

# Focus

November 2013

## Essential Genetics for Life Insurance Underwriters



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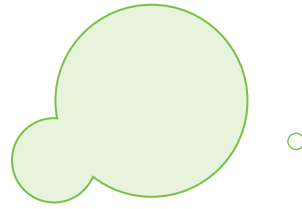
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The page features several decorative elements: a small green circle at the top left, a larger green circle on the left side, and a cluster of colorful puzzle pieces (green, purple, blue, yellow) at the bottom left. The right side of the page has a green curved border.

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# Presentation



## R&D Centre for Medical Underwriting and Claims Management

One key way that insurers can manage risk is through applicant selection. Our International R&D Centre for Medical Underwriting and Claims Management manages our risk selection and acceptance policy and ensures its implementation across all SCOR Global Life divisions. In addition, the R&D Centre monitors medical discoveries and advances, and measures their impact on the insurance industry. It conducts analysis into claim causes and circumstances and verifies risk assessment rules compliance.

### Doctor John Ifor Evans

Is a cardiologist, a former Attaché Consultant des Hôpitaux de Paris and a partner of the Groupe Médical Mas-séna in Paris. He qualified M.B. B .Ch. at the Welsh National School of Medicine (Cardiff, UK). He is an Associate Member of the European Society of Cardiology and a Full Member of the French Society of Cardiology. He joined SCOR Global Life as an Associate Medical Director, in 1993 and is an Associate Member of the American Academy of Insurance Medicine and of "l'Association des Médecins Conseils en Assurance des Personnes" since 1997.

A long-term cooperation in the field of cardiovascular disease between SCOR Global Life and the Assmann Foundation for Prevention dates back to 2006. This cooperation was agreed to strengthen SCOR's special expertise in risk assessment in the field of cardiovascular disease, in particular through the development of an evidence-based calculator for cardiovascular risk factors derived from an analysis of the PROCAM study, the scientific data of which is the intellectual property of Professor Assmann, the principal investigator. This on-going partnership is also the basis for the promotion of other scientific projects of which the writing of this brochure *Essentials of Genetics for Life Underwriters* is the first example.

# ASSMANN

Stiftung für Prävention

“Prevention is better than cure”. The aim of the Assmann Foundation for Prevention is to promote medical research and the education of the public with special focus on prevention. Prevention and health promotion improves health, quality of life, mobility and fitness. The life expectancy of many people can be prolonged through the detection of early stages of disease, for example by means of health check-ups, heart attack tests or other screening examinations and early therapies.

## Professor Assmann

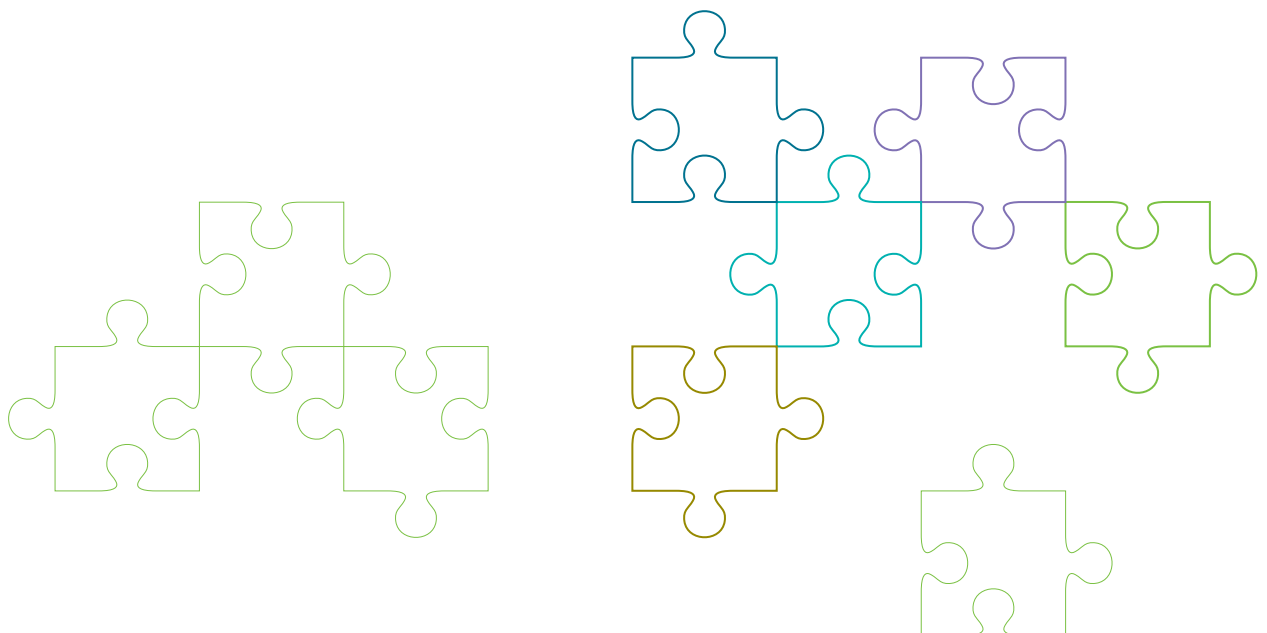
Is the President of the Board of the Assmann-Foundation for Prevention. He is a Fellow of the Royal College of Physicians, Member of the Leopoldina, Executive Director of the International Task Force for Prevention of Coronary Heart Disease, and honorary member of the American Association of Physicians. Professor Assmann is also an honorary member of the Atherosclerosis Society in Turkey and Poland and Vice-President of the European Society of Cardiovascular Prevention. The important professional and scientific positions to which he has been appointed include the Presidency of the German Society of Arteriosclerosis Research, Chairman of the International Task Force for Prevention of Coronary Heart Disease, and Presidency of the Germany Society of Laboratory Medicine. Professor Assmann obtained his medical degree at the University of Düsseldorf. His postdoctoral training included three years with Donald Fredrickson at the National Heart and Lung Institute, Bethesda. In 1977, Professor Assmann became Head of the Central Laboratory of the University of Münster, Germany, and subsequently Director of the Institute of Clinical Chemistry and Laboratory Medicine, and of the Institute of Arteriosclerosis Research at the same University. Professor Assmann is also the lead investigator in the ongoing Prospective Cardiovascular Münster (PROCAM) study initiated in 1979. The PROCAM Study is the largest prospective evaluation of cardiovascular risk markers in Europe and has recruited more than 50,000 participants to date. Professor Assmann's major research interests lie in lipoproteins, lipid transport and metabolism, medical genetics, biotechnology, academic and industrial as well as epidemiology of atherosclerosis. Throughout his career Professor Gerd Assmann has won numerous academic honors including the Heinrich-Wieland price, the Morgagni price, and the Outstanding Achievement Award for Contributions to Atherosclerosis Research by the International Symposium Atherosclerosis Society. Professor Assmann has published over 1,000 original research papers and reviews in medical journals.

### Professor Paul Cullen

Is a specialist in Internal Medicine and Clinical Chemistry. He qualified in medicine at University College, Dublin in 1983. After spells at the Medizinische Hochschule in Hanover, Germany and the Hammersmith Hospital in London, he joined the Institute of Arteriosclerosis Research at the University of Münster, Germany, in 1992. Since then, a main focus of his research has been macrophage foam cell formation and the regulation of gene expression during this process. Professor Cullen formerly led a research group at the Institute of Arteriosclerosis Research. In addition, he was the founder and Chief Executive Officer of Ogham GmbH, a company specialising in the development of DNA arrays for medical diagnostic purposes. Professor Cullen currently is Director of a private diagnostic laboratory.

### Professor Udo Seedorf

Is a member of the Board of Trustees of the Assmann-Foundation of Prevention. He studied Biochemistry and received his Ph.D. degree at the University of Constance, Germany. Subsequently he served as Research Officer at Harvard Medical School in Boston, USA, and Senior Scientist at the Institute of Arteriosclerosis Research, University of Münster, Germany. In 2004, he was appointed Professor of Molecular Biology and Biochemistry at the University Hospital Hamburg-Eppendorf, Germany. In 2006, he became leader of a research group at the Leibniz-Institute of Arteriosclerosis Research, University of Münster. Throughout his career, Professor Seedorf has been engaged in the study of mendelian and complex genetic disorders affecting lipid metabolism and risk of heart disease. Professor Seedorf participated in genome-wide association studies and genome-wide quantitative trait (QTL) analyses of coronary heart disease and myocardial infarction, stroke, diabetes, hypertension, body mass index, blood lipid and lipoprotein (a) level and biomarker level (i.e. homocysteine, a known cardiovascular risk factor). Professor Seedorf is member of the Steering Committee of the PROCARDIS study and contributor to the PROCAM Study.



# Introduction

If the first half of the twentieth century was known as the “era of physics”, then the second half can be described as the “era of biology”. All living things are composed of cells, and since the 1950s fundamental discoveries have been made about the composition of cells at a molecular level and how these molecules interact with each other throughout life.

Perhaps the crowning discovery of this era was the unravelling of the structure of deoxyribonucleic acid, or D.N.A. also known as the “molecule of life”. Since then, genetics and related concepts such as “genetic engineering” and “cloning” have entered popular culture and such terms are often bandied around in the media and in common parlance with little regard for scientific accuracy. As a result, the general public often has a poor understanding of the field of genetics, and tends rather to associate it with connotations of mystery and fate.

The aims of this brochure are to provide the reader with a simple introduction to genes and genetic processes in humans and an insight as to how this rapidly developing field of science could impact on the insurance industry. We hope to provide answers to the following:

- *What is heredity and what are genes? How do our genes affect us? Do my genes map out my destiny? What does it mean to say that someone “carries a gene” for a certain disease? If I “have the gene” for a particular disease, does that mean that I am certain to get that disease? How is genetic testing used and is it valuable in predicting common diseases such as heart attack and stroke? If my genetic risk for a particular disease is high, is there anything I can do to reduce this risk?*
- *With respect to the life insurance industry, would genetic testing be useful when writing insurance premiums? And, if it were useful, should it be allowed? Should people who know they carry a genetic risk for a particular disease be obliged to disclose this risk before they take out an insurance policy? What exactly are the current regulations regarding genetic testing in insurance medicine?*

One important issue in this field is that of “genetic exceptionalism”, a concept that genetic information is inherently unique and should be treated differently to other forms of personal or medical information. Genomics applies a new technology to risk prediction but it does not necessarily provide information that is inherently different from the other predictors commonly used in health care. This brochure aims to remove much of the mystery presently surrounding the field of genetics and to encourage readers to consider that genetic tests are not so different from biochemical tests, X-ray investigations or other forms of medical diagnosis that have been around for many years.

# Chapter 1

## Basic concepts

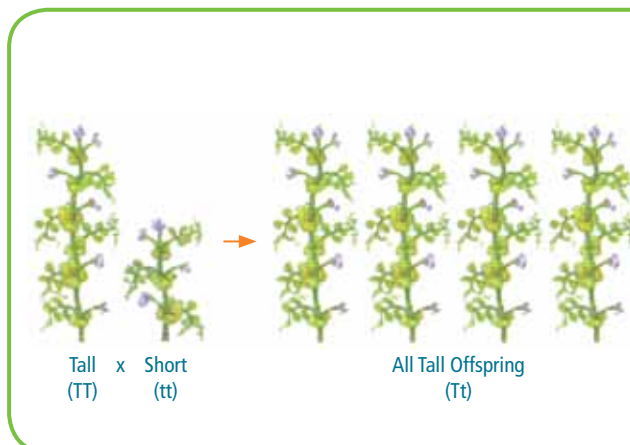
A

### Heredity

Let us begin by stating the obvious: in the living world, offspring resemble their parents. This is true in two respects. Firstly, offspring are both the same species as their parents and the same race: if a male and a female cocker spaniel mate, they will always produce cocker spaniel pups. Secondly, within that species and race, offspring tend to share many of their parents' characteristics: if your mother and father are taller than average, then the odds are that you will be too. This process of transmitting specific characteristics from parents to offspring is referred to as heredity.

Practical knowledge of heredity has existed since the beginning of civilisation and formed the basis of selective breeding that led to the development of agricultural plants and domesticated animals. However, it was not until the mid-nineteenth century that Charles Darwin first published *On the Origin of Species* in which the transmission of variable factors from one generation to the next was described in detail. Darwin believed that all species evolved from a common ancestor by means of natural selection, according to the law of survival of the fittest.

Following Darwin's writings, an Augustinian monk named Gregor Mendel formulated several underlying principles of heredity based on a series of plant breeding experiments he performed in the garden of his monastery in Brno, Czech Republic. With the patience that

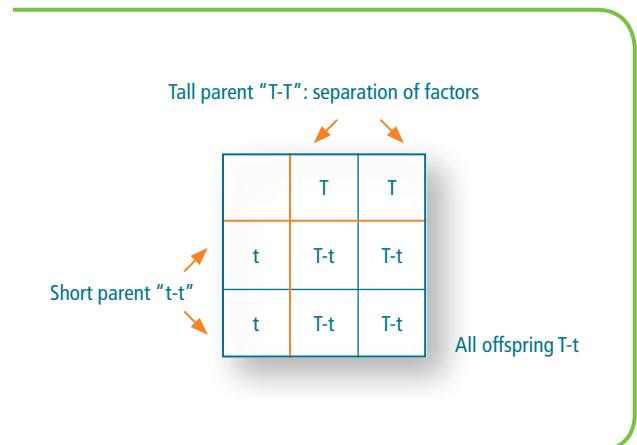


probably only a monk can muster, Mendel painstakingly cross-pollinated by hand several varieties of the ordinary garden pea to produce hybrids, then collected and cultivated these hybrid seeds as those of the following generation.

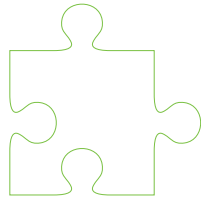
In doing so, Mendel was the first to make several fundamental observations about heredity. He noticed that every individual carries two factors for each physical characteristic observed and that "mother" and "father" plants each transmit one of these two factors to form the "child" plant. To put it another way, the factors separate to form the germ cells. One factor is inherited from each parent at fertilisation. The offspring plant therefore carries two factors for each characteristic. For example, when purely-bred tall pea plants are crossed with purely-bred short pea plants, Mendel observed that all the "offspring" plants were tall. He concluded that for the HEIGHT characteristic, there was one factor which coded for tallness and another for shortness, and the offspring had clearly inherited one factor from each parent plant. Furthermore, when factors were mixed, he observed that the tallness factor dominated the shortness factor, resulting in all of the first generation offspring plants being TALL.

In order to simplify these observations, geneticists today often use abbreviations that are taken from the first letter of the dominant trait, such that if tallness is a dominant factor in height, then tallness is represented by capital "T" and shortness by small "t". In this way, we can describe Mendel's three fundamental laws of heredity with some simplicity.

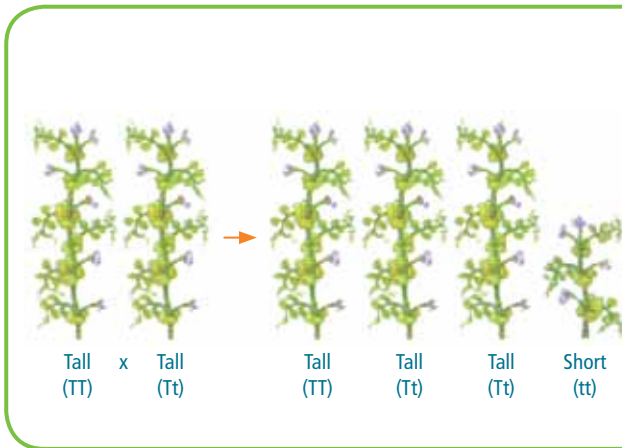
The first of Mendel's laws states that crossing pure-bred tall (T-T) and pure-bred short (t-t) plants, results in all of the offspring inheriting the factor T from one parent and factor t from the other, so they all have a T-t code for their height which results in them all being tall (their phenotype) as T is the dominant factor.







The second of Mendel's laws was based on the observation that when two first-generation hybrids are crossed (two plants each with the phenotype "tall" and the genotype "T-t"), both tall and short offspring plants are obtained, showing that in this second-generation, the characteristic "short" factor must have been present, albeit concealed, in the parent plant.



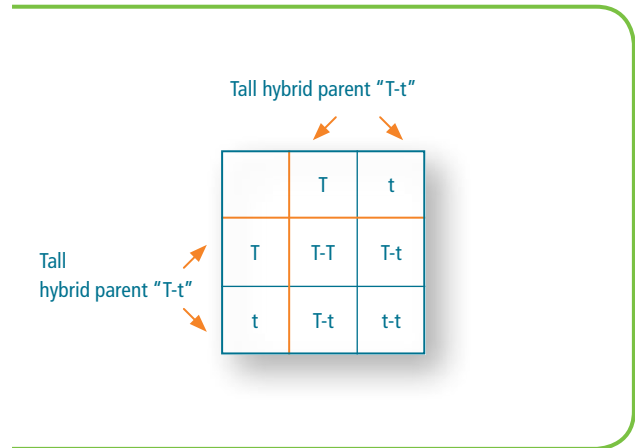
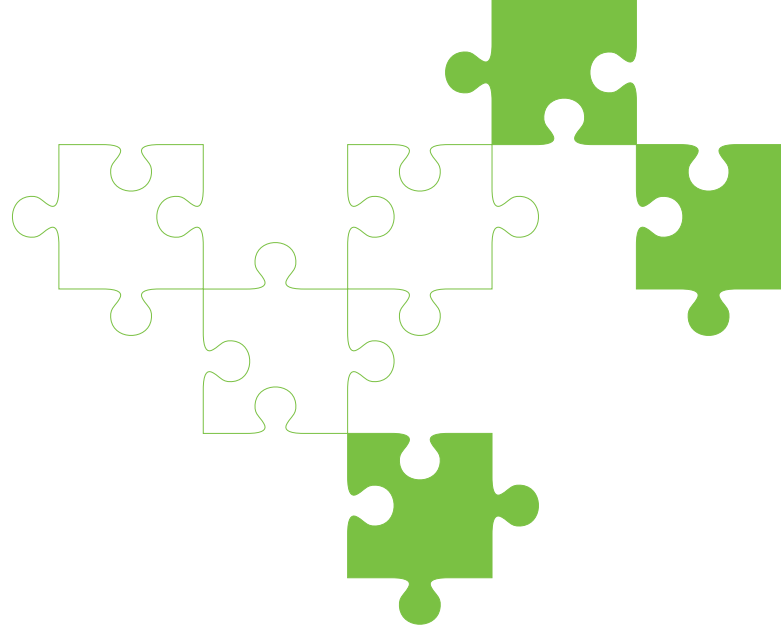
In this situation, three quarters of offspring are always tall because they contain the dominant T factor (genotype "T-t" or "T-T") and one quarter are short because they have the recessive t factor only (genotype "t-t"). Importantly, Mendel noticed that the height of the short offspring of the two tall hybrids was the same as that of their short parent plants, in other words, the characteristic "short" had not been altered during the transmission process. The two factors had segregated independently during the formation of the gametes.

Finally, Mendel observed that factors coding for different traits, such as height and colour, are also inherited independently of each other, and consequently, Mendel's third law simply refers to his work with the transmission of such multiple traits.

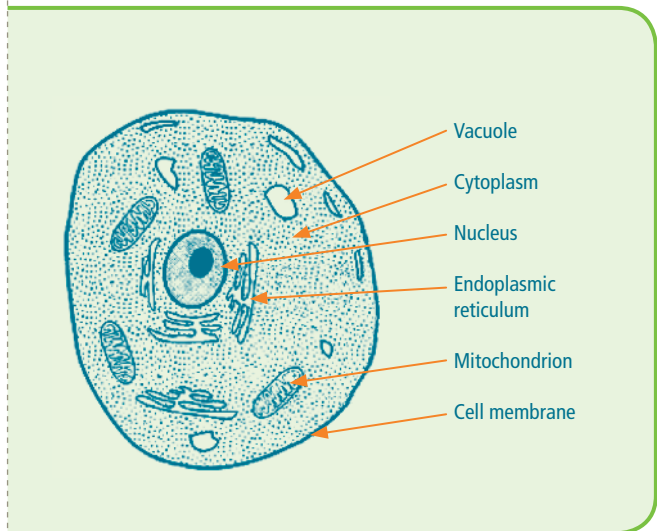
**B**

**"Chromosomes – our hereditary carriers"**

By the time Mendel's ground-breaking work was finally recognised in the early 20th century, scientists were now benefitting from the use of more powerful microscopes enabling them to study cellular make-up and division in plants and animals with greater detail. The interior of the cell was seen to be divided into the nucleus and the cytoplasm. The nucleus is the spherical or oval shaped structure at the centre of the cell. The cytoplasm is the region outside the nucleus that contains cell organelles

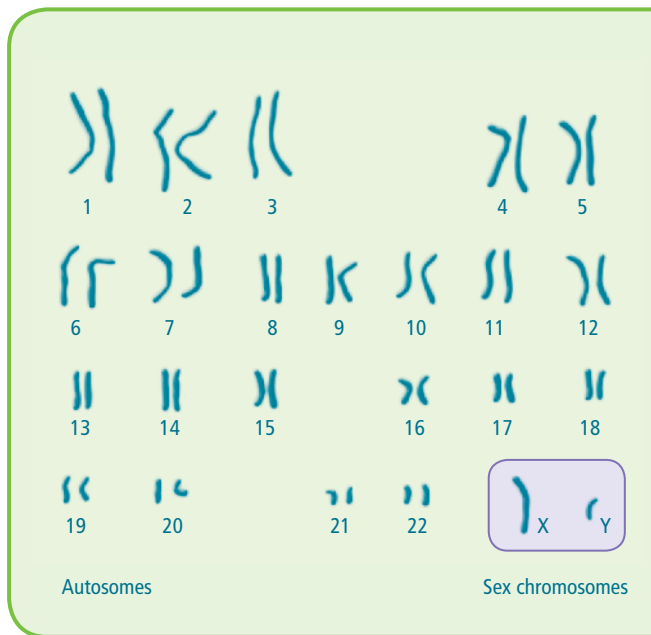


and cytosol, or cytoplasmic solution. Intracellular fluid is collectively the cytosol and the fluid inside the organelles and nucleus.

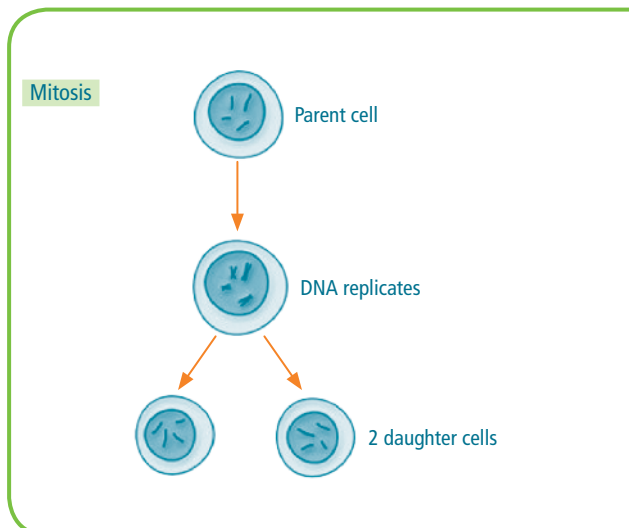


Because the material within the nucleus of resting cells absorbed the staining chemical used at that time, scientists decided to call this material **chromatin** (from the Greek "chroma", meaning colour). When the cells started to divide - a process called mitosis - the chromatin condensed into thick, rod-like forms that today we recognise as **chromosomes** or coloured bodies. These structures were found to carry the "hereditary factors"

of Mendel's earlier work. In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Women have two copies of the X chromosome, while men have one X and one Y chromosome, so defining their genders.



As scientists observed these cells divide, the chromosomes split in half lengthwise, and each half chromosome (or **chromatid**) was drawn into one of the two newly formed cells, after which they dissolved again into chromatin.



As a result, each new cell had the same number of chromosomes as its parent cell and the same nuclear material. This form of reproduction is known as **asexual** and results in cloning of the original cell.

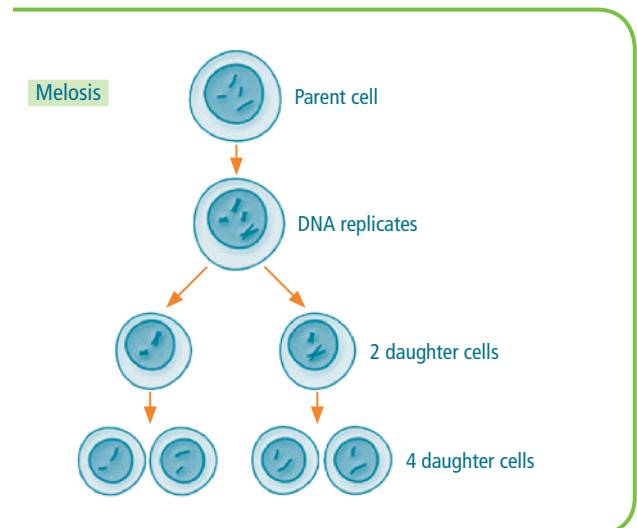
Asexual reproduction is the primary form of reproduction for single-cell organisms such as bacteria and may have short term benefits when rapid population growth is important in stable environments.

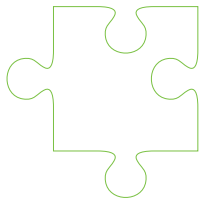
However, more advanced forms of life, including animals, require diversity to be able to adapt to their changing environments, and therefore reproduce sexually by combining multiple hereditary characteristics from two different individuals. Specialised cells in this particular form of sexual reproduction called **gametes**, (male spermatozoa and female ova), are formed by a separate process of cell division called meiosis.

Meiosis is a two-step process of cellular division. Firstly, similar to mitosis, pairs of chromatids align themselves but, at this stage, some parts of the chromosome may be swapped, a process called "crossing-over", so that the resulting cells already contain some genetic diversity.

At the second stage of meiosis, rather than duplicating themselves chromosomes separate and migrate individually into the cells which will become gametes. For this reason, the gametes are so-called **haploid** cells, and when male and female gametes unite to reproduce a new organism, the number of chromosomes is restored to the original **diploid** number.

In this way, sexual reproduction enables genetic traits from both female and male parents to mix and produce an unique variety of chromosomal material in the following generation.

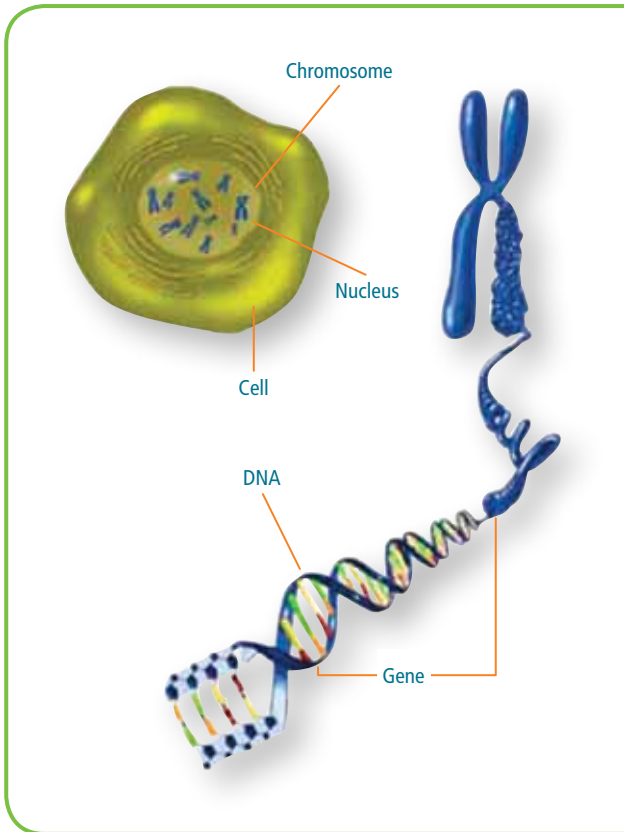




C

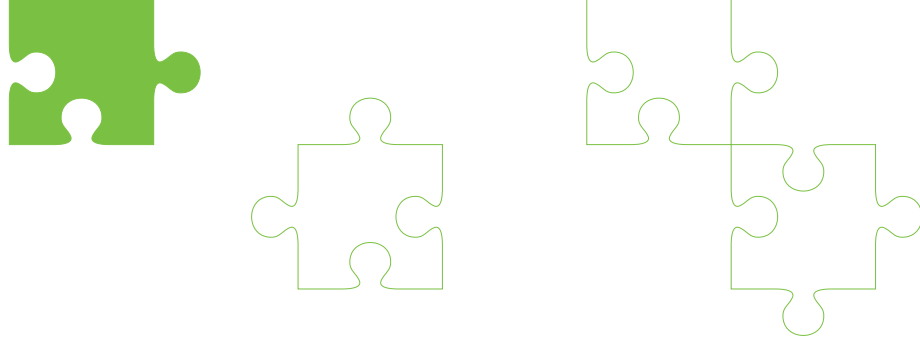
## The Discovery of D.N.A. and Genes

How did we get from chromosomes, the carriers of hereditary traits, to D.N.A. or, to use its full name, deoxyribonucleic acid? Scientists have now established that chromatin is in fact D.N.A. and chromosomes are therefore its condensed form, and have adopted the convention of referring to units of heredity in living organisms as **genes**.



In 1953, Watson and Crick finalised the researches of many others and unravelled the structure of D.N.A., the “heredity molecule”, and found that genes are typically represented by contiguous sequences of DNA transmitted as complete units from one generation to the next.

Perhaps the simplest way to consider the structure of D.N.A. is as a sort of spiral staircase or ladder. The ladder’s structural backbone is made up of a polymer of sugar and phosphate groups and its rungs or steps consist of four molecules called **nucleobases**. The symmetry of the D.N.A. structures is explained by the fact that each molecule or base always combines in the same way: **adenine** binds to **thymine** and **cytosine** to **guanine**.



The sequence of these four letters (A, C, T & G) is the blueprint of all the myriad life-forms on our planet, from the humble bacterium to the mighty whale. In 1998, the complete D.N.A. sequence of a human being was read for the first time in what was known as the **human genome project**.

One way to think of human D.N.A. is as a library of 3 billion letters (the human genome), some of which are organised into 23,000 books (the genes), which are themselves set out onto 23 shelves (the chromosomes).

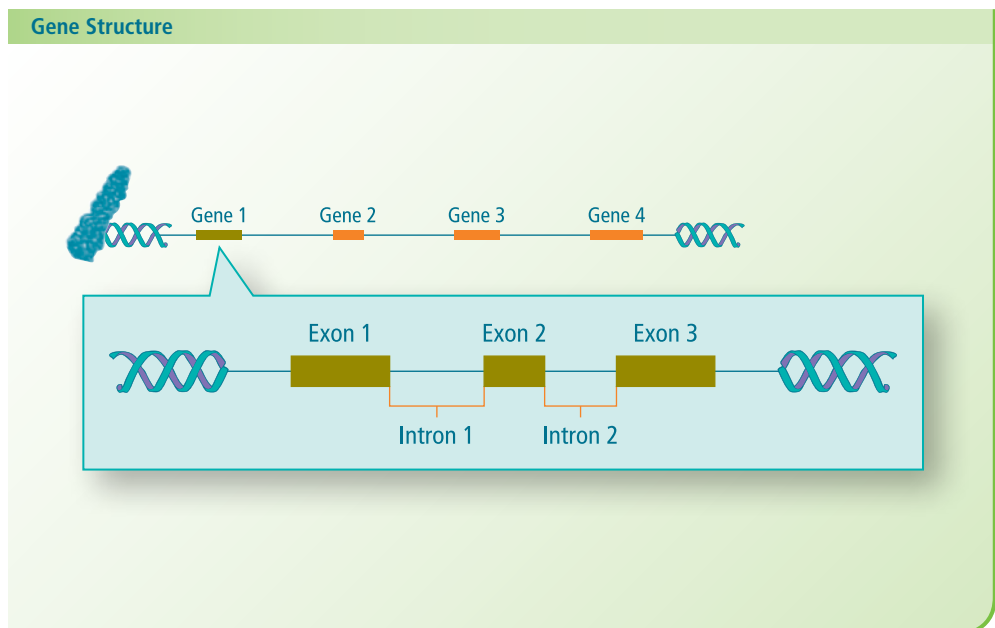
**D**  
**Genetic variability**

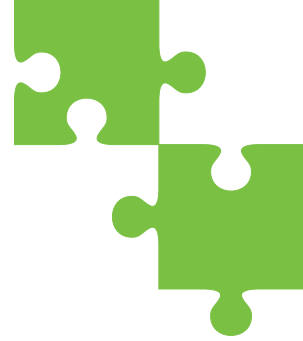
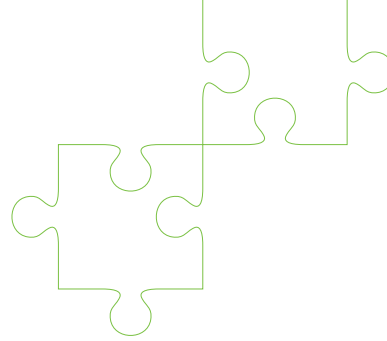
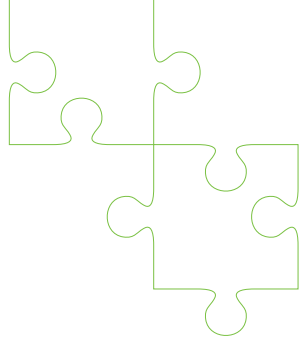
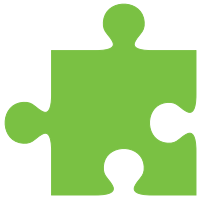
Heredity is responsible for shared characteristics between parent and child. However, within a species, no two individuals are identical. This variability is both due to genetic differences between individuals and to differences in their developmental environment. For the moment we will concentrate on the former: those components of variability which are said to be due to our genetics. As we have just mentioned, the human genetic code (**genome**) contains about 3 billion "letters" made up of the nucleobase pairs. Some of these letter sequences are invariable, such as those which encode enzymes critical to an organism's survival, whereas others vary from individual to individual. Recent scientific evidence suggests that of the 3 billion letters in the genome, about 3 million (0.1%) vary between

individuals, of which about 10 thousand occur within the regions of the genome that contain genes.

These differences, in addition to a number of other minor variations that may occur such as areas of repetition or deletion, form the basis of variability between all human beings. This small degree of genetic variability may seem inadequate to account for the wide variability observed between humans. However, it is important to remember that apparently small differences can have very large effects. For example, the human genome shares roughly 99% of the genetic make-up of that of our nearest relative in the animal kingdom, the chimpanzee.

As we have discussed above, genes may, in simple terms, be thought of as a stretch of D.N.A. on a chromosome. However, while this simple correspondence between a gene and a trait works in some cases, most traits are more complex and are controlled by multiple interacting genes within and among organisms. Interactions in genetic networks and communication among cells can also lead to heritable variations that may underlay some of the mechanics in developmental plasticity. Moreover, the situation is more complex as most genes are coded not by one contiguous stretch of D.N.A., but are broken into different sections. Those sequences of D.N.A. that are destined to be read out and decoded are called "exons", and the intervening sequences are called "introns". A little less than a third of the human genome is used in this way to encode genes. The function of the remaining two-thirds is not completely known at present and is the focus of intense research interest.





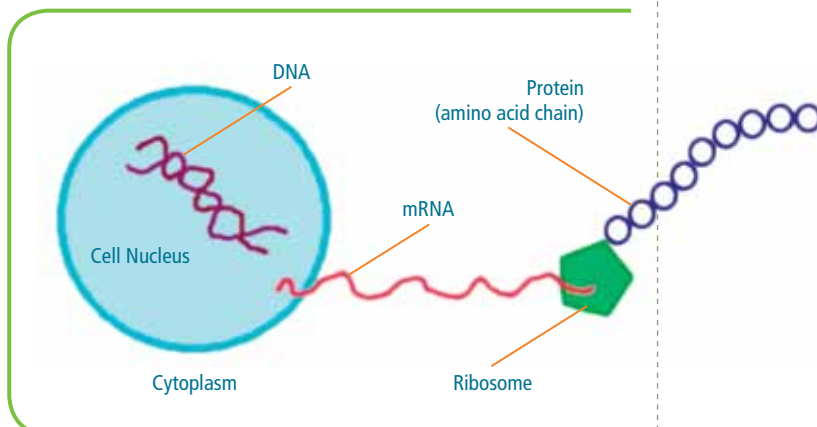
E

## Molecules and Proteins

Inside all living cells, the molecular machines that carry out nearly all of the chemical reactions are called **enzymes** and are comprised themselves mainly of **proteins**. Additional proteins form the structural components of the cell, while still others carry out a wide variety of tasks, including cell motility, signalling within and between cells, the transport of chemicals within cells and between cells and their environment and regulation of the reading of genes, a process known as **gene expression**. Clearly, therefore, proteins can be described as the most important molecular components of the cell.

So what exactly are proteins? Proteins are molecules that are made up of 22 separate chemical building blocks called **amino acids**. These building blocks each have different chemical properties such that the resulting proteins have an almost endless range of characteristics. Some proteins are very strong, such as those which are a constituent of silk and spider's webs, and are impressively much stronger than steel on a weight-for-weight basis. Some proteins are springy, others are rigid, and others still can act as molecular motors, by moving components around inside a cell or by enabling muscles to contract.

As mentioned above, an important group of proteins, the enzymes, catalyse and thus control chemical reactions inside each cell. Following the unravelling of the structure of D.N.A., an additional finding advanced our understanding of how specific proteins are coded for by the D.N.A. itself. It turns out that three letter sequences of D.N.A. - so-called "triplets" - code for each amino acid. In addition, some amino acids are coded for by more than one triplet, and there are further triplets which code for "start reading here" and "stop reading here" on the D.N.A. molecule.



More specifically, the D.N.A. contained in each cell is tightly packed within its **nucleus**. If a particular gene is to be read, then the section of D.N.A. containing that gene is unpacked and read by a special molecule called an R.N.A. **polymerase**.

The D.N.A. is not transformed directly into protein, but is first copied as a sort of mirror image into a secondary molecule called R.N.A. or **ribonucleic acid**. R.N.A. is chemically very similar to D.N.A., but is far more "unstable".

This is a positive characteristic because it means that an R.N.A. "message" within the cell is degraded very quickly after it is read, preventing it from stagnating in the cell.

Once these messenger R.N.A. molecules (mRNAs) move out of the nucleus into the main body of the cell, known as the **cytoplasm** where they enter large molecular "factories" called **ribosomes**. As mRNA moves through these factories, little shuttles continually arrive and depart, each transporting the amino acid that corresponds to the particular R.N.A. triplet.

These shuttles are also made up of R.N.A. but in this case they are referred to as **transfer R.N.A.** Proteins are thus built, block by block, in the ribosome in the process referred to as "translation".

In summary then, the human genome contains about 23,000 different genes. "It was once believed that each gene codes for a single protein. However, experimental and computational evidence (partly obtained at ORNL - Oak Ridge National Laboratory) shows that many genes produce an average of three different proteins and as many as ten protein products".

# Chapter 2

## Genetics and its influence on health and disease in humans

Genes are involved in virtually all of the processes occurring in the human organism. They not only determine obvious features such as eye and hair color but also subtle traits such as an individual's blood type or their risk for a particular disease. In fact, all diseases are influenced, to a certain degree, by genes and their variation.

1

### Genetic Disorders

A genetic disorder is a disease that is caused by a specific variant in an individual's gene. The D.N.A. variations which cause genetic disorders can range from a small mutation in a single gene to multiple variations in a defined set of several genes, through the deletion or addition of entire chromosomes. According to the nature of the mutation, genetic disorders are categorised broadly into four different groups: **chromosomal diseases**, **monogenic disorders**, **mitochondrial disorders** and **polygenic disorders**.

A

### Chromosomal diseases

Chromosomal diseases occur when an entire chromosome, or large segments of a chromosome, are missing, duplicated or otherwise altered.

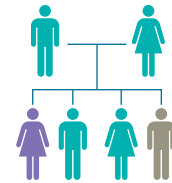
These chromosomal abnormalities usually result from an error in cell division following meiosis or mitosis in the germ cells. When newborn infants are screened, roughly 1 in 200 possess this type of chromosomal abnormality. Some of these infants appear to be normal but most children have obvious and often severe manifestation of disease. A prominent example of a chromosomal disease is Down Syndrome, also known as Trisomy 21, as an individual with Down Syndrome has three, rather than two copies of chromosome 21.

B

### Monogenic diseases

Genetic disorders resulting from small modifications in a single gene are known as monogenic diseases. When the mutation is located on the **autosomes** (the 22 non-sex chromosomes), the mode of inheritance obeys the Mendelian laws described previously. Recessive genes only cause disease in **homozygous** genotypes (i.e. both alleles carry the mutation) and never in a **heterozygous** genotype. Examples of autosomal recessive genetic disease are sickle cell anaemia and cystic fibrosis. Both parents have to be heterozygous carriers of the disease and the risk of the two disease alleles being inherited by an offspring is 1:4.

	A	a
A	AA	Aa
a	Aa	aa



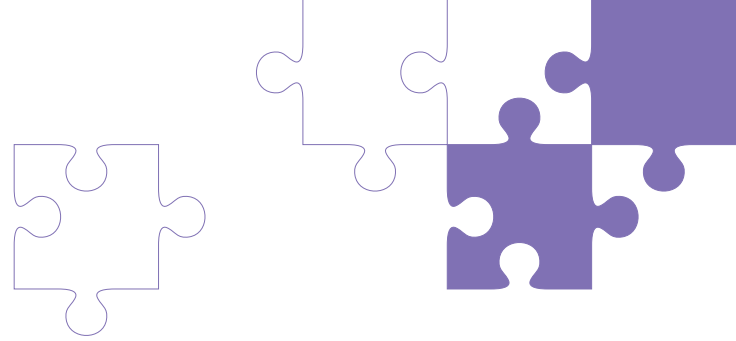
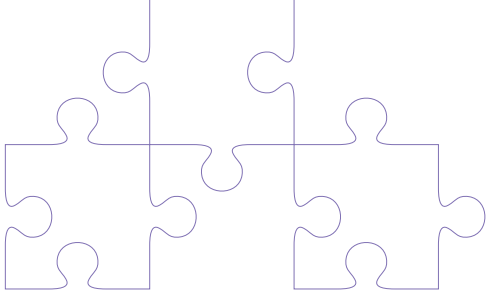
If both parents are carriers of the recessive allele for a disorder, all of their children will face the following odds of inheriting it:

25% chance of having the recessive disorder,

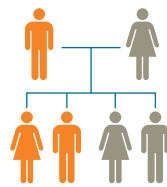
50% chance of being a healthy carrier,

25% chance of being healthy and not have the recessive allele at all.

In dominant autosomal disorders, the trait is displayed even when individuals are heterozygous or have only one copy of the mutated allele. This is the case with Huntington's Disease. If one parent has a single copy of the mutated gene, not only will he or she be affected by the disease but there is a 1:2 risk of passing it on to any offspring.



	A	a
a	Aa	aa
a	Aa	aa

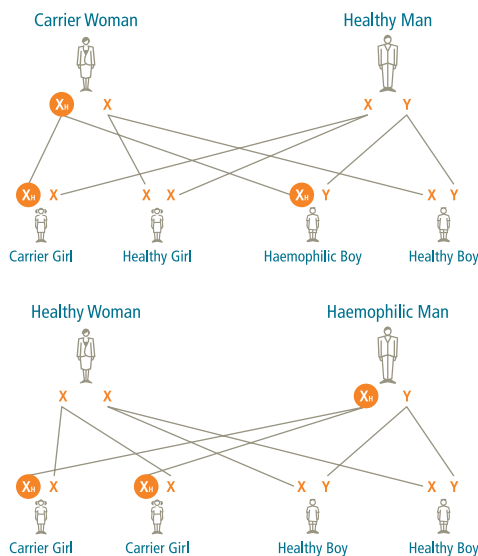


If only one parent has a single copy of a dominant allele for a dominant disorder, their children will have a 50% chance of inheriting the disorder and 50% chance of being entirely normal.

Some genetic diseases are transmitted on the sex chromosomes. Hemophilia, the blood clotting disorder due to Factor VIII deficiency, is caused by a defective gene on the X chromosome. It is an X-linked recessive disorder.

Male offspring of a female carrier have a 1:2 risk of being affected by the disease because they inherit the Y-chromosome from the father and one of the X chromosomes of the mother.

Unfortunately, the Y-chromosome does not carry most of the genes of the X chromosome and therefore does not protect the male offspring. Female offspring of a normal father and a carrier mother have 1:2 chance of being normal and 1:2 of being themselves carriers but not affected by the disease (they have a normal X chromosome which protects them).

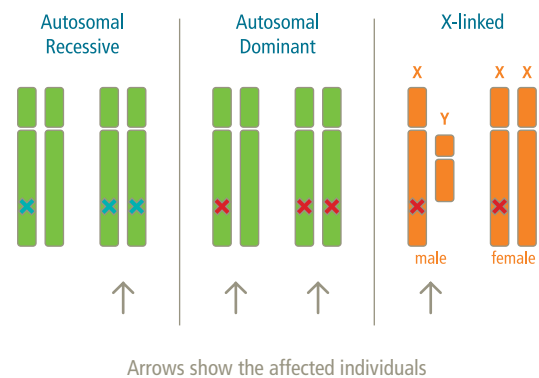


Though relatively rare, monogenic disorders affect millions of people worldwide and scientists currently estimate that over 10,000 human diseases have a monogenic cause. The global prevalence of all monogenic diseases combined is approximately 1 in 100 newborns. The specific abnormalities associated with monogenic diseases depend on the functions performed by the affected gene. As such, some monogenic disorders lead to severe manifestations which are clearly manifest at birth and require lifelong medical care; others have milder consequences and clinically relevant symptoms appear only later in life. Prominent examples of monogenic disorders include **cystic fibrosis**, **sickle cell anemia** and **familial hypercholesterolemia**.

C

### Mitochondrial diseases

Mitochondrial diseases are rare disorders caused by inherited or spontaneous mutations in non-chromosomal D.N.A., that is, D.N.A. which is located within **extra-nuclear** sub-cellular organelles called **mitochondria**. These rare disorders can result in a wide range of anomalies, including poor growth, hearing and visual problems, loss of muscular coordination, muscular weakness, learning disabilities, dementia and heart disease. Although the precise prevalence of mitochondrial disorders is unknown, it has been estimated that in Europe, about 1 in 10,000 adults may suffer from a mitochondrial disorder.



D

**Polygenic disorders**

Polygenic disorders are multi-factorial disorders and are therefore often referred to as **“complex disorders”** because they result from mutations in multiple genes and are frequently associated with environmental causes. Examples of multi-factorial disorders include diabetes, hypertension, cancer, asthma, epilepsy, manic depression, schizophrenia and heart disease.

A common feature of these disorders is that the risk of inheritance is lower compared with monogenic disorders. For example, less than 5% of blood relatives of diabetics also have diabetes. This is a much lower fraction than observed for a monogenic disorder such as cystic fibrosis. The reason for this difference is that a polygenic disorder such as diabetes only penetrates if a specific set of variants of several genes comes together. Importantly, penetrance depends on environmental factors, such as poor diet and sedentary lifestyle. Because of this, it is thought that, in the healthy state, there is a balance between gene variants and environmental factors with both positive and negative effects. If too many negative factors, both genetic and environmental, are present, the balance is then tipped towards disease.

Results of large twin and adoption studies indicate that genetic variation accounts for about 25 to 50% of the risk of most polygenic disorders and the residual risk is due to environmental causes. For example, it has been

estimated that 40% of the risk of coronary heart disease is due to genetic inheritance. Recent technological advances in D.N.A. array technology and gene sequencing have made it possible to identify many genetic variants in the human genome that influence the risk of polygenic disorders. In coronary heart disease for instance, these variants have been found in (or near) 28 genes.

Whereas the precise mechanisms leading to increased coronary heart disease risk have not yet been elucidated for the majority of these variants, about 1/3rd are explained by previously established risk factors, such as LDL-cholesterol, smoking behavior, lipoprotein(a) level and blood pressure and these factors explain, at least in part, their association with coronary heart disease risk.

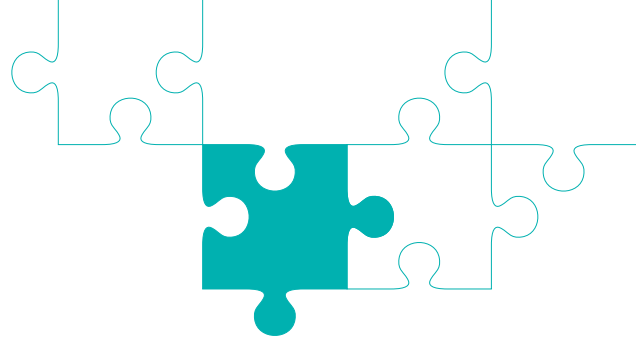
Genome-wide association studies have recently been used to identify genetic variants which affect coronary heart disease risk in humans. The variants were located in 28 genetic loci on specific chromosomes. About one third (9 of 28) of all known genetic variants affecting the risk of coronary heart disease have been shown to influence known risk factors of coronary heart disease.

Locus	Gene	Protein	>	Effect on:
1p13	SORT1	Sortilin		LDL-cholesterol
1p34	PCSK9	Proprotein convertase, subtilisin/kexin type 9		LDL-cholesterol
6q27	LPA	Apolipoprotein (a)		Lipoprotein (a)
9q34	ABO	ABO gene		LDL-cholesterol
10q23	LIPA	Lysosomal lipase A		Cholesterol ester & triglycerides
10q24	CYP17A1	Steroid-17-alpha-monooxygenase		Blood pressure
11q23	APOA5-A4-C3-A1	Apolipoproteins A5, A4, C3, A1		HDL-cholesterol & LDL-cholesterol
15q25	ADAMTS7	Disintegrin metalloproteinase with thrombospondin motif 7		Smoking habit
19p13	LDLR	LDL receptor		LDL-cholesterol



# Chapter 3

## Genetic Testing



A

### Definition and forms of genetic testing

One definition of genetic testing is “the analysis of, chromosomes (D.N.A.), proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes”. Screening of new-born infants for the presence of phenylketonuria, a genetic disease which may cause a severe brain disorder, has been widely used for many years. However, diagnostic testing is used to investigate specific genetic conditions, for example certain forms of cardiomyopathy, when the condition is suspected on finding borderline physical changes or because of a positive family history. Genetic testing also refers to D.N.A.-based tests used to diagnose genetic disorders by direct examination of the D.N.A. molecule itself.

Predictive testing is used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person’s chances of developing disorders with a genetic basis, such as certain types of cancer. For example, an individual with a mutation in BRCA1 has a 65% cumulative risk of breast cancer. Hemochromatosis is another condition in which mutation of the HFE gene located on chromosome 6 causes an iron overload disorder. The results of predictive and pre-symptomatic testing can provide information about a person’s risk of developing a specific disorder and help with making decisions about medical care.

To answer the question of whether some such newly-identified gene variants may be useful in predicting coronary heart disease, the CARDIoGRAM study (a large international genomic study aimed at identifying gene variants affecting coronary heart disease risk) recently developed a weighted genotype score that included 23 of the 28 gene variants. It was demonstrated that of those who scored in the top decile of the genotype score distribution, their mean risk was three times as high as those in the bottom decile. These results are encouraging as they support the feasibility of predictive diagnostics with genetic markers. However, it should be noted that in comparison with this genotype score, risk assessment schemes that rely exclusively on traditional

risk factors, such as the PROCAM Health Test, have greater than ten-fold predictive power. Whether combining genotype information with test results based solely on traditional risk factors would lead to a significant improvement remains to be established.

Importantly, the sum of all newly-identified gene variants combined can account for only about 10% of the total assumed heritable coronary heart disease risk. One plausible reason for this low fraction of explained risk may be that the methods employed so far can only detect the most prevalent variants. Therefore, it is currently presumed that there may be many additional variants, each being relatively rare, that have a more pronounced influence on risk than common variants. Future studies are aimed at identifying such rare variants, employing highly-advanced sequencing methods which will enable large-scale sequencing of the entire human genome (next generation sequencing).

In view of these limitations, predictive genetic diagnostics involved in coronary heart disease appear to be premature at this stage. This also holds true for other polygenic diseases, such as diabetes, hypertension, cancer, asthma, epilepsy, manic depression and schizophrenia, because, for such disorders, the known gene variants currently explain only a small fraction of entire heritable risk.

B

### How are genetic tests performed?

Gene variants can be detected by a number of different methods which differ according to the complexity of the generated data and costs. Currently, there are three best practice techniques that are widely used in genetic laboratories:

- A low-cost and technically simple method for detecting gene variants involves Real-time PCR (description), a high-throughput screening method used to detect a small number of gene variants in large sample numbers. Data interpretation is relatively straight-forward as only a small number of known and presumably relevant variants can be determined.
- In contrast, **high-density D.N.A.** arrays allow simultaneous determination of up to 1,000,000 gene variants in a single individual. Particular DNA arrays have been developed to detect up to 50,000 gene variants which may be relevant for various disorders, including cardiovascular disease.

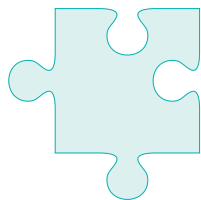
- Thirdly, highly efficient D.N.A. sequencing techniques (next generation sequencing) have recently been developed allowing large-scale sequencing of the entire human genome.

High density D.N.A. arrays and next generation sequencing typically generate vast amounts of data where hundreds to thousands of gene variants can be detected in each examination. However, at this stage it is impossible to fully predict or quantify the effects of most of these variants on any particular disease risk.

Today scientists are using novel and highly efficient techniques of functional genomics, proteomics and metabolomics to elucidate the functional defects that are caused by gene variants.

The aim is to further understand how gene variants alter metabolic processes and to develop future strategies for “personalised” medicine, a new concept in which knowledge about genetic features of the individual patient are included in therapeutic decisions.

It is hoped that such therapies will be more appropriately targeted, will have less side-effects and will be more effective than currently-used therapies which often can be highly unspecific.



# Chapter 4

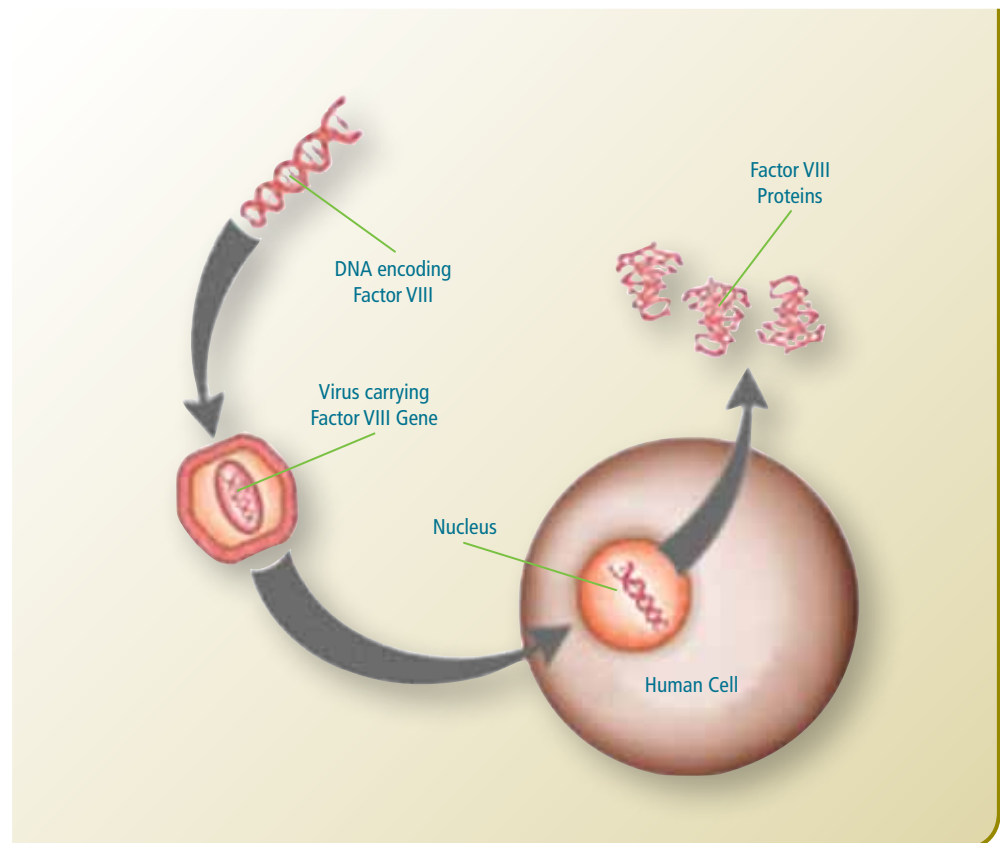
## Gene Therapy

An emerging approach to the treatment of genetic disorders in man is gene therapy. This is a technique whereby the absent or faulty gene or D.N.A. sequence is replaced by a working gene so that the body can make the correct enzyme or protein and consequently prevent or cure the disease which would have resulted from the genetic disorder. In order to carry this out, the healthy gene requires a form of transport to the cell's nucleus where the chromosomes and DNA reside. Viruses are obvious candidates for this function because they invade cells as part of the natural infection process.

Although simple in its concept, there remain many obstacles and some distinct questions concerning the future of gene therapy. Viral vectors must be carefully controlled to prevent infecting the patient with a viral disease. Some retroviruses can enter cells functioning properly and interfere with the natural biological

processes, possibly causing other diseases. Other viruses, like the adenoviruses, may be recognised and destroyed by the immune system so that their therapeutic effects are short-lived. Maintaining gene expression so it performs its role properly after vector delivery is difficult. As a result, some therapies may need to be repeated often to provide longer-lasting benefits.

Ethical concerns over the use and ramifications of gene therapy have been expressed by both scientists and lay people. For example, since much needs to be learned about how these genes actually work and their long-term effect, is it ethical to test these therapies on humans, where they could have a disastrous result? Another questionable evolution of gene therapy is the manipulation of genes to genetically control traits in human offspring that are not health related. For example, perhaps a gene could be inserted to ensure that a child would not be bald, a seemingly harmless goal. However, what if genetic manipulation was used to alter skin colour or ensure good looks? If a gene was to be found that could enhance intelligence of unborn children, would everyone in society have access to the technology or would it be so expensive that only the elite could afford it?



# Chapter 5

## Implications for Insurance Medicine

Patients who have a strong genetic predisposition for chronic diseases usually experience a much earlier onset of clinically relevant complications and they have a higher chance to die prematurely than patients who have no genetic predisposition. As we have noted above, genetic variants contribute importantly to most chronic diseases and predictive genetic diagnosis, although premature today, may well be feasible in the near future. It is important for an insurer to evaluate risk according to the likelihood that claims will occur. Facts increasing the likelihood of claims should theoretically be considered and result in a higher premium. For instance, older people usually pay significantly higher premiums than younger people for term life insurance because older people are likely to die sooner than young people. In analogy, people with a genetic disease or a genetic predisposition leading to a lower life span and more claims per time unit, should theoretically also pay higher premiums than genetically normal people.

In addition, genetic disorders present a significant burden not only for the patients and their families but also for the health care system. It is estimated that 15% of all cancers have an inherited susceptibility and that at least 10% of chronic diseases, such as heart disease, diabetes and arthritis, which occur in the adult populations have a significant genetic component. Lifetime cost of care varies depending on the nature of the condition; but these costs are usually significantly higher compared with the average population. For instance, the costs of care for a patient with Down syndrome in the United States are around \$500,000, whereas those for a patient with cystic fibrosis may exceed \$1,000,000. Newly developed therapies, such as enzyme replacement therapies for the treatment of lysosomal disorders, may be expected to lead to further cost increases in the future. These factors have significant implications for the cover of health and disability insurance.

A

### Implications of asymmetry of genetic information between the insurer and the insured

Basic legal principles of insurance include that the insured and the insurer are bound by a good faith bond of honesty and fairness, requiring that material

facts must be disclosed prior to contracting insurance. With respect to genetic issues, the existing ethical and legal framework values the privacy of individual genetic information higher than the interest of an insurance company to consider all material facts, including genetic data, before entering into a binding insurance contract. This situation may theoretically lead to moral hazard on the side of persons who have been informed about being affected by a genetic condition. They may look to insure undisclosed, excessive event risks for low premiums typically applying for risk-free persons. Since insurance companies are not allowed to perform genetic tests and the obligation to disclose previously obtained genetic test results is restricted by law and remains vague, there may be an asymmetry of information between insurer and the insured.

Such an asymmetry of information may potentially have serious consequences for insurers and the insured. However, it would only generate significant financial implications when individuals who have returned a positive genetic test not only have an increased likelihood of purchasing insurance but also request significantly higher amounts of insurance coverage.

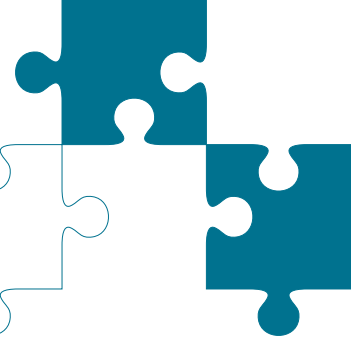
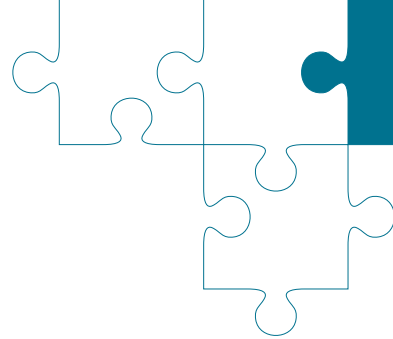
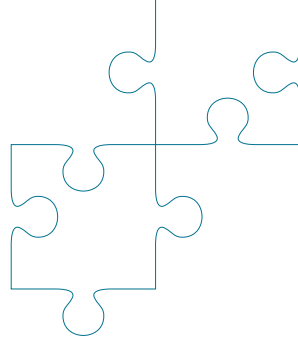
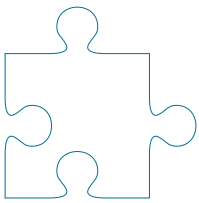
B

### Ethical and Legal framework of genetic testing

During recent years, ethical standards have been developed that should be adhered to while dealing with genetic issues:

- Individual genetic data have to be handled responsibly and precautions have to be taken to adhere to a strict level of data privacy.
- Predictive genetic testing is only allowed upon a patient's request and must be in her or his interest.
- Predictive genetic testing is only warranted if a disease can be predicted with a high level of probability and if the disease can be treated and prevented effectively.
- Genetic testing must always go along with appropriate expert individual consultation.
- Individuals may by no means be disadvantaged on the basis of their special genetic features.

*In 1989, the European Union adopted a resolution in which a complete ban on the use of genetic testing in insurance matters. The Charter of Fundamental Rights prohibited the discrimination based on genetic features*



and the same policy was adopted by the Council of Europe in the Convention. It explicitly prohibits any form of discrimination on the grounds of genetic heritage and the carrying out of predictive tests for reasons other than health-related research, even with the assent of the person concerned. **Insurers are prohibited from conducting genetic tests on insurance applicants and to make distinctions based on people's genomes.**

Some countries have legislated to prohibit insurance companies from using genetic tests. This has been the case in Belgium, Denmark and France. Such a strategy faces definitional problems, namely what actually constitutes genetic information and a genetic test.

The adoption of voluntary moratoria on the use of genetic testing has been a widespread response of the insurance industry. The reason is that there are very few relevant and accurate genetic tests available. Moratoria are either indefinite or for a limited number of years or limited to insurance policies under a certain value (e.g. the United Kingdom).

Other countries have taken the middle road, only authorising the use of genetic susceptibility tests beyond a certain level of insurability and with the consent of the individual concerned. This is the case in the Netherlands and Sweden. The attraction of a ceiling system of insurance is that it reduces the effects of adverse selection by permitting the insured to seek bargains or to transfer risks but only within well-defined financial limits.

The United Kingdom is an example of mandated self-regulation of the use of genetic information by the insurance industry. However, there are obvious problems with relying on self-regulatory systems which exist when there is no external sanction imposed on a financially powerful institution. Since October 2001 the self-regulation concerning genetic information has been turned into a moratorium. In Germany, genetic testing is regulated by the "Gendiagnostikgesetz" ("gene diagnostics law", abbreviated GenDG) and basically similar laws apply in Austria and Switzerland. The most important regulations of the German law include:

- Only especially certified laboratories are allowed to perform genetic tests (in Germany, an ISO 17025 certification is required).
- Predictive genetic testing may only be performed by physicians specialised in human genetics or other physicians who have completed advanced training in genetics.
- Informed consent has to be documented for each examination.

- The patient has a right to be informed about the results, but she or he can also choose to remain uninformed about the results.
- Special regulations apply for genetic tests aimed at determining parentage.
- Employers are not allowed to ask for results of genetic tests or perform genetic tests.
- Insurance companies are not allowed to ask for results of genetic tests or perform genetic tests before contracting insurance. An exception relates to contracts for life insurance, disability insurance and nursing care insurance if insurance sums exceed 300,000 euros one-time payment or yearly payments exceeding 30,000 euros. In such cases, the applicant is obliged to inform the insurer about existing genetic test results before contracting insurance.

In the United Kingdom, the Association of British Insurers (ABI) and the government's Department of Health did establish a voluntary moratorium on the use of predictive genetic testing by insurers. The moratorium means the results of a predictive genetic test will not affect a consumer's ability to take out any type of insurance other than life insurance over £500,000. Above this amount, insurers will not use adverse predictive genetic test results unless the test has been specifically approved by the Government. Only around 3% of all policies sold are above these limits. The only test that is approved is for Huntington's Disease. The moratorium was initially scheduled to expire in 2011. It was extended until 2014 in 2008 and it was recently extended to 2017. The moratorium is scheduled to be revisited again in 2014.

In Ireland, under the provisions of Part 4 of the Disability Act 2005, an insurer cannot request, take into account or process the results of genetic tests. This applies to both positive and negative tests. Under the legislation, an insurer may not take into account a negative test result even if asked to do so by an applicant.

In the United States, the Genetic Information Nondiscrimination Act (GINA) prohibits discrimination on the basis of information derived from genetic tests for health insurance but life, disability and long term care insurance are not included. Moreover, GINA legislation does not protect symptomatic individuals.

Genetic testing in the operation of life insurance business in Australasia is governed by policy statements and Standard issued by the Investment and Financial Services Association (IFSA) and the Financial Services Council (FSC) dating from December 2005. This Standard applies to all IFSA Members who are a registered life insurance

company or have a subsidiary that is a registered life insurance company. All life insurance companies registered by APRA (Australian Prudential Regulation Authority) who are not IFSA members are encouraged to follow this Standard.

Members of this Association have agreed to abide by an industry standard document which specifies, amongst other things, that applicants should not be required to undergo genetic testing when applying for insurance. However, results of previously undertaken tests should be made available to the insurance company on request.

This information must not be used for assessing other family members or for pricing preferred products but it can be used to assess the risk of the applicant. Any such decisions must be fully documented and made available to the applicant on request. A competent and efficient internal dispute resolution system must be implemented to deal with complaints relating to underwriting decisions involving a genetic test result. Responses to any complaints must include a reference to the legal remedies available to the applicants.

Members of the Association have agreed to regular collection of de-identified data by the Association and to allow such data to be made available to the public to aid future research initiatives.

Despite the introduction of this Standard, the Human Genetics Society of Australasia issued a statement on Genetic Testing and Life Insurance in Australia in February 2008 in which it urged the industry to implement a moratorium on the use of predictive genetic testing pending improved actuarial estimates of the impact of such information on adverse selection. It also stated that it supported the implementation of legislation for the purpose of protecting individuals and their families against infringements of privacy and against discrimination arising from access to and abuse of predictive genetic information. However, to date, no such legislation has been passed.

But is genetic testing a legitimate, actuarially sound means of risk assessment?

Currently, a large range of genetic tests is offered via the internet directly to consumers (so called direct-to-consumer or DTC tests) as a commercial service. These services provide an unregulated means for almost everyone to obtain personal genetic data. However, the offered tests rarely if ever have a scientifically sound basis. Their sensitivity and specificity to detect disease risk is either exceedingly low or non-existent and their analytical accuracy is often low. Moreover, the results are rarely accompanied by expert consultation. Therefore,

these tests do currently not constitute a threat for insurance companies by leading to any significant asymmetry of information regarding predisposition to disease and risk of increased claims.

Although genetic testing has become a routine procedure in the diagnosis of many monogenic diseases, these diseases are mostly very rare and genetic testing is not an absolute requirement for their diagnosis because the vast majority can also be diagnosed traditionally based on clinical means.

Polygenic diseases, such as coronary heart disease, cancer or stroke, are caused by complex interactions between genes and the environment. Although a large number of risk modulating gene variants have recently been identified, their combined effects on risk are too low to be employed in a sound prediction of event risk. Traditional risk assessment schemes, such as for instance the PROCAM Health Test which does not involve genetic testing, have a pronouncedly higher sensitivity and specificity to predict cardiovascular events compared with all currently existing risk assessment schemes relying on genetic testing.

# Conclusion

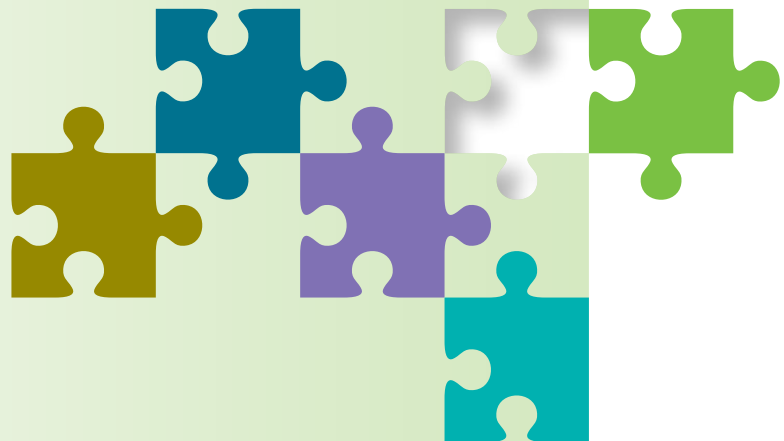
Genetic testing in its present state does not have major practical implications for insurance medicine. Even if legal and ethically acceptable, performing genetic testing at this stage meet strong opposition, whereas potential benefits would be at the most marginal.

However, it is not a question of if but rather when predictive genetic testing will be improved to practically relevant levels. Eventually, genetic testing can be expected to become an important tool in accurately predicting risk for a large range of frequent and devastating disorders.

Once this has been achieved, the current legal frame work which prohibits genetic testing by insurance companies will require adaptation.

Otherwise, the result could, in certain countries, lead to asymmetry of relevant genetic information between insurers and the insured which could have negative consequences for the whole insurance industry

At present, insurers should be highly aware of data arising from research in the field of genetics and monitor all new developments very closely.



# Glossary of genetic terms

## A Alleles

Alternate forms or varieties of a gene. The alleles for a trait occupy the same locus or position on homologous chromosomes and thus govern the same trait. However, because they are different, their action may result in different expressions of that trait.

## Amino acids

20 molecules that contain nitrogen and together form the building blocks of proteins.

## Autosomes

Non-sex chromosomes. Humans have 22 pairs of homologous autosomal chromosomes and one pair of sex chromosomes (X and Y chromosomes).

## B Base pairs

A set of two-bonded nucleotides on opposite strands of DNA. Adenosine and Thymine are one pair and Cytosine and Guanine are the other.

## Blending theory

An incorrect 19th century theory about the inheritance of characteristics. It proposed that inherited traits blend from generation to generation. Through his plant cross-breeding experiments, Gregor Mendel proved that this was wrong.

## C Carrier

An individual who is heterozygous for a trait that only shows up in the phenotype of those who are homozygous recessive. Carriers often do not show any signs of the trait but can pass it on to their offspring. This is the case with females carrying the gene of haemophilia but who have no bleeding tendency themselves.

## Catalysts

Catalysts are agents that increase the rate of a chemical reaction without themselves being consumed in that reaction. In practice, the speed of most chemical reactions that take place in living cells is so slow as to be considered negligible. It is only in the presence of enzymatic catalysts that the rate of reaction increases sufficiently for this reaction to be significant: an increase of several-thousand-fold over baseline is not unusual. Thus, in effect, enzymes act as molecular "switches" that can activate chemical reactions within a cell.

## Centromere

Acentromere is a region of DNA typically found near the middle of a chromosome where two identical sister chromatids come closest in contact.

## Chromatid

One of the two identical copies of DNA into which the chromosome divides during mitosis, joined at their centromere. When they separate during cell division, the strands are called daughter chromosomes.

## Chromosome

A rod-shaped structure of tightly coiled DNA found in the cell nucleus of plants and animals. Humans have 46 chromosomes in each somatic cell and 23 in each sex cell or gamete.

## Cloning

The process used to make genetically identical copies of an organism.

## Cytoplasm

Substance within the cell but outside the nucleus in which various cell parts are suspended.

## D Diploid

Most animal cells are diploid, meaning that their chromosomes exist in homologous pairs. A human somatic cell contains 46 chromosomes which make up 23 homologous chromosome pairs.

## DNA

Deoxyribonucleic acid, a large organic molecule that stores the genetic code for the synthesis of proteins. DNA is composed of sugars, phosphates and bases arranged in a double helix shaped molecular structure. Segments of DNA in chromosomes correspond to specific genes.

## Dominant allele

An allele that masks the presence of a recessive trait in the phenotype. Dominant alleles for a trait are usually expressed if an individual is homozygous dominant or heterozygous.

## E Expressivity

Expressivity measures the extent to which a genotype shows its phenotypic expression. Variable expressivity is a phenomenon of different phenotypic display of the same mutated allele in different individuals.

## G Gamete

An organism's sex cell, which contains half the total number of chromosomes.





### Gene

The fundamental unit of heredity : a section of a chromosome or stretch of DNA which codes for an RNA chain that has a function in the organism.

### Gene markers

Landmarks for a particular gene, either detectable traits that are inherited along with the gene or distinctive segments of DNA.

### Gene mapping

The process of determining the positions of genes on a chromosome and the distance between them.

### Gene therapy

The treatment of disease by replacing or changing non - functioning genes.

### Genetics

The scientific study of heredity.

### Genetic test

The National Human Genome Research Institute definition of genetic testing is "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes." Such purposes include predicting risk of disease and establishing prenatal and clinical diagnosis or prognosis.

### Genome

All the genetic material in the chromosomes of a particular organism.

### Genome map

A chart that shows the arrangement of the genes or other DNA markers on the chromosomes.

### Genotype

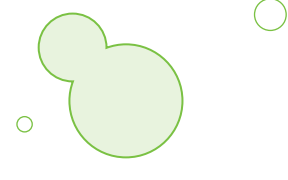
The genetic make-up of an individual.

### Genotypic heterogeneity

Genetic variability among individuals with similar phenotypes.

### Genotype-phenotype plasticity

The concept that the link between genotype and phenotype is subject to broad variability with as yet limited predictability.



### H Haploid

The number of chromosomes in a gamete of an individual. During meiosis, diploid sex cell precursors have their number of chromosomes halved by random "choice" of one homologue, resulting in haploid gametes.

### Helix

A winding shape, similar to a spiral; the DNA molecule has a double - helix shape, which is two helices twisted around each other.

### Heterozygous

A genotype consisting of two different alleles of a gene for a particular trait (Aa).

### Homologues

Homologous chromosomes are chromosome pairs of approximately the same length, and centromere position with genes for the same characteristic or trait at corresponding loci.

### Homozygous

Having the same allele at the same locus on both members of a pair of homologous chromosomes. Homozygous also refers to a genotype consisting of two identical alleles of a gene for a particular trait. An individual may be homozygous dominant (AA) or homozygous recessive (aa). Individuals who are homozygous for a trait are referred to as homozygotes.

### Human genome

The collection of genes needed to produce a human being.

### Human Genome Project (HGP)

The international research effort to identify and map all the genes in the human body.

### Hybrids

Offspring that are the result of mating between two genetically different kinds of parents - the opposite of purebred.

### I Incomplete penetrance

The situation in which an allele is expressed only if certain factors are present in the environment. The triggering of genetically inherited diabetes by obesity and possibly severe emotional stress is an example.

### L Locus (plural loci)

The location of a gene or of a significant sequence of DNA on a chromosome.

### M Meiosis

The division of the genetic information in reproductive cells, so that they have only half the number of chromosomes of somatic cells.

## Glossary of genetics terms

### **Mendelian genetics**

Inheritance patterns which can be explained by simple rules of dominance and recessiveness of genes.

### **Mitochondria**

“Cellular power plants” located in the cytoplasm of cells which generate most of the adenosine triphosphate (ATP) used as a source of energy. Although most of a cell’s DNA is contained in the nucleus, the mitochondrion has its own independent DNA which shows substantial similarity to that of bacteria.

### **Mitochondrial DNA**

Mitochondria appear to be primarily inherited through the maternal lineage. Typically, a sperm carries mitochondria in its tail as an energy source for its long journey to the egg. When the sperm attaches to the egg during fertilisation the tail falls off so that the only mitochondria the new organism gets are from the egg its mother provided. Unlike nuclear DNA, mitochondrial DNA doesn’t get shuffled every generation and so it is presumed to change at a slower rate which is useful for the study of human evolution.

### **Molecule**

A combination of atoms, and also the basic building - block of DNA and RNA. Each molecule has its own shape and attaches only to certain other molecules to form the DNA helix.

### **Mutation**

A change in the genetic code to produce new alleles of a gene that can occur because of environmental reasons or over long periods of time as part of evolution.

### **N Nucleotide**

A unit of DNA or RNA, consisting of one chemical base plus a phosphate molecule and a sugar molecule.

### **Nucleus**

The centre of a cell, where all of the DNA, packaged in chromosomes, is contained.

### **P Penetrance**

The same mutation is not always expressed in all individuals who carry it; moreover, when the mutation is expressed, it is not always expressed in the same way. Penetrance measures the proportion of a population of individuals who carry a disease-causing allele and express the related disease phenotype. Expressivity measures the extent to which a genotype shows its phenotypic expression. Moreover, both the penetrance and expressivity of different diseases can be partially explained by the action of gene modifiers.

### **Phenotype**

An organism’s inherited observable or detectable characteristics of its genotype.

### **Phenotypic heterogeneity**

Phenotypic variability among individuals with similar genotypes.

### **Polymerase chain reaction**

Agentic engineering technique used to reproduce segments of DNA millions of times; it is used in forensics and chemical and biological experiments.

### **Proband**

The first individual in a family who presents with clinical disease, sometimes referred to as the index case.

### **Protein**

A chain of amino acids; examples include hormones, enzymes, and antibodies.

### **R Recessive allele**

An allele that is masked in the phenotype by the presence of a dominant allele. Recessive alleles are expressed in the phenotype when the genotype is homozygous recessive (aa).

### **Ribosome**

An organelle that produces protein in cells.

### **RNA**

Ribonucleic acid, similar to DNA, except that it has ribose instead of deoxyribose sugar, and uracil instead of thymine as a nitrogen base.

### **S Sex chromosomes**

Chromosomes that determine an organism’s sex. Human females have two X chromosomes ; males have one X chromosome and one Y chromosome.

### **Somatic cells**

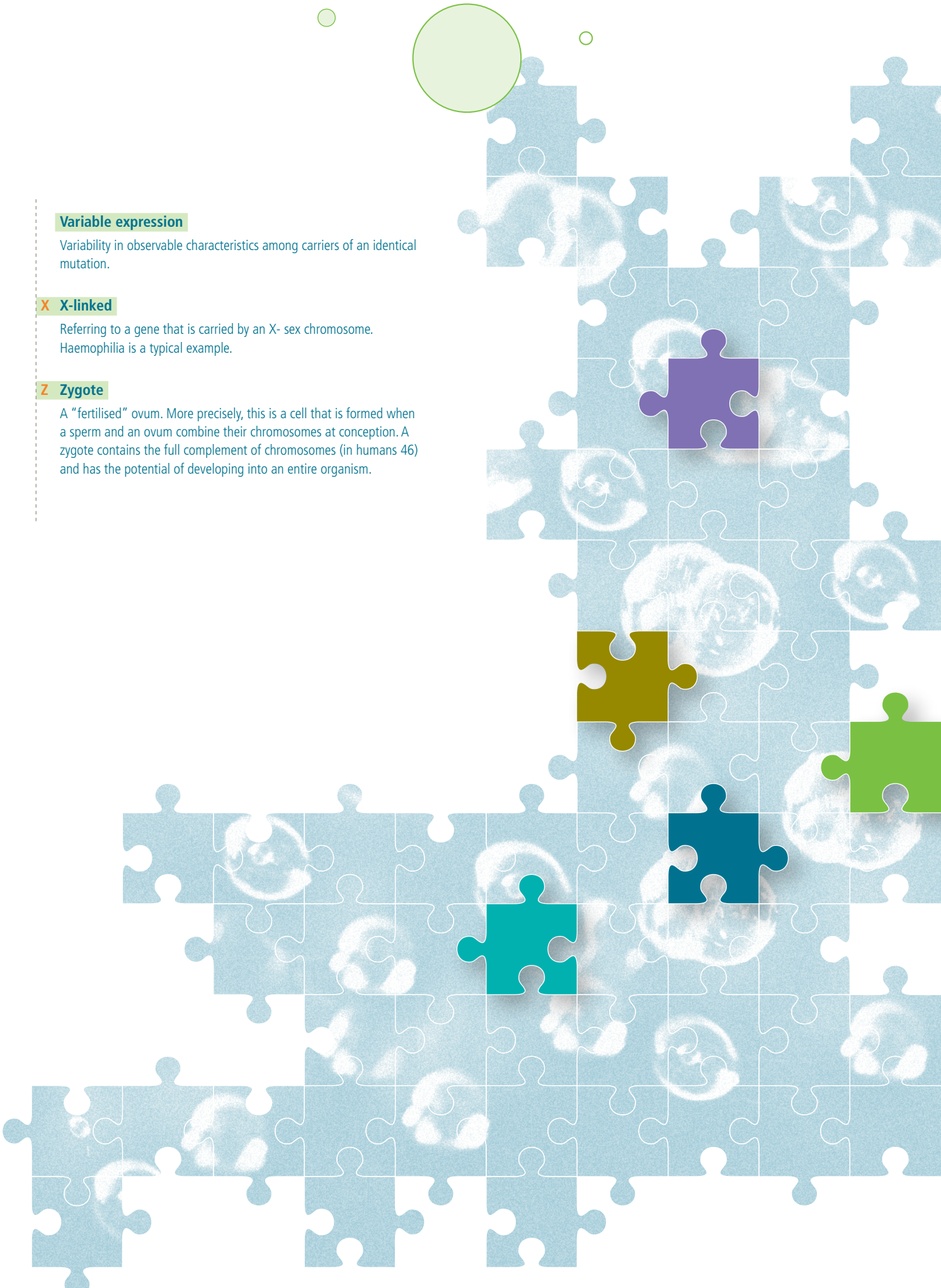

All body cells, except for the reproductive cells.

### **T Trait**

An organism’s physical feature, determined by a gene.

### **V Variable penetrance**

Variability in the proportion of genotypically identical individuals who express the disease phenotype.



### Variable expression

Variability in observable characteristics among carriers of an identical mutation.

### X X-linked

Referring to a gene that is carried by an X- sex chromosome. Haemophilia is a typical example.

### Z Zygote

A "fertilised" ovum. More precisely, this is a cell that is formed when a sperm and an ovum combine their chromosomes at conception. A zygote contains the full complement of chromosomes (in humans 46) and has the potential of developing into an entire organism.



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