Disclosures

- **Relationships with commercial interests:**
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  - **Other:** Royalties from Henry Stewart Talks Ltd.

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Genetics of Frontotemporal Lobar Degeneration (FTLD)

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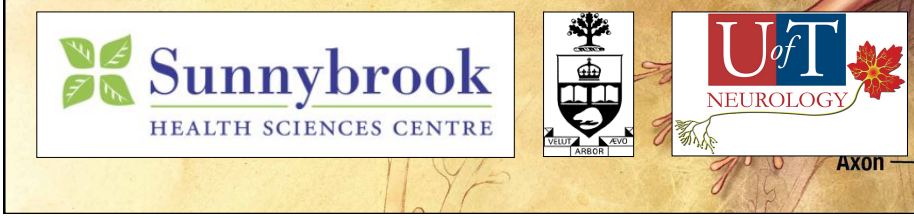
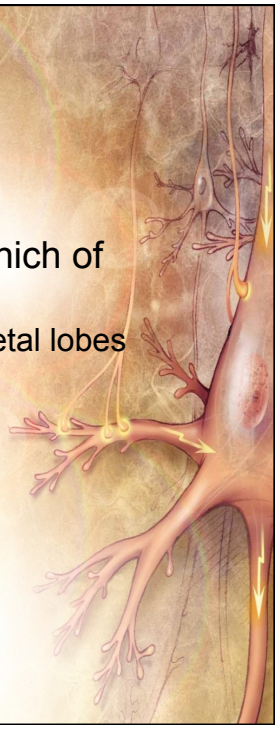
Staff Neurologist, Sunnybrook Health Sciences Centre

Behavioural Neurology Clinic Day & Toronto Neurology Update
October 16, 2015



Pre-test 1

- *PGRN* mutations are associated with which of following:
  - RED: asymmetric atrophy involving the parietal lobes
  - BLUE: midbrain atrophy
  - WHITE: ALS
  - BLACK: long disease course



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Pre-test 2

- *C9ORF72* hexanucleotide repeat expansions are associated with which of following:
  - RED: shorter disease course when ALS is not present
  - BLUE: midbrain atrophy
  - WHITE: ALS
  - BLACK: striking asymmetry on MRI

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Objectives

- Cases
- Review the most common genetic causes of FTLD
- Clinical features associated with different genetic groups
- Ethical issues that should be considered in genetic testing

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Case 1

Case 1

- ID: 57 y.o. R-handed M; working as engineer; 18 years of education (M.Sc. Engineering); bilingual, fluent ESL
- CC: “progressive language disturbance”
  - AOO 55 y.o.
- PMH:
  - hypercholesterolemia
- Family history:
  - +ve for FTD

Case 1

HPI (age 57):

- Insidious onset and gradual decline in speech fluency
- Frequent word-finding difficulties - interrupted verbal output
- Preferred to use native language
- Intermittent echolalia
- No loss of word meaning
- No behavioural or personality change
- No neuropsychiatric symptoms
- No memory or visuospatial troubles

Case 1

Examination (age 57):

- MMSE = 22/30 (limited by aphasia)
- BNA:
  - Spontaneous speech output reduced; struggled to find words
  - Comprehension, repetition, naming of both high and low frequency words, and reading – intact
  - semantically- (animal) and phonemically-cued (f) word list generation in one minute – impaired
  - Written description of cookie theft picture – use of simplified sentences with sparse, but accurate description
  - Mild impairment of working memory and executive functions
- DAD – ADLs and iADLs intact
- Early right hand ideomotor apraxia – hand as comb
- General and neurological exam - normal

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Where is the lesion?

- Left frontal – particularly posterior inferior (Broca's)
- Left insula
- ± Left parietal

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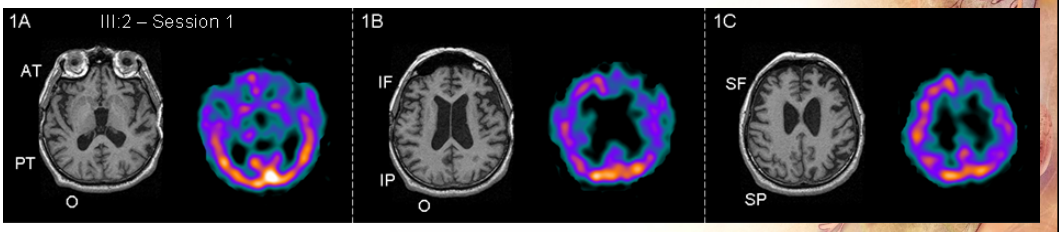
Neuroimaging



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What is the clinical diagnosis?

- Primary Progressive Aphasia – Progressive Non-fluent Aphasia (PNFA)

What is the lesion?

- FTD (Tau or U/TDP-43)
- Pick's disease
- CBD
- PSP
- AD (logopenic variant)
- R/O structural lesion

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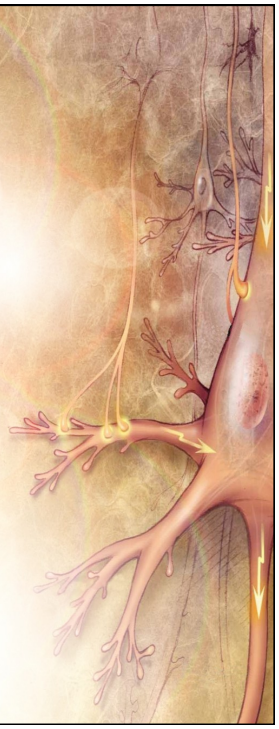
Case 2



Case 2

- ID: 64 y.o. R-handed M; working as managing director; 16 years of education
- CC: “slowness, apathy, and somnolence”
  - AOO 62 y.o.
- PMH:
  - None
- Family history:
  - +ve for FTD

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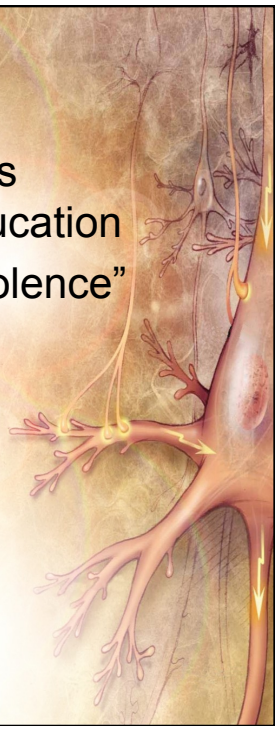

Case 2

HPI (age 64):

- Insidious onset and gradual change in personality and behaviour
- Initially withdrawn; less talkative
- Gave up his hobbies
- Troubles with handling familiar objects
- Months later, social judgement deteriorated:
  - Breakdown in formalities – poor table manners
  - Disinhibited
  - Irritability when opposed

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Case 2

Examination (age 64):

- Cognitive testing:
  - Impaired executive functions
  - Difficulties switching between categories
  - Poor attention
  - Visuospatial difficulties
  - Relatively intact delayed memory
  - NPI = 23/144
- Impaired ADLs and iADLs

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Case 2

Examination (age 64):

- General exam - normal
- Neurological exam:
  - moderately impaired monotone, slurred speech
  - minimal hypomimia
  - resting tremor of upper extremities, moderate in amplitude
  - moderate rigidity
  - severe motor slowness of gait
  - multi-step turning with postural instability

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Where is the lesion?

- Early on - medial and dorsolateral prefrontal
- Later on – orbitofrontal and right anterior temporal
- Right parieto-occipital
- Basal ganglia

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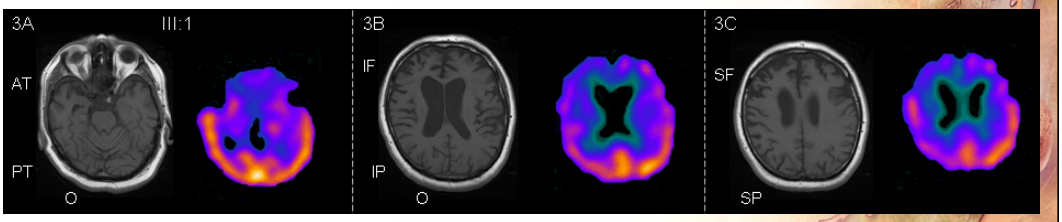
Neuroimaging



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What is the clinical diagnosis?

- bvFTD with parkinsonism

What is the lesion?

- FTD (Tau or U/TDP-43)
- FTDP-17
- Pick's disease
- CBD
- PSP
- DLB
- AD

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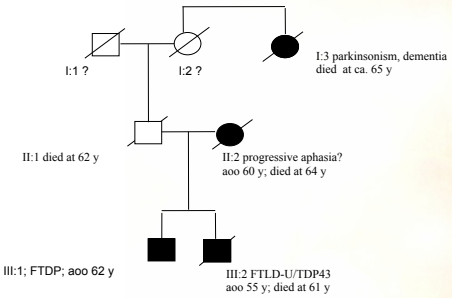
Family-genetic study

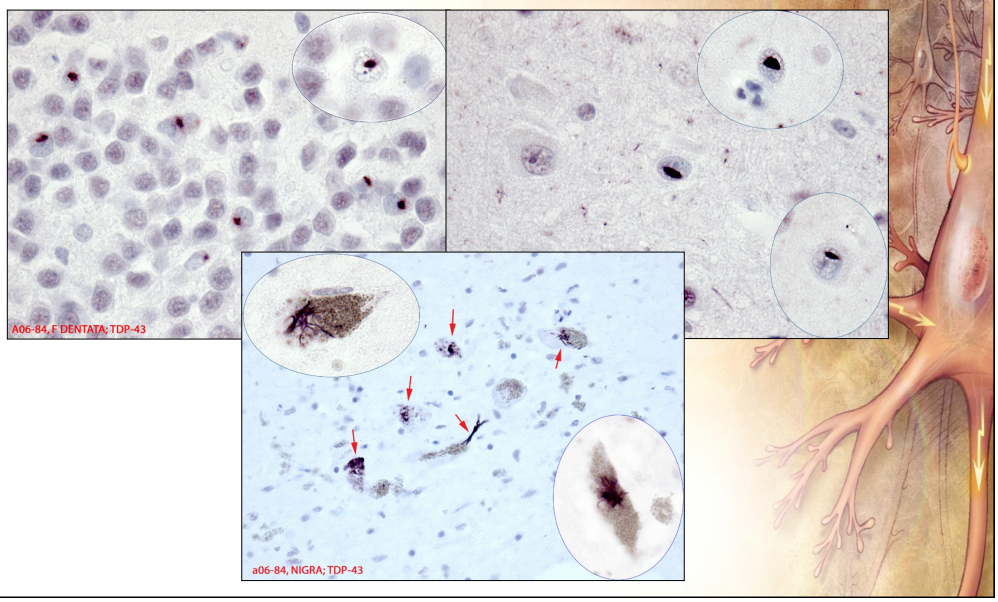


Novel PGRN mutation – CA dinucleotide deletion

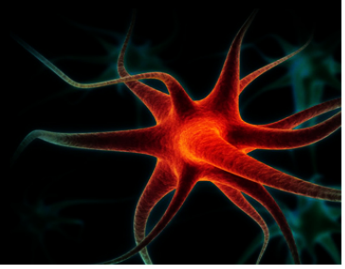
g.2988_2989delCA, c.1536_1537delCA, P439_R440fsX6

Pathology

TDP-43 Neuropathology of Case 1



Case 3

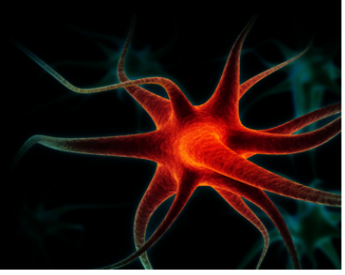


2001

- ID: 63y, left-handed caucasian male
  married with 3 children, 18 yrs of education,
  senior engineer for 37 years

- CC: forgetful, easily angered, paranoid thoughts

- PMH: - depression since Feb 2000
  - concussion (1988)
  - TIA? (April 2000)
  - no cardiovascular risk factors

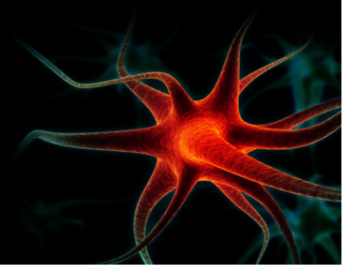


- Meds: - Zyprexa (2.5mg Bid)
  - Ativan (prn)

- Allergy: none

- Habits: non smoker, 5 drinks/wk, no drugs

- Family history: dementia (father)



HPI:

- Age 62: Insidious onset - short term memory impairment
  - irritable & defensive
  - poor concentration
- Diagnosed with depression, no response to Rx
- Age 63: worsening of symptoms, unable to work
- New symptoms:
  - delusions (paranoia, persecutory)
  - obsessive compulsive behavior
  - inappropriate social behavior
  - needed direction for iADLs
  - unable to distinguish fiction from reality
  - perseverative behaviors
  - word finding difficulties

Examination:

- General exam unremarkable
- MMSE: 27/30
  - recall memory
  - orientation
- Neuropsychological testing:
  - short term memory deficits (benefit from cueing)
  - impaired visual memory (immediate and delayed)
  - impaired executive functions
  - anomia
  - visuospatial impairment
  - neuropsychiatry inventory (NPI) score: 34/144
- Increased tone and cogwheeling Rt arm
- Positive Glabellar and palmomental reflexes
- Right cortical sensory deficits
  - impaired extinction and astereognosis

2002-2004

- Slowly declining with fluctuating course
  '' his mental ability is all over the map''

- New cognitive symptoms:
  - more apathetic
  - socially withdrawn,
  - decreased speech, conversation limited to yes and no
- on Zyprexa, Celexa and vitamin B12 supplements

- MMSE: 26/30
- Neuropsychological testing:

- worsening of previous deficits (esp. naming, semantic fluency)
  plus impairments in: - abstract thinking/inductive reasoning
  - Ideomotor praxis
  and perseverative errors in memory testing

2005-2006

- more rapid decline, completely dependent for his iADLS & ADLs
- MMSE: 23/30
- New neurology findings: brisk reflexes, decreased arm swing, poor saccade

April 2007

Interruption in his day program, refused eating and drinking, severe dehydration, admit to hospital,
further complications: pneumonia, VRE (+)

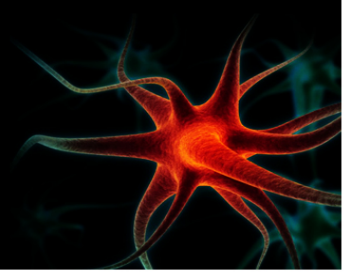
July 2008

Transferred to long term care
Very flat affect, completely mute, very disinhibited and agitated, restrained most of the time, ignoring visitors

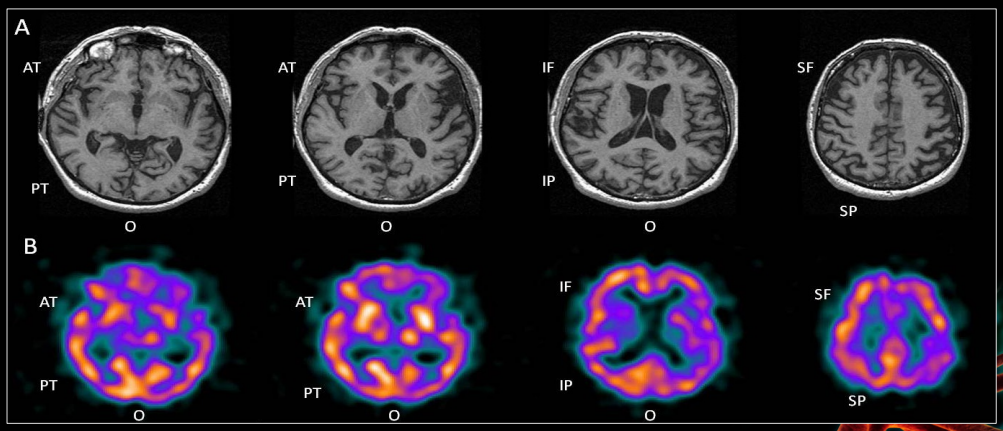
Sep 2009 passed away, complications of dementia

Where are the lesions?

- Right parietal lobe
- Left parietal lobe
- Left peri-sylvian
- Frontal lobe
- Limbic system

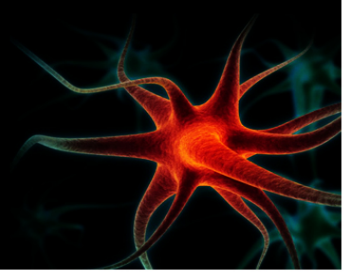


Neuroimaging:



Differential diagnosis?

- **bv-FTD with parkinsonism**
- CBS
- DLB
- AD



Genetic testing

an expanded GGGGCC hexanucleotide repeat in the noncoding region of chromosome 9 open reading frame 72 *(C9ORF72)* (>60 repeats)

(presence of the mutation: repeat lengths >30)

Mutations of other genes e.g. *MAPT*, *PGRN, FUS* were excluded

Frontotemporal Dementia(s)

- Second most common cause of dementia under age 65 – Age At Onset = 45 to 65
- Predominant frontal and/or temporal lobe symptoms:
  - Frontal or behavioural variant
  - Language variant (Neary et al., 1998)
- May be associated with motoneuron disease and/or Parkinsonism
- Up to 40% of cases are familial

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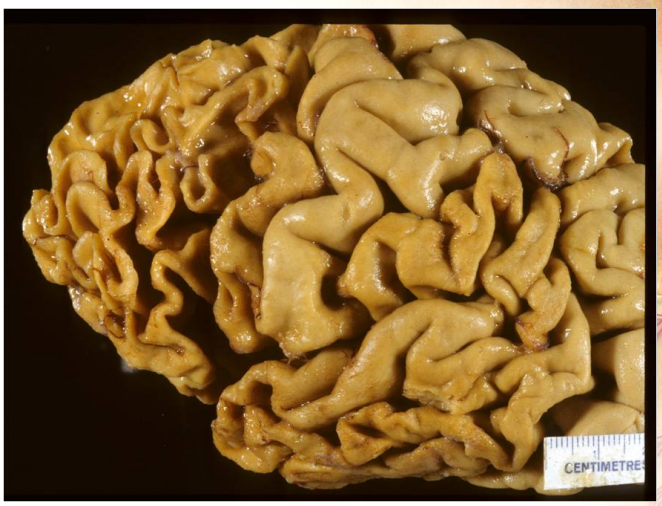
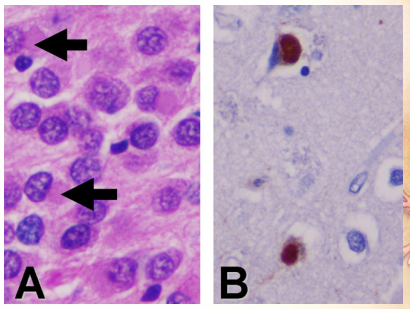
Frontotemporal Atrophy

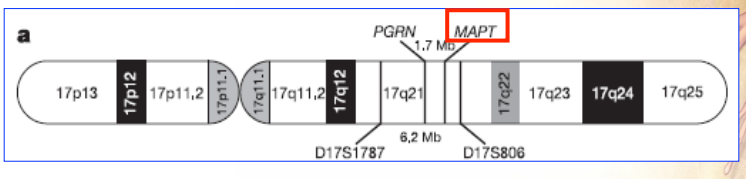


Frontotemporal Dementia(s) II

- < ½ of familial cases show TAU-positivity
  Autosomal dominant linked to chromosome 17q21

Pick Bodies (Tau)





Frontotemporal Dementia(s) III

The genetic puzzle emerges….

- MAPT mutations were excluded in several FTD families linked to chromosome 17q21
- TAU-neg, Ubiquitin-pos cytoplasmic and intranuclear inclusions
- Suggested another disease locus existed on chromosome 17q21 linked to MAPT

doi:10.1038/nature05016 nature

LETTERS

Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

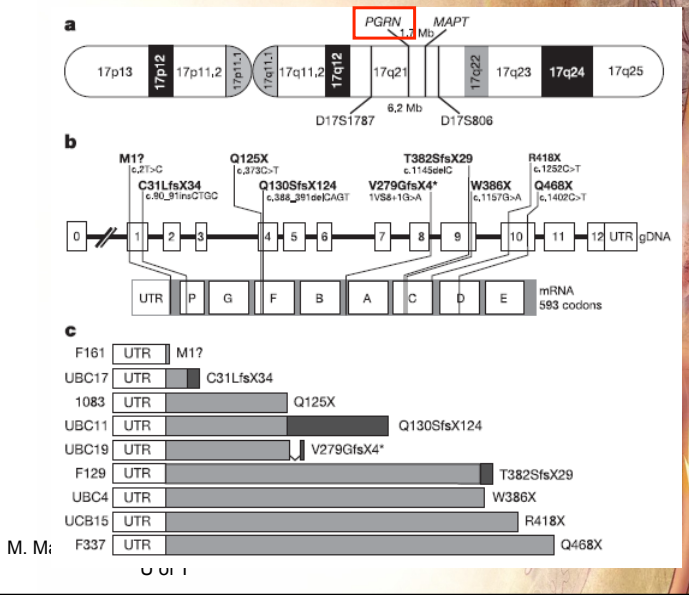
Matt Baker[1]*, Ian R. Mackenzie[2]*, Stuart M. Pickering-Brown[5,6]*, Jennifer Gass[1], Rosa Rademakers[1], Caroline Lindholm[3], Julie Snowden[6], Jennifer Adamson[1], A. Dessa Sadovnick[3,4], Sara Rollinson[5], Ashley Cannon[1], Emily Dwosh[4], David Neary[6], Stacey Melquist[1], Anna Richardson[6], Dennis Dickson[1], Zdenek Berger[1], Jason Eriksen[1], Todd Robinson[1], Cynthia Zehr[1], Chad A. Dickey[1], Richard Crook[1], Eileen McGowan[1], David Mann[6], Bradley Boeve[7], Howard Feldman[3] & Mike Hutton[1]

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

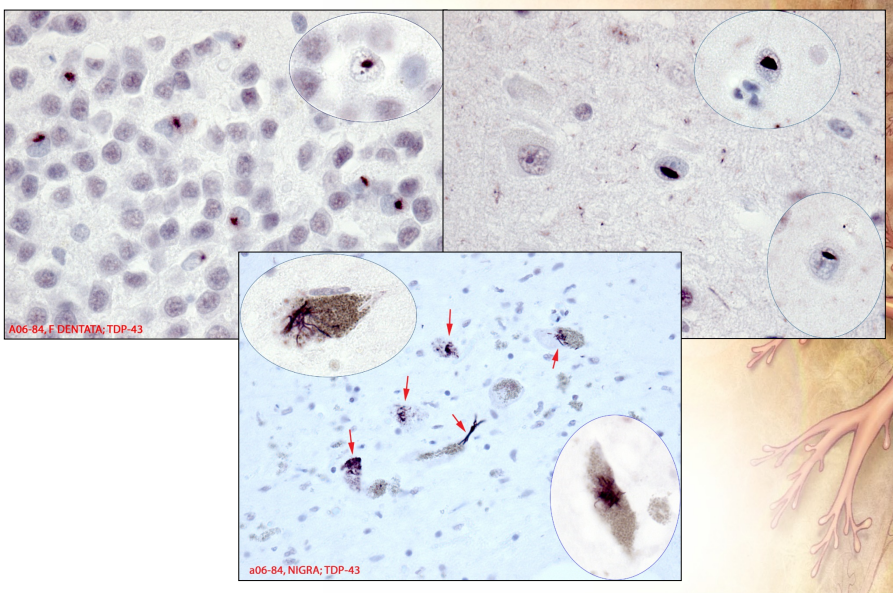
Frontotemporal Dementia(s) IV

- Based on Human Genome Map, they identified about 100 candidate genes in the linked region on chr 17q21
- After sequencing roughly half of the candidate genes….

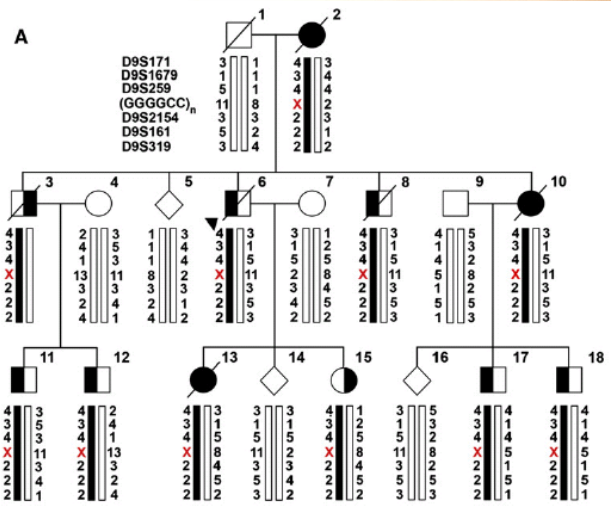


M. Ma

GRN TDP-43 Neuropathology



Chromosome 9 Linkage



DeJesus-Hernandez et al., 2011

Neuron
Article

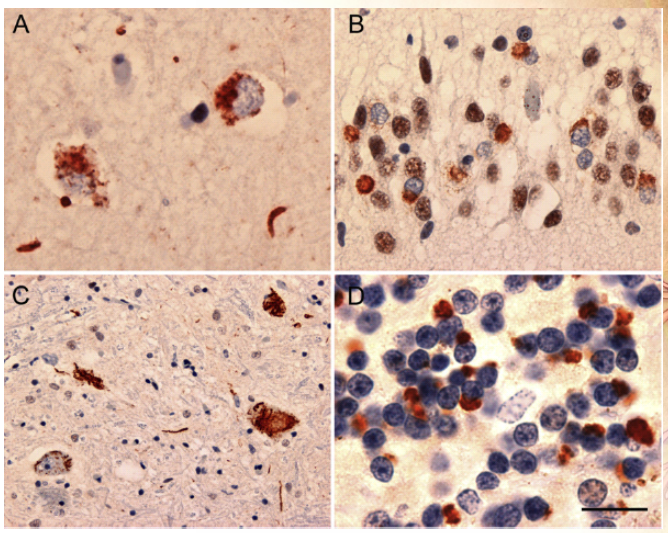
Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8] and Rosa Rademakers[1,*]

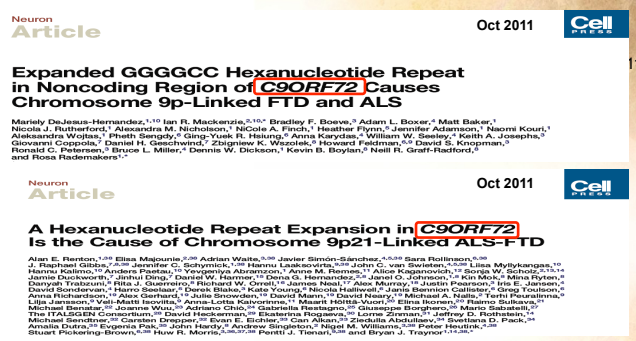
A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

Alan E. Renton,[1,38] Elisa Majounie,[2,38] Adrian Waite,[3,38] Javier Simón-Sánchez,[4,5,38] Sara Rollinson,[6,38] J. Raphael Gibbs,[7,8,38] Jennifer C. Schymick,[1,38] Hannu Laaksovirta,[9,38] John C. van Swieten,[4,5,38] Liisa Myllykangas,[10] Hannu Kalimo,[10] Anders Paetau,[10] Yevgeniya Abramzon,[1] Anne M. Remes,[11] Alice Kaganovich,[12] Sonja W. Scholz,[2,13,14] Jamie Duckworth,[7] Jinhui Ding,[7] Daniel W. Harmer,[15] Dena G. Hernandez,[2,8] Janel O. Johnson,[1,8] Kin Mok,[8] Mina Ryten,[8] Danyah Trabzuni,[8] Rita J. Guerreiro,[8] Richard W. Orrell,[16] James Neal,[17] Alex Murray,[18] Justin Pearson,[3] Iris E. Jansen,[4] David Sondervan,[4] Harro Seelaar,[5] Derek Blake,[3] Kate Young,[6] Nicola Halliwell,[6] Janis Bennion Callister,[6] Greg Toulson,[6] Anna Richardson,[19] Alex Gerhard,[19] Julie Snowden,[19] David Mann,[19] David Neary,[19] Michael A. Nalls,[2] Terhi Peuralinna,[9] Lilja Jansson,[9] Veli-Matti Isoviita,[9] Anna-Lotta Kaivorinne,[11] Maarit Hölttä-Vuori,[20] Elina Ikonen,[20] Raimo Sulkava,[21] Michael Benatar,[22] Joanne Wuu,[23] Adriano Chiò,[24] Gabriella Restagno,[25] Giuseppe Borghero,[26] Mario Sabatelli,[27] The ITALSGEN Consortium,[28] David Heckerman,[29] Ekaterina Rogaeva,[30] Lorne Zinman,[31] Jeffrey D. Rothstein,[14] Michael Sendtner,[32] Carsten Drepper,[32] Evan E. Eichler,[33] Can Alkan,[33] Ziedulla Abdullaev,[34] Svetlana D. Pack,[34] Amalia Dutra,[35] Evgenia Pak,[35] John Hardy,[8] Andrew Singleton,[2] Nigel M. Williams,[3,38] Peter Heutink,[4,38] Stuart Pickering-Brown,[6,38] Huw R. Morris,[3,36,37,38] Pentti J. Tienari,[9,38] and Bryan J. Traynor[1,14,38,*]

C9ORF72 TDP-43 Neuropathology



DeJesus-Hernandez et al., 2011



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Cell PRESS

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Cell PRESS

A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

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- most common genetic abnormality;
11.7% of familial and 3.0% of sporadic FTDs

- *PGRN*: 7.6% of familial and 3.0% sporadic FTDs
- *MAPT*: 6.3% of familial and 1.5% sporadic FTDs.

- The most common phenotype: bvFTD in 25 /26 cases

- In Finnish cohort: bvFTD (64.0%), PNFA (26.7%) and semantic dementia (9.3%)

BRAIN
A JOURNAL OF NEUROLOGY

Feb 2012

Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations

Julie S. Snowden,[1,2] Sara Rollinson,[3] Jennifer C. Thompson,[1,2] Jennifer M. Harris,[1,2] Cheryl L. Stopford,[1,2] Anna M. T. Richardson,[1,2] Matthew Jones,[1,2] Alex Gerhard,[1,2] Yvonne S. Davidson,[2] Andrew Robinson,[3] Linda Gibbons,[3] Quan Hu,[3] Daniel DuPlessis,[3] David Neary,[1,2] David M. A. Mann[2] and Stuart M. Pickering-Brown[3]

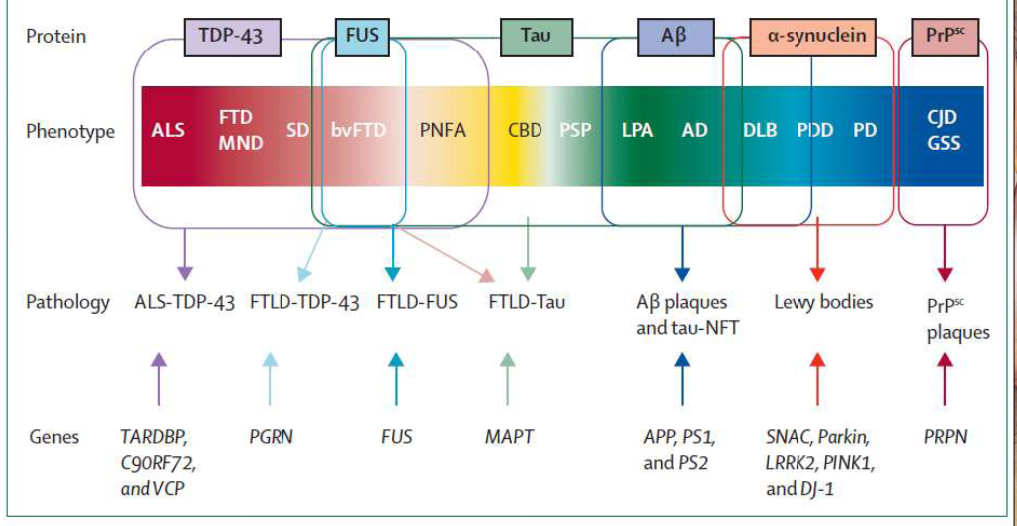
- Neurological signs:
parkinsonian feature (25%), grasp reflex (40%), normal neurological exam (34%)

- Psychotic symptoms:
Psychosis (38%), paranoid or irrational thinking (28%), high rate of complex repetitive behavior

-Non mutation bearer : <4% presented similarly

- Post-mortem pathology (5/32):
TDP-43 A (1/5) and B (3/5), CBS (1/5)

Localizing FTLDs among others



Villemagne et al., Lancet Neurol 2015

Genetic Testing

Approach to FTD genetic testing

- Ensure clinical diagnosis of FTD is correct
- Take detailed family history and ensure that autosomal dominant pattern is confirmed**
- Referral to clinical geneticist/ genetic counselor
- After discussion with index case and caregiver, obtain consent about index case genetic testing
- Send blood for genetic analysis to certified genetics lab
- Obtain and communicate results
- If positive, presymptomatic genetic testing may be offered to relatives, but only after thorough discussion

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Genetic Counseling

- Review family and medical history
- Assessment of risk
- Education – clinical and genetic aspects of FTD
- Discuss benefits, risks, and limitations of genetic test
  - Psychological, social (i.e., insurance, employment), and familial implications
- Discuss medical and advanced planning options based on possible test outcomes
- Ensure family member/ patient has support in making decision to find out result
- Link patients and families with resources

Roberts & Uhlmann, 2013

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Disease	Causative Gene Mutations	Genetic Risk Factors
Frontotemporal Dementia-TDP	*GRN*, *C9ORF72*, *VCP* (rare), *TARDBP* (rare)	*TMEM106B*
Frontotemporal Dementia-Tau	*MAPT*	-
Frontotemporal Dementia-Ubiquitin	*FUS* (rare), *CHMP2B* (rare)	-
Corticobasal Degeneration/ Progressive Supranuclear Palsy	*MAPT* (rare)	MAPT H1 haplotype
Corticobasal Syndrome-TDP	*GRN*, *C9ORF72*	-

Masellis et al. (2013). Alzheimer's Research and Therapy. 5(Suppl 1):S7

Conclusions

- Three major genes causing familial FTLD: *MAPT*, *PGRN*, *C9ORF72*
- Decision to pursue genetic testing should be made after careful consideration of benefits, risks and limitations
- Should be done preferably with the help of a clinical genetics team and with family members involved

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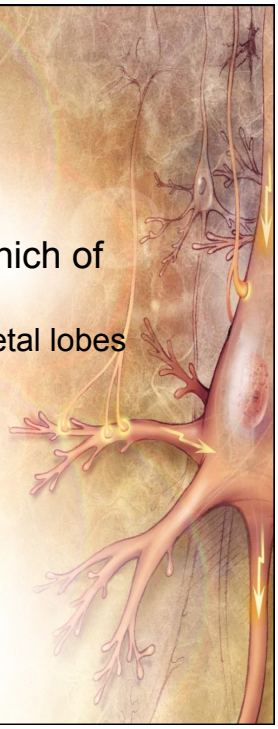
Post-test 1

- *PGRN* mutations are associated with which of following:
  - RED: asymmetric atrophy involving the parietal lobes
  - BLUE: midbrain atrophy
  - WHITE: amyotrophic lateral sclerosis
  - BLACK: long disease course



Post-test 2

- *C9ORF72* hexanucleotide repeat expansions are associated with which of following:
  - RED: shorter disease course when ALS is not present
  - BLUE: midbrain atrophy
  - WHITE: ALS
  - BLACK: striking asymmetry on MRI


Research highlights in genetic AD

Studies in genetic AD

- China-Canada CIHR-funded study of genetic AD
- Dominantly Inherited Alzheimer's Network-Trials Unit (DIAN-TU)

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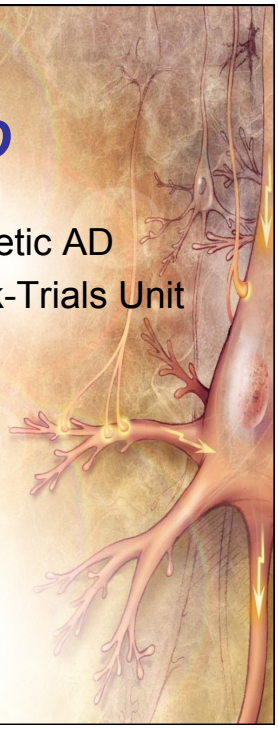

Research highlights in genetic FTD

GENFI 1 – Initial results

- Data Freeze 1 – up to September 2013
- Initial analysis (published in Lancet Neurology March 2015):
  - Cognitive and behavioural measures
  - Volumetric T1 imaging: cortical and subcortical parcellation
  - Main analysis: All mutation carriers vs noncarriers
  - Subgroup analysis: Each genetic group, mutation carriers vs noncarriers

Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis

Jonathan D Rohrer, Jennifer M Nicholas, David M Cash, John van Swieten, Elise Dopper, Lize Jiskoot, Rick van Minkelen, Serge A Rombouts, M Jorge Cardoso, Shona Clegg, Miklos Espak, Simon Mead, David L Thomas, Enrico De Vita, Mario Masellis, Sandra E Black, Morris Freedman, Ron Keren, Bradley J MacIntosh, Ekaterina Rogaeva, David Tang-Wai, Maria Carmela Tartaglia, Robert Laforce Jr, Fabrizio Tagliavini, Pietro Tiraboschi, Veronica Redaelli, Sara Prioni, Marina Grisoli, Barbara Borroni, Alessandro Padovani, Daniela Galimberti, Elio Scarpini, Andrea Arighi, Giorgio Fumagalli, James B Rowe, Ian Coyle-Gilchrist, Caroline Graff, Marie Fallström, Vesna Jelic, Anne Kinhult Ståhlbom, Christin Andersson, Håkan Thonberg, Lena Lilius, Giovanni B Frisoni, Michela Pievani, Martina Bocchetta, Luisa Benussi, Roberta Ghidoni, Elizabeth Finger, Sandro Sorbi, Benedetta Nacmias, Gemma Lombardi, Cristina Polito, Jason D Warren, Sebastien Ourselin, Nick C Fox, Martin N Rossor

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Subject numbers at Data Freeze 1

	Number of families	Mutation negative	Mutation carrier	Totals
C9orf72	27	24	34	**58**
GRN	32	60	58	**118**
MAPT	17	18	26	**44**
TOTALS	*76*	*102*	*118*	***220***

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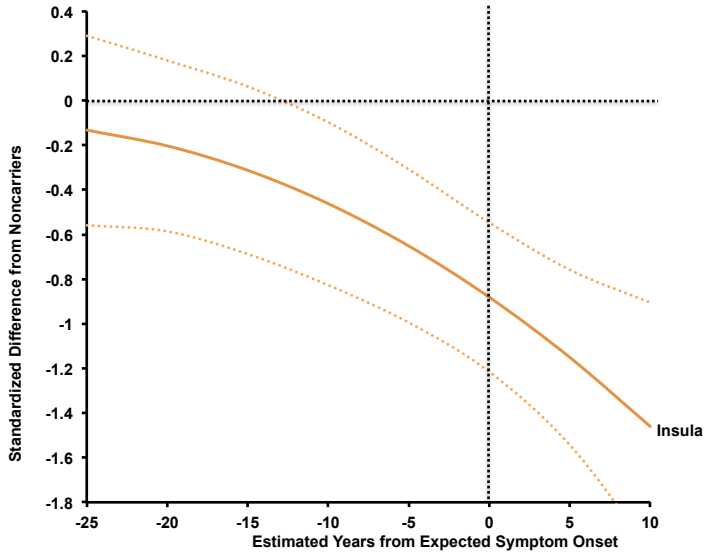
GENFI 1 – Cortical volumes



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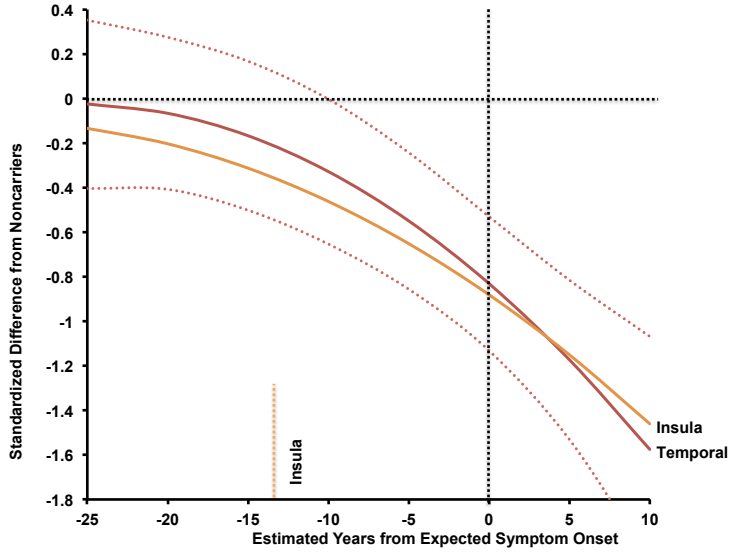
GENFI 1 – Cortical volumes



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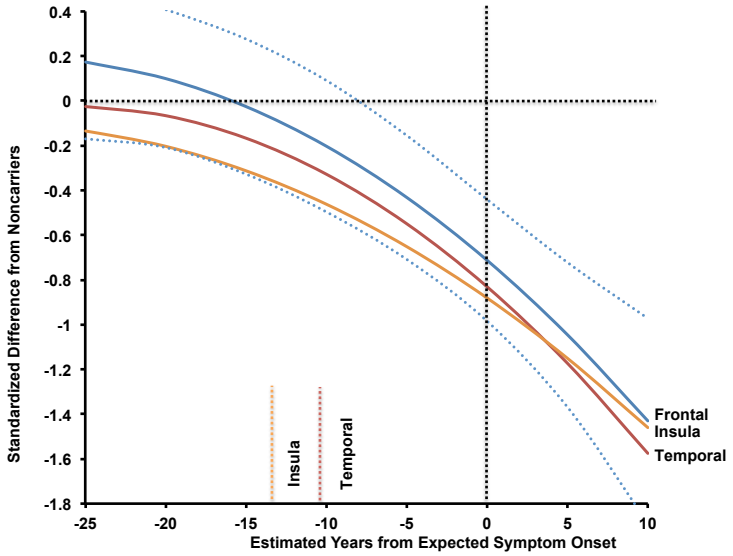
GENFI 1 – Cortical volumes



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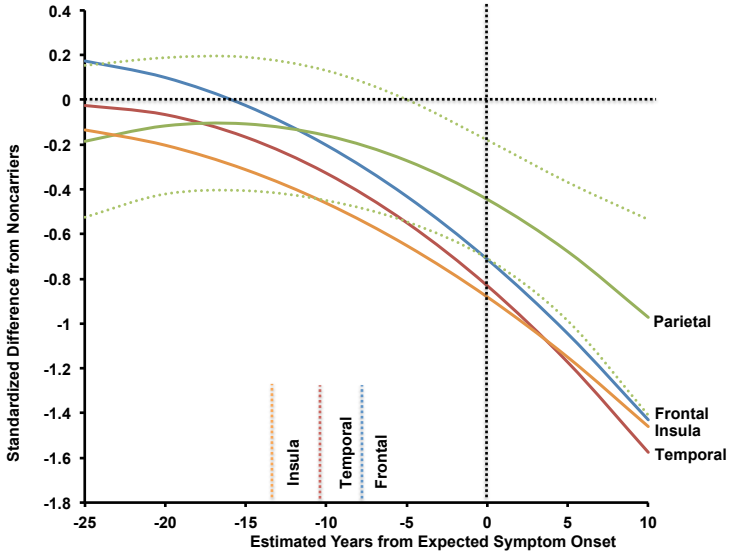
GENFI 1 – Cortical volumes



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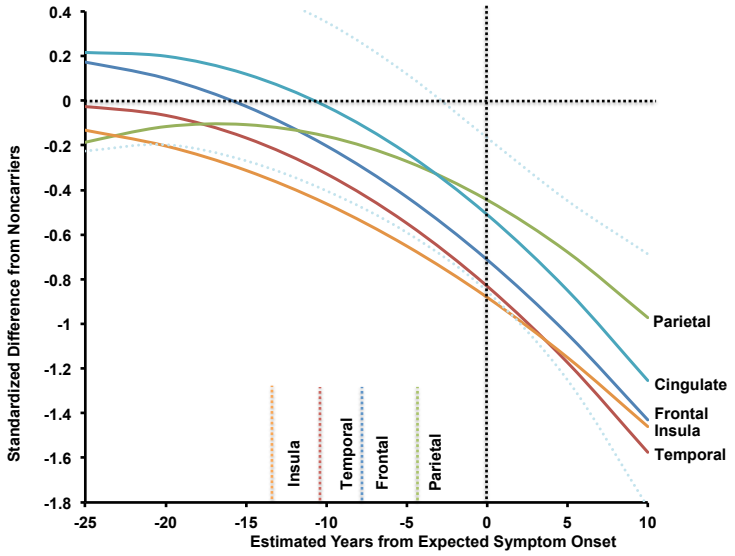
GENFI 1 – Cortical volumes



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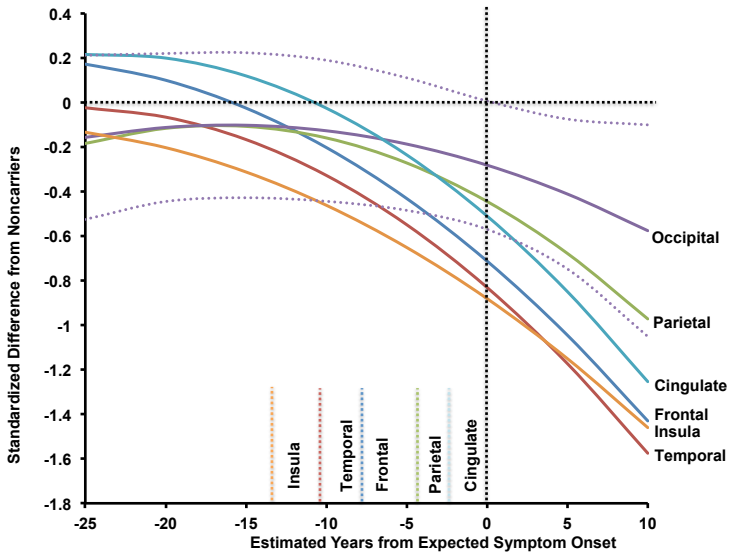
GENFI 1 – Cortical volumes



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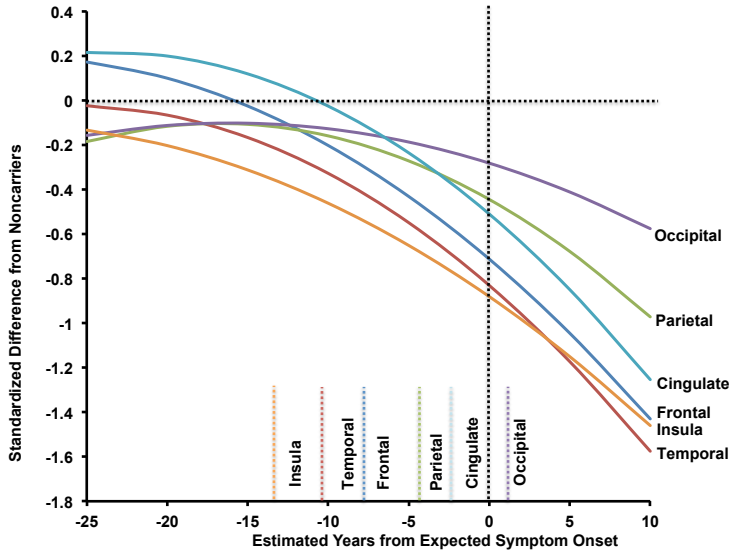
GENFI I – Cortical volumes



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Progranulin (PGRN)

Periphery

- Involved in wound repair and inflammation
- High levels of expression promote tumorigenesis (He & Bateman, 2003)

Central Nervous System (Ahmed et al., 2007)

- Involved in embryonic forebrain development
- PGRN - neurotrophic factor to promote growth of certain neuronal cells (Van Damme et al., 2008)
- Produced by activated microglia and may play a role in neuroinflammation → Granulins
- Reduced PGRN from haploinsufficiency thought to cause FTD

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Reasons for vs. against genetic testing

For

- To further scientific research
- To know if children at risk
- Decrease future uncertainty
- To plan future finances and prepare for medical expenses
- Family planning

Against

- No treatments available
- Psychological impact – stress/ anxiety/ depression/ suicide
- Genetic discrimination – insurance and career

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Health related QoL after genetic testing

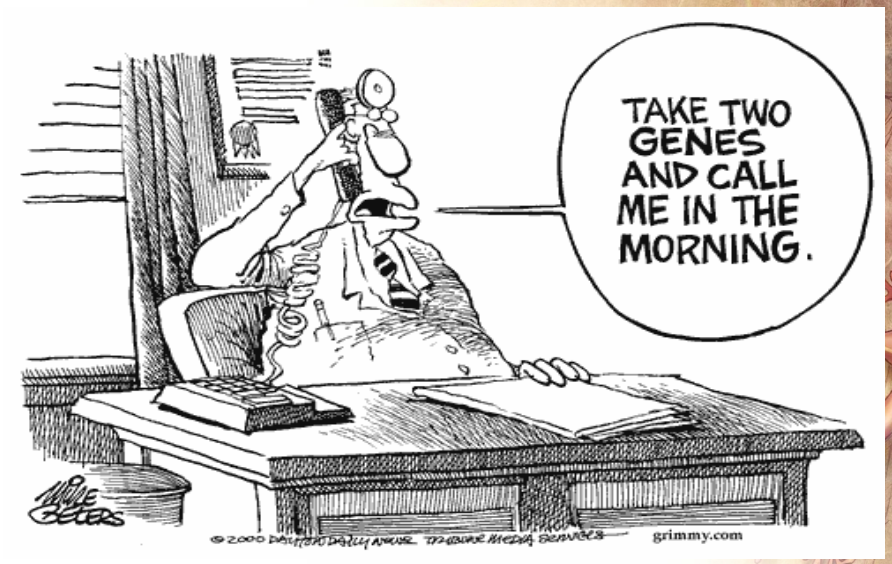
"Forty-one studies examining health-related outcomes following predictive genetic testing for neurodegenerative disease suggested that

1) extreme or catastrophic outcomes are rare;
2) consequences commonly include transiently increased anxiety and/or depression;
3) most participants report no regret;
4) many persons report extensive benefits to receiving genetic information; and
5) stigmatization and discrimination for genetic diseases are poorly understood and policy and laws are needed."

Paulsen et al., 2013

Current uptake for genetic testing in FTD is estimated to be around 7-17%

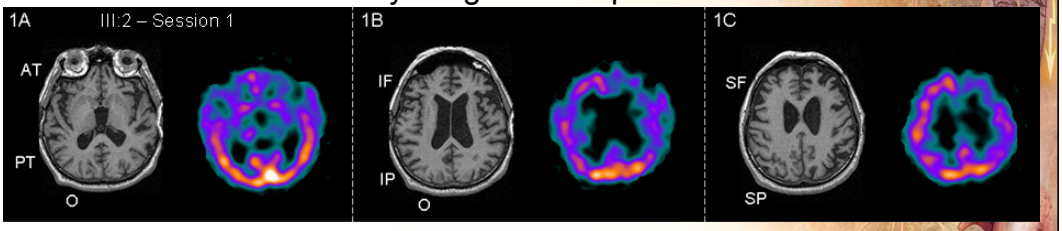
Riedijk et al., 2009



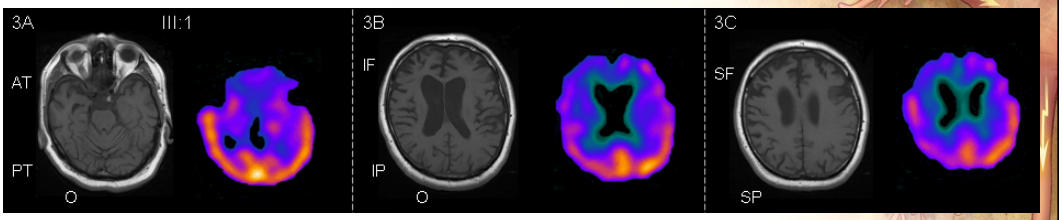
ESTABLISHING THERAPEUTIC EFFICACY
in Familial Frontotemporal Degeneration

Variable phenotype

Primary Progressive Aphasia



Behavioural Variant FTD



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The influence of clinical trials…

'Forty-four percent of subjects expressed a baseline interest in undergoing revealing testing which increased to 85% in order to be eligible for a study of an oral drug "felt to be very safe." If there were a 50% chance of receiving placebo, this number dropped to 62%.'

Hooper et al., 2013


23andMe
DNA TRIBES
Navigenics
IDENTIGENE
HOMEDNA


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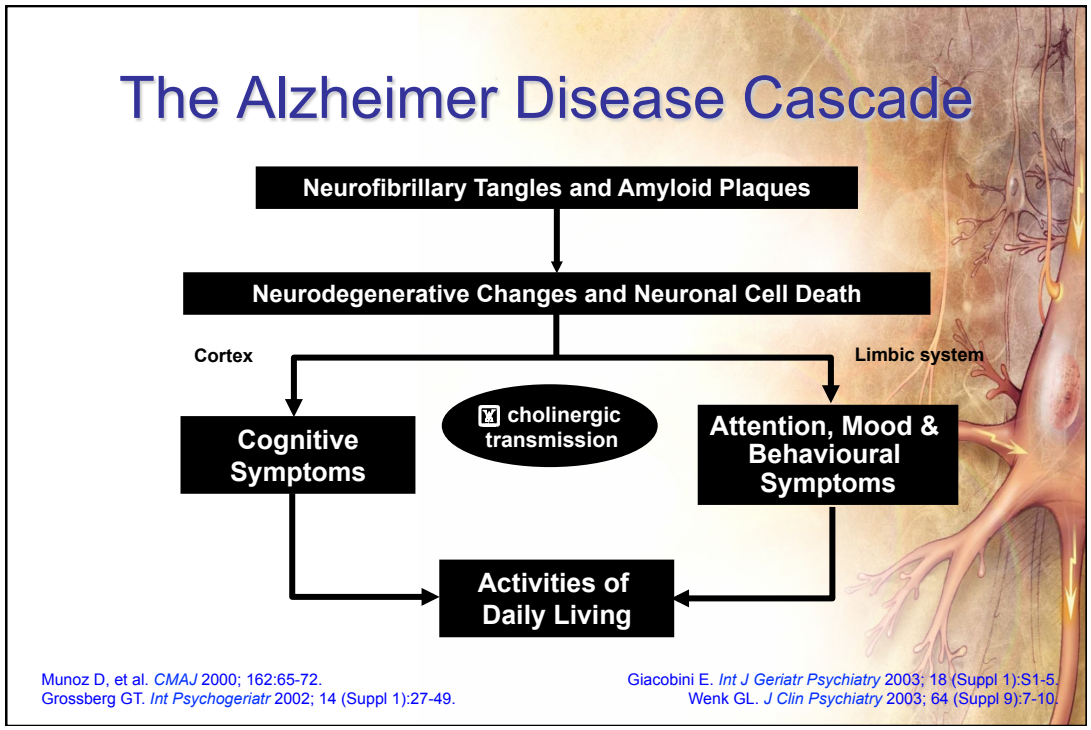
The Alzheimer Disease Cascade
Neurofibrillary Tangles and Amyloid Plaques
Neurodegenerative Changes and Neuronal Cell Death
Cortex
Limbic system
cholinergic transmission
Cognitive Symptoms
Attention, Mood & Behavioural Symptoms
Activities of Daily Living
Munoz D, et al. CMAJ 2000; 162:65-72.
Grossberg GT. Int Psychogeriatr 2002; 14 (Suppl 1):27-49.
Giacobini E. Int J Geriatr Psychiatry 2003; 18 (Suppl 1):S1-5.
Wenk GL. J Clin Psychiatry 2003; 64 (Suppl 9):7-10.


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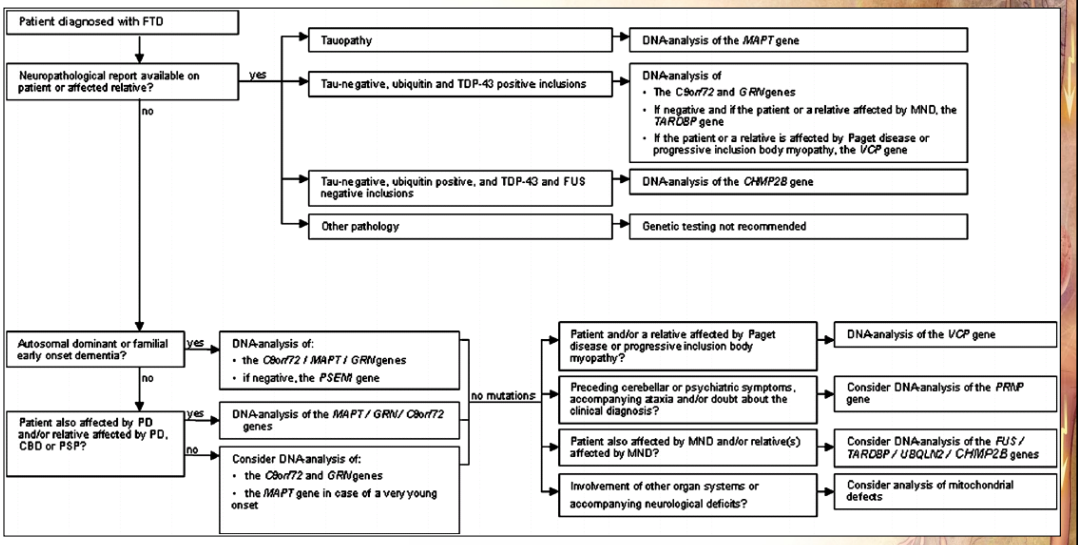
Genetic Testing Algorithm



Cohn-Hokke et al., 2012

Progranulin (PGRN)

- 593-amino acid cysteine rich precursor protein (68.5 kDa)
- Proteolytic cleavage → 7 smaller peptides = Granulins

(Ahmed et al., 2007)


Case 1

Case 1

- ID: 57 y.o. R-handed M; working as engineer; 18 years of education (M.Sc. Engineering); bilingual, fluent ESL
- CC: “progressive language disturbance”
  - AOO 55 y.o.
- PMH:
  - hypercholesterolemia
- Family history:
  - +ve for FTD

Case 1

HPI (age 57):

- Insidious onset and gradual decline in speech fluency
- Frequent word-finding difficulties - interrupted verbal output
- Preferred to use native language
- Intermittent echolalia
- No loss of word meaning
- No behavioural or personality change
- No neuropsychiatric symptoms
- No memory or visuospatial troubles

Case 1

Examination (age 57):

- MMSE = 22/30 (limited by aphasia)
- BNA:
  - Spontaneous speech output reduced; struggled to find words
  - Comprehension, repetition, naming of both high and low frequency words, and reading – intact
  - semantically- (animal) and phonemically-cued (f) word list generation in one minute – impaired
  - Written description of cookie theft picture – use of simplified sentences with sparse, but accurate description
  - Mild impairment of working memory and executive functions
- DAD – ADLs and iADLs intact
- Early right hand ideomotor apraxia – hand as comb
- General and neurological exam - normal

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Where is the lesion?

- Left frontal – particularly posterior inferior (Broca's)
- Left insula
- ± Left parietal

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What is the clinical diagnosis?

- Primary Progressive Aphasia – Progressive Non-fluent Aphasia (PNFA)

What is the lesion?

- FTD (Tau or U/TDP-43)
- Pick's disease
- CBD
- PSP
- AD (logopenic variant)
- R/O structural lesion

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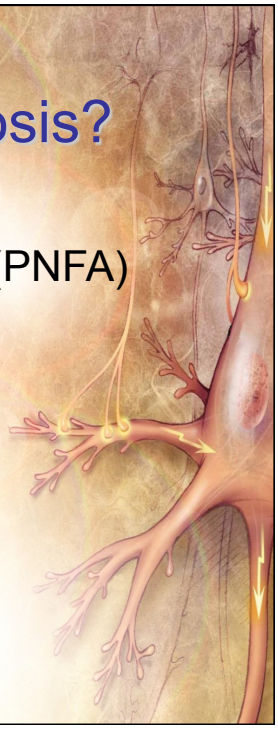
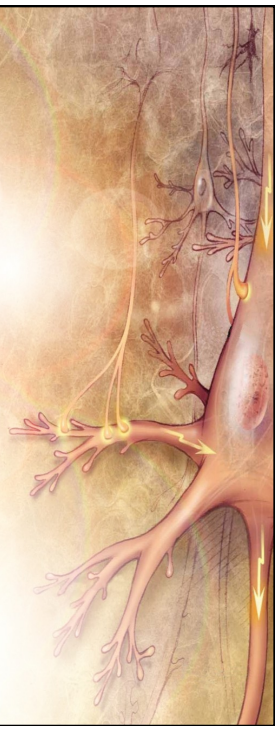


Case 2



Case 2

- ID: 64 y.o. R-handed M; working as managing director; 16 years of education
- CC: “slowness, apathy, and somnolence”
  - AOO 62 y.o.
- PMH:
  - None
- Family history:
  - +ve for FTD

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Case 2

HPI (age 64):

- Insidious onset and gradual change in personality and behaviour
- Initially withdrawn; less talkative
- Gave up his hobbies
- Troubles with handling familiar objects
- Months later, social judgement deteriorated:
  - Breakdown in formalities – poor table manners
  - Disinhibited
  - Irritability when opposed

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Case 2

Examination (age 64):

- Cognitive testing:
  - Impaired executive functions
  - Difficulties switching between categories
  - Poor attention
  - Visuospatial difficulties
  - Relatively intact delayed memory
  - NPI = 23/144
- Impaired ADLs and iADLs

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Case 2

Examination (age 64):

- General exam - normal
- Neurological exam:
  - moderately impaired monotone, slurred speech
  - minimal hypomimia
  - resting tremor of upper extremities, moderate in amplitude
  - moderate rigidity
  - severe motor slowness of gait
  - multi-step turning with postural instability

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Where is the lesion?

- Early on - medial and dorsolateral prefrontal
- Later on – orbitofrontal and right anterior temporal
- Right parieto-occipital
- Basal ganglia

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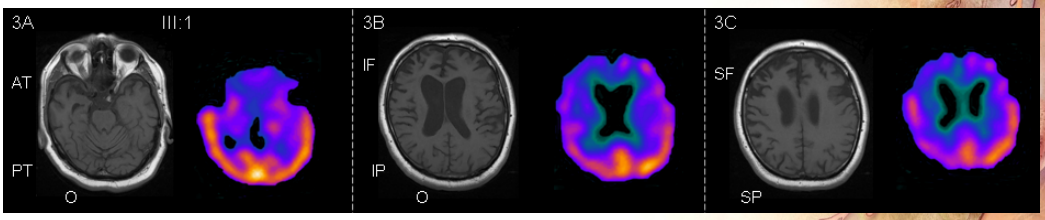
Neuroimaging



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What is the clinical diagnosis?

- bvFTD with parkinsonism

What is the lesion?

- FTD (Tau or U/TDP-43)
- FTDP-17
- Pick's disease
- CBD
- PSP
- DLB
- AD

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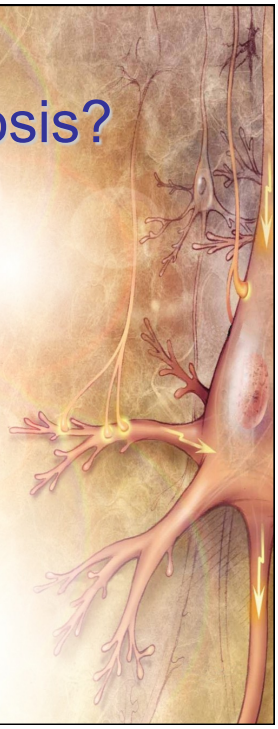

Are these patients related?

- YES!

What would you do now?

- Get more family history
- Get blood for DNA testing!!

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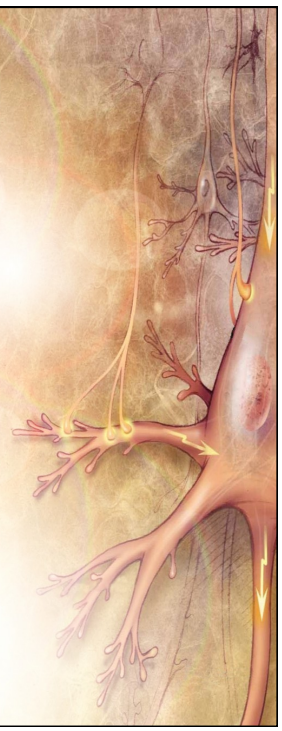
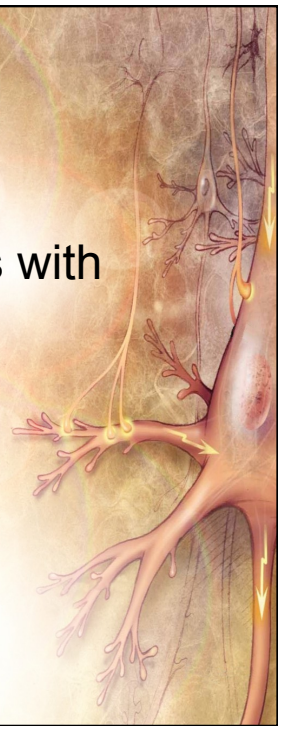
Our study



Objectives

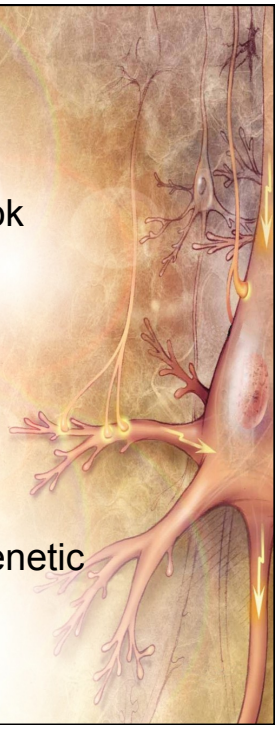
- To characterize the clinical heterogeneity of two brothers with FTD spectrum disorders
- To identify a causative gene mutation
- To identify the underlying pathological substrate



Methods (I)

Subjects

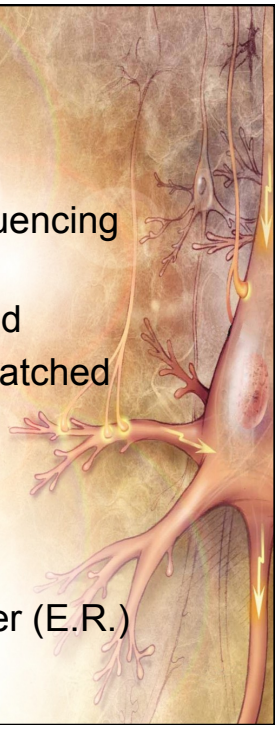
- Case 1 - recruited through the Sunnybrook Dementia study
- Longitudinal study:
  - Neuropsychological testing
  - Brain SPECT
  - Dementia protocol MRI
- Case 2 - recruited in Warsaw, Poland
- Blood obtained for DNA extraction and genetic analysis



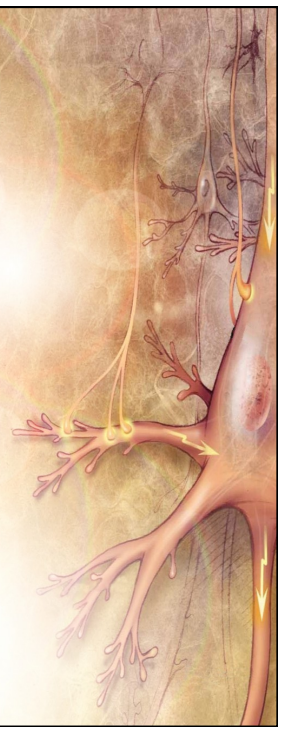
Methods (II)

Genetic Analysis (C.Z.)

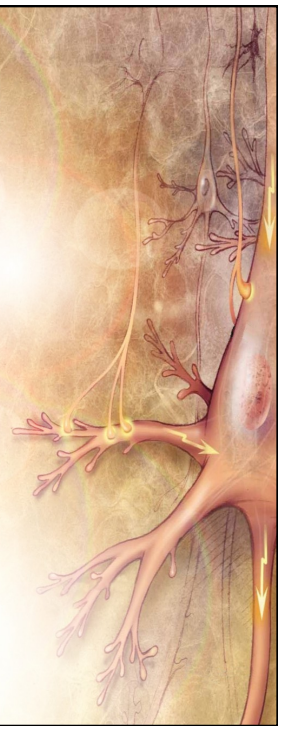
- Mutation screening by direct DNA sequencing of brothers
- 200 normal controls, ethnically matched
- 90 FTD subjects, ethnically and age matched
- Candidate genes
  - MAPT x
  - PSEN1 x
  - PGRN ✔
- Identified mutation genotyped in brother (E.R.)



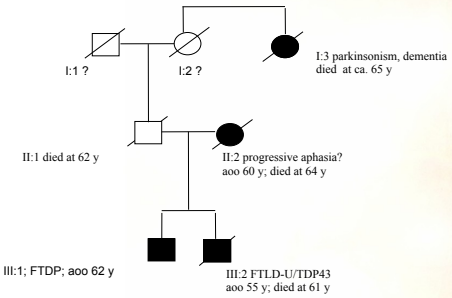
Results



Genetic



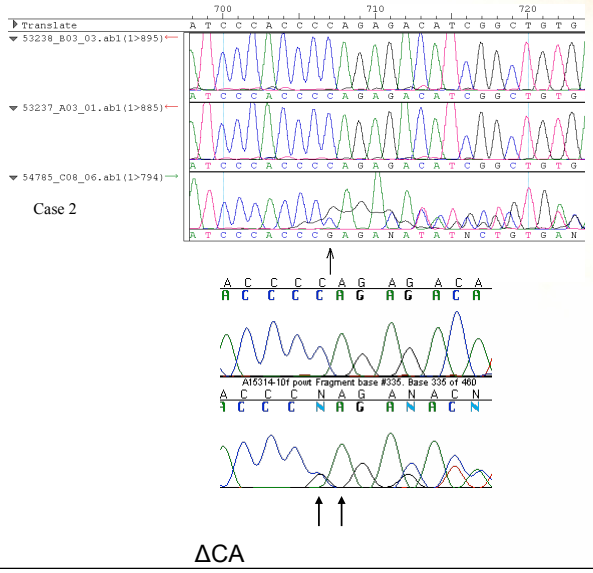
Family-genetic study



Novel PGRN mutation – CA dinucleotide deletion

g.2988_2989delCA, c.1536_1537delCA, P439_R440fsX6

Novel PGRN CA deletion



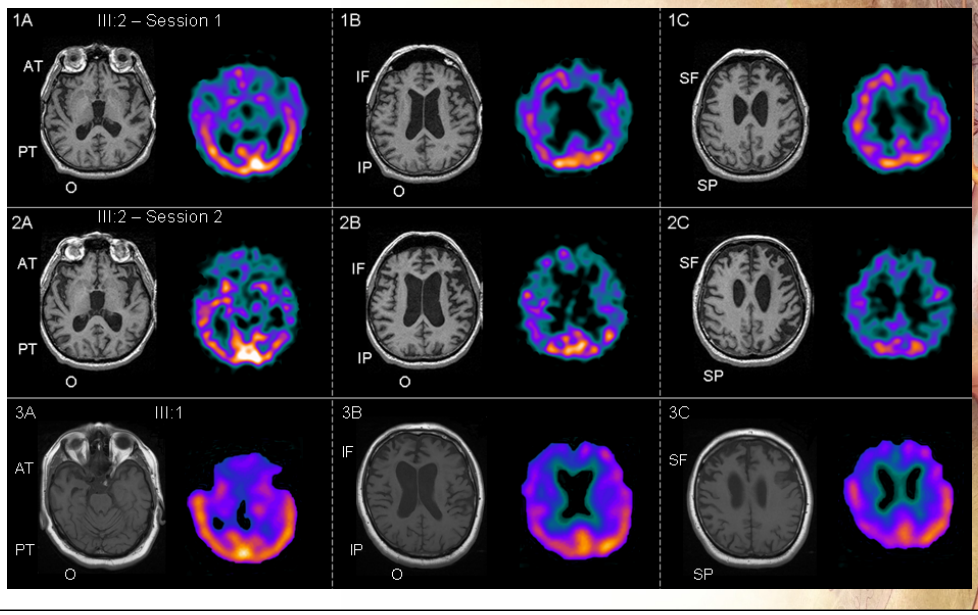
CA deletion

- Causes frameshift, and introduces a premature stop codon
- RT-PCR analysis of *PGRN* mRNA levels from proband revealed a two-fold decrease of the cDNA transcript as compared to healthy subjects.
- haploinsufficiency mechanism confirmed

Clinical

Demographic/Clinical Characteristics	Case 1	Case 2
Hemisphere most affected	Left	Right
Age of Onset (years)	55	62
Duration of disease at testing (years)	2	2
Duration of disease until death (years)	6	-
Extrapyramidal Features		
Parkinsonism	N	Y
Dementia		
Memory	N	N
Language	Y	N
Executive functions	Y	Y
Attention	N	Y
Visuospatial function	N	Y
Praxis	Y	N
Behaviours		
NPI	4	23
Diagnosis	**PNFA**	**bvFTDP**

Neuroimaging



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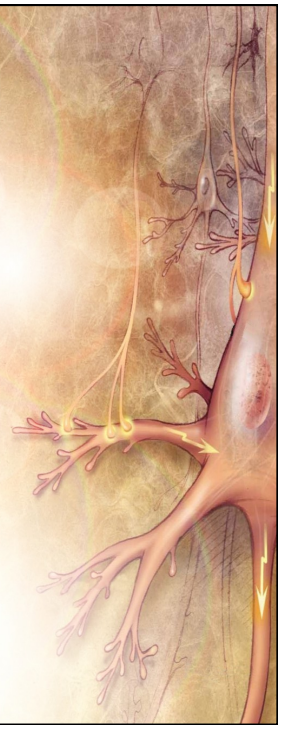
Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,[1,11*] Deepak M. Sampathu,[1*] Linda K. Kwong,[1*] Adam C. Truax,[1] Matthew C. Micsenyi,[1] Thomas T. Chou,[2] Jennifer Bruce,[1] Theresa Schuck,[1] Murray Grossman,[3,4] Christopher M. Clark,[3,4] Leo F. McCluskey,[3] Bruce L. Miller,[6] Eliezer Masliah,[7] Ian R. Mackenzie,[8] Howard Feldman,[9] Wolfgang Feiden,[10] Hans A. Kretzschmar,[11] John Q. Trojanowski,[1,4,5] Virginia M.-Y. Lee[1,4,5]†

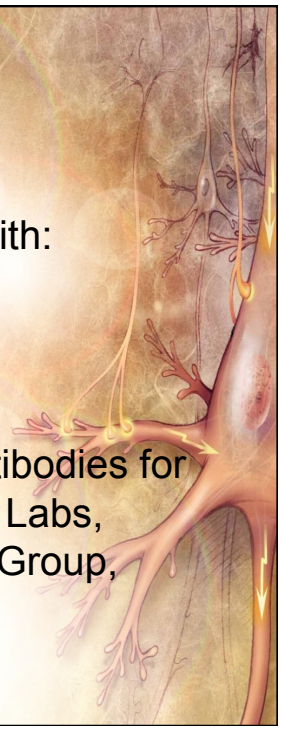
Pathology



Methods

Neuropathology

- Paraffin-embedded sections stained with:
  - Haematoxylin and eosin
  - Luxol fast blue
  - Bielschowski and Gallyas
  - Immunostains using commercial antibodies for tau (Dako, A0024), ubiquitin (Vector Labs, ZPU576) and TDP-43 (ProteinTech Group, Inc.)



Conclusions

- This novel CA deletion in PGRN causes familial FTD spectrum disorders
- This mutation caused typical FTD-U/ TDP-43 +ve intranuclear and intracytoplasmic inclusions
- It is the location of the pathology and not the mutation or pathology itself that produces the clinical dementia syndrome (Lang, 2003)

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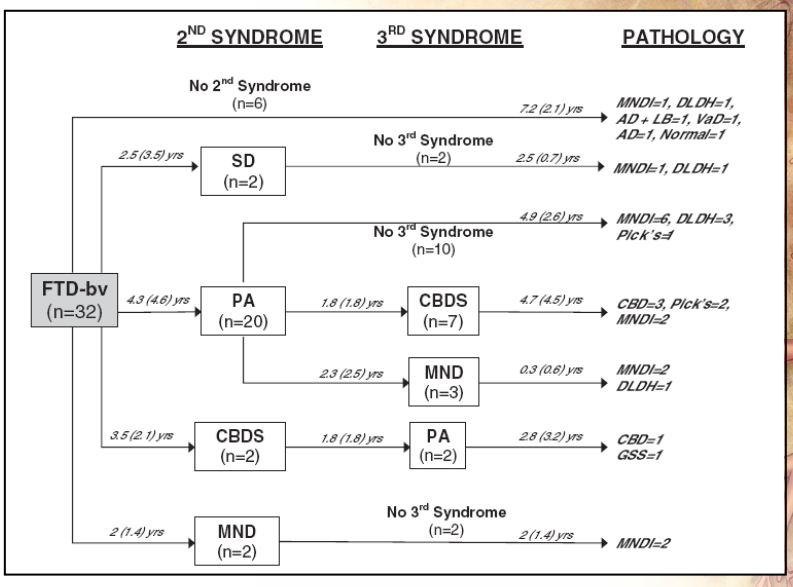
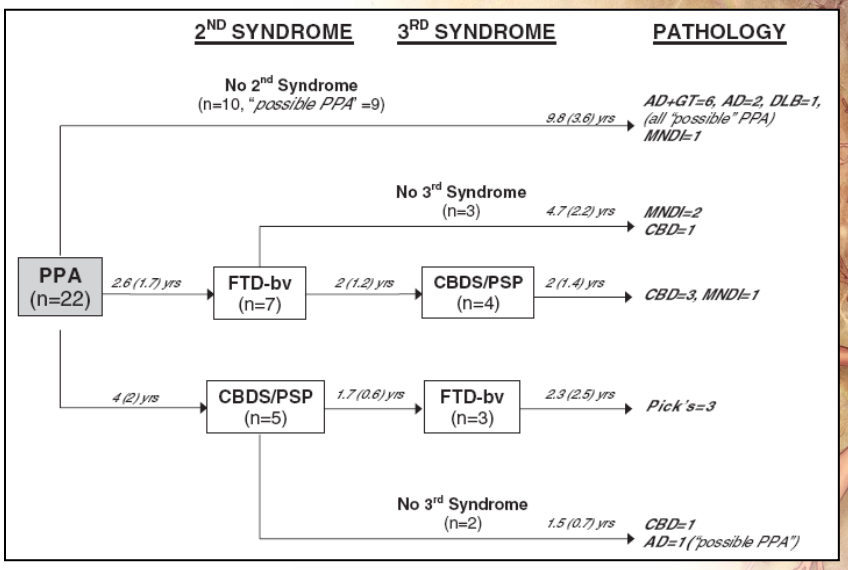
U of T



Kertesz et al. (2005)



Kertesz et al. (2005)

What is really going on?

- Specific diagnoses:
  - hemispheric and specific lobar involvement
- Variable age of onset
- Variable severity of disease
- Variable duration of disease
- Mixed pathologies

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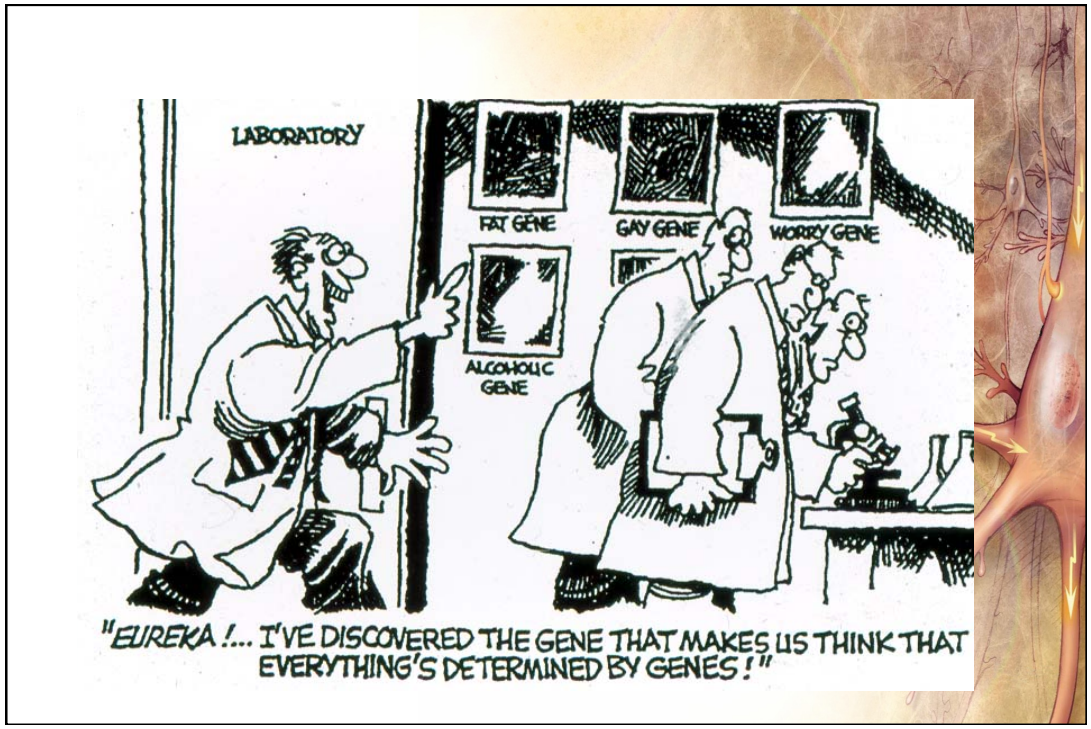
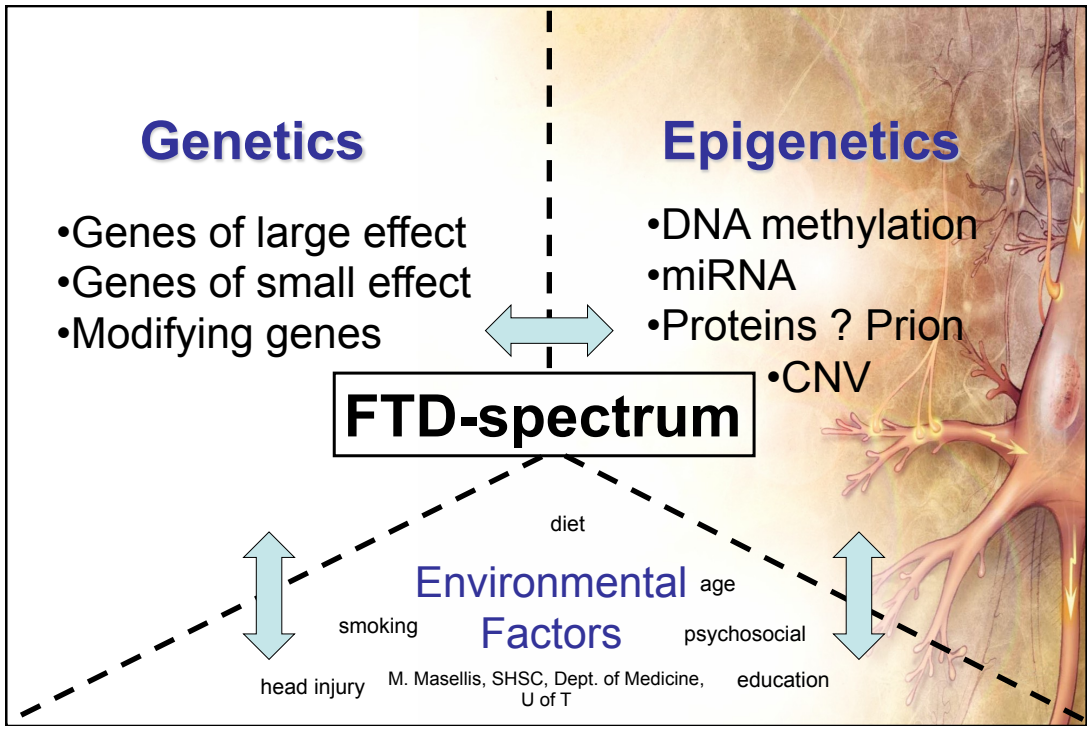

LABORATORY
FAT GENE
GAY GENE
WORRY GENE
ALCOHOLIC GENE
"EUREKA !... I'VE DISCOVERED THE GENE THAT MAKES US THINK THAT EVERYTHING'S DETERMINED BY GENES !"


Genetics
•Genes of large effect
•Genes of small effect
•Modifying genes
Epigenetics
•DNA methylation
•miRNA
•Proteins ? Prion
•CNV
FTD-spectrum
diet
Environmental Factors
age
smoking
psychosocial
head injury
education
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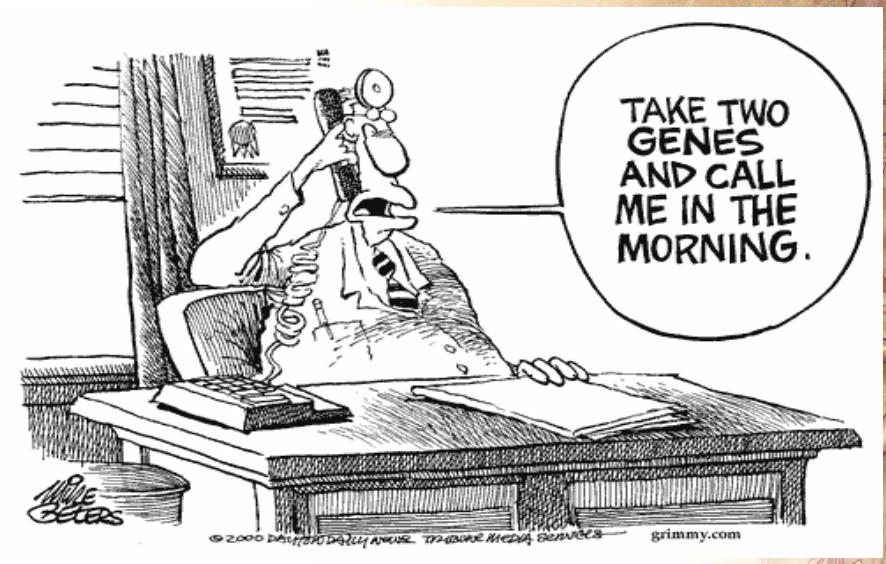

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