Rishi Vansh

All India institute of Medical Science Rishikesh (AIIMSR)

Volume 6, Issue 5, May 2025

Author: Prashant Kumar Verma[1]

[1] Department of Pediatrics, Chairperson of Medical Genetic division, AIIMS Rishikesh, Uttarakhand, India.

Reviewer: Dr. Raksha Ranjan

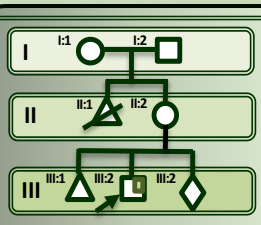
1 Department of Pediatrics, AIIMS Bathinda, Punjab, India

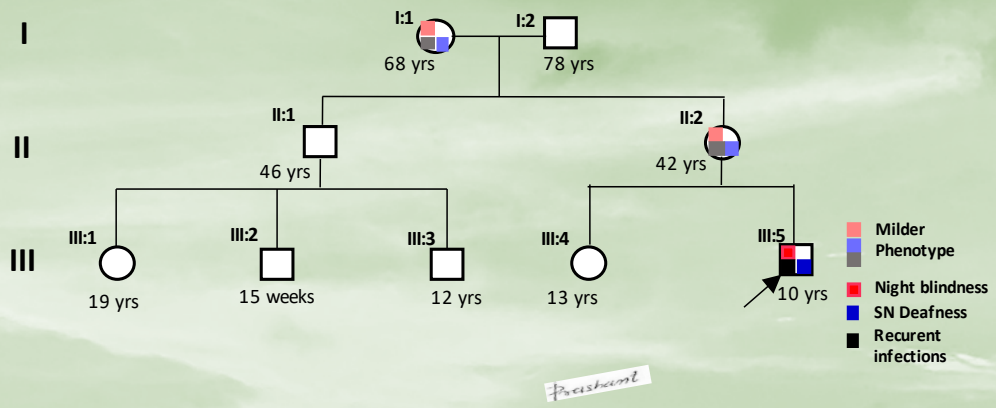
DOI:10.13140/RG.2.2.12374.36163

Pulmogenetics-XII - Syndromes associated with Bronchiectasis / Retinitis pigmentosa, X-linked, and sinorespiratory infections, with or without deafness- RPGR related disorders

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.





The Tunnel vision

- **Normal retina color: red or orange** & leads to red reflex by examination with a retinoscope/ ophthalmoscope
- **Change in retina is always a hard sign &** must to evaluate in all birth defect cases as per guidelines
- **In pediatrics age group ERG** can detect presymptomatic stage
- **Retinitis pigmentosa:** actually, a misnomer, it is secondary changes, not the primary pathology
- Initially night blindness, followed by gradual loss of peripheral vision leading to Tunnel vision
- High degree of suspicion for change in night habit, change in visual gaze, & parents complaining about vision

Insight:

1. When would you clinically suspect a case of RPSRDF?
2. How many other syndromes have the classical triad of RPSRDF?
3. When do you clinically suspect tunnel vision in the pediatric age group?
4. How would you counsel **Case III: 4**?
5. Is the reverse tunnel vision also associated with the RPGR gene?

Plausible tenets:

Gene: RPGR (retinitis pigmentosa GTPase regulator) Xp11.4, genomic coordinates (GRCh38): X:38,269,163-38,327,509

- Belongs to protein having a tandem repeat of **RCC1-like domains** (RLDs), which are conserved guanine nucleotide exchange factors.
- Co-located with RPGRIP1 on the Golgi body, outer segments of photoreceptors, cochlea, & epithelial lining of airways.
- Gene : 257 orthologues, 9 paralogues , and 19 splice variants.
- Transcript: 15 exons, 46 domains and features, transcript length 4,733; Protein: 1,020 AA with 113,387 Da molecular mass.
- Functions: role in ciliogenesis, guanine-nucleotide releasing factor, cell integrity & vesicle transportation.
- Account for approximately 70% of XL RP, around 3.4-4.4 per 100,000 males (western data), and reported as one of the five (ABCA4, USH2A, RPGR, PRPH2, and BEST1) common genes reported with retinal diseases.

Phenotype: X-linked disease, carrier females may show an attenuated ocular and/or respiratory phenotype.

Phenotype	Onset/Clinical Features	OMIM	MOI
Cone-rod dystrophy, X-linked, 1	2nd to 4th decade / first reduced central vision followed by night blindness after a few years later**; mutation especially in an alternative terminal exon 15 (ORF15)**	304020	XR
Macular degeneration, X-linked atrophic	Variable loss of peripheral vision **(reverse tunnel vision)**	300834	XR
Retinitis pigmentosa **(RP)** 3	3rd to 4th decade, first night blindness	300029	XLR
Retinitis pigmentosa, X-linked, and sinorespiratory infections, with or without deafness	Variable onset (1st to 2nd decade), hearing & respiratory first, followed by eye **Preserved fertility**	300455	XLR

- Affected individuals also experience severe recurrent sinorespiratory infections, and some develop progressive hearing loss.
- Typical features of RP: night blindness, constricted visual fields, progressive reduction in visual acuity, bone-spicule pigmentation, and extinguished responses on electroretinography.
- The CEP290 gene may be a modifier for respiratory phenotype. (PMID: 38534367; PMCID: PMC10968961)

Phenotypic Series of RP - PS268000

Sex-linked RP: X-linked are **six** (? 23, ?6, 2, 3, 24, and 34), and Y-liked is only **one**.

RPGRIP1 (Retinitis Pigmentosa GTPase Regulator-Interacting Protein)

Phenotype reported with RPGRIP1: Leber congenital amaurosis 6 and Cone-rod dystrophy 13; MOI- AR
This gene has variable expression in different tissues (high in the retina, and less in the testis), which partially explains the tissue-restricted phenotype expression of RPGR-related disorders.

Syndromes have a classical triad of RPSRDF

- **((Retinitis AND pigmentosa AND infections AND deafness)) Mesh term** search by OMIM provides only three more entries with AR inheritance; but these entries additionally have neurological, renal, endocrinal, and gastrointestinal involvement**.**

1. **Infantile-onset multisystem neurologic, endocrine, and pancreatic disease 2- YARS1** gene, onset with GIT involvement as cholestatic hepatitis & pancreatic dysfunction
2. **PERCHING syndrome –KLHL7** gene, predominantly neurological presentation as ID & axial hypotonia
3. **Alstrom syndrome - ALMS1** gene, Obesity, type 2 DM, with progressive renal and cardiac failure

Counsel the family for Case III: 4 - First to do a routine clinical evaluation and confirm genotype in proband (Case III:5), followed by clinical examination of Case III:4 for similar phenotype. Genotyping is indicated after proper counselling (about negative and positive outcome) for RP because of specific treatment available as gene therapy, even in the trial phase (PMID: 38871269)

Thought Riveting:

- ***What are the domains of RPGR protein related to retina-restricted phenotype?***
- ***How can the Comparative Toxicogenomic Database (CTD) help with research of drug repurposing or off-label use?***
- ***What could be the functional explanation for the highest median expression of RPGR RNA-Seq 9.58 Reads Per Kilobase per Million mapped reads (RPKM) in the pituitary gland?***
- ***What are other possible interacting proteins besides RPGRIP1 for RPGR for reactivating the protein?***
- ***What other proteins have RCC1-like domains (RLDs), and what is their specific role in protein domains?***