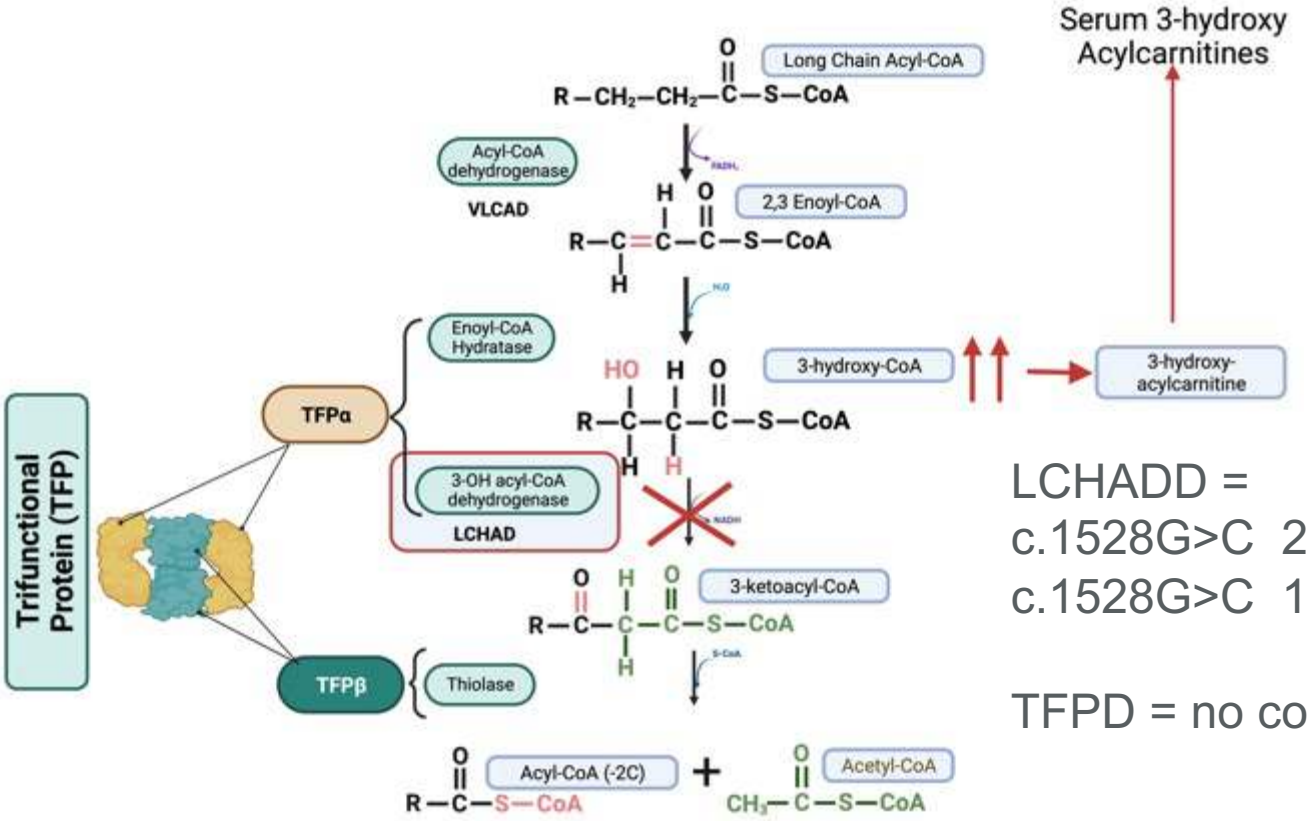
LCHADD Retinopathy Update: Moving Toward a Treatment

DATE: November 1th 2023 PRESENTED BY: Melanie B. Gillingham PhD, RD

LCHAD Deficiency



LCHADD =
c.1528G>C 2 copies
c.1528G>C 1 copy

TFPD = no common allele

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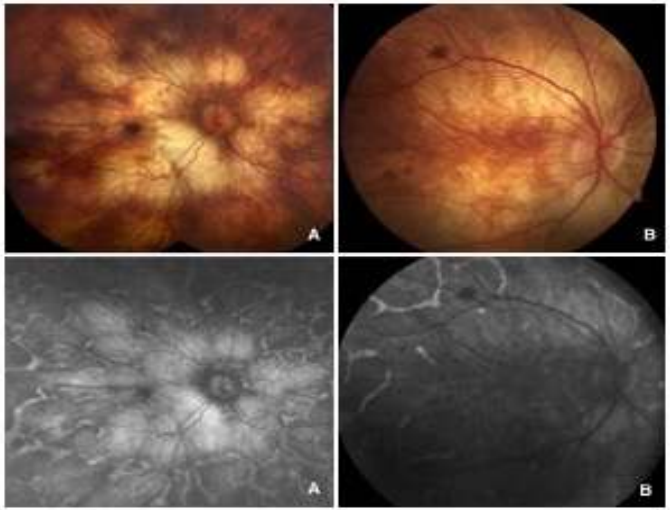
Natural History of LCHAD



- Dx of LCHAD or TFP deficiency
- Age 2 - 60 years
- 40 subjects of all ages
- 2-3 days of ophthalmologic tests at OHSU or UPMC
  - Retinal imaging
  - Visual acuity
  - Retinal function by electroretinogram (ERG)
  - Visual Fields

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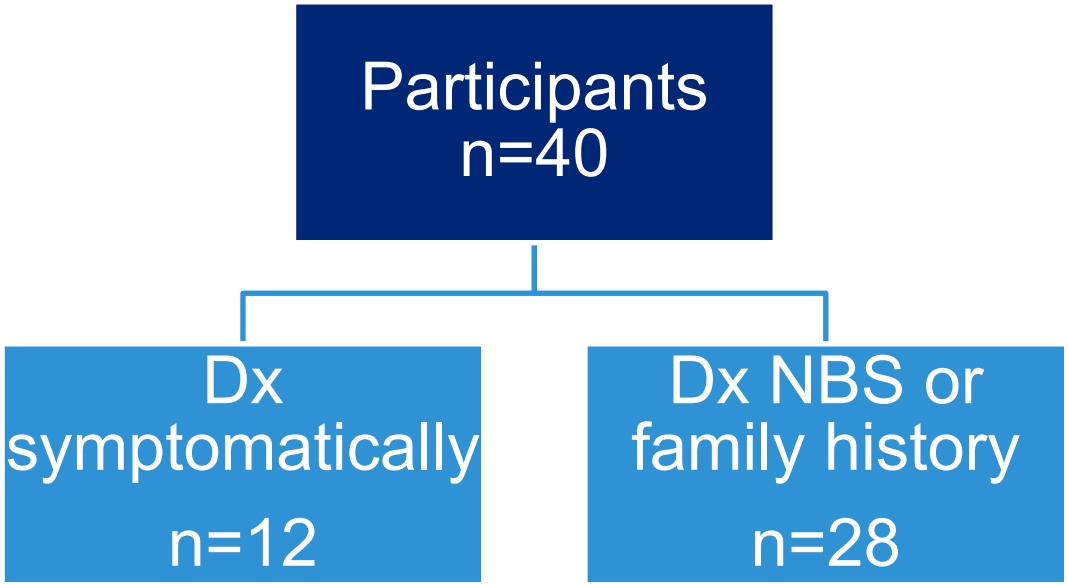
Participants

Age Stratification	n	Sex	Presentation	Genotype
2-7 years	8	6 Male 2 Female	6 NBS or Family Hx 1 Symptomatic	TFP = 1 G1528C 1 copy = 5 G1528C 2 copies = 2
8-14 years	10	5 Male 5 Female	9 NBS or Family Hx 1 Symptomatic	G1528C 1 copy = 8 G1528C 2 copies = 2
15-21 years	13	8 Male 5 Female	8 NBS or Family Hx 5 Symptomatic	G1528C 1 copy = 7 G1528C 2 copies = 6
> 21 years	9	2 Male 7 Female	4 NBS or Family Hx 5 Symptomatic	TFP = 2 G1528C 1 copy = 3 G1528C 2 copies = 4

Presentation:



Is early dx and treatment related to better visual outcomes?

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Participant characteristics

	NBS/Family History	Symptomatic Dx
Average age (range)	14 (2 -36)	21 (7-31)*
LCHADD symptoms (%)		
cardiomyopathy	10.71%	25.00%
rhabdomyolysis	85.71%	100.00%
hypoglycemia	64.29%	75.00%
neuropathy	25.00%	58.33%
chorioretinopathy	67.86%	91.67%
premature birth (%)	42.86%	33.33%
maternal HELLP (%)	17.86%	33.33%
diet treatment (%)		
low fat	100.00%	100.00%
MCT	78.57%	66.67%
carnitine	42.86%	75.00%
C7	50.00%	33.33%

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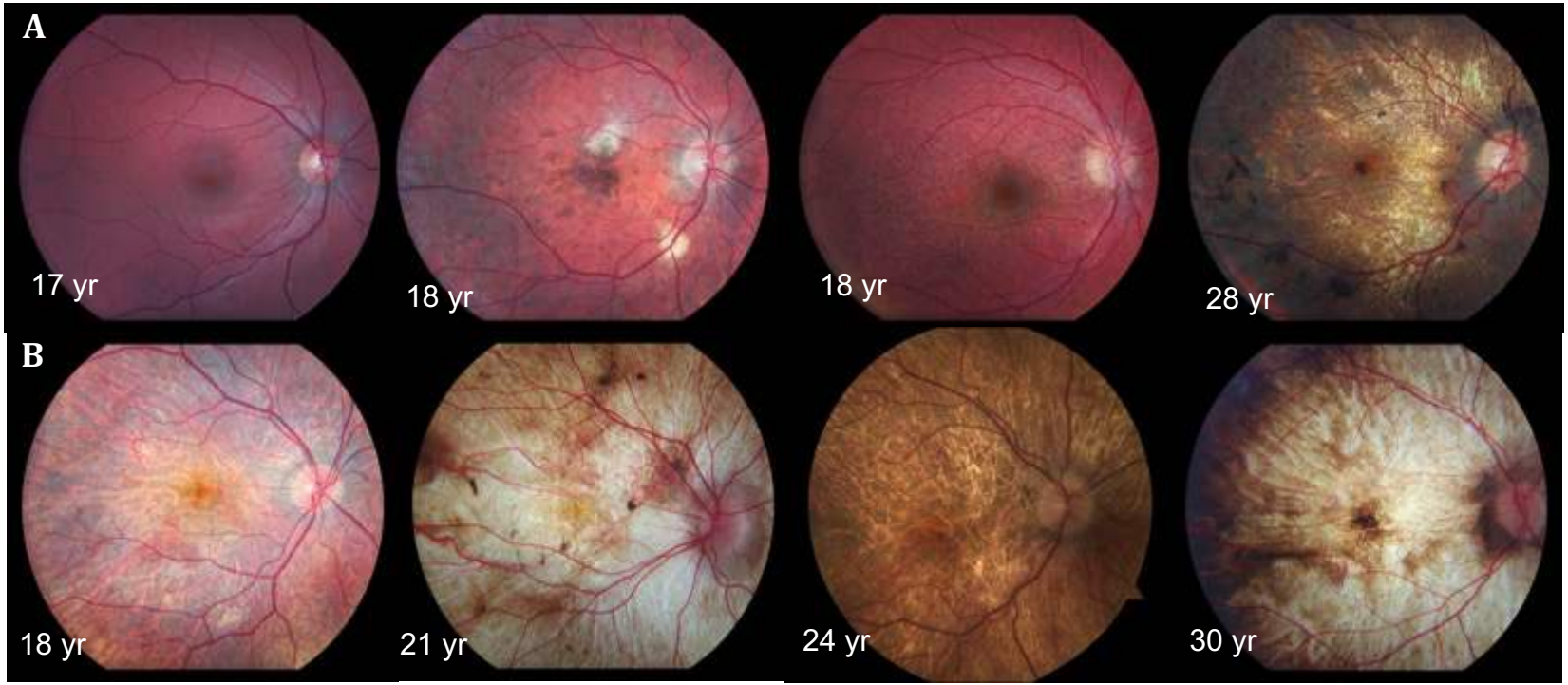
Fundal Images:



Family History Symptomatic

Dx by NBS/family history and younger age associated with preservation of fundal pigment and choroidal vessels

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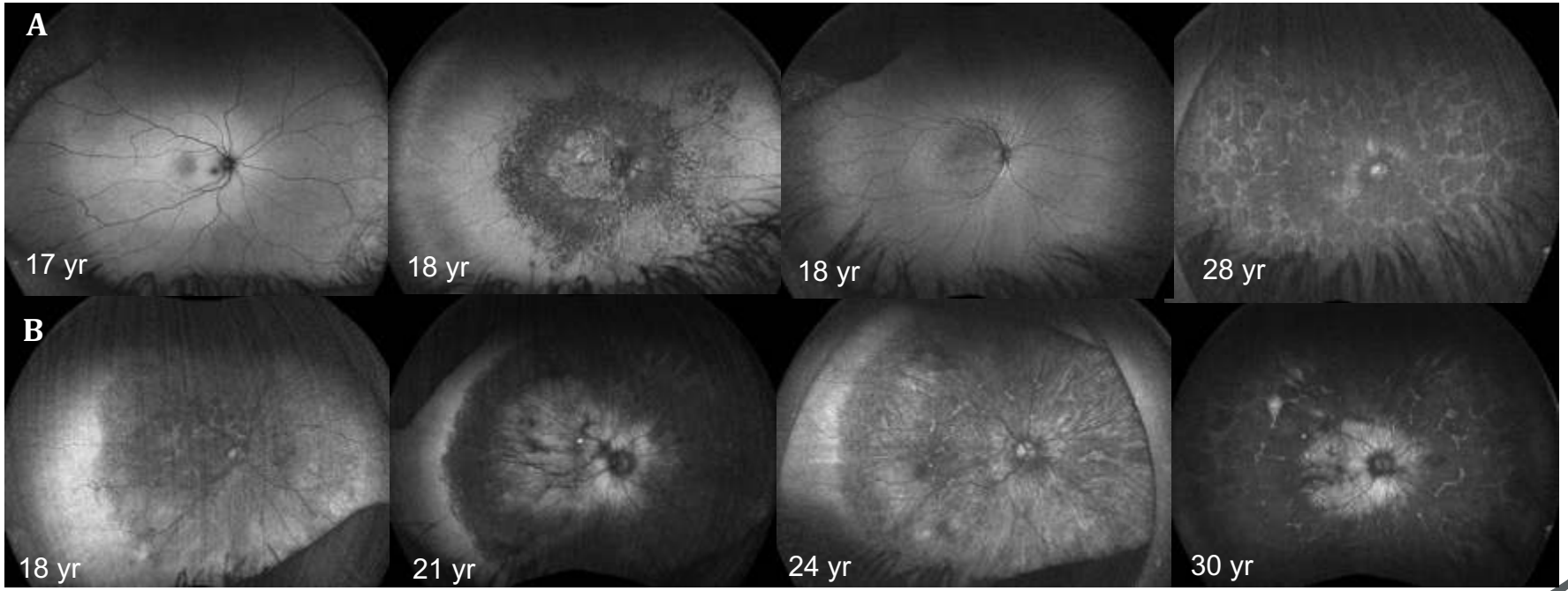
Fundus Autofluorescence



Family History Symptomatic

Dx by NBS/family history and younger age associated with preservation of RPE autofluorescence

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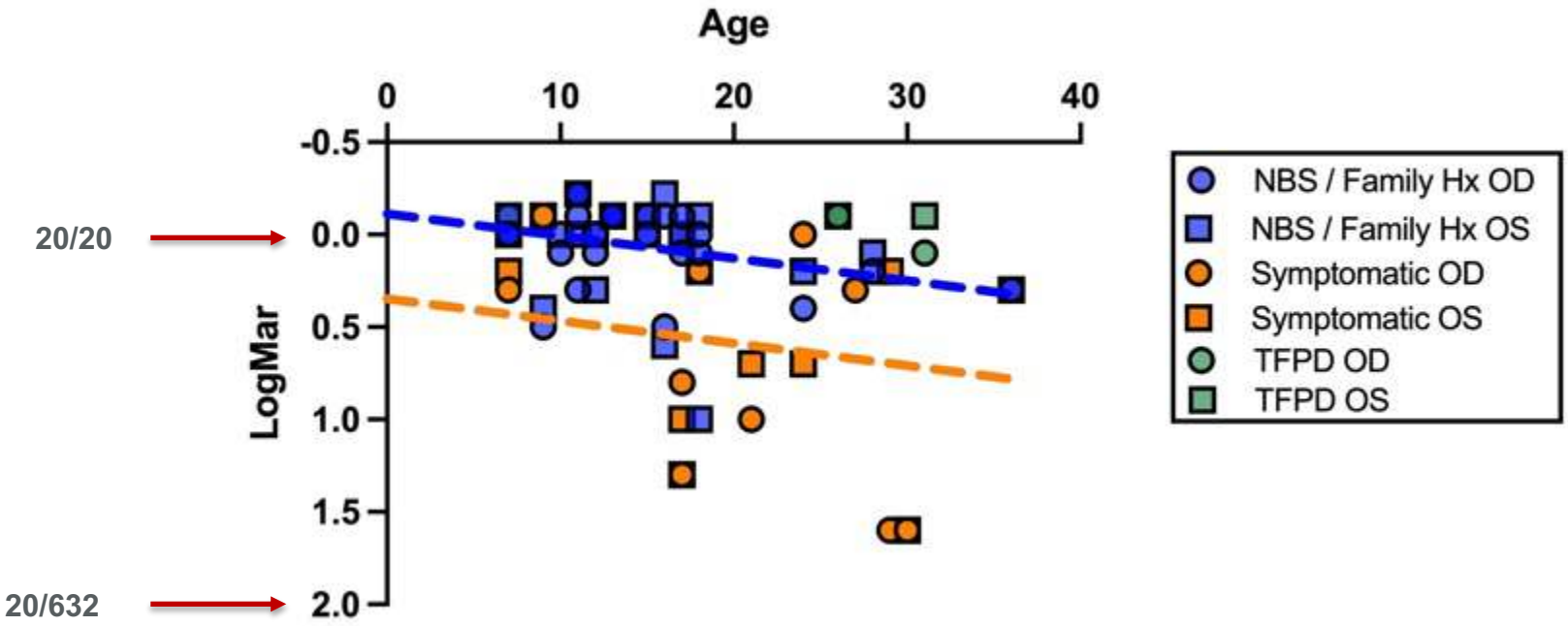
Visual Acuity



Dx by NBS/family history and younger age associated with better visual acuity

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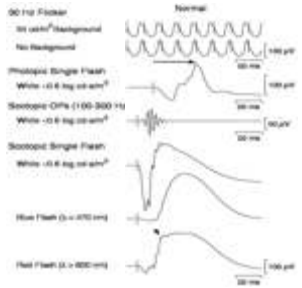
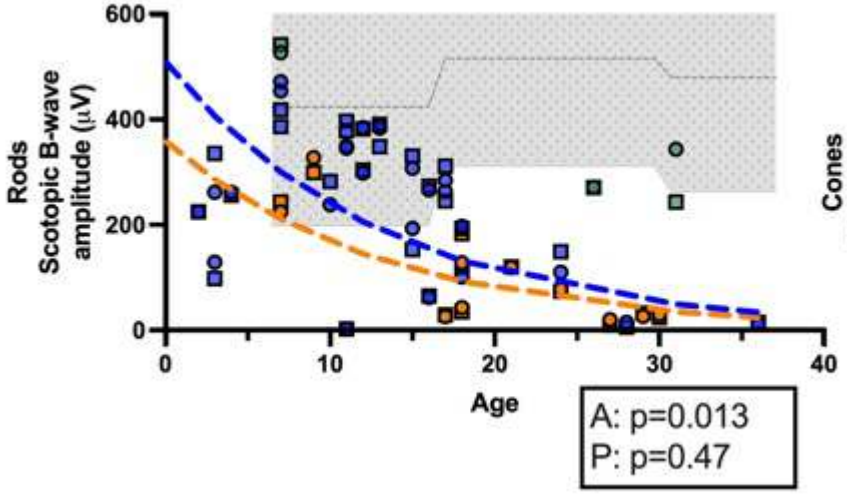
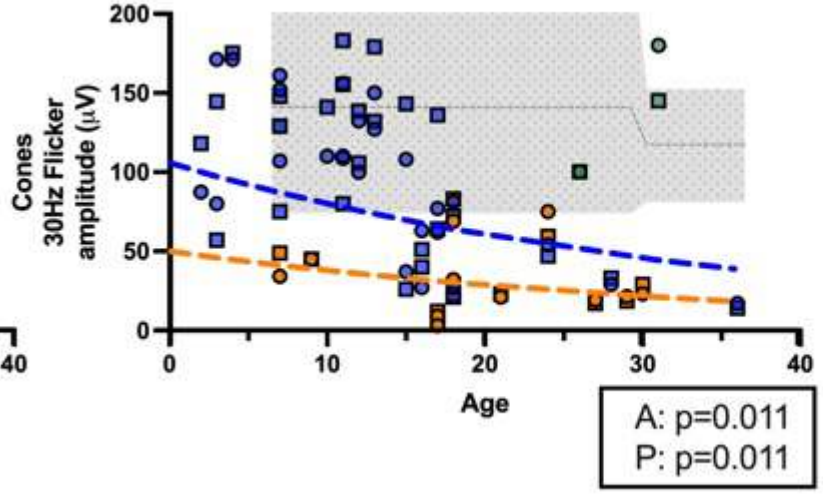
Electroretinogram:







NBS

Symptomatic

Dx by NBS/family history and younger age associated with increased Cone (not Rod) amplitudes with ERG

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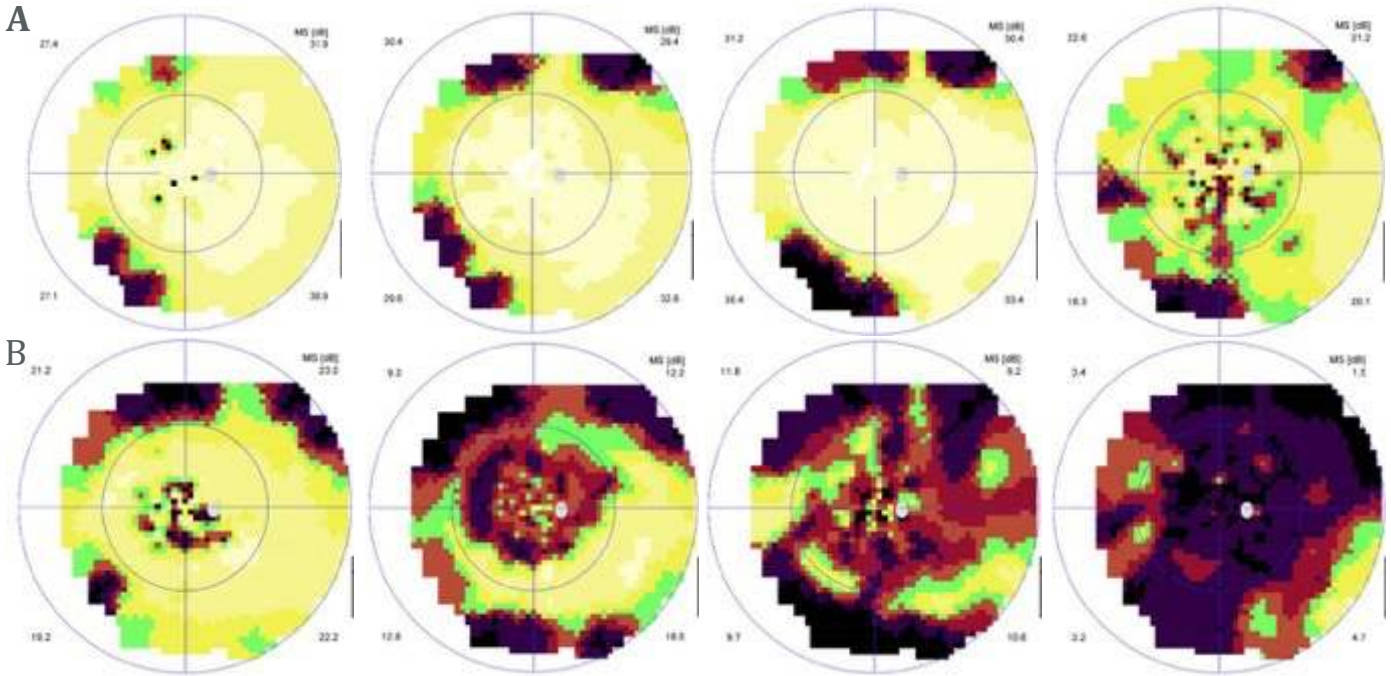
Static perimetry visual fields



Dx by NBS/family history associated with better visual fields

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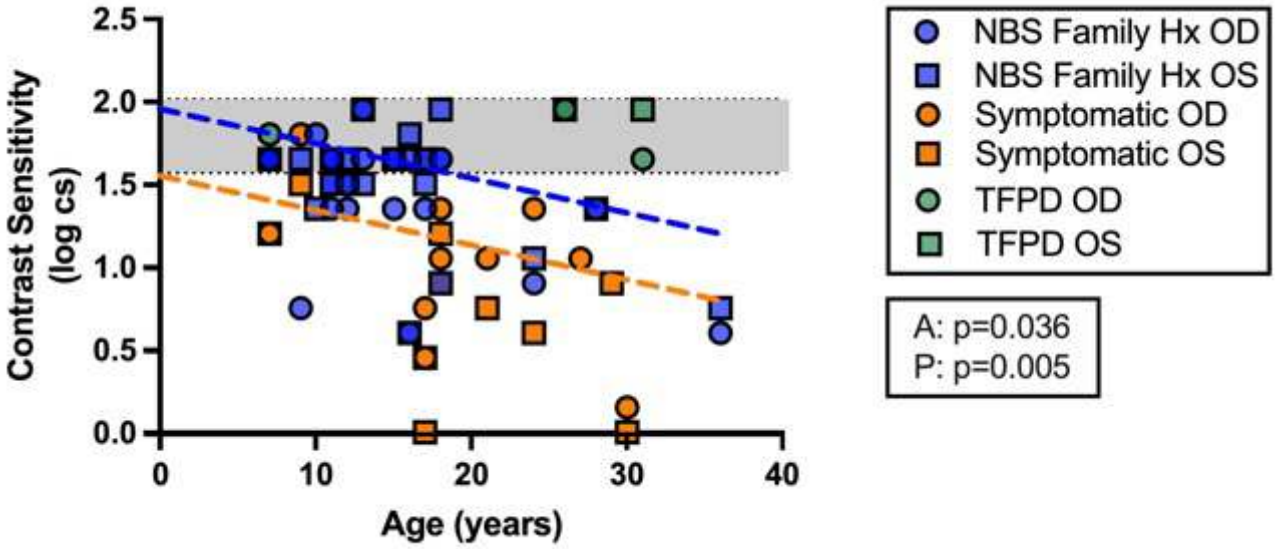
Contrast Sensitivity



Dx by NBS/family history and younger age associated with better ability to distinguish contrasting shades of light

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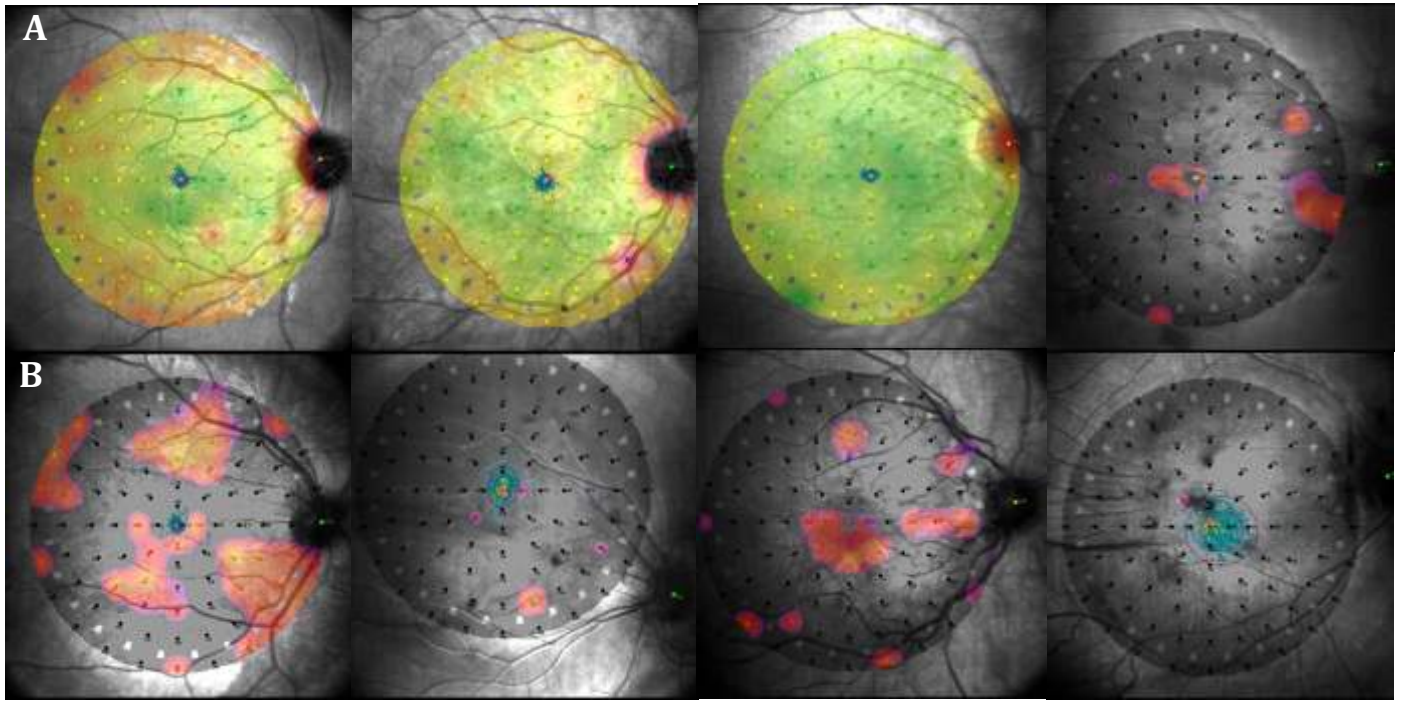
Macular visual fields



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Early Dx and treatment associated with

- Improved fundal images and structure
- Improved visual acuity
- Improved Cone function (color vision)
- Increased contrast sensitivity
- Improved visual fields

Early Dx and treatment

Symptomatic

- Symptomatic participants dx from 7d to 3 yr; majority between 4-6 mo
- All had catastrophic event that led to dx
  - Hypoglycemia (8)
  - Cardiomyopathy/arrest (3)
  - Liver dysfunction (1)
  - FTT, lethargy, feeding difficulties (3)

NBS/Family History

- 8 dx by family history; 20 by NBS
- 2 dx at 3 yr of age; asymptomatic at time of dx due to family testing
- Remainder dx at birth/newborn period
  - Hypoglycemia prior to NBS results (7)
  - Feeding difficulties, temperature instability prior to NBS results (2)

Treatment recommendations similar after diagnosis

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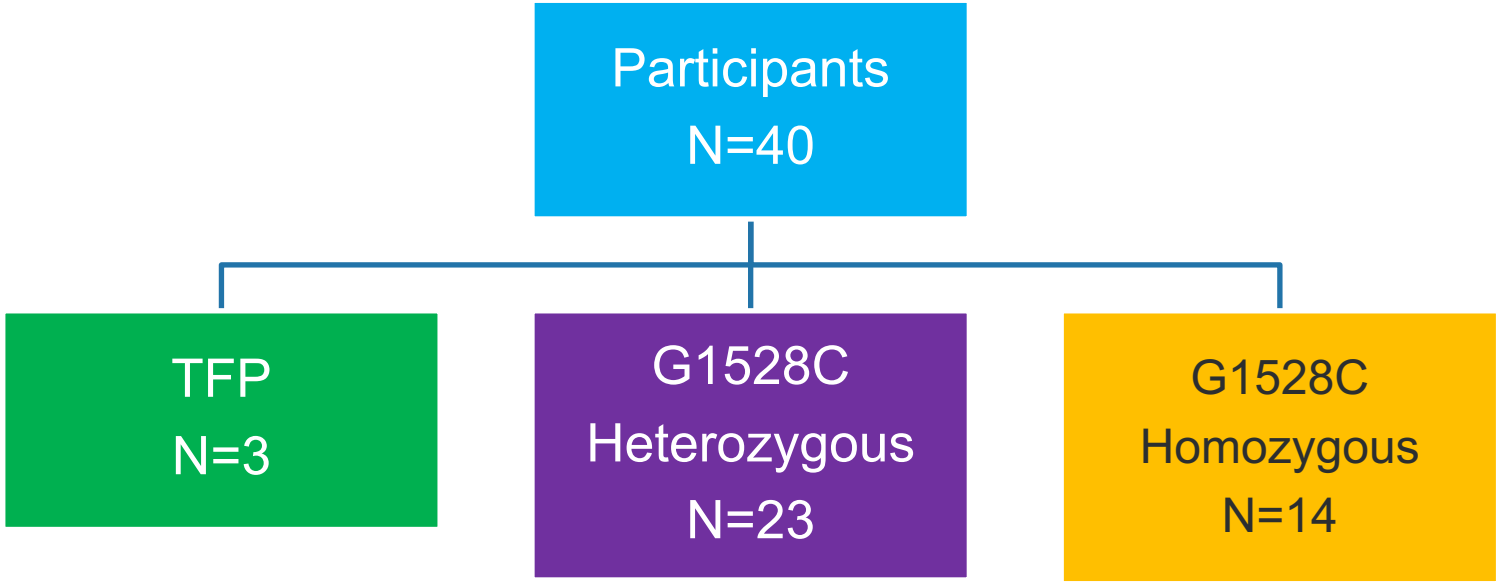
Conclusions

- Dx in the newborn period associated with improved visual structure and function.
- Despite the benefits of NBS on visual outcomes, retinopathy is more advanced with age.

- What to do with this data?
- **Continue to be a newborn screening advocate.**
- We will continue to pursue new treatment approaches.

Genotype



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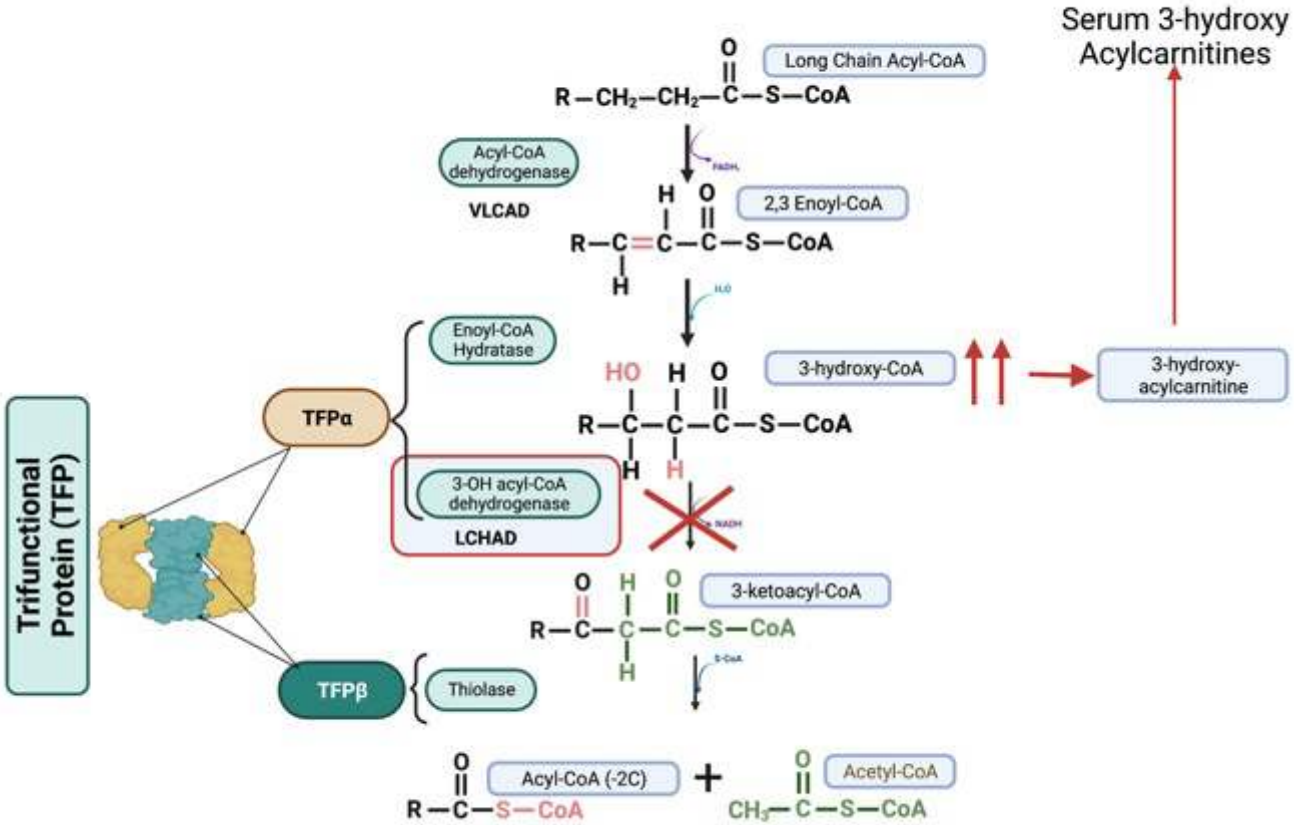
LCHAD Deficiency



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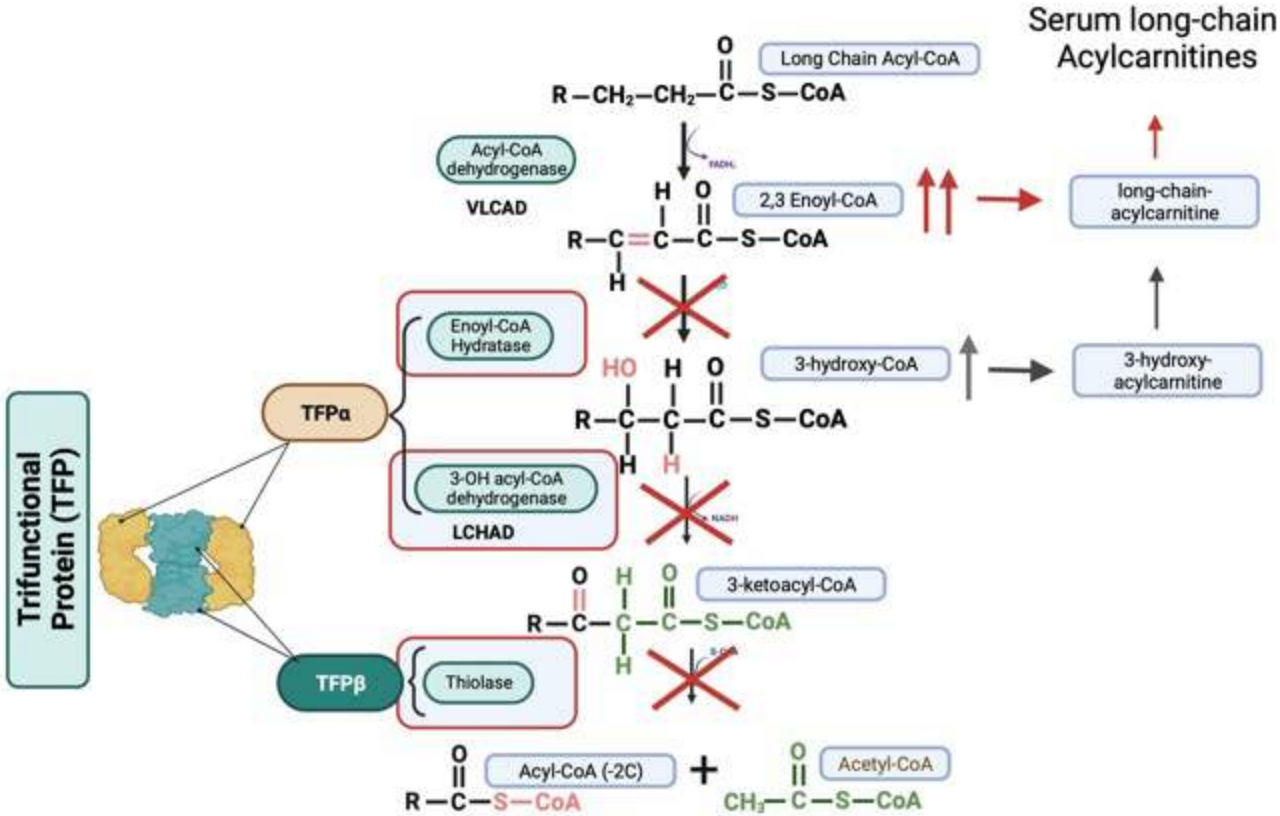
TFP Deficiency



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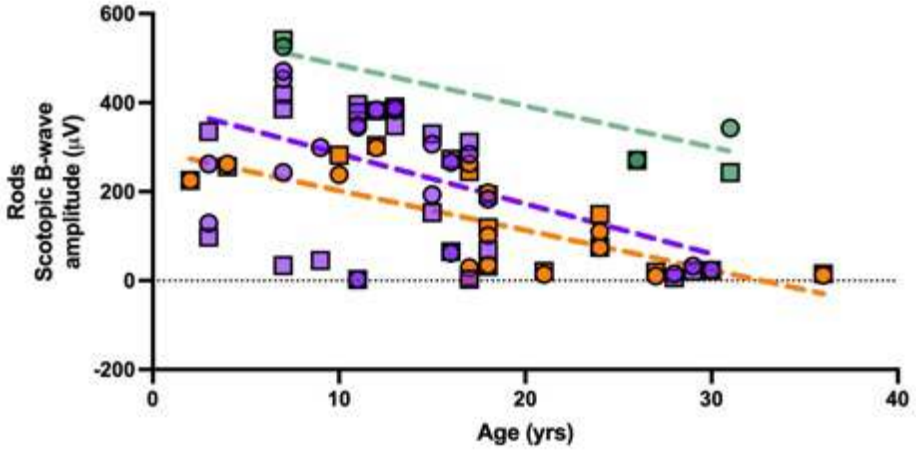
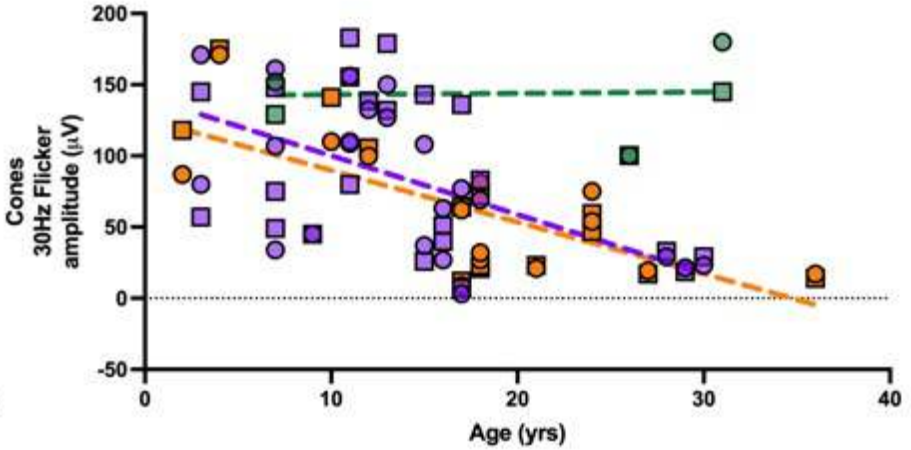
Electroretinogram

Black and White Vision



Color Vision



Genotype G1528C & older age associated with decreased Rod & Cone amplitudes with ERG

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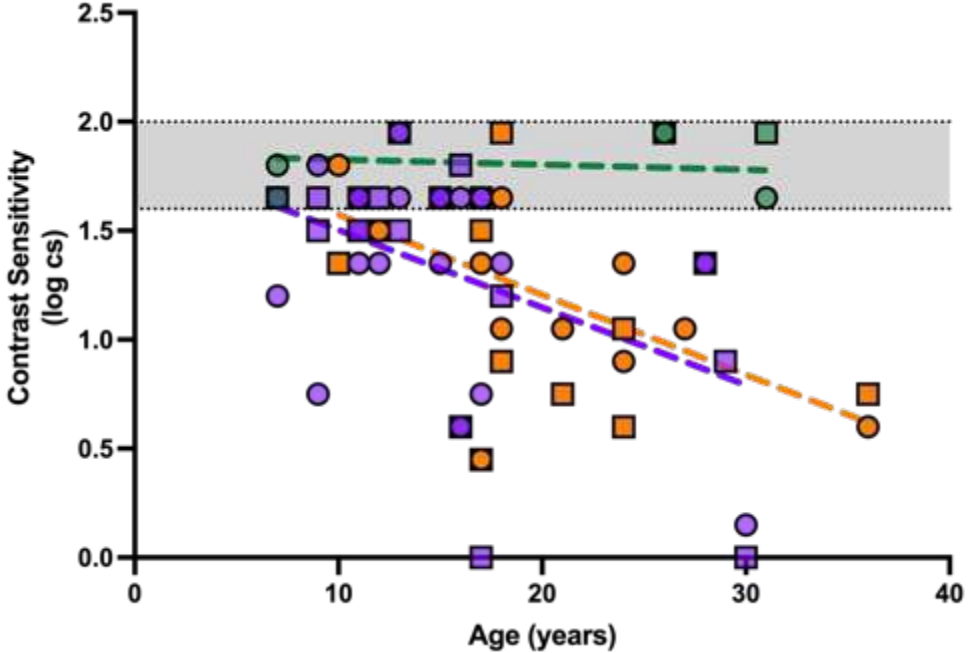
Contrast Sensitivity



Genotype G1528C & older age associated with decreased ability to distinguish contrasting shades of light

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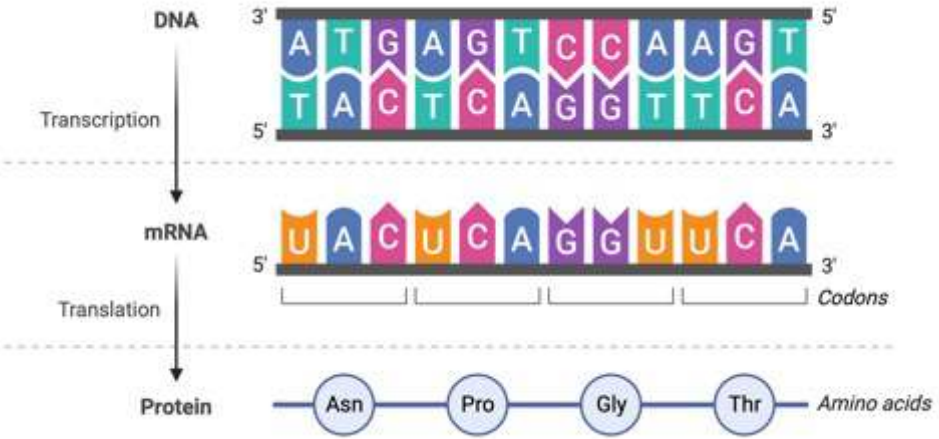
Conclusions

- Common G1528C associated with
  - Decreased vision
  - Lower retinal function
- Older age is also associated with lower visual and retinal function

- <u>What to do with this data?</u>
- Known your genotype



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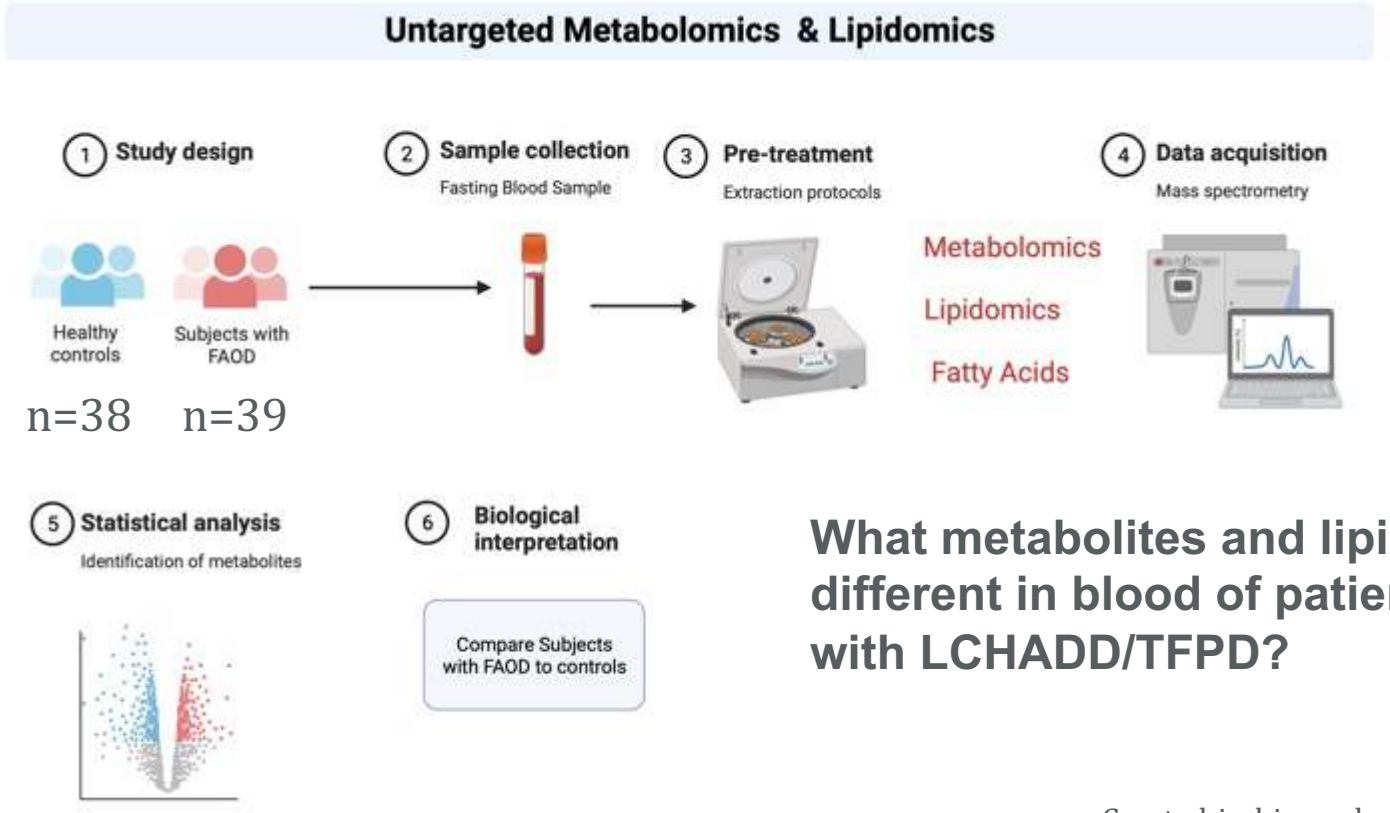
Metabolomics/Lipidomics



What metabolites and lipids are different in blood of patients with LCHADD/TFPD?

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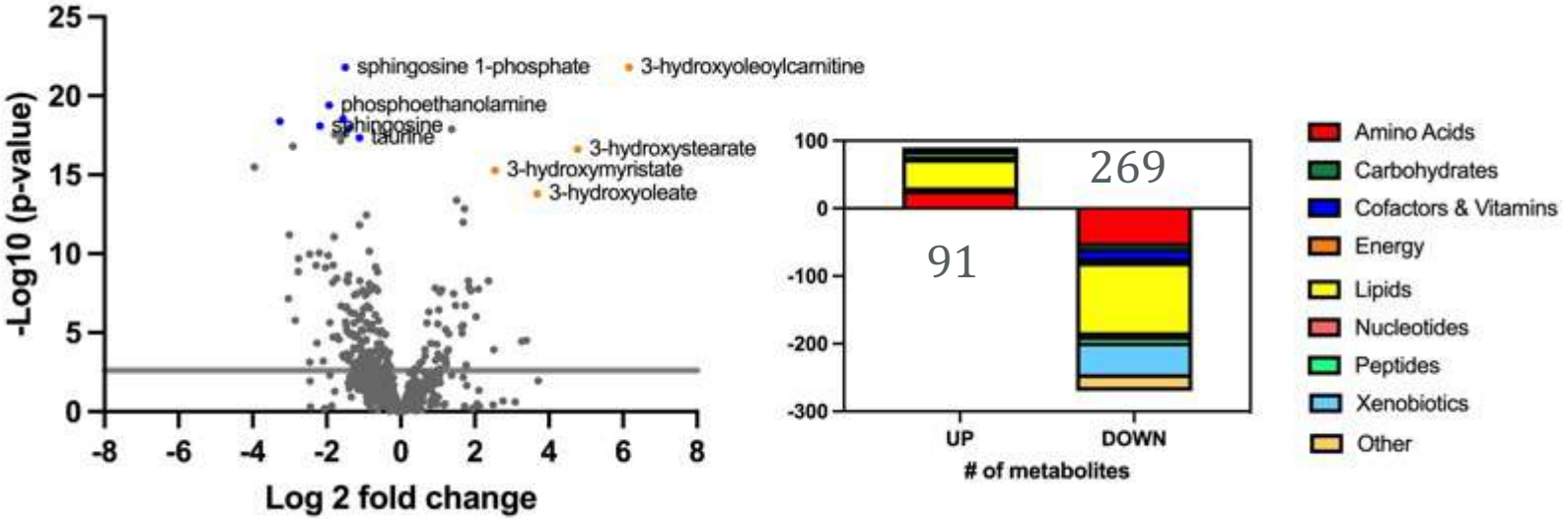
Metabolomics



- 3-hydroxy long-chain fatty acids and acylcarnitines elevated
- short and medium chain fatty acids and acylcarnitines lower
- All TCA intermediates low
- Complex lipids like sphingolipids low

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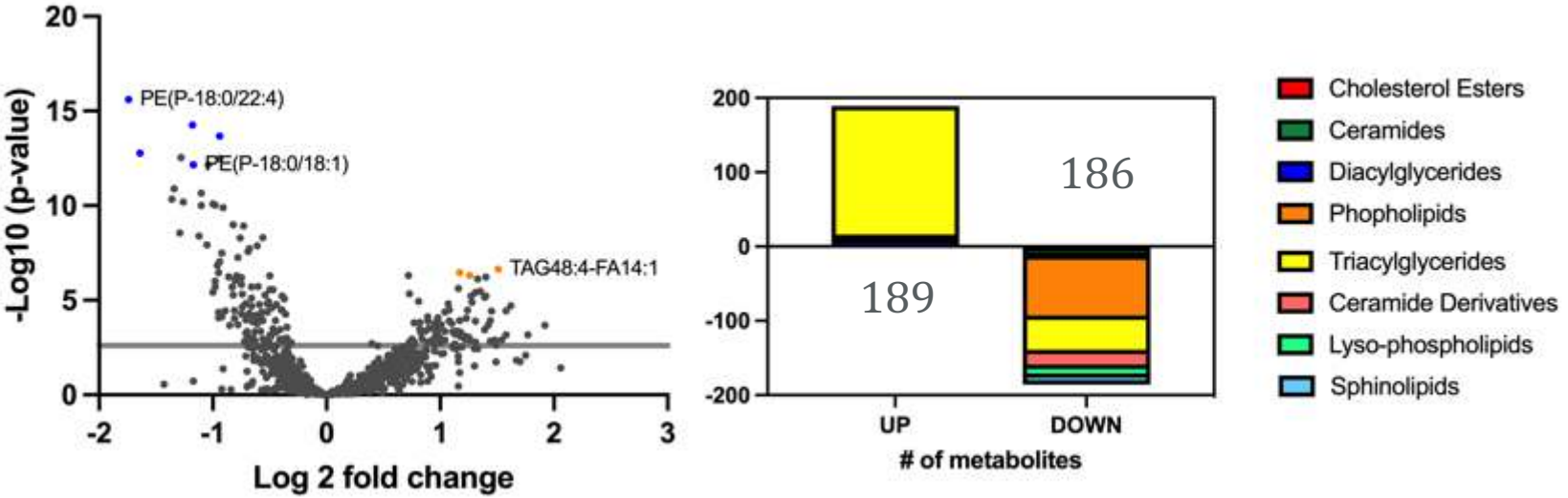
Lipidomics



- Some simple triglyceride species higher
- Complex lipids like phospholipids, ceramides and sphingolipids lower

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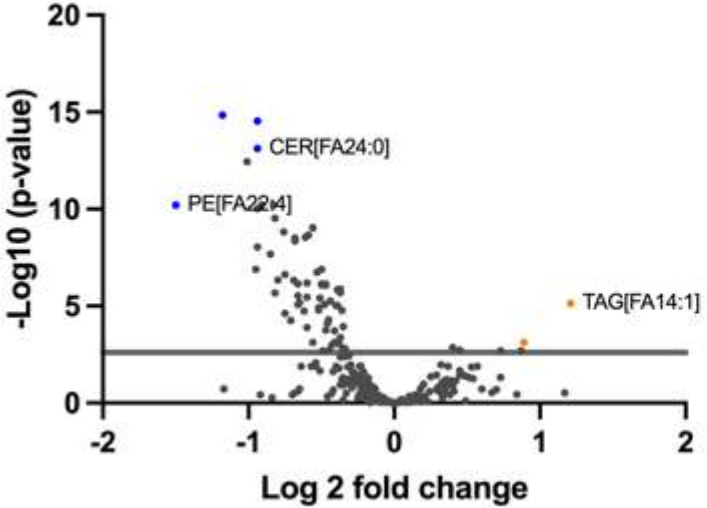
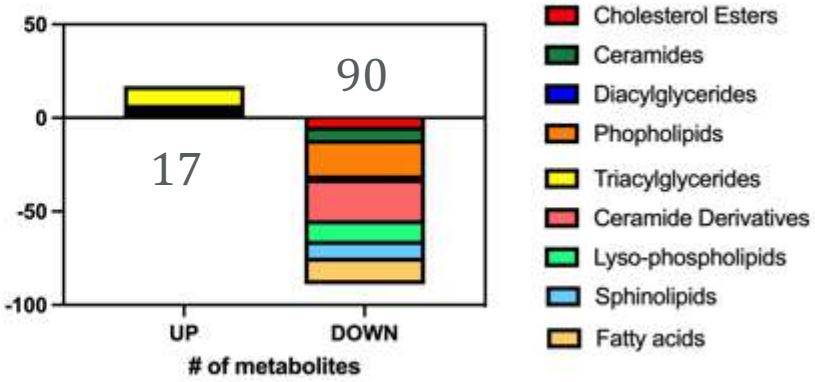
Fatty Acids





- Some simple triglyceride species higher
- Complex lipids like phospholipids, ceramides and sphingolipids lower
- Most of the total fatty acids lower

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Conclusions

- 3-hydroxy fatty acids and 3-hydroxy acylcarnitines most different compared to controls
- Acylcarnitine profiles continue to be primary measure of metabolites specific to LCHADD

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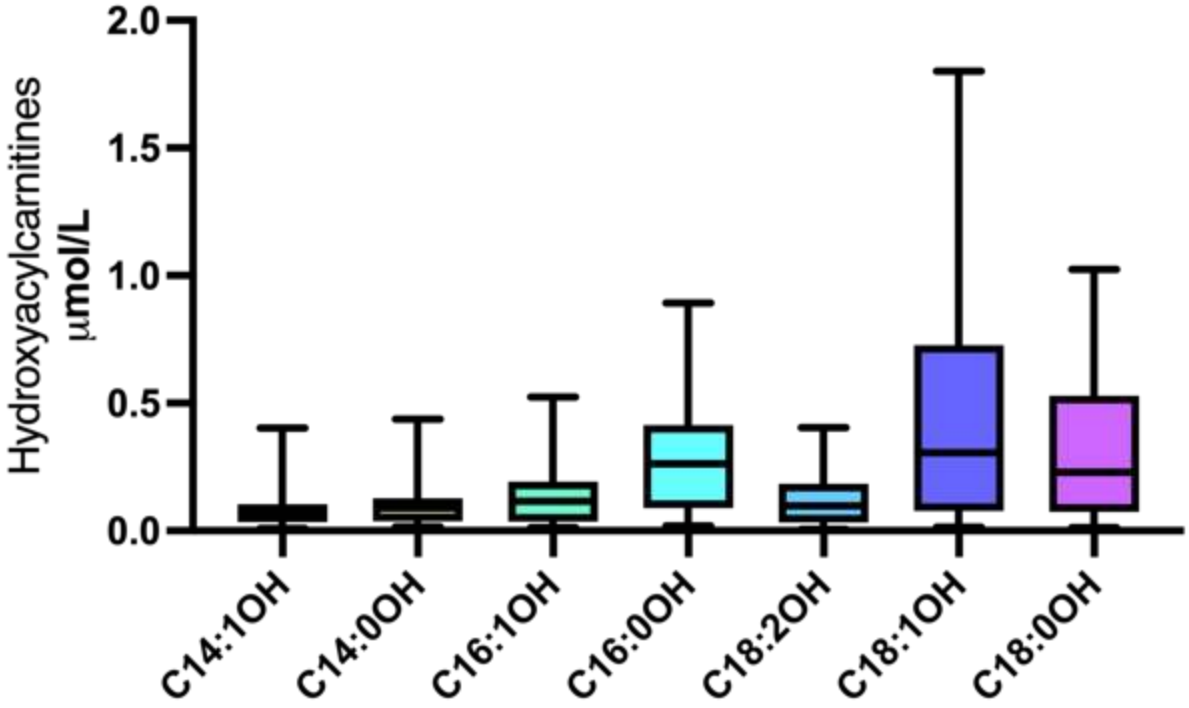
Fasting acylcarnitines



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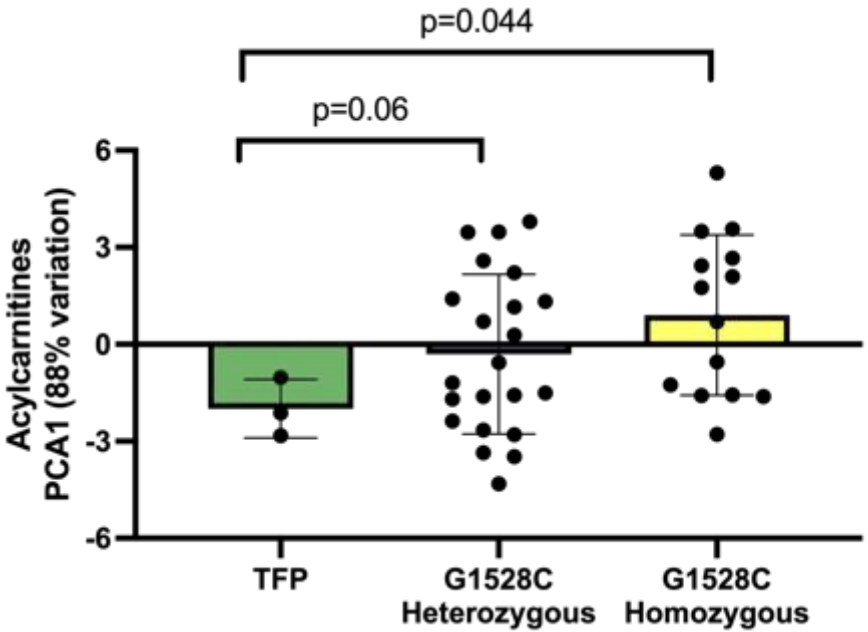
Acylcarnitines, genotype



G1528C variant associated with higher hydroxyacylcarnitines

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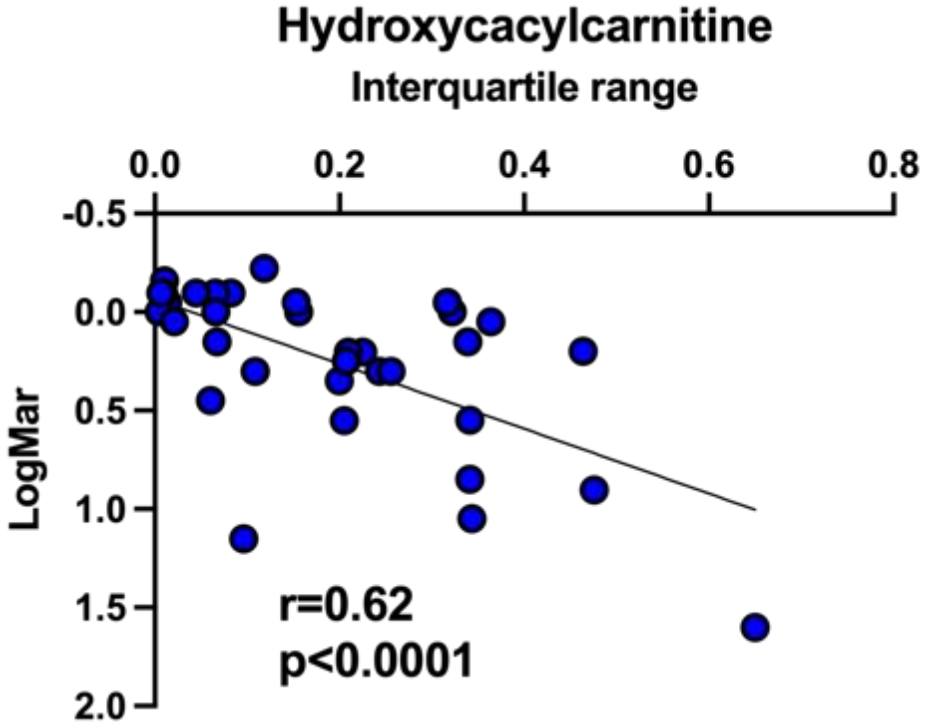
Acylcarnitines and vision



3-Hydroxy acylcarnitines correlate with visual acuity

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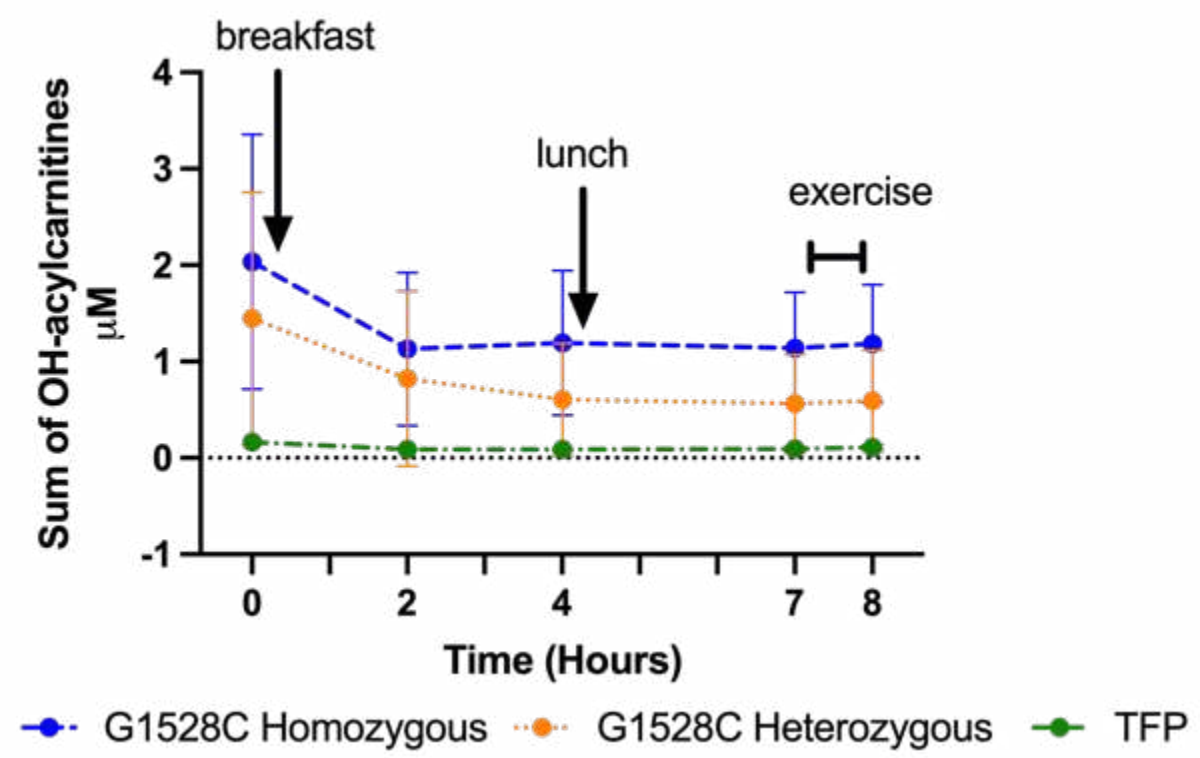
How can you lower 3-hydroxy acylcarnitines in blood?

Eating lowers 3-hydroxy acylcarnitines



Elizondo et al Molecular Genetics and Metabolism 131 (2020) 90-97

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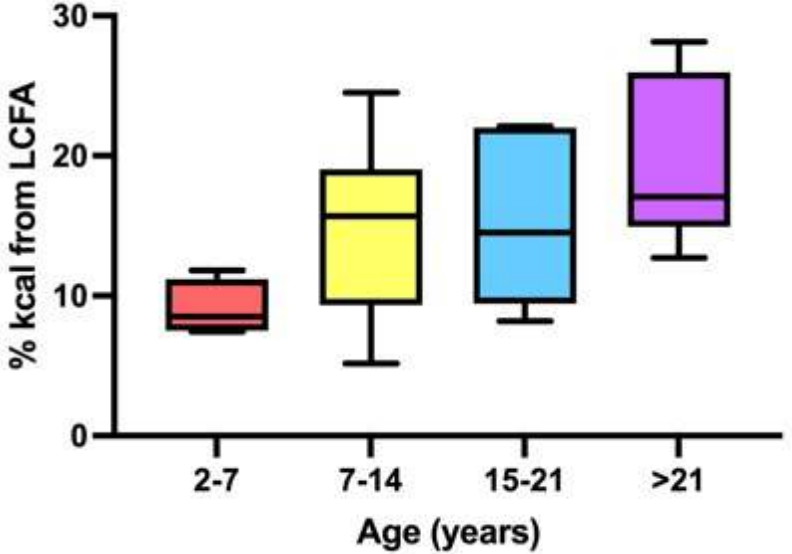
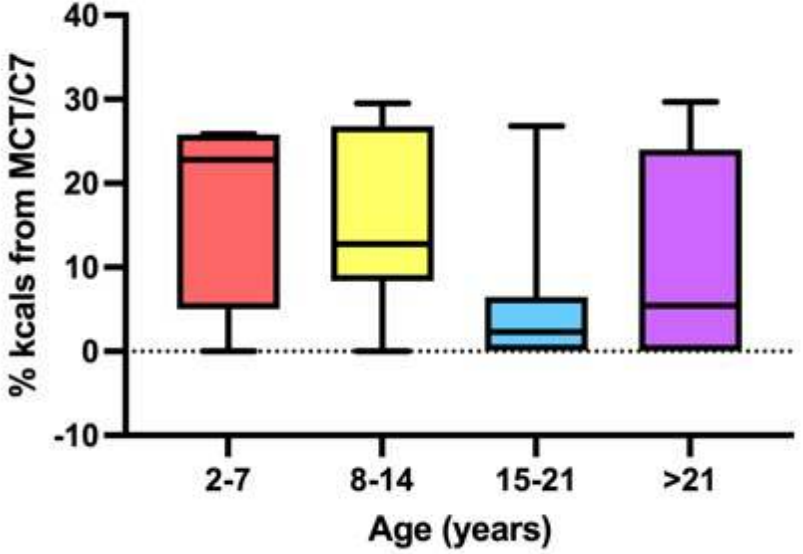
3-day diet records- preliminary results





- % of calories from long-chain fat increases with age
- % of calories from MCT or C7 is highly variable

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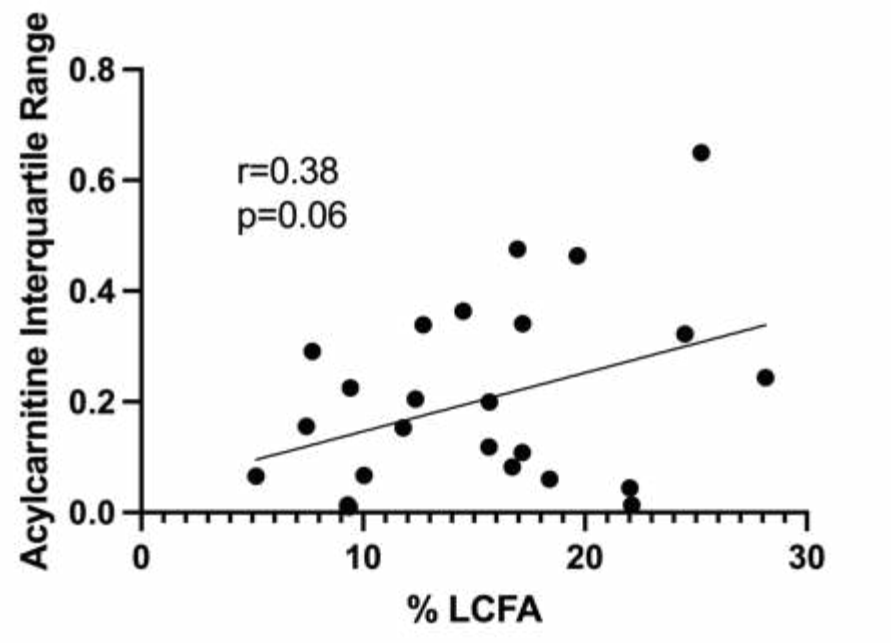
LCFA intake and acylcarnitines



- Higher intake of long-chain fat associated with higher 3-hydroxy acylcarnitines

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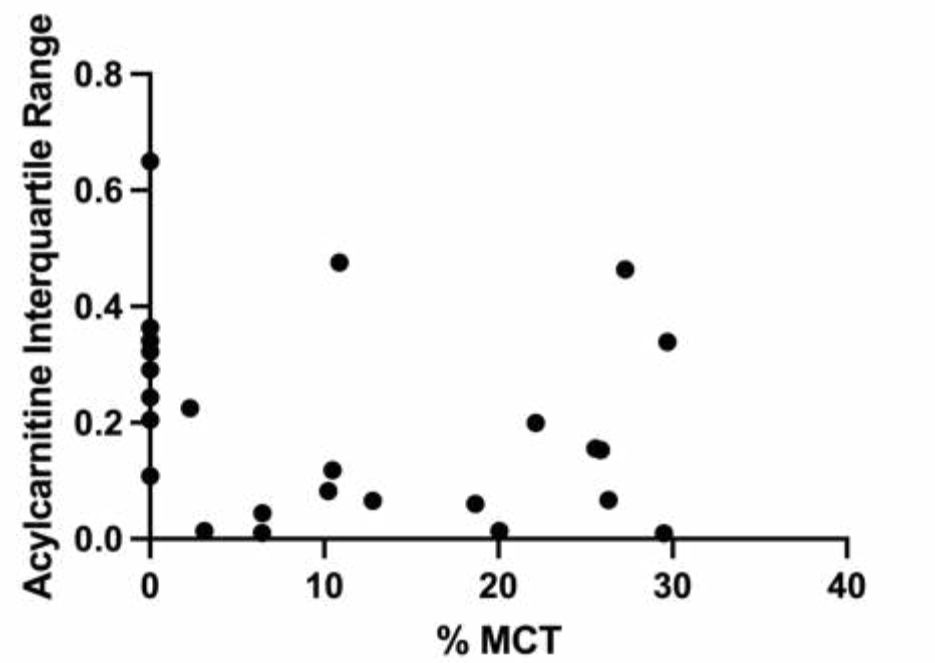
MCT intake and acylcarnitines



- % MCT does not appear to impact acylcarnitines
- MCT/C7 provides needed energy

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Conclusions

- Genotype & Diet influence 3-OH acylcarnitine concentrations
- High 3-OH acylcarnitines associated with lower visual acuity
- Low long-chain fat intake associated with lower 3-OH acylcarnitines
- MCT may not lower 3-OH acylcarnitines but does provide energy

- What to do with this data?
- Eat regular meals & snacks
- Follow a low-fat, healthy diet
- Follow-up with your metabolic physician routinely

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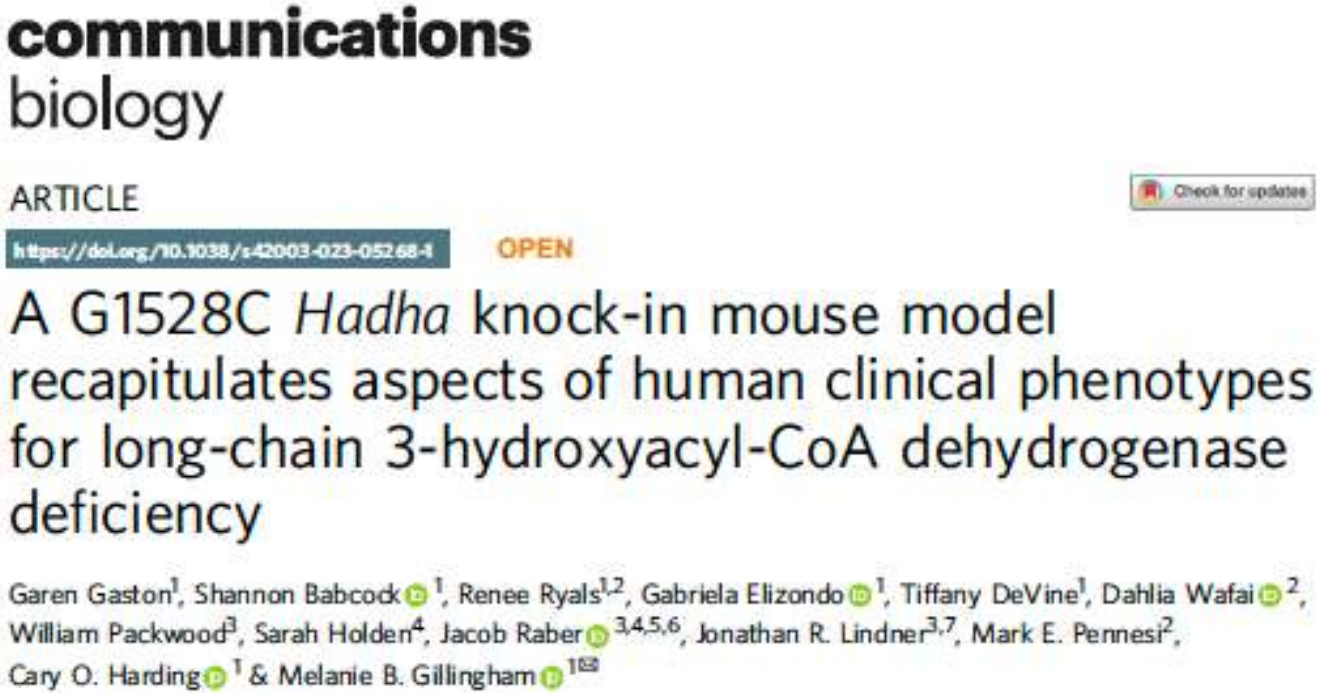
Pre-clinical models



communications biology

ARTICLE

https://doi.org/10.1038/s42003-023-05268-8 OPEN

A G1528C *Hadha* knock-in mouse model recapitulates aspects of human clinical phenotypes for long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

Garen Gaston[1], Shannon Babcock[1], Renee Ryals[1,2], Gabriela Elizondo[1], Tiffany DeVine[1], Dahlia Wafai[2], William Packwood[3], Sarah Holden[4], Jacob Raber[3,4,5,6], Jonathan R. Lindner[3,7], Mark E. Pennesi[2], Cary O. Harding[1] & Melanie B. Gillingham[1]✉

Published mouse manuscript in communications biology

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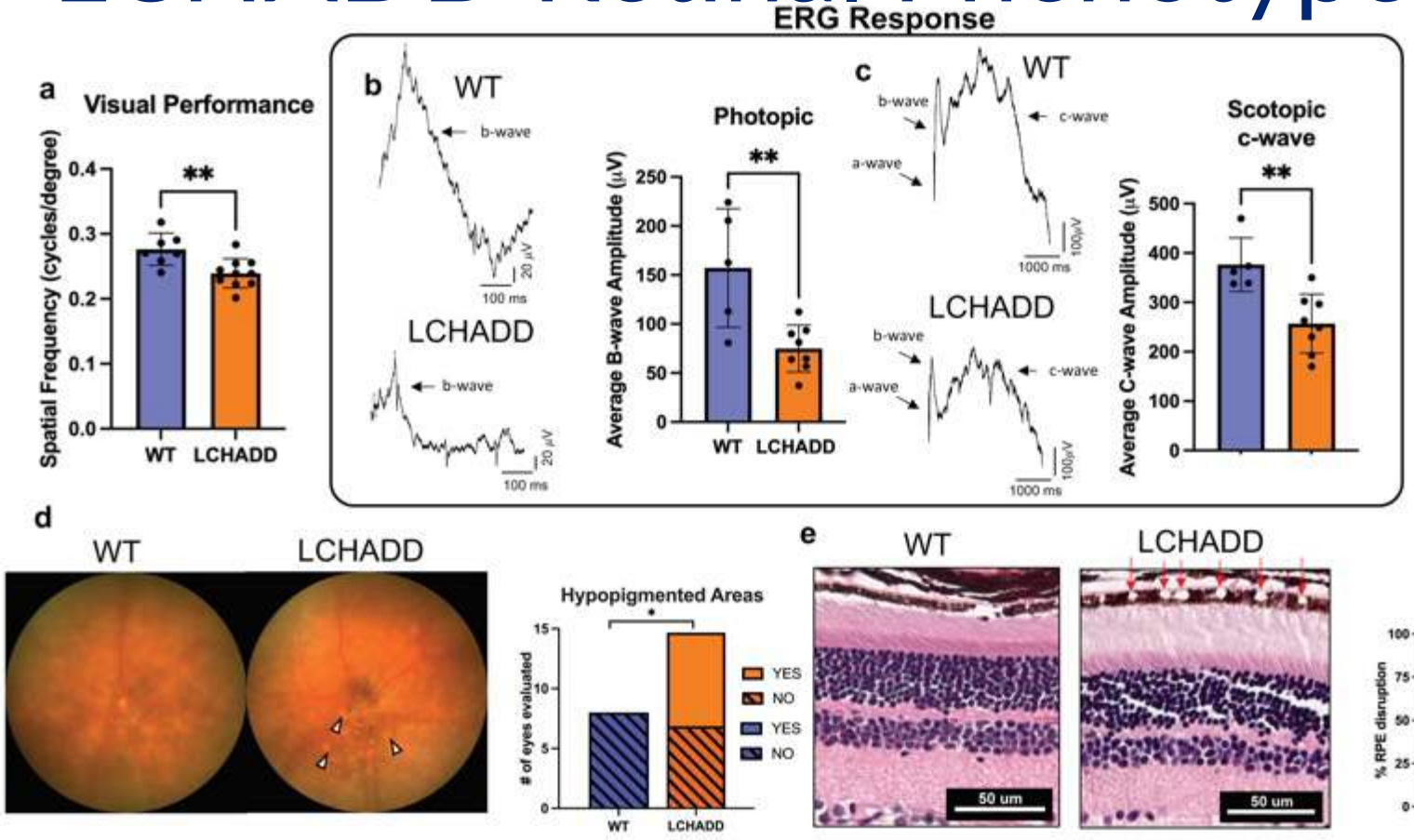
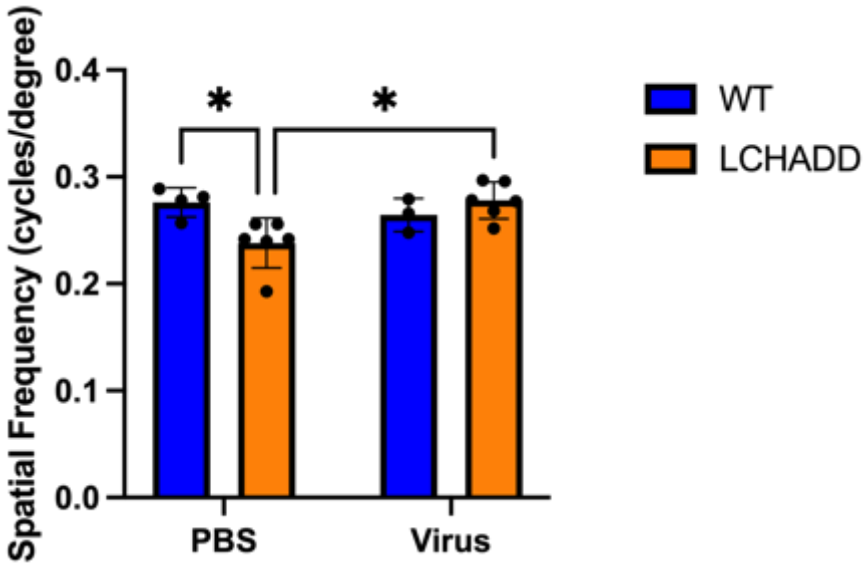
LCHADD Retinal Phenotype



Renee Ryals, PhD

Retinal Gene therapy-preliminary data

- Created a mouse *HADHA* vector in a virus
- Injected into the retina of 2 month old mict
- Checked vision 8 months later



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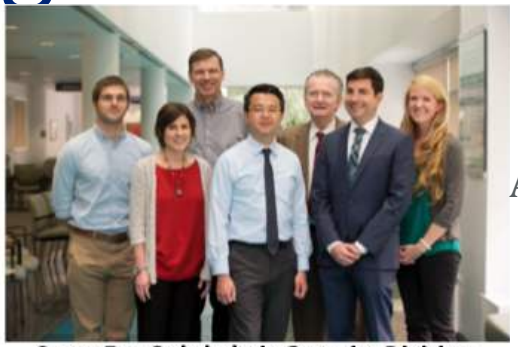
Acknowledgements

Gillingham lab



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- **Funding**
  - **Peterson/Scully Family foundation**
  - **Marcello Miracle Foundation**
  - **Myers, Held**
  - **NICHD-R01HD095968**
  - **NEI-R01EY032889**

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