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The History and Future of Cystic Fibrosis

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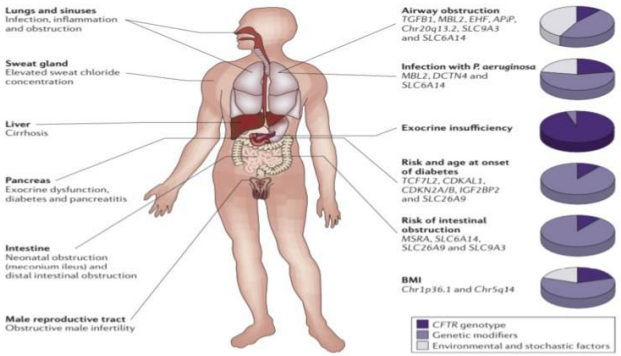
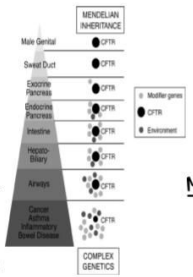
Clinical Presentation



Genotype and Phenotype

- Cystic Fibrosis is an autosomal recessive(1) disease that overwhelmingly affects caucasian populations, often with european descent.
- Single gene(2) disorder: most common allele responsible is a single amino acid deletion(3) at codon position 508 within the first nucleotide binding domain transmembrane conductance regulator (CFTR) gene.
- CFTR is a cAMP dependent chloride channel expressed within the plasma membrane of secretory epithelia in the airways, pancreas, intestine, testis, and exocrine glands.
- This loss of function(5) mutation of the CFTR results in an inability for the mutant delta F508del CFTR protein to leave the ER(4) and is unable to discharge chloride ions across cell membranes.
- An analysis of 36, 696 individuals attributed 70% of CF affected individuals to the F508del. 22 other variants were found to have a frequency of 0.1% or higher and made up for 17.5% of CFTR cases, leaving the remaining variants at a frequency of 0.01-0.1%(9)
- The F508del phenotype is variable with respect to lung function and pulmonary disease but less so with pancreatic function. Lung function variability may be due to the modifying gene transforming growth factor beta(TGFβ1)(8)



Risk of Inheriting CF (11)

- One study based on 3 million CF tests placed the pan-ethnic carrier frequency for Cystic Fibrosis at 1 in 37 people. This leaves the chance of inheriting CF at 0.00018 or about 1 in 5,500 births(11)

References (20)

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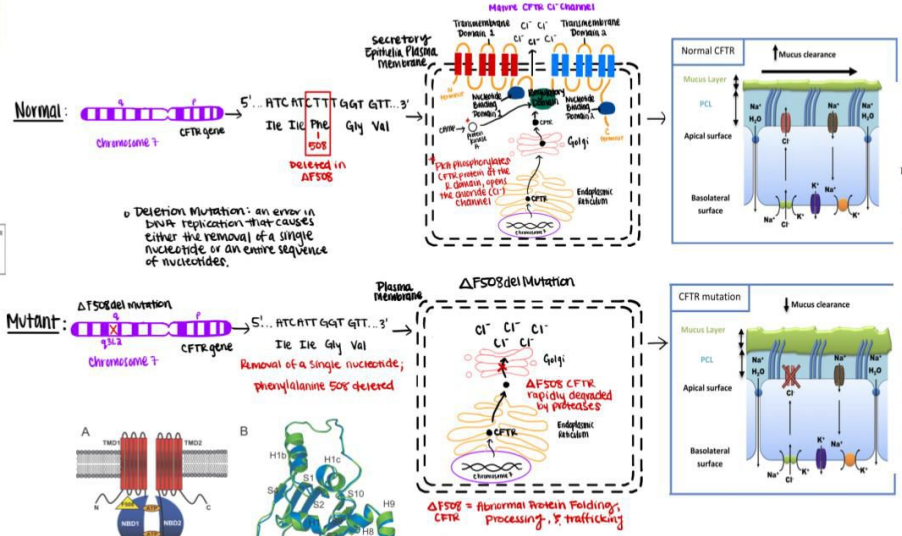
Cystic Fibrosis in Populations (7, 12, 13)

TABLE 1. Filtered Data for CF Incidence Across the Globe[a]

Country or population	Incidence (1 case per X births)[b]	Mutations >0.5%[c]	ΔF508 percent[d]	Reference
These regions passed both Fiber 1 and Fiber 2:				
Finland	25000	4	46.2	Lucotte et al. [1995]; Kere et al. [1994]
Mexico	8500	15	41.6	Grebe et al. [1994]
Sweden	7300	10	66.6	Lucotte et al. [1995]; Schaedel et al. [1999]; Romeo et al. [1989]
Poland	6000	11	57.1	Lucotte et al. [1995]
North Ireland	5350	7	56.6	Romeo et al. [1989]
Russia	4900	12	54.5	Lucotte et al. [1995]
Denmark	4700	6	87.5	Lucotte et al. [1995]
Norway	4500	6	60.2	Lucotte et al. [1995]
Netherlands	3650	9	71.2	Lucotte et al. [1995]; Collee et al. [1998]
Spain	3500	21	52.7	Lucotte et al. [1995]
Greece	3500	22	52.9	Lucotte et al. [1995]
Germany	3300	17	71.8	Lucotte et al. [1995]; Romeo et al. [1989]
United States	2835	10	68.6	Kosorok et al. [1996]; Romeo et al. [1989]
Czech Republic	2833	10	70.0	Lucotte et al. [1995]; Romeo et al. [1989]
United Kingdom	2600	5	75.3	Lucotte et al. [1995]; Romeo et al. [1989]
Australia	2500	8	76.9	Romeo et al. [1989]
Italy	2438	9	50.9	Lucotte et al. [1995]; Gasparini et al. [1999]; Romeo et al. [1989]
France	2356	12	67.7	Lucotte et al. [1995]
Switzerland	2000	9	57.2	Hergenrather et al. [1997]
Ireland	1800	7	70.4	Lucotte et al. [1995]
The following five regions did not pass Fiber 2 Criterion:				
United Arab Emirates	15876	n/a	26.9	Frossard et al. [1998]; Frossard et al. [1999]
Brazil	6902	n/a	47.7	Cabello et al. [1999]; Raskin et al. [1999]; Bernardino et al. [2000]
Estonia	4500	n/a	51.7	Klaassen et al. [1998]
Chile	4000	n/a	29.2	Rios et al. [1994]
Scotland	1984	n/a	71.3	Shrimpton et al. [1991]; Gilfillan et al. [1998]

- The enrichment of Cystic Fibrosis in European descendents is thought to be in part due to past selection imposed by *Mycobacterium tuberculosis*. Heterozygotes were thought to have increased resistance to this bacterium
- CF demonstrates considerable genetic heterogeneity with 1,044 variants known
- 127 CF variants are fully penetrant(F508del included)
- 19 CF variants are indeterminate as to their role in CF
- 12 CF variants have been found be to be entirely non-penetrant(7)

Molecular, Biochemical, and Physiological Pathways (6)



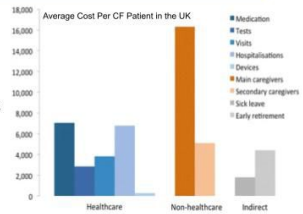
Treatment (16)

General Treatments	Purpose
Airway clearance	Prevent mucus build up
Inhaled medicines	Diluting the mucous
Pancreatic enzyme supplement	Additional nutrients
**CFTR modulators	Fix protein defect

Surgical Treatments	Purpose
Nasal and sinus surgery	Remove clot in airway
Oxygen therapy	Prevent High BP
Noninvasive ventilation	Provide positive pressure
Feeding tube	Treat weight loss and nutritional deficiences
Bowel surgery	Remove blockage
Lung transplant	Perform during respiratory failure
Liver transplant	Perform when cirrhosis occurs

Social Impact

- CF patients have reduced life spans, report lower on scores of quality of life and are rarely able to have their own offspring(19)
- Economic repercussions in countries disproportionately affected by CF, such as Europe and the U.S
- Segregation in the workplace



1606 — First record of symptoms: Children have salty foreheads when kissed on forehead. Reported by Spanish professor of medicine Juan Alonso (Ref: Edelman,A *et al.)*

1938 — Cystic Fibrosis has first official medical report written up - diagnosis done solely by pathological examination

1953 — During a heat wave in New York City, Paul di Sant'Agnese, M.D., and others connect the extra loss of salt by people with CF to the disease's underlying cellular problem

1955 — National Cystic Fibrosis Research Foundation is established

1962 — Cystic Fibrosis has a median age of survival of just 10 years old

1983 — Paul Quinton used microperfused sweat ducts to show CF patients had abnormally low Cl- permeability, led to poor reabsorption of NaCl in sweat Duct(15)

1986 — Frizzell et al. reported for the first time presence of Cl- channels in apical membranes of airway epithelial cells; showed regulation of channels was cAMP (not Ca2+) dependent; resulted in two alternative Cl- channels investigated

1989 — Cystic Fibrosis gene discovered - derived from the sweat duct. Gene discovery confirmed via linkage analysis with F508del. (14)

2000 — Foundation-supported scientists map the entire genome of the most common cause of CF lung infections, the bacteria *Pseudomonas aeruginosa*. This pathogen has increased prevalence at locations closer to the equator and during the summer months(10)

2003 — 3D structure of a portion of the CFTR protein is determined allowing for direct intervention at the level of the protein

2006 — Ivacaftor developed - first biochemical intervention that directly targets the faulty CF protein - small molecule that allows for better function of correctly localized proteins(now used in a 3 drug combination known as Trikafta)

2015 — Median survival ages at birth in F508del homozygous were 46 years (males) and 41 years (females), and similar in non-homozygotes diagnosed at birth. F508del heterozygous had median survival ages of 57 (males) and 51 (females)

2015 — CRISPR Therapeutics and Vertex Pharmaceuticals establish partnership to target CFTR gene

2019 — The FDA approves the lumacaftor/ivacaftor combination drug (Orkambi) for people with CF ages 12 and older who have two copies of the most common CF mutation, F508del

Today — The FDA approves the first triple-combination therapy, for people with CF ages 12 and older who have at least one copy of the F508del mutation. 90% of people with CF could eventually have a highly effective treatment

Future — STOP 2 trial Researchers are trying to determine the ideal amount of time to administer IV antibiotics to treat pulmonary exacerbations(17)

Future — Verona Pharma developing Ensifentrine: acts as bronchodilator and an anti-inflammatory agent in single molecules (18)

Future — In development of miniature organoids that replicate the structure of different tissues using cells from patients with cystic fibrosis (19)