Concepts, definitions and ideas of interest to biologists are explained in *what is...?* Please tell us of any topics you would like to see included.

A chromosome

KEY WORDS
Cell division
Genetic control
Chromatin
Human disease

In a prokaryote, all the genes are carried in a circular DNA molecule in the cytoplasm. In a eukaryote, however, the genes are contained in a number of separate linear DNA molecules in a membrane-bound nucleus. Each of these molecules, together with associated proteins, makes a chromosome. When the nucleus is not dividing, the chromosomes are unravelled and genetically active. But when the nucleus divides at mitosis, genetic activity is switched off and the chromosomes are packaged up into highly condensed structures, which can be seen in the light microscope. The study of chromosomes is an important field of research. Preparations of condensed mitotic chromosomes, including those of humans, are easy to produce (Box 1). These have provided, and are continuing to provide, a huge amount of information about the genetic control of cell function and the mechanisms of cell division. This *What is...?* reviews the genetic content, composition, structure and packaging of chromosomes, and some of the consequences of variations in their number and structure, which include human disease.

How are chromosomes put together?

The total DNA in a newly divided human cell measures around 1.5 m in length — enough to accommodate a sequence of 3 billion bases. However, all the 23 600 human genes would fit into just 2 cm of our DNA, which leaves 98.5% unaccounted for. This excess was originally considered 'junk' DNA, but is now called 'non-coding' DNA (see Biological Sciences Review, Vol. 23, No. 4, pp. 11–14). Evidence suggests that some of the non-coding DNA is needed for gene regulation. Non-coding DNA is certainly important to the cell — damage restricted to non-coding regions is as effective at causing cell death as that in coding regions. It has been suggested that non-coding DNA may also be a reservoir for novel genes that have arisen over an evolutionary lifetime, including incorporation of viral DNA.

As most nuclei are only around 5 μm in diameter, it is clear that the chromosome must be packaged in a sophisticated way. Packaging such a long molecule presents two main problems. First, genes must normally be accessible to allow for protein production. Second, before the cell can divide again, the entire DNA molecule must be duplicated. Once duplicated, each identical copy of DNA must be packaged for distribution to each daughter cell with absolute precision. So the packaging must allow the DNA to be exposed, if only briefly, during the times it is being transcribed, to produce messenger RNA. The same is true during replication in interphase — between successive mitoses — so that two identical molecules can be produced. The rest

BOX 1

How to study human chromosomes

A blood sample is the most convenient starting point, using white cells called T lymphocytes. These cells do not usually divide, but are stimulated to do so in liquid suspension. Only a small percentage of cells enter division, so the number is increased by the addition of agents such as colcemid. This disrupts the mitotic spindle, so preventing the separation of daughter chromosomes and holding cells in metaphase. The cells are then swollen in a hypotonic solution, chemically preserved, then burst by dropping them onto a cooled microscope slide, dried and stained. The chromosomes are then sorted into pairs according to size to produce a karyotype. The cells may also be treated to produce bands shown by stains such as Giemsa — G-banding (Figure 1). These bands are used to produce an international standard map for each chromosome known as an idiogram. Preparations can also be prepared for examination in the scanning electron microscope.

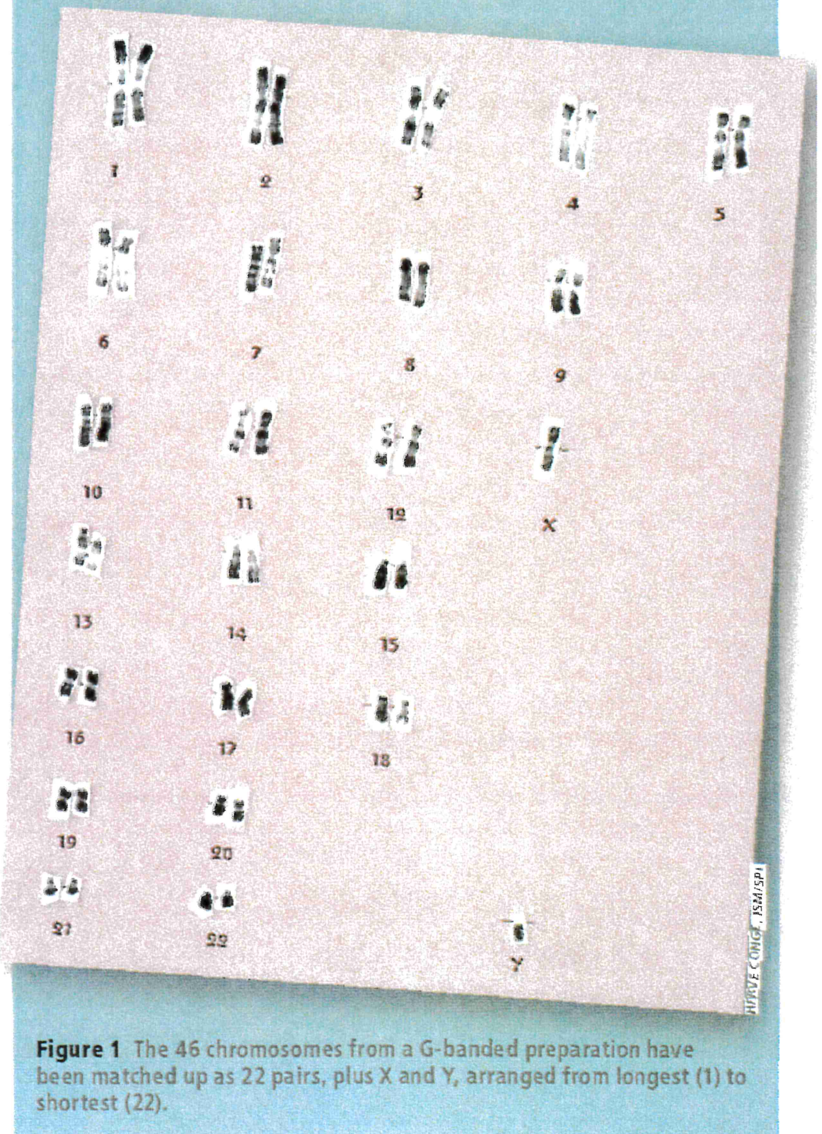

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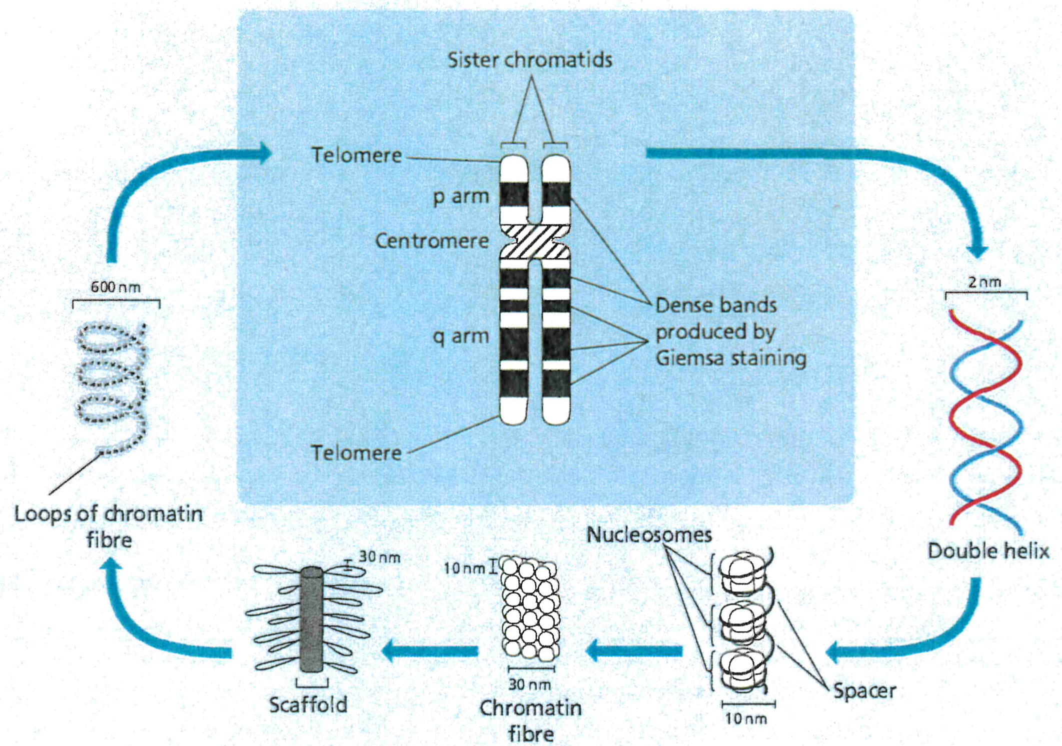
Figure 1 The 46 chromosomes from a G-banded preparation have been matched up as 22 pairs, plus X and Y, arranged from longest (1) to shortest (22).

Figure 2 Stages in the packaging of DNA into chromosomes. Clockwise from top right: naked DNA is packaged by first wrapping around nucleosome cores, then into the 30 nm diameter chromatin fibre found in the interphase nucleus. For further packaging, chromatin becomes arranged on a scaffold and is then coiled and supercoiled into a metaphase chromosome, which has two sister chromatids joined at the centromere with telomeres at each end. Both p and q arms have dense 'G' bands produced by Giemsa staining. These form an internationally standard map called an idiogram for the positioning of genes on each chromosome. (Modified *NCBI Human Molecular Genetics Chromosomes in Cells*, Bios Scientific Publishers, 1999)



of the time the DNA can be held in some form of packaging combined with associated proteins (Figure 2).

The first stage of DNA packaging leads to a 'beads on a string appearance' with the string being the 2 nm diameter DNA molecule. Each bead is formed from a negatively charged group of eight protein molecules called histones. The positively charged DNA binds firmly to the surface of the histones, encircling each bead twice to form a structure known as a nucleosome. The 'spacer' DNA separating adjacent nucleosomes shortens so that the nucleosomes become arranged in a zig-zag to make an 10 nm diameter fibre. This fibre is then coiled to form a cylindrical 30 nm diameter fibre called chromatin. The chromatin fibre is the standard configuration of packaging of nuclear DNA in non-dividing cells. This is what constitutes the apparently haphazard network of structures seen in light microscope images of the interphase nucleus (Figure 3).

As division approaches, the 30 nm chromatin fibre shortens by becoming successively looped, folded, coiled and supercoiled. This involves attachment to a central scaffold formed from non-histone proteins (Figure 2). This complex feat is assisted by the presence in the scaffold of an enzyme with the ability to pass one DNA helix through another by cutting a gap and repairing it. A fully condensed metaphase chromosome has a packing ratio for its DNA of 10 000 to one — it is reduced to one ten-thousandth of its original length. A good analogy to appreciate this amazing organisation would be to take a thread the length of a football field and fold it down to a length of 2 cm.

Fully condensed chromosomes are robust, and this feature has been important in their study. They remain intact even when a dividing cell is preserved and then burst open by an experimenter. They can then be stained for examination under a light microscope or in a scanning electron microscope. As seen at metaphase of mitosis, each chromosome consists of the two future daughter chromosomes, known as chromatids, joined together by a structure known as the centromere (Figure 2). The position of the centromere, together with the number and length of the chromosomes, all go to make the chromosome complement a characteristic feature of each species. The chromatids are 'capped' by structures called telomeres, which protect their ends and stop fusions with other chromatids (which would upset their distribution at cell division). With every division, telomeres lose a small part of the repetitive DNA that forms them. Once this DNA has 'run

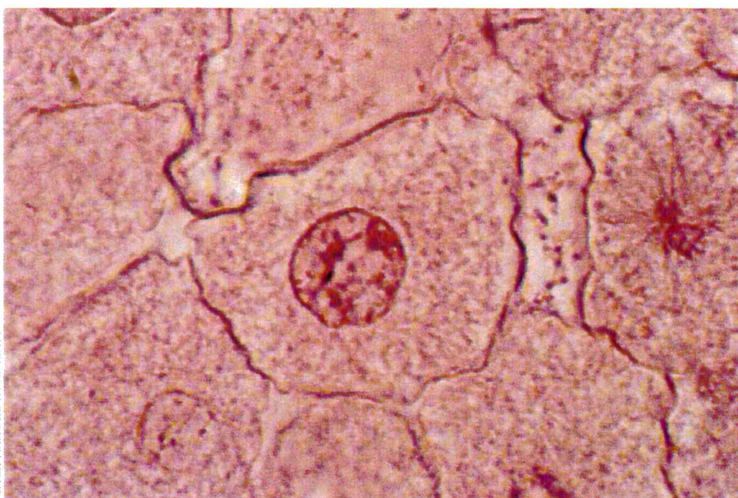

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Figure 3 Light microscope image of interphase of mitosis in a whitefish cell (centre). The denser material at the centre of the cell, in the nucleus, is chromatin. ×700

out', the cell stops dividing. Tumour cells have increased levels of an enzyme called telomerase, which repairs telomeres, allowing unlimited divisions.

Human chromosome preparations are usually produced from lymphocytes in a blood sample, photographed, and then arranged in pairs from largest to smallest, to produce a karyotype (Box 1). This process used to be a skilled and time-consuming task for trained cytogeneticists (Biological Sciences Review, Vol. 23, No. 3, pp. 16–19), but is now routinely automated by computers. In addition, various biochemical treatments performed during the staining of metaphase preparations produce visible bands across the chromatids. Those produced by a stain called Giemsa (G-banding) are used to produce internationally accepted maps of each chromosome known as an idiogram (Box 1).

Chromosome numbers and sex determination

Chromosome number is fixed for each species, but this number is quite variable. Pigs and cats both have 38, cows have 60, fruit flies 8, but some butterflies have 200 and some ferns have several hundred. In all our somatic (body) cells, each of our chromosomes is represented twice, one donated originally from each parent — we are diploid. Sperm and eggs are produced by meiosis, separating each pair of chromosomes into two sets, thus halving the chromosome number — they are haploid. So when sperm and egg combine to produce a fertilised egg, it is diploid, with one set of chromosomes from each parent. Technical difficulties meant that the actual number of human chromosomes was uncertain for a long time, but in 1956 it was finally agreed at 46. The 46 chromosomes form 22 pairs, numbered 1 to 22, plus two sex chromosomes, X and Y (Figures 4 and 5), which determine gender. Males have an X and a Y chromosome, females have two X chromosomes. A gene on the Y chromosome called SRY (for sex-determining region on the Y chromosome) triggers male development in the fetus. In females, one X chromosome is inactivated so that both men and women have the same number of active X chromosome genes.

Chromosomes and disease

It is now over 50 years since the presence of an extra (third) chromosome 21 in Down's syndrome was reported. This was followed, in 1960, by the first chromosomal abnormality associated with cancer, the Ph chromosome, named after its discovery in Philadelphia. The Ph chromosome is an abnormally short chromosome 22, which is formed as a result of breaks in chromosome 22 and chromosome 9, where material is 'swapped' between them (a translocation). People with this abnormality suffer from chronic myeloid leukaemia. During the formation of the Ph chromosome, a gene at the breakpoint from chromosome 9 becomes activated. This gene codes for a protein called Abl and produces excessive tyrosine kinase enzyme, which causes the affected cells to become cancerous (see pp. 38–41). In the 1990s, new tyrosine kinase inhibitors were discovered, which have been useful in limiting the progress of the disease if not curing it. These drugs were found using screening experiments on yeast. Clearly yeast is not closely related to human leukaemia, but the use of such a model system demonstrates how problems can be tackled by studying the basic cell biology from many angles (see pp. 26–29).

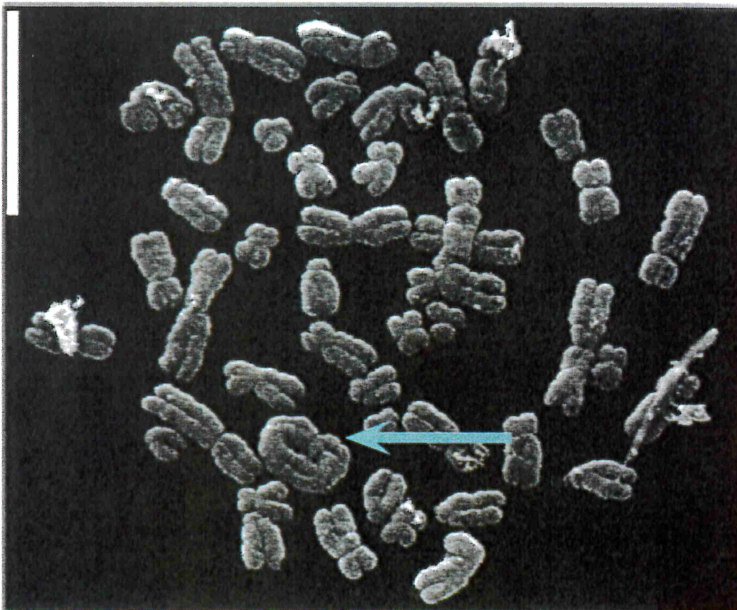

Figure 4 Human chromosome spread viewed in the scanning electron microscope. Ridges in the surface of the chromosomes correspond with Giemsa staining bands. The ends of chromosome 5 (arrowed) have fused, forming a ring (probably due to telomere malfunction), an abnormality that can lead to severe growth retardation. ×6000

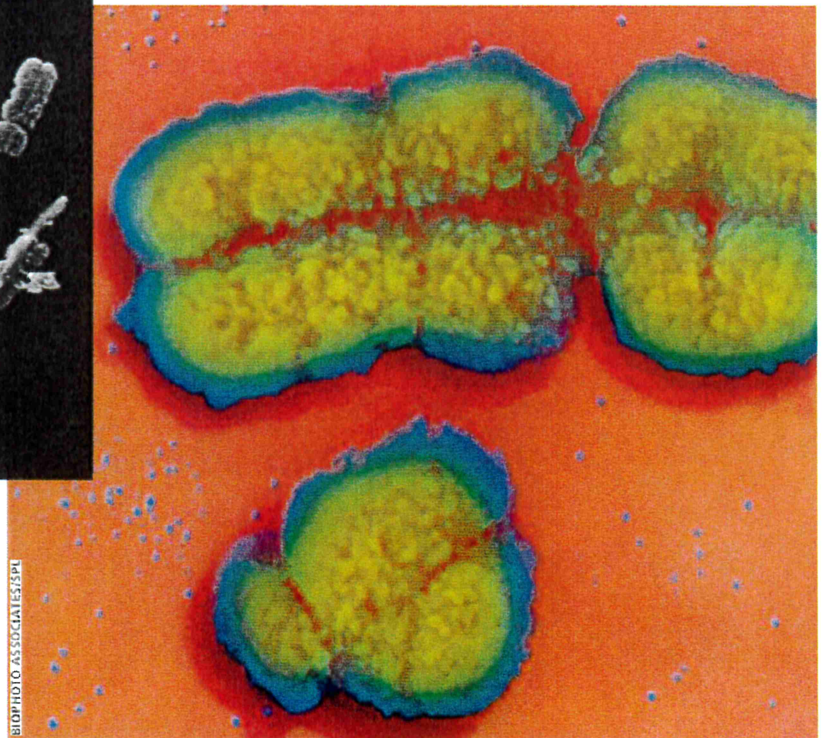

Figure 5 Coloured scanning electron micrograph of a human X chromosome (top) and a Y chromosome. ×17 500

FURTHER READING

Lima-de-Faria, A. (2003) *One Hundred Years of Chromosome Research and What Remains to be Learned*, Kluwer Academic Publishers.

O'Connor, C. (Ed.) Chromosomes and cytogenetics: **www.nature.com/scitable/topic/chromosomes-and-cytogenetics-7**

Information and free posters are available from: **www.ornl.gov/hgmis/posters/chromosome**

Good fact sheets are available from: **www.ghr.nlm.nih.gov/handbook/basics/chromosome**

Which genes are on which chromosome?

We now know how many base pairs of DNA there are in each of our 22 pairs of chromosomes — 246 million in the largest (1), 46 million in the smallest (21). Most genes have now been pinpointed to a particular place on a particular chromosome. Chromosome 1 is six times longer than the smallest human chromosomes (21, 22 and Y). It has 3141 genes and 991 pseudogenes (defective copies of normal genes), some 8% of all human genetic information. It is not surprising therefore that chromosome 1 is medically very important — some 350 human diseases are associated with disruptions in its DNA sequence, including cancers and neurological and developmental disorders.

Now that the entire human genome has been sequenced, one might suspect that the chromosomes themselves might become less relevant, because a patient's DNA can be analysed, compared with normal, and problems diagnosed by computer. But, as we have seen with the Ph chromosome, the behaviour of even normal genes can be altered by translocation and result in disease. It is also worth pointing out that, so far, few complete human genome sequences have been determined, making comparisons between individuals with and without disease difficult.

The first human genome sequence was completed in 2003, after 13 years of sequencing and at a cost of around $500 million. In July 2010 the Wellcome Foundation announced that 10 000 human genomes would be sequenced, 4000 from sufferers of genetic conditions, to be compared with 6000 healthy volunteers. Currently, the main difficulty in the medical value of genomes is that diseases such as cancer, diabetes and Alzheimer's are caused by a large number of different DNA variations. However, the exponential pace of increase of knowledge provides a firm expectation that the idea of specifically targeted medical treatment based on an individual's genome — so-called 'personalised medicine' — may not be too far into the future.

Professor Terry Allen spent his working life at the Paterson Research Institute at the Christie Hospital in Manchester. His research concerned the ultrastructure of cells and the mechanisms of nuclear/cytoplasmic interaction via nuclear pore complexes. Now retired, he writes popular science books and articles.