Human Genomics

What were the aims of the human genome project?

To identify all the approximately 20,000-25,000 genes in Human DNA.

To find where each gene is located

To determine the sequences of the 3 billion chemical base pairs which make up human DNA.

Store this information in databases.

The sequence is not that of one person, but is a composite derived from several individuals. Therefore, it is a 'representative' or generic sequence.

Sequencing DNA

A proportion of DNA is chosen and many copies are synthesised.

DNA polymerase, primer, the four DNA nucleotides and 'modified' nucleotides are added

When a modified nucleotide binds to the DNA strand it halts the process

As this is carried out on many copies, eventually all the strands will have stopped at every possible position

After all 3 billion base pairs were sequenced there was more work to do

Scientists now had to 'understand' the message and identify causes of disease, such as cancer, and then generate effective treatments.

Human genomics

Human genomics is the study of the human genome.

It involves determining the sequence of nucleotide bases, 'genomic sequencing'.

Differences in genomes

Single Nucleotide Polymorphism is variation in DNA sequence that affects a single base pair.

SNPs are one of the ways in which genomes differ from one individual to another.

Two out of three SNPs involve the replacement of cytosine with guanine.

Scientists have catalogued more than a million SNPs, found their exact location and made a 'SNP Map'.

Hopefully the 'map' will help to understand the workings of genes associated with disease.

It could be that people with a certain disease always inherit a particular group of SNPs – unaffected people do not.

'Out of Africa' theory

Examination of genetic differences that do exist between different human populations shows the greatest variation occurs among populations in Africa - this supports the 'Out of Africa' theory.

Humans originated in Africa and underwent early evolutionary divergence in that continent over millions of years.

Small groups migrated out of Africa relatively recently, 100,000 years ago and gave rise to all other Human populations.

'Polymerase Chain Reaction'

PCR is used to create many copies of a piece of DNA for forensic and medical purposes.

The 'amplification' of DNA involves the use of primers – so, the DNA sequence must be known so that primers can be made.

Each primer is a piece of DNA complementary to a specific target sequence at the 3' end of the DNA to be replicated.

Heat tolerant DNA polymerase adds nucleotides to the primers at the 3' end of the original DNA strand.

First cycle produces two identical molecules of DNA

Second cycle produces four identical DNA molecules

And so on 8, 16, 32,

A tiny quantity of DNA can be amplified for forensic and medical purposes.

The specificity of the reaction is very impressive.

This is made possible because each primer is the exact complement of a short length of DNA to which it is to become attached.

The primer, therefore, is able to locate the specific DNA sequence that has to be amplified.

This enables the primer to find 'the needle in a haystack'.

DNA probe

DNA Probe is a short, single stranded fragment of DNA and the DNA, under investigation, is the 'target DNA'.

DNA probe is used to detect the presence of a specific sequence of nucleotides in a sample.

A probe is able to carry out its function because its base sequence is complementary to the base sequence in the target DNA – when a probe combines with its 'target' it 'glows'.

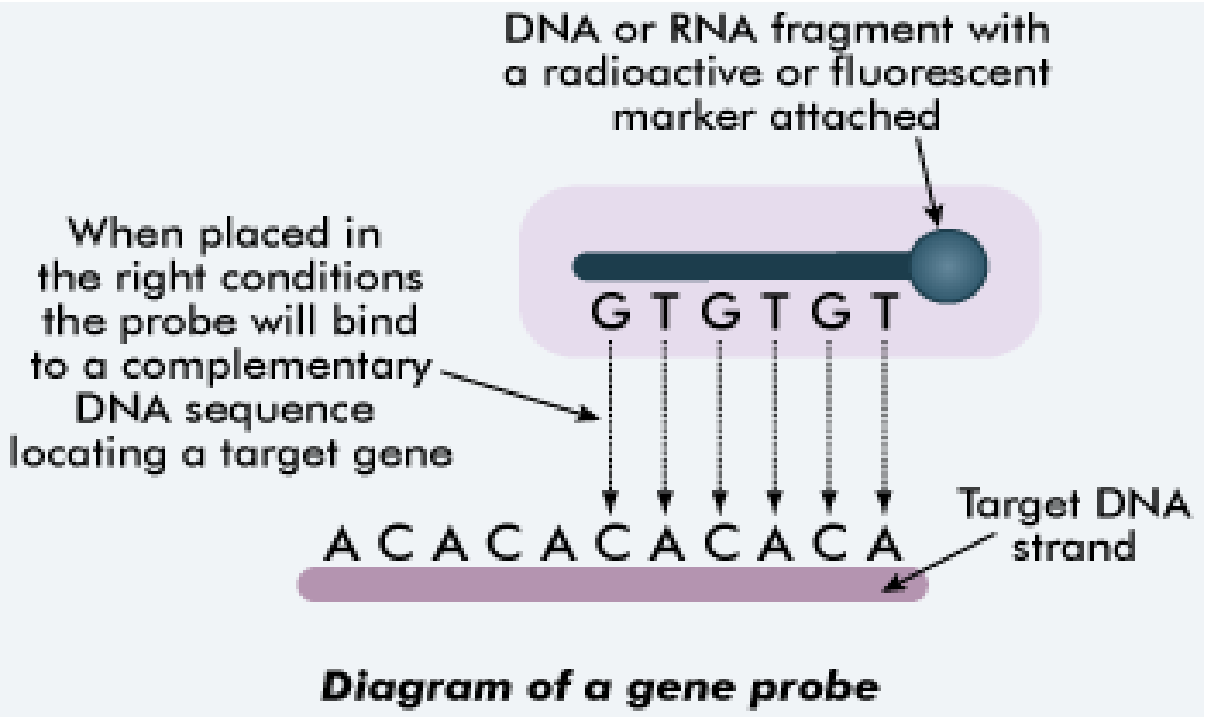

Diagram of a gene probe

DNA microarray

This is an orderly arrangement of thousands of different DNA probes as tiny spots on a glass slide.

Fluorescent labelling indicates those spots where a probe has successfully combined with its complementary target DNA.

PCR can amplify DNA from a cell sample taken from a patient.

Sufficient DNA is generated to allow it to be screened for, by gene probes, the presence or absence of a specific sequence known to be characteristic of a genetic disease.

This -

1. Enables medical experts to estimate risk of onset and

2. Confirm a diagnosis

Forensics

Each human genome possesses many non-coding regions of DNA composed of a number of repetitive sequences.

Each repetitive sequence is unique to an individual.

These regions can be used to construct a person's DNA profile, 'genetic fingerprint'.

Forensic scientists amplify DNA samples from a crime scene as well as DNA from the victim and suspects.

The components of the samples are compared.

Paternity dispute

PCR and gel electrophoresis can also be used to confirm genetic relationships.

As we inherit 50% of our DNA from each parent, the DNA profile, 'genetic fingerprint,' must match 50% of their information to their mother and the other to their father.

Personal Genome Sequence

Personal genome sequence involves a complete sequencing of a person's DNA.

The process of sequencing DNA is rapidly becoming faster and cheaper.

Sequencing an individual's DNA for medical reasons will soon become a real possibility.

In the future, a person's genome may be sequenced in early life and stored as an 'electronic medical record'.

Genetic disorders

A genetic disorder/disease comes about as a result of a variation in genomic DNA sequence.

Challenge for scientists is to establish a link between a mutant variant in genomic sequence and a specific disorder.

So far, causal genetic sequence has been identified for around 2200 genetic disorders in humans.

It is important to distinguish between altered genetic sequences that are 'harmful' and those that are 'neutral'.

Pharmacogenetics

Pharmacogenetics is the study and effects of pharmaceutical drugs on the genetically diverse members of the human population.

It is known that one in ten drugs e.g. warfarin varies in effect depending on differences in a person's DNA profile.

In the future, it may be possible to use genomic information and customise medical treatment.

The most suitable drug and the correct dosage would be prescribed.

This would increase drug efficacy and reduce the 'one-size fits all' approach.

Rational Drug Design

Is the process of creating new medication based on knowledge of the structure of the 'target molecule'.

It acts in one of the following ways –

It binds to the particular region of DNA in the mutant gene that causes the disorder and prevents transcription of abnormal mRNA.

If transcription happens . . .

It binds to the abnormal mRNA and prevents it being translated into abnormal protein.

If translation happens . . . .

It binds to and renders inactive the protein whose presence causes the genetic disorder.'Markers'

When the location of 'markers' have been established it should be possible to scan an individual's genome for a predisposition to a disease and predict a risk

Reduction in risk could be achieved by appropriate drug treatment.