# Genetics and IBM: What we know – what we hope to learn

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# Definitions

- Gene
  - Piece of DNA that codes for a specific protein (humans have ~20,000 genes)
- Protein
  - Large molecules composed of amino acids that perform specific functions in body
  - Examples: albumin, creatine kinase (CK), keratin

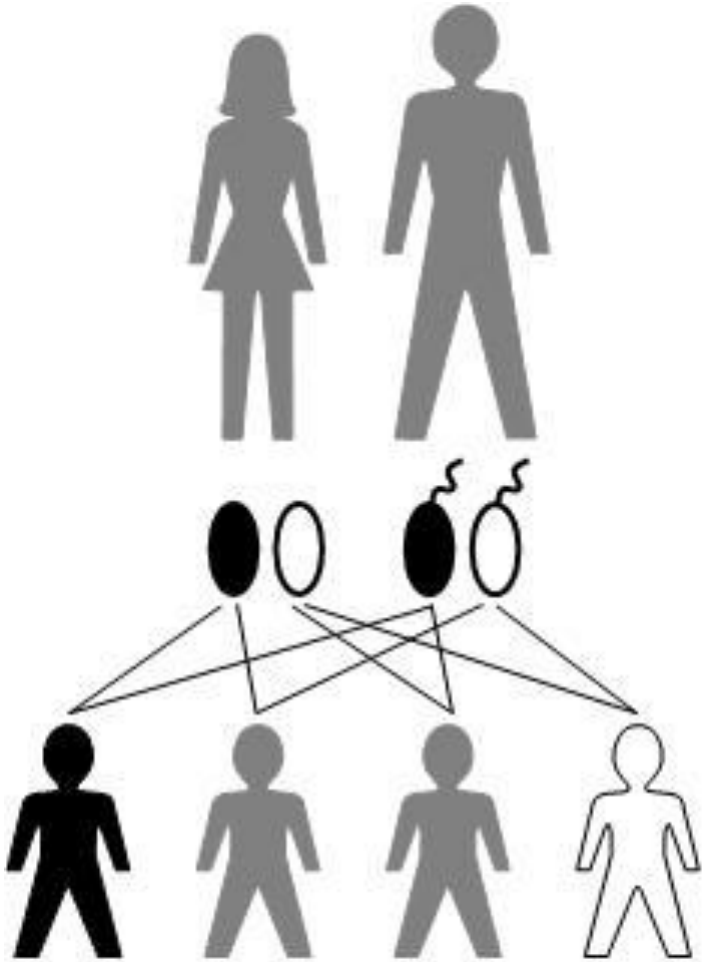
# Definitions

- Mutation or variant
  - Alterations in DNA code that is specific to an individual
  - Some mutations or variants can cause disease or increase risk of disease
  - Example:  ApoE4 variant increases risk of getting Alzheimer's disease
  - Example:  Mutations in a gene named Presenilin-1 cause early onset Alzheimer's disease

# Definitions

- Heredity
  - Passing of “traits” from parents to offspring
    - Traits are “genetic variants”
  - Everyone gets one set of chromosomes from their mother and one set from their father
  - Therefore everyone has two copies of each gene (one from mom and one from dad)

# Genetic inheritance



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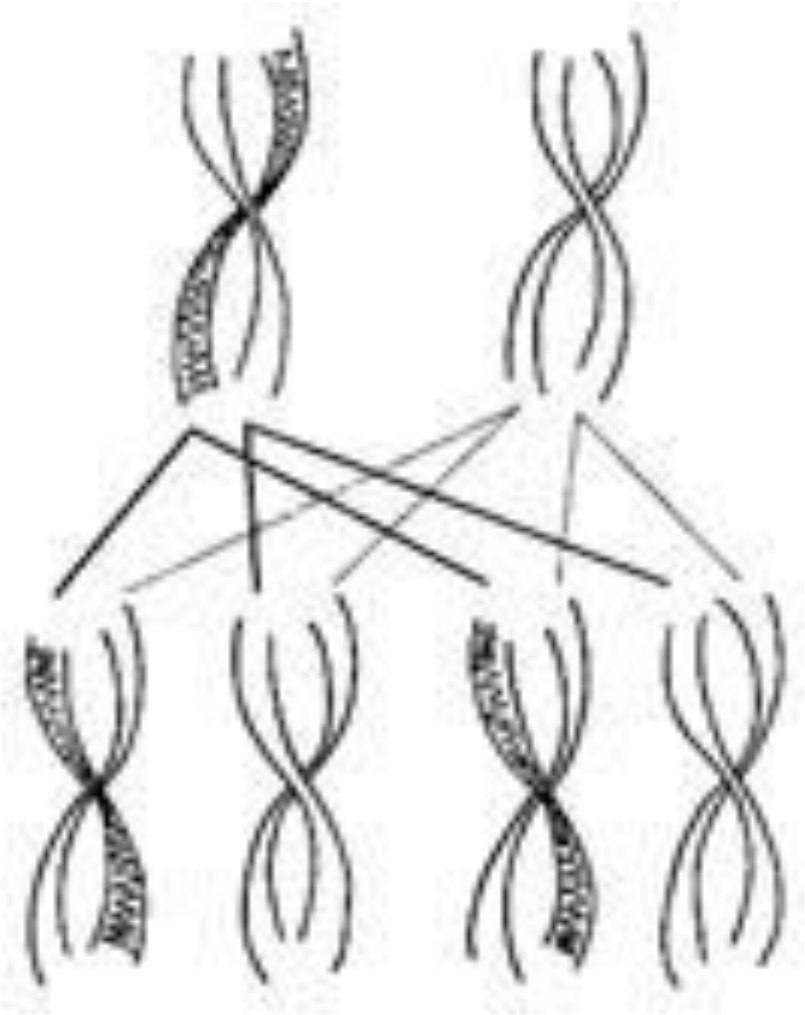

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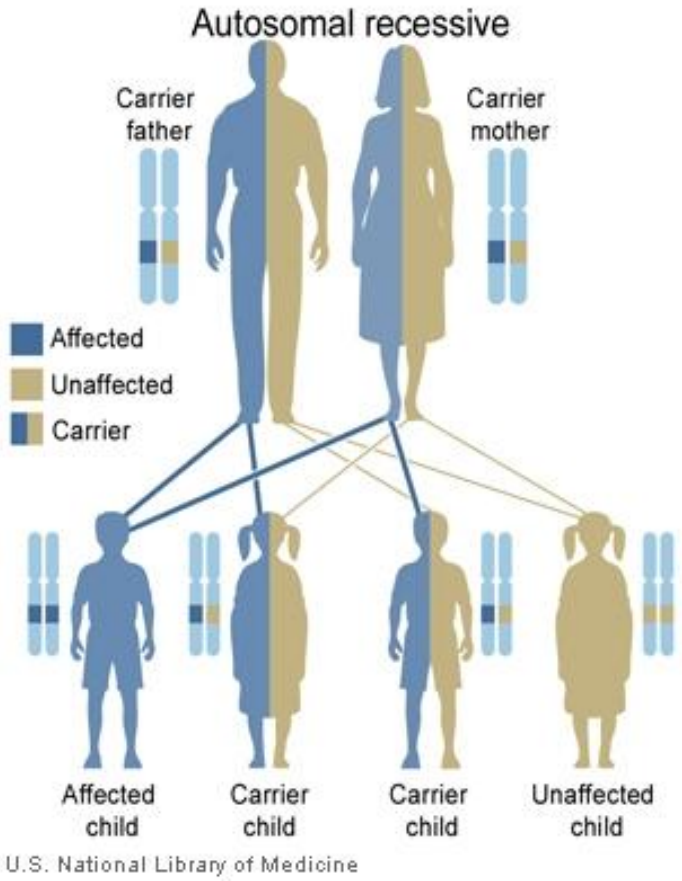


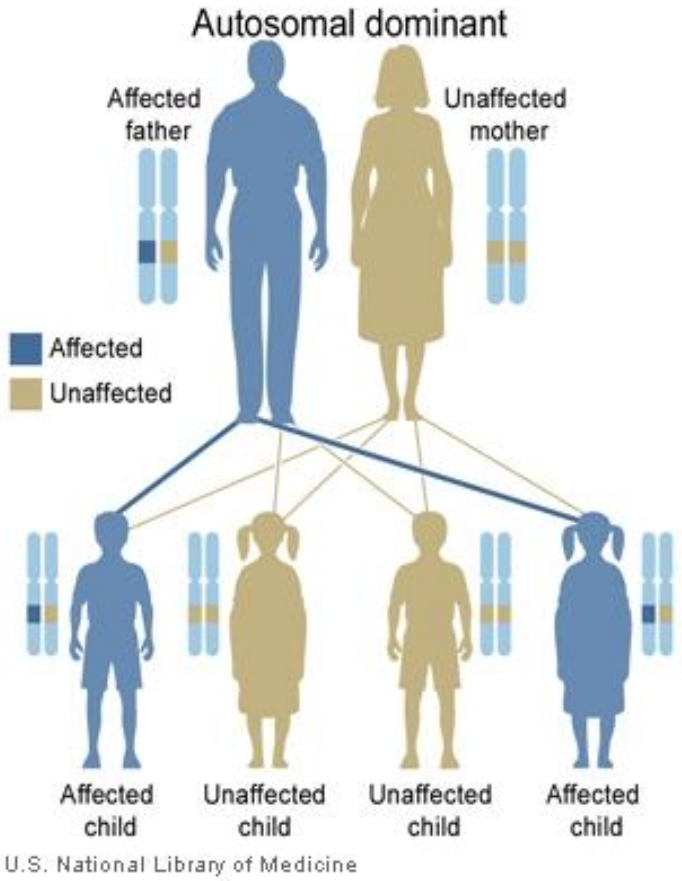

# Definitions

- Recessive mutations
  - Need a disease causing mutation on gene from mom and gene from dad
  - Parents will not be affected
- Dominant mutations
  - Need only one disease causing mutation on one gene
  - One parent will be affected

# Exceptions to the rule

- Some traits are caused by multiple variants in multiple genes (polygenic inheritance; e.g. coronary artery disease or hypertension)
- Some traits have “variable penetrance.” Even if you have the disease causing mutation you may not get the disease (idea of a disease “skipping a generation”)
- Environmental interaction with genetic traits

# Next generation sequencing

- We can sequence the entire genome of an individual for ~$2,000

- Is this helpful?

# Genetic variants

- Common variants
  - Present in >5% of the population
- Non coding variants
  - Genetic variants that do not change a protein's structure
- Coding variants
  - Genetic variants that alter a protein's structure
- Rare variants
  - Present in <0.5% of the population

# Is whole genome sequencing helpful?

- You have ~400 rare coding variants in your 20,000 genes
- ~50 of these rare coding variants are on both genes (one from mom and one from dad)
- ~10 of these pairs of rare coding variants (one variant on both genes) is predicted to be disease causing

# Summary

- Humans have much more genetic variation than originally thought
- It is difficult to interpret disease causing gene variants in a single individual

- Understanding what genes are causal in a disease like sIBM has specific challenges

# IBM genetics

- Some clear genetic causes of diseases with pathology similar to sporadic IBM exist
  - These are rare and are distinct from sIBM
- Termed hereditary IBM (hIBM)
  - Mutations in GNE, VCP, myh2 and likely others
  - No evidence of inflammation on muscle biopsy
- Genetic mutations were identified by finding large families with hIBM

# Sporadic IBM genetics

- No known genetic etiology has been identified

- Challenges
  - Rare disease
  - Sporadic; no clear family history
  - Phenotypic variability
  - May be polygenic
  - May have gene-environment interactions
  - Expensive

# How to study sIBM genetics using next generation sequencing?

- Acquire lots of DNA from patients with well characterized sIBM
- Perform whole genome sequencing
- Utilize bioinformatics to compare genetic variation in patients with sIBM and healthy controls

# What will we find?

- Variants that increase risk of sIBM
- New pathogenic mechanisms aimed at treating sIBM
- Variants that correlate with disease course (e.g. disease prognosis)
- Novel drug targets aimed at treating sIBM

# Thank you!

- Washington University Neuromuscular Genetics Project
- Myositis Association
- Patient Participants