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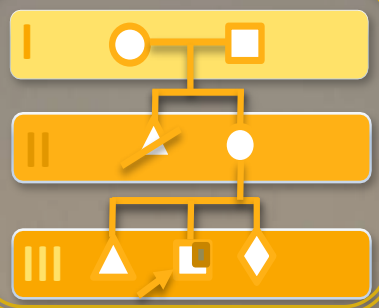

From the desk of Editor

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.

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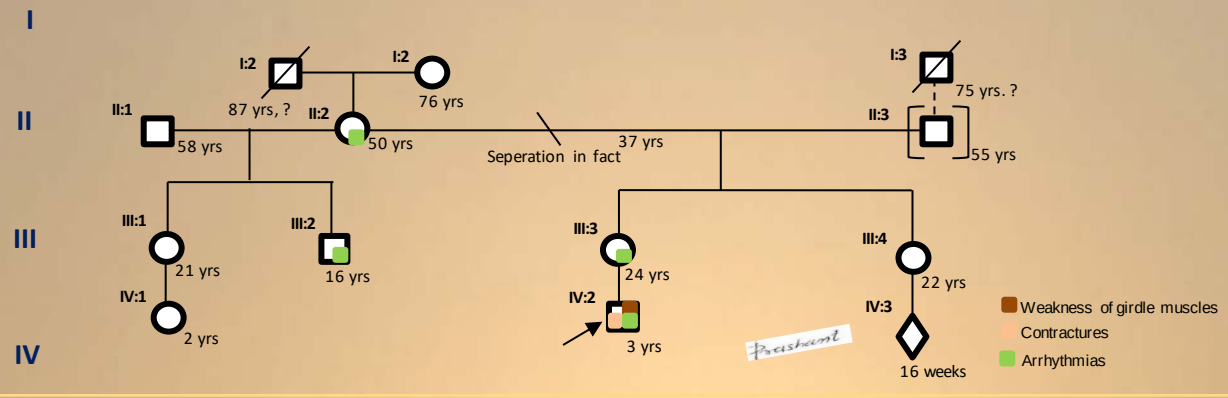
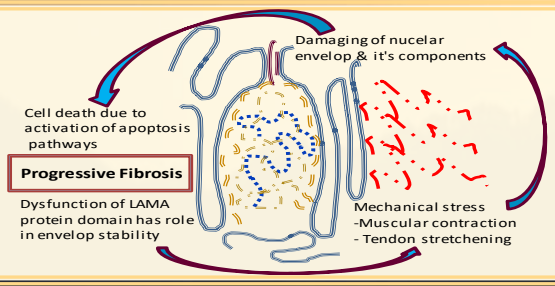
Progeroid Syndromes Like (PSL)-II / LAMIN A/C related disorders/ Emery-Dreifuss Muscular Dystrophy (EDMD) Type 2 & 3



Possible mechanism for EDMD with LAMA1 mutations

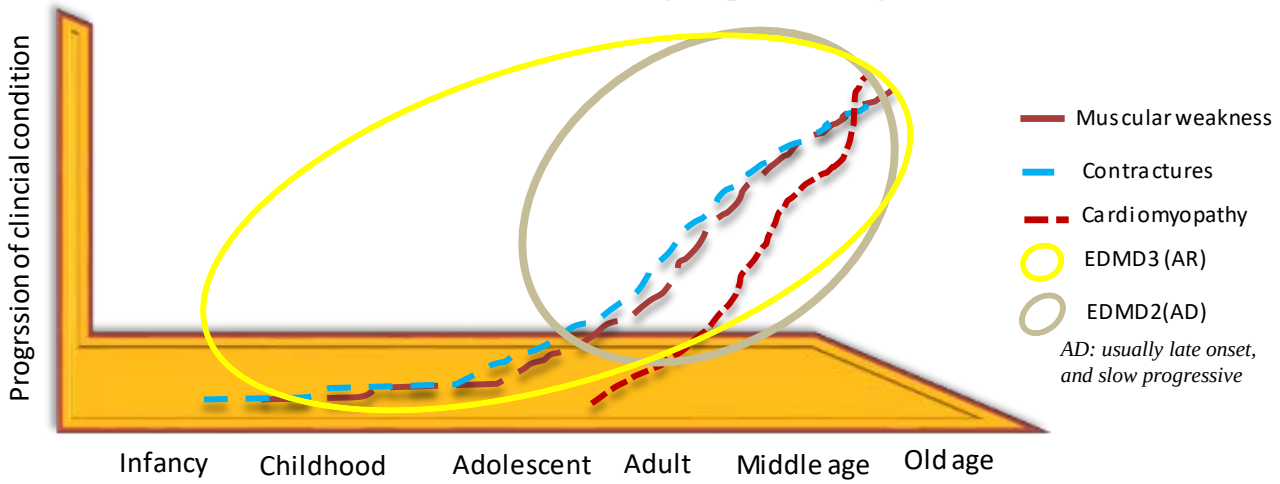


- Mammalian Lamins have multiple functions.
- Mutations in the sequence responsible for a domain, which is responsible for nuclear membrane mechano-stability (interacting with the LINC complex), and the homeostatic function of this protein could be responsible for the EDMD phenotype.
- Sustaining other domain functions might rescue patients from progeria features

Insight:

1. What are the characteristic clinical features of EDMD?
2. What is the molecular mechanism for the genotype-phenotype relationship in EDMD?
3. How would you plan for the antenatal diagnosis of Case IV: 4?
4. What is the possible explanation for having the predominant musculoskeletal findings with mutations of LAMA1 leads to EDMD2/3?

EDMD 2, 3: Clinical Triad and Their Age Dependent Progression



Clinical phenotypes:
EDMD: a triad of weakness of girdle muscles (**the shoulder and the pelvic**), contractures (**the elbows, neck, and Achilles tendon**), and cardiac involvement (**dilated cardiomyopathy & arrhythmias**). In selected cases, cardiomyopathy could be present earlier. Significant inter- and intrafamilial variability even for the similar mutation.
(Key findings help to distinguish EDMD from the Becker: Absence of muscle pseudohypertrophy, association of the forearm muscles, cardiac conduction defects, and development of early contractures in involvement of the neck or paravertebral muscles.

Two broad phenotypes for EDMD2 (AD) inheritance:

Phenotypes	**Clinical findings***	**Molecular Mechanism**
Milder	Late onset and a mild degree of weakness and contractures	**Haploinsufficiency**
Severe	Early presentation and a rapidly progressive course	**Dominant-negative or toxic gain-of-function**

*An increased frequency of sudden death in both groups

Phenotypic Series - PS310300: Emery-Dreifuss muscular dystrophy – eight entries
EMD & FHL1 [X (1, 6 & XMPMA*), LMNA [AD (2) & AR (3)], SYNE 1 & 2[(4, 5) AD], TMEM43 [(7), AD].
- Genes are primarily components of the nuclear envelope protein, which coordinates nuclear-cytoplasmic communication
***Myopathy, X-linked, with postural muscle atrophy**

Counsel the family for antenatal diagnosis of case IV: 4- Before planning for antenatal testing, the proband must be tested (case IV:2), but in this family, "isolated arrhythmias" need to be investigated (cases II:2, III:2, and III:3) for proper antenatal testing. If variants have been detected, then the mother (case III:4) and the fetus (amniotic fluid) samples have to be planned together because of the time-bound test. Meanwhile, clinical and lab data need to be collected for case II:2 and case III:2 for further analysis to know the extent of disease phenotype and variable presentation. Evidence-based data helps in the overall genetic counselling process.

Thought Riveting:

- ***What are the differences between a Genogram and a Pedigree?***
- ***Is there any possible therapeutic role of Crenolanib in EDMD?***
- ***What are the specific repertoire variances between LMNA A/C in EDMD?***
- ***What epigenetic cascades transpire with the malfunctioning of the LINC complex?***
- ***What are the progeria features that need to be monitored in LMNA-related EDMD?***