FTD Genetics: for patients and families

Kirk Wilhelmsen, M.D., Ph.D
The Human Genome

• 22 Pairs of Chromosomes
• 2 Sex Chromosomes
• 3,300,000,000 basepairs of DNA
• 7-14 picograms of DNA per cell
• ~20,000 transcripts (genes)
Genetics is the branch of science that deals with inheritance.

DNA → RNA → Proteins

DNA (green arrow) → RNA (green arrow) → Proteins

DNA (green arrow) → RNA (green arrow) → Proteins (green arrow)
Meiosis

Perception

Reality

30 crossovers per meiosis
Mapping Mutations to Chromosomes
Genotype determination for segregation analysis

• Affected individuals all carry a 2 allele (●)
• This experiment was the first evidence that Turcot’s was due to a mutation at APC on 5q
DDPAC

Family Mo
Clinical Syndrome

• Disinhibition first sign (onset age 27-56) usually manifested predominantly by personality change
• Dementia with relative preservation of language, memory and praxis
• Parkinsonism without tremor or response to L-DOPA progressing to akinetic mutism
• Amyotrophy which is frequently subtle
• Complex, with all of the above features present to varying degrees
Pathology in Family Mo

Frontal Temporal Atrophy

Cortical Neuronal loss layer I

Loss Pigmented Cells in Substantia

Rare ballooned neurons

Swollen Vacuolated Anterior Horn Cells

Gliosis of perifontent pathway into the

(R Defendini, A Sima, C Kohan)
Multipoint Lod Score
DDPAC → Frontotemporal dementia and Parkinsonism linked to chromosome 17

- THRA1
- Tau
- HOX2B/GP3A

Genetic markers:
- D17S946
- D17S250
- D17S800
- D17S934, D17S950
- D17S810, D17S971
- D17S934, D17S950
- D17S800
- D17S806, D17S979, D17S931
- D17S943
The Tau and Aβ in Alzheimer’s Disease
Neurofibrillar tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein

Jada Lewis¹, Eileen McGowan², Julia Rockwood³, Heather Melrose¹, Parimala Nacharaju¹, Marjon Van Slegtenhorst¹, Katrina Gwinn-Hardy¹, M. Paul Murphy¹, Matt Baker¹, Xin Yu¹, Karen Duff³, John Hardy¹, Anthony Corral¹, Wen-Lang Lin¹, Shu-Hui Yen¹, Dennis W. Dickson¹, Peter Davies² & Mike Hutton¹
Genes Known to Cause FTD

- **TAU**
  - Big AD families
- **Progranulin (GRN)**
  - The most common cause of FTD, also 17q21 often in smaller AD families with ubiquitin inclusions
- **FUS**
  - Next most common
- **TDP-43**
  - Most associate with ALS
- **Vasolin (VCP)**
  - Rarer big AD families with muscle (myopathy) and bone (Paget’s) disease with vcp inclusions
- **CMP22**
  - Very rare AD (single Danish family)
Genes Known to Cause Alzheimer’s

- AD Familial disease
  - Amyloid precursor protein (APP)
  - Presenilin 1 (most common)
  - Presenilin 2 (most common)
- AD complex
  - APOE
Molecular Basis of APOE Variation

Site 1
aa 112
Cys
Cys
Arg

Site 2
aa 158
Cys
Arg
Arg
E2
E3
E4
Relationship Between APOE Genotypes And Alzheimer’s Disease

Adapted from Roses 1995
Can we tell which mutation a patient has by their disease?

- The short answer is no.
- The pathology of a patient is correlated with the type of mutation.
- Some patients have similar pathology without having mutations.
Pathology in Family Mo

Frontal Temporal Atrophy

Microvacuolar changes

Cortical Neuronal loss layer I-III

Loss Pigmented Cells in Substantia Nigra

Swollen Vacuolated Anterior Horn Cells

Rare ballooned neurons

Gliosis of perforent pathway into the hippocampus

(R Defendini, A Sima, C Kohan)
What fraction of FTD and related disorders are caused by mutations?
Screening the tau gene for mutations

- 186 subjects sequenced
  - FTD 89 Sporadic 17 Familial
  - 23 PSP, 2 CBD
  - 55 Misc.

- All mutations confirmed by second method
Results

• **10%** of familial (2-3 affected relatives) FTP cases have mutations

• **~1%** of sporadic FTD and PSP cases have mutations in Tau or GRN

• **90%** of highly penetrant autosomal dominant families have mutations Tau of GRN
FTD Epidemiology
Prevalence

• Autopsy series from Lund and Manchester
  – 10-15%

• Probable AD Autopsy series from CERAD
  – 3-6%

• Behavioral Neurology Clinics
  – 0 to 20%

• Population Survey for Pick-like Disease
  – 0.1 per 100,000 between ages 30 and 40
  – 0.3 per 100,000 between ages 40 and 50
  – 1.1 per 100,000 between ages 50 and 60
  – 2.8 per 100,000 between ages 60 and 70
FTD Familial Aggregation

• 10-20% have a positive family history of a affected first degree

• 5% have a history of highly penetrant autosomal dominant disease ($\geq 3$ affected relatives)
First Degree relatives of FTD patients are 3.5 times more likely to become demented by age 80.

Sibling relative risk ($\lambda_s$) (of non-dominant form)

$100 - 300000$

$0.1 \text{ to } 0.3$

$0.001 \text{ to } 0.000001$

Figure. Estimated incidence of dementia in first-degree relative of control subjects, of frontotemporal dementia (FTD) patients with unknown linkage, of all FTD patients, and of patients with FTD linked to chromosome 17 (FTD-17).
Conclusion I

• The known mutations account for a small fraction of the FTD/Pick spectrum.

• There are more genes to find
The San Francisco B Family

*Evaluated by KCW and UCSF
Is DNA diagnosis available?

- DNA diagnosis is being done for by clinical labs
  - Cost ~$1-3K/gene
  - A Genetic Counselor should be involved when a decision is made about whether to do a genetic test
  - Genetic test to confirm the diagnosis of an affected individual can have a major impact on a family.
Cloning

Sequencing

Automation
Advances in DNA sequencing technology

• The first human genome cost ~$1 billion
• Genomes 2-5 cost ~$100,000
• My lab is now sequencing the whole genome of ~100 subjects per month at a cost of $5,000
• The cost is dropping very fast
• It is almost cheaper to resequence a genome than to store the data for long term use.
Guidelines for Genetic Testing

• Until there is treatment or preventative care
  – Confirmation of diagnosis
  – Reproductive planning
  – Life planning?

• When there is treatment
  – It would be helpful to know if genetic diagnoses to start early treatment of children
  • It is possible to save DNA of patients for future testing (see for example http://www.in.gov/isp/files/DNA.pdf)
We thank our patients and NINDS

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