1 # Midterm Results

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3 # Traits of Simple Inheritance (cont.)

4 ## Other Red Blood Groups

- About 27 different blood group systems recognized for human blood

5 ## Rh (Rhesus) Blood Group

- Discovered in 1940 by Karl Landsteiner and Alexander Weiner
- One of the most complexly inherited and clinically important blood group systems
- Involves 45 different antigens on the surface of red blood cells all inherited through Mendelian inheritance

6 ## Two Theories As To the Inheritance of the Rh System

- Fisher and Race Theory of Inheritance
- Weiner Theory of Inheritance

7 ## Fisher and Race Theory

- Three closely **linked** sets of genes
- Each loci with two or more alleles:
  - Locus 1: 2 alleles: C, c
  - Locus 2: 2 alleles: D, d
  - Locus 3: 2 alleles: E, e

8 ## Linkage

- Two or more alleles located at loci close to one another on the same chromosome

9 ## Linkage

- Because of linkage, alleles are passed to the offspring as **haplotypes**
- **Haplotypes:** combinations of genetic traits that can be inherited as a block due to their presence on the same chromosome (usually closely positioned together)
- In this example the haplotype is AB or ab

10 ☐ ## Haplotypes in the Rh System

- Because the genes are closely **linked** the alleles are inherited in blocks called **haplotypes**
- 8 possible haplotypes: CDE, CDe, CdE, Cde, cDE, cdE, cde, and cDe
- Each individual has two haplotypes (one from each parent) for the Rh system (CDE/cde, CdE/Cde, etc. – these too are sometimes referred to as haplotypes)

11 ☐ ## Haplotypes in the Rh Factor (Fisher and Race)

- So an individual with the genotype CDE/cde crossed with an individual of the genotype Cde/cdE:

Gametes	Cde	cdE
CDE	CDE/Cde	CDE/cdE
cde	cde/Cde	cde/cdE

12 ☐ ## The Rh Factor: Positive vs. Negative

- The Rh positive and Rh negative is a function of the D and d alleles only, where D is dominant over d and the phenotype is Rh positive in the homozygous dominant form (DD) or the heterozygous form (Dd). The genotype dd results in a phenotype of Rh negative.

13 ☐ ## Antigens and Antibodies

- Rh+ individuals carry Rh+ antigens
- Rh- individuals carry Rh- antigens
- Rh- individuals can produce antibodies against Rh+ antigens but only through exposure as in transfusions or pregnancy

14 ☐ ## Weiner Theory

- A single locus with eight allelic genes (R^O, r', r", R^1, R^2, R^Z, r^y, r – these correspond to the eight haplotypes of Fisher and Race) each responsible for determining an antigen that can combine with three or more kinds of antibodies

15 ☐ ## Location of the Rh Factor

- Since the two theories were proposed, scientists have located the Rh system on Chromosome 1 where there are three closely linked loci in the order of DCE

16 ☐ ## Selective Mechanisms in the Rh Blood System

- Rh Incompatibility (*Erythroblastosis fetalis*)

- Selective Interaction: Rh factor and ABO

- Non-Infectious Disease – Rheumatic Fever

17 Rh Incompatibility

- In the Rh factor, antibodies are induced following exposure to antigens of the opposite blood type (as opposed to those antibodies genetically determined for in the ABO Blood System)

- Rh Incompatibility can result when a Rh negative mother (d/d) and a Rh positive father (D/D or D/d) produce an Rh positive fetus (D/d)

18 Rh Incompatibility

- The Rh positive fetus carries the antigen D which the mother lacks (she's d/d).

19 Rh Incompatibility

- Disruption of the placenta at parturition allows some of these D-positive fetal cells to enter the maternal bloodstream
- The mother's body responds by producing anti-D antibodies)

20 Rh Incompatibility

- In subsequent pregnancies anti-D antibodies may cross the placental barrier and damage the red blood cells of the fetus

- The fetus can be born with severe anemia (**haemolytic disease of the newborn**, HDN – **Erythroblastosis fetalis**) – occurs in one out of 150 to 200 newborns – can range from mild to a fatal form and when fatal usually kills shortly before or after birth

21 Modern Medicine and Rh Incompatibility

- Rh Incompatibility can be treated if discovered through blood typing

- It can be remedied through injections of antiserum (anti-D) in the mother during the first pregnancy that destroys the fetal blood cells before antibodies can be made.

22 Rh Incompatibility as a Selective Force

- Rh Incompatibility is a selective force acting on the Rh factor specifically through selection against the heterozygote (D/d) in infants

- Consequently, over time the rarer allele should be eliminated first from the population and the more frequent allele should become fixed at 1.

- However an examination of the world distribution of both alleles indicates that neither alleles has reached fixity suggesting other balancing factors.

23 ☐ **World Distribution of the Rh Factor**
CDe and cDE (both Rh Positive)

24 ☐ **World Distribution of the Rh Factor**
cde (Rh negative) and cDe (Rh Positive)

25 ☐ **World Distribution of the Rh Factor**

- Haplotypes CDe, cDE, cDe, and cde are the most common, all others are rare
- CDe and cDE are in very high frequencies in Europe and hits their lowest levels in sub-Saharan Africa. Also very common in Native Americans and Asiatics
- cDe reverses the pattern, being found most often in sub-Saharan Africa and rare elsewhere
- cde reaches its highest frequency in Europe and is uncommon in Africa and absent in Asia and the Americas

26 ☐ **Selective Interaction: Rh and ABO**

- ABO Incompatibility more common in Africa; Rh Incompatibility more common in western Europe
- Maternal-fetal pairs doubly incompatible for ABO and Rh actually run less risk of fetal death than those incompatible for only one system
- Presence of anti-A or anti-B antibodies in mothers may destroy the red blood cells carrying the Rh positive antigens before the mother can develop antibodies

27 ☐ **Correlation of Non-Infectious Diseases and Rh Factor**

- Higher than expected frequencies of the D allele amongst sufferers of Rheumatic fever (balanced polymorphism) probably through a selection for the heterozygote but we don't yet know the selective advantage of the heterozygote over the two homozygous genotypes

28 ☐ **Minor Blood Groups**

- A large number of less well-known groups
- Often these groups are under control of a single pair of alleles
- Little clinical value because they are rare or have no debilitating effect
- Are of anthropological interest because they are valuable as genetic markers and allow comparison of populations to infer relationships and past histories and may present evidence of selective mechanisms involved in their maintenance at polymorphic levels

29 ☐ **MN(S) Blood Group**

- Discovered in 1927 by Karl Landsteiner and Levine
- MN is a codominant system
- No medical importance because no antibodies are induced or occur genetically
- Presence of a second linked-trait called S – two alleles S and s which are codominant
- Thus there are four potential complexes or haplotypes: MS, Ms, NS, Ns

30 ☐ **World Distribution of the MNS Blood System (M allele)**

31 ☐ **World Distribution of MNS System**

- Seemingly neutral selection of the MNS system has produced an even distribution among most worlds populations
- Notable exceptions include Native Americans who have a high frequency of haplotypes MS and Ms and Australian Aborigines who have an extremely high frequency of N
- Scientists are unsure of the selective mechanisms involved in maintaining this polymorphism

32 ☐ **Duffy Blood Group**

- Located on the first chromosome
- A single locus system with three alleles (Fy^a, Fy^b, Fy^o – also sometimes 4)
- a and b are codominant and o(4) is recessive

33 ☐ **World Distribution of the Duffy Blood System**

- World distribution is at first glance confusing
- Europeans and Asians are primarily Fy^a (about 90%) with the remainder Fy^b. Fy^o is rare.
- Highest frequencies of Fy^o are found in West and Central Africa (often reaching 100%) and high frequencies have been noted in Middle Eastern populations

34 ☐ **Selective Mechanisms for the Duffy Blood Group - Malaria**

- Unsure of the selective value of Fy^a and Fy^b but a selection mechanism for Fy^o has been identified
- Individuals that are homozygous recessive (Fy^o/Fy^o) are completely resistant to a form of malaria caused by the parasite *Plasmodium vivax*. It has been suggested that the vivax parasite enters the blood by clinging to the Fy^a and Fy^b antigens but not to the Fy^o (they carry no antigens)
- Vivax however, is absent in West and central Africa where the highest frequency of Fy^o occurs (but may be so because of past evolution -- genetic drift – fixed o in these populations and prevented the migration of the parasite into these regions)

35 ☐ **Xg Blood Group**

- Single locus, two allele system: Xga and Xg with Xga being dominant (carries the antigen) over Xg (lacks the antigen)
- **Sex-linked condition** (found on the short arm of the X chromosome) but not found on the Y chromosome

36 ☐ **Xg Blood Group in Females and Males**

	Genotypes	Phenotypes
Females	XgaXga	Xg+
	XgaXg	Xg+

	XgXg	Xg-
Males	XgaY	Xg+
	XgY	Xg-

37 ☐ **Xg Mating Cross:**

Xga- male with Xga+ female (homozygous)

- 100% of sons are positive
- Sons are said to be hemizygous for Xga
- 100% of the daughters are heterozygous positive

38 ☐ # White Blood Cell Antigens

39 ☐ ## White Blood Cells

- Leukocytes – White Blood Cells – fight infections – not confined to the blood vessels – several types of WBCs but granulocytes and macrophages are the most common
- WBC are a highly variable antigen system able to respond to millions of "non-self" substances over the course of an individuals lifetime
- Scientists have identified a large complex system of WBC antigen types known as the Human Leukocyte Antigens (HLA) or the Histocompatibility System

40 ☐ ## Histocompatibility System (HLA)

- Most polymorphic system of inherited traits known so far in humans
- Antigen types are determined by several closely linked loci on chromosome 6 and are designated: HLA-A, HLA-B, HLA-C, HLA-D, HLA-DQ, and HLA-DR
- Eight to 40 alleles at each locus creating a huge number of different haplotypes

41 ☐ ## Distribution of the HLA Haplotypes

42 ☐ ## Linkage Disequilibrium and HLA

- The occurrence of some genes together more often than is expected by chance

- HLA A1 is commonly associated with B8 and DR3 and A2 with B7 and DR2, presumably because the combination confers some selective advantage.

43 ☐ **Histocompatibility Haplotypes and Selective Mechanisms**

Frequent associations reported between HLA haplotypes and specific diseases:

A3 antigen	haemochromatosis	
B27 antigen	ankylosing spondolitis (chronic	inflammation of tendons and ligaments
B8 antigen	Celiac disease (inflammation of the	intestinal tract)
DW2	Multiple sclerosis	
BW53, DRB1, DQB1	Some protection against malarial	infection

Some association reported for HLA haplotypes with rheumatoid arthritis, type I diabetes, Hodgkin's disease, acute lymphatic leukemia, thyrotoxicosis, and schizophrenia

Very useful for tracking human variability including reconstructing population migrations and ancestral relationships

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Serum Protein Polymorphisms

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Protein Polymorphisms

- Polymorphisms found in proteins found within the blood serum
- Proteins are numerous and include albumins, groups specific (GC), globulins, lipoproteins, transferrins, and haptoglobins

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Immunoglobulins (Gamma Globulins)

- Antibodies associated with fighting foreign antigens introduced as mold, pollen grains, or the proteins of infectious organisms
- Five types of immunoglobulins (IgG, IgA, IgM, IgD, and IgE)
- IgG is the most extensively studied and shows a great deal of polymorphism and is described as the **GM System**

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GM System (IgG)

- Not clear how many loci are involved but all are closely linked on the 14^{th} chromosome and each loci carries several codominant alleles
- All are inherited as haplotypes such as Gm (1, 17, 21); Gm (1, 2, 17, 21); Gm (3, 5, 13, 14)
- Gm numbers from 1 to 23 and then Inv 1 to 3 represent different antigen types (+ and -)

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Gm System (IgG)

- The Gm system is incredibly useful in exploring population relationships and histories

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Bushman Admixture (Gm 1, 13) Haplotype

50

Haptoglobins

- Haptoglobins are part of the $Alpha_2$ globulins and have the capacity to combine with hemoglobin to recycle it and are also a resource of amino acids for protein synthesis
- Three types of haptoglobins controlled by a pair of non-dominant alleles (Hp1 and Hp2) at a single locus on Chromosome 16:
  - Hp1Hp1 Haptoglobin 1-1
  - Hp1Hp2 Haptoglobin 1-2
  - Hp2Hp2 Haptoglobin 2-2

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World Distribution of Haptoglobin Variation

52

Haptoglobin Distribution

- Wide variation in gene frequencies from as little as 20% to 80% for either gene
- Hp1 appears to be the most frequent allele in tropical populations (have a high parasite load that increases the rate of red blood cell destruction)
- Hp1 has a greater affinity for hemoglobin and hence higher binding capacity – therefore an advantage in these areas

53 ☐ ## Transferrins

- Transferrins are beta-globulins – they bind atoms of iron and transports them to tissues as needed and also assists in the absorption of iron through tissue membranes
- Transferrin exists in at least 17 different variants and each seems to be under genetic control by an autosomal nondominant allele
- Variants are defined into three haplogroups:
  - TfC Most variants
  - TfD Slower group
  - TfB Only a few variants

54 ☐ ## Transferrins

- Possibly like Haptoglobins found in regions with high parasite loads – increase rate of red blood cell destruction
- Increase in combining capacity would be advantageous in areas where chronic anemia is common

55 ☐ # Non-Blood Related Polymorphisms

56 ☐ ## Inborn Errors of Metabolism

- Phenylketonuria
- Albinism (occulocutaneous type)
- Variations in Sugar Metabolism
  - Deficiency in Lactase Enzyme
  - Galactosemia
- Other Metabolic Defects
  - Errors in Purine Metabolism
  - Errors in Pyrimidine Metabolism
  - Tay-Sachs Disease
  - Cystic Fibrosis

57 ☐ ## Other Polymorphisms

- Taste Sensitivity
- Cerumen (Ear Wax)