

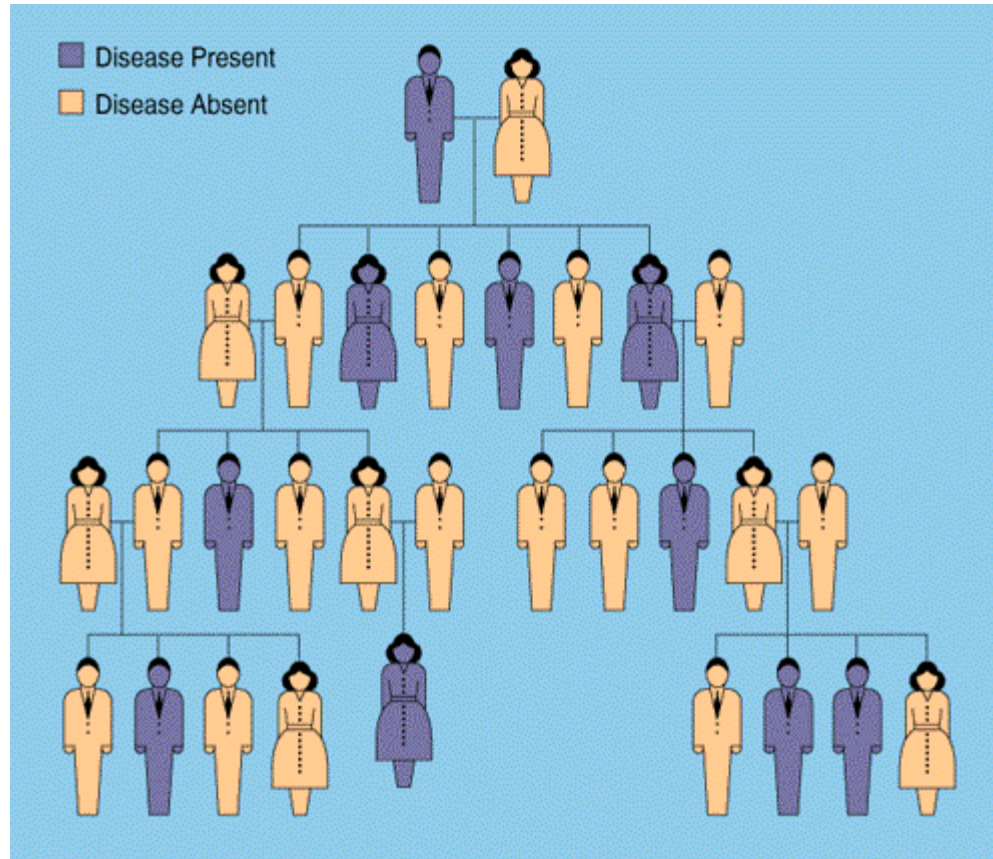
THE GENETICS OF FTD

Jill Goldman, MS, MPhil, CGC

Sergievsky Center and Taub Institute

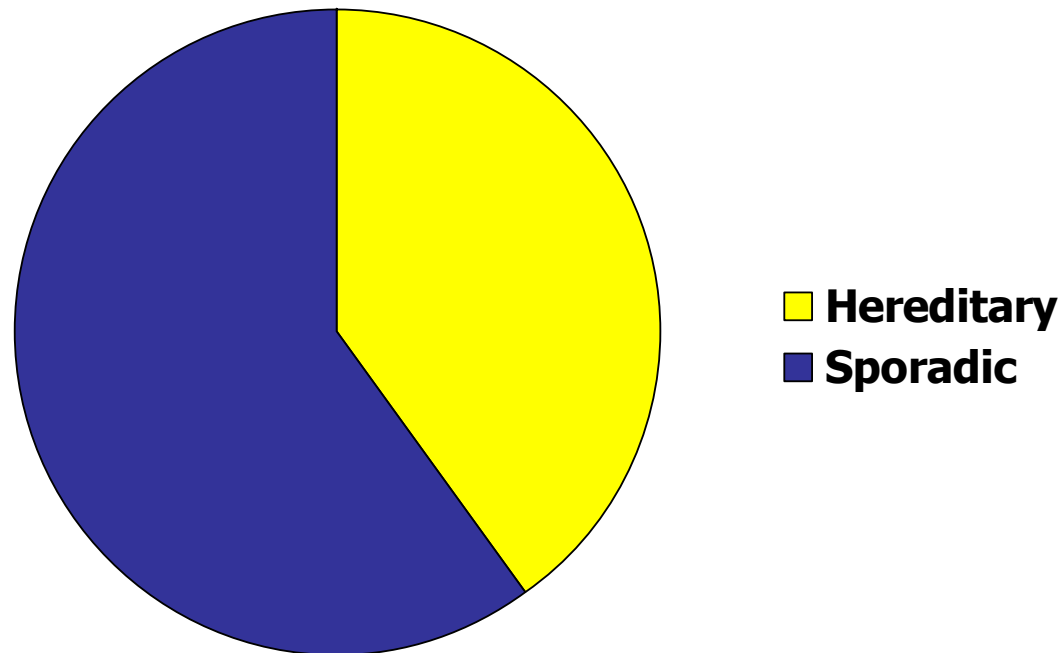
Columbia University

Is the FTD in my family hereditary?



How much of FTD is hereditary?

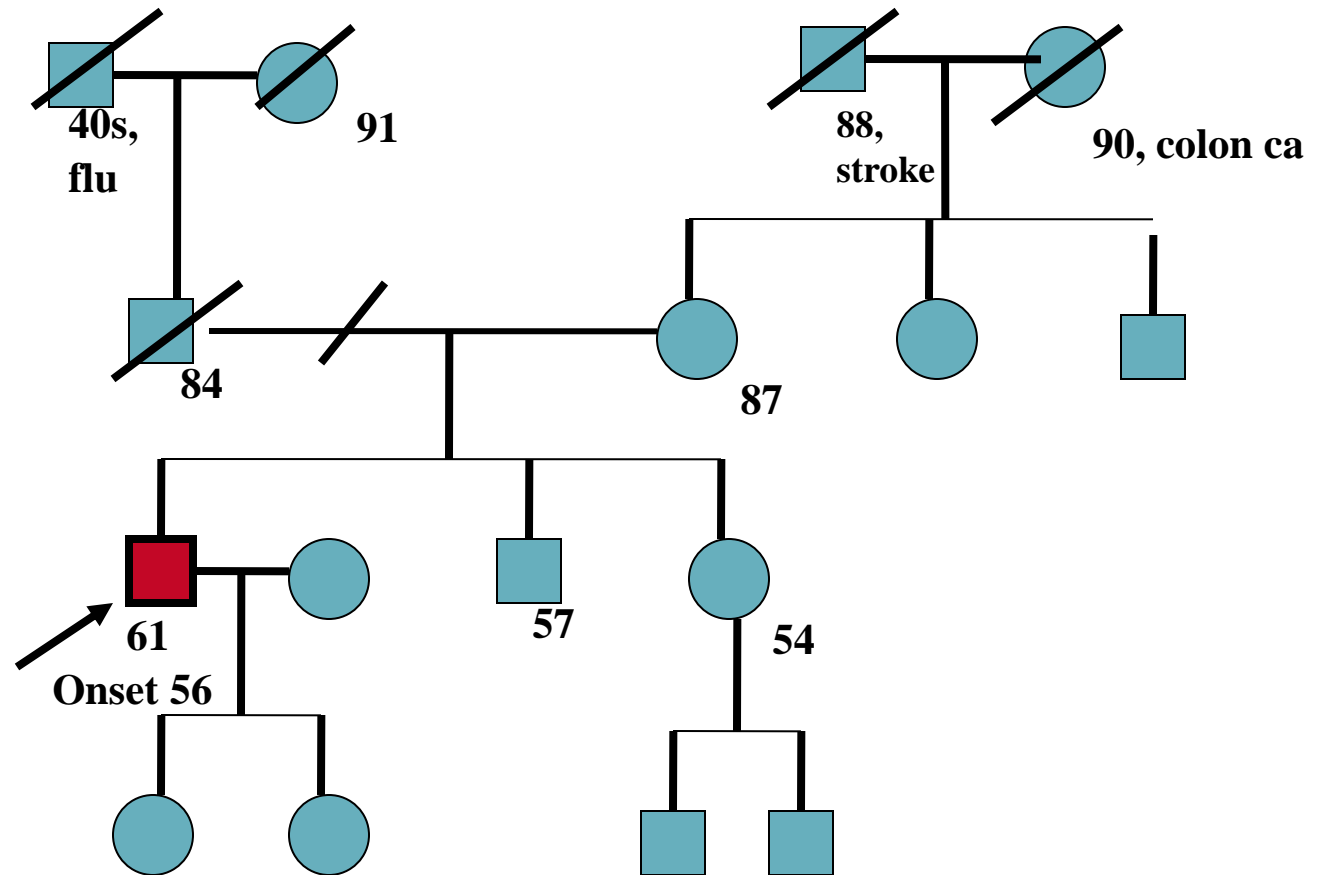
- ~40% of FTD is inherited
 - Deterministic
- vs
- Susceptibility



What does your family history look like?

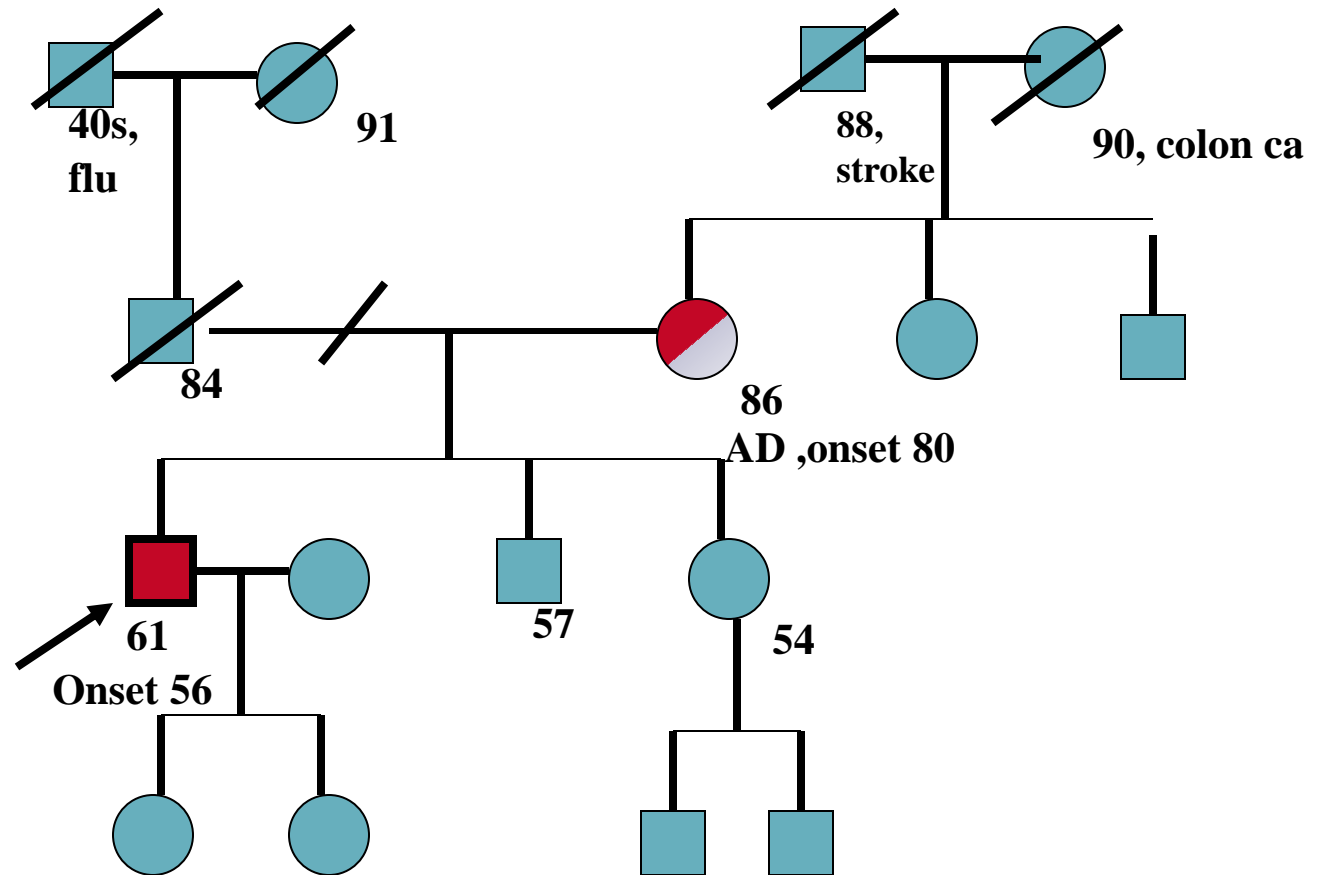
- Sporadic: 1 case of dementia only
- Familial: More than 1 case of dementia (of some kind) but not typical strong inheritance pattern
- **Autosomal dominant: At least 3 affected people in at least 2 generations with 1 affected person being the 1st degree relative of 2 other affected people. (Dementia, ALS, PD)**

Sporadic history



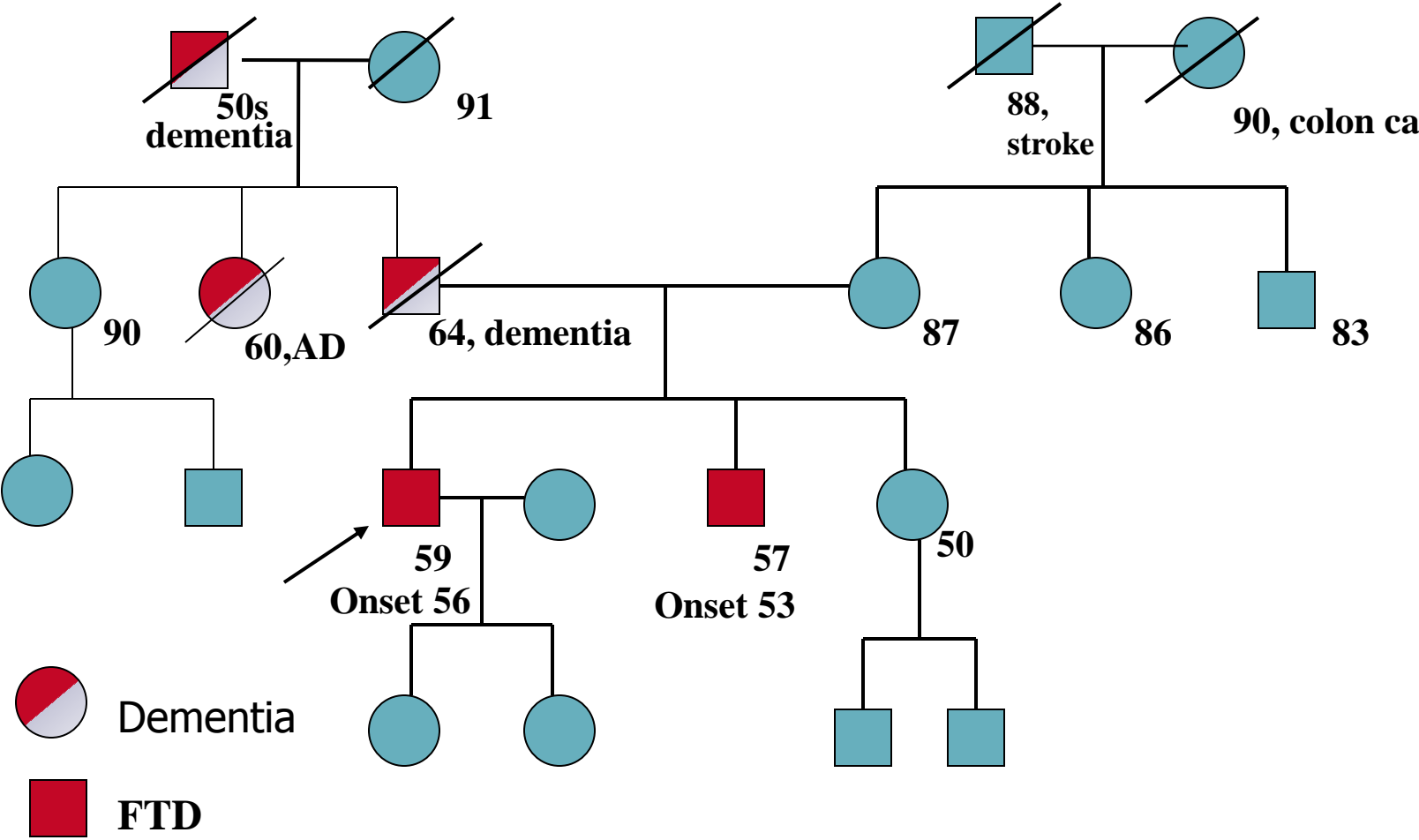
 FTD

Familial history



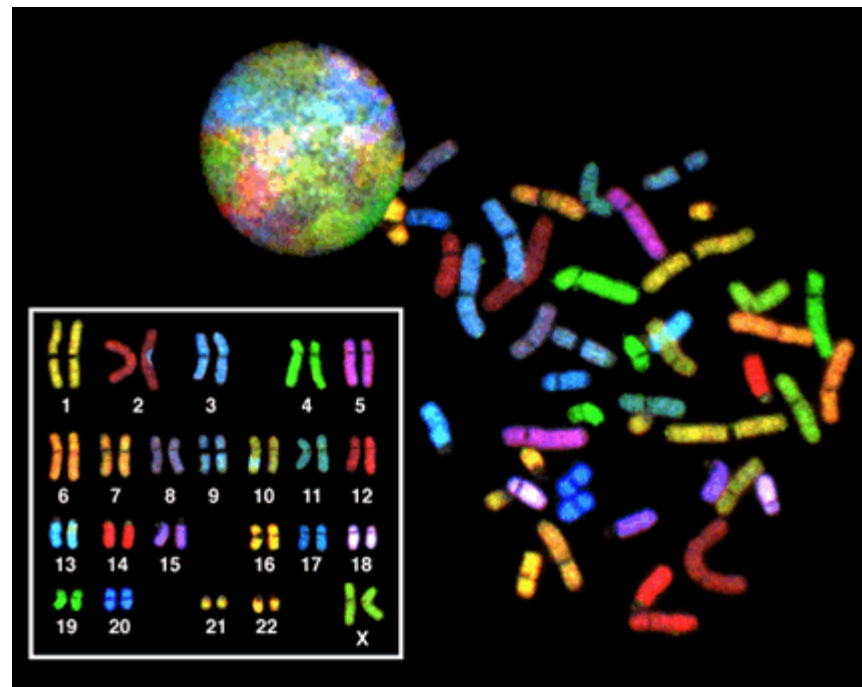
 FTD

Autosomal dominant inheritance



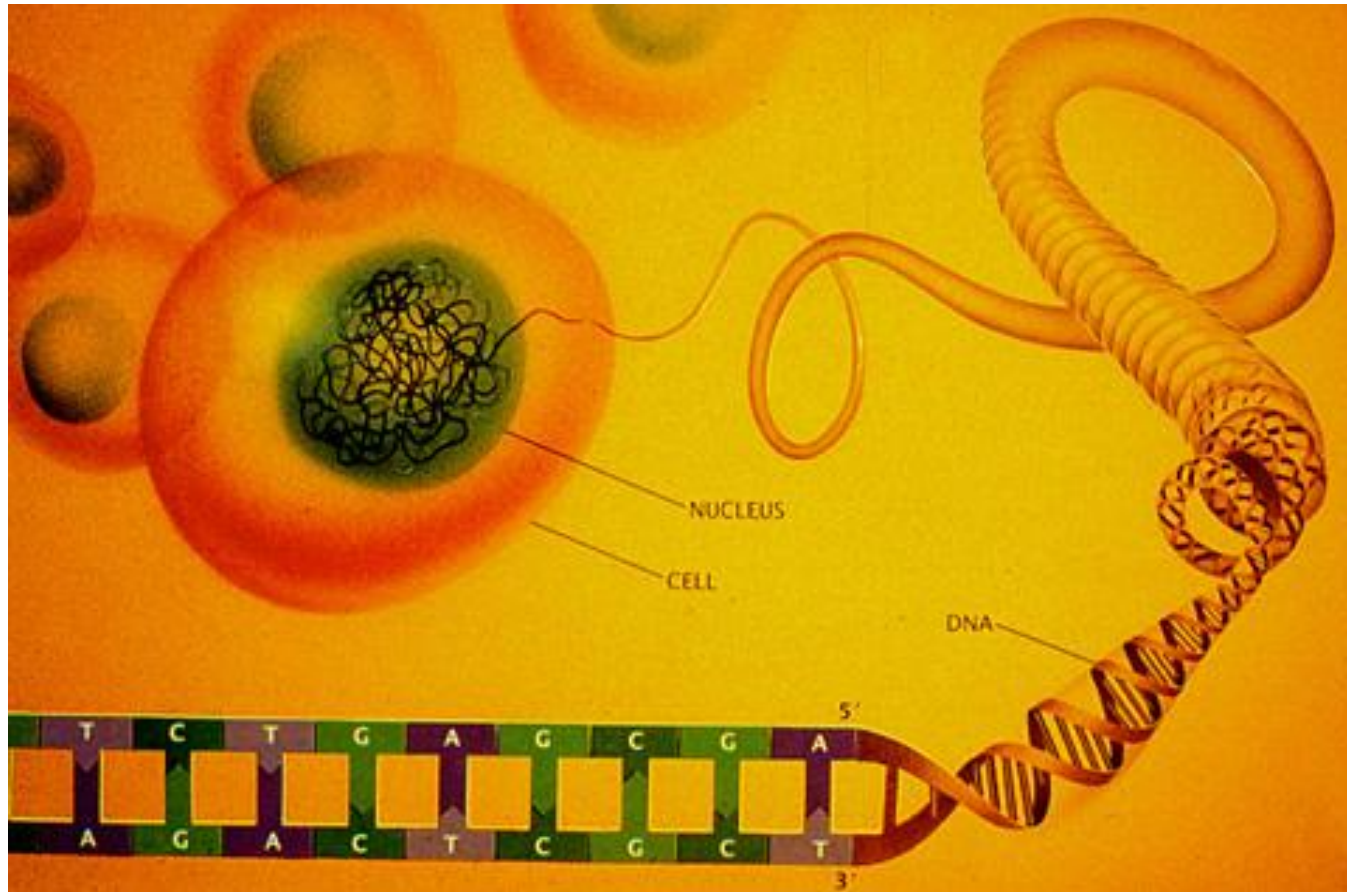
Genetics 101

Genes are part of chromosomes(23 pairs/cell)



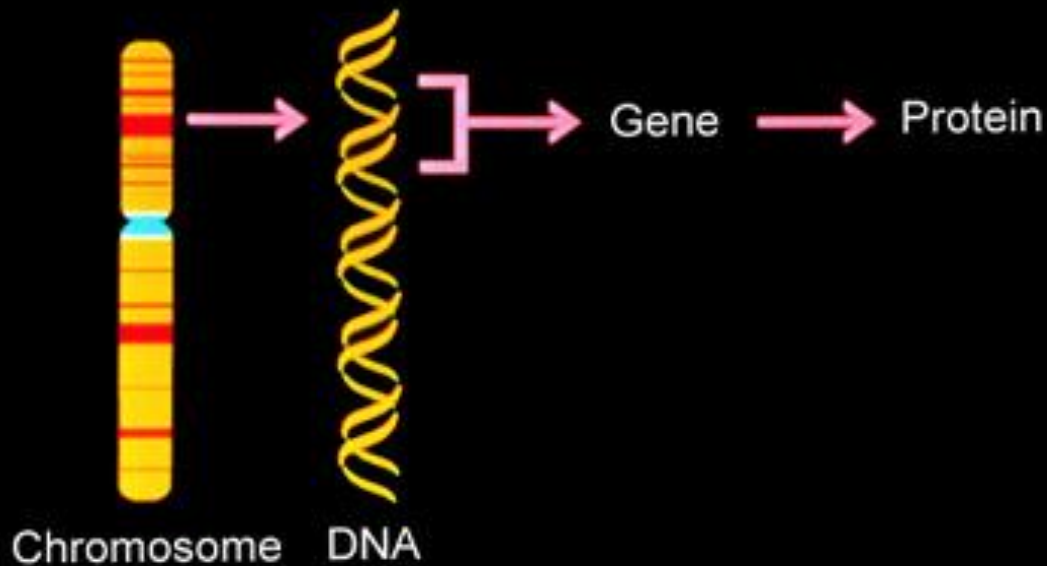
Genetics 101

Chromosomes are made of DNA



Gene Function

Each Chromosome Contains
Thousands of Genes



Genetics 101

Terminology

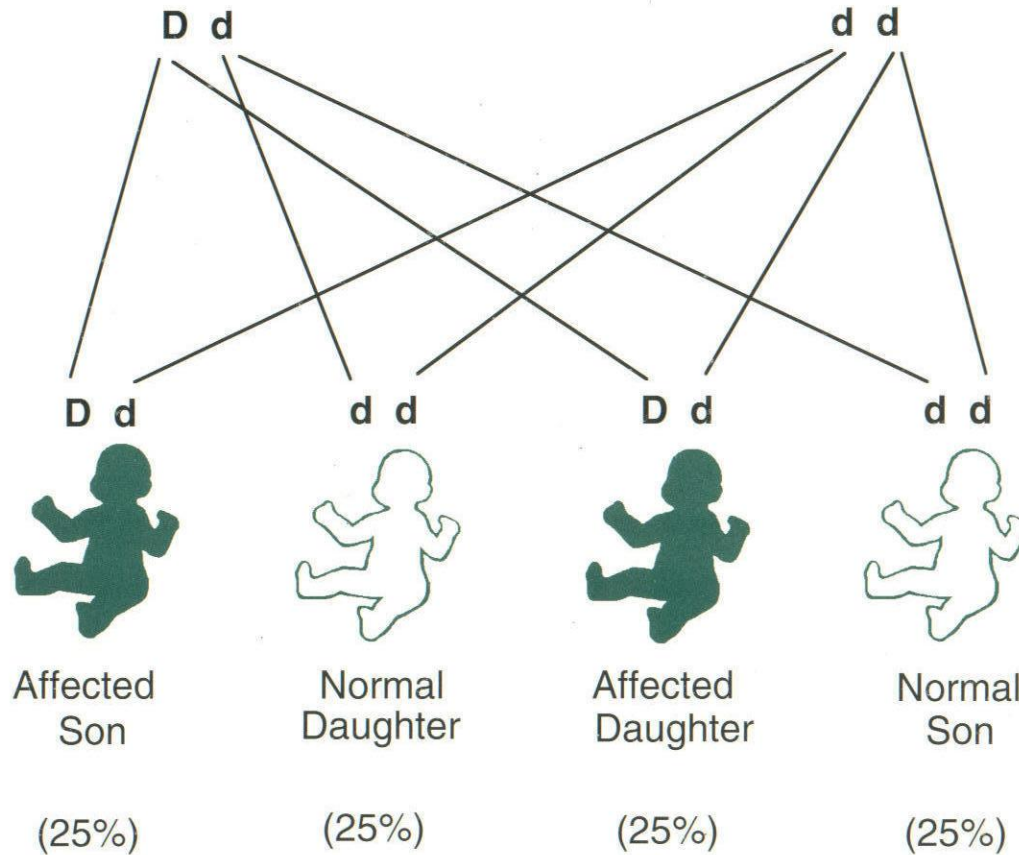
- **Mutation:** an alteration in the DNA sequence of a gene that causes a disease
- **Polymorphism:** a normal variation in the DNA sequence that does not cause a disease
- **Genotype:** the sequence of DNA within a gene
- **Phenotype:** the clinical expression of the gene (Symptoms)
- **Penetrance:** 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



Mutations

- Mistakes in the DNA sequence

e.g.

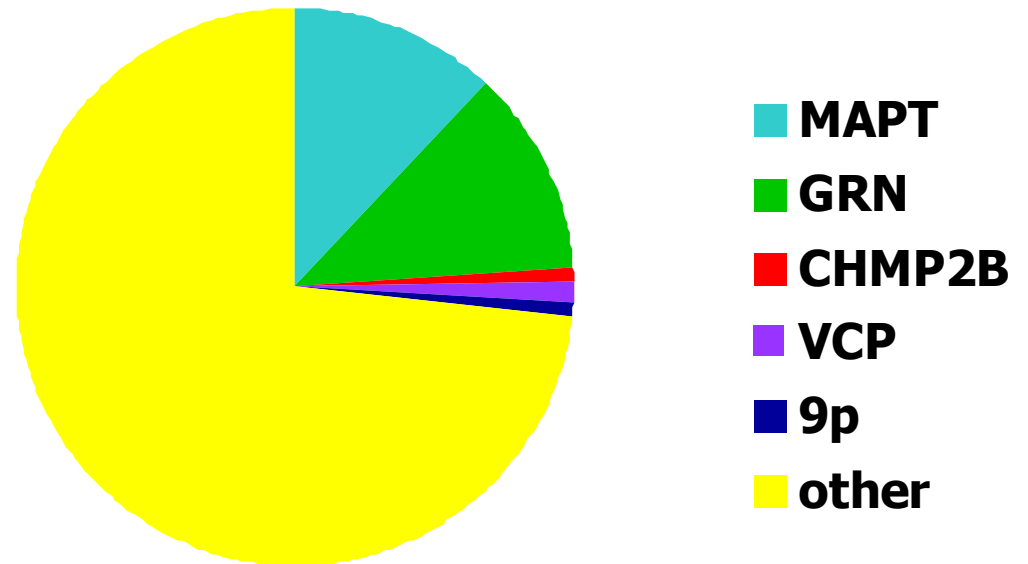
Normal gene: CATGAT

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

FTD Genetics

- We still know very little about the genetic causes of FTD.



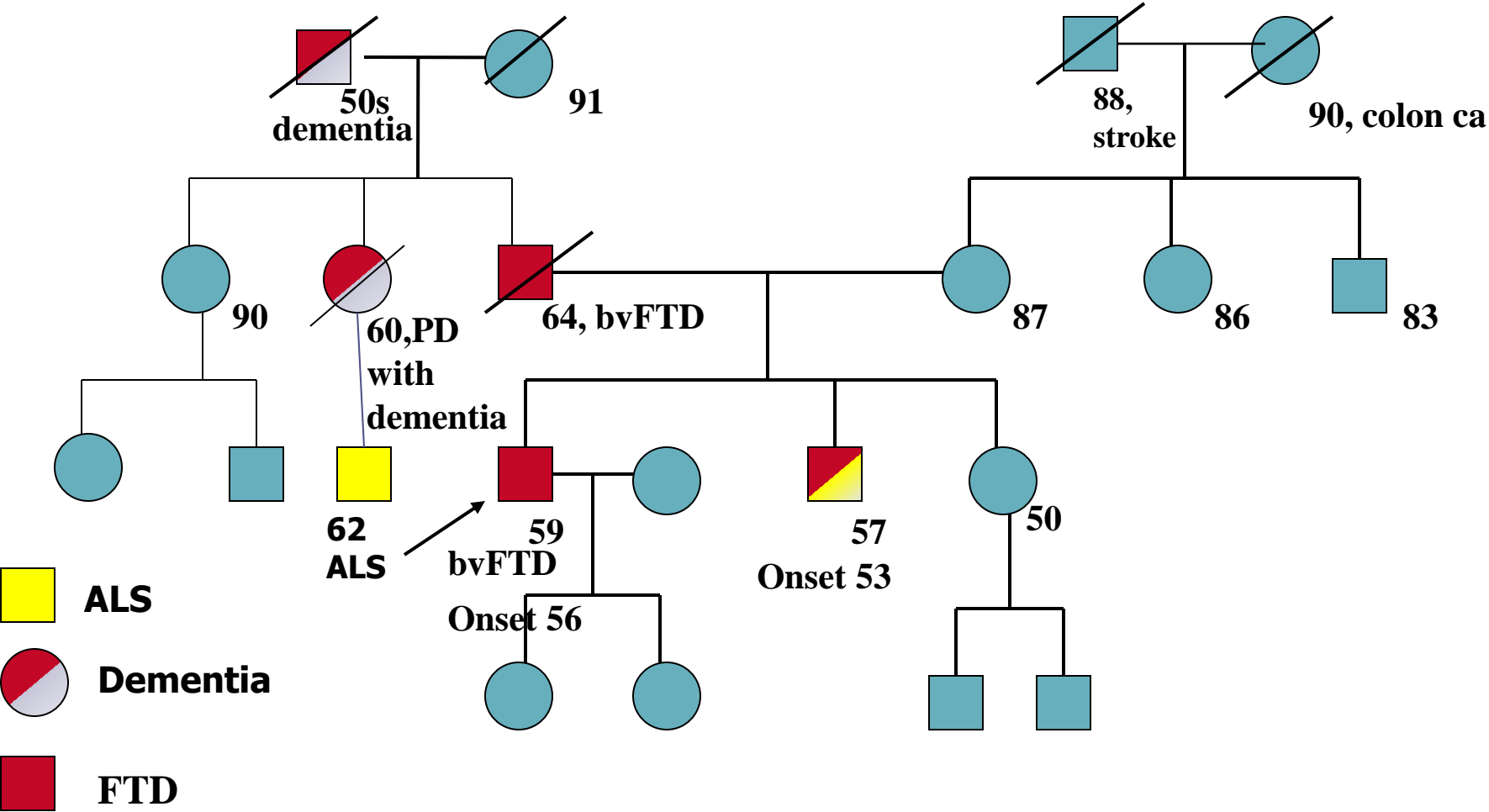
Tau Mutations

- 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



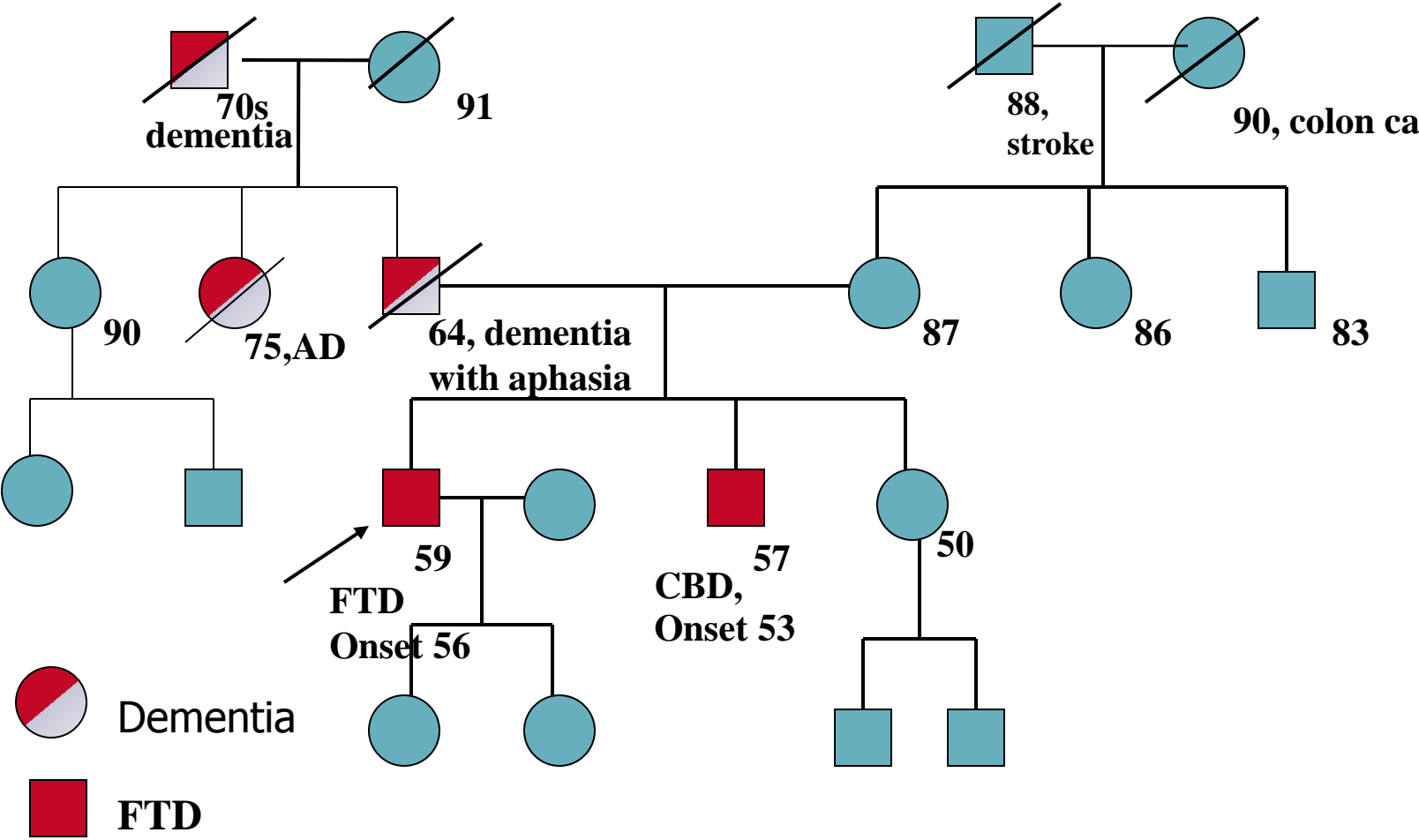
Progranulin Mutations

- 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

Autosomal dominant inheritance



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!