FTD Genetics:
for patients and families

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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.
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

Gliosis of perifrontal pathway into the

Rare ballooned neurons

Swollen vacuolated anterior horn cells

(D. Defendini, R. Sima, C. Kohan)
Multipoint Lod Score
The Tau and Aβ in Alzheimer’s Disease
Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein

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Genes Known to Cause FTD

• TAU
  – 5-10% of FTD cases almost all are from big families with lots of affected individuals

• Progranulin (GRN)
  – 5% of FTD, also 17q21 often in smaller AD families with ubiquitin inclusions

• 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 FTD-ALS

• Superoxide Dismutase 1
  – 20% familial ALS with usually mild symptoms of FTD

• C9orf72
  – 20% familial ALS; 5% Sporadic ALS; 1% Sporadic FTD; rare large familial FTD-ALS

• Fused in Sarcoma 1% of Familial ALS.
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
- Rare ballooned neurons
- Swollen Vacuolated Anterior Horn Cells
- Gliosis of perforent pathway into the hippocampus

(R Defendini, A Sima, C Kohan)
What fraction of FTD and related disorders are caused by mutations?
Conclusions

• 10-20% of familial (2-3 affected relatives) FTP cases have mutations
• ~1% of sporadic FTD and PSP cases have mutations in Tau or GRN or c9orf72
• 90% of big highly penetrant autosomal dominant families have mutations Tau or GRN
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 $2,000 and dozens of whole exomes at $800
• 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)
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