Genetics for orthopaedics☆

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Abstract

A sound knowledge of basic genetic concepts and definitions needs to be at the fingertips of every practicing orthopaedic surgeon and not least for final professional examinations. A review of the general principles of genetics and inheritance is presented, along with illustrations of some common, and less common, relevant orthopaedic conditions.

Keywords bone deformities; DNA; genetics; genome; heredity

Introduction

The word 'genetics' derives from the ancient Greek "genesis" meaning "origin". The modern science of genetics began with the work of Gregor Mendel in the mid-19th century on the mechanisms of trait inheritance. Subsequently, the molecular structure and function of genes was defined. Clinical Genetics is now a branch of medicine intrinsically linked to almost every clinical specialty. The first draft of the human genome was published in 2001.[1] Diploid human genomes, found in somatic cells, are now know to contain around 6 billion DNA base pairs, equivalent to about 2 m of linear DNA. While there are significant variations among the genomes of humans (in the order of 0.1%), these are appreciably less than the variation between humans and their closest relatives, the chimpanzees (approximately 4%).[2]

Diseases of genetic origin are numerous (Table 1). They are often incurable and may cause considerable morbidity. Once a diagnosis has been made, the management involves genetic counselling, including familial recurrence risks, surveillance and management of any associated disease complications in an affected patient.

Genetic disease prevalence

Genetic disorder	Prevalence per 1000 population
Single gene	
Autosomal dominant	2–10
Autosomal recessive	2
X linked recessive	1–2
Chromosomal abnormalities	6–7
TOTAL	**≤21**

Table 1

Common genetic terminology and definitions

DNA (deoxyribonucleic acid)

DNA is a nucleic acid molecule, which encodes the genetic information of nearly all living organisms and many viruses. Most DNA (~90%) is located in the cell nucleus (nuclear DNA), stored as nuclear chromosomes (Figure 1). The remainder is found in the mitochondria of cells (mitochondrial DNA). DNA is composed of two polymer strands. The 'backbone' of DNA is made up of 2-deoxyribose pentose (5 carbon) sugar units and phosphate groups (the sugars are linked via phosphodiester bonds between adjacent 3′ and 5′ carbon atoms). The orientation of the phosphate group defines the 3′ (three prime) and 5′ (five prime) ends of the molecule, meaning that DNA has orientation, which dictates the direction of its replication. The two DNA strands are wound around each other in a double helix and are linked together by hydrogen bonds between the bases (nucleobases), which are attached to each sugar (deoxyribose) unit.

The genetic information of DNA is encoded in the sequence of bases along the molecule. DNA can make identical copies of itself by the process of replication, passing on its genetic information to daughter cells when that cell divides. Watson and Crick produced their model for the double helical structure of DNA in 1953 and proposed a method for replication.

Nucleotide

A nucleotide is the basic repeating unit of the DNA strand, consisting of a nitrogen-containing base (a purine or pyrimidine) covalently linked to a deoxyribose sugar unit and a phosphate group.

Base

The bases are nitrogen-containing compounds with either a two-ring or a single ring molecular structure.

- **purines** adenine (A) and guanine (G), have a two-ring structure
- **pyrimidines** thymine (T), cytosine (C) and uracil (U; the RNA replacement for T), have a single ring structure.

The actual sequence of the bases along the DNA molecule constitutes the genetic code. When held together by hydrogen bonds within the DNA double helix specifically, adenine is always paired with thymine A=T and cytosine with guanine C≡G.

Gene

A gene is defined as a molecular unit of heredity and is a section of DNA that encodes the amino acid sequence, and controls the formation of, a single polypeptide chain in protein synthesis. However, not all genes encode proteins and some are involved in regulation of other genes' expression via the production of non-coding mRNA. Humans have approximately 24 000 genes, accounting for less than 5% of the total genomic DNA. The rest is 'non-coding' DNA, the function of which is not yet entirely defined. Genes are made up of exons and many also contain

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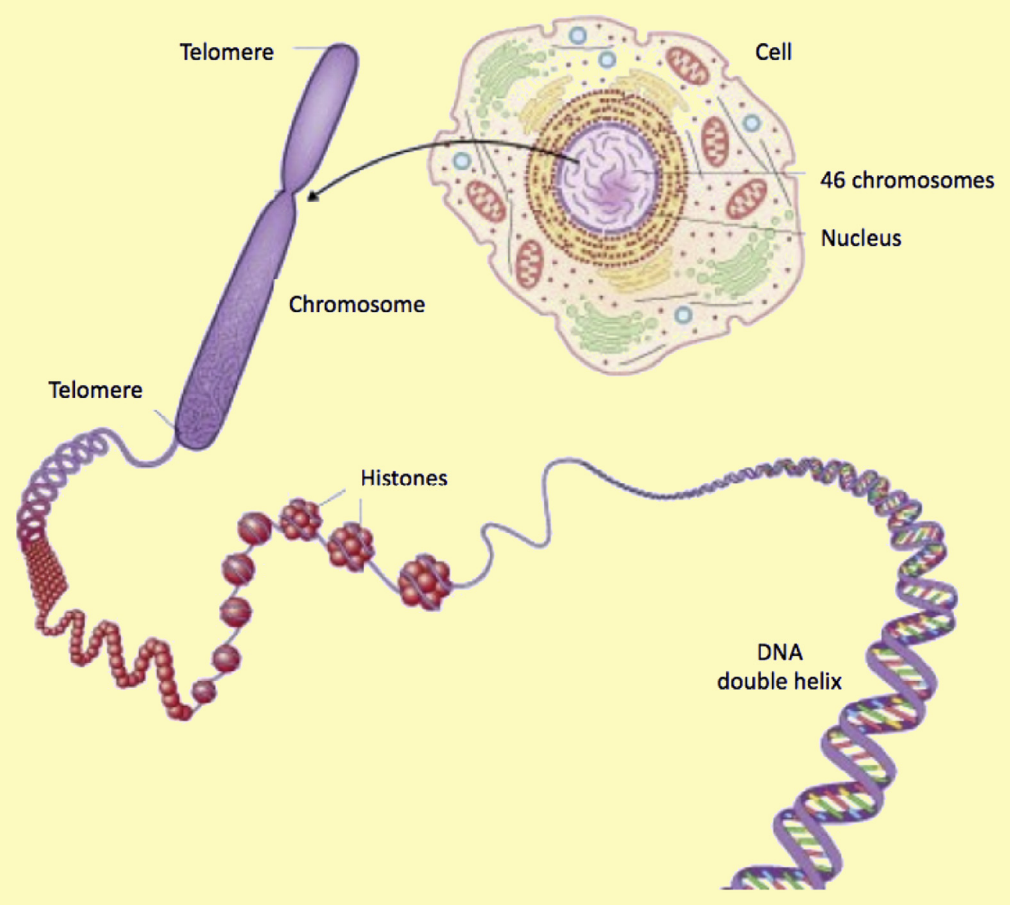

Figure 1 Cell, chromosome and DNA structure www.geneticseducation.nhs.uk.

introns. The protein-coding sequence of a gene is located in the **exon(s)**. When a gene contains multiple exons, these are interrupted by varying sizes & numbers of non-coding sequences, known as **introns** (Figure 2).

Some regions of non-coding DNA are "regulatory regions", which control gene expression (i.e. they control which genes are transcribed in specific cells at specific times). Mutations in certain regulatory regions have been shown to cause specific disorders (e.g. mutations in the regulatory region of the gene *SHH* cause preaxial polydactyly).[3]

The number of genes identified in humans is considerably smaller than was anticipated prior to the sequencing of the human genome. Recently, the field of epigenetics has focused on heritable factors that do not result from a change in the DNA sequence of an organism. Examples of epigenetic mechanisms include DNA methylation, which alters gene expression without changing the sequence of DNA.

Some genes are expressed at low levels in all cells and control basic cellular functions ("housekeeping genes"). Others are tissue and/or developmental stage-specific and are expressed only in

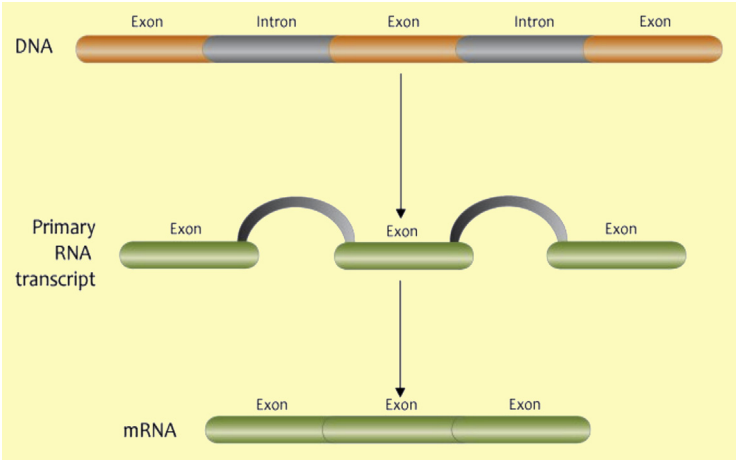

Figure 2 Splicing www.geneticseducation.nhs.uk.