understanding genetics in FTD and PPA

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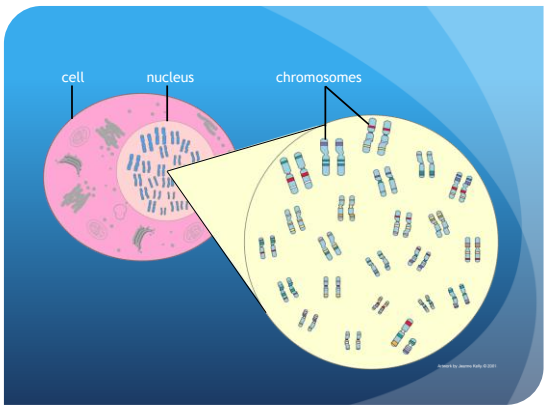
agenda

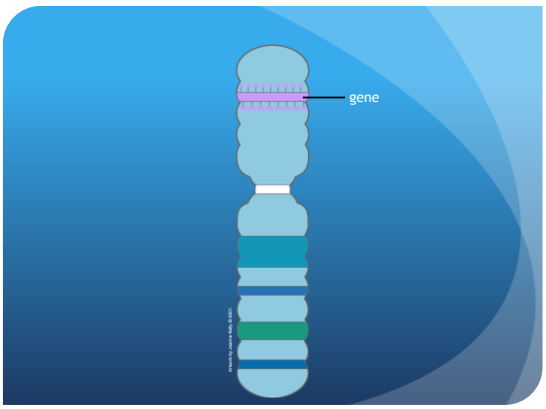
- genetic counseling
- genetics 101
- genetics of FTD and PPA
- genetic testing
- research
- how does my family fit in?
- what to expect

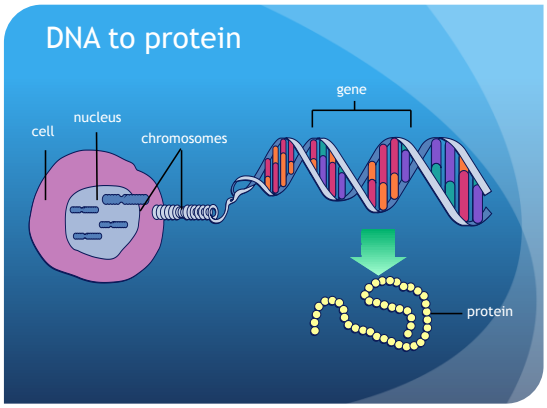
what is a genetic counselor?

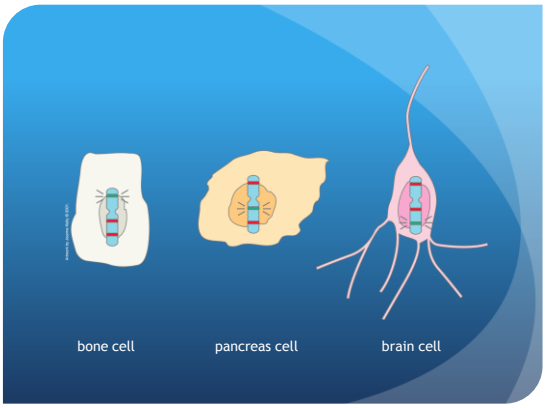
- translator
- patient advocate
- resource negotiator
- educator
- decision facilitator

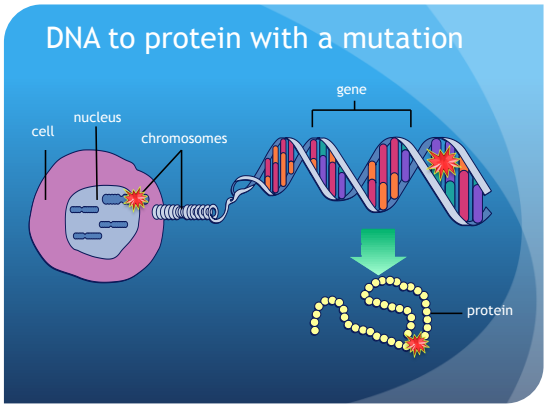
genetics 101

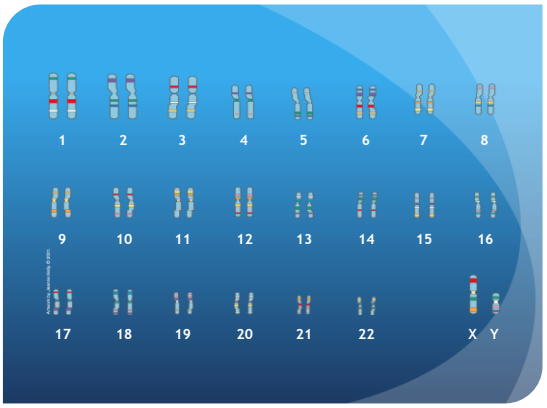


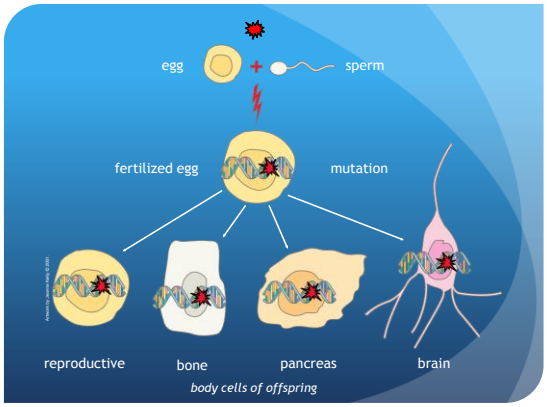








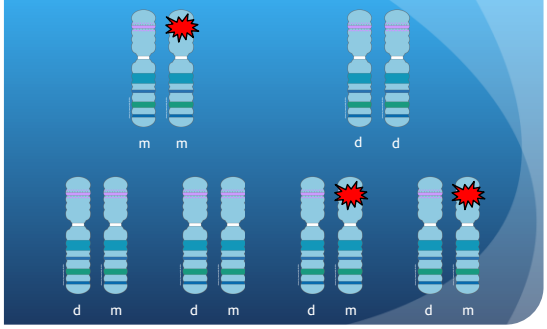




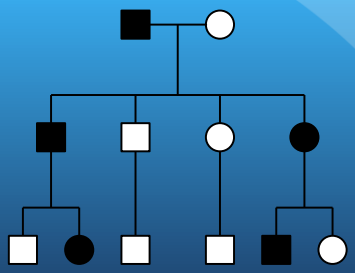
autosomal dominant inheritance

- males and females affected equally
- cannot skip a generation
- 50% chance to pass mutation on
- use pedigree to look for patterns of inheritance

autosomal dominant inheritance



autosomal dominant inheritance



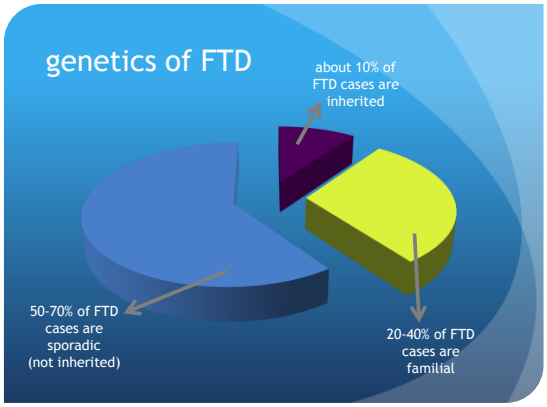
pedigree helps with…

- pattern of inheritance
- identification of individuals at risk
- genetic testing strategies
- screen for other medical risks

polymorphisms

- change in a gene that does not affect function
- color vs. colour

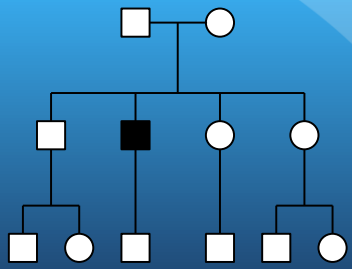
genetics of FTD



sporadic FTD

- ~50-70%
- not inherited
- no other affected family members
- no increased risk for family members

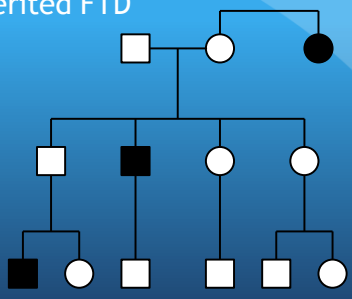
sporadic FTD



Inherited FTD

- about 10% of all FTD
- affected parent means 50% risk to first degree relatives
- lower age of onset and more rapid course than sporadic FTD

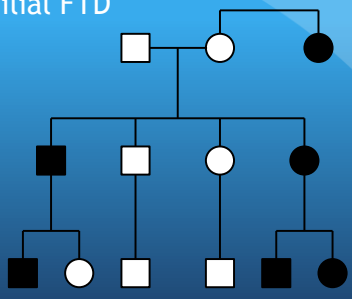
inherited FTD



familial FTD

- 20 - 40%
- has a heritable component
- intermediate risk to family members
- lower age of onset
- quicker disease course
- multifactorial disease

familial FTD



Inheritance

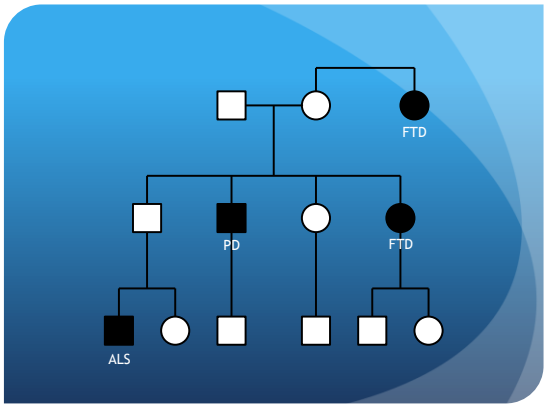
- the thought of inheriting and/or passing down a mutation associated with FTD is scary
- we know some, but not all about FTD genetics

which type of FTD is my family?

- work with genetic counselor
- limitations - early death of relatives, adoption, no information
- any and all medical information is helpful!

medical history

- accurate medical history means more accurate risk estimation
- medical records, autopsy reports, tissue blocks, etc
- any and all conditions, especially neurological
  - ALS, FTD, PD



gray areas of genetics

- much of genetics is not a simple yes or no
- we inherit risk levels for any given condition
- this risk is modified throughout our lives
  - some genes are known
  - not much is known about environmental factors

gray areas of genetics

- many families fall within the middle area
  - no testing available
  - no specific risk number
- research participation is an option
- keep in touch with neurologist and genetic counselor

genetic research

- blood and/or tissue samples
- look for similar changes in many people
- helpful to have affected and unaffected family members
- some genes have been found so far

MAPT

- microtubule associated protein tau
- chromosome 17
- makes a protein called 'tau'
  - present in the brains of people with neurodegenerative disorders
  - healthy tau removed by normal processes
  - abnormal tau has altered function and cannot be removed like normal tau
  - this leads to symptoms

MAPT families

- FTDP-17
- dementia and/or parkinsonism
- brain atrophy
- more than 2 family members affected in an AD pattern

MAPT mutation

- around 40 mutations reported
- unique vs. common mutations
- genotype/phenotype correlations?
  - disease course, symptoms, age
  - useful for genetic counseling of families
- still variation within families - why?
- polymorphisms
  - CBD, PSP or modified FTD risk

PGRN

- progranulin
- chromosome 17
- progranulin sends a message to increase cell growth
  - helps would repair, related to cancer
  - lots of other functions
  - function in FTD is unclear
- mutation leads to not enough functional progranulin

PGRN families

- increased chance for PPA
- decreased chance for MND
- more variable than MAPT
  - aphasia
  - behavior disorders
- reports of individuals in their 70s with no symptoms

PGRN mutation

- brain protein is also common in ALS
- polymorphims in PGRN lead to susceptibility
- more studies are needed!

future directions for research

- genotype/phenotype correlations
- progranulin and TDP-43 proteins
  - related substances may mean drugs for treatment

genetic counseling session

- family history and analysis
- natural history, genetics and inheritance education
- data update
- discuss recurrence risks
- review genetic testing
- psychosocial support

genetic testing

- complex!
- who to test?
- research vs. clinical testing
- what gene?
- testing strategies

presymptomatic testing

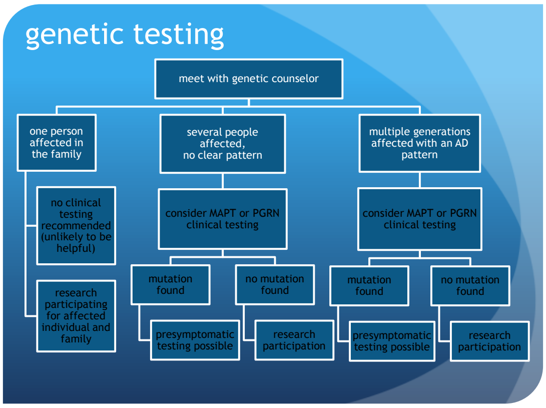
- only possible with a known gene
- "true negative" test result
- other considerations

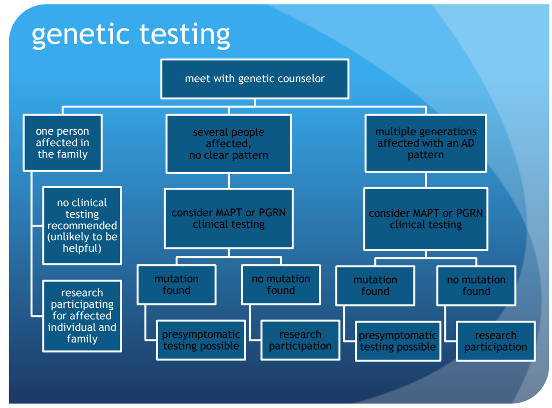
testing: yes or no?

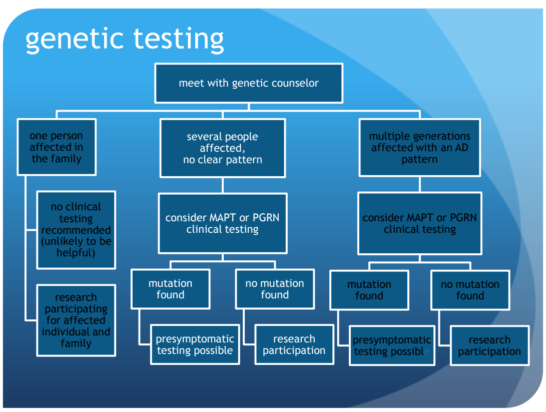
reasons to test	reasons not to test
need to know	no treatment
plan finances	no cure
insurance	hypervigilance for symptoms

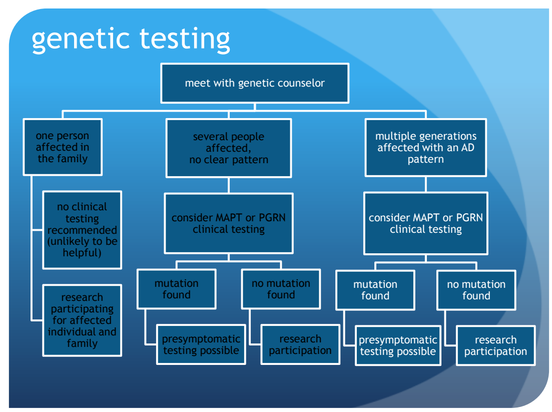
family communication

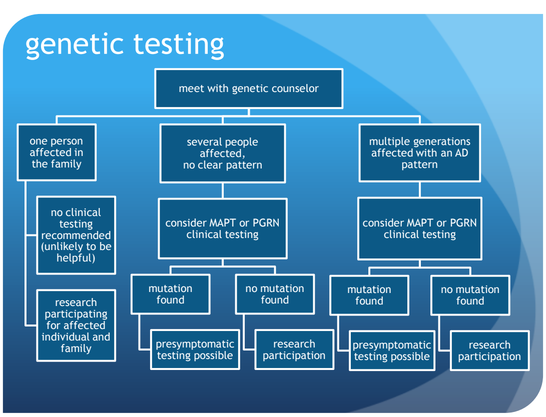
- open and honest, ideally
- include a discussion of genetic testing
- have a meeting with family and genetic counselor
- lots of possible reactions, all are normal and okay
- this is a very individual decision!











summary

- majority of FTD/PPA is not inherited
- accurate medical histories
- risk assessments
- currently known genes
- testing strategies
- research participation
- genetic counselors are your friends!