FTD Genetics…where is it leading us?

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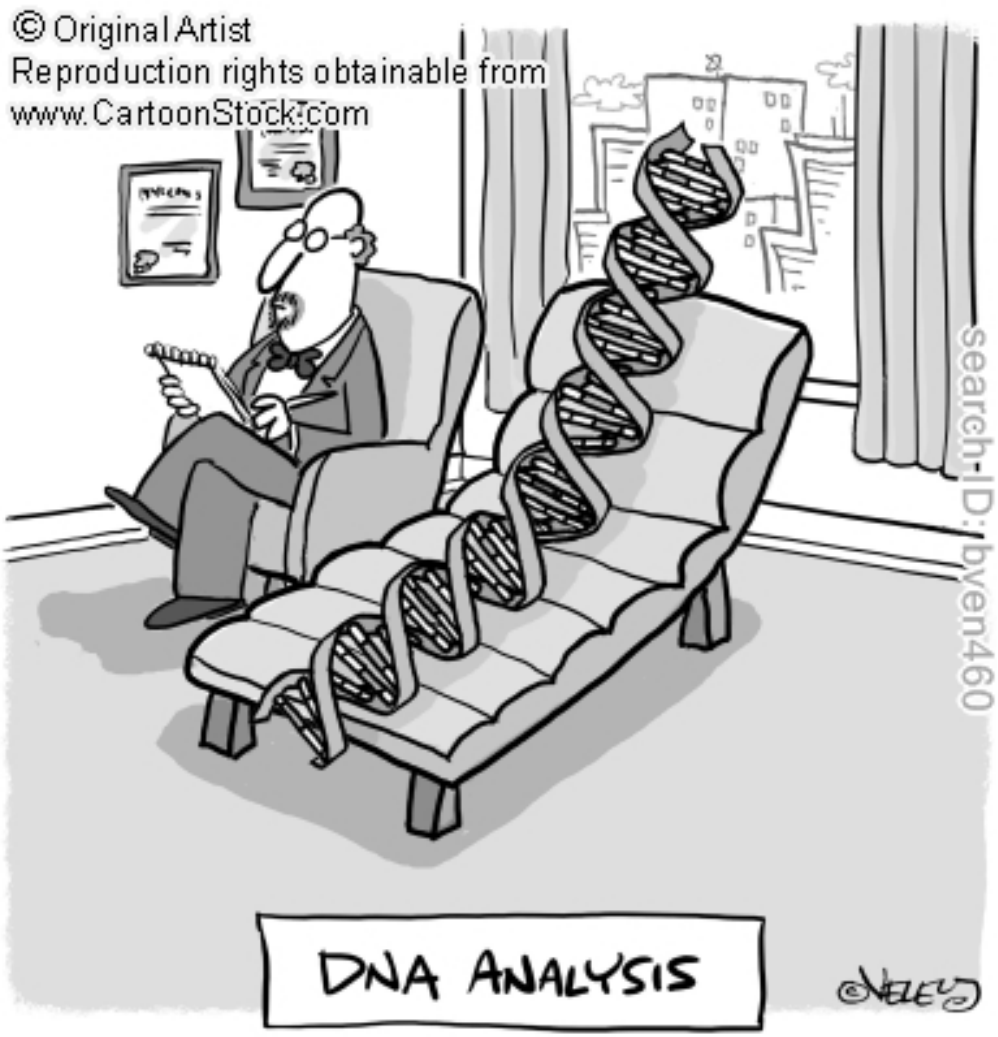
Overview

- 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)?

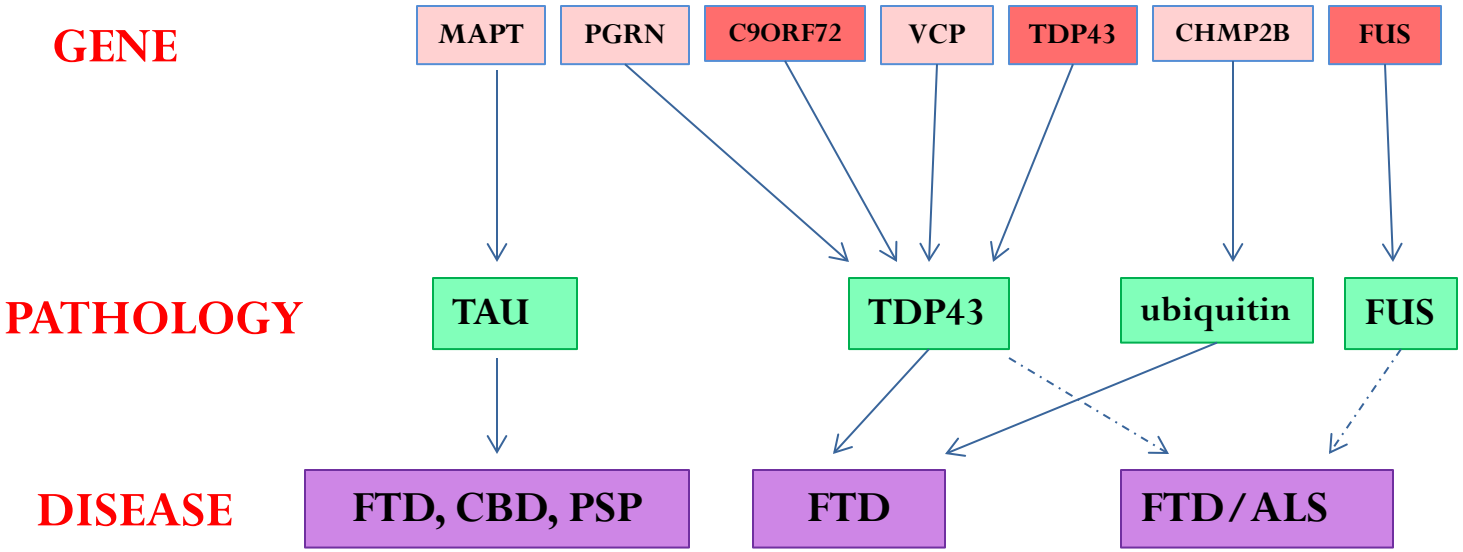


What comes first  or  ?

- 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

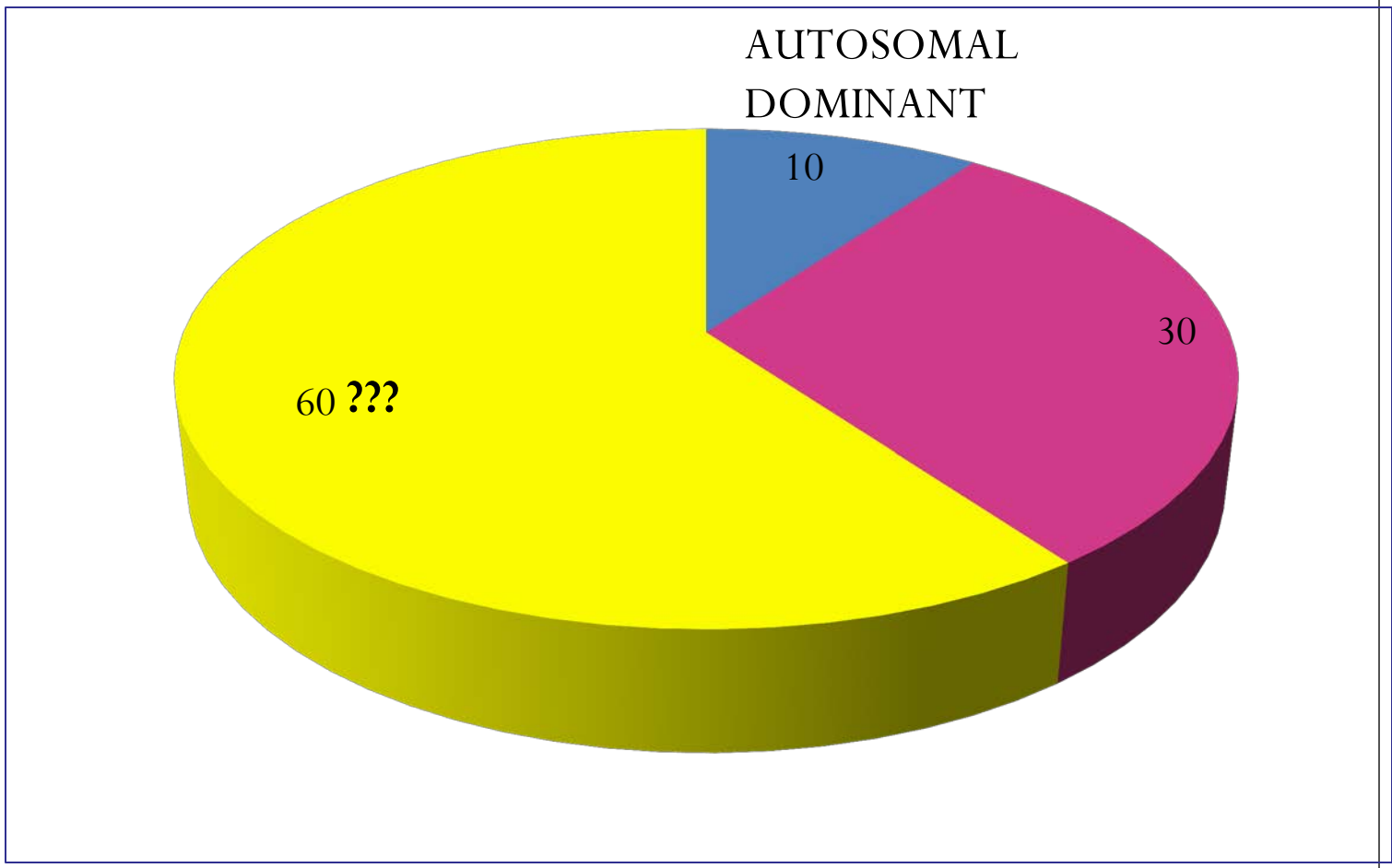
What do we know?

GENE → PATHOLOGY → DISEASE

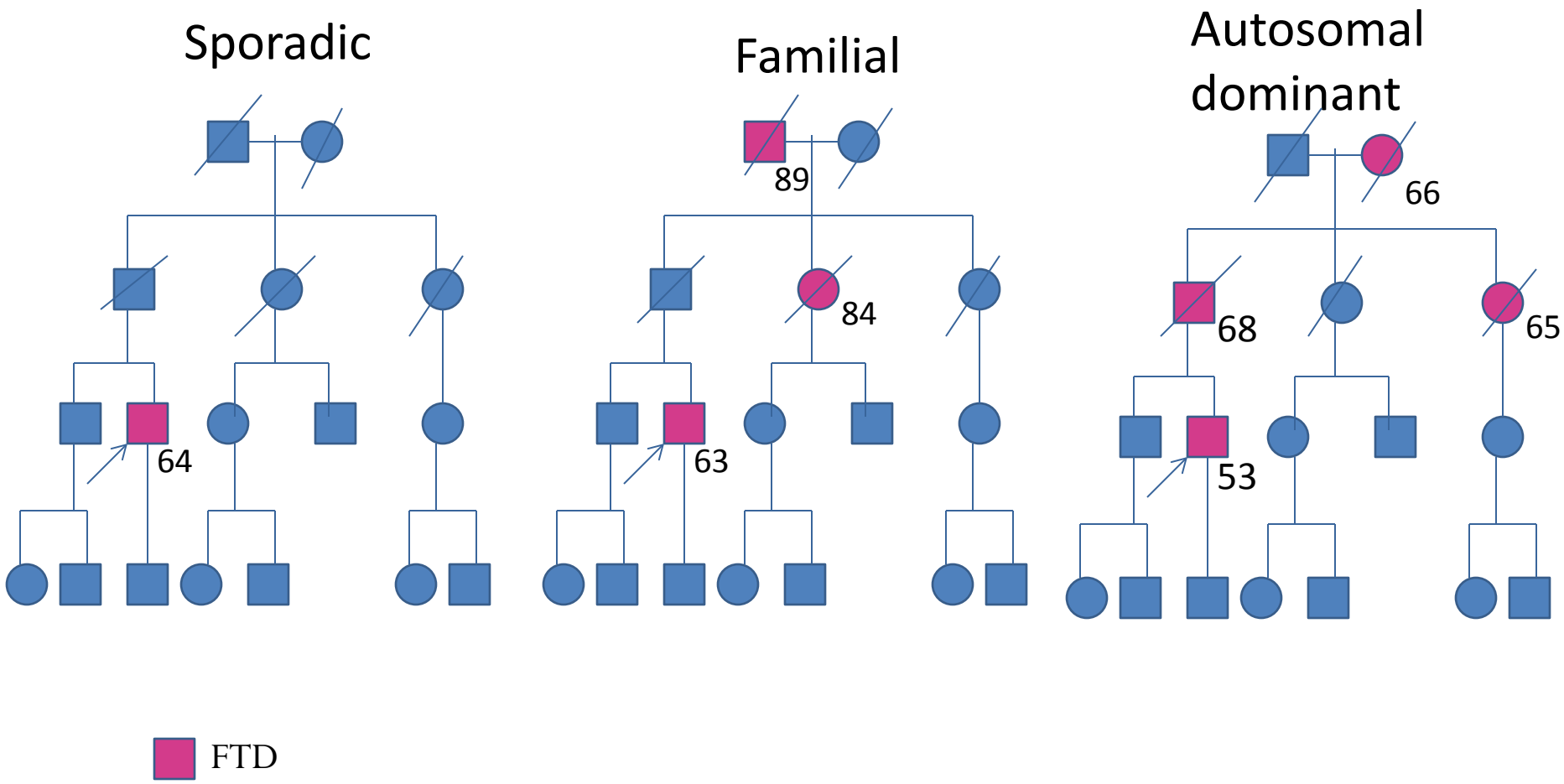


How much of FTD is genetic?

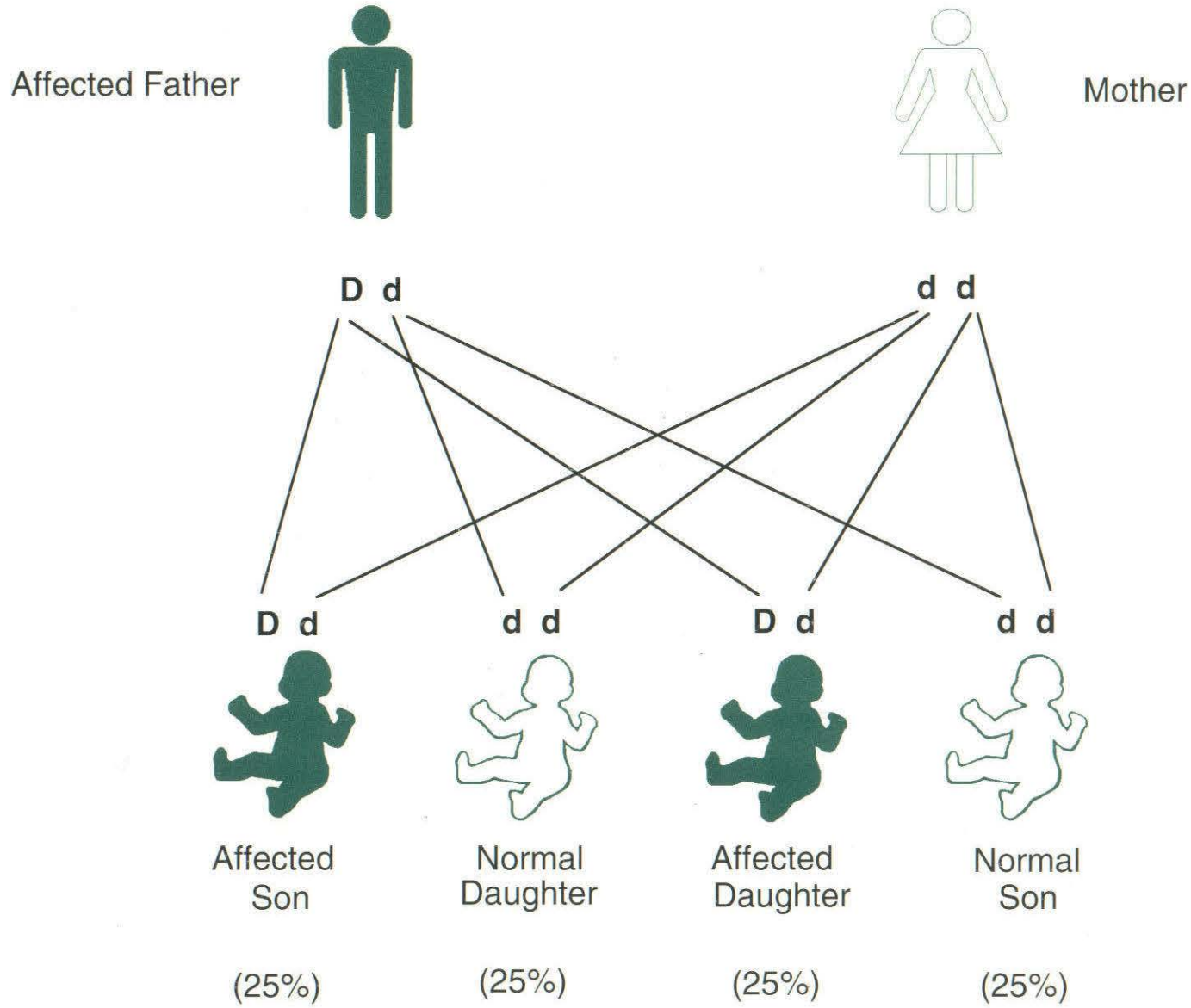
???



Family History

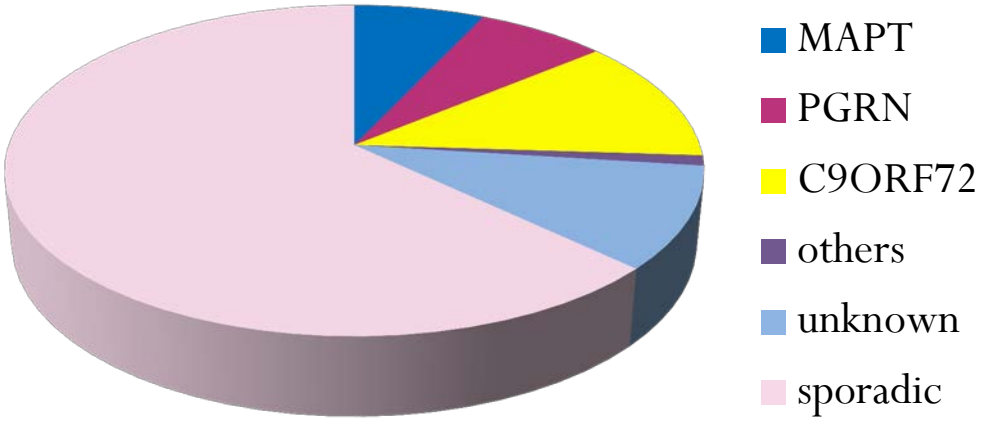


(ONE PARENT AFFECTED)



Autosomal dominant FTD

- ***MAPT***
- ***PGRN*** (~3% sporadic)
- ***C9ORF72***: ~90% FTD with ALS (~4% sporadic)
- Paget's disease/FTD:VCP
- CHMP 2B: Chrom. 3
- TDP-43 (associated with ALS)
- FUS (associated with ALS)

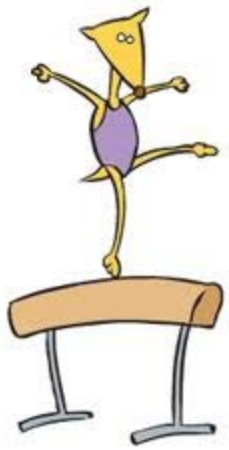


How do we know for sure if it's genetic?

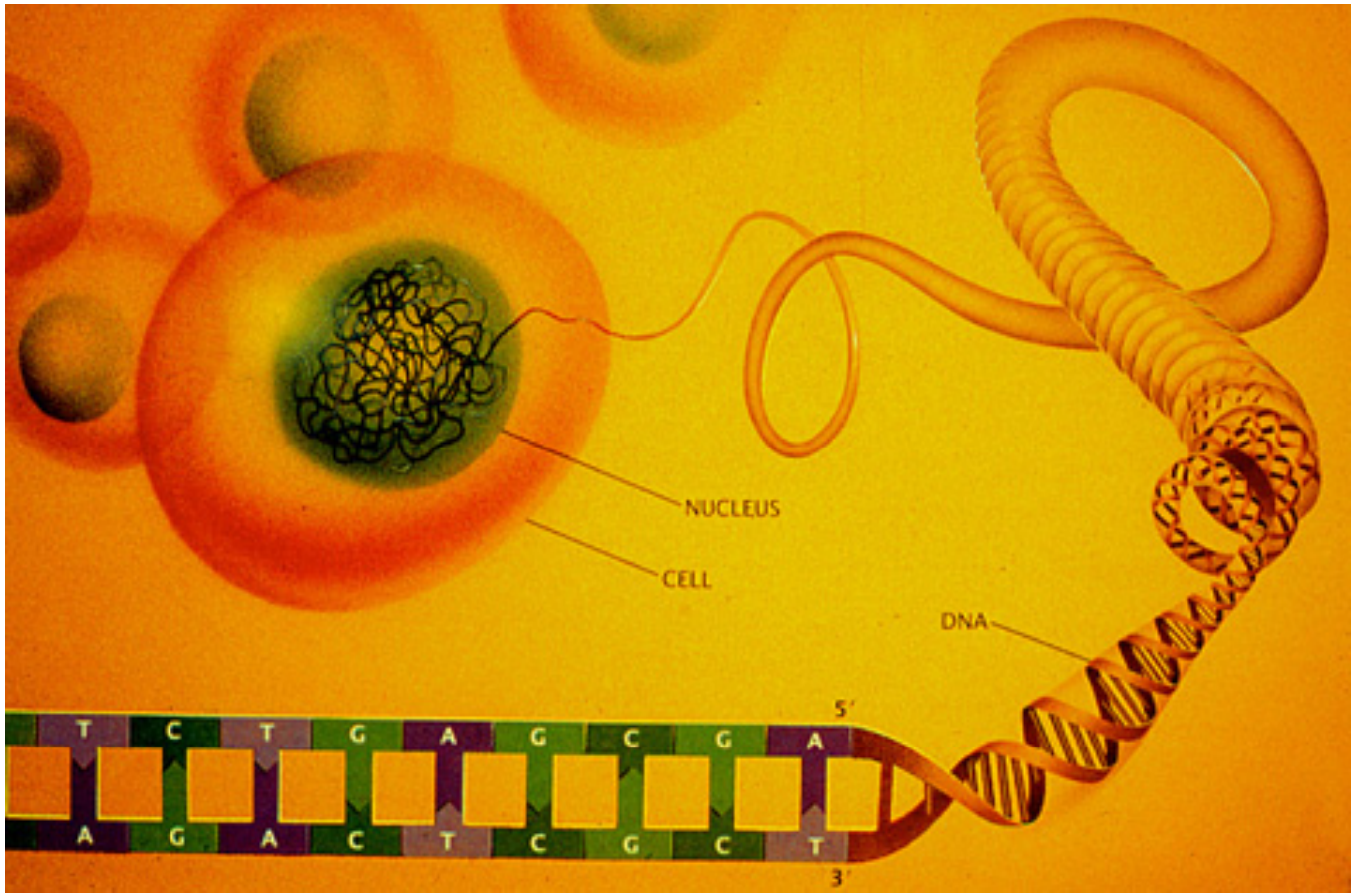
- Must first test an affected person to determine a specific causal gene mutation
- THEN if an at-risk family member wants presymptomatic testing, they can ask for genetic counseling and then testing

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: CATGAT, GGGGCCGGGGCC

  Mutated gene: CAGGAT, CAGAT, CATTGAT, CATGATCATGAT,

  GGGGCCGGGGCCGGGGCCGGGGCCGGGGCC…

- Result of mutation: change in amino acid sequence of protein, hence change in function of protein OR inability to produce protein or production of a toxic molecule

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**