Rishi Vansh

All India Institute of Medical Science Rishikesh

AIIMSR Department of Pediatrics Genetic -

H1 H2A H2B H3 H4

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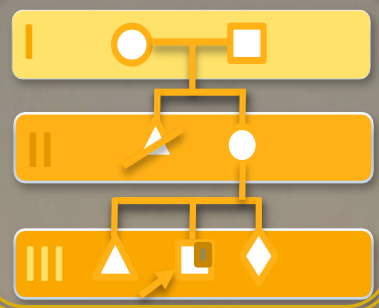

From the desk of Editor

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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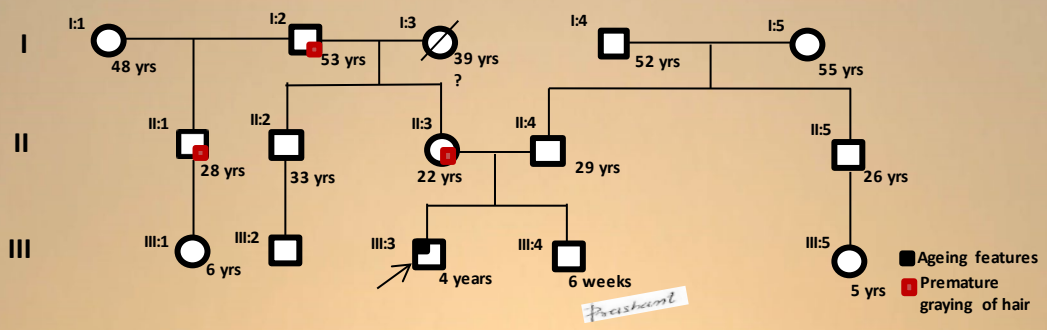
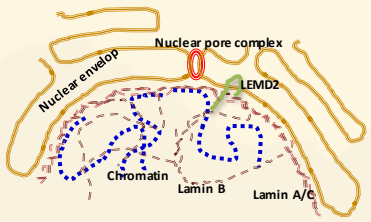
Progeroid syndromes (PS)-I / LAMIN A/C/ Hutchinson-Gilford progeria (HGP) or PROGERIA SYNDROME, CHILDHOOD-ONSET, INCLUDED



Localization of LAMIN A/C & B

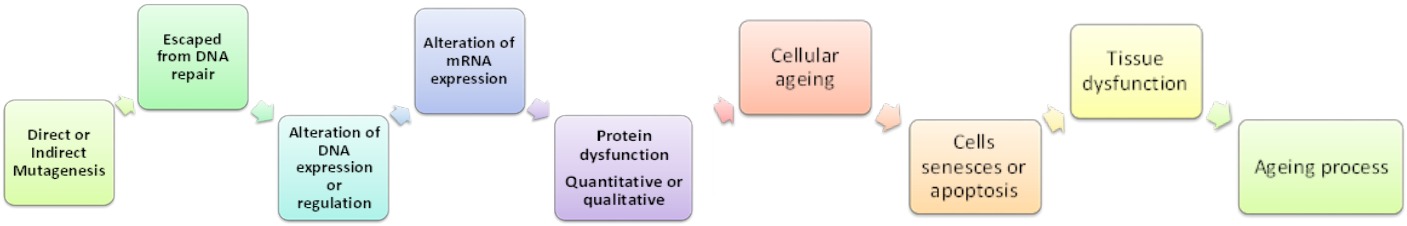


- **Mammalian Lamins encoding Genes:** LMNA, LMNB1 and LMNB2
- **In Somatic cells:** major isoforms of LMNA: A & C (lack of the CAAX box), and B1 & B2 by LMNB1/2
- **Germ-cell-specific lamins:** lamin B3 (isoform of LMNB2) and C2 (isoform of LMNA)
- Have extensive Post-Translational Modifications (PTMs) for specific functions at particular cell cycle stage as reversibly disassembled in mitosis

Insight:

1. What are the clinical phenotypes of HGP?
2. What is the aging process at cellular level?
3. How would you counsel the family for case III: 3?
4. What are key genomic interactions of the LAMA gene for selected phenotypes?

Ageing process (Nuclear & cellular)



Plausible tenets:

Gene: LMNA (1q22) Genomic coordinates (GRCh38) **1:156,082,573-156,140,081 (from NCBI)**

- **LMNA (Lamin A, included Lamin C), a complex protein network beneath the nuclear membrane responsible for nucleus resilience,** having 42 splice variants, 261 orthologues, 68 paralogues
- **Lamin A & C are present in approx. in equal ratio as a fibrous layer, hold the chromatin after DNA breaks and indirectly help in DNA repair.**
- Transcript: **Coding exons: 12**; length of **3,178 bps**, 74 domains, and features, Protein has 664 amino acids, with a molecular weight of 74139 Da.
- **Nuclear function:** maintain normal morphology, organization, stability and support for chromatin structure and gene expression, nuclear steadiness, nuclear assembly, nuclear membrane establishment, part of LINC (links the nucleoskeleton and cytoskeleton) complex & telomere dynamics.
- **Growth & Developmental role:** skeletal muscle, peripheral nervous system, osteoblastogenesis, & muscle satellite cell proliferation, regulate myoblasts into myocytes, & preadipocyte differentiation.
- **Homeostatic role in-** cardiac myocytes, fat distribution, skeletal muscle and bone strength, vascular smooth muscle cells (VSMCs)

Clinical phenotypes: AD inheritance for HGP

- Infantile onset premature aging syndrome with severe failure to thrive; Predominantly involved systems: ectodermal (including dental), cardiovascular, musculoskeletal and endocrine systems. There is no Immune dysfunction, Normal gut, liver & kidney functions, normal cognition without Alzheimer disease & No higher cancer risk.
- **Dysmorphic features**: disproportionately large head, microretrognathia and secondary facial changes because of ectodermal aging (loss of fat, elasticity and hairs) and "Sclerodermatous" skin changes (also reported with chronic graft-versus-host disease in generalized form)

Key genomic interactions (Rational Pleiotropy):

- **Binding site for SREBP1 (adipocyte differentiation factor)** activate PPAR-gamma, leads to adipocyte priming **(explain: lipodystrophy partially)**
- **Regulate downstream pathways of TGF-beta-1-**explain partially dysmorphic features
- **LINC** (Nuclear localization in cytoplasm)**: LMNA, SUN & Nesprin –**for various process **– (excess SUN1 explain premature cellular ageing)**
- **ZMPSTE24-** dispersion of farnesyl-prelamin A **(HIV-Protease inhibitors –inhibit it & leads to lipodystrophic changes in patient)**

Counsel the family for case III: 3- Pediatrics Premature ageing (PPA) is a genetically heterogeneous disorder with different modes of inheritance and needs to be clinical evaluation thoroughly to know exact system wise phenotyping. Isolated premature graying is reported as autosomal dominant inherited without other PPA features, but syndromic form of graying of hair needs to be ruled out clinically in each case as hypomorphic phenotype (Skin/hair/eye pigmentation, variation in – PS227220 – 23 types).

Recurrence risk HGP is almost nil (De novo mutation), but scope of prenatal testing needs to be discussed with family, for chances of germ line mosaicism.

Thought Riveting:

- ***Why there are, only selected systems show accelerating ageing.***
- ***Can the ectodermal changes with physiological aging decelerate by activating Serine-type endopeptidase?***
- ***How the megakaryoblastic leukemia-1 (MKL1) protein is related to cardiac disease pathophysiology?***
- ***What are binding sites for microRNA on the Lamins precursors and what are their principal functions?***
- ***What is possible explanation for sparing the neural tissue from aging phenomenon?***