BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
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Programme: M.Sc., Biomedical science

Course Title : Molecular medicine

Course Code : BM48C16M

Unit-I

TOPIC: Genetic Polymorphism

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Genetic Polymorphism

History

- Originally defined by *Ford* in 1940.
- *E. B. Ford* and his co-workers from(1920-70s) worked on it.
- Later *Cavalli-Sforza & Bodmer* defined in 1971.

- Occurrence of multiple alleles at one locus in same population, where at least two alleles occur with minimum frequency is 1%.

Introduction

- **Genetics** derived ——— genetikos meaning "generative" derived , genesis meaning "origin".
- Study of Genes ,Genetic variation and Heredity in living organisms.

➢ **Polymorphism**

- Combination of Greek words poly (multiple) and morph (form).
- Multiple forms of a single gene , exists in an individual or group of individuals.
- Majority are silent , not alter function or expression of a gene .

•Some polymorphisms are visible.
•e.g dogs E locus, five different alleles(E, Em, Eg, Eh, e)contribute to pigmentation and patterns in dog coats.

➢ **Genetic Mutation**

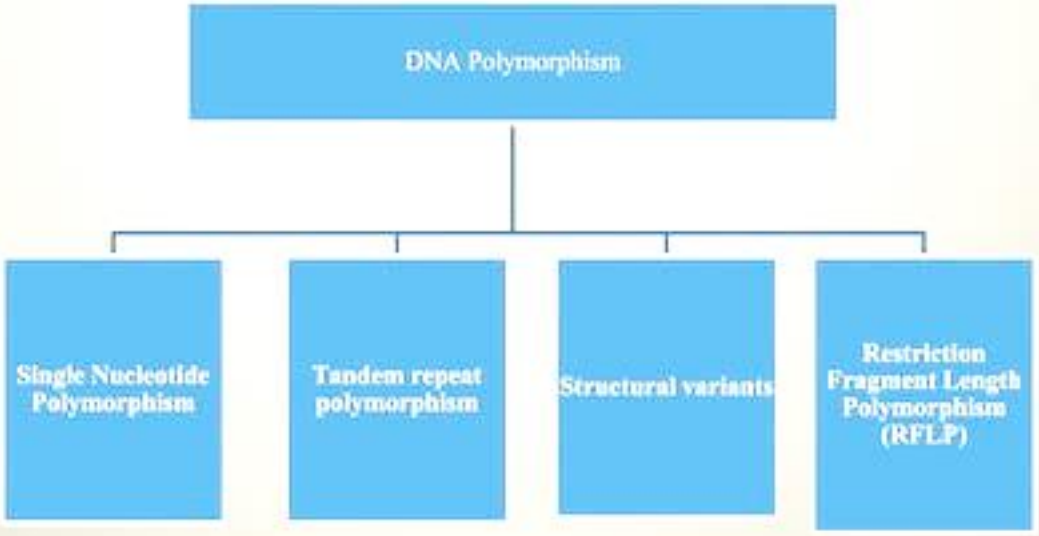
- DNA sequence not present in most individuals of species either associated with disease or resulted from damage caused by external agents.

Types of Genetic Polymorphism

1.**DNA Polymorphism.**

Polymorphisms that detect Slight variations at the level of DNA .

2. **Protein/Enzymes Polymorphism**



Types of DNA Polymorphism

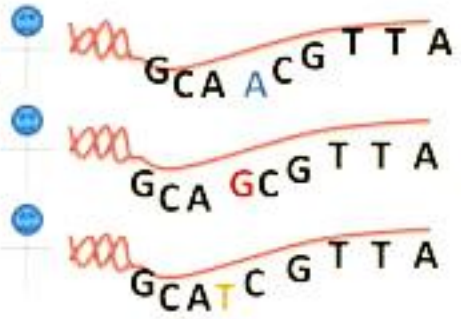
1.Single Nucleotide Polymorphism

- A single nucleotide (A,T,C,G) in genome sequences is altered .
- Detect in highly automated by using DNA 'Chip'
- Most common and simple , accounting 90% human genetic variation.
- 500-1,000 bases to several millions SNPs in human population.
- May occur in Coding and Non Coding region of genome.
- May cause disease, used to search and isolate disease-causing gene.

SNP

These are position in a genome where some individual have one nucleotide (e.g.a.**G**) and others have different nucleotide (e.g.a. **C**)

Each SNP could,potentially,have four alleles (because there are four nucleotides)



TCTAAGTCCGTATAA
AGATTCAGGCATATT

Normal
AGATTCAGGCATATT
TCTAAGTCCGTATAA
Green

TCTAAGTCCGTATAA
AGATTCAGGCATATT

Carrier
AGATTCAGGCATATT
TCTAAGTCCGTATAA
Yellow

TCTAAGTCCGTATAA

Disease
AGATTCAGGCATATT
AGATTCAGGCATATT
Red

TCTAAGTCCGTATAA

General population
96%

A C T C A T T G A

A C T C A T T T A

Single Nucleotide polymorphism

SNPs and Its Types

•Most SNPs are not responsible for a disease state.

➢**Alzheimer's disease:**

•Genes associated are ApoE.

•Two SNPs in 3 alleles for this gene: ε2, ε3, and ε4.

•Individual with ε4 allele have greater chance.

• Two ε4 alleles never but two ε2 alleles may develop disease.

• Directly responsible for genetic disease

➢**Types of SNPs:**

▪ **Transition**

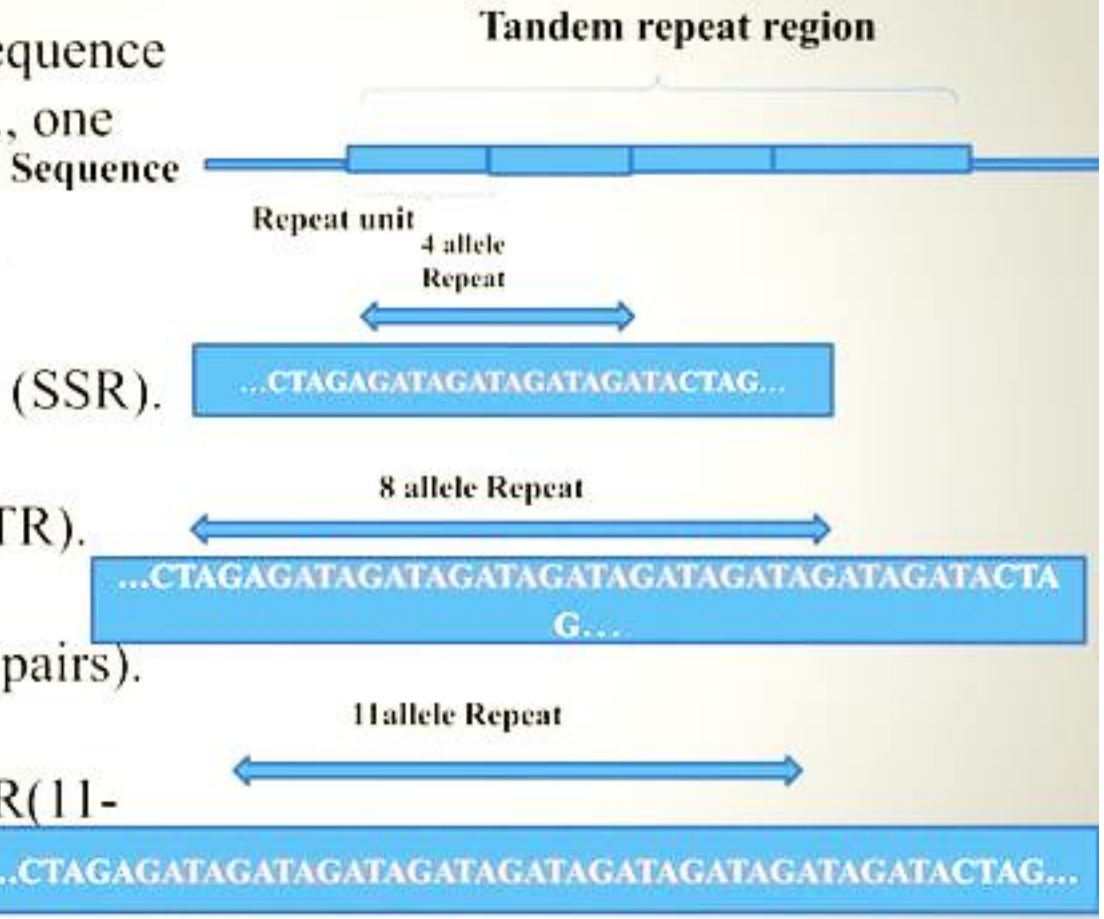
Substitution between purine (A, G) or pyrimidine (C, T). Constitutes 2/3 of all SNPs.

▪ **Transversion:**

Substitution occurs between purine and pyrimidine

2.Tandem repeat polymorphisms

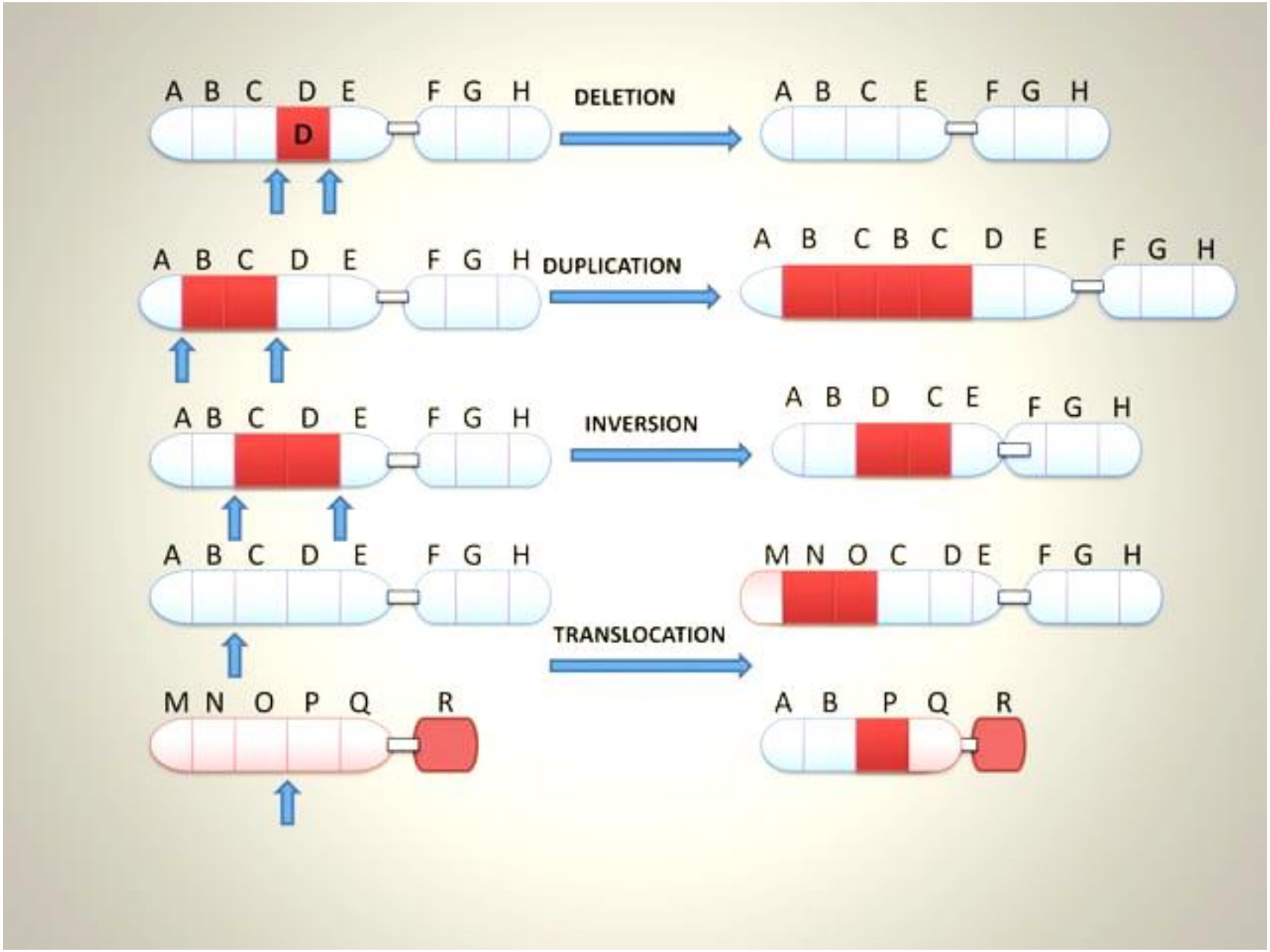
- Series of nucleotides Sequence repeated in tandem (i.e., one time after another).
- (6.6×109bp in genome)
- GATA sequence.
- Simple sequence repeat (SSR).
- Short tandem repeat (STR).
- Microsatellite(2-6 base pairs).
- Mini satellite and VNTR(11-60 base pairs).



3.Structural variants

Slight variation of nucleotide sequence.

- **Deletion**
- **Inversion**
- **Duplication**
- **Translocation**


A B C D E F G H
D
DELETION
A B C E F G H
A B C D E F G H
DUPLICATION
A B C B C D E F G H
A B C D E F G H
INVERSION
A B D C E F G H
A B C D E F G H
M N O P Q R
TRANSLOCATION
M N O C D E F G H
A B P Q R

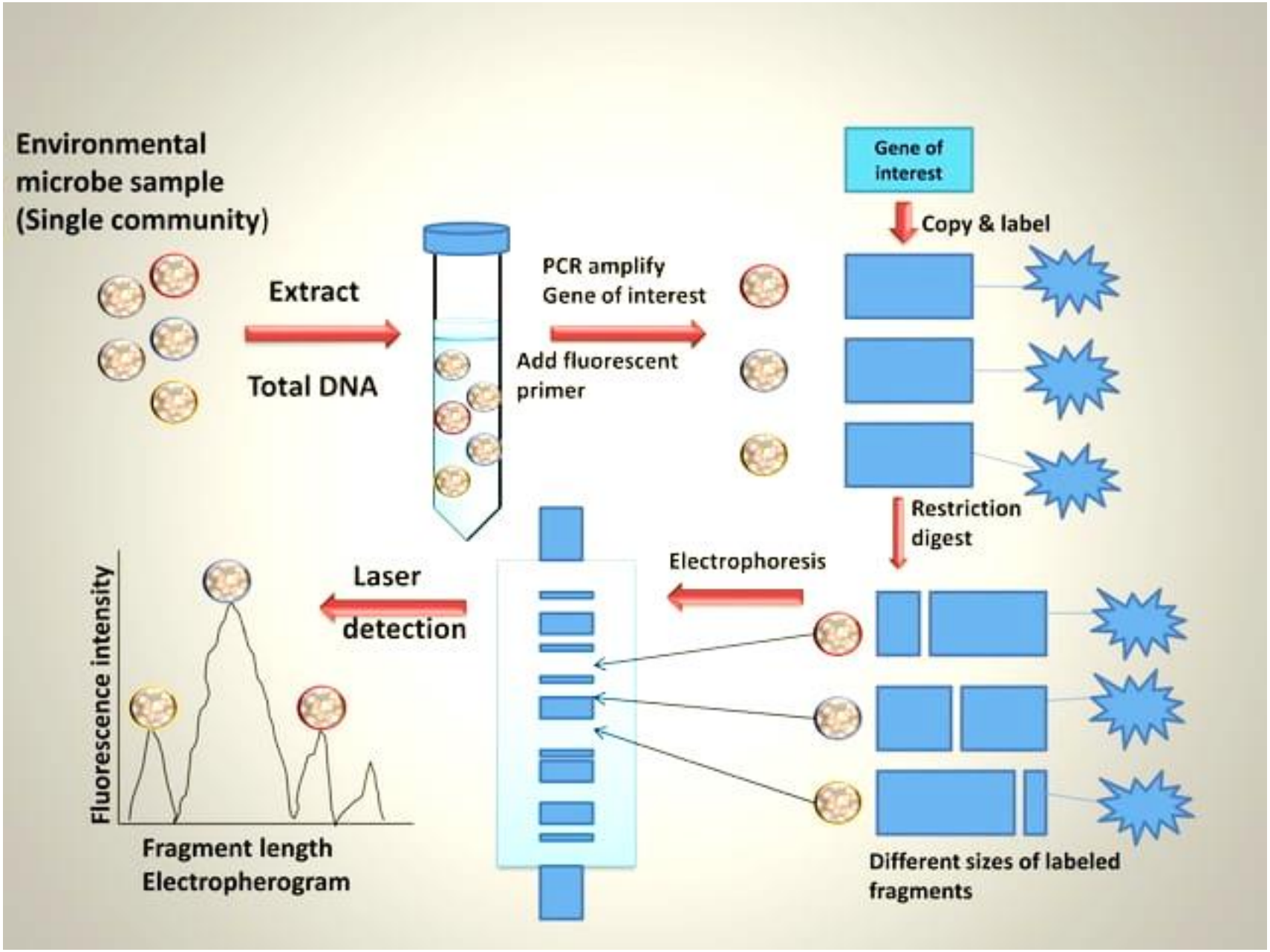
4.Restriction Fragment Length Polymorphism (RFLP)

➢ **Process**

- Analysis.
- Enzyme(restriction endonuclease).
- Length Variation.
- Identification.

➢ **Applications:**

- Criminal cases.
- Disease status.
- Biotechnology

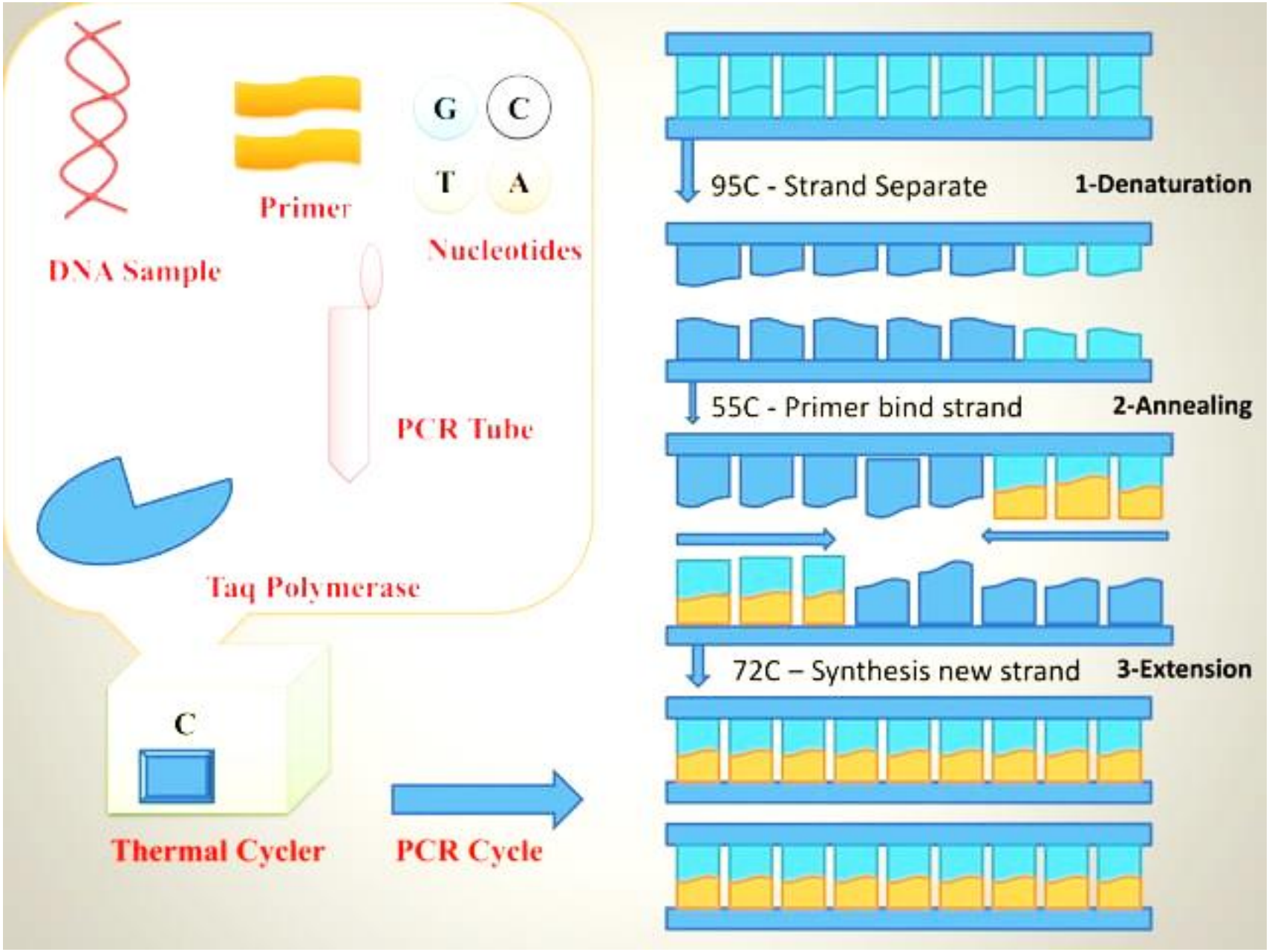

Environmental microbe sample (Single community)
Extract
Total DNA
PCR amplify Gene of interest
Add fluorescent primer
Gene of interest
Copy & label
Restriction digest
Electrophoresis
Laser detection
Fluorescence intensity
Fragment length
Electropherogram
Different sizes of labeled fragments

2.Protein/Enzyme Polymorphism

- Majority associated with proteins and enzymes.
- Detection of polymorphism and genotype.
- Detection of blood group,
- A,B,AB or O etc
- Phenotype and Rhesus factor
- Blood transfusion
- Modren genetic research

Identification

- Identified in laboratory using variety of methods.
- PCR amplify sequence of gene.
- Amplification of specific DNA sequence.
- Polymorphism and mutation detected by DNA sequencing.
- **PCR Steps:**
- Denaturation.
- Annealing.
- Synthesis.
- Target sequence copied and amplified at an exponential rate.
- Qualitative method for identifying DNA.


DNA Sample
Primer
G
C
T
A
Nucleotides
PCR Tube
Taq Polymerase
C
Thermal Cycler
PCR Cycle
95C - Strand Separate
1-Denaturation
55C - Primer bind strand
2-Annealing
72C – Synthesis new strand
3-Extension

Clinical Significance

➢Lungs Cancer

Polymorphism discovered in multiple XPD exons.

- 'XPD' involve ⟶ DNA repair mechanism during replication
- **Two common polymorphism**
- Asp312Asn
- Lys751Gln
- Both result in a change of single Amino acid

➢Asthma

- Inflammatory disease of lungs
- There are many genes for asthma as, one is CD14
- Cause polymorphism in which increase of CD14 protein with low IGE serum

Applications

- **Gene Mapping**
- **Pharmacogenomics.**
  - (I) Pharmacodynamics
  - (II) Pharmacokinetics
- **Forensics.**
  - (I) Crime Scene
  - (II) Paternity
- **Agriculture.**
- **Biological research.**
- **Disease Identification.**

Pharmacogenomics

- Role of genome in drug response.
- Pharmaco-genomics reflects combination of pharmacology and genomics.
- Genetic makeup of an individual affects his response to drugs.
- Genomics and epi-genetics dealing with effects of multiple genes on drug response.

Conclusion

- It Provides opportunity to integrate selection studies with knowledge about molecular genetics and their target.
- Polymorphism of gene-regulatory region is one of major contributors of phenotypic variation between and within population.
- Future studies in genetics will determine genes residing in these phenotypes to map genes functions.

References

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