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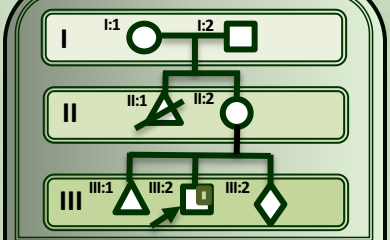
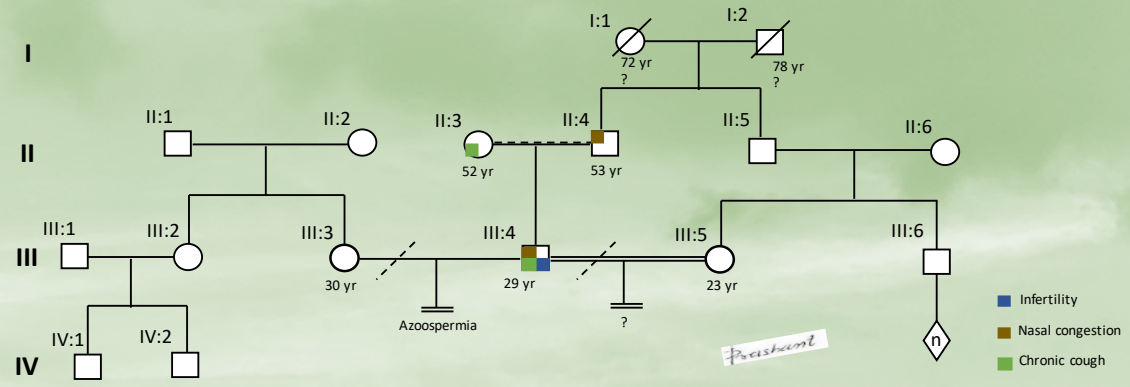
Pulmogenetics-XI - Syndromes associated with Bronchiectasis / Syndromes overlap with CF / Young's Syndrome

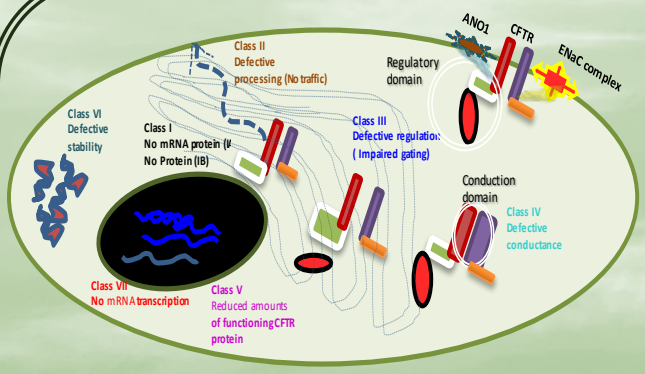


From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.



Genotype and Phenotype of CFTR



Class	Mutations	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 (≥ 1 year)**, **Tezacaftor/ivacaftor (≥6 yrs)** for homozygous ΔF508
Ivacaftor (≥4 months) for even having one CFTR mutation
Elexacaftor/tezacaftor/ivacaftor (≥6 yrs) for compound heterozygous mutations with one should be ΔF508 for therapy

- ANO1-anoctamin 1, calcium-activated chloride channel, ENaC- epithelial sodium channel complex inhibit -SCNN1D, SCNN1B and SCNN1G

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

Insight:

1. Is the Young syndrome a CFTR gene spectrum disorders or atypical ciliopathy?
2. How to approach a case having recurrent infections (especially respiratory tract) with infertility with a normal baseline immunological and dysmorphology workup?
3. How would you counsel the **Case III: 4 for infertility**?
4. What are the key differences between various generations of NGS?
5. What are the steps of doing NGS (next-generation sequencing)?

Plausible tenets:

Approach: A case with recurrent infections (especially respiratory tract) with infertility with normal baseline immunological and dysmorphology workup Clinical phenotypes:

Features/ Diagnosis	Cystic fibrosis	Immotile -cilia syndrome	Young's Syndrome
Onset	Early	Early	**Late**
Gametogenesis	Normal	Normal	Normal
Vas deferens	**Obstructive**	Normal/ **May be**	**Obstructive**
Pancreatic Exocrine insufficiency	Yes /**variable**	Normal	**Normal**
Recurrent URTI	Yes/ **variable**	Yes	**Yes**
Recurrent LRTI	Yes/ **variable**	Yes	Yes
Bronchial biopsy	**Inflammatory changes**	Abnormal cilia	**Inflammatory changes**
Sweat Chloride test	Normal to high values	Normal	Normal

Overlapping conditions:

Bronchiectasis and nasal polyposis (BENP) OMIM No. 620984 (Gene **WFDC2**): recurrent infections (especially respiratory tract) with **only FEMALE** infertility with normal baseline immunological workup

Leptin deficiency or dysfunction (LEPD) OMIM No. 614962 (Gene LEP): recurrent infections (especially respiratory tract) with infertility (hypothalamic **hypogonadism**) with or without immunological dysfunction, **AND EARLY-ONSET SEVERE OBESITY**

X-linked congenital bilateral aplasia of the vas deferens (CBAVDX) OMIM No. 300985 (Gene ADGRG2): Obstructive azoospermia

Molecularly sequencing could be classified in three broad categories

Features / **Generation sequencing**	**Frist**	**Second**	**Third / four**
Number of sequencings	Single	Multiple & parallel	Multiple Single
High throughput data	No	Yes	Yes
Base pair fragment (Approx)	500-1 kb	50-500	300 kb to 10^6
Short/Long/ultra long read sequencing	Short & **SGS#**	Short	Long-ultra
Cost per base pair for large data	Very costly	Costly	Cost effective
Can sequencing any part of genome	No	No	Yes
Error rate per base pair	Very low	Low	High
Molecular technique	Chain termination	*SBH, SBS, & RTS	@SSS by ZMW & BN
Examples	Sanger, Maxam & Gilbert	Illumina, Solexa, Ion torrent	Oxford Nanopore, PacBio

#SGS- Sanger based short-gun sequencing used for a large read, @SSS single-strand sequencing by (ZMW) zero-mode wavelength, and biological nanopore (BN). *SBH- sequencing by hybridization, SBS- sequencing by synthesis, RTS- reversible terminal sequencing

Four basic steps of doing NGS (next generation sequencing)

Key points/ Steps	**First**	**Second**	**Third**	**Fourth**
Name	Sample preparation	Library Preparation	Sequencing	Data analysis
Initial action	DNA isolation	Ligation of adaptor & Barcoding	Shift the PCR product in flow cells	Quality check of Base calling (data Acquisition)
Further actions	Quality check	1. Size selection 2. Amplification 3. Purification 4. Quality check	Massive Parallel sequencing of PCR products	1. Read alignment 2. Variant calling 3. Variant annotation
Time	4 to 24 hrs.	24 hrs.	1-11 days*	1-11 days*

***Depends upon system, data and technique**

Counsel the family for Case III: 4- After completing the basic workup for infertility, the management plan could be the microsurgical process, which has a high success result for obstructive causes. Because common genetic diseases can present with a rare and unusual phenotype, NGS-based tests can be planned with proper counselling for their yielding and limitation even if there is a lack of guidelines after doing a literature review.

Explanations for mismatch between genotype & phenotype – final expression of a single gene depends upon various factors from mRNA to protein synthesis, and post synthesis various secondary modification processes. Besides that, RNAs, and proteins interact with each other more than what we know even at present knowledge. In our life span, protein function and even gene expression are continuously influenced by external genetic environment (metagenomics), internal environment (stress-induced mutagenesis) and physical factors (temperature, nutrients, UV light, microfibers and toxins).

Thought Riveting:

- ***What is the impact on CFTR protein structure and function with the 5T allele of intron 8?***
- ***Can the 12TG-5T-470V haplotyping be used as a first-line screening tool for obstructive azoospermia?***
- ***Is Young's syndrome an environmental disorder because of poor hygiene? How is mercury exposure relate to the recurrent sinopulmonary infections and later obstructive azoospermia?***
- ***Could Elexacaftor/tezacaftor/ivacaftor be used for other protein trafficking disorders?***
- ***Are complex diseases representing a spectrum of epimutations?***