Natural History of Visual Loss in USH1C

Madelaine (Lainey) Pickens[1], Dongjoon Kim[1], Goreth Leite[2], Glenda Vargas[2], Mona Hijazi[2], Thales Guimaraes[3], Wadih M. Zein[4], Michel Michaelides[3], Maria Reinoso[5], Robert K. Koenekoop[2], Jennifer J. Lentz[1,6]

[1]Neuroscience Center of Excellence, LSUHSC, New Orleans, LA, USA; [2]Depart. of Pediatric Surgery, Montreal Children's Hospital, McGill University Health Center, Montreal, CA; [3]Moorfields Eye Hospital, London, UK; [4]Ophthalmic Genetics and Visual Function Branch, National Eye Institute, Bethesda, MD, USA; [5]Depart. of Ophthalmology, LSUHSC, New Orleans, LA, USA; [6]Depart. of Otorhinolaryngology and Biocommunications, LSUHSC, New Orleans, LA, USA

Introduction

Usher syndrome (USH) is a rare genetic disorder characterized by the **multi-sensory loss of hearing, balance, and vision**; however, the natural clinical course—when these losses begin and how quickly they progress—is not known. Four clinical types (USH1-4) and 10 genes (subtypes) are associated with the disease based on the severity and age of onset of the symptoms. Approximately **10% of USH1, the most severe form, is caused by mutations in the USH1C gene**; however, nearly all cases are caused by the **USH1C c.216G>A founder mutation among the Acadian populations** in Canada and Louisiana. We are conducting a multicenter, **prospective natural history study (NHS) of visual loss in USH1C** at all stages of disease to improve our understanding of the natural progression and identify potential clinical trial participants and robust outcome measures that can be used to guide future clinical trials.

Methods

- ***Current/planned enrollment:*** 21/50; 1 participant excluded due to nystagmus
- ***Sites:***
  - Louisiana State University Health Sciences Center Eye Clinic (New Orleans, LA, USA)
  - McGill University Health Centre (Montreal, QC, Canada)
  - Moorfields Eye Hospital (London, UK)
- ***Participant Selection***
  - ***Inclusion criteria:*** (1) genetic confirmation of 2 pathogenic mutations in the *USH1C* gene, (2) age 12 – 70 years, and (3) ability to perform the vision assessments
  - ***Exclusion criteria:*** concurrent ocular or retinal disease (such as nystagmus) or inability to perform the tests
- ***Total # clinic visits/participant:*** 4 (baseline and 3 more every 6 months)
- ***Vision clinical data:*** See table to the right.
- ***Patient-reported outcomes:*** Visual Function Questionnaire (VFQ-25)
- ***Data entry, storage, analysis, and sharing:*** All demographic, ocular history, clinical, and patient-reported data (including source files) are entered and stored in a REDCap database. Deidentified data are exported for visualization and analyses using POD-Vis.

Vision Clinical Data

Vision Test	Protocols & Instruments
1. Refraction	Autorefraction, hand-held
2. Visual Acuity (VA)	ETDRS^ Protocol
3. Low Luminance Visual Acuity (LLVA)	EDTRS^ Protocol
4. Contrast Sensitivity	Pelli-Robson Protocol
5. Visual Fields	Static Humphrey, Kinetic Goldmann
6. Reading Speed Test	IReST* Protocol
7. Color Vision	Ishihara
8. Microperimetry	MAIA
9. Full-Field Stimulus Threshold (FST)	Diagnosys LLC Color Dome *(LSUHSC and MUHC only)*
10. Dark-Adapted Chromatic Perimetry (DAC)	Medmont Int PTY LTD *(LSUHSC only)*
11. Optical Coherence Tomography (OCT)	Heidelberg Spectralis
12. Fundus Photography	Optos
13. Fundus Autofluorescence (FAF)	Optos
14. Eye and Retinal Exam	Slit lamp, undilated and dilated

^Early Treatment Diabetic Retinopathy Study
*International Reading Speed Text

Demographics

Age, Sex, and Genotype

Total enrolled participants	n=21
Age range	
Adolescent (12-17 years)	*n=6*
Young adult (18-39 years)	*n=11*
Adult (40-66 years)	*n=4*
% female	43%, n=9/21
# participants with c.216G>A	17/21 (81%)
Homozygous for c.216G>A	*11/21 (52%)*
Heterozygous for c.216G>A	*6/21 (29%)*

***USH1C* Alleles Present in Cohort**

	Total Alleles	Mutation Type
c.216G>A (p.Val72Val)	28/42	Splicing
c.238dupC (p.Thr78ins1aC)	6/42	Small Indel
c.496+1G>T	4/42	Intron/Splicing
c.463C>T (p.Arg155*)	1/42	Nonsense
c.2401G>T (p.Glu801*)	1/42	Nonsense
c.364C>T (p.Gln122*)	2/42	Nonsense

Reading Speed and Contrast Sensitivity

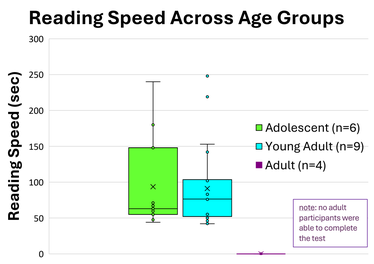

Fig. 1. Reading speed across age groups. Results of the reading speed test (OU, IReST) in 6 adolescents (11/24 visits completed), 9 young adults (22/36 visits completed), and 4 adults (13/16 visits completed). Standard IReST time = 55 sec. Sec, seconds

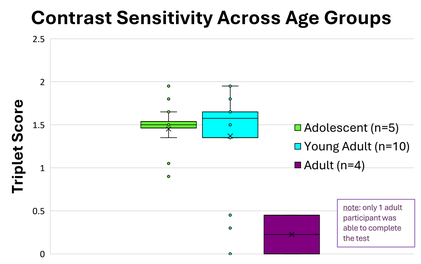

Fig. 2. Contrast sensitivity across age groups. Results of the contrast sensitivity test (OD, OS, Pelli-Robson) in 5 adolescents (11/20 visits completed), 10 young adults (24/40 visits completed), and 4 adults (12/16 visits completed). Normal Triplet Score = 2.0, mild impairment = 1.5-2.0, moderate impairment = 1.0-1.5, visual disability < 1.0.

Visual Acuity and Low Luminance Visual Acuity

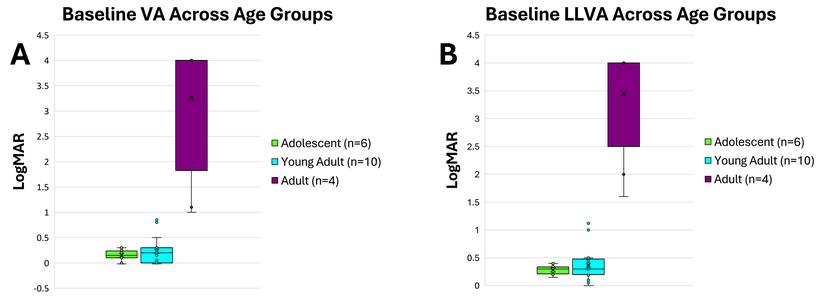

Fig. 3. Baseline Visual Acuity (VA) and Low Luminance Visual Acuity (LLVA) across age groups. Average ETDRS (**A**) VA (OD, OS) and (**B**) LLVA (OD, OS) at baseline was 0.15 and 0.28 (adolescents), 0.23 and 0.36 (young adults), and 3.26 and 3.45 (adults) LogMAR, respectively. LogMAR, Logarithm of the Minimum Angle of Resolution (normal vision = -0.2-0.56; low vision = 0.6-1.3; counting fingers = 2.0; hand motion = 3.0; light perception = 4.0).

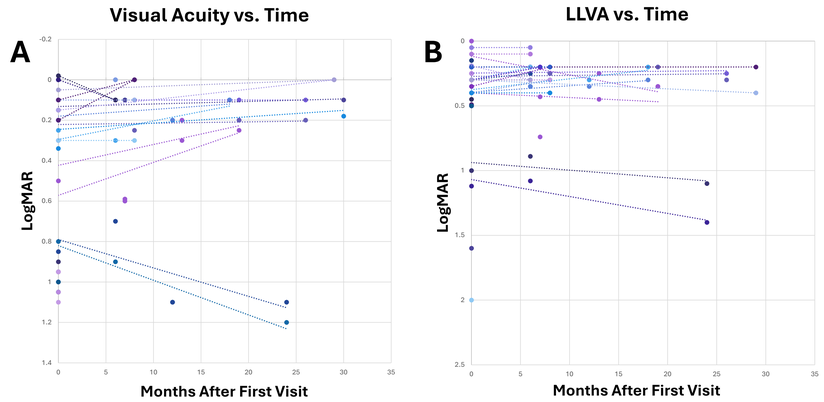

Fig. 4. Visual Acuity and Low Luminance Visual Acuity over time. ETDRS **(A)** VA and **(B)** LLVA (OD, OS) over the course of 1-4 visits for adolescents (n=6), young adults (n=10), and adults (n=1). Two young adult participants (aged 22 and 39 years) showed a decrease in VA over the course of 18 months. Two young adult participants (aged 22 and 33 years) showed a decrease in LLVA over the course of 18 months. Adult participants with light perception only (LP, logMAR = 4.0) were not included (n=3, aged 56, 59, and 66 years).

Full-Field Stimulus Threshold

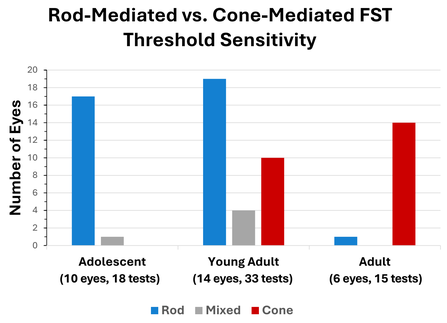

Fig. 5. Rod- vs. cone-mediated full-field stimulus threshold (FST) sensitivity. FST retinal sensitivity thresholds to blue and red light from adolescent (n=5), young adult (n=7), and adult (n=3) USH1C eyes. Average blue-red difference in sensitivity threshold[#] showed mainly rod-mediated threshold sensitivity in adolescents; rod-, mixed-, and cone-mediated in young adults; and mainly cone-mediated in adults.

[#] (Shi et al., 2024), ≤10 dB, cone-mediated (similar sensitivities to blue and red); 10-19 dB, mixed-mediated; and ≥19 dB, rod-mediated (higher sensitivity to blue than red).

FST Threshold Mediated Responses by Age Group

Age Group	Average Blue-Red Difference in Sensitivity Threshold (dB)	Retinal Cell Mediating Response
Adolescent (n=5)	23.81	Rod
Young adult (n=7)	17.45	Mixed
Adult (n=3)	3.97	Cone

Fig. 6. FST threshold mediated responses by age group. Averaged FST blue-red differences in sensitivity threshold indicate rod-mediated threshold sensitivity in adolescent (n=5), mixed-mediated in young adult (n=7), and cone-mediated in adult (n=4) USH1C patients.

Acknowledgments

We gratefully acknowledge support from the National Institutes of Health (NIH Grant R01EY03049901, NIH Grant (JHU) UG1EY033293), Usher 2020 Foundation, USH One See Foundation, Fighting Blindness Foundation Canada, Eye on Jacob Foundation, Vision Health Research Network, MCH Foundation, and Fonds de recherche du Québec (FRQ).

Microperimetry

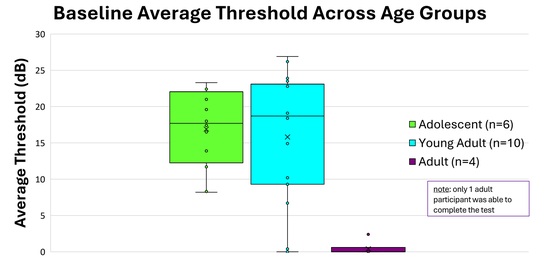

Fig. 7. Microperimetry average thresholds at baseline across age groups. The average Macular Integrity Assessment System (MAIA) light sensitivity threshold (dB) at baseline was similar for the adolescent and young adult groups (16.9 and 15.8 dB, respectively); however, only 1 of 4 adult participants had a threshold greater than 0 dB, indicating a loss of retinal function in USH1C patients as they age. dB, decibel

Color Fundus Photos and Fundus Autofluorescence

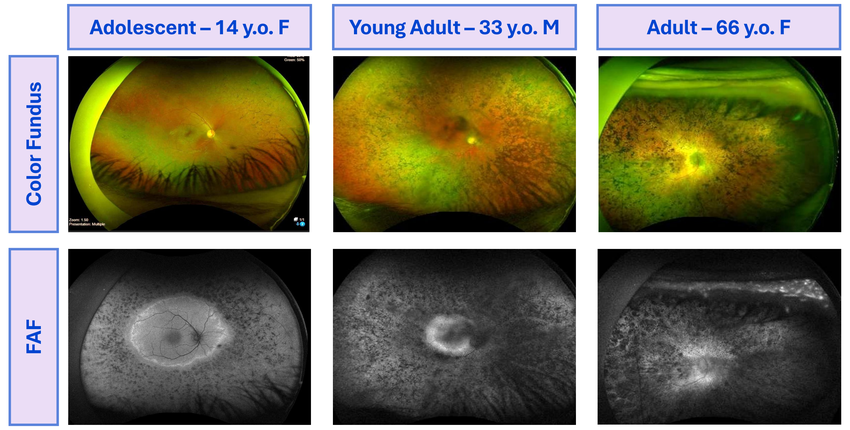

Fig. 8. Color fundus photos and fundus autofluorescence show progression of retinitis pigmentosa in USH1C patients as they age. Representative color fundus and FAF images from USH1C patients at various stages of disease progression. All color fundus photos exhibit arteriolar attenuation, disc pallor, and bone spicule-like pigmentation, which are classic findings in patients with retinitis pigmentosa. Bone spicule-like pigmentation becomes denser as the age of participant increases, as seen in both color fundus and FAF images. FAF images show the perifoveal ring of hyperautofluorescence becomes progressively more constricted as the disease progresses.

Preliminary Results & Conclusions

- 21/50 consenting participants (adolescent (n=6), young adult (n=11, 1 excluded due nystagmus), adult (n=4)) with genetic confirmation of USH1C disease are enrolled. 43% are female, and 81% (n=17/21) have at least one copy of the Acadian *USH1C* c.216G>A mutation.
- Natural history and outcome measures data for USH1C patients are important to guide clinical trials and improve our understanding of the natural disease progression.
- Reading speed is decreased for both adolescents and young adults with USH1C compared with normal vision readers. No USH1C adults were able to complete the test.
- Contrast sensitivity is decreased for all USH1C participants compared with normal vision.
- Average VA and LLVA at baseline was 0.15 and 0.28 (adolescents), 0.23 and 0.36 (young adults), and 3.26 and 3.45 (adults) LogMAR, respectively. VA and LLVA are in the normal vision range in adolescent and young adults with USH1C and in hand-motion range in adults. LLVA was worse than VA, indicating difficulty with low luminance vision.
- Blue-red FST sensitivity threshold difference suggests that retinal light sensitivity thresholds transitioned from rod-mediated to cone-mediated as the age of participants increased, indicative of a loss of rod function before loss of cone function.
- The decline in microperimetry thresholds indicates a loss of retinal function in USH1C patients as they age.
- The color fundus and FAF images show that the bone spicule-like pigmentation becomes denser and the perifoveal ring of hyperautofluorescence progressively became more constricted as the age of participants increased.
- Intraocular pressure was within normal limits for all visits across all patients, and patients did not exhibit a loss of color vision unrelated to their loss of visual acuity (data not shown).
- Kinetic visual field isopter area declined as the age of the participant increased (data not shown).
- Additional analyses of retinal structure and sensitivity using optical coherence tomography are ongoing.

References

1. Birch, D. G., et al ... Foundation Fighting Blindness Consortium Investigator Group (2020). The RUSH2A Study: Best-Corrected Visual Acuity, Full-Field Electroretinography Amplitudes, and Full-Field Stimulus Thresholds at Baseline. Translational vision science & technology, 9(11), 9. https://doi.org/10.1167/tvst.9.11.9.
2. Charng, J., Sanfilippo, P. G., Attia, M. S., Dolliver, M., Arunachalam, S., Chew, A. L., Wong, E. N., Mackey, D. A., & Chen, F. K. (2020). Interpreting MAIA Microperimetry Using Age- and Retinal Loci-Specific Reference Thresholds. *Translational Vision Science & Technology*, 9(7), 19–19. https://doi.org/10.1167/tvst.9.7.19.
3. Delmaghani, S., & El-Amraoui, A. (2022). The genetic and phenotypic landscapes of Usher syndrome: from disease mechanisms to a new classification. Human genetics, 141(3-4), 709–735. https://doi-org.lsuhscno.idm.oclc.org/10.1007/s00439-022-02448-7
4. D'Esposito, F., Gagliano, G., Gagliano, C., Maniaci, A., Avitabile, A., Giglio, R., Reibaldi, M., Cordeiro, M. F., & Zeppieri, M. (2025). Usher Syndrome: New Insights into Classification, Genotype–Phenotype Correlation, and Management. Genes, 16(3), 332. https://doi.org/10.3390/genes16030332
5. Koenekoop, R. K., Arriaga, M. A., Trzupek, K. M., & Lentz, J. J. (1999). Usher Syndrome Type I. In M. P. Adam (Eds.) et. al., GeneReviews®. University of Washington, Seattle.
6. Shi, L. F., Hall, A. J., & Thompson, D. A. (2024). Full-field stimulus threshold testing: A scoping review of current practice. Eye, 38(1), 33–53. https://doi.org/10.1038/s41433-023-02636-3.