Human Genetic Variation

Lisa Brooks, Ph.D.

NHGRI

Why Do We Care about Genetic Variation?

Genetic differences among people lead to differences in disease risk and response to treatment.

Genetic variation is used to find genes and variants that contribute to disease.

Studying how these variants cause disease (including interacting with the environment) provides insight into diagnosis and treatment.

Types of Variants

SNPs = Single Nucleotide Polymorphisms
= One-base spelling differences

...ATCGACCACATGAC...

...ATTGACCACAT___C...

...ATCGACCTCATGAC...

Indels = Insertions / Deletions

Amount of Variation

Chromosomes from two people differ at about 5 / 1000 sites in DNA
= 99.5% the same.

> 30 million variable sites per pop

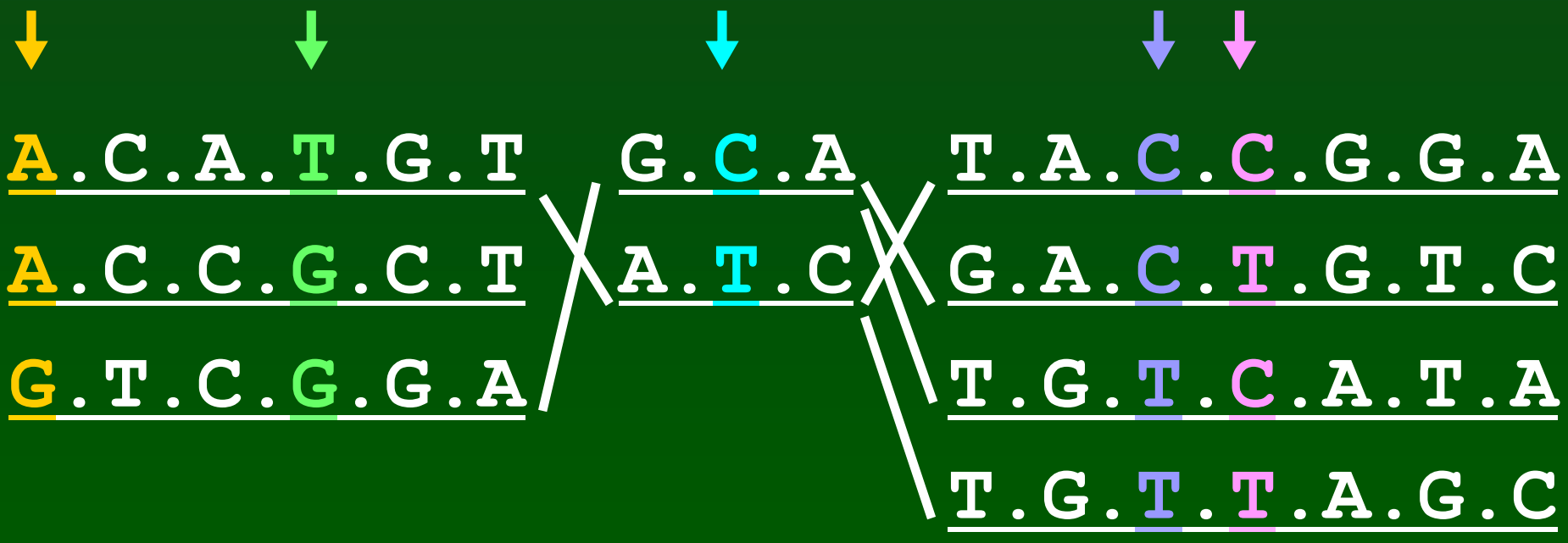
> 80 million variable sites in world

Haplotypes

Sets of variants on the same chromosome

..A..C..A..T..G..T..	40%
..A..C..C..G..C..T..	30%
..G..T..C..G..G..A..	20%
several others	10%

Haplotype Blocks and Tag SNPs



The HapMap Shows the Pattern of Variation in the Genome

Genome-Wide Association Studies (GWAS) to Find Candidate Disease-Gene Regions

People without a disease

..A.C.A.T.G.T.. 40% ..G.C.A.. 60%

..A.C.C.G.C.T.. 30% ..A.T.C.. 35%

..G.T.C.G.G.A.. 20%

People with a disease

..A.C.A.T.G.T.. 40% ..G.C.A.. 30%

..A.C.C.G.C.T.. 30% ..A.T.C.. 50%

..G.T.C.G.G.A.. 20% ..A.T.A.. 15%

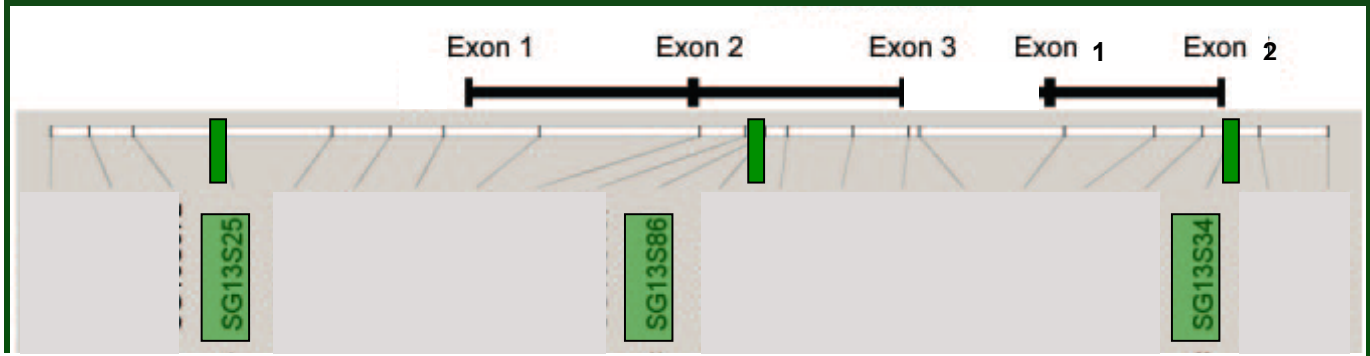
candidate region

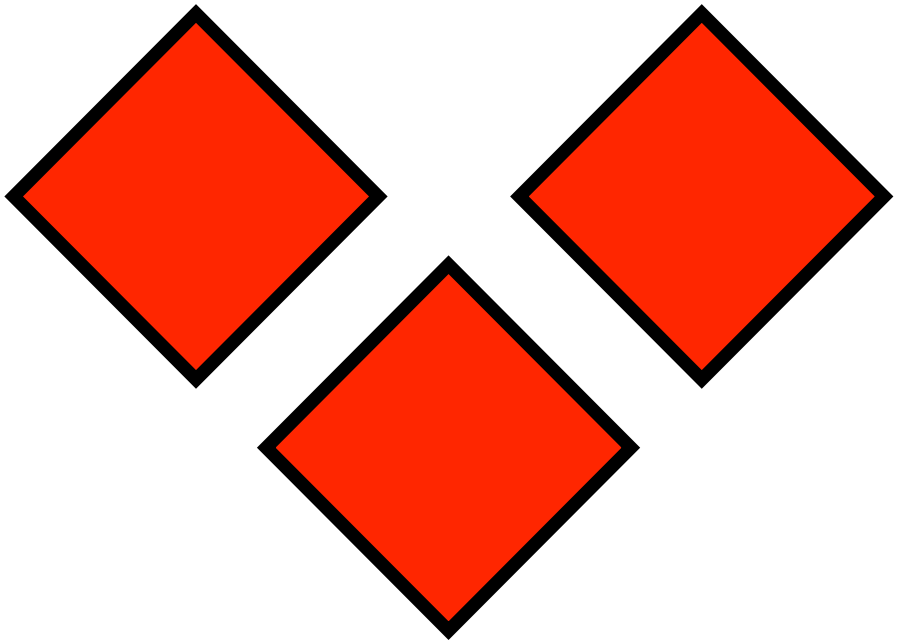
The 1000 Genomes Project Is Looking for Most Variants

Is sequencing samples from 2500 people from 27 populations around the world.

Will find almost all variants with a frequency of 1% or higher.

GWAS Finds Regions Associated with a Disease





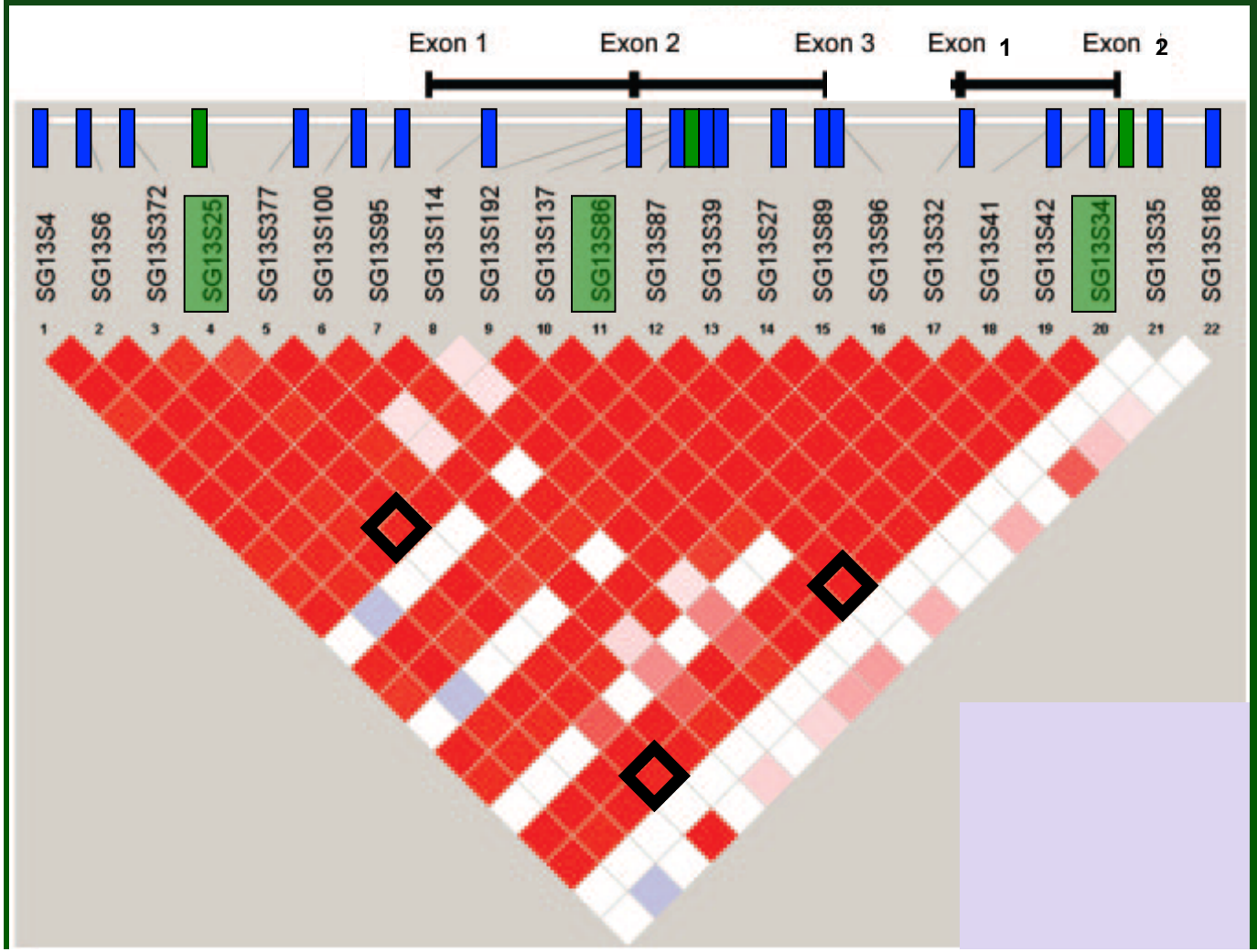
Genes

Tag SNPs from HapMap

Associations with other SNPs

http://stroke.ahajournals.org/cgi/content/full/36/4/731

Sequence or Use 1000 Genomes Data to Find All Variants in Region



Genes

Variants

Associations with other SNPs

Which variants are causal?

http://stroke.ahajournals.org/cgi/content/full/36/4/731

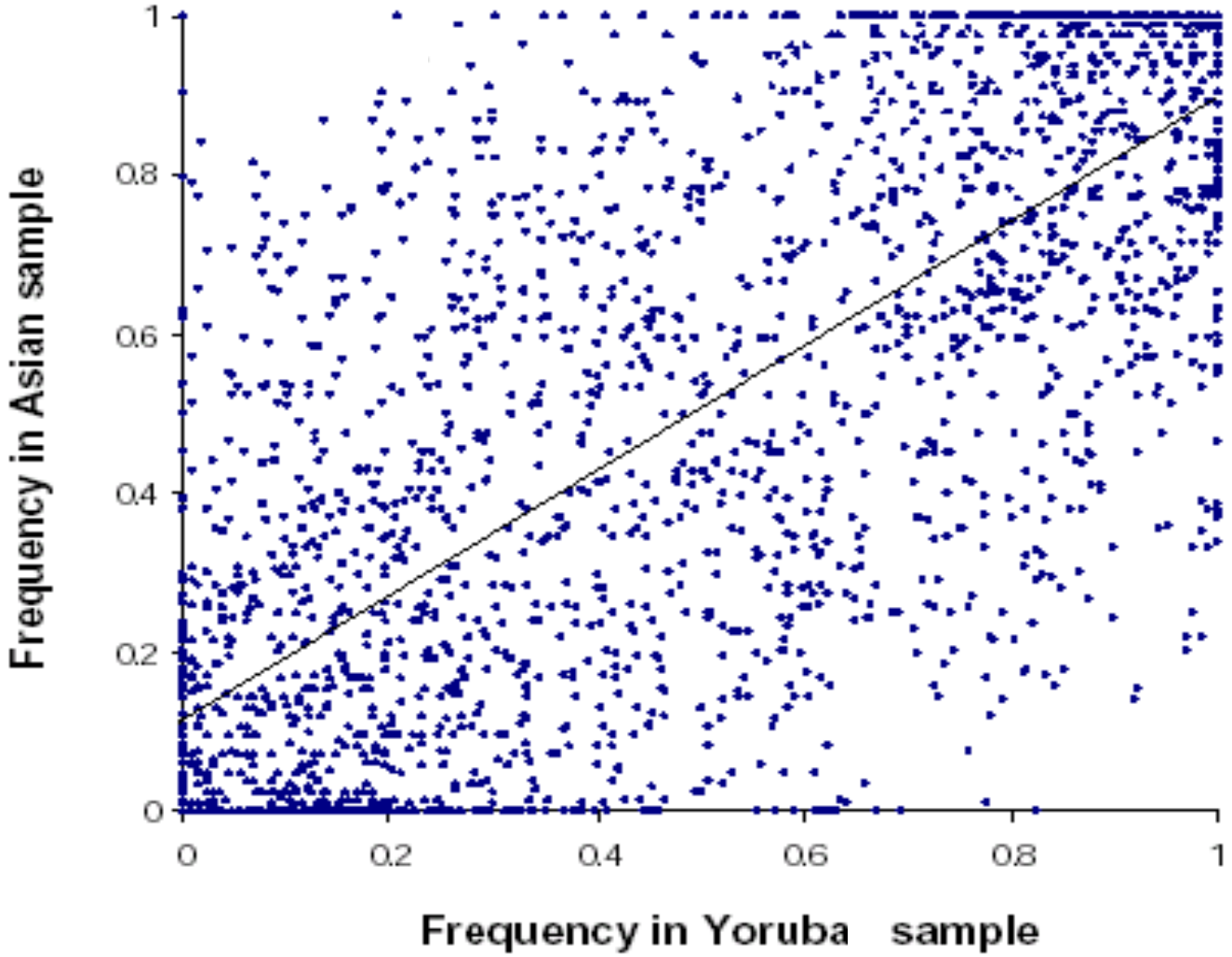
That Was the Easy Part…

Study the set of variants experimentally

- to identify the causal variants;
- to understand their function and interaction (including with the environment);
- to prevent, diagnose, and treat disease.

Allele Frequencies in Japanese / Chinese vs Yoruba Samples

Gabriel et al.



Comparing Populations

Jeff Barrett, Paul de Bakker, Stacey Gabriel, David Altshuler, Mark Daly