Frontotemporal dementia: Insights into its genetic etiology and molecular biology

Julie van der Zee, PhD
**MAPT: Microtubule Associated Protein Tau**

- 1892: A. Pick → Pick’s disease
- Accumulation of filamentous, hyperphosphorylated MAPT protein in neurons and glia = FTLD-tau
- 1998: mutations in MAPT gene

- MAPT protein:
  - abundantly expressed in CNS
  - interacts with microtubules
  - regulates axonal transport

- MAPT gene:
  - on chromosome 17q21
  - mutations: missense, deletion, silent, splice-site

(binding microtubules, form filaments, alter 4R/3R tau)

**Neurodegeneration**
Genetic discoveries in dementia research

Alzheimer dementie

Aloïs Alzheimer

1906

1980

1990

2000

2010

MAPT

VCP

CHMP2B

C9orf72

PSEN1, PSEN2

APP

CLU, CR1, PICALM

TREM2

PTK2B, SORL1, SLC24A4-RIN3, DSG2, INPP5D, MEF2C, NME8, NYAP1, MADD, FERMT2, CASP4, ZCWPW1 locus, HLA-DRB5/HLA-DRB1 locus, CELF3 locus

Frontotemporale dementie

Arnold Pick

1892

1980

1990

2000

2010

FTLD-TDP

FTLD-tau

GRN

MAPT

VCP

UBQLN2, SQSTM1

Molecular pathology of FTLD

--- protein inclusions in degenerating neurons

3R, 3 repeat tau isoform; 4R, 4 repeat tau isoform; aFTLDU, atypical FTLD with ubiquitin-positive inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; FET, fused in sarcoma, Ewing’s sarcoma, TATA-binding protein-associated factor 15; GGT, globular glial tauopathy; NIFID, neuronal intermediate filament inclusion disease; PiD, Pick’s disease; PSP, progressive supranuclear palsy; TDP, transactive response DNA binding protein; UPS, ubiquitin proteasome system.

Mackenzie and Neumann, J Neurochem 2016
Molecular pathology of FTLD

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Mackenzie and Neumann, J Neurochem 2016
<table>
<thead>
<tr>
<th>FTLD-TDP Classification</th>
<th>Cortical Pathology</th>
<th>Common Phenotype</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type A</strong></td>
<td>- many intraneuronal cytoplasmic inclusions (NCI)</td>
<td>bvFTD</td>
<td>GRN Tbk1 (C9orf72)</td>
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<tr>
<td></td>
<td>- many short dystrophic neurites (DN)</td>
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<tr>
<td></td>
<td>- few neuronal intranuclear inclusions (NII)</td>
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<td></td>
<td>- in superficial cortical layers (predominantly layer II)</td>
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<tr>
<td><strong>Type B</strong></td>
<td>- many NCI</td>
<td>bvFTD</td>
<td>C9orf72 Tbk1</td>
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<tr>
<td></td>
<td>- few DN</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- no NII</td>
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<tr>
<td></td>
<td>- in both superficial and deep cortical layers</td>
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<tr>
<td><strong>Type C</strong></td>
<td>- few NCI</td>
<td>SD</td>
<td>None</td>
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<td>- many long DN</td>
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<td></td>
<td>- no NII</td>
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<td></td>
<td>- in superficial cortical layers (predominantly layer II)</td>
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<td><strong>Type D</strong></td>
<td>- few NCI</td>
<td>Familial IBMPFD</td>
<td>VCP</td>
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<tr>
<td></td>
<td>- many short DN</td>
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<td></td>
<td>- many lentiform NII</td>
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<td></td>
<td>- most abundantly in neocortex</td>
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<tr>
<td><strong>Type E</strong></td>
<td>- granulofilamentous neuronal inclusions</td>
<td>bvFTD</td>
<td>(C9orf72)</td>
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<tr>
<td></td>
<td>- grains</td>
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<td></td>
<td>- oligodendroglial curvilinear inclusions</td>
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<td></td>
<td>- widespread distribution</td>
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Progranulin, GRN

Belgian FTD founder family identifies progranulin gene

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

**GRN IVS1+5 G>C; p.0 null mutation**

**GRN mutations are loss of function mutations**

- **Loss-of-function mutations (LOF)**
  - frameshift, nonsense, splice site mutations → create a premature termination codon (PTC)
  - PTC transcripts are preventively degraded by Nonsense Mediated RNA Decay or MND
  - → 50% loss of protein levels → leads to disease through haploinsufficiency
Belgian GRN IVS1+5 G>C founder mutation

- 29 branches (families and index patients)
- DNA of 175 relatives, incl. 79 carriers
- So far, Belgium-Flanders-only
- Onset age: (n=79)
  - $63 \pm 8$ yrs, range 45 - 80 yrs
- Disease duration: (n=66)
  - $6.1 \pm 3.8$ yrs, range 1 - 20 yrs
- Age at death: n=72
  - $70 \pm 7$ yrs, range 49 - 85 yrs
Clinical heterogeneity

Wauters, Van Mossevelde et al., 2018

ALS-FTD or FTD – ALS spectrum

ALS patients
- 15% have FTD (with TDP43-positive inclusions in cortical neurons)
- 50% have evidence for more subtle cognitive and/or behavioral dysfunction
  -> ALS patients with some cognitive or behavioral changes but that do not meet the criteria for FTD: ALS-Ci/Bi (ALS with cognitive or behavioral impairment).

FTD patients
- 15% also have ALS
- many more have some evidence of lower motor neuron involvement.
  -> FTD patients with evidence of mild motor neuron involvement (clinically or on electromyographs) without developing ALS: FTD-MND

Patients with clinical evidence for both disorders are said to have ALS-FTD or FTD-ALS

Adapted from Robberecht & Philips, Nat Rev Neurosc 2013
Chromosome 9 open reading frame 72, **C9orf72**

- **Repeat expansion in C9orf72**

  - 2011: hexanucleotide repeat (GGGGCC) expansion in C9orf72
  - Chromosome 9 open reading frame 72
    - Chr9p21, non-coding repeat in promotor region
  - Most common genetic cause of FTD and ALS
    - general
      - FTD: 4-29%
      - ALS: 11%
      - FTD-ALS: 17-28%
    - familial
      - FTD: 29%
      - ALS: 38%
      - FTD-ALS: up to 88%

*Dejesus-Hernandez et al., Neuron 2011; Renton et al., Neuron 2011; Gijselinck et al., Lan Neurol 2012*
FTD – ALS spectrum

Repeat expansion mutation: like for C9orf72 (GGGGCC repeat)

- unaffecteds: 2 – 24 copies of GGGGCC
- patients: 100eds – 1000ends copies of GGGGCC

Mutation mechanism

C9orf72 gene

Exon 1a 1b 2 3 4 5 6 7 8 9 10 11 2 Kb

3X → >60X → >1000X

AGTGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCCCGGGCC

CGATAA GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC

CGATAA GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC

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CGATAA GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC GGGGCC
C9orf72 repeat size and disease anticipation

- Expansion varies in patients from 45 to 1000 ends of repeat units.
- Onset age: 29 to 80 years (average 56.1 yrs)

Research question: Is there clinical evidence for disease anticipation?

- Investigated 36 extended families including 222 C9orf72 expansion carriers
- Over 4 generations, average onset decreases from 62 years to 49 years

Onset Age in Successive Generations

Van Mossevelde et al., JAMA Neurol 2017

Tank-binding kinase 1, TBK1
**TBK1** a novel player in the FTD-ALS spectrum

- 13 patients: 10 FTD or Dem, 2 ALS, 1 FTD-ALS
- Onset 69.1 ± 7.7 years
- Duration 6.4 ± 3.9 years
- Early memory loss and disorientation
- Early behavioral problems

*Gijselinck et al.,* *Neural 2015*
Large-scale genetic screen of $TBK1$

- 2538 patients: 1873 FTD, 111 FTD-ALS and 554 ALS
- 2864 control individuals

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2017$

Conclusion $TBK1$ loss-of-function

- PTC mutations $\rightarrow$ loss-of-transcript
- Inframe deletions $\rightarrow$ loss-of-protein
  - Belgian FTD-ALS family: $TBK1$ p.Glu643del
- Some missense mutations $\rightarrow$ loss-of-function

- Pathology: TDP-43 type B

- Mutation frequency for $TBK1$ LoF mutations
  - 0.7% overall (19/2538)
    - 0.4% in FTD
    - 1.3% in ALS
    - 3.6% in FTD-ALS patients
Variability in onset age and disease penetrance

FTD genetic diagnostics, where are we today?

- Up to 43% of FTD patients have a positive family history
  - 10-27% autosomal dominant
- Known genes explain
  - 45% - 50% of familial FTD
  - 20% of all FTD
  - Mutations also regularly found in 'isolated' patients
    - small families
    - reduced penetrance
    - FTD-ALS spectrum phenotypes

Explained: 47%
Unexplained: 53%
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