

Postmortem, Dye-free Identification Of Potential RNA Granules In A Retina Of An Individual With FTLD-TDP

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TAKE AWAY AND SUMMARY

THE FIRST POSTMORTEM, DYE-FREE IDENTIFICATION OF POTENTIAL RNA GRANULES IN A RETINA OF AN INDIVIDUAL WITH FTLD-TDP. *IN VIVO* DETECTION OF THESE GRANULES, WHICH MAY TRIGGER TDP-43 FORMATION INTO LARGER DEPOSITS, COULD BE AN EARLY DIAGNOSTIC

BACKGROUND AND INTRODUCTION

Previously, dye-free, with polarized light, we differentiated presumed TDP-43 deposits in 6 postmortem retinas from individuals with ALS and/or FTLD-TDP from deposits in retinas of those with Alzheimer's Disease. Here we describe additional small deposits, imaged in the retina with the largest number of presumed TDP-43 deposits from an individual with FTLD-TDP. The small deposits appear consistent with RNA granules, including stress granules, which have recently been suggested to trigger TDP-43 aggregation into fibrillar deposits. Retinal stress granules have only previously been reported in association with light or chemical damage, optic nerve injury or ocular hypertension. This novel, patented method of retinal imaging in the living eye could provide an inexpensive, dye-free, differential diagnostic that would be accessible to underserved populations. It would also enable appropriate, early treatments and interventions.

METHODS

Eyes and brains were donated by 2 individuals with ALS, including 1 with concurrent FTLD-TDP, and 4 individuals with FTLD-TDP. Retinas were fixed and flat-mounted and deposits were imaged using polarized light, dye-free. Here in only one of those retinas (of an individual with FTLD-TDP), we saw and imaged, in polarized light, additional much smaller, approximately spherical deposits. We compared the sizes and strengths of the polarized light signals of smaller with larger deposits.

RESULTS

The smallest deposits, found only in the retina with the largest concentration of previously reported TDP-43 deposits (and brain tau of ageing), were significantly smaller than presumed TDP-43 deposits (**Fig 1**), and were approximately spherical, consistent with reports of RNA protein assemblies, including small stress granules (**Figs 1,2**), and had surprisingly strong polarimetric signals, similar to larger deposits (**Fig 3**).

Extracellular fibrils and small elongated deposits were also found in the vicinity of these deposits (**Fig 1**), consistent with a previous suggestion that TDP-43 combining with stress granules is a first step in forming larger TDP-43 deposits.

RESULTS CONTINUED

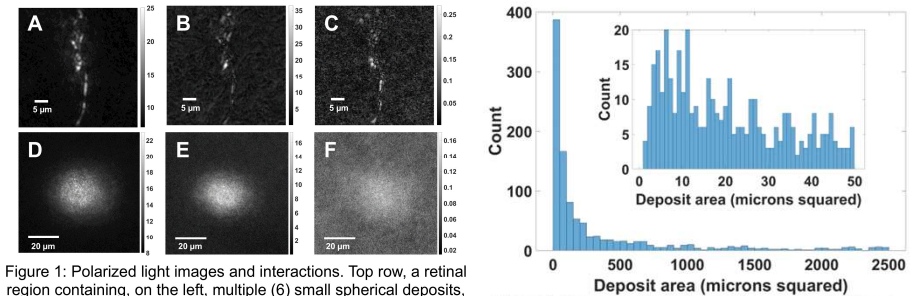


Figure 1: Polarized light images and interactions. Top row, a retinal region containing, on the left, multiple (6) small spherical deposits, consistent in size with stress granules, with small fibrils nearby. Bottom row, a larger, presumed TDP-43 deposit. All are visible in crossed polarized light (A and D) and when displaying linear retardance (B and E), and an additional property: (C, linear diattenuation, and F, depolarization power)

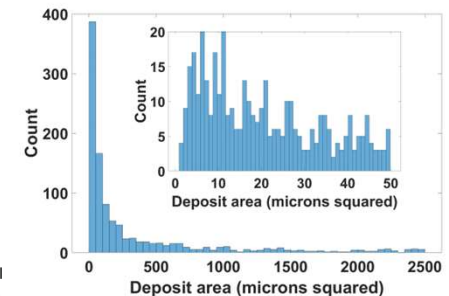


Figure 2: Histogram of retinal deposit areas. For display, we have removed 73 deposits larger than 2500µ². Inserted is an enlarged view of the numbers of deposits with less than a 50µ² area. Stress granules have been reported in brain as large as 20µ² with RNA granules having areas up to 50µ².

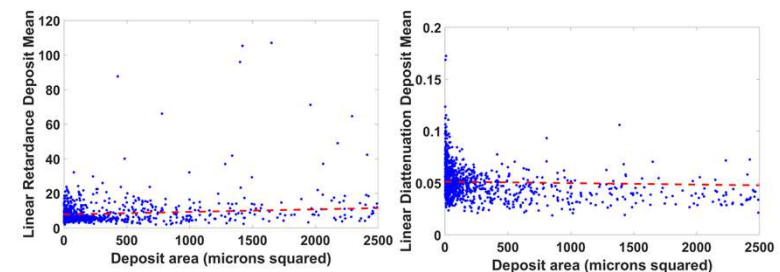


Figure 3: On the left and right are plots of deposit interactions with polarized light, mean linear retardance (left) and mean linear diattenuation (right) vs deposit area (for deposits up to 2500 µ²). With increasing size, there is a small, significant increase in mean linear retardance and a small significant decrease in mean linear diattenuation.

DISCUSSION AND CONCLUSIONS

The shapes and sizes of the smallest deposits in the retina are consistent with stress granules, a subset of RNA granules, not previously identified in the retina in FTLD or ALS. Given their sizes, their polarized light interactions are surprisingly strong and suggest that they may contain TDP-43. Polarized light may facilitate the identification in the living eye, of stress granules and small TDP-43 deposits, (in addition to the larger deposits we previously reported) as earlier retinal diagnostic markers living of those with ALS and FTLD.

REFERENCES, ACKNOWLEDGEMENTS AND CONFLICTS OF INTEREST

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