Retrospective natural history of retinitis pigmentosa due to *RHO*, *PDE6A*, or *PDE6B* mutations: The PHENOROD 1 study

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Purpose

The PHENOROD 1 study aimed at better understanding the natural history of rod-cone dystrophy, in order to optimize the design of clinical studies and the selection of endpoints assessing the efficacy of novel therapies.

Methods

- Retrospective longitudinal study
- Investigational site: national reference center for rare diseases (REFERET) at the *Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts*, Paris, France.
- Included patients with RP due to mutations in *RHO*, *PDE6A*, or *PDE6B* gene.
- Structural and functional visual parameters were collected from medical records. Among them: BCVA, kinetic VF, OCT and FAF imaging.
- Annual progression rates were estimated using a mixed error-component model. Non-parametric regression was performed using Locally Estimated Scatterplot Smoothing (LOESS).

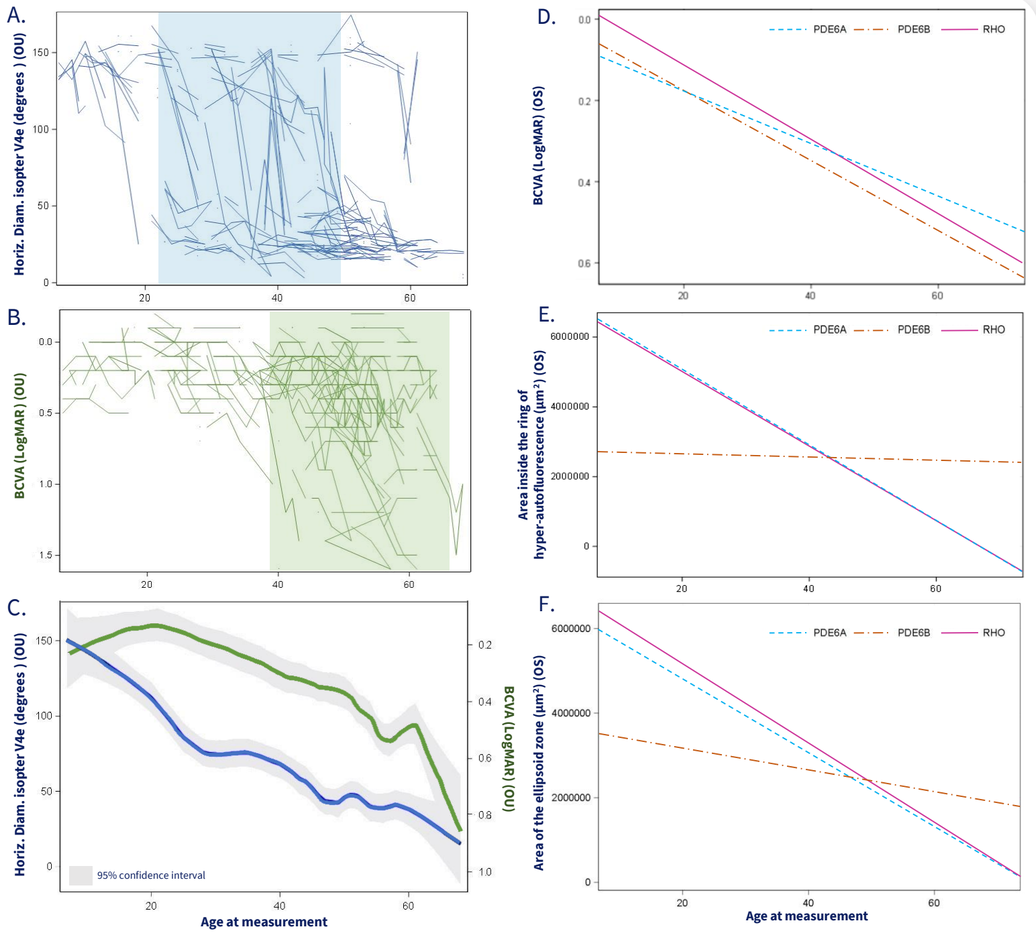
Results

Demographics and Patient Distribution

- 110 RP patients enrolled : 68% *RHO*, 13% *PDE6A*, 19% *PDE6B.*
- Balanced gender distribution : 58% F / 42% M.
- Mean age at onset of first symptoms (20.6 years) : slightly lower in *PDE6A* and *PDE6B* patients, compared to *RHO* patients (13.9 and 16.2 years, vs. 23.4 years).
- Large majority of patients with known history of RP (80.9%), mostly pathogenic missense mutations (81.3%).
- Mean age at time of first visit to investigational center : 38.4 years (range: 7-73).
- Medical records included a mean of 4.2 visits (range: 2-16), spanning on average 6.2 years of follow-up (range: 0.4-31.5).

Structural and Functional Visual Parameters

- Substantial constriction of isopter V4e was observed mostly between the ages of 25 and 50 (Figure A), whereas patients generally showed a drop in BCVA between the ages of 40 and 70 (Figure B).
- Non-parametric regression models corroborated this dynamic of visual function loss: VF constriction precedes BCVA deterioration (Figure C).
- Strong correlations were reported between structural and functional parameters (Chung DC. *et al.*, ARVO 2021 abstract issue of IOVS, Vol.62, 3539).
- The following annual decline rates were calculated between 20 and 60 years of age:
  - BCVA -3.1% (+0.01 LogMAR/year or -0.5 ETDRS letters/year)
  - Area inside the hyperAF ring -2.6% (-90,227 mm^2/year)
  - Area of the EZ – 2.2% (-83,888 mm^2/year)
- Linear regression models reported no difference between genotypes in the overall rate of BCVA decline (Figure D). However, *PDE6B* patients (n=21) showed slower decline rates of the EZ area and area inside the hyperAF ring, compared to *RHO* and *PDE6A* patients (n=73 and 14) (Figures E and F).



LogMAR axes were inverted to represent BCVA worsening going down

Conclusions

This retrospective natural history study PHENOROD 1 reported the slow progression of visual loss in patients with retinitis pigmentosa. Sample sizes were too small to allow meaningful statistical comparisons between genotypes. Annual progression rates were calculated assuming a linear evolution of the parameters, but non-parametric regression models showed that the evolution of visual function parameters BCVA and VF was dynamic: constriction of VF occurred earlier than decline in BCVA. These results are of particular interest in the development of treatments aiming at protecting photoreceptors, such as SPVN06, a novel dual gene therapy based on the expression of neurotrophic factor RdCVF and thioredoxin RdCVFL. A proof-of-concept study showed that SPVN06 dramatically reduced vision loss in the *rd10* mouse model of rod-cone dystrophy (Presentation Number - Posterboard Number: 56 – A0029).

Abbreviations: BCVA = best-corrected visual acuity ; EZ = ellipsoid zone ; FAF = fundus autofluorescence ; hyperAF = hyper-autofluorescence ; OCT = optical coherence tomography ; OS = *oculus sinister* (left eye) ; OU = *oculus uterque* (both eyes) ; RP = retinitis pigmentosa ; VF = visual field

Disclosures: ALM, DC, LT, PAV = (E) ; TL, JAS = (I)(P) ; SMS, IA = (C)

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