GENES

Genetics is the study of variation and inheritance. The basic unit of inheritance is the **gene**. *A gene is a heritable factor that controls a specific characteristic.*

A typical animal or plant cell nucleus contains thousands of genes. The total number of genes in humans is not yet known but is probably between 30 000 and 40 000. All of the genes of an organism are known collectively as the **genome**. *A genome is the whole of the genetic information of an organism.*

CHROMOSOMES

Genes are made of DNA. They are part of much larger DNA molecules called **chromosomes**. In eukaryotes, proteins are always associated with the DNA in chromosomes.

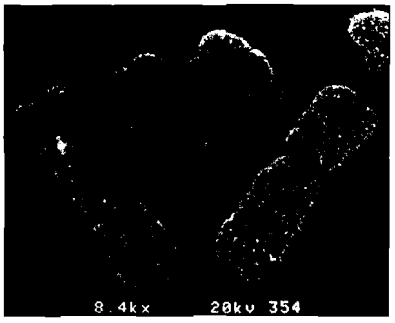
A typical animal or plant chromosome contains about a 1000 genes, which are arranged in a linear sequence. In any particular type of chromosome the same genes are found arranged in the same sequence. The position of a gene on a chromosome is called the **gene locus**.

ALLELES

Although one particular chromosome type always has the same genes in the same sequence, the genes themselves can vary. Different forms of many genes can be found. These are called **alleles** of the gene. *An allele is a form of a gene, differing from other alleles of the gene by a few bases at most and occupying the same locus as the other alleles of that gene.*

REPLICATION OF CHROMOSOMES

If a nucleus is going to divide by mitosis or meiosis, all DNA in the nucleus is replicated. When mitosis or meiosis begins, each chromosome is visible as a double structure (see below). The two parts are called **chromatids** and are connected by a centromere. Some types of chromosome have a **centromere** in the centre and others have a centromere nearer to one end.



HAPLOID AND DIPLOID

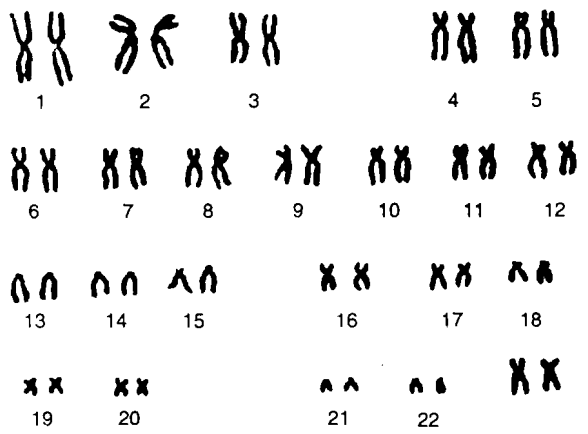
In most cells the nucleus contains two of each type of chromosome (top right). The cell therefore has two full sets of chromosomes. This is called **diploid**. Some cells only contain one of each type of chromosome and therefore have just one set. This is called **haploid**.

In diploid cells each pair of chromosomes have the same genes, arranged in the same sequence. However, they do not usually have the same alleles of all of these genes. They are therefore not identical but instead are **homologous**.

Homologous chromosomes have the same genes as each other, in the same sequence, but not necessarily the same alleles of those genes.

The number of chromosomes in a cell can be reduced from diploid to haploid by the process of meiosis. Meiosis is described as a **reduction division**. Living organisms that reproduce sexually have to halve their chromosome number at some stage in the life cycle because the fusion of gametes during fertilization doubles it.

HUMAN FEMALE KARYOTYPE



KARYOTYPES AND KARYOTYPING

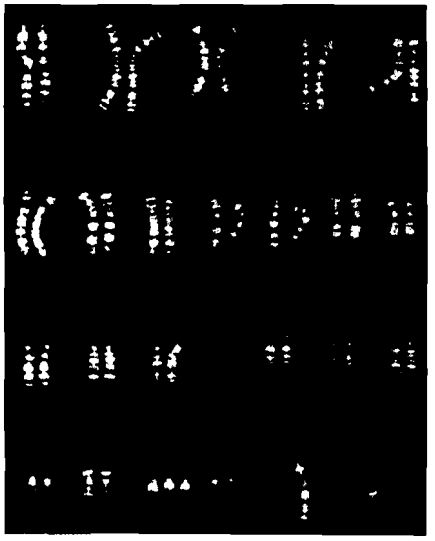
The number and appearance of the chromosomes in an organism is called the **karyotype**. Living organisms that are members of the same species usually have the same karyotype. The karyotype of a human female is shown above. A small proportion of humans have a different karyotype.

A procedure called karyotyping is used to test for this. One example is the testing of babies before birth (fetuses) to find out if they have Down's syndrome.

- A sample of amniotic fluid is removed from the mother. It contains cells from the fetus.
- The cells are incubated with chemicals that stimulate them to divide by mitosis.
- Another chemical is used which stops mitosis in metaphase of mitosis. Chromosomes are most easily visible in metaphase.
- A fluid is used to burst the cells and spread out the chromosomes.
- The burst cells are examined using a microscope and a photograph is taken of the chromosomes from one cell.
- The chromosomes in the photograph are cut out and arranged into pairs. This is called karyotyping.

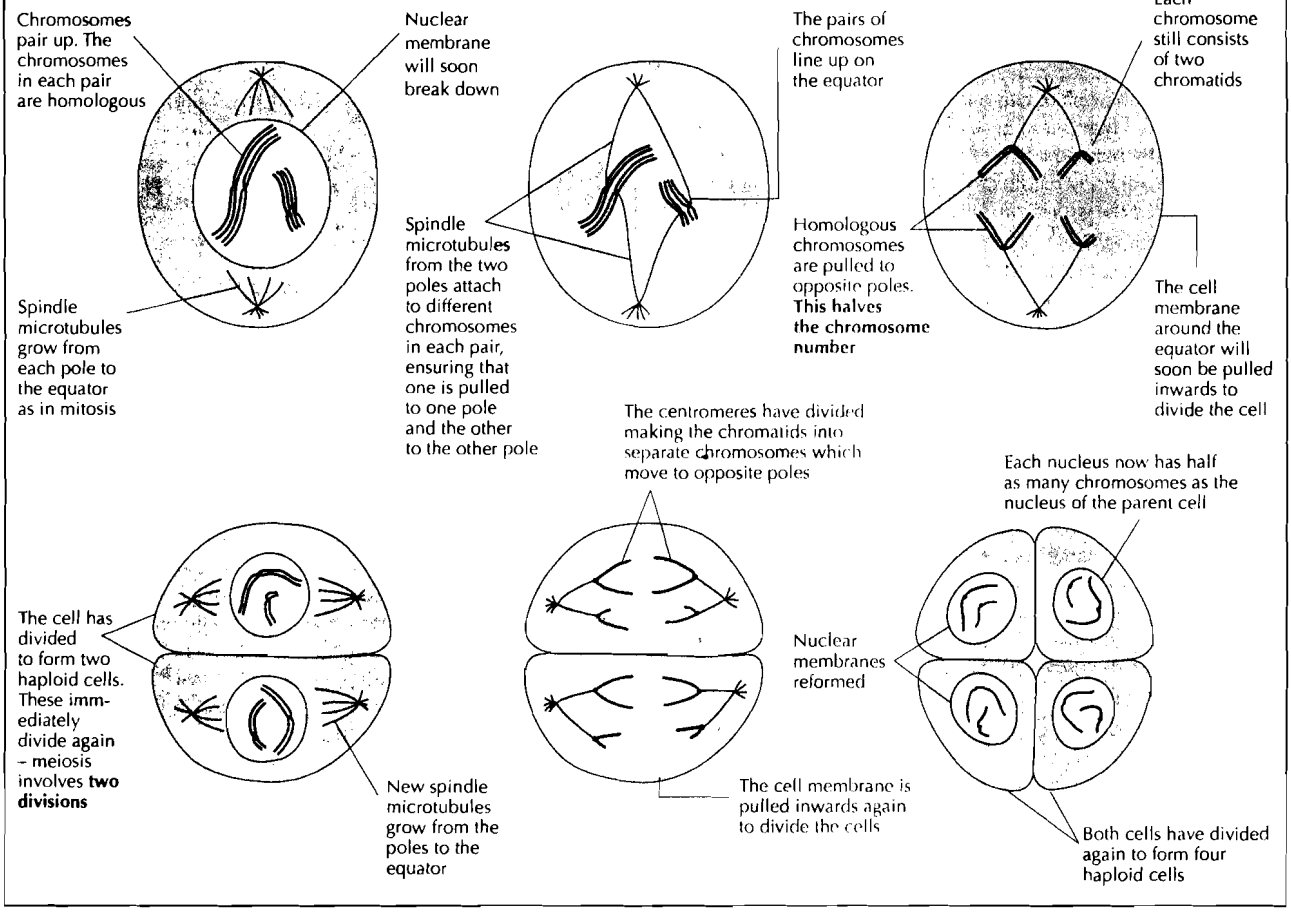
The chromosomes of a boy with Down's syndrome are shown (below). There is an extra chromosome 21 – three are present instead of the usual two.

Karyotype of a person with Down's syndrome



Meiosis

STAGES OF MEIOSIS



CHROMOSOME MOVEMENTS IN MEIOSIS AND GENETIC VARIATION

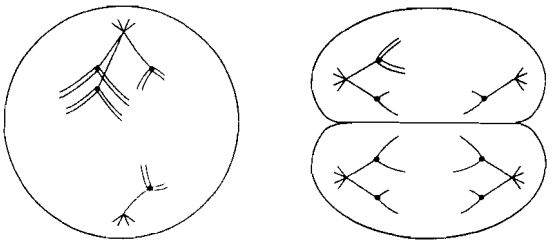
During the first division of meiosis one chromosome of each pair moves to one pole and the other chromosome to the other pole of the cell. The position of each pair of chromosomes in the nucleus when the spindle microtubules become attached is random. This is called **random orientation**. Microtubules from each pole attach to whichever chromosome of a pair is closer.

Because of random orientation, each pole could receive either chromosome of a pair – there are two equally likely possibilities. All cells have at least two pairs of chromosomes. The second pair is also randomly orientated, giving two possibilities and therefore in total each pole could receive four (2 × 2) possible combinations of two chromosomes.

With three pairs of chromosomes there are eight possible combinations (2 × 2 × 2). If the number of pairs of chromosomes is *n* the number of possible combinations of chromosomes that can be formed because of random orientation during meiosis is 2^n. In humans for example, where *n* is 23, there are over 8 million possible combinations. Each of these is genetically different, so the movements of chromosomes in meiosis generate much genetic variety.

NON-DISJUNCTION AND DOWN'S SYNDROME

Sometimes chromosomes that should separate and move to opposite poles during meiosis do not separate and instead move to the same pole. This can happen in either the first (left) or the second division of meiosis (right).



Non-separation of chromosomes is called **non-disjunction**. The result is that gametes are produced with either one chromosome too many or too few.

Gametes with one chromosome too few usually quickly die. Gametes with one chromosome too many sometimes survive. When they are fertilized, a zygote is produced with three chromosomes of one type instead of two. This is called **trisomy**. Down's syndrome is usually caused by trisomy of chromosome 21. It can be due either to non-disjunction during the formation of the sperm or egg. The chance of Down's syndrome increases with the age of the parents.

MENDEL'S MONOHYBRID CROSSES

Gregor Mendel investigated inheritance by crossing varieties of pea plants that had different characteristics. For example, he crossed a variety that had round seeds with a variety that had wrinkled seeds. He found that all the offspring (called the F_1 generation) had the same characteristic as one of the parents. He allowed the F_1 generation to self-fertilize – each plant produced offspring by fertilizing its female gametes with its own male gametes. The offspring (called the F_2 generation) contained both of the original parental types. The characteristic that disappeared in the F_1 generation reappeared in a quarter of the F_2 generation.

From the results of monohybrid crosses, Mendel discovered the Law of Segregation. The figure below shows an example of Mendel's monohybrid crosses.

DEFINITIONS OF TERMS USED BY GENETICISTS

There are two pairs of terms that are often used by geneticists:

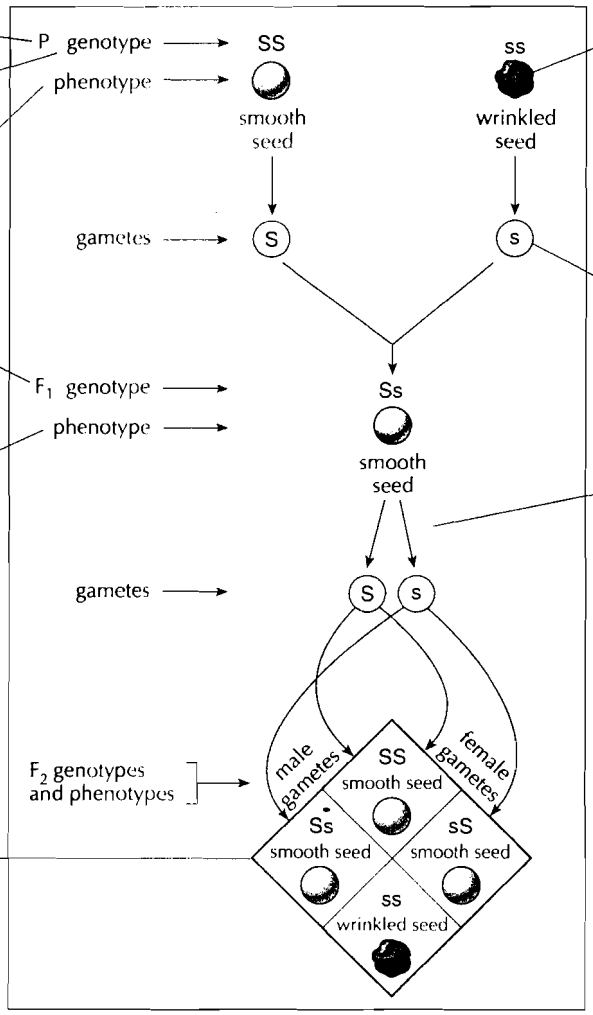
- **Homozygous** – *having two identical alleles of a gene.* All the gametes of a homozygote have the same allele.
- **Heterozygous** – *having two different alleles of a gene.* Half of the gametes of a heterozygote have one of the alleles and half have the other allele.
- **Dominant allele** – *an allele that has the same effect on the phenotype in a heterozygous individual* (where it is combined with a recessive allele) *as in a homozygous individual* (where there are two copies of the dominant allele).
- **Recessive allele** – *an allele that only has an effect on the phenotype in homozygous individuals* (where there are two copies of the recessive allele). In heterozygous individuals the recessive allele is hidden by the dominant allele.

Monohybrid cross between smooth and wrinkled seed pea plants

P = parental generation.

Genotype = *the alleles possessed by an organism.*

Phenotype = *the characteristics of an organism.*



Seed shape is determined by a single gene. One allele of this gene (S) gives smooth seeds and the other (s) gives wrinkled seeds. The pea plants are diploid so they have two copies of each gene. The parental varieties are both homozygous.

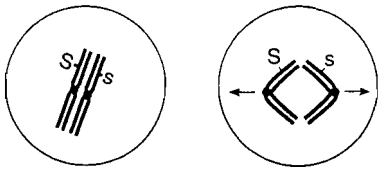
Gametes are produced by meiosis so are haploid and only have one copy of each gene.

F_1 = the first filial generation– the offspring of the P generation.

F_1 plants are heterozygous but all have smooth seeds because S is the dominant allele and s is recessive.

When the F_1 hybrid plants produce gametes, the two alleles separate. This is called **segregation**. Mendel's Law of Segregation states that *two alleles of each gene separate into different gametes, when the individual produces gametes.*

Segregation occurs during meiosis. The two alleles of a gene are located on homologous chromosomes which move to opposite poles, causing the segregation (see below).



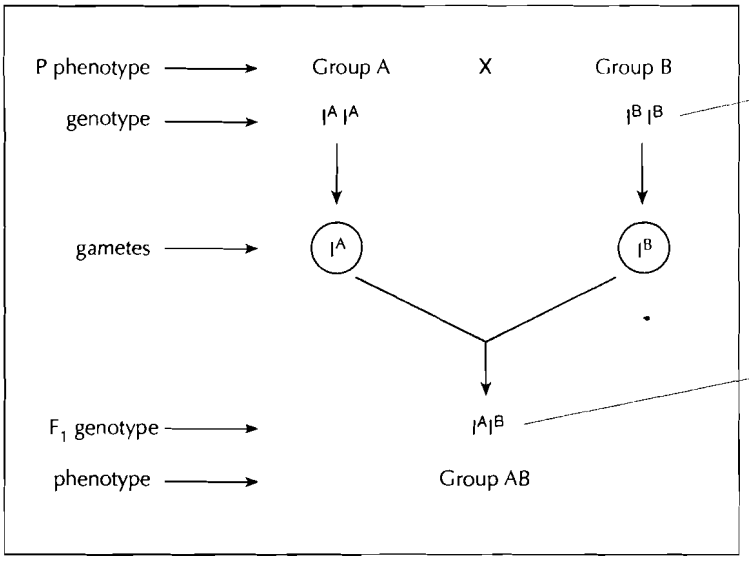
The grid shown here is called a **Punnett grid**. It is used to show all the possible outcomes in a cross. In this case both the male and female gametes can be (S) or (s), giving four possible F_2 genotypes.

There is a 3:1 ratio of smooth and wrinkled seed F_2 plants. Crosses between two heterozygous individuals give a 3:1 ratio if one of the alleles is dominant and the other is recessive.

Inheritance of blood groups

The principles of inheritance discovered by Mendel in pea plants also operate in other plants and in animals. There are, however, sometimes differences and two of these are demonstrated by the inheritance of ABO blood groups in humans –codominance and multiple alleles.

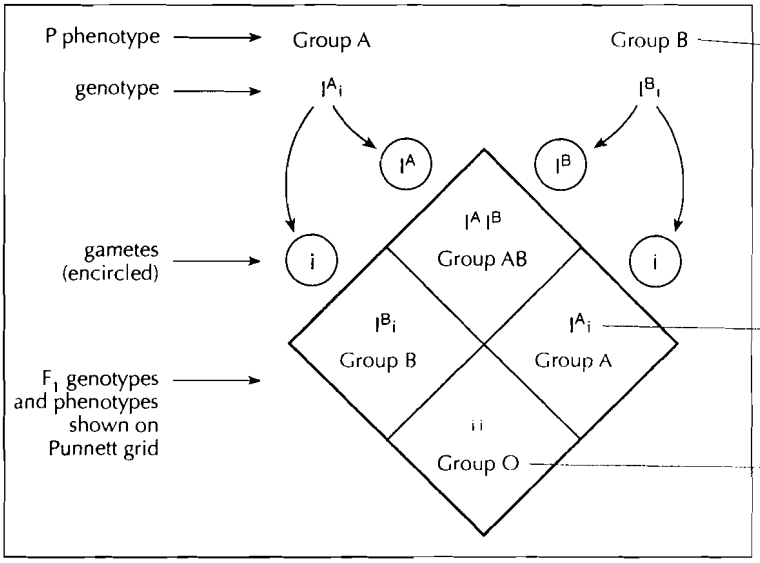
CROSS INVOLVING CODOMINANT ALLELES



I^A is the allele for blood group A and I^B is the allele for blood group B. Neither allele is recessive, so both are given upper case letters as their symbol.

If I^A and I^B are present together, they both affect the phenotype because they are codominant. Codominant alleles are pairs of alleles that both affect the phenotype when present together in a heterozygote.

CROSS INVOLVING MULTIPLE ALLELES



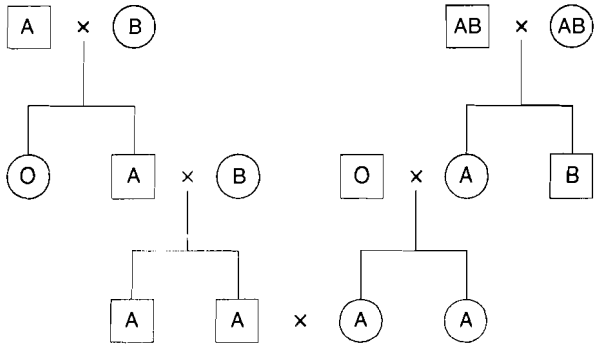
The gene that controls ABO blood groups has a third allele: i If there are more than two alleles of a gene, they are called *multiple alleles*.

i is recessive to both I^A and I^B so $I^A i$ gives blood group A and $I^B i$ gives blood group O.

Individuals who are homozygous for i are in blood group O.

DEDUCING GENOTYPES FROM PEDIGREE CHARTS

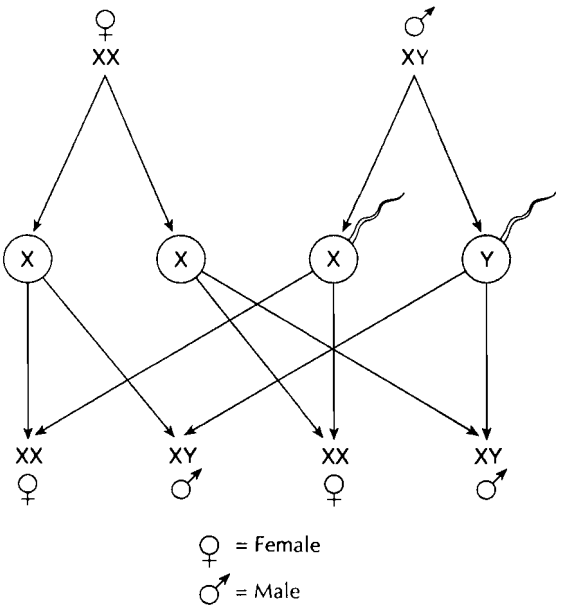
A pedigree chart shows the members of a family and how they are related to each other. Males are shown as squares and females as circles. If the phenotypes of the members of the family are known, the genotypes can often be deduced. The figure (right) is a pedigree chart that shows the blood group of each individual. All of the genotypes can be deduced. It is also possible to deduce the probability of the first child of the parents in the third generation being blood group A, B, AB and O.



SEX CHROMOSOMES AND GENDER

- Two chromosomes determine the gender of a child (whether it is male or female). These are called the sex chromosomes.
- The X chromosome is relatively large and carries many genes
- The Y chromosome is much smaller and carries only a few genes.
- If two X chromosomes are present in a human embryo and no Y chromosome, it develops into a girl.
- If one X chromosome and one Y chromosome are present, a human embryo develops into a boy.
- When women reproduce, they pass on one X chromosome in the egg.
- When men reproduce, they pass on either one X or one Y chromosome in the sperm, so the gender of a child depends on whether the sperm that fertilizes the egg is carrying an X or a Y chromosome (right).

Inheritance of gender in humans



SEX LINKAGE

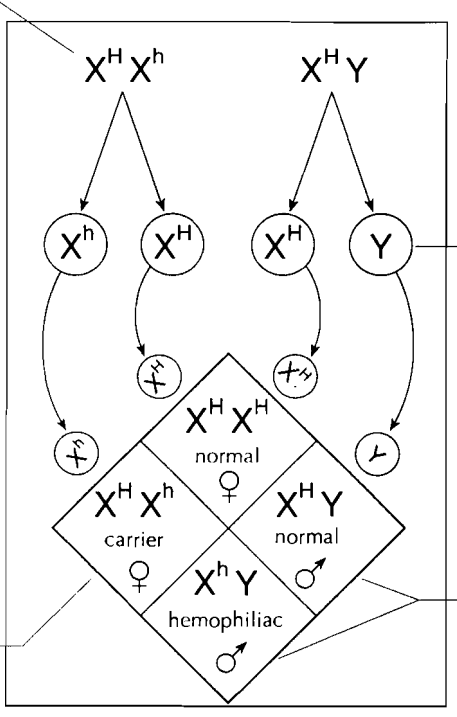
If a gene is carried on the X chromosome, the pattern of inheritance is different for males and females – there is sex linkage. *Sex linkage is the association of a characteristic with gender, because the gene controlling the characteristic is located on a sex chromosome.* Sex-linked genes are almost always located on the X chromosome. Females have two X chromosomes and therefore have two copies of sex linked genes. Males only have one X chromosome and therefore only have one copy of sex linked genes. In humans, hemophilia (below) and red–green colour blindness are examples of sex-linked characteristics.

Example of a cross involving sex linkage

The diagram below shows how two parents who do not either have hemophilia could have a hemophiliac son.

The mother is heterozygous but is not a hemophiliac because H is dominant and h is recessive. She is a **carrier** of the allele for hemophilia.

A carrier has a recessive allele of a gene but it does not affect the phenotype because a dominant allele is also present.



KEY

X^H X chromosome carrying the allele for normal blood clotting

X^h X chromosome carrying the allele for hemophilia.

The Y chromosome does not carry either allele of the gene.

None of the female offspring are hemophiliac because they all inherited the father's X chromosome which carries the allele for normal blood clotting (H), but there is a 50% chance of a daughter being a carrier.

There is a 50% chance of a son being hemophiliac as half of the eggs produced by the mother carry X^h. The chance of a daughter being hemophiliac is 0%, so the overall chance of offspring being hemophiliac is 25%.

Pedigree analysis

USING PEDIGREE CHARTS

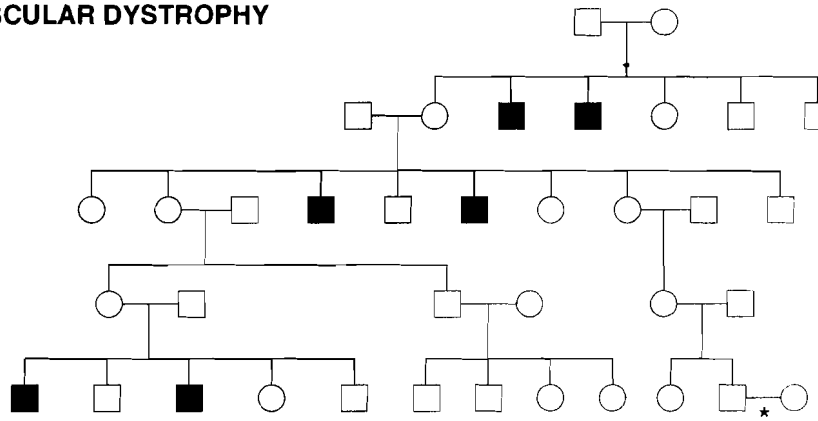
Pedigree charts can be used to study the inheritance of a characteristic:
– whether it is caused by a dominant or recessive allele
– whether it is sex-linked or not.
The figures below are pedigree charts that each show a different pattern of inheritance. The most likely pattern of inheritance can be deduced in each case. Squares represent males and circles represent females. Black symbols represent individuals affected by the condition and white symbols represent unaffected individuals. In the bottom chart the grey symbols represent individuals who are partly affected.
The probability of the different phenotypes in the offspring of some of the couples in the pedigrees (marked with an asterisk *) can also be determined.

CHOOSING SYMBOLS FOR ALLELES

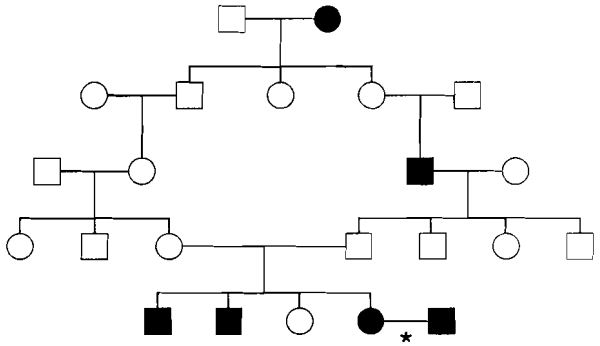
These rules are usually followed:

1. *Dominant and recessive alleles of a gene*
   One letter of the alphabet is chosen. The dominant allele is represented by the upper-case letter and the recessive allele by the lower-case letter (e.g. A and a).
2. *Codominant alleles*
   One letter of the alphabet is chosen. This letter and a superscript letter represent each allele (e.g. C^W and C^r).
3. *Sex-linked dominant and recessive alleles*
   The letter X is used to symbolize the X chromosome. Each allele is shown superscripted (e.g. X^H and X^h).

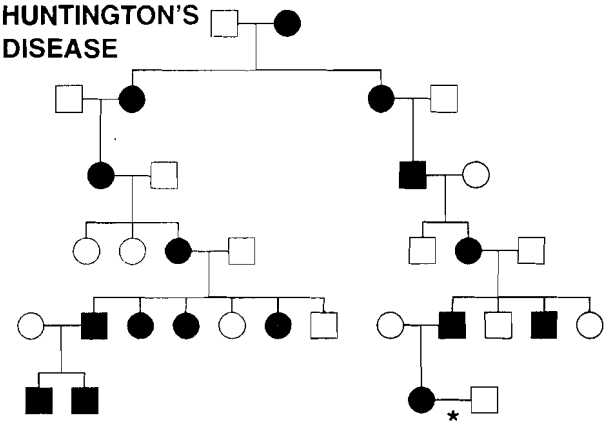
MUSCULAR DYSTROPHY



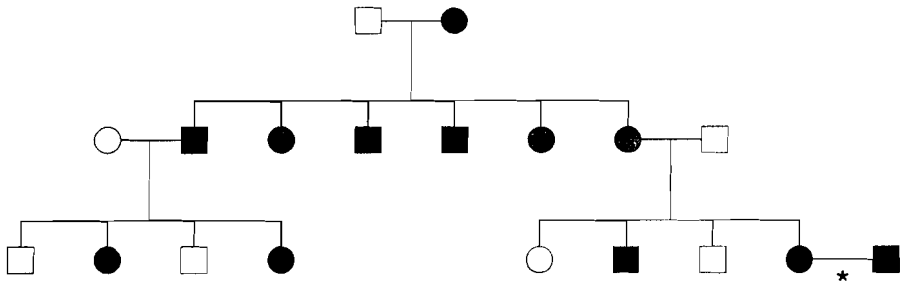
ALBINISM



HUNTINGTON'S DISEASE



GLUCOSE PHOSPHATE DEHYDROGENASE DEFICIENCY



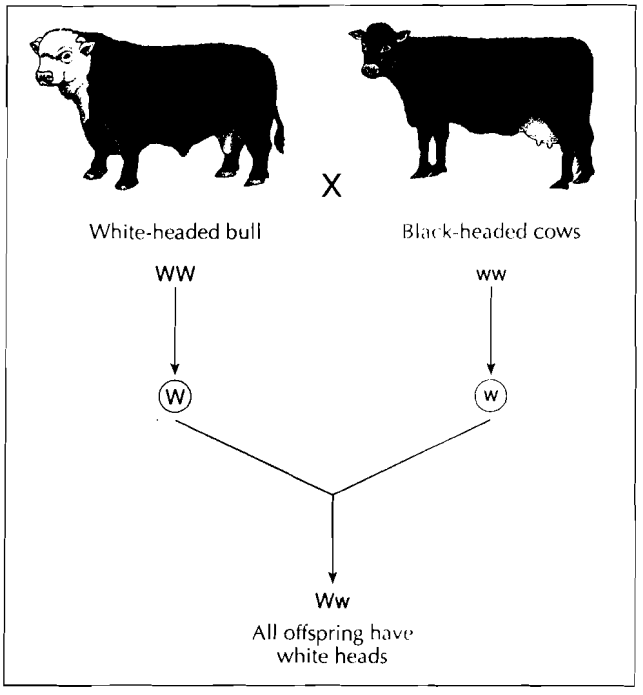
Genetic screening is the testing of an individual for the presence or absence of a gene. Plant and animal breeders can test for the presence of a recessive allele using a test cross. Genetic screening for humans involves more modern analytical techniques but is a more controversial procedure.

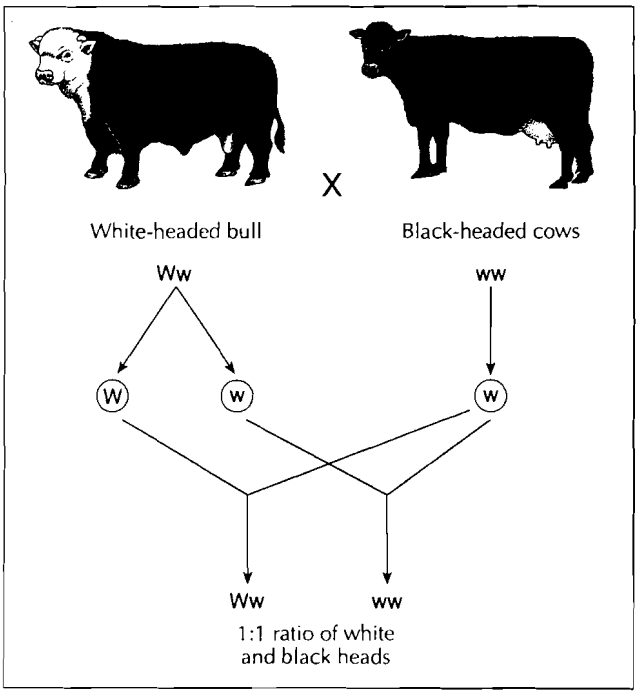
TEST CROSSES

It is not always possible to discover whether an individual does or does not have a gene by looking at the individual's phenotype. If one allele of a gene is dominant and another allele is recessive, an individual with two copies of the dominant allele has the same phenotype as an individual with one dominant and one recessive allele. These two genotypes can be distinguished by carrying out a test cross. *In a test cross an individual that might be heterozygous is crossed with an individual that is homozygous recessive.*

AN EXAMPLE OF A TEST CROSS

A farmer is unsure whether his bull is a pure-bred Hereford or whether it is a Hereford x Aberdeen Angus hybrid. Hereford cattle have a white head caused by a dominant allele (H). Aberdeen Angus cattle have black heads caused by a recessive allele of the same gene (h). The farmer crosses his bull with 100 Aberdeen Angus cows. The figure (below left) shows the outcome if the bull is pure-bred Hereford and the figure (below right) shows the outcome if the bull is a Hereford x Aberdeen Angus hybrid.





GENETIC SCREENING IN HUMANS

The question of whether genetic screening techniques should be used in human populations has been widely discussed. There are potential advantages but also possible disadvantages. Some of these are shown in the table below.

Advantages of genetic screening

1. *Fewer children with genetic diseases are born*
   Men or women who are carriers of an allele that causes a genetic disease could avoid having children with the disease by choosing a partner who has been screened and found not to be a carrier of the same allele
2. *Frequency of alleles causing genetic disease can be reduced*
   Couples who know that they are both carriers of a recessive allele that causes a genetic disease could use IVF to produce embryos and have the embryos screened for the allele. Embryos that do not carry the allele could be selected for implantation
3. *Genetic diseases can be found and treated more effectively.*
   If some genetic diseases are diagnosed when a child is very young, treatments can be given which prevent some or all of the symptoms of the disease. PKU is an example of this

Disadvantages of genetic screening

1. *Frequency of abortion may increase*
   If a genetic disease is diagnosed in a child before birth, the parents may decide to have it aborted. Some people believe that this is unethical
2. *Harmful psychological effects*
   If a person discovers by genetic screening that they have a genetic disease or will develop a disease when they are older, this knowledge might cause the person to become depressed
3. *Creation of a genetic underclass*
   People who are found to have a genetic disease may be refused jobs, life insurance and health insurance and be less likely to find a partner

Genetic disease and gene therapy

GENE MUTATION AND GENETIC DISEASE

Genes are almost always passed from parent to offspring without being changed. Occasionally genes do change and this is called **gene mutation**.

Gene mutation is a change to the base sequence of a gene. The smallest possible change is when one base in a gene is replaced by another base. This type of gene mutation is called a **base substitution**. Although only one base is changed, the consequences can be very significant. Many gene mutations cause a genetic disease. More than 4000 genetic diseases have been discovered. One example is sickle cell anemia.

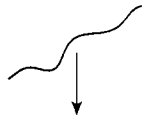
GENE THERAPY

Gene therapy is the treatment of genetic disease by altering the genotype. It might be possible in the future to eliminate genetic disease by changing the base sequence of the allele causing the disease. An easier possible technique, if the allele causing the disease is recessive, is to insert the dominant allele that prevents the disease into affected cells. This could be done at various stages in the human life cycle – in sperm, eggs, early embryos or body cells. The best body cells to use are stem cells. Stem cells can divide again and again to replace body cells that have been lost.

Most attempts at gene therapy so far have not been successful. There has been some success in treating patients with severe combined immune deficiency (SCID) caused by lack of an enzyme called ADA. If this enzyme is not present, healthy lymphocytes cannot be produced by bone marrow and the immune system cannot fight diseases. The gene causing SCID is a recessive allele of a gene on chromosome 20. Most people have a different allele of this gene and can use it to make ADA. A famous case of gene therapy involved a baby called Andrew.

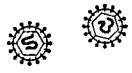
Gene therapy for SCID

Genetic screening before birth shows that Andrew has SCID

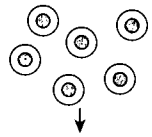


The allele that codes for ADA is obtained. This gene is inserted into a retrovirus

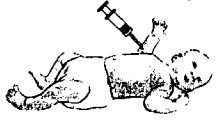
Blood removed from Andrew's placenta and umbilical cord immediately after birth contains stem cells. These are extracted from the blood



Retroviruses are mixed with the stem cells. They enter them and insert the gene into the stem cells' chromosomes



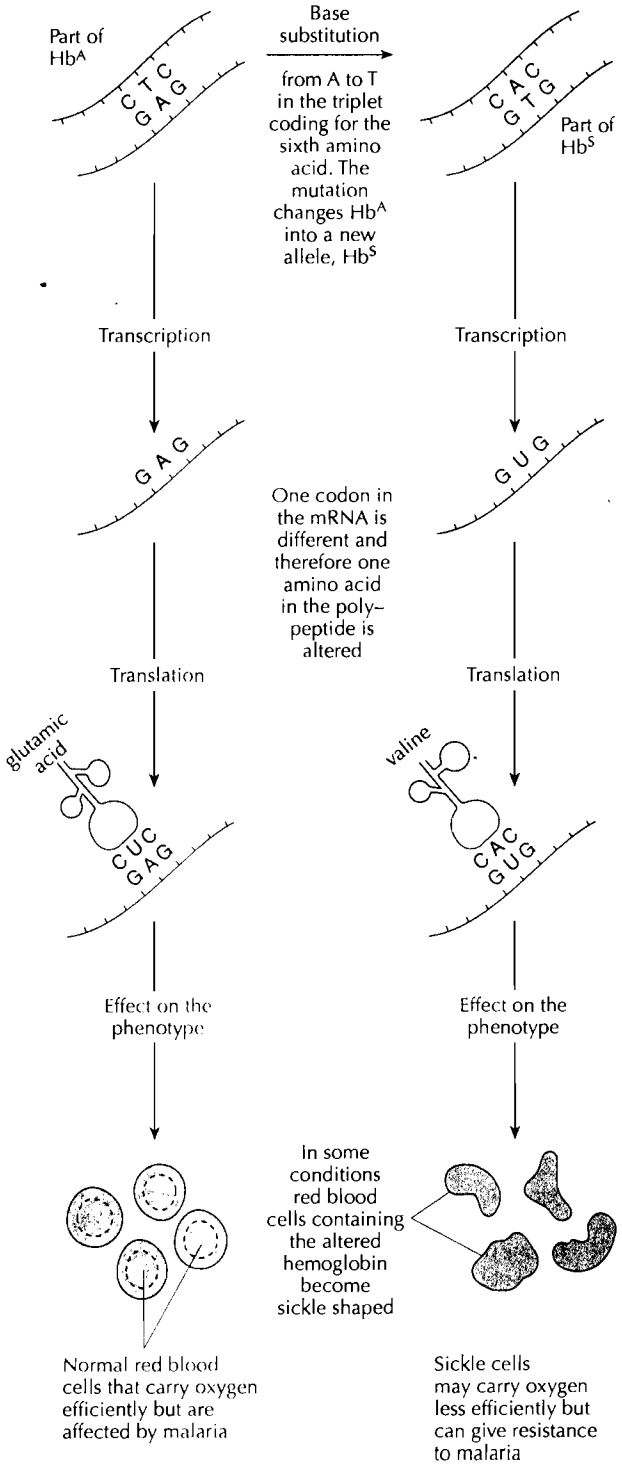
Stem cells containing the working ADA gene are injected into Andrew's blood system via a vein.



For four years T-cells (white blood cells), produced by the stem cells, made ADA enzymes, using the ADA gene. After four years more treatment was needed.

Sickle cell anemia – the consequences of a base substitution mutation

Hb is a gene that codes for a polypeptide of 146 amino acids forming part of hemoglobin

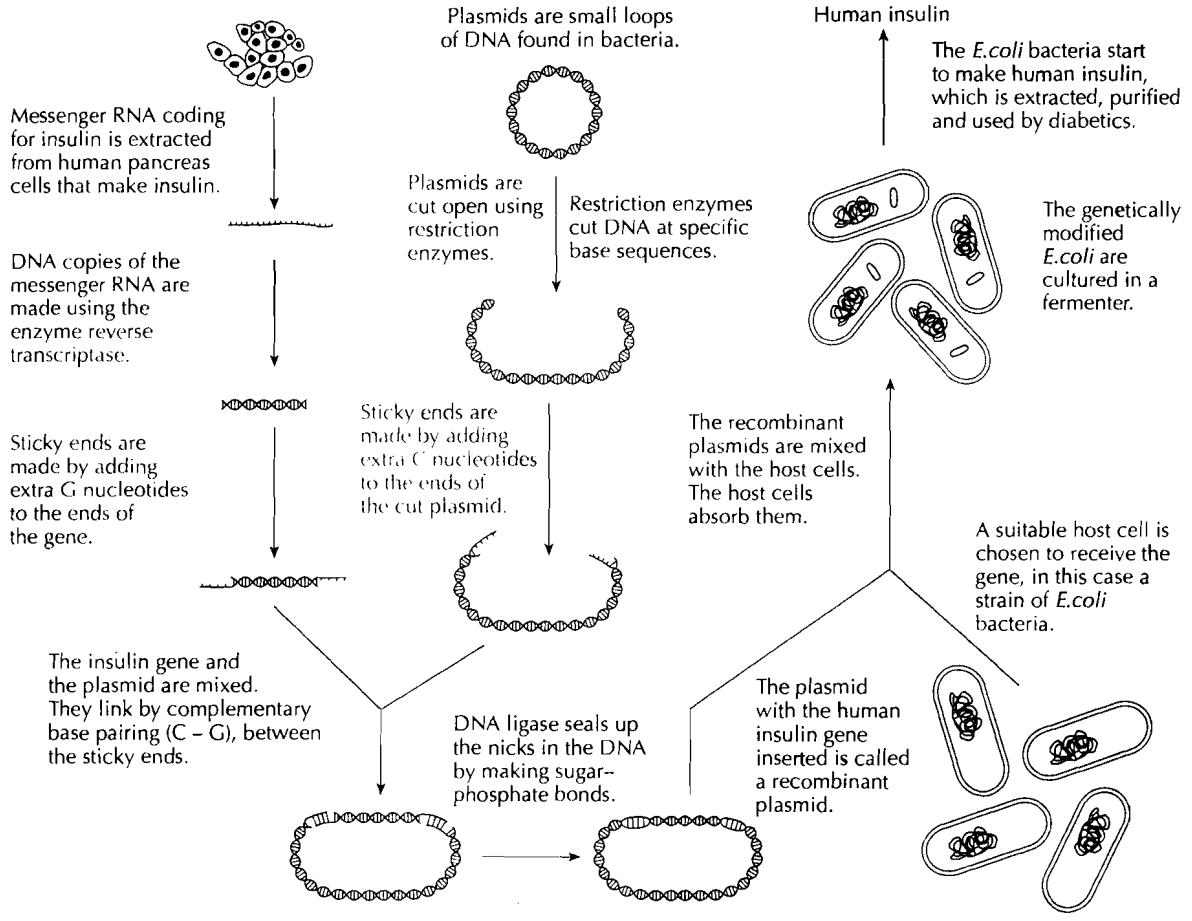


The allele Hb^S that causes sickle-cell anemia has become quite common in some parts of the world affected by malaria. In these regions the malaria resistance that it causes is an advantage

GENETIC MODIFICATION AND ITS USES

The genetic code is universal, so genes can be transferred from one organism to another, even if they are members of different species. A gene codes for the same polypeptide whether it is in a human cell, a bacterium or any other cell. Organisms that have had genes transferred to them are called **genetically modified organisms** (GMO) or transgenic organisms. The process of transferring genes is called genetic modification. An example is the transfer from cattle to chickens of a gene for making growth hormone. Another example is the transfer of the gene for making human insulin to bacteria (see below).

Techniques used for gene transfer into bacteria



BENEFITS AND RISKS OF GENETIC MODIFICATION

The production of human insulin using bacteria has enormous benefits and no obvious harmful effects. There are other examples of genetic modification that are more controversial. Maize crops are often seriously damaged by corn borer insects. A gene from a bacterium (*Bacillus thuringiensis*) has been transferred to maize. The gene codes for a bacterial protein called Bt toxin that kills corn borers feeding on the maize.

Potential benefits of Bt maize

1. Less pest damage and therefore higher crop yields to help to reduce food shortages
2. Less land needed for crop production, so some could become areas for wildlife conservation
3. Less use of insecticide sprays, which are expensive and can be harmful to farm workers and to wildlife

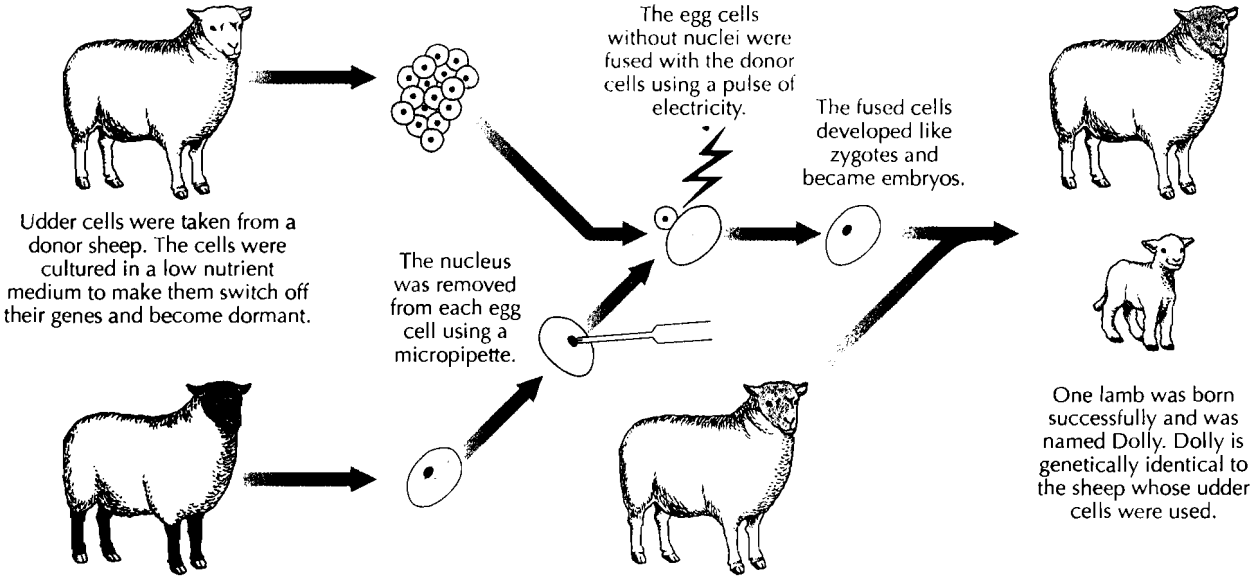
Possible harmful effects of Bt maize

1. Humans or farm animals that eat the genetically modified maize might be harmed by the bacterial DNA in it, or by the Bt toxin
2. Insects that are not pests could be killed. Maize pollen containing the toxin is blown onto wild plants growing near the maize. Insects feeding on the wild plants, including Monarch butterfly caterpillars are therefore affected even if they do not feed on the maize
3. Populations of wild plants might be changed. Cross-pollination will spread the Bt gene into some wild plants but not others. These plants would then produce the Bt toxin and have an advantage over other wild plants in the struggle for survival

Cloning

Cloning is producing identical copies of genes, cells or organisms. The products of cloning are called a **clone**. *A clone is a group of genetically identical organisms or a group of genetically identical cells derived from a single parent.* Cloning is very useful if an organism has a desirable combination of characteristics, and more organisms with the same characteristics are wanted. Most plants can be cloned quite easily from pieces of root, stem or leaf. Animals cannot be cloned in the same way from parts of their bodies. If animal embryos are divided up at an early stage into several pieces, each piece can develop into a separate animal. (This happens naturally when identical twins are formed.) However, it is hard to predict which embryos will develop into animals with desirable characteristics and should therefore be cloned. The first successful cloning of an adult with known characteristics produced Dolly the sheep (see below).

Techniques for cloning using differentiated cells



CLONING IN HUMANS

Experiments have shown that it is possible to clone humans, but there are many ethical issues and human cloning has been banned in many countries.

Arguments for cloning in humans

1. Happens naturally when identical twins are formed, so it is not a new phenomenon
2. Cloning of embryos would make screening of embryos for genetic disease easier
3. Infertile couples might have more chance of success with IVF if their embryos were cloned

Arguments against cloning in humans

1. Groups of genetically identical people might suffer psychological problems of identity or individuality
2. Cloning using differentiated cells would often cause suffering because it carries a high risk of fetal abnormalities and a high rate of miscarriage
3. DNA taken from differentiated cells has already begun ageing and humans cloned from it might therefore grow old more quickly than is usual

THE HUMAN GENOME PROJECT

The human genome has been estimated to consist of between 30 000 and 40 000 genes. The Human Genome Project aims to find the location of all of these genes on the human chromosomes and the base sequence of all of the DNA that makes them up. The project is an international cooperative one, with laboratories in many countries involved.

The sequencing of the entire human genome will make it easier to study how genes influence human development. It will allow easier identification of genetic diseases. It will allow the production of new drugs based on DNA base sequences of genes or the structure of proteins coded for by these genes. It will give us new insights into the origins, evolution and migrations of humans.

PCR –THE POLYMERASE CHAIN REACTION

In the polymerase chain reaction, DNA is copied again and again to produce many copies of the original molecules. Millions of copies of the DNA can be produced in a few hours. This is very useful when very small quantities of DNA are found in a sample and larger amounts are needed for analysis. DNA from very small samples of semen, blood or other tissue or even from long-dead specimens can be amplified using PCR.

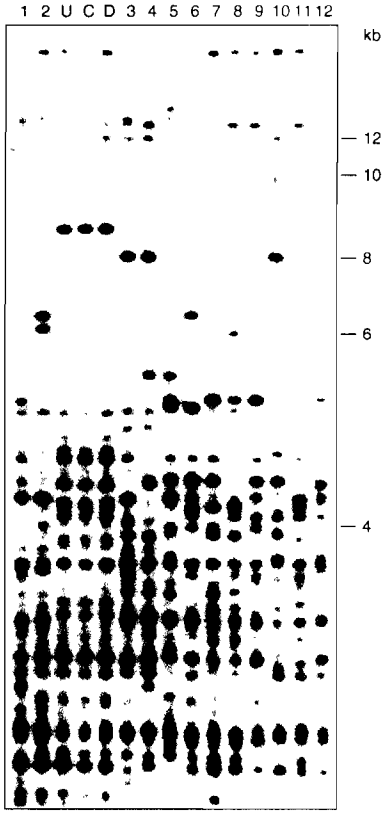
GEL ELECTROPHORESIS

Gel electrophoresis is a method of separating mixtures of proteins, DNA or other molecules that are charged. The mixture is placed on a thin sheet of gel, which acts like a molecular sieve. An electric field is applied to the gel by attaching electrodes to both ends. Depending on whether the particles are positively or negatively charged, they move towards one of the electrodes or the other. The rate of movement depends on the size and charge of the molecules – small and highly charged molecules move faster than larger or less charged ones.

DNA PROFILING

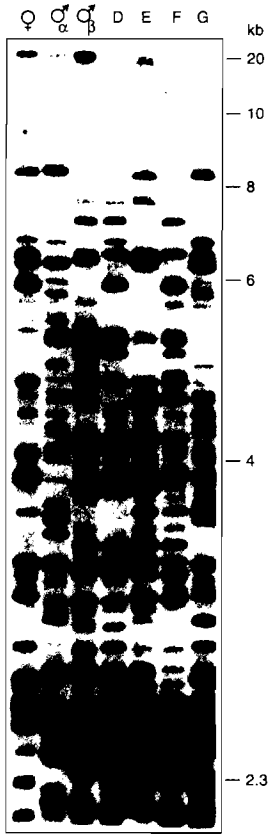
Humans and other organisms have short sequences of bases that are repeated many times, called satellite DNA. This satellite DNA varies greatly between different individuals in the number of repeats. If it is copied using PCR and then cut up into short fragments using restriction enzymes, the lengths of the fragments vary greatly between individuals. Gel electrophoresis can be used to separate fragmented pieces of DNA according to their charge and size. The pattern of bands on the gel is very unlikely to be the same for any two individuals. This technique, called DNA profiling or DNA fingerprinting has many applications. These include criminal investigations, research into variation in populations and tracking individuals in populations such as migrating whales. Figures below show two examples of DNA profiling.

Testing whether samples of DNA show differences using DNA profiling



The results of DNA profiling of Dolly the sheep are shown above.
U = the udder cells from the donor sheep
C = cells in the culture derived from the udder cells
D = blood cells from Dolly the sheep
1 – 12 = results from 12 other sheep for comparison.
The results confirm that Dolly is a clone of the donor udder cells.

Testing parentage using DNA profiling



The DNA profiles of a family of dunnocks (*Prunella modularis*) are shown above. Dunnocks are small birds found in Europe, North Africa and Asia. The tracks from left to right are: the female, two resident males that might have been the father of the offspring and four offspring. The results show that the β male fathered three of the four offspring (D, E and F), despite being less dominant than the α male.