Rishi Vansh

All India Institute of Medical Science Rishikesh

AIIMSR Department of Pediatrics Genetic -

H1 H2A H2B H3 H4

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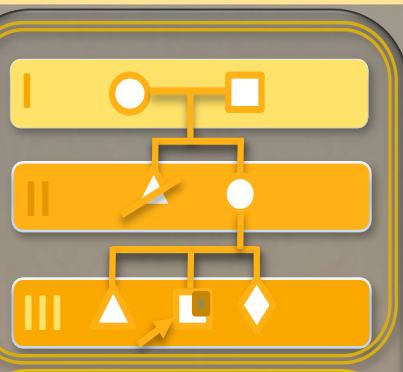

From the desk of Editor

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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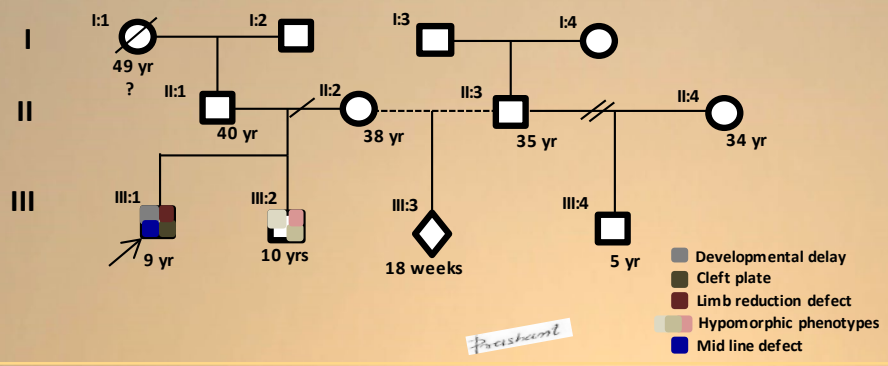
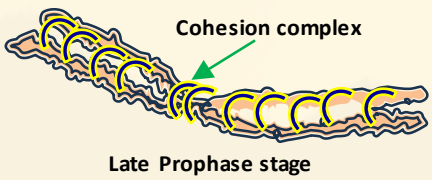
Neurogenetics -XV- Neurometabolic/ Intellectual Disability/ X-Linked/ de Lange syndrome (dLS) 2 & 5 (SMC1A & HDAC8)

Brachmann (1916)-Cornelia (1933) dLS



Cohesion Complex



- Chromatin has a pivotal role in nucleic acid stability, regulation, and maintenance.
- Cohesion proteins make complex molecules with combinations of structural maintenance of proteins (**SMC**) and non-SMC proteins.
- Cohesion complex orchestrates chromatin stability during the cell cycle and has extended non-canonical functions.
- More than thirteen genes have been recognized related to the cohesion complex, but their exact complex interactions and in vivo topological dynamics are still evolving

Insight:

1. What are the cohesinopathies?
2. What is the clinical presentation of CdLS or BdLS?
3. What is the genetic mechanism for CdLS or BdLS?
4. What are the key anomaly scan findings suggestive of CdLS for **Case III: 3**?
5. What are the management guidelines for CdLS or BdLS?

Plausible tenets:

Gene: SMC1A (Xp11.22) Genomic coordinates (GRCh38) **X:53,374,149-53,422,728 reverse strand. (located in an area of the X-chromosome that escapes X inactivation) (GRCh38:CM000685.2)**

- Cohesin is a part of a protein complex [SMC1, SCC1 (RAD21), SMC3], and either SA1 (STAG1) or SA2 (STAG2); might be more in the future]. Cohesin proteins are able to bind with chromatin and RNA, so they actively participate in cell division and DNA repair.
- Transcript: **8 transcripts (splice variants), Coding exons: 25**; length of **9,710 bps**, Translation length: 1,233 residues, 46 domains, and features, Protein has 1233 amino acids, with a molecular weight of 143233 Da.

Phenotypic Series CDLS - PS122470 – 6 enteries

Phenotype	MOI	Gene /Location	Gene function	Phenotype
CdLS 1	AD	NIPBL/ 5p13.2	Part of the Cohesin loading complex	Classical
CdLS 2	XL	**SMC1A***/ Xp11.22	Intricate in Chromosome cohesion	Mild
CdLS 3	AD	SMC3/ 10q25.2	Intricate in Chromosome cohesion	Mild
CdLS 4	AD	**RAD21#**/ 8q24.11	DNA repair, & intricate in sister chromatid cohesion	**Va** +/- **MBD**
CdLS 5	XL	HDAC8/ Xq13.1	Epigenetic repression of transcription, & regulation of SMC3	Mild + Plus%
CdLS 6	AD	BRD4/ 19p13.12	Epigenetic inheritance, regulation of transcription, chromatin insulator	Mild

Other phenotype *Developmental and epileptic encephalopathy 85, with or without midline brain defects**; #-**?Mungan syndrome (? – Not a definite relationship); **%-** hypertelorism, telecanthus, bulbus nasal tip, long philtrum, hooded eyelids, **delayed fontanel closure**, less growth affected; **MBD**- midline brain defects; **Mild** – less facial dysmorphology, lack of limb reduction defects & growth, and lack of other major anomalies, **Va**- variable (Dominant negative variants have more severe than loss-of-function variants).

CdLS first recognized **cohesinopathies,** mutation in the **NIPBL gene (60 %)** is the **most common** cause of **CdLS. SMC1A** is responsible **for 4 to 6%** of CdLS cases. Majority of cases are due to de novo mutations, but recurrence risk is calculated around **1.5%** (**Germline Mosaicism**).

Clinical phenotypes: Involve various body systems with variable phenotype severity. **An international consensus** has been established for characteristic and suggestive features for setting up a **clinical diagnosis.**

Cardinal features: **Hypertrichosis with peculiar facial dysmorphism**(arched thick eyebrows with synophrys, upturned nasal tip with short nasal bridge, high arched palate +/- cleft palate, widely spaced small teeth, micrognathia, thin upper lip with downturn corner of mouth, microbrachycephaly); **Limb anomalies** (upper > lower, variable reduction defect of large bone to digital anomalies), **Intellectually different** (mild to severe), **Growth failure**. 80% of cases have hearing loss (>40% profound), which may imrpove later. **Other Midline defects**: congenital heart disease (pulmonary stenosis), GERD, diaphragmatic hernia, genital anomalies, hypoplastic umbilicus, **variable MBD**, and scoliosis.

Key mechanism for Condensation of 3.4 billion bp in the nucleus

Looped DNA forms a large-scale (0.1-1 Mbp) loop to DNA reeling (many loops of 50-100 kb), and is considered one of the highly organized folding techniques for genomes. SMC mediated genomic structure formation is a loop extrusion function.

Yielding of genetic testing

- **75 % by gene panel or WES-based testing with blood**
  - ? 20-30 % might be missed because of somatic mosaicism
  - Variants in regulatory regions of the genome
  - Undiscovered regulatory Cohesin proteins

Key anomaly scan findings suggestive for CdLS for Case III: 3- Anomaly scan usually is planned around 18 weeks due to adequate clear amniotic fluid, and better resolution of fetus organs to define the dysmorphology as a screening tool. CdLS fetus has a triad of facial dysmorphisms (Hypoplastic nasal and mandible bones, long philtrum, & upper lip anomalies), limb reduction defects (micromelia, ulnar ray defects, transverse defects), and visceral anomalies **with variable severity**. Normal fetal ultrasound can not rule out CdLS.

Thought Riveting:

- ***Are the Cohesin proteins mutations associated with increased risk of cancers?***
- ***What is the actual prevalence of cohesinopathies in the community?***
- ***How do genes reported with CdLS-like phenotypes (AFF4, TAF1, MAU2, ANKRD11, and EP300) topographically interact with the Cohesin complex?***
- ***Is there any theoretically beneficial role of antioxidants, and mitochondrial cocktail in CdLS?***
- ***What kind of dietary modification can benefit the management of behavioral issues in a CdLS case?***