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Programme: M.Sc., Biomedical Science
(5 Year Integrated Program)

Course Title : Genomics

Course Code : BM47C12

Unit-III
Identification of Markers

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Markers from Candidate Gene / Pathway

Candidate gene

- A candidate gene is a gene that is believed to have a potential role in contributing to a particular trait, disease, or phenotype based on its known biological function, location in the genome, or results from prior research.
- Genes selected based on known or suspected association with a trait or disease.
- Chosen due to biological relevance or previous studies.

Purpose of candidate gene

- Identify Genetic Risk Factors: Candidate gene studies aim to discover genetic variations (e.g., SNPs, Indels) associated with diseases or traits.
- Understand Biological Mechanisms: By studying specific genes that are part of known pathways, researchers can gain insights into how these genes influence biological functions.
- Facilitate Personalized Medicine: Identifying variations in candidate genes related to drug metabolism helps tailor drug treatments to individuals, improving efficacy and reducing side effects.

- Improve Agricultural Breeding Programs: In plant and animal breeding, candidate gene studies help in identifying genes linked to traits like yield, disease resistance, and stress tolerance.
- Support Functional Validation: By selecting specific genes of interest, candidate gene studies make it easier to conduct functional validation experiments, testing the real-world impact of these genes on traits or diseases.

Candidate gene markers

1. Single Nucleotide Polymorphisms (SNPs)
2. Microsatellites (Short Tandem Repeats, STRs)
3. Insertions/Deletions (Indels)
4. Copy Number Variations (CNVs)
5. Epigenetic Markers

Single nucleotide polymorphism

- Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation and play a significant role in candidate gene studies.
- A SNP occurs when a single nucleotide (A, T, C, or G) in the DNA sequence is altered at a specific position.
- In the context of a candidate gene, SNPs can help researchers identify genetic variations that may influence the function or expression of that gene, potentially linking the gene to a particular trait or disease.

Role of SNPs in Candidate Gene Studies

- Association with Traits or Diseases.
- Impact on Gene Function:

1. Coding Regions (Exons): SNPs here may lead to a missense mutation or a nonsense mutation, which can alter protein function
2. Non-Coding Regions: SNPs may affect gene expression levels by influencing transcription factor binding or RNA splicing, potentially altering when and how much of the gene is expressed.

Steps to Identify and Study SNPs in Candidate Genes:

1. Gene Selection: Choose candidate genes based on prior biological knowledge or hypothesis. These are often genes involved in known biological pathways related to the disease or trait of interest.
2. Genetic Variation Identification: Use sequencing technologies such as whole-genome sequencing (WGS), whole-exome sequencing (WES), or targeted sequencing to identify SNPs within the candidate gene.

3. Genotyping and Association Studies: Genotype the SNPs in a large sample population to assess the association between the SNP and the trait/disease. This can be done using SNP arrays or other genotyping platforms.

4. Statistical Analysis: Perform statistical tests (e.g., logistic regression) to evaluate whether specific SNPs are significantly associated with the trait or disease.

5. Functional Validation: Validate significant SNPs through laboratory experiments to determine their functional impact on the gene’s activity, protein production, or biological pathway involvement.

Microsatellites

- Microsatellites consist of short DNA motifs repeated in tandem (e.g., CA repeated several times).
- Location in Candidate Genes: Microsatellites can be found within or near candidate genes, where they may influence gene function, expression, or contribute to genetic variation.

Function and Impact

- Variability in the number of repeats can affect gene regulation or protein function if located in coding or regulatory regions.
- Useful in mapping genetic associations with diseases or traits in candidate gene studies.

Indels

- Insertions/Deletions (Indels) in candidate genes are small mutations where nucleotides are either inserted or deleted from the DNA sequence.
- These variations can have significant effects on gene function and are important markers in genetic studies.

Impact on Gene Function

- Coding Regions: Indels may cause a frameshift mutation, potentially leading to a nonfunctional protein or altered gene function.
- Non-Coding Regions: Indels in regulatory regions can affect gene expression by altering transcription factor binding or splicing.

Epigenetic markers

- Epigenetic markers in candidate genes refer to heritable modifications to the DNA or histones that affect gene expression without altering the DNA sequence itself.
- These markers can influence how candidate genes are regulated, impacting traits or disease risk.

Types of Epigenetic Modifications

- DNA Methylation: Addition of a methyl group to DNA, typically at CpG sites, which can silence gene expression.
- Histone Modifications: Changes to histones (e.g., methylation, acetylation) that influence how tightly DNA is wound around histones, affecting gene accessibility.

Copy Number Variations

- Copy Number Variations (CNVs) in candidate genes refer to structural variations in the genome where sections of DNA, including entire genes, are duplicated (gained) or deleted (lost).
- CNVs can affect gene dosage and lead to significant differences in phenotype or disease risk.

- **Impact on Gene Function:** Gene Dosage: Increased copies of a candidate gene can lead to overexpression, while deletions can reduce or eliminate gene function, potentially contributing to disease or altered traits.
- **Role in Candidate Gene Studies:** CNVs in candidate genes can be linked to various diseases, traits, or conditions by altering gene expression or disrupting gene regulation.

Identifying Markers in Candidate Gene Pathways

- Selection of candidate genes based on biological pathways.
- Detection of genetic variations via sequencing.
- Genotype-phenotype association studies.
- Validation through functional assays.

Tools for Marker Identification

- Key Databases: KEGG, Reactome, Gene Ontology for pathway information. dbSNP, ClinVar for genetic variation data.
- Bioinformatics Tools: ANNOVAR, VEP for variation annotation. DAVID, GSEA for pathway enrichment analysis.

Applications of Candidate Gene Markers

- Disease Association Studies: Identify genetic risk factors for diseases.
- Pharmacogenomics: Predict drug response based on genetic markers.
- Agricultural Genomics: Marker-assisted breeding for desirable traits.
- Functional Genomics: Understanding the role of genetic variations in biological functions.

Example of Candidate Gene Marker:

- BRCA1 and BRCA2 (Breast Cancer Susceptibility Genes): SNPs within these genes are used as markers to assess the risk of developing breast and ovarian cancer.
- APOE (Apolipoprotein E) in Alzheimer's Disease: SNPs within the APOE gene are associated with the risk of Alzheimer's disease.

Thank you.!!