# Rishi Vansh

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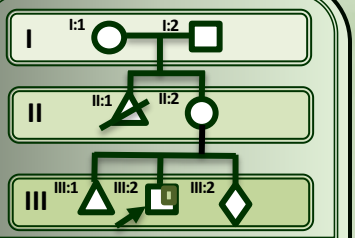
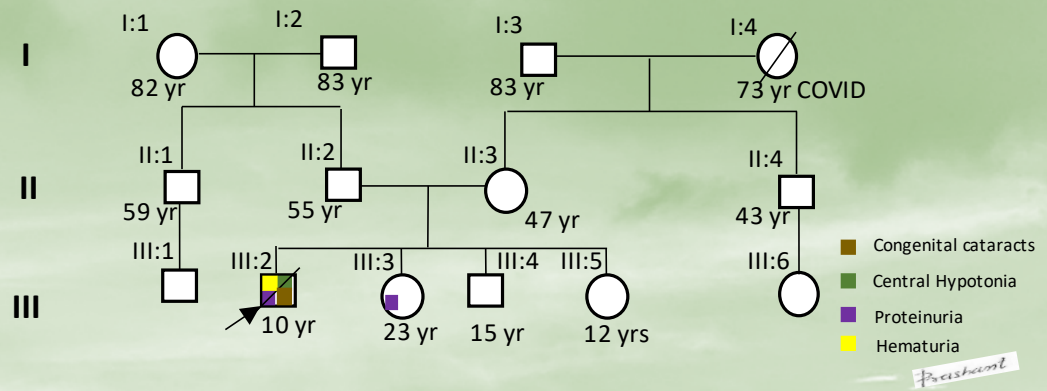
## Neurogenetics - XIX - Dysmorphic/ Intellectual Disability/ X-Linked / Phosphatidylinositol 4,5-bisphosphate-5-Phosphatase (OCRL)spectrum disorder; Including Lowe & Dent disease2



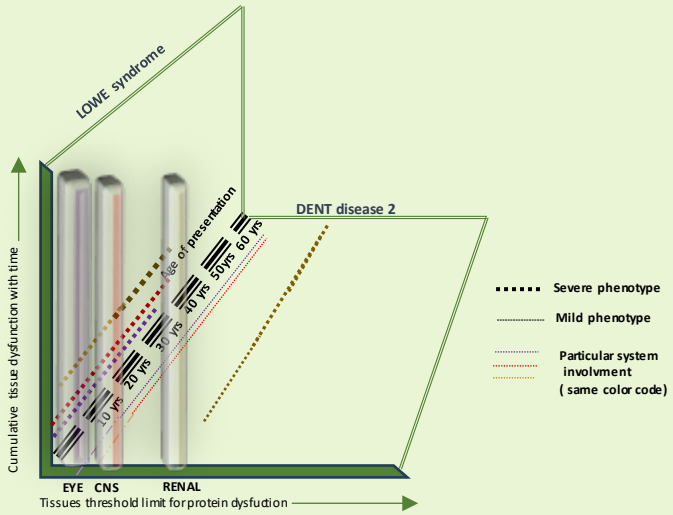






**From the desk of Editor**

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.

## Possible Mechanism of OCRL phenotype spectrum




## *Insight:*

1. What is the potential molecular process leading to OCRL spectrum disorders?
2. What are the various phenotypes of the OCRL spectrum?
3. How would you counsel the family for **Case III: 5**?
4. Is there any role of growth hormone (**GH**) in the management of Lowe syndrome?
5. How would you counsel a X-liked disease with variable phenotypic penetration with an asymptomatic mother with negative somatic cell genotype for a disease?

**Plausible tenets:**

**Gene: OCRL (Xq26.1)** Genomic coordinates (GRCh38) **X:129,540,259-129,592,556 (from NCBI)**

- **Inositol polyphosphate 5-phosphatase (endosomal trafficking regulator, a member of the inositol-5-phosphatase family)** regulates the availability of phosphatidylinositol 4,5-bisphosphate to endosomes by catalying the hydrolysis of the 5-position phosphate of phosphatidylinositol 4,5-bisphosphate (**PtdIns(4,5)P2**) and (**PtdIns(3,4,5)P3**). Which leads to defects in the transport of various proteins and lipids.
- It has been reported to be involved in primary cilia formation, phagocytosis, α-actinin signaling, and proper plasma membrane function.
- Possible Hypothesis for different tissue penetration and severity depends upon tissue-specific other housekeeping functions.
- **Gene: 52,713 bases (normal orientation) variants**; 10 transcripts, 223 orthologues, and 13 paralogues.
- Transcript: **Exons & Coding exons: 24**; length of **5,173 bps**, 28 domains, and features, Protein has 901 amino acids, with a molecular weight of 104205 Da.

**Clinical phenotypes: Lowe syndrome & Dent disease 2**

| Organ | Disease | Frequency of Phenotype in cases | Management |
|---|---|---|---|
| Eye | B/L dense Congenital cataracts & impaired vision (< 20/100) | Almost | Cataract removal**, glaucoma treatment<br>Personalized education programme |
| | Infantile glaucoma | Half cases | Need six monthly monitoring |
| Neurological | Central Hypotonia - Feeding issue, joint hypermobility | Almost | NG feeding, GERD treatment, and scoliosis standard treatment |
| | Seizure | | Antiepileptic |
| | DTR -Absent | Almost | |
| | Intellectual differences | Almost but variable* | |
| | Behavior problem | Variable | Behavioral therapy |
| Renal (Dent disease) | Chronic and progressive Proximal tubular dysfunctions# | All cases in late infantile period | Replacement of lost mineral, and Vit D3, observe for secondary complications |
| | Glomerulosclerosis (1st decade) | | Dialysis |
| | CKD (2nd to 4th decade) | | Renal transplantation |

** They cannot tolerate artificial lens implants (Glaucoma), and Corneal contact lenses (corneal keloid)

*APPROX: Severe (60%) > Mild to Moderate (20%) > Low Normal (20 %)

#Progressive proximal tubular dysfunctions (Fanconi syndrome-like) which lead to proteinuria (Low molecular weight type- indicating tubular function), renal tubular acidosis (RTA), and Ca (calcium/creatinine mg/mg >2 SD), PO4, Na, K, water, HCO3 wasting (secondary rickets), & aminoaciduria. Possible secondary complications of hypercalciuria: Nephrocalcinosis, Nephrolithiasis, and Hematuria

Rx : Annually follow up. Growth failure is a secondary manifestation due to multifactorial reason. In selected cases, **GH** could be use with managing all other complications.

**Principal differences in Dent disease and Lowe syndrome**: Lowe syndrome has mild spectrum with predominantly proximal renal tubular dysfunction; all renal pathological changes appear 2-4 decades late; females usually do not develop CKD. Only below average to mild MR, behavior abnormality, and mild ocular nuclear density.

**Types of dent disease (X-linked hypercalciuric nephrolithiasis)**

**Type 1: CLCN5 related disorders spectrum/ Dent disease complex (Xp11.23)**

**Type 2: OCRL (Xq26.1)- usually a mild phenotype of Lowe syndrome**

**Key counselling facts related to "X-liked disease" with variable phenotypic penetration**

**Prime mover: study** the statistical data (SD) of **denovo mutation & germ line mutation for a particular phenotype of a gene (for Lowe 32 % & 4.6% respectably), & SD of disease penetrance in both sex in the population**

**With Four Possible Outcomes**

| | **X** | **X** |
|---|---|---|
| **Y** | **XY (25% Normal male***)** | **XY (25% affected male)** |
| **X** | **XX (25% Normal female***)** | **XX (25%** a heterozygous female with **variable phenotype**) # |

*** **for that phenotype, # usually mild and late onset, depends upon gene product functions,** ***for Lowe 95% start to develop mild progressive clinical features in second decades***

*In case of a lack of data for **XX**, it is better to say "**We do not have exact figures but likely a mild & late onset phenotype with uncertainty to complete penetration."*

**Counsel the family for Case III: 5**- In spite of asymptomatic parents and having a negative test for somatic mutations (in lymphocytes), there is always a risk to have a germline mutation in gametes (4.6% with Lowe syndrome) in all genetic disorders. So, in each pregnancy, the antenatal testing should be discussed with family. Case III:5 might have a pathological variant and need to test for asymptomatic disease-carrying variants because it is a medically actionable disease.

## Thought Riveting:

- ***What are the key differences between Dent disease and Fanconi renotubular syndromes?***
- ***How does the inositol phosphate interact with a voltage-gated chloride ion channel?***
- ***Will upregulating the Synaptojanin-1 ameliorate a few features of Lowe syndrome?***
- ***Is endosomeopathy a new emerging group of cellular organelle dysfunction disorders?***
- ***What could be the possible overlapping phenotypes of pathological variants of 'Ph Domain-Containing Endocytic Trafficking Adaptor (PHETA1/A2)', a strong possible interactor of OCRL?***