A Case of Leber Congenital Amaurosis in Two Sisters

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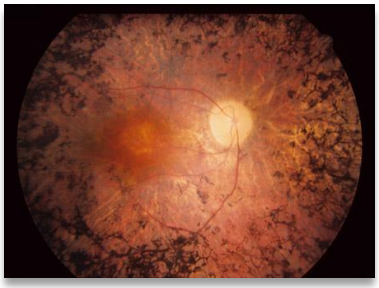
Case Presentation

- Sisters (age 7 & 9) with sickle cell trait and healthy birth were evaluated for low vision.
- Ocular history was significant for OU horizontal nystagmus, alternating exotropia, hyperopia, and photophobia.
- Nystagmus began ~6 weeks of age with low amplitude, medium frequency, horizontal and occasional rotary beats, was unaffected by light/dark, head position, or OKD, and gradually subsided by age 2, yet has persisted.
- Family history of nystagmus in other siblings, and parents are first degree cousins who immigrated from Somalia.
- They were given a diagnosis of congenital familial nystagmus.
- VA remained significantly impaired, and they were registered for legal blindness.
- ERG showed atypical flatline wave forms OU, possibly representing nystagmus artifact vs true pathology.
- Thereafter (ages 6 & 9), retinal exam revealed new pigmentary changes
- As such, both sisters underwent retinal dystrophy genetic testing which revealed two homozygous pathological variants of RPGRIP1 (c.2024del [p.Leu675Profs*9]).
- RPGRIP1 gene is associated with autosomal recessive Leber Congenital Amaurosis and Cone-Rod Dystrophy.
- They were then seen in retina clinic (last visit), where bone spicules and pallor were newly noted in the periphery.

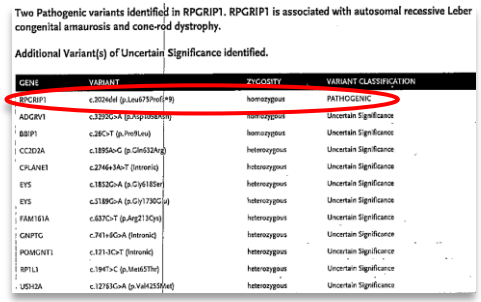
Exam Findings and Testing

9-year-old VA: **20/150 OD; 20/400 OS**
7-year-old VA: **20/300 OD; 20/300 OS**
Combined exams:

- External and Slit Lamp: low amp horizontal nystagmus OU, otherwise grossly normal
- DFE: **peripheral bone spicules and pallor**



Retinal Dystrophy Genetic Panel Results



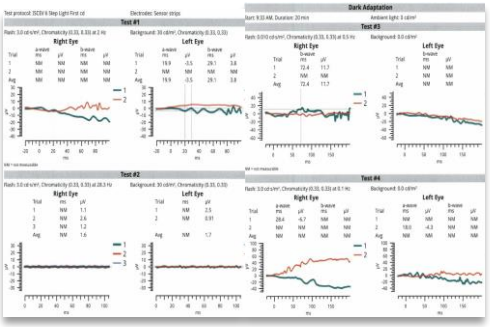
Two Pathogenic variants identified in RPGRIP1. RPGRIP1 is associated with autosomal recessive Leber congenital amaurosis and cone-rod dystrophy.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
RPGRIP1	c.2024del (p.Leu675Profs*9)	homozygous	PATHOGENIC
ADGRV1	c.3293G>A (p.Asp1098Asn)	homozygous	Uncertain Significance
BBIP1	c.286C>T (p.Pro9Leu)	homozygous	Uncertain Significance
CCDC2A	c.1895A>C (p.Gln632Arg)	heterozygous	Uncertain Significance
CPLANE1	c.2746+3A>T (Intronic)	heterozygous	Uncertain Significance
EYS	c.1852G>A (p.Gly618Ser)	heterozygous	Uncertain Significance
EYS	c.5189G>A (p.Gly1730Glu)	heterozygous	Uncertain Significance
FAM161A	c.637C>T (p.Arg213Cys)	heterozygous	Uncertain Significance
GNPTG	c.741+6C>A (Intronic)	heterozygous	Uncertain Significance
POMGNT1	c.1211-1C>T (Intronic)	heterozygous	Uncertain Significance
RP1L1	c.1847>C (p.Met615Thr)	heterozygous	Uncertain Significance
USH2A	c.12763>A (p.Val4255Met)	heterozygous	Uncertain Significance

Electroretinogram Testing

ERG with borderline reliability. There are generally atypical flatline wave forms OU, which may represent true pathology vs artifact from nystagmus.



Discussion

- Leber Congenital Amaurosis (LCA) is one of the most common inherited retinal dystrophies and is considered by some to be a severe form of Retinitis Pigmentosa.
- Hallmark presentation includes onset in the first year of life, nystagmus, hyperopia, poor VA, flat ERG, and can include keratoconus and sluggish pupillary responses (1, 2).
- Pathophysiology arises from degeneration, dysplasia, or aplasia of the RPE and outer segments of photoreceptors leading to impaired phototransduction (3).
- Multiple genes have been associated with LCA, including RPGRIP1 (Retinitis Pigmentosa GTPase Regulator Protein 1), and typically have autosomal recessive inheritance.
- These genes are associated with photoreceptor morphology, phototransduction, Vitamin A metabolism, and ciliary transport (RPGRIP1) to varying degrees (4).
- There is currently no cure; gene therapy trials are ongoing.

Follow up and Prognosis

- The sisters will follow up for a 6-month retina visit in June 2022 for OCT, HVF, and Fundus photos to monitor progression.
- They have learned to cope via home spatial awareness, regular outdoor patterns, reading braille, and benefit from a teaching aid at school.
- Prognosis for visual improvement is quite poor
- Given autosomal recessive inheritance, their siblings and future partners should undergo genetic testing/counseling to advise on likelihood of passing on the trait.
- Gene therapy clinical trials for specific LCA mutations offer promising results.

References

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(5) Fundus Photo: Dr. Dylan Griffiths https://eyewiki.aao.org/File:Retinitis_Pigmentosa_fundus.jpg

This study was funded in part by unrestricted grants from Research to Prevent Blindness, Inc. New York, New York and Lions District 20-Y1, Syracuse, New York. No other significant financial interests or relationships to disclosure

SUPPORTED BY Research to Prevent Blindness