Medicine for Managers

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It's All In The Genes

Imagine an Augustinian Friar at St Thomas' Abbey in Austria, a keen gardener and bee-keeper, who became fascinated by the fact that, when yellow peas and green peas were bred together, their offspring were always yellow. However, in the next generation, green peas reappeared at the ratio 1:3. Over 40 years he was to recognise most of the principles behind modern day genetics.

That Friar, Johann Mendel, who took the name of Gregor when he became a Friar, is now recognised as the founder of modern genetics, all published in the early 1860s.

Animal farmers had known for years that interbreeding animals could produce strains with particular characteristics but the process was hit-and-miss with no scientific basis.

Mendel made the process predictable and defined ***offspring invisible plant factors***, now called ***genes.*** He worked with characteristics of peas; height, colour, pod shape, pod colour, seed shape, seed colour flower position and flower colour. He worked out how to produce exactly the sort of pea plant for which he was asked simply by manipulating those plant factors.

Now, 150 years later, everyone has heard of genes and DNA, and many understand about genetic mapping and its huge applications in everything from disease resistant plants to, probably, cancer cures.

But the actual mechanics is still obscure. Teaching about fruit flies with different wings soon fades from the memory. Below Ishall try to refresh the memory about what genes do and how inheritance works.

We all inherit characteristics and features from our parents. Those characteristics are passed on in our ***genes***.

We have many thousands of genes, which are made of ***deoxyribonucleic acid (DNA)*** and which are within ***chromosomes*** in the nucleus of each cell in the body.

The human has 46 chromosomes (2x23 sets). During conception each parent contributes a set of 23 chromosomes to form a fertilised ovum. 23 chromosomes come from the sperm, 23 from the unfertilised ovum. That single fertilised ovum divides repeatedly, eventually developing into a child. Those forty-six chromosomes form the complete blueprint of the child.

OK, so the 23 chromosomes from the father will be different from the 23 chromosomes from the mother. The combination of the

two sets will define the features of the child. The child will display some features from the mother, some from the father and some which appear to be from neither and which are the result of the result of the union of the two sets of chromosomes to produce a third option different from both the existing.

As one generation produces the next generation a particular characteristic may be observable across the family, e.g. a protruding jaw or hair of a particular colour. Other features may disappear.

I hope you are with me so far.

Of course, inherited features are much more than just physical characteristics. For example, many people have a predisposition to a particular disease or illness because they have inherited a gene which makes them more vulnerable.

In some conditions, the patient needs to inherit the gene from both parents to have a disease, in some from one only and in some the individual has no symptoms but simply carries the gene which can potentially be passed to another generation. Needless to say this inheritance of disease may be very complex and may involve a number of genes and may also require the presence of environmental factors for the gene to have its effect.

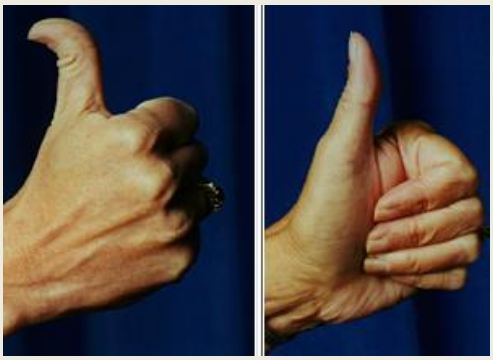
For example, a smoker is forty times more likely than a non-smoker to suffer lung cancer.

But not every smoker gets lung cancer. Genetic vulnerability to lung cancer is the initiator (predisposing to risk) and agents in the smoke are the promoter (making the cancerous change occur). In simple terms, if the patient has the gene and smokes, he or she will most likely get lung cancer. If someone smokes but does not have the gene, he will probably not get the lung cancer.

For the relatively occasional non-smoker who gets lung cancer, it is probably the result of having the gene and either passive smoking (remember Roy Castle) or encountering pollution, e.g. car fumes.

Some patients have a tendency to heart disease but healthy eating, controlling blood pressure, keeping cholesterol low, etc. can considerably reduce the adverse effect of the gene.

Things are a bit more difficult now. How is a characteristic determined? Consider a simple feature which is controlled by a set of genetic information. This set of information is called the ***allele.*** Think of a simple feature controlled by one set of genetic information, such as hitch-hiker's thumb (thumb extension trait)



The thumb on the left, 'hitch-hikers thumb' has set of genetic information 'h'. The normal thumb on the right has set of genetic information 'H'.

If both parents have the ‘H’ set of genetic information (allele) the result is thumb ‘H’ (H-H)

If both parents have the ‘h’ allele then the offspring will have a hitch-hiker’s thumb

(thumb h-h)

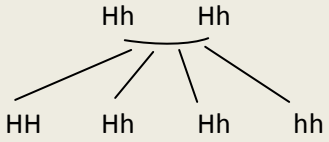
If the child inherits one characteristic from one parent and one characteristic from the other parent, then the child will have straight thumbs (H-h) because the straight thumb (H) is dominant and the hitch-hiker’s thumb (h) is recessive. Therefore if one ‘H’ set of information is present, then that will set the nature of the characteristic in the child.

Someone with the same allele from both parents is said to be ***homozygous***. Someone with different alleles from the parents is said to be ***heterozygous***.

Let us now consider what the chances are of the child getting either form of thumb.

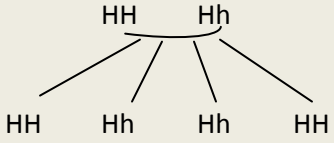
Let us assume that the mother was heterozygous (i.e. had ‘H’ and ‘h’) alleles. Let us assume that the father was also heterozygous and had ‘H’ and ‘h’ alleles.

The child could have one of the following:



If the parents had four children it would be possible using the random law of averages that they could have one with ‘HH’ alleles, two with ‘Hh’ alleles and one with ‘hh’ alleles. If the child was ‘HH’ or ‘Hh’ he or she would have a straight thumb; if the child was ‘hh’ he or she would have a hitch-hiker’s thumb. On average therefore the parents in this example would have a 75% chance of a child with a straight thumb and a 25% chance of a child with a hitch-hiker’s thumb. Of course, genetic information combinations are random and, even if they had four children all might have straight thumbs or all might have hitch-hiker’s thumbs or any combination of the two. The 75-25% is a prediction only.

Now consider if either parent was homozygous (i.e. had the same genetic information from both parents). The child could therefore have:



As all offspring would be either ‘HH’ or ‘Hh’, all would have a straight thumb. On average half would be homozygous (pure straight thumb) and half would be heterozygous (‘Hh’ – one straight thumb gene, one hitch-hiker’s thumb gene)

Few characteristics depend solely on one gene and the result may be a mixture of the influence of all the involved genes. The outcome is therefore the tremendous diversity which we see in the population.

Deoxyribonucleic Acid (DNA) is a series of complex protein strands (46 in all) made up of a huge number of genes.

Each gene or set of genes provides the instructions to body cells to tell them what their role will be in the body. The chromosomes are stored in the nucleus of each cell.

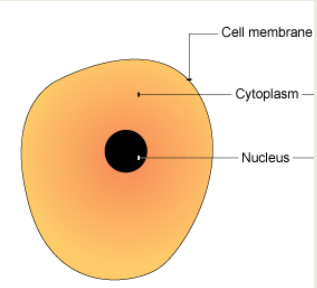


Diagram of a cell

Each chromosome is composed of a ***double helix*** of strands of protein. The two strands which form each helix are linked across by four proteins.

They are ***Adenine, Guanine, Thymine*** and ***Cytosine***.

Any of the four proteins is found in each strand of the double helix and may be in any order. The proteins are each linked across the helix. However, Adenine can only link with Thymine and Guanine can only link with Cytosine.

Purple – Adenine, Blue – Thymine
Yellow – Guanine, Green – Cytosine

Therefor only the purple adenine can link with the blue thymine and the yellow guanine can only link with the green cytosine.

Each chromosome holds a part of the blueprint for the whole body. The combinations of proteins that form genes 'instruct' the body to make special proteins which enable individual cells to perform their specific functions. Organs may be composed of many different sorts of specific cells each undertaken special functions.

The nature of the DNA molecule has been established for many species and the function of each part of the molecule has been established.

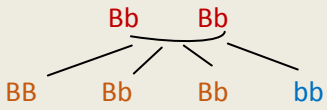
This may herald exciting possibilities in terms of identifying genes that may be defective and which could be changed to prevent offspring developing specific diseases.

Whenever anyone talks of genetics they try to explain eye colour. Let us try to understand it.

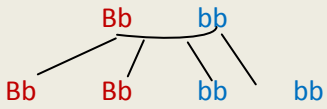
Consider a set of genetic information (called an allele – remember?) from each parent for eye colour.

Brown is dominant and blue is recessive. Therefore if we consider a Brown eyed person they may have the alleles 'BB' or 'Bb' because 'B' is dominant. A blue-eyed person can only have 'bb' because 'b' is recessive and there must be no dominant 'B' gene set or the eyes would be brown.

Thus:



Or:



The above combinations show what would happen on average if four children were born to parents with eye colours as shown.

So why do some people have green or hazel eyes? Well, it is because eye colour is not as simple as I have made it out to be above. If it was single gene effect then it would be exactly as above.

But, the fact is there are other genes for other colours and, because the degree of dominance varies, so will the colours. Imagine another eye colour gene 'G' which confers green or hazel eye colour. To have green eyes the child would need to inherit the bG gene from each parent.

I hope I haven't confused you.

Perhaps the most interesting fact about eye colour is that the relative preponderance is changing. Blue is believed to be a mutation which developed about 8-10,000 years ago. Brown eyes are predominant, about 63% of the world population has brown eyes and the figure increases to 90% if amber and hazel are included (because they are variants of brown). Some populations only have brown eyes. Dark eyes have large amounts of melanin which has a protective effect for the retina. Blue eyes are common in northern Europe.

Nearly 50% of the British have blue eyes. The Scots and Irish have the most blue eyes with brown much more common in the South of England. Over 80% of the Icelandic community have blue eyes. Before the mutation, everyone had brown eyes. 30% of British people have green eyes leaving only 22% of the British with the brown colour.

Of course, the more we learn about genetics, the more complex it becomes. It is hard to believe that it was only discovered in about

1958 by the Cambridge scientists James Watson and Francis Crick who, with Maurice Wilkins, received the Nobel Prize having uncovered the double helix shape of the DNA molecule in 1962. So the start of acquiring the truth about the genesis of life really only started in the lifetime of many of us.

And, look what has happened in fifty-five years! I cannot imagine where genetics will be by 2050 but perhaps we should be afraid, very afraid. On the other hand perhaps everyone will be well if NICE approves genetic techniques on the health service? Who knows?

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