Genetics Advances in FTD

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Layout

• Background – Genes, Chromosomes and DNA

• Genetic mutations in FTD

• Practical Implications
What is genetics?

- Genetics is the field of study that is concerned with heredity and how particular qualities or traits are passed on from parents to offspring. These can be simple physical traits such as height or hair colour as well as complex disease susceptibilities.

- Medical genetics is both a clinical specialty and a basic science.

- The molecule of study in genetics is the gene.
What exactly is a gene?
What do genes do?

The size and code of the genes determine the size and the characteristics of the protein.
Why are proteins important?

• Proteins – building blocks of cells
  – Structure of cells
  – Regulate reactions
  – Enzymes
  – Hormones
Where do our genes come from?

• 46 Chromosomes
• Arranged in pairs
  – 1 from mother
  – 1 from father
• Each chromosome in a pair contains the same genes. For example eye colour but the details may be different
Where do our genes come from?

Mom and Dad have 23 pairs of chromosomes. They inherited one from each of their parents. Here is one of their pairs.

To make the next generation, DNA is mixed up for genetic diversity during meiosis.

Each mixed-up chromosome goes into its own sex cell.

The next generation gets one chromosome from each parent. The baby has its own unique combination of its parents’ DNA.
When genes go wrong ......
One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder.

- Each affected person usually has one affected parent.
- Autosomal dominant disorders tend to occur in every generation of a family.

50% of children will carry the gene.
It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal dominant disorder, the chance of having another child with the gene is still 50% (or 1 in 2).

Although the chances of inheriting a genetic condition appear straightforward, factors such as a person’s family history, environment, presence of other diseases can sometimes modify those chances.

Having one child with an abnormal gene does not “protect” future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder.
Is FTD hereditary?

- Firstly, we know that FTD has a strong familial basis in approximately 20% of cases.
- A strong family history – at least one family member (1st degree) with FTD or a related condition.
- One gene in particular can occur in a small proportion of apparently sporadic disease.
Do we know what genes are involved?

• Yes, we know most of them!

• C9orf72 expansion
• Tau mutation
• Progranulin mutation
What do we know about our patients?
BvFTD
BvFTD
BvFTD
Familial BvFTD
C9orf72

• The most recently discovered – 2011

• The commonest genetic cause of FTD and Motor Neurone Disease

• The gene provides instructions for making a protein called TDP-43 which is involved in cell structure and development

• For some unknown reason abnormalities in this gene cause a build-up of abnormal TDP-43 protein.

• Autosomal dominant condition
Characteristics of *C9orf72* mutation carriers

- Family history of FTD and MND
- bvFTD > PNFA
- Can occur in association with MND
- Can occur in people without a family history (*rare*)

**What is MND**

- Motor neurone disease
- Overlaps with FTD
- Also caused by C9orf72
- Progressive weakness of limb muscles and muscles involved in speech and swallowing.
- Muscles of breathing are affected later on in the disease course
**MAPT**

- Located on chromosome 17

- The *MAPT* gene provides instructions for making a protein called tau. This protein is involved in assembling and stabilizing cell structures.

- In ways that are not fully understood, the *MAPT* gene mutations lead to an accumulation of abnormal tau in neurons and other brain cells.

- Autosomal dominant inheritance
Characteristics of *MAPT* gene carriers

- Family history of FTD
- Behavioural variant FTD is by far the commonest
- Occasional language variant – PNFA
- Also CBS > PSP (Progressive Supranuclear palsy)
- Age of onset – 40-60 years
- Parkinsonism is common
  - Rigidity, Bradykinesia
Progranulin

- Located on chromosome 17

- The progranulin gene provides instructions for making TDP-43.

- For some unknown reason mutations in this gene cause a build-up of abnormal TDP-43 protein. This builds up over time and results in cell death

- Autosomal dominant condition
Characteristics of Progranulin gene carriers

- Family history of FTD
- bvFTD > PNFA > Semantic dementia
- Age of onset – average of 60 years, between 37 and 75 years
- Parkinsonism also common
- Delusions and hallucinations occasionally
What has our research taught us?
Table 1. Baseline Demographic Characteristics of Patients With Behavioral-Variant Frontotemporal Dementia, Comparing C9ORF72 Mutation Carriers, Noncarriers, and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers (n = 10)</th>
<th>Noncarriers (n = 19)</th>
<th>Controls (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>54.1 (9.4)</td>
<td>57.2 (7.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of symptoms at presentation, mean (SD), y</td>
<td>4.7 (3.5)</td>
<td>2.6 (1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Education history, mean (SD), y</td>
<td>10.6 (1.6)</td>
<td>11.3 (3.2)</td>
<td>11.8 (2.3)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>ACE-R score, mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75.7 (8.4)</td>
<td>67.3 (22.1)</td>
<td>94.2 (3.1)</td>
</tr>
<tr>
<td>FTDFRS Rasch score, mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.8 (1.8)</td>
<td>-1.1 (1.5)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-R, Addenbrooke's Cognitive Examination-Revised; FTDFRS, Frontotemporal Dementia Functional Rating Scale; NA, not applicable.

<sup>a</sup> P < .001 for carriers vs controls and for noncarriers vs controls.
How do C9orf72 carriers present?

Misdiagnosis of late-onset schizophrenia

IMPLICATIONS FOR:
• ACCURATE and TIMELY DIAGNOSIS
• APPROPRIATE REFERRAL FOR GENETIC COUNSELING

Psychosis at Presentation

Psychiatric Family History

Variability in MRI Findings
Psychosis in FTD and MND

36 FTD
- 9 C9orf72
- 14 C9orf72

20 FTDMND
- 5 C9orf72

42 Sporadic

Psychosis Present
- 50%
- Average Psychosis Score per Patient: 23.1%

Psychosis Present
- 29%
- Average Psychosis Score per Patient: 8.1%

*p < 0.05
*p < 0.005
What are the brain regions involved?

Thalamus
Cerebellum
Striatum
Frontal/temporal lobes
Psychiatric Family History - 1,143 Relatives

C9 Positive vs Negative

[Graph showing relative risk for various psychiatric disorders]
Majority of sporadic cases are explained

‘Psychosis phenotype’ exists within families
Practical Implications

• Visit to research centre
  – Blood taken for *C9orf72* expansion
  – If you have a positive family history – also test for *Tau* and *Progranulin* mutations

• **A positive finding without a family history is rare**

• Blood is only taken after informed consent

• If we find an abnormality this needs confirmed in a clinical laboratory

• We will inform you of any positive result
Referral to the geneticist

- Medical Doctor
- Works within a team – in close association with a genetic counselor
- Confirm the findings if they are positive
- Offer genetic counseling to make patients and carers aware of the positives and negatives involved in finding a positive result
Referral to a geneticist

• Genetic consultation is free
• Offer family counseling
  • 3 sessions
  • 6-12 month process
  • 2/3 of people decide against testing
  • Useful to discuss implications
Pre-implantation Genetic Diagnosis (PGD)

• IVF process
• In PGD testing, one or two cells are removed from a day-3-5 embryo and tested for a specified gene.
• Only those embryos diagnosed as being unaffected will be transferred in the IVF cycle, maximising the chance of not passing on the gene.
Why is it important to study genes?

• Information for doctors, carriers and their families

• Important for research
  – Progression and survival
  – Develop markers of early features of the disease
  – Provide important information for developing disease models and testing pharmaceutical therapies
Summary

• Frontotemporal Dementia is hereditary in approximately 20% of cases
  – Most common is behavioural variant FTD
• C9orf72 is the most common genetic abnormality in our patients
• *It is very rare to find a genetic abnormality without a positive family history*
• Genetic counseling is advised for family members