Frontotemporal Dementia Update:

Pearls and Pitfalls of Diagnosis and Management Recommendations

CCNA Webinar
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Disclosures

- Dr. Finger has received personal compensation for serving on a PSP Scientific Advisory or Data Safety Monitoring board for Biogen, for Vigil Neuro, for Denali Therapeutics, for serving as a section editor for NeuroImage Clinical, and for serving as a course director for the AAN Annual Meeting.

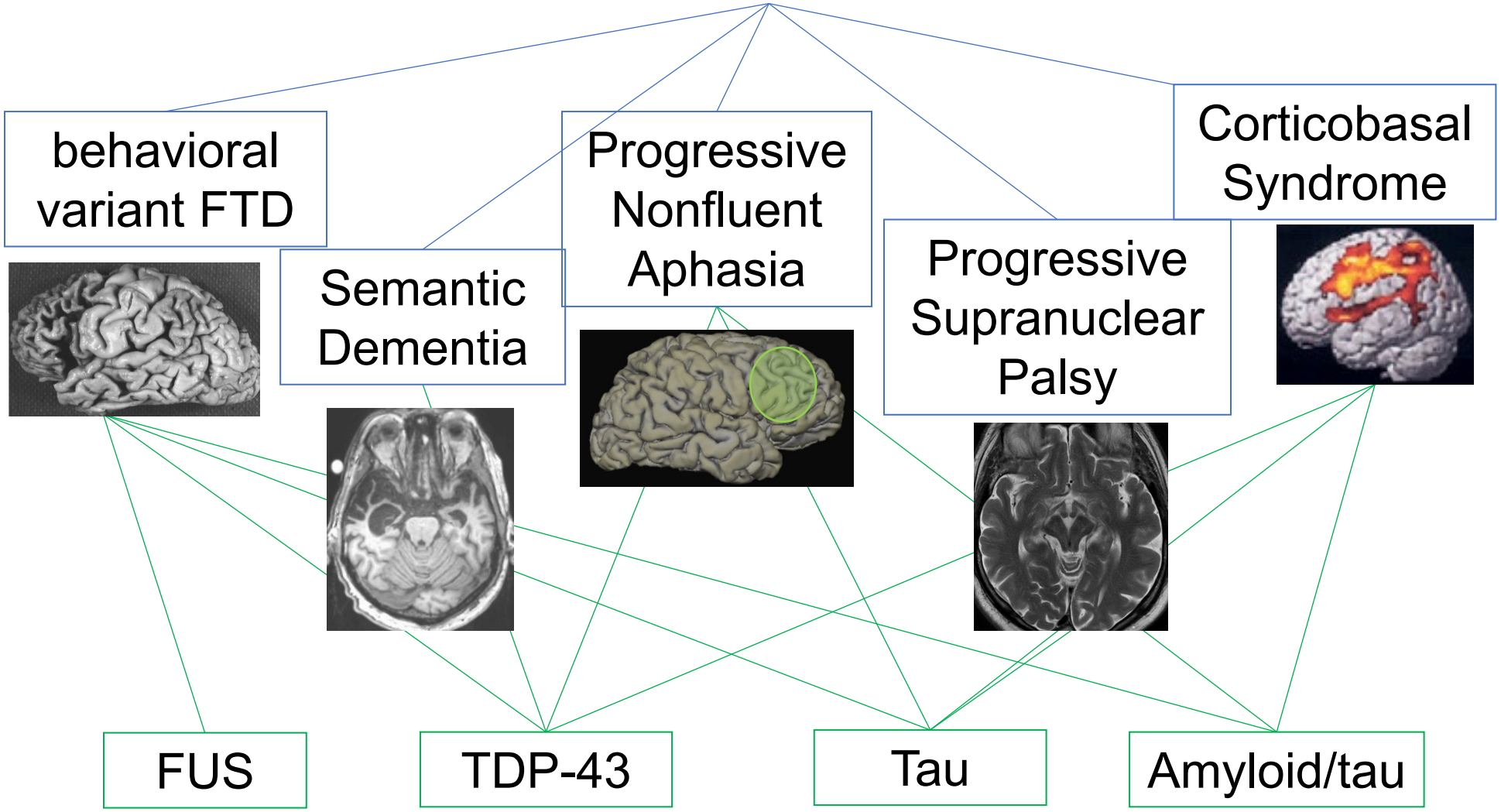
- Dr. Finger has received research support paid to her institution (UWO) from CIHR and the Weston Foundation to conduct an ongoing study of oxytocin in FTD, from Alzheimer Society of Canada, and the Physicians and Services Incorporated Foundation, the Ministry of Research and Innovation of Ontario for research, and for site participation in clinical trials sponsored by Alector, Biogen, and TauRx.

- Dr. Finger will discuss therapies currently in clinical trials including oxytocin for FTD for which she is the PI, nabilone (co-investigator).

Objectives

- Review the current diagnostic criteria and approach for FTD, with a focus on bvFTD
- Understand the key differential diagnosis in patients being evaluated for possible bvFTD
- Improve health care providers distinction between bvFTD and phenocopies
- Highlight current best practices in the management of FTD

Frontotemporal Dementias

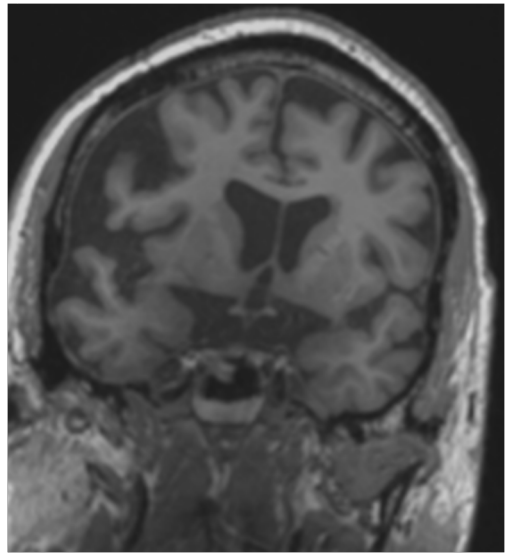


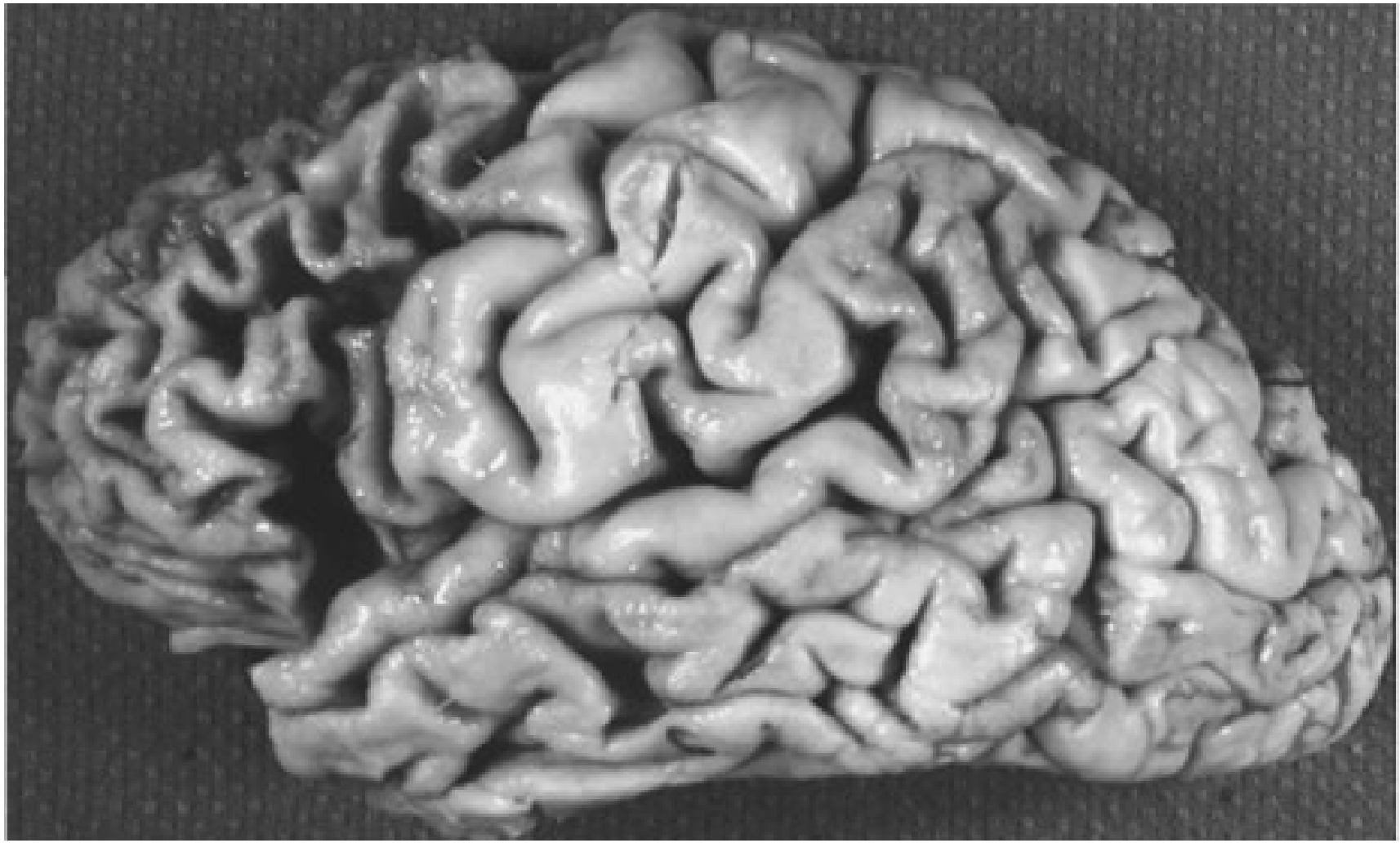
42 y.o. with strong family history of FTD

- 42 y.o. presented at insistence of family, convinced she did not have what her brother did
- At age 40 developed poor taste in jokes, uncertainty, forgetfullness
- Fired from managerial position
- Calling people 6-7x a day
- Craving sugary beverages and desserts
- Introducing self to strangers, city hall officials
- Flat affect
- “ Come see my brother, he is cute”

Neuroexam

- Giggles at reflexes. Makes risque comment. Hugs neurologist.
- Mild inattention. MMSE 29/30. Normal Trails and Wisconsin card sort
- Imaging: right temporal and frontal atrophy
- Pathology- TDP-43 (+p62) type B pathology
- * no familial mutation identified yet

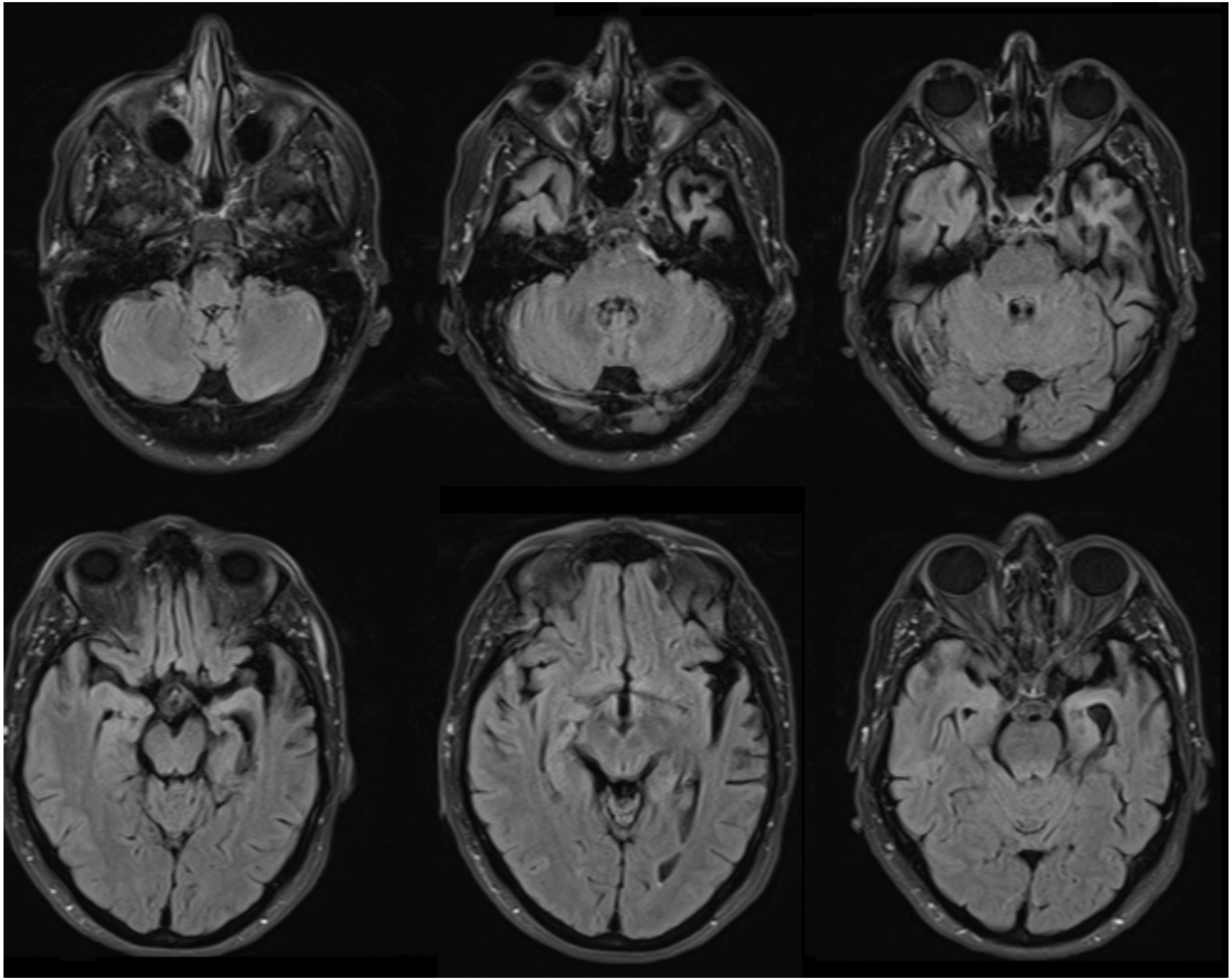


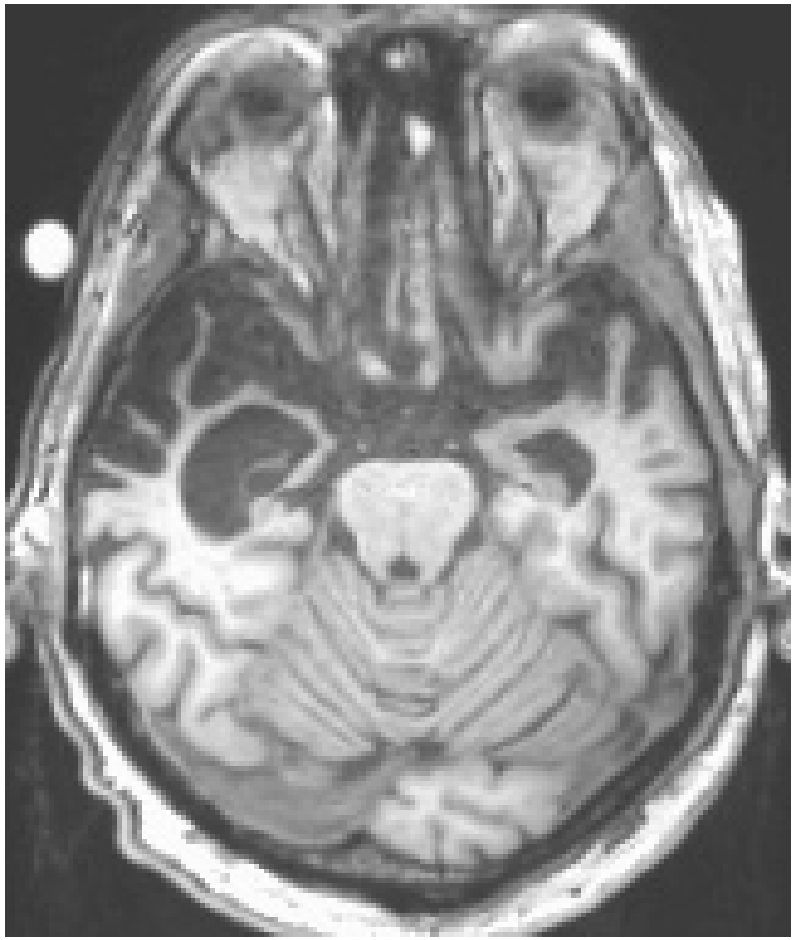


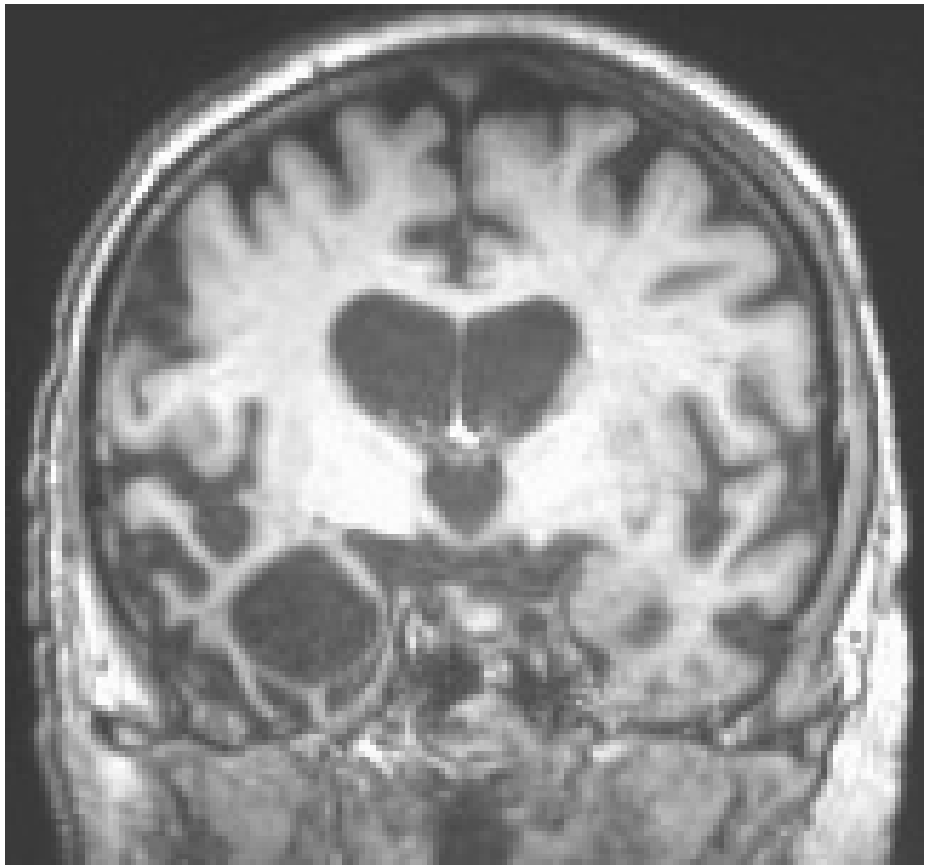
64 y.o. successful accountant who “picks the wrong words”

6-7 years of

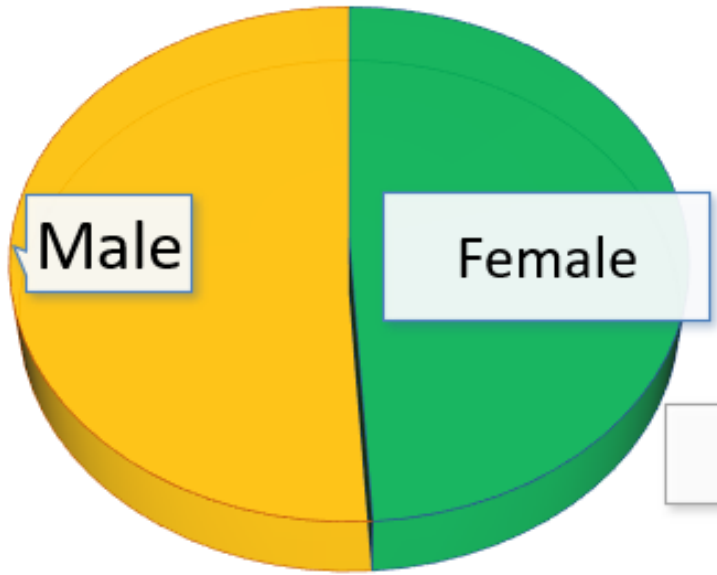
- decreased emotional engagement with family
- Increased candy and alcohol intake
- Calling people in restaurant ugly and fat
- Increased swearing and irritability
- Fired from job for always being out of his seat and talking excessively
- Driving excessively (hours for a 20 min visit)



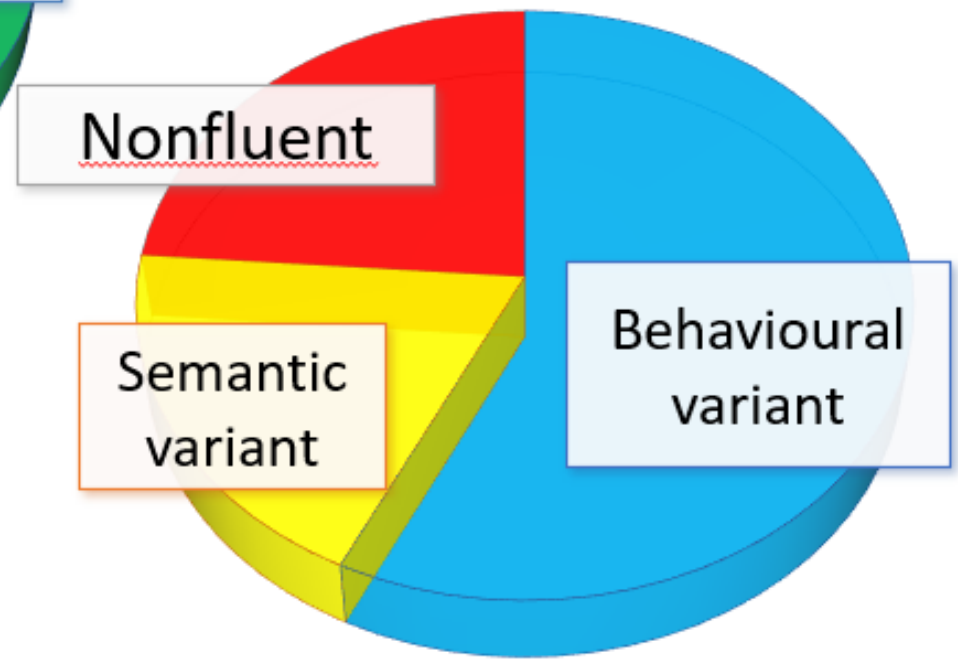




FTD SEX DISTRIBUTION



FTD Subtype Frequency



Epidemiology of Frontotemporal Dementia

Prevalence:

~20+ cases per 100,000 in people age 45-64 y.o.

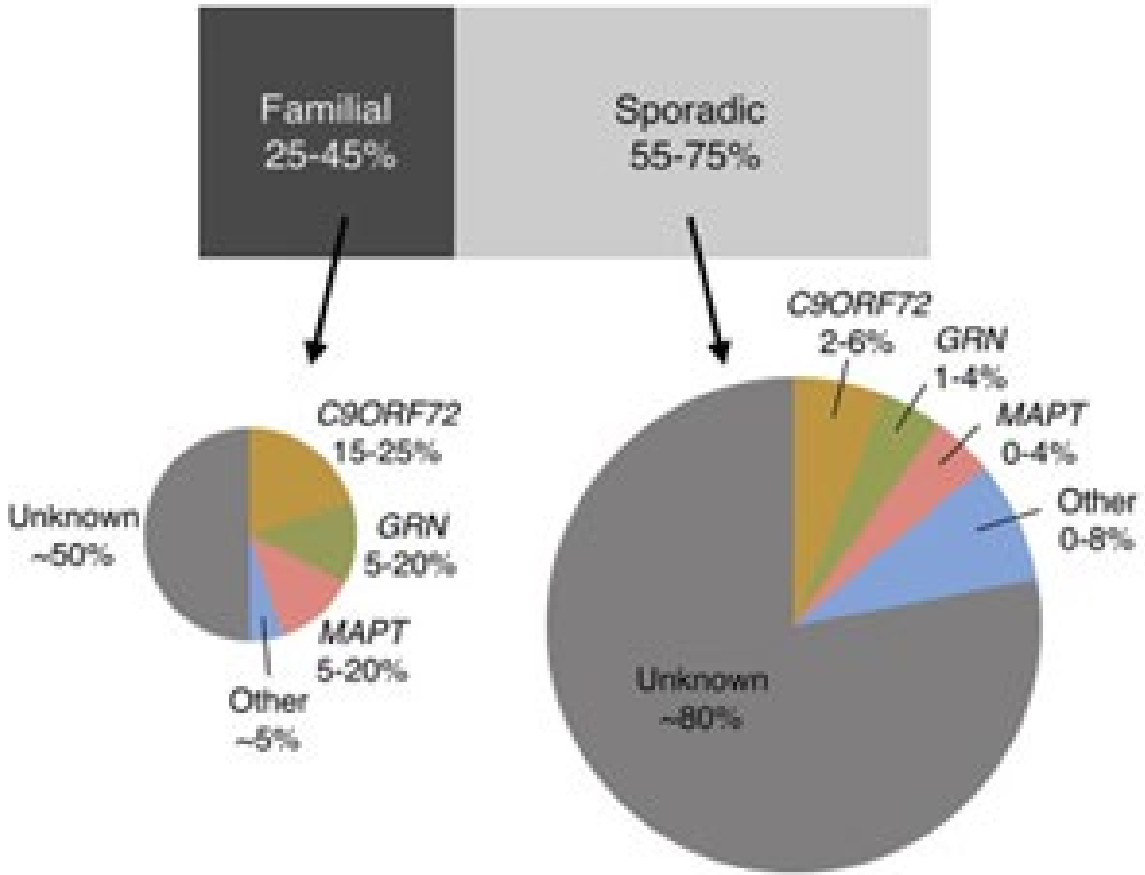
~ 40% with positive family history of dementia, ALS or Parkinson's Disease

~ 10-27% with autosomal dominant inheritance pattern

~ 15% of patients with FTD develop ALS

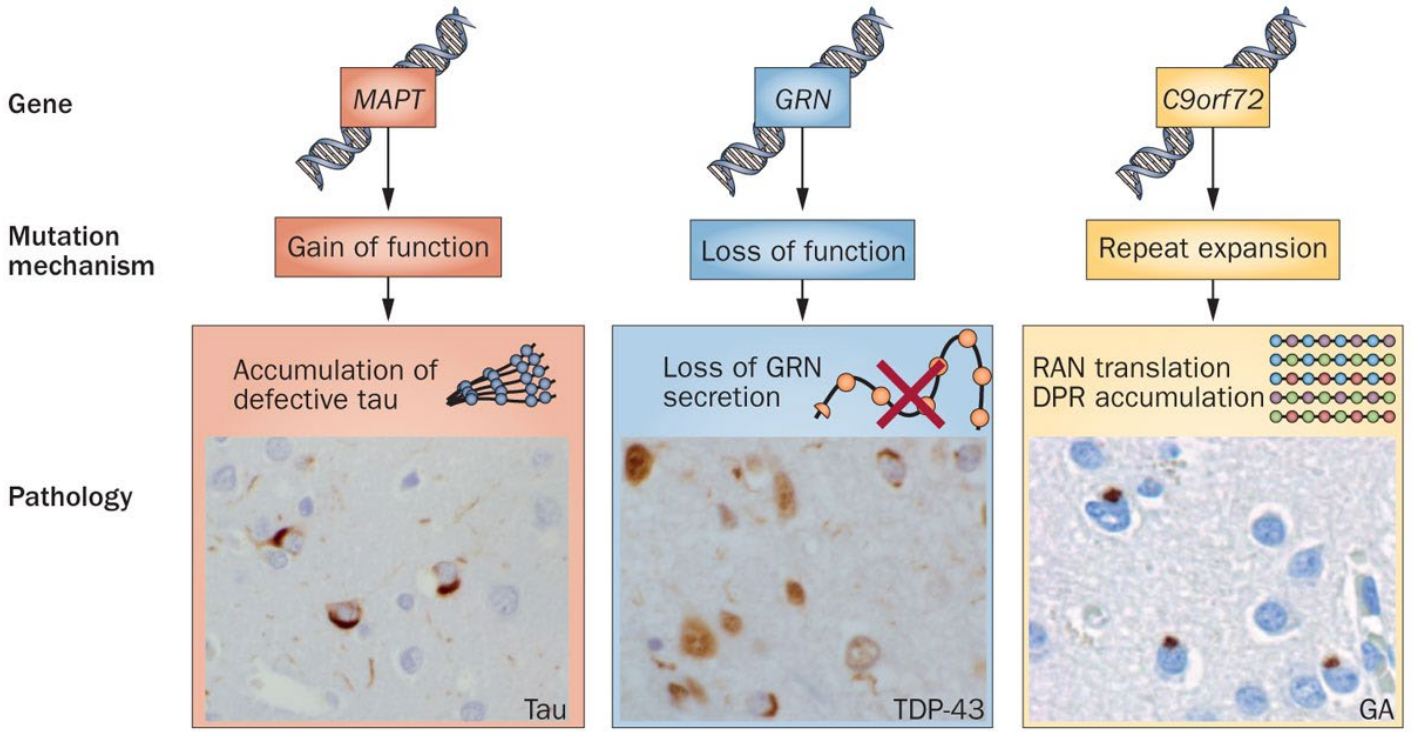
The only known environmental risk factor is head injury (FTD patients 3.3 x more likely to have had a head injury)

Causes of FTD



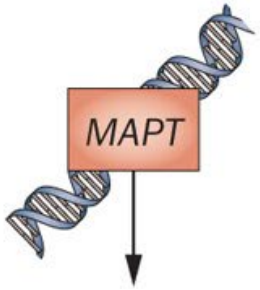
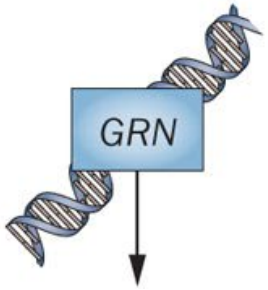
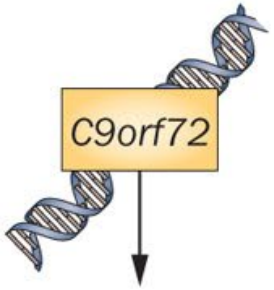
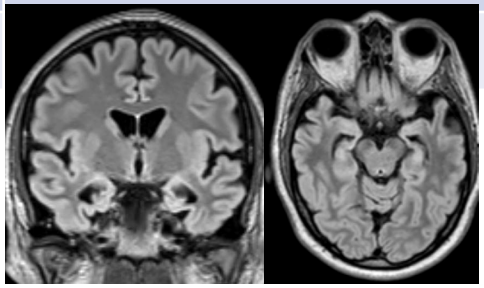
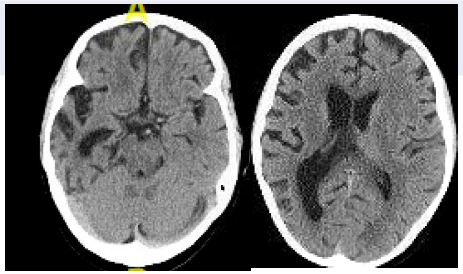
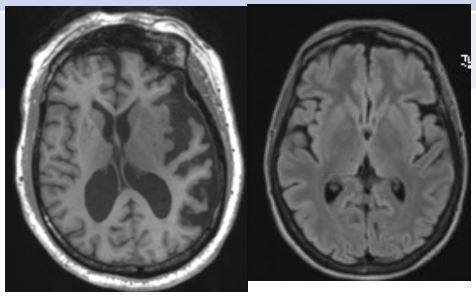
Carr, Sirkis and Yokoyama 2020

Three most common genetic subtypes of frontotemporal lobar degeneration



van der Zee, J. & Van Broeckhoven, C. (2014) Frontotemporal lobar degeneration—building on breakthroughs
Nat. Rev. Neurol. doi:10.1038/nrneurol.2013.270

nature REVIEWS NEUROLOGY

Gene			
Earliest symptoms	Naming difficulty, memory deficits		
Common symptoms	Apathy, disinhibition	Apathy, loss of volition	• Visual or tactile hallucinations • May develop ALS
Imaging	• Anterior temporal lobe/sylvian fissue atrophy	• Atrophy may be asymmetric • White matter hyperintensities	• Early thalamic atrophy • Variety of imaging patterns
			

Neurodegeneration or Neurodevelopment?

- 58 y.o. woman with schizophrenia presents for question of neurodegenerative disorder

Delusions dating from 20s and 30s:

- People at her work were following her.
- Her daughter's dentist was "cruising" their neighborhood.
- Believed sermons at church were directed specifically to her.
- House bugged by neighbors.

Behavioural Changes at age 55

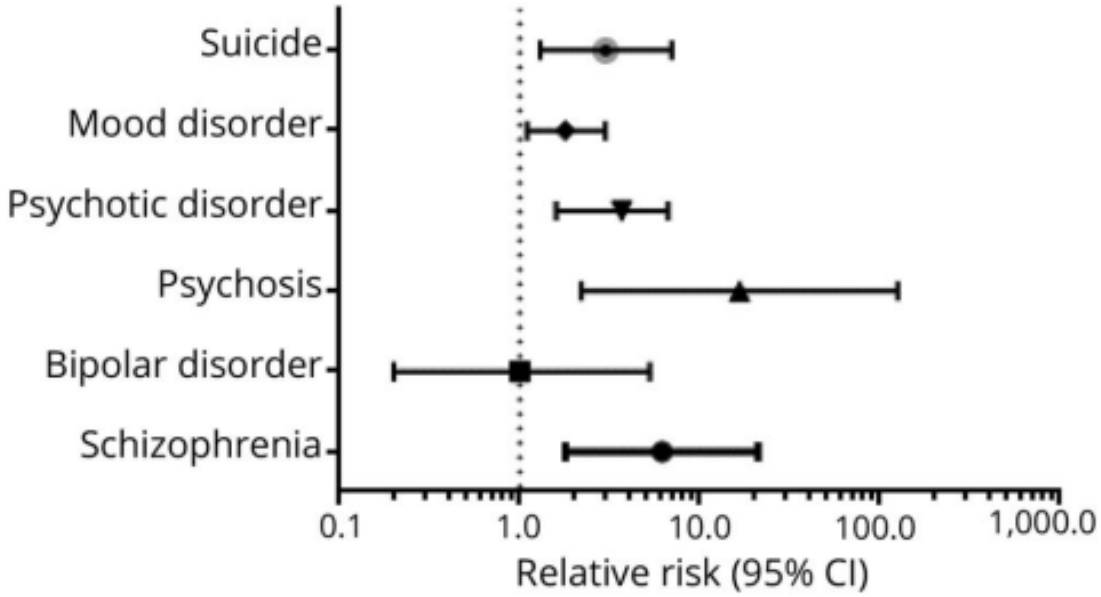
- People standing at the foot of her bed.
- Auditory hallucinations to kill self or husband.
- Eating all meals within 5 minutes.
- At buffets, put food straight into mouth
- Took 2 showers per day but wore same clothes and underwear each day.

+ C9orf72 repeat expansion carrier= genetic FTD

ARTICLE

Psychiatric disorders in *C9orf72* kindreds

Figure 3 Relative risk for psychiatric diagnoses in *C9orf72* kindreds

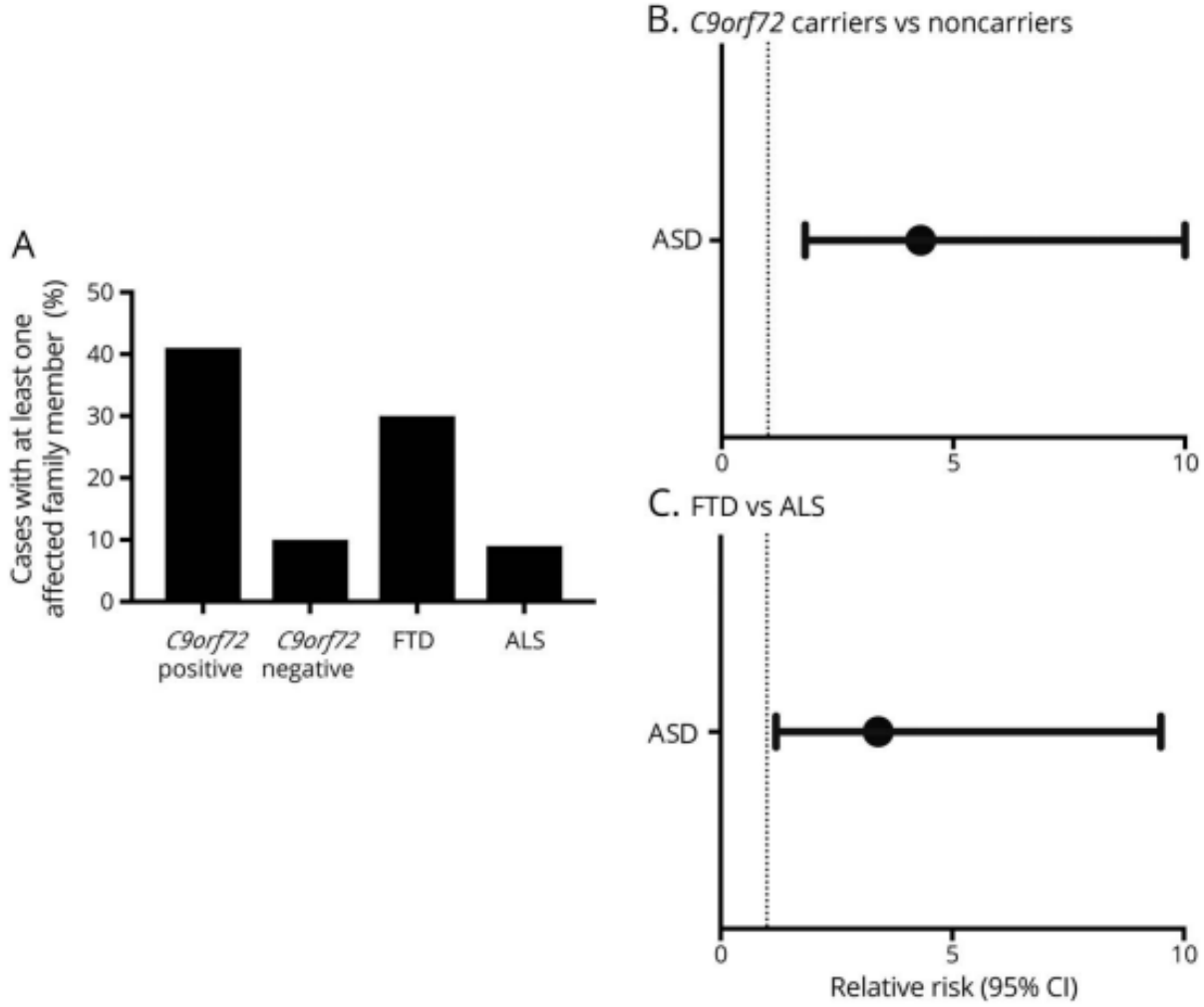


Relative risk, and 95% CIs, for a family history of psychiatric disorders (in at least 1 family member) in *C9orf72* carrying probands compared with probands without the *C9orf72* expansion. ALS = amyotrophic lateral sclerosis; CI = confidence interval; FTD = frontotemporal dementia.

Mean Age at diagnosis of Schizophrenia:
***C9orf72*+ 23 years old**
***C9orf72*- 27 years old**

C9orf72 and autism family history

Figure 2 ASD in *C9orf72* and FTD-ALS kindreds



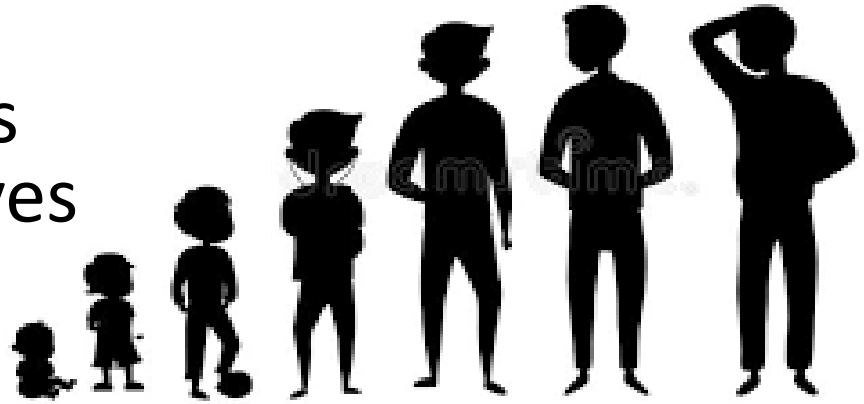
Relative Risk = 4.3

Mean Age at diagnosis of ASD= 6 years old

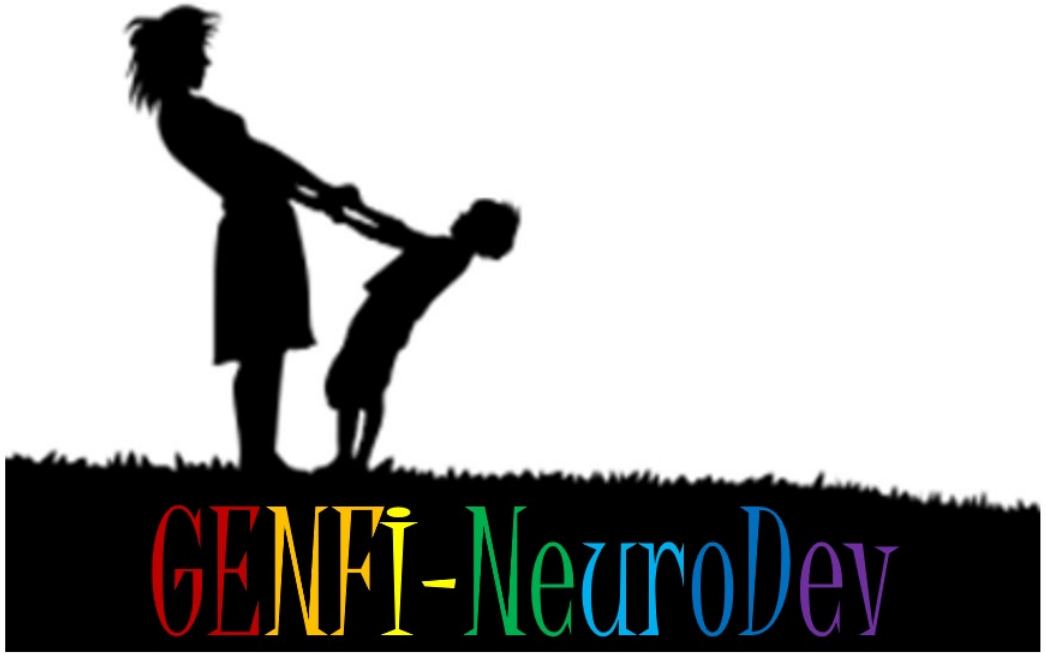
(A) Percentage of cases with at least 1 family member diagnosed with ASD for *C9orf72* carriers and noncarriers and patients with FTD and ALS. (B) Relative risk, and 95% CIs, for a family history of ASD (in at least 1 family member) in *C9orf72* carrying probands compared with noncarriers. (C) Risk for probands with FTD vs ALS. ASD = autism spectrum disorder; ALS = amyotrophic lateral sclerosis; CI = confidence interval; FTD = frontotemporal dementia.

Hints of Neurodevelopment in FTD

- Prior reports of patients who develop PPA having language related learning issues in childhood
  - *Mesulam and Weintraub 1992*
- Increased frequency of Learning Disabilities in patients with PPA and first degree relatives
  - *Rogalski et al. 2008*

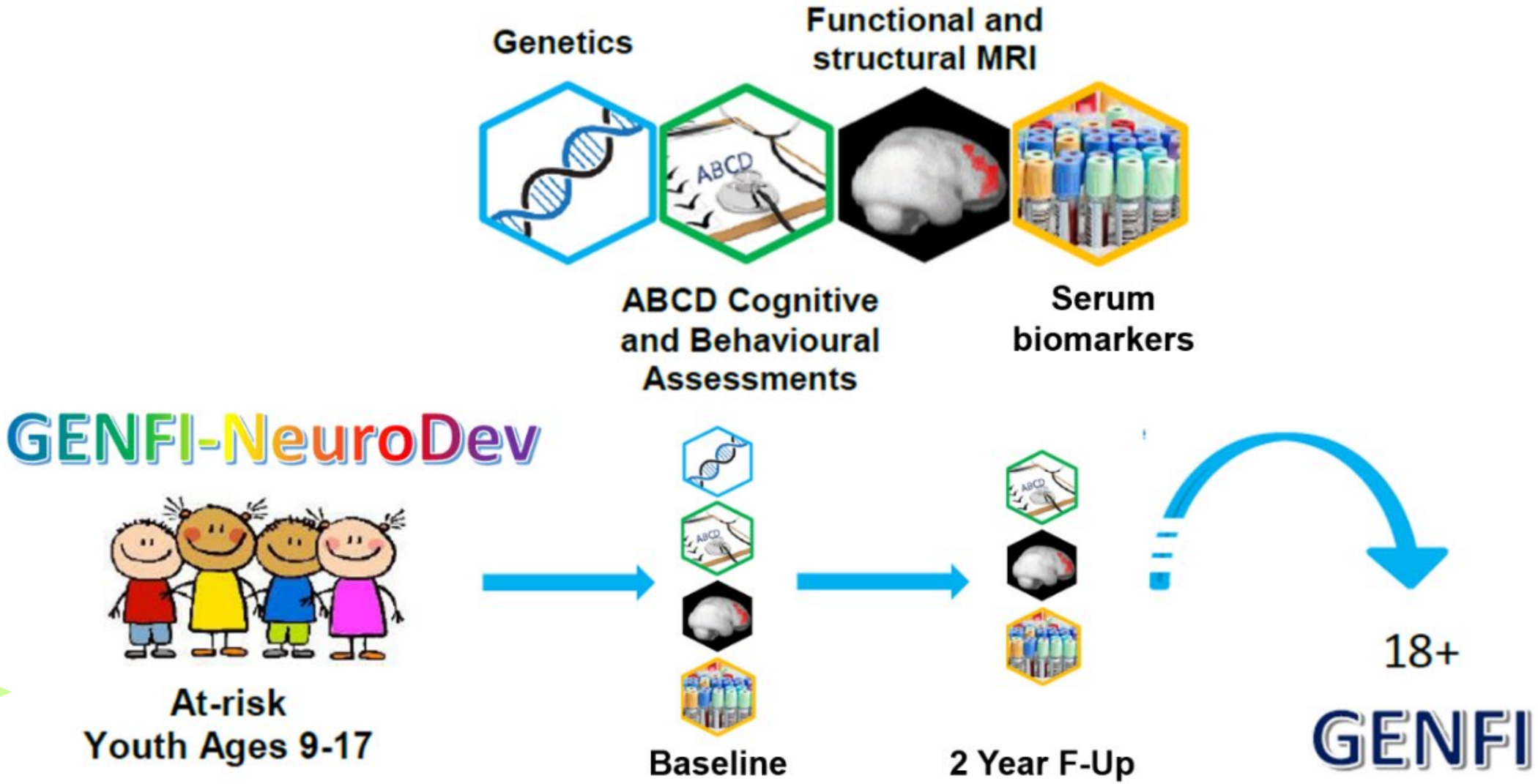


- Genetic FTD studies with differences at baseline between mutation carriers vs. non-carriers
  - *Geschwind et al. 2001, Boroni et al. 2008, Boroni et al. 2012, Tavares et al. 2019, Chu et al 2021;. Young et al. 2022*



Hypothesis:

Genetic mutations causing autosomal dominant Frontotemporal Dementia have neurodevelopmental effects on brain structure and function that can be detected in youth.



GENFI

Parents do not need to know genetic status

GENFI-NeuroDev Sites

McGill University, Simon Ducharme

Universite Laval, Robert La Force

University of Toronto, Mario Masellis

Western University, Elizabeth Finger

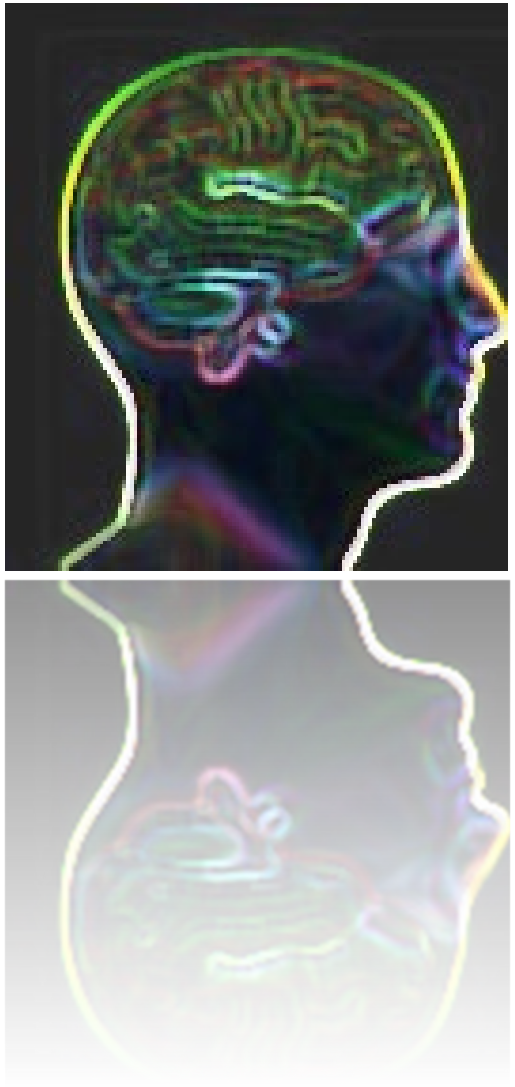
UCL, Jon Rohrer

Karolinska Institutet, Caroline Graff

University Halle-Wittenberg, Markus Otto

University of Tübingen, Matthis Synofzik

Leipzig University, Matthias Schroeter



FTD Phenocopy

The Problem

57 y.o. man presenting with inappropriate behaviour, referred for query FTD

- Patient reports decreased mood for 3-4 years.
- Cites stressors at work and did not return after cataract surgery
- Wife (second) and adult daughter report several years of new “child-like” behaviour
- Discussing bowel movements at dinner, otherwise polite
- Hypersexual grabbing of wife
- Hyperorality with larger portions, increased sweets and soda pop
- Wife notes new negativity, anger, vagueness of emotions
- Indifferent/ emotionally flat
- Requires reminders to cut his nails

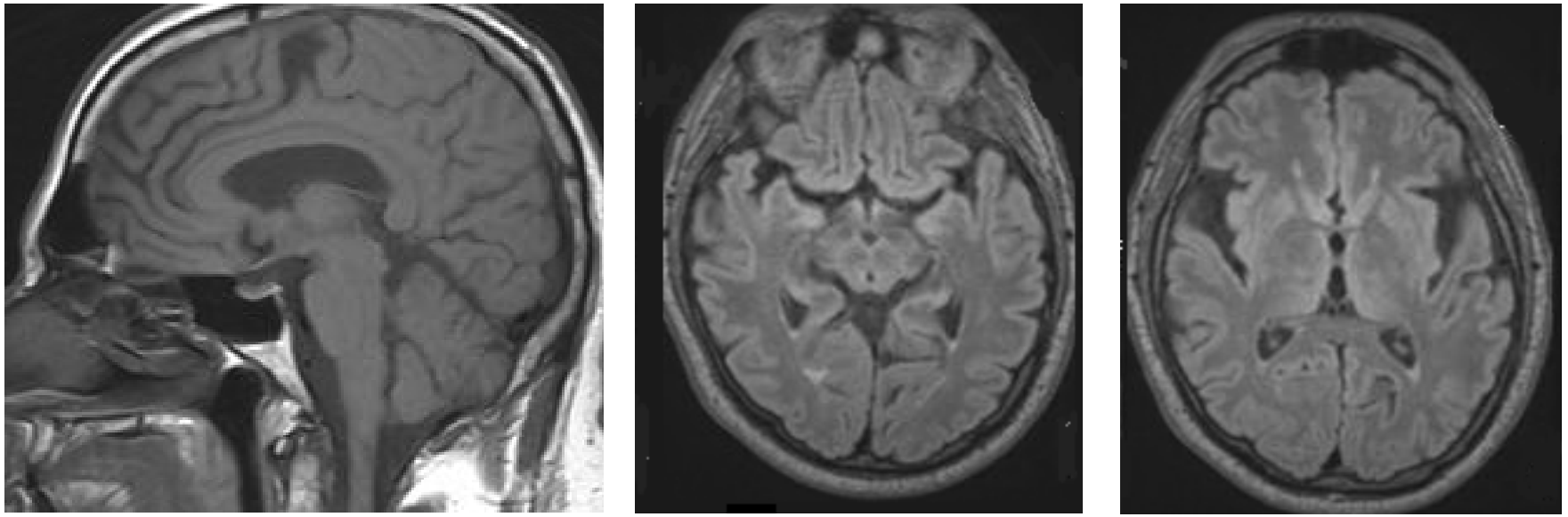
- Disorganized
- At work, difficulty with concentration.
- Would text rather than assisting customers.
- Decreased empathy for wife.
- Babysits for grandchildren ages 1 and 3 without incident or concerns.

57 y.o. man presenting with inappropriate behaviour, referred for query FTD

- Frontal behavioural inventory score= 53
- Normal language, cranial nerves, motor, sensory and coordination
- No snout or grasp reflex, performs Luria hand sequence well
- Cognitive screening: MoCA 29/30. Trails B normal
- Full Neuropsychological testing: Mild difficulty with one card-sorting executive function tasks, otherwise normal memory, visuospatial, executive and language function

57 y.o. man presenting with inappropriate behaviour, referred for query FTD

Formal MRI read by radiology as mild frontal atrophy



Criteria for bvFTD

Rascovsky et al Brain 2011

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. **Early behavioural disinhibition**
- Socially inappropriate behaviour
- Loss of manners or decorum
- Impulsive, rash or careless actions

B. **Early apathy or inertia**
- Apathy
- Inertia

C. **Early loss of sympathy or empathy**
- Diminished response to other people's needs and feelings
- Diminished social interest, interrelatedness or personal warmth

D. **Early perseverative, stereotyped or compulsive/ritualistic behaviour**
- Simple repetitive movements
- Complex, compulsive or ritualistic behaviours
- Stereotypy of speech

E. Hyperorality and dietary changes
- Altered food preferences
- Binge eating, increased consumption of alcohol or cigarettes
- Oral exploration or consumption of inedible objects

bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions:

- Deficits in executive tasks
- Relative sparing of episodic memory
- Relative sparing of visuospatial skills

Rascovsky et al Brain 2011

*** Loss of insight**

Possible, Probable and Definite bvFTD

Possible bvFTD

Gradual onset, recurrence and progression of >=3 of the behavioural/cognitive sx.

Probable bvFTD

- Meets criteria for possible bvFTD
- **Exhibits significant functional decline**
- **Imaging results consistent with bvFTD**
  - Frontal and/or anterior temporal atrophy on MRI or CT

    OR
  - Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Behavioural variant FTD with definite FTLD Pathology

- Meets criteria for possible or probable bvFTD

  PLUS
- Histopathological evidence of FTLD on biopsy or at post-mortem

  OR
- Presence of a known pathogenic mutation

Rascovsky et al Brain 2011

57 y.o. man presenting with inappropriate behaviour, referred for query FTD

Follow up

- Attended Alzheimer Day program. Staff noted entirely normal behaviour, high functioning level. Started a relationship with another client.

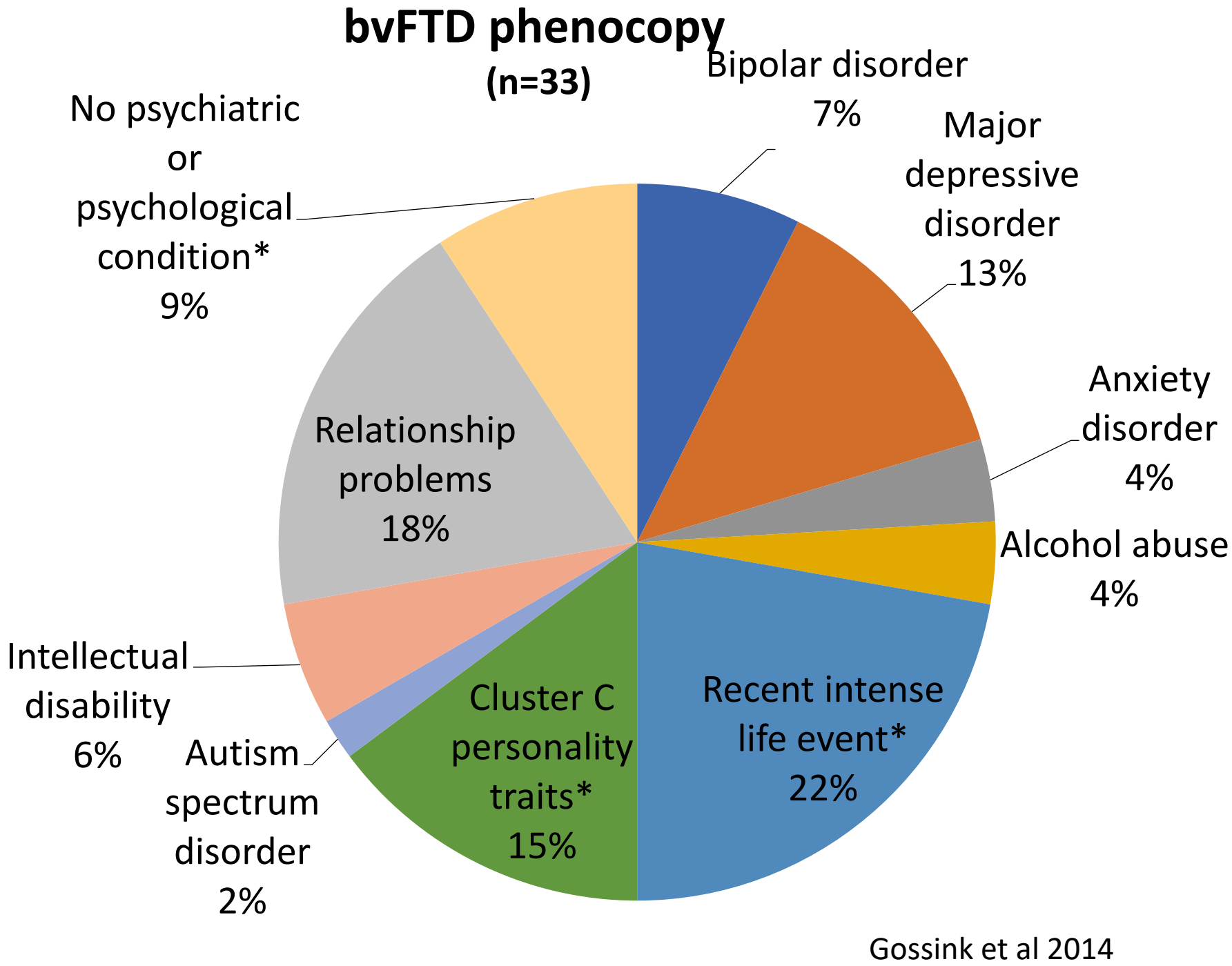
- Subsequently separated from wife, moved into own apartment, independently managed all finances, meals etc. without problem.

- During psychiatric evaluation, revealed violent traumatic incident just prior to onset of behavioural changes.

FTD Phenocopy definition

- Patients presenting with behavioural changes meeting criteria for possible bvFTD with onset in mid to late life, but who do not progress.

(Hornberger et al. 2008), (Kipps et al. 2010)

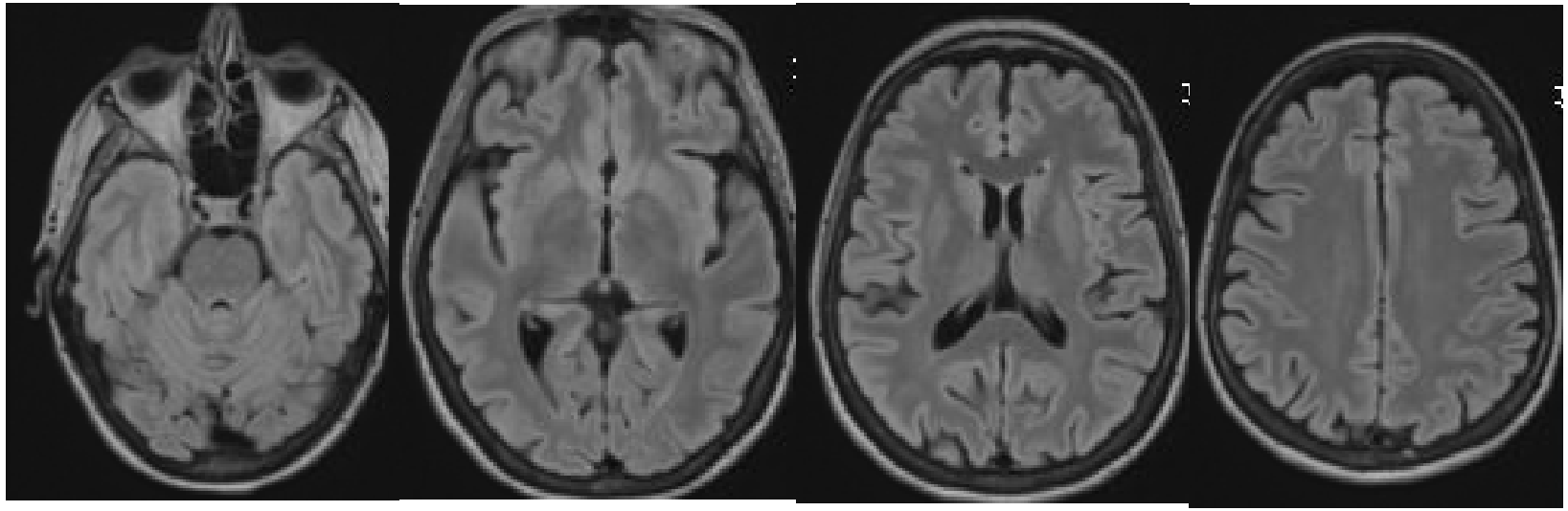


Gossink et al 2014

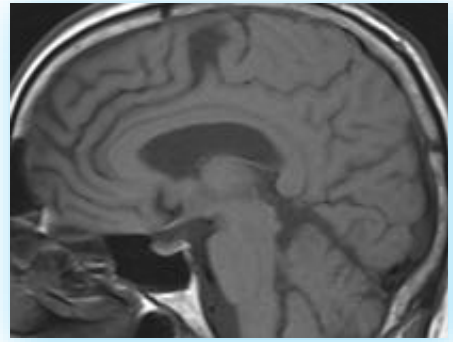
Pitfalls in diagnosis of bvFTD

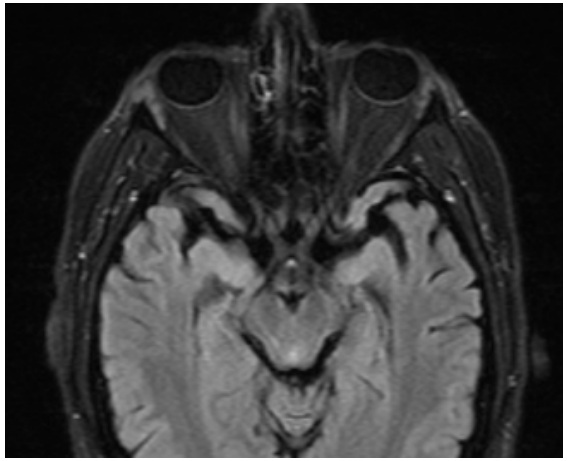
- Patient's lack of insight means they are unreliable reporters -> heavy reliance on carer reports of symptoms
- Carer ratings of function may be low, but performance in clinic high
- 25% may perform normally on cognitive testing in early stages
- 25% may have normal brain volumes at early stages
- Some subtypes and genetic mutations associated with slow progression
  - (*C9orf72, MAPT R406W, early right temporal predominant*)

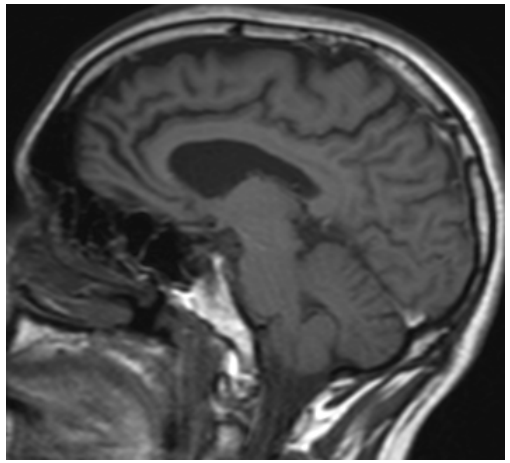
Kipps et al. 2010; Power et al 2021



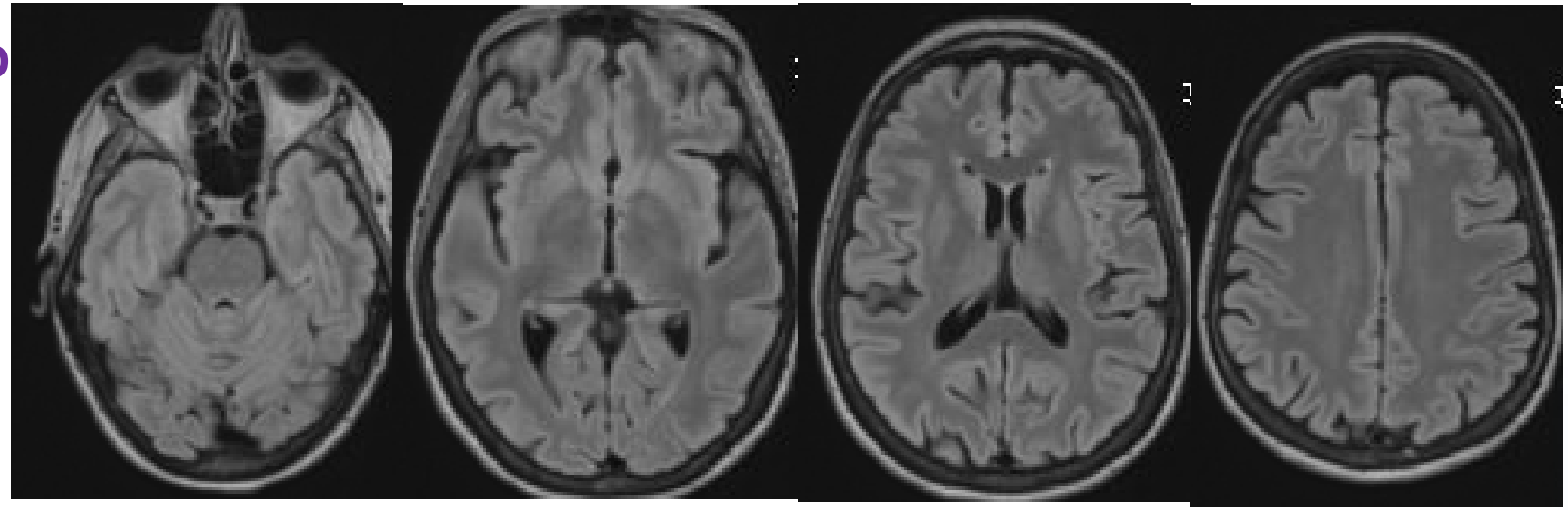
phenocopy







C9orf72 FTD



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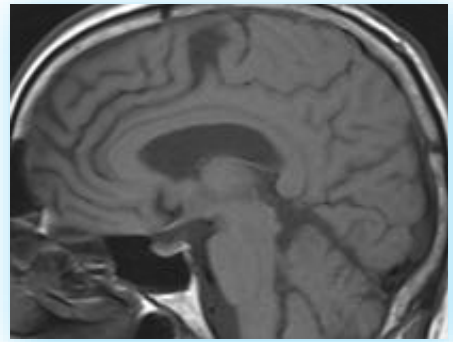
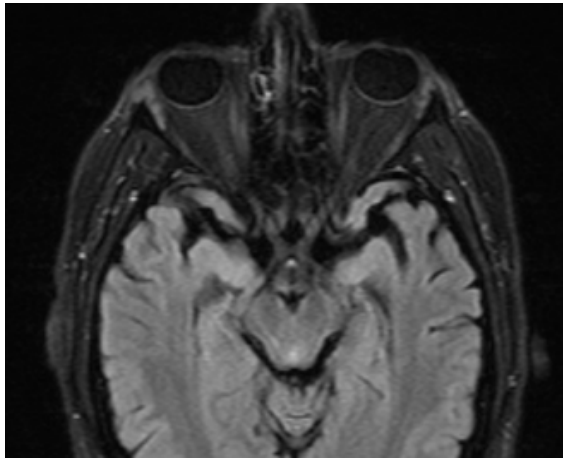
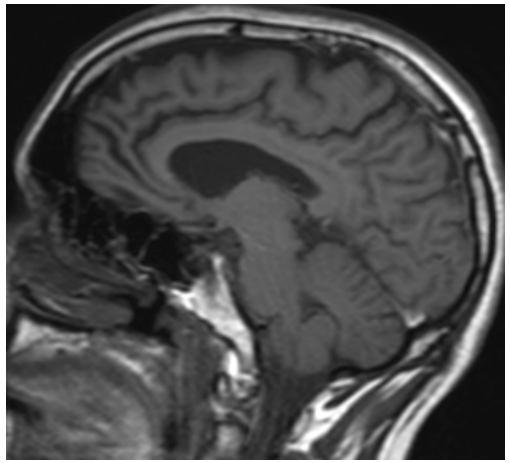


Progressive bvFTD





bvFTD vs. phFTD

bvFTD

- Decline in ADLs over 12 months
- ~ Equal prevalence males: females
- Often positive family history
- ~50% with prior mental health/psychological condition
- May have snout, grasp reflex
- FDG-PET frontotemporal hypometabolism

phenocopy

- Stable ADLs over 12 months
- 10:1 male predominance
- Usually negative family history of FTD
- ~85% with prior mental health/psychological condition
- Normal frontal reflexes
- FDG-PET typically normal

Valente et al. 2019; Power et al. 2021

Distinguishing bvFTD from mood disorders

FTD vs. Depression

- bvFTD may be apathetic, emotionally blunted, socially withdrawn *but: :*
  - ***Are rarely*** *subjectively sad**
  - ***Rarely*** *have guilty ruminations, feelings of worthlessness*
  - *Typically not suicidal*

(Woolley et al 2011; Ducharme et al 2015)

Distinguishing bvFTD from mood disorders

- Useful symptoms to distinguish bvFTD from mood disorders include:

  - Insidious onset and progressive nature
  - Absence of symptom periodicity
  - Stereotyped movement and speech
  - Prominent disinhibition without remorse
  - Profound loss of empathy and social sensitivity
  - Overeating or compulsive eating fads
  - Lack of insight and concern (i.e. "*la belle indifference*")

(Woolley et al 2011; Ducharme et al 2015)

Approach

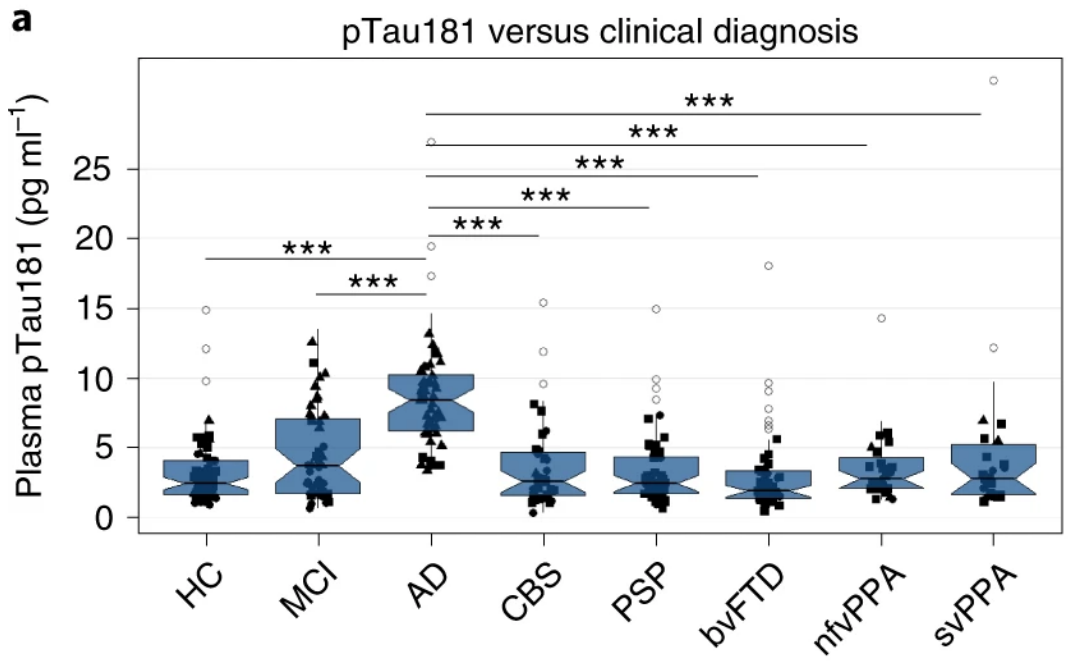
When you do not observe direct evidence of progressive frontotemporal dysfunction…

- Corroborate long term personality traits, symptom and behaviour histories
- Follow up ADLs and consider performance measures*
- Review brain images directly
- Be cautious about making a diagnosis of bvFTD---> refer to specialist for confirmation
- Follow for progression over time***

Update on Fluid Biomarkers for FTD

- CSF for amyloid/tau ratios to rule out Alzheimer's pathology (Irwin et al. 2012)

- Serum testing of phospho-tau isoforms to r/o AD coming soon!



Thijssen et al. Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) investigators. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med. 2020

Treatment and Management of FTD

To date, for FTD we have no "disease modifying" treatments that:

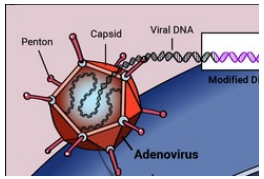
- Delay or prevent onset of FTD
- Slow progression
- Reverse neurodegeneration

Current approaches in trials to modify FTD

Anti-sense Oligonucleotides

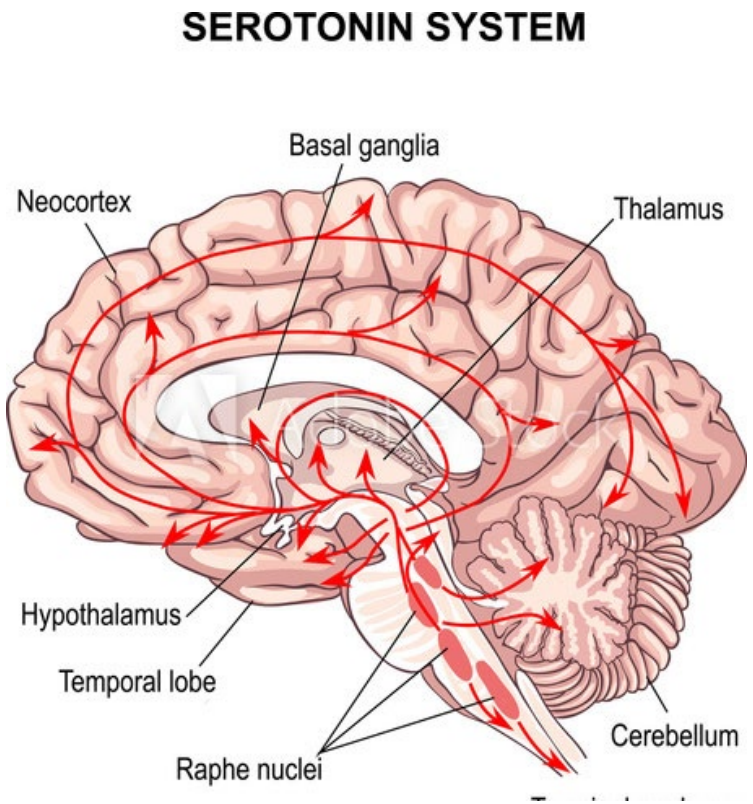
Small molecules

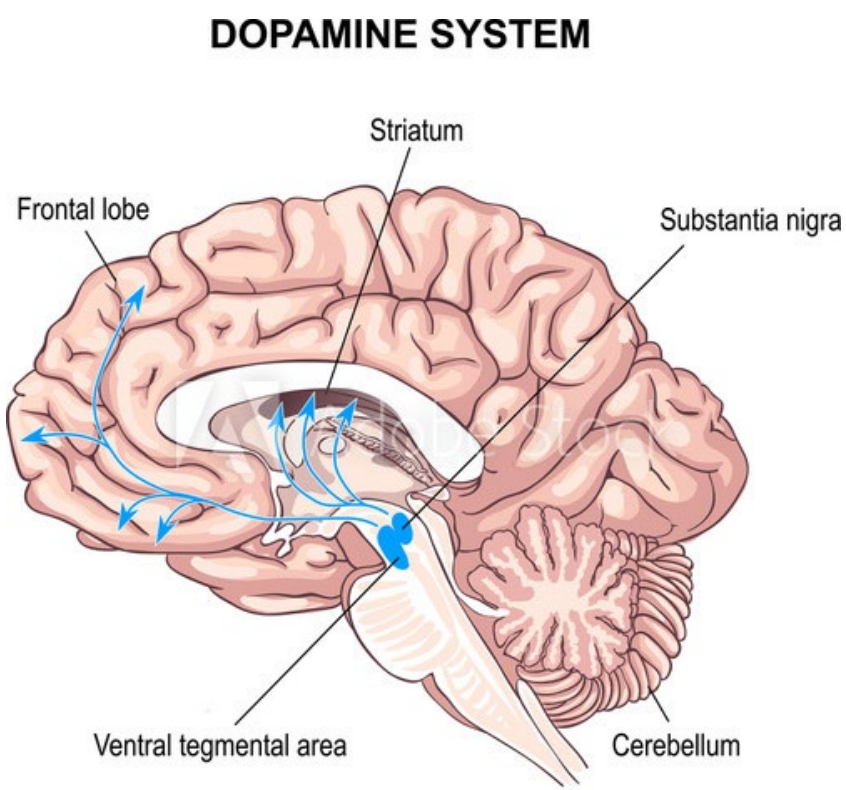
Viral vectors



Monoclonal antibodies

Treatment of symptoms for FTD





Treatment of symptoms for FTD

- Some evidence for efficacy in FTD for reducing agitation, aggression, disinhibition, and compulsive behaviours
  - SSRIs and anti-psychotics
- No effective treatments for empathy deficits or apathy in FTD
- Difficult to predict individual patient's response

Disinhibition and Impulsivity

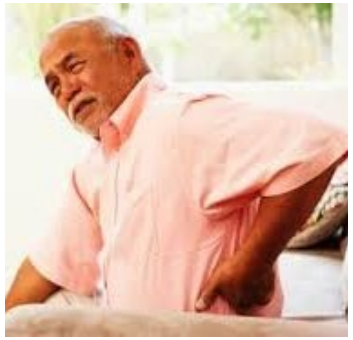
Non-Pharmacologic

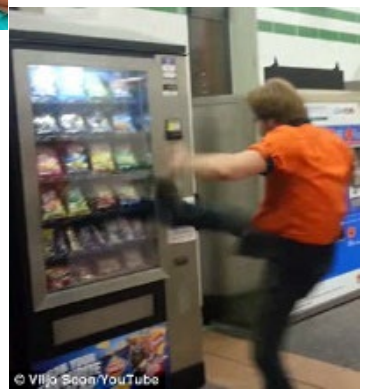
- Early driving cessation
- Power of attorney, limits on spending
- Manage safety issues at home- power tools, guns, ladders, cooking
- Antecedant-behavioural-consequence model (Merrilees 2007)
- Apology cards in caregiver's pocket.

Agitation

Non-Pharmacologic

- Screen for pain
- Activities for boredom
- Music, exercise

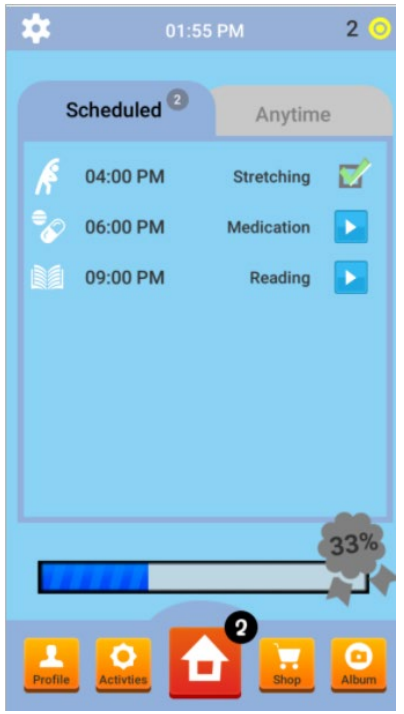




Apathy

Non-Pharmacologic

- **Tailored Activities Program**
- (O'Connor et al. 2015; Gitlin 2008)
  - Physical prompts of activities
  - Modeling of activities
  - Capitalize on routines, structured environments
- **Incentives**

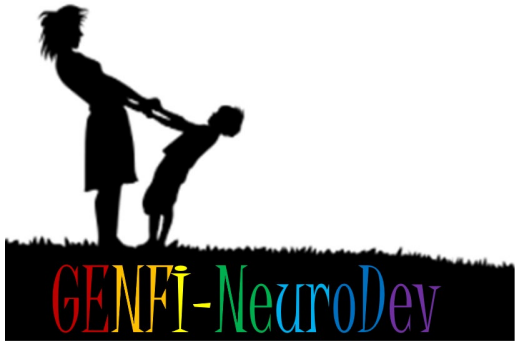


"Clinical trials offer hope for many people
and a chance to help researchers ***find better treatments***
for others in the future*."*

www.clinicaltrials.gov

https://www.nih.gov/health-information/nih-clinical-research-trials-you

Thank you



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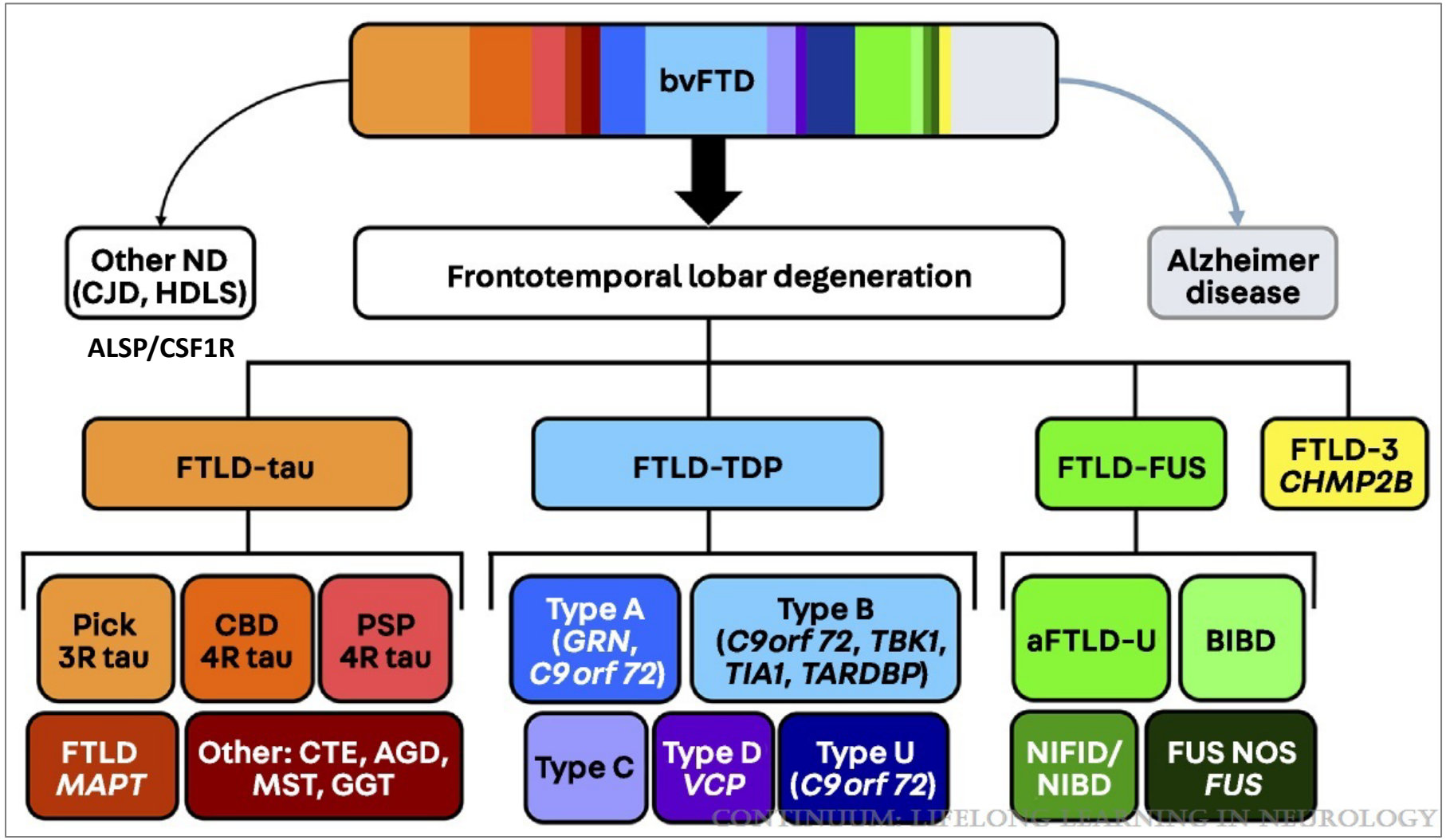
Why Brain Autopsy is still critically important in 2021

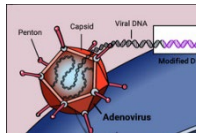


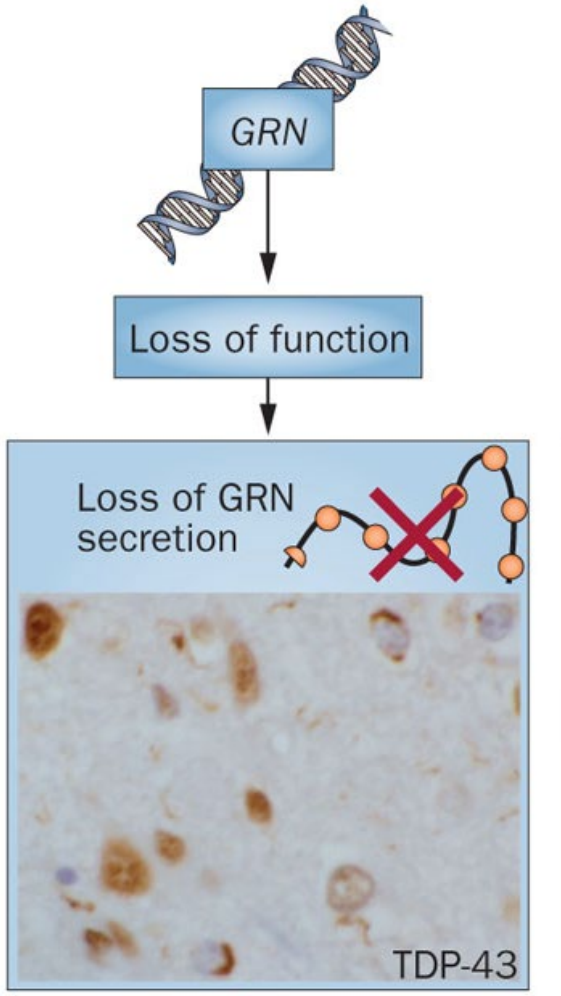
Seeley, William W.

CONTINUUM: Lifelong Learning in Neurology25(1):76-100, February 2019.

Emerging Clinical trials for Disease Modification in FTD

Viral vectors

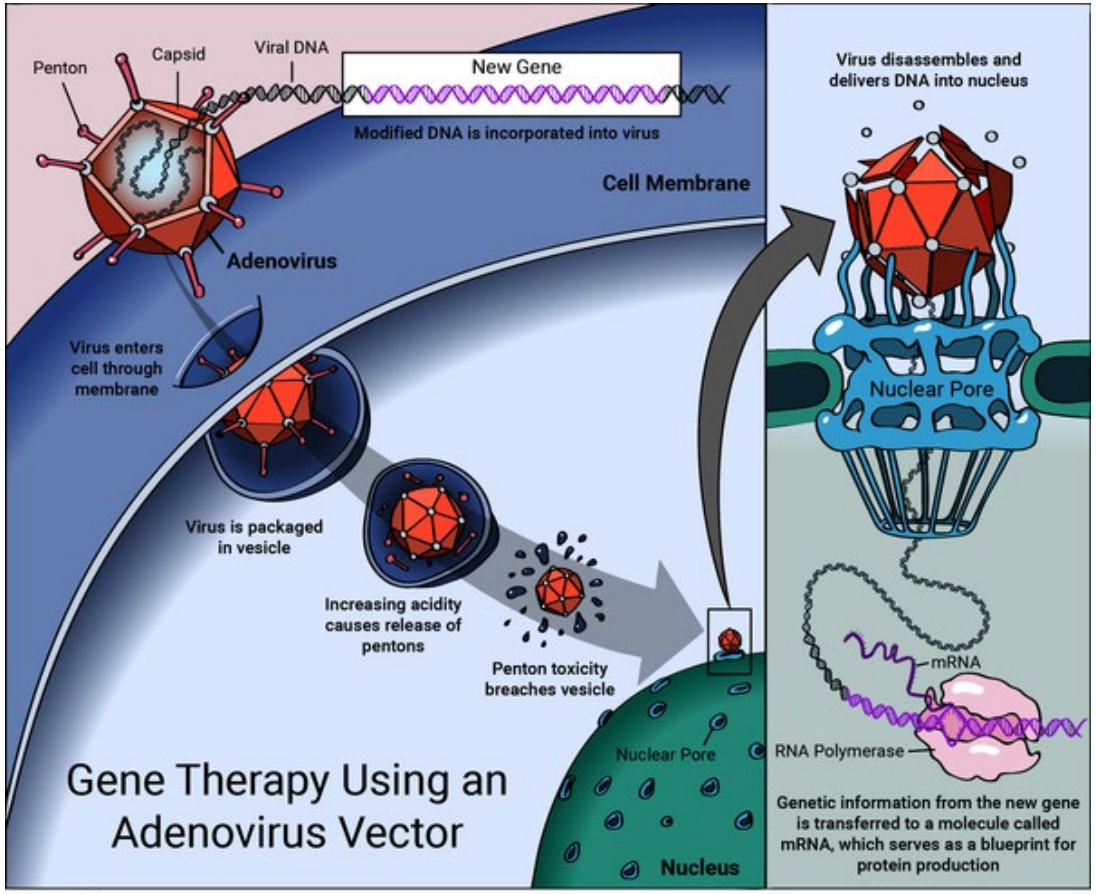




Small molecules

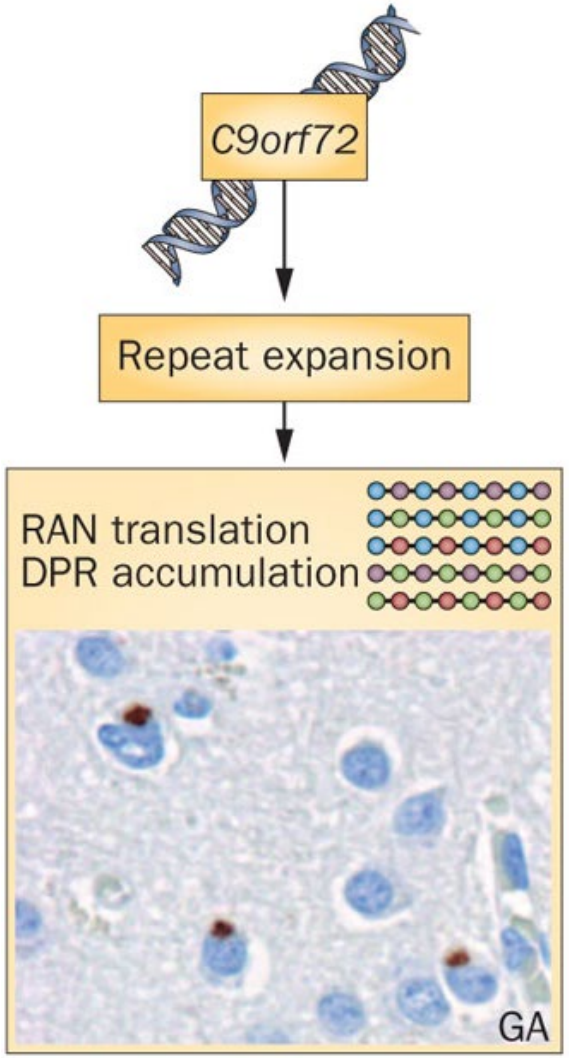
Monoclonal antibodies

Gene therapy with viral vectors



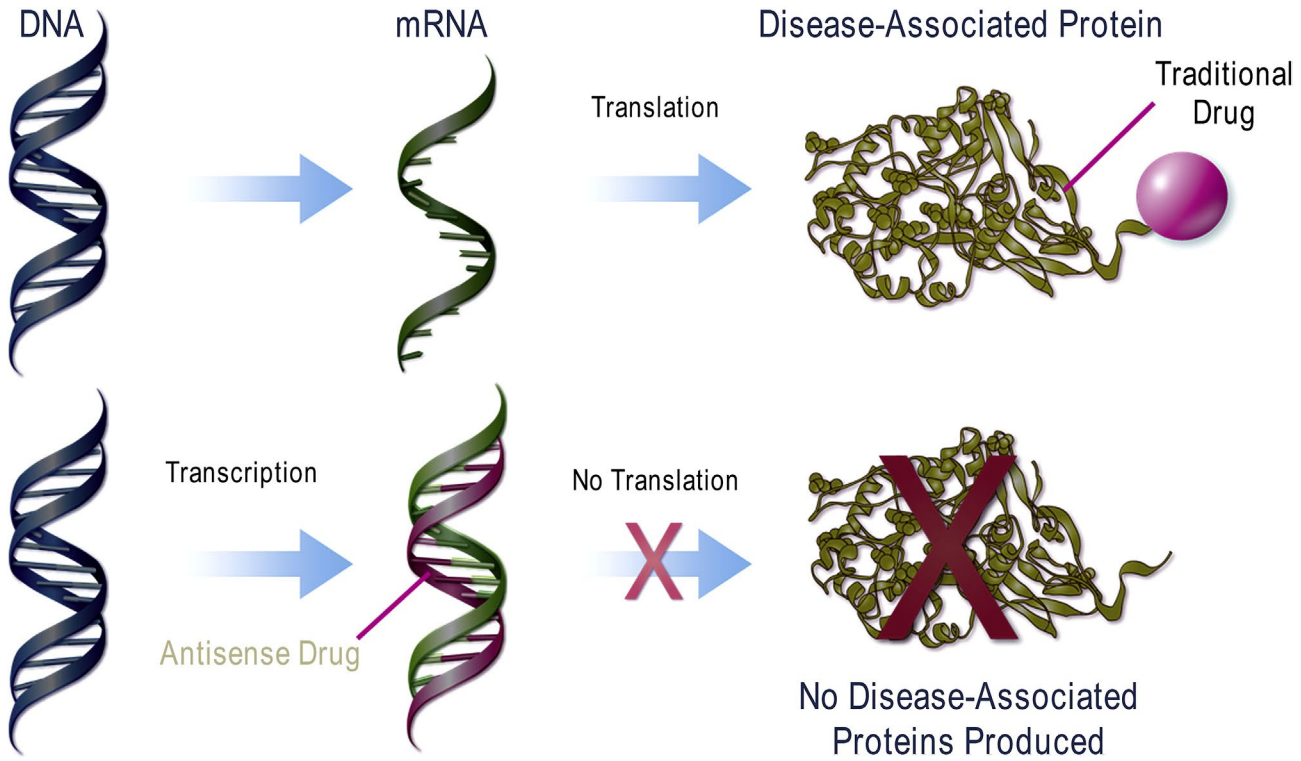
NIH U.S. National Library of Medicine

Anti-sense Oligonucleotides



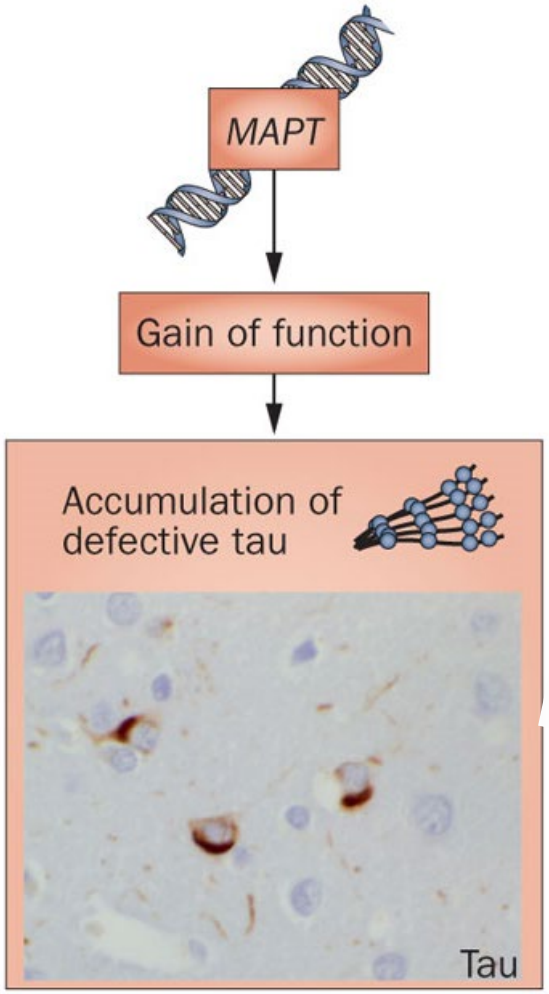
Monoclonal antibodies

Anti-sense Oligonucleotides (ASOs)



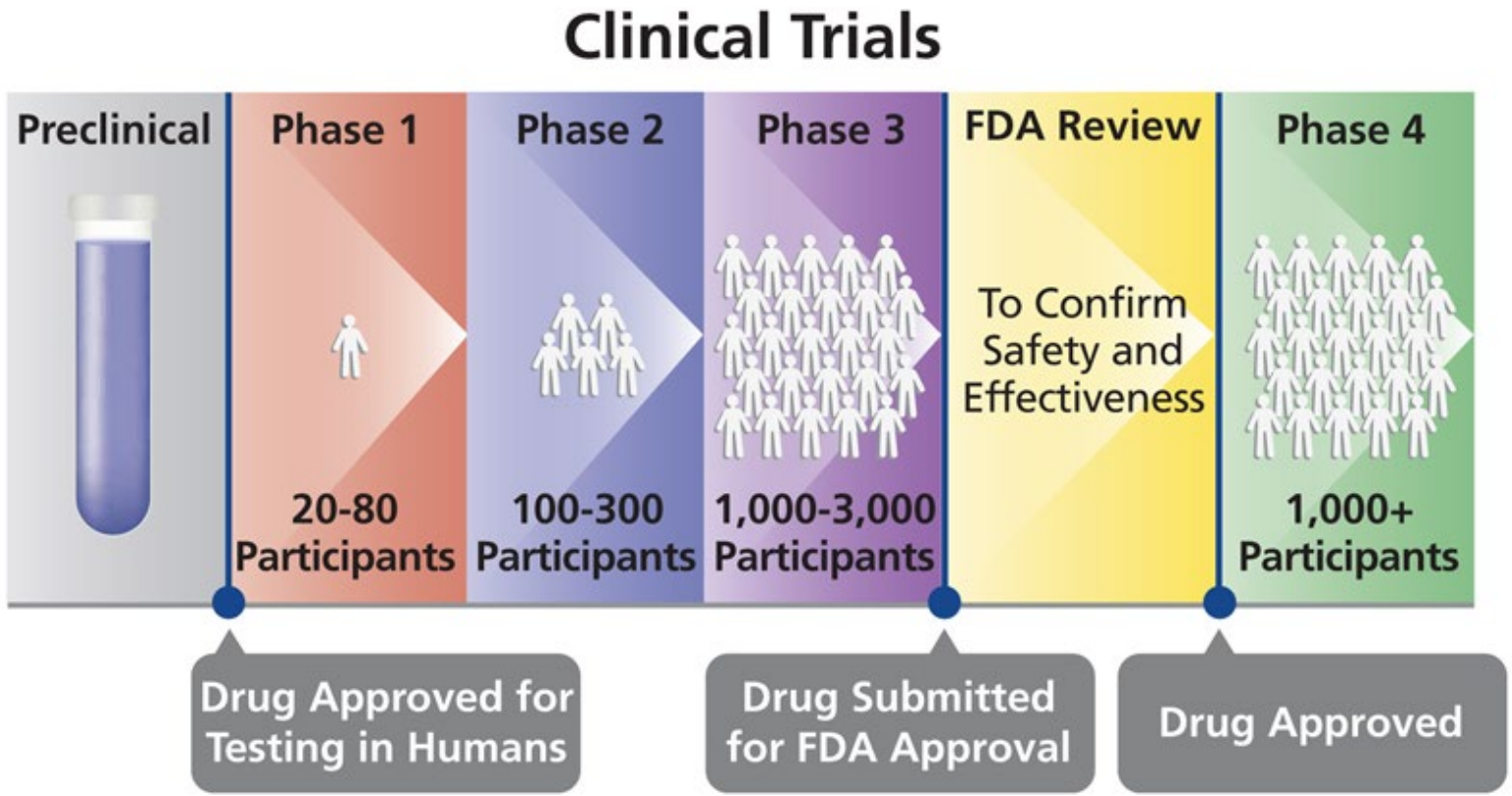
AC Goldberg 2010

Anti-sense Oligonucleotides



Small molecules

Monoclonal antibodies



https://clinicalinfo.hiv.gov/en/glossary/clinical-trial