Disclosures

• Relationships with commercial interests:
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  – Honoraria: Novartis, EMD Serono
  – Consulting Fees: Bioscape Medical Imaging CRO, GE Healthcare, UCB
  – Other: Royalties from Henry Stewart Talks Ltd.

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U of T

Genetics of Frontotemporal Lobar Degeneration (FTLD)

Mario Masellis, MSc, MD, PhD, FRCPC
Clinician Scientist & Assistant Professor,
Dept of Medicine (Neurology), University of Toronto
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 the following:
  - RED: asymmetric atrophy involving the parietal lobes
  - BLUE: midbrain atrophy
  - WHITE: ALS
  - BLACK: long disease course

Pre-test 2

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

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

Where is the lesion?
• Left frontal – particularly posterior inferior (Broca’s)
• Left insula
• ± Left parietal
Neuroimaging

What is the lesion?

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

What is the clinical diagnosis?

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

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
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

Where is the lesion?
• Early on - medial and dorsolateral prefrontal
• Later on – orbitofrontal and right anterior temporal
• Right parieto-occipital
• Basal ganglia
What is the lesion?

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

What is the clinical diagnosis?

- bvFTD with parkinsonism
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)
  - 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, admitted 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

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

Matt Baker1, Ian R. Mackenzie2, Stuart M. Pickering-Brown3, Jennifer Gass1, Rosa Rademakers3, Caroline Lindholm1, Julie Snowden5, Jennifer Adamson1, A. Dessa Sadovnick2,4, Sara Rollinson1, Ashley Cannon1, Emily Dwoish5, David Neary6, Stacey Meilquist7, Anna Richardson9, Dennis Dickson1, Zdenek Berger9, Jason Erikson1, Todd Robinson5, Cynthia Zehr1, Chad A. Dickey8, Richard Crook5, Eileen McGowan2, David Mann1, Bradley Boeve1, Howard Feldman8 & Mike Hutton7

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

Marc Cruts1,2,5, Ilse Gijselink1,2,5, Julie van der Zee2,5, Sebastiaan Engelenborgh1,2,5, Hans Wils1,2,5, Daniel Pinto3,4, Rosa Rademakers3,4,5, Rik Vandenberghe1, Bart Dermaut1, Jean-Jacques Martin1,5, Cornelia van Duijn5, Karen Peeters3,4, Raf Sciot6, Patrick Santens3, Tim De Pooter3,4, Maria Matthijs3,5, Marleen Van den Broeck1,2,5, Ivy Cuyp1,2,5, Kristl Vennekens1,5, Peter P. De Deyn5,5, Samir Kumar-Singh1,3,5, & Christine Van Broeckhoven1,2,5

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....
GRN TDP-43 Neuropathology

Chromosome 9 Linkage

DeJesus-Hernandez et al., 2011
Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS

DeJesus-Hernandez et al., 2011

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

2015-11-01
• 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%)

• 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)
Other genes:
- Valosin-containing protein (VCP)
- Chromatin modifying protein 2B (CHMP2B)
- Trans active DNA-binding protein (TARDBP)
- Fused in Sarcoma (FUS)

Genetic Testing

Villemagne et al., Lancet Neurol 2015
**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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutations</th>
<th>Factors</th>
</tr>
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<tbody>
<tr>
<td>Frontotemporal Dementia-TDP</td>
<td>GRN, C9ORF72, VCP (rare), TARDBP (rare)</td>
<td>TMEM106B</td>
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<tr>
<td>Frontotemporal Dementia-Tau</td>
<td>MAPT</td>
<td>-</td>
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<tr>
<td>Frontotemporal Dementia-Ubiquitin</td>
<td>FUS (rare), CHMP2B (rare)</td>
<td>-</td>
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<tr>
<td>Corticobasal Degeneration/Progressive Supranuclear Palsy</td>
<td>MAPT (rare)</td>
<td>MAPT H1 haplotype</td>
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<tr>
<td>Corticobasal Syndrome-TDP</td>
<td>GRN, C9ORF72</td>
<td>-</td>
</tr>
</tbody>
</table>


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### 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)

Research highlights in genetic FTD
GENFI I – 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, Jeffrey van Swieten, Elke Depper, Ljuba Jakovandic, Rudi van Meel, Serge Aherns, R J Jorge Cardoso, Shone Dagg, Mikaela Podali, Simon Mood, Daniel Thomas, Anna De Vito, Mario Ambatiello, Sandro F Black, Alberto Feinman, Ron Koren, Bradley J MacIntosh, Xiaotian Ma, Danial Tong-Wai, Alana Cardwell Tartaglia, Robert Lafenestre, Fabrice Tassaour, Pietro Tsimbuchi, Veronica Watson, Sara Potts, Matteo Groppi, Daniele Gallelli, Elke Siappari, Andrea Angelini, Giorgio Passamani, James R Rowe, Ken-Cycle Czachor, Caroline Goff, Marie Falkeborn, Vanessa J, Anne-Kathrin Stadlbauer, Christina Anderson, Håkan Thamberg, Lena Liddle, Giovanni P Frisoni, Michele Piazza, Martina Basetti, Luisa Benvenuti, Roberto Ghidoni, Elisabetta Foger, Sandro Sohl, Benedetta Nava, Genna Lombardi, Cristina Polito, Jason D Warren, Sebastien Ourselin, Nick C Fox, Martin N Rossor

Subject numbers at Data Freeze 1

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of families</th>
<th>Mutation negative</th>
<th>Mutation carrier</th>
<th>Totals</th>
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<tbody>
<tr>
<td>C9orf72</td>
<td>27</td>
<td>24</td>
<td>34</td>
<td>58</td>
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<tr>
<td>GRN</td>
<td>32</td>
<td>60</td>
<td>58</td>
<td>118</td>
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<tr>
<td>MAPT</td>
<td>17</td>
<td>18</td>
<td>26</td>
<td>44</td>
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<tr>
<td>TOTALS</td>
<td>76</td>
<td>102</td>
<td>118</td>
<td>220</td>
</tr>
</tbody>
</table>
GENFI I – Cortical volumes

Estimated Years from Expected Symptom Onset

Standardized Difference from Non-carriers

-25 -20 -15 -10 -5 0 5 10

-1.8 -1.6 -1.4 -1.2 -1.0 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4

Insula

GENFI I – Cortical volumes

Estimated Years from Expected Symptom Onset

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-25 -20 -15 -10 -5 0 5 10

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Insula

Temporal
GENFI I – Cortical volumes

Standardized Difference from Noncarriers

Estimated Years from Expected Symptom Onset

Frontal
Insula
Temporal

Parietal
Frontal
Insula
Temporal
GENFI I – Cortical volumes

[Graph showing standardized difference from non-carriers over estimated years from expected symptom onset for different brain regions: Parietal, Cingulate, Frontal, Insula, Occipital, Temporal.]

GENFI I – Cortical volumes

[Graph showing standardized difference from non-carriers over estimated years from expected symptom onset for different brain regions: Parietal, Cingulate, Frontal, Insula, Occipital, Temporal.]
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Estimated Years from Expected Symptom Onset

Occipital
Parietal
Cingulate
Frontal
Insula
Temporal

GENFI 1 – Cortical volumes
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
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

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
Variable phenotype

Primary Progressive Aphasia

Behavourial Variant FTD

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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
The Alzheimer Disease Cascade

Neurofibrillary Tangles and Amyloid Plaques

Neurodegenerative Changes and Neuronal Cell Death

Cortex

Cognitive Symptoms

Attention, Mood & Behavioural Symptoms

Activities of Daily Living

Genetic Testing Algorithm

Progranulin (PGRN)

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

(Ahmed et al., 2007)  M. Masellis, SHSC, Dept. of Medicine, U of T
Case 1

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- AD (logopenic variant)
- R/O structural lesion

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Case 2
Case 2

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- **PMH:**
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- **Family history:**
  - +ve for FTD

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
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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?

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- Later on – orbitofrontal and right anterior temporal
- Right parieto-occipital
- Basal ganglia

Neuroimaging
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

Are these patients related?

- YES!

What would you do now?

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

\[\Delta \text{CA}\]

haploinsufficiency mechanism confirmed
### Demographic/Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemisphere most affected</td>
<td>Left</td>
<td>Right</td>
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<tr>
<td>Age of Onset (years)</td>
<td>55</td>
<td>62</td>
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<td>Duration of disease at testing (years)</td>
<td>2</td>
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<tr>
<td>Duration of disease until death (years)</td>
<td>6</td>
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</table>

### Extrapyramidal Features

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<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Parkinsonism</td>
<td>N</td>
<td>Y</td>
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### Dementia

<table>
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<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
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<td>Memory</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Language</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Executive functions</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Attention</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Praxis</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

### Behaviours

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

### Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td></td>
<td>bvFTDP</td>
</tr>
</tbody>
</table>
Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,1,11* Deepak M. Sampathu,1* Linda K. Kwong,1,2 Adam C. Truax,1 Matthew C. Milcsenyi,3 Thomas T. Chou,2 Jennifer Bruce,2 Theresa Schuck,2 Murray Grossman,1,4 Christopher M. Clark,3,4 Leo F. McCluskey,3 Bruce L. Miller,5 Eliezer Masliah,7 Ian R. Mackenzie,6 Howard Feldman,6 Wolfgang Fellen,1,9 Hans A. Kretzschmar,11 John Q. Trojanowski,1,4,5 Virginia M.-Y. Lee1,4,5†
Pathology

Methods

Neuropathology

• Paraffin-embedded sections stained with:
  • Haematoxylin and eosin
  • Luxol fast blue
  • Bielschowsk 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)

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
M. Masellis, SHSC, Dept. of Medicine, U of T

**Genetics**
- Genes of large effect
- Genes of small effect
- Modifying genes

**Epigenetics**
- DNA methylation
- miRNA
- Proteins? Prion
- CNV

**FTD-spectrum**

Environmental Factors
- diet
- age
- smoking
- psychosocial
- education
- head injury
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- Zbigniew Wszolek (Mayo)
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- Family