THE GENETICS OF FTD

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Is the FTD in my family hereditary?
~40% of FTD is inherited

- Deterministic
- Susceptibility

Pie chart showing a comparison between hereditary and sporadic FTD.
What does your family history look like?

- Sporadic: 1 case of dementia only

- Familial: More than 1 case of dementia (of some kind) but not typical strong inheritance pattern

  - Autosomal dominant: At least 3 affected people in at least 2 generations with 1 affected person being the 1st degree relative of 2 other affected people. (Dementia, ALS, PD)
Sporadic history

FTD
Familial history

- 40s, flu
- 91
- 84
- 61, Onset 56
- 57
- 54
- 86, AD, onset 80
- 88, stroke
- 90, colon ca
- FTD
Autosomal dominant inheritance

- **Onset 56**
- **Onset 53**
- **Onset 50**

- **Dementia**
- **FTD**
Genetics 101
Genes are part of chromosomes (23 pairs/cell)
Genetics 101
Chromosomes are made of DNA
Gene Function

Each Chromosome Contains Thousands of Genes

Chromosome -> DNA -> Gene -> Protein
Genetics 101
Terminology

- **Mutation**: an alteration in the DNA sequence of a gene that causes a disease.
- **Polymorphism**: a normal variation in the DNA sequence that does not cause a disease.
- **Genotype**: the sequence of DNA within a gene.
- **Phenotype**: the clinical expression of the gene (Symptoms).
- **Penetrance**: how often someone with the genotype expresses the phenotype.
- **Phenotypic variability**: difference in symptoms even though the genotype is the same.
- **Autosomal dominant inheritance**: one copy of the disease gene is sufficient for passing on the risk of disease. Each 1st degree relative has a 50% chance of inheriting the disease.
(ONE PARENT AFFECTED)

Affected Father

Mother

D d

D d

d d

d d

Affected Son
Normal Daughter
Affected Daughter
Normal Son

(25%)
(25%)
(25%)
(25%)
Mutations

- Mistakes in the DNA sequence
  e.g.
  Normal gene: CATGAT
  Mutated gene: CAGGAT, CAGAT, CATTGAT, CATGATCATGAT

- Result of mutation: change in amino acid sequence of protein, hence change in function of protein OR inability to produce protein
We still know very little about the genetic causes of FTD.
Tau Mutations

- MAPT (Chromosome 17q21-22)
- FTDP-17
  - >60 mutations
  - Mutations cause abnormal tau
- 5-15% of all FTD
- 10-25% of familial FTD
- Seems to be nearly fully penetrant
- Age of onset 25-65 years (mean 40-60)
- Duration: 3-10 years
Phenotypic Variation of Tau Mutations

- Behavioral change: disinhibition, OCD etc.
- Language dysfunction
- Parkinsonism, CBS
- ALS/motor neuron disease
Autosomal dominant inheritance

ALS

Dementia

FTD

50s dementia

60, PD with dementia

59, bvFTD

Onset 56

57, Onset 53

Onset 56

87

88, stroke

90, colon ca

83

86

85

64, bvFTD

91

60, PD

62, ALS

90

50, PD

86

87
Progranulin Mutations

- PGRN or GRN, (Chromosome 17q21-22)
  - >50 mutations
  - Loss of function
- 5-10% of all FTD
- 10-24% of familial FTD
- 70-90% of mutation carriers have a family hx
  - Lost family history
  - Incomplete penetrance
  - Late onset variability
  - De novo mutation
  - Non-paternity
Phenotypic variability of PGRN mutations

- Age of onset: 35-89 years (mean 60)
- Duration: 3-22 years (mean 6-7)
- Clinical presentation
  - Change in behavior most common presentation
    - Especially apathy, social withdrawal
  - Language dysfunction, aphasia
  - Memory problems (like AD)
  - Hallucinations, delusions
  - Parkinsonism
    - Rigidity, slowness, tremor
    - Corticobasal syndrome
  - ALS very UNCOMMON
What do you do if there is an autosomal dominant inheritance?

- Genetic testing for symptomatic patients
  THEN if a mutation is found genetic testing for asymptomatic relatives is possible

- Clinical vs. Research genetic testing
  - Clinical testing: CLIA lab, payment required, results are available to patient
  - Research testing: Free but results are NOT given to patient
Things to consider for symptomatic testing

- What are/were the patient’s desires?
- Who in the family should be consulted before the testing?
  - Who would want to know results?
  - Is the result going to be shared? If so, how?
Things to consider for presymptomatic testing

**BENEFITS**
- Reduce anxiety
- Reduce uncertainty
- Make future plans for self and children

**LIMITATIONS**
- Emotional impact
- Family issues
- Possible insurance/job discrimination
- No treatment or prevention
- Cost
- Need to test affected family member
Protocol for Genetic Testing

- For **presymptomatic testing**, use HD protocol:
  - Several counseling sessions
  - Baseline neuropsych and neuro exam
  - Psych assessment if mental status is questionable
  - Support person encouraged for all sessions—For results, must bring support person

- **Nobody under the age of 18 can have presymptomatic testing for an adult-onset disease.**
Interpretation of Predictive Gene Test Results

- **True Positive**: previously identified pathogenic mutation found
- **True negative**: affected family member’s mutation not found
- **Positive with unknown significance**: new mutation found: polymorphism or pathogenic?
- **Negative with unknown significance**: affected family member not previously tested
The Testing Decision

“You think about this constantly, I want to set my mind at rest one way or another”

“Choosing not to take the test is a decision one can easily revoke, unlike the situation after testing...’Once you have the information, you cannot give it back.’”

(Alice Wexler: Mapping Fate)
AND MOST IMPORTANTLY…

- MAINTAIN HOPE:
- There are still many unknown genetic factors (+ and -) to be found
- FTD research is expanding rapidly!
- Think about getting involved in genetic research
- Think about brain donation
- Get support!