All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

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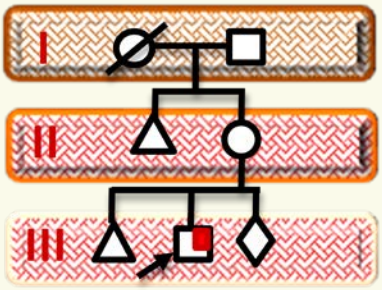
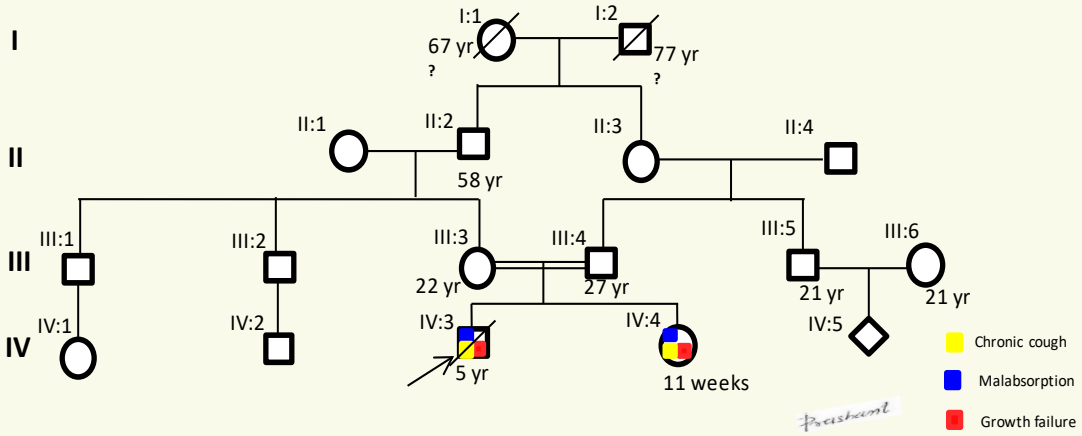
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and a deliberate attempt to enhance awareness for genetic disorders with recent updates.

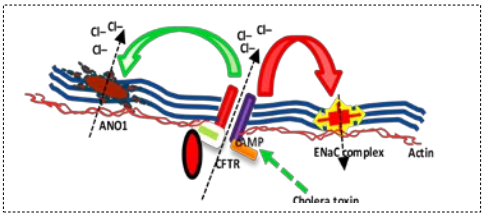


Pulmogenetics-I

Cystic fibrosis (**CF**)/ Mucoviscidosis – **Part (I)**



CF transmembrane conductance regulator (CFTR) Protein cellular interaction in lung epithelium



Green (Stimulatory), Red (inhibitory effect)

Interaction of Cholera toxin with CFTR

- ANO1-Anoctamin 1, calcium-activated chloride.
- δβγENaC- Epithelial sodium channel complex (subunits SCNN1D, SCNN1B, & SCNN1G).
- Chloride loss with cholera toxin might be less severe with CFTR mutation; cholera toxin indirectly acts through CFTR protein.

Insight:

1. How to calculate the risk for CF in fetus IV:5?
2. What is the method for calculating the carrier status of an AR genetic disease in the community?
3. Is there any personalized therapy for CF?
4. Is there any protective effect of mutant CFTR in the community?
5. What is the Genotype-Phenotype Correlation for CFTR?
6. What are cystic fibrosis-like syndromes?

Plausible tenets:

Gene: CFTR (7q31.2); 189.36 kb & 27 Exons

- **Belongs to ATP-binding cassette (ABC) transporter superfamily**
- Transcript length: 6070 bps, 133 domains, and features, thirty-eight splice variants, 218 orthologues, 11 paralogue
- An regulatory anion channel[(1480 AA), Mol. mass: 168,138 D
- Regulate other channels through ATP hydrolysis
- **δβγENaC channel** Inhibitory & non-inihibitory with **αβγENaC**
- Overall, maintain pH, ions & water homeostasis
- Regulate HCO_3^- transportation by SLC4A7
- Role in proper development of Vasa epididymis.

--- Clinical phenotypes of CFTR gene---

Phenotype	MIM number	MOI (Mode of inheritance)
Cystic fibrosis	219700	AR (Autosomal
Congenital bilateral absence of vas deferens	277180	AR
{Bronchiectasis with or without elevated sweat chloride 1, modifier of}	211400	**AD**
{Pancreatitis, hereditary}	167800	**AD**
Sweat chloride elevation without CF	-	-
{Hypertrypsinemia, neonatal}	-	-

(AR- Autosomal recessive, AD- autosomal dominant)

Genotype-Phenotype Correlations for CFTR

System wise	Correlation	Other features
Pancreatitis	Strong	Pancreatic sufficient (PS) or pancreatic insufficient mutations,; behave dominantly (either one or two PS alleles)
Chronic lung disease	Variable	Various modifiers for phenotype
CAVD	Strong	Very high penetration rate and least mutation tolerance

Severity of mutation α phenotype: **(mild mutation) Asymptomatic > CAVD> non-classic > classic (severe mutation)**

Class	Mutation	Phenotype
I	G542X, R553X, W1282X, R11162X, 621– 1G → T, 1717–1G → A, 1078 ΔT, 3659 ΔC	Severe
II	**ΔF508**, Δ1507, N1303K, S549N	Severe*
III	G551D, R560T	Severe**
IV	**R117H, R334W, G85E, R347P	Mild - Moderate
V	3849 + 10 kbC → T,2789 + 5G → A, A455E	Mild - Moderate
VI	120del123, rPhe580del	Mild - Moderate

Personalized medicine: *Ivacaftor/lumacaftor or combined (≥ 12 years), **Ivacaftor (≥2 years)

Ivacaftor [VX-770; N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide]

Syndromes overlap with CF

- Homozygous mutation in **the GUCY2C gene (601330)** on chromosome 12p12 leads to **isolated meconium ileus. GUCY2C,** an intestinal transmembrane receptor, regulates chloride secretion **through the CFTR.**
- **αβγENaC channelopathy** (Mutations in different subunits epithelial sodium channel (SCNN1) B, A, G- beta, alpha & gamma) lead to bronchiectasis **with or without** elevated sweat chloride 1,2,3**(BESC1,2,3)-** This group of disorders does not have non-pulmonary components) -previously classified as **'nonclassical' cystic fibrosis**
- **Young Syndrome (279000)** azoospermia, obstructive, and chronic sinopulmonary infections (sinusitis-infertility syndrome) **clinically overlap with CF but without GIT features & CAVD.**

Risk calculation of CF in fetus IV:5- 1st calculate the **carrier frequency** (CF) by Hardy Weinberg Equilibrium: **2pq**
q2 ≈ disease incidence (AR) ≈ 1/3600, so q = 1/60
p = (1-q) so, 59/60 ≈ 1; SO, 2pq = 2 X 1/60 X1 = 1/30 in the population
Risk of CF in IV:5 = 1/2 X 1/30 X 1/4 = 1/ 240

Protective role of CFTR gene mutation for GIT infection: microbial toxins (Like cholera toxin) work through overactivation of chloride channel, so mutant CFTR protein shows resistance to these toxins.

Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut. 2007 Aug;56(8):1153-63. doi: 10.1136/gut.2004.062786. Epub 2007 Apr 19. PMID: 17446304; PMCID: PMC1955522.

Thought Riveting:

- ***Is it true that cystic fibrosis pathological variants are significantly less in Asian as compared to Caucasians on the ground? If yes, why?***
- ***What are obstacles in using cholera toxins as therapeutic agents for CF?***
- ***What are the newer read-through agents (modified aminoglycosides) for CF & DMD?***
- ***How does the poly T tract of intron 9 affect the CFTR phenotype?***
- ***What is the role of ivacaftor in the treatment of other channelopathies?***

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