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

Rishi Vansh

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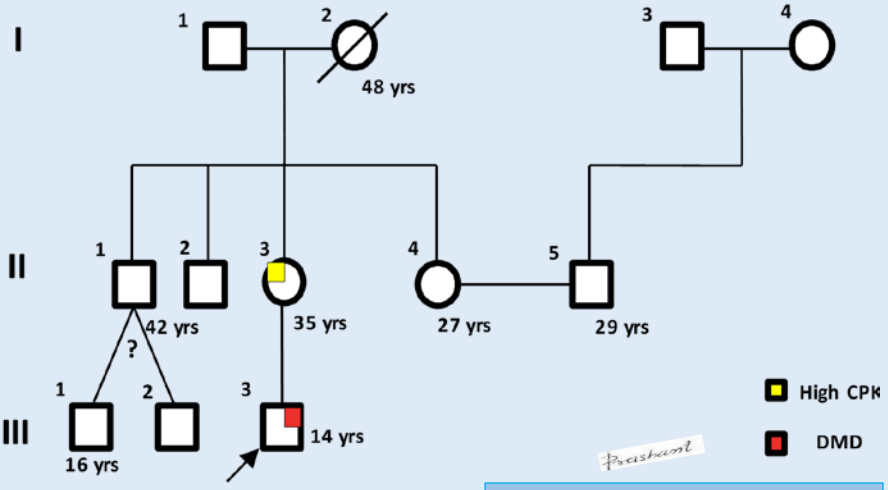
From the desk of Editor

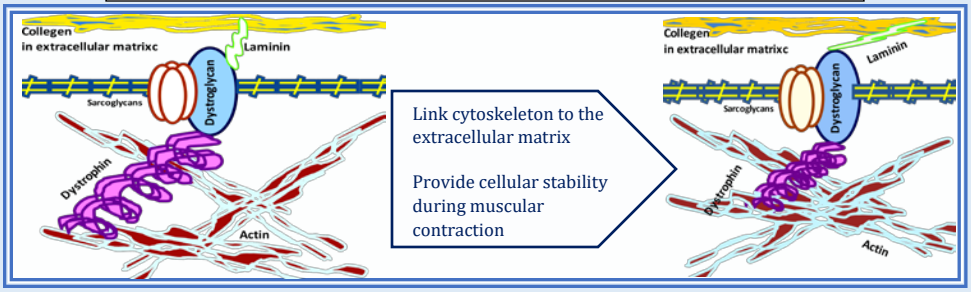
The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and deliberate attempt to enhance awareness for genetic disorders with recent updates

Neurogenetics -I: Duchenne muscular dystrophy (**DMD**)



DMD– Duchenne muscular dystrophy
CK/ CPK - creatine phosphokinase

Dystrophin restoring cell membrane with other proteins



Insight:

1. What is the surveillance guideline for a mother having a child with DMD [**Case II (3)**]?
2. What is the success status of gene therapy in DMD?
3. What is the current medical practice recommended for DMD?
4. Why DMD gene has high mutation rate?
5. What is the CRISPR gene editing?

Plausible tenets:

Dystrophin gene: Cytogenetic band: **Xp21.1** (as per Ensembl), 79 exons, >2.2 Mb** (Inheritance **X Linked**)

- The **largest** homo sapien gene, with several spectrin repeat sequences, high germline mosaicism
- **Phenotypes:** DMD, Becker MD & **Cardiomyopathy-dilated 3B** (Only **X-linked** dialted cardiomyopathy)
- **17 Isoforms**(functionally similar proteins) because of **alternative promoters** & **peculiar splicing** events involved
- **In Nervous System** : stabilizes the sarcolemma & synapses by anchoring postsynaptic receptors in transducing signals. Dystrophin **isoform Dp427c,** especially expressed in neural tissue
- High de novo mutation rate (33%) due to genomic location, large size, high recombination rate & repeats
- **Mutations type**: Approx 65-80 % **CNV***(65% deletions & 5% dupications) & remaining point mutations

Dystrophinopathies

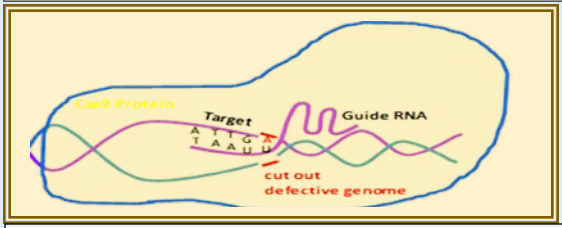
- **The commonest** muscular dystrophy in childhood (Incidence - 1 in 3,500 live male births)
- **DMD:** Symptomatic **< 5yrs** of age, Nonambulatory **<13 yrs**, CPK level **>10 times**
- **Becker MD**: Milder phenotype due to partial preservation of protein function, ambulatory till **16 yrs,** neck flexor muscle strength is preserved & CPK level **>5 times**
- **Cardiomyopathy, dilated, 3B** : More severe & early onset **CHF between 20 to 40 yrs**
- **Surveillance for apparently asymptomatic females**: CPK level **(≥ 2 to 10 times),** education for disease, detailed cardiac evaluation & monitoring (every five years after 25 years of age)
- **Therapy**: **Symptomatic, physiotherapy** & **steriod**(therpay of choice between 5 to 15 years)

***CNV (copy number variation)**: loss or gain of genomic sequences as deletions or duplication resulting in gene imbalance; ****1 Mb = 10^6 base pairs**

Gene Therapy (Two types)

- **Genomic editing** (Mutation specific): Exon skipping of **Exon 51** with **Eteplirsen** [Morpholinos antisense oligonucleotides], CRISPR gene editing
- **Gene transfer (mini Gene copy):** "micro" or "mini" dystrophin, utrophin

Concerns: Cost, ethics, production, limited correction, immunogenicity, not curative, long term outcome, effects on non-muscular tissues with added copy (Not a target tissue therapy), still evolving, FDA approval, development phase 1/2 /...3



CRISPR (Cas-9 most common enzyme) gene editing technique

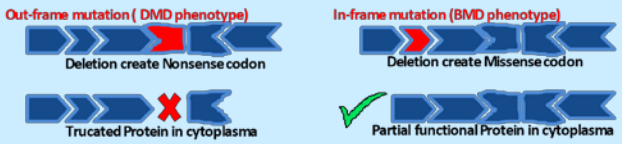
- Adapted from genome editing system in bacteria
- Replaces normal genome with abnormal
- Prospective adequacy in treatment
- Need high doses of vector and high fidelity

Initial results of small oral molecule compounds like Ataluren (RTC), Idebenone (adenosine triphosphate [ATP] modulation), Ezutromid (utrophin modulation) and Givinostat (histone deacetylase inhibition) are not much encouraging

Read-through compounds (RTCs): Certain substances provide the ability for nonrecognition of stop codon in the translation machinery leading to a read-through to produce a functional protein. Two types: aminoglycoside & no aminoglycoside compounds (Ataluren)

Genetic Counselling for Case II (4), 27yrs lady

- **Up to 50 % chance to be a carrier**
- **CPK & carrier testing** (MLPA for CNV)
- **scenario 1-**50% males to be affected if positive
- **scenario 2-**comparable population risk if negative



Thought Riveting:

- ***Is it possible to alter the clinical disease course with any non-steroid or non -molecular medicine?***
- ***How to evade ethical predicament in germline gene therapy?***
- ***Is it ethical to enroll the patient for a gene therapy research project? Who will pay post-research?***
- ***What is the feasibility of CPK based test in universal screening of carrier state in low resource areas?***
- ***How safe are small molecule medicines like ezutromid, idebenone & givinostat with respect to their affects on the whole genome?***
- ***Are modifiers of splicing machinery the emerging therapy for DMD?***

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