MND Factsheet 3A
Introducing Genetics

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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.

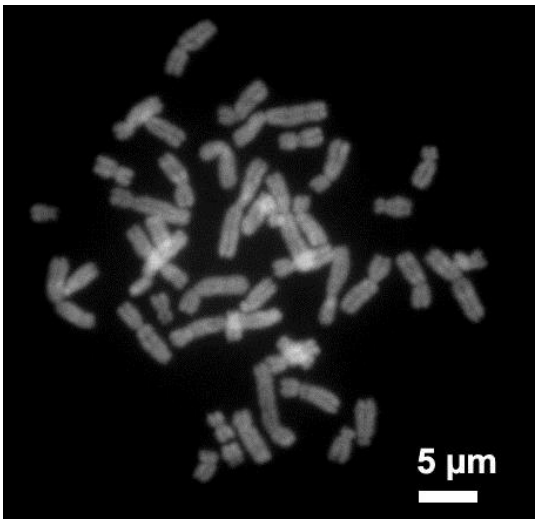
The detail of how all these processes and functions are controlled is beyond the scope of this factsheet. Suffice it to say that there is a substantial body of evidence to support the theory that DNA encodes instructions on how and when to make certain proteins that a living organism might require, and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

The products 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 smaller volumes called chromosomes. Humans have 46 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.

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

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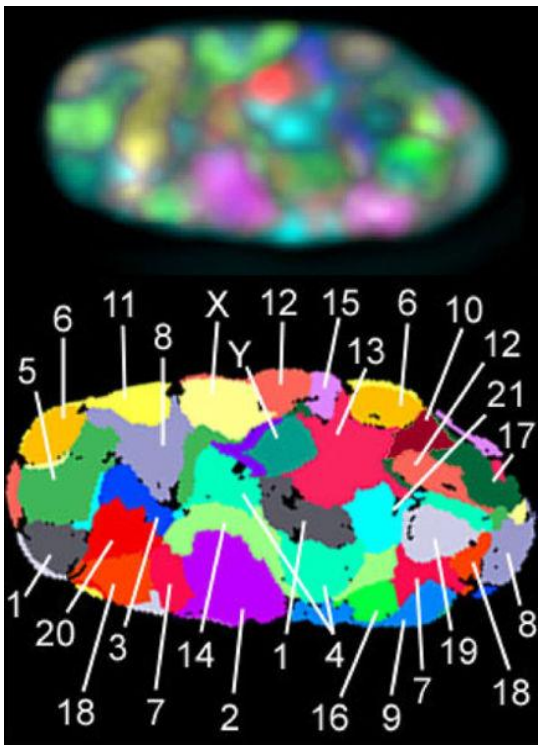
before a cell divides. (Cell division is how we make more cells to let us grow and repair.) At this stage the visible structures look like various kinds of "**X**" shape as they are made up of two copies of each chromosome joined, more or less, near their middles. These will eventually separate to form 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**."



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

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."

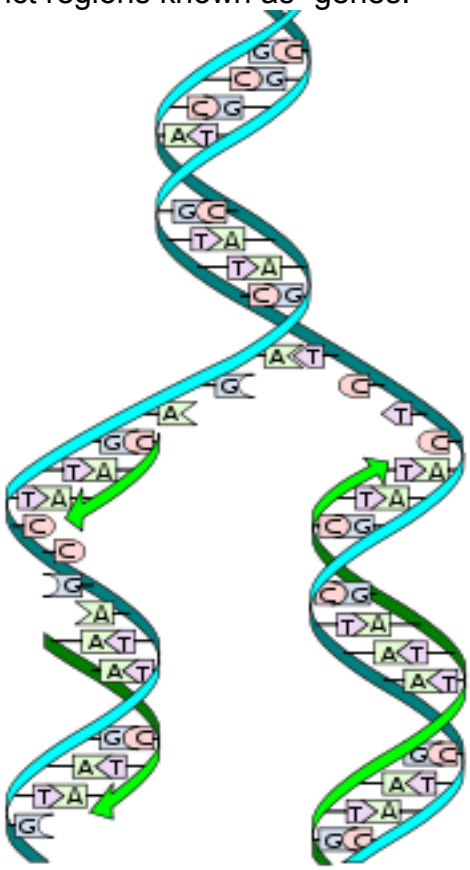
When DNA is analysed chemically it is found that the amount of T and A are always equal, as are the amount of C and G. This has led to the conclusion that within the double helix A always pairs with T and C always pairs with G so that if one strand of DNA had the sequence "CCGAAT" then the other strand 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 GG**G**TTA and 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.

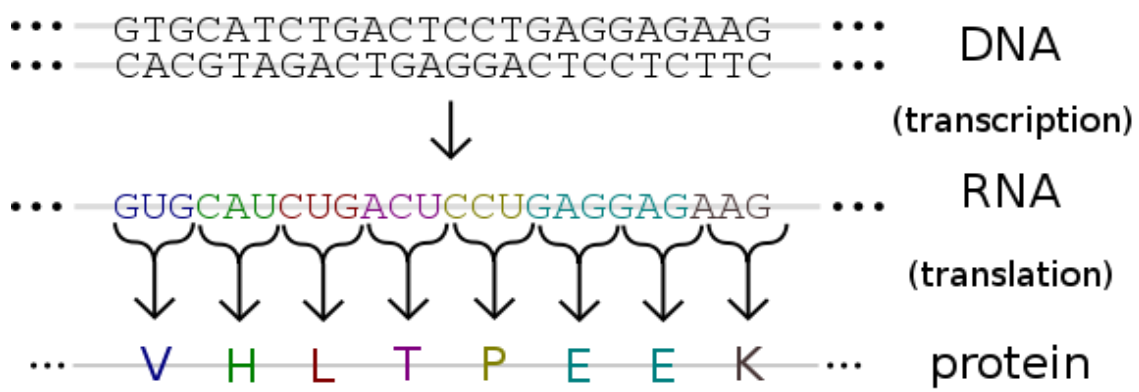
It is thought the 23 human chromosomes contain a total of about 20,000 or so functional genes. Not every gene is active all the time and some require the presence of particular signals to switch them on or off. For example, the processes required to make the chemical melanin, which is the brown pigment 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 the 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



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".

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 reactions to take place between specific chemicals.

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 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 in excess of two dozen genes are involved in MND, most of them 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."

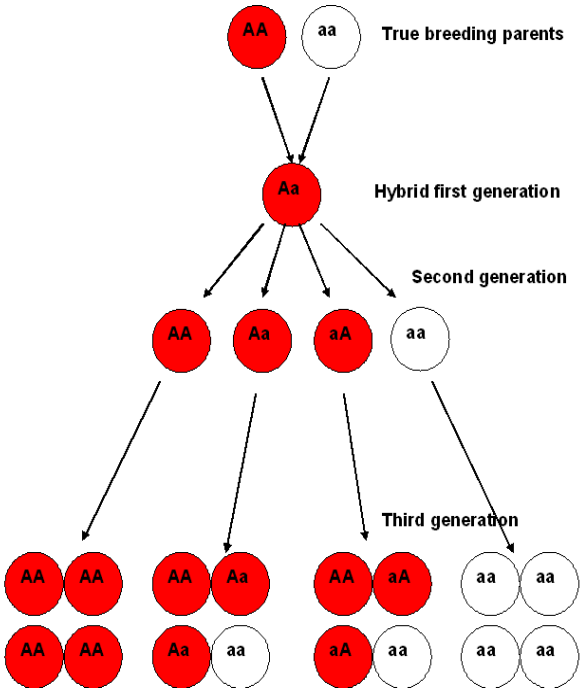
Simple Inheritance

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 ¼ white-flowered plants and ¾ 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 ¼ white-flowered plants and ¾ 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. Unfortunately most of the genes known to be causative in developing ALS/MND are dominant when mutated.

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 ¼ white-flowered, ¼ red-flowered and ½ 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.

An equivalent mechanism is seen in human blood groups where three different forms of the gene that defines blood group are known. These forms of this gene are called "A," "B" and "O". Any one person can only have a maximum of two of these different forms of the gene.

"O" is a recessive gene, while "A" and "B" are co-dominant. The nine possible combinations of pairs of these genes gives rise to four possible blood groups in humans since everyone receives only a single copy of one of these genes from each parent.

	A	O	B
A	AA	AO	AB
O	OA	OO	OB
B	BA	BO	BB

Different ways to make up the four human blood groups, Type A, Type B, Type AB and Type O.

Normally there are two copies of each gene in healthy human cells. However, sometimes one of the copies can be damaged in some way in which case it is referred to as being a mutated form of the gene. Mutated genes are often associated with disorders because the protein that is made from them is not necessarily the protein they should be making. The mutated protein might have no effect on the cells at all, or could actually be poisonous in some way. In some cases, when one gene of a pair is mutated the cells may only get half the amount they need of what it makes and some cell processes run at half speed.

Gene mutations can happen and accumulate as we go through life and most go unnoticed. Sometimes, though, the mutation can give the cell an unexpected vigour causing it to reproduce in an uncontrolled way, causing tumours.

While there is still much to be learned about ALS it is thought that some of the genes involved in inherited ALS can be toxic to the cell when mutated, while others may fail to remove chemical by-products that can be toxic; yet other "genes" might fail to switch on certain essential processes. With these and other mechanisms it is clear that the mechanisms underlying different people's ALS is more complex than first imagined and it will take time to understand how each of the genes actually precipitates the onset of ALS when mutated.

Further Information

Factsheet 2	Inherited MND
Factsheet 3b	Disease Inheritance