Rishi Vansh

All India Institute of Medical Science Rishikesh AIIMSR

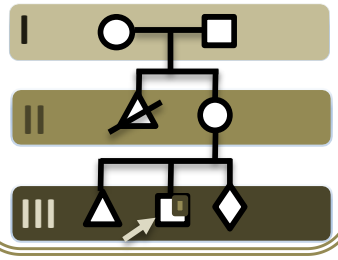
Department Of Pediatric Genetic -division

Volume 4 **Issue 32, Jan 2023**

Editorial Board

Chief Patron
Prof. Meenu Singh
(Executive Director)
Patron
Prof. Jaya Chaturvedi
(Dean academic)
President
Prof. N. K. Bhat
(HOD)

Editor
Dr. Prashant Kumar Verma
Asso. Editor
Dr. Swathi Chacham
Assi. Editors
Dr. Vinod Kumar
Dr. Pooja Bhadoria

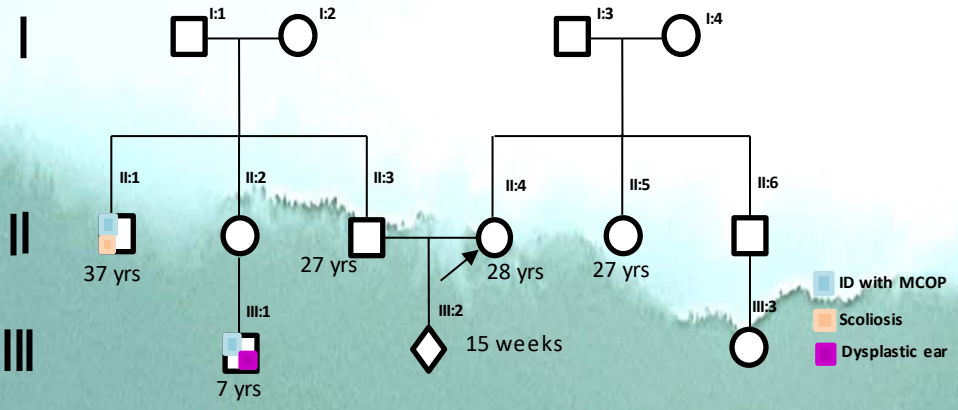


From the desk of Editor

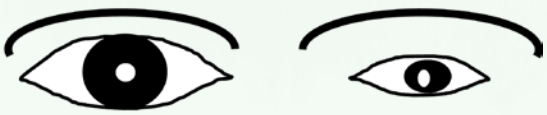
The genetic division of the Pediatric Department is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Neurogenetics-(X)

X Intellectual Disability/ X-Linked/(IDXL)/ Microphthalmia, Syndromic 1; MCOPS1



Microphthalmia



Gross asymmetry between both eyes

- Small and usually structurally disorganized eye
- Eighteen Syndromic MCOPs are reported as MCOPS I- XVIII
- 276 clinical synopses entries in OMIM with MCOP
- Wide clinical phenotype: Anophthalmia ⇢ coloboma
- Majority of "extreme MCOP" recognized as Anophthalmia

Insight:

1. How to approach a male child (X-linked) with learning difficulties with microphthalmia?
2. What are the characteristic features of MCOPS1?
3. What is the Phenotypic series (PS) in OMIM entries?
4. What is the Nanophthalmos?
5. How would you counsel the family for case III:2 if affected family members are not approachable?

Plausible tenets:

- **Gene: NAA10 (Xq28): Catalytic subunit of the "N-alpha-acetyltransferase complex";** a member of the acetyltransferase family
- Location on X: **153,929,225-153,935,037**
- Exons: 8, 5856 bps, 15 domains and features, 202 orthologues, 16 splice variants or transcripts, 4 paralogues.
- Transcript length: 1603 bps. Protein has 235 amino acids, with a molecular weight of 26459 Da.
- Need for proper growth & development of neural, vascular & hematopoietic systems.
- Anticancer role: Inhibits metastasis by acetylation of MYLK kinase & blocks cancer through stabilizing TSC2
- Support chaperone activity & regulate the 5856sister chromatid cohesion
- **Clinical phenotypes:**
- **A. Microphthalmia, syndromic 1(XL) [Lenz MCOPS]:** No formal diagnostic criteria; **Variable phenotype severity,** Microphthalmia or anophthalmia (U/L or B/L) unilateral or bilateral.
- **Nonocular clinical features:** Intellectual disabilities, Orofacial anomalies [(Dysplastic ears (+/- skin tag), palatal anomalies (high or cleft), dental anomalies], urogenital anomalies, and skeletal changes in spins and hands [scoliosis, lordosis, clinodactyly, syndactyly, brachydactyly, and abnormal thumbs]. **Recurrent abortions in a carrier.**
- **B. Ogden syndrome (XLD, XLR): Phenotype differences from MCOPS1: Prominent eyes,** course features, Noonan-like phenotype (**face, dermal & cardiac anomalies**)
- **Rx: Symptomatic, surveillance & supportive**

X linked -Microphthalmia with ID

Syndrome	Gene & MOI	Key clinical features
Renpenning Syndrome 1; RENS1	**PQBP1 (XLR)**	Small testes, Overhanging columella and Sparse lateral eyebrows
Intellectual Development Al Disorder, X-Linked, Syndromic, Turner Type; MRXST	**HUWE 1 (XL)**	deep-set eyes, hypotelorism & bitemporal narrowing
Linear Skin Defects with Multiple Congenital Anomalies 1; LSDMCA1	**HCCS (XLD)**	Corpus callosum agenesis, Absence septum pellucidum, sclerocornea, External urogenital anomalies, CHD, cardiac conduction defect
Microphthalmia, syndromic 1, MCOPS2	**NAA10(XL)**	Agenesis of upper lateral incisors, ankyloblepharon, neural tube defect
Microphthalmia, Syndromic 13; MCOPS13	**HMGB3(XL)**	Diastema of incisors, microcephaly, short stature, coloboma, ptosis
Exudative Vitreoretinopathy 2, X-Linked; EVR2	**NDP9(XLD, XLR)**	Retinal detachment, vitreous degeneration, avascular peripheral retina
Cataract 40; CTRCT40	**NHS(XL)**	Congenital nuclear cataract in males, severe visual impairment, suture cataracts in female
Nance-Horan Syndrome; NHS	**NHS(XLD)**	Posterior Y-sutural cataract, screwdriver blade shaped incisors, mesiodens, diastema
Developmental And Epileptic Encephalopathy 2; DEE2	**CDKL5(XLD)**	Breath-holding episodes, infantile spasm, hypotonia, myoclonus, autistic features
Chondrodysplasia With Platyspondyly, Distinctive Brachydactyly, Hydrocephaly, And Microphthalmia	**HDAC6 (XLD)**	Rhizomelic shortening, hypoplasia of iliac wings, metaphyseal cupping of metacarpals and phalanges
Norrie Disease; ND	**NDP (XLR)**	SN deafness, Progressive disease, retinal dysgenesis and dysplasia, corneal and vitreal opacities
Focal Dermal Hypoplasia; FDH	**PORCN 9 (XLD)**	Arborescent Papillomas, enamel & midclavicular hypoplasia, supernumerary nipples, bifid ureter, hypoplastic digits, linear hypopigmentation
Aicardi Syndrome; AIC	**GRCh38 (XLD)Xp22**	Agenesis of corpus callosum, optic nerve coloboma, absent fused or bifid ribs, butterfly vertebrae, proximally placed thumbs
Linear Skin Defects with Multiple Congenital Anomalies 2; LSDMCA2	**COX7B (XLD)**	microcephaly, reticulolinear skin defect, arched eyebrows, asymmetric thorax, widely spaced nipples, clinodactyly, sandal gap
IFAP Syndrome 1, With or Without Bresheck Syndrome; IFAP1	**MBTPS2 (XLR)**	Unilateral chest hypoplasia, multicystic dysplastic kidneys, renal agenesis, ectodermal dysplasia, lack of eyebrows and eyelashes
Lowe Oculocerebrorenal Syndrome; OCRL	**OCRL(XLR)**	Glaucoma, cataract, hypotonia, areflexia, mental retardation, proximal RTA, renal Fanconi syndrome
Linear Skin Defects with Multiple Congenital Anomalies 3; LSDMCA3	**NDUFB11 (XLD)**	Linear skin defect on face & neck, lacrimal duct atresia, cardiomyopathy, VT and fibrillation, linear atrophic hyperpigmented streak on left index finger
Brachydactyly, Coloboma, And Anterior Segment Dysgenesis	**(XL) or (AD)**	Iridocorneal adhesions with overlying corneal opacity, brachydactyly, clinodactyly, hearing loss

Mesiodens: a supernumerary centrally situated upper incisor

Nanophthalmos: Symmetrically small functional eyes without any dysplastic changes. In literature, few previously defined them as 'partial microphthalmos' or 'posterior microphthalmos.' A mean axial length: is **16-18** mm for the full-term new-born & **22-25** for adult

Phenotypic series (PS): For various well-defined phenotypes or features, OMIM have created a table for that feature which included all OMIM entries having that phenotype or trait. So, it displays genetic heterogenicity and genomic locations for that phenotype or feature.
OMIM entry as PS is given a unique six-digit number with initiate "**PS**":
Microphthalmia, isolated, with coloboma - PS300345 - 13 Entries, Microphthalmia, isolated - PS251600 - 8 Entries & Microphthalmia, syndromic - PS309800 - 18 Entries

Counsel the family for case III:2- Lack of proband genotype leads to uncertainty for antenatal molecular diagnosis. Still family wants to do antenatal testing for the proband's specific phenotype or feature. First, Mother needs to be evaluated clinically with molecular testing for genes provided with Phenotypic series (PS******). Fetus molecular testing will be decided after the mother carrier status. If the time limitation is the factor, the fetus sample must be tested simultaneously.

Thought Riveting:

- ***Might protein kinase-targeted acetylation be used against tumor cell migration?***
- ***Can True or primary anophthalmia be compatible with early fetal development?***
- ***What could be the genotype and phenotype relationship for Ogden syndrome versus MCOPS1?***
- ***Can a screen for eye glove size be used as one of the standard parameters during level II antenatal ultrasound?***

Could it be ethically and socially better to use the "intellectually different" word for "intellectual disability"?

Author: Dr Prashant Kumar Verma, Dr. Md Danish
Reviewer: Dr. Raksha Ranjan