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Clinical characteristics and management of retinitis pigmentosa

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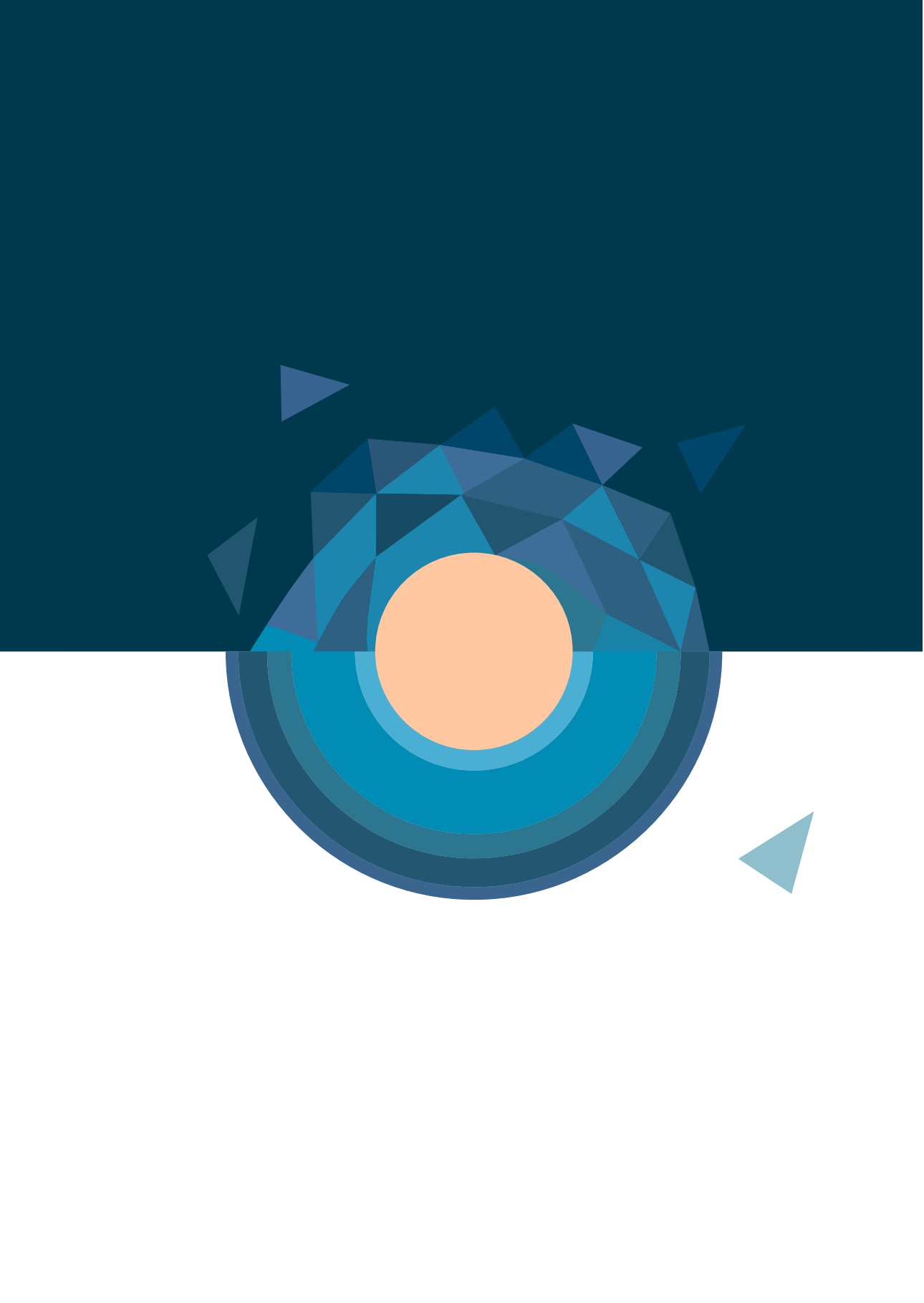
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APPENDIX

ENGLISH SUMMARY

DUTCH SUMMARY

ACKNOWLEDGEMENTS

CURRICULUM VITAE

LIST OF PUBLICATIONS



ENGLISH SUMMARY

Chapter 1 provides a comprehensive overview of the anatomy of the eye and the retina, with a particular focus on the phototransduction and visual cycle processes. In addition, this chapter goes into detail on RP and sheds light on our current understanding of the pathophysiology behind this complex retinal disease. Given the clinical and genetic variability associated with RP, it often presents with overlapping symptoms with other IRDs, making an accurate diagnosis challenging. Hence, establishing the correct diagnosis through clinical and genetic testing is essential for effective management of RP. This chapter delves into the different clinical and genetic testing tools that should be utilized to confirm an accurate RP diagnosis, and the implications of genetic testing for family planning.

In **Chapter 2.1**, we evaluated the natural history of *RHO*-associated RP using one of the largest cohorts to date. One of the first genes to be discovered to cause RP was *RHO*, causing an autosomal dominant form of RP. We found that *RHO*-associated RP is associated with a mild form of RP with regards to disease onset, severity and progression. Also, *RHO* is known to cause a very peculiar form of RP called sector RP, which shows minimal to no progression. As it is difficult to assess treatment efficacy in a disease that is slowly progressive, we propose the use of surrogate endpoints, such as the outer retinal thickness for the measurement of treatment efficacy in future trials.

In **Chapter 2.2**, we investigated the clinical phenotype of male *RPGR* affected individuals using modern psychophysical testing tools, such as the microperimetry and FST. This information is pivotal since several clinical gene therapy trials are currently underway for this genetic subtype of RP. *RPGR* variants typically result in a severe, early-onset form of RP with visual impairment at a young age. Our results reveal several different phenotypes, RP, CRD and MD; with the latter two phenotypes associated with the '3 end of *RPGR*, more specifically, exon ORF15. In the retina of a donor patient with a *RPGR* variant, histopathological evaluation showed that inner remodeling may already take place in regions without macroscopic signs of degeneration. As such, it is important for therapies to be applied at the earliest signs of degeneration.

Chapter 2.3 describes the clinical and genetic characteristics of a rare syndromic form of RP called PHARC syndrome, with less than 50 patients described worldwide. It is caused by variants in *ABHD12*, which plays a vital role in lipid metabolism. There was a variable severity in terms of visual acuity, fundus findings and multimodal imaging with no clear genotype-phenotype correlations. We found that from an ophthalmic perspective, patients with PHARC syndrome did not exhibit characteristic signs of RP, such as bone-spicule-like pigmentation, although the diagnosis rod-cone degeneration could be established using ffERG. Early macular involvement was present in patients with PHARC syndrome. Given the variability of symptom onset

of ophthalmic, neurological and audiological symptoms, it will be difficult to initially diagnose PHARC syndrome. A multidisciplinary approach, consisting of neurologists, geneticists, audiologists and ophthalmologists, is required to accurately diagnose PHARC syndrome.

Chapter 2.4 reports the first prospective, multicenter natural history study for patients with *CRB1*-associated retinal dystrophies. Variants in the *CRB1* gene cause a spectrum of IRDs phenotypes, with the most common being early-onset RP. The first proof of concept of gene therapy for *CRB1* has been established in the LUMC, paving the way for a potential treatment for this form of RP. In preparation for future clinical trials, this study evaluated the 2-year clinical course of *CRB1*, in order to determine time-sensitive progression markers. We found that *CRB1* has a variable disease expression, but most commonly results in visual impairment at a young age. A common finding is the thickening of the retina – which is in contrast with other subtypes of RP – which is almost pathognomic for this specific type of RP. We found that conventional parameters, such as visual acuity and visual fields, did not show any progression during follow-up, and may not be suitable to measure treatment efficacy. Significant progression was observed on microperimetry, suggesting that microperimetry is a more sensitive outcome measure in this disease. As fERG were not detectable in the majority of patients in this study, we employed the use of the FST, which allowed us to measure residual photoreceptor function, and thus FST can be used as treatment efficacy measure, or as inclusion criterion.

In **Chapter 3.1**, we evaluate the visual outcome of cataract surgery in patients with RP, and we discuss potential risk factors. Cataract is one of the most common complications found in patients with RP. Lens opacities, together with ongoing retinal degeneration can aggravate the loss of visual function, and in turn, significantly reduce patient's quality of life. In our study, cataract surgery leads to a significant improvement in visual acuity, and also improvements in subjective visual function in the majority of patients. However, surgeries should be performed with caution, as patients with RP are also relatively higher at risk for complications such as CME, PCO and zonulysis. If necessary precautions are undertaken for this population, cataract surgery can prove a valuable treatment.

In **Chapter 3.2**, we measured the effectiveness of the OrCam MyEye 2.0 on the quality of life in patients with IRDs. The OrCam MyEye is a low vision aid that converts visual stimuli to audio using an optical sensor mounted on a patient's glasses. Using the NEI-VFQ and D-AI, we demonstrated that the OrCam mainly improved activities related to 'near distance', and did not improve other subdomains of the NEI-VFQ or other rehabilitation goals on D-AI. Further improvements are needed in the OrCam to make the device serviceable for a broader audience.

In **Chapter 3.3**, we present a four-year report on the quality of life changes in patients with *CRB1*-associated retinal dystrophies. While objective outcome measures are essential for measuring treatment efficacy in upcoming trials, it's equally important to consider subjective outcome measures that reflect a patient's own experience. Unfortunately, subjective outcome measures are not adequately addressed in current clinical trials. Our study found that patients with *CRB1*-associated IRDs experienced a general decline in vision-related quality of life on the NEI-VFQ, in the absence of treatment. Therefore, we recommend that future clinical trials include patient-reported outcome measures as a relevant endpoint for disease progression and treatment efficacy.