Gillingham Lab

RESEARCH NEWSLETTER

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WE HAVE A WEBSITE!

We are excited to announce that we now have a website! Some of the content you'll find on the website includes lab member profiles, an overview of our basic research and clinical study participation opportunities, and copies of past and current newsletters. If you would like upcoming newsletters or information on study participation opportunities delivered straight to your email inbox, there is a contact form on the website to sign up for this option. Please visit our website by typing the address below into your browser or by scanning the QR code to the right.

https://www.ohsu.edu/school-of-medicine/gillingham-lab

PRELIMINARY RESULTS FROM THE LCHAD RETINOPATHY NATURAL HISTORY STUDY

We're very pleased to have reached our enrollment goal of 40 participants in our LCHAD retinopathy natural history study and to have completed all baseline testing. Participants in this study undergo an extensive array of eye tests at baseline and 2 years later at either OHSU or University of Pittsburgh. We have been analyzing our baseline data to answer questions about how early diagnosis, treatment, genotype, and plasma hydroxyacylcarnitines affect vision. Summarized are some of our early findings, which have been presented at INFORM 2022 and SIMD 2023 conferences.

WHAT IS LCHAD RETINOPATHY?

LCHAD retinopathy is a disease characterized by damage to the retina, the layer of tissue located at the back of your eye, occurring in patients with LCHAD deficiency. The retina contains photoreceptors that sense light and then send these signals via nerves to your brain which interprets what you are seeing. Early in the retinopathy disease progression, damage to the retina affects the central field of vision first and then moves toward the periphery. We can see in photos of the back of the eye this progression of retinal damage, as shown by the increasing areas of white, occurring in patients with LCHADD over time, compared to a patient with TFPD, which shows relative normal retinal health (Figure 1) (1).

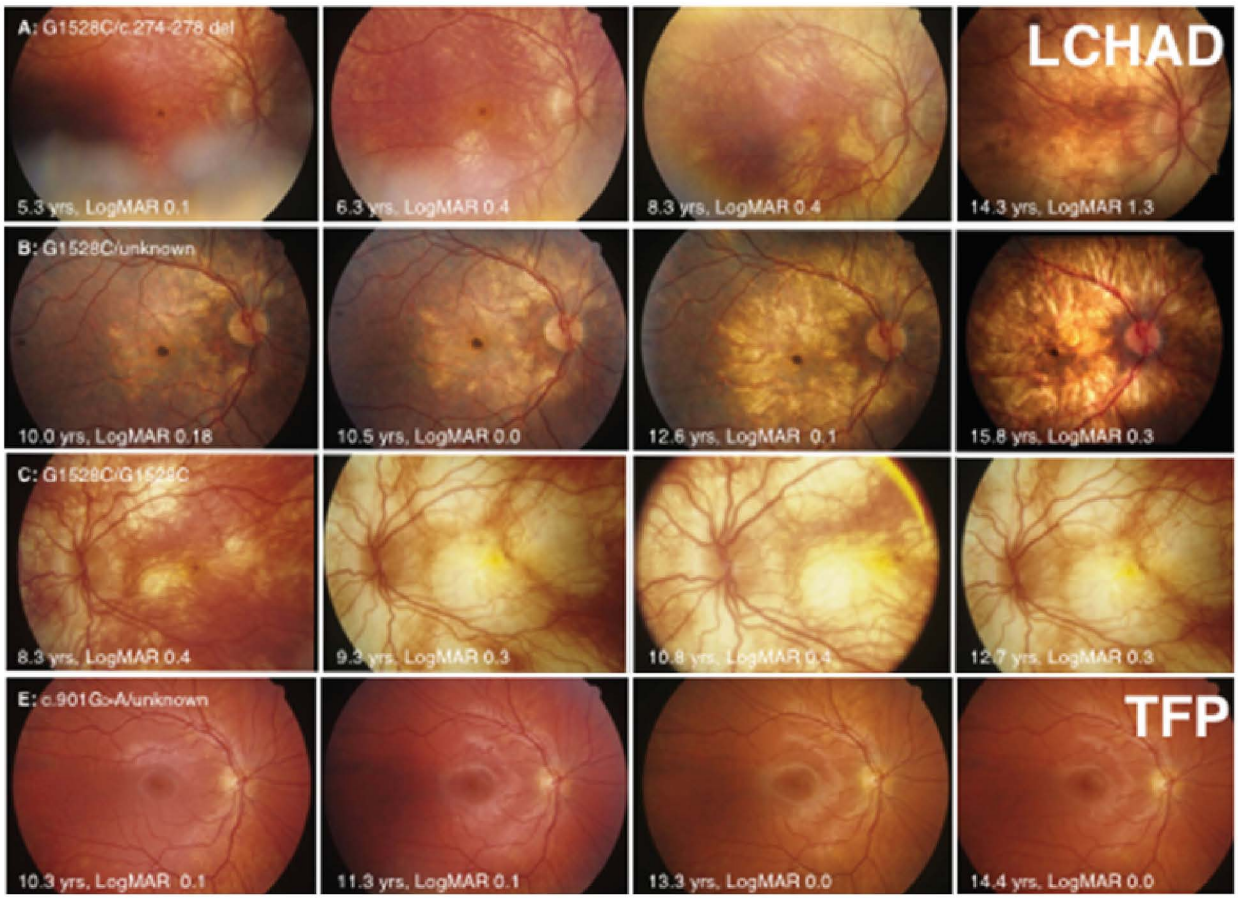

Figure 1. Color fundus photos showing retinopathy disease progression over time in patients with LCHADD and a patient with TFPD.

DOES EARLY DIAGNOSIS AND TREATMENT IMPACT VISUAL ACUITY AND RETINAL FUNCTION?

Visual acuity is the ability of the eyes to see things with clarity or sharpness at a specific distance. We can test visual acuity with a letter chart where the sizes of the letters are varied. There are two types of photoreceptors in the retina: rods and cones. Rods are responsible for low light vision and cones are responsible for color vision. We can test the function of these rod and cone cells with an electroretinography (ERG), a test which measures the electrical activity of your retina to different light stimuli. ERGs conducted under light-adapted conditions measures the cone response and ERGs conducted in dark-adapted conditions measures the rod response. The larger the ERG response (amplitude) to the light stimulus during the test, the better the rod or cone function. From our data, we can see that earlier diagnosis by newborn screening or family history of LCHAD/TFP deficiency and earlier start of FAOD treatment, resulted in better visual acuity and rod and cone amplitudes compared to subjects who were diagnosed symptomatically (Figure 2). These findings support the importance of early detection and start of treatment for preserving vision.

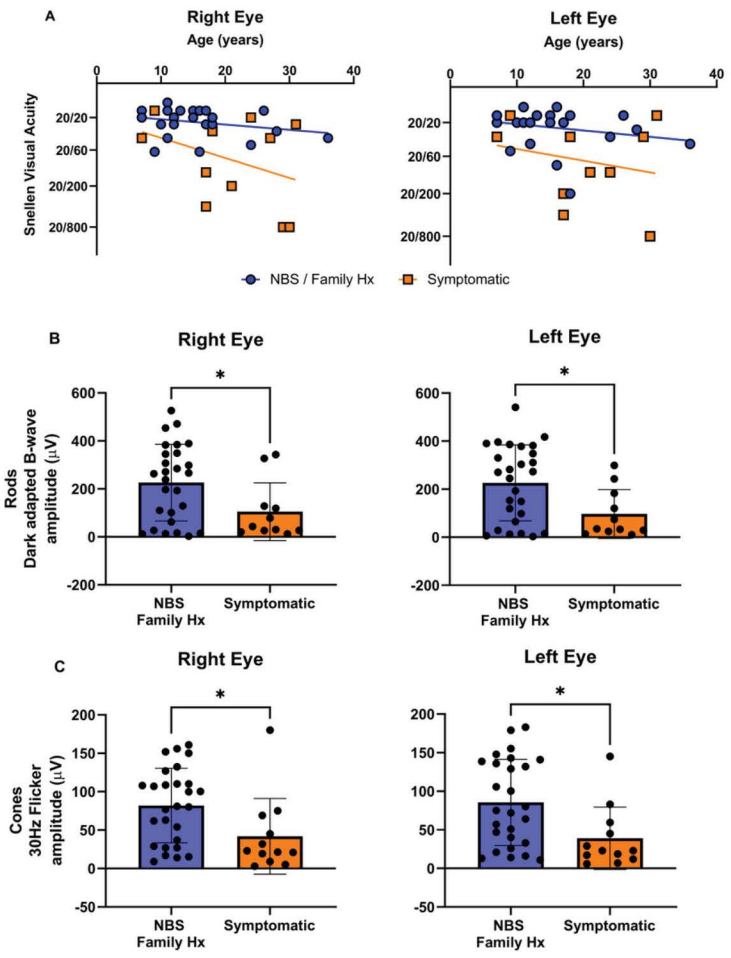

Figure 2. Visual acuity and ERG amplitudes in right and left eyes by diagnosis via NBS/family history or symptomatic presentation. A) Subjects diagnosed by NBS/family history have better visual acuity. B) Subjects diagnosed by NBS/family history have higher Rod responses. C) Subjects diagnosed by NBS/family history have higher Cone responses.

WHAT IS THE IMPACT OF GENOTYPE ON VISUAL ACUITY AND RETINAL FUNCTION?

We all inherit two copies of each gene; one from our mom and one from our dad. There is a common genetic change we call G1528C in the LCHADD gene. We enrolled 23 patients with one copy of the common mutation G1528C (heterozygous), 14 patients with two copies of the common mutation (homozygous) and 3 patients without a copy of the common mutation (TFPD). We wanted to know if there is an impact of having 0, 1 or 2 copies of the common mutation on visual acuity and retinal function. We found that there weren't significant differences in visual acuity; however, rod and cone ERG amplitudes were lowest in subjects homozygous for the common mutation and highest in subjects with TFPD (Figure 3). This suggests that the G1528C variant is associated with poorer retinal function.

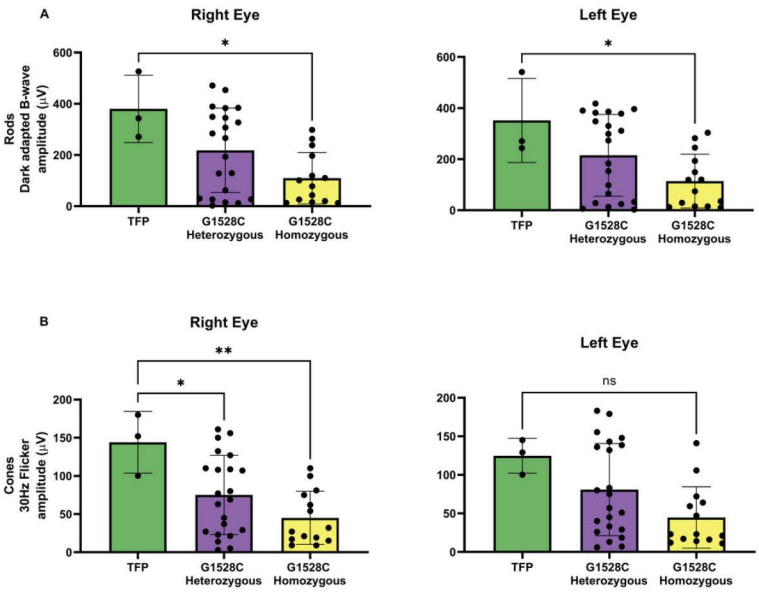

Figure 3. ERG responses by genotype in right and left eyes. A) Rod amplitudes and B) Cone amplitudes were lowest in subjects with 2 copies of G1528C, intermediate in subjects with 1 copy of G1528C and highest in subjects with TFPD.

WHAT IS THE RELATIONSHIP OF VISION AND GENOTYPE TO PLASMA HYDROXYACYLCARNITINES?

Defects in enzyme function in the fat metabolism pathway leads to a buildup of plasma acylcarnitines. These excess acylcarnitines can be measured in an acylcarnitine profile. Elevated long-chain 3-hydroxyacylcarnitines are a marker of LCHAD and TFP deficiency. In a previous study, we found a relationship between chronically high levels of hydroxyacylcarnitines and decreased retinal function (2). In this study, we measured acylcarnitines after an overnight fast and examined if the variability measured in 7 hydroxyacylcarnitines were related to genotype or visual acuity. We found that the greatest abundance of fasting plasma hydroxyacylcarnitines were found in subjects with two copies of the common mutation and least abundance in TFPD subjects (Figure 4A). Higher levels of hydroxyacylcarnitines were also correlated with poorer visual acuity (Figure 4B). This data supports our hypothesis that increased levels of circulating hydroxyacylcarnitines are associated with the progression of LCHAD retinopathy.

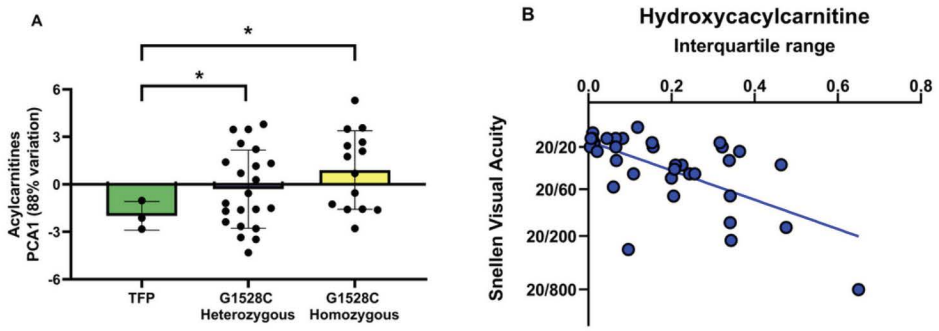

Figure 4. A) Principal components analysis of 7 hydroxylated species of acylcarnitines by genotype. Hydroxyacylcarnitines were lowest in subjects with TFPD and highest in subjects with 2 copies of G1528C. B) Decreases in visual acuity are correlated with higher levels of fasting hydroxyacylcarnitines.

Sources:

1. Boese EA, Jain N, Jia Y, Schlechter CL, Harding CO, Gao SS, Patel RC, Huang D, Weleber RG, Gillingham MB, Pennesi ME. Characterization of Chorioretinopathy Associated with Mitochondrial Trifunctional Protein Disorders: Long-Term Follow-up of 21 Cases. Ophthalmology. 2016 Oct;123(10):2183-95. doi: 10.1016/j.ophtha.2016.06.048. Epub 2016 Aug 2. PMID: 27491397; PMCID: PMC5035590.

2. M.B. Gillingham, R.G. Weleber, M. Neuringer, W.E. Connor, M. Mills, S. van Calcar, J. Ver Hoeve, J. Wolff, C.O. Harding. Effect of optimal dietary therapy upon visual function in children with long-chain 3-hydroxyacyl CoA dehydrogenase and trifunctional protein deficiency. Mol. Genet. Metab., 86 (2005), pp. 124-133. doi:10.1016/j.ymgme.2005.06.001