

Introduction

A complex organism such as a human being is composed of somewhere between one million-million cells and one hundred million-million cells; no-one is quite sure exactly how many there are.

In a complex organism many of these cells specialise and form themselves into groups of tissues and organs which undertake particular functions on behalf of the organism as a whole.

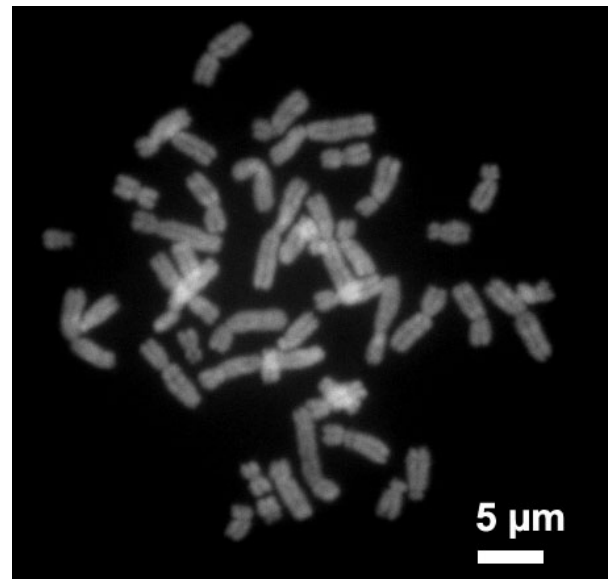
The detail of how all these processes and functions are controlled is beyond the scope of this factsheet. Suffice it to say that there is a substantial body of evidence to support the theory that DNA encodes instructions on how and when to make certain proteins that a living organism might require, and that there are other mechanisms to control when these processes are switched on and off.

The proteins that are made might be used directly as building blocks in the cell or other parts of the body, or they might be used to help with, and control, chemical reactions to make other building blocks such as sugars and lipids that are not coded for directly in DNA.

DNA (Deoxyribonucleic Acid)

DNA is not randomly distributed around the cells but is very closely controlled and protected. With the exception of red blood cells, every cell of the body contains a nucleus within which the cell's DNA is found.

This DNA is not stored as one large "lump" in the nucleus; instead it is divided into 46 smaller volumes called chromosomes. (See photograph below).

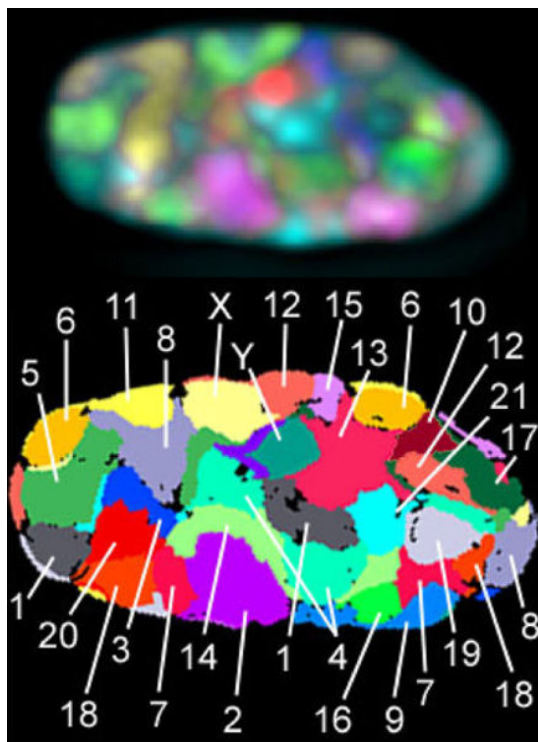


Chromosomes "condense" and become visible just after they have copied themselves prior to cell division. The two copies remain joined together by a structure called the centromere (arrowed below) until shortly before the cell divides.



MND Scotland is the working name of the Scottish Motor Neurone Disease Association, the only charity funding research and providing care and information for those affected by MND in Scotland.

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The locations of the 46 chromosomes immediately before they condense as revealed by fluorescent probes attached to the chromosomes.

Each of the structures in the above photographs is actually two copies of the same chromosome. Normally the chromosomes are not visible until they have been copied and then condensed before a cell divides. (Cell division is how we make more cells to let us grow.) At this stage the visible structures look like various kinds of “X” shape as they are made up of two copies of each chromosome joined, more or less, near their middles. These will eventually separate to form two separate chromosomes that move apart in order that each of the cells arising from cell division contains one copy of each chromosome, i.e. half of each “X.”

Each individual chromosome is composed of a double strand of DNA, (therefore the “X” structures contain four DNA strands, two in each half. Each double strand of DNA has been likened to

a rope ladder, which is then twisted into a helix; the two sides of this “ladder” forming a “double helix.”

Each of these long DNA molecules is composed of a class of chemical known as a nucleotide. DNA is made up of only four types of nucleotide (Adenine, Cytosine, Guanine and Thymine) known by the first letters of their names as “A,” “C,” “G” and “T.”

When DNA is analysed chemically it is found that the amount of T and A are always equal, as are the amount of C and G. This has led to the conclusion that within the double helix A always pairs with T and C always pairs with G so that if one strand of DNA had the sequence “CCGAAT” then the other strand would be the converse of that code and would consist of “GGCTTA”. These two strands are often referred to as the “Sense” and “Antisense” strands since, only one of the strands is “transcribed” or “re-written” as RNA when the gene is being used by the cell. (RNA will be discussed later, but since RNA is only ever copied from one strand of the DNA double helix we call the strand that is copied the “sense” strand.)

The importance of the double helix is due to the fact that if only one strand is present the sequence of the missing strand can be worked out from the “rules of pairing,” (“C” matches with “G” and “T” matches with “A” across the rungs of the ladder). This is an important mechanism to help maintain accuracy when copying the strands.

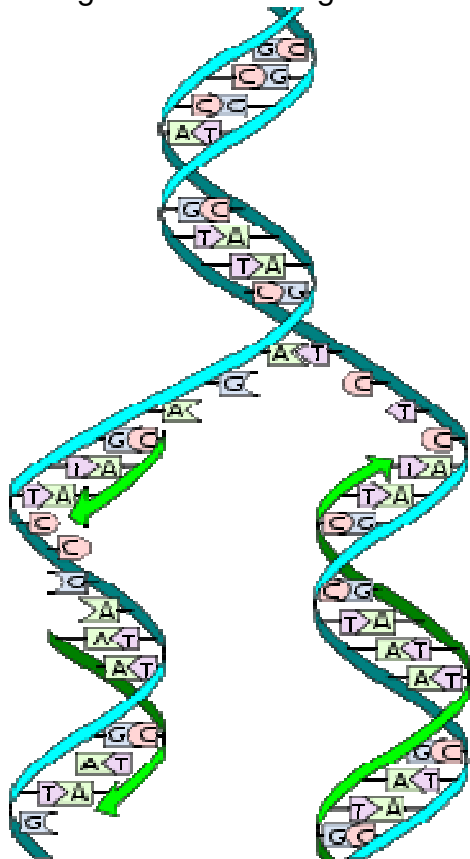
When DNA is being reproduced it “Unzips” and each strand acts as a template for the creation of its new partner strand. If, by accident, during this process a “G” was placed at position 3 instead of a C the other strand in the above example would read GGGTTA and

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the two “G”s at position 3 would not fit together properly. An error like this would be picked up and corrected by mechanisms in the cell which check for errors.

In normal humans the chromosomes are found to consist of 22 matched pairs and two sex chromosomes. In females the sex chromosomes consist of a matched pair called the “X” chromosomes, while in males the sex chromosomes consist of one “X” (the same as a female has) and one “Y” chromosome

Chromosomes are not uniform along their length, but are divided into a number of distinct regions known as “genes.”



An original strand of DNA “unzips” and each strand is used as a template to manufacture the opposite strand.

It is thought the 23 human chromosomes contain a total of about 30,000 or so

functional genes. Not every gene is active all the time and some require the presence of particular signals to switch them on or off. For example, the processes required to make the chemical melanin, which is the brown pigment of a sun tan, is switched on in skin cells when they are exposed to ultra-violet light. Skin protected from UV light contains less melanin and remains untanned.

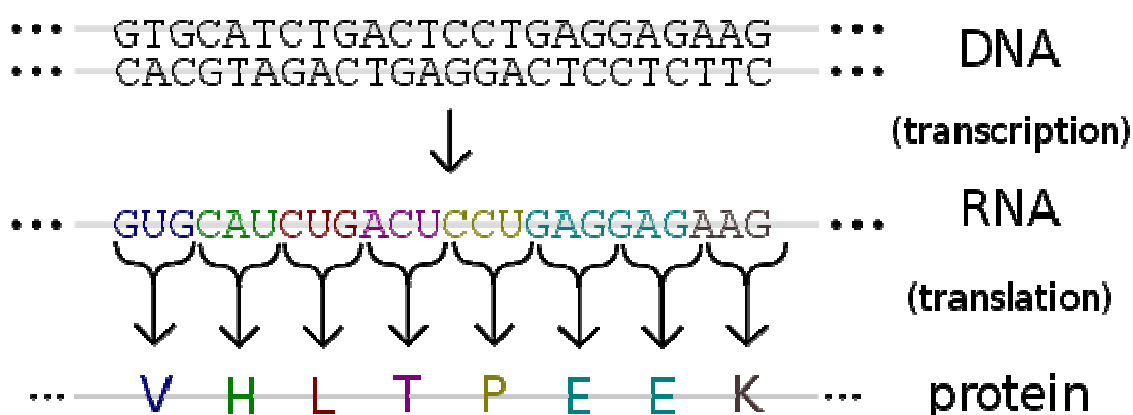
What Genes Do

Each gene is responsible for making a protein that contributes to the wellbeing and functioning of the whole organism. In some cases this protein might be a “structural protein” that is used directly in building the body cells themselves. In other cases the protein produced may be of a kind known as an “Enzyme.” Irrespective of their role, proteins are built up from simpler compounds called amino acids.

Specialised cellular processes are capable of finding the start and end of a gene and can make expendable “copies” of the “sense strand” using a recyclable chemical similar to DNA called RNA (Ribonucleic acid). This RNA copy is of one strand only and is exported from the nucleus to be read by yet other cell structures called a ribosome. While DNA contains the four bases coded for by C, G, T & A, the T (Thymine) is replaced by Uracil (U) in RNA.

It is the job of ribosomes to read the transcribed “letters” of the genetic code in the RNA in groups of three (known as a triplet) and to bring in the amino acid coded for by each triplet. Having added that amino acid the ribosome moves to the next group of three and adds the amino acid they code for and so on until it reaches the end of the RNA copy of

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The sense strand of DNA is transcribed into RNA. A specialised structure, called a ribosome “reads” the RNA bases in groups of three (a triplet) and translates them into protein by adding the amino acid coded for by each “triplet”.

gene. Ultimately this process translates the information coded in the DNA into a protein which can then be used by the cell as required. Some proteins, such as digestive enzymes or hormones like insulin, are exported from the cell. Others can be used directly to build or repair a growing cell; while others have a very brief life, being used for a very short period to make intermediate metabolites from other building blocks in a cell and then broken down again to be recycled.

Enzymes

Enzymes are biochemicals which act as catalysts and encourage other kinds of chemical reactions to take place.

Enzymes fall into two broad groups: one group helps to combine simpler chemicals into more complicated structures, while the other group breaks down complicated chemicals into their building blocks.

It is thought that enzymes help these chemical reactions because any one enzyme has a unique shape into which the chemicals it causes to react can fit in

a specific way. The analogy of a “lock and key” is often used to describe how enzymes and their substrates fit together.

Once the enzyme has locked on to its substrates it helps the chemical reaction take place by holding the chemicals in a particular way that allows them to either join together or break apart more efficiently. Once the chemical reaction has happened the enzyme then releases the products of the reaction and is available to help, or catalyse, another reaction of the same kind.

In many instances enzymes work in partnership with each other: the products of the first enzymatic reaction can be picked up by a second, different, enzyme to be further modified and so on. Chains of reactions like this, involving sequential modifications by a series of enzymes, can build up very complex chemicals from simpler building blocks or, as in the digestive system, break down very complex chemicals into their simpler components.

At the cellular level energy is released from digested foods such as sugars and

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fats when the energy rich food is passed along a chain of chemicals, during which enzymes gradually break down the food molecule. At each stage high energy products can be passed into other chains to have their energy captured for use by the cell. Professor Pam Shaw at Sheffield University is investigating a chain called the Cytochrome Chain for its possible involvement in MND. If the DNA coding for one of the enzymes used in the chain has an error then, ultimately, that cell will not be able to derive usable energy from food sources and will die. Professor Shaw's investigations have identified several genes that have gone wrong in the motor neurones of some people with MND.

At the time of writing it is thought about 24 genes are involved in MND, sixteen of the 24 being associated with Familial ALS due to the way in which they appear to be passed on from generation to generation by what is known as either "Simple Inheritance," or "Mendelian Inheritance."

Simple Inheritance

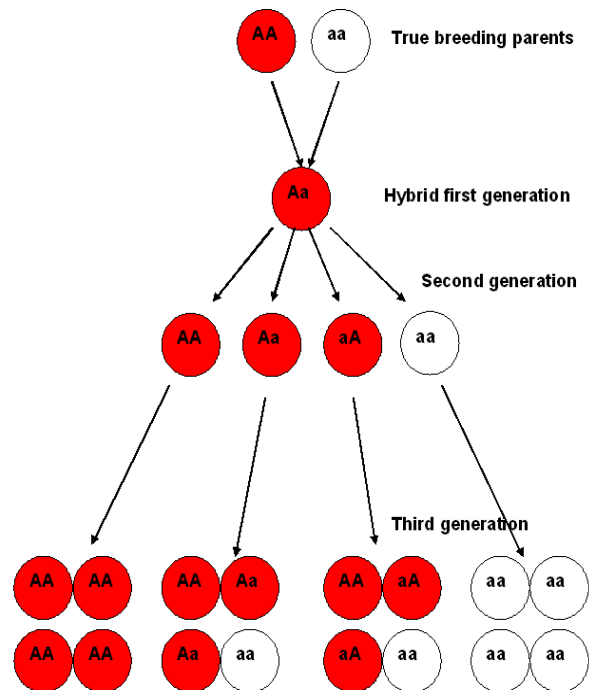
Gregor Mendel, often referred to as the father of genetics, was a monk who studied how characteristics are passed on to subsequent generations of pea plants. Among the characteristics he tracked from generation to generation were the colour of the pea seeds (green or yellow) whether the seeds had wrinkled seed coats or smooth seed coats and the colour of the flowers.

Mendel discovered that in pea plants some characteristics were always expressed while others could be hidden for a generation and then re-appear in subsequent generations. For example, if two true-breeding strains of pea plants, one having red flowers and the other having white flowers, are crossed with

each other all the offspring have red flowers.

If plants from these first generation red-flowered plants are self-fertilised their offspring (second generation) are found to consist of about $\frac{1}{4}$ white-flowered plants and $\frac{3}{4}$ red-flowered. The only explanation for this is that the first generation plants contained the gene for white flowers, but its effects were not seen.

If white flowers from the 2nd generation are self fertilised and used to start a new true breeding strain red flowers never appear in this strain. However, if the red flowers are self fertilised some of them can give rise to true breeding red strains, but the majority will act like the first generation and give $\frac{1}{4}$ white-flowered plants and $\frac{3}{4}$ red-flowered offspring.



Today we describe characteristics like these as Dominant and Recessive characteristics and explain the apparent "disappearance" of the recessive characteristic in the first generation by it being overwhelmed by the dominant

characteristic.

Years later, when the same experiment was repeated using red and white flowered snapdragons it was found that the first generation offspring were all pink and the second generation offspring segregated out to $\frac{1}{4}$ white-flowered, $\frac{1}{4}$ red-flowered and $\frac{1}{2}$ pink-flowered. In the snapdragons flower colour is said to be "Co-dominant." It is now believed that the differences between colour inheritance in snapdragons and peas is due to the white colour of snapdragons being due to a white pigment, whereas white pea flowers lack a pigment, i.e. the pink snapdragon flowers arose from the mixing of two different pigments from two forms of the gene; in contrast the "Aa" peas are red instead of pink since there is only one working gene which is making red pigment, the other gene is making nothing at all.

Inherited forms of ALS

Seven of the named inherited forms of ALS are relatively rare or unknown in the UK (ALS 2 – 8). The eighth gene, known as the Copper-zinc superoxide dismutase-1 gene, (thankfully abbreviated to SOD1,) is associated with both FALS and some cases of sporadic ALS. With the exception of sporadic ALS all eight of these named conditions appear to follow the rules of simple inheritance in the ways in which they are transmitted through the generations. Some are attributable to dominant genes while others are attributable to recessive genes.

It is believed that in the best known example of inherited MND, attributable to the SOD1 gene, both the healthy SOD1 and the mutant SOD1 protein are produced in those who carry a SOD1 mutation, but the effects of the mutant SOD1 eventually predominate in the

motor neurones of the person with a SOD1 mutation. This conforms to dominant inheritance patterns.

Between 20 and 30% of familial cases are attributable to the SOD1 gene. The remaining 70 to 80% of familial cases are not associated with mutations to the SOD1 gene but are attributable to other genes that can be passed on to future generations in a way similar to the SOD1 gene. Two new genes, TDP43 and WNT3 have very recently been identified as also being involved in inherited MND. More will be learned about them in the coming years.

SOD1

Genes and proteins very often share the same name to indicate that the gene and the protein are in some way connected. The "Copper-zinc super-oxide dismutase 1" gene (SOD1), makes the SOD1 enzyme which is designed to mop up and neutralise the free-radical "superoxide" (O^-), which is a negatively charged oxygen atom. Superoxide is produced as a normal by-product of cell metabolism.

If free radicals are not mopped up and neutralised they can cause considerable damage to the cells themselves as well as the DNA they contain. It is for this reason the SOD1 protein is found in all body cells.

A small number of people who develop ALS do so because of mutations to one copy of their SOD 1 gene. It is believed that the mutation causes the SOD 1 protein it makes to take on a shape that is difficult for the cell to break down afterwards so allowing SOD1 protein to build up and, eventually, poison the cell. Why motor neurones should be preferentially damaged, as opposed to any other cell-types, is not clear.

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Genetic research in MND is still at a relatively early stage and it is more than probable the larger picture has still to be uncovered.

Due to the relatively recent development of genetic testing and the possibility that there are many other genes involved in FMND/FALS, it is not possible for the majority of people diagnosed as having

Familial MND/FALS to have a genetic test to identify their risks as there are no currently known “genetic markers” for the majority of these inherited genes. As with the much more common sporadic MND/ALS, the exact causes of the inherited form of the disease remain unknown – although there is increasing research worldwide on the subject.

Further Information

Factsheet 2	Inherited MND
Factsheet 3b	Inherited Disease