Rishi Vansh

All India Institute of Medical Science Rishikesh

AIIMSR Department of Pediatrics Genetic -

H1 H2A H2B H3 H4

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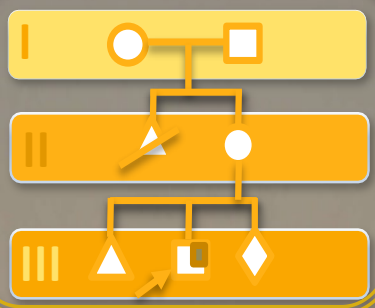

From the desk of Editor

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.

Author: Prashant Kumar Verma[1],
[1] Department of Pediatrics, Chairperson of Medical Genetic division, AIIMS Rishikesh, Uttarakhand, India

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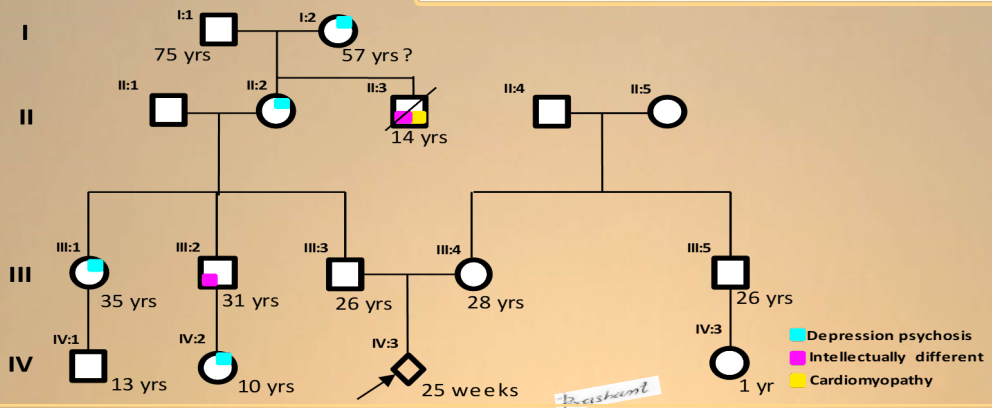
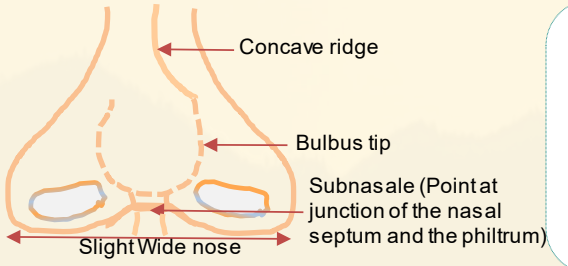
Reviewer: Dr. Raksha Ranjan
[1] Department of Pediatrics, AIIMS Bathinda, Punjab, India

Neurogenetics -XVIII- Dysmorphic/ Intellectual Disability/ X-Linked/ RPS6KA3 related disorders



Pugilistic nose of Coffin Lowry syndrome



- **Nasal, Bulbous/Potato Nose/Pear-shaped**: globular shape anteroinferior aspect (the lower third) of the nose with increased volume, Broad nasal tip If only the width of the nasal tip increased
- **Nose, Wide**: > 2 SD Interalar distance
- **Nasal Ridge, Concave/Saddle /Ski Jump nose**: curving posteriorly nasal ridge (points connecting the nasal root and tip)
- ***Pugilistic nose*** *- a wide nose with bulbus tip and concave ridge* ***(a coarse nose)***
- Nares, Anteverted/ **Pug Nose/** Nasal Tip, Upturned: anteriorly facing, or superiorly positioned nasal tip in the Frankfurt plane

Insight:

1. What is the clinical phenotype spectrum of the RPS6KA3-related disorders?
2. What is the pugilistic nose?
3. What are the major anatomical landmarks for defining facial dysmorphism?
4. What is the practical utility of +/- operators in different search engines?
5. How would you decide the novelty of any new genomic data variant?

Plausible tenets:

Gene: RPS6KA3 (Xp22.12) Genomic coordinates (GRCh38) **X:20,149,911-20,267,097 (from NCBI)**

- **Ribosomal protein S6 kinase A3, belong to the RSK (ribosomal S6 kinase) family, which regulates serine/threonine kinase.** It **increases** various transcriptional factors **(CREB1, ETV1/ER81, and NR4A1/NUR77)** directed through MAPK pathways, inhibiting BAD and DAPK1(Pro-apoptotic proteins), and modulating mTOR signaling. It has 16 splice variants, 247 orthologues, 7 paralogues.
- Transcript: **Exones & Coding Exons: 22**; length of **7,987 bps**, 56 domains, and features, Protein has 740 amino acids, with a molecular weight of 83736 Da, protein structure- https://alphafold.ebi.ac.uk/entry/P51812
- Variant database: https://gnomad.broadinstitute.org/gene/ENSG00000177189?dataset=gnomad_r4

Clinical phenotypes: Xlinked disease, predominantly involved **neurodevelopment, and skeletal system with charecteristic facial dysmorphism.** The majority **(2/3)** are **de novo** mutations.

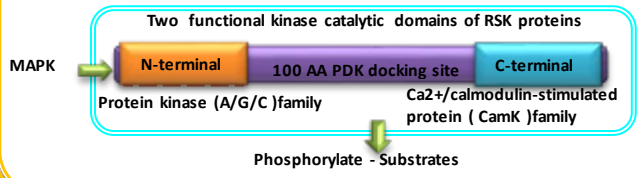
Phenotype, disease and trait	Description
Coffin-Lowry Syndrome (RPS6KA3) XD	Female affected / Symptomatic form of Coffin-Lowry syndrome in female
Coffin-Lowry Syndrome (RPS6KA3) XLR	Female not affected
Intellectual Developmental Disorder, X-Linked 19	Non-syndromic intellectual disability

- **Neurodevelopment:** microcephaly, hypotonia, sensorineural hearing loss, intellectual differences, cataplexy like drop attacks, and growth failure
- **Dysmorphism:** course facies, bulbous **tapering fingers**, small nail, dental dysplasia, **prominent** brows, chin, mouth, ear, and nose (pugilistic) [generalized increase in subcutaneous fat]
- **Skeletal:** sternum changes, delayed bone age, thick calvarium, spinal deformity, iliac wings narrowed, hyperlaxity of joints, metacarpal pseudoepiphyses
- **Altered metabolism of complex molecules** (**Progressive**): coarse features, mitral valvulopathy, radiculomyelopathy, kyphoscoliosis, and progressive neurological features (seizures, spastic paraplegia, etc.)

Management: https://www.ncbi.nlm.nih.gov/books/NBK1346/#cls.Management , Symptomatic, multidisciplinary, and

The Genome Aggregation Database (gnomAD) – online database of human variants (from various resources like HGDP, 1KG, etc.) for various purposes such as research, study, analysis, and comparing for novelty.
https://gnomad.broadinstitute.org/, https://gnomad.broadinstitute.org/downloads, https://gnomad.broadinstitute.org/help#general

Kinase catalytic domains of RPS6KA3



+/- Operators: Adding

- **A '+' (plus) as +X +Y: search all the entries must have X, & Y**
- **A '-' (minus) as +X +Y –Z:** search all the entries must have X, & Y, **but not Z**
- **Use of parentheses as +(X Y Z): search any of X/Y/Z**
- **Use of parentheses as -(X Y Z): exclude entries having any of X/Y/Z**
- **A '+' (plus) operator to a phrase as +"X Y Z": search all the entries must have phrase "X Y Z"**
- **Operator for CLS: +tapering +fingers +microcephaly +coarse +pectus**

Counsel the family for Case IV:3- If father is clinical normal, then there is less possibility of inheritance for a paternal side phenotype, although they need to follow standard operation procedure (**SOP**) for definite confirmation. Affected person should be tested first for variant/s detection, followed by any clinically asymptomatic family member could be tested for the same variant/s **(SOP).**

Thought Riveting:

- ***Can protein replacement therapy (PRT) treat the progressive features of CLS?***
- ***What are the translation factors? What is the role of cytosolic non-translated cntRNAs in the regulation of mRNA?***
- ***Can biologic medicines, like monoclonal antibodies against p90 (rsk) alter or modify the cancer outcome even in the late stages?***
- ***What could be the possible phenotypic differences between N and C-terminal variants?***
- ***Are there any therapeutic role of modafinil (Provigil) or armodafinil (Nuvigil) for cataplexy like the drop attack associated with CLS?***