Frontotemporal dementia: clinical syndromes and pathobiology

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Frontotemporal Dementia (FTD)

• In 1892, Arnold Pick describes a focal neurodegenerative condition involving the frontal and anterior temporal lobes
• Alois Alzheimer, Pick’s student, observes that some patients harbor argyophilic “Pick bodies” unlike the neurofibrillary tangles of AD

Take home points

• FTD is a common and under-diagnosed form of early age-of-onset dementia strongly linked to ALS
• FTD refers to a canon of unique clinical syndromes that (1) reflect focal network-based neurodegeneration and (2) generate a pathological DDX (length varies by syndrome)
• FTLD refers to a spectrum of FTD-associated pathological entities: FTLD-tau, -TDP-43, and -FUS; these misfolded proteins may act as prion-like “strains” that seed network-based disease spread
• Most FTD is sporadic, but the genetics of familial FTD are helping to shed light on disease pathogenesis

FTD Prevalence

Common cause early age-of-onset dementia
• 1:1 with AD 45-64 years (Ratnavalli et al., Neurology 2002)
• More common than AD when symptoms begin before age 60 years (Knopman et al., Neurology 2004)
• Broader FTD spectrum, including CBD/PSP and ALS, even more common

Less common in older patients?
• 25% had symptom onset after 65 in one FTLD series (Barborie 2011)
• May present with less focal cortical atrophy and a higher rate of hippocampal sclerosis (Barborie 2012)
Frontotemporal lobar degeneration (FTLD)

FTLD-tau

FTLD-TDP*

FTLD-FUS

FTLD-3

CHMP2b

Pick's
3R tau

CBD
4R tau

PSP
4R tau

Type A (PGRN)
(C9orf72)

Type B
(C9orf72)

TARDP?

aFTLD-U

BIBD

Type C

Type D

VCAP

???

FUS

FTDP-17

MAPT

Other
CTE, AGD, MST

Type C

Type D

VCAP

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FUS

FTDP-17

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Other
CTE, AGD, MST

Type C

Type D

VCAP

???
Patient D.C.

58 y.o. business executive with 2 high school children

Brought in by wife for increasingly uncharacteristic behaviors:

- No longer interested in son’s school and sports activities
- Rises to board aircraft during each boarding call
- Repeatedly takes out wallet to illustrate the shape of Kansas
- New penchant for sweets; overeating in general, gains weight

Language, memory, navigation, skilled movements all normal.
Frontotemporal lobar degeneration (FTLD)

- svPPA
- nfvPPA
- FTD-MND
- CBS
- PSPS

Frontal Insula (FI)

bvFTD due to Pick’s Disease (FTLD-tau)

- H & E
- GFAP

Pick’s
3R tau
4R tau
3R tau
Pick’s
FTDP-17 (APAP)
Tau NOS
MST/AGD
Type A
(FGRRN)
Type B
(C9ORF72)
Type C
Type D
(VCP)
FTLD-U
NIFID
???
(FUS)

FTLD-tau
FTLD-TDP*
FTLD-FUS
FTLD-3
(FTMD2b)

Type A
Type B
Type C
Type D

- bvFTD
- svPPA
- nfvPPA
- FTDD-MND
- CBS
- PSPS

*Mackenzie harmonized scheme, 2011
In healthy subjects, baseline low frequency fMRI BOLD signal fluctuations in Right FI are correlated with:

- Frontal pole (Frontal pole)
- ACC (Anterior Cingulate Cortex)
- SLEA (Sphenolateral Eminence)
- VSP (Ventral Striatum Putamen)
- Hypothalamus
- Lat OFC (Left Orbitofrontal Cortex)
- Right OFC (Right Orbitofrontal Cortex)

Intrinsic connectivity measured with fcMRI

3T fcMRI
19 healthy controls

“Salience Network” (Intrinsic connectivity network)

Seeley et al J Neurosci 2007

Structural covariance measured with “scMRI”

Across healthy subjects, gray matter volume in Right FI is correlated with:

- S1 (Primary somatosensory cortex)
- S2 (Secondary somatosensory cortex)
- S3 (Somatic motor cortex)
- S4 (Supplementary motor area)
- S5 (Sensory motor cortex)
- S6 (Primary motor cortex)
- S7 (Secondary motor cortex)

“Salience Network” (Intrinsic connectivity network)

1.5T T1 MRI
65 healthy controls
bvFTD atrophy pattern
VBM, patients < controls
N = 24

Functional connectivity
Right FL seed
fMRI, healthy controls
N = 19

Structural covariance
Right FL seed
VBM, healthy controls
N = 65

Overlap
Seeley et al Neuron 2009

bvFTD atrophy pattern
VBM, patients vs. controls
N = 24

Which regions serve as a gateway to the network?

bvFTD pattern
N seed-based maps

bvFTD-vulnerable “salience network”

Does a node’s connectivity predict its vulnerability?

bvFTD pattern
Healthy correlation matrix
Healthy network graph

Zhou et al 2012
Patient C.N.

- 47 y.o. RH former foundation group leader with no complaints other than “mild memory problems”

Brought in by wife for 10-15 years slowly progressive behavior change:
- Brought home books on death and dying to read to 3 y.o. daughter at bedtime
- Took up computer Solitaire, counted white cars
- Failed to initiate job search when laid off
- Urination ritual: To and from BR x 4 QHS
- Mild verbal memory impairment; no executive, language, or motor deficits
Patient C.N.

bvFTD due to aFTLD-U (FTLD-FUS)

Working model: anatomical convergence
Different diseases, same onset, same spread

Tau, TDP-43, or FUS

bvFTD

Pick's (Tau)

TDP-43

Type B

aFTLD-U

(FUS)
Early psychiatric mis-diagnoses

• Bipolar illness
• Schizophrenia
• Major Depression
• Addiction Disorder (multiple types)
• Personality Disorders
  – Borderline
  – Passive-aggressive
  – Antisocial
  – Schizoid
  – Schizotypal

Patient A.T.

61 y.o. high school counselor with 5 years of word-finding and word recognition difficulties. Asks husband to explain words in the newspaper.

Later:
• Approaches strangers for idle conversation
• Obsessed with vitamins, takes 15/day
• Prefers sweets and chips, gains 10#

Patient A.T.

Exam:
• Surface dyslexia, questions meaning of individual words
• Fluency and repetition spared until late
• No motor or visuospatial/ navigation deficits

Relationship between bvFTD anatomy and psychiatric disease

Imaging (VBM, PET) meta-analyses

1 bvFTD

2 bipolar disorder

3 schizophrenia
Object knowledge regresses to category prototypes

“horse”

“dog”

Semantic variant PPA due to FTLD-TDP, Type C

H & E

TDP-43

- Long, swollen, dystrophic neurites in superficial > deep layers: Type C
- Relatively few neuronal cytoplasmic inclusions, except in dentate gyrus and nucleus accumbens

Frontotemporal lobar degeneration (FTLD)

- bvFTD
- svPPA
- svPPA
- FTD-MND
- CBS
- PSP

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FTLD-TDP

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FTLD-3 (TARDP?)

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CBD 4R tau

PSP 4R tau

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Type B (C9ORF72) (TARDP?)

Type C

Type D (VCP)

eFTLD-U

BIBD

NIFID

???

*Mackenzie harmonized scheme, 2011

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- Long, swollen, dystrophic neurites in superficial > deep layers: Type C
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Semantic Variant PPA

R Insula
L Insula
Anterior Cingulate
Orbital Frontal
R Amy/Tpole
L Amy/Tpole
Orbital Frontal

Right
Left

Rosen et al 2002

Semantic-appraisal network: decoding and evaluating context

vmPFC
TPole
vent striatum
VTA


Network-based neurodegeneration

Syndrome-specific regional atrophy patterns: patients vs. controls

AD
bvFTD
svPPA
ntvPPA
CBS
R Amy/Tpole
L TPole

"atrophy" = seed ROI

Time (sec)

Single subject

Seeley et al, Neuron 2009

Does each vulnerable network harbor a key epicenter or epicenters?
Relationship between intrinsic connectivity in health and vulnerability to disease

Connectomic prediction of regional vulnerability
Connectomic prediction of regional vulnerability

Healthy connectivity graph

Intrinsic functional connectivity

AD pattern  bvFTD pattern  SD pattern  PNFA pattern  CBS pattern

Shortest path to epicenter in health

ROIs in AD pattern  bvFTD pattern  SD pattern  PNFA pattern  CBS pattern

Connectomic prediction of regional vulnerability

Healthy connectivity graph

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FTLD-TDP

FTLD-FUS

FTLD-3 CHMP2b

Pick’s 3R tau

CBD 4R tau

PSP 4R tau

Type A (C9orf72)

Type B (C9orf72)

Type C

Type D (VCP)

Type U

NIFID

???

FTDP-17 (MAPT)

Other CTE, AGD, MST

FTLD-U

BIBD

FTDP-17 (MAPT)

Type A (PGRN)

Type B (C9orf72)

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Type U (C9orf72)

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???
A midbrain-anchored network vulnerable in progressive supranuclear palsy

ROI seed = rostral midbrain tegmentum

Reduced network connectivity in PSP-S

Gardner et al, Annals of Neurology 2013

Frontotemporal lobar degeneration (FTLD)

FTLD-tau

FTLD-FUS

FTLD-TDP

FTLD-3

CHMP2b

PSP

CBD

PSP

FTDP-17

(FTDP-17)

Other

CTE, AGD, MST

Pick's

3R tau

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4R tau

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(TARDP?)

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BIBD

BIBD

???

(VCP)
**C9ORF72**

- **Gene/mutation:** GGGGCC repeat expansion (normal 2–23, abnormal 400–1600)
- **Epi:** 12% all FTD, 24% familial ALS or familial FTLD (> 50% familial FTD at UCSF)
- **Syndrome:** bvFTD, FTD/MND, ALS, less often PPA/PSP/CBS/HD
- **Path:** TDP-43 type B (less often A or U), dipeptide repeat protein inclusions
- **MRI:** symmetric atrophy dorsolateral, medial and orbital frontal, insular, anterior temporal, parietal, occipital, thalamus, +/- cerebellum

### RNA-mediated Neurodegeneration

- **RNA noncoding regions; toxic gain-of-function**
  - *C9ORF72*
  - Myotonic dystrophy
  - Fragile X-tremor ataxia syndrome
- Transcriptional alterations generate sense and antisense repeat transcripts, sequester mRNA-associated protein complexes; lead to aberrant mRNA splicing and processing

*Todd, Paulson, Ann Neurol 2010*

#### Nuclear RNA Foci in Brain and Cord

- **A** cortex expanded repeat
  - probe: (GGCCCG)$_n$
- **B** spinal cord expanded repeat
  - probe: (GGCCCG)$_n$
- **C** cortex normal repeat
  - probe: (GGCCCG)$_n$
- **D** spinal cord expanded repeat
  - probe: (CAGG)$_n$

*Dejesus-Hernandez et al., Neuron 2011*

#### Anti-C9RANT immunoreactivity is specific to C9FTD/ALS

Some mRNA translated (non-ATG) into dipeptide repeat proteins that aggregate in cytoplasm

*Ash et al., Neuron 2013*
**MAPT**

- **Gene/Mutation:** Microtubule associated protein tau, Chr 17.
  - In most cases, intron mutation, splice in exon 10, or mutations in exons 9–13
- **Epi:** 3–14% all FTD, 17% familial FTD at UCSF
- **Syndrome:** Usually bvFTD, PSP preceded by depression, addiction, mood instability
- **Path:** Unclassifiable tauopathy
- **MRI:** Symmetric, anteromedial temporal lobes, anterior insula, OFC, fornix

**GRN**

- **Gene:** GRN, encoding progranulin, Chr 17
- **Epi:** 1–16% all FTLD, 8% familial FTLD at UCSF
- **Syndrome:** Usually bvFTD, PNFA, or less likely CBS. 10% > 70 without symptoms
- **Path:** TDP-43 type A (NCIs and threads, NII)
- **Sx/Signs:** mean onset 62, episodic memory impairment, parkinsonism
- **MRI:** more dorsal asymmetric atrophy affecting inferior frontal, temporal, inferior parietal lobes, medial thalamus, and basal ganglia

**Progranulin**

- Secreted glycoprotein with growth factor-like and immunomodulatory activities
- TNF receptor antagonist-like activity; also binds Sortilin receptor→master regulator of inflammation?
- Contains 7 full and one ½-length granulin domains, which are released following proteolytic cleavage
- > 60 pathogenic GRN mutations reported in FTD, all expected to result in haploinsufficiency

<table>
<thead>
<tr>
<th></th>
<th>C9orf72</th>
<th>MAPT</th>
<th>GRN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Dx</strong></td>
<td>56</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>bvFTD, ALS, or FTD-ALS</td>
<td>bvFTD, PSP, CBD</td>
<td>bvFTD, nfvPPA, CBS, AD</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Mild, symmetric, dorsal, thal &amp; cereb</td>
<td>Symmetric ATL-OFC</td>
<td>Asymmetric fronto-parietal, temporal in some</td>
</tr>
<tr>
<td><strong>Unique clinical</strong></td>
<td>Postural tremor, ALS, smoldering psychiatric prodrome</td>
<td>Suicide, addiction</td>
<td>Posterior deficits: overlap with AD</td>
</tr>
<tr>
<td><strong>Unique biology</strong></td>
<td>RNA-mediated, RAN translation</td>
<td>3R/4R tauopathy, tau dysfunction</td>
<td>Haploinsufficiency</td>
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Lingering questions and challenges

- Anatomical convergence = pathological heterogeneity for a given syndrome. Unifying principle?

- Anatomical divergence = syndromic heterogeneity for a given pathology. Protein strains?

- Variable age-of-onset and disease kinetics. Background genetics? Strain diversity?

Progranulin: A New FTD Gene

- Hutton & Van Broeckhoven independently found PRG mutations in families linked to 17q21 (Cruts 2006; Baker 2006)

- 5–10% of all FTLD cases and 23% of familial cases seen at the Mayo Clinic have mutations (Gass 2006)

- 24% of these cases have primary language dysfunction (others with FTD, CBS, AD picture)

- Family members with the same mutation can have strikingly different phenotypes (FTD vs. PNFA) (Snowden 2006)

Tau Mutations

- 44 mutations, 132 families

- Exon mutation or deletion exon 9–13 (maybe 7) causes tau loss of function

- Introns increase 4R tau

- Glial/neuronal tau inclusions

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Stanford University

Michael Greicius

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Menlo Park

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**Progranulin**

- Double function: PGRN: Neuron growth anti-inflamm (neutrophil, IL-10) Granulin: inflam
- Two receptors: sortilin (neuronal), TNF α (neuronal, microglial, neutrophils)
- Tightly regulated
  - SLPI (block PGRN breakdown), elastase
- Master regulator of inflammation?

**Sporadic CBS due to FTLD-TDP, Type 3**

- Copious short, angulated neurites in superficial > deep layers
- Numerous round or crescentic neuronal cytoplasmic inclusions
- Occasional “cat’s eye” neuronal nuclear inclusions

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**Patient D.C.**

58 y.o. business executive with 2 high school children

Brought in by wife for increasingly uncharacteristic behaviors:

- Disinterest in kids’ school and sports activities
- Speaking out of turn, commenting on strangers’ weight or hairstyle
- Circles the kitchen island 3 times (counterclockwise) upon entering room
- New penchant for sweets; overeating in general

Language, memory, navigation, skilled movements all normal. Denies low mood, sleep disturbance, life stressors.
Premotor cortex, TDP-43 antibody

bvFTD-MND, Stage 1, Right FI, stained for TDP-43

MR voxel-based morphometry

FTD and SD vs. controls

Rosen et al, Neurology
Tau immunohistochemistry shows abundant cortical and subcortical white matter tauopathy

Astrocytic plaques, neuropil threads, ballooned tau-immunoreactive Layer 5 neurons, & coiled bodies

Also seen: tufted and thorny astrocytes in numerous cortical and subcortical regions (not shown)

UCSF Neurodegenerative Disease Brain Bank
Patients with known mutations (n = 25)

Kim et al, Cerebral Cortex 2011
S. Gaus, unpublished
FTD Genetics

- Genetic (40%) sporadic (60%)
  - Predominantly FTD, CBD or PSP (Chromosome 17)
    - Tau – exon/intron mutations tau aggregates
    - Progranulin – nonsense mutation nuclear TDP-43
  - ALS and FTD
    - Chr 1 – TDP-43 mutations (uncommon)
    - Chr 9 – C9ORF72 (common)
    - Chr 9 – Valosin (TDP43) FTD with Paget’s IBM/ALS
    - Chr 16 – FUS (still only ALS)
      - X-linked – ubiquilin-2 (uncommon)
    - Rare!
      - FTD – Chromosome 3 CHMP2b
      - ?FTD with bone tumors – EXT2 – Chromosome 9

Frontotemporal dementia

- Behavioral variant
- "Language" variants
- FTD-MND

- Semantic Dementia
- Progressive Nonfluent Aphasia

RTLV LTLV

Visit #1 Visit #2 Visit #3

Henry et al 2014
**Patient DM**

- 56-year-old right-handed woman referred for progressive reading difficulties and falls
- First symptoms at age 50: "eyes tired" when reading, trouble navigating stairs, fell down an escalator
- Following 6 years: almost daily falls, uncontrollable laughter/crying, difficulties with swallowing
Single patient imaging-pathology correlation analysis

36 months prior to death

56 y.o. woman with PSP

Single patient connectivity to rostral midbrain < 24 age-matched healthy women

Dissected tissue blocks
<table>
<thead>
<tr>
<th>Regions of interest to match dissected tissue blocks</th>
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<td>PostCG PreCG STN</td>
<td>rMT intrinsic connectivity: Which pathological events disrupt connectivity?</td>
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<td>Cortex Limbic BG Cereb/brainstem SC</td>
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Which pathological events disrupt connectivity?

- Tau burden
- Astrogliosis
Tau burden predicts rMT connectivity disruption

\[ \rho = 0.6, p = 0.001 \]

Composite tau burden

Cortical nucleus

bvFTD involves distributed salience network connectivity disruptions

Zhou et al. Brain 2012