FTD 101: Genetics
The Importance of Family Histories & Gene Discoveries

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Introduction

Genetic counselling for FTD at UBCH-CARD:
• newly diagnosed FTD patients
• FTD research participants

What is our role?
• provide information about FTD and the genetics of FTD
• interpret family histories
• review genetic testing options and implications
• facilitate genetic testing if available and desired
Introduction

“Will my children get FTD?”
Introduction

“What about my grandkids?
Does it skip a generation?”
Is there genetic testing?
Introduction

How do we answer these questions?

What do we know about the genetics of FTD?

Is there genetic testing?

What else can we talk about with these patients and their families?
From a genetics standpoint, there are two main subtypes of FTD:

- 60% Sporadic
- 40% Familial
FTD Genetics: Sporadic FTD

• ~60% of FTD cases are sporadic

• caused by a complex combination of environmental factors and susceptibility genes (i.e. multifactorial)
  • mostly still unknown and under investigation

• sporadic FTD does not “run in the family”

• recurrence risks for relatives are low
FTD Genetics: Familial FTD

• ~40% of FTD cases are familial

• can be caused by alterations in specific causative genes

• these genes can be directly passed on from parent to child

• if carry one of these genes, you will almost certainly develop FTD (i.e. they are almost completely penetrant)

• 50% recurrence risk for children and siblings of affected individuals (i.e. autosomal dominant inheritance)
FTD Genetics: Familial FTD

FTD: Is it sporadic or familial?

How can we tell if FTD is sporadic or familial?

Specific symptoms?
• not really
• sporadic and familial FTD demonstrate similar and overlapping clinical features

Specific autopsy findings?
• yes, some autopsy findings are highly suggestive of familial FTD
• BUT, autopsy results are often unavailable or from many years ago
FTD: Is it sporadic or familial?

- Behavioral Variant FTD
- svPPA semantic variant
- naPPA Nonfluent/agrammatic variant
- FTD-ALS
- Sporadic or Familial
- FTD-Tau FTD-TDP43
- FTLD-TDP43 FTLD-FUS
- ALS
- Mostly sporadic
- TDP43, SOD1,FUS
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- Mostly sporadic
- Sporadic or Familial
- FTLD-TDP43 FTLD-FUS
- Mostly sporadic
- TDP43, SOD1,FUS

FTD: Is it sporadic or familial?

We need to look at the family history:

- three generations
- ages and causes of death
- dementia or other neurological diseases?
- other medical problems?
- medical records and autopsy reports whenever possible
Interpreting Family Histories

Can be complicated by:

• early ages-of-death
• adoptions/non-paternity
• family dynamics/cultural considerations
• inaccurate/antiquated diagnoses
• population prevalence of other forms of dementia (especially Alzheimer disease and vascular dementia)
• no autopsy confirmation of reported dementia cases
• rare incomplete penetrance of familial FTD genes
Interpreting Family Histories

Hallmarks of sporadic FTD:

• just one person in the family affected

• no known family history of FTD or related neurological conditions (i.e. parkinsonism, ALS)

• affected individual has unaffected parents
Hallmarks of familial FTD:

- multiple family members with FTD or related conditions (i.e. parkinsonism, ALS)
- affected parents having affected children over at least 3 generations
- multiple siblings affected in the same family
- age of symptom onset may vary
Interpreting Family Histories

“Will my children get FTD?”
Interpreting Family Histories

- no known family history of FTD or related conditions
- patient most likely has sporadic FTD
- likelihood for her children or siblings to develop FTD is low
- small possibility that this is a brand new mutation in a familial FTD gene
Interpreting Family Histories

“What about my grandkids? Does it skip a generation?”
Interpreting Family Histories

- no known family history of FTD or related conditions
- patient most likely has sporadic FTD
- likelihood for children and siblings to develop FTD is low
- likelihood for grandchildren to develop FTD is even lower!
- small possibility that this is a brand new mutation in a familial FTD gene
Interpreting Family Histories

“Organic Brain Disease”

Alzheimer Disease
Strokes

EtOH
Depression

“Will my children get FTD?”
Interpreting Family Histories

• are medical records/autopsy reports accurate?

• patient could have sporadic FTD in context of a family history of dementia due to different causes

• in this scenario, the likelihood for her children or siblings to develop FTD would remain low

• small possibility that this is a brand new mutation in a familial FTD gene
Interpreting Family Histories

“Organic Brain Disease”

“Pick’s Disease”

“Dementia”?

“Will my children get FTD?”
Interpreting Family Histories

- are medical records/autopsy reports accurate?
- family history is highly suggestive of familial FTD
- likelihood for patient’s children or siblings to develop FTD could be as high as 50%
Interpreting Family Histories

“Organic Brain Disease”

“Pick’s Disease”

“Dementia”?

FTD

FTD

“Is there genetic testing?”
Familial FTD: Genetic Testing

Three most common familial FTD genes:
• MAPT, progranulin (PGRN), C9ORF72
• together account for more than 50% of familial FTD cases
• clinical genetic testing is available

Rare familial FTD genes:
• FUS, CHMP2B, TARDP, others?
• only a few families identified around the world
• research testing may be available
Familial FTD: Genetic Testing

MAPT, PGRN, and C9ORF72 genetic testing:
- available at commercial and clinical laboratories
- physician ordered
- ~$250-$1200 CDN per gene
- cost coverage may vary by country/region/health plan
- turn around time = 2-4 weeks

In Canada:
- C9ORF72 testing available at Edmonton clinical lab
- MAPT, PGRN testing available at US commercial labs

Autopsy findings and clinical symptoms can help identify candidate genes for testing
Familial FTD: Genetic Testing

- C9ORF72
- FUS, ?
- CHMP2B, ?
- MAPT
- PGRN
- VCP, TARDP, ?

Legend:
- Green: Tau pathology
- Blue: TDP43 pathology
- Purple: Fus pathology
- Black: Other pathology
## Familial FTD: Genetic Testing

### Most Common Familial FTD Genes

<table>
<thead>
<tr>
<th>MAPT</th>
<th>PGRN</th>
<th>C9ORF72</th>
</tr>
</thead>
<tbody>
<tr>
<td>codes for a protein (tau) stabilizes structure of brain cells</td>
<td>precursor of a protein that stimulates cell growth and wound repair</td>
<td>disease-causing mechanism unknown</td>
</tr>
<tr>
<td>9-21% of familial FTD</td>
<td>4-23% of familial FTD</td>
<td>18-30% of familial FTD</td>
</tr>
<tr>
<td>FTD-tau pathology (variable findings)</td>
<td>FTD-TDP43 pathology (unique protein structure and location)</td>
<td>FTD-TDP43 pathology (with additional GA dipeptide protein)</td>
</tr>
<tr>
<td>Can be associated with parkinsonism</td>
<td>Can be associated with parkinsonism</td>
<td>Can be associated with ALS</td>
</tr>
<tr>
<td>Almost complete penetrance</td>
<td>Reduced penetrance</td>
<td>Reduced penetrance</td>
</tr>
</tbody>
</table>

*Almost complete penetrance* suggests that almost all individuals with the gene will develop the disease. *Reduced penetrance* indicates that the gene may be present without causing the disease in some cases. The specific penetrance may vary depending on the individual.

Familial FTD: Genetic Testing

- Genetic testing for familial FTD is usually only relevant *if a family history is suggestive of this condition*.

- Testing process needs to start with a DNA sample from an affected individual (i.e. **diagnostic** testing).

- Pre-test **genetic counselling** recommended to ensure families are aware of all test limitations and implications.

- Negative test result does not rule out possibility of familial FTD.

- Positive test result:
  - Confirms familial FTD diagnosis and 50% recurrence risk.
  - Option of **predictive** genetic testing for at-risk family members.
  - Participation in clinical trials?
Familial FTD: Predictive Genetic Testing

- pre-test genetic counselling recommended in accordance with guidelines established for Huntington disease

- pre-test neuromedical assessment for neurological symptoms and risk factors for depression/anxiety/suicide

- review of motivations for testing and potential genetic, medical, family planning, psychosocial, and insurance implications…

- how will test results impact mood, confidence, relationships…?

- additional considerations: no cure, variable symptoms, reduced penetrance
Familial FTD: Other Considerations

- DNA banking
  - for future clinical genetic testing or research purposes

- autopsy arrangements
  - confirmation of diagnosis and pathology subtype
  - more accurate interpretation of family history
  - clarify candidate genes for genetic testing
Familial FTD: Other Considerations

- baseline cognitive testing for at-risk relatives
  - may allow for earlier diagnosis should FTD develop in the future

- research participation
  - gene discovery
  - genetic/environmental modifiers
  - clinical trials
What is the importance of gene discovery?

• genetic testing
  – confirmation of diagnosis
  – confirmation of recurrence risks for concerned relatives
  – options for predictive testing

• further understanding of disease mechanisms
  – treatments
  – preventative measures
  – a cure?
Conclusions

• most FTD cases are sporadic; ~40% are familial

• determining the genetic implications of an FTD diagnosis requires documentation and interpretation of family history information

• clinical genetic testing for familial FTD is available and relevant for families suggestive of this condition

• genetic testing for familial FTD should only be completed upon consideration of all implications; pre-test genetic counselling is recommended
Conclusions

• genetic counselling services are available across Canada, the US, Australia, and several European countries

• additional information available on-line or from your family physician

• BC residents concerned about a family history of FTD can be referred for genetic counselling at UBCH-CARD:
  
  Phone: 604-822-7031
  Fax: 604-822-7191