Molecular Genetics & Neuropathology of Frontotemporal Dementia

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Neurodegenerative diseases

- slow, progressive, permanent loss of neurologic function.
- cause unknown.
- sporadic, familial or inherited.
- degeneration of specific brain region → clinical syndrome.
- pathology: abnormal accumulation of disease specific protein.
Neurodegenerative diseases

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Neurodegenerative diseases

disease | gene | biochemistry | protein deposits
---|---|---|---
early-onset fAD | •APP | •β-amyloid | ↑ senile plaques
| •PS1 | | |
| •PS2 | | |
late-onset fAD | •ApoE | | |
Frontotemporal dementia (FTD)

Clinical syndrome:
- progressive change in behaviour, personality and/or language.
- often associated with movement disorder (parkinsonism or ALS).
- 25-50% have family history, most autosomal dominant.
Neuropathology of FTD

- selective atrophy of frontal & temporal lobes
Neuropathology of FTD

- Selective atrophy of frontal & temporal lobes
Neuropathology of FTD

Microscopic pathology:
- Pick’s disease
- corticobasal degeneration (CBD)
- progressive supranuclear palsy (PSP)
- frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U)
- FTD with ALS
- atypical FTLD-U
- neuronal intermediate filament inclusion disease
- basophilic inclusion body disease
- dementia lacking distinctive histopathology (DLDH)
Neuropathology of FTD

Microscopic pathology:
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Protein:
- tau
- TDP-43
- FUS
- none
Neuropathology of FTD

- aFTLD-U
- NIFID
- BIBD

FTLD-TDP
- FTLD-U
- FTD+ALS

FTLD-FUS

FTLD-tau
- PiD
- CBD
- PSP

other
Tau protein

- a microtubule associated protein.
- gene on chromosome 17.
- forms cytoskeleton of neurons, important for axonal transport.
- abnormal tau accumulates in neurons and glial cells (inclusion bodies).
Pick’s disease

- usually presents as FTD.

- Pick bodies.
Corticobasal degeneration (CBD)

- May present as parkinsonism or FTD.

- Abnormal accumulation of tau in neurons and glia.

- Cortex, subcortical grey and white matter.
Progressive supranuclear palsy (PSP)

◆ most often presents as parkinsonism but may cause FTD.

◆ abnormal accumulation of tau in neurons and glia.

◆ cortex, subcortical grey and white matter.
MAPT mutations

- 44 mutations in >130 families.
- 10-20% familial FTD.
- FTD + parkinsonism.
- FTLD-tau pathology.
FTLD with ubiquitinated inclusions

- originally identified as cerebral pathology in patients with ALS and dementia.
- now recognized as most common FTD pathology.
- neuronal inclusions only recognized with immunohistochemistry for ubiquitin (non-specific).
- TDP-43 recently identified as abnormal (ubiquitinated) protein in most FTLD-U and ALS.
abnormal protein deposits in neurons.

stain for ubiquitin but not tau or other proteins.
- nuclear protein involved in mRNA processing.
- abnormally fragments accumulate in neurons and glia.
FTLD-U subtypes

- neurites & NCI in layer II.
- 32%.
- bvFTD or PNFA.
- NCI in neocortex.
- 20%.
- ALS-FTD.

• neurites in layer II.
• 27%.
• SD.
• NCI in HC.
• 22%.
• bvFTD or ALS-FTD.
GRN mutations in FTD

- progranulin = secreted neuronal growth factor.
- GRN gene on chromosome 17.
- 68 mutations in 226 families.
- all cause ↓ functional PGRN.
- 12-25% of familial FTD.
- clinical = bvFTD or PPA, no ALS.
- pathology = FTLD-TDP type 1 with neuronal intranuclear inclusions.
Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members

Nicole Finch,† Matt Baker,† Richard Crook,† Katie Swanson,† Karen Kurtz,‡ Rebecca Suttees,† Gina Bisceglio,† Anne Rovelet-Lecrux,§ Bradley Boeve,∥ Renald C. Petersen,∥ Dennis W. Dickson,† Steven G. Younkin,† Vincent Desnuescourt,† Julia Crook,† Neill R. Graff-Radford‡ and Rosa Radesmaiers†
FTD/ALS linked to chromosome 9

- multiple families reported with combination of FTD and ALS showing genetic linkage to region on chromosome 9.

- FTLD-TDP type 3 and ALS.
Inclusion body myopathy with Paget’s disease of bone and FTD

- rare autosomal dominant syndrome.
- myopathy (80%), Paget’s disease of bone (50%), early-onset FTD (30%).
- mutations in the gene for valosin-containing protein (VCP).
- FTLD-TDP type 4.
**TARDBP** mutations in ALS

- 38 missense mutations in 78 families.
- ~3% FALS and ~1.5% SALS.
- clinically and pathologically typical ALS.
- rare mutations in familial and sporadic FTD +/- ALS.
Neuropathology of FTD

- aFTLD-U
- NIFID
- BIBD
- DLDH
- CHMP2B

FTLD-TDP
- FTLD-U (type 1, 2, 3)
- FTD+ALS
- GRN
- VCP
- chrom 9p

FTLD-tau
- PiD
- CBD
- PSP
- MAPT

other
Mutations in the \textit{FUS/TLS} Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis


Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6

Caroline Vance, Boris Rogelj, Tibor Hortobagyi, Kurt J. De Vos, Agnes Luni Nishimura, Jemeen Sreedharan, Xun Hu, Bradley Smith, Deborah Rubly, Paul Wright, Jeboon Ganesalingam, Kelly L. Williams, Vimeeta Tripathi, Safa Al-Saraj, Ammar Al-Chalabi, P. Nigel Leigh, Ian P. Blair, Garth Nicholson, Jackie de Belieerde, Jean-Marc Gallo, Christopher C. Miller, Christopher E. Shaw.

\textbf{Science, Feb. 27, 2009}

\begin{itemize}
  \item \textbf{fused in sarcoma / translocated in liposarcoma.}
  \item RNA/DNA binding protein with similar function to TDP-43.
  \item mutations $\rightarrow$ $\sim$4\% FALS and <1\% SALS.
  \item pathology = TDP-43-negative, FUS-positive inclusions.
\end{itemize}
Neuropathology of FTD

- aFTLD-U
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- FTD+ALS
- GRN
- VCP
- chrom 9p

FTLD-tau
- PiD
- CBD
- PSP
- MAPT

Other

FUS?
FTLD-FUS

“Atypical” FTLD-U

Basophilic inclusion body disease

Feuronal intermediate filament inclusion disease

Most tau/TDP-negative FTLD is FUS+.
FTD linked to chromosome 3

- Single Danish family with FTD caused by mutation in CHMP2B gene.

- Ubiquitin+ inclusions do not label for tau, TDP-43 or FUS.
Neuropathology of FTD

- aFTLD-U
- NIFID
- BIBD
- (FUS)

FTLD-FUS

FTLD-TDP
- FTLD-U (type 1, 2, 3)
  - FTD+ALS
  - GRN
  - VCP
  - chrom 9p
  - (TARDBP)

FTLD-tau
- PiD
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other
- DLDH
- CHMP2B