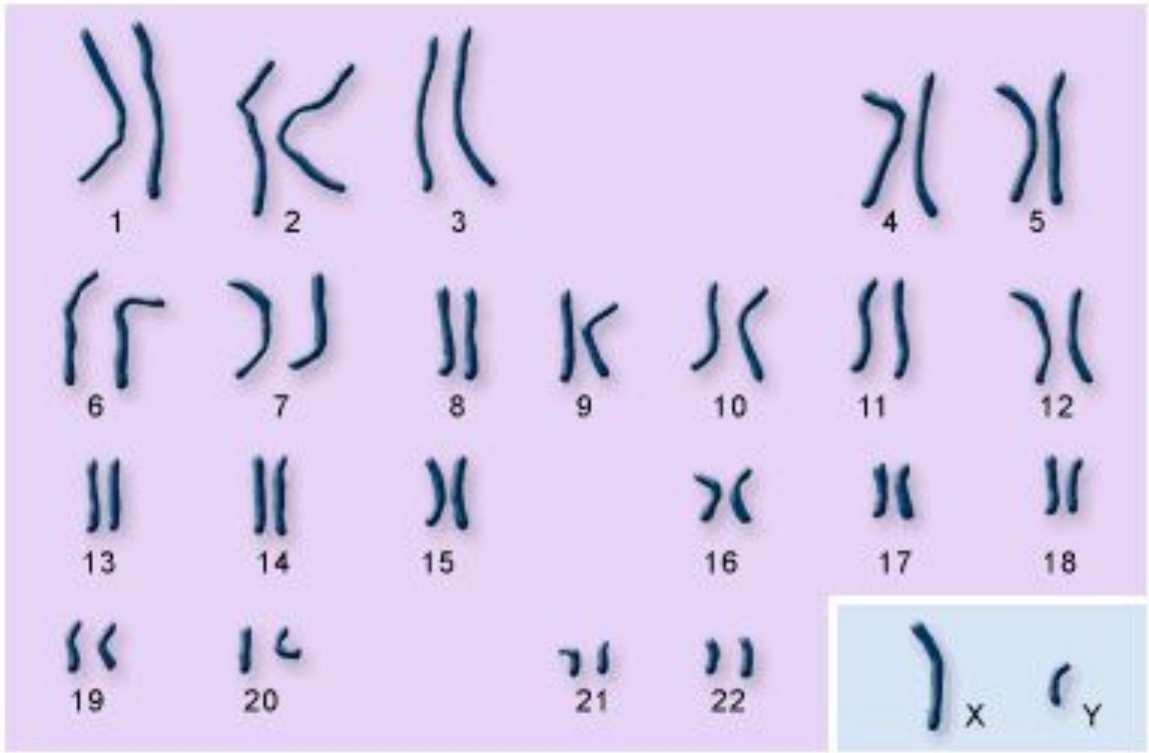
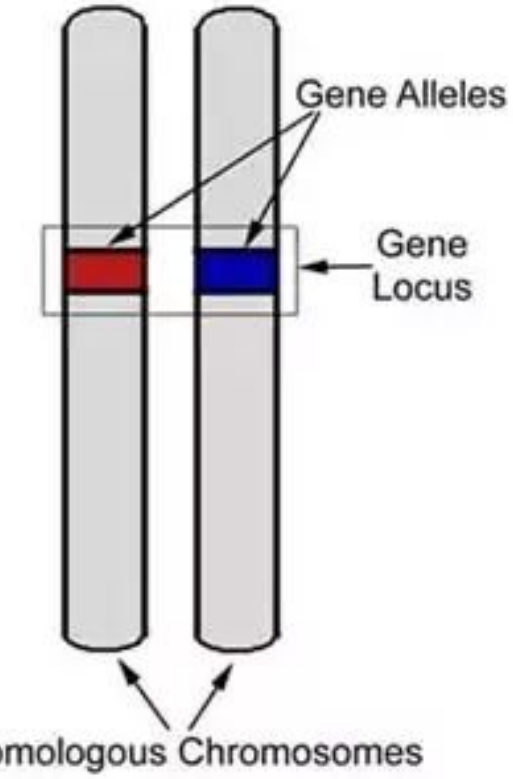
Practical 1
APOL1 variants

Karyotype



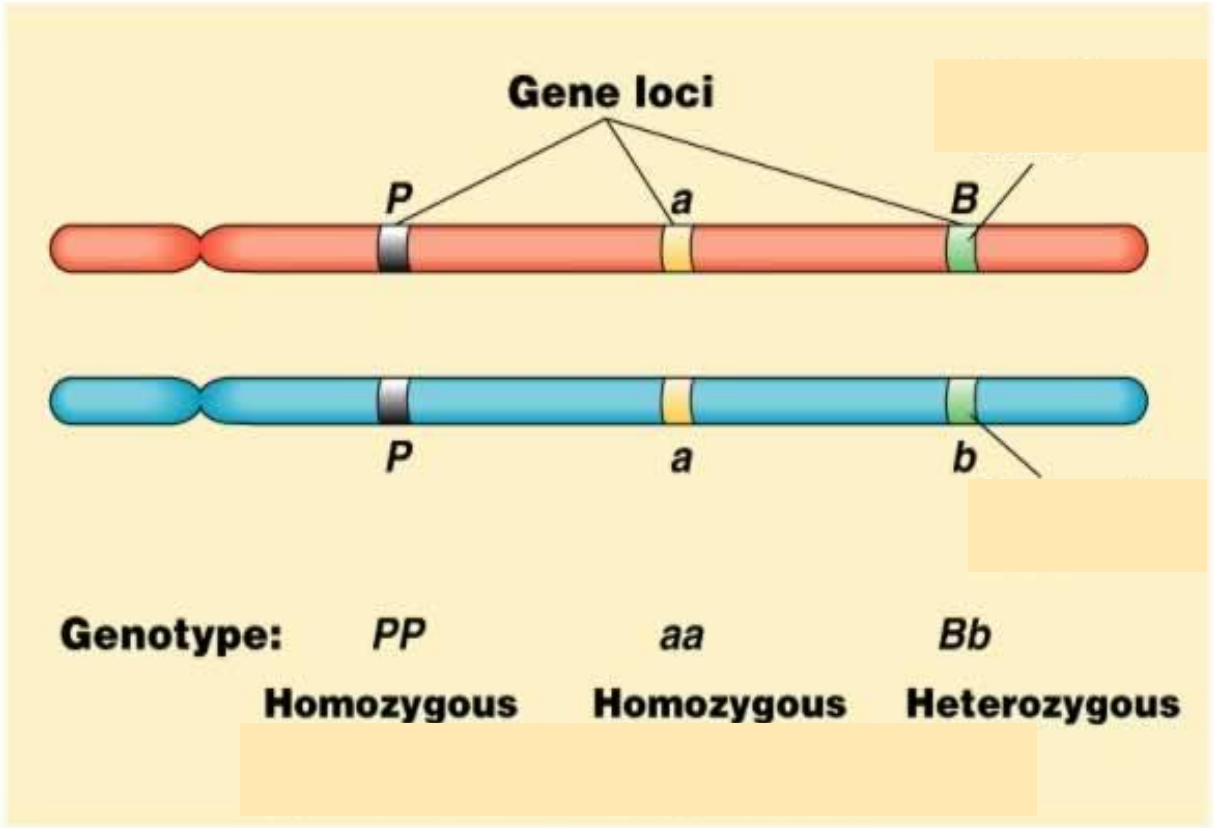
U.S. National Library of Medicine
Image © Genetics Home Reference, US National Library of Medicine: http://ghr.nlm.nih.gov

Locus and allele



A locus does not have to be a gene, it can be a single DNA base

One chromosome pair
Three loci (P, A, B)
Each locus has two alleles
- P and p
- A and a
- B and b



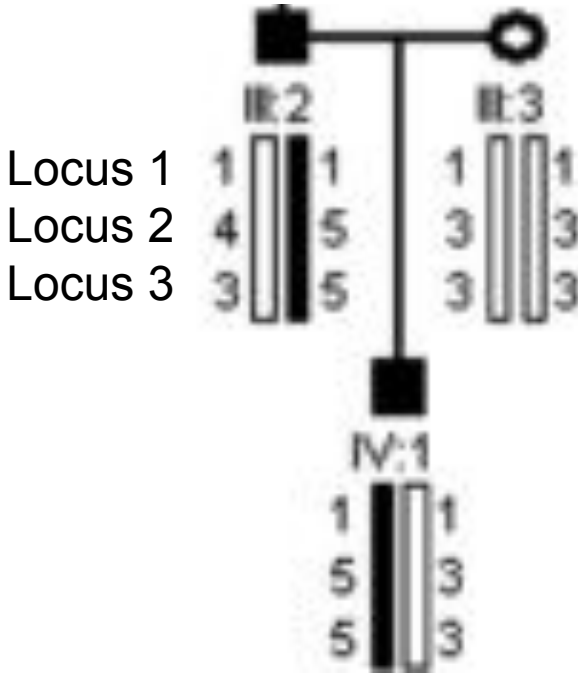
Haplotype: The co-occurrence of a group of alleles from loci that are closely linked and inherited together from a single parent (i.e they are in linkage disequilibrium).

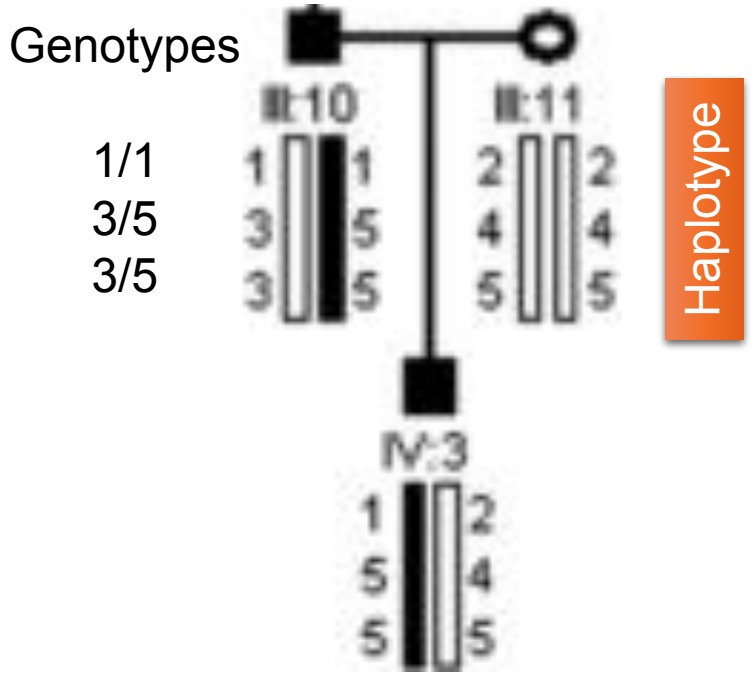
Example: Three loci in two nuclear families

Locus 1 has 2 alleles “1” and “2”

Locus 2 has 3 alleles “3” “4” and “5”

Locus 3 has 2 alleles “3” and “5”





Objectives

- To use raw genotype data to derive APOL1
  - alleles (G0, G1 and G2)
  - genotypes (G0/G0, G1/G0, G2/G0, G1/G2, G1/G1 and G2/G2)
- To understand allele and genotype frequencies
- To understand genetic association and causality

Three loci that are each bi-allelic are involved

For each locus at ***APOL1***

Locus	Alleles	Genotypes
rs73885319 A/G S342G	A or G	A/A or A/G or G/G
rs60910145 T/G I384M	T or G	T/T or T/G or G/G
Rs71785313 TTATAA(ins)/del N388Y389/del	ins or del	ins/ins or ins/del or del/del

S-serine
G-glycine
I-isoleucine
M-methionine
N-asparagine
Y-tyrosine

Haplotypes (Every person has 2 and therefore they have a diplotype) (one haplotype from each parent)

Which are the high risk variants?

Haplotype	rs73885319 A/G S342G	rs60910145 T/G I384M	rs71785313 TTATAA(ins)/del N388Y389/del
G0	A	T	ins
G1	G	G	ins
G1	G	T	ins
G1	A	G	ins
G2	A	T	del

S-serine; G-glycine; I-isoleucine ; M-methionine; N-asparagine; and Y-tyrosine

High risk genotypes

- G1/G1
- G2/G2
- G1/G2

More nuanced – could also be associated with increased risk

- G1/G0
- G2/G0

This is confusing ……..

For *APOL1* the main literature is as follows:

- G0, G1, and G2 are referred to as alleles (but they are actually haplotypes)
- G0/G0, G1/G0, G2/G0, G1/G2, G1/G1 and G2/G2 are referred to as genotypes but they are diplotypes (the 2 haplotypes in an individual)

Part 1

Table 1: Raw genotypes – not phased

Individual	rs73885319 A/G	rs60910145 T/G	rs71785313 TTATAA/del
ID 1	A/A	T/T	ins/ins
ID 2	A/G	T/T	ins/ins
ID 3	A/A	T/T	ins/del
ID 4	A/A	T/T	del/del
ID 5	A/A	T/G	ins/ins
ID 6	A/G	T/G	Ins/ins
ID 7	A/G	T/T	Ins/del
ID 8	A/G	T/T	Ins/ins

Task: Work out the diplotypes

Questions:

- Could you resolve all the '**genotypes**' – actually haplotypes?
- How many individuals are 'high risk' *APOL1* **genotypes**?
- What are the *APOL1* G0, G1 and G2 frequencies?

Part 2

Questions

- What conclusions can you draw about genotype frequencies in different African populations?
- Are the associations with the genotypes/haplotype or with the alleles?
- Is the APOL1 risk genotype causal of chronic kidney disease? Motivate your response
- Do G1 and G2 contribute equally to the kidney function phenotype?