

An Introduction to DNA and Inherited Disease

How is a disease inherited?

DNA is passed down through the generations in the cells of the germ line. These are the **ova** in females and the **sperm** in males. The DNA is wound in a remarkably compact way to form **chromosomes**. Each of the germ line cell types, carry one half set of the chromosomes (**haploid**) which normally exist as pairs (**diploid**) in the other cells of our bodies. Humans have 23 pairs of chromosomes in each cell other than the germ line cells, one set inherited from our mother, the other from our father.

Scattered about the chromosomal DNA are the **genes**, currently estimated to comprise around 35,000 different codes. This represents less than 2% of the total DNA contained in the chromosomes with the remaining 98%, often described as 'junk' DNA, yet to be understood. These genes are stretches of DNA that the cell's machinery can read (**transcribe**) and in turn, make (**translate**) into **proteins**.

Proteins are chains of **amino acids** that take on a form and function able to undertake a particular job within the cell and, more generally, within the body. There are 20 different amino acids available and can be assembled in many different combinations. The size of the chain may vary from a few amino acids to a few thousand. It is not hard to see that the number of combinations available is enormous although most of these are not stable and therefore not used.

The tasks undertaken by proteins include breaking down a wide range of chemicals for re-use or disposal, transport, growth, control and communications, structure and many other roles. An important type of protein is referred to as an **enzyme**. These are enablers and accelerators (**catalysts**) of chemical reactions and there is considerable evidence of their presence in our everyday life. They may be referred to as chemical scissors as they cut large molecules into smaller ones for processing. Some examples of enzymes in action are:- fruit going bad, the action of yeast in brewing or baking, the digestion of our food, milk going sour.

Diseases can arise as a result of errors (**mutations**) in the DNA, the biochemical molecule that make up our genes which define how we are made, how we grow and how we die. This DNA is inherited in the cells of all living things through countless generations and is copied to each generation almost without error. However errors do and must occur or nothing would ever change and, change is essential for evolution to operate. Many of the errors are catastrophic and result in early death of those unfortunate enough to inherit them. Many other errors can be tolerated and, in certain circumstances, may even prove advantageous.

The variation in our DNA code accounts for the differences between individuals, and whether we are people, mice, worms, yeast or other life form. The code, which consists of four letters (the names of chemical molecules called bases), A, T, C and G, defines all life, past, present and future. There are about **3 billion of these four letters** in the human **genome** and so it is easy to see how errors can arise when making a copy. Current understanding is that the errors arise as a result of mistakes made by the copying machinery of the cell and by environmental factors such as radiation or chemical contamination. It is thought that each of us harbour a number of disease causing errors in our DNA and these may result in a range of physical and mental illnesses in our lifetime, or may pass unnoticed to our children along with all the good points we like to see such as good health, family likeness and other physical and mental attributes.

The main point about mutations of the genomic DNA is that they specify changes in the construction of associated proteins. At worst this may mean that the protein is not made at all, or more often, is made with a wrong combination of amino acids and as a result, has impaired function. For example, if a gene was to specify how to make a pint glass (a protein), then a mutation may specify a glass with a hole in the bottom. This looks close to a normal glass but clearly would not carry out its function. This could be the result of a simple substitution of one amino acid for another or the addition/deletion of one amino acid. Proteins have great complexity and their chains of amino acids may contain a number of functions such as addresses, sensors, plug in type connections with other proteins or substrates. If one of these functions is badly impaired, then a disease state will result. Some mutations do not disturb the primary function of the protein and it can do its job with no noticeable problem. Such mutations are called **polymorphisms** and many exist in the human genome. These contribute towards the diversity in appearance and health of individuals.

Diseases due to mutations are diseases of the cell and hence apply to all life in all forms, from microbes to men.

The Cells of Inheritance

We can easily see from families with a number of children that an inherited disease does not in general, affect them all.

Why should this be?

The answer lies with the DNA/genes contained in the male sperm and female ova sex cells (**gametes**) and, also whether a particular gene expression is dominant or recessive.

These cells are produced in both male and female from pre-cursor cells which each contain 23 pairs of chromosomes (diploid). In order to produce the gametes, the pre-cursor cells undergo a special form of cell division described as **meiosis**. This results in the production of gametes, which contain just one set of 23 chromosomes (haploid). These chromosomes will be a random mix of the original two sets in each case. If one of the original chromosomes contained a disease gene, then 50% of the haploid sex cells will also contain this gene. This figure will be the same for both males and females. If an ovum (singular of ova) containing a disease causing gene is then fertilised by a sperm containing the same disease gene, then the embryo and subsequently the child, will inherit two disease genes in each of its cells. This is because the fertilised ovum (**zygote**) grows by another type of cell division described as **mitosis**. Each mitotic cell division produces two daughter cells each containing copies of the original 23 pairs of chromosomes. In terms of chance or in mathematical terms, probability, the sum is 'any one from one pair, with any one from a second pair'. This provides for four different combinations as may be seen in the graphic. One combination results in a disease condition, two of the combinations result in carrier status, and one combination is free of any of the disease genes.

When both parents are carriers of Niemann-Pick Disease, there is a 1 in 4 chance (25%) with each pregnancy that both parents will pass on the affected gene to their child and therefore have a child with the disease. There is a 2 in 4 chance (50%) that only one parent will pass on the affected gene to their child, making the child a carrier of the disease. There is also a 1 in 4 chance (25%) that neither parent will pass on the affected gene, the child will not be a carrier and will not be affected by the disease. This is demonstrated in the diagram below.

I = Unaffected gene **X = Affected gene**

Father
II

Mother
II

Child
II

In this case neither parent is a carrier of the affected gene and so they cannot pass it on to their child.

Father
IX

Mother
IX

Child
XX

In this case both parents carry the affected gene and both pass it on to their child.
This child has Niemann-Pick Type C

Father
IX

Mother
IX

Child
IX

If only one parent, either parent, passes the affected gene to their child, the child will be a carrier of the disease like their parents. Currently there is no known adverse health affects associated with being a carrier of NPC.

Father
IX

Mother
IX

Child
II

If neither parent passes on the affected gene to their child, then that child will neither have the disease nor carry it.

[For a definition of the words highlighted in blue, please refer to Our Glossary of Terms on the Website.](#)