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The New Zealand Genetic Frontotemporal Dementia Study (FTDGeNZ): Baseline retinal characteristics

Hannah M. Kersten [1], Brigid Ryan [2,3], Kiri L. Brickell [2,3], Christina Ilse [2,3], Ehsan Vaghefi [1], Donna Rose Addis [2,3,4], Lynette Tippett [2,3,5], Maurice A. Curtis [2,3], Helen V. Danesh-Meyer [6]

[1] School of Optometry and Vision Science, University of Auckland [2] Centre for Brain Research, University of Auckland [3] Brain Research New Zealand, Rangahau Roro Aotearoa
[4] Rotman Research Institute, Baycrest Health Sciences, Canada [5] School of Psychology, University of Auckland [6] Department of Ophthalmology, University of Auckland

BACKGROUND

- The key to combating dementia is early detection. Prospective longitudinal studies to search for pre-clinical dementia are required.
- Genetic FTD provides an opportunity to identify pre-clinical markers because the causative mutation can be identified decades before expected symptom onset.
- FTDGeNZ is one of the largest, single-family longitudinal FTD studies internationally.
- OCT imaging has been shown to be a marker of disease progression in other neurodegenerative disorders.
- There are reports of retinal layer thinning in patients with sporadic FTD, and individuals with pre-symptomatic FTD caused by progranulin mutations.[1-3]
- Cerebral hypoperfusion has been documented in patients with FTD. Assessment of the retinal microvasculature will help to determine whether retinal hypoperfusion is an early feature of FTD.

OBJECTIVE

Identify retinal biomarkers of pre-clinical FTD in a longitudinal cohort study of a kindred with genetic FTD caused by a tau mutation

FTDP-17 COHORT

Pre-clinical carriers
MAPT IVS 10+16 C>T
(Autosomal dominant mutation with complete penetrance)

Non-carrier controls

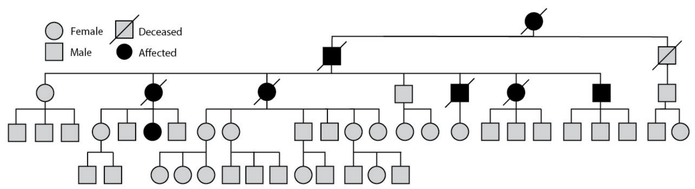

Figure 1: FTDP-17 Pedigree. Participants include members of the two youngest generations. There are 24 participants in the current study, including 6 carriers (not indicated in the pedigree for reasons of confidentiality).

REFERENCES

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2. Kim BJ, Irwin DJ, Song D, et al. Optical coherence tomography identifies outer retina thinning in frontotemporal degeneration. *Neurology.* 2017;08:08.
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METHODS

- Genotyping of FTDP-17 cohort:
  - Isolated DNA from 500 µL buffy coat (Gentra Puregene Blood Kit, QIAGEN)
  - Sanger sequencing (ABI 3130XL Genetic Analyzer) using custom primers
  - Validated using a TaqMan Genotyping Assay specific to SNP ID:rs63751011
- Carrier participants pre-symptomatic at baseline, based on neurological and neuropsychological examination
- Comprehensive neuro-ophthalmic examination including SD-OCT (Zeiss Cirrus™) and OCT-A (Angioplex®) (Figure 2)
- Support vector machine (SVM) image analysis of vessel density and vessel distribution
- One eye of each participant used in analysis

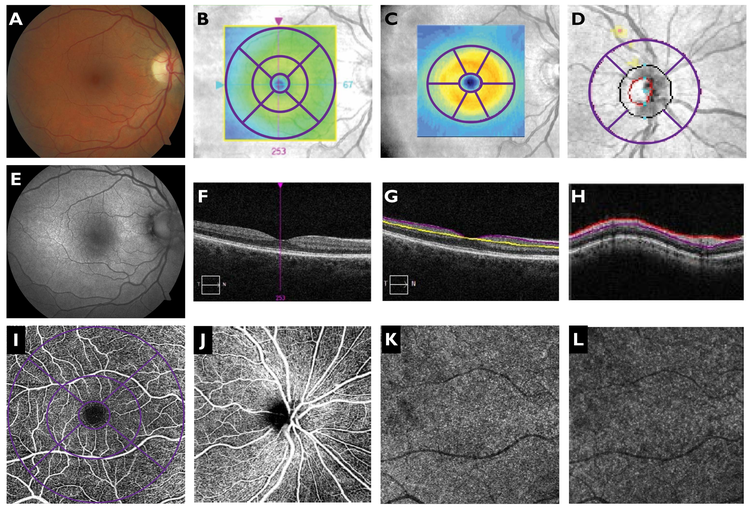

Figure 2: Imaging sequence. A and E - Colour fundus photography and fundus autofluorescence; B and F - OCT macular segmentation; C and G - OCT ganglion cell complex segmentation; D and H - OCT retinal nerve fibre layer segmentation; I and J - OCT-A superficial retinal vessel plexus at macula and optic nerve; K and L - OCT-A of choriocapillaris and choroid

SUMMARY

At baseline, there were no significant differences in OCT or OCT-A measurements between carriers of the tau mutation for FTD and non-carriers.

Longitudinal analysis will determine the role of OCT/OCT-A as a retinal marker of FTD

RESULTS

- Included in analysis were 6 carriers and 18 non-carrier controls.
- Both groups had similar baseline ophthalmic and refractive characteristics (Table 1).
- There were no statistically significant differences between carriers and non-carriers for peripapillary and macular OCT and OCT-A measures (Tables 2 and 3).
- These findings were consistent across age-matched paired T-test analysis
- SVM analysis was not sufficient to determine the genetic status of participants.

Table 1: Baseline age and ophthalmic characteristics

	Carriers, N=6 (SD)	Non-carriers, N=18 (SD)	*p* value
Age (years)	41.2 (12.0)	40.5 (14.3)	0.58
LogMAR VA	-0.07 (0.04)	-0.04 (0.05)	0.22
IOP (mmHg)	13.8 (2.6)	13.8 (3.6)	0.92
CDR (OCT)	0.45 (0.13)	0.50 (0.08)	0.58
Mean Sphere (D)	-0.19 (0.84)	-0.15 (0.89)	0.77

Table 2: Baseline OCT measures

	Carriers, N=6 (SD)	Non-carriers, N=18 (SD)	*p* value
RNFL (µm)			
Average	100.2 (8.1)	94.6 (6.1)	0.14
Superior	121.2 (17.0)	113.6 (9.7)	0.63
Nasal	77.2 (11.1)	76.0 (8.7)	0.92
Inferior	131.3 (11.1)	125.3 (14.3)	0.20
Temporal	71.7 (10.3)	63.5 (9.3)	0.18
Macula (µm)			
Total volume (mm^3)	10.49 (0.35)	10.40 (0.35)	0.63
Superior outer	292.0 (10.7)	284.4 (8.6)	0.08
Superior inner	331.7 (12.6)	333.2 (12.2)	0.87
Nasal outer	309.9 (9.1)	305.6 (13.1)	0.54
Nasal inner	332.5 (12.9)	335.9 (12.3)	0.67
Inferior outer	278.0 (7.7)	273.3 (12.7)	0.45
Inferior inner	328.8 (11.2)	328.6 (12.5)	0.97
Temporal outer	271.3 (10.3)	269.8 (12.2)	0.63
Temporal inner	316.3 (13.7)	321.4 (11.4)	0.44
Fovea	257.7 (14.8)	264.8 (14.4)	0.38
GCC (µm)			
Average	85.6 (2.8)	82.9 (5.6)	0.25
Minimum	83.4 (2.8)	81.2 (6.1)	0.38

Table 3: Baseline OCT - Angiography (Zeiss Angioplex®) measures

	Carriers, N=6 (SD)	Non-carriers, N=18 (SD)	*p* value
6x6 macular vessel density (mm/mm^2)			
Superior outer	18.88 (0.52)	18.21 (0.91)	0.09
Superior inner	18.00 (0.86)	17.82 (0.93)	0.72
Nasal outer	19.70 (0.55)	19.74 (0.67)	0.82
Nasal inner	17.73 (0.92)	18.08 (1.11)	0.45
Inferior outer	18.53 (0.68)	18.32 (1.42)	0.97
Inferior inner	17.40 (0.94)	17.66 (1.10)	0.67
Temporal outer	17.28 (0.50)	16.87 (1.60)	0.63
Temporal inner	17.62 (1.07)	18.03 (0.91)	0.58
Central	9.37 (1.39)	10.13 (1.64)	0.20
Inner average	17.70 (0.87)	17.91 (0.78)	0.67
Outer average	18.60 (0.47)	18.29 (0.92)	0.58
Full average	18.13 (0.52)	18.02 (0.89)	0.67
FAZ	0.26 (0.05)	0.24 (0.07)	0.58

Note: All comparisons performed with the Mann Whitney U test. Abbreviations: *FAZ* foveal avascular zone; *GCC* ganglion cell complex; *RNFL* retinal nerve fibre layer

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Contact: h.kersten@auckland.ac.nz

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