Rishi Vansh

All India Institute of Medical Science Rishikesh

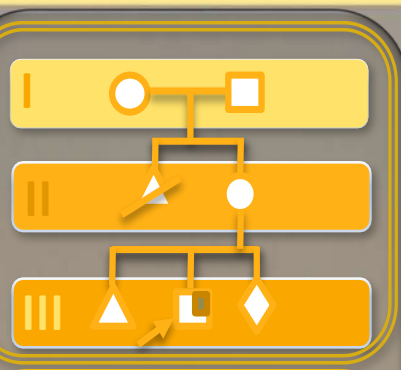
AIIMSR

Department of Pediatrics Genetic -division

H1 H2A H2B H3 H4

Volume 5

Issue 51, Aug 2024



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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DOI: 10.13140/RG.2.2.16691.44320

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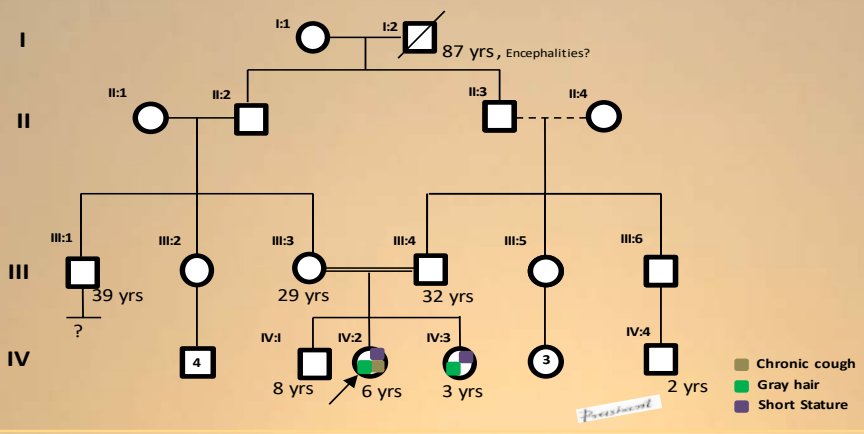
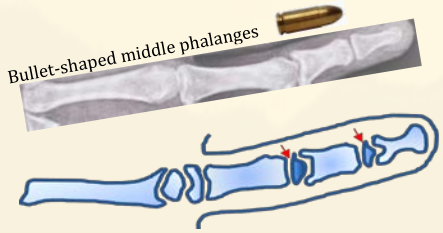
Pulmogenetics-IX/ Syndromes associated with Bronchiectasis / Cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD)



Cone-shaped Epiphyses (CSE)



- Isolated sporadic non-syndromic CSE: presence of CSE in the distal phalanx of the thumb, and the middle phalanges of the fifth finger.
- Syndromic CSE: presence of CSE in middle phalanges of fingers 3 and 4, & proximal phalanges
- There are various types of CSE, and few of them have diagnostic value (Pseudo-pseudo-hypoparathyroidism, Tricho-rhino-phalangeal syndrome, type I & type II, Cleidocranial dysplasia, cartilage-hair hypoplasia, etc.).

Insight:

1. What are the key findings of CHH-AD?
2. How do you approach a child with CSE?
3. What is the treatment protocol for case IV: II?
4. What is the role of Long noncoding RNA (lncRNA) in growth and development?
5. How would you counsel the family for case IV: 3?

Plausible tenets:

Gene: RMRP (RNase MRP): 9p13.3, Genomic coordinates (GRCh38) **9:35,657,750-35,658,022**

- **Mitochondrial RNA-processing endoribonuclease, an RNA Gene, belongs to the lncRNA (Long noncoding RNA).**
- Transcript: **Coding exon: 1**; **273 bases**
- **It cuts mitochondrial RNA for processing;** also forms double-stranded RNAs by forming a distinctive ribonucleoprotein complex with the telomerase reverse transcriptase catalytic subunit. **Essential components for handling of "Viperin," which has a significant role in innate immunity.**

Clinical phenotypes: A ribosomopathies, AR recessive MOI, Classically: Four components: Short stature (short-limb), hair hypoplasia, immunodeficiency**(88%),** and defective erythrogenesis **(80%).**

- Not having established clinical diagnostic criteria, intra- and interfamilial phenotypic variability for the same mutation

Phenotype	Severity of the phenotype	Genotype	Radiographic evidence (Mosaic Pleiotropy)
Metaphyseal dysplasia without hypotrichosis	Milder	Partial loss of function	Metaphysis changes
Cartilage-hair hypoplasia	Moderate	Founder mutation 70A-G (50%–90%)	Metaphysis and epiphysis changes
Anauxetic dysplasia 1	Severe	Minimum with one null mutation	Metaphysis, epiphysis, & spinal changes

- Additional findings(**Rational Pleiotropy**): Bronchiectasis **(29%-52%)** Gastrointestinal dysfunction (congenital megacolon, intestinal malabsorption), Hirschsprung disease **(8%)**, hypogonadism, impaired spermatogenesis, and increased risk for malignancy **(11%)** (various type, most common NHL)
- Treatment Protocol for Combined Immunodeficiency: Preventive strategies as using facemask, proper hand hygiene, vaccination as per protocol, and physiotherapy; prophylactic antibiotic therapy; Acyclovir; immunoglobulin replacement therapy; & stem cell transplantation.

Surveillance: Growth monitoring by CHH-specific growth curves; six monthly follow-ups in the initial two years for infections; annual clinical and radiographic examination of the spine in individuals (AD); HRCT for the suspecting bronchiectasis; & lung MRI for disease progression.

Anauxetic (Greek "not to permit growth"): severe short stature phenotype (<1 meter adult height); It is a type of spondylometaepiphyseal dysplasia. The majority of cases have mid face hypoplasia and are intellectually different. It can be detected in an antenatal anomaly scan.

- **Anauxetic dysplasia 2(617396):** AR, POP1 (endoribonuclease for mitochondrial RNA processing complex) on 8q22
- **Anauxetic dysplasia 3(618853):** AR, NEPRO (positive regulation of Notch signalling pathway) on 3q13. Brachydactyly, joint hypermobility with dislocations, sparse hair, and skin laxity are additional findings in these cases.

Long noncoding RNA (lncRNA) : > 200 nucleotides of untranslated RNA (ncRNA), further divided into subcategories based on size, genomic location, and structure; lncRNA has a significant role in embryonic development (especially in the brain), and in various epigenetic regulations. Malfunctions of lncRNA are also strongly linked with neuropsychiatric disorders and premature aging.

Genetic counseling for case IV: 3- In view of positive family history with clinically findings, she has variable possibilities for pulmonary involvement, but early intervention helps for disease course modification. The mutation study will definitely help in future phenotyping. After the post-test, the standard investigation plan (primary evaluation & surveillance) needs to be discussed with family with regard to their clinical relevance.

Thought Riveting:

- ***What is a non-molecular mechanism for the mild ID with Anauxetic dysplasia 1(AD1)?***
- ***Can the TRECs test be useful for other medical conditions besides SCID-related disorders?***
- ***Does a gene with a single exon have a high mutation rate?***
- ***Is the epistasis mechanism responsible the development of Hirschsprung disease in CHH cases?***
- ***Should there be an individual vaccination plan for the CHH case?***
- ***What is the lifetime risk of having acquired Ribosomopathies?***