Chapter 3

Chromosomes

What is the physical unit of inheritance? When asked this question, most people will answer "genes" or "DNA," but they would be wrong. We humans have some 20,000 some genes but we do not inherit 20,000 plus separate physical units. Neither do we simply inherit a big piece of DNA. Instead we inherit "packaged genes" or "packaged DNA" and those packages are called *chromosomes* (from the Greek *chroma* or χρωμα meaning "color" and *soma* or σωμα meaning "body"). Hence, the physical unit of inheritance is the chromosome. To understand genetics, we must first understand chromosomes.
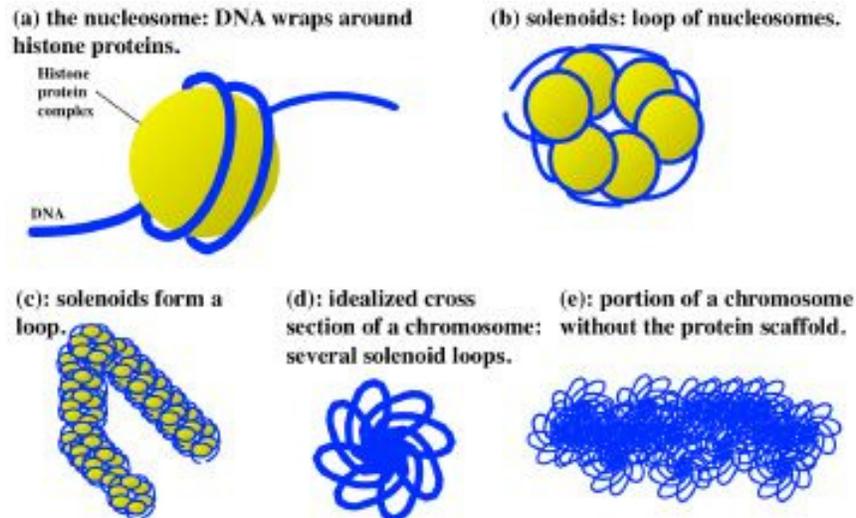
This is a short chapter. We want to introduce terminology to talk about genes, their locations, and DNA structure. More information about chromosomes and chromosomal anomalies may be found in Chapter X.X.

3.1   DNA packaging

To appreciate the way that DNA is packaged, we should first think of three types of objects—a very, very long piece of twine, several million donuts, and the Eiffel tower. Taking the twine in one hand and a donut in the other, wrap the twine twice around the donut in the way shown in panel (a) of Figure 3.1. Leaving a few inches of twine free, grab another donut and loop the twine around it twice. Repeat this process until you have about six donuts with twine wrapped around them, giving a structure similar to that in panel (b). Arrange these donuts in a circle on the ground right next to the bottom of the tower. Repeat this with another six donuts and place them, again in a circle, almost on top of the first six donuts. Continue repeating this process until there is a loop of these twine-donut complexes as depicted in panel (c).

Eventually, the pile of twine and donuts will become high enough to make it unstable and in danger of toppling over. To prevent this, have a few helpers take the pile of donuts and start circling it around the Eiffel tower to give it support, gluing it to the tower if necessary. Proceed with this strategy of looping twine around donuts, arranging circles of donuts, and snaking these piles in and

Figure 3.1: Packaging of DNA into chromosomes (from HGSS).

(a) the nucleosome: DNA wraps around histone proteins.

Histone protein complex

DNA

(b) solenoids: loop of nucleosomes.

(c): solenoids form a loop.

(d): idealized cross section of a chromosome: several solenoid loops.

(e): portion of a chromosome without the protein scaffold.

around all the rigid structure of the tower. When you finally run out of string, jelly donuts, and tower space, you will have created a chromosome. An electron microscope image of the human X and Y chromosomes immediately prior to the cell division is given in Figure 3.2.

The twine in this procedure is the DNA molecule and the donuts are composed of eight small proteins called *histones*. The DNA-histone complex is called a *nucleosome*. Not simply a physical structure, modification of the histone proteins plays a role in the dimmer switch of gene regulation and expression. Hence, it is important to know the term nucleosome and its definition–DNA wound around a histone protein complex.

The term *chromatin* is used for the packaging of the nucleosomes around the protein scaffolds. The actual state of the chromatin depends on the cell cycle. The description given above applies to the chromosomes when they are at their greatest

Figure 3.2: Electron microscope image of the human X and Y chromosomes immediately prior to cell division.

From http://www.snv.jussieu.fr/vie/ dossiers/ky/chromosome%20X%20et%20Y.jpg

density–right before cell division. At other times in the cell cycle–and also in cells like mature neurons that do not ordinarily divide–the Eiffel tower protein

scaffolding is not present, leaving the chromatin as a more thread-like structure. Also, a single chromosome will have sections of densely packed DNA interspersed with more loosely packed areas.

When the cell is not in the process of replication, the density and looseness of the chromatin is associated with gene expression. In the looser areas, genes are usually being expressed (i.e., the dimmer switch is ratcheted up) while genes in the denser sections are often being repressed (the dimmer switch is turned down and sometimes may be shut off completely).

3.2   Studying chromosomes

Chromosomes were discovered in the middle of the 19th century when early cell biologists were busily staining cell preparations and examining them under the microscope. It was soon recognized that the number of chromosomes in sperm and egg was half that in an adult organism, and by the 1880s it was conjectured that the chromosomes carried the genetic material. Theorizing about genetics and chromosomes abounded and generated one of the more interesting curiosities in the history of science. Despite the ability to actually see the genetic material under the microscope, for over 20 years early cell biologists were unable to derive the simple laws of segregation and independent assortment postulated by an unknown Austrian monk, Gregor Mendel. Mendel worked these laws out because of the properties of a mathematical model and to the best of our knowledge never even saw a chromosome!

Today, the study of chromosomes–both in the research lab and in clinical settings–is called *cytogenetics*. There are two major tools used in cytogenetics today. The first is the *karyotype* which is literally a picture of the stained chromosomes that can be viewed under the light (or fluorescent) microscope. The second is a procedure called *fluorescent in situ hybridization* or FISH that is used to detect chromosomal microdeletions, i.e., deletions that are too small to see under a light microscope. Here, we discuss the karyotype and leave FISH for a later section after we have learned more about molecular genetic techniques.

A typical karyotype is given in Figure 3.3. Karyotypes are most often used in clinical, pediatric settings. The first major reason is to confirm or refine a suspected diagnosis of a known chromosomal anomaly. Testing for Down's syndrome in a newborn is a classic example. A second use occurs when a newborn or infant exhibits wide series of physical and medical irregularities. Here, the pediatrician will order a karyotype to see if there is a gross chromosomal abnormality.
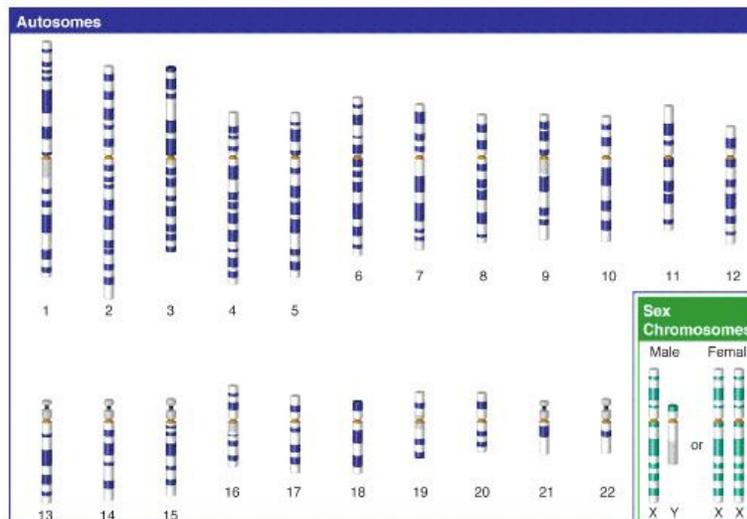
Construction of a typical karyotype begins with living tissue, usually a particular type of white blood cell called the *lymphocyte* obtained from a blood sample. The lymphocytes are kept alive and dividing in a culture and then, in a series of complicated steps, are stained and examined under the microscope. Pictures are taken of the chromosomes under the microscope. The chromosomes are then cut out of the photographs and pasted onto paper in a certain order. Today, the process is greatly aided by computer imaging technology, reducing

Figure 3.3: A typical karyotype.

From http://www.genome.gov/Glossary/resources/karyotype.pdf
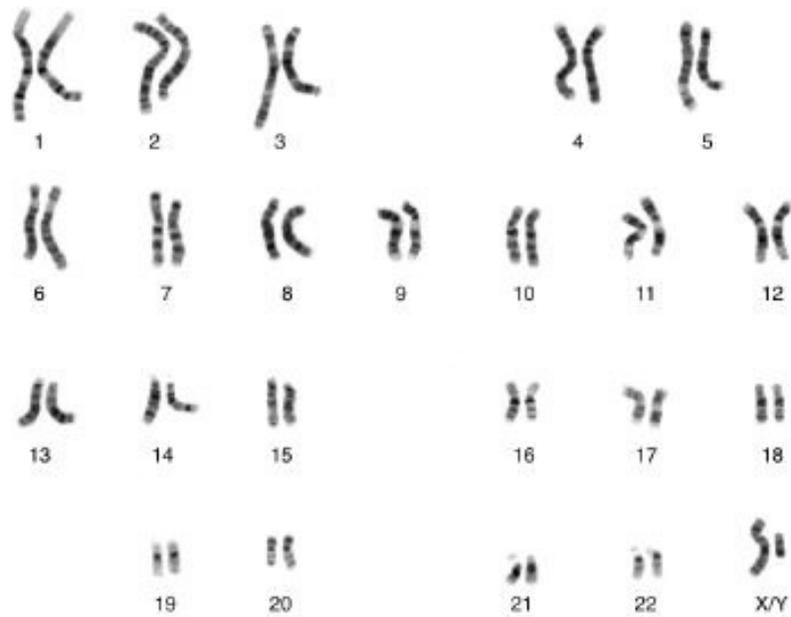
Figure 3.4: Schematic for the banding patterns of the human chromosomes.

From http://www.genome.gov/Glossary/resources/x-chromosome.pdf

the need for the tedious photographic and cut and paste steps.

Different sections of chromosomes absorb the stain better than other sections, leading to a characteristic banding pattern for every chromosome. There are several different staining techniques used to generate a karyotype, each one having its advantages and limitations. In clinical cytogenetics, it is not unusual to perform more than one karyotype to determine whether someone has a chromosomal abnormality.

3.3   Nomenclature

There is a standard terminology used among cytogeneticists for ordering and numbering chromosomes, referring to the bands of a chromosome, and describing any chromosomal abnormalities. Humans have 23 pairs of chromosomes. They are divided into the sex chromosomes (i.e., the X and Y chromosome) and the *autosomes* (i.e., the other 22 pairs). The term *autosomal* is frequently encountered in genetics to refer to a gene or chromosomal anomaly involving an autosome. The autosomes are ordered by height, position of the centromere (the region separating the two arms of the chromosome), and banding patterns. Figure 3.4 provides a schematic of the banding patterns for the 22 autosomes and the sex chromosomes

Karyotypes are abbreviated by the total number of chromosomes, a comma, and the sex chromosomes of an individual. Thus, the notation 46,XX denotes

a normal female; 46,XY, a normal male; and 45,X (or sometimes 45,XO) an individual who has only one X chromosome, a condition that produces Turner's syndrome. Karyotypes followed by a plus and then a number indicate trisomy, the inheritance of a whole extra chromosome. For example, 47,XX,+21 denotes a female with a trisomy of chromosome 21 which results in Down syndrome. Similarly, a minus sign followed by a number denotes monosomy or the loss of an entire chromosome.

Figure 3.5 provides a schematic for the banding pattern of chromosome 18. The ends of the chromosome, that is the "top" and the "bottom," are called the telomeres. The section corresponding to the "over tightened" belt on the chromosome is called the centromere.

Far from being mere physical structures both the telomeres and centromeres have functional significance. The spindles that "drag" one copy of the chromosome onto one daughter cell and the other copy into the other daughter cell attach to the centromere. Telomeres are the topic of active research in aging. Telomere lengths shorted as a cell undergoes more and more cell divisions until eventually the cell dies. Evidence is accumulating that shortened telomeres are associated with a number of diseases (e.g., Aviv and Levy, 2013, X.X).

Figure 3.5: Banding schematic for human chromosome 18 (adapted from HGSS).

The short arm of a chromosome, conventionally placed at the top, is called the p arm and the long arm, the q arm. Numbering of the bands begins at the centromere and progresses to the terminal of an arm. The number of bands depends upon the type of staining and the particular stage of cell division at which the cells are arrested in culture. The high resolution bands, shown in the chromosome on the right hand side of Figure 3.5, are derived from cells where the chromosome is more elongated. As the process of cell division progresses, the chromosomes become more compacted and dense, leading to the banding pattern on the left hand side of the figure.

Bands are denoted by the chromosome number, arm, and band number(s). For instance, Often a range of bands may be specified. For example, 15q11-13 denotes bands 11 through 13 of the long arm of chromosome 15. Deletions in this region can result in Prader-Willi syndrome or Angelman syndrome.

There are many other notational devices for chromosomal anomalies. They are too detailed for our purpose here, so the interested reader should consult a standard textbook on medical genetics.