Keynote: Frontotemporal Degeneration: Overview, Trends and Development
AFTD Annual Meeting Salt Lake City April 12, 2013

FRONTOTEMPORAL DEGENERATION: OVERVIEW, TRENDS AND DEVELOPMENTS

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UNIVERSITY OF UTAH HEALTH CARE

Talk Outline

- Definitions – FTD 101
- The complicated story of FTD
- Recent advances
  - New clinical diagnostic criteria
  - Brain imaging
  - Proactive care
- Investing in family health history

Definitions

Cognitive complaint or symptom ≠ cognitive deficit

Deficit is a medically significant problem identified during an examination

Definition of Mild Cognitive Impairment

A syndrome with many causes

- Objective evidence of an acquired deficit in one or more cognitive domains insufficient to impair everyday activities.
- Prognosis variable
- Mild cognitive impairment involving memory (amnestic MCI) is a risk factor for Alzheimer's disease dementia; approximately 15%/yr
- This classification also can apply to very mild forms of other diseases leading to dementia

Definition of Dementia

A syndrome with many causes

- A decline in intellectual function (2 or more cognitive domains) from a previous level of performance sufficient to impair daily activities in someone who is alert and cooperative

Dementia ≠ Alzheimer's disease

Alzheimer's Disease Dementia

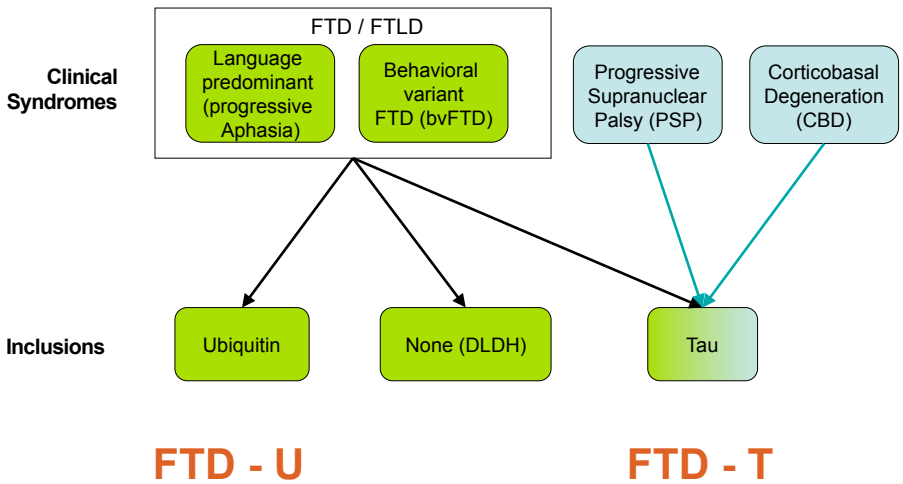
- Insidious onset of gradual, progressive dementia
- Memory loss usually initial and most prominent symptom
- No focal weakness or sensory loss
- Gait normal and continent until late in the illness
- Familial in about 10%, several genetic defects
- Validated criteria available

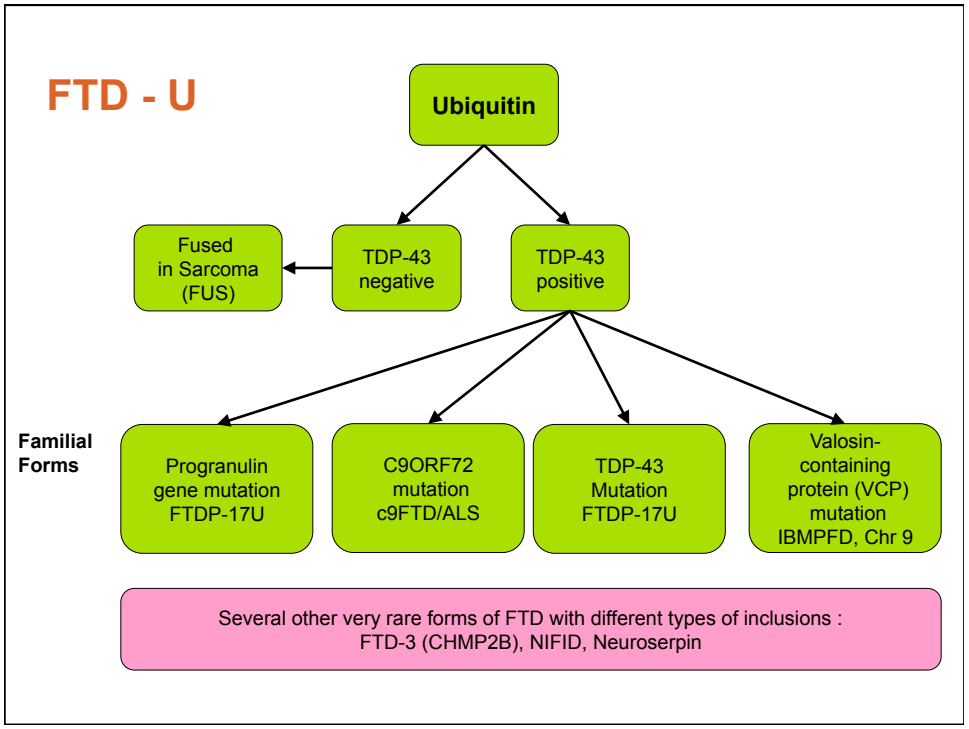
Frontotemporal Degeneration (FTD)

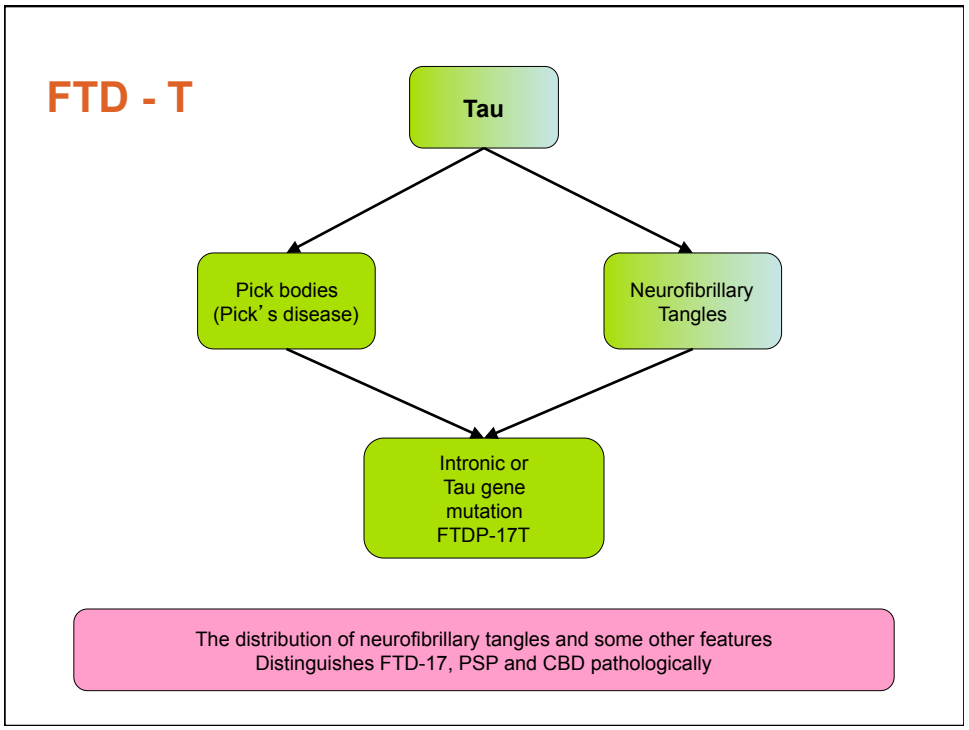
- Insidious onset of progressive dementia
- Disturbing behavior and speech problems most prominent, less evident memory loss
- Perseveration, decreased verbal fluency
- Typical behavioral changes including apathy, unrestrained and inappropriate social conduct
- Memory loss often not prominent; AD screening tests may be insensitive
- May be associated with motor neuron disease
- 2nd most common dementing disease if age <65

The Complicated Story of Types of FTD

Two "Flavors" of FTD







New Clinical Diagnostic Criteria

Language Impairment FTD (Progressive Aphasia)

- **Gorno-Tempini et al. Neurology 2011;76:1006-1014**

Behavioral Variant FTD

- **Rascovsky et al. Brain 2011;134:2456-2477**

Progressive Aphasia Classification

- Agrammatic variant (non-fluent)
- Semantic variant (impaired naming and single word comprehension)
- Logopenic variant (impaired repetition and single word retrieval)
- Further modifiers
  - Imaging supported
  - With definitive pathology

Gorno-Tempini et al. Neurology 2011;76:1006-1014

Behavioral Variant FTD

- Definite bvFTD – typical clinical features and genetic or autopsy confirmation
- Probable bvFTD – requires imaging confirmation
  - FTD phenocopy – no imaging abnormalities, has a better prognosis
- Possible FTD – no imaging abnormalities or other features decreasing diagnostic confidence

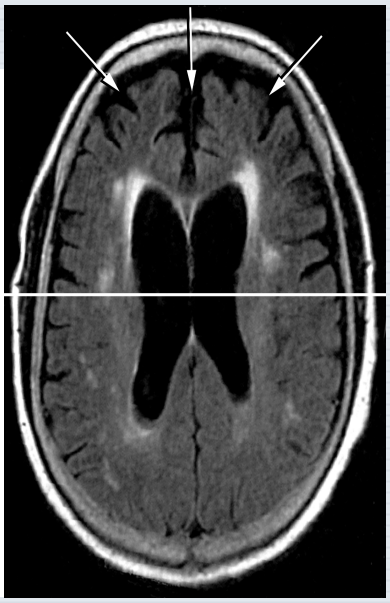
Rascovsky et al. Brain 2011;134:2456-2477

Advances in Molecular Imaging

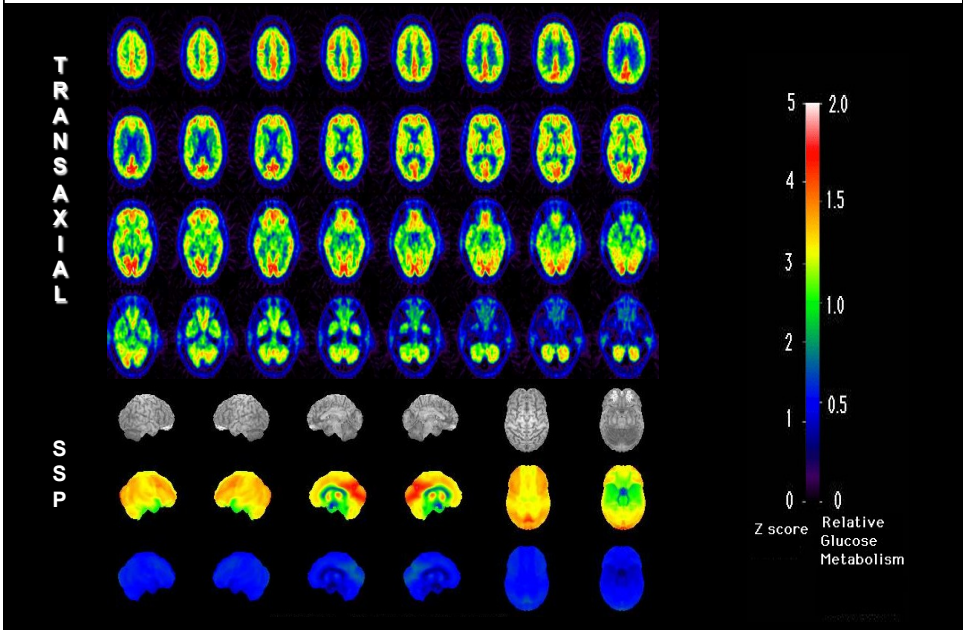
MRI scans
FDG-PET imaging
Amyloid PET imaging

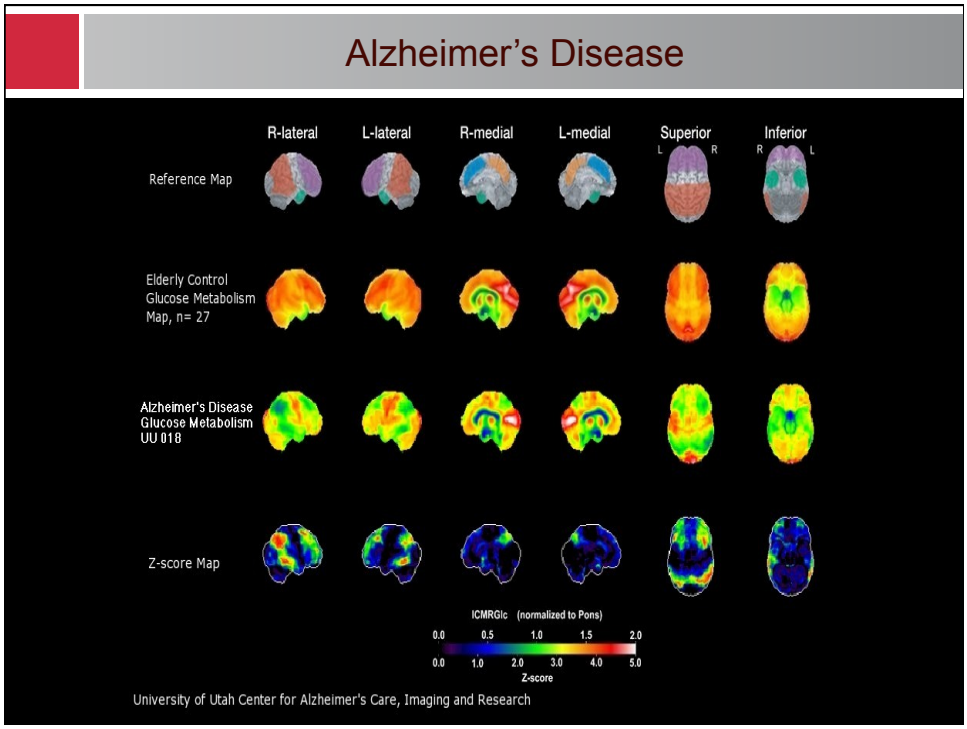
MRI Scan in a Patient with FTD

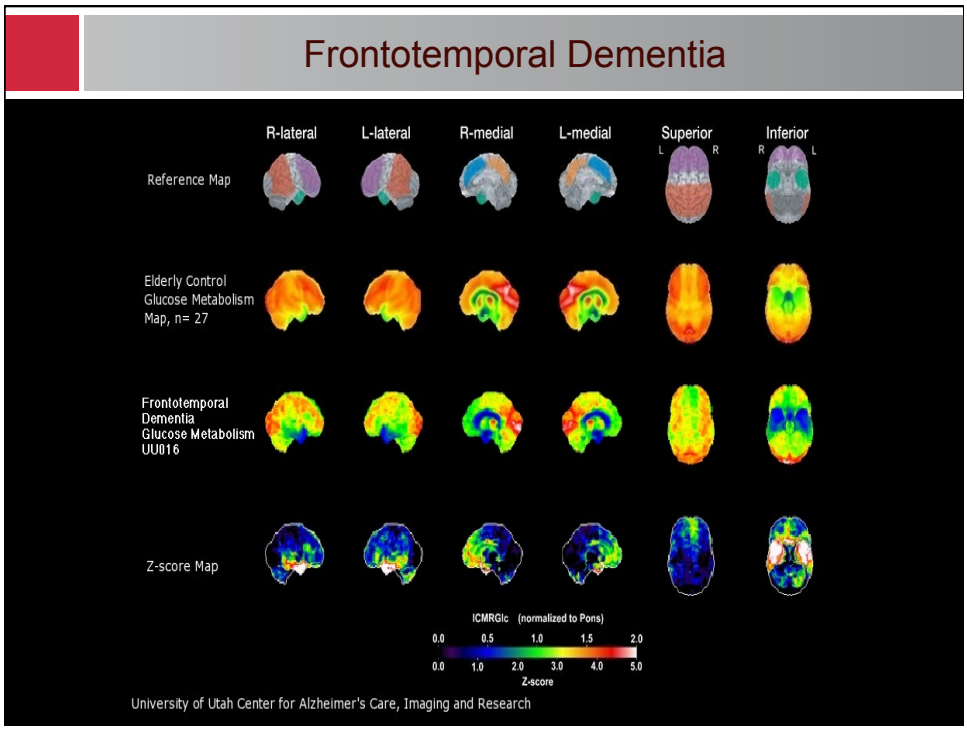
Compare size of sulci and ventricles in the anterior and posterior half of the brain



Powerful Quantitative Individual Analysis Methods





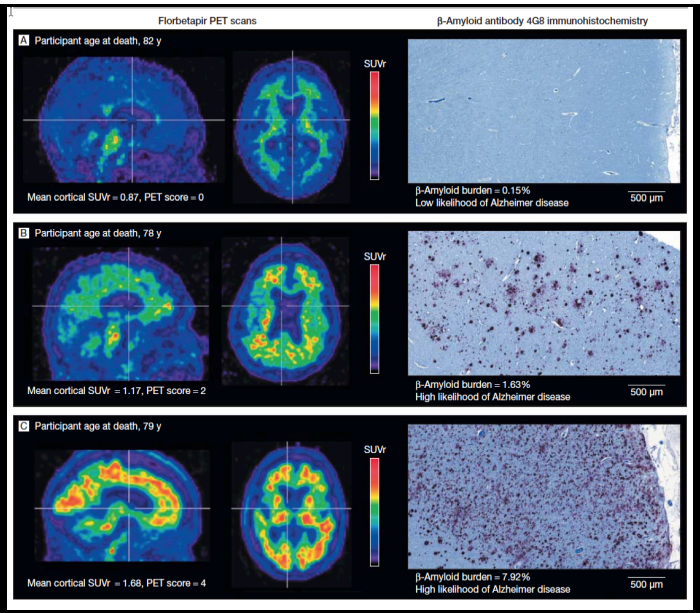


Typical Patterns of Atrophy and Hypometabolism with FTD Mutations

Type of Mutation	Predominant area affected	Bilateral or asymmetric involvement	Other features
Tau	Anteromedial temporal	symmetric	Frontal sometimes spared
Progranulin	Frontal and temporal	asymmetric	
C9orf72 expansion	frontal	symmetric	Parietal also involved
Sporadic	frontal +/or temporal	either	Lateral temporal and parietal spared

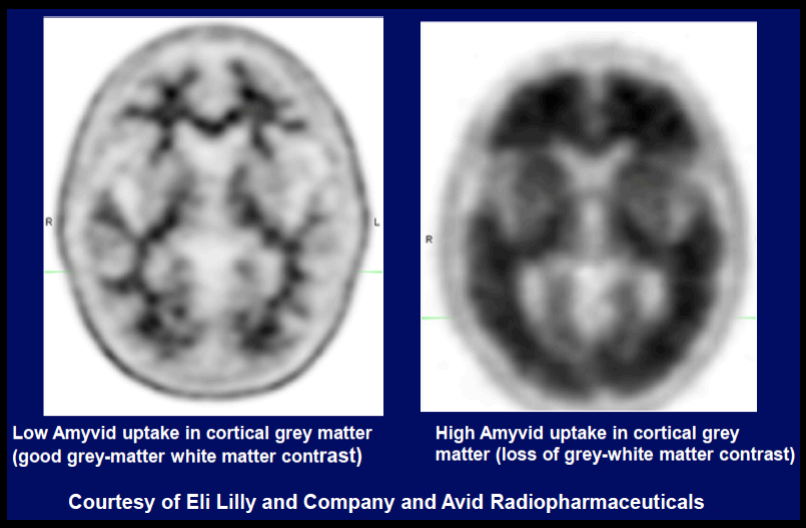
Whitwell et al. Brain 2012; 135:794-806

Correlation of Florbetapir and AD pathology



Clark JAMA 2011;305:275-283

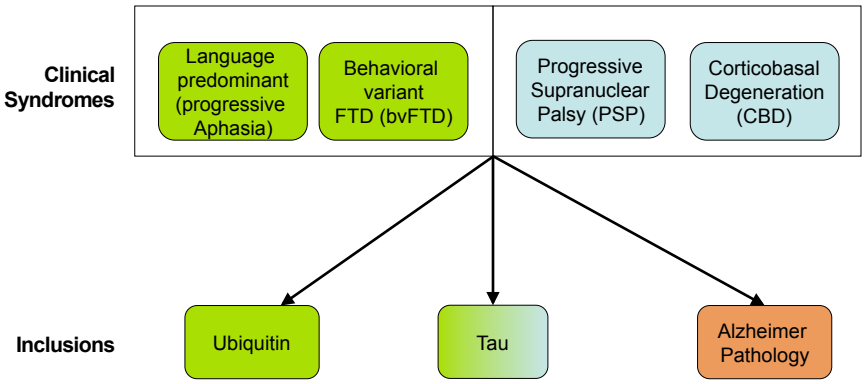
Florbetapir Amyloid PET



Amyloid PET FDA Labeling

- "to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline."
- "A negative scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD"
- "A positive scan indicates moderate to frequent amyloid neuritic plaques…but may be present in ... older people with normal cognition"

FTD can be misdiagnosed as AD, but …



Rarely Alzheimer's can mimic FTD
These now can be identified with amyloid PET, not just at autopsy

Proactive Care

Integrates medical care with health education, social work who share information and treatment goals

Individualizes and streamlines care

Education and planning begin at point of evaluation

Players on the PDC Team

- Physician
  - Cause of impairment
  - Education prescription
- Health Educator
  - Self-management education
- Social Worker (Family support)
  - Unified family plan of progressive support

University of Utah
Dept. of Neurology Cognitive Disorders Clinic
Center for Alzheimer's Care, Imaging & Research

Name
MRN
Date

MD NAME

DIAGNOSIS: _____

PDC STATUS: ORIENTATION WITH PDC WITHOUT PDC NON-STUDY

Accompanying Names & Relationships: _____

_____

EDUCATION PRESCRIPTION

RISK ASSESSMENT SECTION

LEGAL/FINANCIAL
Risk Level: High Medium Low
- Adv Health Dir in EMR — Yes **No**
- Financial implications of care — Yes **No**

❑ Advanced Health Care Directive
❑ Financial Aspects of Care

SAFETY
Risk Level: High Medium Low
- Driving despite disability or AMA — **Yes** No
- Driving ability may be impaired — **Yes** No
- Wandering/becoming lost — **Yes** No
- Other safety risks — **Yes** No
- Specify: _____

❑ Driveability Program
❑ Alternative Transportation Options
❑ Safe Return Program

PHYSICAL DEBILITY AND FALLS
Risk Level: High Medium Low
- Exercise daily (1 mile/30 mins) — Yes **No**
- Sufficient and healthy diet — Yes **No**
- Maintaining weight — Yes **No**
- Falling <1x month — Yes **No**

❑ Exercise Plan
❑ Meals on Wheels / Nutrition Plan

MOOD AND UNNECESSARY FUNCTIONAL DECLINE
Risk Level: High Medium Low
- Mentally stimulating activities — Yes **No**
- Recreational activities — Yes **No**
- Achieving functional potential — Yes **No**
- Medical issues controlled — Yes **No**

❑ Cooperative Activities

SOCIAL ISOLATION
Risk Level: High Medium Low
- Socially engaged 3x weekly — Yes **No**
- Current supervision adequate — Yes **No**
- Weekly contact w/ 3+ people — Yes **No**

❑ Attend Senior or Adult Day Center
❑ Expand Social Network

CARE CRISES
Risk Level: High Medium Low
- Knowledgeable about disease — Yes **No**
- Plan for unexpected (short & long) — Yes **No**
- Normal sleep — Yes **No**

❑ Home Health / Respite Services
❑ Support Groups & Newsletters
❑ Sleep Hygiene
❑ Disease Information

EDUCATION SECTION

www.utahmemory.org
❑ Advocacy Association _____
❑ Research **(Memory Study Line: 801-587-7888)**
❑ PET Scan
❑ Gift to Life
❑ Memory Skill Book/Calendar

Other: _____

FOLLOW-UP PLAN

_____

HEALTH EDUCATOR: 801-585-9924

BILLED TIME: _____ Minutes

Version 8/31/10

Investing in Family Health History

- Brain autopsy
  - Clinical examination not a brain donation
  - Definitive information now, and tissue for review in the future (Gift to Life outpatient autopsy planning)
- Family-oriented DNA banking
  - Clinical banking, not a research donation
  - Families have control, make deposits and withdrawals and send for testing (e.g. Prevention Genetics)

More About FTD Genetic Errors

- Tau
  - Structural protein, also affected in AD
  - Normally an equal balance of 3R and 4R tau an imbalance causes FTD
- Progranulin
  - Growth factor that sustains frontal and temporal lobes
  - Misense mutation interferes with function
- C9orf72
  - Controls transcription of proteins from RNA
  - Expansion of repeat sequences in gene

C9orf72 Genetic Error Mechanism

- Expansion of hexanucleatide repeat sequences in gene (GGGGCC)
  - Number of repeats is sometimes so large they are impossible to measure by usual techniques
- Abnormal proteins accumulate from the products of these expansions
  - Not produced by conventional transcription
  - Repeat-associated non-ATG (RAN) translation
  - C9RANT insoluble protein aggregates TDP-43 - inclusions (in addition to TDP-43 + inclusions)
  - Likely alter function of RNA binding proteins

Ash et al., Neuron 2013:77:639-646

C9orf72 Genetic Error Mechanism

- Found only in CNS
- RAN transcription presumed to be possible because of new tertiary gene structure
- Repeats are usually non-coding regions
- Repeat-associated non-ATG (RAN) translation also occurs in:
  - Myotonic dystrophy type 1
  - SCA type 8
- Abnormal RAN proteins likely alter function of RNA binding proteins

Ash et al., Neuron 2013:77:639-646