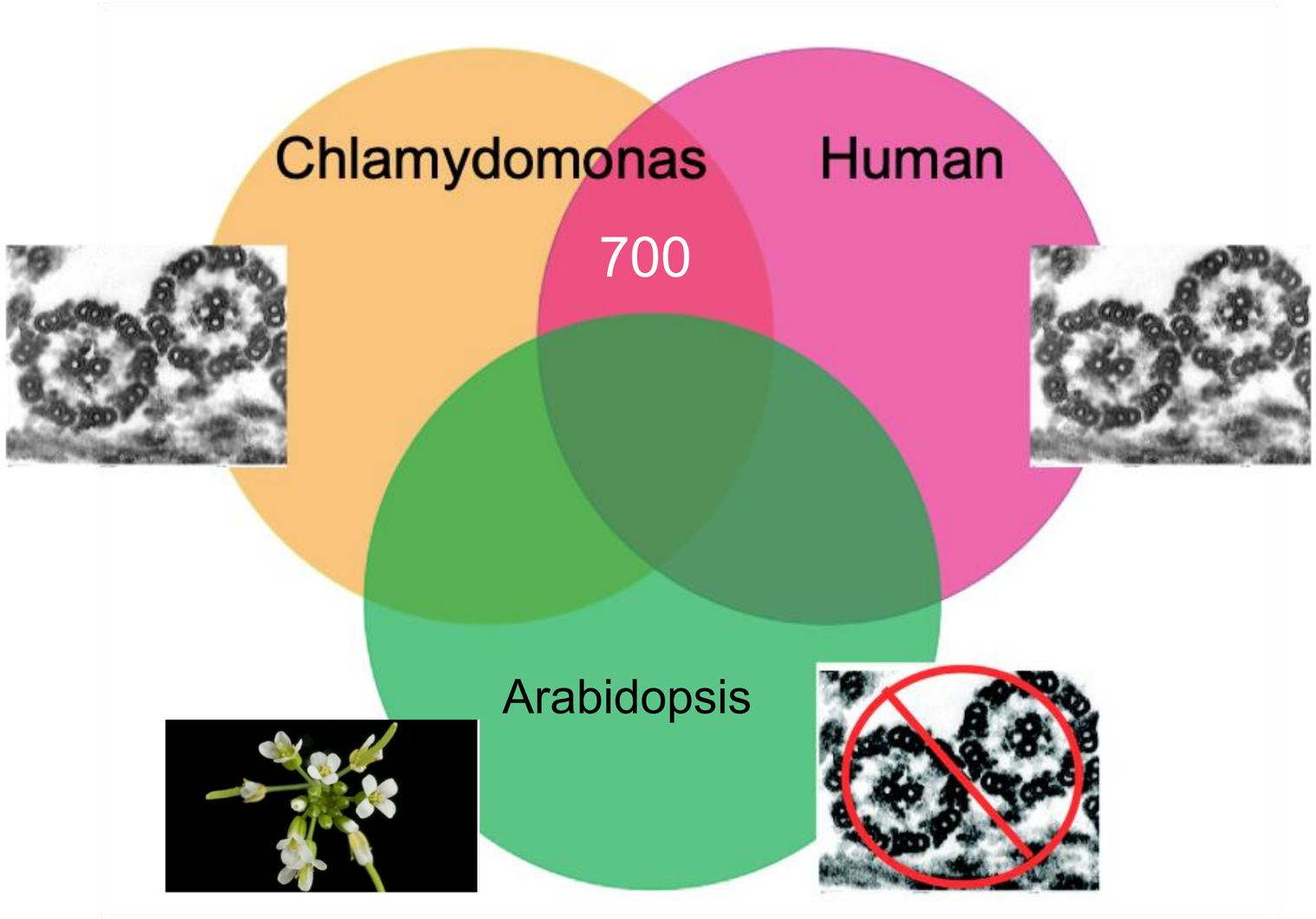
Simpson and Rogers, Curr. Biol. 14:R694 (2004)

Comparative genomics to find genes for cilia

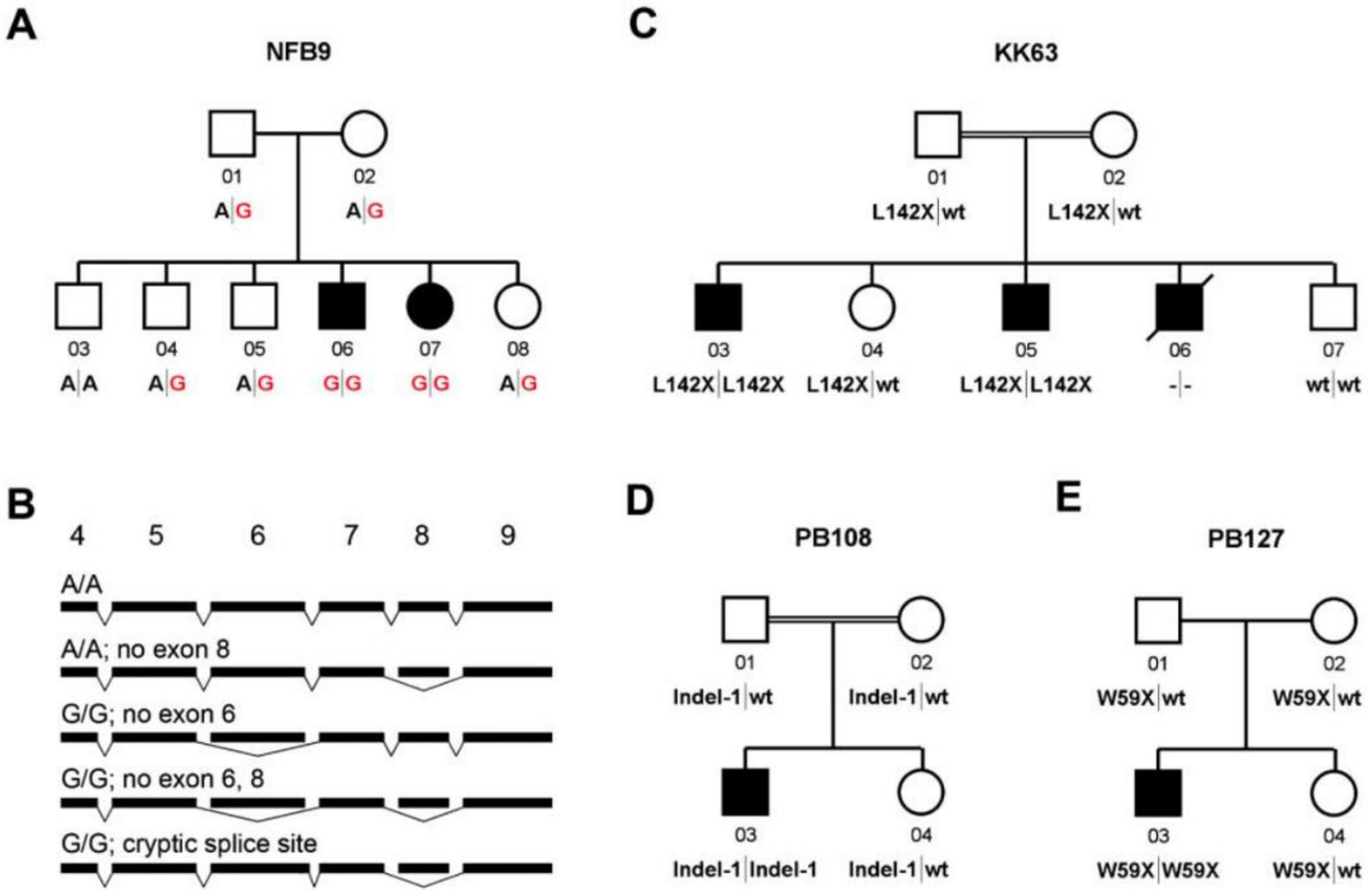


Li et al., 2004

Comparative genomics identifies ~700 proteins that are only in organisms with cilia



Human disease genes (BBS5, MKS1, LRRC6) in the cilia comparative genomics list



Bardel Biedl Syndrome

Central Obesity

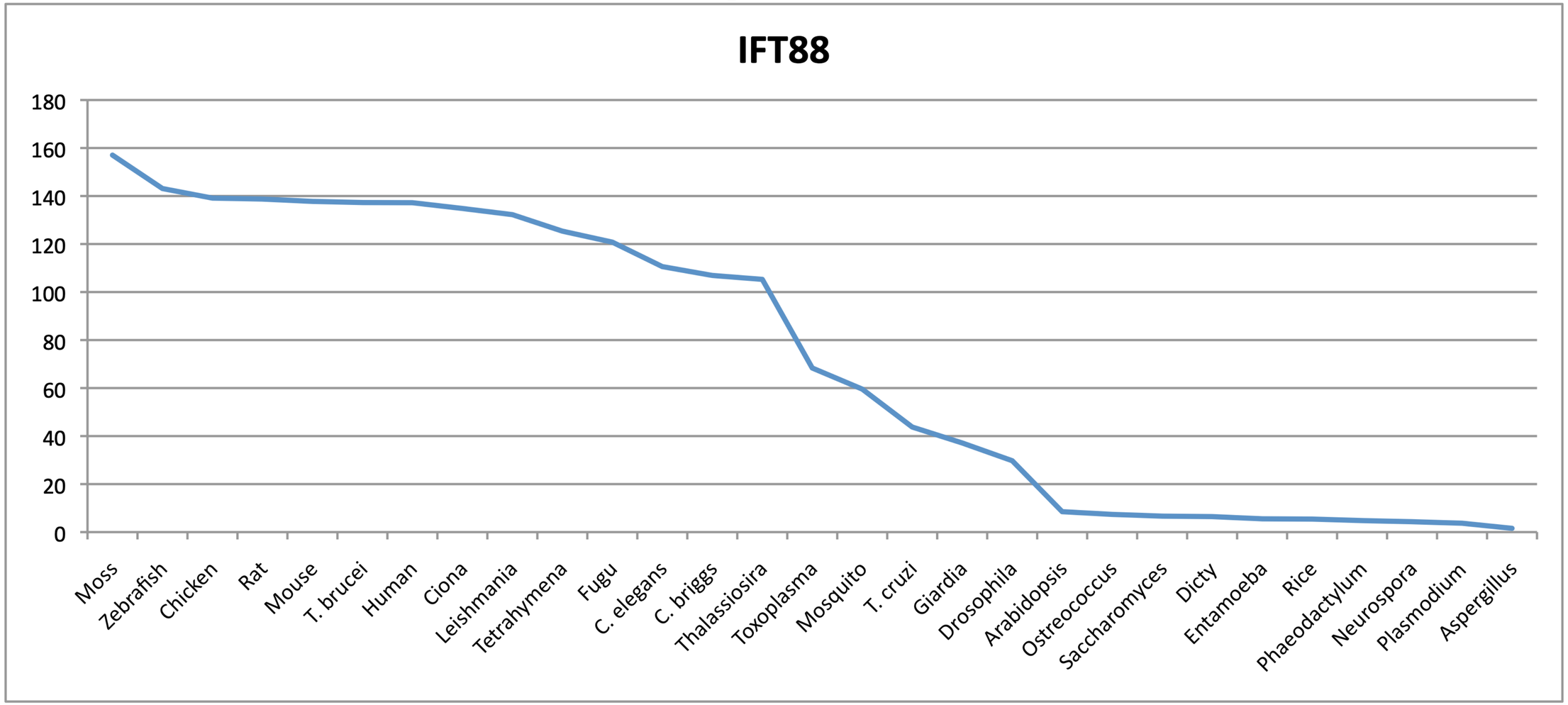
Retinal Degeneration

Kidney Disease

Mental Retardation

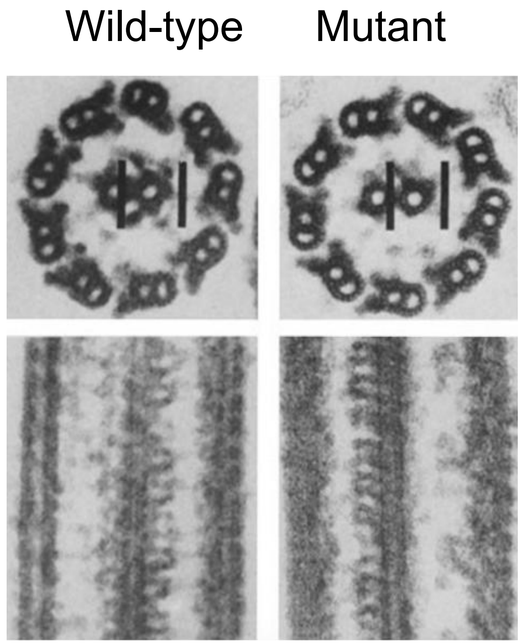
Li et al., 2004
Kyattala et al., 2013
Horani et al., 2013

Many proteins show this cilia-specific pattern over 40 species

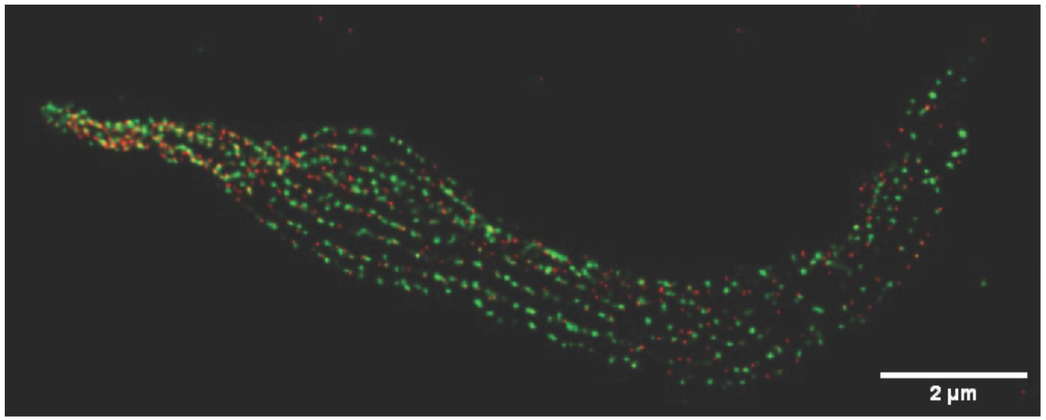


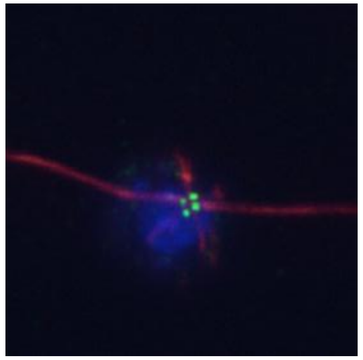
Kwan, Stormo, and Dutcher 2010

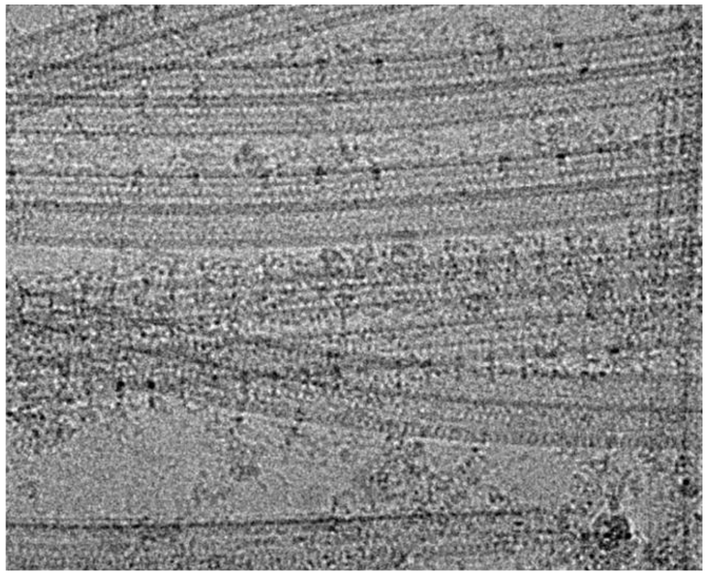
Changing Technologies:
Single particle cyro-electron microscopy



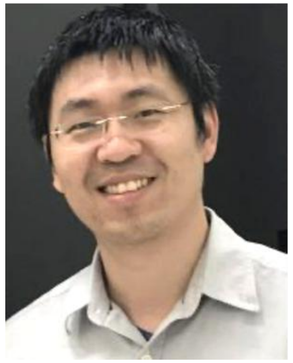
Dutcher et al., 1984





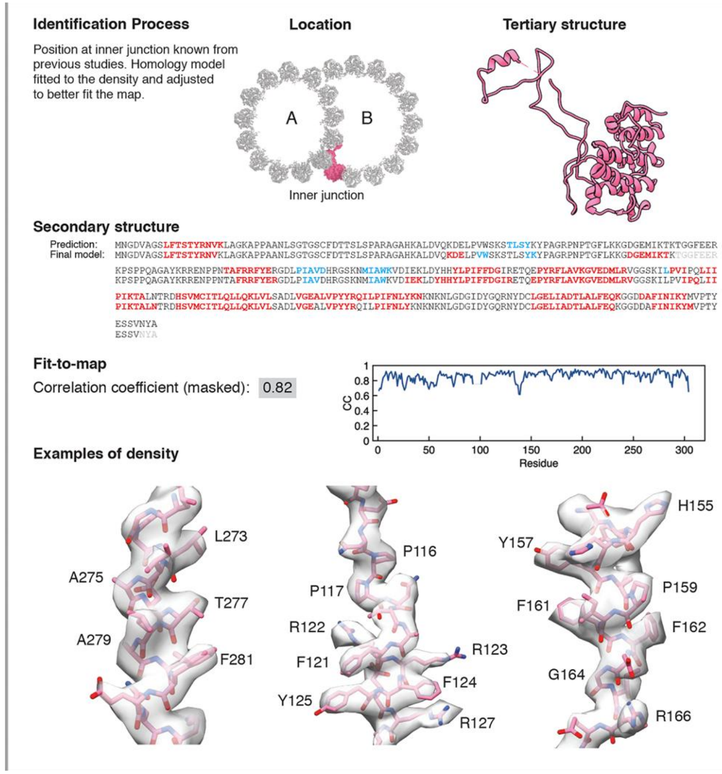


Ma *et al*., 2019

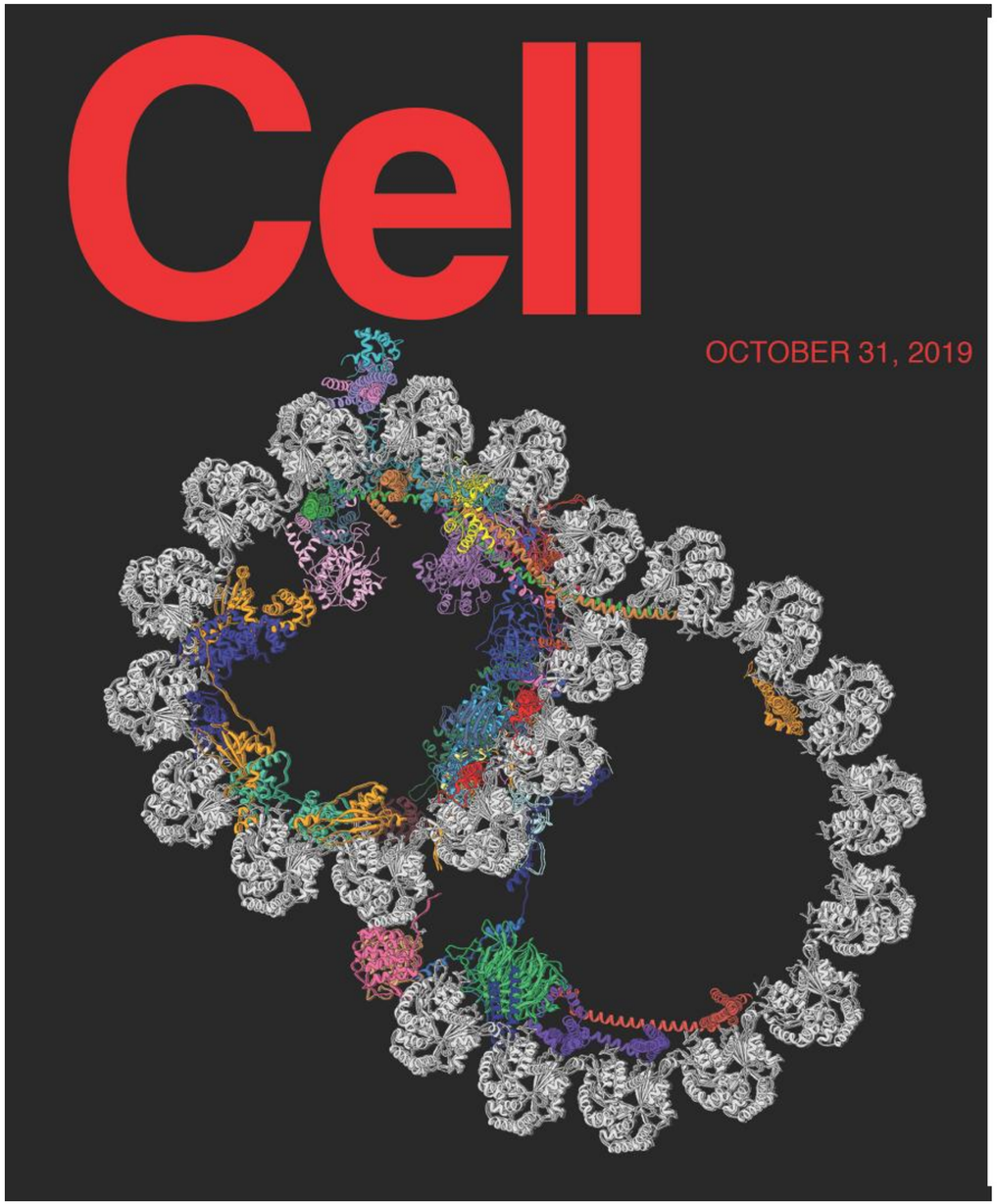


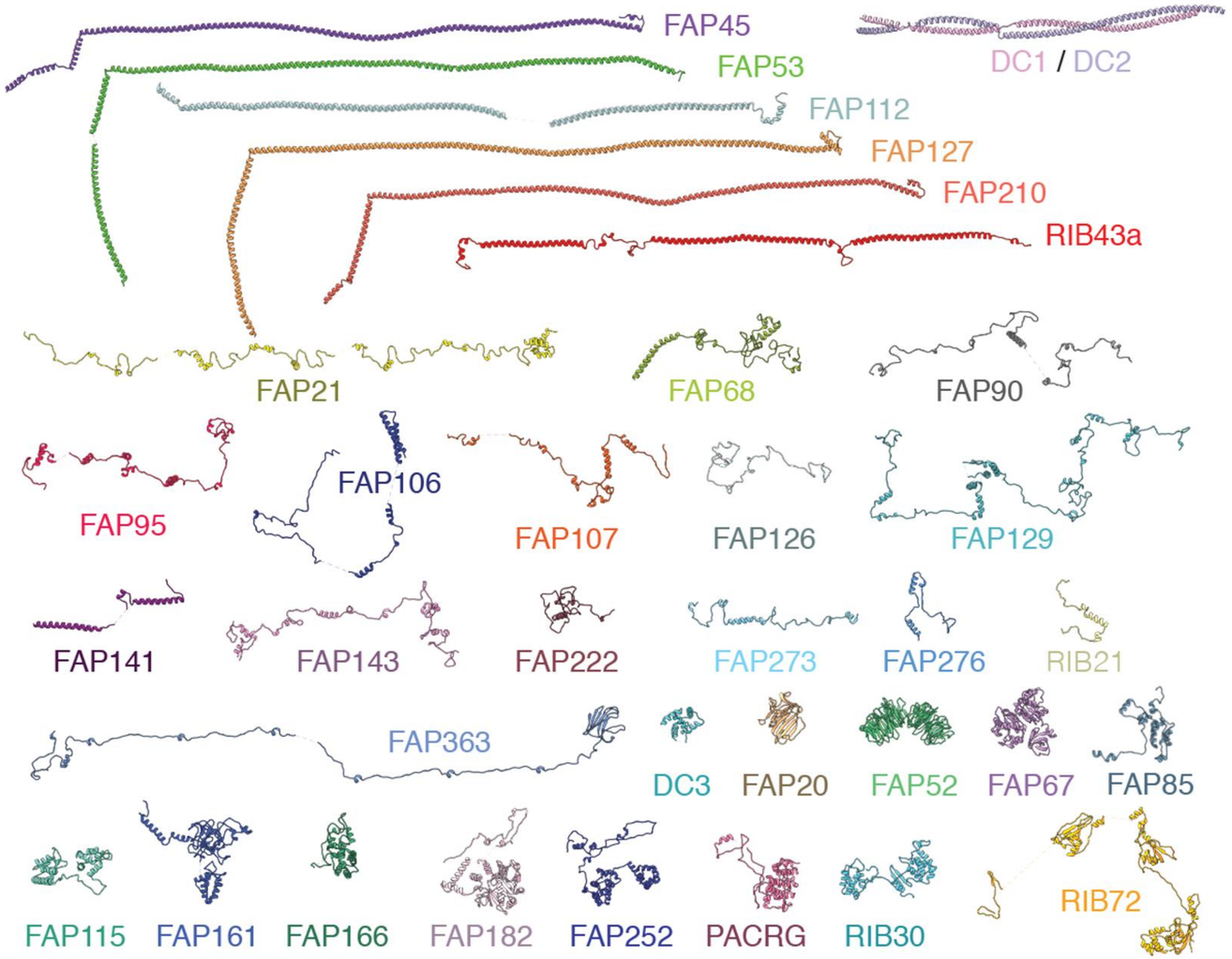
Rui Zhang

Biochemistry and Molecular Biophysics, Wash U

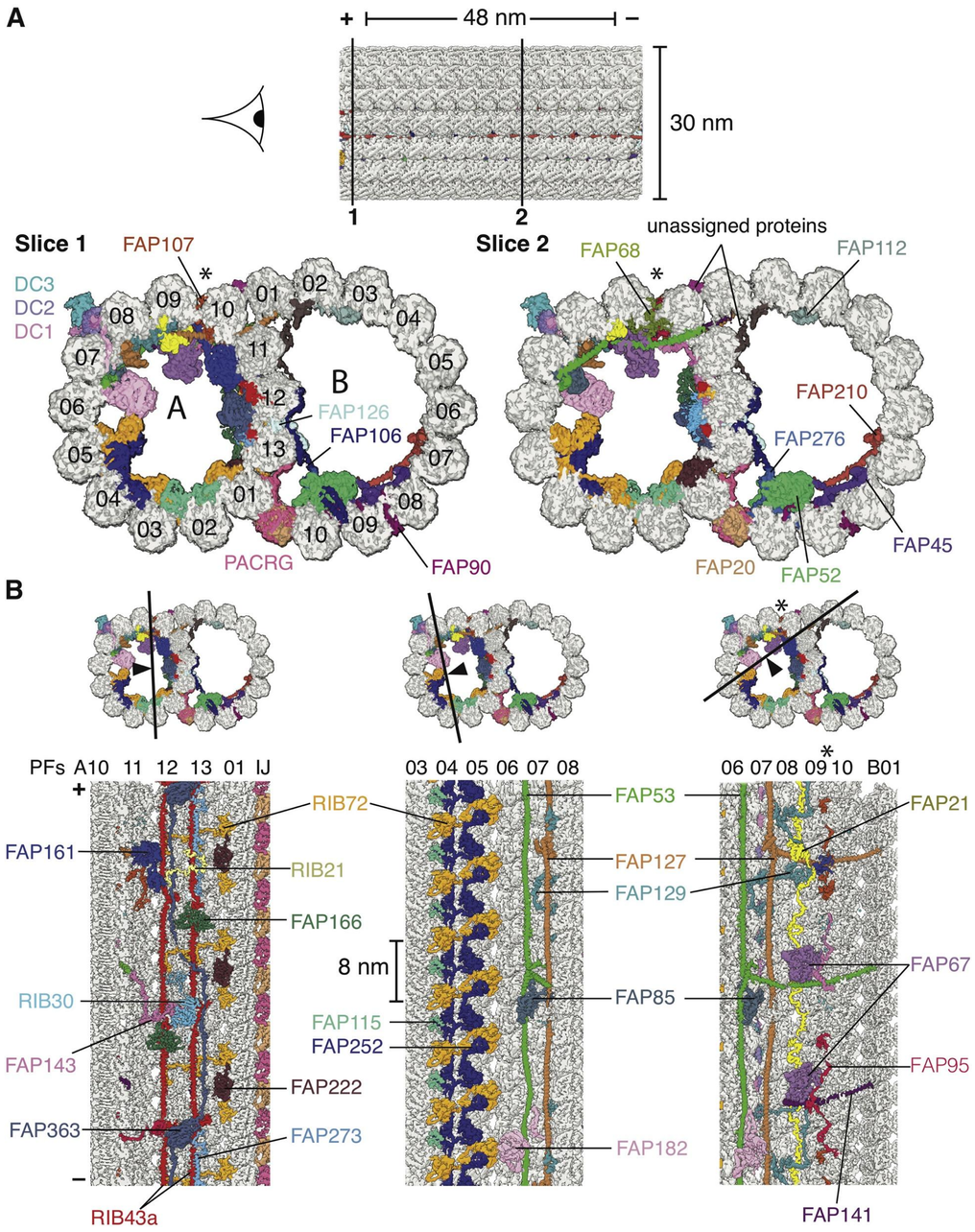


Microtubule Inner Proteins

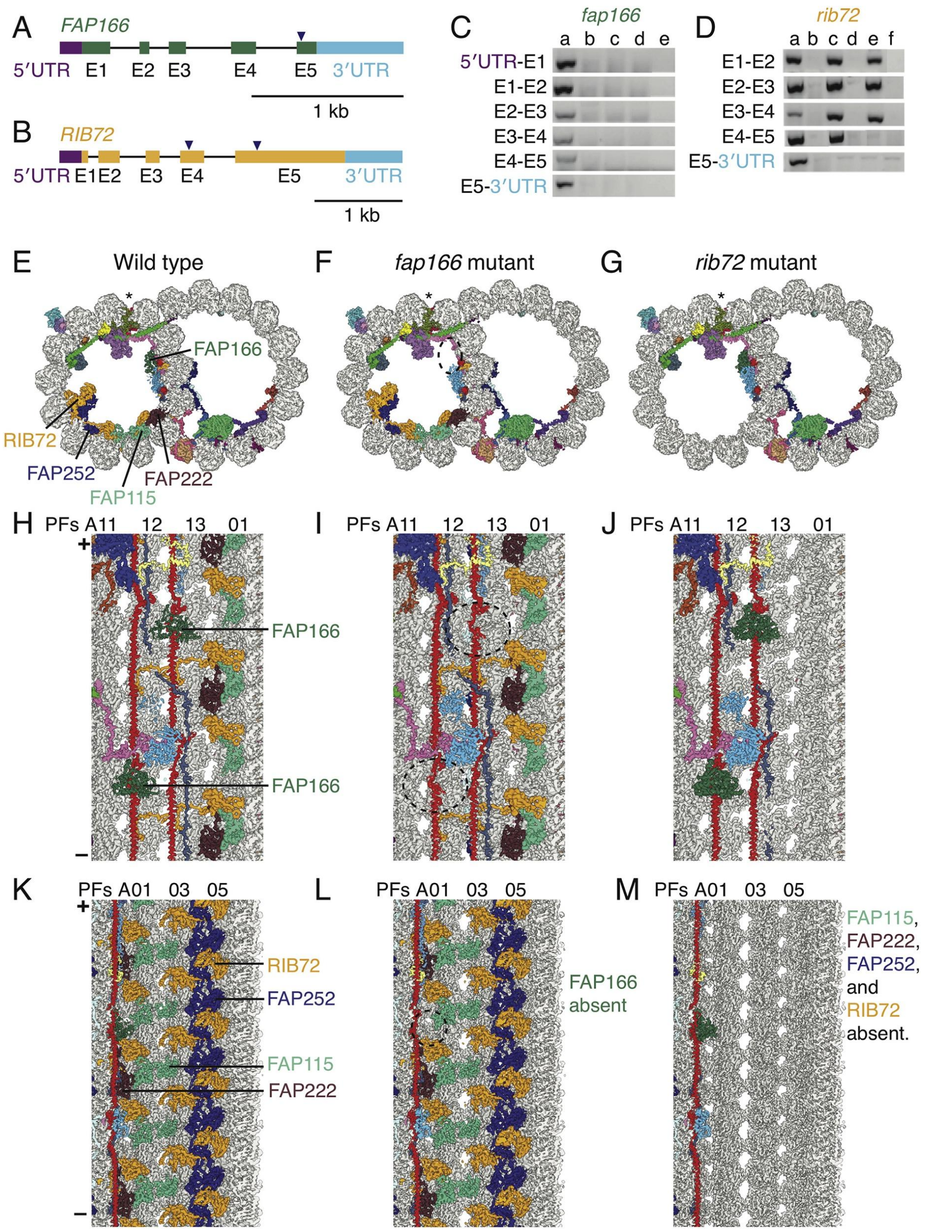


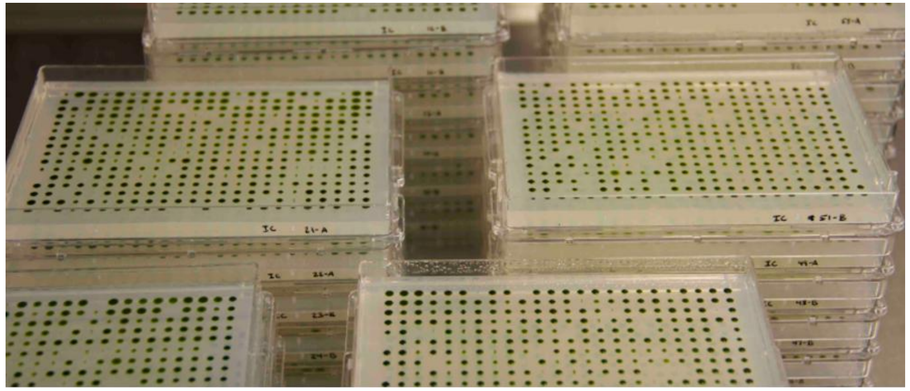


Microtubule Inner Proteins —-MIPS



Mutants in *MIP* genes



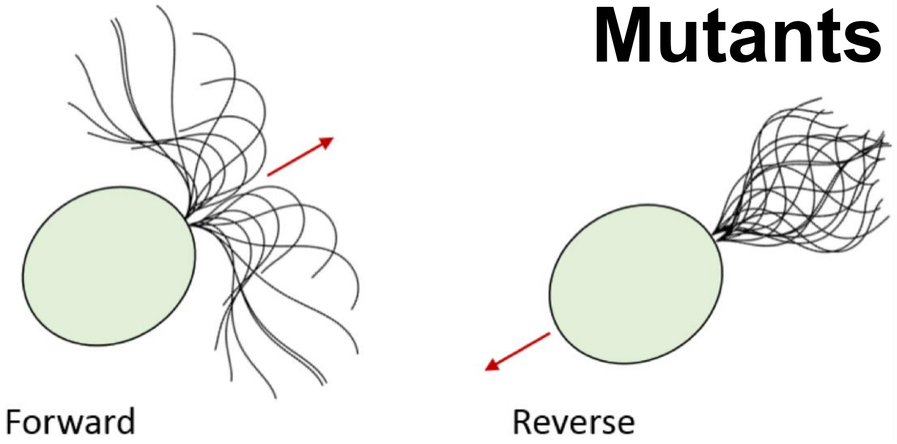


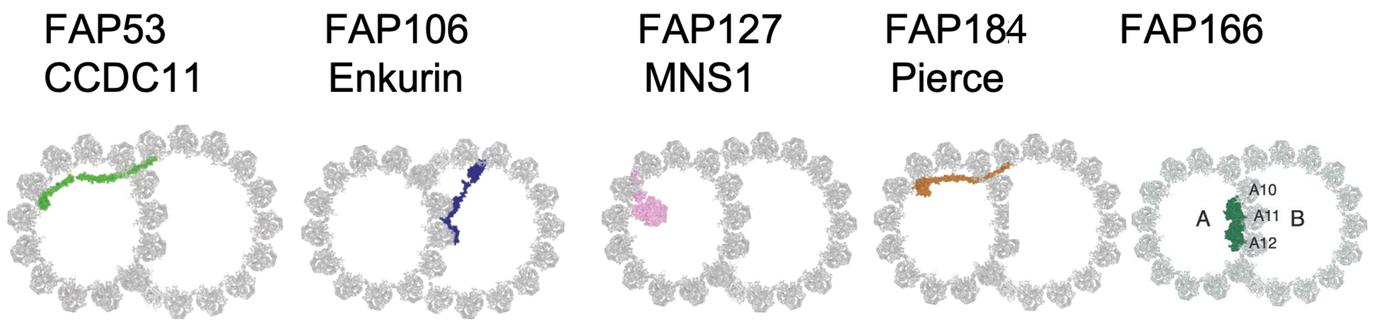
The *fap166* mutant is missing only one protein: FAP166

The *rib72* mutant is missing four proteins: RIB72, FAP115, FAP222, and FAP252

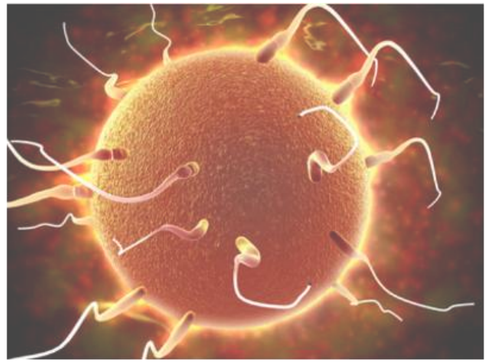
Ma et al., 2019
Li et al., 2018

Mutants in Microtubule Inner Proteins

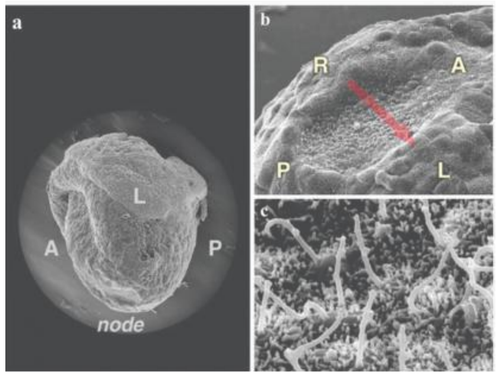




Genotype	Low Light	Hight Light
Wild-type	**Swim (WT)**	**Reverse Swimming**
fap53	**Swim (WT)**	**Immotile**
fap106	**Swim (WT)**	**Immotile**
fap127	**Swim (WT)**	**Immotile**
fap184	**Swim (WT)**	**Immotile**
fap166	**Swim (WT)**	**Slow Reverse Swimming**



- Sperm



- The node

The study of human biology as discussed in Nature, News and Views, 1986

The proper study of mankind

Molecular biology has made the human genome accessible to laboratory investigation. But does that mean that the sequence of the human genome would be worth the effort?

THERE is no scientific reason for studying man. Thus one of the 120 speakers at this year's Cold Spring Harbor Symposium on the molecular biology of *Homo sapiens* from 28 May to 4 June. The issue arises because, as the programme was designed to demonstrate, there are now few fundamental questions in biology that cannot be explored using human genes and human cells.

This in itself is scarcely sufficient reason for overlooking the rather obvious shortcomings of man as an object of investigation. But there is one reason, just the same: the human species alone preserves its rare defective variants. Mouse mothers, whose matings are manipulable and whose generation times are manage-

and Goldstein have built up a picture of the cellular and, more recently, the molecular biology of receptor-mediated endocytosis which has provided fundamental insights into these processes as well as clarifying the mechanism of atherosclerosis.

This has been possible only because Brown and Goldstein worked up to the molecular biology from classical genetics via biochemistry. More characteristic of latter-day triumphs were the papers presented by Louis Kunkel (Boston Children's Hospital) and Stuart Orkin (Harvard Medical School), both published in this issue of *Nature* (pp 73 and 32). They have arrived directly at the genes responsible for two human genetic diseases without engaging with the intervening bio-

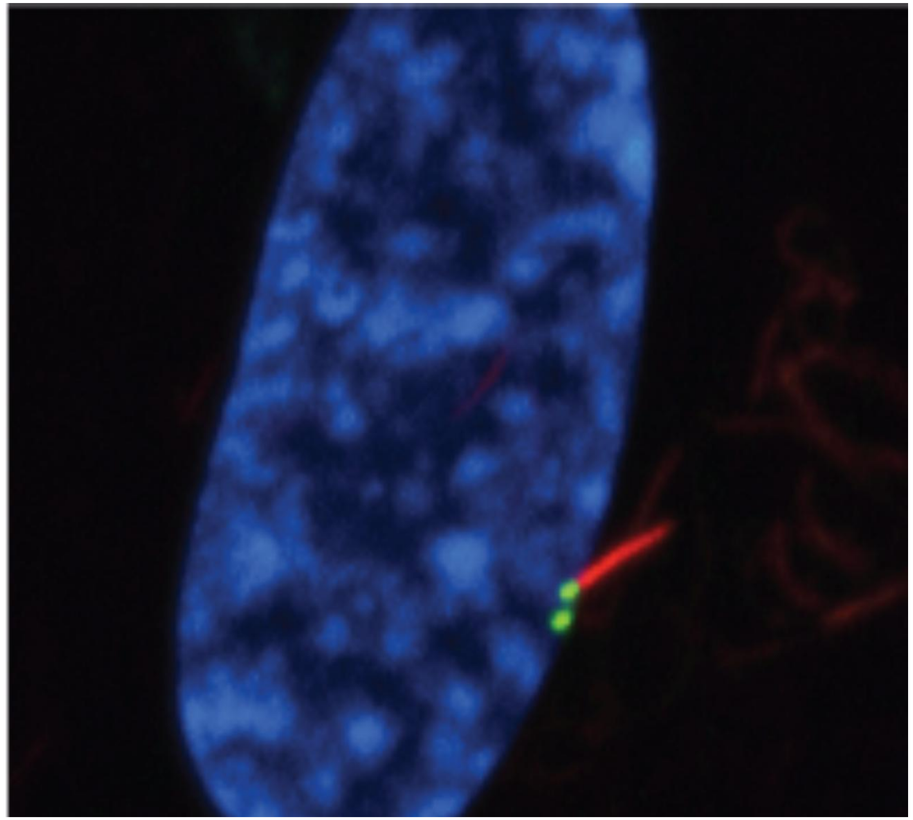
may require some ingenuity, as well as some biochemistry, to discover.

The substantial challenge now facing Orkin and Kunkel and their collaborators is in no sense a reflection on the quality of the work or the validity of their approach. But it is an inevitable consequence of approaching the DNA directly, and thus has a direct bearing on the desirability of sequencing the rest of the human genome.

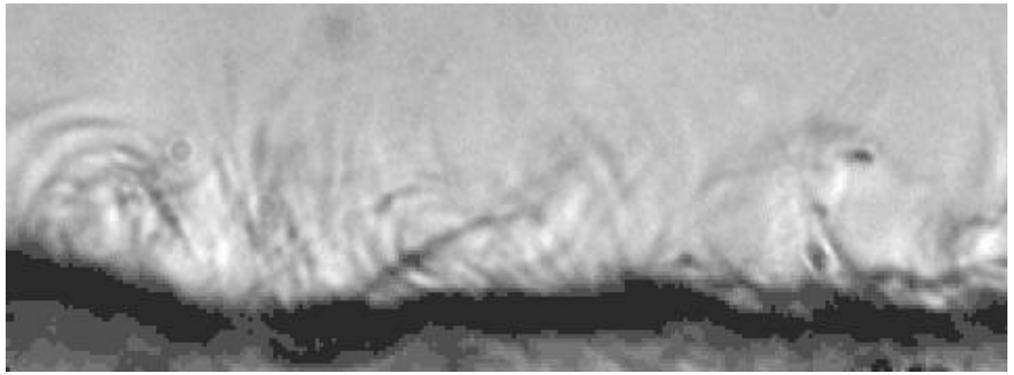
In the discussion on that topic at the symposium, Paul Berg (Stanford) set out the issues — is it feasible, who will pay and is it worth it? Walter Gilbert (Harvard) seraphically chalked up the tally — three thousand million bases at 10^5 bases per year equals 30,000 person-years or, at the current rate of 2×10^6 bases per year, but

The human species preserves its rare variants

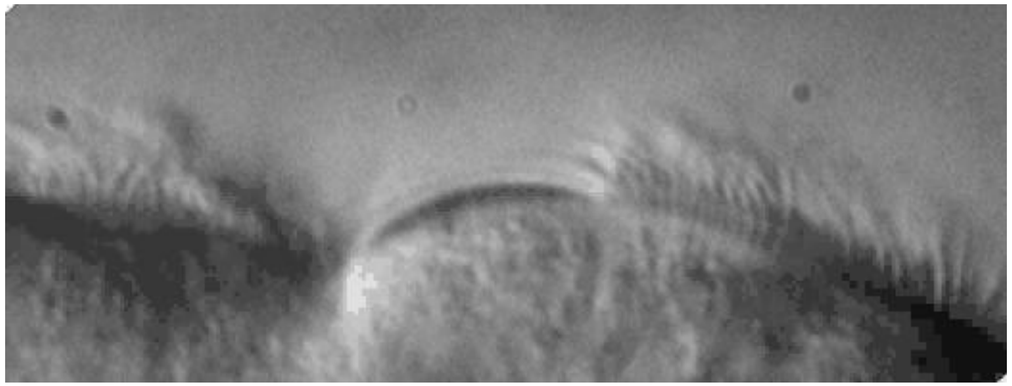
Two Types of Mammalian Cilia



Alison Albee



Mouse Ependymal Cilia

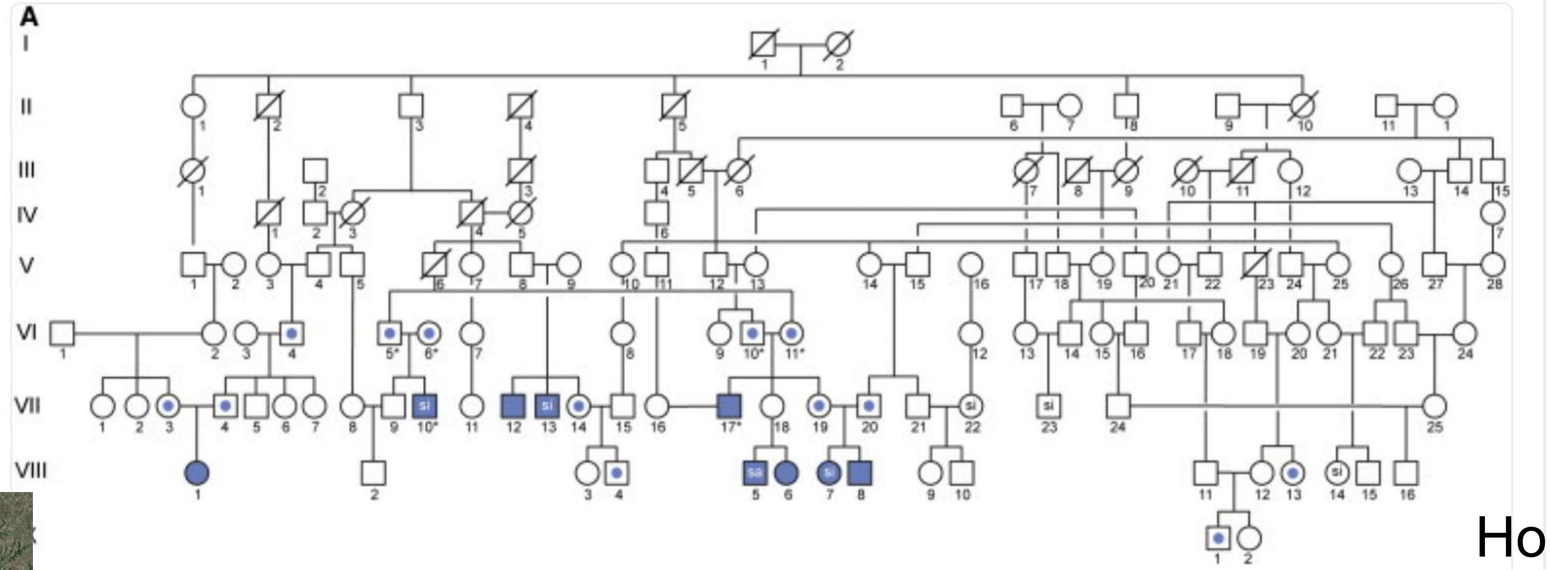


Mouse Tracheal Cilia
Karl Lecktreck

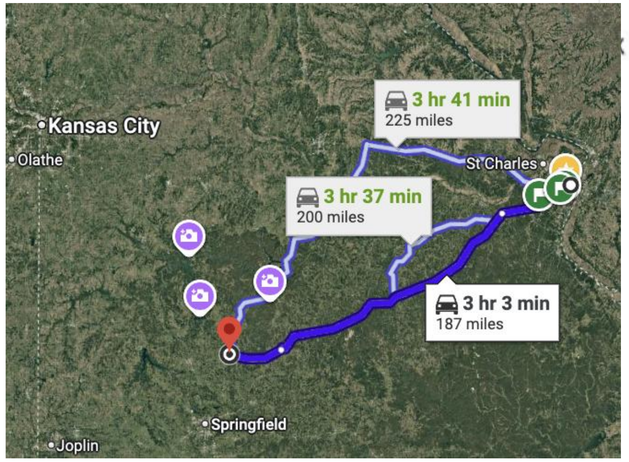
Sensory Cilia

Motile Cilia

Primary Ciliary Dyskinesia (PCD)



Horani et al., 2013



- Respiratory distress
- Laterality/CHD
- Nasal obstruction
- Pneumonia

- Chronic cough
- Rhinosinusitis
- Otitis/hearing loss
- Bronchiectasis
- Pneumonia

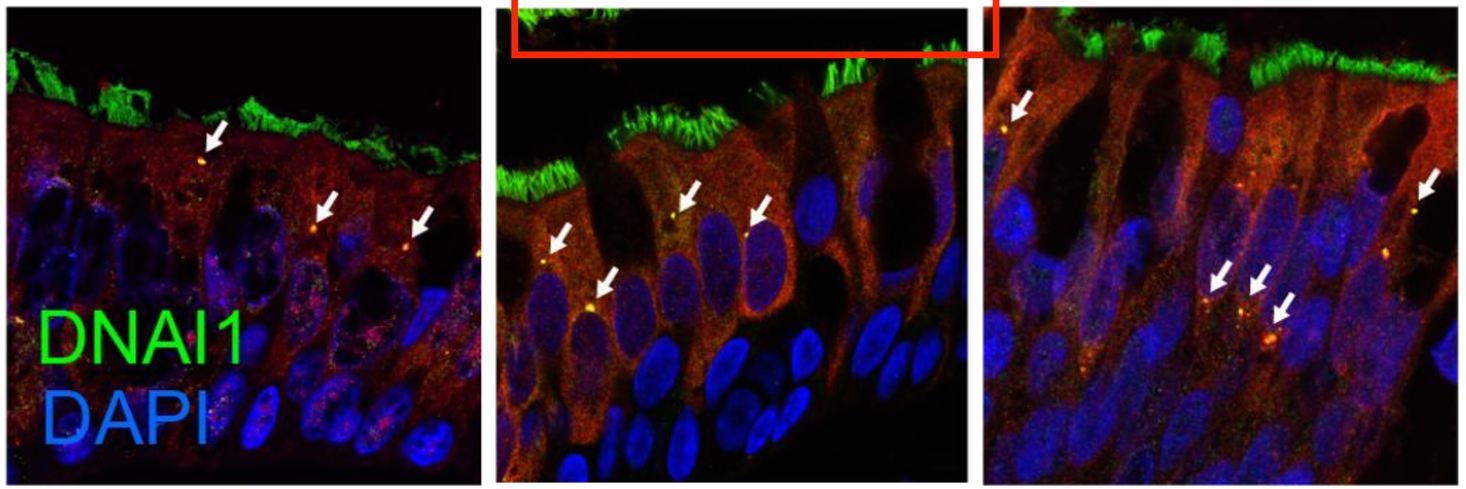
- Chronic cough
- Rhinosinusitis
- Hearing loss
- Bronchiectasis
- Pneumonia
- Sub/Infertility
- (Hydrocephalus)

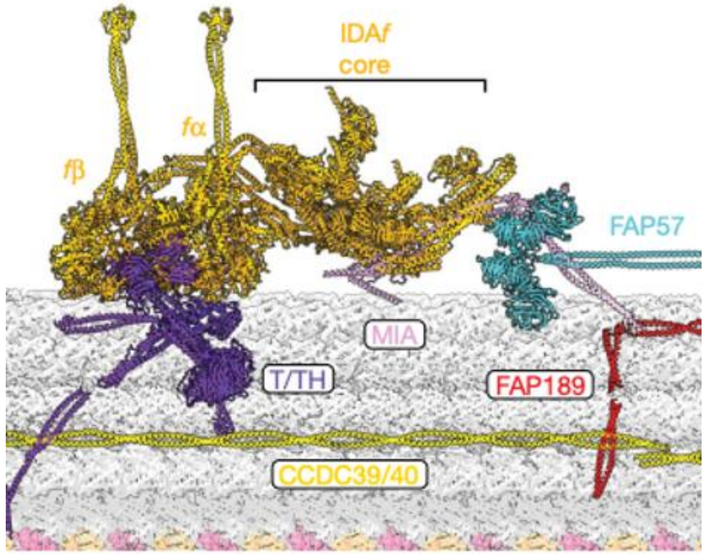
Steve Brody

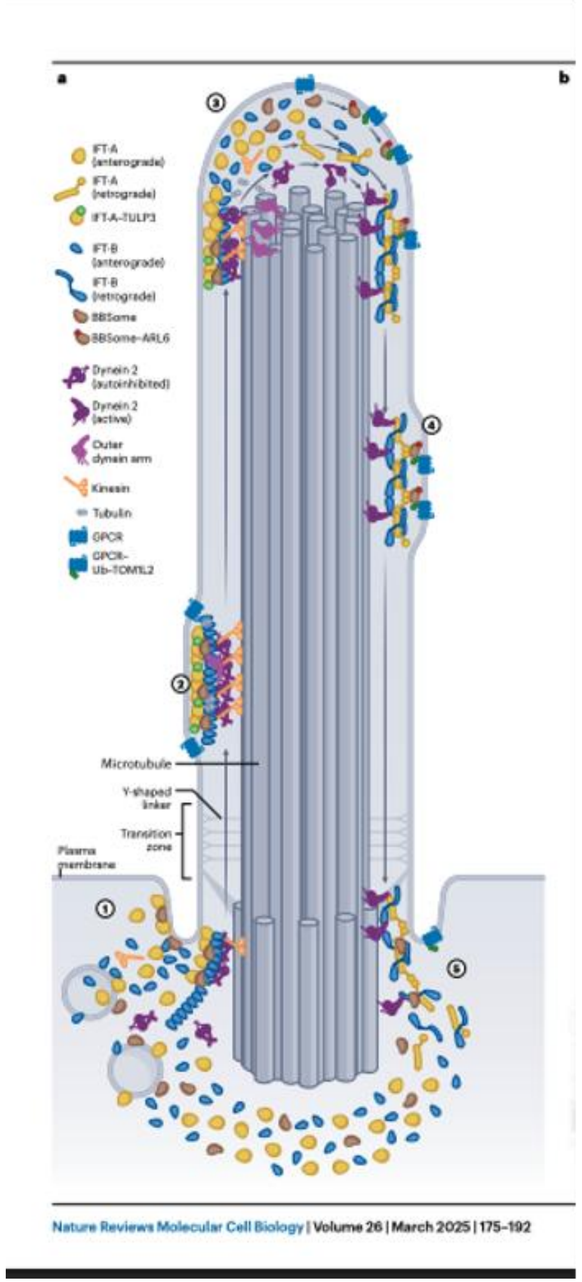
Amjad Horani

Primary Ciliary Dyskinesia (PCD) from a large family in Buffalo Missouri

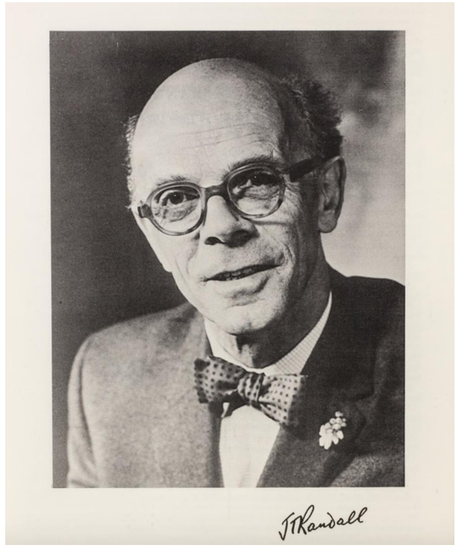
DNAAF2 HEATR2 LRRC6



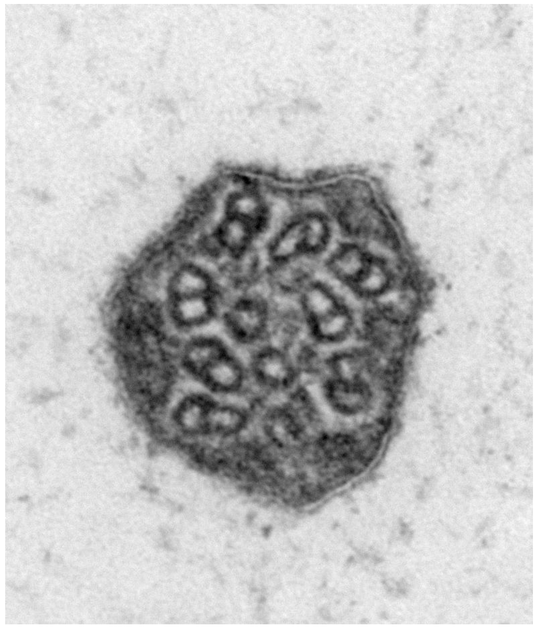




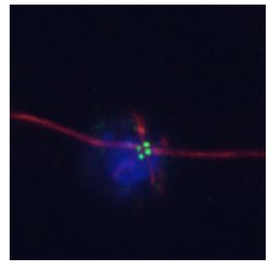
Paralyzed Cilia Collection



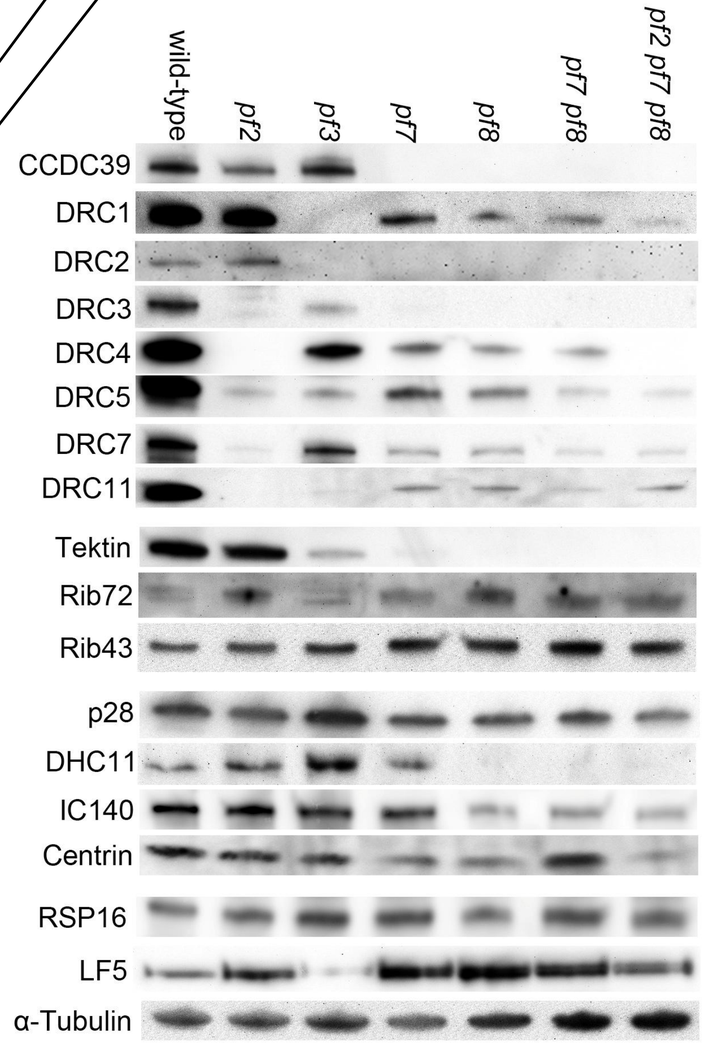
Sir John Randall. University of Edinburgh, 1968-1978



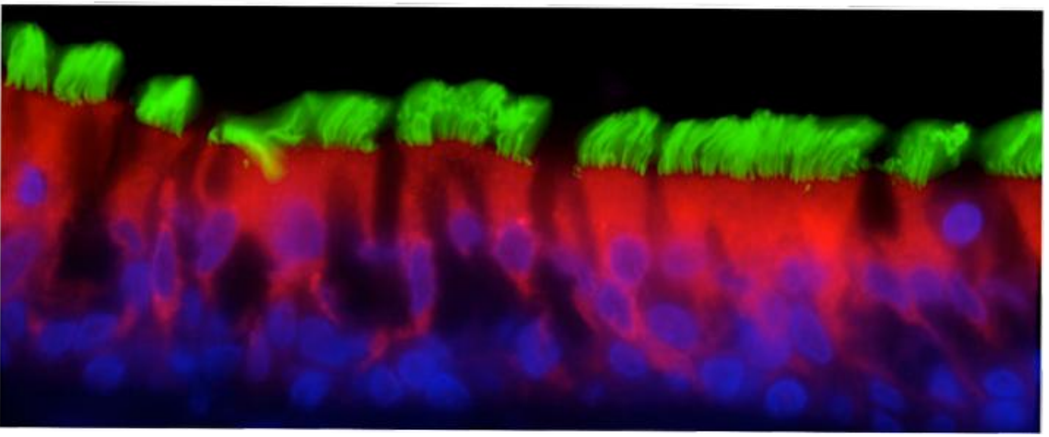
PF1	✓ RSP4	RSPH
PF2	✓ DRC4	N-DRC
PF3	✓ DRC1	N-DRC
PF4	✓ PP2A/IDA	IDA f
PF5	✓ LC8	RSPH
PF6	✓ SPAG17	Central pair
PF7	✓ CCDC39	ADDRESS
PF8	✓ CCDC40	ADDRESS
PF9	✓ DNAH10	IDA f
PF10		UNKNOWN
PF12	✓ PACRG	MIP
PF13	✓ DNAAF2	DNAAF
PF14	✓ RSPH14	RSPH
PF15	✓	Central pair
PF16	✓ SPAG6	Central pair
PF17	✓ RSPH9	RSPH
PF18		Central pair
PF19	✓	Central pair
PF20	✓ SPAG16	Central pair

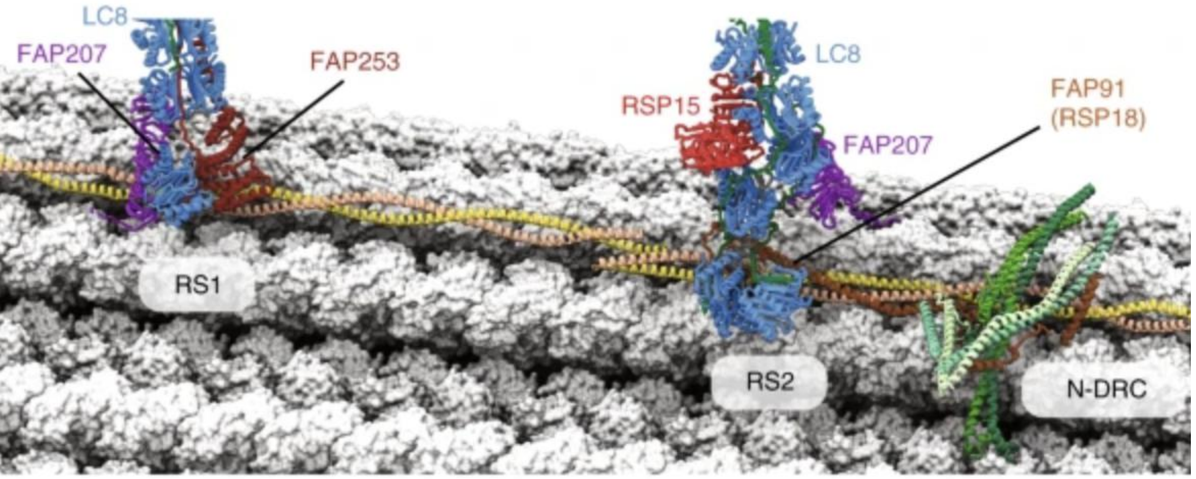


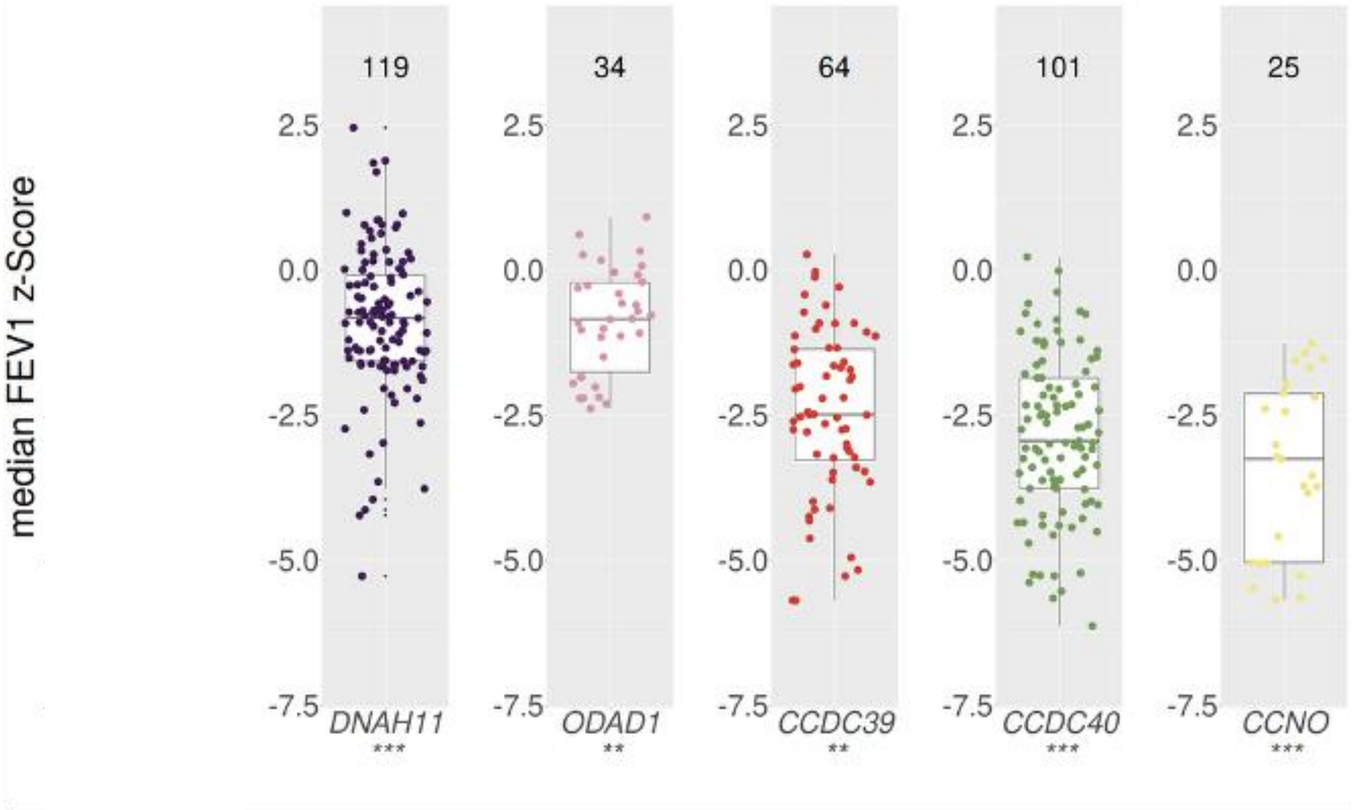
CCDC39 and *CCDC40* mutants



CCDC39 and CCDC40 are a 96 nm long heterodimer

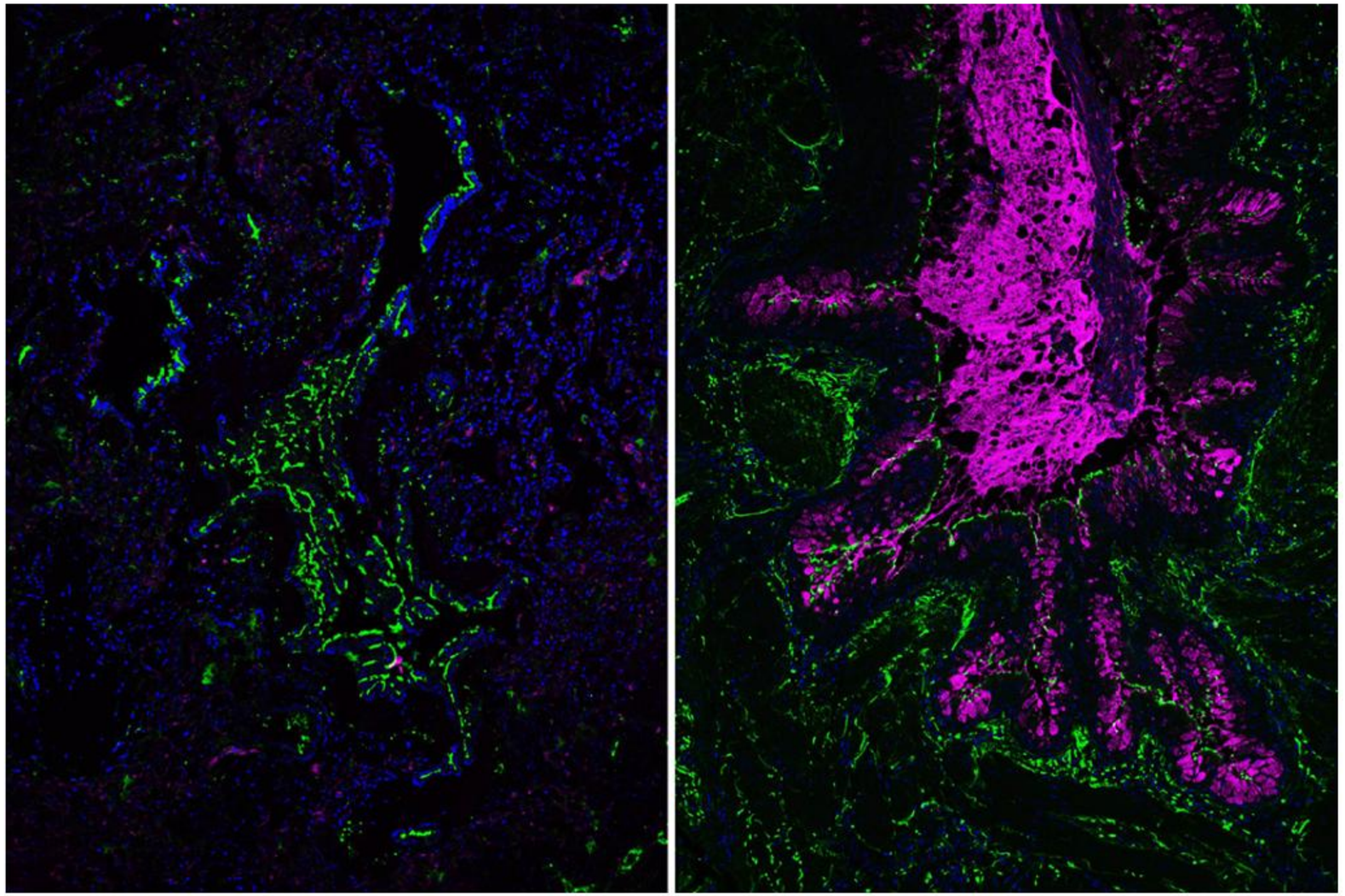






Raidt et al., 2025

CCDC39 and *CCDC40* patients have more mucus in their small airways

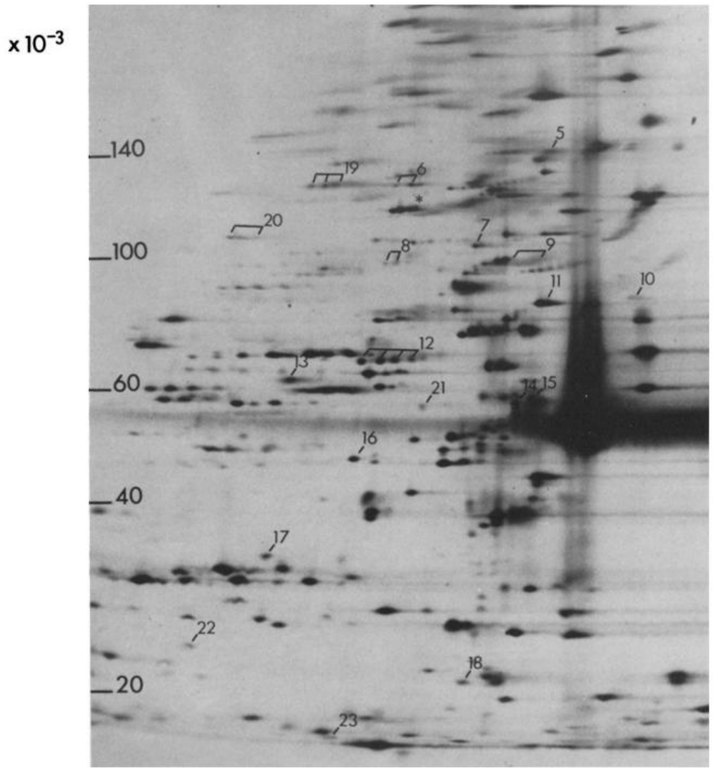


Control

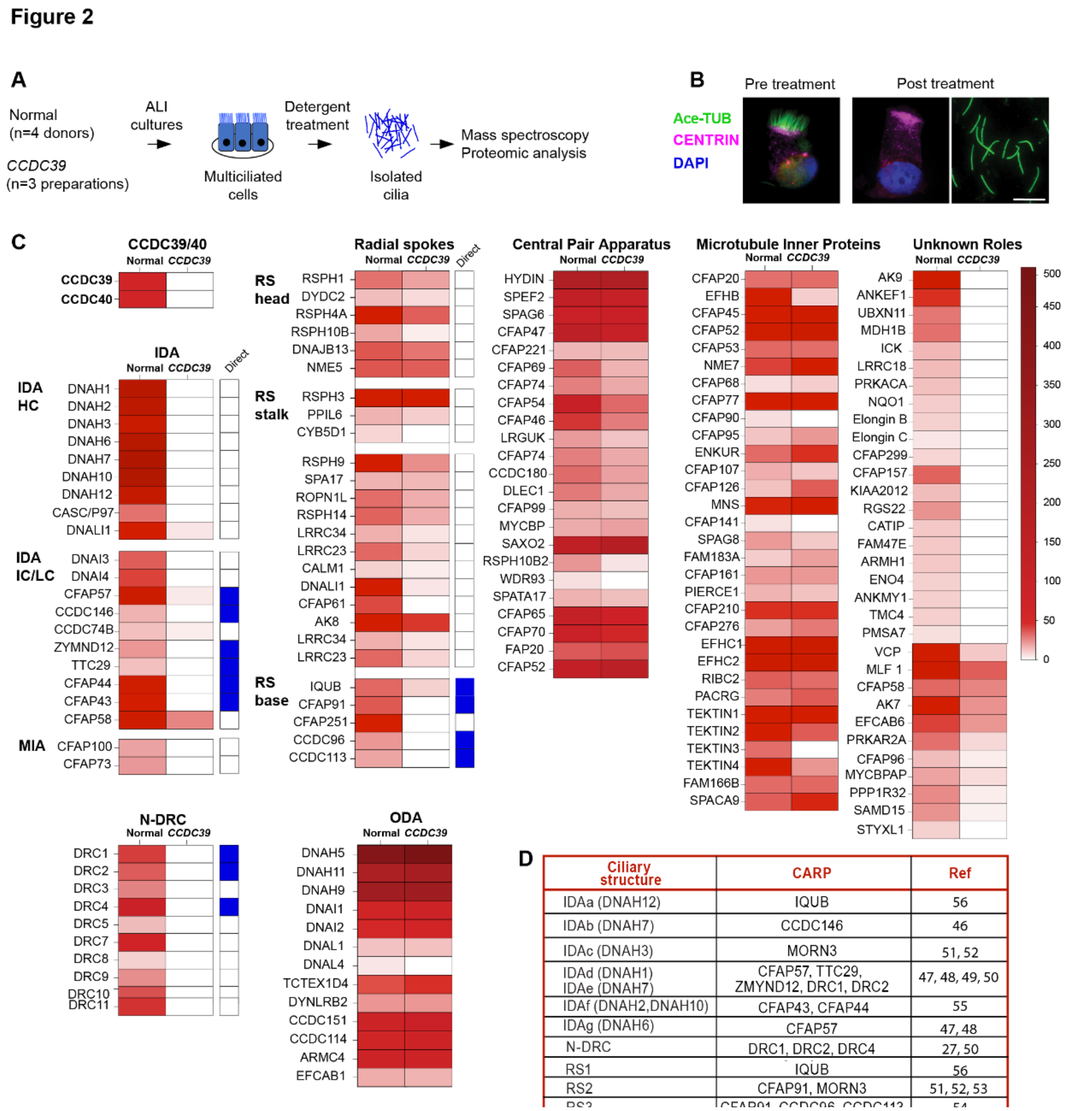
CCDC39-/-

Cilia Mucus DNA

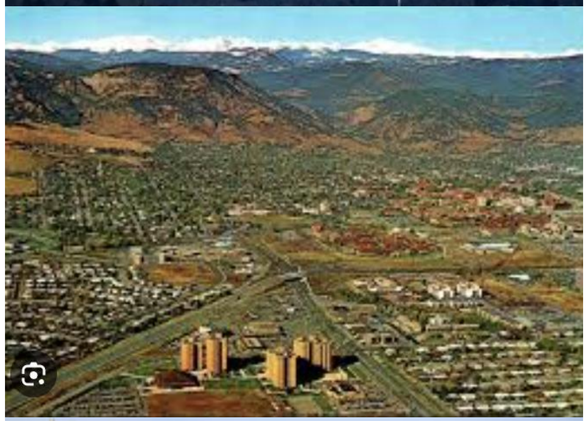
Changing Technologies: 2D gels to Proteomics



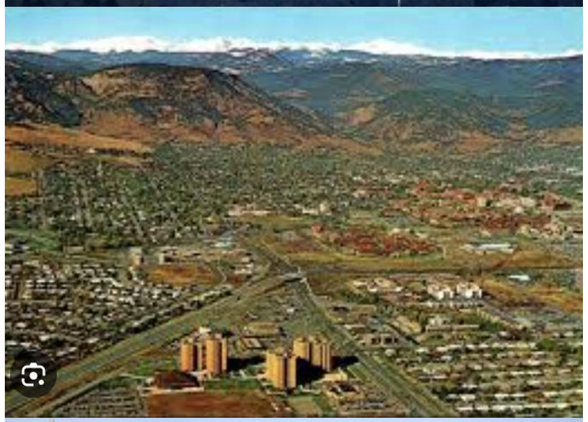
Dutcher et al., 1984



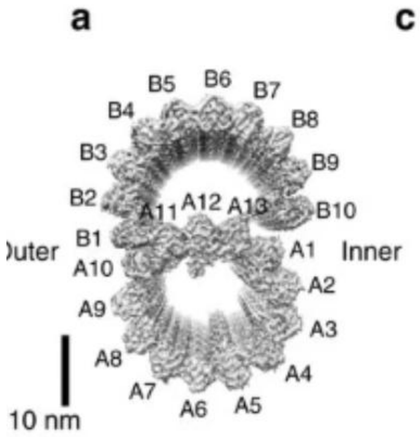
Brody et al., 2025

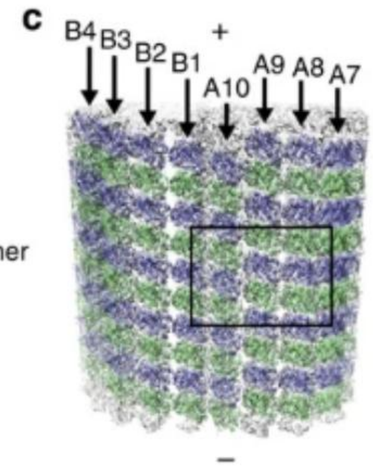


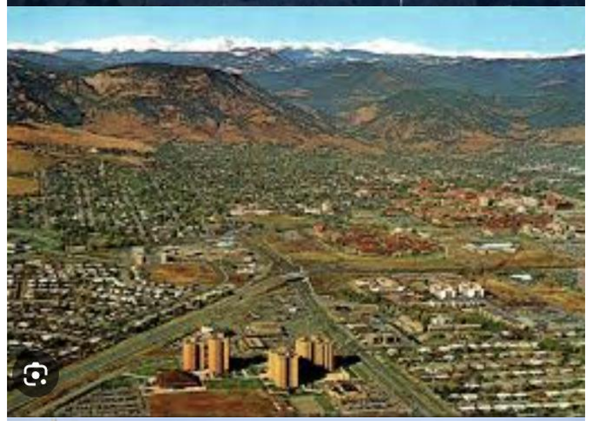
Finding addresses for ciliary proteins



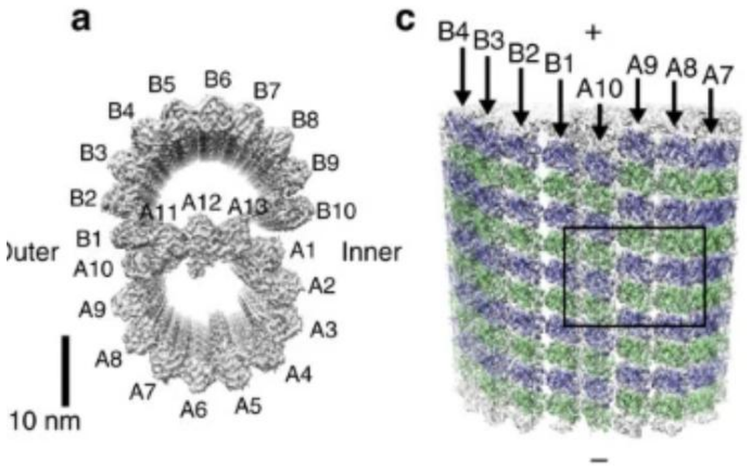
Finding addresses for ciliary proteins





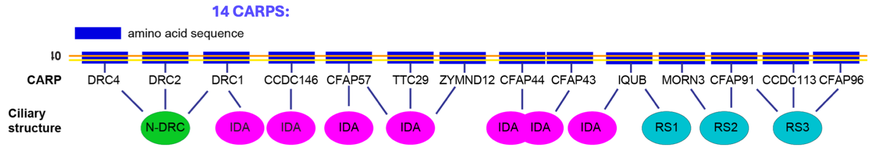


Finding addresses for ciliary proteins



CCDC39/CCDC40 heterodime

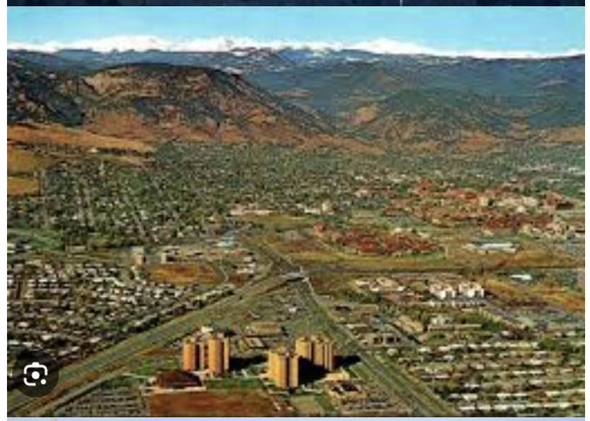
CARPS: **Cilia Address Recognition Proteins attached to CCDC39/40 heterodimer**



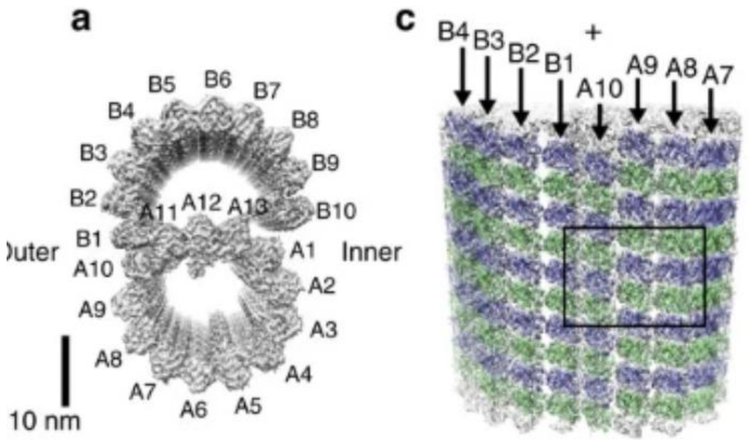
Major structures missing:

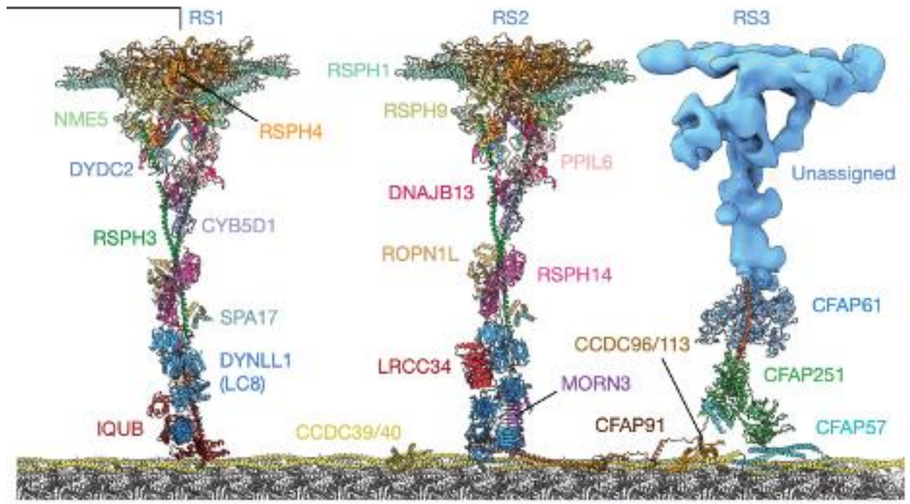
- Nexin-dynein regulatory complex
- Inner dynein arms
- Radial spokes

Brody et al., 2025



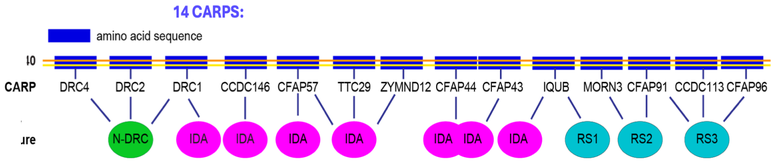
Finding addresses for ciliary proteins





CCDC39/CCDC40 heterodimer

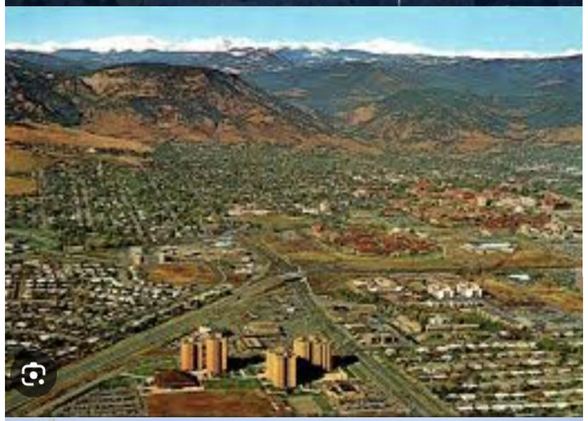
CARPS: **Cilia Address Recognition Proteins attached to CCDC39/40 heterodimer**



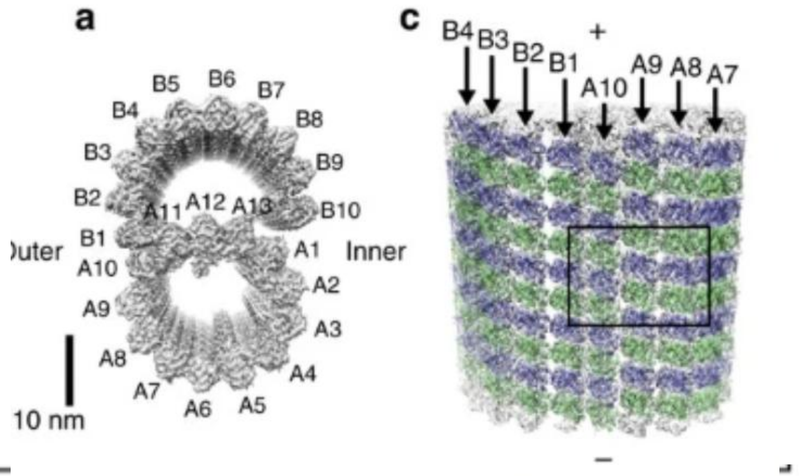
ajor structures
ssing:

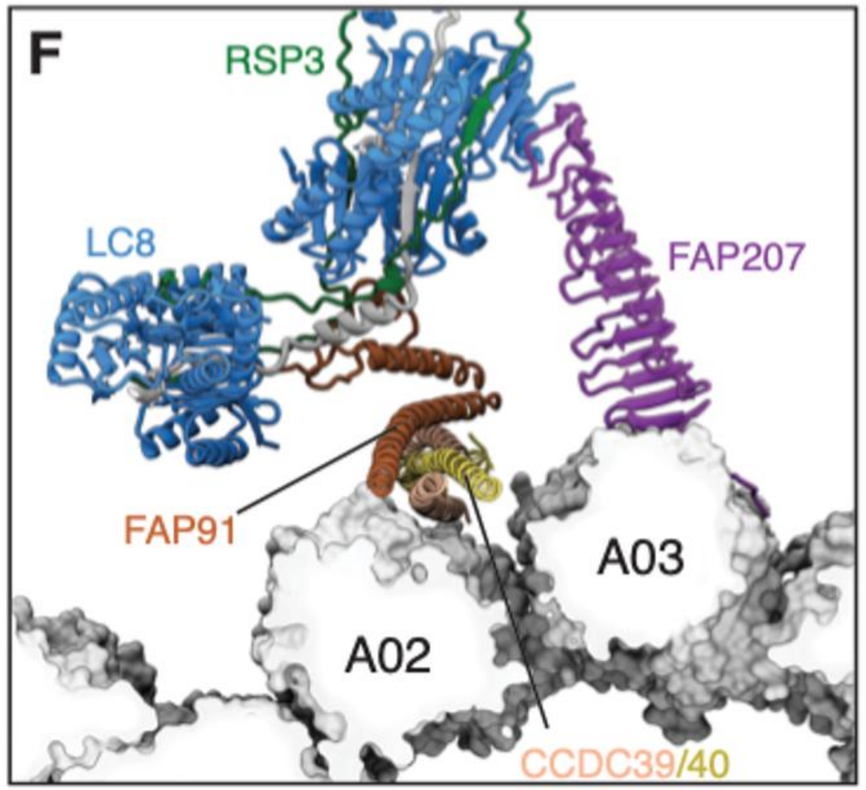
- Nexin-dynein regulatory complex
- Inner dynein arms
- Radial spokes

Brody et al., 2025



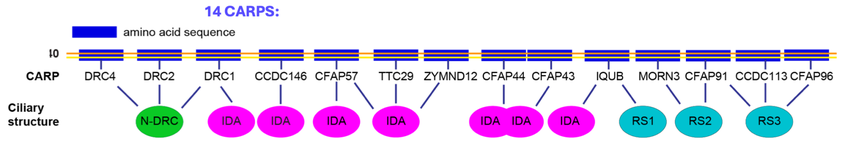
Finding addresses for ciliary proteins





CCDC39/CCDC40 heterodimer

CARPS: **Cilia Address Recognition Proteins attached to CCDC39/40 heterodimer**



Major structures missing:

- Nexin-dynein regulatory complex
- Inner dynein arms
- Radial spokes

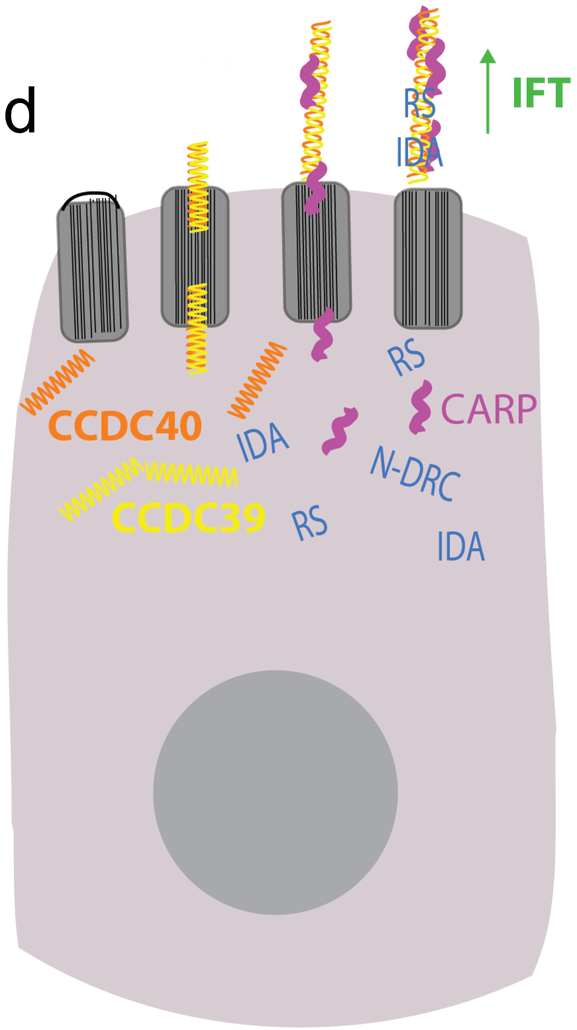
Brody et al., 2025

Timing of events during cilia assembly

3. Complexes enter and dock

2. CARPs enter and bind CCDC39/40 heterodimer

1. CCDC39/40 enter

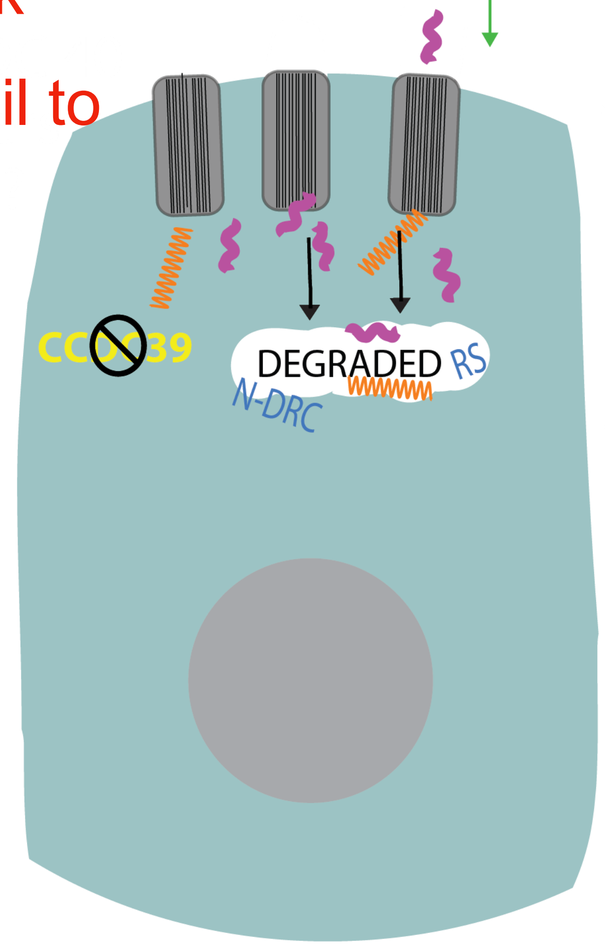


Control cells

2. CARPs enter but do not dock

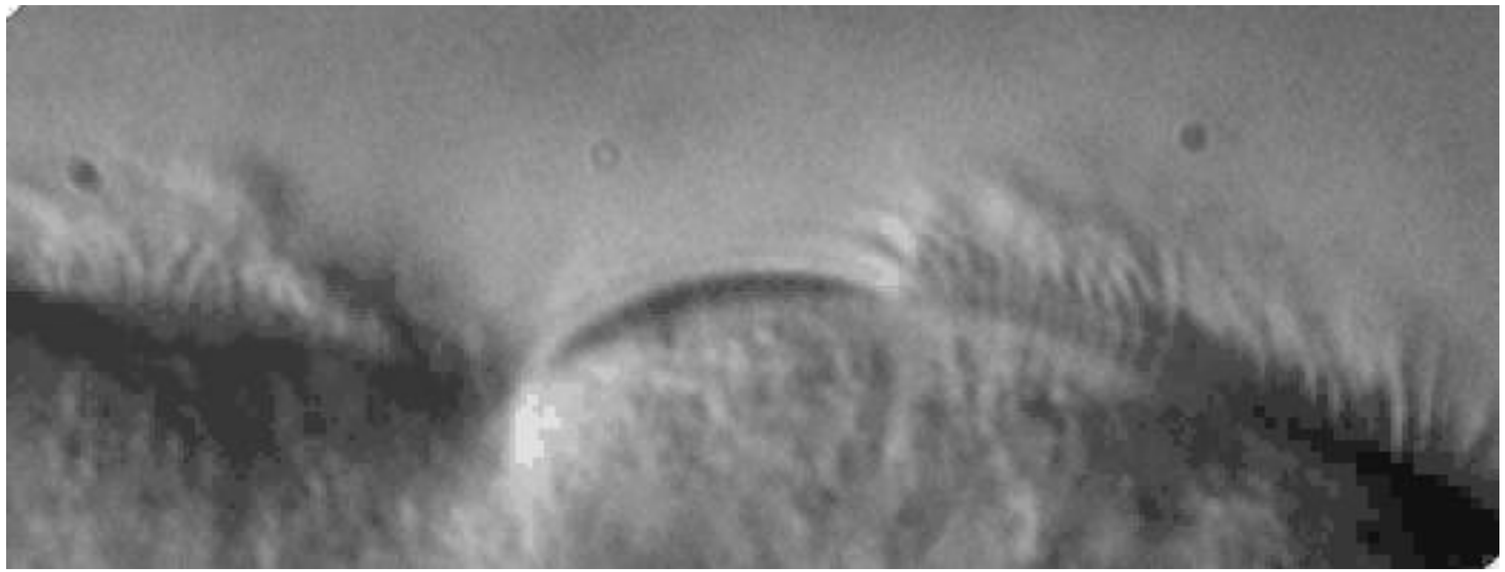
1. CCDC39/40 fail to enter

3. Complexes enter and do not dock



Variant cells

Why do patients with *CCDC39* and *CCDC40* variants show more severe disease than PCD patients with variants in other genes?



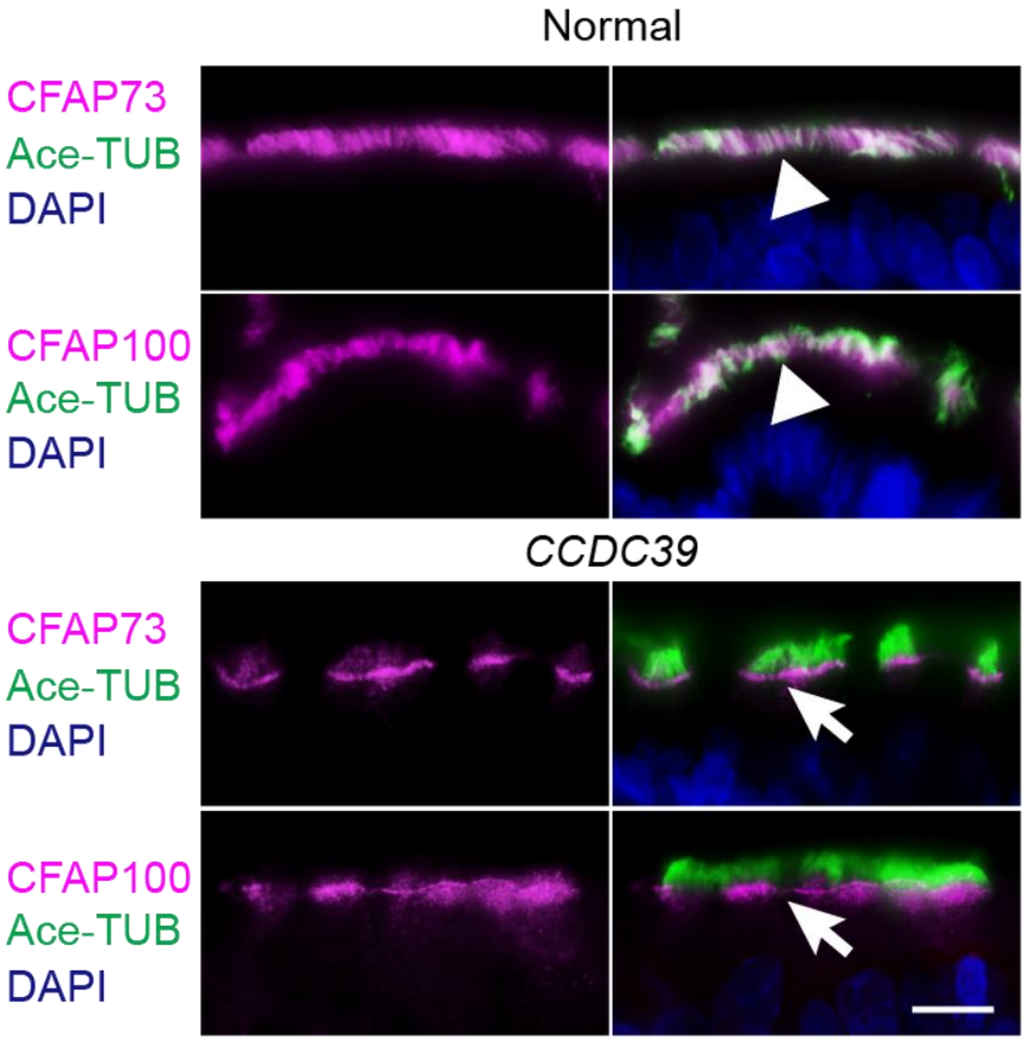
Disease is caused by more than just loss of ciliary movement

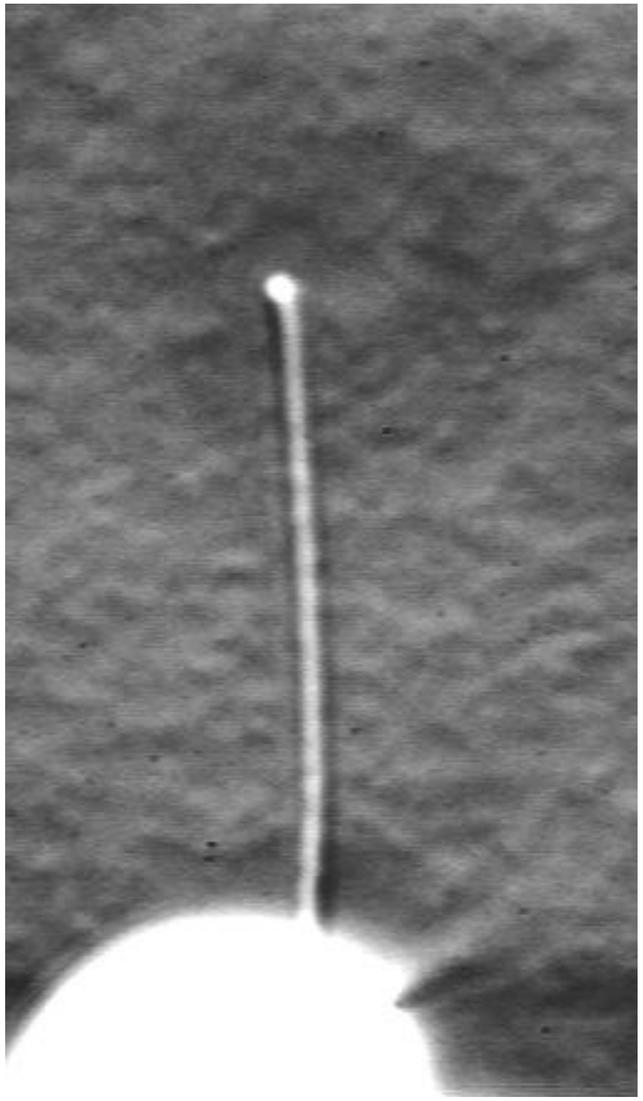
Why do patients with *CCDC39* and *CCDC40* variants show more severe disease?

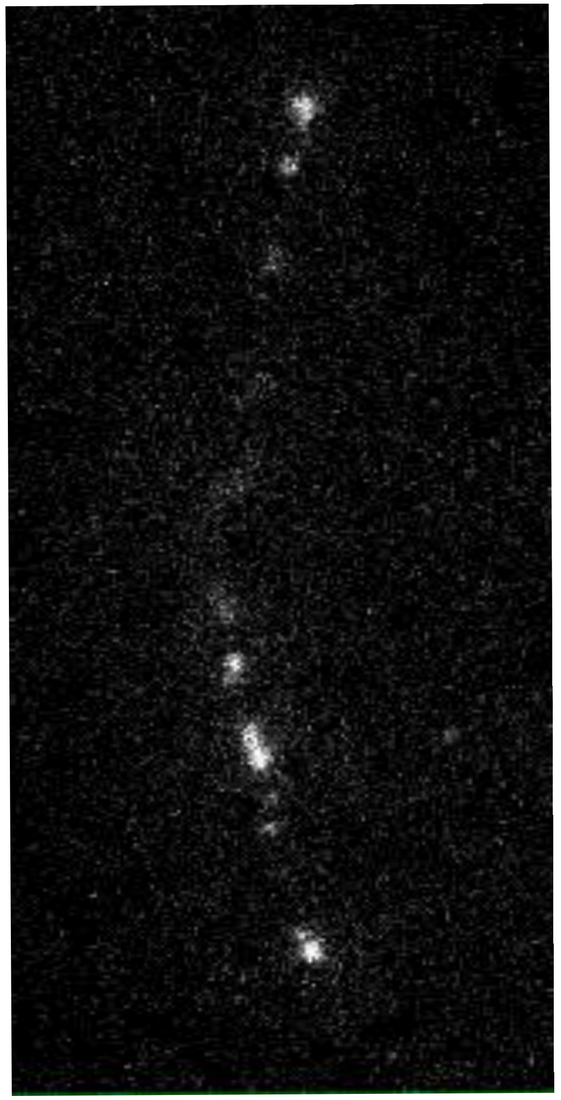
Motility independent phenotype

Cleaning and recycling up the ”trash”

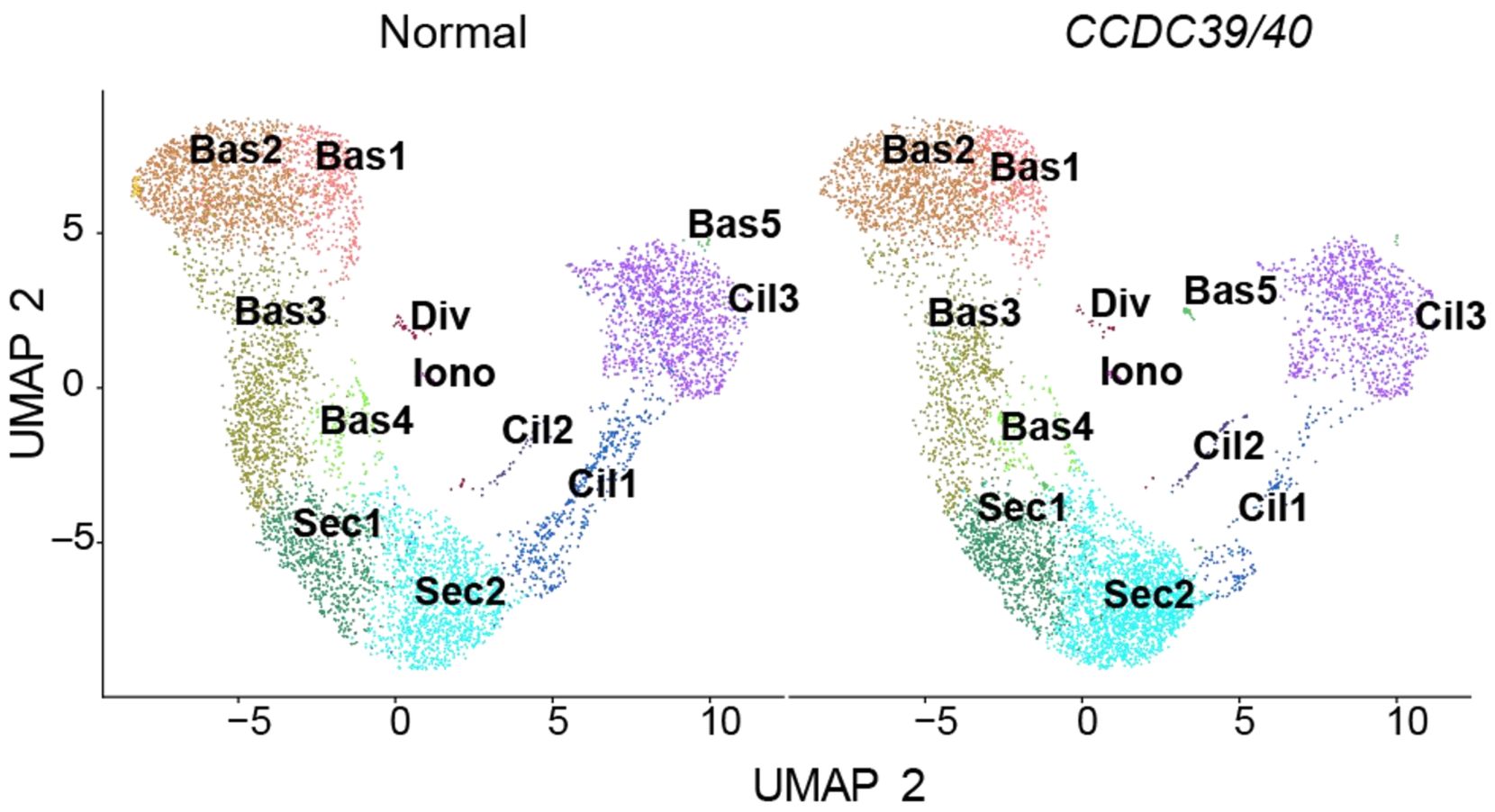
Motility independent phenotype: Cleaning and recycling up the ”trash”



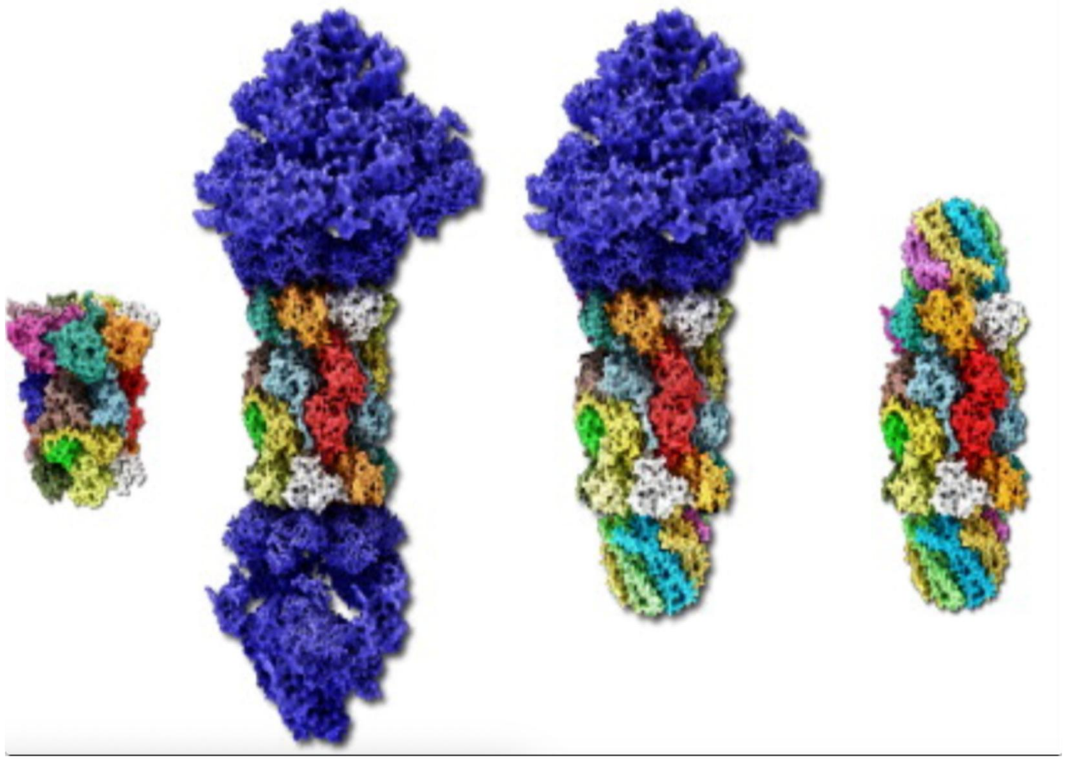


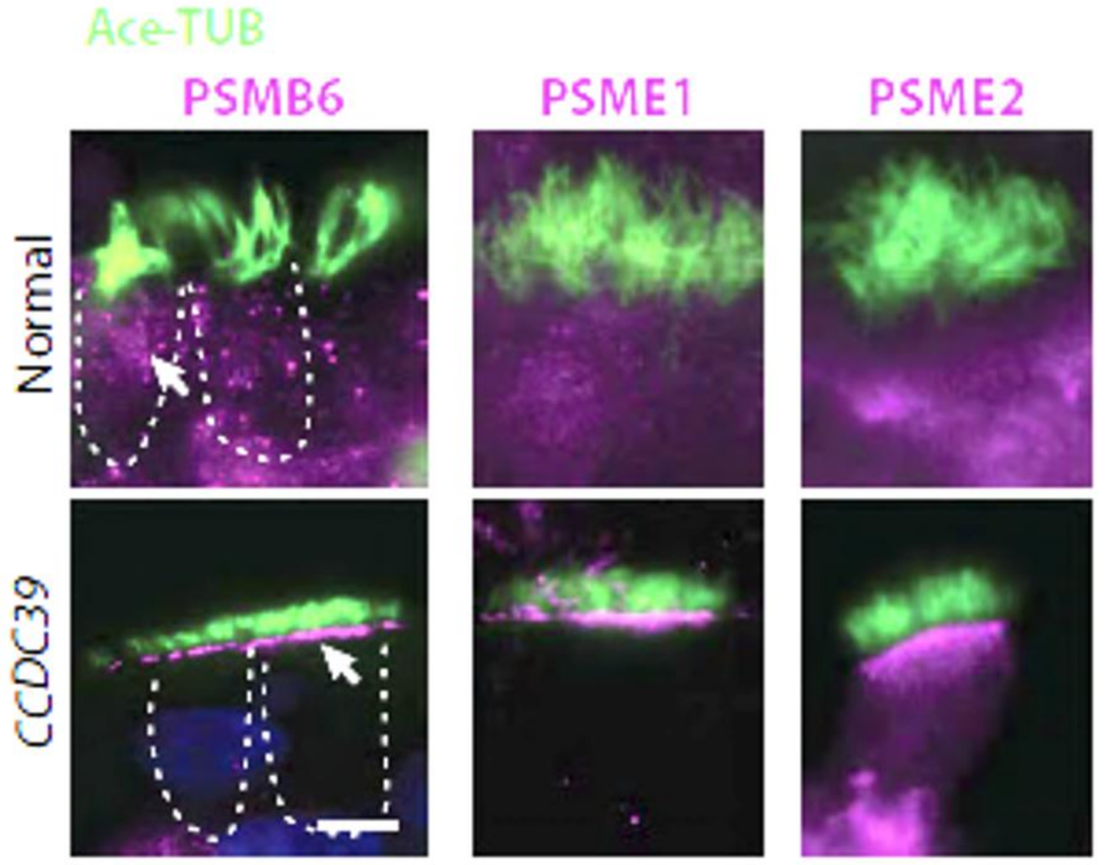


Motility independent phenotype: Cleaning and recycling up the ”trash”



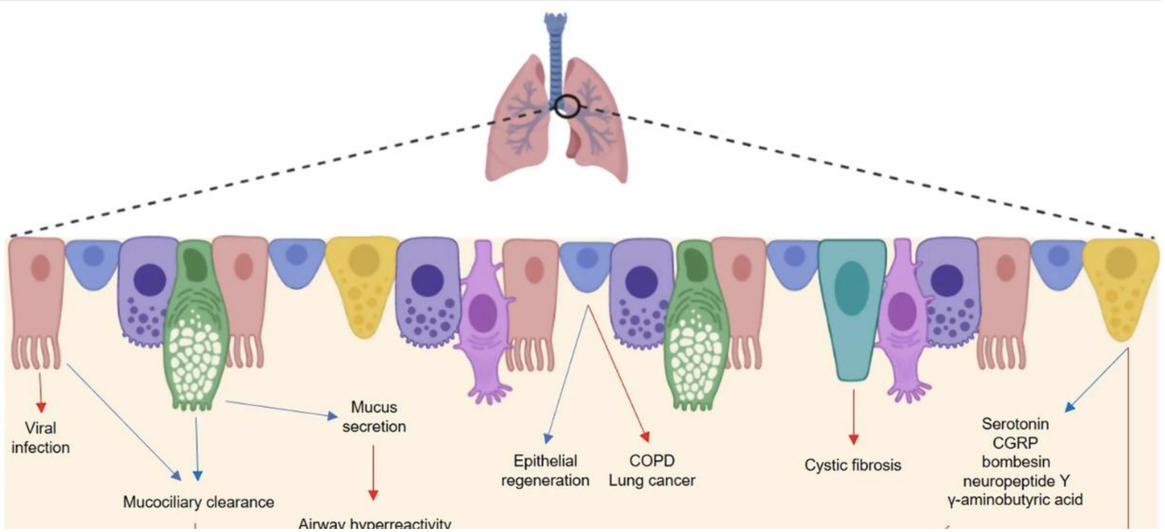
The immunoproteasome is turned up in the disease cells



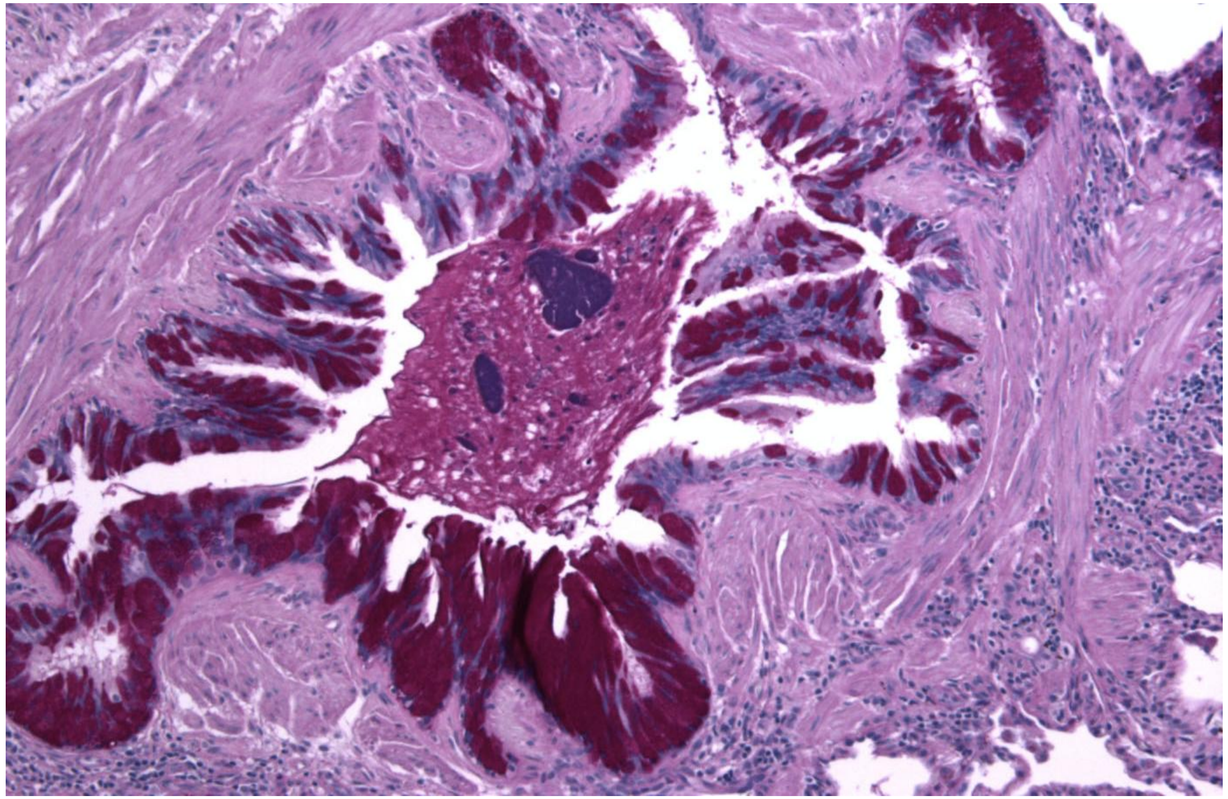


19S 26S Hybrid Immunoproteasome

Why do patients with *CCDC39* and *CCDC40* variants show more severe disease?

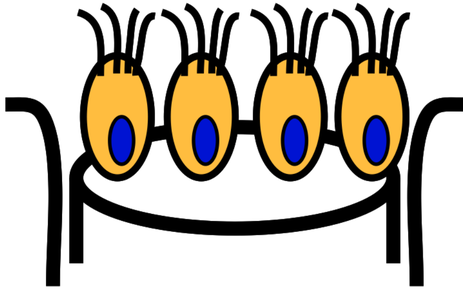


Davis and Wypych, 2021

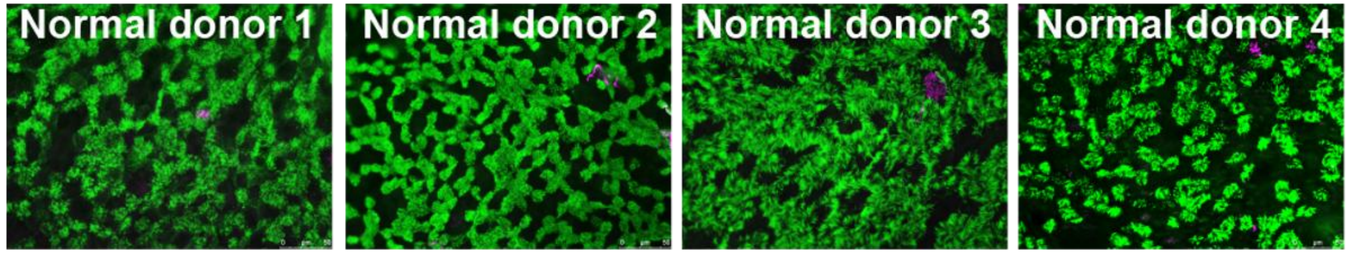


Change the cell fate of the multicilaited cells to secretory cells

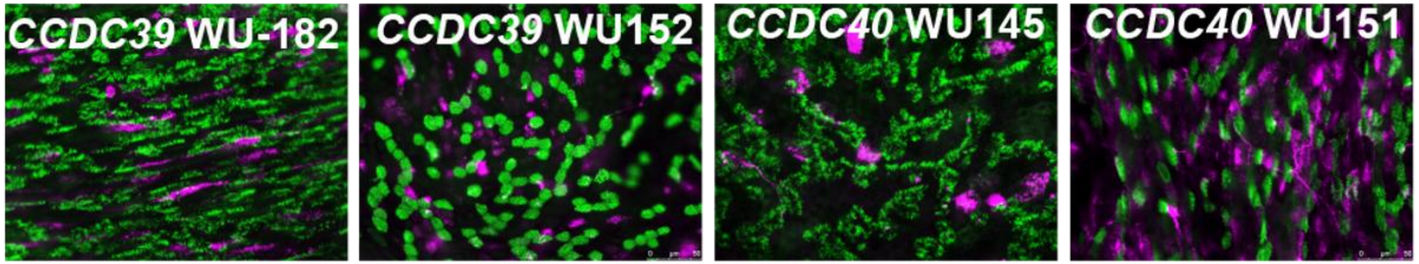
Motility independent phenotype: Transdifferentiation of multicilated cells



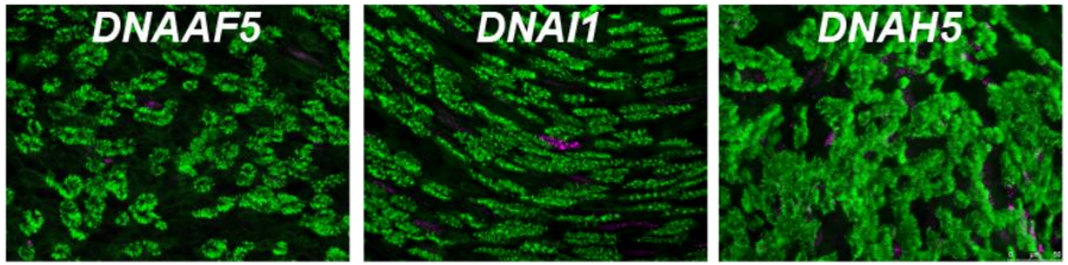
Normal

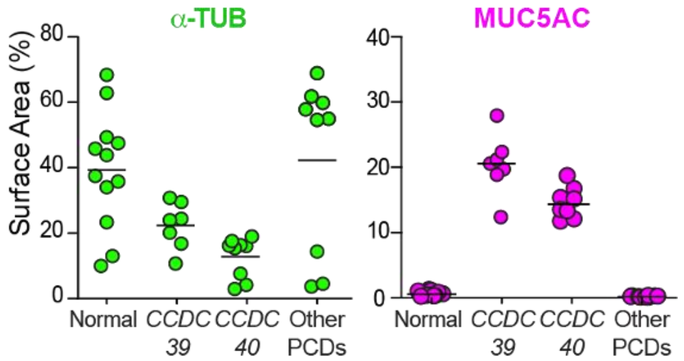


Patient



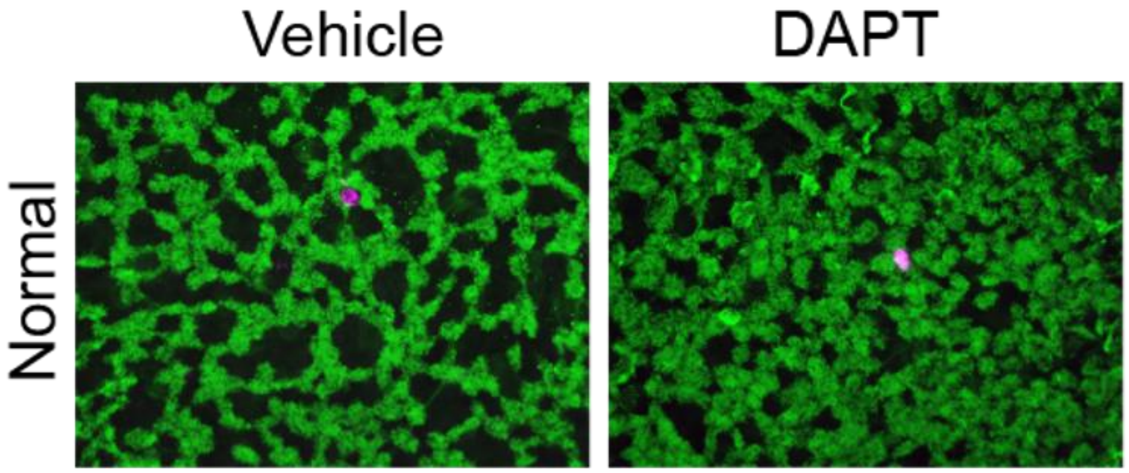
Patient

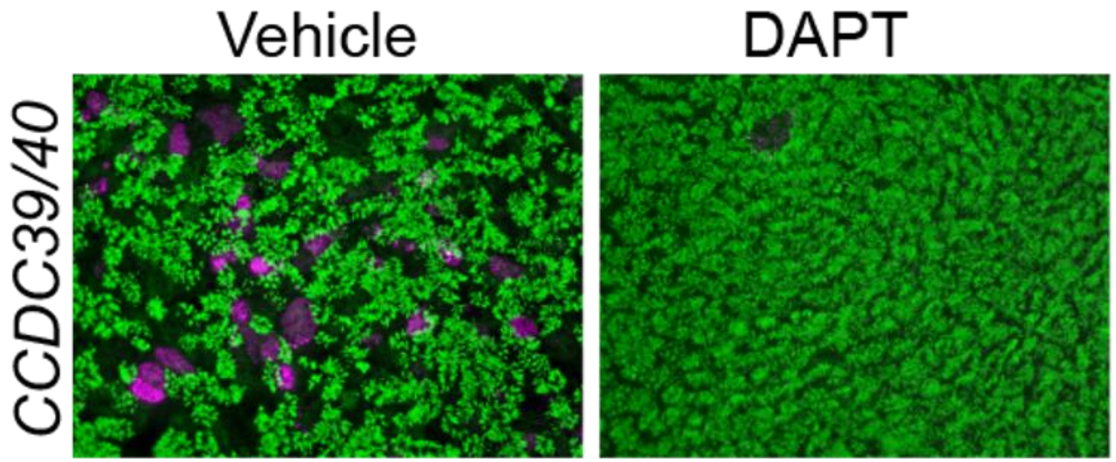




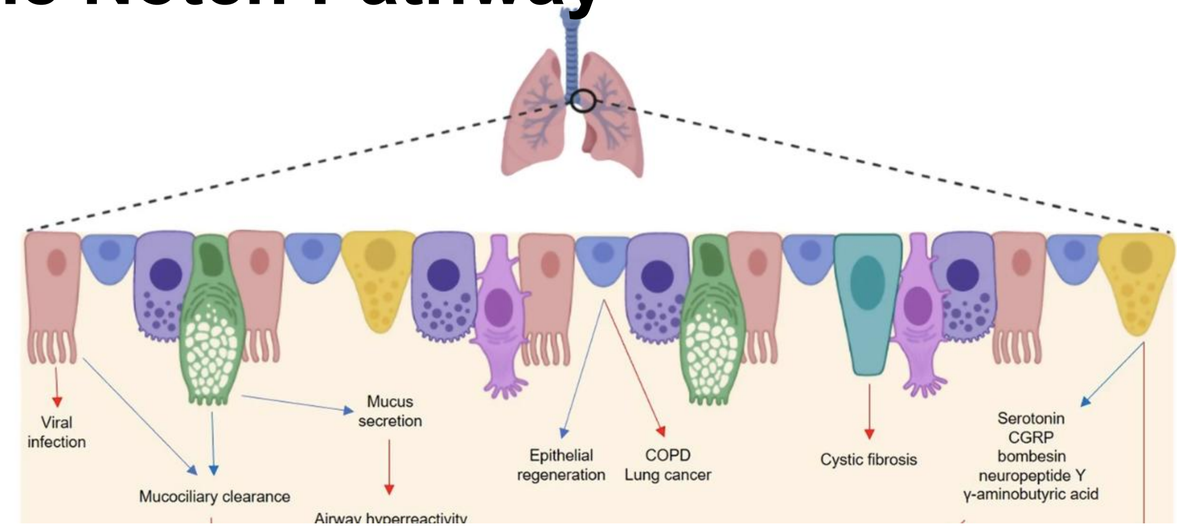
Cilia Mucus

Motility independent phenotype: Transdifferentiation of multicilated cells via misregulation of the Notch Pathway

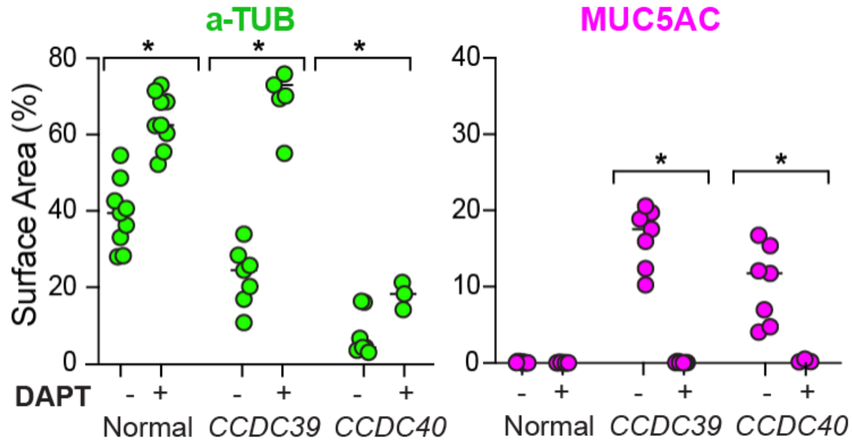




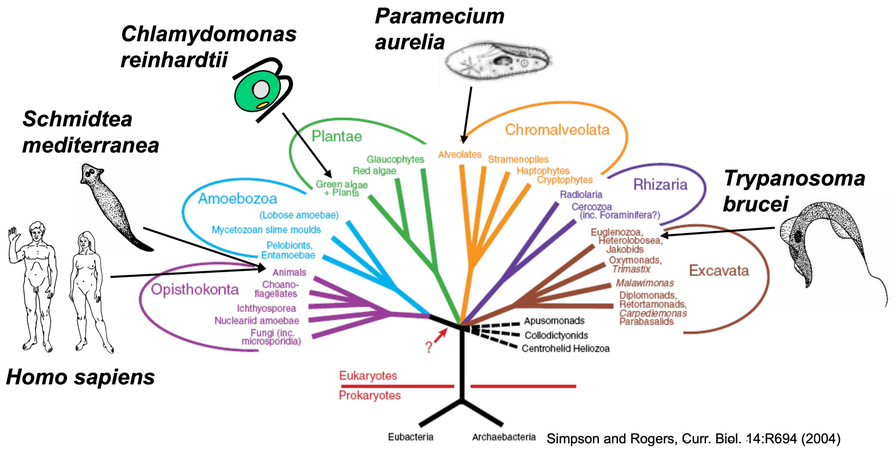
Cilia Mucus



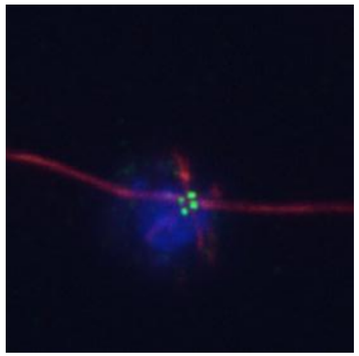
Davis and Wypych, 2021

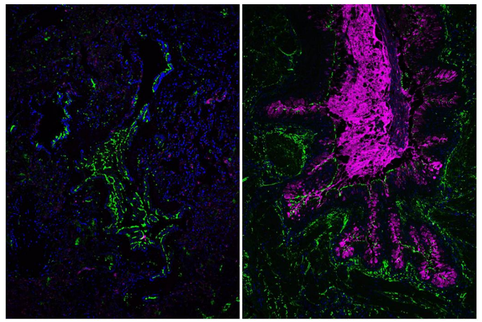


Take home messages



Simpson and Rogers, Curr. Biol. 14:R694 (2004)

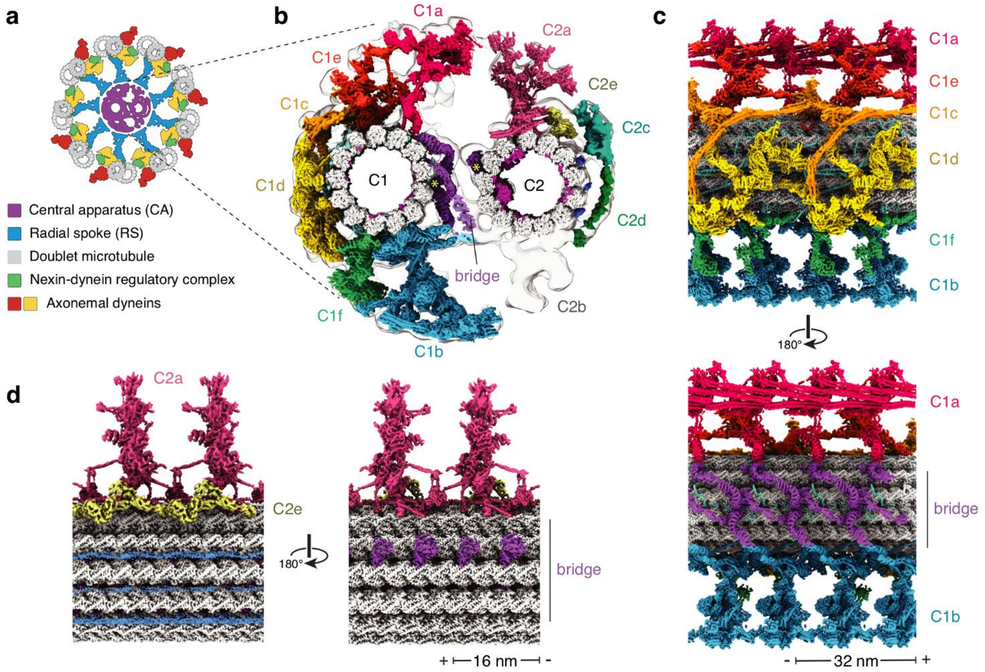


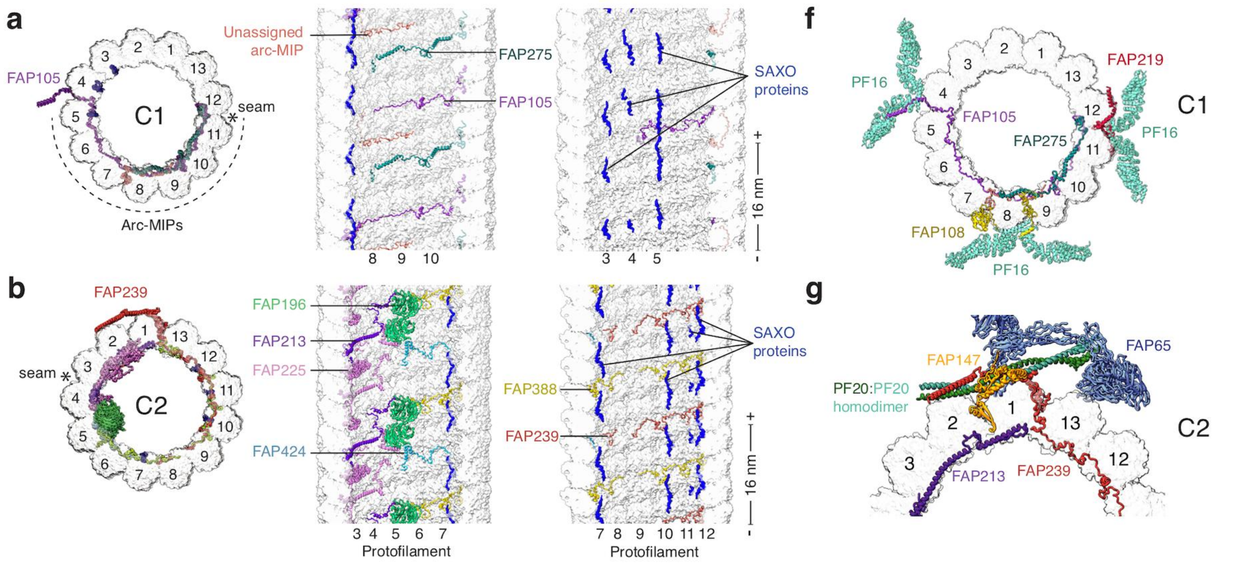


Evolution provides a wealth of information about key genes involved in human disease

Motile organisms provide fast and easy functional assays and therapeutic assays

Human variation and diseases provide additional functional tests and new phenotypes


a
b
c
d
Central apparatus (CA)
Radial spoke (RS)
Doublet microtubule
Nexin-dynein regulatory complex
Axonemal dyneins
C1a
C2a
C1e
C2e
C1c
C2c
C1d
C2d
C1
C2
bridge
C1f
C2b
C1b
180°
C2a
C2e
bridge
+ 16 nm -
C1a
C1e
C1c
C1d
C1f
C1b
- 32 nm +


a
FAP105
C1
seam
Arc-MIPs
Unassigned arc-MIP
FAP275
FAP105
SAXO proteins
16 nm
8 9 10
3 4 5
b
FAP239
seam
C2
FAP196
FAP213
FAP225
FAP424
FAP388
FAP239
SAXO proteins
16 nm
3 4 5 6 7
Protofilament
7 8 9 10 11 12
Protofilament
f
PF16
FAP219
C1
FAP105
FAP275
PF16
FAP108
PF16
g
FAP65
FAP147
PF20:PF20 homodimer
C2
FAP213
FAP239