Genetics for orthopaedics

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Abstract
Basic genetic concepts and definitions need to be at the fingertips of every practising orthopaedic surgeon and not least for those preparing for the FRCS(Tr&Orth) examination. This review covers general principles of medical genetics and patterns of inheritance, illustrated with examples of specific relevant conditions.

Keywords bone deformities; DNA; genetics; genome; heredity; skeletal dysplasias

Introduction

The term 'genetics' derives from the ancient Greek 'genesis' meaning 'origin'. The modern science began with the work of Gregor Mendel in the mid-19th century concerning the mechanism of trait inheritance. Subsequently the molecular structure and function of genes was defined. Clinical genetics is now a branch of medicine intrinsically linked with almost every other 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 those 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 includes genetic counselling, including familial recurrence risks, surveillance and management of any associated disease complications in an affected patient.

Common genetic terminology and definitions

See also the Glossary at the end of the text.

DNA (deoxyribonucleic acid)

DNA is a molecule which encodes the genetic information of nearly all living organisms and many viruses. Most (~90%) is located in the cell nucleus (nuclear DNA), stored as chromosomes (Figure 1). The remainder is found in mitochondria (mitochondrial DNA). Watson and Crick produced their model for the double helical structure of DNA in 1953, composed of two polymer strands. The 'backbones' are made up of 2-deoxyribose pentose (five 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 a direction, which facilitates 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 contained 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.

Genetic disease prevalence

Genetic disorder	Prevalance 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

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).

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; some are involved in the regulation of expression of other genes 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 entirely defined. Genes are made up of exons and many contain 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 and numbers of non-coding sequences, known as **introns**.

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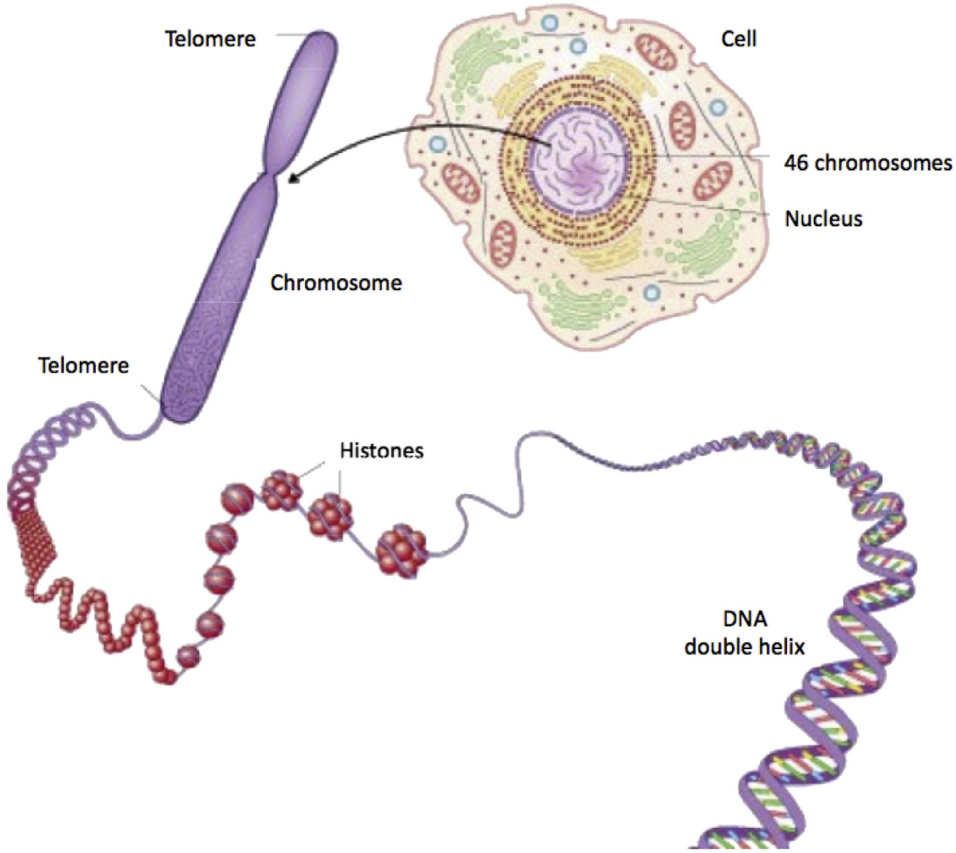

Figure 1 Cell, chromosome and DNA structure. Reproduced with permission from www.geneticseducation.nhs.uk.

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 is considerably smaller than was anticipated prior to the sequencing of the human genome. Recently, the field of epigenetics has focused on heritable factors which 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 certain tissues or cell types and/or at certain times during development (e.g. during limb development).

Genes vary in size, both in the number of bases they contain and in the number of exons. For example, there are 118 exons in the COL7A1 gene (encoding the α chain of type VII collagen), whereas the SRY gene (encoding the SRY transcription factor) has only one exon. The dystrophin gene is one of the largest genes identified. It spans 2.4 million base pairs of genomic DNA, contains 79 exons and takes 16 hours to transcribe into mRNA.[4]

Allele

One of two or more alternative copies of a gene, only one of which may be present in any one chromosome. Two alleles of a particular gene occupy the same relative positions on a pair of homologous chromosomes. A genotype may be described as:

Homozygous: if the two alleles are the same.

Heterozygous: if the two alleles are different.

Replication

The specific base pairing A=T and C≡G is elemental to DNA replication, whereby the two DNA helices separate along the base's hydrogen bonds and each then acts as a template for the synthesis of a new strand. (Figure 2).

Codon

An amino acid coding unit, consisting of three nucleotide bases. For example, UUC codes for phenylalanine. Signaling codons are three nucleotide bases that signal the start (AUG) and stop (UAA, UAG and UGA) of translation. As there are four bases (A, T, C and G), there are 64 possible codon configurations. Therefore, most of the 20 amino acids have at least two codons. Methionine and tryptophan have only one codon (Figures 2 and 3).

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