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# Fronto-subcortical hypoperfusion in presymptomatic FTD is associated with behavioral measures, but not cognitive deficits – the GENFI study

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*Nothing to disclose*

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# FRONTO-TEMPORAL DEMENTIA(S)-FTD

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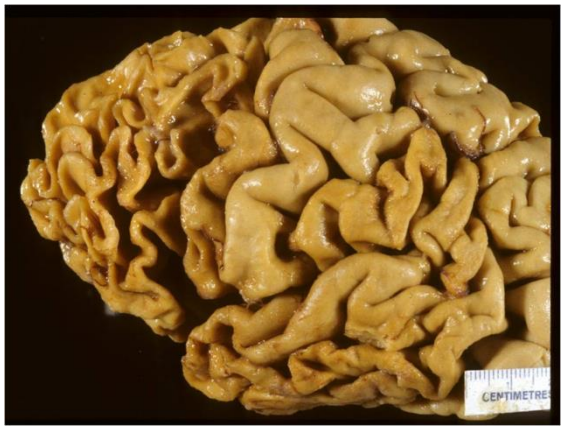
GENETIC FTD INITIATIVE

- A group of rare neurodegenerative disorders
- Age of Onset 45 to 65 years
- Primarily affecting frontal and temporal lobes
  - Behavioral variant (bvFTD)
  - Primary progressive aphasia (PPA)
    - Semantic variant of PPA
    - Non-fluent variant of PPA
  - Disturbances of motor function-ALS or parkinsonism

Frontotemporal Atrophy




*Seelaar et al.2011; Onyike and Diehl-Schmid 2013; Gorno-Tempini et al. 2011*

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# GENETICS AND PATHOLOGY OF FTD

Sporadic cases, 50-80%

Fa
20

Single gene mutations. Autosomal dominant

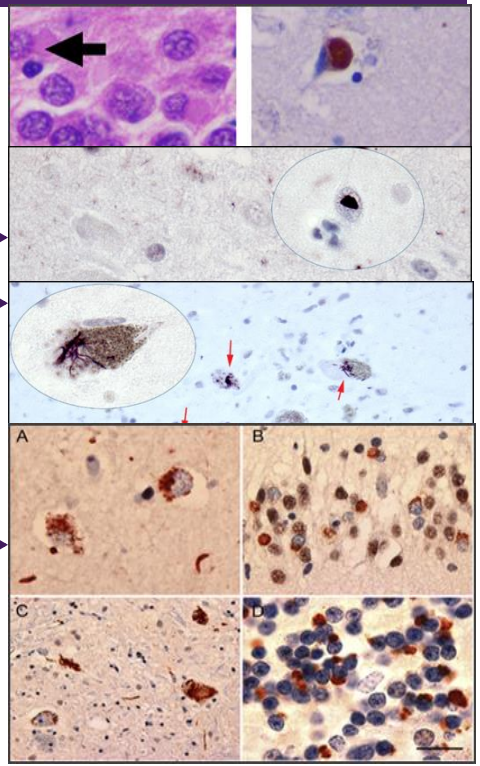
17q21

9p21

*MAPT* — Tau

*PGRN* — *PGRN* TDP-43

*C9ORF72* — *C9orf72* TDP-43




*Rohrer et al. 2009; Mackenzie et al. 2010; DeJesus-Hernandez et al. 2011; Gasca-Salas et al. 2016*

# PRESYMPTOMATIC MUTATION CARRIERS

- Presymptomatic mutation carriers - a very important group to understand the long preclinical phase of FTD
- In presymptomatic mutation carriers of these genes, identifying (Imaging) biomarkers of disease before the onset of clinical symptoms is crucial
  - To predict disease onset
  - To monitor disease progression, and
  - To guide use of future disease modifying therapies

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# IMAGING AND PRESYMPTOMATIC FTD

- Volumetric Magnetic Resonance Imaging (MRI) – volume changes e.g. atrophy
  *Rohrer et al. 2015*
- 18F-Fluorodeoxyglucose Positron Emission tomography (FDG-PET) – hypometabolism
  *Jacova et al. 2013*
- Resting-state functional MRI – information on functional networks
  *Premi et al. 2014*
- Diffusion Tensor Imaging (DTI) – structural connectivity of white matter
  *Dopper et al. 2013*
- Arterial Spin Labelling (ASL) – cerebral perfusion
  *Dopper et al. 2016*
  - Increasing evidence suggests that perfusion changes precede structural brain changes in FTD

# AIMS AND OBJECTIVES

- In pre-symptomatic family members of FTD cases [non-carriers: n=100; carriers: n=95 (*MAPT*=17, *GRN*=48, *C9orf72*=30)], we aimed to:

I. Explore differences in cerebral perfusion in mutation-carriers compared to non-carriers in same families utilizing Arterial Spin Labeling MRI data

II. Investigate if differences in perfusion (if any) identified in aim I are associated with cognitive or behavioral measures

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# METHODS

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# SETTING

GENFI
GENETIC FTD INITIATIVE

-Multicentre consortium for tracking evolution of genetic FTD

-Common methodological platform across all sites

-13 centres across Europe and Canada

-Includes FTD cases and unaffected family members

-Clinical, functional, neuropsychological, MRI, blood and CSF assessments

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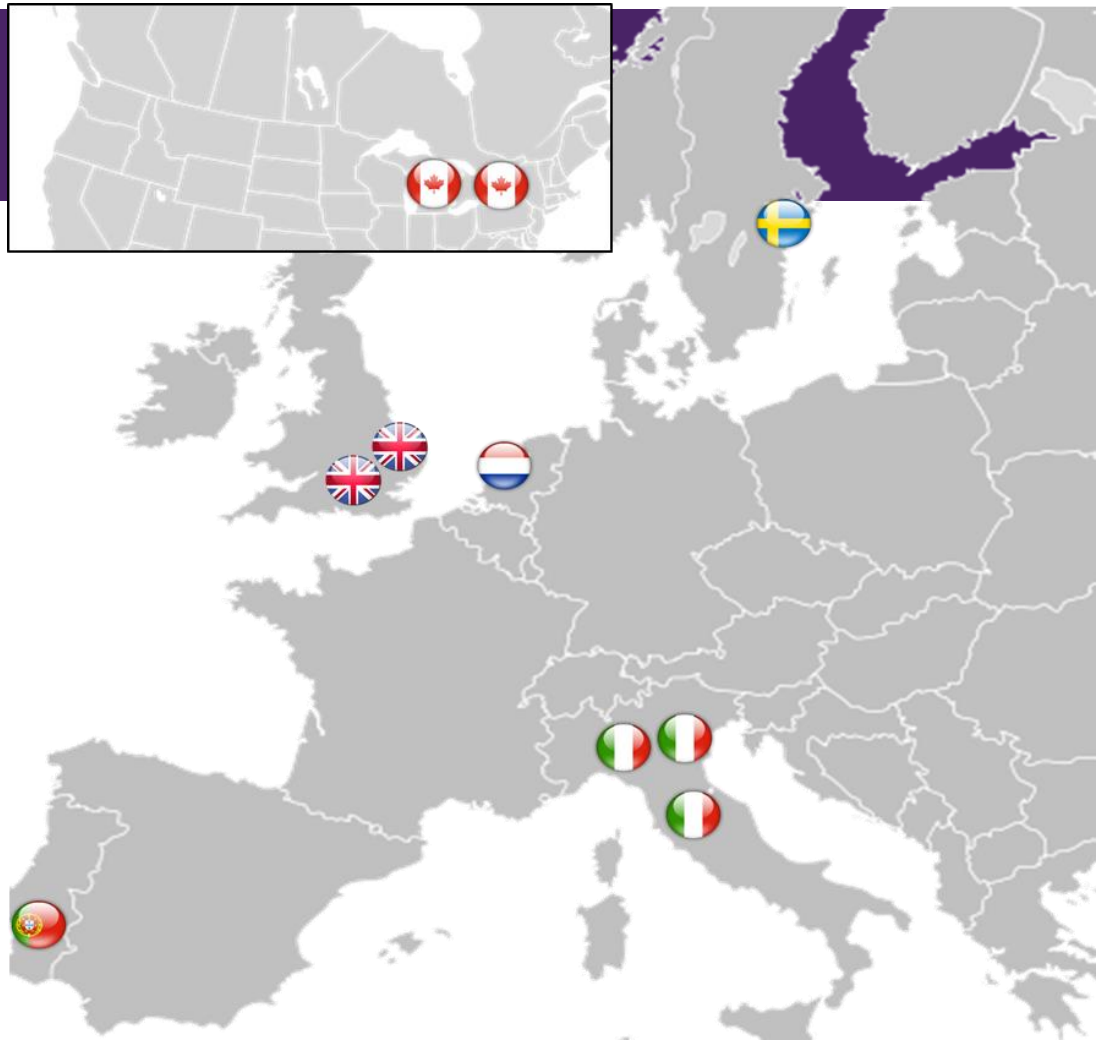

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# STUDY POPULATION AND ASSESSMENTS

- Presymptomatic family members of FTD cases, N=195 [100 non-carriers; 95 carriers (*MAPT=17, GRN=48, C9orf72=30*)]
- Cerebral perfusion data
- Cognitive measures
- Behavioural measures

- Global cognition:
*MMSE*
- Executive function:
*Trail making test A & B*
- Language
*Boston Naming & Verbal Fluency*
- Memory
*Logical memory-Immediate and delayed recall*
- Working memory
*Forward and backward digit span*

**Cambridge Behavioural Inventory-CBI**
- *Memory and orientation*
- *Everyday skills*
- *Self-care*
- *Abnormal behaviour*
- *Mood*
- *Beliefs*
- *Eating habits and sleep*
- *Stereotype and motor behaviours*
- *Motivation*

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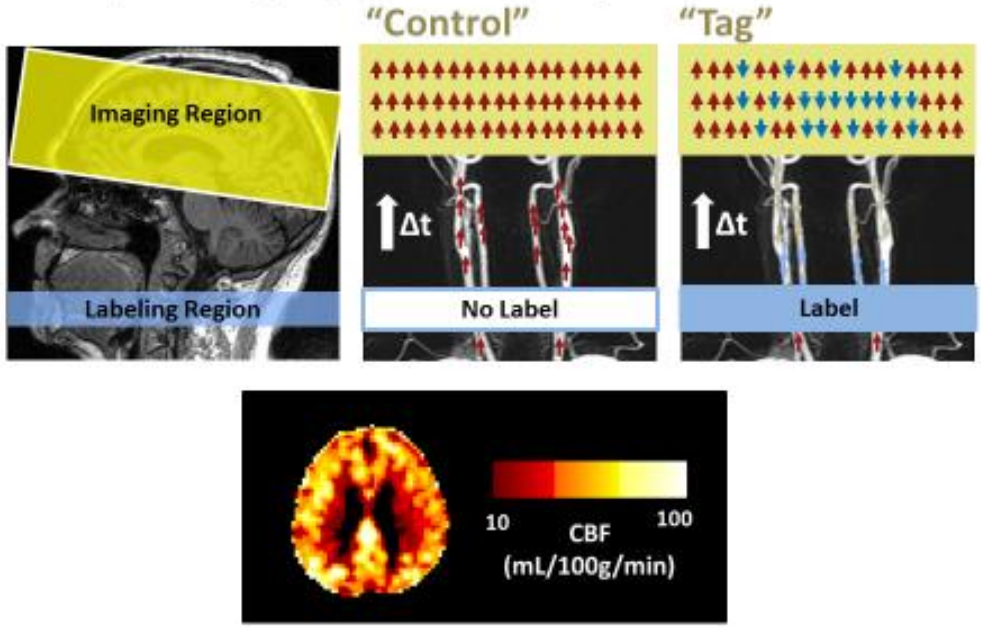
# CEREBRAL (HYPO)PERFUSION-ASL

*Aim I: To explore* *same families*

- Cerebral perfusion
- In a voxel-based a non-carriers and mutation carriers
- Linear mixed mod
  - Account for
  - Fixed effect **et (YAO),** YAO*mutati
  - YAO=age o
  - Analyses ac r artifacts
- Regions of hypop riers were identified on VBA, and then olume effects



# ASSOCIATION OF CEREBRAL HYPOPERFUSION WITH COGNITION AND BEHAVIOUR

*Aim II: Investigate if regional hypoperfusion in regions of interest (ROIs) identified in aim I is associated with cognitive or behavioral measures*

- To test associations of the identified ROIs of cerebral hypoperfusion with cognitive and behavioral measures, we used:
  - Multiple linear regression models
    - Adjusted for age, sex, and education
- First, we tested interactions between cerebral perfusion and mutation carrier-status in analyses of ROIs with both cognitive and behavioural measures
- Second, analyses were repeated stratified for carrier status (carriers and non-carriers) and subsequently stratified on mutation: *MAPT=17*, *GRN=48, C9orf72=30*)

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# RESULTS

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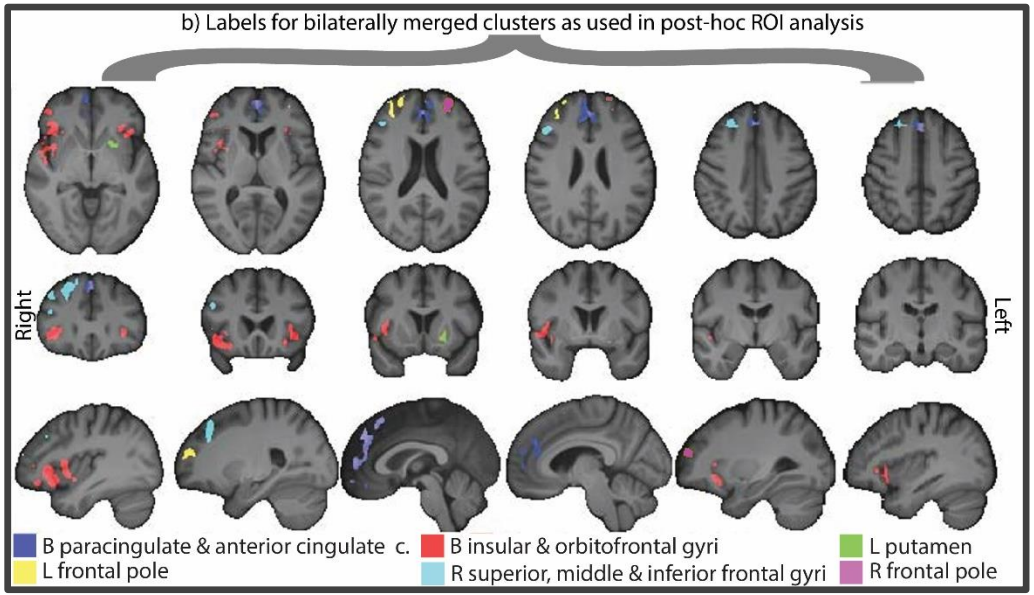
# RESULTS I-REGIONS OF HYPOPERFUSION

- Six regions of interest (ROIs) of cerebral hypoperfusion in carriers compared to non-carriers were identified named according to their overlap with the Harvard-Oxford atlas 35

- C1: Paracingulate gyri (B)
- C2: Orbitofrontal gyrus/insula (B)
- C3: Frontal pole (R)
- C4: Putamen (L)
- C5: Frontal pole (L)
- C6: Middle, Inf, and Sup frontal gyri (R)




B: bilateral; R: right; L: left

# RESULTS II-CEREBRAL HYPOPERFUSION AND COGNITION

- When testing perfusion in identified ROIs with cognitive tests:
  - We did not find any associations between cerebral perfusion and cognitive test scores in any ROIs in mutation carriers or non-carriers

# RESULTS II-CEREBRAL HYPOPERFUSION AND BEHAVIOUR

| | CBI TOTAL SCORE, Difference (95% confidence interval) P-value | | | | |
|---|---|---|---|---|---|
| | Non-carriers n=100 | All carriers n=95 | *C9ORF72* n=30 | *PGRN* n=48 | *MAPT* n=17 |
| **Paracingulate (B)** | -0.01 (-0.06, 0.04) 0.59 | 0.16 (0.08, 0.23) **<0.001** | 0.03 (-0.08, 0.14) 0.56 | 0.03 (-0.08, 0.14) 0.54 | 0.33 (-0.19, 0.47) **<0.001** |
| **Orbitofrontal/insula (B)** | -0.005 (-0.05, 0.04) 0.83 | 0.10 (-0.002, 0.18) 0.056 | -0.04 (-0.16, 0.07) 0.42 | -0.02 (-0.15, 0.10) 0.70 | 0.36 (0.07, 0.65) **0.02** |
| **Frontal pole (R)** | 0.02 (-0.01, 0.07) 0.25 | 0.14 (0.06, 0.22) **<0.001** | -0.01 (-0.11, 0.09) 0.84 | 0.07 (-0.04, 0.19) 0.21 | 0.35 (0.17, 0.54) **0.001** |
| **Putamen (L)** | -0.01 (-0.09, 0.07) 0.80 | 0.20 (0.06, 0.34) **0.006** | -0.006(-0.19, 0.18) 0.95 | 0.04 (-0.15, 0.23) 0.68 | 0.76 (0.30, 1.21) **0.003** |
| **Frontal pole (B)** | 0.02 (-0.03, 0.06) 0.46 | 0.14 (0.06, 0.22) **<0.001** | -0.03 (-0.14, 0.08) 0.61 | 0.08 (-0.03, 0.19) 0.15 | 0.41 (0.23, 0.60) **<0.001** |
| **Middle, inferior, and superior frontal gyri (R)** | 0.02 (-0.03, 0.06) 0.43 | 0.13 (0.06, 0.21) **<0.001** | -0.01 (-0.10, 0.08) 0.82 | 0.03 (-0.08, 0.15) 0.53 | 0.36 (0.22, 0.49) **<0.001** |

All estimates are adjusted for age, sex, and education

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# CONCLUSION

- Cerebral hypoperfusion within frontal-subcortical regions in presymptomatic FTD is associated with early behavioral changes but not cognitive deficits.
- This may be consistent with the natural history of FTD which most commonly shows behavioural dysregulation as an early feature.
- The current approach uses an ROI analysis.
- Future work will look at a direct voxel-based analyses associating perfusion with CBI and neuropsychological test scores.

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