All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

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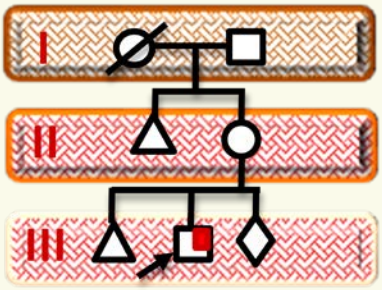
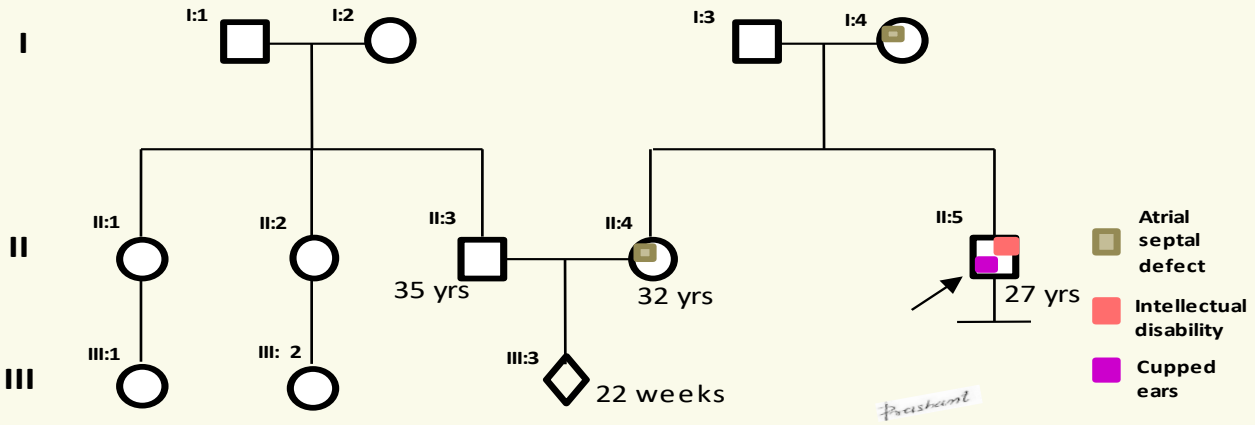
From the desk of Editor

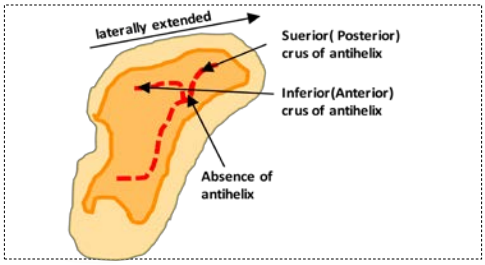
The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and a deliberate attempt to enhance awareness for genetic disorders with recent updates.



Neurogenetics -IX
Intellectual Disability/ X-Linked/(IDXL)/ Renpenning syndrome



Cupped ear (cup-shaped ears)



- Cupped Ear Definition:
- Laterally extended ear that deficit antihelical [A **Y**-shaped arched cartilaginous ridge (- - - - - - -)]

Hunter A, Frias JL, Gillessen-Kaesbach G, Hughes H, Jones KL, Wilson L**. Elements of morphology: standard terminology for the ear.** Am J Med Genet A. 2009 Jan;149A(1):40-60. doi: 10.1002/ajmg.a.32599. PMID: 19152421.

Insight:

1. What is the checklist for antenatal genetic counseling for III:3?
2. What is the approach for a X-linked intellectual disability case with a cupped ear?
3. Is there any specific phenotype within the Renpenning syndrome?
4. How would you recognize Renpenning syndrome clinically?
5. Is there any immunological role of PQBP1 protein?

Plausible tenets:

Gene: PQBP1 (Xp11.23), Exons: 7

- **An intrinsically disordered protein (IDP), a nuclear polyglutamine-binding protein and having a WW domain**
- Help in different complex processes, such as transcription activation, pre-mRNA splicing, neuron development
- Role in innate immunity- **recognize the reverse-transcribed DNA in the cytosol lead to activate the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway which, set off type-I interferon production**
- Regulates alternative splicing of cell-specific target pre-mRNA species. The mutation hot spot: **AG hexamer in exon 4**

Clinical phenotype:

- Recognizable dysmorphic feature: **Short/Small** (stature, head circumference, testis, eye, eyebrows, philtrum, face width), and apparently long face, upslanting palpebral fissure, overhanging columella
- Less common features: **Fusion defects** [cardiac malformations (TOF, ASD, VSD), cleft palate, ocular colobomas], anal anomalies(atresia), and progressive muscular atrophy around the spine lead to scoliosis. It might be expressed in female
- **Neurological:** All unspecified XLID (IQ: 30-70 %) cases were labeled as Renpenning syndrome before discovering the gene. Still, no consensus on clinical diagnostic criteria, so molecular testing is a must.
- **Management:** Follow national guidelines for Intellectual disability cases plus symptomatic management

WW domain: A compressed; antiparallel beta-sheet arranged in three-stranded ("W" like shape) gives space for protein-protein interfaces by attachment to xPPxY-based protein ligands (**Building for Multiprotein interaction**)

Koepf EK, Petrassi HM, Ratnaswamy G, Huff ME, Sudol M, Kelly JW. **Characterization of the structure and function of W --> F WW domain variants: identification of a natively unfolded protein that folds upon ligand binding.** Biochemistry. 1999 Oct 26;38(43):14338-51. doi: 10.1021/bi991105l. PMID: 10572009.

Intrinsically disordered proteins (IDPs): Specific proteins having a very complex tertiary structure and provide critical platform in their intrinsically disordered regions (**IDRs**) for various cellular signaling, assembling various membrane-less organelles & post-translational modification of other proteins. **(Communicator for Building of Multiprotein interaction)**

Wright PE, Dyson HJ. **Intrinsically disordered proteins in cellular signalling and regulation**. Nat Rev Mol Cell Biol. 2015 Jan;16(1):18-29. doi: 10.1038/nrm3920. PMID: 25531225; PMCID: PMC4405151.

X linked intellectual disabilities with cupped ear

Syndrome **(OMIM)**	Gene	Key feature
Intellectual developmental disorder, X-linked syndromic, Turner type **(309590)**	HUWE1(XL)	Highly variable phenotype with deep-set eyes & brachydactyly
Intellectual developmental disorder, X-linked syndromic, Abidi type **(300262)**	___ (XL)	sloping forehead & deafness
Intellectual developmental disorder, X-linked 93 **(300659)**	BRWD3 **(XLR)**	Autism spectrum disorder, & kyphosis
Corpus callosum, agenesis of, with impaired intellectual development, ocular coloboma and micrognathia **(309500)**	IGBP1 **(XLR)**	Ocular coloboma, agenesis of the corpus callosum, & micrognathia
Allan-Herndon-Dudley syndrome **(300523)**	SLC16A2 (XL)	Spastic paraplegia, dysarthria, & athetoid movements
Kabuki syndrome 2 **(300867)**	KDM6A**(XLD)**	Long & everted lateral third of the lower eyelids
Trichothiodystrophy 5, nonphotosensitive **(300953)**	RNF113A (XL)	Structural brain anomalies & sparse and brittle hair

Checklist for antenatal genetic counseling for III:3- The prerequisite for antenatal counseling of any family: Besides taking care of **Privacy**, the Physician needs to follow a **checklist**: **1**. Understanding family psychological status (body language and attitude and understanding) **2.** Family social and cultural value, including religion, **3.** Pedigree drawing and analysis, **4.** Medical data analysis (carrier/disease status in the couple or in the family, investigations as radiology and biochemical markers for genetic diseases), **5**. Proband diagnosis (Proband medical data)

Thought Riveting:

- ***Would it be possible ethically and socially to do the pre-conceptional molecular carrier testing for X-linked disorder at a population level?***
- ***What is the possible molecular mechanism for PQBP1 gene-related mosaic pleiotropy?***
- ***How can maternal higher education grade and subtle dysmorphology help antenatal counseling in a low-resource center?***
- ***Can recombinant PQBP1 protein be a futuristic medicine for HIV?***
- ***Does the gene dosage of PCBP1 protein affect pleiotropy?***

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