understanding genetics in FTD and PPA

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agenda
• genetic counseling
• genetics 101
• genetics of FTD and PPA
• genetic testing
• research
• how does my family fit in?
• what to expect

what is a genetic counselor?
• translator
• patient advocate
• resource negotiator
• educator
• decision facilitator

genetics 101

cell
chromosomes
nucleus

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DNA to protein

- **Cell**
- **Nucleus**
- **Chromosomes**
- **Gene**
- **Protein**

DNA to protein with a mutation

- **Gene**
- **Protein**

Autosomal dominant inheritance

- Males and females affected equally
- Cannot skip a generation
- 50% chance to pass mutation on
- Use pedigree to look for patterns of inheritance
autosomal dominant inheritance

pedigree helps with...
• pattern of inheritance
• identification of individuals at risk
• genetic testing strategies
• screen for other medical risks

polymorphisms
• change in a gene that does not affect function
• color vs. colour

genetics of FTD
• about 10% of FTD cases are inherited
• 50-70% of FTD cases are sporadic (not inherited)
• 20-40% of FTD cases are familial

sporadic FTD
• ~50-70%
• not inherited
• no other affected family members
• no increased risk for family members
sporadic FTD

- about 10% of all FTD
- affected parent means 50% risk to first degree relatives
- lower age of onset and more rapid course than sporadic FTD

Inherited FTD

- 20 – 40%
- has a heritable component
- intermediate risk to family members
- lower age of onset
- quicker disease course
- multifactorial disease

inherited FTD

familial FTD

- 20 - 40%
- has a heritable component
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Inheritance

- the thought of inheriting and/or passing down a mutation associated with FTD is scary
- we know some, but not all about FTD genetics
**which type of FTD is my family?**
- work with genetic counselor
- limitations - early death of relatives, adoption, no information
- any and all medical information is helpful!

**medial history**
- accurate medical history means more accurate risk estimation
- medical records, autopsy reports, tissue blocks, etc
- any and all conditions, especially neurological
  - ALS, FTD, PD

**gray areas of genetics**
- much of genetics is not a simple yes or no
- we inherit risk levels for any given condition
- this risk is modified throughout our lives
  - some genes are known
  - not much is known about environmental factors

**gray areas of genetics**
- many families fall within the middle area
  - no testing available
  - no specific risk number
- research participation is an option
- keep in touch with neurologist and genetic counselor

**genetic research**
- blood and/or tissue samples
- look for similar changes in many people
- helpful to have affected and unaffected family members
- some genes have been found so far
MAPT
- microtubule associated protein tau
- chromosome 17
- makes a protein called ‘tau’
  - present in the brains of people with neurodegenerative disorders
  - healthy tau removed by normal processes
  - abnormal tau has altered function and cannot be removed like normal tau
  - this leads to symptoms

MAPT families
- FTDP-17
- dementia and/or parkinsonism
- brain atrophy
- more than 2 family members affected in an AD pattern

MAPT mutation
- around 40 mutations reported
- unique vs. common mutations
- genotype/phenotype correlations?
  - disease course, symptoms, age
  - useful for genetic counseling of families
- still variation within families - why?
- polymorphisms
  - CBD, PSP or modified FTD risk

PGRN
- progranulin
- chromosome 17
- progranulin sends a message to increase cell growth
  - helps would repair, related to cancer
  - lots of other functions
  - function in FTD is unclear
- mutation leads to not enough functional progranulin

PGRN families
- increased chance for PPA
- decreased chance for MND
- more variable than MAPT
  - aphasia
  - behavior disorders
  - reports of individuals in their 70s with no symptoms

PGRN mutation
- brain protein is also common in ALS
- polymorphisms in PGRN lead to susceptibility
- more studies are needed!
future directions for research

- genotype/phenotype correlations
- progranulin and TDP-43 proteins
- related substances may mean drugs for treatment

genetic counseling session

- family history and analysis
- natural history, genetics and inheritance education
- data update
- discuss recurrence risks
- review genetic testing
- psychosocial support

genetic testing

- complex!
- who to test?
- research vs. clinical testing
- what gene?
- testing strategies

presymptomatic testing

- only possible with a known gene
- “true negative” test result
- other considerations

testing: yes or no?

<table>
<thead>
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<th>reasons to test</th>
<th>reasons not to test</th>
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<tbody>
<tr>
<td>need to know</td>
<td>no treatment</td>
</tr>
<tr>
<td>plan finances</td>
<td>no cure</td>
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<tr>
<td>insurance</td>
<td>hypervigilance for symptoms</td>
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family communication

- open and honest, ideally
- include a discussion of genetic testing
- have a meeting with family and genetic counselor
- lots of possible reactions, all are normal and okay
- this is a very individual decision!
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**Summary**

- Majority of FTD/PPA is not inherited
- Accurate medical histories
- Risk assessments
- Currently known genes
- Testing strategies
- Research participation
- Genetic counselors are your friends!