Genetic Polymorphism

Mutations lead to:

Genetic diversity among individuals

Deleterious mutations

Disease

Many mutations are not deleterious

May effect phenotype

Over generations, the influx of new nucleotide variations has ensured a high degree of genetic diversity and individuality.

Genetic Variation

Some mutations in the gene(coding sequence) → Variant protein

Variant protein → Altered structure and

Altered structure and → Altered properties

Some mutation in the gene DNA (coding sequence) → Variant protein

Variant protein → No major change in structure

No major change in structure → Normal properties

Some mutations in DNA (non-coding regions) → No effect on proteins

Estimates of gene mutation rates

Mutation Rates: are expressed as the number of new mutations per locus per generation (These are calculated using deleterious mutations with an obvious effect on phenotype)

Calculated to range from 10^{-4} to 10^{-7} mutations per locus per generation.

Based on mutation rates it is calculated that each new zygote is expected to contain around 100 new base pair combinations not present in the genome of either parents.

~100 new base pair combinations

Genetic Polymorphism

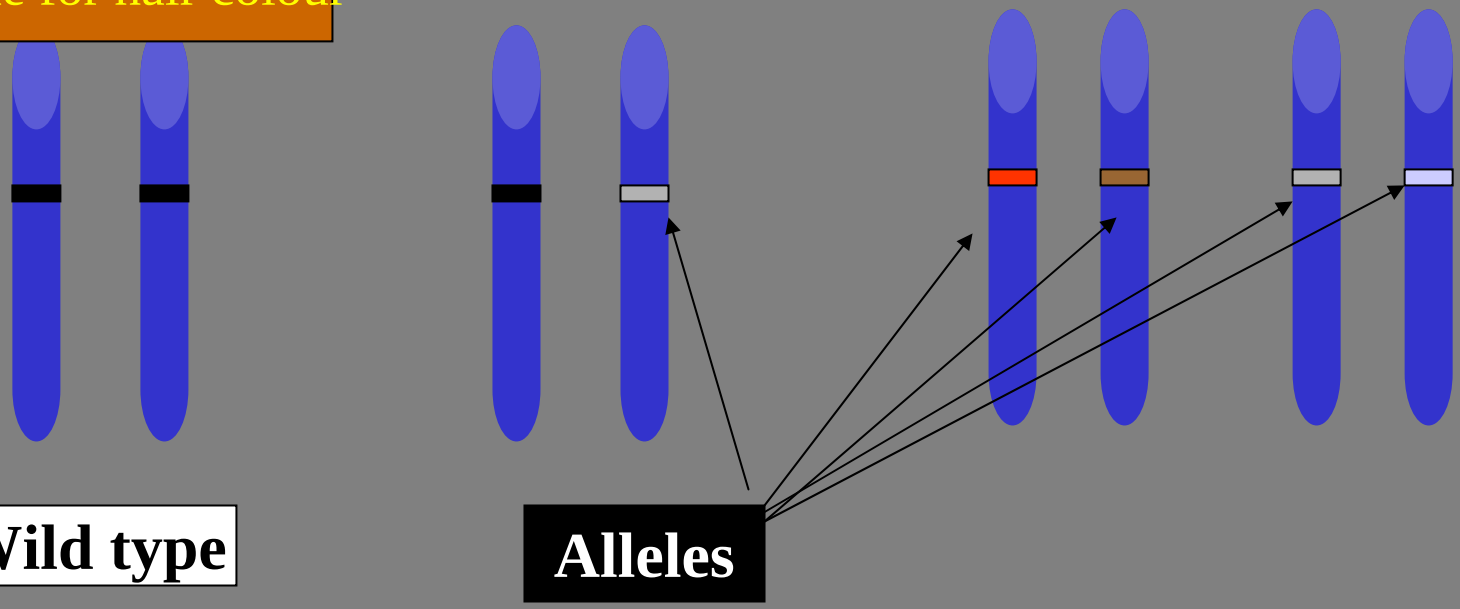
Many genetic loci are characterised by a number of relatively common alleles, thus producing many phenotypes in normal population

Alleles that occur at a frequency of > 1% are said to be **polymorphic variants**

Alleles that occur at a frequency of < 1% are said to be **rare variants**

Polymorphisms are common, particularly in non-coding regions of DNA

e.g. Gene for hair colour



If there are two or more alleles and the rarest occurs at a frequency of more than 1% then this loci will be considered polymorphic.

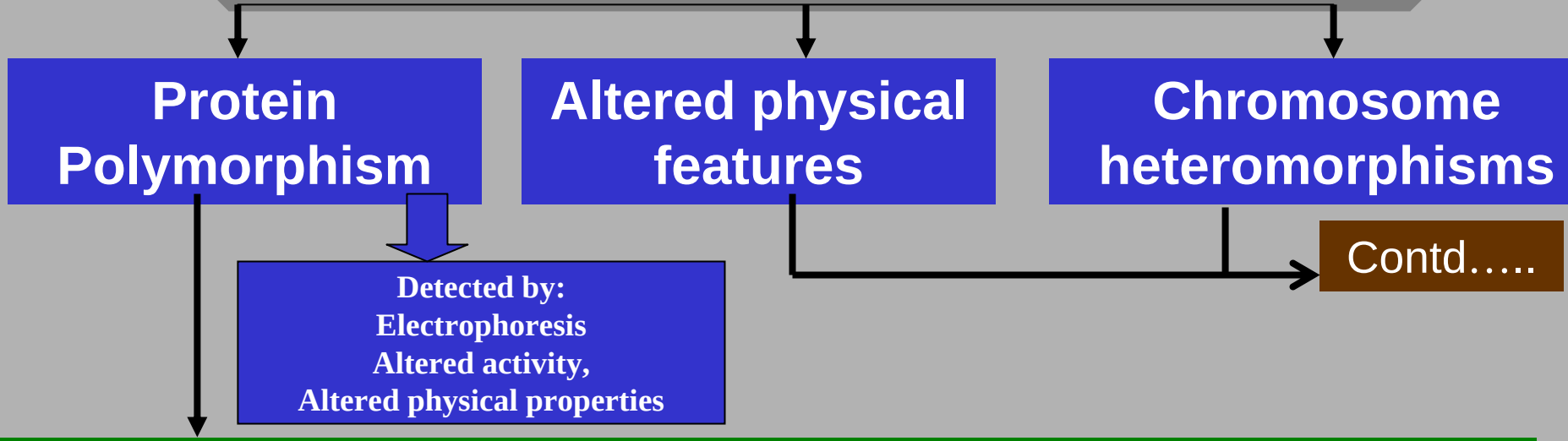
Types of Polymorphisms (Defined by the method of detection)

- DNA Polymorphism
  - Detected by altered DNA sequences
- Protein Polymorphism
- Altered physical features
- Chromosome heteromorphisms

Contd…..

- **Restriction fragment length polymorphism (RFLPs):**
  - Inherited variations in DNA sequence, resulting in gain or loss of a site recognised in the number of nucleotides between such sites (see next slide – Figure)
- **Variable number of tandem repeats (VNTRs):** Involve variations in the number of short, repeated DNA sequences between restriction sites (Extremely polymorphic, valuable in forensic medicine)

Types of Polymorphisms (Defined by the method of detection) Contd…



- Enzyme variant: altered enzyme activity, electrophoretic mobility, thermostability or other physical properties e.g.G-6-PD deficiency.

- Antigenic variants: altered antigenic properties: e.g. ABO blood groups.

Protein Polymorphism

- Several proteins exist in two or more relatively common, genetically distinct and structurally different form.
- The causes of polymorphic forms:

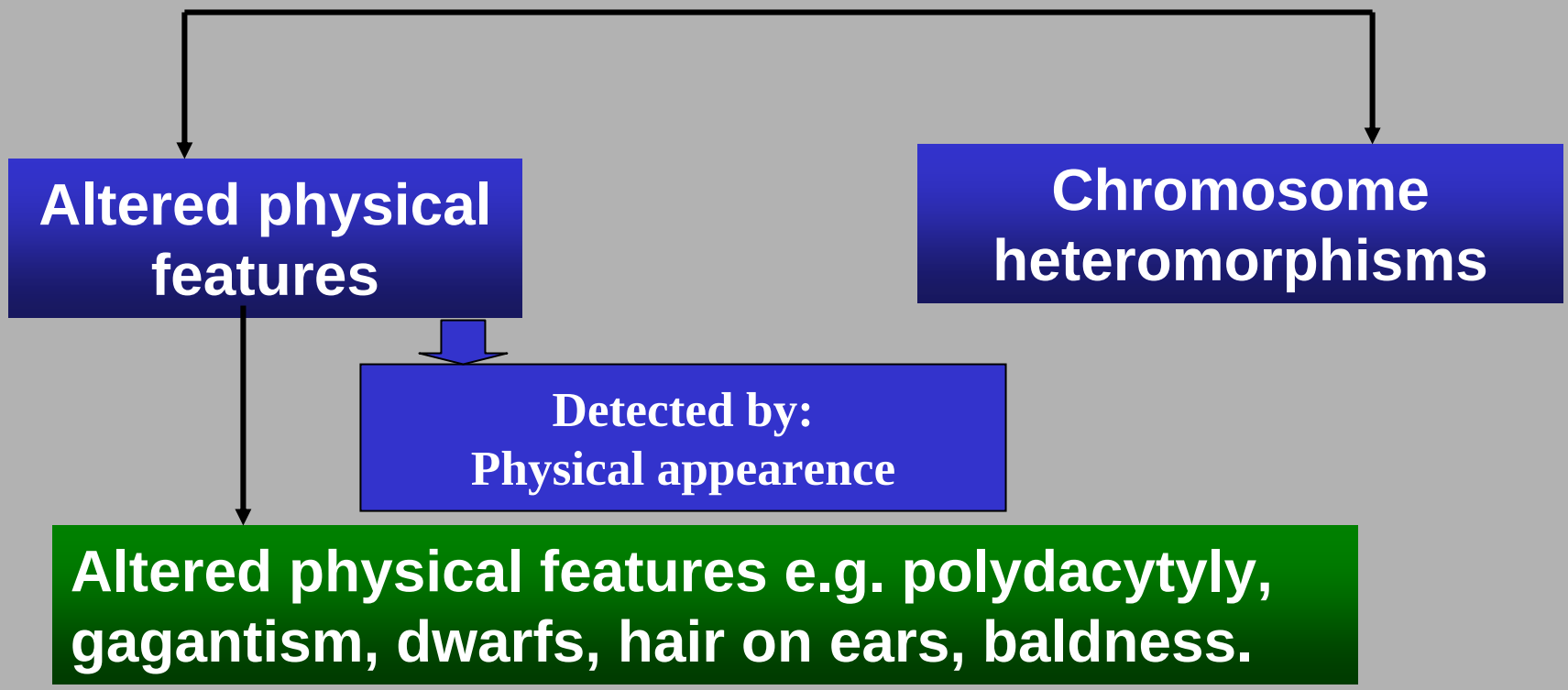
  Mutation in or around gene.
- The polymorphic forms may or may not be:

  Structurally and functionally distinct.

  e.g. ABO Blood groups, Transferrin, Hb, α1 antitrypsin.

Not all variant proteins have clinical consequences

Types of Polymorphisms (Defined by the method of detection) Contd…



Types of Polymorphisms (Defined by the method of detection) Contd…

Chromosome heteromorphisms

→ **Detected by:**
Cytogenetic studies
FISH

- **Heritable differences in chromosomal appearances, e.g.**
  - **Variations in the size of the Y chromosome long arm.**
  - **Variation in the size of the centromeric heterochromatin.**
  - **Variation in satellite size and structure.**
  - **The occurrence of fragile sites.**

Genetic diversity among normal individuals

Chromosome heteromorphisms

- Generally, the karyotype of normal persons of the same sex are quite similar.
- However, occasional variants are seen on staining. These are called heteromorphisms.
- These reflect difference in amount or type of DNA sequence at a particular location along a chromosome.

- In long arm of chromosome.
- In chromosomes 1, 9, 16.
- In short arm of acrocentric chromosomes

Protein variations

- Almost 25% are silent mutation with effect on protein structure.
- Most mutations alter amino acid sequence but do not have phenotypic effect (e.g. ABO blood groups).
- Rare mutations produce severe phenotype effect or influence survival (e.g. phenylketonuria)

Uses of Polymorphism

- As genetic “Markers”:
  - To distinguish inherited forms of a gene in a family.
  - Mapping gene to individual chromosomes by likage analysis.
  - Presymptomatic and prenatal diagnosis of genetic disease.
  - Evaluation of high and low – risk persons.
  - Paternity testing and forensic applications.
  - Matching of donor-recipient pairs of tissue and organ transplantation.

Advantages of Polymorphism

- **Polymorphic forms** are produced as result of mutation in the genetic loci.
- The **advantages** are possibly:
  - Production of more **stable** forms.
  - Production of such forms that give **resistance against disease.**

    e.g. HbS Trait are resistance to malarial plasmodia.
  - **Natural selection** for survival of the fittest.

* **ABO System:**

  - **First identified by Landsteiner in 1900. Human blood can be assigned to one of four types according to presence of two antigens, A and B, on the surface of Red Blood Cell and the presence of two corresponding antibodies, Anti A and Anti B in the plasma.**

* **RBC Antigen Polymorphism:**

  - **Useful marker for:**

    - **Family and population studies.**

    - **Linkage analysis.**

  - **Different frequencies in different population.**

Contd.

Polymorphism:

- Can by revealed by:
  - Electrophoresis.
  - Cytogenetic studies.
- Important in:
  - Blood transfusion.
  - Tissue typing.
  - Organ Transplantation.
  - Treatment of Hemolytic disease of new born.

* **Blood Group Substances:**

- Blood group substances are encoded by allelic genes A and B.
- Blood group substances exhibit polymorphism.

Polymorphic System	Chromosomal Location	Common Alleles
ABO	9 q34	A, B and O
MNSs	4q28 – 31	M and N;S and s
Xg	Xp 22.3	Xg^a and Xg.

ABO Blood groups and Reaction with Antibodies

Group	Geno Type	Anti A	Anti B	Cellular Antigen	Serum Anti	Frequencies
O	O/O	-	-	NO	Anti A+B	45%
A	A/A, O/A	+	-	A	Anti B	42%
B	B/B, O/B	-	+	B	Anti A	10%
AB	A/B	+	+	A + B	Neither	4%

Haptoglobins

- α2-globins which contain a relatively high content of carbohydrate (glycoproteins) and have an affinity for haemoglobin (Hb).
- Function as transporters of free Hb and removes it from the circulation.
- Synthesized in the liver.
- Exist in 3 phenotypic forms, determined by 2 allelic genes Hp, Hp2, which are codominant.
- The genotypes of the three polymorphic forms are Hp1, Hp1Hp2, and Hp2Hp2.
- Each molecule of Hp (hepatoglobin) is formed of 4 subunits.

Transferrin

- β-globin consisting of glycoproteins.
- They are synthesized in the liver.
- They are present in several genetically distinct variant.
- The transferrins carry plasma iron and release it to the receptor on the tissue and bone marrow.
- Binds to two atoms of Fe^{3+}, and prevent toxic concentrations of iron to accumulate in the blood.
- There are several variants that are controlled by a series of alleles at the Tf locus. The commonest is transferrin C which is controlled by Tfc.
- Electrophoresis shows that transferrin B is the fastest, then comes C and the slowest one is transferrin D.

Clinical Importance of Polymorphism

Some disease genes occur with polymorphic frequencies

e.g.
- **HbS in African, Saudi Arabia**
- **Thalassaemia in Mediterranean region Saudi Arabia**
- **Cystic fibrosis in Europeans**

Genetic polymorphisms may produce disease

e.g.
On exposure to drugs or environmental factor
- **G-6-PD deficiency**
- **Malignant hyperthermia.**

Some polymorphisms determine antigenic differences

e.g.
- **Blood group**
- **HLA antigen for tissue typing.**

Clinical Importance of Polymorphism Contd…..

Forensic Medicine

e.g.
DNA fingerprint of each individual differs due to polymorphic sites in many non-coding sequences

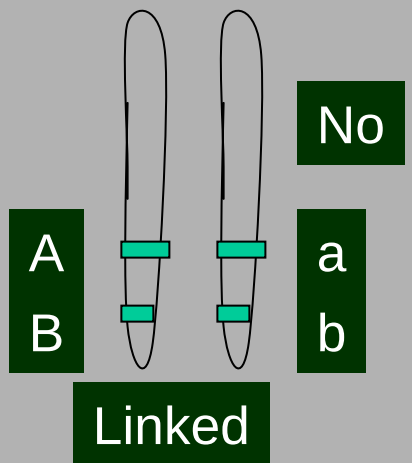
As genetic markers

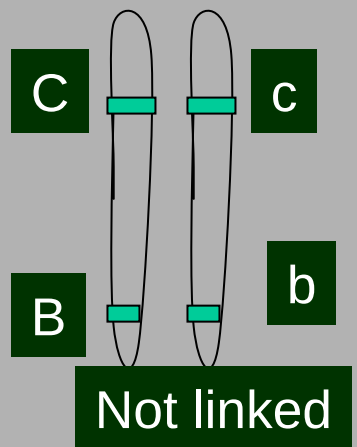
e.g.
Predisposing to a disease within families or populations

Genetic Linkage

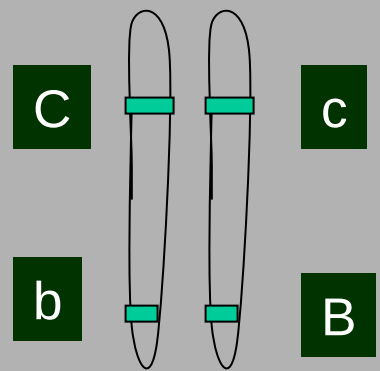
The occurrence of two or more genetic loci in such close physical proximity on a chromosome that they are more likely to assort (or segregate) together and not independently during meiosis

Crossing over does not take place between closely situated loci – So they are said to be linked





Crossing During meiosis



No

Concept of Genetic Linkage

Linkage refers to loci, not to alleles

Measurement of genetic linkage can only take place in family studies

Statistical method of measuring linkage is by calculation of lod score

Contd….

Closeness of a genetic linkage is expressed in Cente Morgans (cM) or percent recombination

Loci separated by crossing over in 1% of gametes are 1 cM apart

Loci close to each other, so they never separate are linked at a genetic distance of OcM

Unlinked loci are separated by a genetic distance of 50 cM as a given allele at one locus has a 50% of being transmitted with either allele at an unlinked loci.

Concept of Genetic Linkage
Contd…..

Lod Score

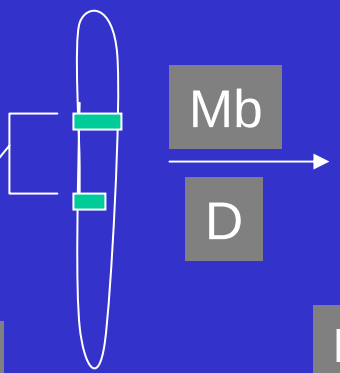
- Lod is a acronyn for “Logarithm of the Odds” (Lod score is a Logirithm of the likelihood ratio).
- Lod score of +3 or greater at recombination distance of less than 50 cM between two loci is considered to be a strong evidence of linkage (1000 : 1 odds for linkage.
- Lod score of –2 or less is taken as a strong evidence there is no linkage (100: 1 odds against linkage).

Concept of Genetic Linkage
Contd…..

Linkage disequilibrium

Measure in populations, not in families

This is the tendency for certain alleles at two linked loci to occur together more often than expected by chance. e.g.



Distance=5cM

If the mutant allele at D occurs on the same chromosome as Mb more often than expected within a certain population linkage disequilibrium is said to exist.

Disease locus = D
Marker = M
Alleles of Marker Ma and Mb.

Centi Morgan

Defines the distance between two gene loci

If two loci are IcM apart, there is a 1% change of recombination between these loci as the chromosome is passed from parent to child

It gives a rough unit of distance along the chromosome

- Different chromosomes have different sizes.
- Average chromosomes contain about 150 cm.
- There are about 3300 cM in the whole human genome. This corresponds to $3x10^9$ bp.
- On average IcM is about 1 millionbp (1000 kb).

Markers tightly linked to a disease

- The marker linked to a disease gene, must be on the same chromosome.
- They must be on the same region on the chromosome (within < 1 cm distance).

Markers that are a long distance away on the same chromosome may not appear to be linked because of relatively frequent recombination between the two loci.

Importance of Gene Mapping

The gene map is the anatomy of the human genome

To develop optimal strategy for gene therapy by improved knowledge of genomic organization

Analysis of heterogeneity and segregation of human genetic diseases

Provides information about linkage

Gene Mapping

This is the assignment of genes to specific chromosomal locations. Mapping is done by:

- Family studies to demonstrate linkage between loci
- Somatic cell genetic method to show that two loci are not linked (demonstrate synteny) or that an unmapped loci resides on a chromosome
- Cytogenetic techniques e.g. in situ hybridization
- Gene dosage studies
- Indirect means of identifying location of a agene

Clinical Applications of Linkage

Linkage is clinically useful as it may permit

- More precise determination of the genotype at an unidentified gene locus on the basis of readily identified linked markers
- Determination of the pattern of inheritance or specific for disease that exhibits genetic heterogeneity
- Gene mapping by determining the recombination distance between two genes on a chromosome

Used in

- Prenatal diagnosis
- Carrier detection
- Presymptomatic diagnosis
- Elucidation of genetic factors in multifactorial disorders