FALL/WINTER 2025

Gillingham Lab

RESEARCH NEWSLETTER

A LOOK BACK AT 2025 AND INTO 2026

Despite what has felt like an uphill battle in the field of clinical research right now, we are proud of what we have accomplished in 2025. Included in this list of accomplishments are five new publications and several research presentations at international conferences and to the FAOD patient community. You can find recent updates on our Featured News page and an updated list of selected peer-reviewed publications, with a link to pubmed.gov for full-text articles, on our Publications & Presentations page.

Pictured: Lauren Ahmann

We also recently welcomed a new PhD student to our lab, Lauren Ahmann! Lauren is a graduate student researcher in the PhD Program for Biomedical Sciences. Originally from the San Francisco Bay Area, she earned her bachelor's degree in Genetics and Genomics from the University of California, Davis. In her free time, Lauren enjoys exploring new hiking trails, baking sweet treats, and playing with her cat, Echo. Lauren has been a wonderful addition to the team.

As we enter 2026, we continue our focus on ongoing projects and efforts to secure funding for new projects, including trying to get closer to a clinical treatment trial for LCHADD retinopathy. Some of the readers of this newsletter may have been participants in our Natural History of LCHADD Retinopathy study, which completed data collection in October 2024.

We previously summarized our preliminary results from the baseline testing in the Spring/Summer 2023 newsletter, followed by our published findings in the *Journal of Inherited Metabolic Disorders*. We've been busy analyzing the data collected from the 2-year follow-up visit. We presented our preliminary findings at the 2025 INFORM and ICIEM meetings in Kyoto, Japan, and are in the editing stage of submitting a paper to a journal for peer review. We hope to announce the publication of this paper soon, but in the meantime, we have summarized some of the main findings in this newsletter.

We've provided a glossary of medical terms used in our summary and a diagram of retinal layers of interest in our research at the end of this document for reference.

LCHADD RETINOPATHY: OUR 2-YEAR FINDINGS

One of the distinct characterizations of LCHAD/TFP deficiency, not present in other fatty acid oxidation disorders, is the presence of chorioretinopathy, a progressive eye disease that results in vision loss. Despite earlier detection and treatment of LCHADD/TFPD with newborn screening, this vision loss still occurs.

GENETICS OF LCHAD/TFP DEFICIENCIES

LCHADD or TFPD is caused by a variant in your DNA or genes. The LCHAD and TFP genes tell your cells how to make an enzyme called mitochondrial trifunctional protein. The mitochondrial trifunctional protein (TFP) is an enzyme complex made up of 4 protein subunits. Two of these subunits are called alpha subunits, and the other two are called beta subunits. The alpha and beta subunits work together to help break down fat in the fatty acid oxidation metabolism pathway. The DNA or gene named *HADHA* tells the cell how to make the alpha subunits, and the gene named *HADHB* tells the cell how to make the beta subunits. The genes are translated to messenger RNA (mRNA), then into proteins (chains of amino acids) to make the enzyme (TFP) that can help break down fat. The LCHAD enzyme is in the alpha subunit.

A common *HADHA* gene variant changes one single amino acid, glutamic acid, to a different amino acid, glutamine, and we call this variant c.1528G>C. It is right in the middle of the LCHAD enzyme, and the different amino acid (glutamine) decreases the LCHAD enzyme activity and causes LCHAD deficiency. This is often referred to as "the common mutation" or the "common variant". Everyone has 2 copies of the *HAHDA* and *HADHB* genes (1 inherited from mom, 1 inherited from dad).

People with LCHADD who have 2 copies of the "common variant" are referred to as c.1528G>C **homozygous** (means 2 of the same variant). People with 1 copy of the common variant, and another different mutation in the *HADHA* gene are c.1528G>C **heterozygous** (means 2 different variants in the same gene). Patients who have other variants (it could be 2 other variants in the *HADHB* gene or other variants in the *HADHA* gene) are traditionally diagnosed with TFP deficiency.

Our study enrolled 40 patients diagnosed with LCHADD or TFPD. The study was conducted at Oregon Health & Science University and the University of Pittsburgh Medical Center. All patients had comprehensive eye exams at enrollment ("baseline"), and then again approximately 2 years later. Ten participants were c.1528G>C homozygous (2 of the common variant), 27 participants were c.1528G>C heterozygous (1 copy of the common variant and 1 other variant in *HADHA*), and 3 participants had TFP deficiency.

FACTORS RELATED TO LCHADD CHORIORETINOPATHY

At Year 2 follow-up, having 1 or 2 copies of the common variant, being diagnosed after presenting with symptoms, and older age were associated with lower visual acuity, contrast sensitivity, visual field sensitivity, and electroretinogram (ERG) rod amplitudes. These factors associated with decreased vision were very similar to what we found when looking at the baseline testing results as well. Together, there is a strong indication that declines in eyesight are related to the specific genetic variants (presence of the common variant), age, and how people are diagnosed, either early with newborn screening or if they presented with symptoms when they were diagnosed.

LCHADD CHORIORETINOPATHY RATE OF PROGRESSION

We measured a small but detectable decrease in visual acuity over 2 years. Eight people with LCHADD had a clinically significant decline in visual acuity of at least 10 feet. This is similar to starting with 20/20 vision and 2 years later having 20/30 vision (indicated below the red line on **Figure 1**). Clinically significant changes in visual acuity were associated with a higher number of hospitalizations in the 2 years between tests.

Nine people with LCHADD had a small increase in LCHADD chorioretinal stage, the ophthalmologist's rating of chorioretinopathy based on eye imaging and the ERG tests. The changes in chorioretinopathy staging were associated with higher LCHADD-specific biomarkers in the fasting blood sample, the 3-hydroxyacylcarnitine levels.

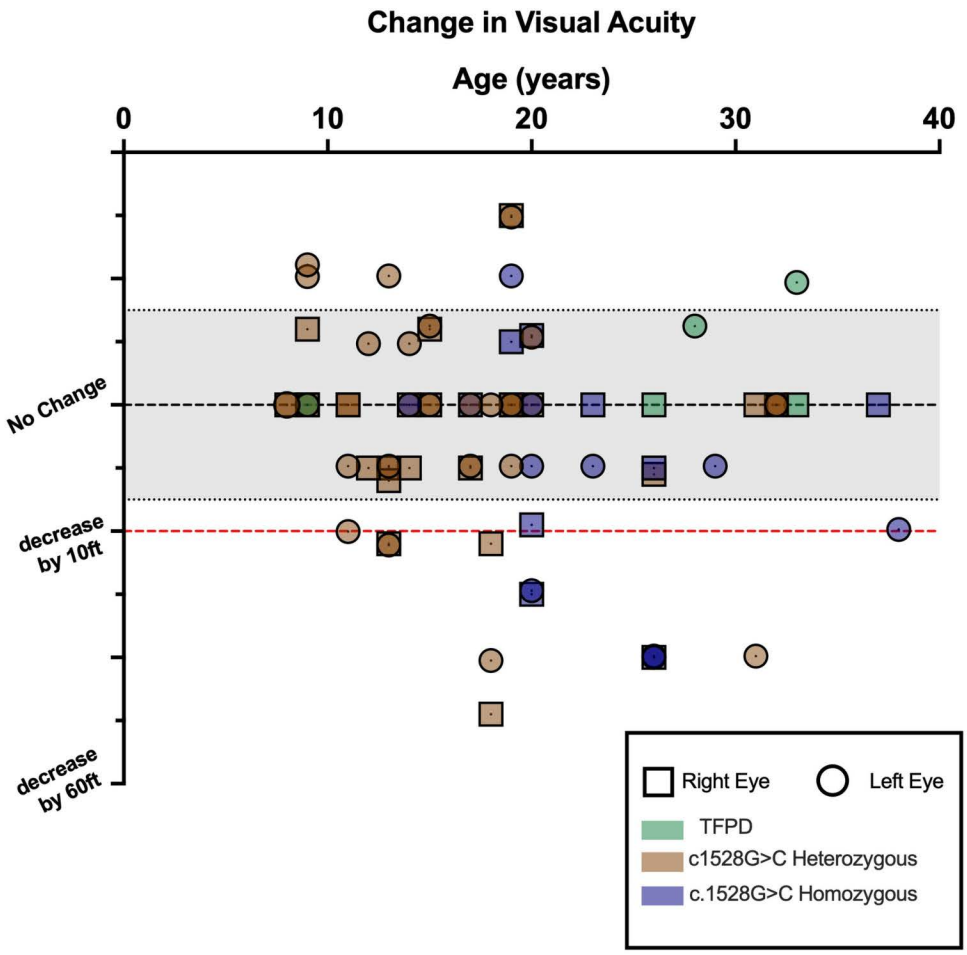

Figure 1: Change in visual acuity over 2 years. Y-axis = change in visual acuity (2-year follow-up - baseline). X-axis = age in years. Squares = Right eye (OD). Circles = Left eye (OS). Colors represent genotypes. The red line indicates a clinically significant decrease in vision of 10 ft or more. The grey shaded area is the normal vision change between repeated tests.

CELL LAYER CHANGES IN THE EYE

We used multiple imaging techniques in this study to look at changes to the structures of the eye, including ophthalmic exam, fundus autofluorescence, fundal photography, and SD-OCT. In our study, participants with two copies of the common variant were more likely to have spotty color/texture (aka "mottling") and degeneration of the RPE, degeneration of the choroid layer, changes to the ellipsoid zone, and an increase in retinal tubulations than participants with 1 or 0 copies of the common mutation (**Figure 2**). In line with previous studies, our imaging data suggests degradation of the RPE layer occurs first, followed by loss of the choroid. Our treatment experiments are targeting the RPE layer to halt LCHADD retinopathy progression.

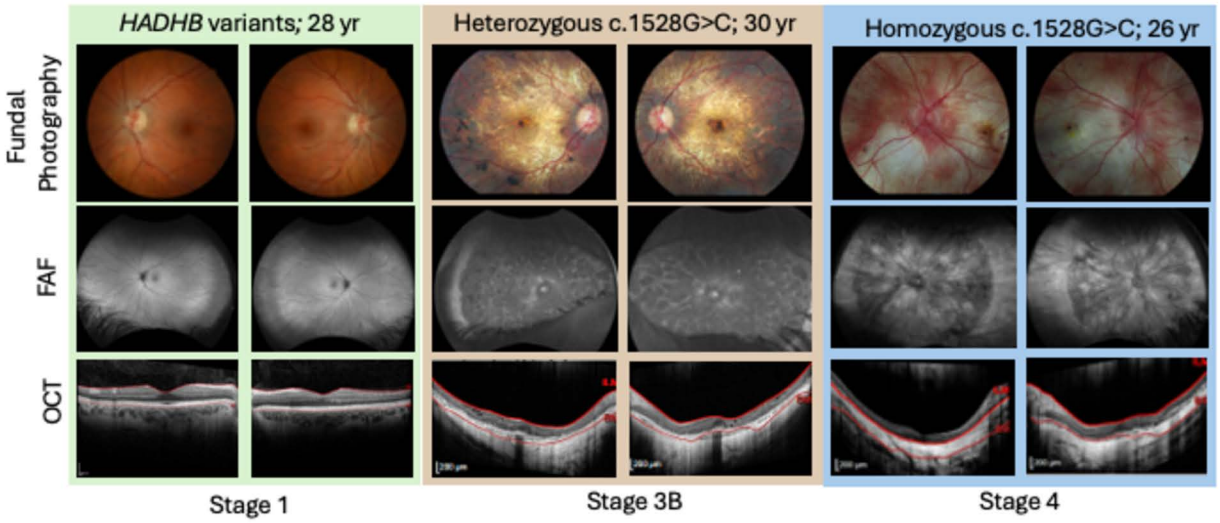

Figure 2: Structural eye differences between different genotypes at Year 2. Shown are the right and left eyes of 3 participants, all of similar ages, but with different genotypes and chorioretinopathy stages. The top row is fundus images. The increased areas of white indicate damage to the retina. The middle row is FAF images, which show increasing speckling and dense dark areas with more advanced stages, indicating RPE cell death. Bottom row is SD-OCT scans showing a cross-section of the retinal layer. Greater loss of retinal layers and loss of structural integrity is shown in later chorioretinal stages.

FINAL THOUGHTS

Despite earlier treatment with newborn screening, chorioretinopathy still progresses with age and to a greater extent in participants with 2 copies of the common *HADHA* mutation, c.1528G>C. Advanced vision loss can be seen within the first 30 years of life, with advanced chorioretinal stages occurring among people with LCHADD aged at least 16 years and older. We are working on treatments designed to slow or halt the progression of LCHADD chorioretinopathy and vision loss, including both small molecule and genetic approaches.

GLOSSARY

- **3-hydroxyacylcarnitines**: metabolic byproducts of fat breakdown. Elevated levels are indicators of long-chain fatty acid oxidation disorders and are a common biomarker used in LC-FAOD diagnosis and clinical testing.

- **Choroid**: the layer containing many blood vessels between the RPE and the sclera, the white outer layer of the eyeball.

- **Contrast sensitivity**: the ability to see outlines of objects clearly and small differences in shading and patterns.

- **Ellipsoid zone**: region of the photoreceptor inner segments that are packed with mitochondria, that shows up as a bright band in the retina on SD-OCT scans. Thinning or loss of this band is an indicator of poor photoreceptor health.

- **Electroretinogram (ERG)**: a test that uses electrodes on or around the eye to measure the retina's electrical response to light.

- **ERG rod amplitudes**: rods are one of two types of photoreceptors. The amplitude is a measure of the strength of the response of these cells to various light intensities. A lower response indicates poor rod health.

- **Fundal photography**: photography of the fundus, the back of your eye. This also includes a picture of your retina.

- **Fundus autofluorescence (FAF)**: imaging of the back of the eye that detects the glow of the pigmented RPE cells of the retina. Hypofluorescence (dark spots) indicates RPE cell death.

- **Ophthalmic exam**: an eye exam performed by an ophthalmologist that includes testing visual acuity, eye pressure and movement, and the use of imaging to view the front and back of the eye for signs of eye disease.

- **Photoreceptors**: layer of cells in your retina that detects light, sends nerve signals to your brain, and the brain interprets what you are seeing. Consists of rod & cone cells. Rods are responsible for low-light vision, cones are responsible for color vision.

- **Retina:** the layer of tissue at the back of the eye that is sensitive to light.
- **Retinal pigment epithelium (RPE)**: pigmented layer of cells in your retina located between the blood vessels and the photoreceptors. Has several important functions relating to maintaining visual function.
- **Retinal tubulations**: tubular structures seen on SD-OCT that appear as dark, oval spaces created when damaged photoreceptors "roll themselves up" due to retina injury and degeneration.
- **SD-OCT**: spectral-domain optical coherence tomography. An imaging test that creates cross-sectional photos of the layers of the retina.
- **Visual acuity**: the ability to see things clearly at specific distances.
- **Visual field sensitivity**: how well your eye detects light in the entire area your eye can see (i.e., field of vision). Visual field testing can help detect blind spots.