CASE STUDY LECTURE SLIDES

How to use these slides:

- **These slides are intended to complement the material presented in Modules 1-6 of the case study.**
- **You can include as many or as few of these slides into your lectures depending on the level of detail into which you wish to explore CF with your students.**
- **Feel free to modify the slides so that they fit with your lecture or course content.**

Tamara Western
McGill University

CASE STUDY LECTURE SLIDES

Modules 1-2

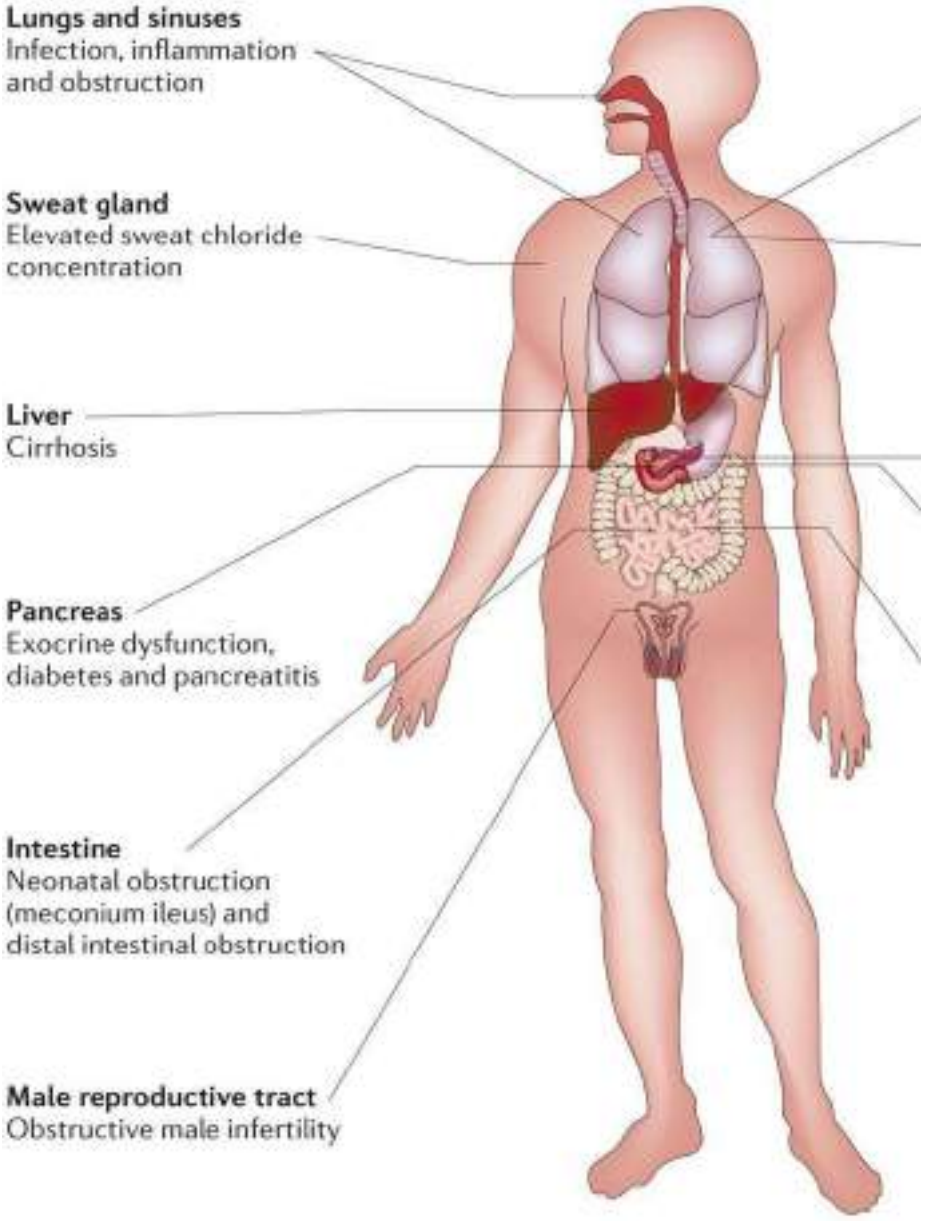
Case Study Assignments (5%)

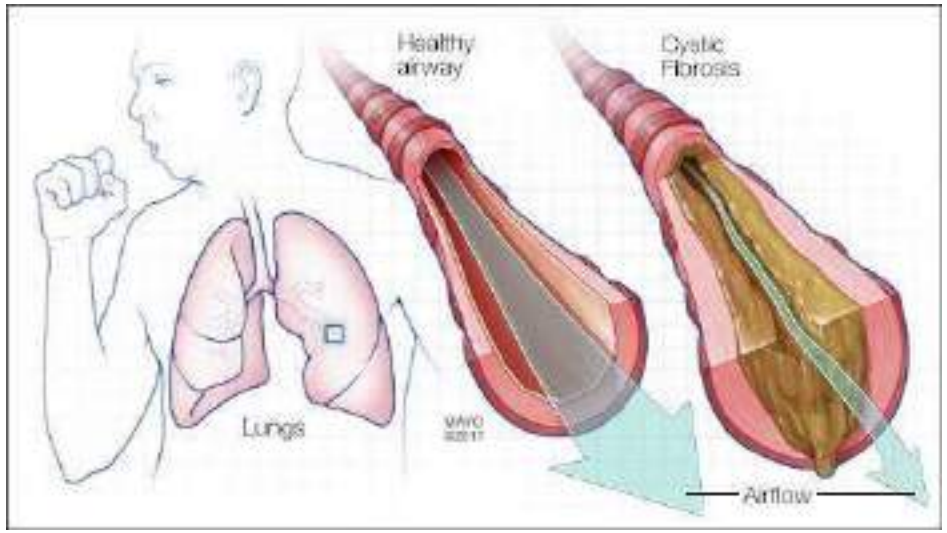
- New this year!
- A case study has been developed to span the course – this year it is on Cystic Fibrosis
- There will be 6 modules – each will include a short assignment (each worth 1% of your final grade (best 5/6)
- It will conclude with a guest lecture on current research in cystic fibrosis at the end of the course

A Case for Cystic Fibrosis - A Québec Perspective

- **Part I: CF as a Mendelian Disorder**
- **Part II: Quebec CF Population Genetics**
- **Part III: From Genotype to Phenotype**
- **Part IV: CF Genetic Screening**
- **Part V: CF Bacterial Genetics**
- **Part VI: Gene Therapy**

A Case for Cystic Fibrosis - A Quebec Perspective



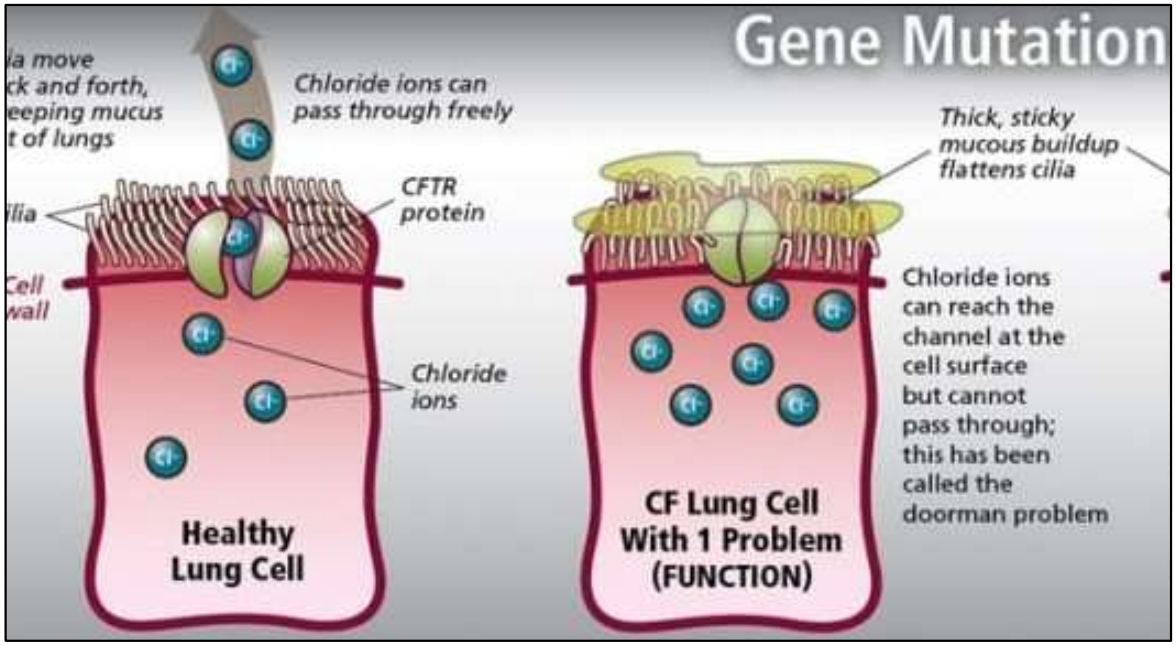


Mayo Clinic

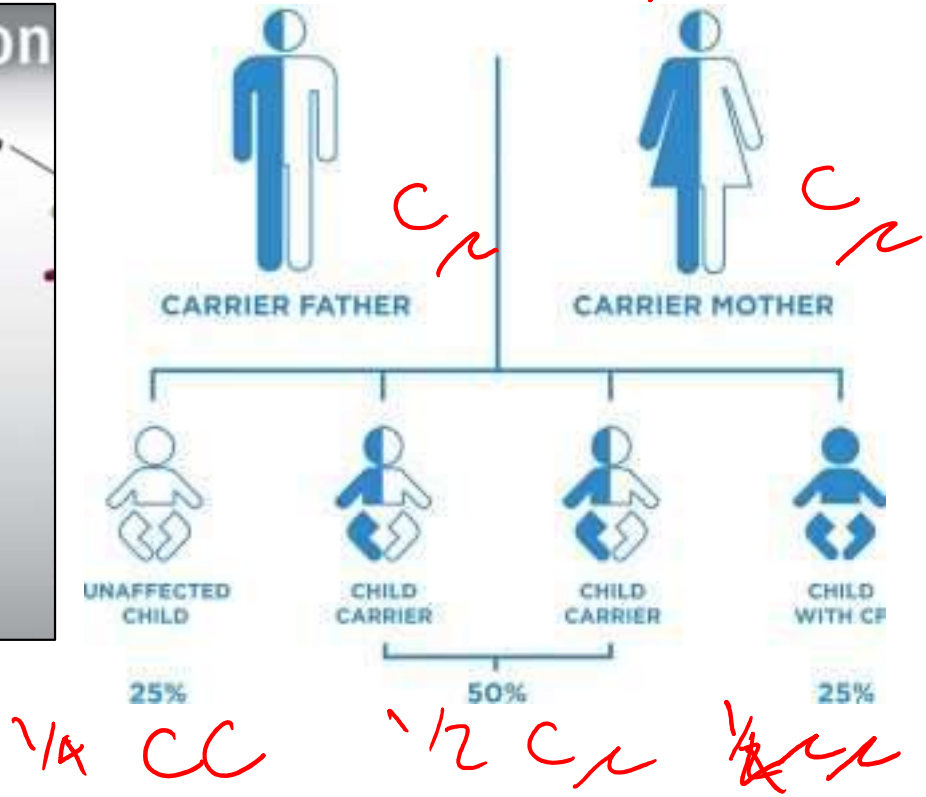
Nat Rev Genet. 2015 Jan; 16(1): 45–56.

Part I: CF as a Mendelian Disorder

- Cystic Fibrosis is a prevalent autosomal recessive disorder in Canada & Quebec
- Mutation in the Cystic Fibrosis Transmembrane Receptor *(CFTR gene)*
  - Cloned by researchers at Hospital for Sick Children - Toronto
- The origins are disputed, but thought to be IndoEuropean



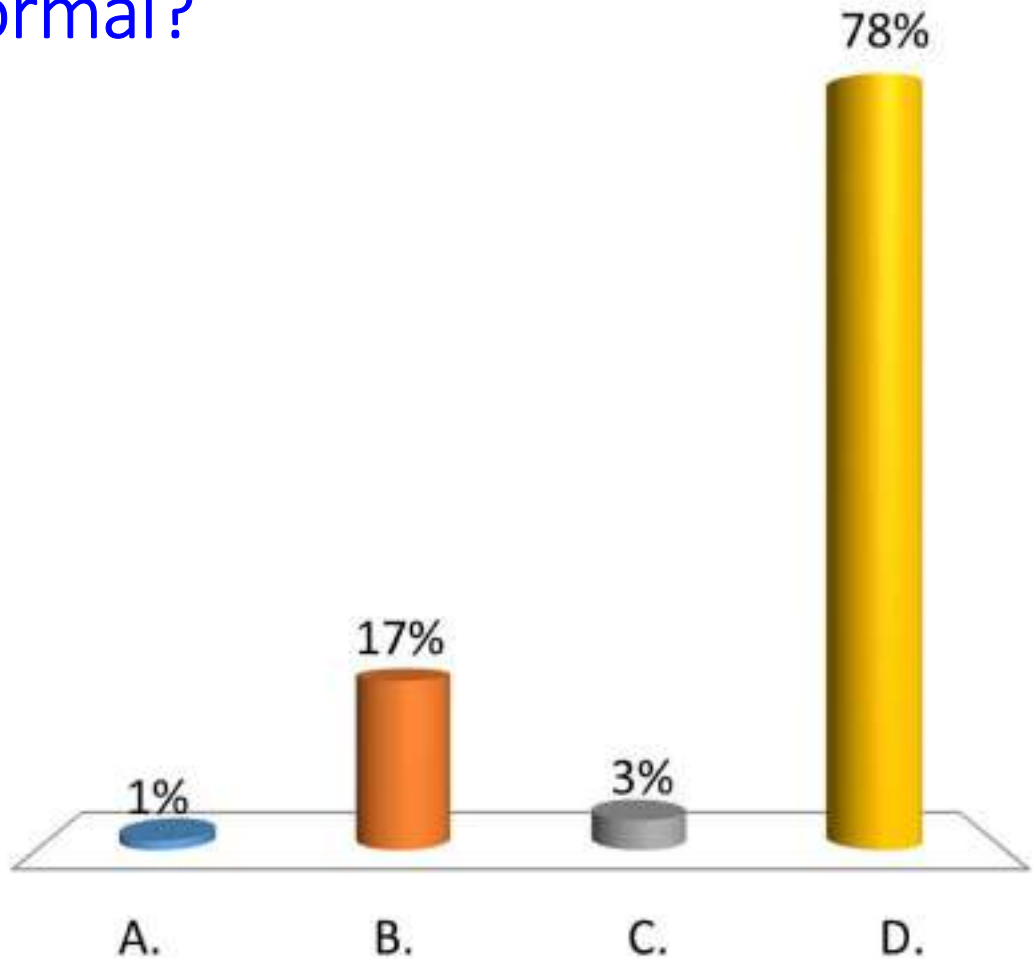
http://cysticfibrosis.com/know-your-cf-mutations/



https://www.cysticfibrosis.ca/about-cf/what-is-cystic-fibrosis

Cystic Fibrosis (CF) is a recessive condition caused by a single mutation. Normal parents have a child with CF. What is the probability that their next child will be normal?

A. 0
B. 1/4
C. 1/2
D. 3/4



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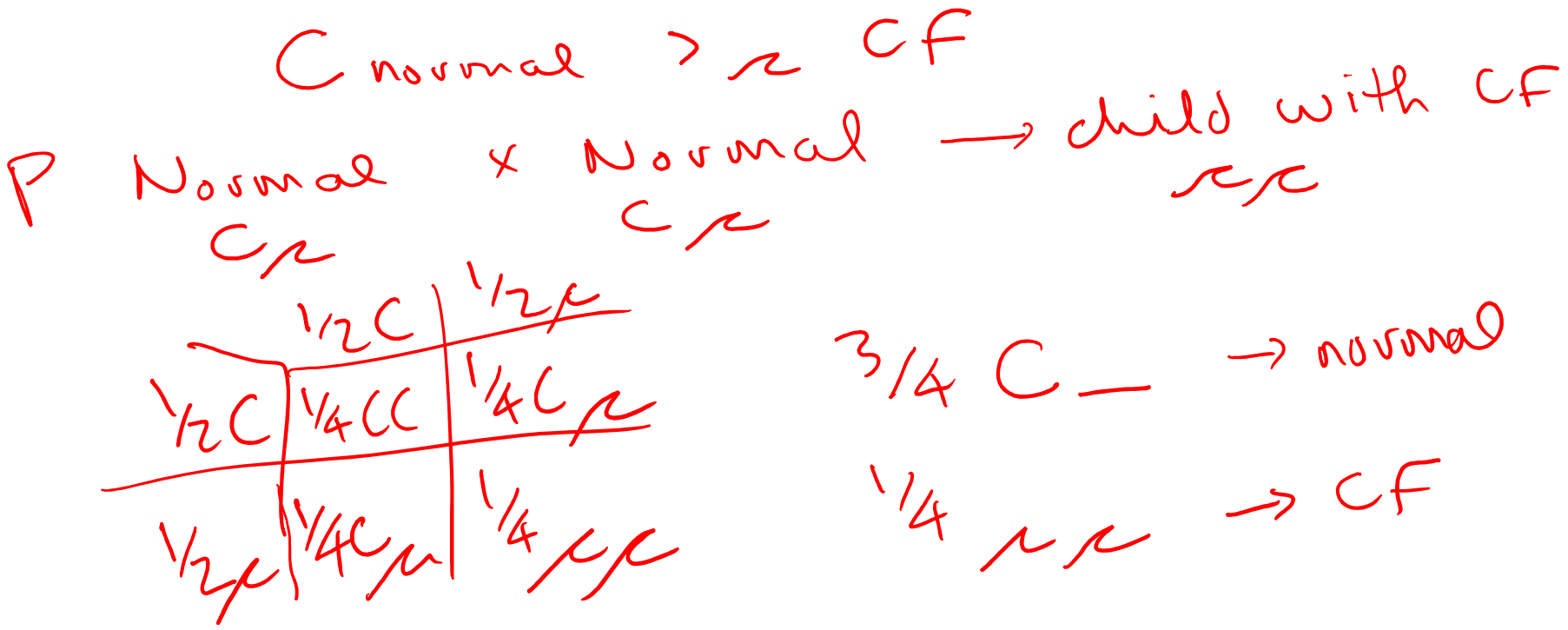
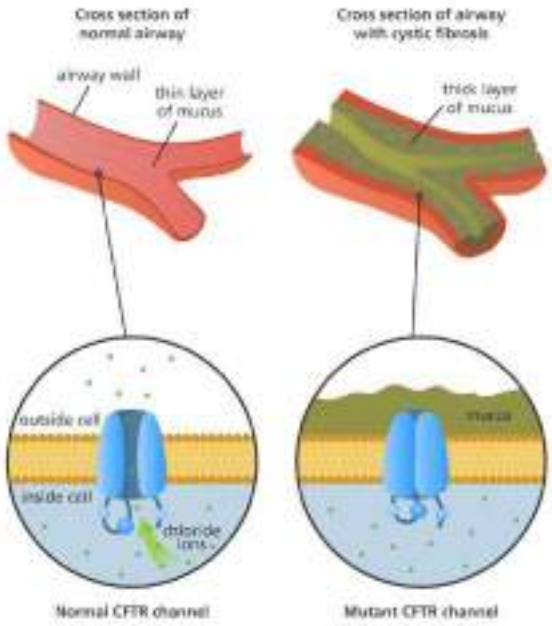
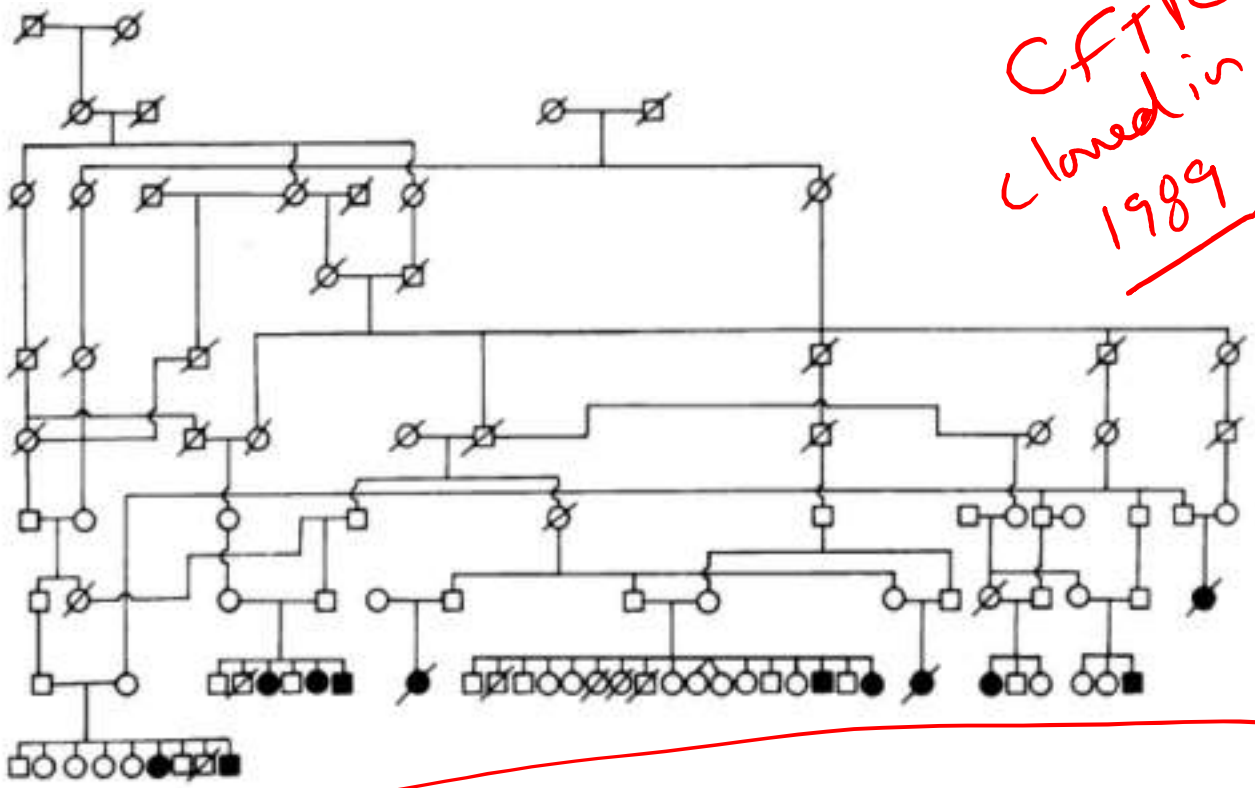


An important application for mapping: Finding the genes underlying genetic diseases

Cystic fibrosis CFTR cloned in 1989



Eva Markvoort; http://65redroses.com/

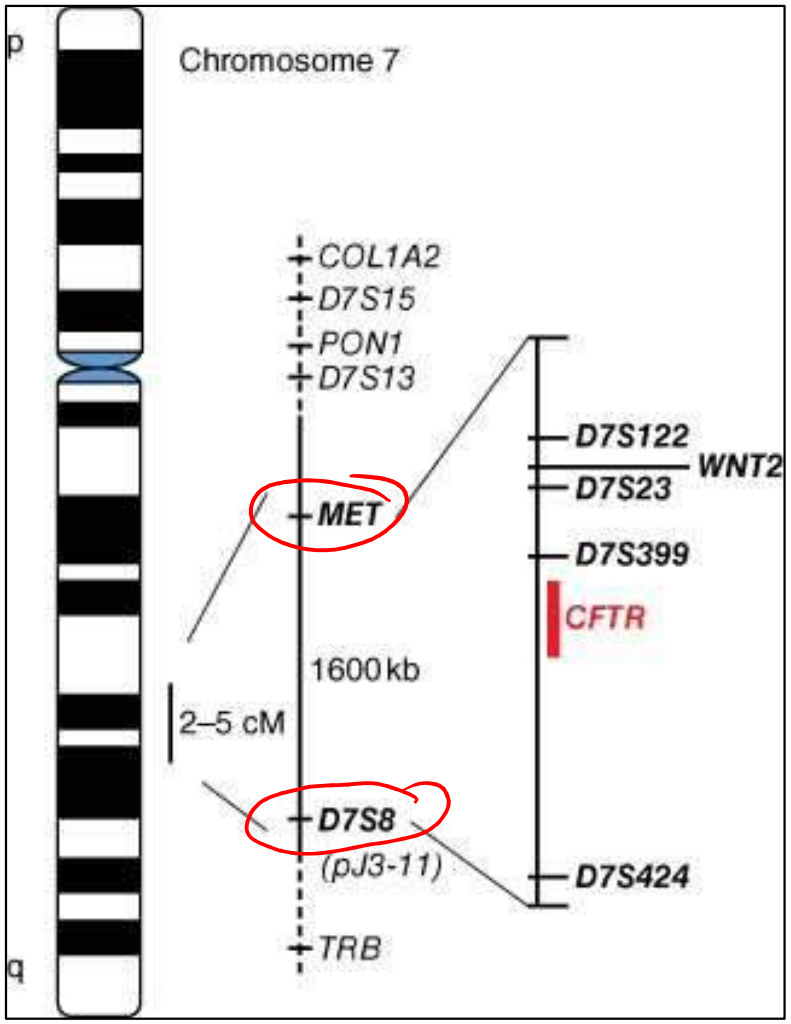


A Linkage Study of Cystic Fibrosis in Extended Multigenerational Pedigrees

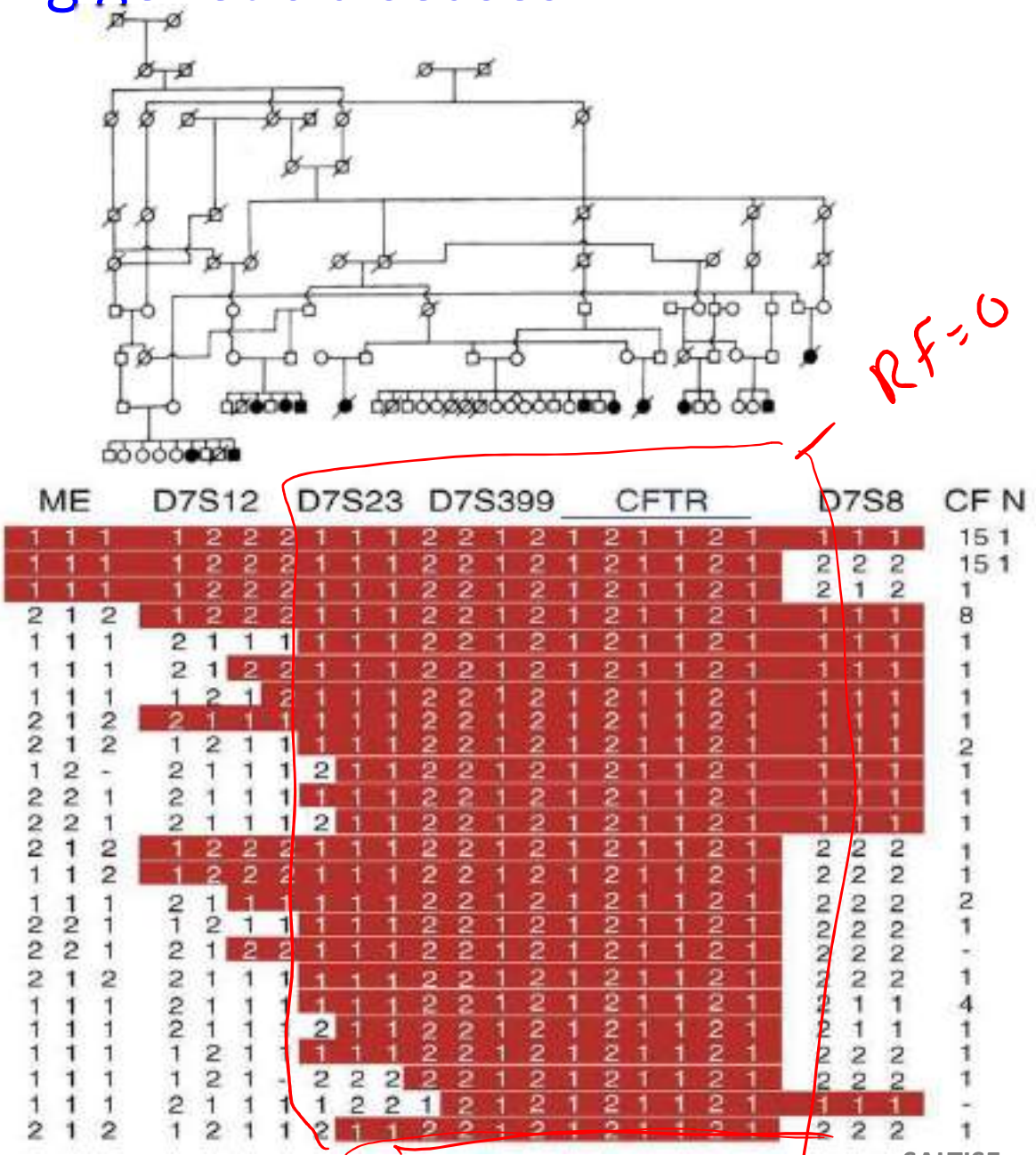
Am J Hum Genet 39:735–743, 1986

↪ DNA markers

An important application for mapping: Finding the genes underlying genetic diseases

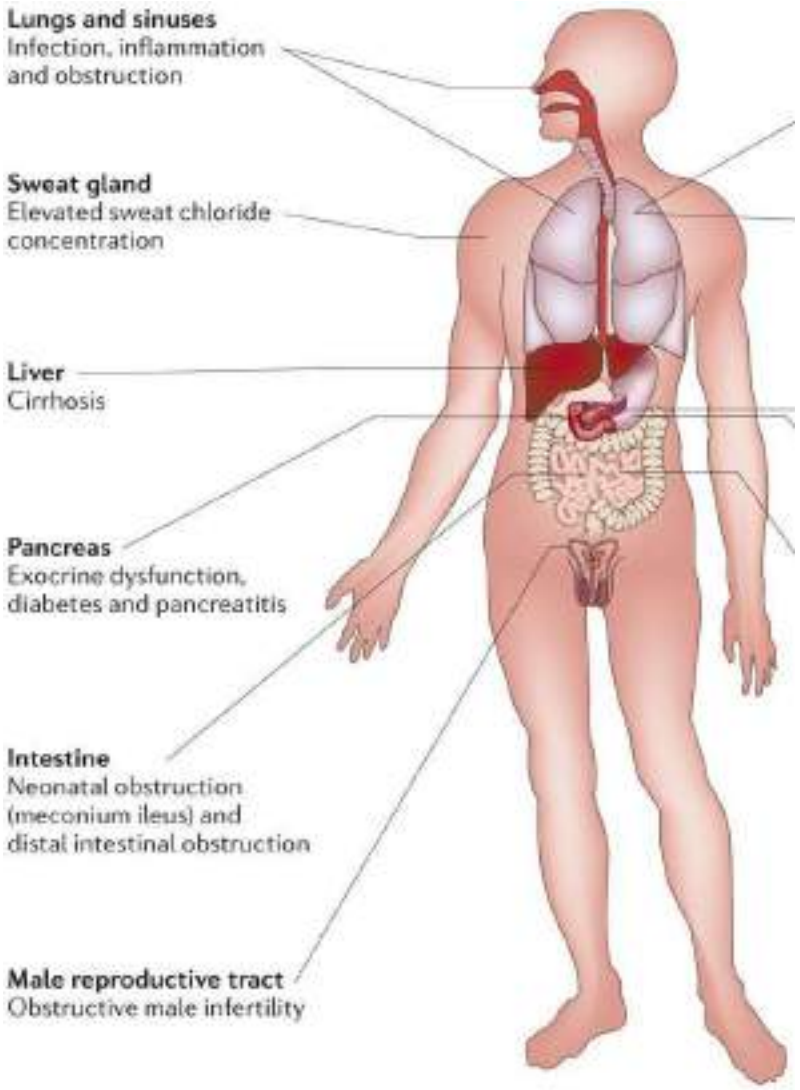


2018 - Encylopedia of Life Sciences – Wiley
https://onlinelibrary.wiley.com/doi/full/10.1002/9780470015902.a0005376.pub2

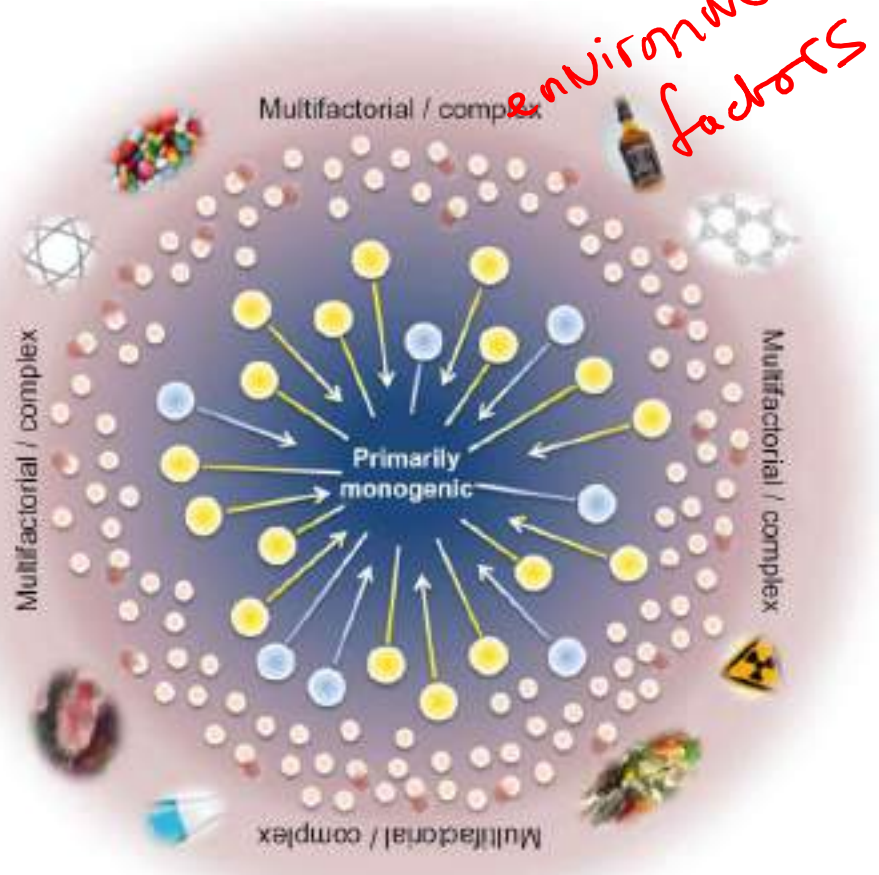


Tsui et al. CSHL Perspect Med 2013;3:a009472

Cystic fibrosis & genetic modifiers



Cutting *Nature Rev Genetics* **16**, pages45–56 (2015)

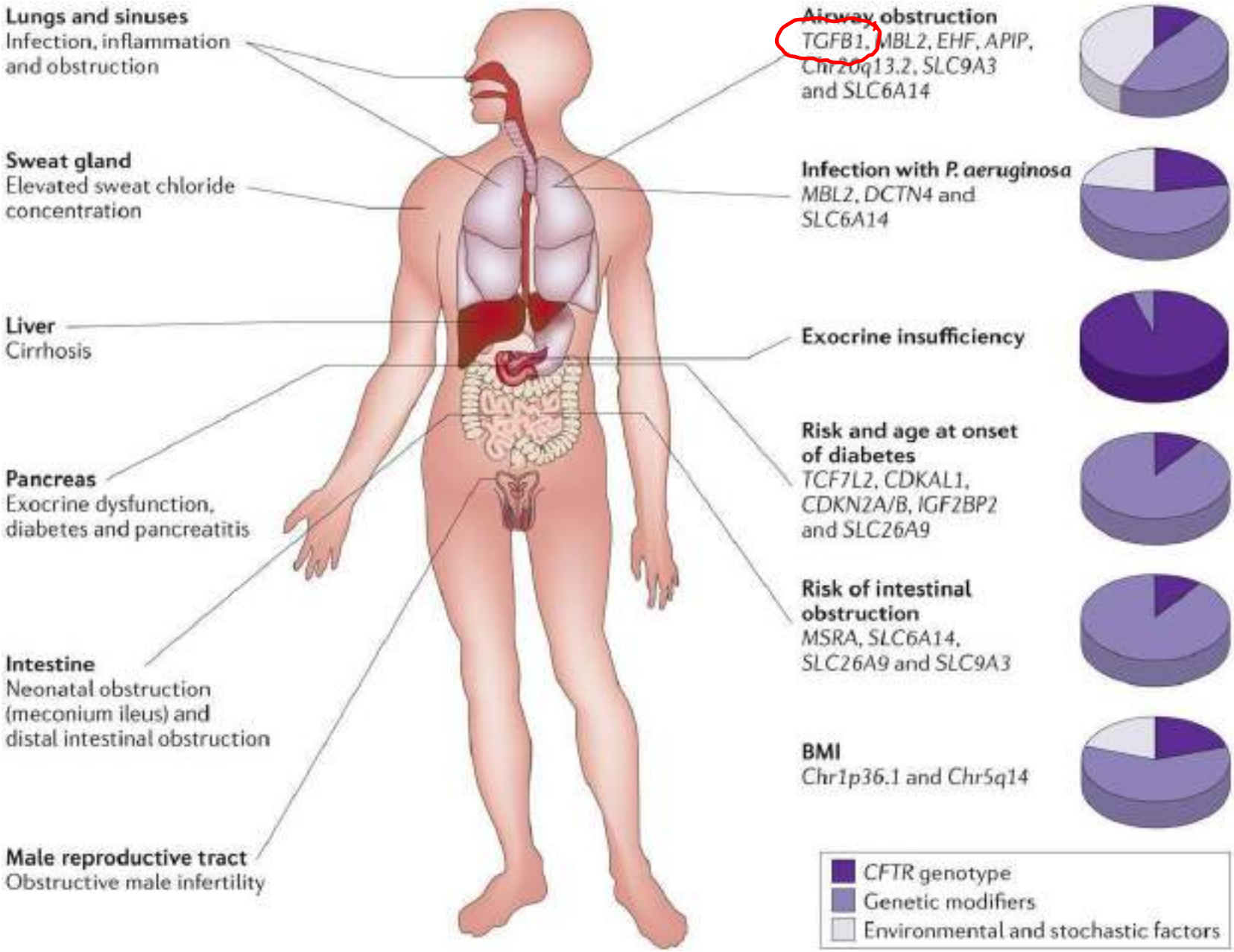


environmental factors

Gallati, Appl Clin Genet. 2014; 7: 133–146.

CF Primarily monogenic severity is influenced by genotype of other genes → modifier genes

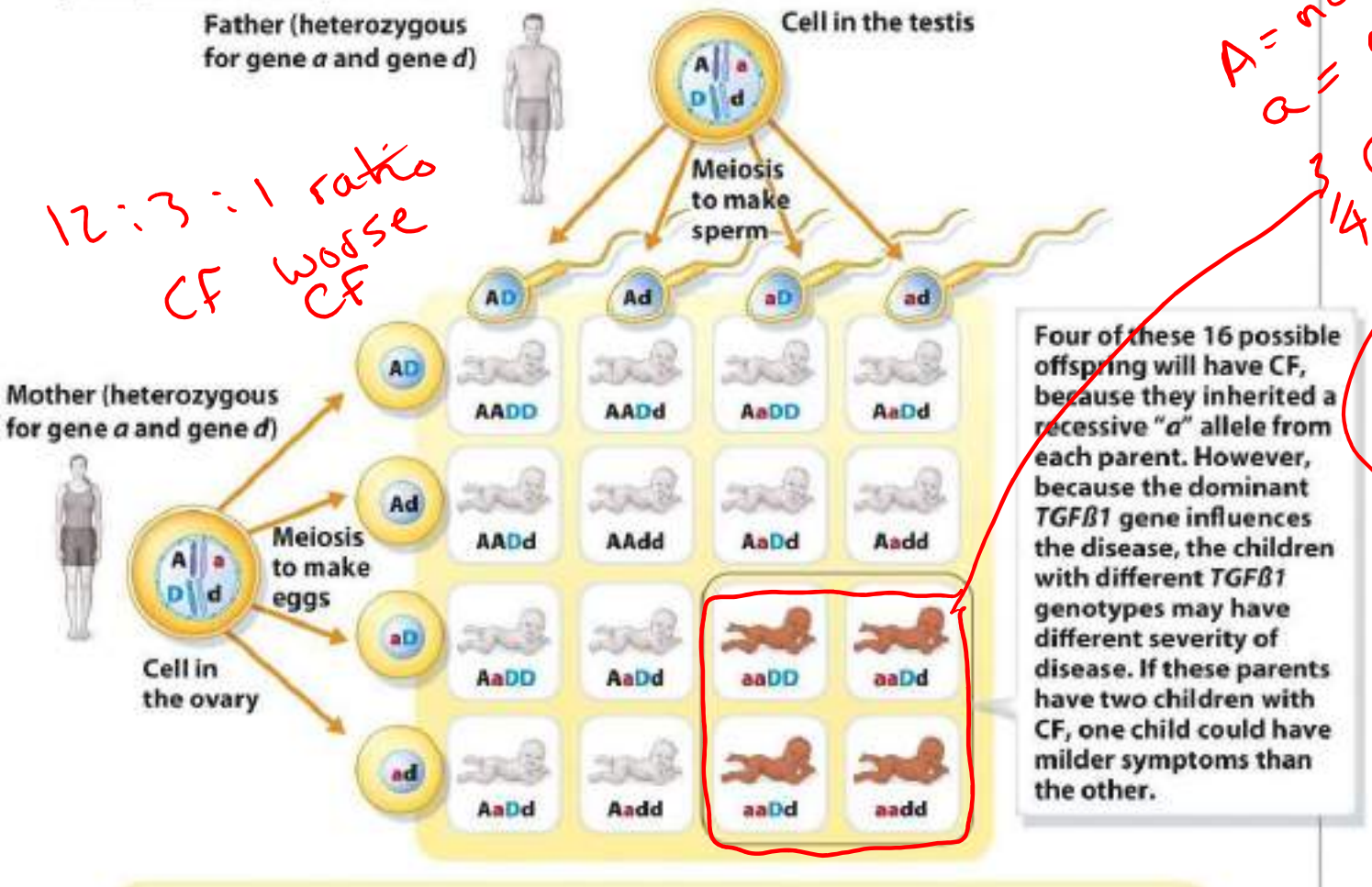
Cystic fibrosis & genetic modifiers



Cutting *Nature Rev Genetics* **16**, pages45–56 (2015)

Cystic fibrosis & genetic modifiers

People with CF differ in the severity of their disease. Some of this variability is influenced by alleles of other genes that sit on other chromosomes. One such gene, called *TGFß1*, is located on chromosome 19, shown here with symbol "*D*." We can also use a Punnett Square to follow the inheritance of two genes, as in the example below.

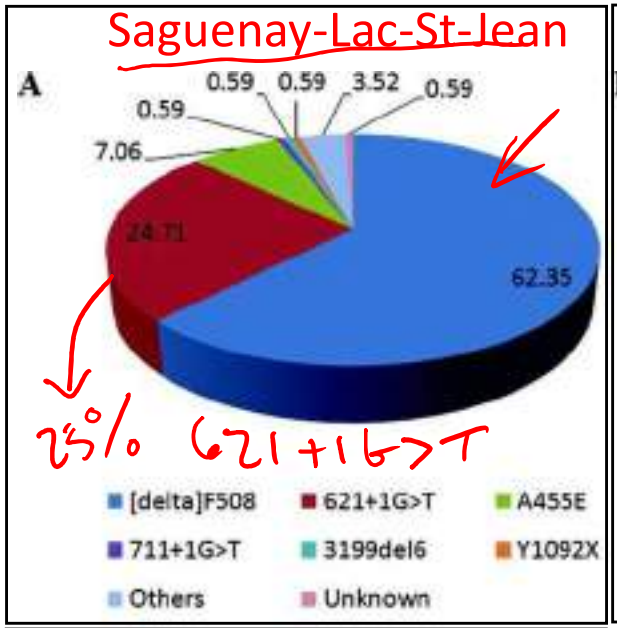


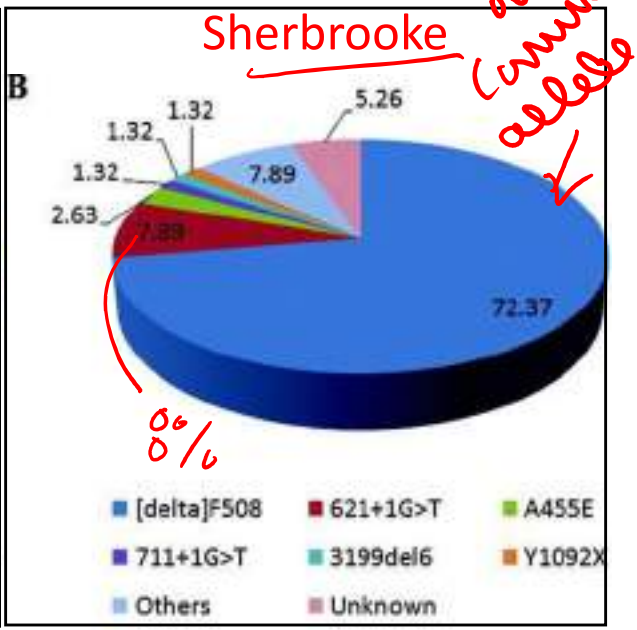
Four of these 16 possible offspring will have CF, because they inherited a recessive "*a*" allele from each parent. However, because the dominant *TGFß1* gene influences the disease, the children with different *TGFß1* genotypes may have different severity of disease. If these parents have two children with CF, one child could have milder symptoms than the other.

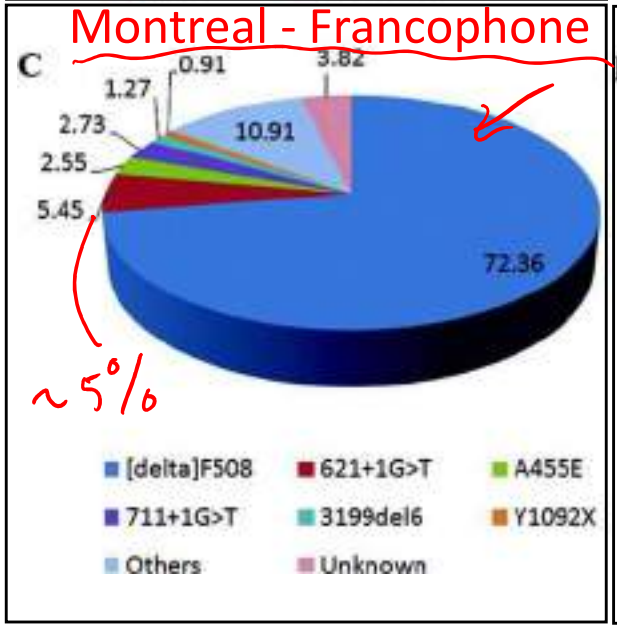
Both parents produce four different allele combinations, with respect to these genes as a result of independent assortment of chromosomes 7 and 19 during meiosis I.

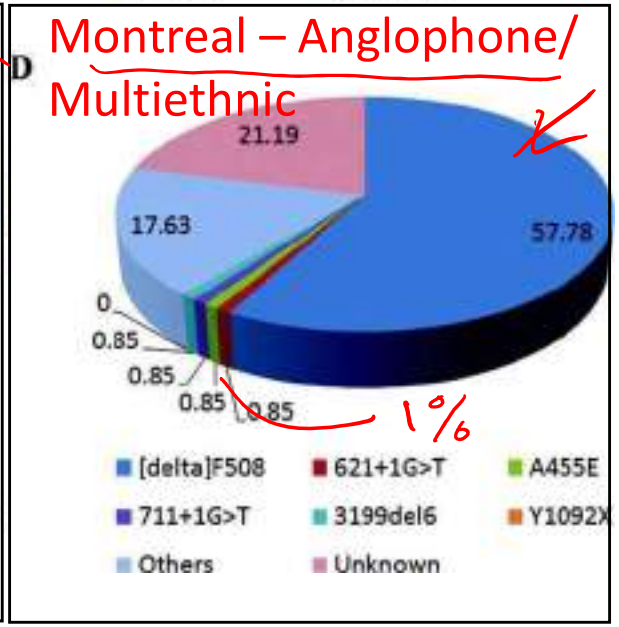
Infographic 11.9
Biology for a Changing World

Population Genetics & Cystic Fibrosis in Quebec





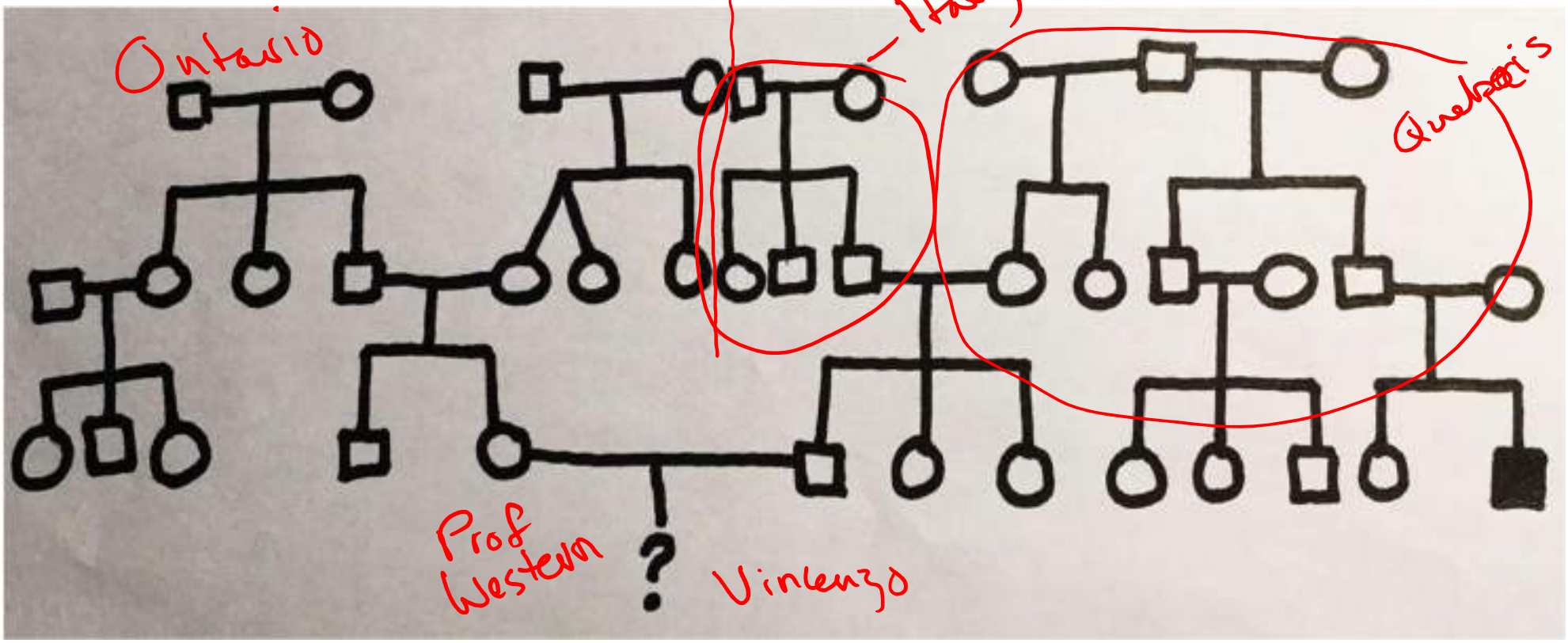




Frequency of CF in Canada ~1/3600
Frequency of CF in Quebec ~1/2500
Frequency of CF in SLSJ ~1/900

Madore A-M, Prévost C, Dorfman R, Taylor C, Durie P, Zielenski J, Laprise C. Distribution of CFTR mutations in Saguenay–Lac-Saint Jean: proposal of a panel of mutations for population screening. *Genet Med* 2008;10:201–216.

Population genetics & genetic counselling

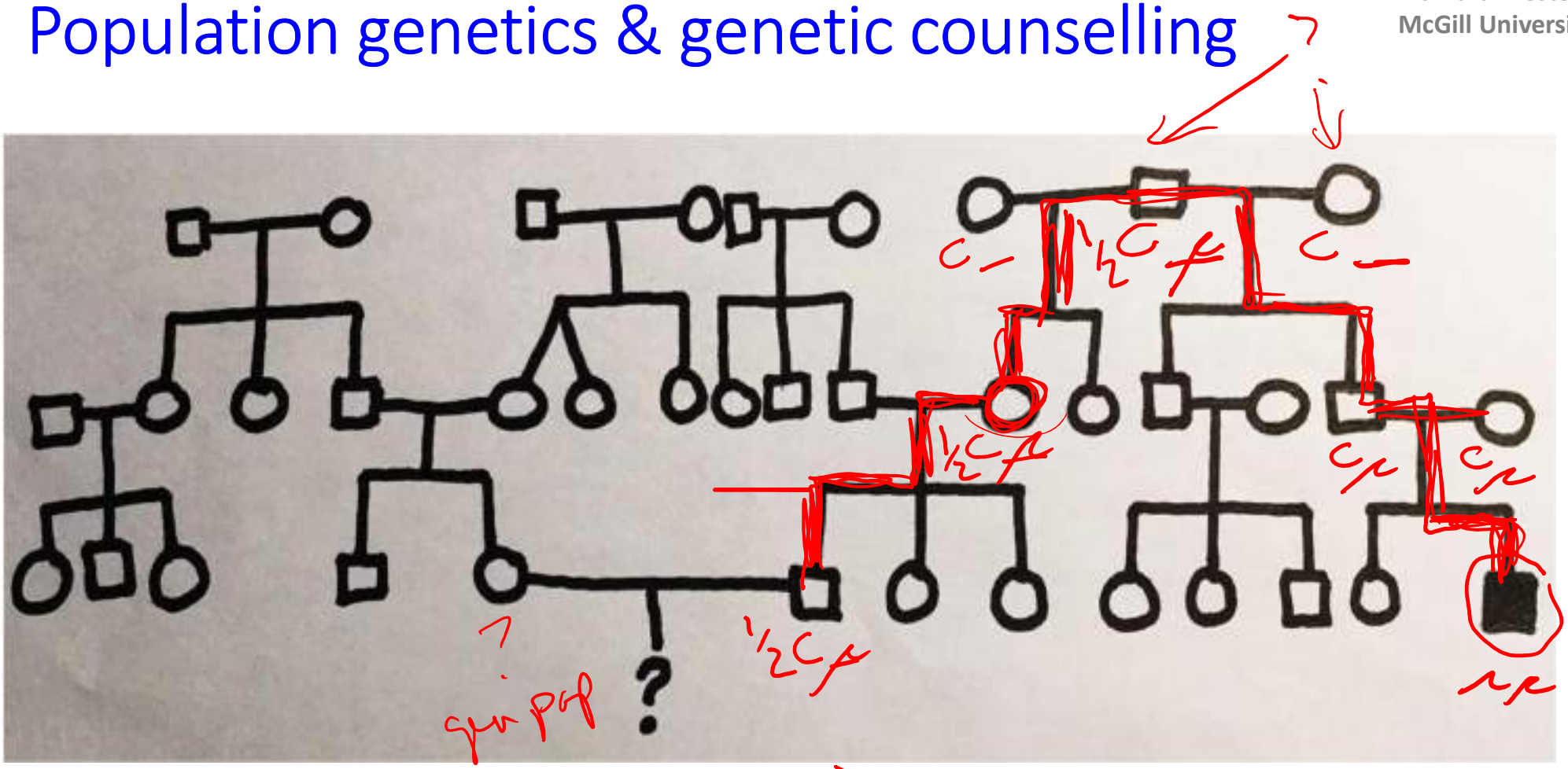


→ P(child) having CF

→ freq of carrier of CF in Canada in gen.
↳ 1/25

A real Quebec pedigree…

Population genetics & genetic counselling



Prob(child w CF $c_f c_f$) = P(Prof W c_f) × P(husband c_f) × P(both pass to child or child is $c_f c_f$)

(General pop of Canadian Carrier for CF = 1/25)

1/25 × (1/2)(1/2)(1/2) × 1/4

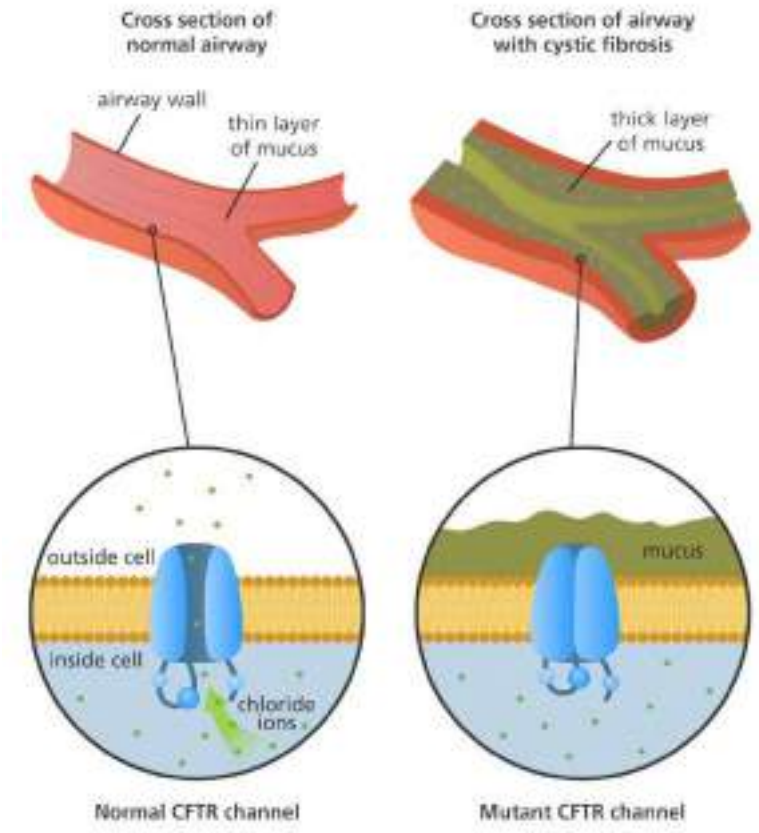
1/25 × 1/8 × 1/4

= 1/800

A real Quebec pedigree…

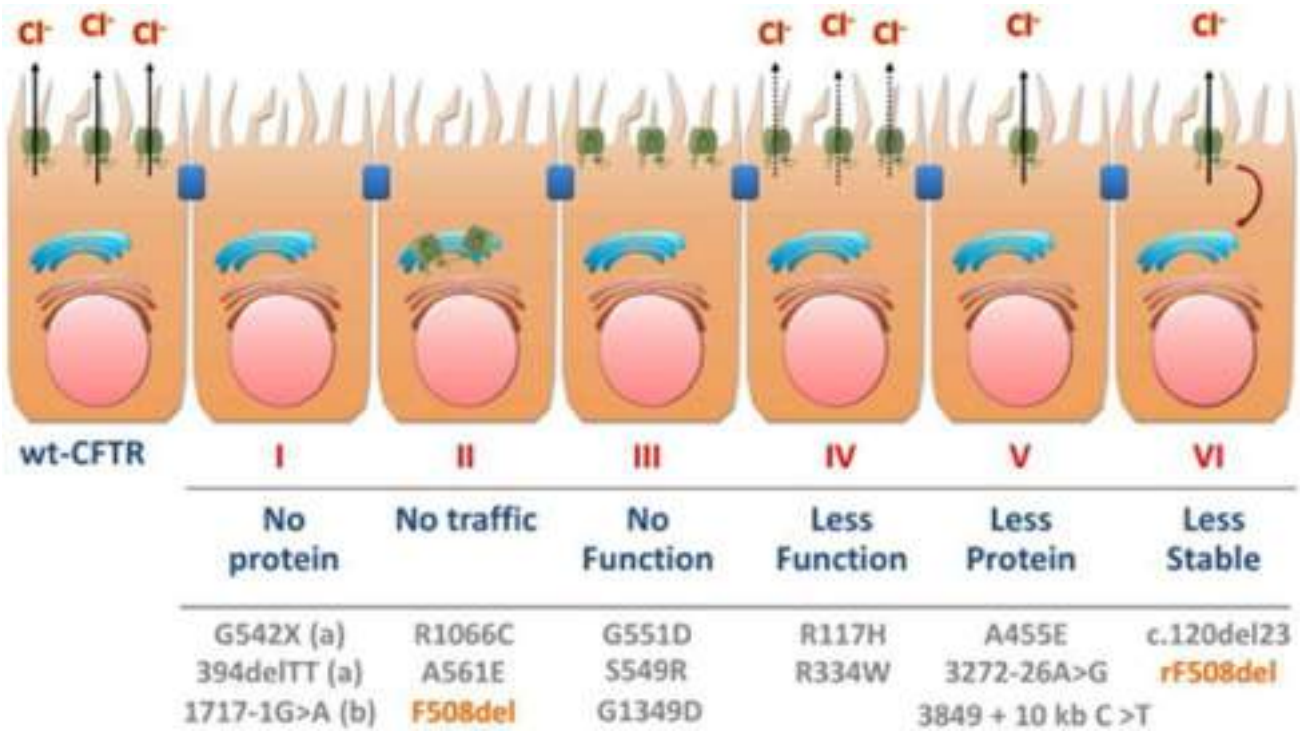
A Case for CF: From Genotype to Phenotype

- Cystic Fibrosis caused by a mutation in the cystic fibrosis transmembrane receptor (CFTR)
- CFTR transports chloride ions across membranes to control transport of liquids and salts
- All mutations cause dysregulation in this chloride transport
- Phenotypes may vary based on the mutation, with varying severity



Genome Research Limited.

A Case for CF: From Genotype to Phenotype



Bell et al., 2015. *Pharmacology and Therapeutics.*

A Case for CF: From Genotype to Phenotype

- Modifier Gene: the expression of one gene alters the expression of another gene often involved in disease pathology
  - Ranges from primary action of target gene to intermediate phenotypes at the cellular organ or system level
  - CFTR mutant mice have differing phenotypes based on the genetic background of the mouse
  - Found a modifier gene in some strains with linkage studies

A Case for CF: From Genotype to Phenotype

Table 1. Genetic modifiers of different features of cystic fibrosis[53]

Gene	Pulmonary Function (FEV_1)	*P. aeruginosa* Acquisition/ Colonization	Intestinal Obstruction	Diabetes	Liver Disease
ADIPOR2			Possible effect[87]		
EDNRA	Probable effect[79]				
IFRD1	Possible effect[74]				
IL8	Possible effect[75]				
MBL2	Probable effect[55,62–64,70,94]	Probable effect[60,70,94]			
MSRA			Probable effect[86]		
SERPINA1	No effect[57,95–98]	Likely no effect[97,99,100]			Possible effect[49]
TCF7L2				Probable effect[37]	
TGFB1	Probable effect[57,59,69,70,73,78]	No effect[70,72,73,78,101]			Likely no effect[49,101]

Probable effect: Association observed in ≥3 independent populations with ≥1000 participants in aggregate.
Possible effect: Association observed in ≥2 independent populations with ≥500 participants in aggregate.
Likely no effect: No association observed in ≥2 independent populations with ≥500 participants in aggregate.
No effect: No association observed in ≥3 more independent populations with ≥1000 participants in aggregate.
N.B.: Some studies include replication populations, which are treated as separate independent populations.

Cutting, 2010. *Ann. N.Y. Acad. Sci.*

Heather Fice, Laura Nilson
McGill University

CASE STUDY LECTURE SLIDES

Modules 3-4

A Case for CF: From Genotype to Phenotype

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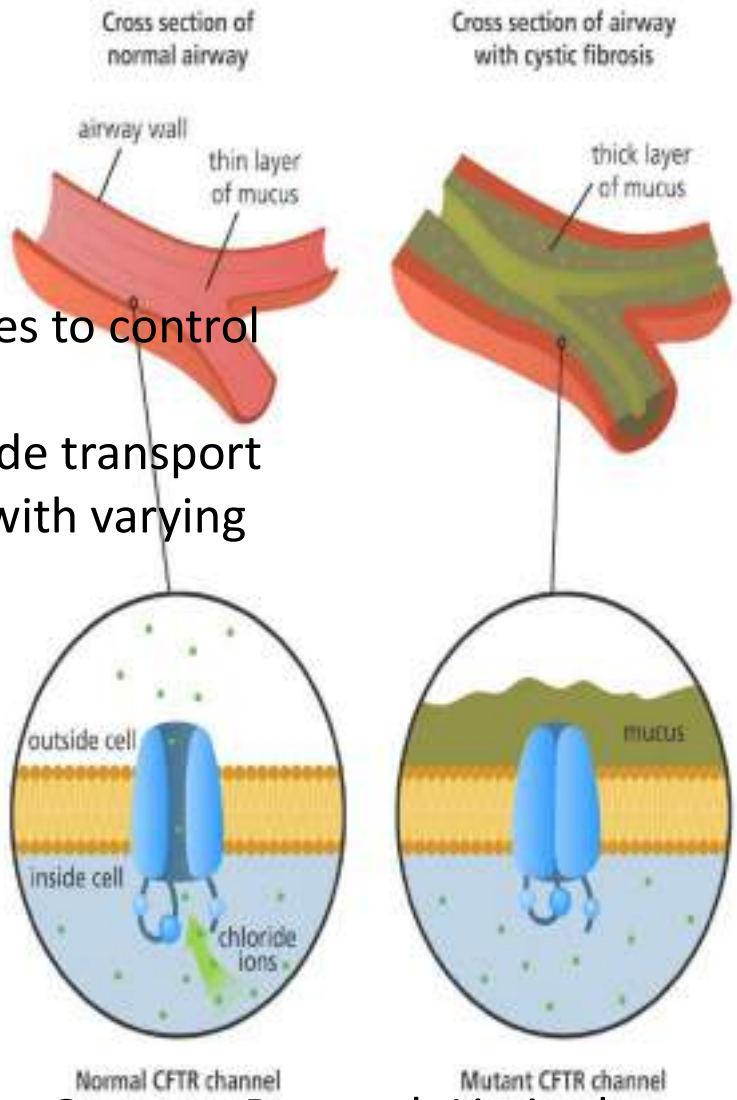
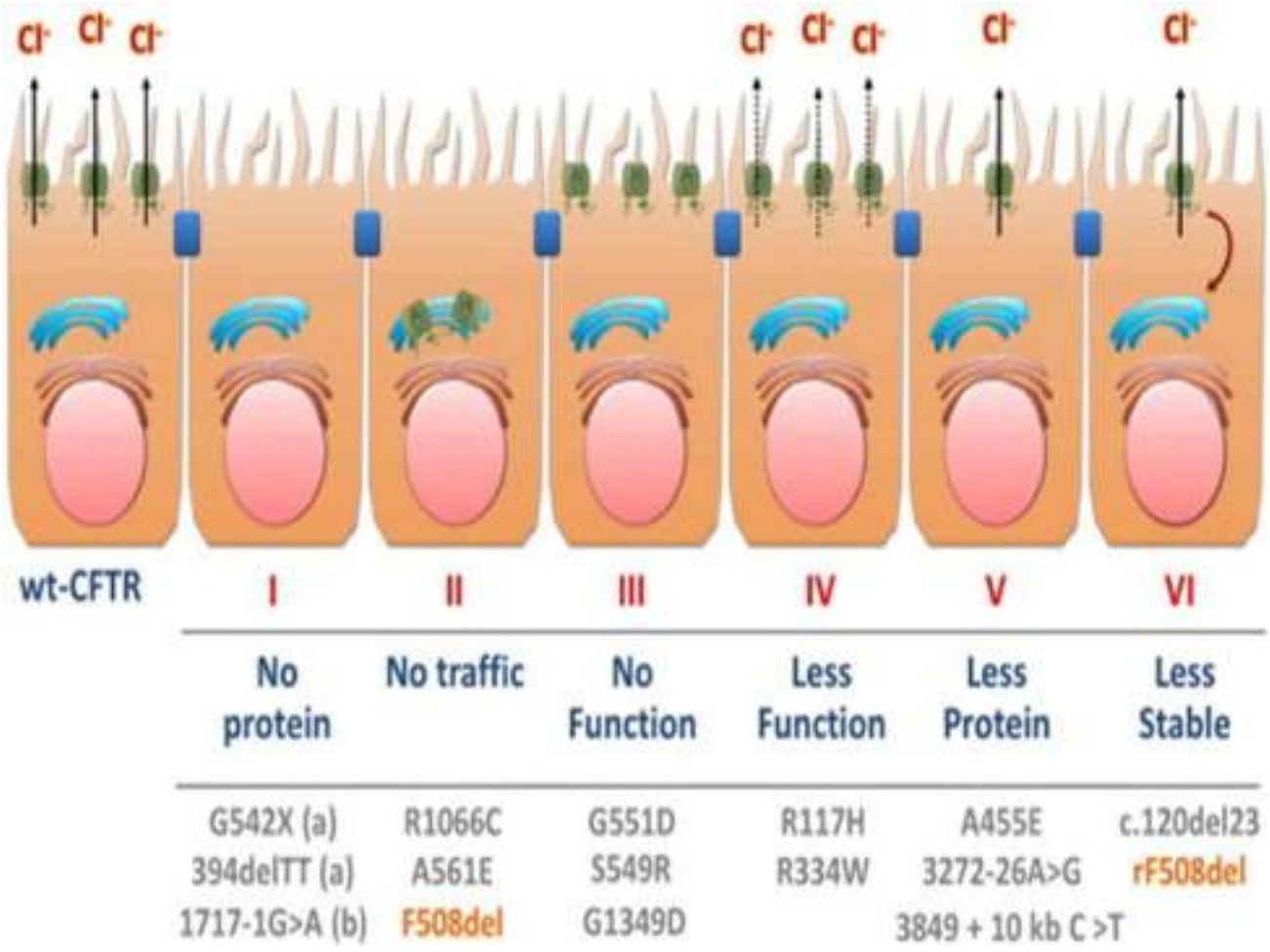


Genome Research Limited.

A Case for CF: From Genotype to Phenotype



Bell et al., 2015. *Pharmacology and Therapeutics.*

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Cutting, 2010. *Ann. N.Y. Acad. Sci.*

A Case for CF: Genetic Screening

Screening for CF will:

- Prevent potentially irreversible consequences on growth
- Potentially decrease risk of contracting lung infections
- Decrease ER visits by families going through diagnosis

Quebec to start screening newborns for cystic fibrosis

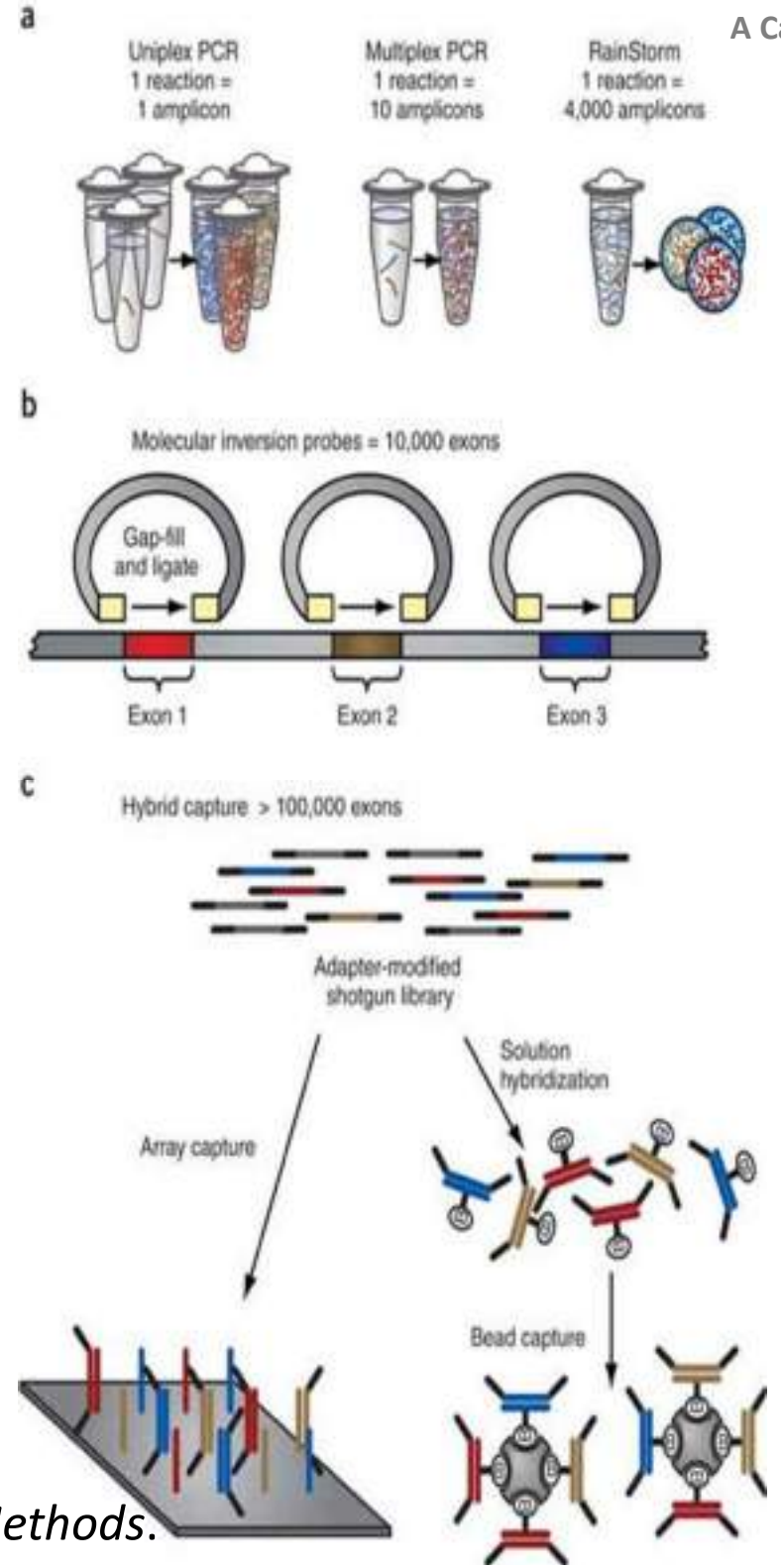
Cystic Fibrosis Canada says this is a "huge win" for the health and well-being of Quebec's children

CATHERINE SOLYOM, MONTREAL GAZETTE Updated: June 8, 2017

Cystic fibrosis affects one in 2,500 babies in Quebec. MICHAEL CONROY / ASSOCIATED PRESS

A Case for CF: Genetic Screening

- Panel Sequencing
  - Targeted gene sequencing for specific mutations related to a disorder
  - Predesigned panels are available for CF, containing the most common mutations



Mamanova et al. 2010. *Nat Methods*.

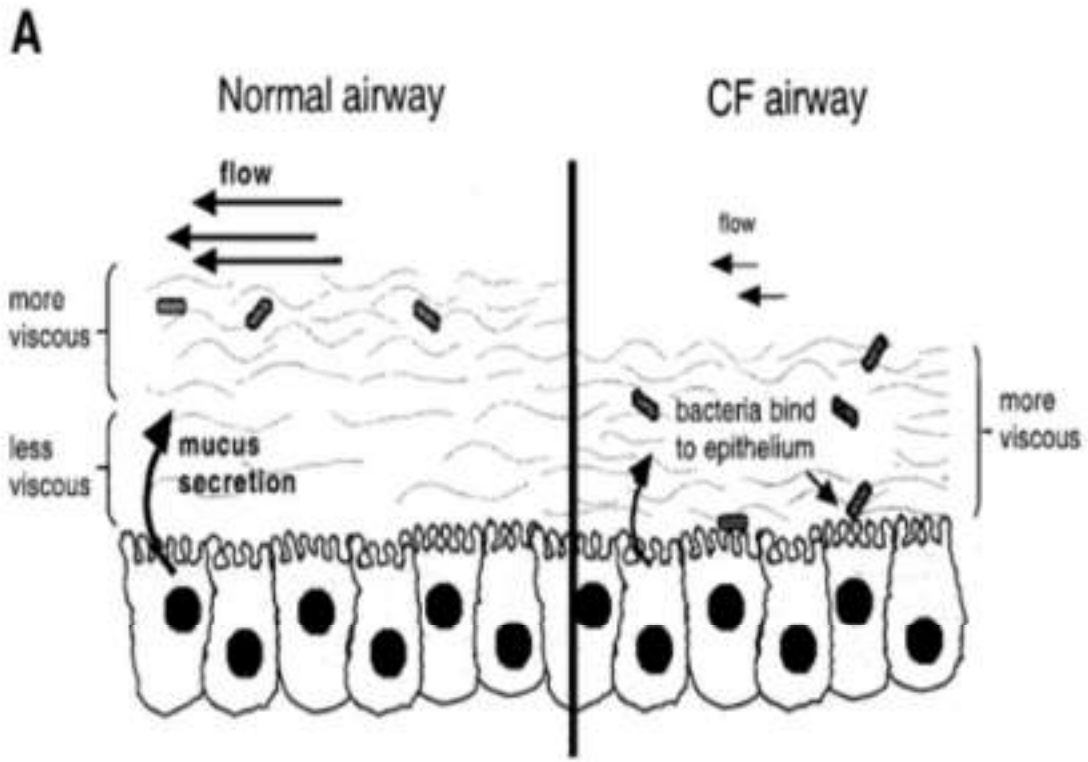
Heather Fice, Nam-Sung Moon
McGill University

CASE STUDY LECTURE SLIDES

Modules 5-6

Drug resistant bacteria and CF

- Lung infection is one of the most common problems with CF because the mucus lining the lungs is thicker and traps bacteria
- Chronic infection with *Pseudomonas aeruginosa* is often the perpetrator in CF patient lung function decline and respiratory failure
- These bacteria can be treated with various antibiotics, but many become drug resistant.



Lyczak, JB. 2002. Clinical Microbio Reviews.

The second immune response is the reason why vaccination works

The **active agent** (the antigen) of a vaccine:

Intact but inactivated (non-infective) pathogen

Attenuated (reduced infectivity) forms of the pathogen

Purified components of the pathogen
that have been found to be highly immunogenic

The vaccine thus induces the primary immune response,
generating the memory cells that are ready
when the (second) infection happens.