

# A beginner's guide to genetics: the basics

In the first of our new series about clinical genetics, **Adrián J González, Heidy R Arrieta, and Osvaldo M Mutchinick** explain the fundamental principles of medical genetics, which provide the basis of prevention and treatment of genetic diseases

**F**ounded by Gregor Mendel in the 19th century, genetics is the scientific discipline that probably has the greatest potential to change the way we practise medicine in the future. Genetics affects many aspects of life—in horse racing, where certain characteristics, such as speed and strength, are chosen to be passed on to the next generation; in crop selection, to allow better vegetables to feed more people; and in recombinant DNA technology, to produce insulin and other chemicals to improve disease treatment.

For medics, the most important area of genetics is human genetics, particularly medical genetics, which deals with the interactions between the human genome and the environment in which we live and how these interactions affect our life in terms of health and susceptibility to disease.

## Molecules of life

Genetic information in most living organisms, including humans, is organised in chromosomes. In human cells, chromosomes are inside the nucleus and are in pairs. Except for gametes (oocytes and spermatozooids), which have 23 chromosomes (the haploid number of chromosomes), our cells have 46 (the diploid number of chromosomes). Among the 23 pairs of chromosomes, one pair is the sex chromosomes—XX in females and XY in males.

The most important constituent of chromosomes is deoxyribonucleic acid (DNA). DNA is made of sugar (deoxyribose) and phosphate as a backbone and four nitrogenated bases: two purines, adenine (A) and thymine (T), and two pyrimidines, cytosine (C) and guanine (G), which are organised along the DNA thread in a fixed pattern.

In 1953, Watson and Crick described the structure of the DNA as a double strand of polynucleotides that coils around a common axis and associates by hydrogen bonding of bases A-T and C-G to form a structure called a double helix.<sup>1</sup> These specific bonds, known as base pairing, result in two strands that are a mirror image of the other, called complementary strands. These characteristics enable the molecule to

separate without breaking covalent bonds, and the specificity of base pairing means that one strand can serve as a template for the synthesis of a new (daughter) strand in a process known as DNA replication.<sup>2</sup>

## Genes create proteins

DNA codes for the proteins that make up our tissues and organs and control cell functions. A gene is a segment of DNA that can produce a functional product—usually a protein. DNA codes for proteins via another molecule—messenger ribonucleic acid (mRNA) (fig 1). mRNA has a sequence complementary to the DNA strand and has had the DNA message transcribed onto it using uracil (U) instead of thymine (T). It has the ability to leave the nucleus to associate with ribosomes, the protein assembling machines. The bases of the mRNA are in groups of three called codons.

The mRNA code (fig 2) is translated into the sequence of amino acids that form a polypeptide. There are two other important ribonucleic molecules, the ribosomal RNA (rRNA) and the transfer RNA (tRNA). rRNA is a component of the ribosomes at the site where proteins are synthesised. tRNA recognises the mRNA codons and adds a specific amino acid to the polypeptide chain.<sup>3</sup>

## Mutations

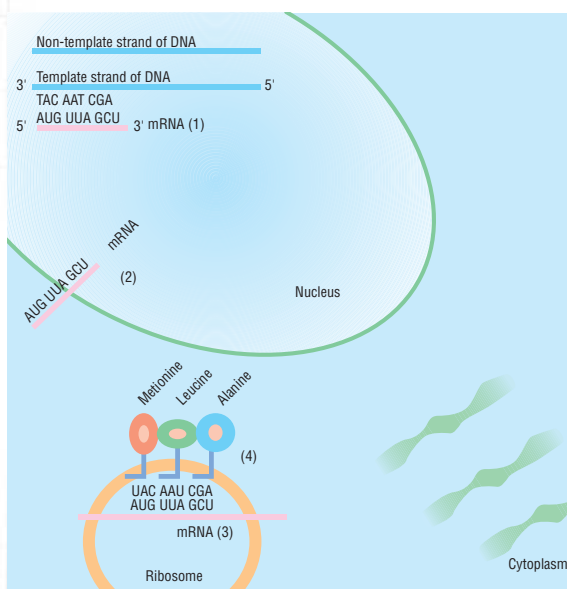
Mutations are permanent changes in the DNA sequence of the genome and can occur spontaneously during DNA replication or can be induced by exposure to chemicals or radiation. DNA sequences often mutate, but almost all are rapidly corrected by DNA repair systems. If a mutation is not repaired, this can change the amino acid that is added to the polypeptide chain. Sometimes this affects the synthesis or structure of the protein and consequently its function. This type of mutation is often found in genetic diseases.

Mutations can be classified in three groups:

- *Genome mutations* refer to loss or gain of chromosomes, giving rise to monosomies and trisomies.
- *Chromosomal mutations* involve structural chromosome changes, such as deletions, translocations, and inversions.
- *Gene mutations* are at a submicroscopic level and can involve single base substitutions, loss of a few base pairs, or the complete loss of the gene; these changes affect protein synthesis and structure.

Mutations in germ cells can be inherited by offspring and give rise to an inheritable trait or disease. New mutations in somatic cells do not generate heritable disorders but are an important cause of ageing and diseases like cancer.<sup>4</sup>

**Fig 1** DNA codes for mRNA, which codes for proteins. (1) Transcription: mRNA is made based on the template DNA strand, changing thymine (T) for uracil (U); (2) mRNA leaves the nucleus; (3) mRNA binds to the ribosome, where proteins are synthesised. (4) Translation: each triplet of bases (codon) is recognised by the anticodon in tRNA, then a new amino acid is added to the polypeptide chain to form the protein



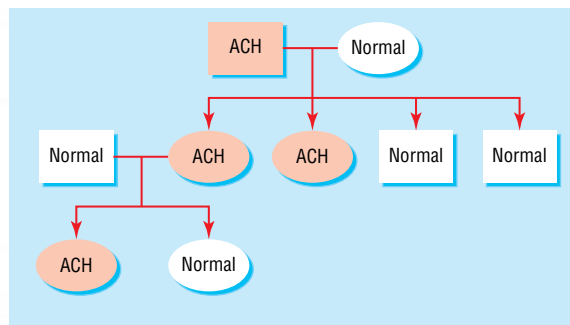
		Second nitrogenated base				
		u	c	a	g	
First nitrogenated base	u	{ uuu } Phe uuc } uua } uug } Leu	{ uuc } Ser ucc } uca } ucg }	{ uau } Tyr uac } uua } Stop uag }	{ ugu } Cys uga } ugc } Stop ugg } Trp	u c a g
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	a	{ auu } auc } aua } aug } Met	{ acu } acc } aca } acg } Thr	{ aau } Asn aac } aaa } aag } Lys	{ aau } Ser aac } aaa } aag } Arg	u c a g
	g	{ guu } guc } gua } gug } Val	{ gcu } gcc } gca } gcg } Ala	{ gau } Asp gac } gaa } gag } Glu	{ gau } gac } gaa } gag } Gly	u c a g

**Fig 2** Groups of three nitrogenated bases (codons) code for a specific amino acid—for example, CUU, CUC, CUA, and CUG code for leu (leucine). The codons of a particular mRNA strand indicate the sequence of amino acids in a particular protein

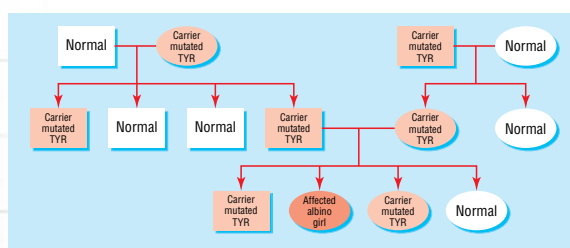
from normal parents who carried the recessive abnormal gene. If both parents are carriers of the mutation for albinism, they have a 25% chance of having a child with albinism (fig 4).

*Sex-linked inheritance*

In the X linked mode of inheritance, the recessive type affects males, and females are normal carriers of the mutated gene (for example, haemophilia), and the dominant type affects both sexes, although more severely in males (for example, vitamin D resistant rickets).



**Fig 3** Autosomal dominant mutations. All patients with the mutated gene FGFR3, responsible for achondroplasia (ACH), will develop the disease. Offspring have a 50% chance of inheriting the abnormal gene



**Fig 4** Autosomal recessive mutations. The gene TYR, responsible for albinism, is inherited as an autosomal recessive trait. Healthy carriers (heterozygous for the mutation) do not develop the disease, but can pass the abnormal gene to their offspring. To have albinism the child must receive the mutated TYR gene from both the mother and father (be homozygous for the mutant gene). The child of a pair of carriers has a 25% of chance of being affected

**Modes of inheritance**

In 1866, Gregor Mendel performed experiments with pea plants and explained how the characteristics of organisms are inherited from one generation to another. His work was rediscovered in 1900, and his principles (Mendel’s laws) were applied to the study of human genetics. Soon after, the mode by which human traits determined by a single gene are inherited was established. These patterns of heredity are called Mendelian patterns of inheritance. Actually we recognise four Mendelian forms by which normal and abnormal traits are inherited—autosomal dominant and recessive and X linked dominant and recessive.

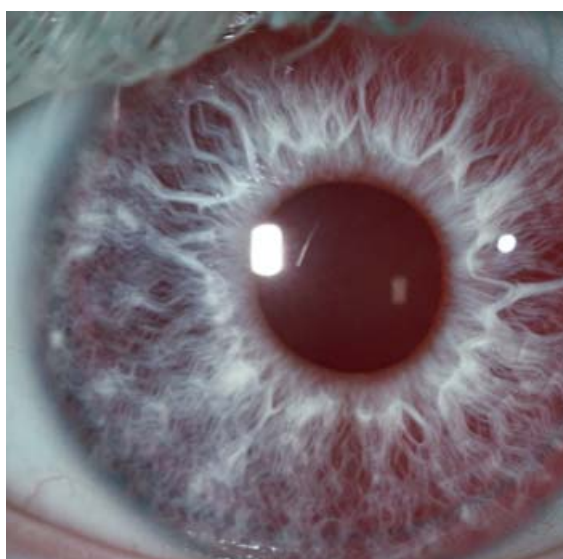
*Autosomal inheritance*

Characteristics caused by a gene carrying dominant mutations are expressed in individuals that bear them, even in the presence of a wild homologous gene. For example, people who inherit the mutation for achondroplasia have the characteristics of the disease and have a 50% chance of transmitting the mutant gene to their offspring (fig 3).

*Recessive inheritance*

Recessive traits are expressed in people who have two of the mutant genes (homologous genes), inherited

Eye of a person with albinism



**Non-Mendelian modes of inheritance**

Unfortunately not everything in medical genetics is so simple. Recently, non-classic patterns of heredity have been described. Mendelian principles imply that the expression of genes is the same whether the genes are inherited from the mother or the father. In some genetic diseases, however, clinical manifestations are different depending from whom the mutant gene was inherited.<sup>4</sup>

This differential expression is known as genetic imprinting and has mostly been associated with DNA methylation. This methylation, which does not happen at random but in specific DNA sequences (CpG islands), is considered an epigenetic mechanism that modifies the expression of the gene by silencing it. Although this epigenetic mechanism does not involve changes in the DNA sequence, it has a characteristic pattern that is transmitted to the next generation.<sup>5</sup>

A clear example is a disease consisting of mental retardation, short stature, abnormal sexual development, polyphagia, and obesity—Prader-Willi syndrome. The most common cause is a submicroscopic deletion in the long arm of chromosome 15 inherited from the father. If this deletion is in the same region of the same chromosome but is inherited from the mother, a different disease with severe mental retardation, lack of speech, seizures, and characteristic laughter—Angelman syndrome—is seen. <sup>5</sup>

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