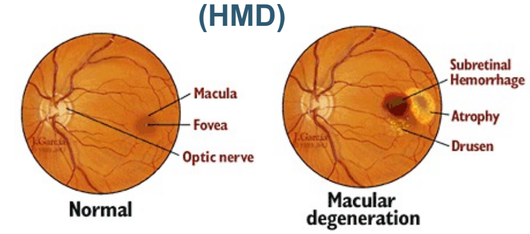
Biallelic Loss of Function Mutations in *PYGM* Cause Presumed Non-Syndromic Macular Dystrophy

Rowaida Hussein[1,2], Erika Tavares[2], Kashif Ahmed[2], Elise Héon[2,3], Ajoy Vincent[2,3]

[1] Institute of Medical Science, University of Toronto
[2] Genetics and Genome Biology, SickKids Research Institute
[3] Ophthalmology and Vision Sciences, University of Toronto

Introduction

Hereditary Macular Dystrophy (HMD)



- HMD leads to degeneration of the central retina resulting in irreversible vision loss
- It is sometimes reported in association with **McArdle Disease**, a glycogen storage disorder resulting from mutations in glycogen phosphorylase (GP)
- GP, encoded by the *PYGM* gene, breaks down stored glycogen into glucose-1-P monomers for use in glycolysis
- Retina expresses two isoforms of GP, *PYGB* and *PYGM*

Aim

? What is the link between HMD and McArdle Disease?

Methods

Whole genome sequencing in family with HMD to identify causative mutation(s)

Immunohistochemistry of *PYGM* in human retina to determine which retinal layers *PYGM* is expressed in

Recruitment and examination of additional McArdle patients (n = 15) to look for any retinal changes

Results

- WGS identified homozygous p.(Arg50*) mutations in *PYGM*
- *PYGM* is expressed in the INL, ONL, OPL, GCL, and NFL (Figure 1)
- 11 of 20 McArdle patients showed evidence of retinal changes (Figure 2)

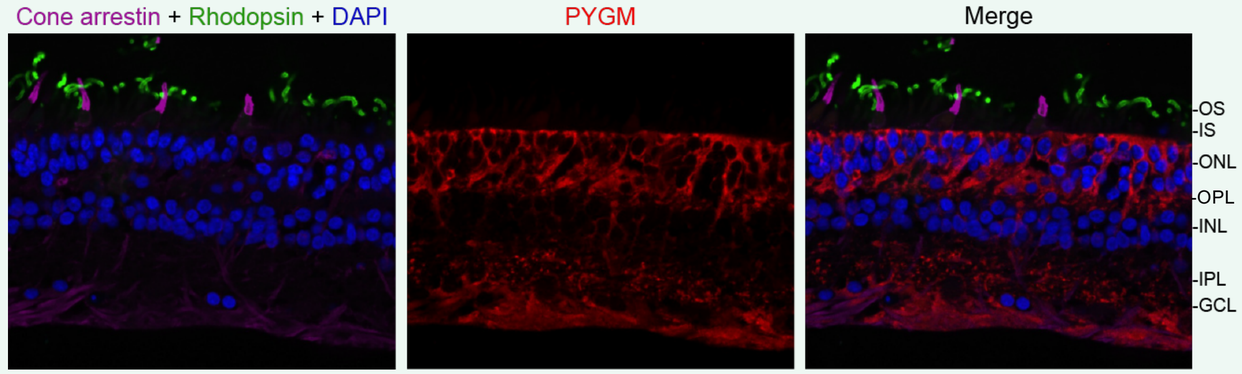


Figure 1: *PYGM* expression in human retina

Nuclei were stained with antibodies specific to cone arrestin (purple), rhodopsin (green), PYGM (red) and DAPI (blue). IPL, inner plexiform layer; IS, inner segment; OS, outer segment. Images were captured at 40x magnification.

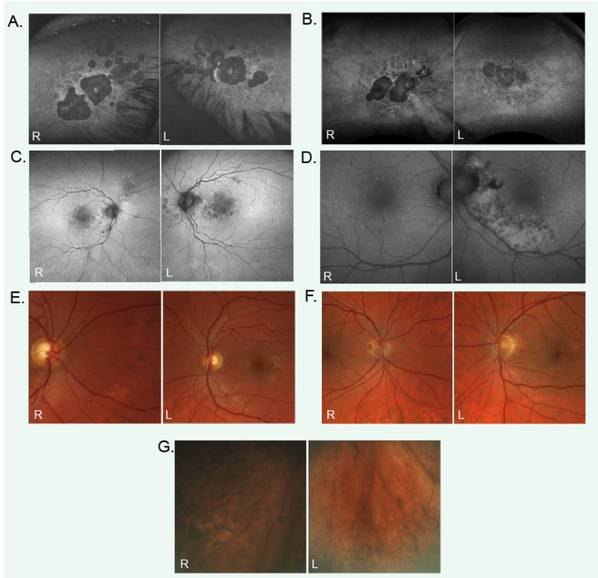


Figure 2: Retinal images of McArdle patients

McArdle patients show evidence of retinal changes, including yellow deposits, reticular changes, pigment hyperplasia and scalloped atrophy.

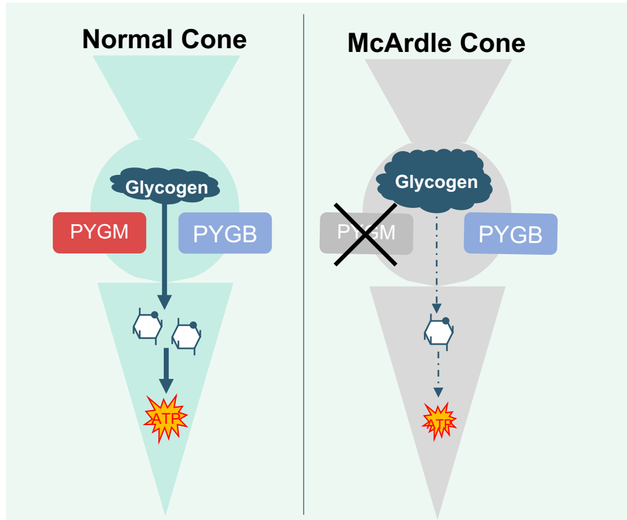


Figure 3: Proposed schematic of etiopathogenesis of retinopathy in McArdle Disease

Unlike healthy cones (right), dystrophic cones in McArdle disease (left) lack *PYGM* for glycogen breakdown, leading to progressive glycogen accumulation and glucose starvation.

Conclusions

- Biallelic mutations in *PYGM* causes McArdle disease and HMD
- HMD is prevalent in nearly half of examined McArdle patients, suggesting that this phenotype is either underdiagnosed or underrecognized
- Our results indicate that patients with McArdle disease would benefit from periodic eye exams as part of their care