

# Wolfram Syndrome: A Rare but Insightful Childhood Condition

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**Background:** Wolfram Syndrome is a rare autosomal recessive genetic condition hallmarked by optic atrophy (OA), diabetes mellitus(DM) and deafness with an average life expectancy of 25-30 years.<sup>1,2,3,4,5</sup> The prevalence of wolfram syndrome has been documented as 1 in 770,000.<sup>1,2</sup> It has been linked to mutations in two genes;WFS1 and ZCD2. The WFS1 gene is located on 4p16.1 while ZCD2 is located on 4q22-25.<sup>1,2,4</sup> The WFS1 gene encodes for a transmembrane protein localized to the endoplasmic reticulum (ER) and ZCD2 encodes the protein endoplasmic reticulum intermembrane small protein; both of which play a key role in calcium(Ca<sup>2+</sup>) homeostasis.<sup>1,2,4</sup> Altered calcium levels causes inability of the ER to fold proteins which in turn causes stress on the ER and triggers the unfolded protein response and leads to apoptosis.<sup>1,2,4</sup>

DM is typically the first manifestation and occurs due to the apoptosis of the pancreatic beta cells as a result of the ER stress from the altered Ca<sup>2+</sup> homeostasis. OA occurs secondary to wolframin expressed in amacrine and muller cells of the retina and the Astrocytes of the optic nerve.<sup>1,2,4</sup> Diabetes Insipidus and Deafness typically occurs in the 2<sup>nd</sup> to 3<sup>rd</sup> decade of life; with deafness manifesting as high frequency sensorineural hearing loss caused by mutated wolframin in inner ear cells.

Additional systemic manifestations include urological, cardiovascular, gastrointestinal, reproductive, and neurological complications. Neurological complications arise from atrophy of the brain and visual pathways and lead to smaller intracranial volume, ataxia of the trunk, and apnea which is typically the cause of mortality. Additional ocular manifestations include: cataracts, Pigmentary retinopathy, abnormal pupillary light reflexes and nystagmus.

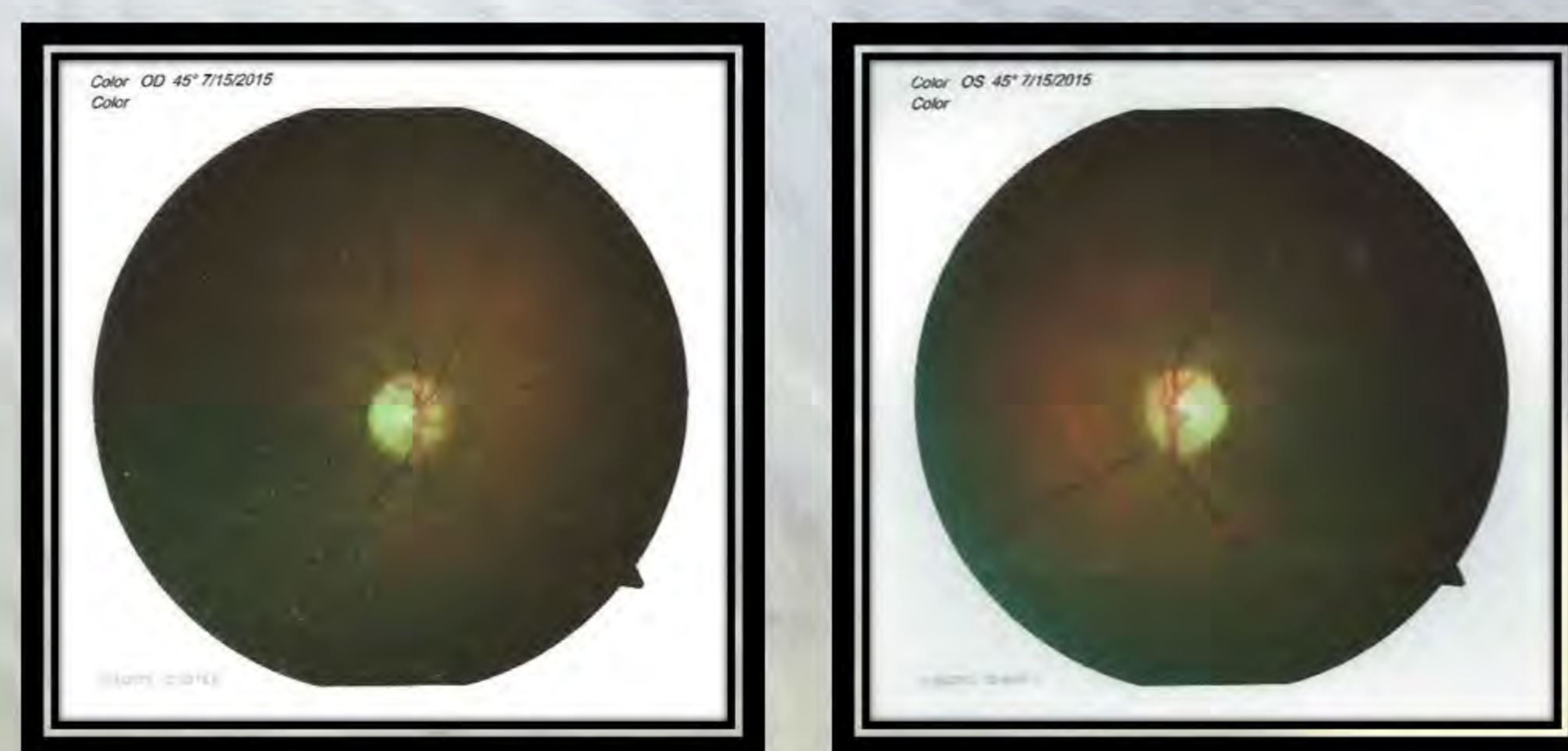


Figure 1: Fundus Photos depicting grade three pallor OD, OS. Taken July 2015 .

**Case Presentation** Twenty-four-year-old female presented to clinic for Wolfram Syndrome follow up with complaints of decreased vision at distance and near in both eyes worsening over the past year. The patient's entering visual acuity was measured to be 20/60 OD, 20/60<sup>+</sup> OS and 20/60<sup>+</sup> OU. Manifest refraction was found to be -0.25 +1.00x090 OD and -0.25 +0.50 x 090 OS yielding acuities of 20/40 and 20/40<sup>-1</sup> respectively. Anterior segment Slit lamp examination was unremarkable, while Posterior segment examination revealed grade 3 pallor of both optic nerves secondary to optic atrophy from Wolfram syndrome(Figures 1 & 2).In addition, updated Ocular coherence tomography (OCT)scans of the Optic nerve, Macular and ganglion cell layer were obtained, along with Hardy Randy Rittler(HRR) Color vision testing's. HRR revealed a severe red green color defect identifying only 1/24 figures OD 4/24 OS.

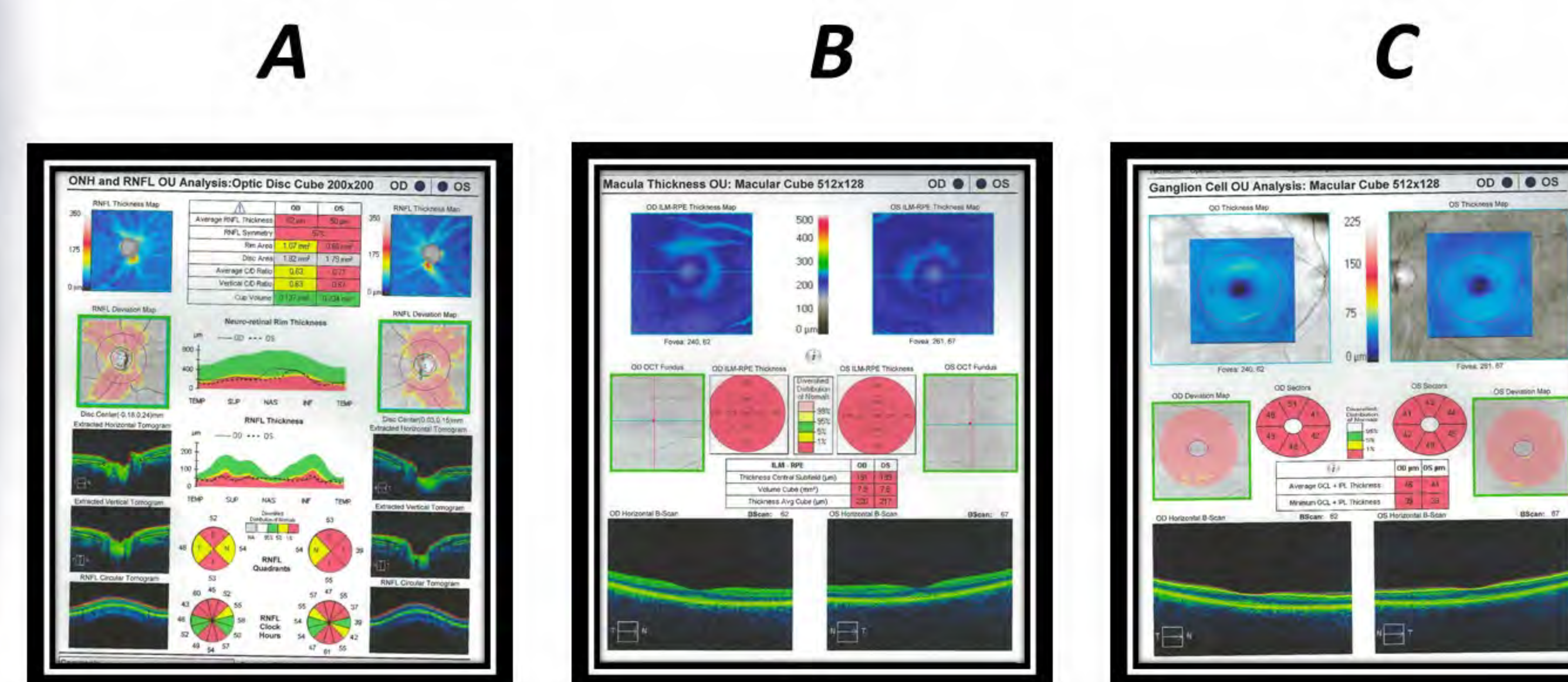


Figure 2: A) OCT of the Optic nerves showing thinning of both optic nerves in all quadrants. B) OCT of the macula, showing general thinning of the macular region of both eyes. C) OCT Ganglion cell layer analysis showing diffuse ganglion cell loss.

**Treatment and Management:** The patient will continue to be followed annually by Radiology, Neurology, Endocrinology, Psychology, Ophthalmology, and other specialties as needed with updated testing as the disease progresses. Systemic management, while there is no currently accepted treatment being used to delay or halt or reverse progression of wolfram syndrome current standard of care includes regular visits with specialists; control of Blood sugar, and Hearing aid or Cochlear implants for hearing manifestations. Standard of care for ocular management consist of regular visits with specialists, Color vision testing, Dilated fundus examination, Visual field testing. Additionally there have been studies on the use of Idebenone and Doxosahexanoic acid in attempt to achieve acuity improvements in patients with vision loss but results have been inconclusives<sup>1,5,7</sup>

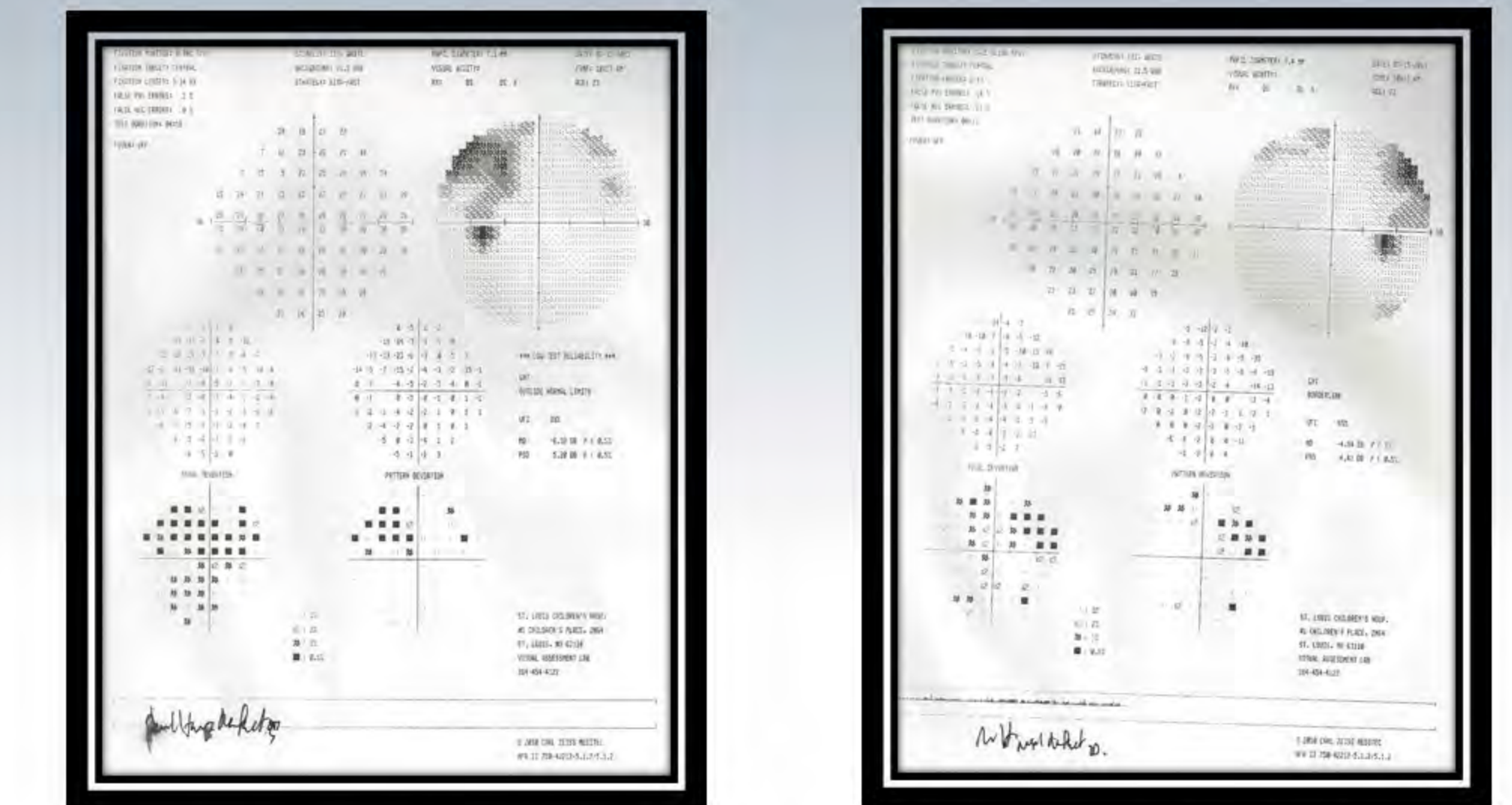


Figure 3: Humphrey visual field 30-2 measurements of the right and left eyes showing mild superior temporal field loss.

**Discussion and Conclusion:** Future Treatments for wolfram should focus on repurposing existing medications and creating new medications that would target the ER and Ca<sup>2+</sup> homeostasis pathways. Repurposing medications like Dantrolene which preserves ER Ca<sup>2+</sup> levels in response to ER stress and in turn can prevent beta cell death. This treatment model has been proven successful in animal models and is now currently under investigation in clinical trials. In addition to Ca<sup>2+</sup> stabilizers, repurposing of Chemical chaperones like 4-phenylbutyric acid (PBA)<sup>1</sup> and Traurosodeoxycholic acid (TUDCA) can stabilize protein conformation during folding which can reduce the ER stress and improve function of beta cells and neuronal cells by preventing cell death<sup>1</sup>

While repurposing medications would provide a more efficient means of finding a treatment, the alternative is to create new drugs that target ER and Ca<sup>2+</sup> homeostasis this maybe achieved by targeting one of the following: the Sarco/Endoplasmic reticulum Ca<sup>2+</sup> atpase (serca), Ryanodine receptors, Inositol triphosphate receptors, REDOX, and protein folding.<sup>1</sup> While wolfram syndrome is a rare condition, awareness of it is key to providing valuable insights into the mechanism of Diabetes that may lead to a cure and more effective treatments in the future.

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