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

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**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

**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