Linking Genetic Variation to Important Phenotypes

BMI/CS 776

www.biostat.wisc.edu/bmi776/

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Outline

- How does the genome vary between individuals?
- How do we identify associations between genetic variations and simple phenotypes/diseases?
- How do we identify associations between genetic variations and complex phenotypes/diseases?

Understanding Human Genetic Variation

- The “human genome” was determined by sequencing DNA from a small number of individuals (2001)
- The HapMap project (initiated in 2002) looked at polymorphisms in 270 individuals (Affymetrix GeneChip)
- The 1000 Genomes project (initiated in 2008) sequenced the genomes of 2500 individuals from diverse populations
- 23andMe genotyped its 1 millionth customer in 2015
- Genomics England plans to sequence 100k whole genomes and link with medical records, 49k so far

Classes of Variants

- Single Nucleotide Polymorphisms (SNPs)
- Indels (insertions/deletions)
- Structural variants

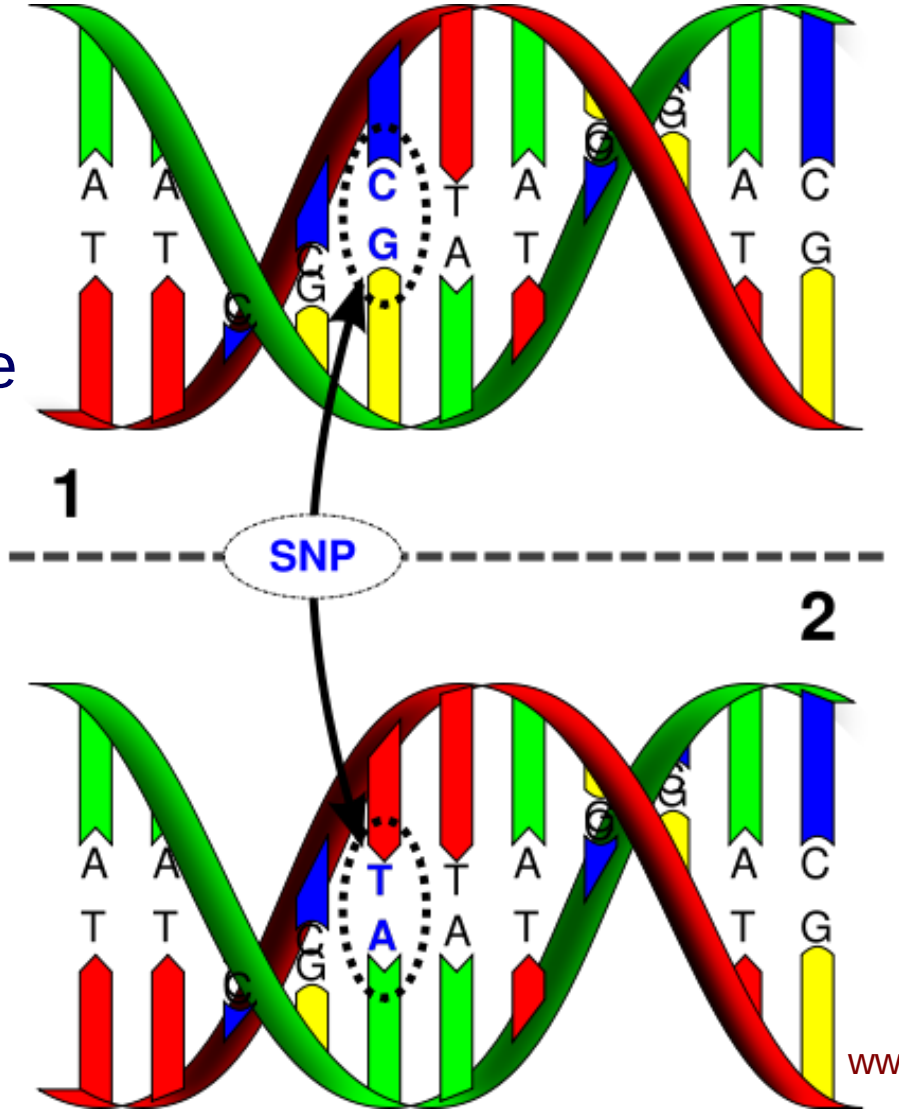
Formal definitions: https://www.snpedia.com/index.php/Glossary

Single Nucleotide Polymorphisms (SNPs)

One nucleotide changes

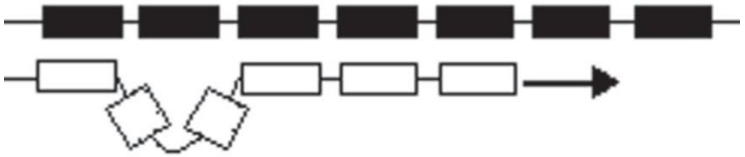
Variation occurs with some minimal frequency in a population

Pronounced “snip”

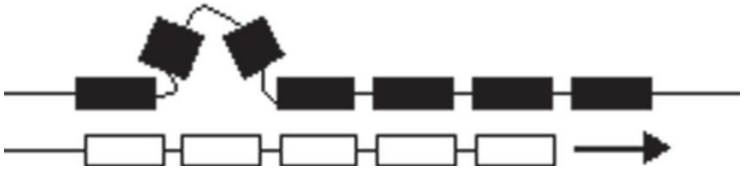


Insertions and Deletions

Black box: DNA template strand
White box: newly replicated DNA



Insertion: slippage inserts extra nucleotides



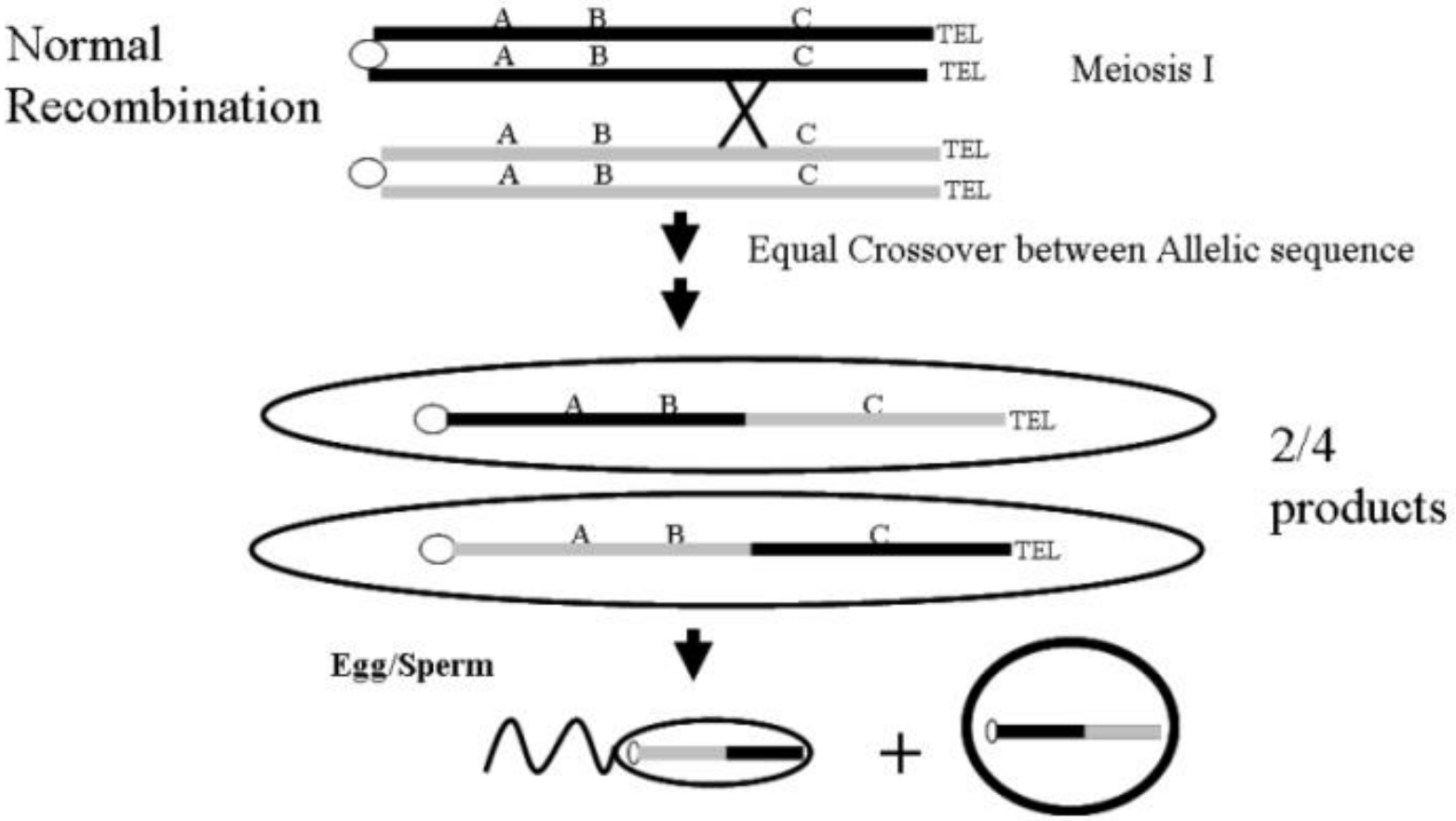
Deletion: slippage excludes template nucleotides

Forster et al. *Proc. R. Soc. B* 2015

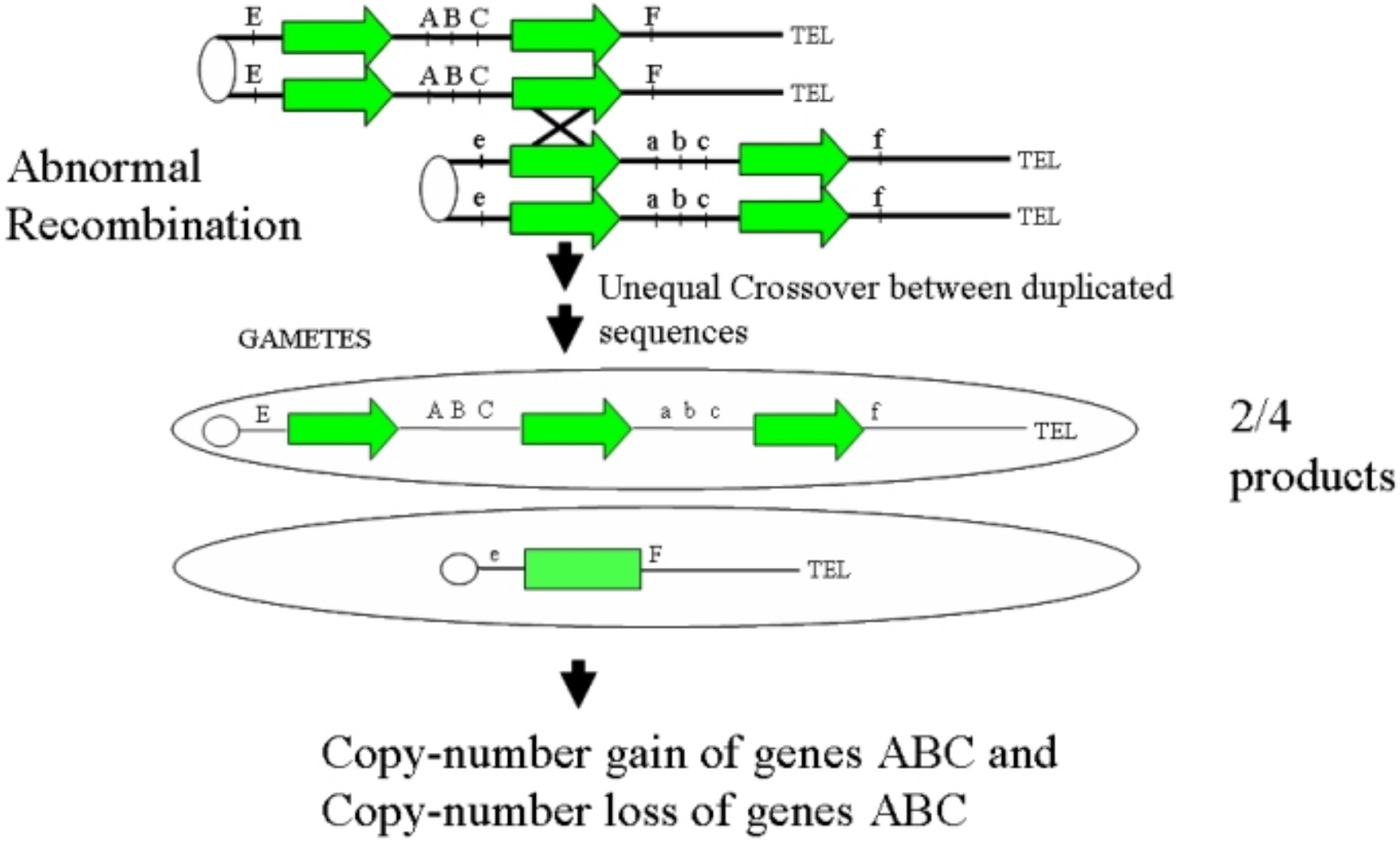
Structural Variants

- Copy number variants (CNVs)
  - Gain or loss or large genomic regions, even entire chromosomes
- Inversions
  - DNA subsequence is reversed
- Translocations
  - DNA subsequence is moved to a different chromosome

Genetic Recombination

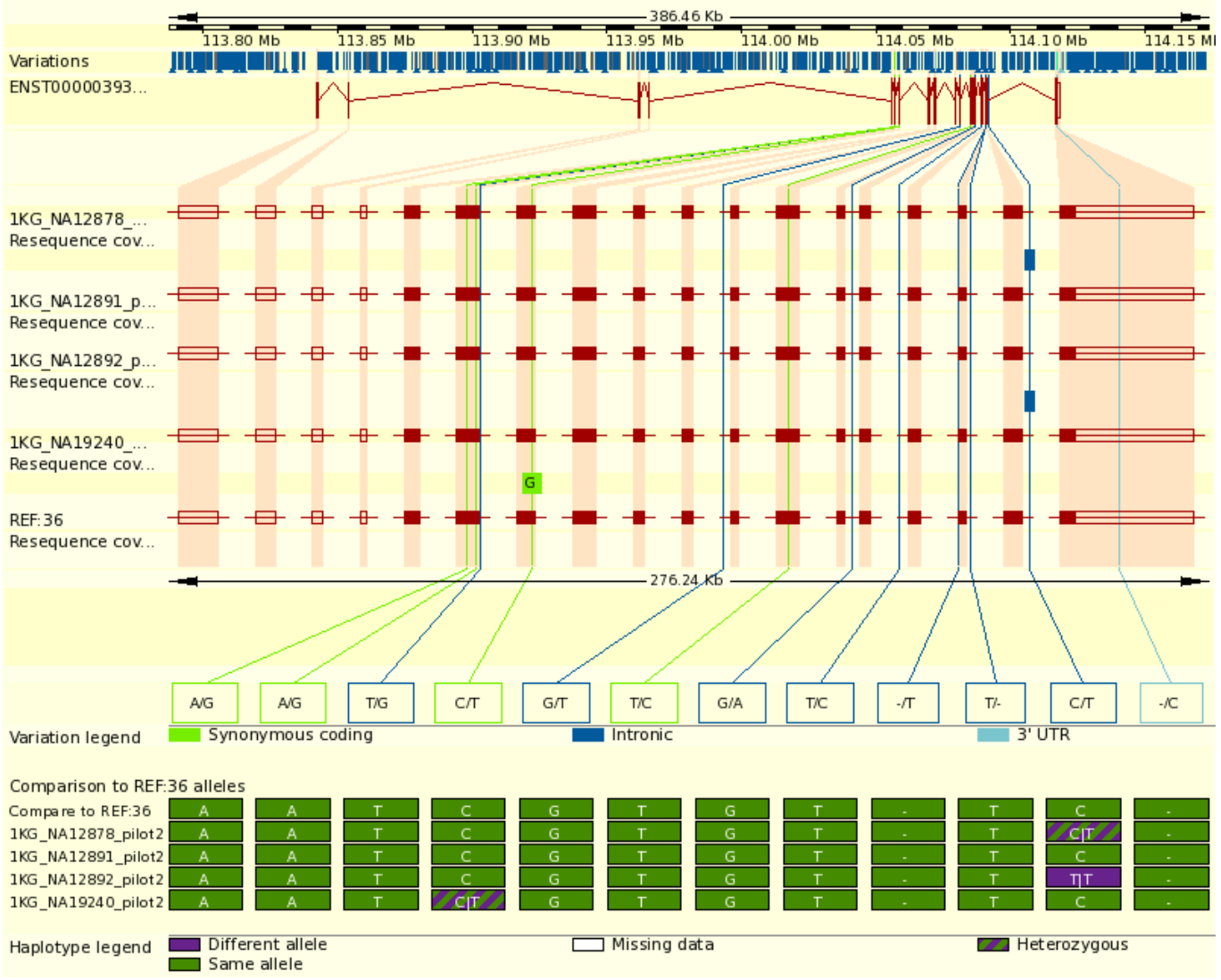


Recombination Errors Lead to Copy Number Variants (CNVs)



1000 Genomes Project

Project goal: produce a catalog of human variation down to variants that occur at >= 1% frequency over the genome



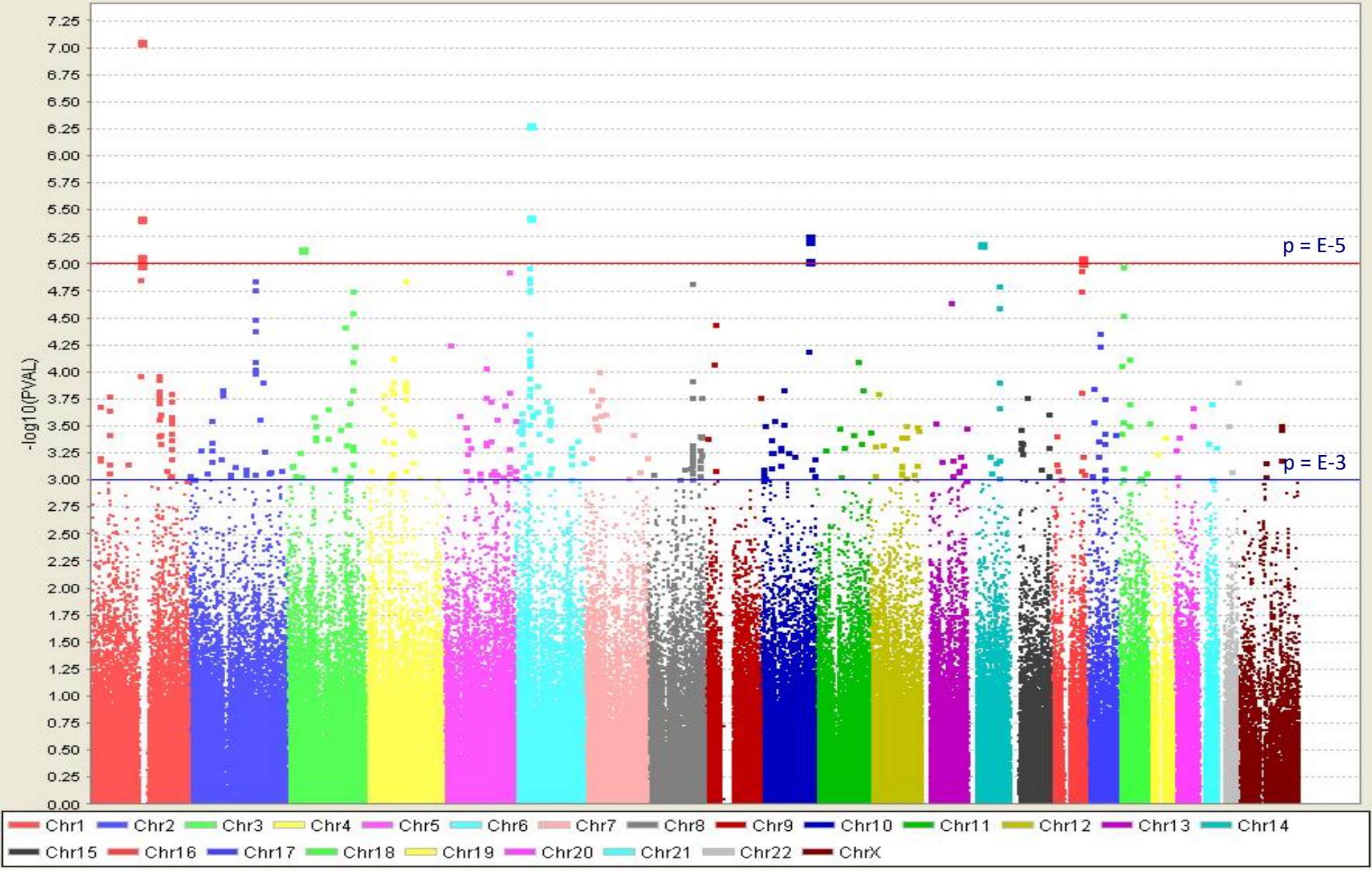
Understanding Associations Between Genetic Variation and Disease

Genome-wide association study (GWAS)

- Gather some population of individuals
- Genotype each individual at polymorphic markers (usually SNPs)
- Test association between *state* at marker and some variable of interest (say disease)
- Adjust for multiple comparisons

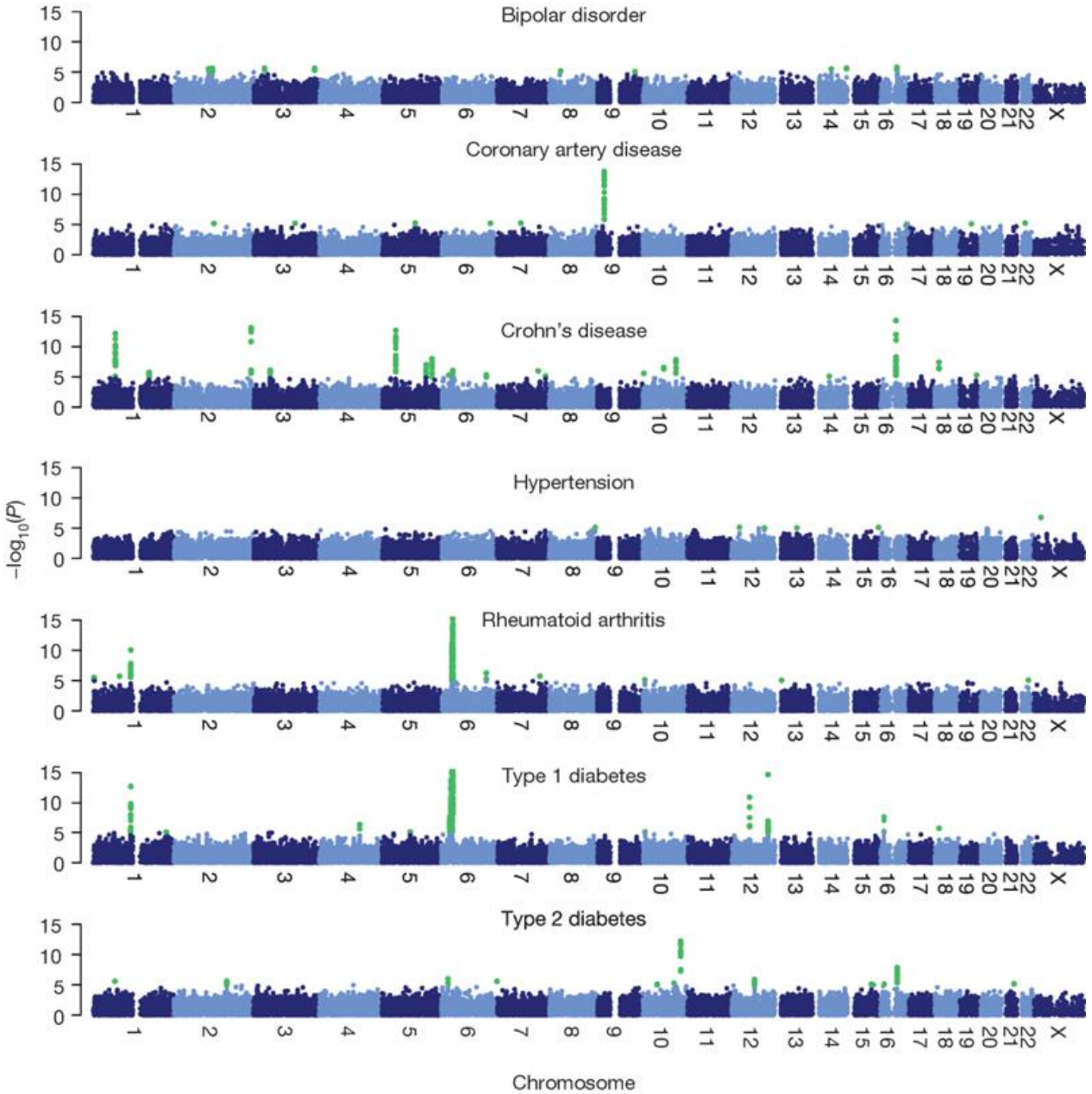
- Phenotypes: observable traits

Type 2 Diabetes Results: 386,731 markers

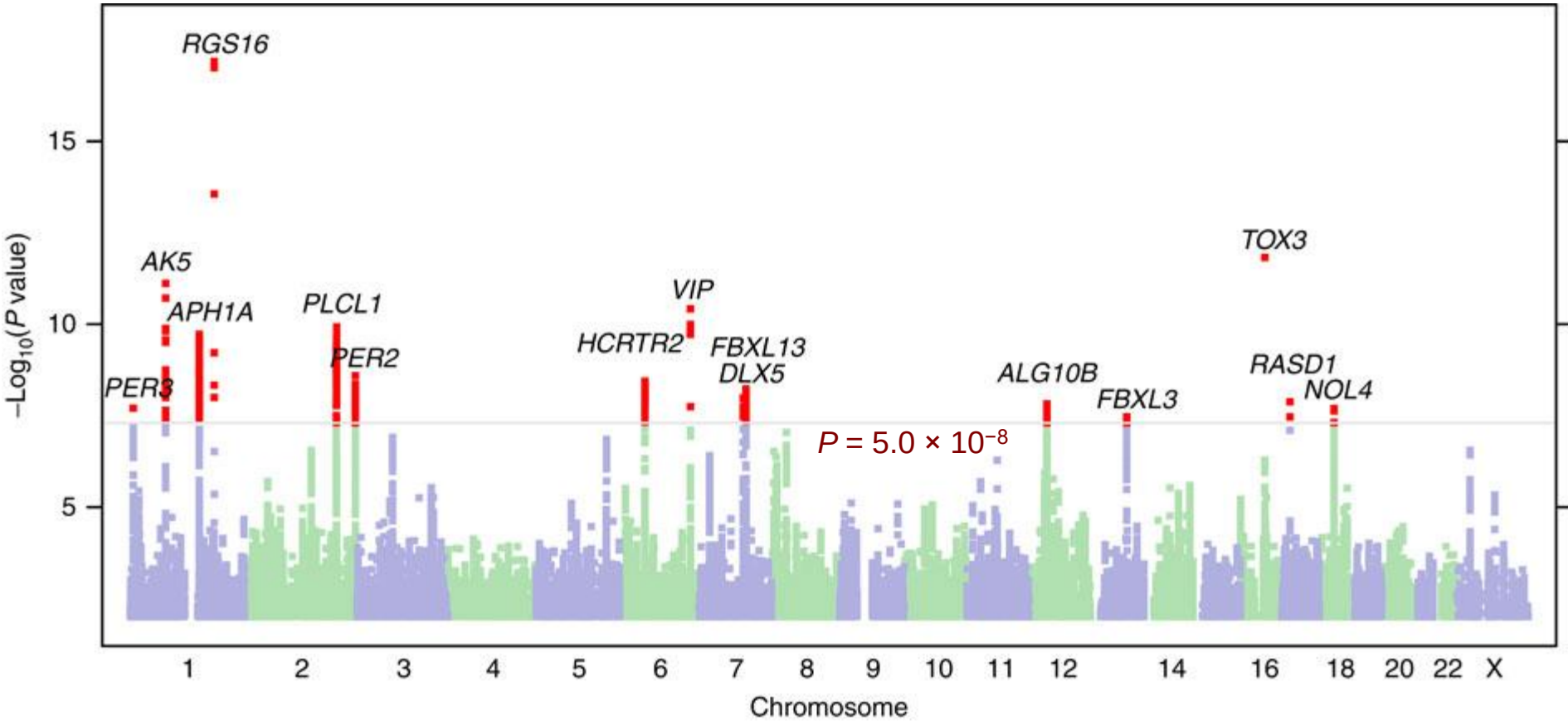


Type 2 diabetes association P values by chromosome (386,731 markers). The x-axis is the genomic position by chromosome 1-22 and X (by color), and the y-axis is the negative base 10 logarithm of the P value.

Wellcome Trust GWAS



Morning Person GWAS



Hu et al. *Nature Communications* 2016

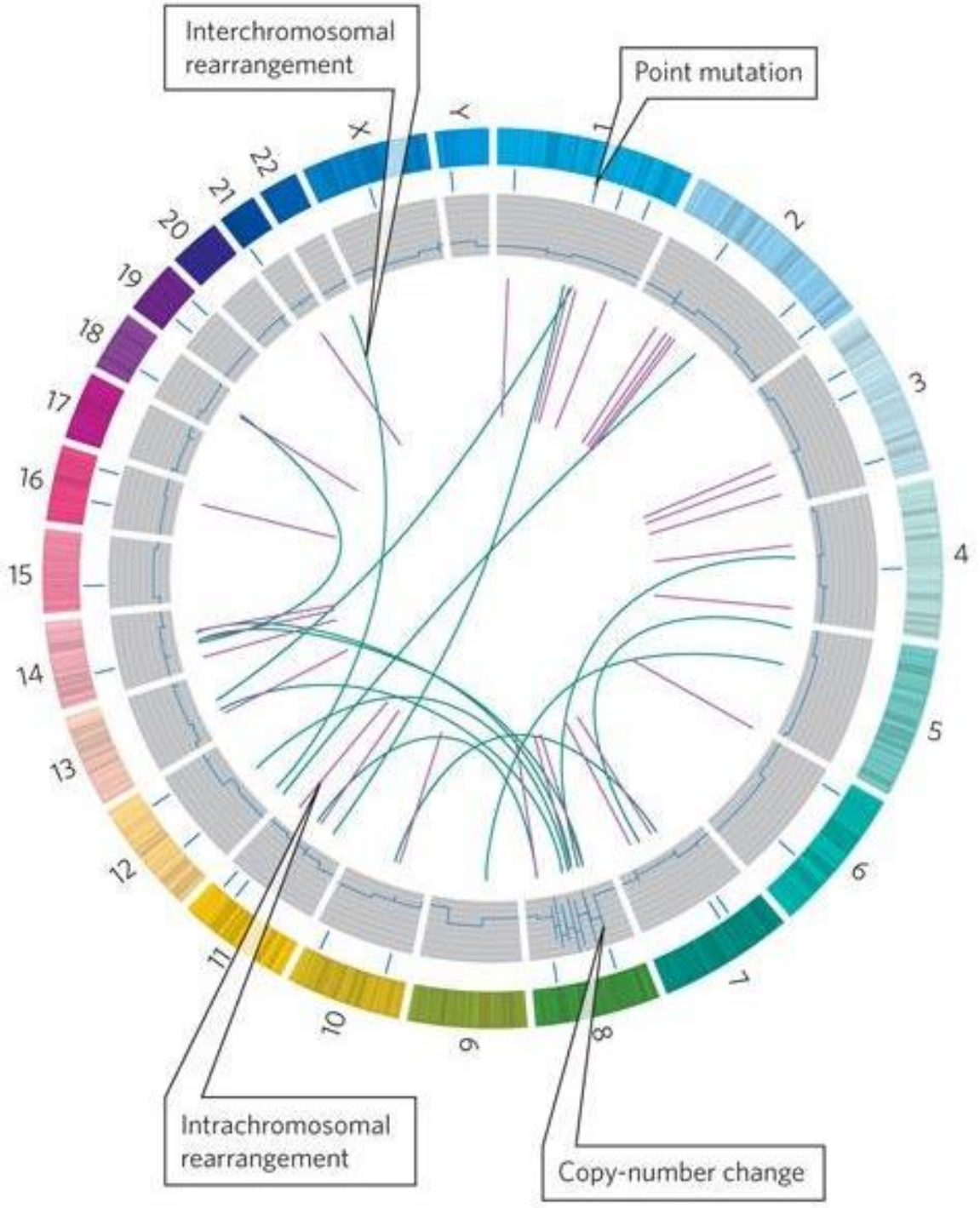
Understanding Associations Between Genetic Variation and Disease

International Cancer Genome Consortium

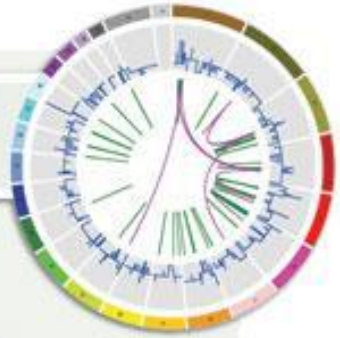
- Includes NIH's *The Cancer Genome Atlas*
- Sequencing DNA from 500 tumor samples for each of 50 different cancers

- Goal is to distinguish *drivers* (mutations that cause and accelerate cancers) from *passengers* (mutations that are byproducts of cancer's growth)

A Circos Plot

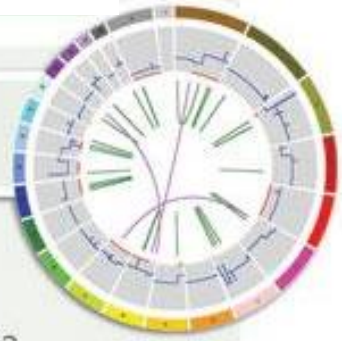


Some Cancer Genomes



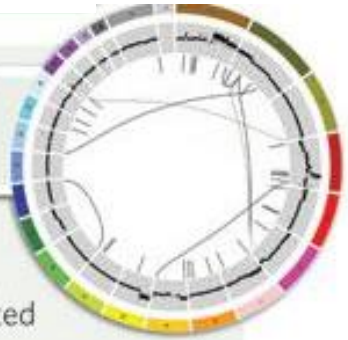
LUNG CANCER
Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334



SKIN CANCER
Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41



BREAST CANCER
Cancer: basal-like breast cancer

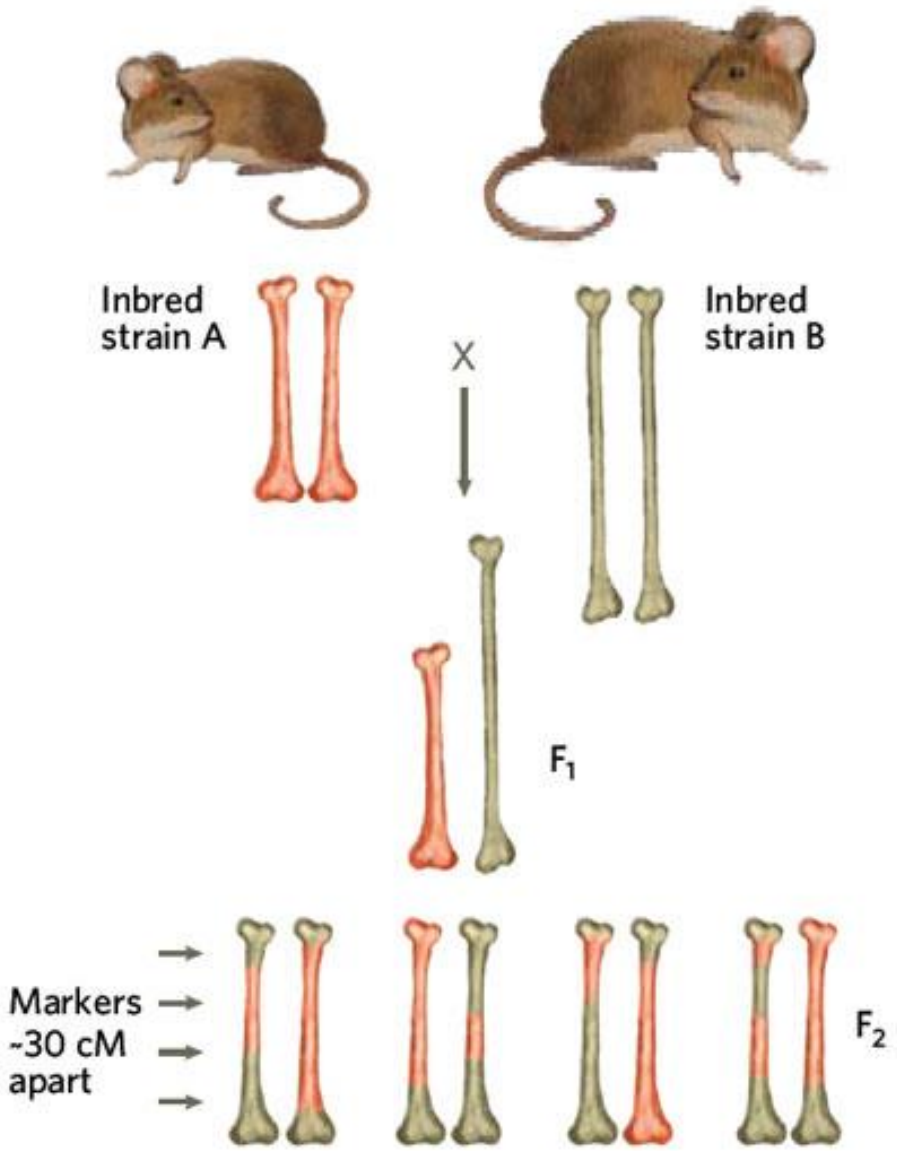
- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

Understanding Associations Between Genetic Variation and Complex Phenotypes

Quantitative trait loci (QTL) mapping

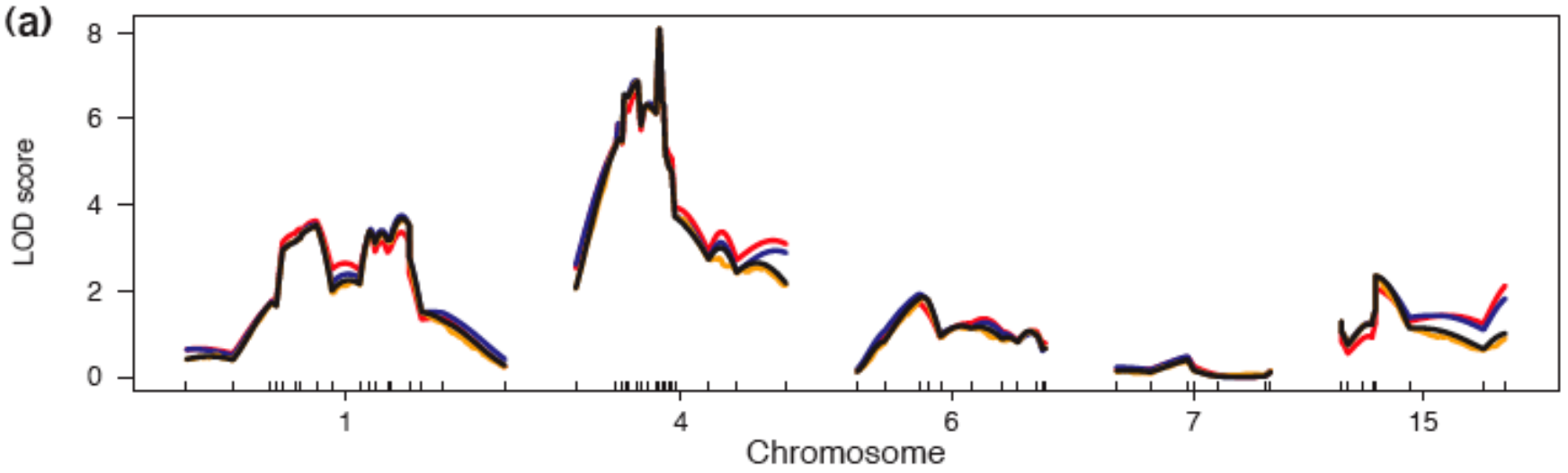
- Gather some population of individuals
- Genotype each individual at polymorphic markers
- Map quantitative trait(s) of interest to chromosomal locations that seem to explain variation in trait

QTL Mapping Example



QTL Mapping Example

QTL mapping of mouse blood pressure, heart rate
[Sugiyama et al., Broman et al.]



Logarithm of Odds

$$\mathrm{LOD}(q) = \log_{10} \frac{P(q \mid \text{QTL at } m)}{P(q \mid \text{no QTL at } m)}$$

quantitative trait

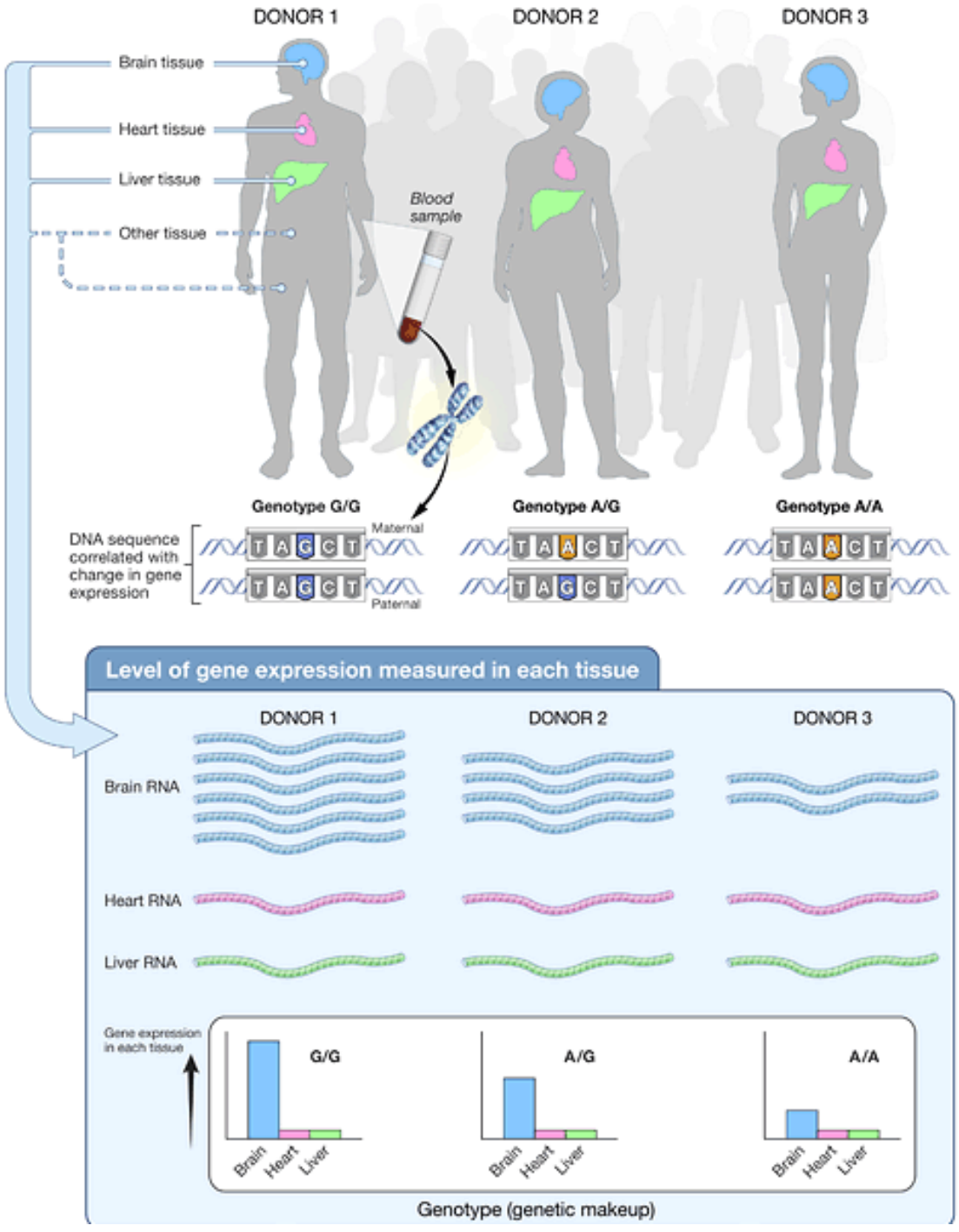
position in the genome

QTL Example: Genotype-Tissue Expression Project (GTEx)

- Expression QTL (eQTL): traits are expression levels of various genes

- Map genotype to gene expression in different human tissues

QTL Example: GTEx



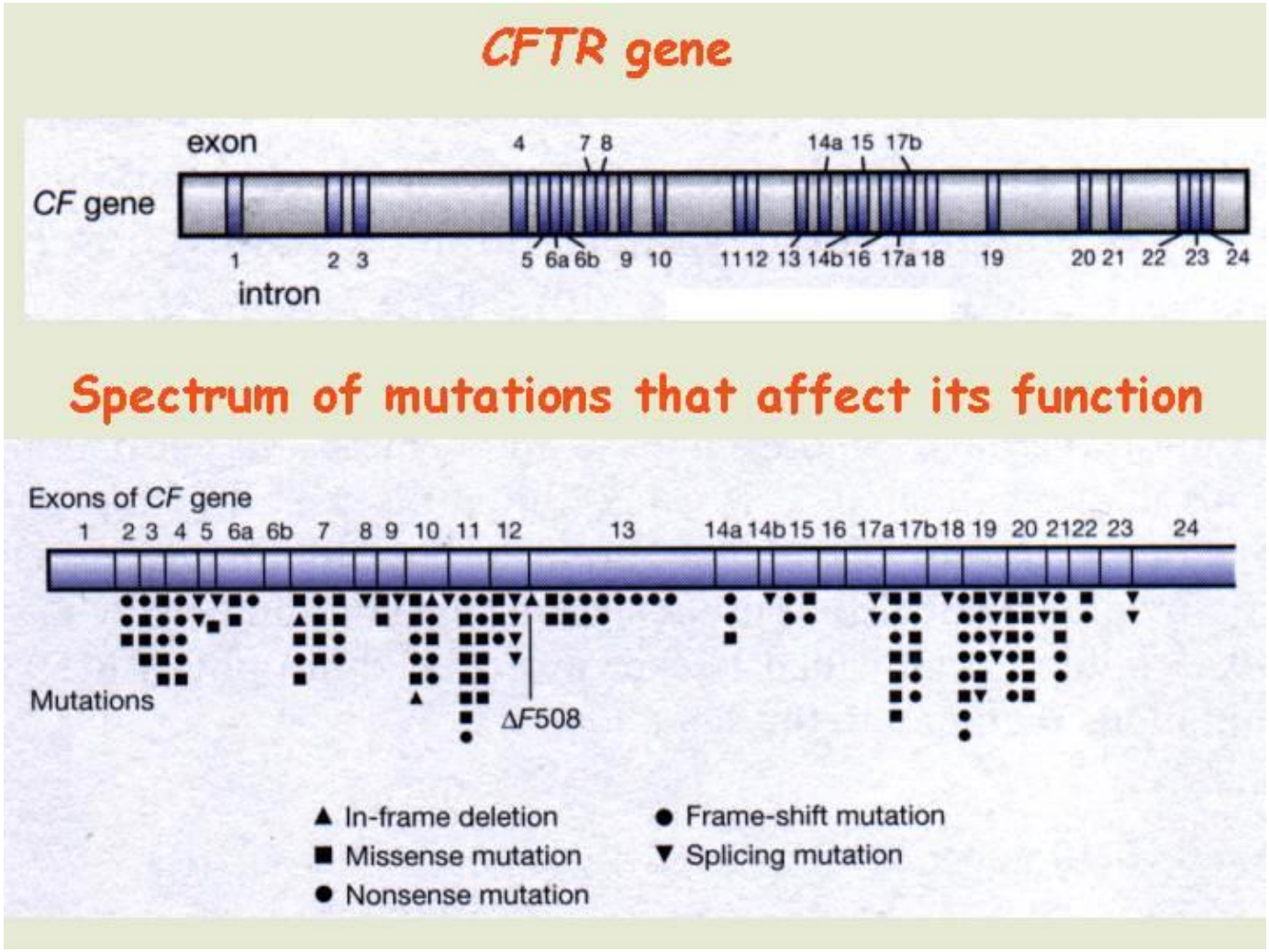
https://www.genome.gov/27543767/

GWAS Versus QTL

- Both associate genotype with phenotype
- GWAS pertains to discrete phenotypes
  - For example, disease status is binary
- QTL pertains to quantitative (continuous) phenotypes
  - Height
  - Gene expression
  - Splicing events
  - Metabolite abundance

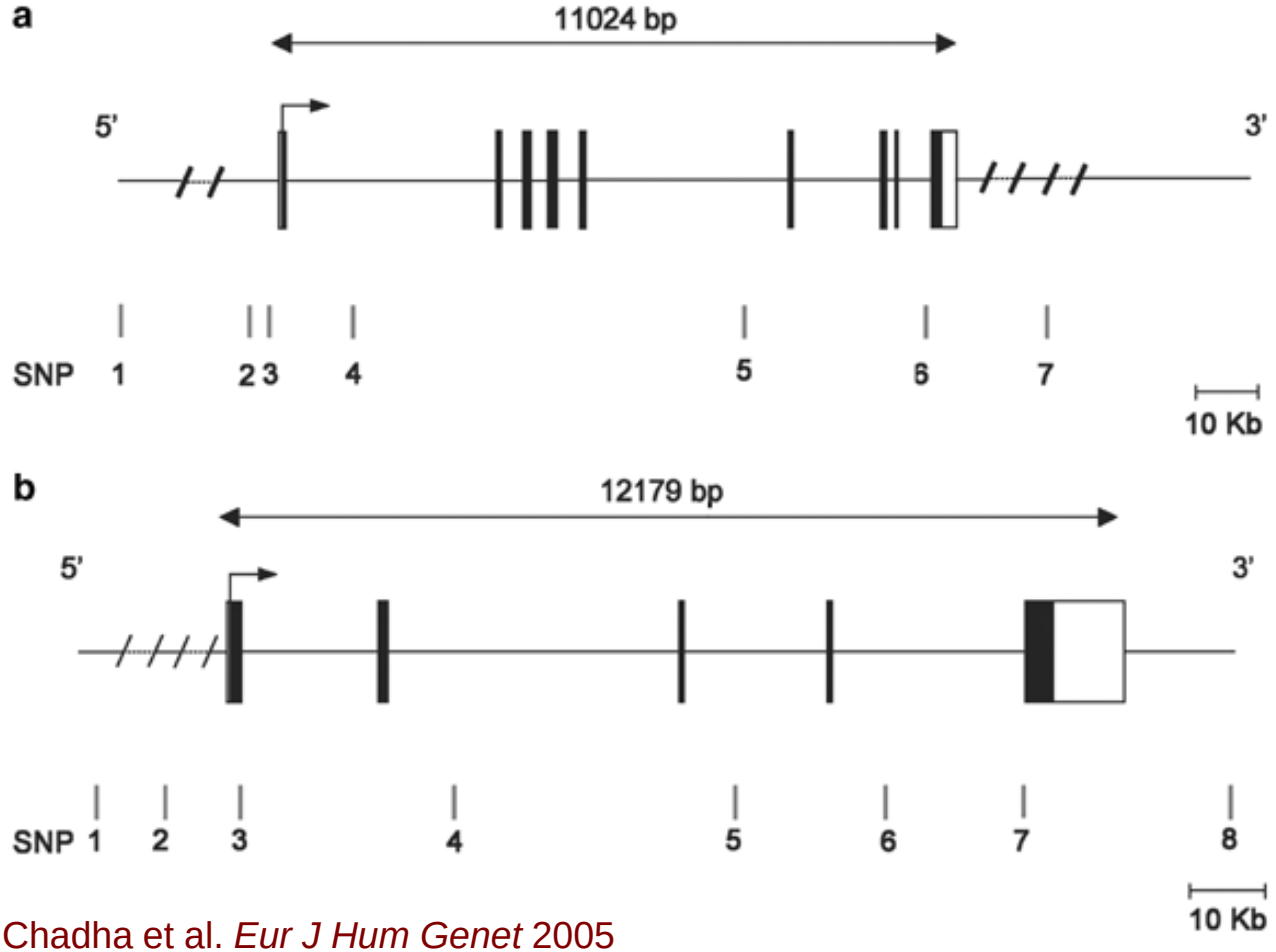
Determining Association is Not Enough

A simple case: CFTR (Cystic Fibrosis Transmembrane Conductance Regulator)



Many Measured SNPs Not in Coding Regions

- Genes encoding CD40 and CD40L with relative positions of the SNPs studied



Chadha et al. *Eur J Hum Genet* 2005

Computational Problems

- Assembly and alignment of thousands of genomes
- Data structures to capture extensive variation
- Identifying functional roles of markers of interest (which genes/pathways does a mutation affect and how?)
- Identifying interactions in multi-allelic diseases (which combinations of mutations lead to a disease state?)
- Identifying genetic/environmental interactions that lead to disease
- Inferring network models that exploit all sources of evidence: genotype, expression, metabolic, etc.
- Detecting large structural variants