Introduction

The common "model" for most of the better known genetic diseases is that of a gene damaged in some way to prevent it from working properly. The knock-on effects of this damage then show up in the person as some form of disease or some kind of deficit that can be traced through the generations to describe its mode of inheritance. This fact sheet explores some of these known mechanisms as these, and others not mentioned here, are areas which researchers are exploring as ways to explain both inherited MND and sporadic MND.

Genetic mutations can arise from a number of different causes, among the better known are exposure to UV light, ionising radiation and exposure to particular kinds of chemicals known as mutagens or carcinogens.

Mutations can also arise from mistakes made when chromosomes are duplicated, either when making the sex cells (sperm or egg) or before cells divide to make new body cells.

Mutations themselves can be of many different kinds ranging from one wrong letter in the DNA coding for one gene to the complete deletion of whole chromosomes and their associated genes. In between these two extremes cases are known where parts of genes have been deleted, duplicated, moved to the wrong place or reversed.

Most mutations result in a loss of function, i.e. the cell can no longer make the intended product from that copy of the gene. Since most chromosomes will have a partner where the gene still functions this is unlikely to be a major problem as far as many genes are concerned. At worst a cell in this position might have to get by on a half dose of the gene's product.

However, some genes, particularly those on the X chromosome in males, have no working partner to back them up, so a mutation in an X-chromosome gene can have serious consequences and, like Duchène Muscular Dystrophy and some forms of colour blindness, can lead to conditions that are carried by females (who have two X chromosomes) and are seen in those male descendants who inherit the faulty X-chromosome.

Very occasionally a mutation can lead to a gain of function. Under these circumstances the mutated protein is made, but far from doing nothing, the mutant protein actually does something else – usually harmful. It is thought that this is what has happened in the known mutations to SOD1 genes that give rise to ALS. The protein the gene should make is made, but with one major exception that totally changes the shape of the protein so that it no longer does its original job. What is worse, the new shape has gained a function which causes it to be damaging to motor neurones and difficult for the cell to dismantle, so allowing it to accumulate and poison the cell.

If the mutation happens when making a

new body cell, then the loss of one copy of that gene from one cell might not be important in any way at all. (There are 10^{12} other cells to compensate). On the other hand, if the mutation happens to a tumour-suppressing gene the results could be very serious if that single cell multiplies out of control to form a tumour.

If the mutation happens when making a sex-cell then all cells that grow from that sex cell and its set of chromosomes will also contain the mutation. In this circumstance the mutation will potentially, be transmissible to future generations since the person's sex-cells will also contain the mutation

In humans, at the moment of fertilisation a sperm from the male parent carries 23 chromosomes into an egg from the female parent, which also contains 23 chromosomes. Following fertilisation these chromosomes match up as 23 "pairs." Thereafter the genetic material of every cell of the embryo, foetus and, ultimately the person, is made by copying the DNA derived from that original fertilised cell – mistakes and all. For the rest of that person's life every new body cell made (except for red blood cells) will contain a copy of each of these 46 chromosomes,

Dominant and recessive traits have been mentioned in detail in Factsheet 3 while a third form of inheritance, "Co-dominant Inheritance," was only mentioned obliquely.

In humans it is known that blood groups A and B both show co-dominance while blood group O is recessive to both A and B. Someone inheriting an A gene from one parent and an O gene from the other would have blood group A, similarly they would have blood group B if they inherited an O and a B (or indeed two Bs). However, inheriting an A from one

parent and a B from the other would give blood group AB as both are equally expressed. Someone with blood group O must have inherited an O gene from each parent. This kind of inheritance is less easy to follow and understand; particularly since there are three forms of the gene and four possible blood groups. None-the-less, it is theoretically possible that some diseases could have a similarly complicated pattern of inheritance that has still to be discovered due to the rarity of the disease.

Gene Inherited from		Child's
Parent 1	Parent 2	Blood Group
A	A	Blood Group A
B	B	Blood Group B
O	O	Blood Group O
A	B	Blood Group AB
A	O	Blood Group A
B	O	Blood Group B

Characteristics that can be described as dominant, co-dominant and sex-linked are relatively easy to follow from generation to generation. In a nutshell, if you can see the characteristic then you know the gene is present.

Recessive traits are more difficult to follow. Some characteristics, such as red hair or blue eyes, can remain hidden by the expression of more dominant genes for many generations and then suddenly appear when two copies of the recessive gene finally come together in the one person again. Some diseases, such as Cystic Fibrosis and Sickle-Cell Anaemia, occur when the person inherits two recessive genes. Neither of their parents may have the disease, but each has a "good" copy of the gene to compensate for their "bad" copy. However, if both give a copy of their damaged gene to any offspring, then the child will develop the condition.

Complications to Simple Inheritance

Simple inheritance can be complicated by "gene-silencing" which is where genes have been effectively switched off and their effects are not seen. Sometimes a cell only needs one copy of a gene and can switch off the other copy. Sometimes the copy that is switched off always comes from the same parent. For example the copy of the gene for "Insulin-Like Growth Factor" (IGF2) that comes from the mother is normally switched off in humans. Similarly Angelman Syndrome and Prader Willi Syndrome arise when the genetic contribution of one parent is lost from the developing embryo. Most often this happens when

> **When half the children of someone with a genetic disease suffer from the same condition as the parent it is most likely that the parent carries a genetic mutation which is dominant for the condition. This is the case with ALS caused by the SOD1 and C9orf72 genes.**
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> **When the condition affects only males, none of their children develop the same condition, but half of their male grandchildren by their daughters show the condition then the mutation is probably carried on the "X" chromosome.**
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> **When the condition appears spontaneously in children from parents who do not have the condition, but each of them know of others with the condition in their ancestry, recessive inheritance should be suspected.**

one of the chromosomes from one parent is accidentally duplicated in the fertilised egg. Sensing that there are three copies of the same chromosome the cell removes one of these chromosomes, leaving behind the two copies that came from the same parent. Since some genes from this parent might normally be silenced the developing embryo lacks the input from these genes leading to these syndromes. Evidence that silencing at the level of the gene can be caused by many different factors is slowly emerging.

Epigenetic Inheritance

This is a special form of gene silencing where the controlling factors are not the genes or DNA as such. The controlling factors in epigenetic inheritance could come from diet, exposure to chemicals, food intake or many other factors.

The best known (and maybe least recognised) example of epigenetic influence is probably shown by the development of a queen honey-bee.

All worker bees and queen bees have exactly the same set of genes when the egg is laid. Those larvae that are fed royal jelly develop into queen bees while the others, who are not fed royal jelly, develop into workers. Queens are larger than workers and are fertile while the smaller workers do not lay eggs. In addition to these physical changes there are also special behavioural patterns that are unique to either worker bees or queens but are not common to both.

In March 2008 an Australian team showed that when a mechanism which silences genes in bees is itself switched off, the larvae then emerged as queens without ever having tasted a drop of royal jelly. It appears, from this evidence, certain genes that promote development into sexually mature females, or queens, are switched off when honey-bee eggs are laid, but switched on in larvae by a diet of royal jelly. The royal jelly, or some chemical contained within it, is therefore directly influencing the expression of genes which would otherwise not be seen. Even more intriguingly, this chemical that switches on the genes to create queens is produced by bees in which the "Queen genes" are switched

off. This suggests that the workers have functioning genes that are switched off in the queens since only worker-bees make royal jelly.

This example illustrates a mechanism by which the same genetic inheritance can lead to two entirely different results when the genes are expressed in one case and silenced in the other and suggests a new mechanism by which disease can be both inherited and influenced by environment.

Some genes could be inherited in their switched off state and can therefore fail to function, so causing disease from an early stage. Conversely, genes that are inherited in a functioning state could be switched off by exposure to some environmental or nutritional factor and, after a normal start, cause disease in later life.

A recent example of this has been seen in mice, where, if the pups are neglected by the mother in infancy certain genes associated with the stress response become switched off leading to heightened anxiety. The chemical changes that caused these genes to be switched off can be reversed by specific drugs and, following the example of the honey bee, they could also potentially be reversed by specific foods. The concept of epigenetics leads to a whole new idea in the way in which disease could be transmitted between generations, despite each new generation apparently receiving genes that have no identifiable damage.

The X chromosome provides a different example of this same idea. Compared to women, how do men get by on a half dose of the genes carried by their two "X" chromosomes?

Or, to look at the question another way, why don't women suffer from diseases caused by having two "X" chromosomes compared to men who have only one copy?

There are several conditions where an extra chromosome causes deviation from the norm in terms of human development. For example an extra chromosome 21 causes Down's syndrome, also known as Trisomy 21 (trisomy = three copies of the chromosome).

Just as in trisomy 21 abnormal numbers of the sex chromosomes can also cause problems. For example only one X chromosome, causes a condition called Turner's syndrome where the development is apparently female, but without female secondary sexual characteristics. Two or more X chromosomes and one Y chromosome leads to Klinefelter syndrome, typified by males with very small genitalia and prostate gland and a tendency to a very feminine body, often with breast development.

So why, when we compare men and women from the viewpoint of the number of copies of genes they have on their respective X chromosomes don't women have problems due to having two X chromosomes when men have only one copy of that chromosome?

Gene silencing or, more accurately, whole chromosome silencing, provides an answer to this question. In the body cells of women it is very possible that the extra X chromosome may cause problems similar to those seen in XXY males due to "too much femaleness". To counter this danger the second copy of the X chromosome is locked away in each cell in a structure called a "Barr Body". Therefore women, like men, have only one working copy of each of the genes of the X chromosome in their body cells.

Even more intriguingly, in the majority of

cases where a woman carries a serious defect on one of her X chromosomes it is most often the chromosome with a defect that is locked away, so sparing her from the expression of the "bad" chromosome's genes.

So, what has this got to do with MND?

There is the perplexing problem of the disparity of the gender ratios in MND. On average, for every two women with MND there are three men with the condition. Is it possible that this gender bias is in some way linked with the mechanisms of both gene silencing and X-chromosome inactivation, even though MND is not known as a sex-linked disorder? Or is this gender disparity due to motor neurones being affected in some way by male hormones? The jury is still out on these possibilities. It is worth noting that all humans produce the same set of hormones, but their proportions and functions differ between males and females. Females have testosterone, but males have more of it. After the menopause, the average female's production of testosterone stays pretty much as it was, but their production of oestrogen and progesterone falls, so allowing the masculisation of features and the growth of facial hair seen in some women as they grow into their pensionable years.

This question of the gender ratio and observations of the possible influences is not posed as part of some rhetorical question; it is a genuine question that deserves exploration in its own right as we learn more about human genetics and the influences of factors other than Mendelian inheritance.

Pseudogenes

Those who accept the theory of evolution as a possible explanation for the gradual changes that would need to take place to allow one species to slowly differentiate from another accept the idea that humans and apes are part of the same, wider family. To them it comes as no shock to discover that some of our human chromosomes are almost identical to those of other apes. More intriguingly, our chromosome 2 looks as though it has developed from the joining together of two smaller ape chromosomes

It is possible that during evolutionary development some chromosomes have joined together while others have split and formed smaller chromosomes.

Occasionally some bits of chromosome become split off from each other during copying and the cell mechanisms don't quite "know" what to do with these separated bits. Equally, genes can be copied to new locations as part of their evolution, consequently requiring that one copy or other should be silenced so as not to produce too much of that gene's product in the cell.

Like a bemused librarian the first cell to encounter these changes away back in our evolutionary past put these extra copies where it "thought" they might fit in the system and put a "Not for Use" sign on them. The mechanism the cell uses to silence genes is called "methylation," in effect the cell covers the silenced gene with "methyl groups," a simple chemical consisting of only carbon and hydrogen, both of which are "cheap" and abundant in the cell. This splitting, joining and duplication of chromosomes and genes means that we have many "pseudogenes" in our DNA. These pseudogenes are extra copies of working genes, usually older, less evolved, forms of the gene that have been locked away and silenced in order that they don't interfere with normal modern development.

In some cases we have over a dozen copies of particular pseudogenes, all of these genes silenced by methylation, just as happens with epigentic factors, leaving only one or, at most, two working copies of the gene as originally intended. What would happen of some of these pseudogenes were re-activated? More importantly, from an evolutionary point of view, what would happen if genes we think of as redundant, including pseudogenes, could be activated in the same way as royal jelly can reactivate the genes for queen-ness in bees?

Each of the above chromosome pairs has the human chromosome on the left and the ape equivalent on the right

Although this is not known to happen, yet,

it is possible that some diseases might arise from reactivated genes. This is the basic principle behind the work of those scientists exploring the theoretical re-activation of viruses incorporated into our DNA as a possible source of disease, including ALS/MND.
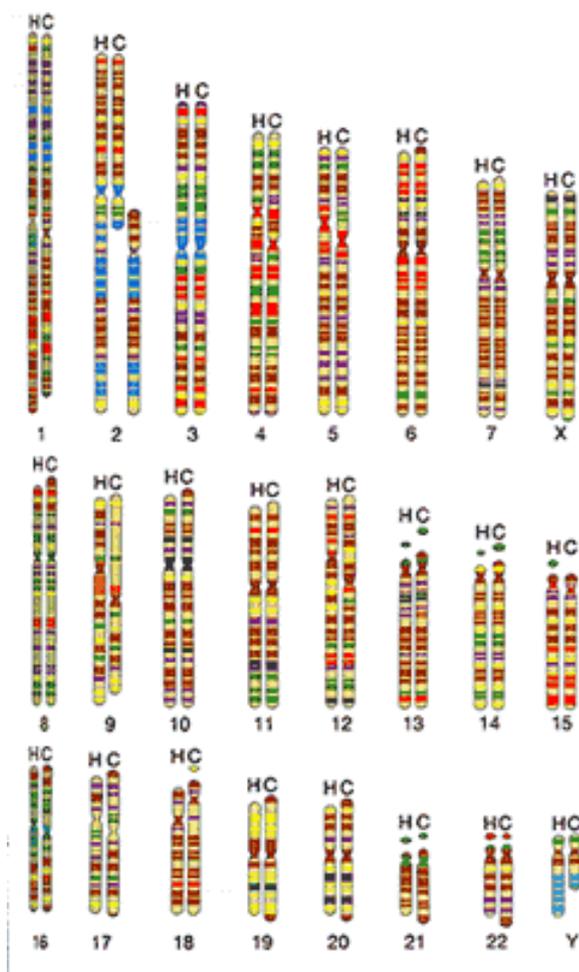
Complex Genetic Inheritance

More complex patterns of inheritance occur when a characteristic is due to the interaction of several genes. This is often described as "Polygenic Inheritance," (many gene inheritance.)

It is possible that some diseases are due to polygenic inheritance. This type of inheritance is very difficult to discover in a non-experimental population, where detailed genetic and medical records over many generations would be required.

Unfortunately, the knowledge of what detail is required to carry out this kind of study has only recently been identified and since there was no need for that kind of information in the past the detail from past generations has not been recorded.

None the less it is theoretically possible that in a disease such as MND, in which many of the cases are apparently "sporadic," polygenic inheritance could be responsible for some of these cases.

Some characteristics, such as skin colour in humans, are thought to be due to at least three genes inherited from each parent (making at least six genes responsible for an individual's skin colour). As each of these genes can have at least two forms, and possibly more, skin colour is incredibly complex and despite more than 100 years of genetic investigations has still not been fully explained. Note: this is different from blood groups where there are three

possible variations of the same gene.

If we assume that a disease could be caused when three "bad copies" of three different genes come together in the one person it is not impossible that such a person may pass on all of the defective genes to one of their offspring, but much more likely that they will pass on only one or two of the genes.

As each "bad gene" will also have a non-disease causing version of the same gene the chances of passing on any one bad gene are 50/50 or 1 in 2.

For every person who gets a copy of the first bad gene their chances of inheriting a copy of the second bad gene are also 50/50 or 1 in 2, therefore half of those with a bad copy of gene one will have a bad copy of gene two and half will have a good copy of gene 2. (At the same time half of these who got a good copy of gene 1 will inherit a bad copy of gene two and a good copy of gene two.) It follows, then, that the chances of inheriting both bad genes are 1 in 4 ($\frac{1}{2}$ X $\frac{1}{2}$ = $\frac{1}{4}$). The chances of all three bad genes being inherited by the one person are $\frac{1}{2}$ X $\frac{1}{2}$ X $\frac{1}{2}$ = 1 in 8. Therefore for each child born to such a parent carrying three "bad" genes there is a 7/8 probability the child will not have all three "bad" genes and will not have the disease that requires all three genes.

If the disease needs all three genes to be present then the probability is that 7 times out of 8 the genes necessary for the disease to develop won't come together in that person's children. As a result the disease might disappear from the family for a couple of generations since only one or two of the genes have been passed on. The disease could reappear several generations later if the missing gene or genes are brought back in by someone with the missing "bad" gene (or genes)

marrying into the family.

There is no reason why polygenic inheritance should be restricted to only 3 genes. If four genes are required they won't come together fifteen times out of sixteen and so on. As you can see from the above examples, the more "bad" genes required to cause the disease the rarer the disease will be and the harder it will be to identify the genes responsible as there will be so many candidate genes.

Recent work involving post mortem analysis of brain tissues from 35 schizophrenics has shown that there might be as many as forty genes involved in schizophrenia and that many of these forty genes were affected by epigenetic factors.

Non coding DNA
"Non coding DNA" is a slight misnomer as it describes DNA which is not translated into proteins, however it does code for specific kinds of RNA. Technically it is the RNA which is non-coding (ncRNA). These stretches of DNA do not have the standard "Start" and "Stop" groups which are typical of genes. There are many different kinds of ncRNA which can act in different ways to influence what is made, or not made, from a gene.

The expression of thousands of genes is controlled by ncRNA, so in addition to the mechanisms whereby genes may be mutated, lost, silenced or otherwise be responsible for a condition there is also the possibility that a gene may be perfectly normal, but the ncRNA which regulates it is somehow not working properly.

The ALS "gene" C9orf72 is a ncRNA whose function is not yet completely understood, yet when mutated by having a section of it repeated many times over it

is responsible for as much as 46% of familial ALS and 21% of sporadic ALS in Finland.

The mechanisms underlying some forms of MND/ALS are only now starting to be understood, but there are many cases where the underlying cause is not yet known. Hopefully within a generation we should know all of the commonly mutated genes and other entities involved in familial inheritance and have made considerable headway in understanding the genetic and other influences underlying all forms of MND.

With our present technology it is unlikely that we can cure MND, in the sense of repairing the damage and making the person better, however it is possible in the near future the application of sensitive screening tests could identify the underlying cause of a person's disease and direct manipulation of the damaged genes by what are known as "antisense drugs" could prevent further damage.

In 2016 Phase 1 and II clinical trials began using an antisense drug developed by Ionis Pharmaceuticals to treat ALS resulting from damage to the SOD1 gene.

A similar kind of drug has received acclaim when it proved to be effective against another neurological condition known as Type 1 Spinal Muscular Atrophy which is usually fatal to very young children. The drug appears to correct the damaged gene and to allow a more normal course of development. Medical advances such as these bring great hope to all those where a genetic condition underlies their disease.

Further Information

New Scientist Issue 2664, 12th July 2008, page 29, or online at:
www.newscientist.com/article/mg19926641.500-rewriting-darwin-the-new-nongenetic-inheritance.html

New Scientist Issue 3094 8th October 2016
www.newscientist.com/article/mg23230943-300-children-with-fatal-muscle-disease-walk-after-drug-breakthrough/

www.ionispharma.com/rd/antisense-technology/discovery-platform/antisense-drugs/

Treating type 1 SMA with antisense drugs www.youtube.com/watch?v=kbMBNi94Wjs

Factsheet 2   Inherited MND
Factsheet 3   Introducing Genetics