The Genetics of Multiple Sclerosis

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Disclosures and Conflicts of Interest

Disclosures – None with regards to this presentation

My use of zebras throughout the presentation is due to the way medical students are trained to consider a “differential diagnosis” where the most likely diagnosis is listed first, and the least likely is listed last, the zebra in the herd of diagnoses. When I was a medical student, the genetic diagnosis was the zebra in the list. Many other geneticists also use zebras to designate genetic disorders and genetic/genomic medicine.

Objectives

- Understand the different modes of inheritance of human disorders
- Learn about risk alleles and other risk factors
- Comprehend the types of studies that have been done to uncover the genetics of Multiple Sclerosis (MS)

References to genetic sex in this talk

- Please note that when male or female sex is mentioned in this talk, I refer only to chromosomal sex, and not gender.

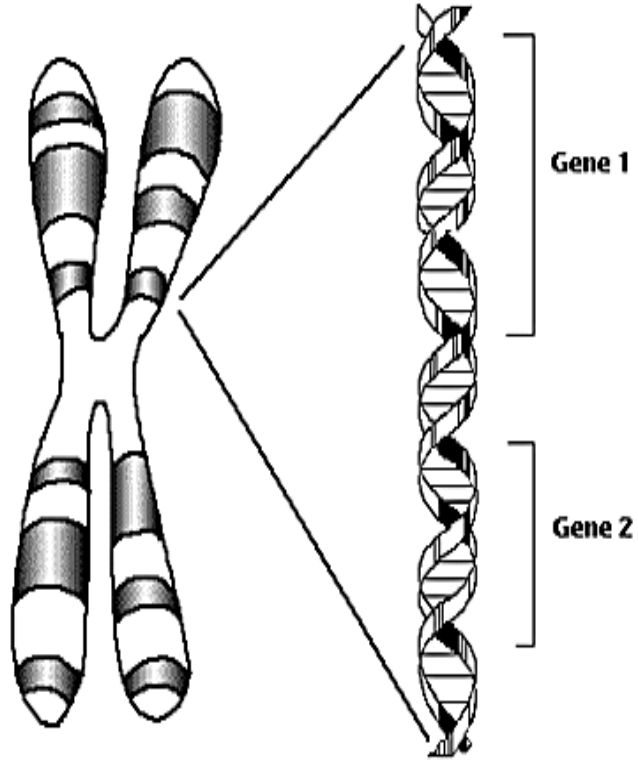
Primer on Genetics: Inheritance

- Nuclear genes are located in specific order on chromosomes, which are packages of DNA
- Chromosomes come in pairs, one of each pair inherited from each parent
- 46 total chromosomes = 22 pairs of autosomes and 1 pair of sex chromosomes
- Most females have 2 X chromosomes, most males have an X and a Y chromosome
- Mitochondrial genes are also in a specific order on circular chromosomes within the mitochondria and are only inherited from the mother

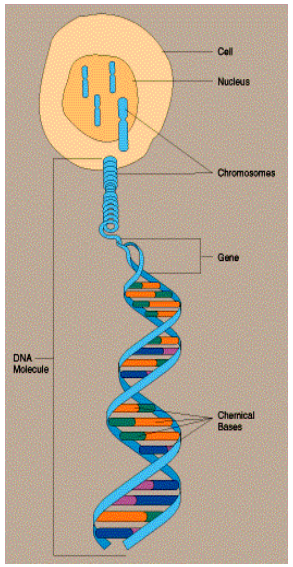
There are hundreds of genes along each chromosome

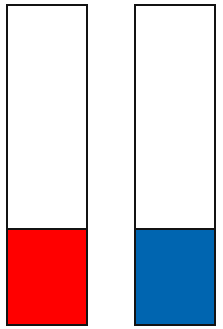
Genes come in pairs

Genes carry the information that is the "recipe for life"



Genes

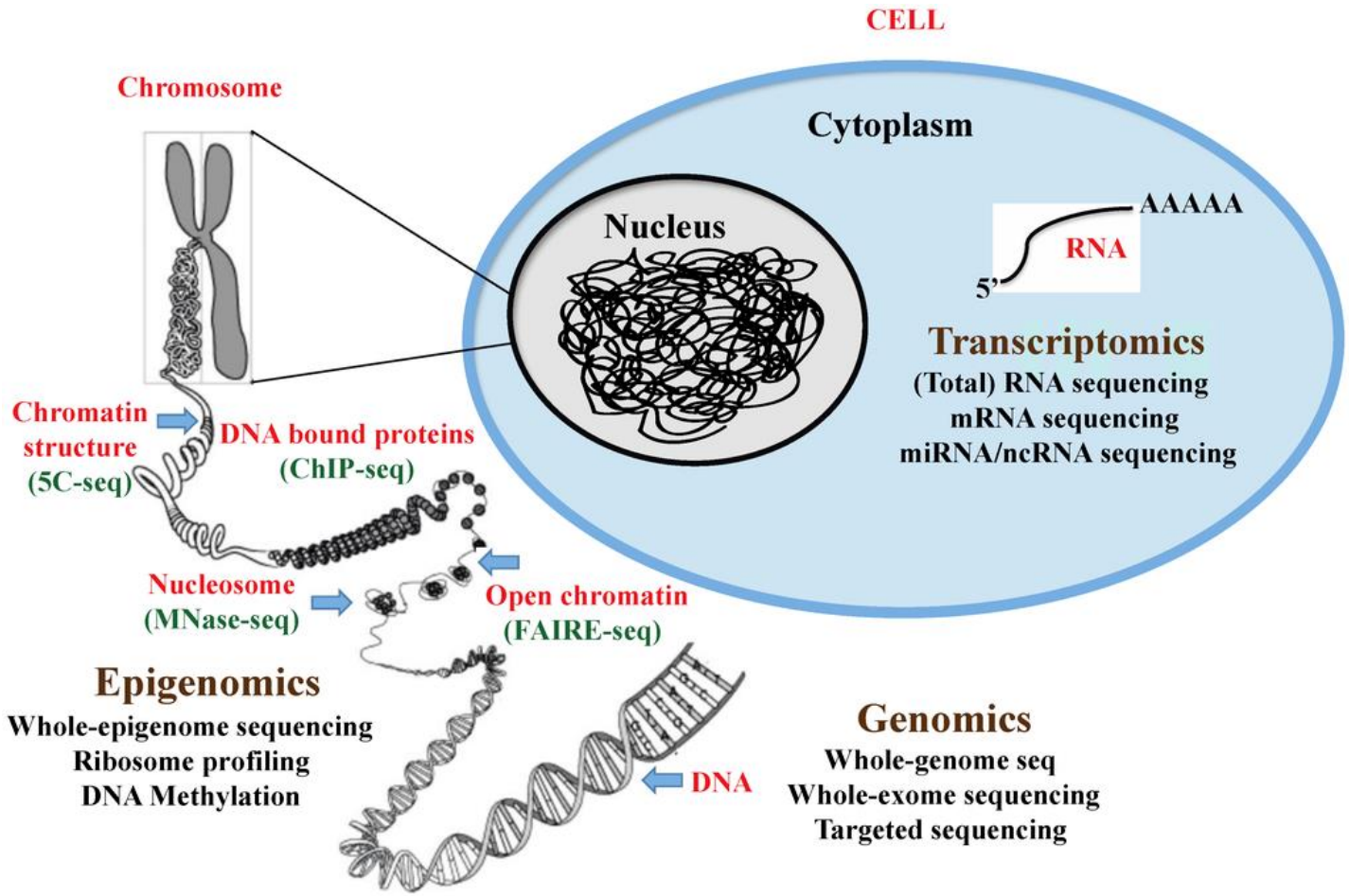




→*1 gene of each pair comes from* ***Mom***

→ *1 gene of each pair comes from* ***Dad***

The State of Genetics 2023: The Era of Multi-omics



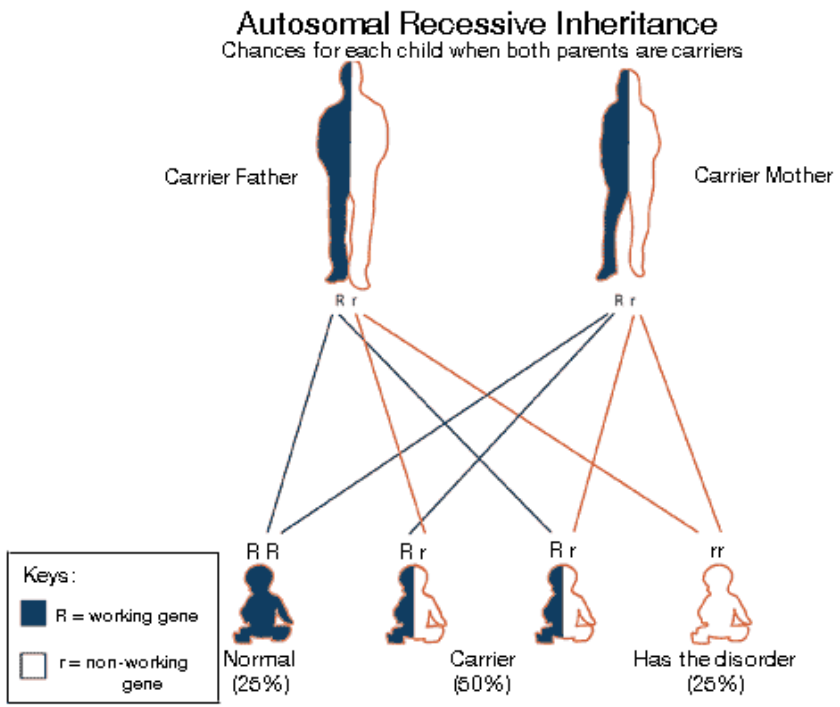
Primer on Genetics: Variants VS Mutations

- In the older literature, the word “mutation” was used to designate a change in the DNA sequence.
- In speaking with patients, clinical geneticists found that using that word to describe what had caused a disorder, especially in a small child, was disturbing to the patient and family.
- The better word, based in science, is variant. We all carry hundreds of variants in our DNA, making us unique.
- A pathogenic variant is one that has been shown to cause a disorder. Molecular geneticists look carefully at many details to decide if a variant is indeed pathogenic.

Primer on Mendelian Genetics: Inheritance Patterns

- Autosomal recessive: usually both parents are silent carriers of pathogenic variants with a 1:4 chance of having an affected child: Tay-Sachs disease and maple syrup urine disease are examples
- Autosomal dominant: a single pathogenic variant causes the disease, and if the parent has the disease, there is a 1:2 chance of passing it on to any child: some types of inherited Alzheimer disease
- X-linked disorders: manifestations are different in males (XY) vs females (XX), with males having significantly more symptoms: Fragile X syndrome

Autosomal Recessive Inheritance

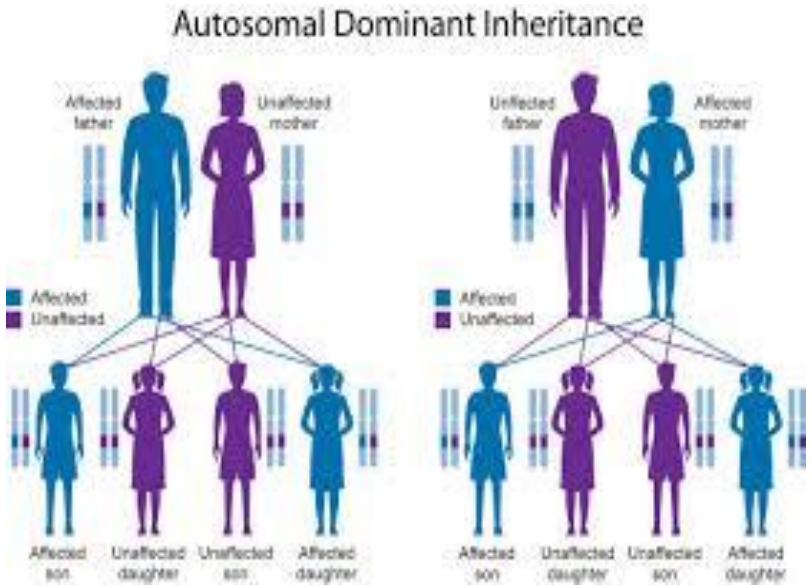


- If both partners are carriers of a pathogenic variant in the ***same*** disease gene, there is a **25%** chance with each pregnancy of having a child affected with the disease.

- If both partners are carriers of a pathogenic variant in ***different*** disease genes, there is *little* increased risk to have a child affected with either disease, although the child can be a carrier for one disease, or the other, or both.

- Males and females are equally likely to be carriers and are equally likely to have the disease.

Autosomal Dominant Inheritance

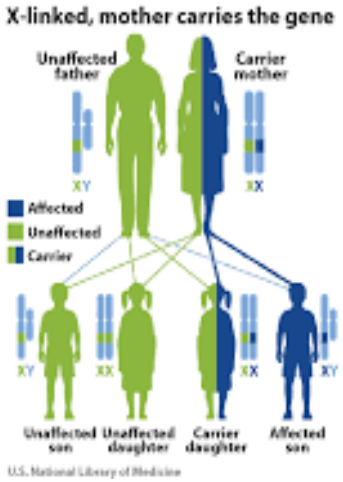


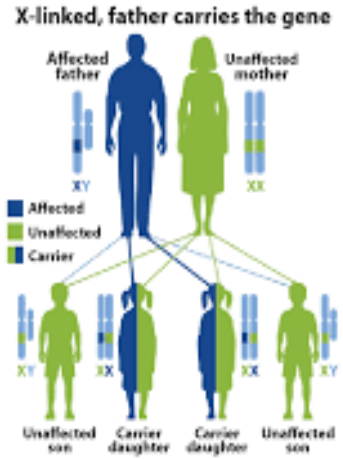
- If one partner in a couple carries a pathogenic variant in a disease gene, there is a **50%** chance with each pregnancy of having a child affected with the disease.

- Sometimes new alterations in genes occur either in the sperm or egg or in the fetus as it develops. These are called ***de novo*** variants.

- Males and females are equally likely to have the disease, although for some diseases, males and females have different presentations.

X-Linked Inheritance



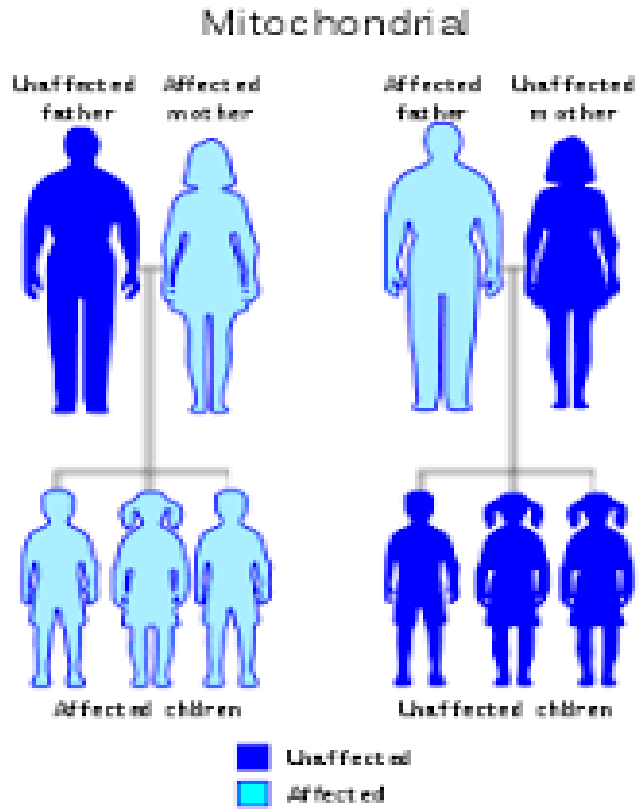


- If a mother carries a pathogenic variant in an X chromosome disease gene, there is a **25%** chance with each pregnancy of having a male child affected with an X-linked recessive disorder.

- If a father carries a variant in an X chromosome disease gene, it is likely that he is affected, and there is no increased risk to have a male child affected with either disease, although all his daughters will be carriers of disorder.

- Rare X chromosome disease genes affect only females, and in families with these disorders, often affected male fetuses are miscarried.

Mitochondrial Inheritance



- Mitochondrial DNA is separate circular structure within the mitochondria of the cells.
- Only oocytes contain mitochondria that are passed to a fetus, and not the part of the sperm that transmits the genome.
- A mother with a pathogenic variant will transmit that variant to all her children, while a father will not.
- There can be a mix of normal and abnormal mitochondrial DNA in every cell.

Additional Genetic Terminology

- Penetrance VS Expressivity
  - Penetrance indicates whether a person with a genetic variant will show features of the disorder associated with the gene. If all individuals with pathogenic variants show features associated with variants in this gene, the penetrance is 100%.
  - To explain further, let's look at a family where a child with a cleft palate is found to have a pathogenic variant in a gene, and the father is found to harbor the same variant, yet has no signs of a cleft. That indicates that the penetrance for this gene is less than 100%, and may be more like 50% to 80%.
  - Expressivity is the degree of difference that may be found in individuals with the same genotype. It is not thought of as a statistic, rather it relates to the individual variability seen in a person with a pathogenic variant.

What is Multiple Sclerosis?

- MS is a neurological condition in which there are areas in the brain and spinal cord that are damaged, causing the layer of protection around nerves, the myelin sheath, to be destroyed.
- MS is considered an **autoimmune disorder**, which means that the immune system is attacking the body due to a malfunction.
- Autoimmune disorders include lupus, type 1 diabetes, and rheumatoid arthritis, among others.
- **The contribution of genetic inheritance in autoimmune disorders is difficult to explain because there are rarely Mendelian presentations in these disorders, and more often affected individuals have inherited risk alleles in a variety of genes.**

However....

- Most geneticists believe that *all human disease is genetic*, or at least influenced by genetic or epigenetic factors.
- For example, how badly injured a person is after a car crash is influenced by genetic inheritance. If an individual has more fragile bones than others, they may have more fractures, even though they may not have a fragile bone disease.
- Teasing out the genetics of common diseases (ie, cancer, type II diabetes) and autoimmune disorders (ie, MS, lupus) has been difficult because we don't always know the impact of a combination of genetic factors, with or without other factors.
- Some ways to work through these difficult problems are through very large studies, meta-analysis of many studies taken together, and adding in GWAS.

Remember…

- The human genome project only published the rough sequence of the human genome 20 years ago.
- The complete human genome sequence was only published last summer.
- There are still refinements underway (T2T or telomere-to-telomere genome)
- We don’t know the impact of alterations in a majority of the DNA that lies between genes. There are many regulatory elements that are still being elucidated.
- We are all still learning.

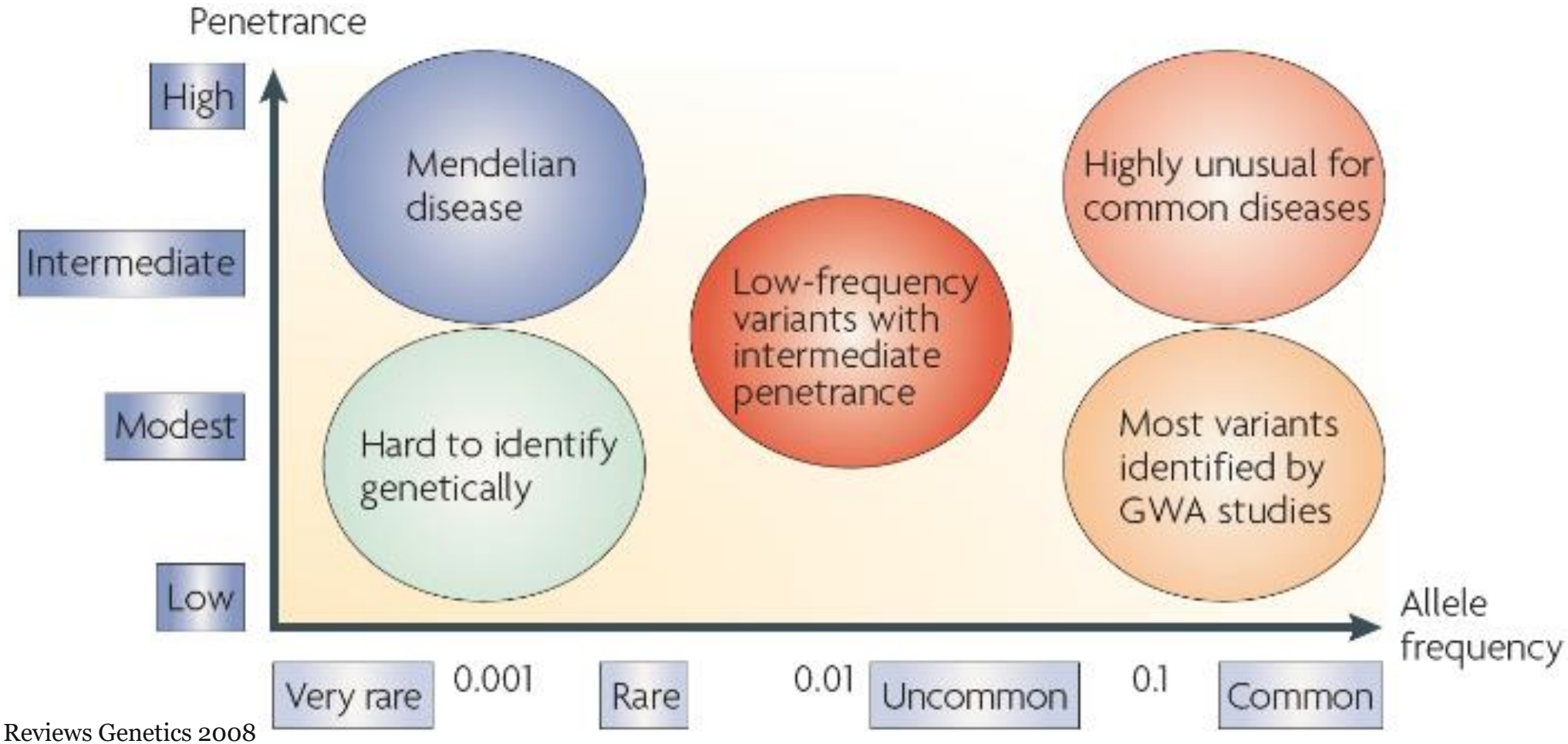
What is GWAS?

- In a **genome-wide association study**, a group of people, often selected because they have a similar ethnic ancestry, disease process, or just because they sign up, undergo testing for a specific set of DNA locations, or single-nucleotide variants (SNVs), (UK Biobank, All-of-US, Geisinger Medical Center, Kaiser system).
- The SNVs are often selected because the lab has the right reagents to test them or because there were prior studies that showed these were useful.
- The test is usually run on a microarray, although DNA sequencing may be used instead.
- An analysis of the data will then show if the SNVs and the disease process are both found in the same individuals.
- GWAS results don't necessarily show a specific correlation of a gene, variant, and disease process, just an association in the tested population.

What does that mean for MS?

- MS is usually not inherited as a Mendelian disorder. Instead, there are risk factors that may be inherited as well as environmental and other factors that influence whether a person develops MS.
- Most gene variants that may increase the risk of MS have been identified by genome-wide association studies (GWAS).
- Very few families with an inherited form of multiple sclerosis have been identified. Some of those families underwent sequencing studies.
- There are many other factors that are associated with MS, including the potential association with later onset infection with Epstein-Barr virus (EBV).

Gauging allele frequency, penetrance, and disease: Low-frequency variants and disease susceptibility



McCarthy Nature Reviews Genetics 2008

Zebras Amid Their Neighbors

Recent research: Creating a risk assessment formula

- Researchers have taken large datasets to tease out which factors are most likely to be combined in patients who are diagnosed with MS.
- For example, taking age plus genetic sex plus a score that is derived from the presence of several specific genetic variants may allow clinicians to better figure out which individuals have a greater risk of developing MS.
- Whether other members of the family have MS is a part of the risk equation with some of the polygenic risk calculators.
- Usually there is one set of data used to figure out the formula, and a second separate dataset used to test whether the formula works.

Sequencing studies, Risk assessment, and MS

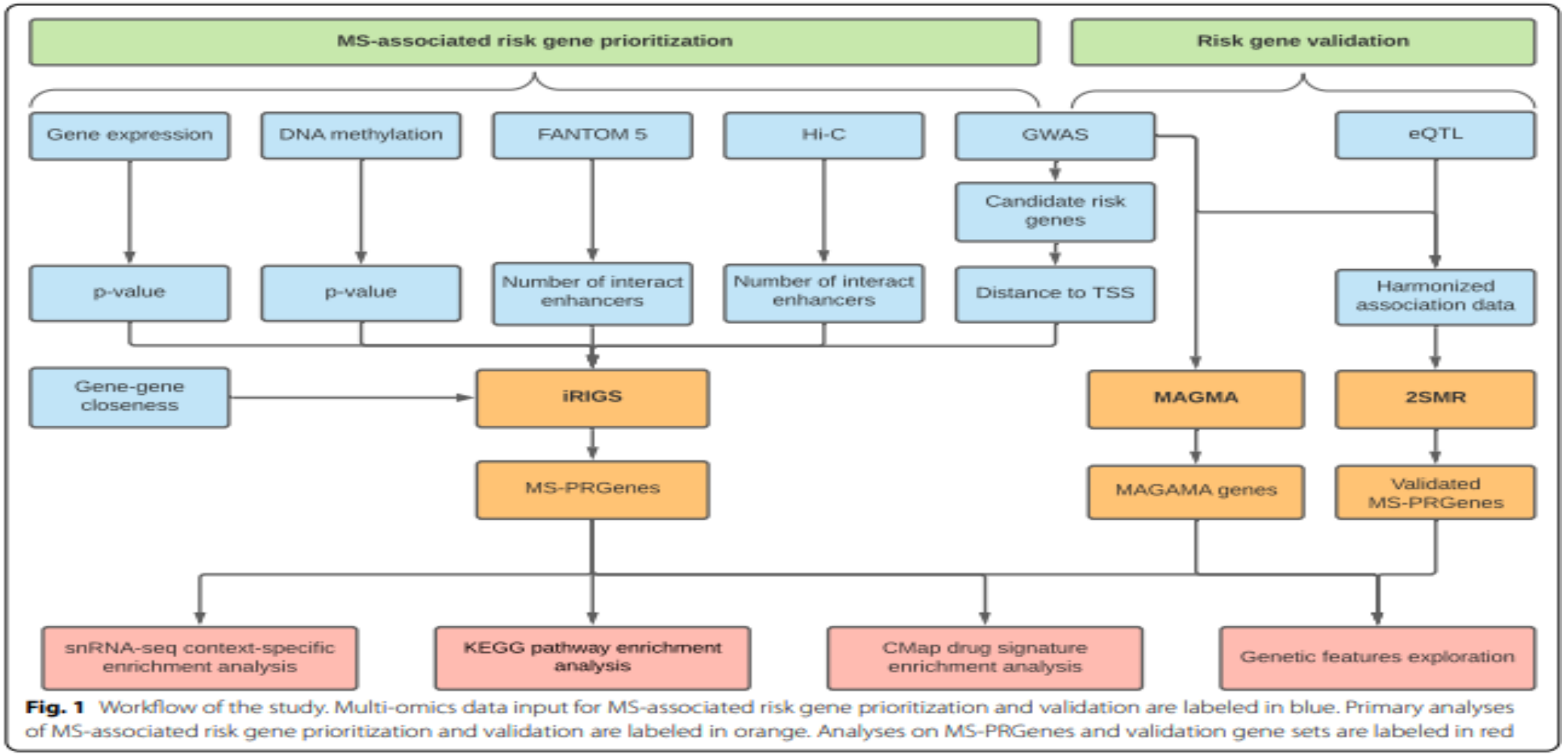
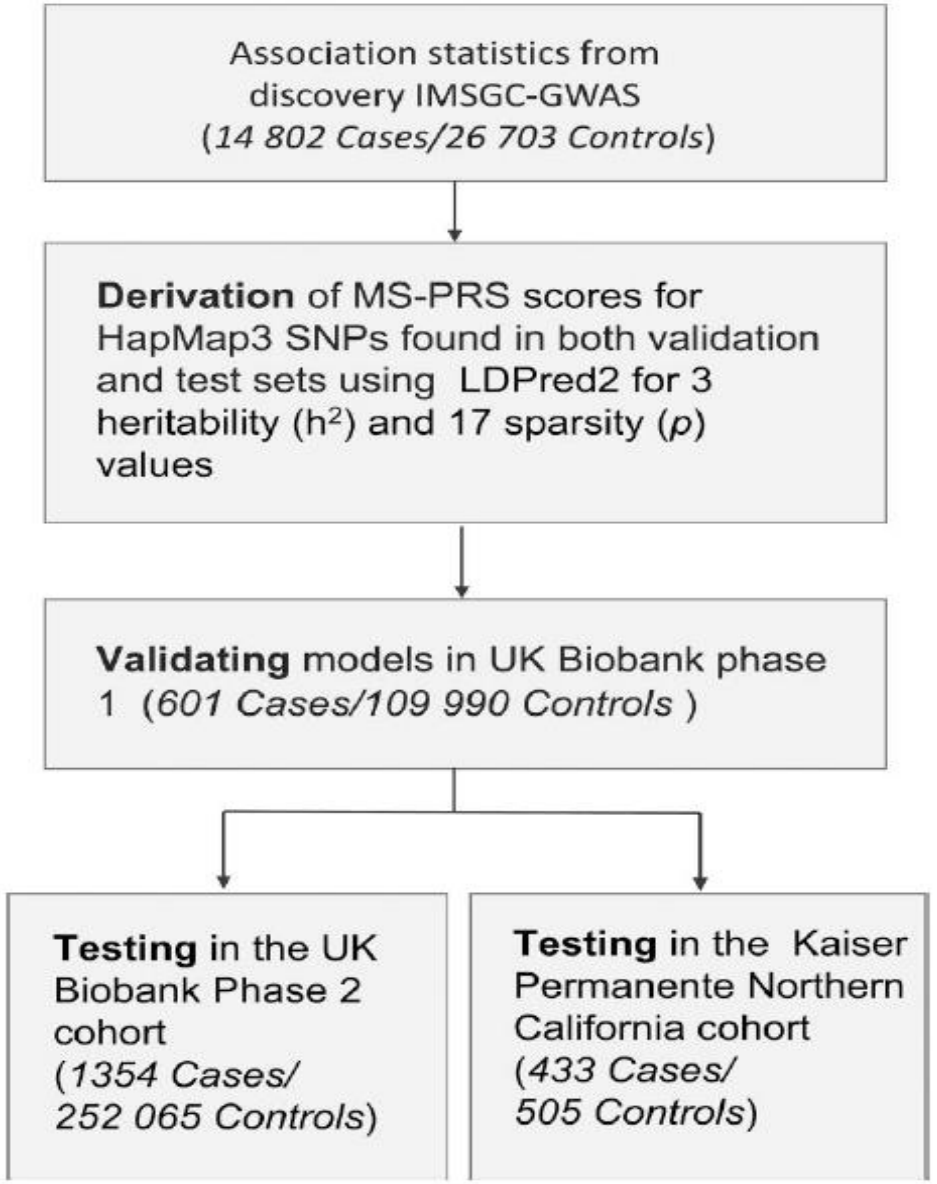


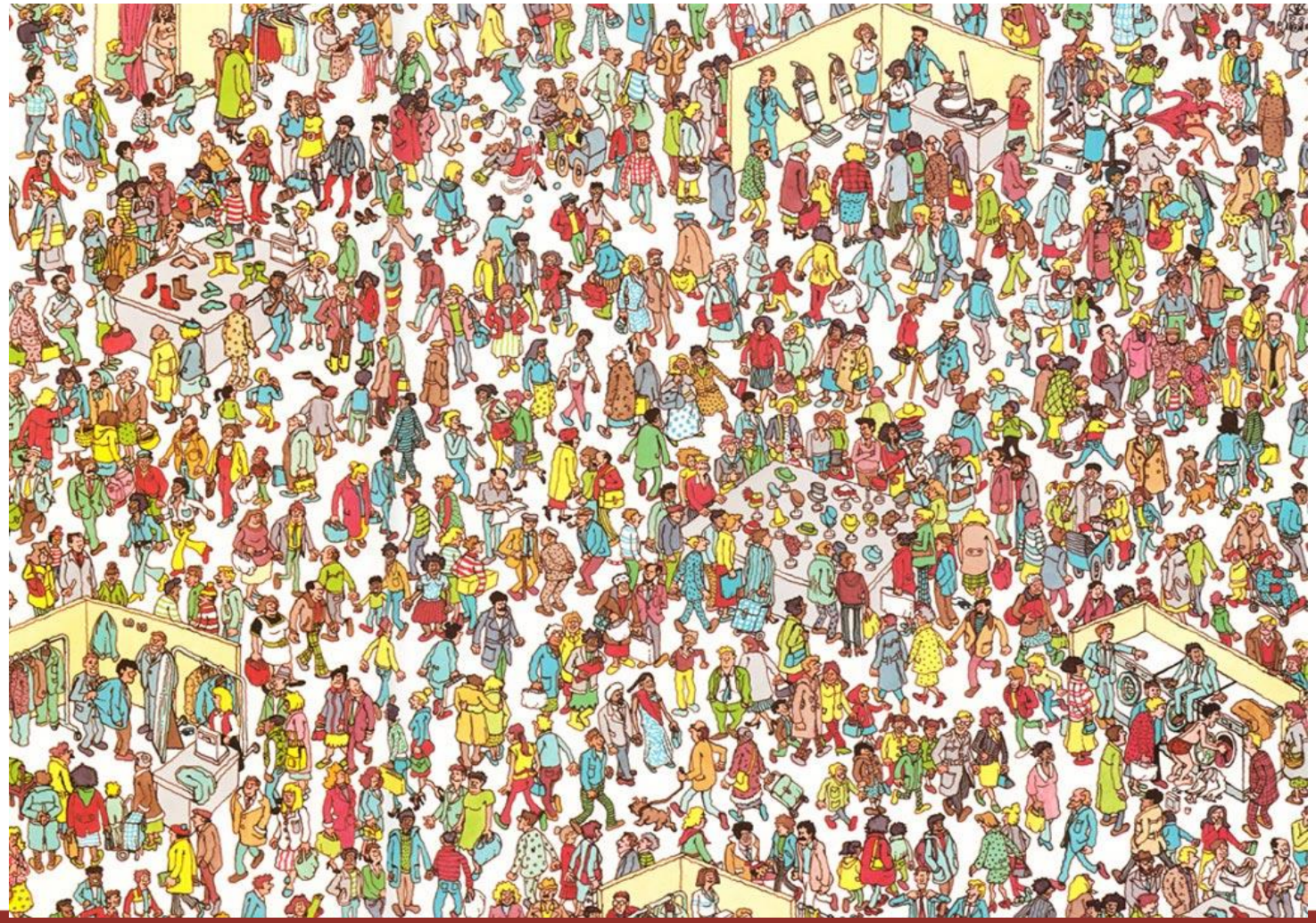
Fig. 1 Workflow of the study. Multi-omics data input for MS-associated risk gene prioritization and validation are labeled in blue. Primary analyses of MS-associated risk gene prioritization and validation are labeled in orange. Analyses on MS-PRGenes and validation gene sets are labeled in red

Liu et al, BMC Genomics 2022

Shams et al Brain 2023
Workflow



Finding the Right Variants is Hard!



What factors were found to increase risk?

- Pathway-specific factors and genes that added risk include:
  - Adaptive immune response (IL-5 and IL-2 signaling)
  - T cell receptor signaling
  - MHC class II antigen presentation
  - Interferon gamma signaling
  - Complement cascade genes
  - Viral and parasitic infection response pathways
  - Pathways identified in other autoimmune diseases like lupus, Hashimoto thyroiditis, type 1 diabetes
  - Cell adhesion and extracellular matrix organization, protein glycosylation genes
  - VEGF and NOTCH pathways
  - Chromosome 6 (where several immune-response genes are located)

Newly published EBV data analysis

- Many papers came out in 2022 that looked at large data sets, for example, military recruits who were tested for exposure to EBV or data from countries where the medical system regularly tests the whole population.
- There were arguments about the quality of the analyses!
- Some of the analyses have suggested that individuals infected with EBV for the first time as young adults may have an *increased risk* of developing MS.
- Most of these studies did not test the participants for genomic data, so there isn't a good list of genes or variants that accompanied these papers.
- **There was no data showing that EBV alone causes MS in every infected individual.**
- *Perhaps there are specific genetic variants that allowed the people with later EBV infections to then develop MS?*

Looking for Zebras Among the Herd

Summary

- Understand the different modes of inheritance of human disorders
  - Mendelian disorders usually follow specific patterns of inheritance: autosomal recessive, autosomal dominant, X-linked
  - There are also mitochondrial disorders caused by mitochondrial DNA variants
  - MS doesn't follow these modes of inheritance
- Learn about risk alleles and other risk factors: EBV?
- Comprehend the types of studies that have been done to uncover the genetics of Multiple Sclerosis (MS)
  - Risk alleles are often uncovered through large population GWAS studies
  - Families with several affected members may undergo sequencing studies
  - Scientists then analyze the data to derive polygenic/multifactorial risk scores

Thank you!

Acknowledgements

- I would like to thank Dr. Taswell and Brain Health Alliance for inviting me to give this talk.
- I also thank all of the MS patients, their families, and the clinicians and researchers who contributed to the studies I have referenced.

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