

coreBio II - genetics: WED 25 April 2018
2018

Stephanie Moon, Ph.D. - GWAS

After this class students should be able to:

1. Compare and contrast **methods used** to discover the genetic basis of traits or diseases including haplotyping
2. Describe what a **GWAS** is
3. Explain why it's important to have **a large sample size** when doing a GWAS
4. Describe **what scientists should do next** using data from GWAS
5. Give one example of **a successful GWAS**

How do we distinguish Mendelian from non-Mendelian traits?

Simple Mendelian genetics → More complex genetics

A trait is a physical characteristic of an organism determined by genetics and/or environment.

What is an example of a simple trait? (penetrance & expressivity)

How is a disease defined?

What is an example of a complex trait?

VANISHING WHITE MATTER DISEASE: a 'simple' disease with clear Mendelian inheritance

OMIM: 603896

Recessive mutations in any of 5 genes, encoding *EIF2B* subunit proteins, can cause progressive loss of brain tissue in childhood

Genealogical studies and haplotyping revealed the genetic basis for vanishing white matter disease (Leegwater et al., 2001)

- Individuals differ in age and severity
 - Question: What determines these factors - a single other gene, or many genes, or environment?
 - How could we figure this out?

We can discover genetic perturbations that contribute to complex traits or diseases by looking at different scales

Chromosome duplications

Partial chromosome deletions

Haplotypes (sets of SNPs)

SNPs

Down Syndrome

Prader-Willi syndrome

Vanishing white matter disease

Schizophrenia

How do we determine a person's genotype?

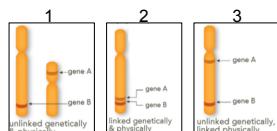
- SNP microarray analysis, **exome** analysis, whole genome sequencing
- When we do an **exome analysis**, what do we miss?
- What are the limits of SNP analysis? (linkage disequilibrium)

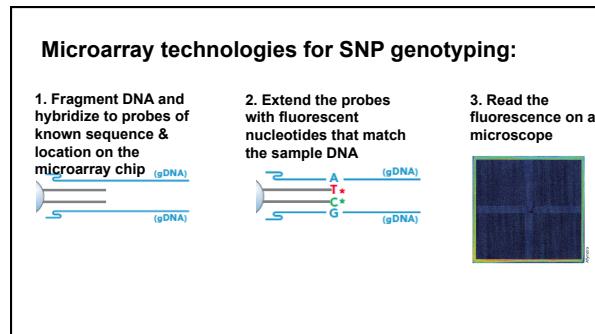
Haplotyping can reveal trait or disease-associated genetic variants (alleles) in diseases with less clear heritability

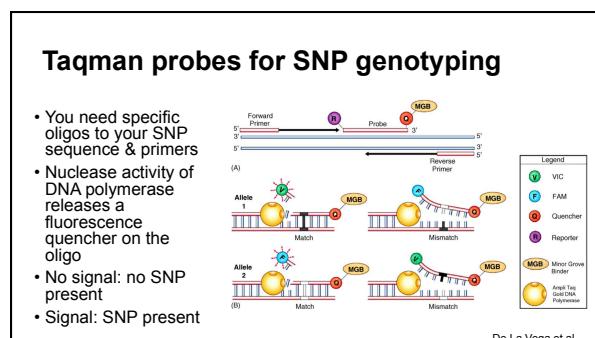
Haplotyping relies on **linkage disequilibrium**: when alleles are present in a combination more frequently than would occur by chance due to recombination events

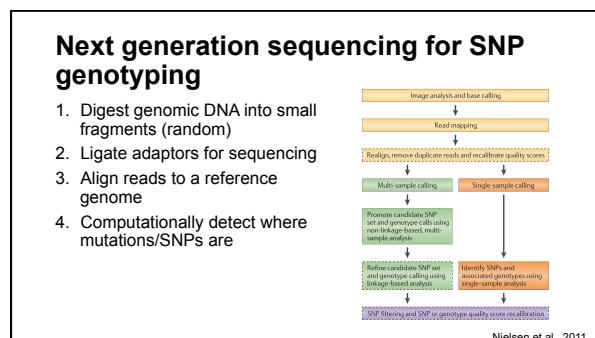
Haplotyping is measuring **clusters of mutations** called **single nucleotide polymorphisms (SNPs)** on linked genes.

In which scenario would genes A and B likely be part of the same haplotype?









How do we determine a person's phenotype?

- Quantitative versus qualitative traits
- Symptoms and disease spectrums
 - Schizophrenia is a psychiatric disease with many symptoms that could be present or absent in a given individual

- Question 1: how might we determine whether different people have the same disease?
- What types of traits are the easiest to identify (define)?

How do we combine phenotype with genotype information? GWAS

- Why do I need lots of people?
- How are GWAS different from Mendelian genetics?
- The presence of a single allele will usually not cause disease in GWAS studies

- Question 2: how would you recognize a trait controlled by allelic differences in multiple genes?

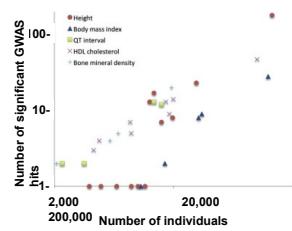
GWAS: genome-wide association studies



- The **genomes** of many individuals are sequenced
- Mutations, aka **single nucleotide polymorphisms** are detected
- The observed SNPs that occur in people with a certain trait or disease are found

The importance of having a large sample size for GWAS

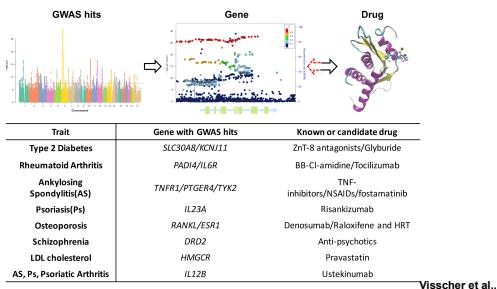
- One SNP (allele) rarely cause all cases of a disease or fully explain a trait/disease
- They would be Mendelian otherwise!



GWAS studies are useful because:

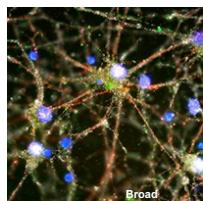
- They can pinpoint new genes to target in a disease
- They point to **new biological pathways** to study in the context of disease or a certain trait
 - Follow-up studies are needed that directly assess these pathways
 - Drug targets with genetic data backing them up have a higher chance of successfully going to market or phase III clinical trials

GWAS can suggest new drug targets



A successful GWAS outcome: Schizophrenia

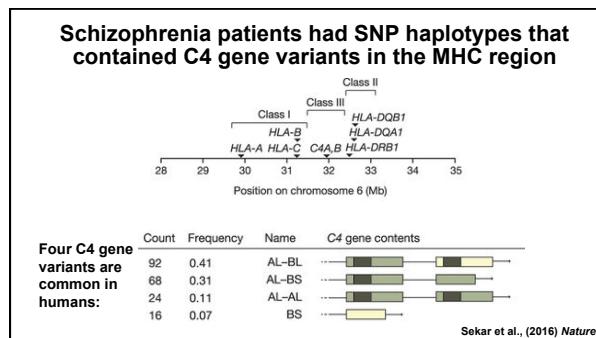
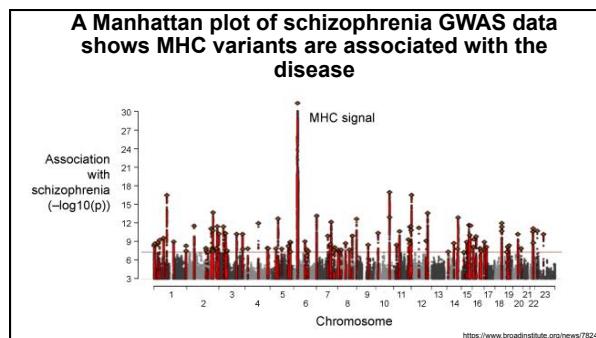
- No animal or cell culture model of schizophrenia
- GWAS used 28,799 schizophrenia patients and 35,986 non-affected people
- Loss of connections between neurons identified as a key biological defect in schizophrenia

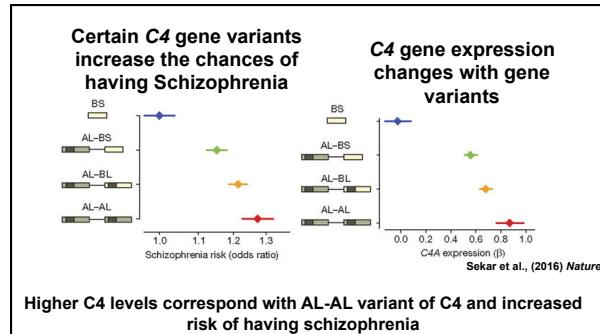


Schizophrenia is a severe mental disorder with genetic and environmental risk factors

- Severe mental disorder
 - Psychotic behaviors
 - Hallucinations, agitated body movements, delusions
 - Disruption of normal emotions/behaviors
 - Unemotional affect, reduced speaking
 - Cognitive symptoms
 - Poor ability to understand information & make decisions
 - Trouble focusing, memory problems
- Potential environmental contributors:
 - Viral infections
 - Malnutrition in utero
 - Problems during birth
 - Psychosocial factors

NIMH.gov

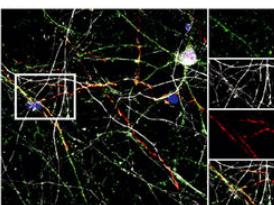




What experiment would you do next to see if increased C4 expression plays a role in schizophrenia?

C4 is important for development of neurons

- Staining brain tissue shows C4 (green) is in a certain type of neurons
 - A process called synaptic pruning is caused by C4
 - Schizophrenia may arise from excessive synaptic pruning



GWAS mini-quiz!

- 1. Explain why it's important to have a large sample size when doing a GWAS**
- 2. Describe what should be done next using data from GWAS**
- 3. Give one example of a successful GWAS**
