GENETIC POLYMORPHISM

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M.SC SEMESTER II CC 08

Genetic approaches complement functional approaches to the study of hereditary disease and have contributed substantially to our understanding of the biology of enterohepatic circulation in health and disease. The basic steps in genetic mapping of a disease gene are reviewed here. They include identification of the mode of inheritance; genetic mapping of the disease gene; identification and screening of candidate genes; and evaluation of the functional consequences of the mutation(s) identified. Ongoing advances in technology and analytic methods have increased the effectiveness and efficiency of genetic mapping approaches.

A gene is said to be polymorphic if more than one allele occupies that gene's locus within a population. In addition to having more than one allele at a specific locus, each allele must also occur in the population at a rate of at least 1% to generally be considered polymorphic.

Gene polymorphisms can occur in any region of the genome. The majority of polymorphisms are silent, meaning they do not alter the function or expression of a gene. Some polymorphism is visible. For example, in dogs the E locus, can have any of five different alleles, known as E, E^m, E^g, E^h, and e. Varying combinations of these alleles contribute to the pigmentation and patterns seen in dog coats.

A polymorphic variant of a gene can lead to the abnormal expression or to the production of an abnormal form of the protein; this abnormality may cause or be associated with disease. For example, a polymorphic variant of the gene encoding the enzyme CYP4A11, in which thymidine replaces cytosine at the gene's nucleotide 8590 position encodes a CYP4A11 protein that substitutes phenylalanine with serine at the protein's amino acid position 434. This variant protein has reduced enzyme activity in metabolizing arachidonic acid to the blood pressure-regulating eicosanoid, 20-Hydroxyeicosatetraenoic acid. A study has shown that humans bearing this variant in one or both of their CYP4A11 genes have an increased incidence of hypertension, ischemic stroke, and coronary artery disease.

Polymorphism can be caused by: ¬ Deletion, duplication, triplication and so on of hundreds of millions of base pairs of DNA ¬ Or it can also be changes in one or a few bases in the DNA located between genes or within introns ¬ Sequence changes may also be located in the coding sequence of genes themselves and result in different protein variants that may lead in turn to different phenotypes ¬ Others are in regulatory regions and may also be important in determining phenotype by affecting transcription or mRNA stability

Identification

Polymorphisms can be identified in the laboratory using a variety of methods. Many methods employ PCR to amplify the sequence of a gene. Once amplified, polymorphisms and mutations in the sequence can be detected by DNA sequencing, either directly or after screening for variation with a method such as single strand conformation polymorphism analysis.

Types

A polymorphism can be any sequence difference. Examples include:

- Single nucleotide polymorphisms (SNPs) are a single nucleotide changes that happen in the genome in a particular location. The single nucleotide polymorphism is the most common form of genetic variation.

- Small-scale insertions/deletions (Indels) consist of insertions or deletions of bases in DNA.

- Polymorphic repetitive elements. Active transposable elements can also cause polymorphism by inserting themselves in new locations. For example, repetitive elements of the Alu and LINE1 families cause polymorphisms in human genome.

- Microsatellites are repeats of 1-6 base pairs of DNA sequence. Microsatellites are commonly used as a molecular markers especially for identifying the relationship between alleles

SUMMARY

The polymorphism occurring while gene replacement is in process is transient, since as soon as the favoured allele is fixed the population becomes monomorphic. However, many characters in human populations are more or less permanently polymorphic. One of the most obvious examples of such 'balanced polymorphism' is sex. Others that occur in many human populations affect the blood-group systems, secretor status, haemoglobins, red cell enzymes and serum proteins. Non-coding regions of DNA from homologous chromosome pairs also demonstrate an average of one nucleotide difference for every 250-nucleotide sequence. The nucleotide differences are called polymorphisms. Humans have such extensive polymorphism that each person's DNA is as individual as his or her fingerprints. These polymorphisms then become genetic markers that can be raced within members of the family just as genes are traced.

The role of genetics is emerging as an increasingly important aspect of health care. A number of RFLPs associated with human diseases are now being used in prenatal diagnosis and to determine delayed-onset diseases and dominant and recessive carriers. Information from a genetic test can be used to diagnose disease, identify risk as for future disease and predict treatment response.

Genetic polymorphisms provide us with the ability to predict inter-individual differences in susceptibility to clinical disease. Biomarkers of susceptibility include: polymorphisms in drug/carcinogen metabolism, in DNA repair capacity, and in genes that control cell growth. Wide variations in drug/carcinogen metabolism have been widely investigated and clearly shown to be an important determinant of individual cancer susceptibility and adverse drug reactions. Such polymorphisms in drug/carcinogen-metabolising enzymes may be due to heritable and/or to environmental factors; and the modern application of metabolic phenotyping and genotyping methods to epidemiological studies has provided new insights into such gene-environmental interactions.