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Baseline Microperimetry and OCT in the RUSH2A Study: Structure-Function Association and Correlation with Disease Severity

Baseline MP and OCT in the RUSH2A Study

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*The comprehensive list of FFB Consortium Investigator Group members participating in this protocol was previously published in Duncan JL, Liang W, Maguire MG, et al. Baseline Visual Field Findings in the RUSH2A Study: Associated Factors and Correlation with Other Measures of Disease Severity. *Am J Ophthalmol.* 2020

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Abstract

Purpose: To investigate baseline mesopic microperimetry (MP) and spectral domain optical coherence tomography (OCT) in the Rate of Progression in *USH2A*-related Retinal Degeneration (RUSH2A) study.

Design: Natural history study

Setting: 16 clinical sites in Europe and North America

Study Population: Participants with Usher syndrome type 2 (USH2) (N=80) or autosomal recessive nonsyndromic RP (ARRP) (N=47) associated with biallelic disease-causing sequence variants in *USH2A.*

Observation Procedures: General linear models were used to assess characteristics including disease duration, MP mean sensitivity and OCT intact ellipsoid zone (EZ) area. The associations between mean sensitivity and EZ area with other measures, including best corrected visual acuity (BCVA) and central subfield thickness (CST) within the central 1 mm, were assessed using Spearman correlation coefficients.

Main Outcome Measures: Mean sensitivity on MP; EZ area and CST on OCT

Results: All participants (N=127) had OCT, while MP was obtained at selected sites (N= 93). Participants with Usher syndrome type 2 (USH2, N=80) and nonsyndromic autosomal recessive Retinitis Pigmentosa (ARRP, N=47) had the following similar measurements: EZ area (median (interquartile range [IQR]): 1.4 (0.4, 3.1) mm^2 vs 2.3 (0.7, 5.7) mm^2) and CST (median (IQR): 247 (223, 280) μm vs 261 (246, 288), and mean sensitivity (median (IQR): 3.5 (2.1, 8.4) dB vs 5.1 (2.9, 9.0) dB). Longer disease duration was associated with smaller EZ area (*P*<0.001) and lower mean sensitivity (*P*=0.01). Better BCVA, larger EZ area, and larger CST were correlated with greater mean sensitivity (r>0.3 and *P*<0.01). Better BCVA and larger CST were associated with larger EZ area (r>0.6 and *P*<0.001).

Conclusions: Longer disease duration correlated with more severe retinal structure and function abnormalities, and there were associations between MP and OCT metrics. Monitoring changes in retinal structure-function relationships during disease progression will provide important insights into disease mechanism in *USH2A*-related retinal degeneration.

Highlights

- Baseline microperimetry and spectral domain OCT were analyzed in the RUSH2A study.

- Better BCVA and larger CST were associated with larger EZ area.

- Longer disease duration correlated with more severe structure-function abnormalities.

- Monitoring these changes will provide important insights into disease mechanisms.

Table of Contents Statement

The international, natural history study Rate of Progression in *USH2A*-related Retinal Degeneration (RUSH2A) enrolled 80 participants with Usher syndrome type 2 and 47 with

autosomal recessive retinitis pigmentosa associated with biallelic variants in the *USH2A* gene*.*
At baseline, longer disease duration correlated with more severe retinal structure (smaller
ellipsoid zone area) and functional abnormalities (lower mean retinal sensitivity on
microperimetry). A structure-function association was identified between microperimetry and
optical coherence tomography metrics.

Usher syndrome is the leading cause of autosomal recessive deaf-blindness and is genetically heterogeneous.[1,2] The most common form of Usher syndrome (56-67%) is Usher syndrome type 2 (USH2), with mild/moderate congenital hearing impairment and inherited retinal degeneration (IRD) beginning in the first or second decade.[3,4] The gene most commonly associated with USH2 is *USH2A*, which accounts for 57-80% of USH2 patients.[5,6] Retinitis Pigmentosa (RP) in *USH2A* shows primary rod and secondary cone photoreceptor degeneration followed by retinal pigment epithelial (RPE) degeneration.[7] *USH2A* mutations result in a wide phenotypic spectrum, with normal function in some patients, especially in the macula.[8] *USH2A* variants can also lead to IRD without hearing loss and represent the most common cause of nonsyndromic autosomal recessive RP (ARRP).[5]

USH2A-related natural history studies of retinal structure and function are limited. Earlier functional data was obtained with older techniques (Snellen acuity charts and Goldmann kinetic perimetry) in several single-center studies that lacked robust genotyping.[9,10] A study of 225 patients with *USH2A*-related IRD showed that individuals with USH2 had more severe symptoms and earlier visual loss than patients with ARRP, likely related to the difference in severity of causative genetic variants.[11] However, this study lacked detailed retinal phenotype data obtained using quantitative, high-resolution modalities for evaluation of structural and functional loss.

Prior studies did not perform assessments using current evaluation modalities, including spectral-domain optical coherence tomography (SD-OCT) and mesopic fundus-guided microperimetry (MP).[12,13] OCT provides non-invasive visualization and allows objective quantification of retinal structure in patients with IRD.[14-16] While these measurements correlate with visual function measures, ellipsoid zone (EZ) band width and area have higher reliability than functional measures such as visual acuity (VA), visual field, and electroretinogram responses.[14,17] Prior studies have not investigated the association of EZ measures with visual function in patients with *USH2A*-associated IRD. Fundus-guided MP, which provides a topographic evaluation of retinal function across the macula with greater precision and resolution than standard perimetry, can also be correlated with OCT measures of macular retinal structure.[18-20]

As new treatments for *USH2A*-related IRD are being evaluated,[21,22] an accurate knowledge of the natural history of *USH2A*-associated IRD is essential to best identify outcome measures suitable for clinical studies of therapies. This multicenter, international, longitudinal study of participants with retinal degeneration associated with *USH2A* sequence variants, the Rate of Progression of *USH2A*-related Retinal Degeneration (RUSH2A) study, was designed with the primary objective to characterize the natural history of *USH2A*-related retinal degeneration over 4 years. The study employs functional, structural, and patient-reported outcome measures to characterize variability in endpoints and possible risk factors (genotype, phenotype, and comorbidities) for disease progression.

The main objective herein is to address the unmet need stemming from the paucity of robust, quantitative structural and functional outcome measures characterizing retinal degeneration related to *USH2A* variants. We report RUSH2A baseline data on OCT and mesopic MP in participants with *USH2A*-related USH2 compared to *USH2A*-related ARRP and explore macular structure-function associations and relationships with baseline participant characteristics.

Materials and Methods

Study Design

Participants were enrolled in the RUSH2A study (NCT03146078) at 16 clinical sites in Europe and North America. The study was approved by the ethics boards at each site and adhered to the tenets of the Declaration of Helsinki. The study design and inclusion and exclusion criteria were previously documented.[12] Briefly, study participants were at least 8 years of age with a clinical diagnosis of rod-cone degeneration associated with at least 2 pathogenic or likely pathogenic sequence variants in *USH2A.* Following informed consent and initial eligibility assessment and informed consent, some individuals without a history of hearing loss and presumed nonsyndromic ARRP underwent additional genetic testing of first-degree relatives to confirm *in trans* inheritance of the variants. After enrollment, an independent audiologist reviewed the history of hearing loss and the results of baseline audiology exams to confirm either the USH2 or the ARRP diagnosis. Disease duration was computed based on age of onset, date of awareness of visual symptoms on participant medical history forms, and date of study enrollment.

Participants with a baseline best corrected visual acuity (BCVA) with Early Treatment of Diabetic Retinopathy Study (ETDRS)[23] letter score of 54 or greater (Snellen equivalent 20/80 or better) in the study eye, kinetic visual field at least 10° diameter in all meridians using the III4e target (Octopus 900 Pro, Haag Streit, Mason, Ohio), and stable fixation were enrolled in the primary cohort with a target sample size of 100. The study was also designed to enroll a secondary cohort of 20 participants with study eye baseline ETDRS letter score of 53 or less (Snellen equivalent 20/100 or worse), central visual field of less than 108 diameter, or unstable fixation. Secondary cohort was designed to complete a baseline visit only. The study eye was defined as the eye with better VA at baseline.

The schedule of assessments and testing procedures for this natural history study have been described previously.[12] This prior report provides details of other measures evaluated for correlation with MP and OCT measures of interest, including BCVA determined by ETDRS letter score and static perimetry total hill of vision (V_{TOT}). All MP and OCT testing was performed by technicians certified by the Duke Reading Center respecting the study-specific protocol and standardized procedures. Fundus-guided mesopic (standard) MP was performed using a Macular Integrity Assessment (MAIA-2) unit (iCare, Raleigh, NC) with software version 1.7 or higher. Sites performed baseline MP in the study eye, in primary cohort participants only. The test was performed three times to evaluate test-retest repeatability and to mitigate a potential learning effect. Two sites did not have the equipment and therefore MP was not performed in the participants from these sites. OCT volume scans were obtained using a Heidelberg Spectralis HRA+OCT unit (Heidelberg Engineering GmbH, Heidelberg, Germany). Sites performed baseline OCT in both eyes of all participants. The OCT and MP measures reported herein are mean retinal sensitivity from MP; and intact EZ area,

central 1 mm subfield thickness (CST), presence of intraretinal cysts, epiretinal membrane (ERM) or vitreomacular traction (VMT) from OCT.

Microperimetry Imaging and Grading

MP testing was administered following pupillary dilation with one drop of tropicamide 1% and phenylephrine 2.5%. Participants were in a mesopic environment for at least 10 min prior to testing and completed a two-minute training session prior to the full test. The full test involved a custom, circular grid consisting of 89 points that covered the macular area and to the arcades. The custom grid was composed of 89 stimuli arranged in concentric crowns located at 2°,4°, 6.5°, 9°, 12° and 15° from the foveal center.

Readers at the Duke Reading Center evaluated all MP images. A retinal sensitivity of <25 dB was considered abnormal, and sensitivity of <0 dB was considered to represent an absolute scotoma. The foveal area was determined based on the red-free fundus image[24] by use of the perimacular vessels and the center of the avascular zone. Eyes with abnormal sensitivity <25 dB in the foveal area were classified as having foveal involvement. Fixation stability was expressed as the bivariate contour ellipse area (BCEA), the area of an ellipse on the retinal surface within which the center of the target was imaged at least 68% of the time; smaller values indicate more precise fixation.[25]

OCT Imaging and Grading

High resolution, macula-centered, spectral domain OCT volume scans consisting of 121 B-scans within a 30° x 25° retinal area using automatic real-time (ART) tracking setting of 9, and one 7-line raster scan with a 30° x 5° area at ART 25 were acquired.

Duke Reading Center readers assessed all OCT scans; grayscale was used for additional contrast. The presence or absence of retinal cystic changes were determined within the retinal layers, not between ERM and the retina or associated with choroidal neovascularization, pigment epithelial detachment, or other area outside the neurosensory retinal tissue. Retinal cystic changes were considered well-defined, black or dark round or oval shapes, and were differentiated from diffuse edema characterized by absence of well-defined round or oval shapes, and from outer retinal tubulations.

ERM and VMT deformation within 1 mm of the foveal center were defined as whether the presence of ERM or posterior hyaloid, respectively, deformed the retina within this area. CST was measured semi-automatically by the HEYEX software version 6.12 (Heidelberg Engineering GmBH, Heidelberg, Germany). Readers first adjusted image centration, and then corrected inner and outer segmentation boundaries ç@ Ág c^¦} æ¦Áã ãã* Á ^{ à¦æ}^¦Áæ} åÁÓ¦˘&@ Á ^{ à¦æ}^¦Dåæ Á^^å^åÈ

The Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP)[26,27] was used to manually annotate A-scans with intact EZ on each B-scan from OCT macular volumes and to calculate intact EZ area. Readers first annotated the foveal B-scan on which the intact EZ is easier to identify, and then annotated the neighboring B-scans. In borderline cases where the presence or absence of the EZ was not clear, the reader assumed EZ continuity from the fovea. A second senior reader reviewed all B-scan gradings of the first reader and corrected the gradings when needed.

Microperimetry-OCT Overlays

To overlay the MP microperimetry sensitivity grid and intact EZ area segmented on the OCT images, a semi-automated software program was developed to register the

Characteristic						
N=70	N=125	None	Outside central 1mm only N=18	Inside central 1mm N=37	P-value
Clinical diagnosis					0.22
USH2	78	39 (50%)	13 (17%)	26 (33%)	
ARRP	47	31 (66%)	5 (11%)	11 (23%)	
Foveal involvement[b]					0.60
Yes	56	32 (56%)	6 (11%)	19 (33%)	
No	14	8 (57%)	2 (14%)	4 (29%)	
Possible	18	13 (72%)	0	5 (28%)	
EZ area (mm^2)	124				0.29
Median (IQR)		1.4 (0.6, 4.3)	1.0 (0.2, 2.6)	1.9 (0.7, 3.2)	
[Min, Max]		[0.0, 33.4]	[0.0, 11.2]	[0.0, 14.5]	
Central subfield thickness[c]	124				**<0.001**
Median (IQR)		252 (226, 279)	238 (225, 280)	271 (247, 300)	
[Min, Max]		[148, 323]	[137, 323]	[212, 519]	
95% BCEA area	88				0.61
Median (IQR)		1.5 (0.8, 2.8)	1.2 (0.7, 2.3)	1.5 (0.8, 2.9)	
[Min, Max]		[0.2, 57.2]	0.5, 2.8]	[0.5, 16.8]	
VA	125				**0.01**
Median (IQR)		83 (75, 87)	75 (69, 82)	79 (75, 83)	
[Min, Max]		[43.0, 94.0]	[18.0, 88.0]	[41, 92]	
Definite VMT with deformation within center 1mm					0.35
Yes	1	0	0	1 (100%)	
No	123	70 (57%)	18 (15%)	35 (28%)	
Ungradable	1	0	0	1 (100%)	
Definite ERM with deformation					0.19

within center 1mm					
Yes	25	12 (48%)	2 (8%)	11 (44%)	
No	100	58 (58%)	16 (16%)	26 (26%)	

[a]2 participants with ungradable cysts were excluded from this analysis

[b]Foveal involvement was not available for 37 participants

[c]CST was missing for 1 participant

Table 7. OCT EZ area stratified by baseline participant characteristics, overall and by clinical diagnosis

Characteristic	Clinical Diagnosis						Univariable[a]	Multivariable[b]
	All		USH2		ARRP			
	N=126	EZ Area Median (IQR), mm^2	N=80	EZ Area Median (IQR), mm^2	N=46	EZ Area Median (IQR), mm^2	P-value	P-value
Gender							0.63	
Female	68	1.8 (0.4, 4.4)	44	1.8 (0.3, 3.8)	24	2.0 (0.6, 5.2)		
Male	58	1.4 (0.6, 3.4)	36	1.2 (0.4, 2.2)	22	2.3 (1.0, 5.7)		
Race/Ethnicity							0.93	
White	112	1.5 (0.5, 3.4)	70	1.4 (0.4, 3.0)	42	2.3 (0.7, 5.7)		
Hispanic	9	1.6 (1.0, 5.1)	7	1.4 (0.4, 5.1)	2	3.6 (1.6, 5.7)		
Asian	5	1.1 (0.3, 2.8)	3	1.1 (0.0, 11.4)	2	1.6 (0.3, 2.8)		
Age at enrollment, yrs							<0.001	
<35	44	2.6 (1.4, 5.9)	36	2.6 (1.4, 5.6)	8	2.6 (2.0, 6.2)		
35-45	44	1.4 (0.6, 2.6)	25	1.2 (0.4, 2.1)	19	1.6 (0.7, 3.5)		
45 years or older	38	0.6 (0.1, 2.8)	19	0.2 (0.0, 0.7)	19	1.8 (0.5, 9.9)		
Duration of Disease, yrs[c]							**<0.001**	**<0.001**
<10	36	4.5 (2.5, 8.5)	20	4.6 (2.6, 6.8)	16	3.9 (2.0, 14.7)		
[10,20)	46	1.6 (0.7, 2.8)	25	1.6 (0.7, 2.5)	21	1.6 (0.7, 2.8)		
>=20	43	0.6 (0.1, 1.3)	35	0.6 @(0.1, 1.3)	8	0.5 (0.0, 1.5)		
Smoking status							0.79	
Yes	32	1.7 (0.5,	20	1.8 (0.5,	12	1.7 (0.6,		

[a]Numeric factors were analyzed using continues version.

[b]Multivariable model adjusted for clinical diagnosis ($P = 0.75$) and other factors included in final model as noted

^c1 participant in the ARRP group was missing age of onset (a participant-reported field based on their awareness of visual symptoms) and duration of disease (computed based on age of onset and date of enrollment)

Table 8. Correlation of baseline OCT EZ area with other functional and structural measurements

Factors to Evaluate	a) All	Clinical Diagnosis	Spearman Correlation Coefficient (95% CI)					P-value^a
	N=126	OCT EZ Area – Median (IQR)	N=80	USH2	N=46	ARRP		
VA ETDRS letter score (approx. Snellen equivalent)							0.61 (0.48, 0.71)	<0.001
<68 (<20/40)	14	0.0 (0.0, 0.2)	11	0.0 (0.0, 0.6)	3	0.0 (0.0, 0.0)		
69-73 (20/40)	14	0.3 (0.2, 0.7)	9	0.2 (0.2, 0.4)	5	0.7 (0.3, 0.7)		
74-78 (20/32)	24	1.4 (0.8, 2.0)	17	1.4 (0.8, 2.1)	7	1.0 (0.5, 1.6)		
79-83 (20/25)	33	2.1 (0.8, 3.5)	18	1.3 (0.4, 2.6)	15	2.8 (2.1, 5.7)		
>=84 (>=20/20)	41	3.4 (1.4, 7.2)	25	3.7 (1.4, 7.2)	16	3.0 (1.3, 9.5)		
Central subfield thickness^b (μm)							0.67 (0.57, 0.76)	<0.001
<230	33	0.3 (0.1, 0.7)	28	0.4 (0.2, 0.8)	5	0.1 (0.0, 0.2)		
[230, 250)	22	1.4 (0.7, 2.6)	13	1.9 (0.8, 2.6)	9	1.0 (0.7, 1.6)		
[250, 280)	33	2.1 (0.9, 4.7)	18	1.8 (0.9, 3.7)	15	2.5 (0.9, 5.7)		
>=280	37	3.4 (1.8, 7.2)	20	3.4 (1.7, 6.9)	17	4.3 (2.1, 9.9)		
Spherical equivalent^c							-0.13 (-0.31, 0.05)	0.16
< -3.25	27	1.3	19	1.4	8	1.2		

		(0.4, 2.8)		(0.4, 3.0)		(0.5, 2.4)		
[-3.25, -1.125)	26	2.6 (1.2, 5.1)	19	2.5 (1.2, 4.5)	7	3.5 (0.7, 9.9)		
[-1.125, -0.125)	28	1.5 (0.8, 5.5)	15	1.1 (0.3, 3.7)	13	2.6 (1.4, 6.8)		
>= -0.125	30	1.0 (0.2, 2.6)	19	0.7 (0.1, 2.5)	11	1.6 (0.5, 2.7)		

[a]Numeric factors were analyzed using continues version

[b]CST was missing for 1 participant

[c]Spherical equivalent was missing for 15 participants

Table 9. Baseline MP-OCT overlay metrics, overall and by clinical diagnosis and disease duration.

	All	Clinical Diagnosis		P-value	Disease duration[b]			P-value
	N	USH2	ARRP		<10	10-20	⁻Ǥ€	
	N= 83	N=51	N=32		N= 29	N=34	N=19	
Average sensitivity within Intact EZ Area				0.17				0.08
Median (Q1, Q3)	23 (21, 25)	22 (21, 25)	24 (22, 25)		22 (21, 25)	24 (22, 25)	20 (18, 24)	
Average sensitivity (interpolated) within intact EZ area				0.13				0.02
Median (Q1, Q3)	21 (19, 24)	21 (18, 23)	22 (20, 24)		21 (19, 24)	21 (20, 23)	18 (15, 23)	
Average sensitivity outside intact EZ area				0.80				0.02
Median (Q1, Q3)	2 (1, 6)	2 (1, 7)	2 (2, 5)		4 (2, 8)	2 (1, 4)	3 (1, 5)	
Average sensitivity (interpolated) outside intact EZ Area				0.64				0.01

Median (Q1, Q3)	2 (1, 5)	2 (1, 5)	2 (1, 4)		3 (2, 6)	1 (1, 3)	2 (0, 4)	
Number of pixels within intact EZ area within the interpolated microperimetry map[a]				0.03				<0.001
Median (Q1, Q3)	21 (10, 43)	16 (6, 36)	24 (14, 60)		37 (23, 62)	16 (10, 34)	7 (3, 16)	
Number of pixels outside intact EZ area within the interpolated microperimetry map[a]				0.04				<0.001
Median (Q1, Q3)	713 (691, 724)	718 (699, 728)	710 (675, 720)		696 (673, 711)	718 (701, 725)	728 (715, 731)	
Number of sensitivity points within intact EZ area				0.03				<0.001
Median (Q1, Q3)	5 (3, 9)	4 (2, 8)	6 (4, 12)		9 (5, 12)	4 (2, 7)	2 (1, 4)	
Ratio of average sensitivity (interpolated) inside vs outside intact EZ				0.11				0.95
Median (Q1, Q3)	8 (3, 16)	6 (2, 15)	11 (5, 17)		6 (3, 13)	16 (4, 18)	6 (3, 13)	

[a]Different scale (all values reported have been divided by 1000)

[b]1 participant in the ARRP group was missing age of onset (a participant-reported field based on their awareness of visual symptoms) and duration of disease (computed based on age of onset and date of enrollment