Characterisation of *RPGR*-associated Retinitis Pigmentosa with Mesopic and Scotopic Microperimetry using the S-MAIA

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Introduction

- Microperimetry (MP) is a potential clinical endpoint for a wide range of retinal conditions including Retinitis Pigmentosa (RP).
- Disease-causing variants in *RPGR* (Retinitis Pigmentosa GTPase regulator) account for the majority of X-linked RP [1], and is the focus of multiple ongoing gene therapy trials.
- We assessed retinal sensitivity in *RPGR*-associated RP using the S-MAIA microperimeter

Methods

- The mesopic retinal sensitivity of 36 patients (32 adults, 4 children; age range 9-37 years) with *RPGR*-associated RP (*RPGR*-RP) and 3 adult subjects (age range 34-55 years) with *RPGR*-associated cone-rod dystrophy (*RPGR*-CORD) was assessed using the S-MAIA (CenterVue, Padova, Italy).
- A subset of 18 adults with *RPGR*- RP also undertook scotopic testing with the S-MAIA.
- Prior to mesopic testing a period of 20 minutes of dark adaption was observed whilst for scotopic, 30 minutes was observed.
- Preset background luminance were: 1.27 cd/m^2 (mesopic) and <0.0001cd/m^2 (scotopic)
- A stimulus of Goldman size III; a 4-2 staircase threshold strategy and a modified 10-2 grid consisting of 68 points with test points spaced 2^0 apart, centred on the fovea was used (see Figure 1). The device has a 36dB dynamic range. Testing was repeated if fixation losses exceeded 15%.

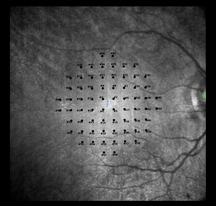


Figure 1
Custom grid overlaid on near infrared fundus photo

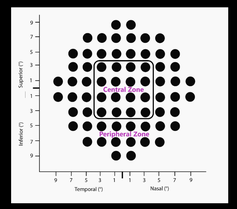


Figure 2
Grid subsections: Central & peripheral zones shown

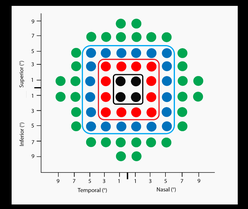


Figure 3 Grid subsections:
Black = central 4 points
Red = inner square rim
Blue – intermediate square rim
Green = outer area

- The mean sensitivity (MS) overall, as well as for the central (16 points across central 6^0) and peripheral (remaining 52 points) macular zones, were calculated (see Figure 2).
- The number of floor effects encountered during scotopic and mesopic testing, according to eccentricity in predefined grid subsections was determined (see Figure 3).

Results

MEAN SENSITIVITY

- The average mesopic MS (SD) for *RPGR*- RP and *RPGR*-CORD is shown in the below Table.

	RPGR-RP		*RPGR*-CORD	
	RE	LE	RE	LE
Central macula MS	9.90 (8.22)	10.07 (8.36)	6.92 (6.44)	4.60 (6.44)
Peripheral macula MS	5.00 (6.93)	5.10 (7.03)	16.93 (4.29)	13.13 (6.11)
Overall MS	6.16 (5.60)	6.27 (5.29)	14.56 (1.28)	11.12 (2.30)

- Under scotopic conditions, 9 of the 18 *RPGR*-RP subjects encountered the floor (i.e. <0.dB) at every tested point during the scotopic cyan component of testing.
  - For the remaining 9 subjects, the average scotopic cyan MS (SD) was 2.18dB (4.98dB), the average scotopic red MS (SD) was 2.90dB; the average pointwise cyan-red difference (SD) excluding the rod free zone was -2.13dB (2.07dB) in the central zone, and 0.74dB in the peripheral macular zones.

POINTWISE SENSITIVITY

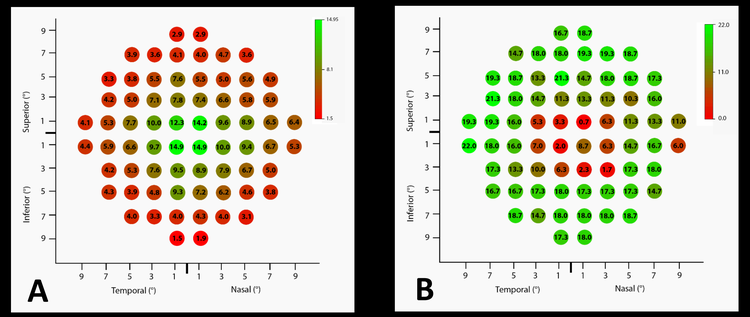


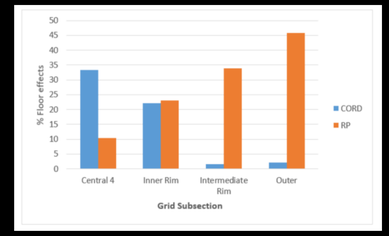
Figure 4
Averaged pointwise sensitivity at each grid point for A) *RPGR*-RP and B) *RPGR*-CORD right eyes. Numerical values shown & displayed according to a colour gradient.

- Retinal sensitivity values at each grid point (i.e. pointwise sensitivity) in mesopic testing were pooled and averages at each grid point is shown for *RPGR*-RP (see Figure 4A) and *RPGR*-CORD (see Figure 4B). For *RPGR*-RP subjects, highest values were at the centre whilst in *RPGR*-CORD, these were located in the more peripheral regions.

FLOOR EFFECTS

Scotopic Microperimetry in *RPGR*-RP

Point Location	Scotopic Cyan		Scotopic Red	
	No. of points reaching floor (i.e. <0dB)	Percentage of points reaching floor	No. of points reaching floor (i.e. <0dB)	Percentage of points reaching floor
Central 0-1° (n=72)	57	79%	11	15%
Inner Square rim 3° (n=288)	178	82%	101	47%
Intermediate square rim 5° (n=648)	307	85%	261	73%
Outer rim 7-9° (n=576)	507	88%	490	85%
All locations (n=1224)	1049	86%	863	71%



- The number of floor effects encountered during scotopic testing, according to grid subsections outlined in Figure 3, are shown in the Table above . Regardless of eccentricity, floor effects during scotopic cyan testing were widespread. Scotopic red testing was also profoundly affected but to a lesser extent.
- The floor effects encountered in mesopic testing are shown in the above Figure. Consistent with the underlying pattern of disease, the number of floor effects was highest at the centre in *RPGR*-RP and lowest in the centre in *RPGR*-CORD. Overall, 37% of all tested points reached the floor in mesopic testing in *RPGR*-RP.

Conclusion

- Severely reduced mesopic and scotopic retinal sensitivity, reflecting impaired mixed rod/cone and rod activity respectively, was evident in this cohort.
- Mesopic sensitivities reflected the underlying disease pattern in *RPGR*-RP and *RPGR*-CORD.
- Owing to the device's floor effect, scotopic evaluation was particularly limited. The present device may be suitable for a subset of RPGR-RP subjects with early or mild disease

Reference

1. Tee JJL, Smith AJ, Hardcastle AJ, *et al* *RPGR*-associated retinopathy: clinical features, molecular genetics, animal models and therapeutic options. *British Journal of Ophthalmology* 2016;**100:**1022-102

Commercial relationships

Yesa Yang, Angelos Kalitzeos, Navjit Singh, James Bainbridge: None declared
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