What can the retina of A53T mice teach us about Parkinson's disease?

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Background & Purpose

- Abnormal alpha-synuclein (α-syn) protein deposition in the central nervous system (CNS) is a key hallmark of Parkinson's disease (PD)
- Eye is an embryological outpouching of the CNS – retina is an accessible place to non-invasively & directly visualise neuronal changes that occur with PD pathogenesis
- We aim to examine how retinal function & structure are altered in a well-characterised α-syn animal model of PD

Materials & Methods

Parkinson's disease (PD) model

- Transgenic homozygous (HOM) knock-in mice (hA53T; Tg(Prnp-SNCA*A53T)83Vle) expressing autosomal dominant mutant human A53T synuclein-alpha (SNCA) gene vs. wildtype (WT) littermates
- *In vivo* assessments conducted at 6 & 14 months of age (n = 15-31 / group)

Histology & Western Blot Protein Assay

- Retinal cross-sections, recombinant anti-phosphorylated α-syn (pSer129) & native anti-α-syn antibodies (Abcam®, Cambridge, MA, USA, Cat no. ab51253 & ab138501)

Electroretinography – Retinal Function

- Dark-adapted & light-adapted responses; photoreceptors: a-wave, bipolar cells: b-wave

Optical Coherence Tomography – Retinal Structure

- Spectralis OCT2 Module, Heidelberg Engineering; retinal nerve fibre layer: RNFL, ganglion cell inner plexiform layer: GCIPL, inner nuclear layer: INL, outer plexiform layer: OPL, outer nuclear layer: ONL, total retinal thickness: TRT

Statistical Analysis

- Two-way ANOVA with Bonferroni correction for multiple comparisons (Prism, GraphPad)
- Data expressed as average ± SEM; * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001

Results

A53T model: α-syn overaccumulates in cortical & retinal tissue

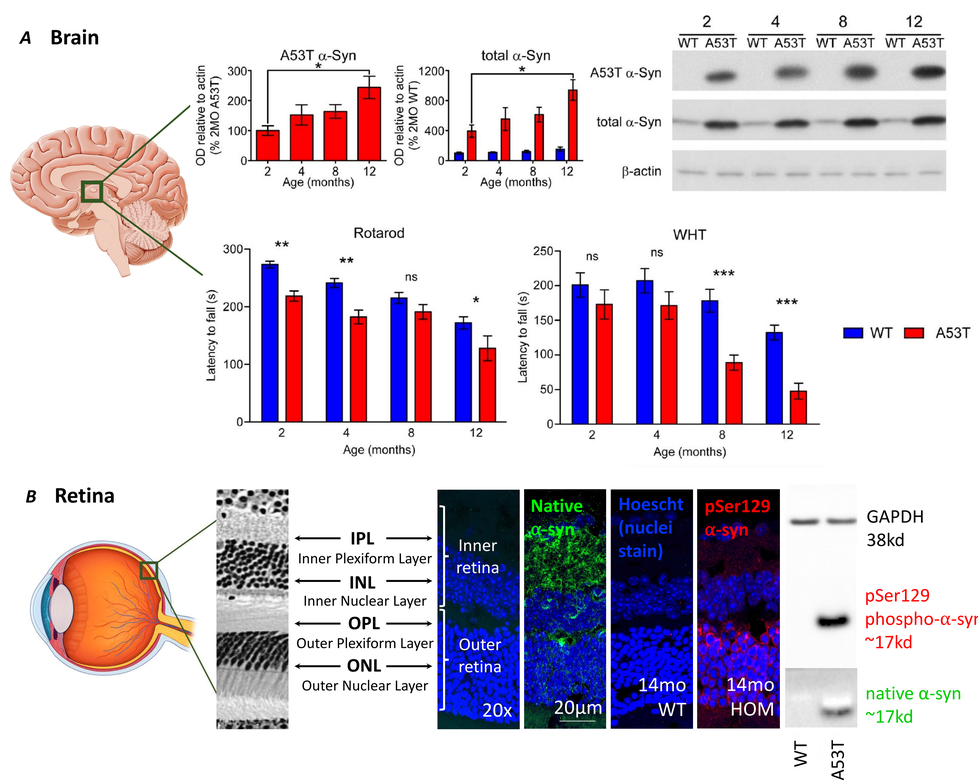

Fig 1. Immunohistochemical & protein assessment of A53T model. (***A***) Oaks et al. 2013 find A53T model shows increasing α-syn accumulation in the brain with advancing age. Behavioral motor assessment with rotarod & wire hang test (WHT) shows severity of motor impairment worsens with advancing age. (***B***) A53T mice show elevated phosphorylated & native α-syn levels in the retina using immunohistochemistry & western blot analyses.

Outer Retinal Layers Degenerate in A53T Mice

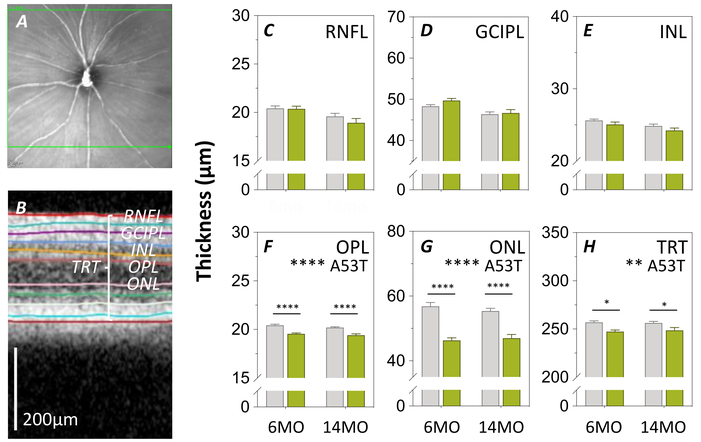

Fig 2. Structural retinal changes in A53T mice. (***A-B***) *In vivo* retinal cross-section with automated layer segmentation. (***C-E***) A53T mice did not exhibit changes in retinal ganglion cell (RNFL, GCIPL), bipolar cell (INL) thickness parameters. (***F-H***) In contrast, A53T HOM mice exhibit significant outer retinal thinning in the outer nuclear layer (ONL) & outer plexiform layer (ONL), an indicator of photoreceptoral neurodegeneration, manifesting in overall decreased total retinal thickness (TRT).

Outer Retinal Function is Reduced & Delayed in A53T Mice

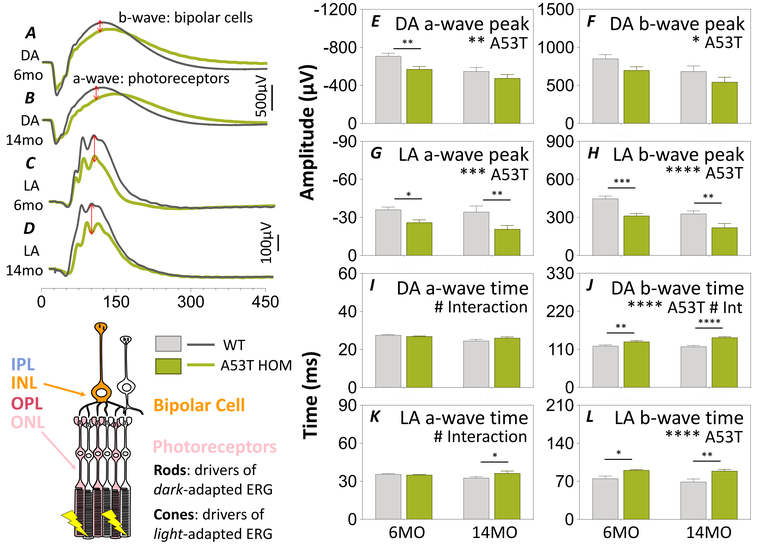

Fig 3. Functional retinal changes in A53T mice. (***A-D***). Representative dark-adapted (DA) & light-adapted (LA) ERG waveforms show compromised photoreceptoral & bipolar cell function in A53T HOM mice at 6 & 14 months. (***E-L***) Photoreceptoral & bipolar cell peak amplitude responses are significantly reduced & delayed in A53T HOM mice. # denotes interaction effect. A larger effect size was observed in LA ERG than DA ERG (Cohen's d = -2.16, effect size r = -0.73).

Conclusions

- A53T mouse model of PD shows α-syn overaccumulation leads to photoreceptoral neurodegeneration & progressive retinal dysfunction
- These retinal deficits in structure & function can be easily identified using non-invasive tools already in clinical use (OCT & ERG)
- Ultimately, these may inform future development of preclinical biomarker endpoints to help triage & fast-track PD drug discovery

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References

1. Oaks et al. (2013) PLoS ONE. DOI: 10.1371/journal.pone.0060378

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