Overview

- Why are there so many research studies on the genetics of FTD?
- How much of FTD is genetic?
- What are the different genes that can cause FTD?
- Why should families get involved with genetic research (even if they don’t have a family history)?

What comes first or ?

- We are used to thinking about the symptoms of FTD, but where do they come from?
- FTD has at least 3 different pathologies…i.e. it is at least 3 different diseases
- What are the mechanisms that cause these pathologies?
- Therapies need to target cause, not symptoms

What do we know?

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<th>GENE</th>
<th>PATHOLOGY</th>
<th>DISEASE</th>
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<td>TAU</td>
<td>FTD</td>
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<td>PGRN</td>
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<td>CHMP2B</td>
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<td>VCP</td>
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<td>C9ORF72</td>
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How much of FTD is genetic?

- Sporadic
- Familial
- Autosomal dominant

Family History

- FTD
Autosomal dominant FTD

- MAPT
- PGRN (~3% sporadic)
- C9ORF72: 9 FTD/ALS (~4% sporadic)
- Paget’s disease/FTD/VCP
- CHMP 2B: Chrom. 3
- TDP-43 (associated with ALS)
- FUS (associated with ALS)

How do we know for sure if it’s genetic?
- Must first test an affected person to determine a specific causal gene mutation
- THEN if an at-risk family member wants presymptomatic testing, they can ask for genetic counseling and then testing

Interpretation of Autosomal Dominant 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

Genetics 101
Chromosomes are made of DNA

- Mistakes in the DNA sequence
  - e.g.
  - Normal gene: CATGAT
  - Mutated gene: CAGGAT, CAGAT, CATGAT, CATGATCATGAT
- Result of mutation: change in amino acid sequence of protein, hence change in function of protein OR inability to produce protein
Options for people at risk of hereditary dementia

- Genetic testing after identification of family mutation through blood or tissue
- DNA banking
- Genetic research study
  - FTD Genetics Research with or without genetic results
  - Autopsy

Importance of genetic research

- To understand mechanisms of disease
- Who can participate in genetic research?
  - Families with autosomal dominant family histories
    - Characterize features of mutations: spectrum of symptoms, biomarkers-imaging changes, CSF profile, etc.
    - Candidates for specific drug trials
    - Identify etiologies of mutational variation (other genetic markers or environment)
  - Sporadic families
    - Identify genetic or environmental risk factors
    - Unaffected family members
    - Controls

Researchers need all of you!

- Volunteer for research studies
- Fund raise
- Advocate

Genetics as a Research Tool

- Patients
- Families
- FTD databases
- Clinical Trials
- Models
- Diagnosis

It starts with you – the patient - the caregiver - the family
Patients and Families Donate Samples
Fill out Surveys and Participate in Research Studies

- NACC-FTLD module (clinical, pathology)
- NY brain bank-Columbia Univ., Troxel brain bank-Mayo clinic, Northwestern Univ. brain bank for PPA/bvFTD
- FTD Stem Cell Consortium at Coriell Cell Repositories
- Longitudinal research studies at FTD medical centers

Diagnosis
Genetics at Work – Learning More About FTD Around the World

- Genetic screening of individuals and families will contribute to clinical trials based on familial FTD cohorts
- Screening increases our knowledge of FTD in other countries – the percentages of C9ORF72, MAPT, GRN can vary by geographic region

Survey Results
Building an International Network of Familial FTLD Cohorts

From: M. Catarina Silva, PhD – AFTD Postdoctoral Fellowship Award, 2013

Genetics at Work
FTD Patient-Derived Stem Cells

- FTD gene mutations can be introduced into the DNA of different animals (mice, fruit flies) or cells in culture to try and recreate the disease
- These animal and cell models allow us to learn about the biological pathways that contribute to FTD and test new drugs
- The newest model is the patient-derived stem cell, which allows us to study and test drugs in human autosomal dominant FTD cells in culture

From: M. Catarina Silva, PhD – AFTD Postdoctoral Fellowship Award, 2013

Genetics at Work
Models

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From: M. Catarina Silva, PhD – AFTD Postdoctoral Fellowship Award, 2013
Nerve cells Grown From FTD Patient iPS Cells

From: M. Catarina Silva, PhD – AFTD Postdoctoral Fellowship Award, 2013

“Disease in a Dish”

Create nerve cells from individual FTD gene mutation carriers and controls

• Study disease biology in a human model
• Test new drugs in human nerve cells

Genetics at Work

More Research advances from FTD genetics
• Gene mutations can be ‘shared’ across diseases
• New findings on toxic pathways
• New approaches to prevent or decrease nerve cell death

From: Jeff Rothstein laboratory – ADDF-AFTD Translational Research Grant Awardee

Getting there - with the support of our patients, caregivers and families