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
Genetic Inheritance
Definitions
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