

# Retinal degeneration in mice devoid of membrane-type frizzled-related protein or adiponectin receptor 1 results in selective fatty acid synthesis impairments

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## Introduction

- Abnormal lipid metabolism is the derivation of multiple retinal degenerative and blinding diseases.
- The omega 3 fatty acids eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6) provide substrate for the fatty acid elongase-4 (ELOVL4) to synthesize VLC-PUFAs.
  - These fatty acids then became part of phospholipids of the outer segments of photoreceptors where they tightly interact with rhodopsin.
  - In the retinal pigmented epithelium (RPE), they serve as precursors to the potent neuroprotective molecules known as Elovonoids.
- The membrane-type frizzled-related protein (MFRP), a protein expressed in the RPE and ciliary bodies, and adiponectin receptor 1 (AdipoR1), a protein expressed in the retina and RPE, were shown to be vital to the maintenance of a healthy retinal lipidome.
  - Given that these lipids are essential for proper vision, it is important to compare the amount of the total fatty acids in the  $\omega$ -3 and  $\omega$ -6 pathways in *Mfrp*<sup>rd6</sup> and *AdipoR1*<sup>-/-</sup>.

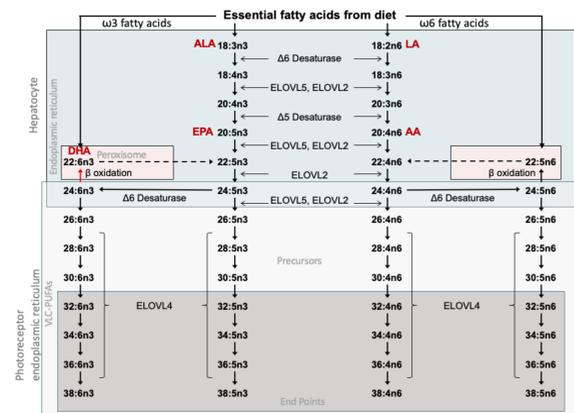
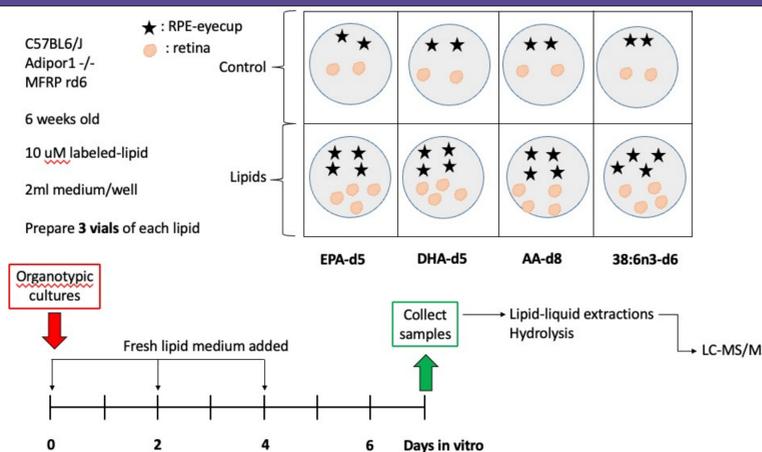


Figure 1: VLC-PUFA lipid metabolism pathway

## Methods



## Results

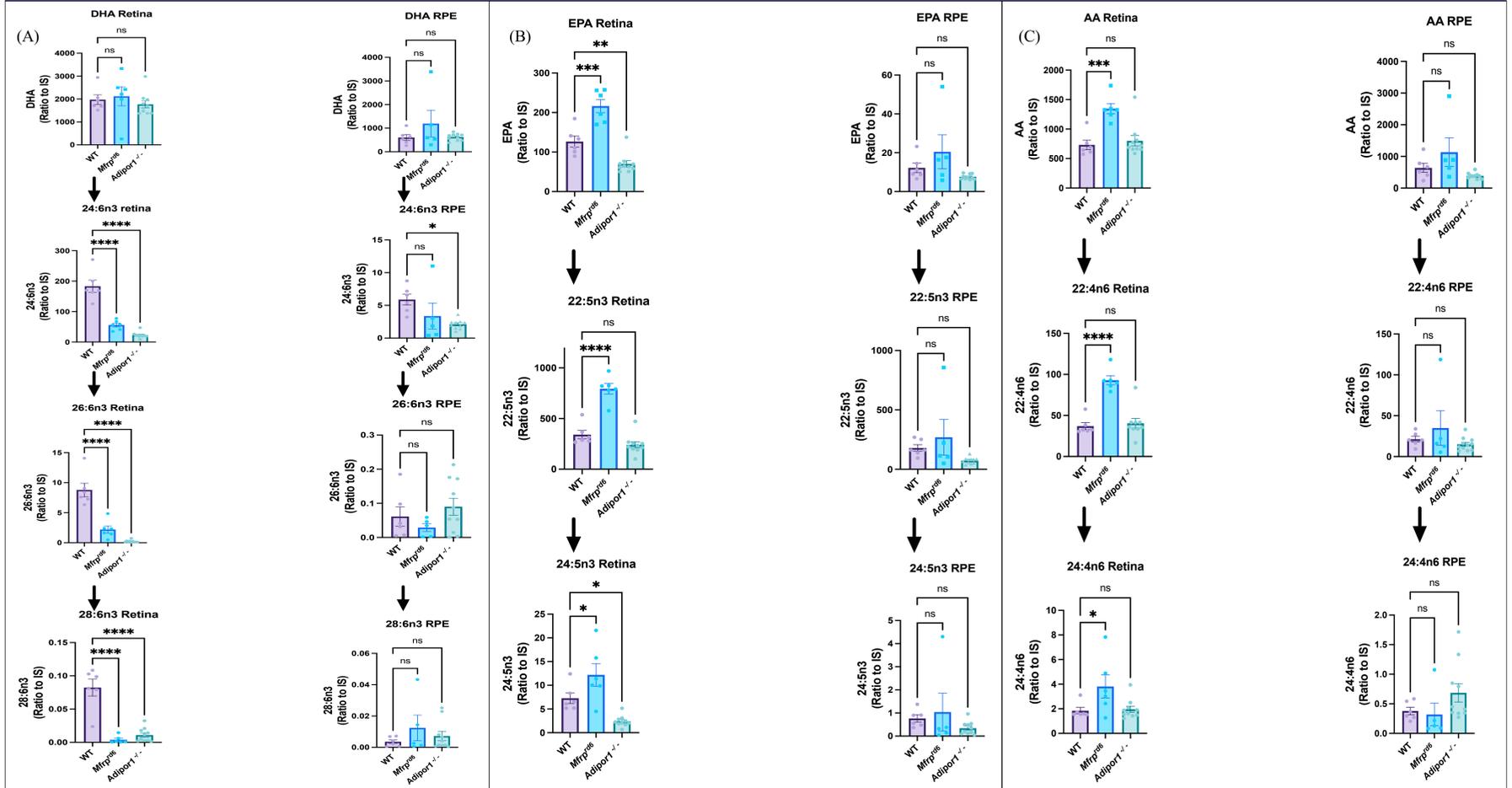


Figure 2. Lipid concentrations in  $\omega$ -3 and  $\omega$ -6 pathways relative to the internal standard starting with DHA (A), EPA (B), or AA (C) for WT, *Mfrp*<sup>rd6</sup> and *AdipoR1*<sup>-/-</sup>. \* $P \leq .05$ , \*\* $P \leq .01$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ .

## Conclusions

- Mfrp*<sup>rd6</sup> and *AdipoR1*<sup>-/-</sup> had depleted levels of VLC-PUFAs from 24:6n3 onwards suggesting a decreased ability to synthesize Elovonoids which require the precursors 32:6n3 and 34:6n3.
- Given that there was a buildup of 24:5n3 in *Mfrp*<sup>rd6</sup> retina, the conversion of 24:5n3 to 24:6n3 seems to be impaired in animals with *Mfrp*<sup>rd6</sup>.
- In contrast, the levels of PUFAs in *AdipoR1*<sup>-/-</sup> retina were low from 20:5n3 to 36:6n3.
- In *Mfrp*<sup>rd6</sup> retina, there were increased levels of arachidonic acid and its downstream products, suggesting a compensatory effect.
- The use of deuterium starting products can help unveil the accurate pathway.
- The lipid concentrations of RPE and retina samples from 4 week and 8-week-old mice will be analyzed for developmental comparison.

## References

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- Rice DS, Calandria JM, Gordon WC, et al. Adiponectin receptor 1 conserves docosahexaenoic acid and promotes photoreceptor cell survival. *Nat Commun.* 2015;6:6228-6242