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- Dr. Sun is a professor in the Department of Biological Sciences in the University of Southern California. He completed his Ph.D in Applied Mathematics from University of Southern California in 1994. Presently, He is the Head of the computational biology group, Associate head of Molecular and Computational Biology Program, Department of Biological Sciences at University of Southern California. He is elected as Fellow in American Association for the Advancement of Sciences and International Statistical Institute in 2012. He is the member of American Society of Human Genetics, American Statistical Association, International Genetic Epidemiology Society etc. He is the editor and reviewer of a number of international Journals.

Biography

Computational Biology

Statistical Genetics

Mathematical Modeling

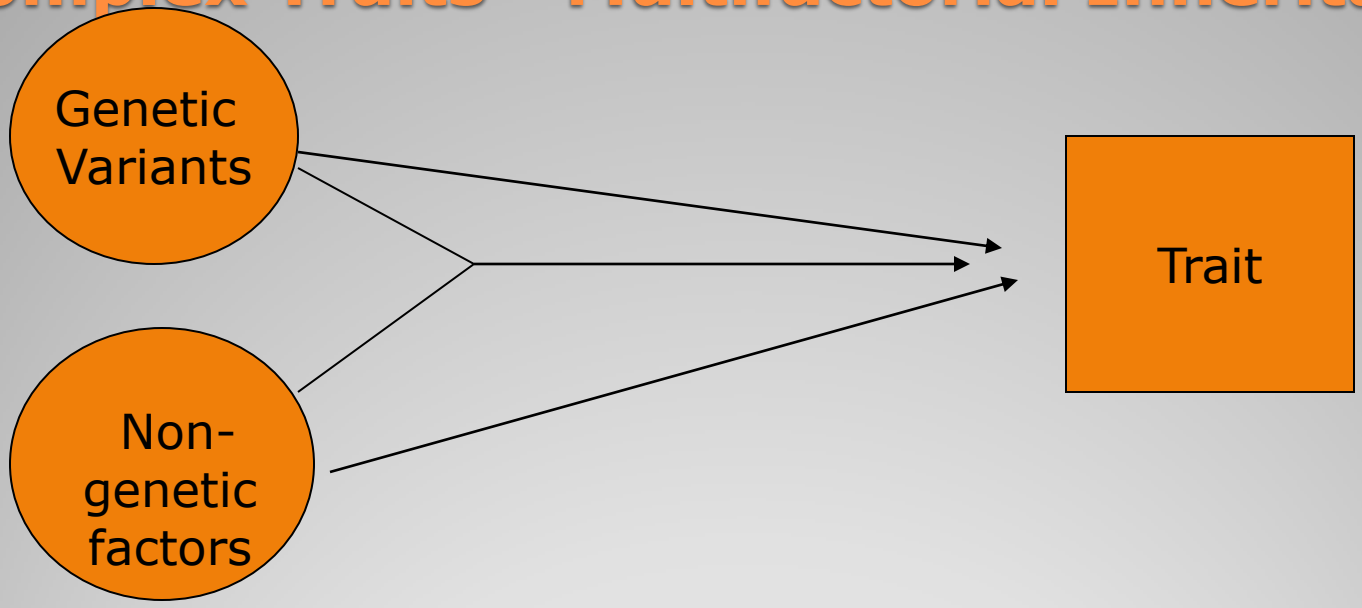
Summary of Research Interests

- **It is a scientific field which is concerned with the development and application of statistical methods for drawing inferences from genetic data**

Statistical Genetics

- Goal of a genetic association study
- Rationale for genome-wide association studies
- Design and analysis considerations for GWAs
- Application to two clinically similar granulomatous lung diseases

Today
Complex Traits - Multifactorial Inheritance



- Examples
  - Some cancers
  - Type 1 diabetes
  - Type 2 diabetes
  - Alzheimer disease
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Schizophrenia
  - Cleft lip/palate
  - Hypertension
  -
  - Asthma

Genetic Association Studies

- Short-term Goal: Identify genetic variants that explain differences in phenotype among individuals in a study population
  - Qualitative: disease status, presence/absence of congenital defect
  - Quantitative: blood glucose levels, % body fat
- If association found, then further study can follow to
  - Understand mechanism of action and disease etiology in individuals
  - Characterize relevance and/or impact in more general population
- Long-term goal: to inform process of identifying and delivering better prevention and treatment strategies

DNA Variation

- >99.9 % of the sequence is identical between any two chromosomes.
  - Compare maternal and paternal chromosome 1 in single person
  - Compare Y chromosomes between two unrelated males

- Even though most of the sequence is identical between two chromosomes, since the genome sequence is so long (~3 billion base pairs), there are still many variations.

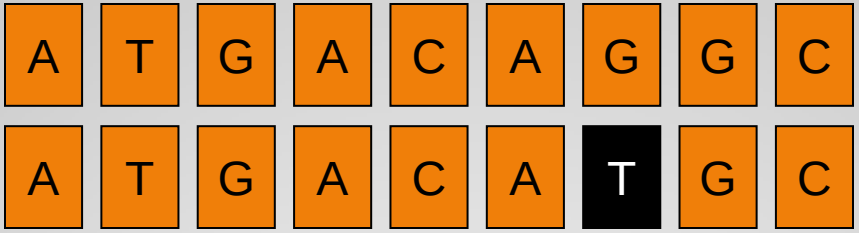
- Some DNA variations are responsible for biological changes, others have no known function.

- Alleles are the alternative forms of a DNA segment at a given genetic location.

- Genetic polymorphism: DNA segment with ≥ 2 common alleles.

Single Nucleotide Polymorphisms: SNPs

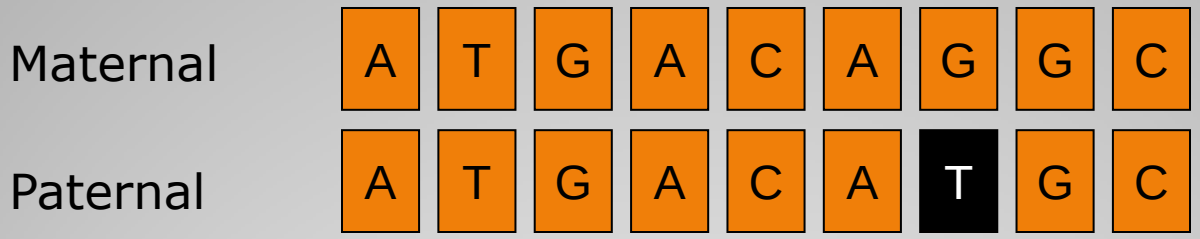
- SNPs – DNA sequence variations that occur when a single nucleotide is altered



- Alleles at this SNP are “G” and “T”
- SNPs are the most common form of variation in the human genome
- SNPs catalogued in several databases

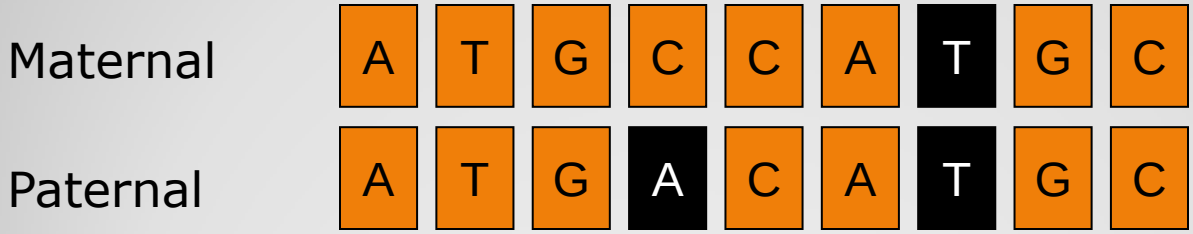
Genotypes and Haplotypes

- Genotype: pair of alleles (one paternal, one maternal) at a locus



Genotype for this individual is GT

- Haplotype: sequence of alleles along a single chromosome

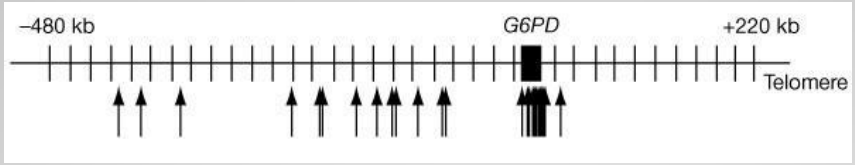


Genotypes for this individual (vertical) : CA and TT

Haplotypes (horizontal): CT and AT

Scope of a Genetic Association Study

- Candidate gene
  - Known functional variants
  - Variants with unknown function in exons, introns, regulatory regions



- Linkage candidate region
  - Functional variants, or those with unknown function in candidate genes
  - More general coverage of region using many markers

* Sabeti PC et al. (2002). *Nature* 419: 832-837

- Genome-wide
  - Test for association with hundreds of thousands (millions) of SNPs spread across the entire genome.
  - Many design strategies possible for distributing markers

Genome-Wide Association Studies

Rationale:

- Linkage analysis using families takes unbiased look at whole genome, but is underpowered for the size of genetic effects we expect to see for many complex genetic traits.
- Candidate gene association studies have greater power to identify smaller genetic effects, but rely on *a priori* knowledge about disease etiology.
- Genome-wide association studies combine the genomic coverage of linkage analysis with the power of association to have much better chance of finding complex trait susceptibility variants.

Why are They Possible Now?

Genotyping Technology:

- Now have ability to type hundreds of thousands (or millions) of SNPs in one reaction on a "SNP chip." The cost can be as low as $200-$300 per person.
- Two primary platforms: Affymetrix and Illumina.

Design and analysis:

- Availability of SNP databases, HapMap, and other resources to identify the SNPs and design SNP chips.
- Faster computers to carry out the millions of calculations make implementation possible.

Design and Analysis Strategies: Moving Target

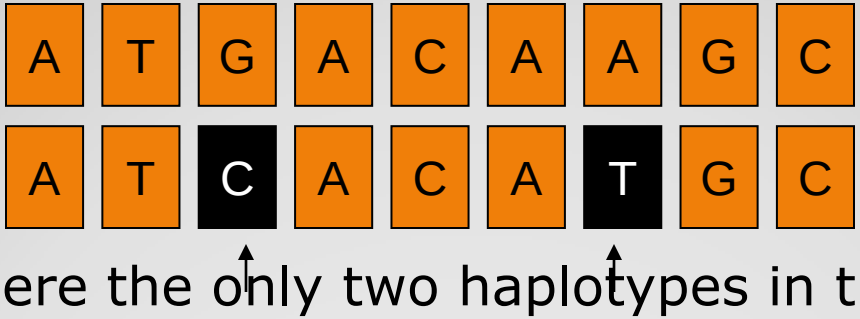
- A genetic factor is like any other potential risk factor and the same study design and analysis principles hold – in addition to those specific to GWAs.
- Standard case-control (matched or unmatched), cohort-based quantitative trait and longitudinal designs are common.
- In what follows, I will talk about current ideas and methods, with a focus on assumptions and quality control.
- Focus today is on case-control design, but many of the principles apply to other designs.

SNP Chips: Number and Placement of SNPs

- A "typical" SNP chip has at least 317,000 SNPs distributed across the genome. Newest: ~1 million.
- The newest chips can also measure (directly or indirectly) some types of copy number variation.
- We do not directly measure genotypes at all genetic polymorphisms, but rely on association between the polymorphisms we do assay and those which we do not assay.
- SNP-SNP association, or linkage disequilibrium, is fundamental to our ability to sample the whole genome with relatively few SNPs.

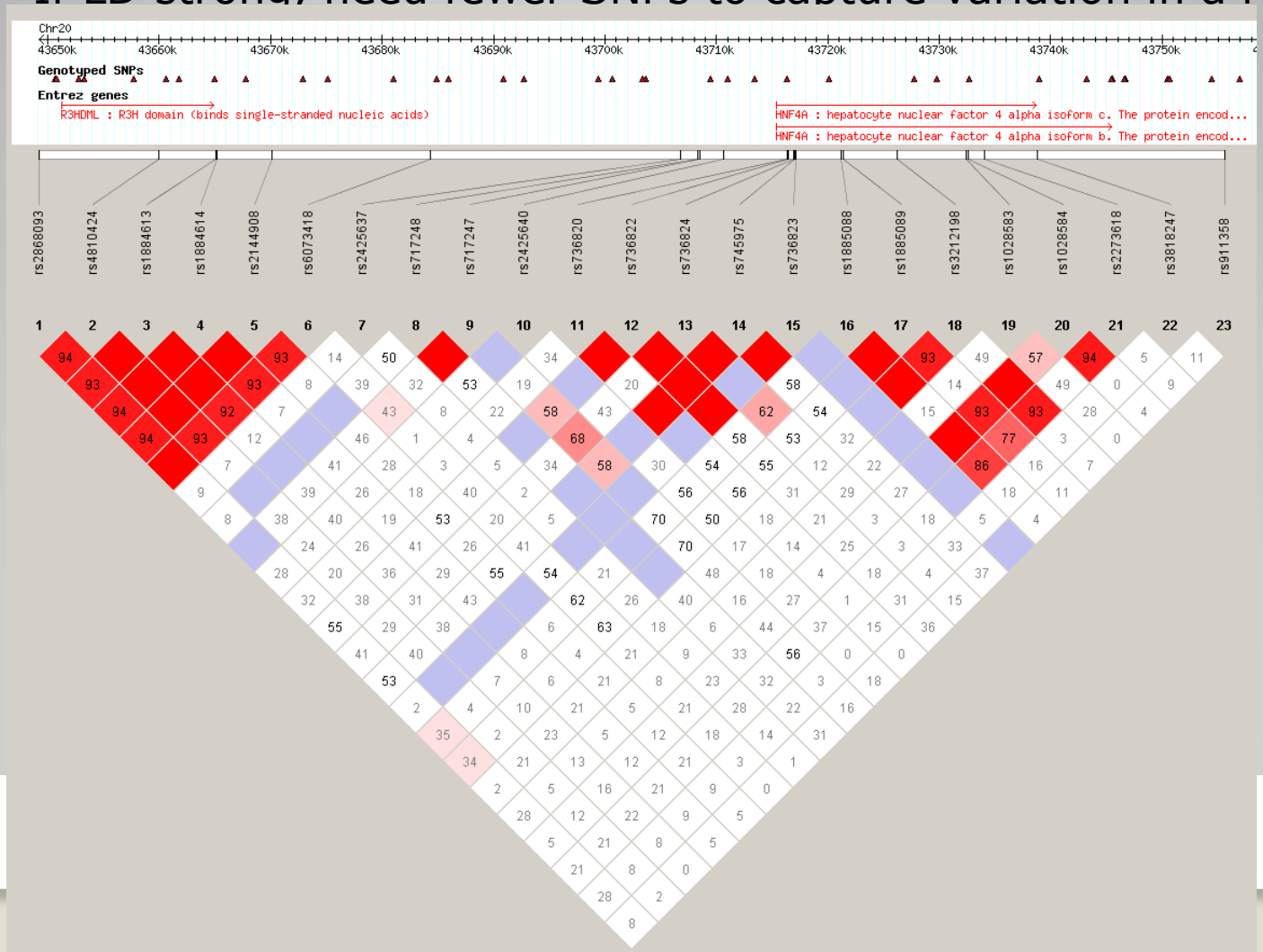
Linkage Disequilibrium (LD)

- Linkage disequilibrium: the non-random association of alleles at linked loci.
- A measure of the tendency of some alleles to be inherited together on haplotypes descended from ancestral chromosomes.



- If these where the only two haplotypes in the population, then alleles G and A (C and T) are in perfect linkage disequilibrium.
- If we genotype the first SNP, we know what the alleles are at the second SNP.

- In general, LD between two SNPs decreases with physical distance
- Extent of LD varies greatly depending on region of genome
- If LD strong, need fewer SNPs to capture variation in a region



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Editor Signature

Fengzhu Sun

Thank you.