Dementias in the Genomic Era:

Current Understanding of Frontotemporal Dementia

Demystifying Medicine Lecture

NIH Campus, Bethesda, MD

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National Institutes of Health

Turning Discovery Into Health

Disclosures

- Patents on the clinical testing and therapeutic interventions for the hexanucleotide repeat expansion of *C9orf72*

- Funding from Merck, CDC, Myasthenia Gravis Foundation, ALSA, Packard Center

Learning Objectives

- To understand the clinicopathological features of frontotemporal dementia
- To review current genetic understanding of frontotemporal dementia
- To delineate how genetic knowledge can be leveraged to advance the precision medicine paradigm

Overview

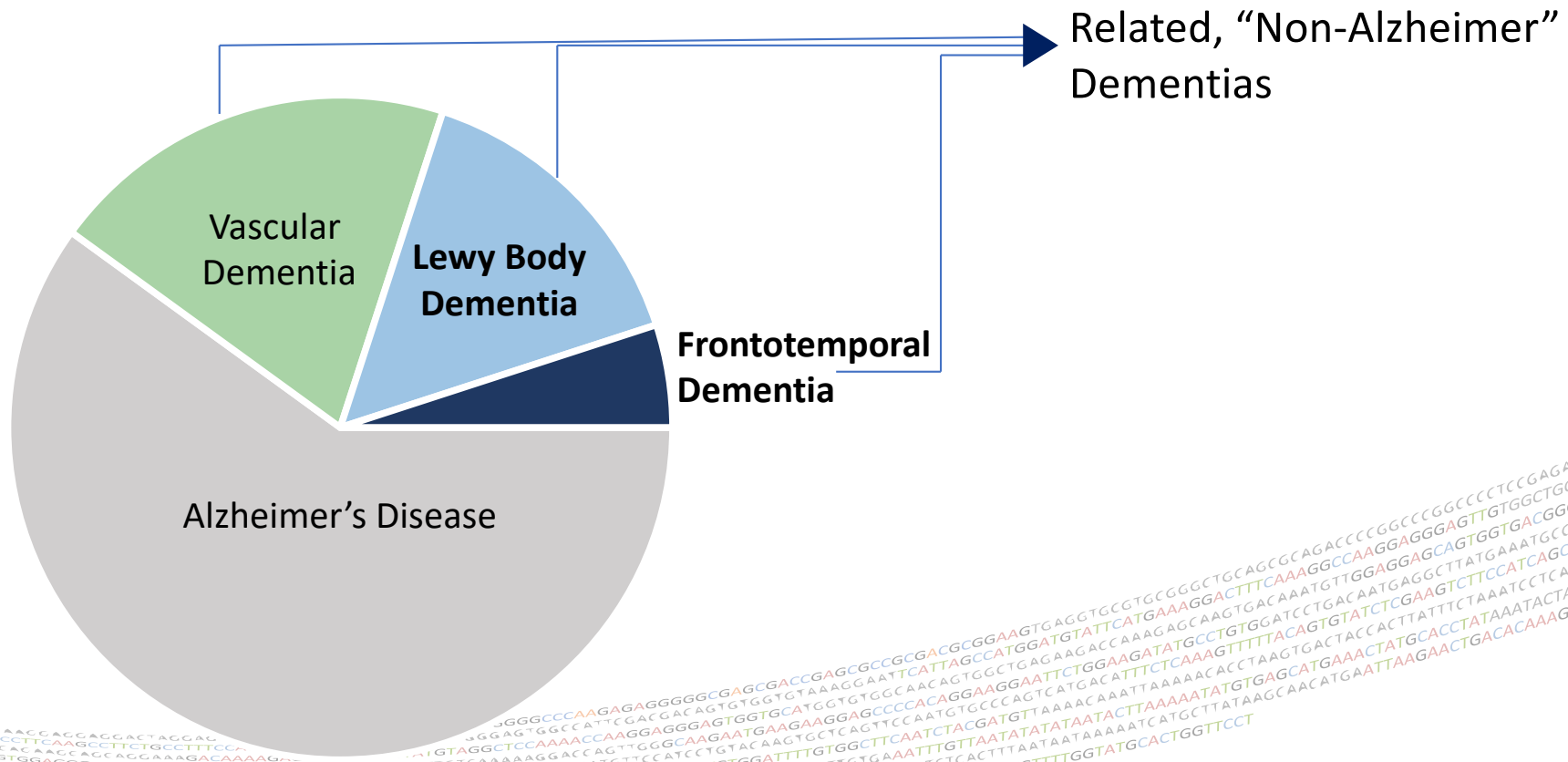
1 Background

2 Illustrative Cases

3 Current Genetics

4 Future Directions

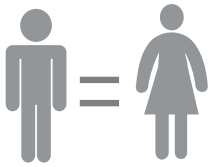
Age-Related Dementias

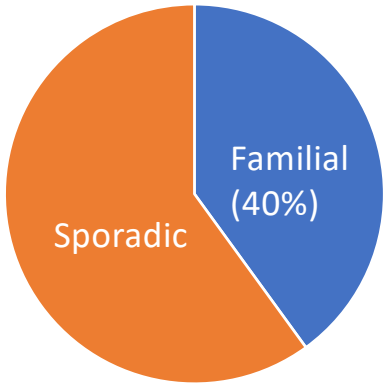


Background

- Second most common presenile dementia (<65 years)
- Middle-age onset dementia (< 65, younger than AD)
- Clinically, pathologically and genetically heterogeneous

Epidemiology of frontotemporal dementia

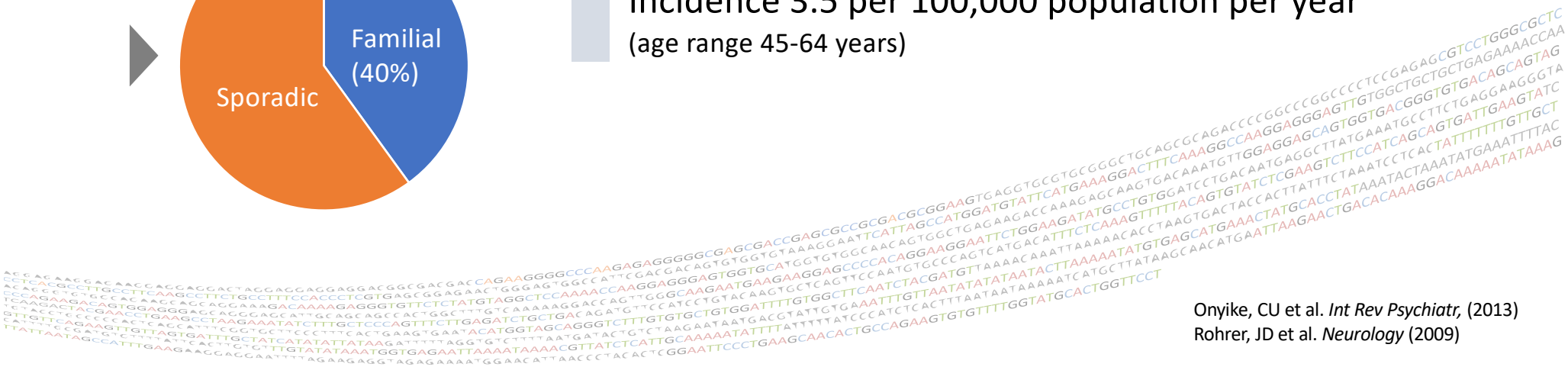




Prevalence 15-20 per 100,000 population

20,000 – 30,000 cases in the U.S.

Incidence 3.5 per 100,000 population per year
(age range 45-64 years)



Onyike, CU et al. *Int Rev Psychiatr,* (2013)
Rohrer, JD et al. *Neurology* (2009)

A Historic View on FTD

1892

1851 - 1924

71 year-old man with

- progressive cognitive decline
- personality change
- speech disorder: *impaired comprehension*
  paraphasias
  partial preservation of repetition

Asymmetric temporal atrophy on pathology

Pick A., Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie, *Prag Med Wochenschr*, 17, 165-7 (1892)
Image source: www.wikipedia.org

A Historic View on FTD

1892 1911

Alois Alzheimer
(1864 – 1915)

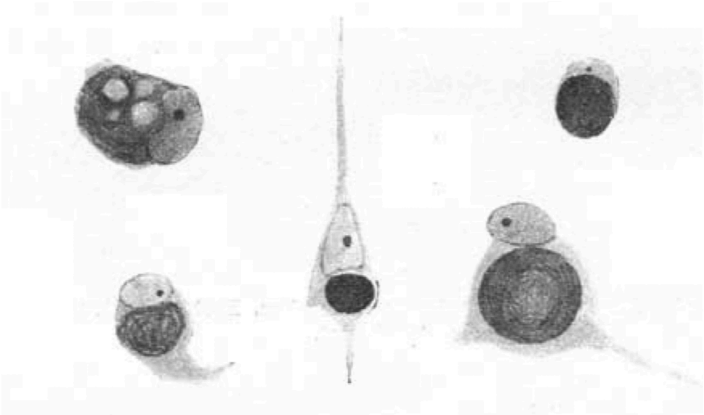


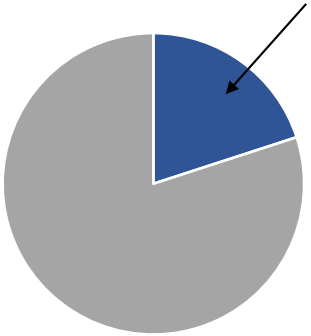
Illustration of argyrophilic Pick bodies by Alois Alzheimer. (*Z Gesamte Neurol Psychiatr* 1911; 4: 356–85).

Image source:
www.wikipedia.org

A Historic View on FTD

1892 — 1956 — 1974

Only 20% of cases have Pick bodies



First pathological classification

Escourolle, R. *La maladie de Pick. Etude D'ensemble et Syntese Anatomo-Clinique,* (1956)
Constantinidis, J. et al. *Eur Neurol* (1974)

A Historic View on FTD

Genetic studies reveal disease-causing mutations

Immunohistochemistry: diverse protein aggregations

Escourolle, R. *La maladie de Pick. Etude D'ensemble et Syntese Anatomo-Clinique,* (1956)
Constantinidis, J. et al. *Eur Neurol* (1974)

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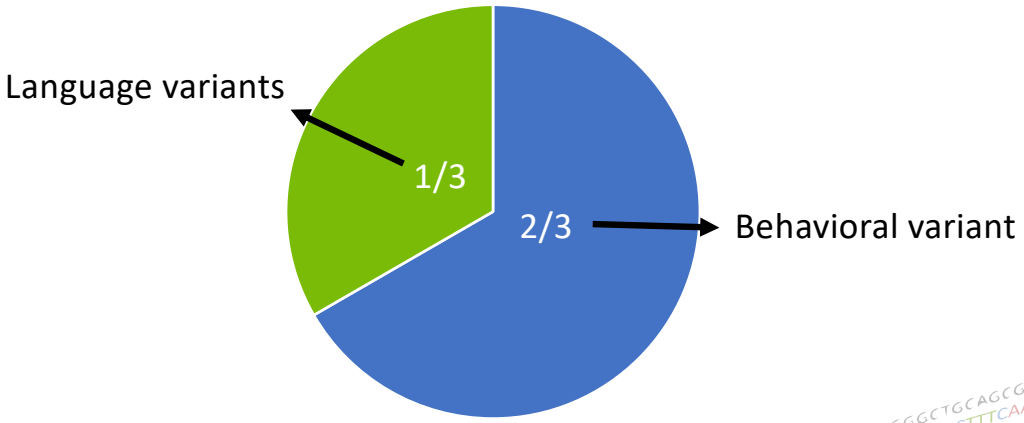
Clinical FTD Subtypes

FRONTOTEMPORAL DEMENTIA



Clinical Features of FTD

FRONTOTEMPORAL DEMENTIA

Behavioral variant
(Pick dementia)

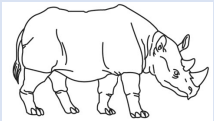
Change in personality:
- Disinhibition
- Apathy
- Loss of empathy

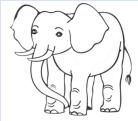
Change in behavior
- Hyperorality
- Obsessive-compulsive
- Stereotypies
- Executive dysfunction

Language variant (Primary progressive aphasia)

Non-fluent variant

Progressive language impairment
- Agrammatism
- Apraxia of speech
- Paraphasias (e.g. “rhinoferus”)
  (e.g. “lelefant”)





Semantic variant

Progressive language impairment
- Anomia
- Impaired comprehension
- Circumlocutious (e.g. ”a yellow food”)

Clinical Features of FTD

FRONTOTEMPORAL DEMENTIA		
Behavioral variant	Language variant (PPA)	
	Non-fluent variant	Semantic variant

Source: https://www.youtube.com/watch?v=14bWXgtvshc

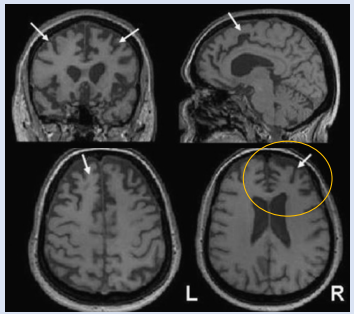
Source: https://www.youtube.com/watch?v=gYUGzCbNmNA

Neuroimaging in Clinical FTD Subtypes

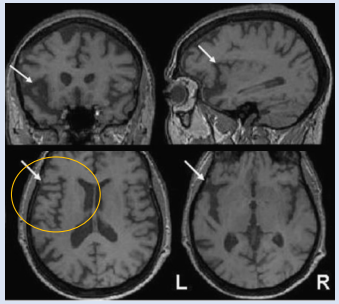
FRONTOTEMPORAL DEMENTIA

Behavioral variant	Language variant (PPA)	
	Non-fluent variant	Semantic variant

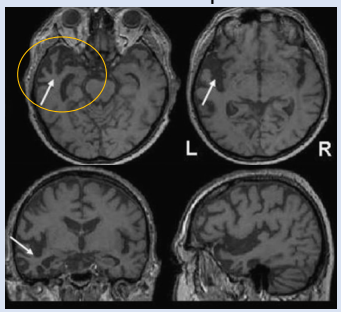
Symmetric or right frontal lobe



Left frontal lobe



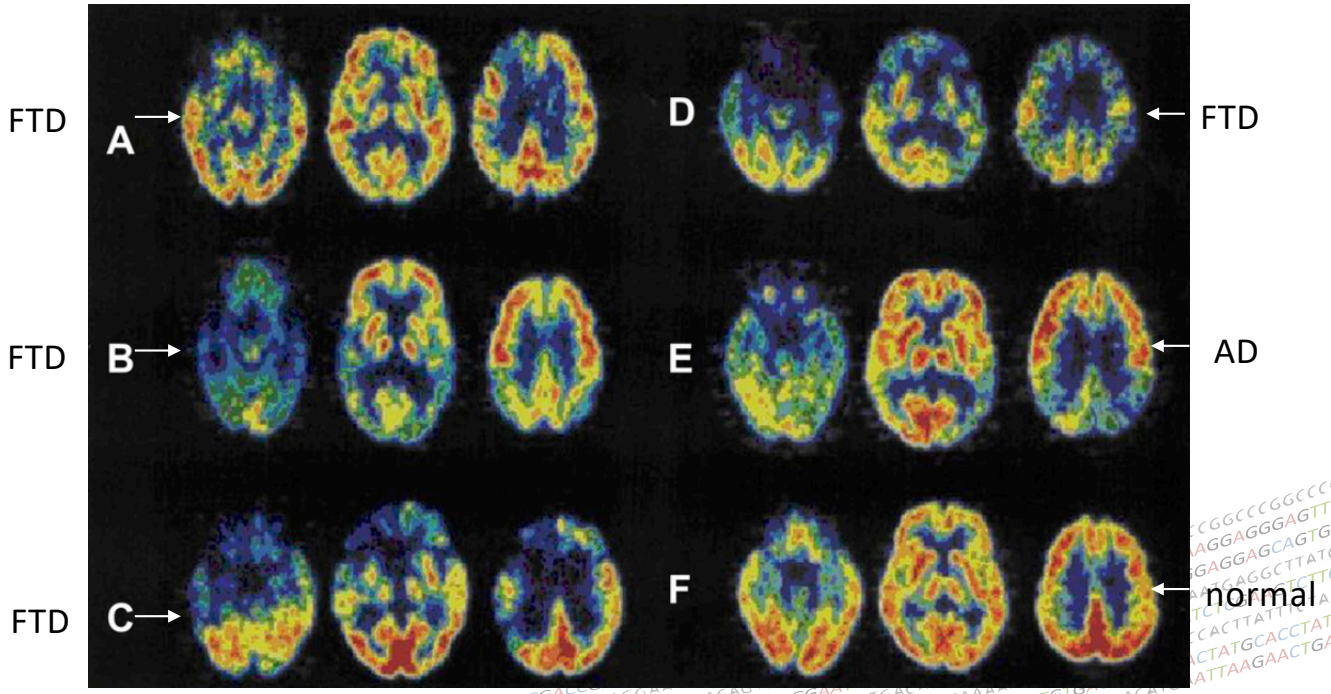
Left anterior temporal lobe



Acosta, F. et al. *Cortex* (2012)

Neuroimaging in Clinical FTD Subtypes

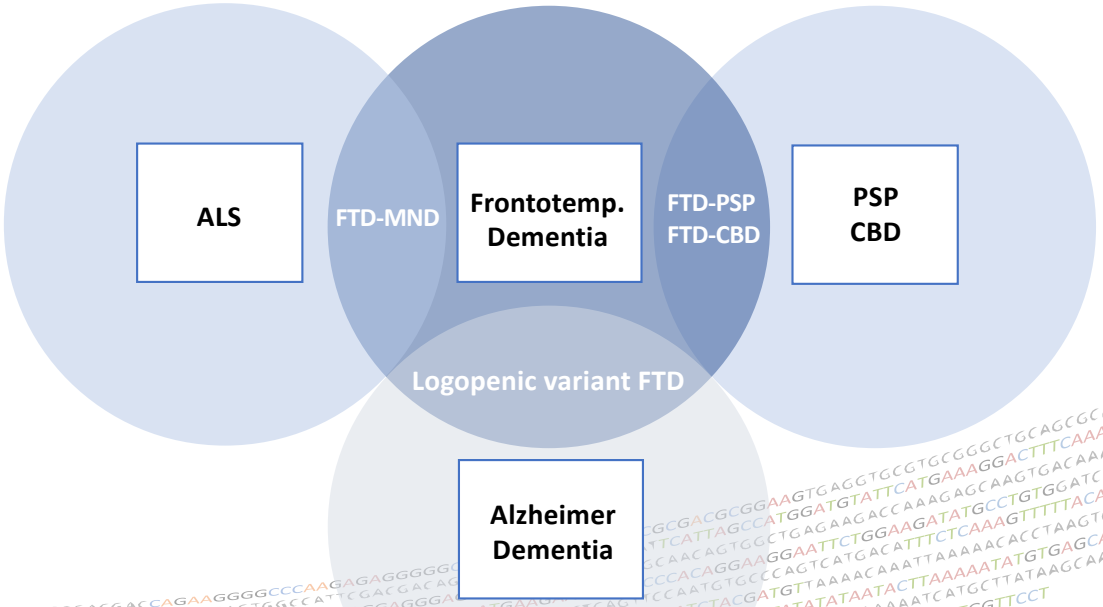
FDG-PET imagine



Acosta, F. et al. *Cortex* (2012)

Frontotemporal Lobar Degeneration Spectrum

- Overlap with motor neuron disease, Alzheimer's and atypical parkinsonism



The Treatment of FTD

Pharmacologic

SSRIs: depression, anxiety, disinhibition
Atypical neuroleptics: aggression, disinhibition
Acetylcholinesterase inhibitors: aphasia
Low dose dopaminergic agents: parkinsonism

symptomatic

Non-Pharmacologic

Social work
Physical therapy, occupational therapy, language therapy
Family counseling, support groups
Home safety inspections
Palliative care
Hospice care

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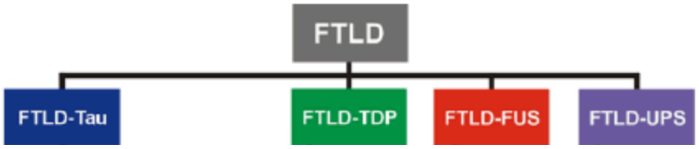
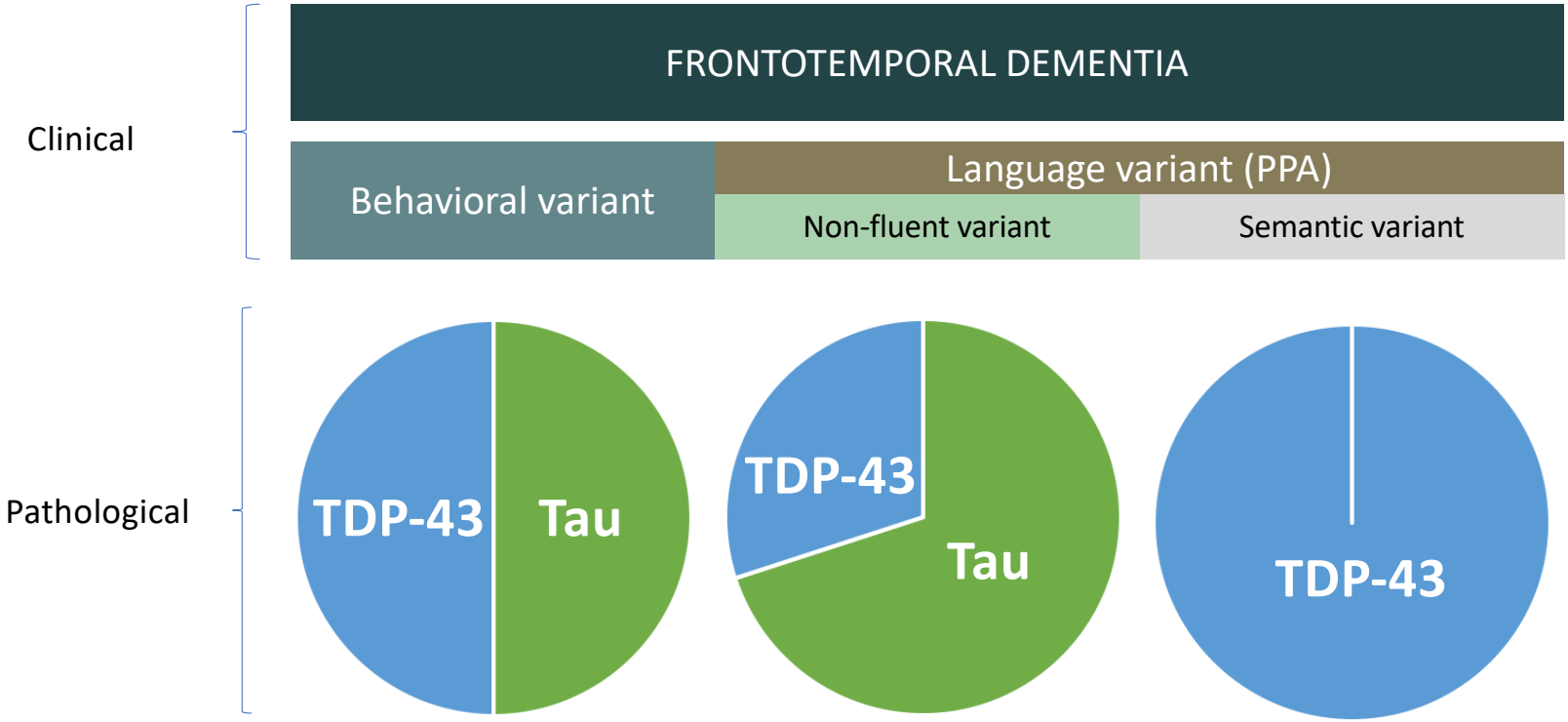
Abnormal Protein Aggregation

FRONTOTEMPORAL LOBAR DEGENERATION



Jellinger K, *Journal of Alzheimer disease and Parkinsonism*, 2017

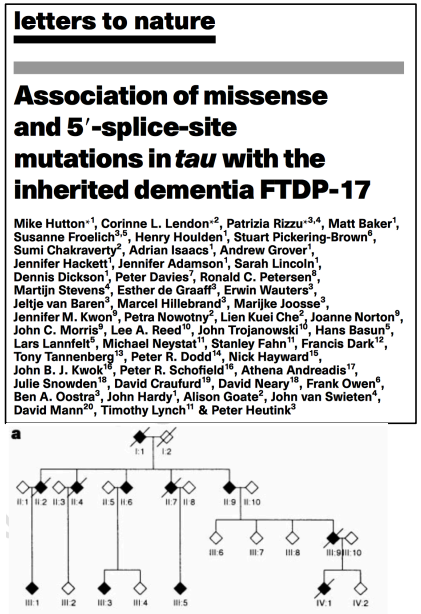
Abnormal Protein Aggregation



Genetics of FTD: *MAPT*

1892

1998

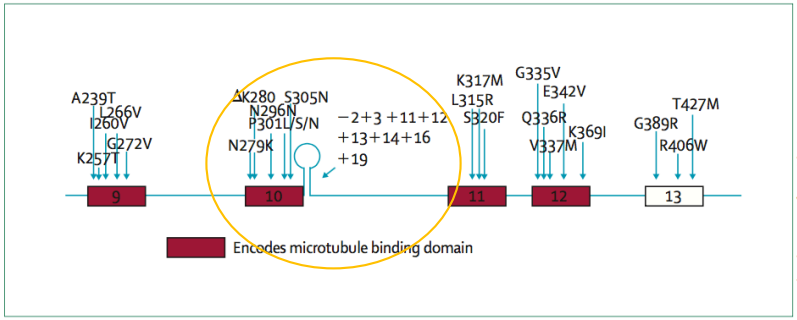


letters to nature

Association of missense and 5′-splice-site mutations in *tau* with the inherited dementia FTDP-17

Mike Hutton[*1], Corinne L. Lendon[*2], Patrizia Rizzu[*3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[7], Peter Davies[7], Ronald C. Petersen[8], Martijn Stevens[4], Esther de Graaff[3], Erwin Wauters[3], Jeltje van Baren[3], Marcel Hillebrand[3], Marijke Joosse[3], Jennifer M. Kwon[9], Petra Nowotny[2], Lien Kuei Che[2], Joanne Norton[9], John C. Morris[9], Lee A. Reed[10], John Trojanowski[10], Hans Basun[5], Lars Lannfelt[5], Michael Neystat[11], Stanley Fahn[11], Francis Dark[12], Tony Tannenberg[13], Peter R. Dodd[14], Nick Hayward[15], John B. J. Kwok[16], Peter R. Schofield[16], Athena Andreadis[17], Julie Snowden[18], David Craufurd[18], David Neary[18], Frank Owen[6], Ben A. Oostra[3], John Hardy[1], Alison Goate[2], John van Swieten[4], David Mann[20], Timothy Lynch[11] & Peter Heutink[3]

10% of familial FTD cases



Missense & splice-site mutations

Gain of function

Neary, D. et al. *Lancet Neurol* (2005)

Tauopathies

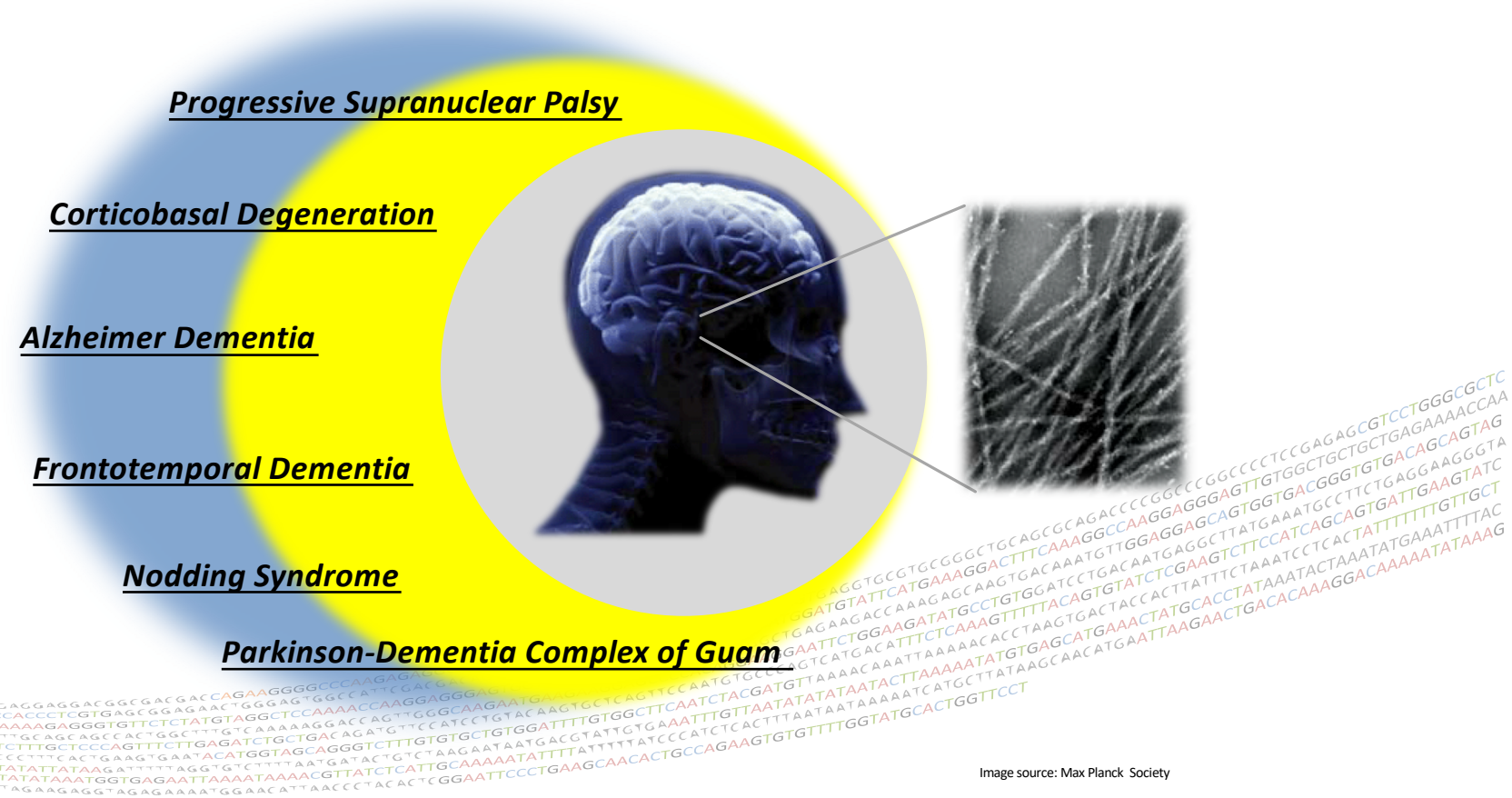


Image source: Max Planck Society

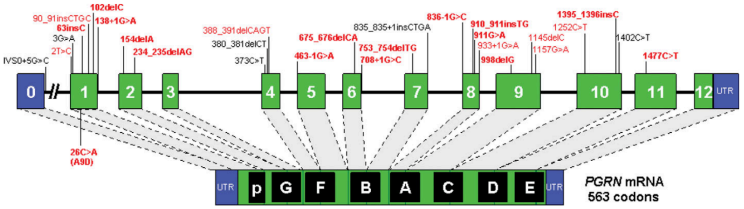
The Genetics of FTD: *GRN*

1892 — 2006

10% of familial cases

Heterozygous missense mutations

Haploinsufficiency



Gass, J et al., *Hum Mol Genet* (2006)

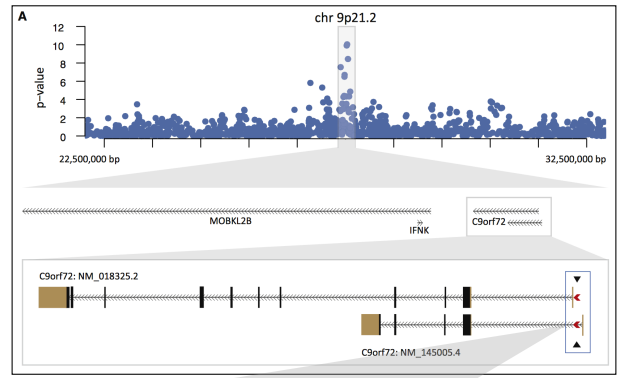
The Genetics of FTD: *C9orf72*

1892 — 2011

30% of familial cases

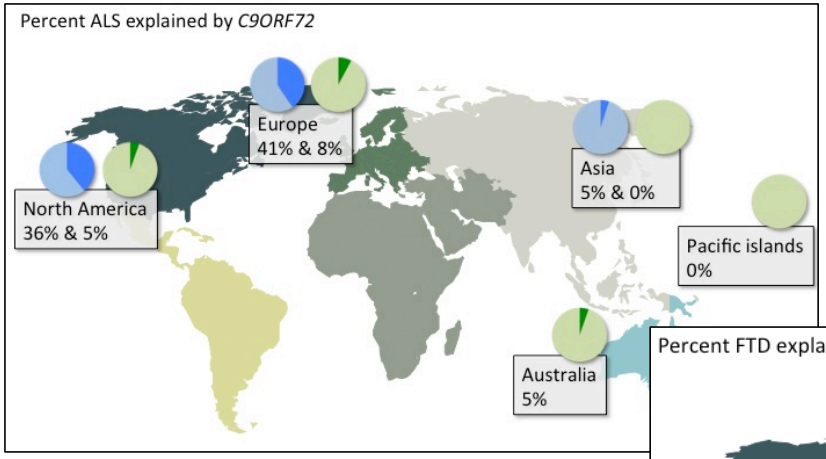
Hexanucleotide repeat expansion
[GGGGCC]n x 700-1600 (nr: <30 repeats)

Molecular link between FTD & ALS

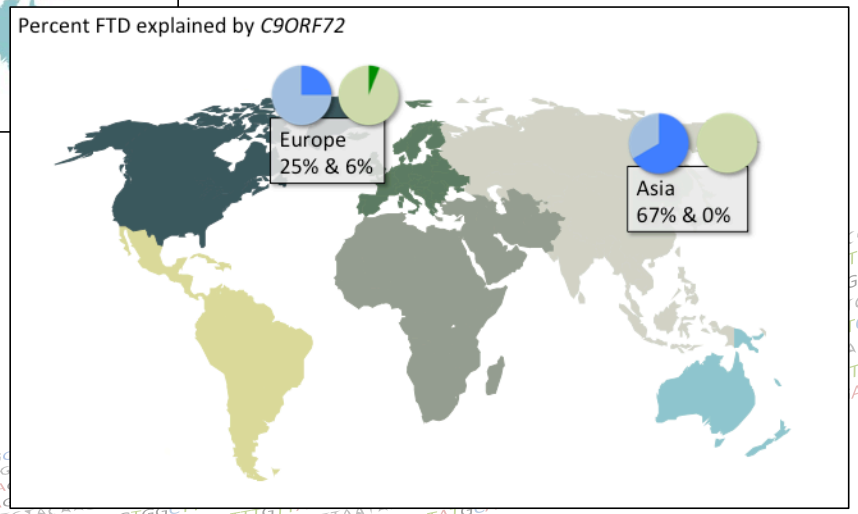


Renton, A et al., *Neuron* (2011)
DeJesus-Hernandez, et al., *Neuron* (2011)

Global Incidence of *C9orf72*



40% of familial ALS
8% of sporadic ALS

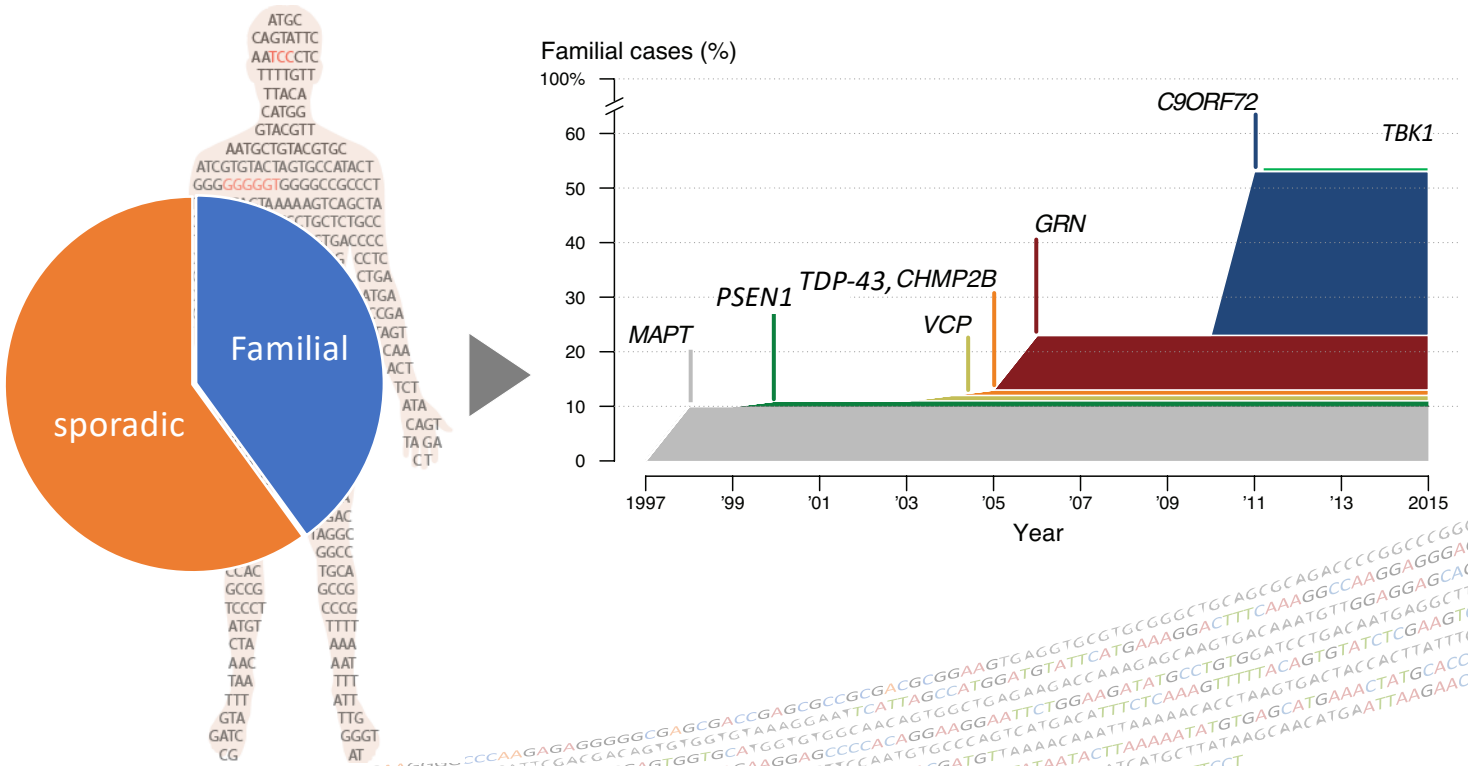


25-67% of familial FTD
6% of sporadic FTD

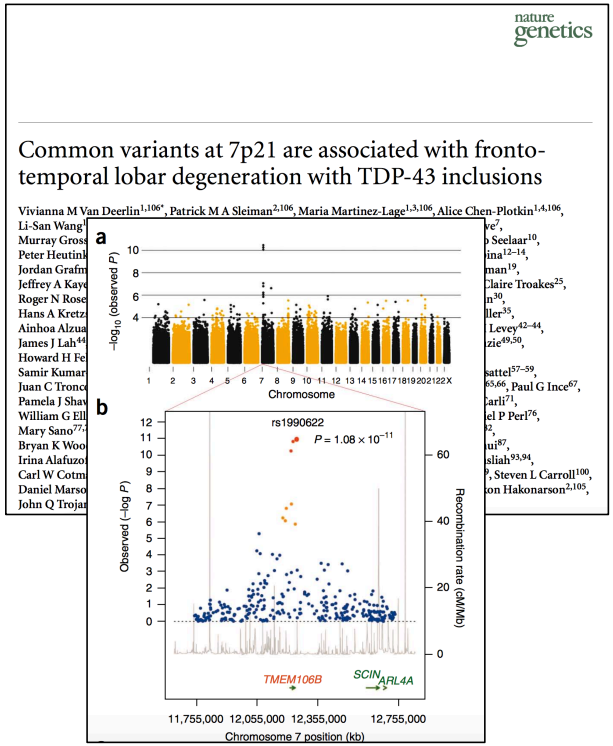
N = 4,448 ALS and 1,425 FTD

Majounie, E et al, *Lancet Neurol* (2012)

The Genetics of FTD



FTD GWAS: a Role for Common Variants?



N=515 FTD-TDP patients, 2509 controls

Replication: 89 cases, 553 controls

European ancestry FTD-TDP cases

Increased expression of TMEM106B

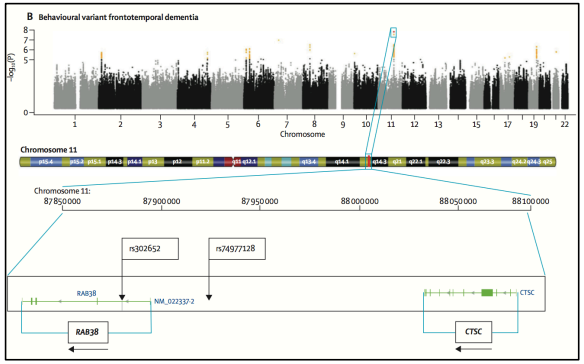
Lysosomal metabolism

Van Deerlin, V et al. *Nature Genetics* (2010)

FTD GWAS: a Role for Common Variants?

Frontotemporal dementia and its subtypes: a genome-wide association study

Raffaele Ferrari, Dena G Hernandez*, Michael A Nalls*, Jonathan D Rohrer*, Adaikalavan Ramasamy, John B J Kwok, Carol Dobson-Stone, William S Brooks, Peter R Schofield, Glenda M Halliday, John R Hodges, Olivier Piguet, Lauren Bartley, Elizabeth Thompson, Eric Haan, Isabel Hernández, Agustín Ruiz, Mercè Boada, Barbara Borroni, Alessandro Padovani, Carlos Cruchaga, Nigel J Cairns, Luisa Benussi, Giuliano Binetti, Roberta Ghidoni, Gianluigi Forloni, Daniela Galimberti, Chiara Fenoglio, Maria Serpente, Elio Scarpini, Jordi Clarimón, Alberto Lleó, Rafael Blesa, Maria Landqvist Waldö, Karin Nilsson, Christer Nilsson, Ian R A Mackenzie, Ging-Yuek R Hsiung, David M A Mann, Jordan Grafman, Christopher M Morris, Johannes Attems, Timothy D Griffiths, Ian G McKeith, Alan J Thomas, P Pietrini, Edward D Huey, Eric M Wassermann, Atik Baborie, Evelyn Jaros, Michael C Tierney, Pau Pastor, Cristina Razquin, Sara Ortega-Cubero, Elena Alonso, Robert Perneczky, Janine Diehl-Schmid, Panagiotis Alexopoulos, Alexander Kurz, Innocenzo Rainero, Elisa Rubino, Lorenzo Pinessi, Ekaterina Rogaeva, Peter St George-Hyslop, Giacomina Rossi, Fabrizio Tagliavini, Giorgio Giaccone, James B Rowe, Johannes C M Schlachetzki, James Uphill, John Collinge, Simon Mead, Adrian Danek, Vivianna M Van Deerlin, Murray Grossman, John Q Trojanowski, Julie van der Zee, William Deschamps, Tim Van Langenhove, Marc Cruts, Christine Van Broeckhoven, Stefano F Cappa, Isabelle Le Ber, Didier Hannequin, Véronique Golfier, Martine Vercelletto, Alexis Brice, Benedetta Nacmias, Sandro Sorbi, Silvia Bagnoli, Irene Piaceri, Jørgen E Nielsen, Lena E Hjermind, Matthias Riemenschneider, Manuel Mayhaus, Bernd Ibach, Gilles Gasparoni, Sabrina Pichler, Wei Gu, Martin N Rossor, Nick C Fox, Jason D Warren, Maria Grazia Spillantini, Huw R Morris, Patrizia Rizzu, Peter Heutink, Julie S Snowden, Sara Rollinson, Anna Richardson, Alexander Gerhard, Amalia C Bruni, Raffaele Maletta, Francesca Frangipane, Chiara Cupidi, Livia Bernardi, Maria Anfossi, Maura Gallo, Maria Elena Conidi, Nicoletta Smirne, Rosa Rademakers, Matt Baker, Dennis W Dickson, Neill R Graff-Radford, Ronald C Petersen, David Knopman, Keith A Josephs, Bradley F Boeve, Joseph E Parisi, William W Seeley, Bruce L Miller, Anna M Karydas, Howard Rosen, John C van Swieten, Elise G P Dopper, Harro Seelaar, Yolande A L Pijnenburg, Philip Scheltens, Giancarlo Logroscino, Rosa Capozzo, Valeria Novelli, Annibale A Puca, Massimo Franceschi, Alfredo Postiglione, Graziella Milan, Paolo Sorrentino, Mark Kristiansen, Huei-Hsin Chiang, Caroline Graff, Florence Pasquier, Adeline Rollin, Vincent Deramecourt, Florence Lebert, Dimitrios Kapogiannis, Luigi Ferrucci, Stuart Pickering-Brown, Andrew B Singleton†, John Hardy†, Parastoo Momeni†*

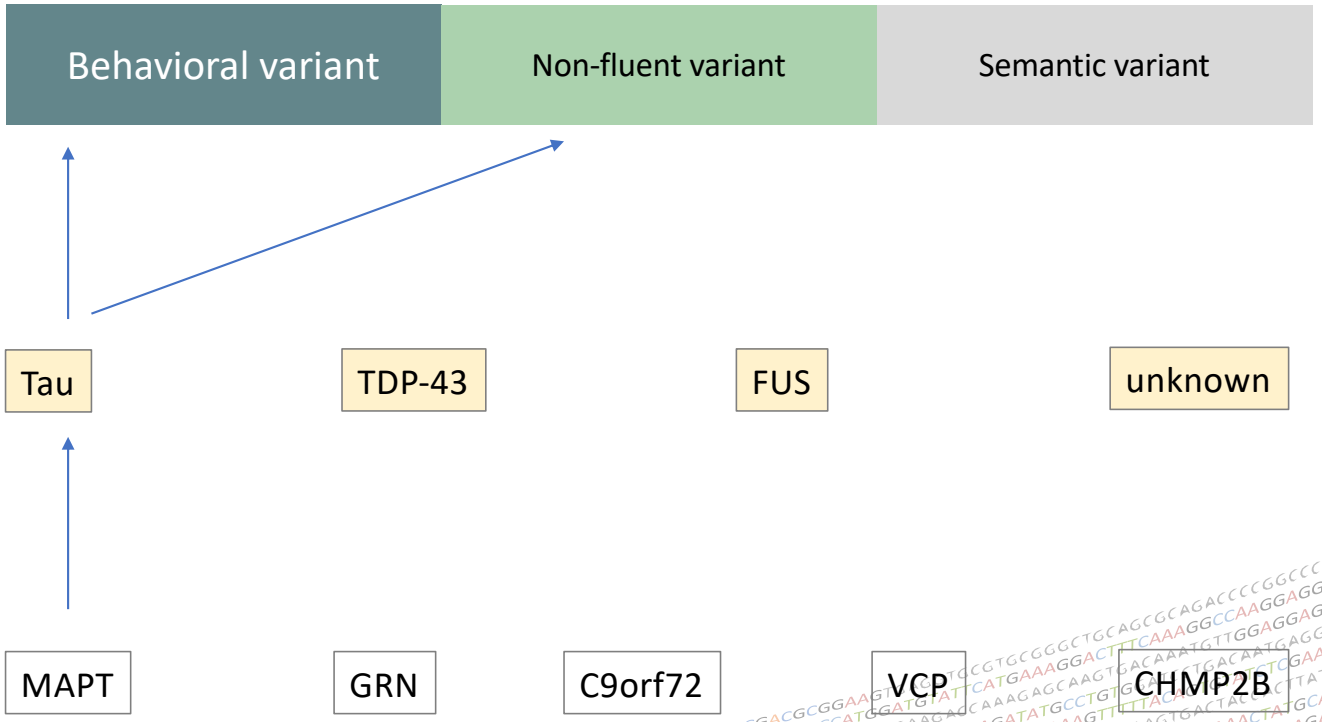


N=2154 FTD patients, 4308 controls

- European ancestry FTD cases
- RAB38/CTSc in bvFTD
- Lysosomal metabolism

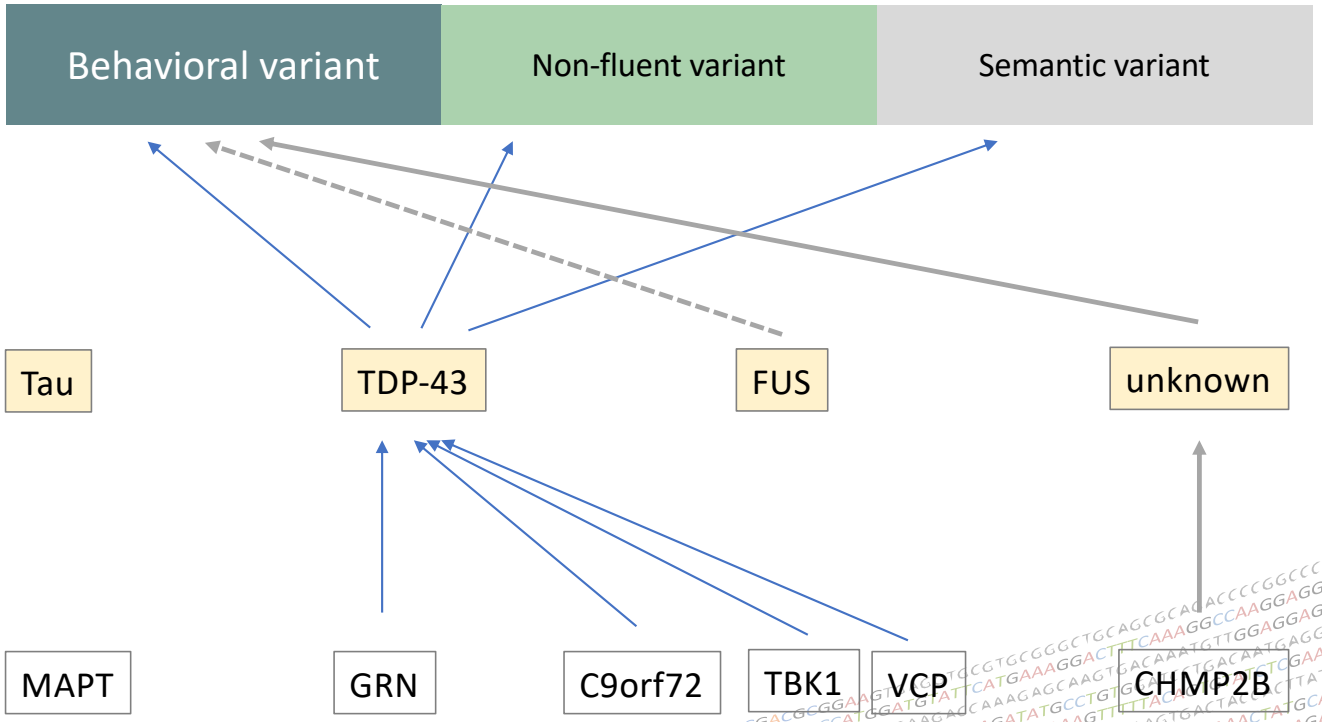
Ferrari, R et al. *Lancet Neurology* (2014)

Genotype-Phenotype Correlations



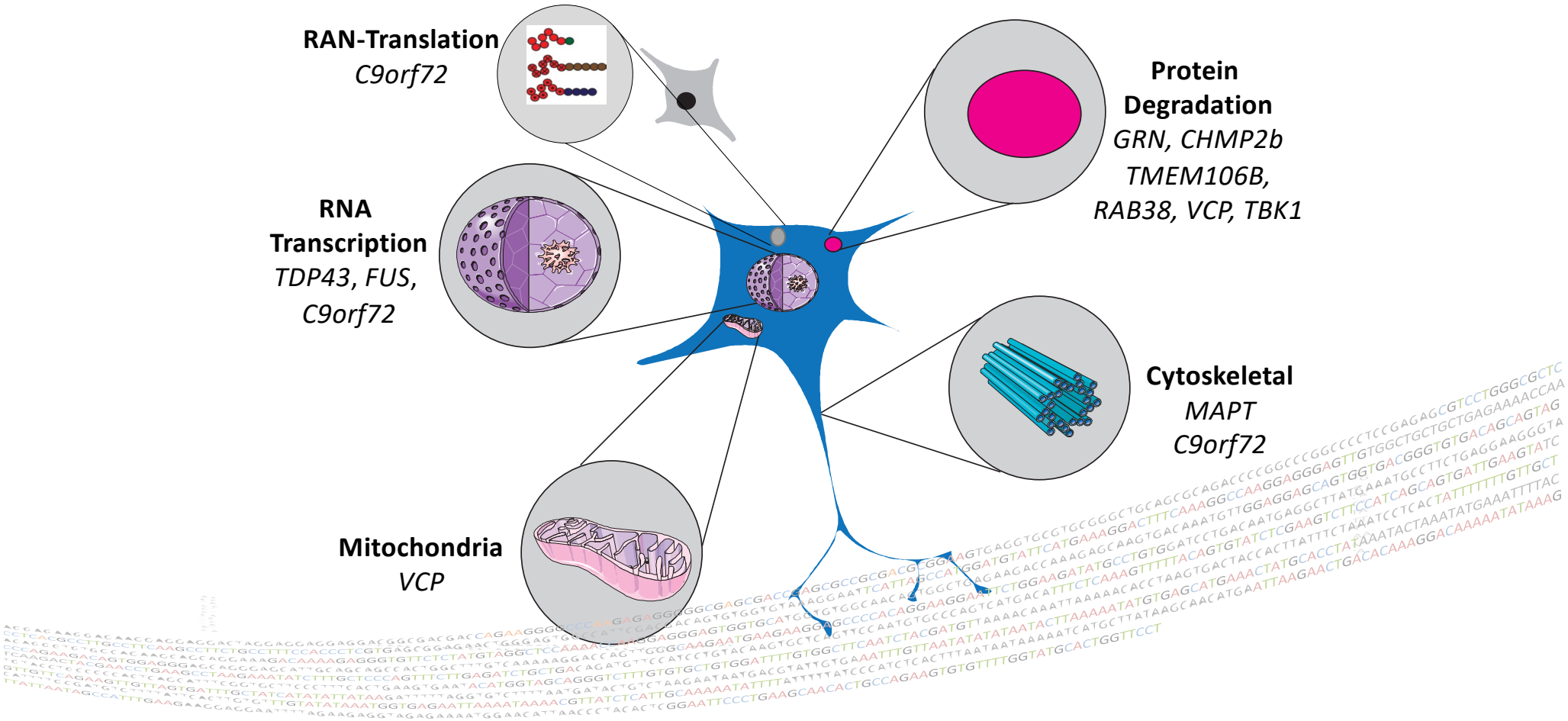
Adapted from Kurz, A et al. *Maturitas* (2014)

Genotype-Phenotype Correlations



Adapted from Kurz, A et al. *Maturitas* (2014)

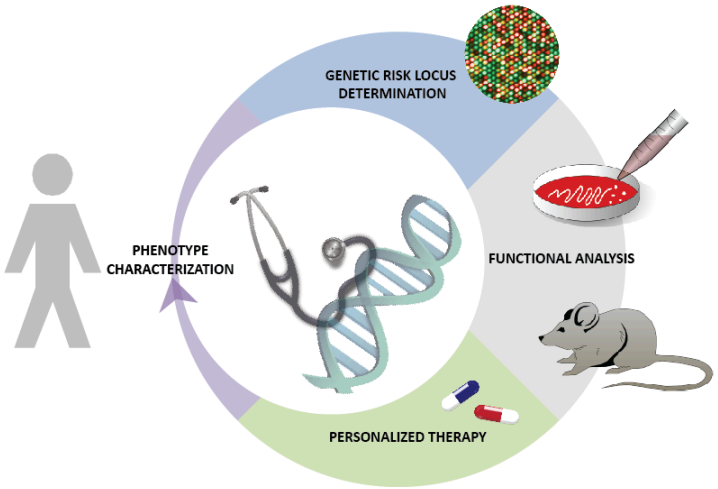
Pathogenic Mechanisms of FTD



Genomics of FTD: Future Directions

- Genomic research highlights molecular defects involved in the pathogenesis of neurodegeneration
- Causative/Risk genes provide clues for rational, targeted interventions
- Ongoing work: Dementia Sequencing Initiative

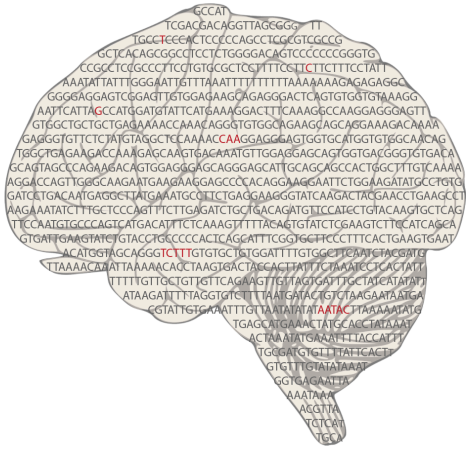
Future Directions in FTD: Disease Modification



- Anti-tau antibodies
- Antisense oligonucleotides
- Progranulin enhancers
- tDCS

Scholz, SW et al. *Cold Spring Harb Perspect Med* (2012)

Summary



- Common form of dementia
- Clinically, pathologically and genetically heterogeneous
- Treatment is supportive
- Pathogenesis is poorly understood

Questions?