HMB265: Human & General Genetics

Lecture 10: Population Genetics

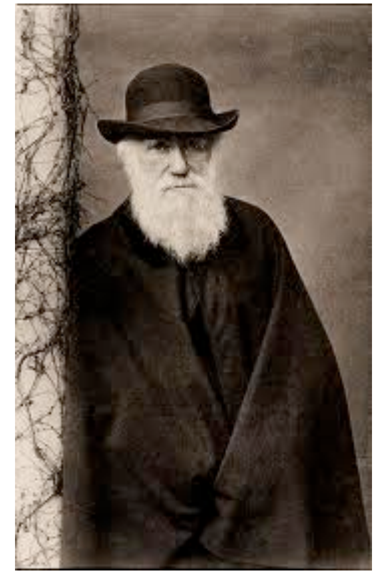
Prof. Stephen Wright

Lecture Outline

1. Human Population Genetics
2. Hardy-Weinberg equilibrium
3. Mutation-selection balance
4. Genetic drift
5. Population genetics and forensics

- Griffiths *et al*., 1st Canadian edition, Chapter 12 (emphasis on pages 391-398)

Genetic Diversity Underlies Both Genetics and Evolution



Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
1	G	G	C	A	T	C	G	C	G	C	C	G	T	T	A	C	G	T	A	G	A	G	A	G	A	G	A	G	G	T	G	A	A	T	C
2	G	G	C	A	A	C	G	C	G	C	C	G	T	T	A	C	G	T	A	G	A	G	A	G	A	G	A	G	G	T	G	A	A	T	C
3	G	G	G	A	T	C	G	C	G	C	C	G	T	T	A	C	G	T	A	G	A	G	A	G	A	G	A	G	G	T	G	A	A	T	C
4	G	C	C	A	T	C	G	C	T	C	C	G	T	T	A	C	T	T	A	G	A	G	A	G	-	-	-	-	G	T	T	A	G	T	C
5	G	C	C	A	T	C	G	C	T	C	-	-	-	T	A	C	T	T	A	G	A	G	A	G	-	-	-	-	G	T	T	A	G	T	C
6	G	C	C	A	T	C	G	C	T	C	-	-	-	T	A	C	T	T	A	G	A	G	A	G	-	-	-	-	G	T	T	A	G	T	C
7	G	C	C	A	T	C	G	C	T	C	C	G	T	T	A	C	T	T	A	G	A	G	A	G	-	-	-	-	C	T	T	A	G	T	C
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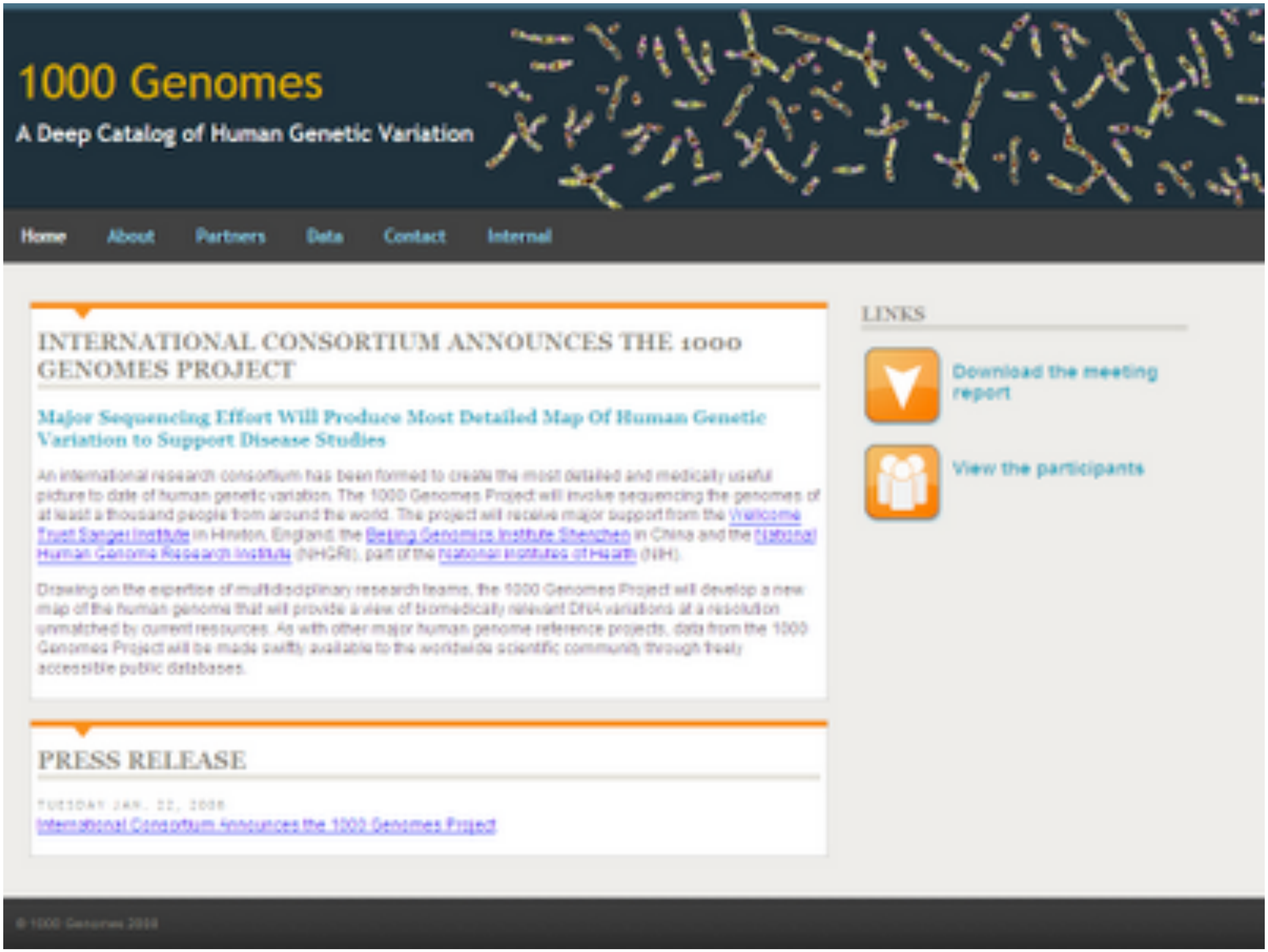
Indel (positions 11–13) — Microsatellite (positions 19–28)

Figure 18-1
Introduction to Genetic Analysis, Tenth Edition

1000 Genomes Project



Questions in Population Genetics

- how much genetic diversity is there?
- what forces act on genetic diversity?
- how do changes within populations lead to the evolution of species?

Questions in Human Population Genetics: 1) Applied Questions

1. How can we predict what proportion of the population will have a disease?
2. What factors influence the frequency of diseases?
3. How can we use genetics to infer guilt in criminal cases?
4. What mutations are responsible for common diseases in human populations?

Questions in Human Population Genetics: 2) Evolutionary Questions

1. What is the evolutionary history of human populations?
2. How much of our genome has been the target of adaptive evolution since we diverged from chimpanzees?
3. What mutations, genes and pathways were the product of adaptive evolution?
4. What genes have contributed to local adaptation?

EHJ 352:
Evolution of the Human Genome

Phenotype Frequencies Vary in Different Populations

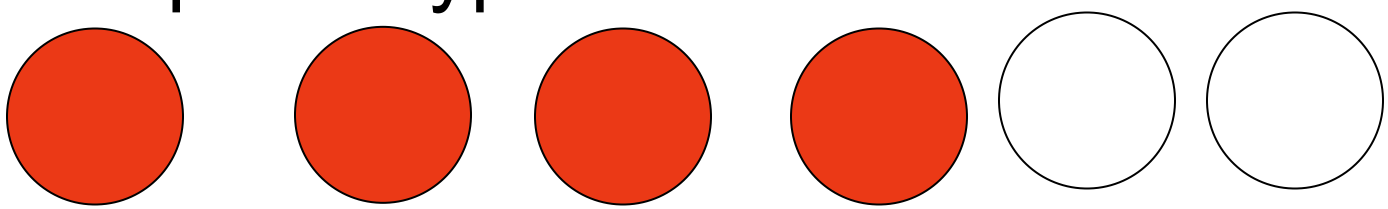
Example: Phenylketonuria (PKU), heritable metabolic disorder, autosomal recessive trait

Frequency of PKU in Various Populations

Population	Frequency of PKU
Chinese	1/16,000
Irish, Scottish, Yemenite Jews	1/5,000
Japanese	1/119,000
Swedes	1/30,000
Turks	1/2,600
United States Caucasians	1/10,000

Population Genetics: Characterizing and Understanding Genetic Diversity in Populations

phenotypes



genotypes

RR Rr Rr Rr rr rr

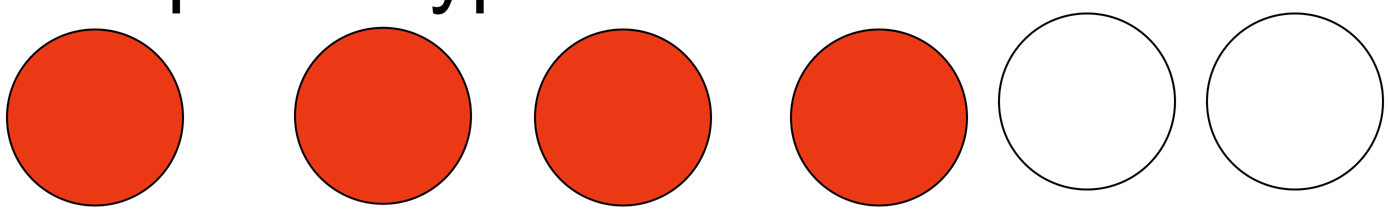
AA AT AT AT TT TT

alleles

A A A T A T A T T T T T

Population Genetics: Characterizing and Understanding Genetic Diversity in Populations

phenotypes



phenotype frequency= 2/3 red, 1/3 white

•cannot determine genotype frequencies directly from phenotypes

Population Genetics: Characterizing and Understanding Genetic Diversity in Populations

genotype frequencies

RR Rr Rr Rr rr rr

RR= 1/6

Rr= 1/2

rr= 1/3

counting allele frequencies:
p = frequency of R, q = frequency of r

RR Rr Rr Rr rr rr

$$p = \frac{\textit{2(\# RR homozygotes) + (\# Rr)}}{\text{total x 2}}$$

=(2+3)/12=5/12

$$q = \frac{\text{2(\# rr homozygotes) + (\#Rr)}}{\text{total x 2}}$$

Genotypes in first generation	RR		Rr	rr
Number of individuals in first generation	N_{RR}		N_{Rr}	N_{rr}
Allele types in first generation		R	r	

Allele frequencies in first generation

$$p = \text{frequency of } R \text{ gametes} = \frac{2N_{RR} + N_{Rr}}{2N_{\text{total}}}$$

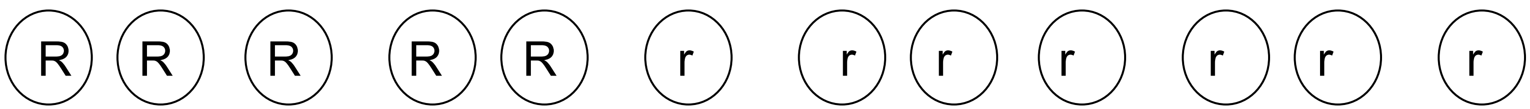
$$q = \text{frequency of } r \text{ gametes} = \frac{N_{Rr} + 2N_{rr}}{2N_{\text{total}}}$$

$$N_{\text{total}} = N_{RR} + N_{Rr} + N_{rr}$$

$2N_{\text{total}}$ = total chromosomes

Predicting Genotype frequencies in the next generation

- depends on allele frequencies
- can use probability theory



Predicting Genotype frequencies in the next generation

- depends on allele frequencies
- can use probability theory

R R R R R r r r r r r r

expected frequency of RR: $(p \times p) = p^2$
expected frequency of Rr: $(p \times q) + (q \times p) = 2pq$
expected frequency of rr: $(q \times q) = q^2$

Predicting Genotype frequencies in the next generation

Sperm

Eggs	Allele R, Frequency p	Allele r, Frequency q
Allele R, Frequency p	RR p^2	Rr pq
Allele r, Frequency q	Rr pq	rr q^2

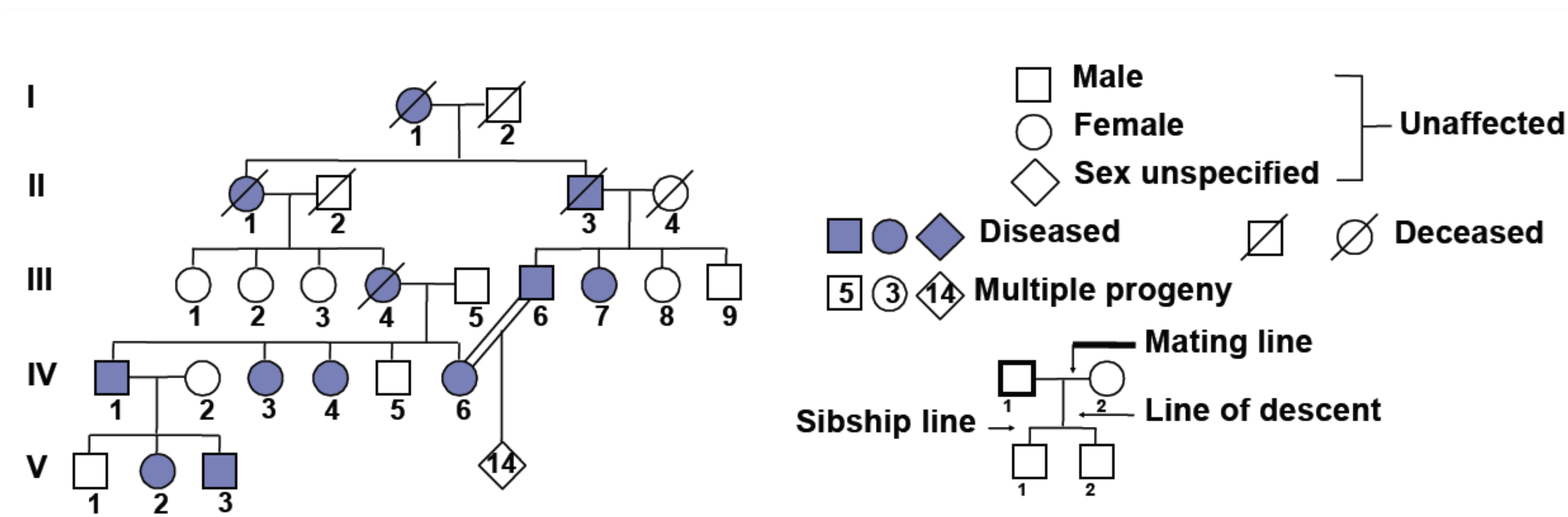
Hardy- Weinberg Equilibrium

Determining Allele Frequencies and Genotype frequencies assuming Hardy-Weinberg equilibrium

The frequency of a recessive disorder is found to be 3% in a population. Estimate the frequency of heterozygous carriers in the population. assuming Hardy-Weinberg equilibrium.

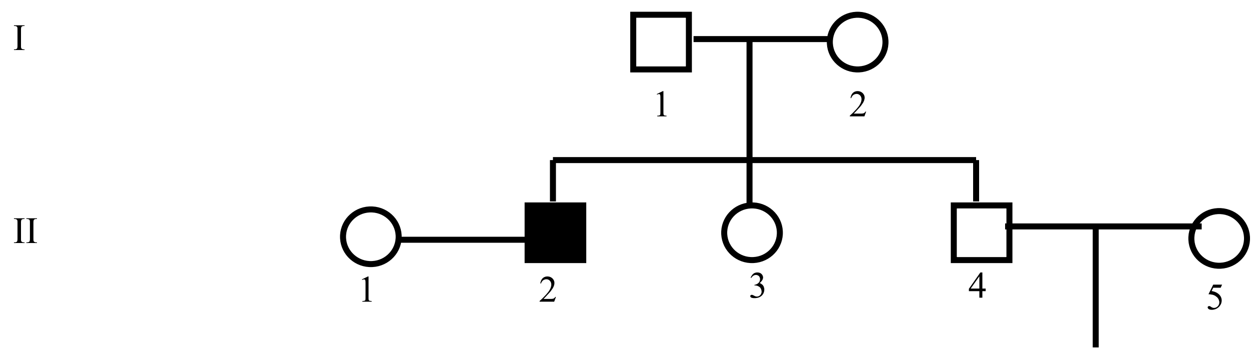
$3\% = q^2$
q=square root (0.03) = 0.17
p= 1-q=0.83
Carriers=2pq=0.28

Rare Diseases and Pedigrees



Incidence of Huntington's disease in US: approx. 5/100,000
Frequency of homozygous wild type= 0.99995 = p^2
p=square root(0.99995)=0.99998
q=1-p=0.00002
homozygote frequency=q^2= approx. 1 in 4 billion!

Common Diseases and Pedigrees



Cystic Fibrosis is caused by a recessive allele at a frequency of 0.025 in Caucasian populations

What is the probability that the first child of II-4 and II-5 has the disease?

Probability that 2-4 has allele: 2/3

Probability that 2-5 has allele: $2pq/(2pq+p^2)=0.04875/0.9994 = 0.04878$

Probability that child has disorder if both parents heterozygous:1/4

2/3 x 0.04878 x 1/4 =0.00813

13 x increased risk compared with general population ($q^2=0.000625$)

Why Hasn't Natural Selection Eliminated Diseases from the Population: 1) Recurrent Mutation

- Disease allele frequency will reflect a balance between the rate of mutations causing the disease and the strength of natural selection
- The weaker selection, or the higher the mutation rate, the higher the incidence of disease
- Recessive mutations are masked in heterozygotes

Why Hasn't Natural Selection Eliminated Diseases from the Population: 1) Recurrent Mutation

- Two forces: mutation rate, u and selection coefficient, s
- E.g. a recessive mutation gives an individual the probability of surviving and reproducing of 1-s
- A severe disease might reduce survival probability by 0.25, giving a fitness of 0.75 relative to wild type

Why Hasn't Natural Selection Eliminated Diseases from the Population: 1) Recurrent Mutation

$$f = \sqrt{\frac{\mu}{s}}$$

- Expected frequency of a recessive deleterious mutation is increased by mutation, decreased by selection

Why Hasn't Natural Selection Eliminated Diseases from the Population: 2) Genetic Drift

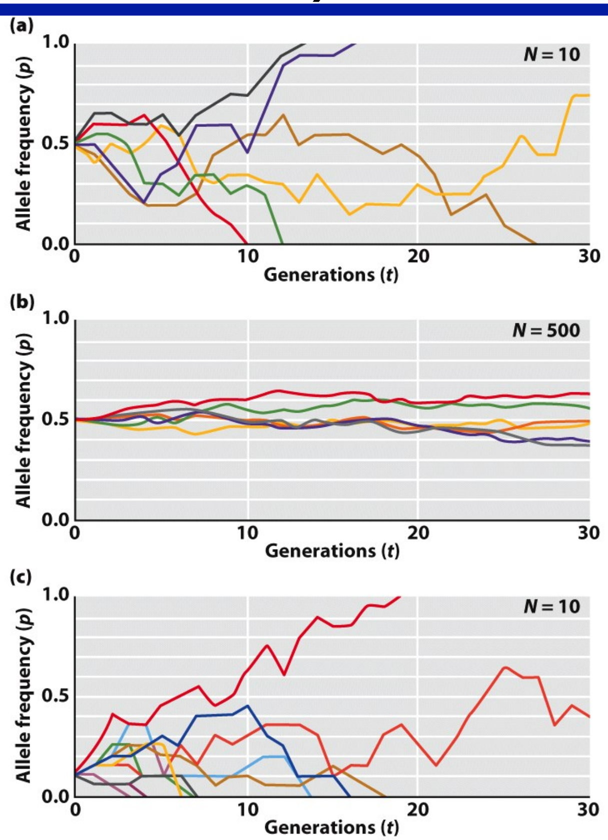


Figure 18-18
Introduction to Genetic Analysis, Tenth Edition

- In particular populations, disease allele frequencies can increase by chance

Genetic Drift May Explain Some Differences in Disease Incidence

The highest frequencies of HD are found in Europe and countries of European origin, such as the United States and Australia. The lowest documented frequencies of HD are found in Africa, China, Japan, and Finland.

Population	Frequency of HD (cases per million people)
South Africa (blacks)	0.6
Japan	1-4
Hong Kong	3.7
Finland	6.0
Europe & countries of European descent	40-100
-Northern Ireland	64
-South Wales	76.1
-Scotland (Grampian Region)	99.4
-United States	100

-frequency of Huntington's Disease by geographic area

Why Hasn’t Natural Selection Eliminated Diseases from the Population: 3) Pleiotropy

- Disease alleles may confer a selective advantage associated with another trait
- Positive selection or balancing selection could maintain disease alleles

Why Hasn’t Natural Selection Eliminated Diseases from the Population: 4) Novel environments

- Alleles that were advantageous in our past environment may now be deleterious
- E.g. sodium retention hypothesis: adaptive allele that maintains sodium in salt-limited diet now causes hypertension

1) In humans, brachydactyly is a dominant condition. 6,400 people in a population of 10,000 exhibit the disease phenotype (1,600 are *BB*; 4,800 are *Bb*) and 3,600 have the normal phenotype (*bb*). What is the frequency of the *b* allele?

A) 0.60

B) 0.40

C) 0.36

D) 0.48