IMPORTANCE OF GENETIC RESEARCH IN FTD

Continuing Education Training
FTD Support Group Facilitators
May 19, 2014
AFTD is Mission Driven

Promote and fund research
Provide information, education and support
Educate physicians and health professionals
Increase public awareness
Advocate for LTC and social services
Facilitate the international exchange of ideas

We envision a world where frontotemporal degeneration is understood, effectively diagnosed, treated, cured and ultimately prevented.
AFTD: Support Encourages Strength

• HelpLine - individual, responsive
• Respite and travel grants
• Telephone support groups (behavior, language, parents, diagnosed)
• Caregiver Connections
• FTD Education Conferences
• FTD support groups
Information Empowers

- Accurate, current and specific to FTD
- Guidance for managing care
- Resources with experience in FTD
- Connection to experts and emerging research

Website
Newsletters
Publications
Partners in FTD Care

Education for healthcare professionals
- Training materials
- Quarterly newsletter - case study, and “What to do About…”
- Intervention focused on-line forum
Hot News from AFTD

AFTD Kids and Teens website  www.aftdkidsandteens.org

Reorganized main website coming early June.
• Same look. Easier access to great information.

Partners in FTD Care Spring Issue – Aggressive behavior

Key dates:
• May 30 – FTD Caregiver Conference, UPenn, Philadelphia
• Oct 5-12 – AFTD’s Food for Thought & FTD Awareness Wk
• Oct. 23-25 - 9th International FTD Conference
Importance of Genetic Research in FTD

Today’s Guest Speakers

Jill Goldman, CGC
Genetic Counselor
Columbia University

Nadine Tatton, PhD
Scientific Director
AFTD
FTD Genetics...where is it leading us?

Jill Goldman, MS, MPhil, CGC
Taub Institute
Columbia University Medical Center
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 \( \text{chicken} \) or \( \text{egg} \)?

- 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?

GENE → PATHOLOGY → DISEASE

GENE
- MAPT
- PGRN
- C9ORF72
- VCP
- TDP43
- CHMP2B
- FUS

PATHOLOGY
- TAU
- TDP43
- ubiquitin
- FUS

DISEASE
- FTD, CBD, PSP
- FTD
- FTD/ALS
How much of FTD is genetic?
(ONE PARENT AFFECTED)

Affected Father

D d

D d

D d

d d

Affected Son

Normal Daughter

Affected Daughter

Normal Son

(25%)

(25%)

(25%)

(25%)
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
Mutations

- Mistakes in the DNA sequence
  
  e.g.

  Normal gene: \text{CATGAT}

  Mutated gene: \text{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
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 at Work
Advancing FTD Research and Therapeutic Development

Nadine Tatton, PhD
Scientific Director - AFTD
Genetics as a Research Tool

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

GENETICS
Genetics at Work – Advancing Research

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 (clinical databank)
- NY brain bank-Columbia University
- Northwestern brain bank for PPA/bvFTD
- FTD Stem Cell Consortium
- Longitudinal research studies
Genetics at Work – Learning More About FTD Around the World

- Genetic screening is used for diagnosis
- Screening expands our current understanding of FTD epidemiology
- Genetic screening can help us design clinical trials for familial FTD
Survey Results

Building an International Network of Familial FTLD Cohorts
Models

Genetics at Work

- FTD genes can be inserted into the DNA of fruit flies or other animals to create a model of FTD
- Models let us study the cellular pathways of FTD
- Models are also used for pre-clinical testing of new drugs
Gene mutation identified-FTD patient

Skin Biopsy

Tissue-punch takes skin sample from forearm

Adult Skin Fibroblasts contain the FTD patient’s gene mutation

Grow biopsy cells in culture to get fibroblasts

From: M. Catarina Silva, PhD – AFTD Postdoctoral Fellowship Award, 2013
Repogram FTD fibroblasts into stem cells

‘Induce’ FTD pluripotent stem cells

Use special culture media to create nerve cells from iPSCs

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

Models

Control Neurons
FTD Neurons

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
• The C9 mutation can cause ALS or FTD
• New approaches to prevent or decrease nerve cell death

From: Jeff Rothstein laboratory – ADDF-AFTD Translational Research Grant Awardee
• **Dose Finding Study of Nimodipine for the Treatment of Progranulin Insufficiency From GRN Gene Mutations** (*NCT01835665*) Dr. Adam Boxer, UCSF, Memory and Aging Center

• **A study to assess the safety, tolerability and effectiveness of Nuedexta (Dextromethorphan 20mg/Quinidine 10mg) in the treatment of Pseudobulbar Affect (PBA)** (*NCT01799941*) Dr. Carol Lippa, Drexel University College of Medicine

• **A Double-Blind, Placebo-Controlled, Randomized, Parallel Group, 12-Month Safety and Efficacy Trial of TRx0237 in Subjects With Behavioral Variant Frontotemporal Dementia (bvFTD)** (*NCT01626378*) TauRx sponsored multi-site trial

• **Natural History and Biomarkers of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia Caused by the C9ORF72 Gene Mutation** (*NCT01925196*) NIH sponsored study, Dr. Mary Kay Floeter, NIH Clinical Center
Getting there - with the support of our patients, caregivers and families
Importance of Genetic Research in FTD

Q & A with Today’s Guest Speakers

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Future Web Training

This training will be archived on AFTD’s website. Please share the link with others.

Watch your email and AFTD’s newsletter for more web-based training for group leaders, family caregivers people with FTD and professionals.

Thank you for all you do to support AFTD’s mission!
A Focus on FTD Care and Cure

AFTD creates:

• A community of and for those affected
• A hub for cross-disciplinary collaboration
• Opportunities to get involved
• Change

http://www.theaftd.org

HelpLine: 866-507-7222
info@theaftd.org

The Association for Frontotemporal Degeneration
Opening the gateway to help and a cure